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ENANTIOSELECTIVE SYNTHESIS OF OPTICALLY PURE S-ISOSERINE

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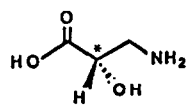
Abstract : KF-promoted addition of nitromethane on (-)-8-phenylmenthyl glyoxylate monohydrate affords, after one purification, optically pure (-)S isoserine in about 50% yield.

Isoserine was found to inhibit several enzymes of serine metabolism in mammals and to interfer with panthotenic acid synthesis from β-alanine in yeast[1]. More recently, it appeared to be a constituent of peptide antibiotics such as edeine[2] and tatumine[3] and to



(-)S isoserine

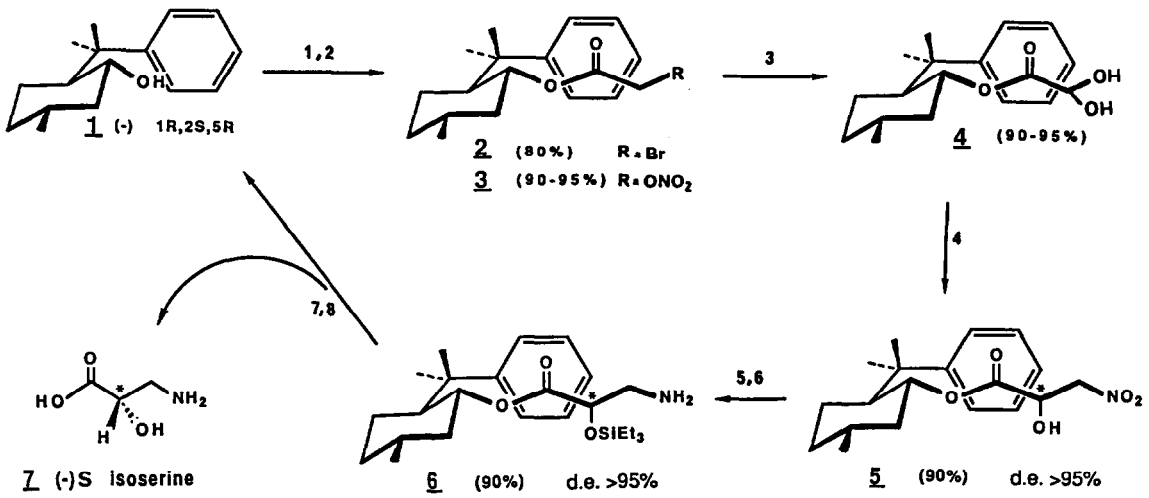
enhance antibiotic activity as in modified butirosin[4] (where isoserine replaces 4-amino-2-hydroxy-butanoic acid). As such S-isoserine is thus an important biologically active β-amino acid.

Racemic isoserine has been synthesized in one step starting from α-chloro-β-hydroxy-propionic acid[5], or in two steps starting from methyl acrylate[6], ethyl glycidate[7] and glyoxylic acid hydrate[8]. S-isoserine has been prepared from S-asparagine[9] or D-mannitol[10], and R-isoserine from S-serine[11] or D-mannitol[10].

We report here the first enantioselective synthesis of S-isoserine (which could also be used for the synthesis of R-isoserine). In this method, scheme 1, the inducer of chirality, (-)-8-phenyl menthol 1[12], is recovered and can thus be used again.

The key material is the (-)-8-phenylmenthol glyoxylate monohydrate 4[13] which is a stable colorless oil prepared in three steps from (-)-8-phenyl menthol 1[14]. Using KF as a catalyst and anhydrous iPrOH as solvent[15] nitromethane addition on 4 proceeds smoothly at 20°C[16] leading to 5 in 90% yield. The use of KF to promote the condensation is also a key point of the synthesis as it allows the presence of an ester function on the substrate and, consequently, permits introduction of a chirality through a chiral ester[17].

The percentage of asymmetric induction at C_α is determined by ^1H NMR (200MHz) on the crude products 5[18] and 6[19]. It appears to be > 95% (fig. 1), as only one diastereomer is detected in both cases.



Scheme 1 : 1) $HOCOCH_2Br/DCC/DMPA$; 2) $AgNO_3/CH_3CN$; 3) $AcONa/DMSO$; 4) CH_3NO_2/KF[16] ; 5) protection ; 6) reduction ; 7) hydrolysis ; 8) epoxypropane/EtOH.

After protection (Et_3SiCl/DMF/Imidazole, overnight, rt) hydrogenation[19] (Raney Ni, EtOH, H_2 35 atm., 50°C, 24 h) and hydrolysis (HCl 6N, 80°C, 18 h) followed by treatment of the hydrochloride with epoxypropane in anhydrous ethanol, (-) S-isoserine[20], is isolated. Therefore, the diastereomer obtained in step 4 (where the new asymmetric carbon C_α is created) is 1R,2S,5R,αS[21].

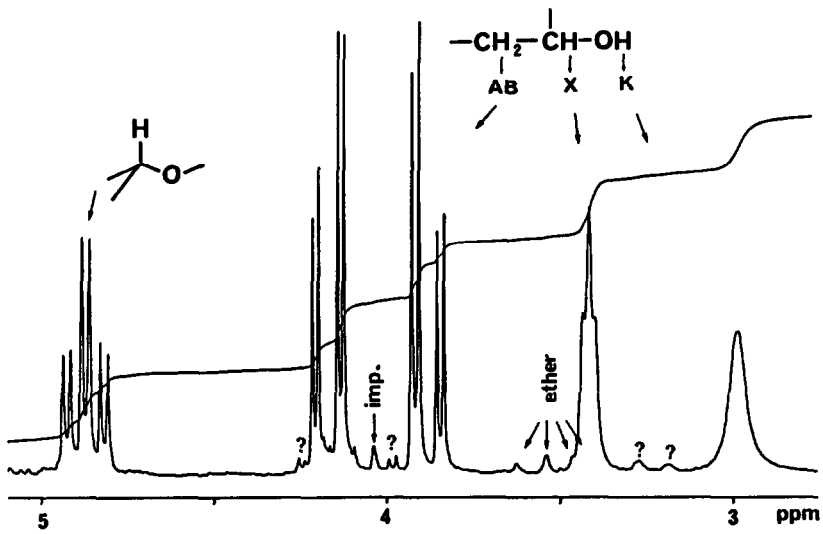
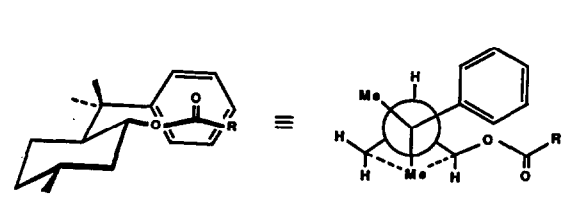
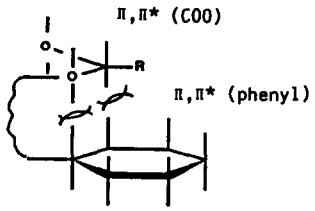
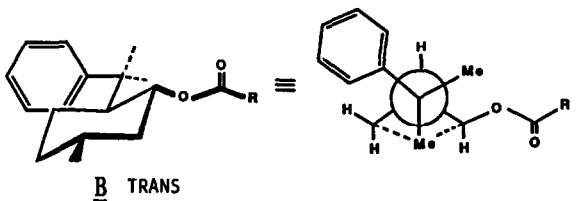


Figure 1 : ^1H NMR (200MHz, $CDCl_3$) of crude product 5.

The observed strong shieldings of the α-H , -1.17 ppm, and of the two β-H, -0.88 and -0.64 ppm, (as compared with the same signals in the corresponding (-) menthyl ester[22]), suggest a conformation, A, where the $CH\alpha-CH_2\beta$ fragment is above the plane of the phenyl ring, i.e. cis to this phenyl group. The stability of this apparently sterically-hindered cis conformation, compared to the trans conformation B, could be due to the presence, in A, of an hyperconjugative stabilizing term of the type $n_O(C-O-C).\Pi,\Pi^*(phenyl)$ and/or $\Pi,\Pi^*(O-CO).\Pi,\Pi^*(phenyl)$[23].







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12) (-) 8-Phenylmenthol (1R,2S,5R) is prepared from (+) pulegone (E.J. Corey and H.E. Ensley, J. Am. Chem. Soc., 97, 6908 (1975)). A 90(1R,2S,5R)/10(1S,2R,5R) mixture which is obtained, is flash-chromatographed (silicagel 60, ethyl ether/pentane 15/85).
13) 4 obtained in 70% overall yield from 1, is more stable than the corresponding aldehyde and easier to handle.

14) The Jurczak method leading to the stable monohydrate proved to be the best (J. Jurczak and A. Zamojski, Roc. Chem. Ann. Soc. Chim. Pol., 44, 2257, 1970).
The bromo ester 2 is obtained in 80% yield after flash chromatography (silica gel 60, ethyl ether/hexane 5/95). ^{1}H NMR (200MHz, $CDCl_3$) δ ppm. 7.27 (m, 4H, arom.) ; 7.15 (m, 1H, arom.), 4.85 (t.d., 1H, CHO cycl., $^3J_{aa}$=10.5Hz twice, $^3J_{ae}$=4Hz); 3.0 (2H, AB system, CH_2Br, $^2J_{AB}$=-12Hz, $\Delta\nu_{AB}$=8Hz) ; 2.07 (m, 1H cycl.) ; 1.85 (m, 2H cycl.) ; 1.7 (m, 1H cycl.) ; 1.47 (m, 1H cycl.) ; 1.30 (s, 3H, CH_3) ; 1.20 (s, 3H, CH_3) ; 0.87 (d, CH_3) ; the 3 other H give multiplets overlapped with methyl.
Compound 3 is prepared in 90 to 95% yield from 2 after one week in the dark.
^{1}H NMR (200MHz, $CDCl_3$) δ ppm : 7.27 (m, 4H, arom.), 7.15 (m, 1H, arom.), 4.92 (t.d., 1H, CH-O cycl., $^3J_{aa}$=10.5Hz twice, $^3J_{ae}$=4Hz), 4.2 and 3.80 (two d., 2H, AB system, CH_2ONO_2, $^2J_{AB}$=-17Hz, $\Delta\nu_{AB}$=80Hz) ; 2.1 (m, 1H cycl.) ; 1.3 (s, 3H, CH_3) ; 1.20 (s, 3H, CH_3) ; 0.90 (d, 3H, CH_3) ; the 7 other H give multiplets between 2 and 0.95 ppm.

15) R.H. Wollenberg and S.J. Miller, Tetrahedron Lett., 3219 (1978).

16) 20 mmoles of 4 are dissolved in 10ml of anhydrous iPrOH, 10mg of KF are added and the mixture stirred for 5 min. (20°C). Then 40 mmol of CH_3NO_2 are added dropwise and stirring is maintained overnight. After evaporation of iPrOH under vacuum, the residue is poured in 100ml ether and washed twice with 5ml water. The ether layer is dried over Na_2SO_4 and the ether removed under vacuum. 90% of crude product 5 which contains no starting material is obtained and analyzed by ^{1}H NMR (200MHz).

17) Addition of $NaCH_2NO_2$ (Henry's method) onto (-)menthylglyoxylate monohydrate at -20°C leads to saponification. However, one must note that in the same conditions, addition of $NaCH_2NO_2$ onto ethyl pyruvate leads to ≈ 100% of the desired compound.

18) ^{1}H NMR (200MHz, $CDCl_3$) δ ppm of 5 (only one diastereomer detected) : 7.3 (m, 4H, arom.) ; 7.15 (m, 1H arom.) ; 4.85 (d.t., 1H, CHO cycl., $^3J_{aa}$=10.5Hz twice, $^3J_{ae}$=4Hz) ; 4.05 (2H, AB part of an ABX system, J_{AB}=-14.5Hz, J_{AX}≈3.5Hz, J_{BX}≈4Hz $\Delta\nu_{AB}$=57Hz) ; 3.41 (1H, X part of an ABX system, OCH-CH_2) ; 3.0 (1H, b, OH) ; 2.17 (m, 1H cycl.) ; 2.0 (m, 2H cycl.) ; 1.77 (m, 1H cycl.) ; 1.61 (m, 2H cycl.) ; 1.27 (s, 3H, CH_3) ; 1.17 (s, 3H, CH_3) ; 0.90 (d, 3H, CH_3) ; The other 3H give multiplets overlapped with the methyls.

19) ^{1}H NMR (20MHz, $CDCl_3$) δ ppm of 6 main signals (only one diastereomer detected) : 7.27 (m, 4H arom.) ; 7.15 (m, 1H arom.) ; 4.77 (t.d., 1H, CHO cycl., $^3J_{aa}$=10.5Hz twice, $^3J_{ae}$=4Hz) ; 3.5 (t., 1H, X part of an ABX system, CH-CH_2NH_2, J_{AX}≈J_{BX}≈3.5Hz) ; 2.55 (2H, AB part of an ABX system, $CHCH_2$-NH_2, J_{AB}=-12Hz) ; 1.3 (s, 3H, CH_3) ; 1.22 (s, 3H, CH_3). Other protons give overlapped signals.

20) ^{1}H NMR spectrum (200MHz, D_2O) of 7, crude product. 4.1 (1H, X part of an ABX system), 3.1 (2H, AB part of an ABX system, $^2J_{AB}$=-13Hz, $^3J_{AX}$ 8.5Hz, $^3J_{BX}$≈4Hz, $\Delta\nu_{AB}$=45Hz).

21) We have shown (A. Solladié-Cavallo and N. Khiar, to be published) that KF-promoted nitromethane additions on carbonyls are equilibrated reactions, but this does not imply that one must think in term of product's stability.

22) KF promoted addition of CH_3NO_2 onto (-)menthylglyoxylate monohydrate at 20°C leads to a 55/45 mixture of the desired addition compound. The $C\alpha H$-$C\beta H_2$ protons give rise to an A_2X system (200MHz, $CDCl_3$) with a doublet at 4.76ppm and a triplet at 4.6ppm.

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