Asymmetric Syntheses of (+)-Diltiazem Hydrochloride

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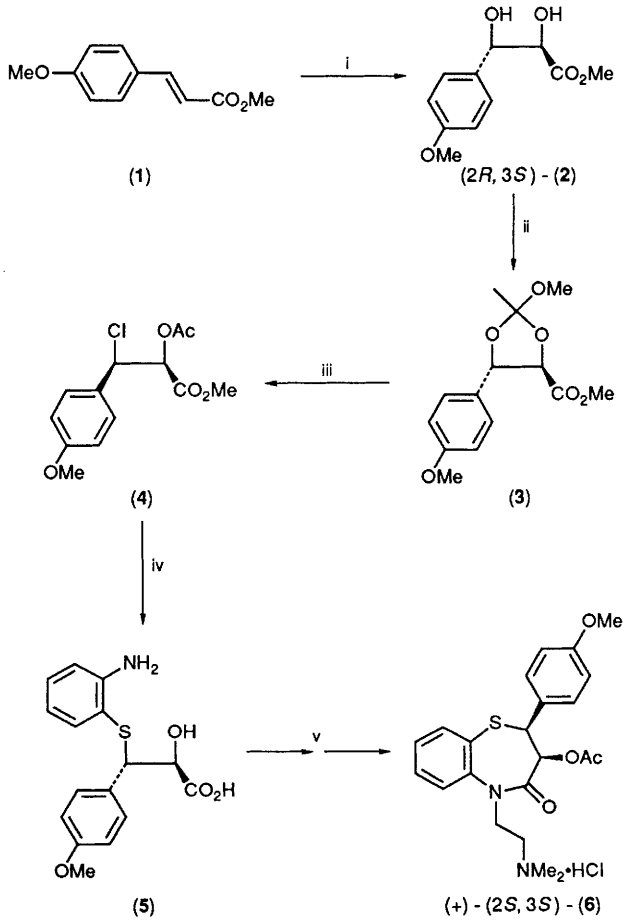
Efficient enantioselective syntheses of the important cardiac drug (+)-*cis*-(2*S*,3*S*)-diltiazem from (*E*)-methyl 4-methoxyphenylpropenoate *via* either the (2*R*,3*S*)- or (2*S*,3*R*)-enantiomers of *threo*-methyl 3-(4-methoxyphenyl)-2,3-dihydroxypropanoate are described.

(+)-(2*S*,3*S*)-*cis*-Diltiazem hydrochloride (**6**) is a potent vasodilating agent discovered by Tanabe Seiyaku Co. Ltd. that possesses calcium channel blocking activity.[1] Several synthetic approaches have been described[2] of which many are in the patent literature.[3] All but one appear to involve a classical resolution. The one asymmetric synthesis was patented by another Japanese pharmaceutical company.[4] It involves an asymmetric Sharpless epoxidation but suffers from having a large number of steps.

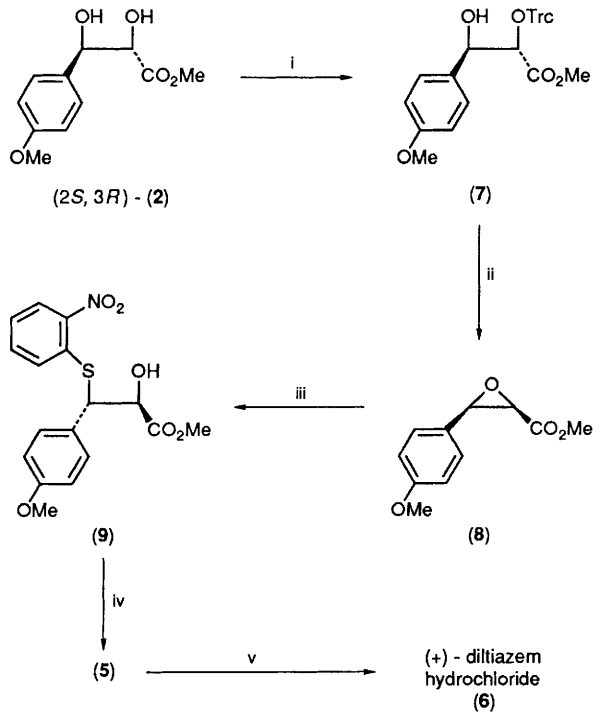
We now report efficient syntheses of (+)-diltiazem (**6**) from (*E*)-methyl 4-methoxypropenoate *via* either of the enantiomers of *threo*-methyl 3-(4-methoxyphenyl)-2,3-dihydroxypropanoate (**2**). Both of these enantiomers are available in excellent chemical yield (>95%) and high optical purity (≥88%) by reaction of the (*E*)-propenoate (**1**) with *N*-methylmorpholine *N*-oxide using catalytic amounts of osmium tetroxide and either dihydroquinine or dihydroquinidine acetates as ligands.[5] Recrystallisation of this material from toluene led to a further increase in enantiomeric purity and material with an enantiomeric excess (e.e.) of ≥97% was obtained in *ca.* 80% yield. The catalytic method used the same ligands as those described by Sharpless for the asymmetric dihydroxylation using stoicheiometric amounts of osmium tetroxide and a chiral ligand.[6] Subsequently, Sharpless described a catalytic method similar to ours with a further modification which generally gives 1,2-diols at a faster rate and in even higher enantiomeric excess.[7]

The enantiomeric diols (**2**) are also available by an alternative synthetic route[8] from (*R*)- or (*S*)-4-methoxybenzaldehyde cyanohydrins which are readily available in high optical purity by hydrocyanation of 4-methoxybenzaldehyde in the presence of Inoue catalyst.[9]

The synthetic strategy involves conversion of the enantiomers of (**2**) into the *threo*-(2*S*,3*S*)-thioether (**5**) which is an intermediate in the Tanabe synthesis of (+)-diltiazem.[10] Conversion of the (2*R*,3*S*)-diol (**2**) involves reactions which lead to *retention* of configuration at both C-2 and C-3. The method by which this has been achieved is outlined in Scheme



Scheme 1. *Reagents and conditions*: i, *N*-methylmorpholine *N*-oxide, OsO_4–dihydroquinine acetate, 80%; ii, $MeC(OMe)_3$, *p*-$MeC_6H_4SO_3H$, *ca.* 100%; iii, Me_3SiCl, $Et_3\overset{+}{N}HCl^-$ (trace), *ca.* 100%; iv, *o*-$H_2NC_6H_4S^-K^+$ in dimethylformamide (DMF), *ca.* 100%; v, reactions as in Tanabe synthesis,[10] 81%.



Scheme 2. *Reagents and conditions*: i, tricsyl (Trc) chloride–pyridine, 95%; ii, NaH–THF, 97%; iii, *o*-$O_2NC_6H_4SH$, $NaHCO_3$, EtOH, 60%; iv, H_2, Pd–C, EtOAc; NaOH, EtOH/H_2O, 95%; v, reactions as in Tanabe synthesis,[10] 81%.

1. The cyclic orthoacetate (**3**) was prepared by the general procedure of Dansette and Jerina.[11] It was shown to react with trimethylsilyl chloride in the presence of a catalytic amount of triethylammonium chloride with both high regio- and stereoselectivity to give the chloroacetate (**4**). Reaction of the chloroacetate (**4**) with potassium *o*-aminobenzenethiolate gave the *threo*-(2*S*,3*S*)-thioether (**5**) which was converted into (+)-diltiazem by the Tanabe route.[10] Use of the *threo*-diol (**2**) with e.e. ≥97% gave (+)-diltiazem hydrochloride with $[\alpha]_D^{21}$ 104.5° (*c* 2.50, $CHCl_3$), {authentic sample, $[\alpha]_D^{21}$ 103.7° (*c* 2.53, $CHCl_3$)}. The overall yield from the propenoate was 65%.

Conversion of the (2*S*,3*R*)-enantiomer of the *threo*-diol (**2**) into the (2*S*,3*S*)-thioether (**5**) involves reactions which lead to the *inversion* of configuration at both chiral centres. This was achieved by reaction of a sample of the diol (**2**), rich in the (2*S*,3*R*)-enantiomer (e.e. 85%), with 2,4,6-trichlorobenzenesulphonyl chloride (tricsyl chloride)[12] (see Scheme 2). This bulky reagent reacted regiospecifically at the C-2-hydroxy group of (**2**) to give the tricsylester (**7**). Treatment of (**7**) with sodium hydride in tetrahydrofuran (THF) gave the *cis*-epoxide (**8**), $[\alpha]_D^{18}$ +5.3° (*c* 0.826, $CHCl_3$). Spectral data for this compound and for a sample of racemic material prepared by the same method were in good agreement with those previously reported for a sample of the racemic epoxide (**8**) prepared by another route.[13] The *cis*-epoxide (**8**) has been previously shown to undergo highly stereoselective *syn*-ring opening in a tin-catalysed reaction with 2-nitrobenzenethiol leading to the *erythro*-diastereoisomer of (**9**).[2,13] However, reaction of (**8**) with 2-nitrobenzenethiol in the presence of a catalytic amount of sodium hydrogen carbonate and in the absence of tin salts was found to give exclusively the *threo*-thioether (**9**) with $[\alpha]_D^{20}$ +123.5° (*c* 0.56, $CHCl_3$). The same enantiomer has recently been prepared by an efficient resolution procedure with $[\alpha]_D^{25}$ +121° (*c* 1, $CHCl_3$).[14] The enantiomeric purity of our sample of this compound was confirmed as being ≥97% by ^1H NMR chiral shift experiments carried out on a sample of the acetate of (**9**). Thus enantiomeric enrichment of the material had occurred during the purification sequence. A sample of (**9**) was hydrogenated and hydrolysed to give the key intermediate, the hydroxy-amino acid (**5**) which had $[\alpha]_D$ +332° (*c* 0.634, EtOH) suggesting an e.e. value of 96% by comparison with the published literature value, $[\alpha]_D$ +346°, EtOH.[10]

Thus highly stereoselective routes to (+)-diltiazem hydrochloride (**1**) are available *via* either of the enantiomers of the *threo*-diol (**2**). Overall yields of enantiomerically pure (+)-diltiazem from 4-methoxyphenylpropenoate are 65% for the orthoester route (Scheme 1) and 43% for the epoxide route (Scheme 2). These yields have not been optimised for either route.

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