Tetrahedron Letters,Vol.30,No.46,pp 6423-6426,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF THE ENANTIOMERS OF FELODIPINE AND DETERMINATION OF THEIR ABSOLUTE CONFIGURATION

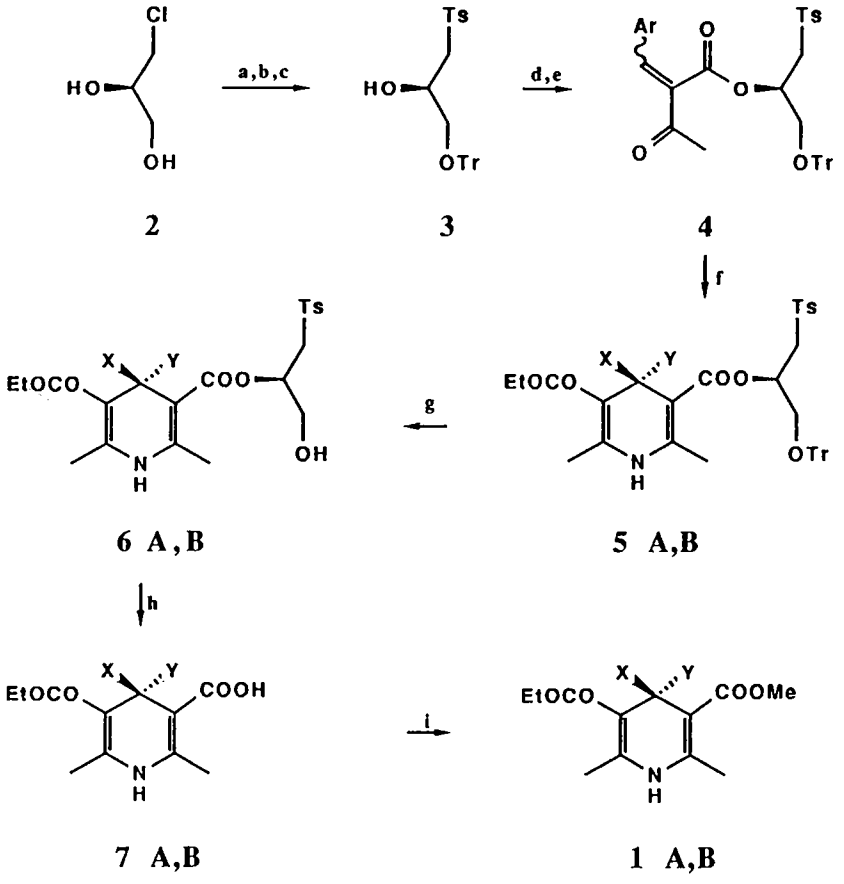
Bo Lamm and Roger Simonsson
Department of Organic Chemistry, CV, AB Hässle
S-431 83 MÖLNDAL, SWEDEN

Staffan Sundell
Department of Structural Chemistry
Faculty of Medicine, University of Göteborg
Box 33031, S-400 30 GÖTEBORG, SWEDEN

Summary: The pure enantiomers of felodipine, 1, have been synthesized by chromatographic separation of diastereomeric esters with (R)-1-(p-toluenesulfonyl)-3-trityloxypropan-2-ol, 3, as an easily removable chiral auxiliary. Absolute configurations have been deduced via X-ray crystallography on a (R)-mandelic acid ester, 9B.

Felodipine, 4-(2,3-dichlorophenyl)-2,6-dimethyl-3-ethoxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine, 1, is a calcium antagonist recently introduced on the market as an antihypertensive drug.[1] The pure enantiomers of 1 were desired for extended pharmacological studies. Classical resolution of the methyl half ester 8 (Scheme 2) with brucine yielded the S form of 1, 1A, upon esterification with iodoethane. Brucine is expensive and toxic, and it would have been difficult to obtain 1B in optically pure form, so we decided to develop a method based on separation of covalent diastereomers. Such methods have been reported for other chiral 1,4-dihydropyridines.[2] Asymmetric synthesis is another possibility.[3,4]

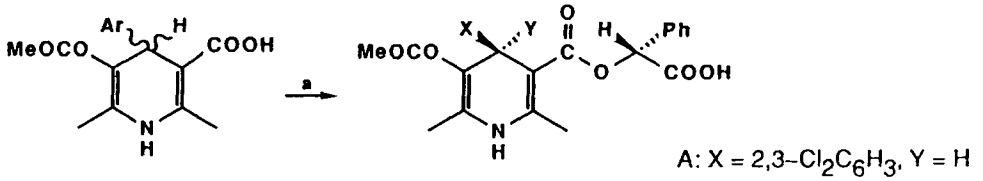
From commercially available 2 (Kanegafuchi), (R)-1-(p-toluenesulfonyl)-3-trityloxypropan-2-ol is obtained in three steps. The further elaboration into diastereomeric esters via Hantzsch synthesis is shown in Scheme 1. The primary alcohols 6 are easily separated by straight-phase chromatography. Serendipitously, one of the tritylated isomers, 5A, crystallized from diethyl ether, facilitating the separation. The chiral auxiliary had been designed to allow mild removal via β elimination in alkaline solution, yielding 7A and 7B[5]. Esterification with iodomethane yielded 1A and 1B. Their specific rotation had the same numerical value and opposite sign.[6] Chiral chromatography[7] showed that the enantiomeric excess of 1B is at least 99 %.



Ts = p-$CH_3C_6H_4SO_2$, Tr = $(C_6H_5)_3C$, Ar = 2,3-$Cl_2C_6H_3$
A : X = Ar, Y = H, B : X = H, Y = Ar

Scheme 1. Route to felodipine enantiomers. Reagents, conditions and (yields) a)p-$CH_3C_6H_4SH$, aq. NaOH, 100°, 2 h (90 %), b)H_2O_2, o-$NO_2C_6H_4SeO_2H$ (cat.), CH_2Cl_2, r.t., 12 h (83 %),[8] c) TrCl, Et_3N, DMAP (cat.), CH_2Cl_2, r.t., 1.5 h)(95 %), d)Diketene, CH_3COCH_3, C_5H_5N (cat.), reflux, 1 h (98 %), e) 2,3-$Cl_2C_6H_3CHO$, C_6H_6, CH_3COOH (cat.), $C_5H_{11}N$ (cat.), reflux (az. water removal), 1 h (94 %), f) Ethyl 3-amino-crotonate, C_5H_5N, reflux, 1 h (81 %), 5A recryst. from ether (optional), g) CH_3COOH, H_2O, 60°, 2 h (85 %), then LC on 40-63 µ Si-60, CH_2Cl_2:CH_3COCH_3:CH_3COOH 87:12:1 (vol.), h) MeOH, KOH, r.t., 2 h (87 %), i)MeOH, KOH, evaporation, then CH_3I in DMF (94 %).

In an attempt at preparing 1A and 1B via (R)–mandelic acid derivatives, we found an outstanding chromatographic separation of 9A and 9B (Scheme 2), but we were unable to remove the mandelic acid part by hydrogenolysis without also removing aromatic chlorine. A crystal of 9B was subjected to X–ray diffraction analysis (Fig.1). The dihydropyridine part had S configuration. Conversion of 7A and 7B to (R)–mandelic acid esters and comparison of spectra and chromatographic elution order allowed us to assign 1A as the S form.



8 9 A,B

Scheme 2. Preparation of diastereomers for X–ray diffraction. Reagents and conditions: a) $SOCl_2$, DMF, –10°, 40 min, then (R).mandelic acid, Et_3N. Diastereomers separated on 40–63 μ Si–60, using CH_2Cl_2 $(CH_3)_2CHOH$: CH_3COOH 190:10:1 (vol). The first eluted compound 9B was recrystallized from acetonitrile–water.

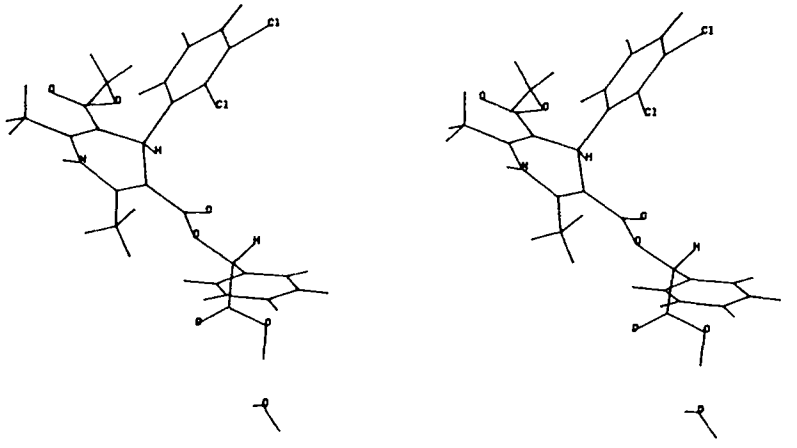


Figure 1. Stereoscopic view of 9B (Scheme 2)[9]

References and notes:

1. Saltiel, E. Ellrodt, A.G. Mon K, J.P. and Langley, M.S. Drugs 36 (1988) 387.
2. Arrowsmith, J.E., Campbell, S.F., Cross, P.E., Stubbs, J.K., Burges, R.A., Gardiner, D.G. and Blackburn, K.J. J. Med. Chem. 29 (1986) 1696.
3. Meyers, A.I., Oppenlaender, T. J. Chem. Soc. Chem. Commun. 1986 920
4. Enders, D., Müller, S. and Demir, A.S. Tetrahedron Letters 29 (1988) 6437.
5. An achiral precedent for this reaction is the rapid hydrolysis of β-methylsulfonyl esters; Hardy, P.M., Rydon, H.N. and Thompson, R.C. Tetrahedron Letters 9 (1968) 2525.
6. 1A: $[\alpha]_{436}^{25}$ - 33.2°, $[\alpha]_{546}^{25}$ - 9.6°, $[\alpha]_{578}^{25}$ - 7.7°, $[\alpha]_{589}^{25}$ - 7.3°

   1B: $[\alpha]_{436}^{25}$ + 32.6°, $[\alpha]_{546}^{25}$ + 9.1°, $[\alpha]_{578}^{25}$ + 7.4°, $[\alpha]_{589}^{25}$ + 6.8°

   (C = 1, MeOH)

   1A: mp. 145.3° , purity 99.5 %; 1B: mp. 145.4°, purity 99.8 % (differential scanning calorimetry).
7. Carried out by Prof. J. Hermansson, using an immobilized α_1-acido glycoprotein column (100 x 4 mm, Chiral AGP (Chrom Tech AB, Stockholm Sweden)). The mobile phase was a 12.5 % (vol) solution of 2-propanol in a 0.01 M phosphate buffer at pH 7.
8. Reich, H.J. Synthesis 1978, 299.
9. Compound 9B crystallizes in the monoclinic space group $P2_1$ with unit cell dimensions a = 12.256(2), b = 7.256 (1), c = 13.816 (2) Å and β = 105.96(1)°. The structure was determined by X-ray single-crystal analysis based on intensity data collected with an Enraf-nonius CAD4F-11 diffractometer. In order to ascertain the absolute configuration anomalous dispersion factors were introduced for the non-hydrogen atoms. After refinement the residuals for the correct enantiomer shown in Fig. 1 were calculated to R = 0.038 and R_w = 0.048 while for the opposite enantiomer the residuals were R = 0.054 and R_w = 0.071. Positional and thermal parameters as well as lists of observed and calculated structure factors can be obtained from the Department of Structural Chemistry, University of Göteborg.

(Received in UK 2 October 1989)