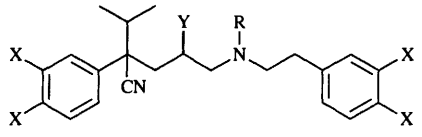
Convenient synthesis of (2*R*)- and (2*S*)-2-(1-methylethyl)-5-oxo-2-phenylpentanenitrile, intermediates in the preparation of phenylalkylamine calcium channel blockers

Jeremy Gilmore,*,[a] Will Prowse,[a] David Steggles,[a] Michael Urquhart[a] and Jennifer Olkowski[b]

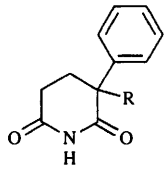
[a] *Lilly Research Centre Ltd, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey GU20 6PH, UK*
[b] *Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285-1513, USA*

The multigram synthesis of (2*S*)- and (2*R*)-2-(1-methylethyl)-5-oxo-2-phenylpentanenitriles 9a and 9b is described, using either (4*R*)-2,2-dimethyl-1,3-dioxolan-4-ylmethanol or (2*R*)-butane-1,2,4-triol as chiral auxiliary. The configuration of an intermediate dioxolane 10b is assigned by X-ray crystallography. The synthetic utility of the aldehydes is demonstrated by conversion to both enantiomers of the calcium antagonist noremopamil in >98% enantiomeric excess (ee). The enantiomeric purity of the final amines is assayed by ^{1}H NMR spectroscopy in the presence of the chiral solvating agent (1*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

The 5-amino-2-alkyl-2-phenylpentanenitrile functionality represents an important pharmacophore in medicinal chemistry, finding particular application in the phenylalkylamine class of L-type calcium channel blockers [1,2] (*e.g.* verapamil **1**, emopamil **2**



1 Verapamil (X = OMe; Y = H; R = Me)
2 Emopamil (X, Y = H; R = Me)
3 Noremopamil (X, Y, R = H)
4 (Y = OH)



5

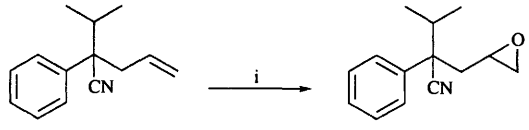
and noremopamil **3**). It has also been utilised when 4-hydroxylated in a series of immunosuppressant agents [3] **4** and, when cyclised, in the structurally related 3-alkyl-3-phenylpiperidine-2,6-dione hypnotics [4] (*e.g.* glutethimide **5**, R = Et). In the case of the phenylalkylamine channel blockers, the majority of the biological activity resides in the (*S*)-(−)-enantiomer.

Historically, the enantiomers of the phenylalkylamines have been separated by classical resolution of their diastereoisomeric *O*,*O*′-di-4-toluoyltartrate salts.[2] The piperidinediones **5** have similarly been resolved but as salts of the precursor 4-cyanobutanoic acids with bases such as brucine and quinine.[5] More recently, a lengthy, eleven-step stereospecific synthesis of verapamil has been reported from (2*S*)-(+)-propane-1,2-diol,[6] giving products of >95% ee. Attempted enantioselective alkylations of 2-(1-methylethyl)-2-(3,4-dimethoxyphenyl)acetonitrile have given only low enantiomeric excesses (ee ≤10%).[7]

To progress a structure–activity relationship study of a series of 5-amino-2-alkyl-2-phenylpentanenitriles, we required a general synthesis of either enantiomer of the precursor 2-alkyl-5-oxo-2-phenylpentanenitrile. We report here two short routes to the versatile aldehyde intermediates **9a,b** from the commercially available (4*R*)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl 4-methylbenzenesulfonate or (2*R*)-butane-1,2,4-triol, and exemplify their use in the formation of either enantiomer of noremopamil in >98% ee.

Results and discussion

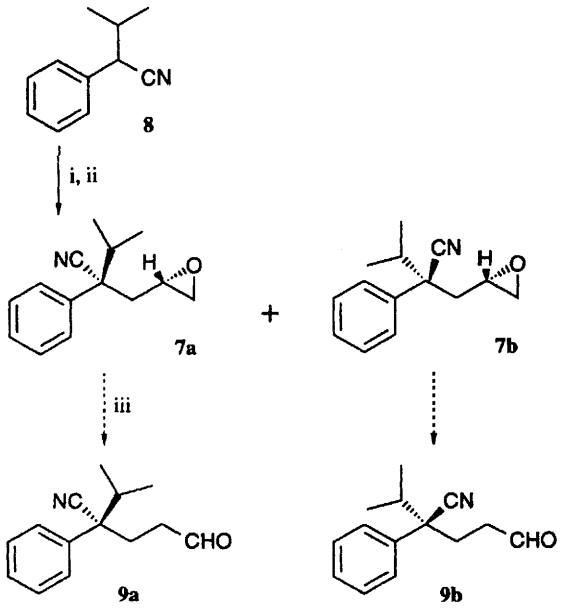
When epoxidising 2-(1-methylethyl)-2-phenylpent-4-enenitrile **6** (Scheme 1), we had observed that the resultant diastereomeric



6 **7**

Scheme 1 *Reagents:* i, 3-chloroperbenzoic acid, $CHCl_3$

oxiranes **7** could be readily separated by flash chromatography on silica. With the commercial availability of homochiral chloromethyloxirane, a potential route to enantiomerically pure aldehydes **9a,b** was envisaged *via* reaction with the anion of 3-methyl-2-phenylbutanenitrile **8**, separation of the diastereomers **7a,b** and a Lewis acid-catalysed oxirane to aldehyde rearrangement (Scheme 2). However, this approach was marred by the poor regiospecificity of attack of the carbanion of **8** at either C-2 of the oxirane or at the chloromethyl carbon, resulting in partial racemisation of the stereocentre. We therefore chose to substitute the chloromethyloxirane with the corresponding homochiral dioxolane where potential for racemisation was effectively removed. Reaction of 3-methyl-2-phenylbutanenitrile **8** with sodium hydride in DMF at *ca.* 50 °C followed by the addition of commercially available (4*R*)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl 4-methylbenzenesulfonate gave a separable mixture of the substituted dioxolanes **10a,b**, in the ratio 40:60 (Scheme 3). Acid hydrolysis of the diastereomer **10a** or **10b**, followed by periodate cleavage of the resultant 1,2-diol, gave the two aldehydes **11a** and **11b**. Reaction



Scheme 2 *Reagents:* i, NaH, DMF; then (*R*)-2-(chloromethyl)oxirane; ii, chromatographic separation; iii, Lewis acid

with (methoxymethylene)triphenylphosphorane gave a mixture of geometric isomers of the methyl enol ethers which was immediately hydrolysed to the homologous aldehydes **9a** and **9b**. The configuration of the substituted dioxolane **10b** was determined by X-ray crystallography, relative to the known stereochemistry of the 1,3-dioxolan-4-yl moiety† (Fig. 1). Reductive amination of the chiral aldehyde **9a** with 2-phenylethylamine yielded (*S*)-noremopamil **3a** (Scheme 4).

The enantiomeric purity of the (*S*)-noremopamil **3a** was determined by ^{1}H NMR spectroscopy using the commercially available chiral solvating agent[8] (1*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE). Method development on the racemic product indicated that preparation of a *ca.* 2:1 TFAE:noremopamil mixture caused chemical shift non-equivalence of the high field methyl doublet (which is in a clear region of the ^{1}H NMR spectrum) of 0.014 ppm. Analysis of (*S*)-noremopamil was performed under identical conditions with the level of the distomer being determined as <1.0% by comparison of its methyl doublet peak height with that of the ^{13}C NMR satellite signal (0.55% abundance) of the eutomer (Fig. 2).

This synthetic approach is viable for the synthesis of gram quantities of the aldehydes **9a,b** and it is noteworthy that conducting this reaction on a larger scale leads to a 1:1 ratio for the dioxolanes **10a,b**. The procedure is only complicated on this increased scale by the chromatographic separation of the diastereoisomeric dioxolanes.‡ The separation can be much simplified on a multigram scale by initial conversion to the cyclic carbonates **12a,b**, where much greater differences in retention time are observed (Scheme 5).

We have observed that on small scale reactions (<2 g) reversing the order of alkylation of the phenylacetonitrile, *i.e.* introducing the dioxolane prior to the isopropyl group, changed the diastereomeric ratio of the resulting dioxolanes from 40:60 to 60:40, but overall poorer yields removed any synthetic benefit. However, increased yields of the (*S*)-isomer **10a** can be successfully achieved by formation of the anion of **8** with LDA in

† Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/77.

‡ Recently we have achieved excellent separations of the dioxolanes **10a,b** on a Biotage FLASH 75^{TM} radially compressed silica column.

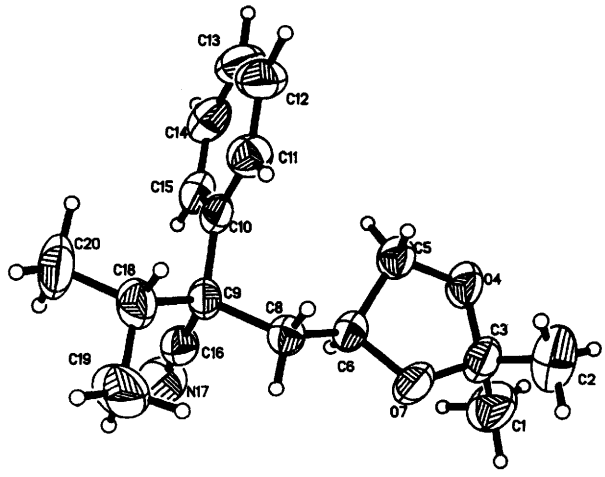
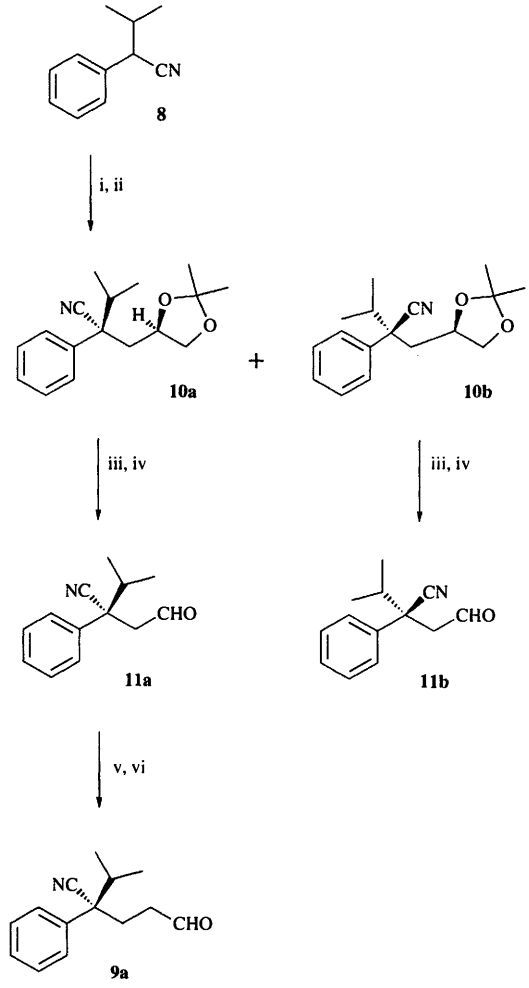


Fig. 1 X-Ray molecular structure of compound **10b**



Scheme 3 *Reagents:* i, NaH, DMF *or* LDA, THF; then (*R*)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl 4-methylbenzenesulfonate; ii, chromatographic separation; iii, aq. AcOH; iv, aq. $NaIO_4$, aq. $NaHCO_3$, CH_2Cl_2; v, $MeOCH{=}PPh_3$, THF; vi, *p*-TSA, Pr^{i}OH, H_2O

THF–1,3-dimethylimidazolidin-2-one at −78 °C. Subsequent reaction with the sulfonate gave the dioxolanes **10a,b** in a comparable overall yield to the sodium hydride method, in diastereomer ratios of from 2:1 to 3:2, depending on reaction scale (*i.e.* gram or multigram quantities).

To avoid the need for homologation of the intermediate aldehydes **11a,b**, the synthesis may preferably be carried out using (2*R*)-butane-1,2,4-triol as chiral auxiliary (Scheme 6). Here, however, conversion of the initially formed dioxolanes **13** to the

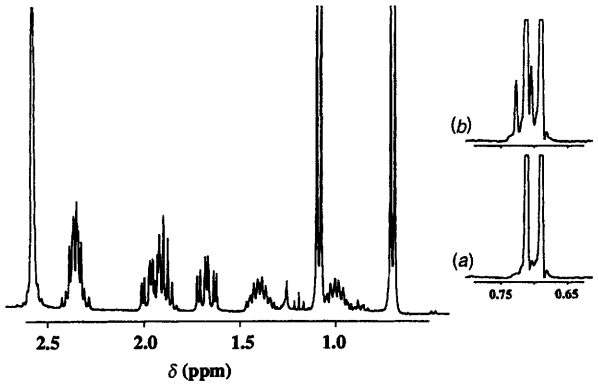
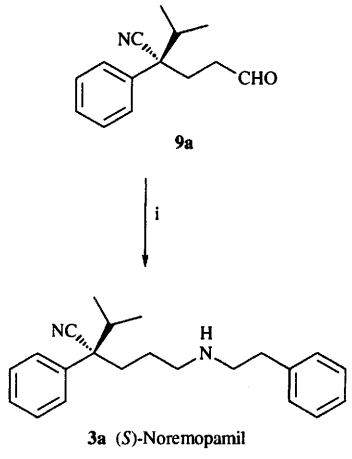
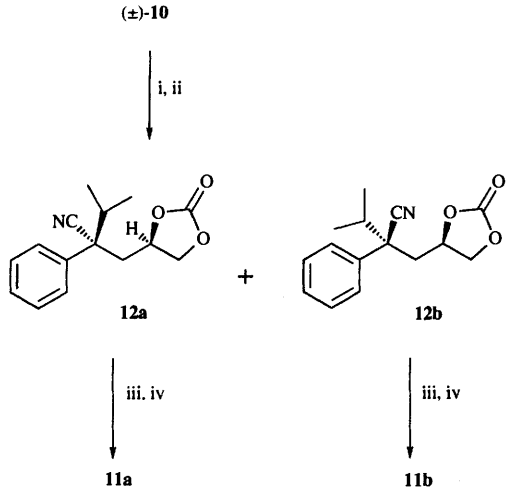


Fig. 2 ^{1}H NMR spectrum of the aliphatic region between 0.5 and 2.6 ppm for (*S*)-noremopamil containing two molar equivalents of the chiral shift reagent TFAE. (*a*) Expansion of the high field doublet of (*S*)-noremopamil **3a**. (*b*) Expansion of the high field doublet of (*S*)-noremopamil **3a** spiked with racemic noremopamil showing the appropriate shift of the (*R*)-enantiomer.

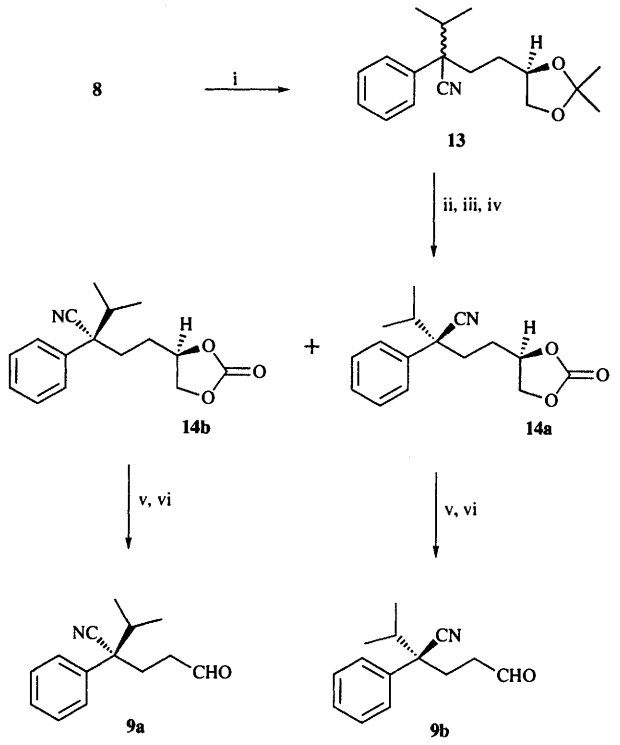


Scheme 4 *Reagents:* i, 2-phenylethylamine, MeOH, molecular sieves, $NaBH_4$



Scheme 5 *Reagents:* i, AcOH, H_2O; ii, diphosgene, pyridine; iii, 1 M NaOH, dioxane; iv, aq. $NaIO_4$, CH_2Cl_2

carbonates **14a,b** becomes a necessity to enable chromatographic separation of the diastereomeric mixture. With the longer alkyl chain, no diastereomeric excess is observed and the order of chromatographic elution of the two diastereomeric carbonates reverses with respect to that observed with the first synthesis.



Scheme 6 *Reagents:* i, NaH, DMF, (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl 4-methylbenzenesulfonate; ii, aq. AcOH; iii, diphosgene, pyridine; iv, chromatographic separation; v, 1 M NaOH, dioxane; vi, aq. $NaIO_4$, CH_2Cl_2

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Bruker IFS-48 spectrometer. NMR spectra were measured in $CDCl_3$, unless otherwise stated, with tetramethylsilane as internal standard on a Bruker AM300 (300 MHz ^{1}H) spectrometer. *J* values are in Hz. Optical rotations were determined on a Bellingham and Stanley P.70-4 polarimeter, and the specific rotations calculated in units of 10^{-1} deg cm^2 g^{-1}. Column chromatography was carried out on Sorbsil C60 silica (40–60 μm). Solvents were dried over 3 Å molecular sieves prior to use. Organic extracts were dried over anhydrous magnesium sulfate. GC analysis was performed on a HP 5890 Series II gas chromatograph with a 5 m × 0.53 mm id × 2.65 μm HP-1 crosslinked methyl silicon gum capillary column and using a 50–250 °C temperature ramp (10 deg min^{-1}).

2-(2,2-Dimethyl-1,3-dioxolan-4-ylmethyl)-3-methyl-2-phenylbutanenitrile 10a and 10b

Method A. To a stirred solution of 3-methyl-2-phenylbutanenitrile **8**[9] (41.9 g, 0.26 mol) in dry DMF (950 cm^3) was added sodium hydride (60% dispersion in mineral oil; 10.5 g, 0.26 mol) under nitrogen and the suspension heated at 60 °C for 3 h. The reaction mixture was cooled to room temperature and (4*R*)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl 4-methylbenzenesulfonate (68.5 g, 0.24 mol) in dry THF (50 cm^3) added dropwise over 10 min. The reaction mixture was stirred for a further 5 h at 60 °C. After cooling, the reaction was quenched with water, extracted into diethyl ether and washed with water (3 ×), then brine. The combined organic extracts were dried, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica, eluting with diethyl ether–hexane (0–1 : 4), to give three fractions of approximately equal mass. Fraction 1 contained diastereomer **10a** (95% purity by GC), fraction 2 contained a mixture of both diastereomers and fraction 3 contained diastereomer **10b** (92% purity by GC). The diastereomers **10a** and **10b** were separately recrystallised.

Successive chromatography of the mixed fraction 2 together with the mother liquors from the recrystallisations allowed further amounts of each diastereomer to be isolated and recrystallised.

Diastereomer **10a** (24.2 g, 34%) as colourless *prisms*, mp 70–71 °C (hexane) (Found: C, 75.1; H, 8.4; N, 5.5. $C_{17}H_{23}NO_2$ requires C, 75.0; H, 8.1; N, 5.1%); $[\alpha]_D^{26}$ −7.4 (*c* 0.76, CH_3OH); ν_{max}(KBr)/cm^{-1} 2231; δ_H 0.77 and 1.21 [3 H each, d, *J* 6.7, CH(CH_3)$_2$], 1.20 and 1.34 [3 H each, s, C(CH_3)$_2$], 2.18 [1 H, septet, *J* 6.7, C*H*(CH$_3$)$_2$], 2.30 (1 H, dd, *J* 8.7 and 14.0, CH_2CHO), 2.42 (1 H, dd, *J* 3.9 and 14.0, CH_2CHO), 3.64 (1 H, m, CH$_2$C*H*O), 3.76 (1 H, dd, *J* 7.4 and 8.3, CH_2O), 4.06 (1 H, dd, *J* 5.5 and 8.3, CH_2O), 7.32–7.41 (5 H, m, Ph).

Diastereomer **10b** (28.3 g, 39%) as colourless *prisms*, mp 77–78 °C (hexane) (Found: C, 74.8; H, 8.4; N, 5.1. $C_{17}H_{23}NO_2$ requires C, 75,0; H, 8.1; N, 5.1%); $[\alpha]_D^{25}$ −23.0 (*c* 1.0, CH_3OH); ν_{max}(KBr)/cm^{-1} 2236; δ_H 0.77 and 1.21 [3 H each, d, *J* 6.7, CH(CH_3)$_2$], 1.24 and 1.35 [3 H each, s, C(CH_3)$_2$], 1.95 (1 H, dd, *J* 7.7 and 13.9, CH_2CHO), 2.20 [1 H, sept, *J* 6.7, C*H*(CH$_3$)$_2$], 2.66 (1 H, dd, *J* 4.7 and 13.9, CH_2CHO), 2.93 (1 H, t, *J* 8.3, CH_2O), 3.11 (1 H, dd, *J* 5.6 and 8.3, CH_2O), 3.98 (1 H, m, C*H*O), 7.3–7.4 (5 H, m, Ph).

Method B. A 2.0 M solution of lithium diisopropylamide in THF (34.8 cm^3, 69.8 mmol) was added dropwise to a stirred solution of 3-methyl-2-phenylbutanenitrile **8** (11.1 g, 69.8 mmol) and 1,3-dimethylimidazolidin-2-one (7.98 g, 69.8 mmol) in THF (100 cm^3) at −70 °C under nitrogen. The resulting dark mixture was stirred at −60 °C for 1 h and treated dropwise with a solution of (4*R*)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl 4-methylbenzenesulfonate (20.0 g, 69.8 mmol) in dry THF (15 cm^3). The mixture was allowed to warm gradually to room temperature over *ca.* 2 h and stirred at this temperature for 15 h. The reaction mixture was quenched with brine, extracted into diethyl ether (3×), and the combined organic extracts were washed with water (3×), brine and dried. Concentration under reduced pressure gave the crude product as a yellow oil and inspection of the GC at this stage showed that the dioxolanes **10a,b** were present in a 3:2 ratio respectively. Flash chromatography on silica, eluting with ethyl acetate–hexane (1:9), gave the dioxolanes **10a,b** as a yellow oil (14.3 g, 75%). This mixture of diastereomers was taken on to the next step (conversion to the cyclic carbonates **12**) without further purification.

(2*S*)-2-(1-Methylethyl)-4-oxo-2-phenylbutanenitrile 11a

A solution of dioxolane **10a** (15.7 g, 57 mmol) in glacial acetic acid (270 cm^3) and water (90 cm^3) was stirred for 18 h at room temperature. The reaction mixture was concentrated under reduced pressure to give the crude diol as a colourless oil. This was taken up in dichloromethane (750 cm^3) to which was then added an aqueous solution (380 cm^3) of sodium hydrogen carbonate (29.1 g, 0.35 mmol). To the stirred biphasic system was added a solution of sodium periodate (49.5 g, 0.23 mmol) in water (250 cm^3) dropwise over 2 h. After addition was complete, the suspension was stirred for a further 2 h at room temperature when GC confirmed the reaction to be complete. The organic phase was separated, washed with water, dried, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica, eluting with diethyl ether–hexane (0–1:4), to yield **11a** (10.3 g, 89%) as a colourless *oil*, bp 106 °C/0.5 mbar; $[\alpha]_D^{34}$ −98.5 (*c* 0.64, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2237, 1730, 1601; δ_H 0.84 and 1.19 [3 H each, d, *J* 6.7, CH(CH_3)$_2$], 2.18 [1 H, septet, *J* 6.7, C*H*(CH$_3$)$_2$], 2.98 (1 H, dd, *J* 3.4 and 16.6, CH_2CHO), 3.13 (1 H, dd, *J* 1.3 and 16.6, CH_2CHO), 7.28–7.43 (5 H, m, Ph), 9.53 (1 H, dd, *J* 1.3 and 3.4, C*H*O). An analytical sample of the 2,4-dinitrophenylhydrazone was prepared by standard procedures,[10] giving yellow *needles*, mp 154–155 °C (ethyl acetate–hexane) (Found: C, 59.6; H, 4.9; N, 18.2. $C_{19}H_{19}N_5O_4$ requires C, 59.8; H, 5.0; N, 18.4%).

(2*R*)-2-(1-Methylethyl)-4-oxo-2-phenylbutanenitrile 11b

Prepared from the dioxolane **10b** as above to yield **11b** (8.5 g, 90%) as a colourless *oil*, $[\alpha]_D^{23}$ +100.0 (*c*. 0.90, $CHCl_3$). An analytical sample of the 2,4-dinitrophenylhydrazone was prepared as above, mp 159–160 °C (diethyl ether–hexane) (Found: C, 59.6; H, 4.9; N, 18.1. $C_{19}H_{19}N_5O_4$ requires C, 59.8; H, 5.0; N, 18.4%).

(2*S*)-2-(1-Methylethyl)-5-oxo-2-phenylpentanenitrile 9a

To a stirred suspension of powdered (methoxymethyl)triphenylphosphonium chloride (33.2 g, 96.8 mmol) in dry THF (500 cm^3) at −78 °C under nitrogen was added butyllithium (1.6 M in THF) (54.7 cm^3, 87.5 mmol) over 10 min. The orange suspension was allowed to warm to 0 °C and stirred for 1 h. The resultant deep red solution was re-cooled to −78 °C and the aldehyde **11a** (9.75 g, 48.4 mmol) in dry THF (50 cm^3) was added dropwise over 10 min. The reaction mixture was stirred at −78 °C for 45 min, allowed to warm to room temp. and quenched with water. The product was extracted into diethyl ether, the organic extracts were washed with water, then brine, dried, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica, eluting with diethyl ether–hexane (0–3:20), to yield the intermediate 5-methoxy-2-(1-methylethyl)-2-phenylpent-4-enenitrile (7.0 g, 63%) as a mixture of geometric isomers (*Z*:*E* ratio of 3:2 by GC).

This was immediately hydrolysed by dissolving in propan-2-ol (60 cm^3) and water (60 cm^3) containing 4-methylbenzenesulfonic acid (0.24 g) and heating under reflux for 3 h. On cooling, the reaction mixture was diluted with water and extracted into diethyl ether. The combined organic extracts were washed with aqueous sodium hydrogen carbonate, then brine, dried, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica, eluting with diethyl ether–hexane (0–1:4), to yield **9a** (4.4 g, 67%) as a colourless *oil*, bp 89–91 °C/0.07 mbar; $[\alpha]_D^{27}$ −57.1 (*c* 1.2, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3061, 3026, 2234, 1718, 1601; δ_H 0.79 and 1.24 [3 H each, d, *J* 6.7, CH(CH_3)$_2$], 2.10–2.24 [3 H, m, C*H*(CH$_3$)$_2$ and CH_2], 2.43–2.68 (2 H, m, CH_2CHO), 7.30–7.43 (5 H, m, Ph), 9.66 (1 H, s, CH$_2$C*H*O). An analytical sample of the 2,4-dinitrophenylhydrazone was prepared by standard procedures,[8] giving yellow *needles*, mp 133–134 °C [diethyl ether–light petroleum (bp 40–60 °C)] (Found: C, 60.9; H, 5.3; N, 17.8. $C_{20}H_{21}N_5O_4$ requires C, 60.7; H, 5.3; N, 17.7%).

(±)-2-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethyl]-3-methyl-2-phenylbutanenitrile 13

To a stirred solution of 3-methyl-2-phenylbutanenitrile **8** (29.1 g, 0.18 mol) in dry DMF (250 cm^3) was added sodium hydride (60% dispersion in mineral oil; 8.0 g, 0.2 mol). The suspension was heated at 60 °C for 40 min after which a solution of (4*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl 4-methylbenzenesulfonate (40 g, 0.13 mol) in dry DMF (70 cm^3) was added dropwise. An exothermic reaction took place and stirring was continued at 50 °C for 2 h. The cooled solution was quenched with brine, extracted into diethyl ether, and the combined organic extracts were washed with water (3×), dried and the solvent was removed *in vacuo*. Flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (1:4), gave **13** (34.0 g, 89%) as a pale yellow oil. This mixture of diastereoisomers was carried on to the next step without further purification.

3-Methyl-2-[2-oxo-1,3-dioxolan-4-yl]methyl-2-phenylbutanenitrile 12a and 12b

A solution of the ketal **10** (41.6 g, 0.15 mol) in acetic acid (680 cm^3) and water (230 cm^3) was stirred at 25 °C for 20 h. The solvent was removed *in vacuo* and the residual oil dissolved in ethyl acetate, washed with water (3×), then saturated aqueous sodium hydrogen carbonate, dried and evaporated to dryness to

yield 4,5-dihydroxy-2-(1-methylethyl)-2-phenylpentanenitrile (29.1 g, 82%) as a yellow oil.

The crude diol (28.7 g, 0.12 mol) was redissolved in dry pyridine (380 cm^3) and diphosgene (trichloromethyl chloroformate) (8.8 cm^3, 0.14 mol) added dropwise to the stirred solution at 0 °C under nitrogen. The resulting suspension was allowed to warm to 20 °C and stirred for 3 h. The reaction mixture was quenched with water, extracted into ethyl acetate, and the combined organic extracts were washed with copper sulfate solution (3×), dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield a yellow oil. Flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (1:4), gave the (*S*)-isomer **12a** (11.5 g, 36%) as an orange–yellow oil which crystallised on standing. Recrystallisation from diethyl ether–hexane gave colourless *prisms*, mp 86–87 °C (Found: C, 69.5; H, 6.6; N, 5.4. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.3%); $[\alpha]_D^{29}$ −32.5 (*c* 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2236, 1806, 1601; δ_H 0.80 and 1.24 [3 H each, d, *J* 6.7, $CH(CH_3)_2$], 2.23 [1 H, septet, *J* 6.7, $CH(CH_3)_2$], 2.56 (2 H, m, CH_2CHO), 4.36 (2 H, m, CH_2O), 4.53 (1 H, m, CHO), 7.35–7.48 (5 H, m, Ph).

Further elution with ethyl acetate–light petroleum (bp 60–80 °C) (1:3) yielded the (*R*)-isomer **12b** (10.8 g, 34%) as brown crystals. Recrystallisation from diethyl ether–hexane gave colourless *needles*, mp 106–108 °C (Found: C, 69.7; H, 6.7; N, 5.4. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); $[\alpha]_D^{29}$ −7.0 (*c* 0.98, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2237, 1792; δ_H 0.80 and 1.28 [3 H each, d, *J* 6.7, $CH(CH_3)_2$], 2.17 and 2.86 (1 H each, m, CH_2CHO), 2.27 [1 H, septet, *J* 6.7, $CH(CH_3)_2$], 3.47 (1 H, t, *J* 8.6, 1 × CH_2O), 3.70 (1 H, dd, *J* 8.9 and 7.6, 1 × CH_2O), 4.63 (1 H, m, CHO), 7.36–7.48 (5 H, m, Ph).

3-Methyl-2-[2-(2-oxo-1,3-dioxolan-4-yl)ethyl]-2-phenylbutanenitrile 14a and 14b

Using the same procedure as that described above for **12a** and **12b**, the ketal **13** (34.0 g, 0.12 mol) gave a crude mixture of the title carbonates **14a** and **14b** as a yellow–brown oil (38.7 g). Flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (bp 60–80 °C) (1:4), gave the (*R*)-isomer **14a** (12.8 g, 39%) as colourless crystals. Recrystallisation from diethyl ether–hexane gave colourless *prisms*, mp 91–93 °C (Found: C, 70.4; H, 7.1; N, 5.3. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%). $[\alpha]_D^{28}$ +39.7 (*c* 0.91, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2234, 1722; δ_H 0.79 and 1.21 [3 H each, d, *J* 6.7, $CH(CH_3)_2$], 1.37 and 1.75 (1 H each, m, CH_2CHO), 2.12 [1 H, septet, *J* 6.7, $CH(CH_3)_2$], 2.22 (2 H, m, CH_2CH_2), 3.92 and 4.49 (1 H each, t, *J* 8.2, CH_2O), 4.70 (1 H, m, CHO), 7.32–7.44 (5 H, m, Ph).

Further elution with ethyl acetate–light petroleum (bp 60–80 °C) (1:3) yielded the (*S*)-isomer **14b** (12.4 g, 38%) as a yellow oil which crystallised on standing. Recrystallisation from diethyl ether–hexane gave colourless *needles*, mp 89–91 °C (Found: C, 70.1; H, 7.0; N, 5.0. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%); $[\alpha]_D^{25}$ −33.7 (*c* 0.69, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2235, 1807; δ_H 0.79 and 1.23 [3 H each, d, *J* 6.7, $CH(CH_3)_2$], 1.38 and 1.88 (1 H each, m, CH_2CHO), 1.92 (1 H, m, CH_2CH_2), 2.15 [1 H, m, $CH(CH_3)_2$], 2.44 (1 H, m, CH_2CH_2), 3.97 (1 H, t, *J* 8.3, CH_2O), 4.44 (1 H, dd, *J* 8.3 and 7.1, CH_2O), 4.56 (1 H, m, CHO), 7.31–7.44 (5 H, m, Ph).

(2*S*)-2-(1-Methylethyl)-4-oxo-2-phenylbutanenitrile 11a

A solution of carbonate **12a** (11.5 g, 44.35 mmol) in 2.0 M sodium hydroxide (290 cm^3) and dioxane (290 cm^3) was stirred for 12 h at room temperature. The reaction mixture was quenched with brine, extracted into ethyl acetate (3×), the combined organic phases were washed with water (2×) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the crude diol (10.4 g, 100%) as a yellow oil. This was taken up in dichloromethane (550 cm^3) to which was then added an aqueous solution (400 cm^3) of sodium periodate (47.3 g, 0.22 mol) dropwise over 2 h. After the addition was complete, the suspension was stirred for a further 2 h at room temperature when GC confirmed the reaction to be complete. The organic phase was separated, washed with water, dried, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica, eluting with diethyl ether–hexane (0–1:4), to yield **11a** (2.8 g, 32%) as a colourless oil. The physical and spectroscopic characteristics were identical to those described above.

(2*R*)-2-(1-Methylethyl)-4-oxo-2-phenylbutanenitrile 11b

Cyclic carbonate **12b** (10.8 g, 41.7 mmol) was reacted by the method described above for **11a** to yield **11b** (3.5 g, 42%) as a colourless oil. The physical and spectroscopic characteristics were identical to those described above.

(2*S*)-2-(1-Methylethyl)-5-oxo-2-phenylpentanenitrile 9a

Cyclic carbonate **14b** (21.5 g, 75.4 mmol) was reacted by the method described above for **11a** to yield **9a** (15.8 g, 98%) as a colourless oil. The physical and spectroscopic characteristics were identical to those described above.

(2*R*)-2-(1-Methylethyl)-5-oxo-2-phenylpentanenitrile 9b

Cyclic carbonate **14a** (15.5 g, 54.2 mmol) was reacted by the method described above for **9a** to yield **9b** (10.0 g, 86%) as a colourless oil, $[\alpha]_D^{23}$ +57.4 (*c* 0.85, $CHCl_3$). An analytical sample of the 2,4-dinitrophenylhydrazone was prepared by standard procedures,[9] giving yellow *crystals*, mp 132–133 °C [diethyl ether–light petroleum (bp 40–60 °C)] (Found: C, 60.7; H, 5.3; N, 17.8. $C_{20}H_{21}N_5O_4$ requires C, 60.7; H, 5.3; N, 17.7%).

(7*S*)-7-Cyano-1,7-diphenyl-8-methyl-3-azanonane [(*S*)-noremopamil] 3a

A solution of aldehyde **9a** (0.29 g, 1.19 mmol), 2-phenylethylamine (0.15 g, 1.19 mmol) and 3 Å molecular sieves (0.65 g) in methanol (20 cm^3) was stirred at 25 °C under nitrogen for 100 min. Sodium borohydride (0.14 g, 3.58 mmol) was carefully added to the mixture and stirring was continued for an additional 16 h. The mixture was filtered and the residue washed with chloroform (100 cm^3). The combined organic extracts were washed with water (100 cm^3), dried, filtered and the solvent was removed *in vacuo* to yield a yellow oil. Flash chromatography on silica gel, eluting with ethyl acetate, gave the (*S*)-isomer of **3a** (0.27 g, 66%) as a pale yellow *oil*, ν_{max}(thin film)/cm^{-1} 3062, 3027, 2236, 1653, 1602; δ_H 0.77 and 1.19 [3 H each, d, *J* 6.7, $CH(CH_3)_2$], 1.11 and 1.51 (1 H each, m, 2 × 5-H), 1.32 (1 H, br s, NH), 1.87 (1 H, dt, *J* 12.8 and 4.5, 6-H), 2.10 (2 H, m, 6-H, 8-H), 2.56 (2 H, m, 2 × 1-H), 2.76 (4 H, m, 2 × 2-H, 2 × 4-H), 7.26 (10 H, m, 2 × Ph). Dissolution in diethyl ether (15 cm^3) and acidification with ethanolic hydrogen chloride gave a white solid. Recrystallisation from methanol–ethyl acetate–hexane gave the hydrochloride salt of (*S*)-noremopamil as colourless crystals, mp 171–176 °C; $[\alpha]_D^{29}$ −10.6 (*c* 1.0, EtOH) {lit.,[2] $[\alpha]_D^{20}$ −10.2 (*c* 1.0, EtOH)}; ν_{max}(KBr)/cm^{-1} 3853, 3748, 3673, 3650, 3443, 2236, 1582; $\delta_H(CD_3OD)$ 0.75 and 1.22 [3 H each, d, *J* 6.7, $CH(CH_3)_2$], 1.31 and 1.71 (1 H each, m, 2 × 5-H), 2.09 (1 H, dt, *J* 12.9 and 6.2, 6-H), 2.26 (2 H, m, 6-H, 8-H), 2.92 (3 H, m, 2 × 1-H, 4-H), 3.02 (1 H, m, 4-H), 3.21 (2 H, m, 2 × 2-H), 7.35 (10 H, m, 2 × Ph).

(7*R*)-7-Cyano-1,7-diphenyl-8-methyl-3-azanonane [(*R*)-noremopamil] 3b

The product **3b** was prepared as described above for **3a** (41%). The hydrochloride salt was prepared as above and recrystallised from methanol–ethyl acetate–hexane as colourless crystals, mp 168–170 °C; $[\alpha]_D^{29}$ +10.4 (*c* 1.0, EtOH).

Crystal data for 2-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)-3-methyl-2-phenylbutanenitrile 10b

$C_{17}H_{23}NO_2$, $M = 273.4$. Orthorhombic, cell dimensions: $a = 10.709(3)$, $b = 10.752(3)$, $c = 14.219(5)$ Å, $V = 1637.2(8)$ Å^3 (by least-squares refinement on diffractometer angles for 15

reflections, $\lambda = 1.541\,78$ Å), space group $P2_12_12_1$, $Z = 4$, $D_c = 1.11$ g cm^{-3}. Crystal dimensions mm $0.35 \times 0.3 \times 0.45$ μ(Cu-Kα) = 0.568, $F(000) = 592$.

Data collection and processing. The intensity data were collected on a Siemens R3/V diffractometer (θ range: 5.16–57.18°; $0 \le h \le 11$, $0 \le k \le 11$, $0 \le l \le 15$) using Cu-Kα X-radiation and θ–2θ scanning. 1303 independent reflections were collected [$1245 > 2\sigma(I)$] and all were used in subsequent structural solution and refinement. The data were corrected for Lorentz and polarisation effects, but not for absorption.

Structural analysis and refinement. The structure was solved by direct methods (SHELXTL86)[11] and refined by full-matrix least-squares methods (SHELXTL93)[12] using anisotropic temperature factors for all the non-hydrogen atoms. All the hydrogen atoms were included at calculated positions with isotropic temperature factors. The number of refined parameters was 182. The weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0780P)^2 + 0.1185P]$, where P is $[2F_c^2 + \max(F_o^2, 0)]/3$, gave satisfactory agreement analysis. R indices are defined in ref. 12. Final R (all data), $R[I > 2\sigma(I)]$, and wR (all data) are 0.0418, 0.0407 and 0.1048 respectively and the goodness-of-fit value on F^2 is 1.078. The final difference Fourier map was essentially featureless (general noise level less than ±0.19 e Å^{-3}). The configuration was determined relative to the known glyceraldehyde synthon.

Acknowledgements

The authors would like to thank C. P. Dell for his constructive criticism in the preparation of this manuscript.

References

1 W. Appel, *Arzneim.-Forsch.*, 1962, **12**, 562.
2 DEP 205 998 5, 1972 (*Chem. Abstr.*, 1972, **77**, 101 248 g); DEP 334 475 5, 1985 (*Chem. Abstr.*, 1985, **104**, 148 554v).
3 USP 524 771 9, 1993 (*Chem. Abstr.*, 1994, **120**, 106 560u).
4 E. Tagmann, E. Sury and K. Hoffmann, *Helv. Chim. Acta*, 1952, **35**, 1541.
5 J. Knabe and D. Reischig, *Arch. Pharm. (Weinheim, Ger.)*, 1984, **317**, 353.
6 L. J. Theodore and W. L. Nelson, *J. Org. Chem.*, 1987, **52**, 1309.
7 H. Brunner and H. Zintl, *Monatsch. Chem.*, 1991, **122**, 841.
8 W. H. Pirkle and D. J. Hoover, *Top. Stereochem.*, 1982, **13**, 263.
9 K. Mitani, T. Yoshida, S. Sakurai, K. Morikawa, Y. Iwanaga, E. Koshinaka, H. Kato and Y. Ito, *Chem. Pharm. Bull.*, 1988, **36**, 373.
10 W. Kemp, *Qualitative Organic Analysis*, McGraw-Hill, London, 1986, p. 58.
11 G. M. Sheldrick SHELXTL PLUS, v 3.4 User Manual, Siemens Analytical X-Ray Instruments, Inc. 1989.
12 G. M. Sheldrick SHELXTL, v 5 User Manual, Siemens Analytical X-Ray Instruments, Inc. 1994.

Paper 6/03597C
Received 23*rd May* 1996
Accepted 16*th August* 1996