Synthesis of (2*S*,3*R*)[3-$^2H_1$]- and (2*S*,3*S*)[2,3-$^2H_2$]-Serines and (1*R*)[1-$^2H_1$]- and (1*S*,2*RS*)[1,2-$^2H_2$]-2-Aminoethanols

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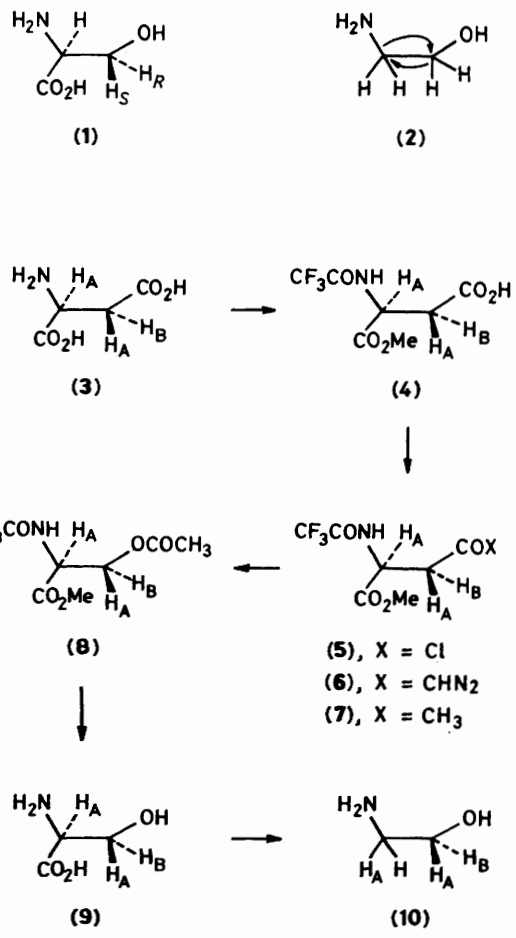
(2*S*,3*R*)[3-$^2H_1$]- and (2*S*,3*S*)[2,3-$^2H_2$]-Serines have been prepared by a route which includes a Baeyer–Villiger oxidation involving rearrangement of a secondary chiral centre; a ^1H n.m.r. assay has been developed to assess stereochemical integrity of *both* prochiral centres in 2-aminoethanol and this shows that decarboxylation of each sample of serine proceeds without loss of chirality at C-3, yielding (1*R*)[1-$^2H_1$]- and (1*S*,2*RS*)-[1,2-$^2H_2$]-2-aminoethanols, respectively.

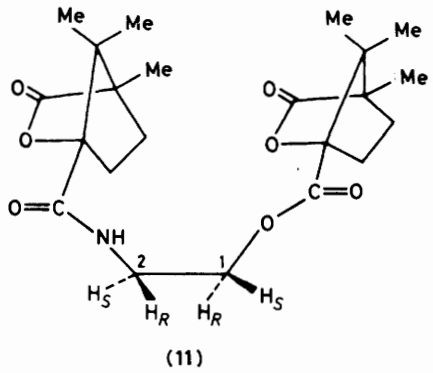
The amino-acid serine (**1**) can be converted in nature into a number of biologically important molecules by pathways involving elimination and replacement reactions at C-3.[1] It is evident therefore that synthesis of serine stereospecifically



labelled at C-3 with isotopic hydrogen would be useful in assessing the overall stereochemistry of these enzymic reactions and indeed some syntheses of the labelled amino-acid have been completed.[2] Decarboxylation of serine would yield 2-aminoethanol. This is the natural substrate for the coenzyme-B_{12}-dependent enzyme ethanolamine ammonia lyase. The substrate undergoes a typical vitamin B_{12}-catalysed rearrangement[3] with this enzyme, the amino-group migrating from C-2 to C-1, and *one* of the hydrogens on C-1 migrating to C-2 as shown in formula (**2**). The synthesis of 2-aminoethanol, stereospecifically labelled at C-1 with isotopic hydrogen, would evidently allow the stereochemistry of this enzymic reaction to be studied.

Because of our interest in the stereochemistry of metabolic reactions of serine and of the ethanolamine ammonia lyase reaction, we determined to synthesise chirally labelled serines by a new route and to investigate the decarboxylation of these compounds as a means of preparing 2-aminoethanol stereospecifically labelled at C-1 with isotopic hydrogen.

We have shown[4] that (2*S*,3*R*)[3-$^2H_1$]- and (2*S*,3*S*)[2,3-$^2H_2$]-aspartic acids [(**3**,H_B = ^{2}H) and (**3**,H_A = ^{2}H)] can be



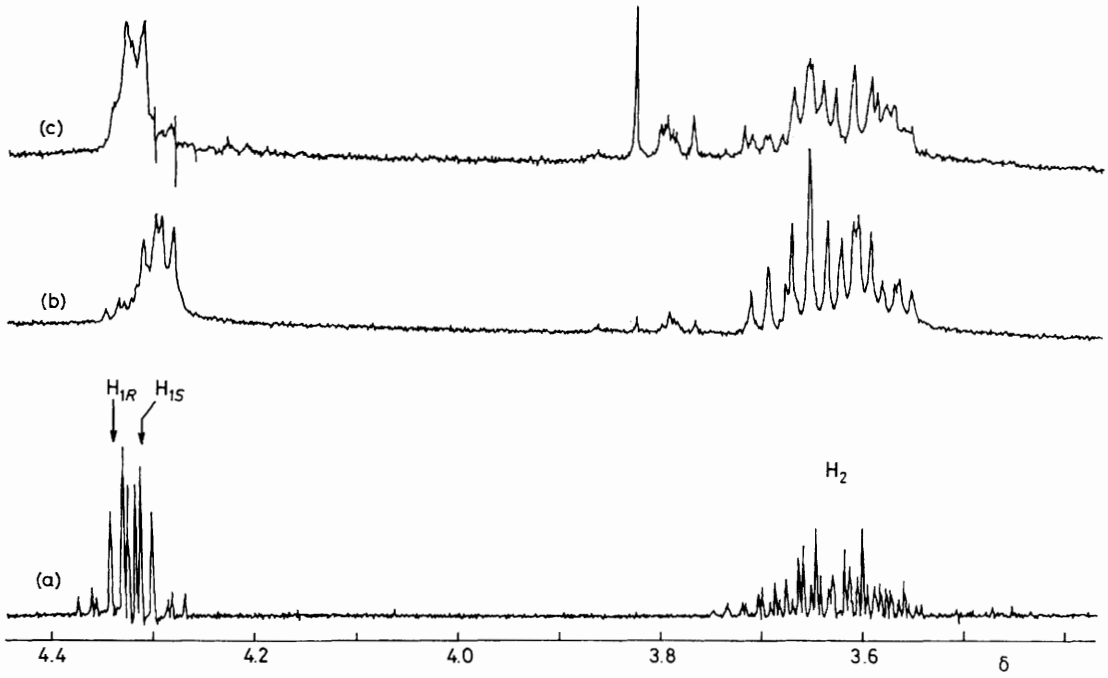


Figure 1. 360 MHz ^{1}H n.m.r. spectra ($CDCl_3$) of (a) the dicamphanoate (**11**); (b) (1*R*)[1-^{2}H]-(**11**); and (c) (1*S*,2*RS*)[1,2-$^2H_2$]-(**11**). The spectrum (a) has been computer line-narrowed, and the spectrum (c) has had the spectrum of a small amount of ethyl camphanoate removed by computer subtraction.

prepared in large quantities using the commercially available enzyme L-aspartase, and that selective protection of amino- and α-carboxylic acid functions can be achieved by reaction with trifluoroacetic anhydride followed by treatment with ethanol. When methanol was substituted for ethanol in this sequence, the esters (**4**,H_B = ^2H)† and (**4**,H_A = ^2H)† were obtained, contaminated with a small amount of the isomeric β-monoesters. Conversion into the acid chlorides (**5**,H_B = ^2H)† and (**5**,H_A = ^2H)† allowed the isomeric contaminant to be removed by crystallisation from dry benzene and the pure acid chlorides were converted into the diazoketones (**6**,H_B = ^2H)† and (**6**, H_A = ^2H)† with diazomethane. Reduction with HI in $CHCl_3$ then afforded the methyl ketones (**7**,H_B = ^2H)† and (**7**,H_A = ^2H).†

Methyl groups are expected[5] to have the lowest migratory aptitude of all alkyl groups in Baeyer–Villiger oxidations so that the methyl ketone (**7**) might be expected to yield the protected serine (**8**). Baeyer–Villiger reactions are also expected to proceed with retention of stereochemistry at the migrating centre[5,6] so that the protected serines (**8**) should be labelled stereospecifically as shown. In the event, treatment of the ketones (**7**) with trifluoroperoxyacetic acid gave mixtures which were hydrolysed directly with refluxing 6M HCl. The serines (**9**,H_B = ^2H)† and (**9**,H_A = ^2H)† were obtained from the hydrolysates by chromatography on Amberlite 1R45, the main by-product proving to be aspartic acid obtained *via* migration of the methyl group in the Baeyer–Villiger reaction. The absolute stereochemistry of the serines (**9**) was confirmed by comparison of the ^1H n.m.r. spectral data with those reported in the literature.[2c] Although the yield in the Baeyer–Villiger step was poor, all other yields were reasonable so that the *overall* yields of the stereospecifically labelled serines (**9**) from the aspartic acids (**3**) were *ca.* 9%.

Decarboxylation of the labelled serines (**9**) was effected in good yield by first heating with *para*-methoxyacetophenone at 160—190 °C and then heating the product with 12M HCl at reflux. It was evident that the samples of 2-aminoethanol obtained were deuteriated but an assay was required to assess the stereochemical purity of the samples. The enantiomeric purity of [1-$^2H_1$]ethanol had been assessed[7] from the ^1H n.m.r. spectra of the camphanic acid ester in the presence of $Eu(dpm)_3$ (dpm = dipivaloylmethanato) and so we prepared the *N*-acetyl-† and *N*-phthaloyl-*O*-camphanic esters† of 2-aminoethanol. The prochiral hydrogens in the former compound could not be resolved even in the presence of shift reagent whilst resolution was observed in the ^1H n.m.r. spectrum of the latter compound on addition of $Eu(fod)_3$ (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionato). When the *N*,*O*-dicamphanic derivative† was made however, the ^1H n.m.r. spectrum showed *all four prochiral protons* separately even in the absence of shift reagent [Figure 1(a)]. When the dicamphanoates of the products of decarboxylation of (2*S*,3*R*)[3-$^2H_1$]- and (2*S*,3*S*)[2,3-$^2H_2$]-serines [(**9**,H_B = ^2H) and (**9**,H_A = ^2H), respectively] were prepared then it was evident that the labelling was indeed stereospecific [Figures 1(b) and 1(c), respectively]. We had therefore synthesised (1*R*)-[1-$^2H_1$]-2-aminoethanol (**10**,H_B = ^2H) and (1*S*, 2*RS*)[1,2-$^2H_2$]-2-aminoethanol (**10**,H_A = ^2H) from (2*S*,3*R*)[3-$^2H_1$]- and (2*S*,3*S*)[2,3-$^2H_2$]-serines, respectively. It is of interest to note that the assay will also serve to assess the enantiomeric purity of 2-aminoethanols labelled at C-2.

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† These compounds had the expected analytical and spectral properties and the stereochemical integrity of the label was confirmed by selective omissions in the ^1H n.m.r. spectra. This was also confirmed by ^2H n.m.r. spectroscopy in the case of the chirally labelled serines (**9**).

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