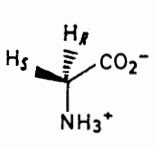
A Highly Stereospecific Synthesis of (*R*)- and (*S*)-[2-$^2H_1$]Glycine

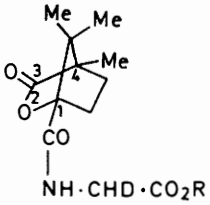
By **Wilfred L. F. Armarego,* Beverly A. Milloy,** and **William Pendergast,** Medical Chemistry Group, The John Curtin School of Medical Research, The Australian National University, Canberra, A.C.T. 2600, Australia

Chirally pure [2-$^2H_1$]glycines were synthesised by the following sequence: *O*-benzylserine (4) ⟶ 3-benzyloxy-2-bromopropionic acid (5) ⟶ 3-benzyloxy[2-$^2H_1$]propionic acid (6) ⟶ 3-benzyloxy[2-$^2H_1$]propionamide (7) ⟶ 2-benzyloxy[1-$^2H_1$]ethylamine (8) ⟶ 2-benzyloxy-*N*-phthaloyl[1-$^2H_1$]ethylamine (9) ⟶ 2-hydroxy-*N*-phthaloyl[1-$^2H_1$]ethylamine (10) ⟶ [2-$^2H_1$]glycine (13). The isotopic, chemical, and optical purity of these compounds was determined by microanalyses and mass, n.m.r., and o.r.d. spectra. Complete retention of configuration in the first and second steps was established by correlation with (*S*)-(−)-2-bromopropionic acid and by conversion into (+)-(*S*)-[2-$^2H_1$]propionic acid, respectively. (*S*)-*O*-Benzyl[2-$^3H_1$]serine was made, and can be used to prepare (*S*)-[2-$^3H_1$]glycine.

We required chiral [2-$^2H_1$]- and [2-$^3H_1$]-glycines for biosynthetic studies, and we first attempted to prepare them by an enzymic method. Jordan and Akhtar [1] found that when an aqueous solution of (*RS*)-[2-$^3H_1$]-glycine was treated with serine hydroxymethyl transferase in the presence of pyridoxal phosphate and tetrahydrofolic acid, but in the absence of formaldehyde, the *pro-S* hydrogen atom at C-2 in glycine (1) was exchanged with hydrogen from the medium stereospecifically. This stereospecificity was consistent with reports from other laboratories.[2] We repeated the enyzmic reaction



(1)



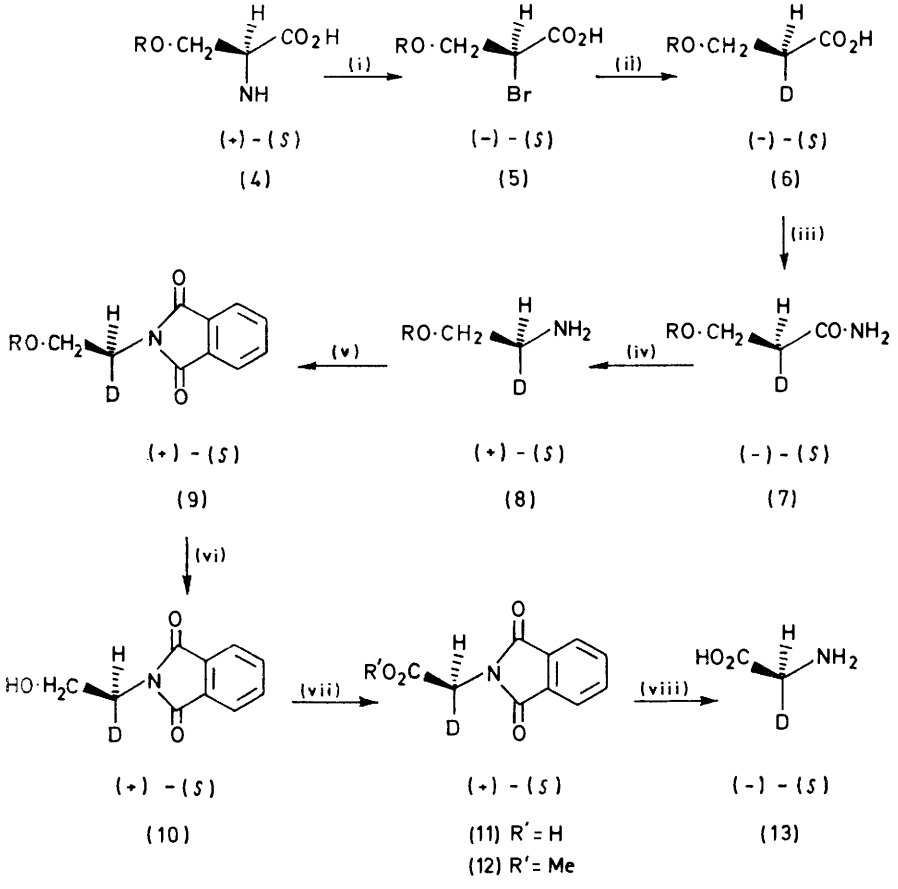
(2) R = H
(3) R = Me

and confirmed that about half the tritium was lost from (*RS*)-[2-$^3H_1$]glycine. When we carried out the experiment with [2-$^2H_2$]glycine in water we obtained a deuteriated glycine, but in this case we had to confirm its optical purity. It was converted into the *N*-benzyloxycarbonyl derivative, which was analysed by mass spectrometry. At 15 eV the ratio of peak heights for undeuteriated, monodeuteriated (*m/e* 210), and dideuteriated glycines was 26 : 59 : 15. These results, however, give no indication of the chiral purity of the monodeuteriated glycine. The derivative also exhibited a plain positive o.r.d. curve in methanol and the specific rotation was small ($[\alpha]_{230}^{20}$ + 28°). Although this rotation was entirely due to chiral *N*-benzyloxycarbonyl-[2-$^2H_1$]glycine, it was not possible to establish the chiral purity from these data. Similar results were obtained when the enzymic reaction was performed with glycine in deuterium oxide except that the o.r.d. curve was of opposite sign. In order to deduce the chiral purity we converted the mixture of glycines into the camphanamides (2) derived from (−)-(1*S*,4*R*)-ω-camphanic acid. In this derivative the n.m.r. signals for the diastereotopic protons of glycine are separated into a quartet in $CDCl_3$ (because of vicinal coupling with the NH) which is centred at δ 4.1 with the *pro-R* hydrogen atom resonating at higher field (see Figure A). In the camphanoyl ester (3) these protons appear as a triplet, but if the shift reagent Eu(dpm)$_3$ is added to the deuteriochloroform solution the resonances are shifted downfield and appear as a clearly separated octet (because of vicinal and geminal coupling) in which all the signals can be integrated. The quartet from the *pro-R* hydrogen atom in this case also occurs at higher field. Gerlach and Zagalak [3] had previously used camphanic esters to identify the diastereotopic protons in α-monodeuteriated alcohols. When the amide (2) from the enzymic preparation of (*R*)-[2-$^2H_1$]glycine was examined, and the integrals of the diastereotopic protons were measured it was found that the ratio of (*R*)- to (*S*)-[2-$^2H_1$]glycine was 45 : 25 (Figure A). The enzymic preparation was, therefore, not completely stereospecific; a result which could be due to contamination of the enzyme preparation with a transaminase. Transaminases are known to labilise α-hydrogen atoms of α-amino-acids in a *pro-R* configuration.[2,4] A cautionary note is warranted here for those who use chiral [2-$^2H_1$]glycines prepared by the enzymic methods; it is advisable that the chiral purity should be confirmed in each case.

Synthesis of Chiral [2-$^2H_1$]*Glycines.*—Several syntheses of chiral [2-$^2H_1$]glycines have been reported, and although they involved chemical sequences, one or two of the steps were mediated by an enzyme.[4-7] We now describe an entirely chemical synthesis of (*R*)- and (*S*)-[2-$^2H_1$]glycines which is highly stereospecific (Scheme 1). The starting material is (*RS*)-*O*-benzylserine, synthesised from methyl acrylate, and resolved as described by Wünsch and Fürst.[8] In later attempts starting from the *S*-enantiomer, material of high optical purity which was available commercially was used. (+)-(*S*)-*O*-Benzylserine (4) was converted into (−)-3-benzyloxy-2-bromopropionic acid (5) by treatment with nitrous acid in the presence of hydrobromic acid—a step which,

[1] P. M. Jordan and M. Akhtar, *Biochem. J.*, 1970, **116**, 277.
[2] H. C. Dunathan, *Adv. Enzymol.*, 1971, **35**, 79.
[3] H. Gerlach and B. Zagalak, *J.C.S. Chem. Comm.*, 1973, 274.
[4] P. Besmer and D. Arigoni, *Chimia (Switz.)*, 1968, **22**, 494.
[5] A. R. Battersby, J. Staunton, and M. C. Summers, *J.C.S. Chem. Comm.*, 1974, 548.
[6] C. Fuganti and M. Mazza, *J.C.S. Perkin I*, 1973, 954.
[7] E. Leistner and I. D. Spenser, *J.C.S. Chem. Comm.*, 1975, 378.
[8] W. Grassmann, E. Wünsch, P. Duefel, and A. Zwick, *Chem. Ber.*, 1958, **91**, 538; E. Wünsch and G. Fürst, *Z. physiol. Chem.*, 1962, **329**, 109.

by analogy with reactions of other α-amino-acids, should proceed with retention of configuration.[9,10] The reductive debromination of the acid (5) was achieved with lithium triethylborodeuteride (' superdeuteride '); according to reported reductive debrominations with this reagent, which was shown to be an exceptionally powerful nucleophile, the reaction should occur with inversion of configuration.[11] The (−)-3-benzyloxy [2-$^2H_1$]propionic acid (6) formed, contained < 5% of non-deuteriated acid (mass spectrum). The ^1H n.m.r. spectrum showed a clear doublet for the two 3-protons and a triplet (broadened by geminal H,D-coupling) for aqueous alkali. In contrast, sodium hypobromite gave low yields of amine together with large amounts of benzyl alcohol and benzoic acid, probably formed from benzaldehyde resulting from benzylic bromination. A quantity of unchanged amide could be recovered from the hypochlorite reaction, but its ^1H n.m.r. spectrum showed that it had lost a lot of its deuterium. Unchanged amide could only be recycled in the Hofmann reaction with the non-deuteriated amide. A Curtius reaction on the acid chloride, on the other hand gave much *NN'*-bis-(2-benzyloxyethyl)urea, and the use of diphenyl phosphorazidate [13] was unsatisfactory.



SCHEME 1 R = CH_2Ph. Reagents (i) HNO_2–HBr, (ii) $LiEt_3BD$, (iii) $(COCl)_2$ then liq. NH_3, (iv) NaOCl–NaOH, (v) *o*-$C_6H_4(CO)_2O$, (vi) Pd–H, (vii) $KMnO_4$–H^+, (viii) N_2H_4, AcOH then H^+

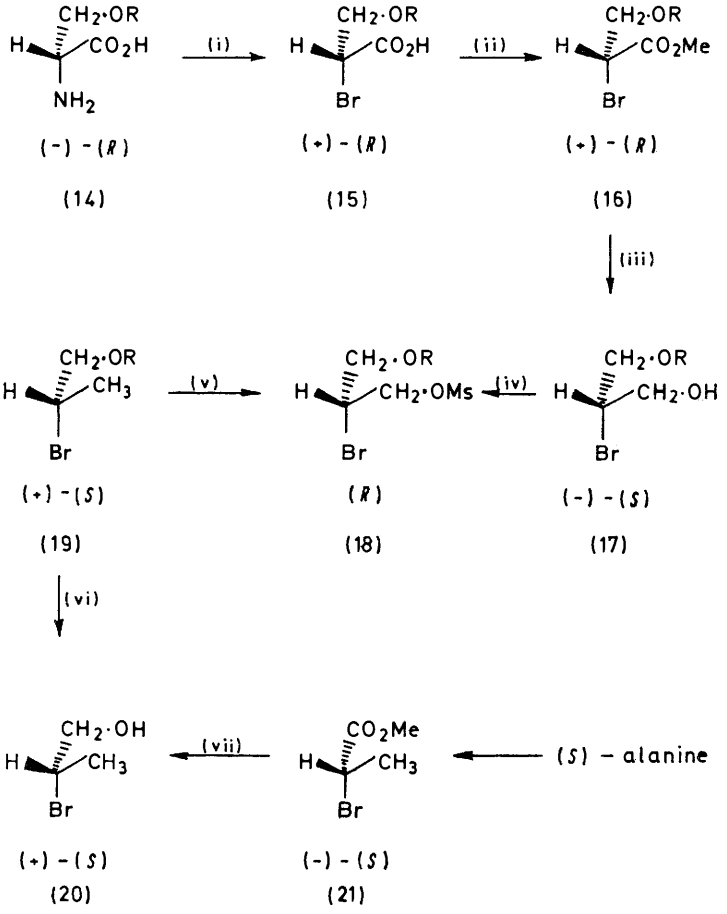
H-2. The (−)-acid (6) gave the (−)-amide (7) on treatment with oxalyl chloride (to give the acid chloride in high yield) followed by liquid ammonia. Attempts to carry out the first step with other reagents, *e.g.* thionyl chloride, led to considerable decomposition involving cleavage of the ether linkage (*cf.* ref. 12). Conversion of the amide (7) into (+)-2-benzyloxy[1-$^2H_1$]ethylamine (8) by a Hofmann reaction was investigated in detail in order to define optimum conditions. The best yields (62%) were obtained with 0.9N-sodium hypochlorite in

Fusion of the (+)-amine (8) with phthalic anhydride provided (+)-2-benzyloxy-*N*-phthaloyl[1-$^2H_1$]ethylamine (9), which was debenzylated quantitatively to (+)-2-hydroxy-*N*-phthaloyl[1-$^2H_1$]ethylamine (10) by hydrogenolysis over palladium black or 50% palladium–charcoal in alcoholic solution. Oxidation of the amine (10) to (+)-*N*-phthaloyl[2-$^2H_1$]glycine (11) was also studied in detail and the best yields were obtained with potassium permanganate in aqueous 2.5N-sulphuric acid

[9] J. P. Greenstein and M. Winitz, ' Chemistry of the Amino Acids,' Wiley, New York, 1961, vol. 1, pp. 160—167.
[10] P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, 1950, **166**, 178.
[11] H. C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, 1973, **95**, 1669.
[12] J. J. Bloomfield, *J. Org. Chem.*, 1962, **27**, 2742.
[13] K. Ninomiya, T. Shioiri, and S. Yamada, *Tetrahedron*, 1974, **30**, 2151; *J. Amer. Chem. Soc.*, 1972, **94**, 6203.

under conditions in which negligible exchange of the hydrogen atoms at C-2 occurred. Attempts to remove the phthaloyl group with hydrazine failed, probably because of the formation of a stable salt. However, after the (+)-acid (11) was esterified, with diazomethane, the (+)-ester (12) could be hydrolysed with hydrazine acetate in methanol to methyl [2-$^2H_1$]glycinate, which on further hydrolysis with 2.5N-hydrochloric acid for a short period gave (−)-[2-$^2H_1$]glycine (13) in 90% yield. The overall yield of glycine from (*S*)-*O*-benzylserine was 15%.

The synthesis was repeated with (−)-(*R*)-*O*-benzylserine, and although the intermediates were not analytically pure their purity was >80% (by ^1H n.m.r.) and



SCHEME 2 R = CH_2Ph. Reagents (i) HNO_2–HBr, (ii) CH_2N_2, (iii) $LiBH_4$, (iv) $MeSO_2Cl$–C_5H_5N, (v) $LiEt_3BH$, (vi) Pd–H, (vii) $LiBH_4$

of its ω-camphanoyl derivative (2) were compared with those of the products obtained from the enzymic synthesis and with data from the literature.[5] It was clear that (−)-[2-$^2H_1$]glycine from (*S*)-*O*-benzylserine had the *S*-configuration (13). Similarly the physical data of our monodeuterioglycine from (*R*)-*O*-benzylserine confirmed that it had the *R*-configuration. In the original synthetic plan it was expected that (*R*)-[2-$^2H_1$]-glycine should be formed from (*S*)-*O*-benzylserine. This was because the three steps (i), (ii), and (iv) (Scheme 1) in which the chiral centres are directly involved in the reactions were presupposed to proceed with retention, inversion, and retention of configuration, respectively. One of these steps, however, did not occur as predicted their optical rotations had signs opposite to those of their enantiomers in the above series.

The design of this synthesis was such that several steps could be studied in detail with non-deuteriated relays. The exchange of the hydrogen atoms, which were later to be replaced by deuterium, with the reaction medium in steps (vii) and (viii) could also be tested for conditions of least exchange with relays in which the intended chiral carbon atom possessed two deuterium atoms.

The negative o.r.d. curve of [2-$^2H_1$]glycine synthesised from (+)-(*S*)-*O*-benzylserine and the ^1H n.m.r. spectrum and the stereochemistry of the odd reaction had to be established.

Stereochemistry of Reactions (i) *and* (ii) *in Scheme* 1.— The first evidence that step (i) took place with retention of configuration was that the reaction of (−)-(*S*)-3-benzyloxy-2-bromopropionic acid (5) with aqueous ammonia gave (−)-(*R*)-*O*-benzylserine with partial racemization. α-Bromo-acids are known to produce α-amino-acids with inversion of configuration.[10] However, the possibility that inversion could have occurred in step (i) and retention in the amination reaction was

not overlooked. Confirmation of retention of configuration in step (i) was obtained from the reaction sequence in Scheme 2 in which the chiral centres were not involved in any of the reactions. (+)-(*R*)-3-Benzyloxy-2-bromopropionic acid (15), prepared from (−)-(*R*)-*O*-benzylserine (14) was esterified and the (+)-(*R*)-methyl ester (16) was reduced with lithium borohydride to (−)-(*S*)-3-benzyloxy-2-bromopropan-1-ol (17) without observable debromination. The alcohol was converted into its methylsulphonyl derivative (18), which was reduced with lithium triethylborohydride to (+)-(*S*)-1-benzyloxy-2-bromopropane (19), again without debromination. The latter reaction was very clean and none of the non-chiral benzyl propyl ether was formed. Hydrogenolysis of the (+)-(*S*)-ether (19) gave (+)-(*S*)-2-bromopropan-1-ol (20) in high yield. This product was identical with the bromopropanol obtained from the reduction ($LiBH_4$) of methyl (−)-(*S*)-2-bromopropionate (21) [14] produced from (−)-(*S*)-2-bromopropionic acid of known absolute configuration, which was in turn prepared from (*S*)-alanine.

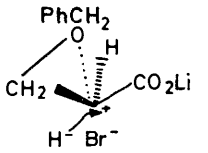
We then investigated the reductive debromination step (ii). Although lithium triethylborohydride is known to displace the bromine atom in halides with inversion of configuration,[11] in the presence of intramolecular interactions hydride reagents are known to substitute a halogen atom with retention of configuration.[15] The reduction in step (ii) (Scheme 1) may well have proceeded with retention of configuration. We examined the reduction of (*S*)-2-bromopropionic acid with lithium triethylborodeuteride and observed that as in the reduction with lithium aluminium deuteride (which was followed by oxidation of the resulting deuteriopropanol [16]) only (−)-(*R*)-[2-$^2H_1$]propionic acid was formed. The absolute configurations of chiral [2-$^2H_1$]propionic acids was firmly established,[17,18] and clearly the above deuteriodebrominations of 2-bromopropionic acid proceeded with inversion of configuration. On the other hand, when (−)-3-benzyloxy[2-$^2H_1$]-propionic acid (4) was treated with hydrobromic acid it gave 3-bromo[2-$^2H_1$]propionic acid. Debromination of the latter with lithium triethylborohydride (' superhydride ') gave (+)-(*S*)-[2-$^2H_1$]propionic acid. Unlike the above reductions of (*S*)-2-bromopropionic acid, the reduction of (5) occurred with high retention of configuration, accounting for the observed configuration of the deuterioglycines obtained. The reason for the unexpected stereochemistry in the reduction of (5) as compared with that of chiral 2-bromopropionic acid is probably the presence of the ethereal oxygen atom in 3-benzyloxy-2-bromopropionic acid. This may stabilize a complex such as (22) in which the bromine atom is replaced by hydride with retention of configuration.

* We assume that relative intensities of peaks in the spectra of deuteriated and nondeuteriated species are within ±3%.

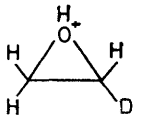
[14] B. Acott, R. B. Bates, and C. D. Green, *Tetrahedron Letters*, 1969, 3465.

[15] J. N. Labows, jun., and N. Landmesser, *J. Org. Chem.*, 1975, **40**, 3798.

Chemical and Chiral Purity of Compounds in Scheme 1.—The chemical purity of the compounds was established by microanalyses (see Experimental section). The error in the H + D analyses, however, was too large to

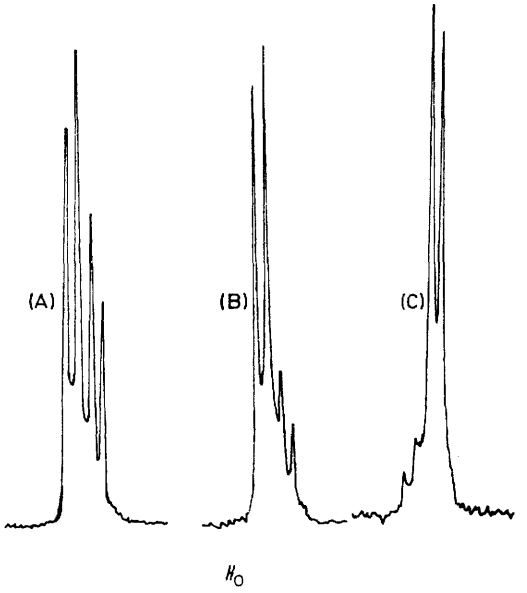


(22)



(23)

give reliable H : D ratios of nondeuteriated to deuteriated molecules. More reliable ratios were obtained from mass spectrometric data.* The spectra were run under conditions which gave adequately intense molecular ion



Deuterium-decoupled 100 MHz ^1H n.m.r. spectra of the diastereotopic protons (near δ 4) of the (1*S*,4*R*)-ω-camphanoyl derivatives of (A) enzymically prepared (*R*)-[2-$^2H_1$]glycine, (B) synthetic (*R*)-[2-$^2H_1$]glycine, and (C) synthetic (*S*)-[2-$^2H_1$]-glycine

peaks (*e.g.* at 15 eV) or fragment ion peaks (present in both deuteriated and non-deuteriated compounds) and had weak or negligible $M - 1$ peaks (see Experimental section). From the peak areas the percentage of non-deuteriated impurity in the deuteriated samples was calculated. Thus (−)-(*S*)-3-benzyloxy[2-$^2H_1$]propionic acid (6) was shown to contain 5(±3)% of 3-benzyloxypropionic acid. The *R*-enantiomer, on the other hand, contained 10(±3)% of nondeuteriated acid. The presence of the latter was attributed to contamination of the reducing agent, lithium triethylborodeuteride (a different batch was used in each case) with the hydride. If any water was introduced into the ' superdeuteride ' solution it would have decomposed the reagent immedi-

[16] D. J. Prescott and J. L. Rabinowitz, *J. Biol. Chem.*, 1968, **243**, 1551.

[17] B. Zagalak, P. A. Frey, G. L. Karabatsos, and R. H. Abeles, *J. Biol. Chem.*, 1966, **241**, 3028.

[18] J. Retey, A. Umani-Ronchi, and D. Arigoni, *Experientia*, 1966, **22**, 72.

ately. (+)-(*S*)-2-Benzyloxy[1-$^2H_1$]ethylamine (8) did not give a molecular ion but gave intense peaks at *m/e* 46 [probably due to the ion (23)] and 32 (probably from DHC=N^+H_2), and did not have peaks at 44 and 29 seen in the spectrum of 2-benzyloxyethylamine run under the same conditions. The percentage of the latter compound in (8) was found to be 7(±3)%. Similarly the spectra of (9), (11), and (12) indicated between 5 and 8% of nondeuteriated species. The spectra of (−)-(*S*)-[2-$^2H_1$]glycine and its (+)-(*R*)-enantiomer contained 8 and 18(±3)% of nondeuteriated glycine, respectively. The high percentage in the latter originated mainly in step (ii) (Scheme 1) and in the Hofmann reaction [step (iv)] which was improved when the synthesis of the *S*-series was carried out. These ratios only tell us that the compounds possessed a very high proportion of monodeuteriated material but give no indication of chiral purity.

The chiral purity of the deuteriated glycines was determined from the ^1H n.m.r. spectra of the respective ω-camphanoyl derivatives (2). The spectra of the diastereotopic protons of the derivatives from (*R*)- and (*S*)-[2-$^2H_1$]glycine are shown in the Figure (B and C, respectively). From the peak heights (particularly the outer peaks), and assuming that the contaminant is nondeuteriated glycine, the percentages of optically pure *R*- and *S*-isomers are about 80 and 92, respectively. Optically pure (−)-(*S*)-[2-$^2H_1$]glycine prepared by Battersby and his collaborators [5] had $[\alpha]_{238}$ −38.8°, and from our o.r.d. curves (max. at 220 nm) the optical purities of (*R*)- and (*S*)-monodeuterioglycines are 80 and 90(±3)%. This is in agreement with the ^1H n.m.r. data and demonstrates that the monodeuterioglycines are almost, if not entirely chirally pure (but contain a little of the nonchiral glycine). It follows that the monodeuteriated intermediates in this synthesis are also chirally pure. They are, however, slightly contaminated with nondeuteriated species—but not with enantiomeric deuteriated species.

The synthesis described is highly stereospecific and should be particularly useful for preparing chiral [2-$^3H_1$]glycines. As a preliminary test of this we prepared (*RS*)-*O*-benzyl[2-$^3H_1$]serine (61% incorporation) by heating (*RS*)-*O*-benzylserine in tritiated water containing benzaldehyde. When a large amount of (*S*)-*O*-benzylserine was recrystallised with the ' hot ' racemate, 50% of the radioactivity was removed and (*S*)-*O*-benzyl[2-$^3H_1$]serine was obtained. This amino-acid was taken through the synthesis (Scheme 1) up to (*S*)-2-benzyloxy[1-$^3H_1$]ethylamine without loss of specific molar radioactivity, which confirms the stereospecificity of the steps involved. By using ' superdeuteride ' in the second step it should be also possible to prepare chiral [2-$^2H_1$,2-$^3H_1$]glycines. Recently Golding, Sargeson, and their co-workers [19] have reported that the diastereotopic protons of glycine in a cobalt complex are selectively exchanged by deuterium; this affords another entirely chemical method for making optically enriched (but not chirally pure) monodeuteriated glycines. The *pro-S* hydrogen atom of glycine in the Λ-(*N*-benzylglycinato)-bis(ethylenediamine)cobalt(III) ion (Λ indicates the absolute configuration at cobalt) exchanges faster than the *pro-R* hydrogen atom ($k_{rel} \geqslant 4$) in deuterium oxide buffer at pH 10.5.

EXPERIMENTAL

All extracts were dried over Na_2SO_4 and evaporated below 35 °C and at *ca.* 18 mmHg unless otherwise stated. I.r. spectra of solids (KBr discs) and liquids (films) were measured on a Unicam SP 1000 spectrometer. Band assignments are tentative and CH str. bands at *ca.* 3 000 cm^{-1} are not always indicated. ^1H N.m.r. spectra were obtained on a Varian T60A spectrometer locked on the Me_4Si signal unless otherwise stated. *J* Values are in Hz. Optical rotations were measured on a Zeiss (366650) photoelectric polarimeter (1 dm tubes; 20 °C), and the o.r.d. curves were measured by Dr. R. D. Frier on a Cary 60 spectropolarimeter (0.1 dm cells; 20 °C). Specific rotations of deuteriated compounds were *not* corrected for the small amounts of optically inactive nondeuteriated species. Concentrations (*c*) are in g per 100 ml. Mass spectra were measured at 70 eV on an A.E.I. MS9 spectrometer unless otherwise stated. The ratios of nondeuteriated to deuteriated compounds were obtained from peak heights or by cutting out and weighing the chart paper. Microanalyses (by the Australian National University Analytical Services Unit) of deuteriated compounds obtained by the conventional C and H method gave the total H + D percentages as determined by the weight of H_2O + HOD formed. For smaller quantities (0.5 mg) a 185B Hewlett–Packard C, H, and N analyser was used in which H + D values were determined, from the H_2O + HOD formed, by g.l.c. (thermal conductivity detector). When glycine and [2-$^2H_2$]glycine were used as standards in the latter method, the area of the HOD peak was 5% larger than that of the H_2O peak. The determined values of H + D in both methods were calculated from the weight or areas of H_2O + HOD produced on the assumption that the H : D atomic ratio was that of the compound analysed. Unless these corrections were made the hydrogen analyses were unsatisfactory. The radioactivity of compounds was measured on a Beckman LS 100 scintillation spectrometer for solutions of 2,5-diphenyloxazole (5%) and naphthalene (10%) in dioxan (10 ml), and corrected for quenching.

(−)-(S)-3-*Benzyloxy*-2-*bromopropionic Acid* (5).—(+)-(*S*)-*O*-benzylserine [8] {21.6 g, 1 mol. equiv.; $[\alpha]_{546}$ +26.8°, (*c* 2 in 0.1N-HCl in aqueous 80% acetic acid)} in cold 2.5N-H_2SO_4 (786 ml) containing potassium bromide (80.1 g, 6 mol. equiv.) was treated (0.5 h) with sodium nitrite (21 g, 2.7 mol. equiv.) at 0 °C. The solution was kept at 0 °C for 1 h and then stirred for 1 h with ether (250 ml). The layers were separated and the aqueous solution was extracted with ether. The combined extracts were dried ($CaCl_2$ and 4A molecular sieves) until clear. Evaporation gave an oil which was dissolved in ether and dried as before if not clear. The residual oil was evaporated at 25 °C and 0.1 mmHg to constant weight (23 g). Attempts to distil large quantities *in vacuo* led to considerable decomposition with the formation of benzyl bromide, *cis*-3-benzyloxyacrylic acid [δ($CDCl_3$) 4.72 (s, CH_2), 6.39 (d, H-2, *J* 2), 7.11 (d, H-3, *J* 2), 7.40 (s, aromatic H), and 7.90 (s, CO_2H)],

[19] B. T. Golding, G. J. Gainsford, A. J. Herlt, and A. M. Sargeson, *Angew. Chem. Internat. Edn.*, 1975, **14**, 495.

and polymeric material. Small quantities (*ca.* 5 g) can be distilled (without a fractionating column; b.p. 166 °C at 0.9 mmHg), without decomposition and yield mainly (*S*)-3-benzyloxy-2-bromopropionic acid containing about 15% of (*S*)-3-benzyloxy-2-hydroxypropionic acid which distilled with it (Found: C, 48.2; H, 4.4; Br, 27.9. Calc. for $C_{10}H_{11}BrO_3$,0.15$C_{10}H_{12}O_4$: C, 47.9; H, 4.5; Br, 27.9%), δ($CDCl_3$) 3.86 (dd, 3-H_2), 4.27 (q, H-2), 4.60 (s, CH_2O), 7.33 (s, aromatic H), and 7.90br (s, CO_2H); $\nu_{max.}$ 705 and 645 (Ph), 1 735 (CO), and 3 100br cm^{-1} (OH). The small amounts of hydroxy-acid in the crude or the distilled material could not be observed in the ^1H n.m.r. spectra because of overlapping peaks. The crude oil was used in the subsequent reduction because it gave yields of product similar to those obtained with the distilled oil. The specific rotations from the preparations of both enantiomers were consistently similar: $[\alpha]_{346}$ −58.4, $[\alpha]_{405}$ −40.4, $[\alpha]_{436}$ −32.0, $[\alpha]_{546}$ −17.3, and $[\alpha]_{578}$ −14.7° (*c* 2.14 in MeOH) for the *S*-isomer.

(S)-3-*Benzyloxy*[2-$^2H_1$]*propionic Acid* (6).—A solution (1M) of lithium triethylborodeuteride in tetrahydrofuran (230 ml, 2.8 mol; Aldrich 'superdeuteride') under dry nitrogen was added (syringe) to the preceding (−)-bromo-acid (21 g, 1 mol. equiv.) under nitrogen at 0 °C and the mixture was then refluxed for 2 h. The solution was cooled and the excess of deuteride was decomposed with water (75 ml); the mixture was acidified and extracted with ether. The residue from the extract was treated with water (100 ml) followed by a 1 : 1 mixture of hydrogen peroxide (100 vol) and 2N-sodium hydroxide until effervescence ceased (*ca.* 100 ml added). The alkaline solution was extracted with ether (discarded), and the aqueous solution was acidified with 2N-sulphuric acid, saturated with sodium chloride, and extracted with ether (6 × 150 ml). The extract was dried ($CaCl_2$) and evaporated. The residual oil was distilled to give (*S*)-3-*benzyloxy*[2-$^2H_1$]*propionic acid* (7.4 g, 50%), b.p. 126 °C at 0.15 mmHg, 116 °C at 0.07 mmHg, which absorbed water slowly from the atmosphere [Found: C, 64.2; H, 6.1 (corrected for D); Br, nil. $C_{10}H_{11}DO_3$,0.33H_2O requires C, 64.15; H, 6.1%. Found after a further period in air: C, 63.5; H, 6.2 (corrected for D). $C_{10}H_{11}DO_3$,0.5H_2O requires C, 63.4; H, 6.4%]; $[\alpha]_{405}$ −7.96, $[\alpha]_{436}$ −6.82, $[\alpha]_{546}$ −4.18, and $[\alpha]_{578}$ −3.74° (neat); $\nu_{max.}$ 705 and 745(Ph), 1 100 (COC), 1 710 (CO_2H), and 3 050br cm^{-1} (OH); δ ($CDCl_3$) 2.68br (t, H-2, *J* 6), 3.82 (d, 3-H_2, *J* 6), 4.62 (s, PhCH_2), 7.42 (s, aromatic H), and 10.07 (s, CO_2H; position varies); *m/e* 179 (0.6%), 180 (15), 181 (100), and 182(14).

3-Benzyloxypropionic acid was prepared from butyrolactone and benzyl alcohol as described in ref. 12 and by reaction of (±)-*O*-benzylserine with 'superhydride', and had δ ($CDCl_3$) 2.68 (t, 2-H_2, *J* 6), 3.82 (t, 3-H_2, *J* 6), 4.62 (s, PhCH_2), 7.42 (s, aromatic H), and 9.80 (s, CO_2H); *m/e* 179 (10%), 180 (100), and 181 (13).

(−)-(S)-3-*Benzyloxy*[2-$^2H_1$]*propionamide* (7).—The acid (6) (5.7 g) was dissolved in freshly distilled oxalyl chloride (6 ml) and stirred at room temperature for 2 h. Volatile material was removed *in vacuo* and the residue was kept in a vacuum (over KOH) overnight. The oil was cooled in liquid nitrogen and liquid ammonia (120 ml) was added slowly. The solution was allowed to warm to room temperature and to evaporate to dryness. Brine (100 ml) was added to the residue, which was then extracted with chloroform (8 × 50 ml). The dried extract was decolourised (charcoal), filtered, and evaporated. The residue was dissolved in a small volume of benzene and on addition of light petroleum (b.p. 60—80°) the (S)-*amide* (4.2 g, 74%) crystallised out as plates, m.p. 57.5—58° (after drying at 20 °C and 0.01 mmHg for 5 h) (Found: C, 66.3; H + D, 7.9; N, 7.6. $C_{10}H_{12}DNO$ requires C, 66.6; H + D, 7.8; N, 7.8%); $[\alpha]_{436}$ −4.97 and $[\alpha]_{578}$ −4.54° (*c* 51 in $CHCl_3$); $\nu_{max.}$ 700 and 755 (Ph), 1 625 and 1 660 (amide), and 3 180br and 3 360br cm^{-1} (NH str.); δ ($CDCl_3$) 2.48br (t, H-2, *J* 6), 3.75 (d, 3-H_2, *J* 6), 4.57 (s, PhCH_2), 6.00br (s, NH_2), and 7.33 (s, aromatic H).

3-*Benzyloxypropionic acid*, m.p. 50—51°, was prepared in a similar way (Found: C, 66.8; H, 7.0; N, 7.9. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%); δ ($CDCl_3$) 2.48 (t, 2-H_2, *J* 6), 3.75 (t, 3-H_2, *J* 6), 4.57 (s, PhCH_2), and 7.33 (s, aromatic H).

(+)(S)-2-*Benzyloxy*[1-$^2H_1$]*ethylamine* (8).—To the (*S*)-amide (7) (3.98 g, 1 mol. equiv.) in water (26.5 ml) at 0 °C was added a freshly prepared solution containing 0.91N-sodium hypochlorite (29.4 ml, 1.2 mol. equiv.) and 1.6N-sodium hydroxide (13.9 ml, 1 mol. equiv.; yield was drastically reduced at lower normalities) and the mixture was stirred at room temperature for 0.75 h. It was then heated at 90—95 °C for 10 min (during which time an oil separated), cooled, acidified with concentrated hydrochloric acid, and extracted with chloroform (4 × 50 ml). Unchanged amide could be recovered from this extract but could not be recycled because it had lost some deuterium (see below). The aqueous layer was basified with 2N-sodium hydroxide, saturated with sodium chloride, and extracted with chloroform (4 × 50 ml). Evaporation of the dried extract gave the (S)-*amine* (2.08 g, 62%), b.p. 67—68° at 1 mmHg (Found: C, 71.0; H + D, 9.2; N, 9.3. $C_9H_{12}DNO$ requires C, 71.0; H + D, 9.3; N, 9.2%); $[\alpha]_{364}$ +0.42, $[\alpha]_{405}$ +0.34, $[\alpha]_{436}$ +0.25, $[\alpha]_{546}$ +0.15, and $[\alpha]_{578}$ +0.11° (*c* 61.5 in $CHCl_3$); $\nu_{max.}$ 700 and 742 (Ph), 1 100 (COC), 1 600 (amide), and 3 300 and 3 400 cm^{-1} (NH); δ ($CDCl_3$) 1.45 (s, NH_2), 2.91br (t, H-1, *J* 5.5), 3.37 (d, 2-H_2, *J* 5.5), 4.60 (s, PhCH_2), and 7.43 (s, aromatic H); *m/e* (15 eV) 46 ($C_2H_4DO^+$, 100%), 45 ($C_2H_5O^+$, 6), 31 (DHC=N^+H_2, 32), and 30 (H_2C=N^+H_2, 2).

2-*Benzyloxyethylamine*, b.p. 100 °C at 6 mmHg, was obtained in a similar way but in higher overall yield because it could be recycled (see above) (Found: C, 71.4; H, 8.8; N, 9.2. $C_9H_{13}NO$ requires C, 71.5; H, 8.7; N, 9.3%); δ ($CDCl_3$) 1.30 (s, NH_2), 2.91 (t, 1-H_2, *J* 5.5), 3.57 (t, 2-H_2, *J* 5.5), 4.60 (s, PhCH_2), and 7.43 (s, aromatic H); *m/e* (15 eV) 45 ($C_2H_5O^+$, 100%), 44 ($C_2H_5O^+$ − 1, 0), 30 (CH_2=N^+H_2, 30), and 29 (CH_2=N^+H_2 − 1, 0).

(+)-(S)-2-*Benzyloxy*-N-*phthaloyl*[1-$^2H_1$]*ethylamine* (9).—The (*S*)-amine (8) (1.11 g) and phthalic anhydride (1.11 g, 1 mol. equiv.; prepared by extracting crude anhydride with cold choroform, filtering, and evaporating), under dry nitrogen in a stoppered vessel, were heated at 175 °C for 1 h, then in a stream of nitrogen for 2 h. The solid obtained on cooling was dissolved in toluene and the solution eluted through an alumina column (3/4 × 5 ft) with toluene. Evaporation gave the (S)-*phthaloylamine* (1.91 g, 93%), m.p. 71.5—72°, which sublimed at 120 °C and 1 mmHg (Found: C, 72.5; H + D, 5.9; N, 4.9. $C_{17}H_{14}DNO_3$ requires C, 72.3; H + D, 5.7; N, 5.0%); $[\alpha]_{405}$ +1.02, $[\alpha]_{435}$ +0.78; $[\alpha]_{546}$ +0.40, and $[\alpha]_{578}$ +0.34° (*c* 51.6 in $CHCl_3$); $\nu_{max.}$ 1 700 and 1 770 cm^{-1} (CONCO); δ ($CDCl_3$) 3.78br (m, H-1 and 2-H_2), 4.55 (s, PhCH_2), 7.32 (s, C_6H_5), and 7.80 (m, *o*-C_6H_4); *m/e* (15 eV) 282 (M^+, 100%) and 281 (M^+ − 1, 8).

2-*Benzyloxy*-N-*phthaloylethylamine*. m.p. 69° (Found: C, 72.4; H, 5.5; N, 4.8. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.4; N, 5.0%), with similarly prepared; δ ($CDCl_3$) 3.88 (octet, 1- and 2-H_2), 4.55 (s, PhCH_2), 7.34 (s, C_6H_5), and 8.86 (m, *o*-C_6H_4); *m/e* (15 eV) (M^+, 100%) and 280 ($M^+ - 1$, 0).

(+)-(S)-2-*Hydroxy*-N-*phthaloyl*[1-$^2H_1$]*ethylamine* (10).—The (*S*)-benzyl ether (9) (1.97 g) in ethanol (240 ml) containing palladium black [20] was hydrogenated at 20 °C and 720 mmHg. Uptake was complete after 1 h; the catalyst was filtered off and the filtrate was evaporated to give the (S)-*alcohol* (quantitative), m.p. 126.5—127°, which sublimed at 125 °C and 1 mmHg (Found: C, 62.5; H + D, 5.5; N, 7.35. $C_{10}H_8DNO_3$ requires C, 62.5; H + D, 5.2; N, 7.3%); $[\alpha]_{364}$ +4.4, $[\alpha]_{405}$ +3.3, $[\alpha]_{436}$ +2.9, and $[\alpha]_{546}$ +1.1° (≤1.36 in $[CD_3]_2SO$ containing 1 drop of D_2O); $\nu_{max.}$ 1 695 and 1 765 (CONCO) and 3 490 cm^{-1} (OH); δ ($[CD_3]_2SO$) 3.58 (s, OH), 3.65 (s, H-1 and 2-H_2, and 7.88 (s, *o*-C_6H_4).

2-Hydroxy-*N*-phthaloylethylamine, m.p. 128° (lit.,[21] 127—128°) was prepared as above and by condensation of 2-hydroxyethylamine with phthalic anhydride; δ ($[CD_3]_2SO$) 3.65 (s, 1- and 2-H_2), 4.50br (s, OH), and 7.90 (s, *o*-C_6H_4).

(+)-(S)-N-*Phthaloyl*[2-$^2H_1$]*glycine* (11).—The (*S*)-alcohol (10) (1.3 g) in 5N-sulphuric acid (78 ml) was heated to 45 °C with stirring to dissolve most of the solid (5 min). The solution was cooled to 30 °C and potassium permanganate (1.61 g) was added (5 min). There was no temperature rise and the solution was stirred at room temperature for 2.5 h and decolourised with sulphur dioxide. The white solid was collected, washed with water, and dried at 70 °C for 2 h to give the pure (S)-*acid* (1.04 g, 74%), m.p. 191—192°, which sublimed at 180 °C and 1 mmHg. More acid (282 mg, 20%) was obtained from the aqueous filtrate by saturating with sodium chloride and extracting with chloroform. The deuterium content of this acid was the same as in the first crop (Found: C, 58.1; H + D, 3.9; N, 7.0. $C_{10}H_6DNO_4$ requires C, 58.25; H + D, 3.9; N, 6.8%); $[\alpha]_{405}$ +2.4, $[\alpha]_{436}$ +1.9, $[\alpha]_{546}$ +1.1, and $[\alpha]_{578}$ +0.94° (*c* 10.7 in MeOH); δ ($[CD_3]_2SO$) 4.05br (s, CO_2H), 4.35 (s, H-1), and 7.93 (s, *o*-C_6H_4); $\nu_{max.}$ 1 725 and 1 775br (CO_2H and CO) and 3 000br cm^{-1} (OH); *m/e* 205 ($M^+ - 1$, 7%), 206 (M^+, 100), and 207 ($M^+ + 1$, 14).

N-Phthaloylglycine, m.p. 192° (lit.,[22] 192—193°), was prepared as above and by fusion of phthalic anhydride and glycine at 185 °C for 20 min; *m/e* 204 ($M^+ - 1$, 0%), 205 (M^+, 100) and 206 ($M^+ + 1$, 14).

(+)-(S)*Methyl* N-*Phthaloylglycinate* (12).—The (*S*)-acid (11) (1 g) suspended in dry ether (30 ml) slowly dissolved with effervescence when diazomethane in dry ether [23] was added. When the yellow colour persisted and nitrogen evolution had ceased, charcoal (0.2 g) was added and the solution was filtered and evaporated. The residue was dissolved in hot benzene (5 ml) and light petroleum (b.p. 60—80°) was added until crystallisation was complete to give the (S)-*methyl ester* (1 g, 92%), m.p. 112° (Found: C, 60.0; H + D, 4.6; N, 6.4%); $[\alpha]_{364}$ +4.0, $[\alpha]_{405}$ +2.6, $[\alpha]_{436}$ +2.0, $[\alpha]_{546}$ +1.1, and $[\alpha]_{578}$ +1.0° (*c* 17.7 in $CHCl_3$); $\nu_{max.}$ 1 720 and 1 775 (CONCO), and 1 750 cm^{-1} (ester); δ ($CDCl_3$) 3.77 (s, OCH_3), 4.47 (t, H-2, J_{HD} 2), and 7.83 (m, *o*-C_6H_4); *m/e* 219 ($M^+ - 1$, 6%), 220 (M^+, 100), and 221 ($M^+ + 1$, 11).

[20] J. P. Greenstein and M. Winitz, 'Chemistry of the Amino Acids,' Wiley, New York, 1961, vol. 2, p. 1233.
[21] H. Wenker, *J. Amer. Chem. Soc.*, 1937, **59**, 422.

Methyl N-phthaloylglycinate, m.p. 114—114.5° (Found: C, 60.1; H, 4.4; N, 6.2. $C_{11}H_9NO_4$ requires C, 60.3; H, 4.1; N, 6.4%); *m/e* 218 ($M^+ - 1$, 0%), 219 (M^+, 100) and 220 ($M^+ + 1$, 13), was prepared as above. The ethyl ester was prepared by treating the acid with thionyl chloride, evaporating, and adding ethanol. Ethyl *N*-phthaloyl-[2-$^2H_2$]glycinate prepared in this way retained all its deuterium atoms (by ^1H n.m.r.).

(−)-(S)-[2-$^2H_1$]*Glycine* (13).—The (*S*)-ester (12) (1.1 g, 1 mol. equiv.) in methanol (8 ml) containing anhydrous hydrazine acetate {506 mg, 1.1 mol. equiv.; prepared in 84% yield by mixing equimolar amounts of hydrazine hydrate and acetic acid, evaporating, and recrystallising from EtOH; m.p. 99.5—100° [Found (dry-box sampling): C, 25.9; H, 8.8; N, 30.4. Calc. for N_2H_4,CH_3CO_2H: C, 26.1; H, 8.8; N, 30.4%]} was refluxed for 0.75 h and cooled. Saturated methanolic hydrogen chloride (2 ml) was added and the phthalazinedione was filtered off. The filtrate was evaporated and the residue dried *in vacuo* (KOH) overnight. Water (6.7 ml) was added and more phthalazinedione (total 781 mg, 96%) was removed. Concentrated hydrochloric acid (1.9 ml; which makes the solution up to 2.5N) was added to the filtrate and the solution was refluxed for 15 min, then evaporated. Water (8 ml) was added to the residue, then charcoal (50 mg); the solution was filtered and evaporated to dryness. The residue, which contains deuterioglycine hydrochloride, was dissolved in water (5 ml) and placed on a Dowex 50W × 4 column (60 ml; 50 × 100 mesh in H^+ form after two cycles with 2N-HCl and aqueous 3M-ammonia). The column was washed with water and eluted with aqueous 3M-ammonia. Evaporation gave the (S)-*amino-acid* (13) (342 mg, 90%), which contained a trace of u.v.-absorbing impurity, removed by extraction with warm methanol (3 × 25 ml). After one recrystallisation (H_2O–MeOH) it had m.p. 234° (decomp.) (Found: C, 31.8, 31.65; H + D, 8.4, 8.2; N, 18.3, 18.3. $C_2H_4DNO_3$ requires C, 31.6; H + D, 7.9; N, 18.4%); o.r.d. $[\alpha]_{215}$ −71.3, $[\alpha]_{220(max.)}$ −76.8, $[\alpha]_{230}$ −54.8, $[\alpha]_{238}$ −35.0, $[\alpha]_{250}$ −17.8, $[\alpha]_{275}$ −11.0, $[\alpha]_{300}$ −4.2, $[\alpha]_{364}$ −1.3, and $[\alpha]_{405}$ −0.88° (114 mg in 5 ml H_2O, *i.e.* *c* 2.28); $\nu_{max.}$ 1 413, 1 525, 1 615 (CO_2), and 3 200br cm^{-1} (NH); ^1H n.m.r. (D_2O) triplet (J_{HD} 2) 50 Hz upfield from HOD; *m/e* 77 ($M + 1$, 4%), 76 (M, 100), and 75 ($M - 1$, 8) [glycine, *m/e* 76 ($M + 1$, 3), 75 (M, 100), 74 ($M - 1$, 2); (*R*)-[2-$^2H_1$]glycine 77 (3%), 76 (100), and 75 (18)].

For the preparation of (+)-(*R*)-[2-$^2H_1$]glycine, (−)-(*R*)-ethyl [2-$^2H_1$]-*N*-phthaloylglycinate ($SOCl_2$ method) was used, and in this case (+)-(*R*)-ethyl [2-$^2H_1$]glycinate hydrochloride (purity 80 ± 3%) was isolated; $[\alpha]_{364}$ +0.7 and $[\alpha]_{436}$ +0.2° (*c* 4.5 in D_2O); δ (D_2O) 1.32 (t, CH_3, *J* 7), 3.95 (t, H-2, J_{HD} 2), and 4.32 (q, OCH_2, *J* 7).

(−)-(1S,4R)-ω-*Camphanoylglycine*.— (1*S*,4*R*)-ω-Camphanoyl chloride [24] {541 mg, 1.5 mol. equiv; $[\alpha]_{364}$ −29.2, $[\alpha]_{405}$ −18.0, $[\alpha]_{436}$ −13.5, $[\alpha]_{546}$ −7.5, and $[\alpha]_{578}$ −6.0° (*c* 0.67 in C_6H_6), derived from (+)-camphor and freshly sublimed at 70 °C and 5 mmHg} in toluene (1 ml) at 0 °C was treated simultaneously with a solution of glycine (150 mg, 1 mol. equiv.) in 2N-sodium hydroxide (1 ml, 1 mol. equiv.) and 3N-sodium hydroxide (1 ml, 1.5 mol. equiv.) and stirred at room temperature for 3 h while keeping the pH above 7 by dropwise addition of 2N-sodium hydroxide.

[22] J. H. Billman and W. F. Harting, *J. Amer. Chem. Soc.*, 1948, **70**, 1473.
[23] F. Arndt, *Org. Synth.*, Coll. vol. II, 1943, p. 165.
[24] H. Gerlach, *Helv Chim. Acta*, 1968, **51**, 1587.

The mixture was extracted with chloroform (discarded) and the aqueous layer was acidified and extracted with chloroform. The extract gave a thick oil which crystallised, with evolution of heat, on addition of a few drops of water to give (1S,4R)-ω-*camphanoylglycine* (507 mg, 80%), m.p. 73.5—75° [from wet ether–light petroleum (b.p. 60—80°) or water] (Found: C, 49.5; H, 7.1; N, 4.7. $C_{12}H_{17}NO_5$,-$2H_2O$ requires C, 49.5; H, 7.3; N, 4.8%); $[\alpha]_{364}$ −78.6, $[\alpha]_{405}$ −51.8, $[\alpha]_{436}$ −42.1, $[\alpha]_{546}$ −22.3, and $[\alpha]_{578}$ −19.7° (*c* 1.55 in MeOH); $\nu_{max.}$ 1 275 (COC), 1 557 and 1 665 (amide CO), 1 705 (acid CO), 1 775 (lactone CO), 2 960, 2 995, and 3 018 (CH str.), 3 470 (NH), and 3 570 cm^{-1} (OH); δ ($CDCl_3$) 1.00 (s, CH_3-4′), 1.71 (s, 7′-Me_2), 1.8—2.8 (m, 5′- and 6′-H_2), 4.10 (d, 2-*pro-R*-H, *J* 2.5), 4.20 (d, 2-*pro-S*-H, *J* 2.5), 7.30br (s, N*H*), and 8.80 (s, CO_2H).

A similar condensation with methyl glycinate hydrochloride gave the above acid. *Methyl* (1S,4R)-ω-*camphanoylglycinate*, prepared quantitatively from the acid and diazomethane in ether, distilled as a thick oil which solidified on cooling, and after recrystallisation [ether–light petroleum (b.p. 40—60°)] had m.p. 84° (Found: C, 58.0; H, 7.1; N, 5.1. $C_{13}H_{19}NO_5$ requires C, 58.0; H, 7.1; N, 5.2%); $[\alpha]_{364}$ −71.3, $[\alpha]_{405}$ −52.7, $[\alpha]_{436}$ −43.3, $[\alpha]_{546}$ −24.7, and $[\alpha]_{578}$ −21.3° (*c* 1.5 in MeOH); $\nu_{max.}$ 1 235 (COC), 1 538 and 1 672 (amide CO), 1 747 (ester CO), 1 763 and 1 799 (lactone CO), and 3 430 cm^{-1} (NH); δ ($CDCl_3$) 0.97 (s, C*H*$_3$-4′), 1.12 (s, 7′-Me_2), 1.6—2.6 (m, 5′- and 6′-H_2), 3.75 (s, OCH_3), 4.03 (d, 2-*pro-R*-H, *J* 4), 4.13 (d, 2-*pro-S*-H, *J* 4), and 6.97br (d, NH) [addition of $Eu(dpm)_3$ caused the d of d at δ *ca.* 4.1 to move progressively upfield, and after addition of *ca.* 0.3—0.5 mol. equiv. of shift reagent the quartet became an octet with J_{vic} 6 and J_{gem} 18, with a separation of 36 Hz between the two quartets making it easy to measure the relative proportions of the two diastereotopic 2-protons].

The camphanoyl derivatives of (*R*)- and (*S*)-[2-$^2H_1$]-glycines were prepared in a similar manner; the ^1H n.m.r. spectra near δ 4 are shown in the Figure (B and C, respectively).

Determination of the Steric Course of Reaction (i) *in Scheme* 1.—(*S*)-Alanine was converted into (*S*)-2-bromopropionic acid as for the preparation of the acid (6) above; the product had b.p. 70 °C at 1 mmHg, $[\alpha]_{405}$ −128.0, $[\alpha]_{436}$ −102.3, $[\alpha]_{546}$ −52.9, and $[\alpha]_{578}$ −45.5° (neat), indicating almost complete purity (lit.,[25,26] $[\alpha]_D^{20}$ −46°; see however ref. 16). Esterification of the acid with diazomethane [23] gave methyl (*S*)-2-bromopropionate, b.p. 68—70° at 40 mmHg, $[\alpha]_{578}$ −69.2° (neat) [lit.,[27] $[\alpha]_D^{20}$ −68.6° (neat)]. This ester (21) (2.3 g) in dry tetrahydrofuran (20 ml) at 0 °C was treated with lithium borohydride (330 mg, 1.1 mol. equiv.) and stirred at room temperature for 3 h. Cold water (12 ml) was added, the solution was extracted with ether, the dried extract was evaporated, and the residual oil was distilled to give (S)-2-*bromopropan*-1-*ol* (20), b.p. 61° at 15 mmHg (1.17 g, 61%) (Found: C, 26.1; H, 5.2; Br, 57.0. C_3H_7BrO requires C, 25.9; H, 5.1; Br, 57.5%); $[\alpha]_{364}$ +54.8, $[\alpha]_{405}$ +42.2, $[\alpha]_{436}$ +35.1, and $[\alpha]_{578}$ +18.2° (*c* 11.2 in $CHCl_3$); $\nu_{max.}$ 1 035, 1 390 and 1 460 (OH bend), 2 880, 2 940, and 2 995 (CH str.) and 3 380br cm^{-1} (OH str.); δ ($CDCl_3$) 1.67 (d, CH_3, *J* 7), 3.07 (s, OH), 3.75 (d, 1-H_2, *J* 6), and 4.25 (q of d, H-2, *J* 6 and 7).

(+)-(*R*)-3-Benzyloxy-2-bromopropionic acid {$[\alpha]_{578}$ +14.0° in MeOH (*c* 2.18); prepared as (5) above from (*R*)-*O*-benzylserine} was esterified with diazomethane [23] to give *methyl* (+)-(R)-3-*benzyloxy*-2-*bromopropionate* (16), b.p. 106 °C at 0.5 mmHg (Found: C, 48.7; H, 4.9. $C_{11}H_{13}BrO_3$ requires C, 48.4; H, 4.8; Br, 29.2%; Br analysis did not give reproducible results but all values were above 23%); $[\alpha]_{578}$ +9.6° (*c* 2.0 in $CHCl_3$); $\nu_{max.}$ 700 and 745 (Ph), and 1 210 and 1 745 cm^{-1} (ester); δ ($CDCl_3$) 3.77 (s, OCH_3), 3.80 (m, 3-H_2), 4.30 (q, H-2, *J* 6.5 and 14), 4.60 (s, PhC*H*$_2$), and 7.33 (aromatic H).

The (*R*)-ester (16) (3 g) in tetrahydrofuran (75 ml) at 0 °C was treated with lithium borohydride (266 mg, 1.1 mol. equiv.) and stirred at room temperature for 3 h. Brine (36 ml) was added to the cooled solution, which was then extracted with ether. The extract gave (S)-3-*benzyloxy*-2-*bromopropan*-1-*ol* (17) quantitatively, b.p. 134 °C at 3 mmHg (Found: C, 49.2; H, 5.4. $C_{10}H_{13}BrO_2$ requires C, 49.0; H, 5.3; Br, 32.6%; Br analyses did not give consistent results but values were always above 28%); $[\alpha]_{578}$ −0.26° (*c* 19.2 in $CHCl_3$); $\nu_{max.}$ 703 and 745 (Ph), 1 380 and 1 460 (OH bend), 2 870 and 2 940 (CH str.), and 3 420br cm^{-1} (OH str.); δ ($CDCl_3$) 2.42br (s, OH), 3.88 (m, H-2 and 1- and 3-H_2), 4.55 (s, PhC*H*$_2$), and 7.30 (s, aromatic H).

The (*S*)-alcohol (17) (1.43 g) at 0 °C was added to methanesulphonyl chloride (0.91 ml) followed by dry pyridine (1.4 ml) and set aside for 18 h. Ice-cold 2N-hydrochloric acid was added and the solution extracted with chloroform. The dried extract gave (R)-3-*benzyloxy*-2-*bromopropyl*-*methanesulphonate* (18) (1.9 g) which decomposed on distillation, was stable at 0 °C for 8 weeks, and had $\nu_{max.}$ 1 180 and 1 370 (OSO_2), 2 878, 2 950, and 3 020 cm^{-1} (CH str.); δ ($CDCl_3$) 2.98 (s, CH_3), 3.78 (m, 3-H_2), 4.23 (m, H-2), 4.53 (d, H-1), 4.75 (s, PhC*H*$_2$), and 7.33 (s, aromatic H); it had a very small rotation probably due to compensation of the $PhCH_2$ group by the $MeSO_2$ group. ' Superhydride ' in tetrahydrofuran (1M; 7 ml, 1.2 mol. equiv.) was added to the ice-cold methylsulphonyl derivative (18) (1.9 g, crude) under nitrogen, and the mixture was stirred at room temperature overnight. Water (5 ml) was added, followed by saturated aqueous sodium carbonate (10 ml) and the mixture was extracted with chloroform. Evaporation gave an oil which contained about 50% of starting material. The reduction was repeated with more ' superhydride ' (7 ml) and gave only (+)-(S)-1-*benzyloxy*-2-*bromopropane* (19) (1.2 g, 90%), b.p. 88—90 °C (Found: C, 52.3; H, 5.8. $C_{10}H_{13}BrO$ requires C, 52.4; H, 5.7; Br, 34.9%; Br values were not reproducible but were above 34%); $[\alpha]_{405}$ +4.2, $[\alpha]_{436}$ +3.1, $[\alpha]_{546}$ +1.6, and $[\alpha]_{578}$ +1.5° (*c* 22.6 in $CHCl_3$); $\nu_{max.}$ 705 and 745 (Ph), 1 100 (COC), 2 888, 2 940, and 2 995 cm^{-1} (CH str.); δ ($CDCl_3$) 1.67 (d, CH_3, *J* 7), 3.63 (m, 1-H_2), 4.21 (m, H-2), 4.57 (s, PhC*H*$_2$), and 7.30 (s, aromatic H). When this ether (474 mg) in methanol (5 ml) containing palladium black [20] was hydrogenated at 20 °C and 712 mmHg, it absorbed 1 mol. equiv. of hydrogen in 8 min, and gave a quantitative yield of (+)-(*S*)-2-bromopropan-1-ol (20) identical with the above sample.

Determination of the Steric Course of Reaction (ii) *in Scheme* 1.—(−)-3-Benzyloxy[2-$^2H_1$]propionic acid (5) (1.5 g) was heated with 48% hydrobromic acid (10 ml) at 100 °C for 2 h. Water (10 ml) was added and the solution was basified with 8N-potassium hydroxide and extracted with ether. The aqueous layer was acidified, saturated with sodium sulphate, and extracted with ether (5 × 50 ml). The dried

[25] E. Fischer and K. Raske, *Ber.*, 1906, **39**, 3981.
[26] E. Fischer, *Ber.*, 1907, **40**, 489.
[27] W. A. Cowdrey, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1937, 1208.

($CaCl_2$) extract gave 3-bromo[2-$^2H_1$]propionic acid (0.4 g), δ ($CDCl_3$) 2.93br (t, H-2, *J* 6.5), 3.56 (d, 3-H_2, *J* 6.5), and 4.70 (s, CO_2H). The α-bromo-acid was treated with a solution of 'superhydride' in tetrahydrofuran (1M; 8 ml) under nitrogen; the mixture was boiled for 2 h and set aside for 18 h. Water (3 ml) was added and the mixture evaporated to two-thirds of its volume. A 1 : 1 mixture of hydrogen peroxide (100 vol) and 2N-sodium hydroxide was added dropwise until effervescence ceased. The solution was extracted with ether (discarded), acidified with 2N-sulphuric acid, saturated with Na_2SO_4, and extracted thoroughly with ether. The oily residue from the dried ($CaCl_2$) extract was distilled to give (*S*)-[2-$^2H_1$]propionic acid (75 mg), $[\alpha]_{364}$ +2.4, $[\alpha]_{436}$ +1.3, $[\alpha]_{546}$ +0.8, and $[\alpha]_{578}$ +0.6° (*c* 1.7 in D_2O) (ref. 17 gave positive o.r.d. curve for neat liquid; see below); δ (D_2O) 1.33 (d, CH_2, *J* 7) and 2.28br (q, H-1, *J* 7).

(R)-[1-$^2H_1$]*Propionic Acid*.—To (*S*)-2-bromopropionic acid (2.2 g; $[\alpha]_{578}$ −45.4°; see above) was added 'superdeuteride' in tetrahydrofuran (1M; 40.2 ml) under nitrogen; the mixture was refluxed for 2 h and worked up as in the preceding reduction to give (*R*)-[2-$^2H_1$]propionic acid (0.5 g); $[\alpha]_{364}$ −2.4, $[\alpha]_{436}$ −1.3, $[\alpha]_{546}$ −0.7, and $[\alpha]_{578}$ −0.6° [neat liquid, but the same specific rotations were obtained in D_2O at *c* 25; ref. 16 gave negative o.r.d. curve for neat liquid prepared by reduction of (−)-2-bromopropionic acid with $LiAlD_4$ followed by oxidation].

(S)-O-*Benzyl*[2-$^3H_1$]*serine*.—(*RS*)-*O*-Benzylserine (0.2 g) and benzaldehyde (0.15 ml) in tritiated water (5 ml; 0.01 Ci ml^{-1}) were heated at 110 °C in a sealed container for 18 h. The solution was cooled, acidified with 5 drops of concentrated hydrochloric acid, diluted with water (5 ml), and extracted with chloroform (5 × 4 ml) to remove benzaldehyde (discarded). The solution was basified with 4N-sodium hydroxide, extracted with chloroform (4 × 5 ml; discarded) and evaporated to *ca.* 2 ml under a stream of air at 110 °C. More water (25 ml) was added and the solution evaporated to dryness (to remove TOH). The residue was dissolved in water (5 ml); the solution was evaporated to 3 ml and allowed to crystallise to give (*RS*)-*O*-benzyl[2-$^3H_1$]serine [76.8 mg; 9.6×10^6 disint. min^{-1}, 2.44×10^{11} disint. min^{-1} mol^{-1} (61% of theoretical incorporation)]. This was dissolved in hot water (50 ml), (*S*)-*O*-benzylserine (2 g) was added, and the clear solution was allowed to crystallise. The first and second crops (298 mg) possessed half the specific molar radioactivity of the starting material, and this was unchanged on further recrystallisation. This material, after appropriate dilution with 'cold' isomer was converted into (*S*)-2-benzyloxy-[1-$^3H_1$]ethylamine without loss (within ±5%) of specific molar radioactivity.

We thank Dr. D. J. Brown for encouragement, Professor A. R. Battersby, F.R.S., for discussions, Dr. J. K. McLeod and Mr. T. Davies for mass spectra, Mr. B. Paal for the deuterium-decoupled spectra and The Australian National University for a Research Fellowship (to W. P.).

[6/775 *Received*, 20*th April*, 1976]