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# A Scaleable Route to the Pure Enantiomers of Verapamil

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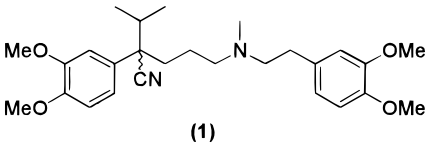
**Abstract:**

**A versatile route to single enantiomer verapamil from readily available raw materials is described. The key intermediate, 4-cyano-4-(3,4-dimethoxyphenyl)-5-methyl hexanoic acid (verapamilic acid), was resolved efficiently with α-methyl benzylamine. Stereochemical integrity at the quarternary carbon centre was preserved through subsequent steps to give either (*R*)-or (*S*)-verapamil in good overall yield. This sequence incorporated a selective borane-mediated reduction of a tertiary amide. Process scale-up to the pilot plant has been demonstrated successfully for the resolution step.**

## Introduction

Verapamil (**1**) has a well-established place in the treatment of cardiovascular ailments.[1] The compound is usually administered as its hydrochloride salt. Currently there is renewed interest in enhancing this drug's portfolio by replacing the racemate with either the pure single enantiomers, or non-stoichiometric mixtures thereof. These isomers differ significantly in their biological effects and pharmacodynamics.[2] (*S*)-(−)-Verapamil has quite specific transmembrane calcium channel antagonist activity, whilst its antipode influences a wider range of cell pump actions, including that for sodium ions. Formulations enriched in the (*S*)-enantiomer are likely to confer greater pharmacological efficacy, with diminished side effects, for cardiac arrhythmia and hypertension. In contrast, angina appears to be better alleviated by (*R*-(+)-verapamil. Unrelated therapeutic targets, such as multidrug resistance in cancer chemotherapy,[3] and migraine,[4] have also been proposed for verapamil. These more speculative outlets may also benefit from an optimisation of the enantiomer ratio.[5]

Lack of a scalable "chiral switch" for verapamil has hindered investigations since, hitherto, there has been insufficient material available to support detailed clinical trials. A number of syntheses have been published, but these have little prospect of providing kilograms of bulk active at an acceptable cost. The substitution pattern at the chiral quaternary centre cannot be readily derived from members of the chiral pool or by asymmetric induction. Efforts to do so have resulted in lengthy syntheses comprising many functional group interconversions, as well as separations of diastereomeric intermediates by column chromatography.[6−8] Verapamil free base has been resolved directly, but to obtain high enantiomeric excesses (ee's) required inefficient, multiple recrystallisatons or very expensive auxiliaries.[9,10] Furthermore, no salt of verapamil has been identified as forming a conglomerate, and bulk synthesis of the parent amine involves only achiral precursors.[11] McCague et al devised an adaptation of the latter that was based around resolution of a secondary amine intermediate, but this tactic distanced the overall route from readily available starting materials.[12] Another approach was based upon the resolution of 4-cyano-4-(3,4-dimethoxyphenyl)-5-methyl hexanoic acid ("verapamilic acid") (**2**), as the key intermediate.[13] The route was unattractive, as described, because it employed the expensive and toxic alkaloid brucine for the resolution step. Additionally, downstream conversion to verapamil involved a low-yielding reduction step and a high-temperature coupling reaction, with neat reactants, whilst purification of the final product was both laborious and indirect. However, this approach shared key feedstocks with manufacture of the racemic verapamil, allowed flexibility in onward conversion to the final product, and did not require column chromatography for any step. We reasoned that should a better resolution be developed for **2** then a means to meet our objectives would follow. Herein, we describe our efforts to

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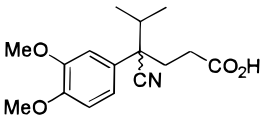


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(1) Cervoni, P.; Crandall, D. L.; Chan, P. S. Cardiovascular Agents. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed.; Kroschwitz, J. L., Executive Ed.; Howe-Grant, M., Ed.; Wiley: New York, 1992; Vol. 5, pp 207−300 and references therein.
(2) Longstreth, J. A. Verapamil: A Chiral Challenge to the Pharmacokinetic and Pharmacodynamic Assessment of Bioavailability and Bioequivalence. In *Clinical Pharmacology*, 2nd ed.; Wainer, I. W., Drayer, D. E., Eds.; Drug Stereochemistry, Vol. 11; Dekker: New York, 1993; p 315.
(3) Eliason, J. F.; Ramuz H.; and Kaufmann, F. *Int. J. Cancer*. **1990**, *46*, 113.
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(5) Longstreth, J. A.; Fakhreddin, J. Int. Patent Appl. WO9744025A1 (U.S. Patent 5,955,500, 1999).
(6) Ramuz, H. *Helv. Chim. Acta*. **1975**, *58*, 2050.
(7) Theodore, L. J.; Nelson, W. L. *J. Org. Chem*. **1987**, *52*, 1309.
(8) Gilmore, J.; Prowse, W.; Steggles, D.; Urquhart, M.; Olkowski J. *J. Chem. Soc., Perkin Trans. I* **1996**, 2845.
(9) Blasche, G.; Doebber, P. Ger. Patent DE 3723684.
(10) Ehrmann, O.; Nagel, H.; Karau, W. Int. Patent Appl. WO9316035 and WO9408950.
(11) Dengel, F. Belg. Patent 615,861, 1962 ; Idem. U.S. Patent, 3,261,859, 1966.
(12) McCague, R.; Wang, S. Int. Patent Appl. WO 9509150.
(13) Trieber, E. J.; Raschack M.; and Dengel, F. Ger. Patent 2,059,923, 1972 .

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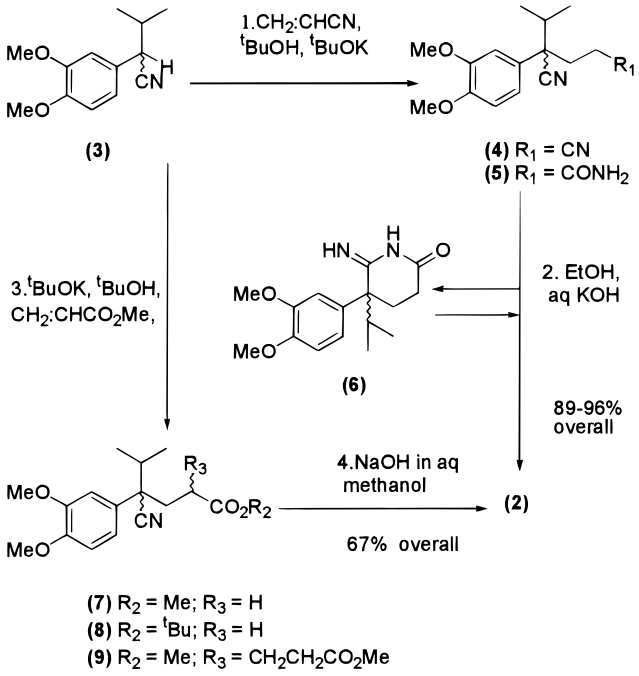
develop a process with the potential to deliver large quantities of pure, single isomer verapamil.

## Results and Discussion

The first hurdle to overcome was to secure a reliable procedure to make racemic **2**. This compound is accessible by Michael addition of either acrylonitrile or acrylate esters to 2-isopropyl homoveratronitrile (**3**), as shown in Scheme . Since **3** is already an intermediate in the commercial synthesis of racemic verapamil, it is available in bulk at low cost. Knoll Pharmaceuticals supplied our 2-isopropyl homoveratronirile, which was used without purification. Reaction of **3** with acrylonitrile proceeded best in *tert*-butyl alcohol with a catalytic amount of potassium *tert*-butoxide as base. After some experimentation, a loading of 0.5 mol % of this base was adopted. HPLC reaction monitoring, which allowed the reagent charges to be adjusted prior to the water quench, assured essentially quantitative conversion to bis-nitrile (**4**). Although **4** could be isolated in high yield

***Scheme 1***




after crystallisation from methanol (mp 97.2−100.1 °C), we pursued a procedure that incorporated the subsequent (primary) nitrile hydrolysis. After drowning out in water, the *tert*-butyl alcohol was distilled out and replaced with ethanol and aqueous potassium hydroxide. The mixture was reheated to distill out the ethanol and then boiled under reflux until the conversion to verapamilic acid was >90% by HPLC (16−18 h). A homogeneous medium was necessary to start conversion of **4** to **5** at a satisfactory rate. Ethanol, but not *tert*-butyl alcohol, solubilised **4** to achieve this: hence the need for two distillation steps. Provision of a phase transfer catalyst in the future may permit ethanol to be dispensed with. Although **4** had disappeared after 2−3 h, the persistence of amide **5** and adduct **6** necessitated long periods at reflux. Both intermediates were isolated from the hydrolysis and identified: the former was extracted into ethyl acetate, whilst the latter was recovered from the aqueous phase. Verapamilic acid was isolated in 89−96% physical yield and 97−99% HPLC purity after controlled precipitation by acidification at 60−65 °C.

The alternative pathway via methyl acrylate proved unsatisfactory. Under the best conditions tried, a 2:1 mixture of esters **7** and **8** was obtained, which was contaminated by solvent (*tert*-butyl alcohol) addition products for example $^{t}BuOCH_2CH_2CO_2Me$. Attempts to perform the reaction in THF/*tert*-butyl alcohol mixtures led to the bis-addition product(s) **9** appearing in significant proportions.

A small screen of eight resolving agents was undertaken for the resolution of **2**, of which three were effective. The particulars of the lead results are highlighted in Table 1. (*R*)-Quinine, the least efficient of the base trio, also shares many of the disadvantages of brucine (expense, availability of only the "natural" enantiomer, and relatively high molecular weight). These two alkaloids give complementary resolutions to the enantiomers of **2**. In contrast, 1-naphthylethylamine and α-methyl benzylamine (α-MBA) are available in either enantiomeric form, which allows access to both **2a** and **2b** with equal ease. However, the cost of chiral 1-naphthylethylamine precludes it from further consideration for large-scale work. Hence, cheap and commercially readily available single isomer α-MBA was identified as the best resolving agent for **2**, in terms of both cost and efficiency (highest *S* factor).[14]

Further development work confirmed that the highest diastereomeric excesses were obtained when the α-MBA salts of **2** were crystallised from ethyl acetate. Processing constraints with this solvent were imposed by formation of *N*-acetyl α-MBA, which became significant above 60 °C. Toluene was an inefficient solvent for the resolution ($S$ = 0.55), but proved ideal for purification of enantiomerically enriched streams of **2**, generated from it. This solvent conferred greater process robustness, being more chemically inert and allowing any moisture carry-over to be easily removed azeotropically. Entrained water had a demonstrable adverse affect on the crystallisation. Careful temperature control during cooling back to 0−5 °C, prior to isolation, was also very important in securing the best crystal forms and diastereomeric excesses (de's) from both ethyl acetate and toluene.

Scheme 2 depicts the overall resolution process we devised, whereby *both* enantiomers of **2** were obtained sequentially in >95% de from single crystallisations, each in ∼40% physical yield. If desired, salts **10a** and **10b** could be purified to 98−99% de by recrystallisation from ethyl acetate. The latter de's were obtained by a single crystallisation in the laboratory on some occasions, and it may be that more precise control of the vessel jacket temperature during the early stages of cooling back will allow this feature to be scaled up too. On our pilot plant the process was run as shown in Scheme 2, but there is no reason **10b** could not be crystallised first, by transposing the addition order of the α-MBA enantiomers. Reuse of the verapamilic acid remain-

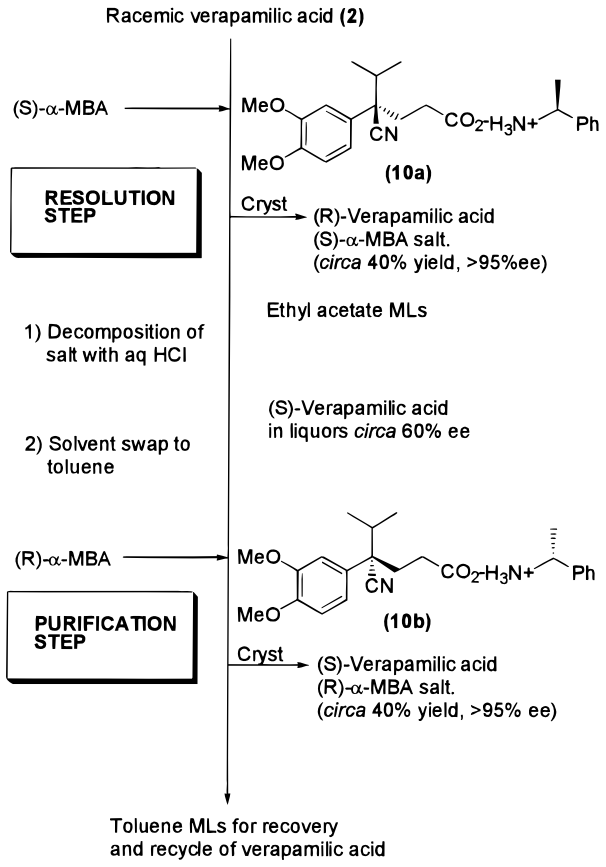
(14) Fogassy, E.; Lopata, A.; Faigl, F.; Darvas, F.; Acs, M.; Toke, L.; *Tetrahedron Lett.* **1980**, *21*, 647.

**Table 1.**

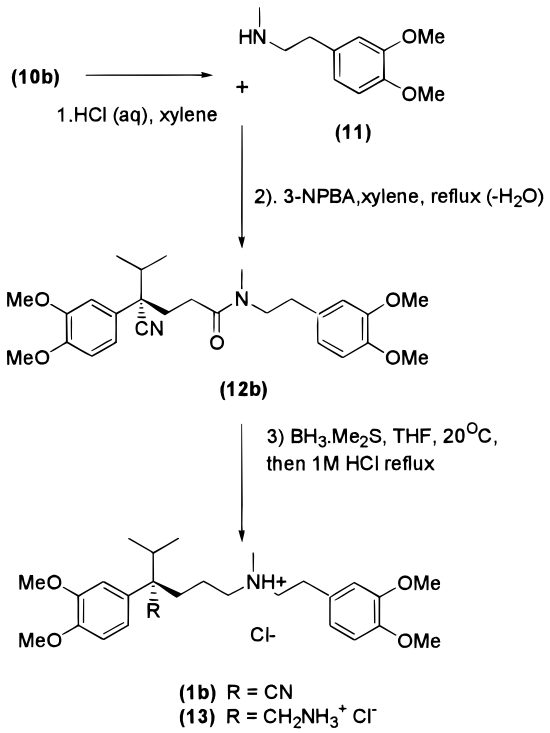
| resolving agent | solvent | yield of salt (d.e. %) | *S* factor[a] |
|---|---|---|---|
| (*R*)-(−)-quinine (MW 324) | acetone | 72% (84.5%) **(2a)** | 0.46 |
| (*R*)-(+)−1-(1-naphthyl)- ethylamine (MW 171) | ethyl acetate | 86% (82.5%) **(2b)** | 0.71 |
| (*S*)-(−)-α-methyl benzylamine (MW 121) | ethyl acetate | 88% (96.6%) **(2a)** | 0.76 |

[a] *S* = efficiency = diastereomeric excess (de)% of solid × yield × 2.

**Scheme 2**




**Scheme 3**




ing in the toluene mother liquors appears to be feasible, and would raise the total utilisation of racemic **2** to above 80%.

Whilst racemic **2** was relatively easy to obtain as a solid, the single isomer forms preferred to oil out under the same conditions. Because of these difficulties, the decomposition of **10a** or **10b**, with aqueous acid, was integrated into downstream processing, and no further attempt made to isolate the liberated acids.

Although resolved **2** has been elaborated to verapamil after reduction to the corresponding alcohol[13] or aldehyde,[15] no synthetic route via coupling with *N*-methyl homoveratrylamine (**11**) at the *same* oxidation level has been reported.[16] We decided to explore this option, shown in Scheme 3, and assess its feasibility for scale-up. Amine **11** is the other feedstock shared with the extant commercial synthesis of racemic verapamil. Uetikon provided our supply of **11**, which was redistilled prior to use (bp 109−110 °C at 1 mBar). Direct coupling of resolved **2** with amine **11** (1.1 mol equiv) was achieved in 85−90% yield, in toluene or xylene solvent, and facilitated by 0.5−1 mol % 3-nitrophenyl boronic acid (3-NPBA).[17] The high efficiency of the latter reagent at least partially offset its high cost. Boric acid itself was also effective as catalyst, but required much higher loadings (10−20 mol %) and gave somewhat lower conversions to verapamilamide (**12**). After removing excess amine **11** with an aqueous acid wash, the organic solution was azeotrope-dried and concentrated to crystallise amides **12a** or **12b**. Once again, the single isomer forms showed greater reluctance to crystallise than racemic **12**, and seeding with authentic material was essential for consistency. The amides crystallised most easily from concentrated xylene solutions ( ∼2.1 volumes). Once the product started to come out of solution, dry xylene was added to the flask to maintain suspension mobility.

Interestingly, the proton NMR spectrum of **12** is complicated by the presence of a 1:1 mixture of rotamers. At ambient temperature, several peaks were doubled up, includ-

(15) Kastner, G.; Hardo, S.; Geiss, K. H. U.S. Patent 4,350,636, 1982.
(16) Bannister, R. M.; Evans, G. R.; Skead, B. M. Int. Patent Appl. WO 9729081.
(17) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196.

ing the *N*-methyl group, which gave two singlets at ($\delta$ 2.73 and 2.80). These resonances coalesced at ~80 °C, indicating that a significant barrier to free rotation about the amide bond exists. The HPLC *chiral* purity of **12** could not be checked accurately, since only partial separation of the enantiomer peaks was obtained, even on a bovine serum albumen (BSA) protein or Chirobiotic T columns. This deficiency was tolerable because fully effective methods were in place for both **10** and verapamil. Further process refinement may allow uncrystallised amide to be charged directly to the reduction step.

The final reduction of **12** was the most chemically challenging step of our route. A wide variety of reagents are capable of converting amides to amines,[18] but our requirement for selectivity imposed significant constraints on the choice. Scouting experiments discounted use of aluminium hydride reagents because they tended to be too aggressive, causing some cleavage of the amide itself. In our hands, the action of borane:THF was confined to reduction, but it failed to discriminate between the amide and nitrile groups to a satisfactory degree; hence, a significant proportion of **12** ended up as the diamine **13**.[7] Borane: dimethyl sulphide complex (BMS) was able to reduce the amide functionality completely, without affecting the nitrile group substantially, and was advantageous in terms of its far greater stability.[19] Use of BMS also allowed a choice of reaction solvent. Robust conditions for reducing **12** in 5 vols of THF with 1.85 equiv of BMS were quickly identified. Although reduction of an amide consumes only two hydride equivalents formally, a second mole of borane complexes to the amine formed; 1.85 equiv therefore represents a 10% mole excess of theory. Over-reduction to **13** was still very limited (10.8 mol %) even after stirring for 60 h with 2.5 equiv of this reagent. 1,2-Dimethoxyethane (DME) provided an equally suitable reaction medium, but 8 vols were required to dissolve **12**. HPLC monitoring showed that the reaction went to completion, and an in-process assay was consistent with 85−90% active ingredient yield of verapamil.

Whilst conditions for the reduction itself were facile, the work-up and product purification required detailed optimisation. Forcing conditions were needed to decompose the verapamil:borane complex and aqueous or methanolic solutions of hydrogen chloride at reflux were the most effective. Both methanolic and the more concentrated hydrochloric acid solutions (3−6 M) appeared to promote side reactions which significantly depressed the quality and physical yield of the product. We were able to suppress, but not eliminate, this deterioration by using 1 M hydrochloric acid in the step. The extent of these side reactions was hard to quantify since their high molecular weights or polarities caused them to be retained on the GC and HPLC columns used for reaction monitoring. In our experience, boiling with lower-strength acid for longer periods gave the best tradeoff, in terms of crude product yields. Despite these measures, the level of impurities was such that most of the product oiled out upon cooling the aqueous solution. This phase was readily miscible with dichloromethane but would not dissolve in ethyl or isopropyl acetate.

Most literature verapamil preparations have isolated the free base, purified it, then appended conversion to, and then crystallisation of, the hydrochloride salt. This approach is disadvantageous for scale-up because of the variety of solvents employed and the lengthy processing it entails. Our shorter work-up exploited the solubility of verapamil hydrochloride in dichloromethane, which also allowed it to be extracted *directly* from the acid quench liquors. Apart from giving better volume efficiency, more polar impurities, such as **13**, which would also have been extracted following basification, remained in the aqueous phase.

Attempts to crystallise the residue obtained from evaporating the dichloromethane extracts, by existing methods, were largely unsuccessful due to the impurity burden. We found that a manageable solid precipitated if a concentrated solution of the residue in 2-propanol was added slowly to a large volume of well-stirred methyl *tert*-butyl ether, which had been seeded with authentic **1a/b**. Although a 73% (net) physical yield was obtained, this material still required a recrystallisation from 10 vols of 2-propanol to raise its specification to >99.5% PAR (HPLC) and mp >130 °C.[20] The latter step proceeded with 85% recovery, making the Stage's overall yield 62.1%. Sticky, inferior crystals precipitated after an attempt to substitute a concentrated dichloromethane solution for one of 2-propanol in the first crystallisation. Optimisation work continues on this step, with a view to obviating the need for a recrystallisation.

Despite the convenience of the reduction procedure, it is still only suitable for large laboratory or small kilo laboratory scale, due to the use of BMS. The disadvantages of this reagent are its expense and the need for specialised handling equipment, when working at higher volumes. We have therefore tried to substitute borane generated in situ (from $NaBH_4$ and HCl) for this transformation. A change in reaction solvent from THF to DME was necessary to accommodate anhydrous hydrogen chloride. Although this method is presently less clean than BMS mediated reduction, we are confident that further development work will deliver a satisfactory process.

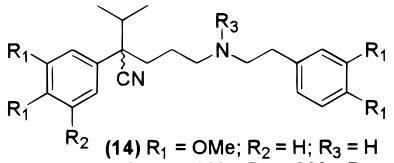
## Conclusions

We believe that our endeavours have provided the basis for a simple and efficient process to both (*R*)- and (*S*)-verapamil hydrochloride which could be run at up to kilo laboratory scale, with little further modification. The overall yield of single isomer verapamil hydrochloride from **3** stands at 35−40% of theory for *each* enantiomer. There are only four steps to the synthetic route. Reuse of the toluene liquors from the resolution, improvements to the efficiency of the amide reduction work-up, and final product crystallisations will probably improve this figure. Our synthetic strategy should permit the preparation of related compounds in single isomer form, such as the pharmacologically active metabolite

(18) Pelter, A.; Smith, K.; Brown, H. C. In *Borane Reagents*; Katritsky, R.; Meth-Cohn, O.; Rees, C. W. Eds.; Academic: San Diego, 1988.

(19) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH: New York, 1991.

(20) For a thorough review on analytical topics related to verapamil see: Chang, Z. L. *Analytical Profiles of Drug Substances* **1988**, *17*, 643.




**(14)** $R_1$ = OMe; $R_2$ = H; $R_3$ = H
**(15)** $R_1$ = OMe; $R_2$ = OMe; $R_3$ = Me
**(16)** $R_1$ = H; $R_2$ = H; $R_3$ = Me

norverapamil (**14**),[2] as well as analogues gallopamil (**15**),[7] emopamil (**16**),[8] and other structural relatives. Since the demand for chiral verapamil hydrochloride is likely to be skewed in favour of the (*S*)-enantiomer, we are presently examining a means to recycle the unwanted isomer. Disassembly of the quarternary carbon centre to facilitate racemisation is not trivial, but we have demonstrated the feasibilty of a retro-Michael reaction on **2**.[21] It is anticipated that further process development will allow the amide reduction step to be run in larger, more general purpose, plant equipment.

## Experimental Section

Proton NMR spectra were obtained from a Bruker AM 400-MHz machine. A VG Platform II spectrometer was used to record mass spectra. A Perkin-Elmer 1600 FTIR spectrometer provided the infrared data. Gas chromatography analysis was performed using a Perkin-Elmer Autosystem 600 model in conjunction with a DB-5 column. Melting points were determined with either a Leica Galen (III) microscope hot stage or a Mettler-Toledo DSC 12E, and are uncorrected. Optical rotations were measured at 589 nm on a Perkin-Elmer polarimeter. CHN combustion data was obtained from a Leeman Labs Inc CE440 elemental analyser. All laboratory reagents were used as supplied, unless stated otherwise. The reactions described below were carried out under a nitrogen atmosphere and routinely monitored for completion by GC or HPLC. Process water was deionised throughout. The xylene solvent used was the commercial mixture of isomers and ethyl benzene.

**Verapamilic Acid (2).** Potassium *tert*-butoxide (0.2 kg, 1.78 mol) was charged to a stirred solution of nitrile **3** (8.0 kg, 36.7 mol) in *tert*-butyl alcohol (31.0 kg, 40 L). The vessel contents were adjusted to 20−25 °C, and then acrylonitrile (2.53 kg, 47.7 mol) was introduced over 2.5 h. After this temperature range was maintained for a further hour, the reaction was sampled for a completion check and then quenched with water (1.0 L). A solvent exchange was performed by distilling out the *tert*-butyl alcohol at atmospheric pressure whilst feeding in water to keep the batch volume approximately constant. Ethanol (16.0 L) and a solution of potassium hydroxide (3.1 kg, 55.4mol) in water (8.0 L) were then added, and distillation was repeated until the pot temperature reached 100 °C. The batch was subsequently boiled under reflux until conversion to product was >90% by HPLC (18 h). The solution was cooled to 50−60 °C prior to careful addition of 6 M hydrochloric acid (5.5 L) to obtain the cloud point (at ∼pH 6). The preparation was seeded with authentic **2** (0.08 kg), and stirred out until crystal growth was evident. Once this had occurred, the pH was reduced to <1.0 with further 6 M hydrochloric acid (10 L), and the resulting suspension cooled to 20 °C, prior to filtration. The solid was washed with water (3 × 12 L) before drying under vacuum at 50−60 °C to afford **2** as an off-white microcrystalline powder (9.7 kg, 33.4 mol, 91.3% yield,) mp 113.7−116.8 °C. $^1$H NMR spectrum ($CDCl_3$): $\delta$ 0.83 (d, 3H); 1.22 (d, 3H); 2.2 (m, 3H); 2.5 (m, 2H); 3.89 (s, 3H); 3.9 (s, 3H); 6.9 (m, 3H); 13.0 (b,s 1H). HPLC purity 99.0% PAR; method: column NovaPak C18, 4 $\mu$m, 3.9 × 150 mm, mobile phase 40 MeCN, 59 $H_2O$, 1.0 trifluoroacetic acid (TFA), flow rate 1 mL/min, temperature 40 °C, detector UV at 230 nm. Retention times: **3**, 6.0 min; **4**, 5.6 min; **2**, 3.1 min; **5**, 1.9 min; **6**, 1.0 min. IR spectrum (KBr disk): 2230.1(w), 1705.2(s) cm$^{-1}$.

**Resolution of Verapamilic Acid. (*R*)-Verapamilic Acid (*S*)-α-MBA Salt (10a).** (*S*)-α-MBA (3.3 kg, 27.3 mol) was added over 10 min to a solution of **2** (7.93 kg, 27.3 mol) in ethyl acetate (35.7 kg, 40.0 L) at 40 °C. The batch temperature was then adjusted to 50 °C prior to seeding with salt **10a** (0.03 kg). After a 2 h stir-out at 50 °C, the preparation was cooled slowly to 0−5 °C, at a rate of no more than 5 °C per hour. Following 1 h at 0−5 °C, the suspension was filtered and the cake washed with cold ethyl acetate (2 × 15 kg, 13.5 L). The solid was dried to constant weight at 35−45 °C in vacuo to give salt **10a** as a white crystalline solid (4.35 kg, 10.6 mol, 38.8%), mp 132.4−134 °C, $[\alpha]^{20}_D = +15.4°$ (*c* 5.2, MeOH). $^1$H NMR ($D_2O$): $\delta$ 0.71 (d, 3H); 1.14 (d, 3H); 1.33 (d, 3H); 1.63 (m, 1H,); 1.98 (m, 1H); 2.18 (m, 1H); 2.29 (m, 2H); 3.8 (s, 6H); 4.17 (q, 1H); 6.93−7.02 (m, 3H); 7.28 (m, 1H); 7.38 (dd, 2H); 7.45 (d, 2H). HPLC: 99.0% PAR; 96.7%ee. Method: column Chiralcel OJ 10 $\mu$m, 4.6 × 250 mm, mobile phase 88 heptane, 11.5 2-propanol, 0.5 TFA, flow rate 1.0 mL/1 min, temperature 30 °C, detector at 230 nm, retention times α-MBA, 5 min; *N*-acetyl-α-MBA, 8.7 min; **2a**, 10.6 min; **2b**, 15.2 min; dimethoxy isobutyrophenone (feedstock impurity) 28 min. Calcd for $C_{24}H_{32}N_2O_4$; C, 69.88; H, 7.82; N, 6.79%. Found: C, 69.61; H, 7.85; N, 6.83%.

**(*S*)-Verapamilic Acid (*R*)-α-MBA Salt (10b).** The combined ethyl acetate mother liquors and washes from the above preparation of (**10a**) were stirred with 1 M hydrochloric acid (18 L) (pH check <2.0) and then water (2 × 10 L). The organic phase was subsequently concentrated by vacuum distillation (200−250 mBar), until the pot temperature reached 60 °C. After a full solvent swap to toluene, with concomitant azeotropic removal of entrained water, the residual solvent charge was adjusted to 4 vols, with respect to the (calculated) free **2** content. After the solution cooled, to 50−55 °C, (*R*)-α-MBA (1.96 kg, 16.2 mol) was added. The solution was heated back to 60−65 °C prior to seeding with authentic salt **10b** (0.03 kg). After stirring out for 2 h, the vessel contents were carefully cooled to 5−10 °C over 19 h. The crystallised solid was filtered off, washed with toluene (2 × 14.0 kg, 16.0 L), and dried in vacuo, as above, to furnish salt **10b**, (4.65 kg, 11.3 mol, 41.4%), (mp 132.2−133.6 °C, $[\alpha]^{20}_D = -14.9°$ (*c* 5.0, methanol). $^1$H NMR

(21) McCague, R. International Patent Appl. WO 9729080.

spectrum ($CDCl_3$) was identical to that of **10a**. HPLC: 99.2% PAR; ee 96.3%, method as above. CHN Found: C, 69.88; H, 7.88; N, 6.55%.

**(*S*)-Verapamilamide (12b).** Salt **10b**, (494 g, 1.2 mol) was partitioned between xylene (3.0 L) and 1 M hydrochloric acid (1.5 L) at 40 °C. After the reaction mixture was washed further with water (2 × 1.0 L), amine **11** (260 g, 1.32 mol) and a solution of 3-nitrophenyl boronic acid (1.0 g, 6.0 mmol) in xylene (0.25 L) were added sequentially, and then the whole was boiled under reflux for 24 h. A Dean−Stark apparatus removed water carried over from the separations and that arising from the condensation. After it was established that the reaction was complete by HPLC, the preparation was cooled to, and then maintained at, 40 °C whilst washing with 1 M hydrochloric acid (1.0 L), water (1.0 L), 5% sodium bicarbonate solution (1.0 L), and finally more water (1.0 L). The organic phase was concentrated and dried by distilling out 2.0 L of wet xylene. Upon cooling back to 50−55 °C, the residual solution was seeded with authentic **12b** (12.5 g). Once crystallisation had initiated, the resulting suspension was carefully cooled to 0−5 °C over 3 h, whilst diluting with dry xylene (1.5 L) to maintain mobility. The crude product was filtered off, washed with xylene (2 × 0.5 L), and then dried in vacuo at 50 °C to afford **12b** as a white microcrystalline solid (479.8 g, 1.03 mol, 85.5% yield; mp 95−97 °C), $[\alpha]^{25}_D = -6.1°$ (*c* 5.18, ethanol).

$^1$H NMR ($d_6$-$Me_2SO$, at 20 °C): $\delta$ 0.71 (2d, 3H); 1.14 (2d, 3H); 1.70 (m, 0.5H); 1.87 (m, 0.5H); 1.99 (septet, 0.5H); 2.1−2.32 (m, 3.5H); 2.60 (2t, 2H); 2.73 (s, 1.5H); 2.80 (s, 1.5H); 3.3 (t, 1H); 3.42 (t, 1H); 3.7−3.8 (4s, 12H); 6.50 (d, 0.5H); 6.67 (s, 0.5H); 6.68 (d, 0.5H); 6.77 (s, 0.5H); 6.78 (d, 0.5H); 6.84 (d, 0.5H); 6.91−7.02 (m, 3H). (at 100 °C): $\delta$ 0.77 (d, 3H); 1.15 (d, 3H); 1.92 (m, 1H); 2.18−2.36 (m, 4H); 2.67 (t, 2H); 2.76 (s, 3H); 3.4 (t, 2H); 3.76−3.81 (4s, 12H); 6.67 (d, 1H); 6.76 (s, 1H); 6.86 (d, 1H); 6.98 (m, 3H). HPLC: 99.0% PAR; Method: Novapak C18 column; mobile phase water 60: acetonitrile 40: TFA 1; 1 mL per min, detection at 230 nm. Retention times: **11**, 1.5 min; **2**, 3.9 min; **12**, 9.7 min. Calcd for $C_{27}H_{36}N_2O_5$: C, 69.21; H, 7.74; N, 5.98%. Found: C, 69.3; H, 7.75; N, 5.86%. Mass spectrum (*m*/*z*) 469.3 $(M + 1)^+$.

**(*R*)-Verapamilamide (12a). 12a** was prepared by the same method from **10a** and **11** in 82.3% yield (mp 94.8−97.1 °C, $[\alpha]^{25}_D = +6.0°$ (c 4.9 ethanol). The $^1$H NMR spectrum was identical to that of **12b** and LC purity was 98.8% PAR. CHN Found C, 69.47; H, 7.69; N, 5.79%. Racemic **12** was also made from **2** in a similar fashion in 88.6% yield and had mp 105−106.5 °C with LC purity 99.5% PAR.

**(S)-Verapamil (1b).** Amide **12b** (100 g, 0.214 mol) was suspended in THF (450 mL) and cooled to 0−5 °C. BMS (30.0 g, 38 mL, 0.395 mol) was then added dropwise over 20 min at this temperature. After a THF line wash (2 × 25 mL), the mixture was stirred out for 2 h before being allowed to warm to 20−25 °C, whilst stirring overnight (16 h). The completed reaction was added over 1 h to 1 M hydrochloric acid (1000 mL), which had been preheated to 80−85 °C. Provision was made for simultaneous THF removal by distillation. Once quenching was complete, the pot temperature was raised to 100 °C, and the residual mixture boiled under reflux for 4 h. After cooling back to 20 °C, the preparation was extracted with dichloromethane (3 × 300 mL). These extracts were combined, back-washed with water (50 mL), then solvent swapped to 2-propanol (300 mL). The 2-propanol solution was subsequently added over 1h to a well-stirred suspension of authentic **1b** (10 g) in methyl *tert*-butyl ether (1500 mL). The resulting mixture was stirred for 2 h, then filtered and the solid washed with methyl *tert*-butyl ether (2 × 100 mL). After drying in vacuo at 50−60 °C, the crude product was obtained as a white powder (76.6 g,[22] 0.156 mol, 73.0% yield); (mp 126−133 °C). This material was purified by recrystallisation from 2-propanol (850 mL) to obtain good quality (*S*)-verapamil hydrochloride (65.1 g, 85% recovery (0.133 mol, 62.0% overall) mp 132−134 °C, $[\alpha]^{25}_D = -9.0°$ (*c* 5.04, ethanol), [lit.[7] 131−133 °C, $[\alpha]^{24}_D = -8.9°$(*c* 5.03, ethanol)]. $^1$H NMR ($D_2O$): $\delta$ 0.76 (d, 3H), 1.19 (d, 3H), 1.34 (m, 1H); 1.71 (m, 1H); 2.01 (septet, 1H); 2.21 (m, 2H); 2.85 (s,3H); 2.87 (m, 2H); 3.08 (m,1H); 3.20 (m, 1H); 3.26(t, 2H); 3.80−3.87 (4s, 12H); 6.73 (dd, 1H); 6.87 (d, 1H); 6.92−7.08 (m, 4H). HPLC 99.7% PAR; >99.5% ee. Method (related substances): Spherisorb ODS II column, 3 $\mu$m, 125 × 4.6 mm, injection volume 10 $\mu$L, mobile phase 7:3 [aqueous acetic acid (0.58 M) and sodium acetate (0.01 M)]:[acetonitrile/2-heptylamine 60:1], flow rate 0.8−0.9 mL/min, detection at 278 nm, run time 40 min, retention times **1** 6.2 min; **12** 38.3 min. Method (ee): Diacel Chiralpak AD column, 10 $\mu$m, 250 × 4.6 mm, injection volume 20 $\mu$L [1.0 mg/1.0 mL], mobile phase 9:1 heptane: 0.1% diethylamine in 2-propanol, flow rate 1.0 mL/min, temperature 20−25 °C, detection at 230 nm, run time 20 min; retention times **1b**, 8.6 min; **1a**, 10.0 min.

**(*R*)-Verapamil (1a). 1a** was prepared from **12a** by the same method in 60.7% overall physical yield,[22] following 2-propanol recrystallisation of the hydrochloride salt (mp 132−134 °C, $[\alpha]^{25}_D = +8.9°$ (*c* 5.0, ethanol), [lit.[7] mp 131−133 °C; $[\alpha]^{24}_D = +8.9°$ (*c* 5.01, ethanol]). $^1$H NMR ($D_2O$): identical spectrum to **1b**; HPLC purity 99.8% PAR; >99.5% ee.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(22) The physical yields quoted are net of the quantity of authentic seed added.