Direct Synthesis of *N*-Protected Chiral Amino Acids from Imidodicarbonates employing either Mitsunobu or Triflate Alkylation. Feasibility Study using Lactate with Particular Reference to ^{15}N-Labelling

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Two novel approaches to *N,N*-diprotected chiral α-amino acid esters, based on selected imidodicarbonates as amine synthons, have been explored. Thus, *N*-alkylation of these substrates was smoothly accomplished by the Gabriel or Mitsunobu methods as well as by the use of triflates. Ethyl (*R,S*)-2-bromopropionate underwent nucleophilic substitution when treated with the potassium salt of selected imidodicarbonates in dry dimethylformamide to furnish the corresponding fully blocked (*R,S*)-alanines in high yield. The chirality of ethyl (*S*)-lactate was largely conserved when it was condensed with free imidodicarbonates and tosylcarbamates under conventional Mitsunobu conditions. The yield of the corresponding *N,N*-di-protected ethyl (*R*)-alaninate was strongly dependent on the electron-withdrawing properties of the imidodicarbonate alkyl groups. Thus, Boc_2NH gave <5% of the product whereas Troc-NH-Z afforded the corresponding analogue in 83% yield under comparable conditions. On the other hand, triflates of various lactic acid esters reacted smoothly with the lithium salt of Boc_2NH, also with clean inversion, as a result of which, after selective removal of two blocking groups, the *N*-protected alanine of opposite configuration could be isolated in high yield and excellent stereochemical purity. Both methods have been used for the synthesis of ^{15}N-labelled *N*-protected (*R*)- and (*S*)-alanines, suitable for direct application to peptide synthesis.

The design of novel, efficient strategies to enantiomerically pure amino acids is a rapidly expanding field in synthetic chemistry.[1] Although all proteinogenic amino acids are produced industrially,[2] the situation is less favourable to their antipodes and also to other analogues of chemical or commercial interest. Besides, various isotope-labelled amino acids and derivatives are often required and, therefore, the elaboration of convenient preparative methods to such compounds from readily accessible, chiral or non-chiral precursors is of vital importance.[3]

As the first step in an investigation aimed at direct routes to chiral, *N*-protected amino acids suitable for application to peptide synthesis,[4] we have conducted a model study leading to derivatives of (*R*)- and (*S*)-alanine. It utilizes chiral lactic acid esters as starting materials.[5] Other authors have described work dealing with related target molecules based on asymmetric synthesis.[6] A recent paper outlines a preparation of some *N*-benzylalanine derivatives based on the stereoselective aminolysis of certain chiral α-halogenopropionates under various conditions involving the use of enzymes.[7] It should also be mentioned that ^{15}N-labelled (*S*)-alanine of high isotopic and enantiomeric purity was obtained by a convenient enzyme-assisted reduction of pyruvate in the presence of $^{15}NH_3$.[8] Our own approaches, providing alanine derivatives **4** carrying two protective groups on the amino nitrogen in one step, rely on the smooth alkylation of miscellaneous imidodicarbonates **1** by (*R*)- and (*S*)-lactic acid esters in accordance with the well established Mitsunobu procedure, or alternatively by reaction of the corresponding triflates as originally described by Effenberger *et al.*[9] In addition, a few corresponding non-chiral derivatives were prepared by alkylation using ethyl (*R,S*)-2-bromopropionate under Gabriel conditions.[10]

$$P^1NCO + HOR^2 \longrightarrow P^1NHCO_2R^2 \equiv P^1NHP^2 \longrightarrow \begin{matrix} P^1 \\ \diagdown \\ N^- K^+ \\ \diagup \\ P^2 \end{matrix}$$

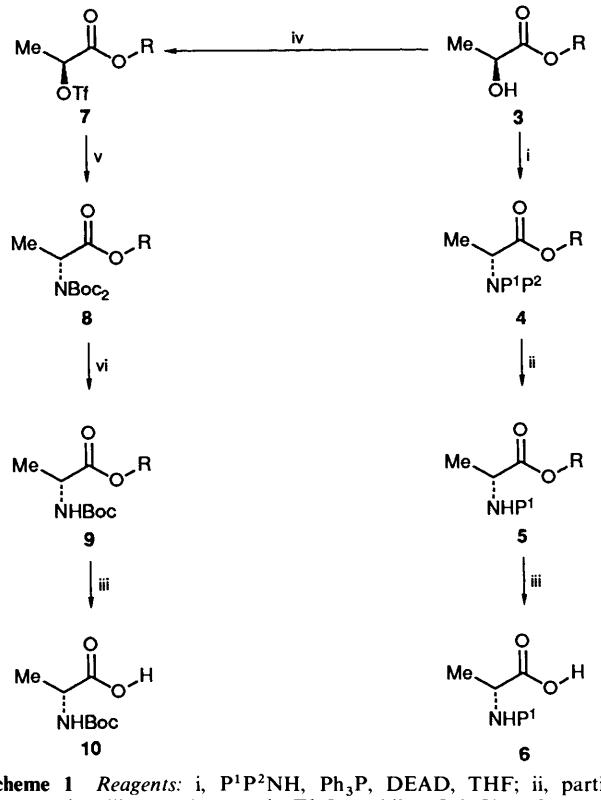
1 **2**

Key: For P^1 and P^2 used: see under compound **4**, Table 1, column 2.

A few years ago we described a convenient synthesis of Boc_2NH† **11** and the value of its potassium salt in the Gabriel synthesis was also demonstrated.[11a] This study was followed by a simple preparation of Boc-NH-Z **1a** and experiments indicated that compound **1a** readily underwent Mitsunobu alkylation under mild conditions.[11b] The versatility of these imidodicarbonates encouraged us to prepare several additional analogues from the pivotal benzyloxycarbonyl isocyanate and a wide range of alcohols in high yield.[11c] A few new additional analogues are to be found in the Experimental section.

Mitsunobu Synthesis.—The Mitsunobu reaction is a method of wide applicability to the functionalization of alcohols and related compounds by using various nucleophiles.[12] Previously, ethyl (*S*)-lactate has been employed as a precursor in this reaction for obtaining (*R*)-alanine derivatives, without protection on the amino group, using azide as the nucleophile and subsequent reduction of the intermediary azide analogue.[13] When, in the presence of a slight excess of ethyl (*S*)-lactate **3a**, imidodicarbonates **1** were treated with triphenylphosphine and diethyl azodicarboxylate (DEAD) under otherwise conventional Mitsunobu conditions, pure, doubly protected ethyl (*R*)-alaninates **4** were obtained after chromatographic work-up. The yield in this conversion was profoundly influenced by the structure of substrate **1**. Earlier work had shown that lactate readily underwent Mitsunobu reaction with phthalimide to furnish the corresponding *N*-phthaloylalaninate.[14] By repeat-

† Abbreviations of protective groups are in accordance with the 1983 Recommendations of the IUPAC-IUB Joint Commission on Biochemical Nomenclature (*Eur. J. Biochem.*, 1984, **138**, 9). In addition, Adoc is 1-adamantyloxycarbonyl, Aloc is allyloxycarbonyl, TCBoc is 2,2,2-trichloro-1,1-dimethylethoxycarbonyl, Troc is 2,2,2-trichloroethoxycarbonyl, Z(Cl) is 4-chlorobenzyloxycarbonyl, Z(*o*-Cl) is 2-chlorobenzyloxycarbonyl, and Poc is 4-pyridylmethoxycarbonyl.



Scheme 1 *Reagents:* i, P^1P^2NH, Ph_3P, DEAD, THF; ii, partial deprotection; iii, ester cleavage; iv, Tf_2O, pyridine, CH_2Cl_2; v, Boc_2NH, BuLi, THF (cooling); vi, TFA (1.5 mol equiv.), CH_2Cl_2.
a–**p**: R = Et. For P^1 and P^2 used, see Table 1, column 2.
q: R = Bzl, P^1 = Z, P^2 = Troc.
r: As in **q** but opposite configuration.
s: R = Bzl, P^1 = P^2 = Boc.
t: As in **s** but opposite configuration.

ing this preparation with our detailed procedure using chiral lactate as substrate, we obtained the desired product in 93% yield. The phthaloyl group, however, suffers from the disadvantage that it is only cleaved under conditions too vigorous to be compatible with sensitive functions.[15] In the present study, imidodicarbonates **1d**, **1e** and **1h** containing electronegative alkyl substituents gave the highest yields of the desired products **4d**, **4e** and **4h**, respectively. When, in the reaction with substrate **1e**, benzyl (*S*)-lactate **3q** and its antipode **3r** were employed as hydroxy components, compounds **4q** and **4r**, respectively, were obtained in similar yields. In striking contrast, analogues **1a**, **1b** and, in particular, **1l** reacted considerably more sluggishly and the expected products **4a**, **4b** and **4l** were isolated in significantly lower yields (see Table 1). Moreover, attempts to enhance the conversion of lactate **1a** into compound **4a** by employing a larger excess of lactate and Mitsunobu reagents in combination with an elevated reaction temperature met with little success. Instead, the accumulation of various side-products led to necessarily more exacting work-up conditions. Preliminary experiments using preformed Ph_3P–DEAD adduct did not increase the final yield of compound **4a**.

The reactivity in the Mitsunobu reaction is obviously related to the acidity of the NH function in substrates **1**, and steric factors seem to be less important. The influence of the acidity is clearly demonstrated by comparing **1l** with the corresponding trichloro analogue **1d**. In addition the reactivity of compounds **1f**, **1g**, **1h** and **1i** is strongly dependent on the electronegativity of the 4-substituent. Details of this study will be presented separately.[16] Furthermore, tosylamides,[17] being more acidic than amides in general, were smoothly alkylated in high yield as corroborated in three cases (**1n**, **1o**, **1p**), to furnish compounds **4n**, **4o** and **4p** in excellent yield. Recent results indicate that the Tos group is selectively removable by electrochemical methods.[18]

Although substrate **1a** readily reacted with benzyl alcohol under Mitsunobu conditions,[11b] the corresponding reaction with a secondary alcohol is not unexpected to be significantly retarded. This feature may be rationalized in terms of a more strained reaction intermediate when secondary alcohols are involved.[19] The high reactivity of the sulfur analogue **1m** in this reaction is notable, providing the corresponding product **4m** in very good yield. The isolated side-product in this case is probably the *O*-alkylated isomer.[12] Presumably, the alkylation has occurred on the 'sulfur side' of compound **1m**. Formally, imidodicarbonates might undergo Mitsunobu reaction to afford *O*-alkylated isomers as by-products and, in the case of asymmetric analogues, there are two possibilities for this undesired side-reaction. However, such side-products were not observed in any other case.

It is also worth mentioning that the Fmoc function appears unstable under these reaction conditions as only the decomposition products Z-NH_2 [$\delta(CH_2)$ 5.10] and dibenzofulvene [$\delta(CH_2)$ 6.07] were detected in the crude mixture from the Mitsunobu reaction of Z-NH-Fmoc with compound **3a**.[20] No trace of the desired Z(Fmoc)-(*R*)-Ala OEt was formed, judging from the ^1H NMR spectrum of the crude product.

Extensive attempts to optimize the reaction conditions in this Mitsunobu alkylation indicated that several solvents other than the commonly employed tetrahydrofuran (THF) were useful. A comparative series of small-scale ^1H NMR experiments revealed 37, 39, 43, 44 and 49% conversions of **1f** into **4f** when THF, toluene, CH_2Cl_2, MeCN and dimethylformamide (DMF), respectively, were used as the reaction medium. Preparative runs in DMF confirmed that the yield was generally slightly enhanced (Table 1) with imidodicarbonates of moderate reactivity, such as **1f** and **1g**, but not with the more reactive substrates **1e** and **1h**.

Gabriel Synthesis.—As the yields of compounds **4a**, **4c** and, especially, **4l** above were rather poor, alternative approaches to these analogues were investigated. The nucleophilic displacement of a halide moiety by the alkali metal salts of certain diacylamides is often referred to as the Gabriel reaction.[10,11] Hence, a selected collection of imidodicarbonates (**1a**, **1c**, **1e**, **1f**, **1h** and **1l**) were conveniently converted in satisfactory yield into the corresponding potassium salts **2a**, **2c**, **2e**, **2f**, **2h** and **2l**, respectively, using a slight deficiency of KOH in MeOH at low temperature. The subsequent reaction of these salts with an excess of ethyl (*R*,*S*)-2-bromopropionate proceeded smoothly in dry DMF and furnished the corresponding fully protected ethyl (*R*,*S*)-alaninates **4a**, **4c**, **4e**, **4f**, **4h** and **4l**, respectively, in good yield. The use of the corresponding sodium salts seemed less favourable, mainly from a practical point of view as their greater hygroscopicity required strictly anhydrous handling. As expected, considering the strongly basic reaction conditions, the formation of the Gabriel product was accompanied by noticeable elimination of HBr from the bromide substrate. Typically, 7–10% of the reaction mixture was estimated to be ethyl acrylate by ^1H NMR spectroscopy. This volatile by-product was easily removed by evaporation and had no detrimental effect on the work-up. Obviously, the liberated HBr partly protonated the anion and minor amounts of unchanged imidodicarbonates always remained in the crude reaction mixture.

Triflate Method.—The favourable properties of the Boc function as the amino protection render such derivatives very useful in preparative work. In particular, Boc amino acids constitute important intermediates in peptide synthesis.[4] As the yield of the Mitsunobu reaction between miscellaneous lactates

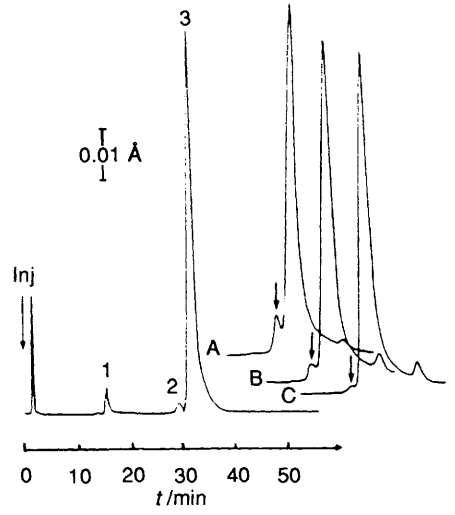


Fig. 1 Elution profile of the diastereoisomeric mixture obtained after acidic hydrolysis of (*R*)-Z_2-Ala-OEt and derivatization with (−)-Flec-Cl. HPLC was performed by using a Spherisorb C_8-column (150 × 4.6 mm; 5 μm) and elution at 1.0 cm^3 min^{-1} with 0.05 mol dm^{-3} aq. NaOAc (pH 4.35)–THF (74:26). Detection wavelength 265 nm. Peak 1 is a system peak, 2 and 3 correspond to (−)-Flec-(*S*)-Ala and (−)-Flec-(*R*)-Ala, respectively. Integration indicated the presence of (*R*)-Ala in 96% ee. Insert: Authentic (*R*)-Ala was spiked with 10, 5 and 2% (*S*)-Ala, treated with (−)-Flec-Cl, and chromatographed similarly to give peaks A, B and C, respectively. Minor component, (−)-Flec-(*S*)-Ala, indicated (arrow).

and Boc_2NH is neglible, alternative approaches were sought for the direct synthesis of ^{15}N-labelled bis-Boc alaninates **8** by employing $^{15}NHBoc_2$[21] as the amine synthon. The optimization of the reaction conditions was carried out with non-labelled Boc_2NH and all intermediary derivatives behaved as previously described.[22] The nucleophilic displacement of appropriate α-substituted carboxylic acids is promising in that respect and we have found that the triflyl analogues **7** readily react with the Li salt of $^{15}NHBoc_2$ in dry THF to furnish the bis-Boc-protected alaninates **8** in excellent yield. The conversion of $^{15}NHBoc_2$ into its Li salt was conveniently accomplished by treatment with a marginal deficiency of BuLi at low temperature under anhydrous conditions.[23] As expected, this nucleophilic substitution proceeds with complete inversion provided that the reaction is conducted at low temperature (−28 °C).[9,24] A higher reaction temperature (0 °C) gave considerable racemization (>10%) and it was somewhat unexpected that the stereochemical integrity was fully preserved when a significantly elevated reaction temperature was employed in a similar case.[25] Generally, the enantiomeric excess in compound **8** was greater than 96% as assessed by the 1-(fluoren-9-yl)ethyloxycarbonyl (Flec) assay after suitable deprotection.[26] Preliminary attempts to use other solvents such as DMF and the corresponding potassium salt **2l** as the nucleophile in this reaction gave lower yields of an impure, occasionally partly racemized, product. In conclusion, the yield of this highly stereoselective nucleophilic displacement of the triflate group seems to be less influenced by the nature of the protective functions P^1 and P^2. Therefore, this procedure appears to be of wider scope than the Mitsunobu reaction, at least for the synthesis of alanine derivatives.

Stereochemical Aspects.—Mitsunobu reactions proceed with complete inversion of the configuration of the α-carbon of the hydroxy component,[12] although certain exceptions have been claimed.[27] Several studies of the stereochemical outcome of Mitsunobu-type condensations, involving chiral lactates and related analogues, have also confirmed that the replacement of the hydroxy group with various nitrogen functions occurs without noticeable loss of asymmetry of this reaction site. Also, the nucleophilic displacement of the triflate group in compound **7** by the Li salt of compound **1l** proceeds with essentially clean inversion. This is in full agreement with various investigations of similar substitutions of miscellaneous chiral triflates using a wide range of nucleophiles under controlled conditions.[9,24,25] In the present study, the degree of racemization was ascertained by using a recent method based on the chromatographic separation of diastereoisomers.[26] Removal of all protective groups in compounds **4** and subsequent derivatization of the amino function with optically active 1-(fluoren-9-yl)ethyl chloroformate (Flec-Cl) provided the corresponding Flec-alanine. If both enantiomers of alanine are present in the mixture, the corresponding diastereoisomers can be separated by HPLC under carefully controlled conditions (see Fig. 1). The favourable properties of the Flec moiety easily permit the detection of 2% of the minor diastereoisomer. With an integrator even 0.1% can be quantitated. In a screening of the optical purity of the Mitsunobu products **4a**, **4b**, **4c**, **4f** and **4g** by utilization of this method, complete deprotection was accomplished by acidolysis under harsh conditions. The subsequent conversion of the liberated alanine into the Flec derivative was achieved as previously described and, in all cases, HPLC analysis revealed (*R*)-alanine in an enantiomeric excess of at least 95%.

The presence of the (*S*)-antipode might originate from three sources: (a) Trace amounts of the (*R*)-isomer as impurity in the starting ethyl (*S*)-lactate; (b) Incomplete inversion in the Mitsunobu condensation; and (c) Racemization in the deprotection steps. During the course of this work we realized that a major part of the (*S*)-alanine present in the HPLC samples originated from the acid-mediated removal of the protective groups. Further careful analytical work is in progress to determine the corresponding contributions.

Applications Related to ^{15}N-*Labelling.*—As evident from the above the Mitsunobu approach employing imidodicarbonates **1** as amine synthons and chiral lactates as precursors provides direct routes to protected chiral alanine derivatives. By the judicious choice of suitable imidodicarbonates a wide range of doubly protected alaninates **4** are readily accessible in high yield. The two amine-blocking functions are in most cases cleavable in optional order by well established standard methods, thus providing the conventional monoprotected derivatives required in peptide synthesis.[4,28] The potential of this novel strategy is exemplified in the convenient preparation of Z-(*R*)-[^{15}N]alanine. The Troc moiety in [^{15}N]-**4e** was selectively removed in excellent yield by zinc-mediated reduction according to a published procedure.[29] The resulting ethyl Z-(*R*)-[^{15}N]alaninate ([^{15}N]-**5a**) was then subjected to alkaline hydrolysis to furnish [^{15}N]-**6a** of high optical purity. The total yield over three steps from **3a** was 86%. Alternatively, Z(Troc)-(*S*)-[^{15}N]Ala-OBzl ([^{15}N]-**4r**) was employed in a convenient preparation of (*S*)-[^{15}N]Ala-OBzl. To our surprise the Z-group was smoothly cleaved completely selectively in the presence of neat trifluoroacetic acid (TFA) (1 h; room temp.) and Troc-(*S*)-[^{15}N]Ala-OBzl was obtained in excellent yield. Evidently, the Z-group is rendered considerably labile by the geminal Troc function, since the removal of the former normally requires strongly acidic conditions (HF or HBr/HOAc) or refluxing TFA for complete reaction. The subsequent deblocking of the remaining Troc moiety with Zn under conventional conditions afforded the desired (*S*)-[^{15}N]Ala-OBzl in fair yield after extractive work-up.

The selective removal of one Boc group in the crude product **8** was readily achieved by a very dilute solution of TFA (1.5 mol equiv.) in dichloromethane.[23] Attempts to purify the bis-Boc derivatives **8** by chromatography on silica sometimes

Table 1 Yields and properties of alkylation products **4a–4p**

Compound	P^1, P^2	Yield (%) Mitsunobu[c]	Yield (%) Gabriel[c]	Remarks[a]	$[\alpha]_D^{25}$[b]/° Mitsunobu
4a	Z, Boc	16[d]	78	oil (4:1)	+18.5[e]
4b	Z, Adoc	13		oil (4:1)	+13.6
4c	Z, Aloc	31	83	Gabriel product: 50 °C (21 h), oil (4:1)	+14.7
4d	Z, TCBoc	73		m.p. 64–64.5 °C (6:1)[f]	+11.7
4e	Z, Troc	83, 76[g]	59	oil (33:1)	+14.1
4f	Z, Z	42, 51[g]	80	Gabriel product: 50 °C (21 h), oil (2:1)	+12.4
4g	Z, Z(OMe)	30, 47[g]		oil (3:1)	+10.2
4h	Z, Z(NO_2)	66, 72[g,h]	62	oil (2:1)	+10.8
4i	Z, Z(Cl)	45		oil (3:1)	+10.4
4j	Z, Z(*o*-Cl)	55		oil (3:1)	+10.5
4k	Z, Poc	50		oil [CH_2Cl_2–acetone (6:1)]	+12.1
4l	Boc, Boc	<5[h]	90	oil (3:1)	
4m	Z, BzlS-CO	90[i]		oil (6:1)	+21.9
4n	Tos, Z(NO_2)	93		m.p. 94.5–95.5 °C [CH_2Cl_2–Et_2O (20:1)][j]	+56.8
4o	Tos, Z	91		oil (2:1)	+47.5
4p	Tos, Boc	93		oil (4:1)	+55.5

[a] Purified by chromatography on silica in light petroleum–diethyl ether mixtures (proportions within brackets). [b] *c* 1, $CHCl_3$. [c] Mitsunobu yield calculated from substrate **1** after chromatography. ^{1}H NMR spectrum of the crude product mixtures indicated losses of less than 5 per cent units in the work-up. Gabriel yield calculated from compound **2** after chromatography. Racemic products. [d] Ethyl (*S*)-lactate (2.0 mol equiv.), Ph_3P (2.5 mol equiv.), DEAD (3 mol equiv.), 16 h, 40 °C. [e] Z(Boc)-(*R*)-Ala-OEt obtained by exhaustive *t*-butoxycarbonylation of Z-(*R*)-Ala-OEt gave the same value. The corresponding (*S*)-enantiomer obtained analogously gave $[\alpha]_D^{25}$ −18.5° (*c* 1, $CHCl_3$).*[33] [f] From pentane (40 cm^3 g^{-1}), active carbon (Found: C, 47.5; H, 4.9; N, 3.1. $C_{18}H_{22}Cl_3NO_6$ requires C, 47.5; H, 4.9; N, 3.1%). [g] DMF as solvent. [h] Estimated by ^{1}H NMR spectroscopy. [i] Minor amounts of a side-product were isolated [R_f < R_f(**4m**)]. δ_H($CDCl_3$) 7.28–7.42 (≈ 10 H, complex), 5.40 (1 H, q), 5.14 (2 H, s), 4.25 (2 H, s), 4.19 (2 H, q), 1.52 (3 H, d) and 1.23 (3 H, t). [j] From hexane–Et_2O (1:1) (100 cm^3 g^{-1}) (Found: C, 53.5; H, 5.0; N, 6.2. $C_{20}H_{22}N_2O_8S$ requires C, 53.3; H, 4.9; N, 6.2%).

resulted in impure samples and somewhat lower yields. This is probably due to the instability of these compounds in the presence of silica, and the main decomposition product in this case appears to be the corresponding mono-Boc analogue **9**. Conventional hydrogenolytic cleavage of the ester benzyl group in compound **9** proceeded smoothly and provided the acid **10** in a satisfactory overall yield (83%) from $^{15}NHBoc_2$ (Scheme 1).

The applicability of our new approach to protected amino acids strongly relies upon ready access to the required α-hydroxy analogues.[30] Therefore, it should offer an alternative route to some protected (*R*)-amino acids and particularly to ^{15}N-labelled amino acids. In particular, (*R*)-alanine occurs in pharmacologically interesting peptides such as the immunosuppressive cyclic undecapeptide cyclosporine[31] and the opioid heptapeptide dermorphin.[32] Work is now in progress to exploit other α-hydroxy acids in this context and, in parallel with this investigation, convenient preparative methods for other suitable hydroxy-containing precursors are being sought.

Experimental

General Methods.—M.p.s were recorded on a Gallenkamp apparatus and are uncorrected. All solvents applied as reaction media were of best commercial grade and dried for several days over molecular sieves (4 Å, activated at 320 °C/0.01 mmHg for 10–15 h). THF was further purified by refluxing with $LiAlH_4$ (10 g dm^{-3}) for 8 h, distilled and stored under dry argon in a dark bottle in the cold. The ethyl (*S*)-lactate used in the Mitsunobu reactions was purchased from Sigma Chemical Company, dried over molecular sieve 4 Å, and redistilled; b.p. 50.5 °C/12.5 mmHg; $[\alpha]_D^{25}$ −11.29° (neat). Ethyl (*R,S*)-2-bromopropionate from Fluka (>98%) was used as such in the Gabriel synthesis. (*S*)-Lactic acid was purchased from Chemalog and (*R*)-lactic acid originated from Rhone Poulenc (Lot 90246-01). Both compounds were used without purification in the preparation of the corresponding benzyl esters by a known procedure.[34] [^{15}N]Ammonia was obtained from Icon Services, USA. Triphenylphosphine was recrystallized from hexane (4 cm^3 g^{-1}; active carbon) to m.p. 80–81 °C before use. Light petroleum refers to the fraction boiling in the range 40–60 °C. TLC analyses were performed on 0.25 mm thick precoated silica plates (Merck DC-Fertigplatten Kieselgel 60 F_{254}) with toluene–MeCN (2:1) or light petroleum–diethyl ether mixtures as developer. Spots were visualized by inspection under UV light at 254 nm or preferentially, after brief heating, by exposure to Cl_2 followed by dicarboxidine spray (violet-blue spots).[35] Preparative chromatography was carried out on silica gel 60 (70–230 mesh). Optical rotations were measured with a Perkin-Elmer 241 polarimeter and IR spectra were recorded on a Mattson Polaris FT IR spectrometer; NMR spectra were routinely recorded with a JEOL FX 90Q or a JEOL FX 100 instrument at 90/100 MHz (^{1}H) and 22.5/25 MHz (^{13}C) in $CDCl_3$ at 22 ± 1 °C unless otherwise stated. The signals were tentatively assigned by comparison of chemical shifts and peak multiplicities. Elemental analyses (CHN) of recrystallized solids were carried out by Mikro Kemi AB, Uppsala, Sweden. Yields, m.p.s, spectroscopic data, and other information about compounds **4a–p** are compiled in Tables 1 and 2.

Benzyl 2,2,2-Trichloro-1,1-dimethylethyl Imidodicarbonate **1d**.—This compound was prepared from benzyloxycarbonyl isocyanate (Z-NCO) and 2,2,2-trichloro-1,1-dimethylethanol (sublimed to dryness) in CH_2Cl_2 by analogy with an earlier procedure.[11c] The yield after chromatography in CH_2Cl_2 was 70%; m.p. 89–90 °C; δ_H 1.96 (6 H, s, Me), 5.21 (2 H, s, CH_2), 7.22 (~1 H, br, NH), and 7.37 (5 H, s, Ph); δ_C 21.3 (Me), 68.0

* A ^{1}H NMR spectrum of (*R*)-Z(Boc)-Ala-OEt (0.125 mol dm^{-3} in $CDCl_3$) mixed with the shift reagent, europium tris(dicampholyl-[$^2H_2$]methanate); [Eu(dcm)$_3$] (1.0 mol equiv.) displayed signals at δ 6.19 and 6.28 (Ph CH_2O). The analogous spectrum of the corresponding (*S*)-enantiomer showed signals at δ 6.61 and 6.66. The spectrum of the Mitsunobu product **4a** was in all respects identical with that of the (*R*)-enantiomer and no (*S*)-antipode could be detected in the sample. The reference specimens were obtained by exhaustive *t*-butoxycarbonylation of (*R*)-Z-Ala-OEt and its (*S*)-enantiomer, respectively, as outlined in ref. 6. For a discussion on Eu(dcm)$_3$ see ref. 33.

Table 2 Spectroscopic data of *N,N*-diprotected alanine derivatives **4a–p**

Compound	^{1}H NMR (δ_H; $CDCl_3$)	^{13}C NMR (δ_C; $CDCl_3$)
4a	1.21 (3 H, t, *Me*CH_2), 1.46 (9 H, s, BocMe), 1.51 (3 H, d, *Me*CH), 4.12 (2 H, q, MeCH_2), 5.02 (1 H, q, MeC*H*), 5.24 (2 H, s, PhCH_2), and 7.37 (5 H, s, Ph)	14.1 (*Me*CH_2), 15.6 (*Me*CH), 27.9 (BocMe), 54.4 (MeCH), 61.2 (MeCH$_2$), 68.7 (PhCH$_2$), 83.6 (Me$_3$*C*), 128.2, 128.4, 128.5, 135.3 (aryl C), 151.1 (Boc CO), 153.5 (Z CO), and 170.7 (ester CO)
4b	1.21 (3 H, t, *Me*CH_2), 1.51 (3 H, d, *Me*CH), 1.64 and 2.10 (~15 H, br, Adoc H), 4.12 (2 H, q, MeCH_2), 5.01 (1 H, q, MeC*H*), 5.24 (2 H, s, PhCH_2), and 7.34 (~5 H, complex, Ph)	14.1 (*Me*CH_2), 15.6 (*Me*CH), 30.9, 36.0, and 41.1 (Adoc C), 54.4 (MeCH), 61.3 (MeCH$_2$), 68.7 (PhCH$_2$), 83.6 (Adoc C–O), 128.3, 128.5, 128.6, and 135.3 (aryl C), 150.5 (Adoc CO), 153.6 (Z CO), and 170.7 (ester CO)
4c	1.17 (3 H, t, *Me*CH_2), 1.54 (3 H, d, *Me*CH), 4.09 (2 H, q, MeCH_2), 4.67 and 4.74 (2 H, 2 t, =CHCH_2), 5.08 (1 H, q, MeC*H*), 5.19, 5.30, and 5.44 (2 H, complex s, CH_2=CH), 5.25 (2 H, s, Z CH$_2$), 5.72–6.14 (1 H, complex s, CH$_2$=C*H*), and 7.36 (5 H, s, Ph)	14.0 (*Me*CH$_2$), 15.5 (*Me*CH), 54.7 (MeCH), 61.3 (MeCH$_2$), 67.9 (=CHCH$_2$), 68.9 (PhCH$_2$), 118.9 (CH$_2$=CH), 128.2, 128.4, 128.5, and 135.0 (aryl C), 131.2 (CH$_2$=CH), 152.9 (Z, Aloc CO), and 170.3 (ester CO)
4d	1.17 (3 H, t, *Me*CH_2), 1.56 (3 H, d, *Me*CH), 1.97 (6 H, s, *Me*$_2$C), 4.09 (2 H, q, MeCH_2), 5.03 (1 H, q, MeC*H*), 5.26 (2 H, s, PhCH_2), and 7.36 (5 H, s, Ph)	14.0 (*Me*CH$_2$), 15.5 (*Me*CH), 21.3 and 21.4 (*Me*$_2$C), 55.0 (MeCH), 61.5 (MeCH$_2$), 69.0 (PhCH$_2$), 91.2 (Me$_2$*C*), 105.5 (CCl$_3$), 128.4, 128.5, and 135.0 (aryl C), 150.0 (TCBoc CO), 152.9 (Z CO), and 170.2 (ester CO)
4e	1.18 (3 H, t, *Me*CH_2), 1.60 (3 H, d, *Me*CH), 4.12 (2 H, q, MeCH_2), 4.81 and 4.86 (2 H, AB q, *J* 11.0 Hz, Troc CH$_2$), 5.13 (1 H, q, MeC*H*), 5.29 (2 H, s, PhCH_2), and 7.37 (5 H, s, Ph)	14.0 (*Me*CH$_2$), 15.5 (*Me*CH), 55.1 (MeCH), 61.6 (MeCH$_2$), 69.4 (PhCH$_2$), 76.0 (Troc CH$_2$), 94.1 (CCl$_3$), 128.4, 128.6, and 134.7 (aryl C), 151.5 (Troc CO), 152.6 (Z CO), and 169.9 (ester CO)
4f	1.12 (3 H, t, *Me*CH_2), 1.52 (3 H, d, *Me*CH), 4.03 (2 H, q, MeCH_2), 5.08 (1 H, q, MeC*H*), 5.24 (4 H, s, PhCH_2), and 7.33 (10 H, s, Ph)	14.0 (*Me*CH$_2$), 15.6 (*Me*CH), 54.8 (MeCH), 61.3 (MeCH$_2$), 69.0 (Z CH$_2$), 128.2, 128.4, 128.5, and 135.0 (aryl C), 152.9 (Z CO), and 170.3 (ester CO)
4g	1.12 (3 H, t, *Me*CH_2), 1.51 (3 H, d, *Me*CH), 3.80 (3 H, s, MeO), 4.03 (2 H, q, MeCH_2), 5.06 (1 H, q, MeC*H*), 5.18 [2 H, s, Z(OMe) CH_2], 5.23 (2 H, s, PhCH_2), 6.85 and 7.28 [4 H, 2 × d, *J* 9.0 Hz, Z(OMe) ArH] and 7.33 (5 H, s, Ph)	14.0 (*Me*CH$_2$), 15.5 (*Me*CH), 54.7 (MeCH), 55.3 (MeO), 61.3 (MeCH$_2$), 68.9 [Z, Z(OMe) CH$_2$], 113.9, 127.1, 128.2, 128.4, 128.5, 130.1, 135.0, and 159.8 (aryl C), 153.0 [Z, Z(OMe) CO], and 170.4 (ester CO)
4h	1.16 (3 H, t, *Me*CH_2), 1.55 (3 H, d, *Me*CH), 4.08 (2 H, q, MeCH_2), 5.10 (1 H, q, MeC*H*), 5.26 (PhCH_2), 5.34 [Z(NO$_2$) CH$_2$], 7.36 (5 H, s, Ph), and 7.47 and 8.15 [4 H, 2 × d, *J* 9 Hz, Z(NO$_2$) ArH]	14.0 (*Me*CH$_2$), 15.5 (*Me*CH), 54.9 (MeCH), 61.5 (MeCH$_2$), 67.4 [Z(NO$_2$) CH$_2$], 69.3 (PhCH$_2$), 123.7, 128.1, 128.5, 128.7, 134.7, 142.2, and 147.7 (aryl C), 152.6 [Z(NO$_2$) CO], 153.0 (Z CO), and 170.1 (ester CO)
4i	1.13 (3 H, t, *Me*CH_2), 1.52 (3 H, d, *Me*CH), 4.05 (2 H, q, MeCH_2), 5.08 (1 H, q, MeC*H*), 5.20 [2 H, s, Z(Cl) CH$_2$], 5.24 (2 H, s, PhCH_2), 7.27 [4 H, s, Z(Cl) ArH], and 7.34 (5 H, s, Ph)	14.0 (*Me*CH$_2$), 15.4 (*Me*CH), 54.7 (MeCH), 61.3 (MeCH$_2$), 68.1 [Z(Cl) CH$_2$], 69.1 (PhCH$_2$), 128.2, 128.5, 128.7, 129.5, 133.4, 134.2, and 134.8 (aryl C), 152.8 [Z(Cl) CO], 152.9 (Z CO), and 170.2 (ester CO)
4j	1.14 (3 H, t, *Me*CH_2), 1.54 (3 H, d, *Me*CH), 4.05 (2 H, q, MeCH_2), 5.10 (1 H, q, MeC*H*), 5.25 (2 H, s, PhCH_2), 5.36 [2 H, s, Z(*o*-Cl) CH$_2$], 7.12–7.50 [4 H, complex, s, Z(*o*-Cl) ArH], and 7.33 (5 H, s, Ph)	14.0 (*Me*CH$_2$), 15.5 (*Me*CH), 54.8 (MeCH), 61.4 (MeCH$_2$), 66.3 [Z(*o*-Cl) CH$_2$], 69.1 (PhCH$_2$), 126.9, 128.2, 128.5, 128.6, 129.5, 129.7, 129.8, 132.8, 133.4, and 134.9 (aryl C), 152.9 [Z(*o*-Cl), Z *C*O], and 170.2 (ester CO)
4k	1.15 (3 H, t, *Me*CH_2), 1.56 (3 H, d, *Me*CH), 4.08 (2 H, q, MeCH_2), 5.11 (1 H, q, MeC*H*), 5.27 (4 H, s, Z, Poc CH$_2$), 7.22 and 8.57 (4 H, 2 × d, *J* 5.8 Hz, Poc ArH), and 7.36 (5 H, s, 5 H, Ph)	14.0 (*Me*CH$_2$), 15.4 (*Me*CH), 54.9 (MeCH), 61.4 (MeCH$_2$), 66.8 (Poc CH$_2$), 69.2 (PhCH$_2$), 121.5, 128.4, 128.6, 134.6, 143.9, and 150.0 (aryl C), 152.6 (Poc CO), 152.9 (Z CO), and 170.0 (ester CO)
4l	1.26 (3 H, t, *Me*CH_2), 1.50 (18 H, s, BocMe), 1.50 (3 H, d, *Me*CH), 4.17 (2 H, q, MeCH_2), and 4.94 (1 H, q, MeC*H*)	14.1 (*Me*CH$_2$), 15.4 (*Me*CH), 28.0 (Boc Me), 53.9 (MeCH), 61.1 (MeCH$_2$), 82.9 (Me$_3$*C*), 151.8 (Boc CO), and 171.1 (ester CO)
4m	1.07 (3 H, t, *Me*CH_2), 1.49 (3 H, d, *Me*CH), 3.96 and 3.97 (2 H, 2 q, MeCH_2), 4.11 (2 H, s, CH$_2$S), 5.22 (2 H, s, PhCH_2), 5.26 (1 H, q, MeC*H*), and 7.21–7.38 (10 H, complex, ArH)	13.9 (*Me*CH$_2$), 15.4 (*Me*CH), 35.8 (CH$_2$S), 53.2 (MeCH), 61.3 (MeCH$_2$), 69.1 (PhCH$_2$), 127.2, 128.5, 128.7, 128.8, 129.2, 134.3, and 136.6 (aryl C), 153.2 (Z CO), 169.9 (ester CO), and 170.7 (SCO)
4n	1.15 (3 H, t, *Me*CH_2), 1.70 (3 H, d, *Me*CH), 2.42 (3 H, s, Tos Me), 4.12 (2 H, q, MeCH_2), 5.17 [2 H, s, Z(NO$_2$) CH$_2$], 5.24 (1 H, q, MeC*H*), 7.25 and 7.84 (4 H, 2 × d, *J* 8.3 Hz, Tos ArH), and 7.29 and 8.15 [4 H, 2 × d, *J* 8.8 Hz, Z(NO$_2$) ArH]	14.0 (*Me*CH$_2$), 16.8 (*Me*CH), 21.6 (Tos Me), 55.5 (MeCH), 61.8 (MeCH$_2$), 67.2 [Z(NO$_2$) CH$_2$], 123.7, 128.4, 128.5, 129.3, 136.1, 141.6, 145.0, and 147.7 (aryl C), 151.1 [Z(NO$_2$) CO], and 169.8 (ester CO)
4o	1.07 (3 H, t, *Me*CH_2), 1.67 (3 H, d, *Me*CH), 2.39 (3 H, s, Tos Me), 4.02 and 4.04 (2 H, 2 × q, MeCH_2), 5.06 (2 H, s, PhCH_2), 5.21 (1 H, q, MeC*H*), 7.06–7.34 (7 H, complex, ArH + Tos ArH), and 7.80 (2 H, d, *J* 8.3 Hz, Tos ArH)	13.8 (*Me*CH$_2$), 16.9 (*Me*CH), 21.6 (Tos Me), 55.3 (MeCH), 61.6 (MeCH$_2$), 68.9 (Z CH$_2$), 128.4, 128.5, 129.0, 134.2, 136.1, and 144.5 (aryl C), 151.3 (Z CO), and 169.7 (ester CO)
4p	1.21 (3 H, t, *Me*CH_2), 1.31 (9 H, s, BocMe), 1.67 (3 H, d, *Me*CH), 2.44 (3 H, s, Tos Me), 4.17 (2 H, q, MeCH_2), 5.17 (1 H, q, MeC*H*), and 7.32 and 7.91 (4 H, 2 × d, *J* 8.4 Hz, Tos ArH)	13.9 (*Me*CH$_2$), 16.9 (*Me*CH), 21.6 (Tos Me), 27.7 (Boc Me), 54.8 (MeCH), 61.5 (MeCH$_2$), 84.7 (Me$_3$*C*), 128.2, 129.0, 136.8, and 144.2 (Tos aryl C), 149.8 (Boc CO), and 170.1 (ester CO)

(CH$_2$), 90.1 (CCl$_3$), 105.5 (Me$_2$*C*), 128.7 and 134.8 (aryl C), 147.8 (TCBoc CO) and 150.4 (Z CO) (Found: C, 43.8; H, 4.0; N, 3.9. $C_{13}H_{14}Cl_3NO_4$ requires C, 44.0; H, 4.0; N, 3.9%).

Benzyl 4-Chlorobenzyl Imidodicarbonate **1i**.—Synthesized as above from 4-chlorobenzyl alcohol and Z-NCO. The yield after recrystallization from light petroleum–diethyl ether was 79%; m.p. 114–116 °C; δ_H 5.15 [2 H, s, Z(Cl) CH$_2$], 5.19 (2 H, s, PhCH_2), 7.14 (~1 H, br s, NH), 7.31 [4 H, s, Z(Cl) ArH], and 7.35 (5 H, s, Ph); δ_C 67.1 [Z(Cl) CH$_2$], 68.1 (PhCH$_2$), 128.5, 128.7, 128.8, 129.8, 133.5, 134.6, and 134.9 (aryl C) and 150.4 (CO) (Found: C, 59.9; H, 4.4; N, 4.3. $C_{16}H_{14}ClNO_4$ requires C, 60.1; H, 4.4; N, 4.4%).

Benzyl 2-Chlorobenzyl Imidodicarbonate **1j**.—By analogy with its isomer **1i**. The yield of recrystallized product was 75%; m.p. 87–89 °C; δ_H 5.18 (2 H, s, PhCH_2), 5.40 [2 H, s, Z(*o*-Cl) CH$_2$], and 7.20–7.50 (~10 H, complex, ArH + NH); δ_C 65.2 [Z(*o*-Cl) CH$_2$], 67.9 (PhCH$_2$), 127.0, 128.5, 128.7, 129.6, 130.0, 130.3, 132.7, 133.9, and 134.8 (aryl C), and 150.3 and 150.5 (CO) (Found: C, 60.0; H, 4.4; N, 4.4%).

Benzyl 4-Pyridylmethyl Imidodicarbonate **1k**.—From recrystallized 4-pyridylmethanol and Z-NCO essentially according to the usual procedure. The yield of purified compound was 61% after chromatography in CH_2Cl_2–Me_2CO (4:1) and recrystallization from hexane–EtOAc; m.p. 154–156 °C; δ_H

5.22 (4 H, s, CH_2), 7.24 and 8.57 (4 H, 2 × d, Poc ArH), 7.37 (5 H, s, Ph), and 7.94 (~1 H, br s, NH); δ_C 65.7 (Poc CH_2), 68.0 (Ph*C*H_2), 121.9, 128.5, 128.7, 134.9, 144.2, and 149.9 (aryl C), and 150.6 (CO) (Found: C, 62.9; H, 4.9; N, 9.8. $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.9; N, 9.8%).

Benzyl N-[(*Benzylthio*)*carbonyl*]*carbamate* **1m**.—Synthesized by reaction of Z-NCO with toluene-α-thiol by analogy with the previous preparations. Preparative chromatography in CH_2Cl_2 followed by recrystallization from light petroleum–Et_2O afforded the *pure product* in 76% yield; m.p. 113–115 °C; δ_H 4.15 (2 H, s, CH_2S), 5.17 (2 H, s, PhCH_2), 7.21–7.35 (complex) and 7.35 (s), (together ≈10 H, Ph), and 7.72 (~1 H, br, NH); δ_C 34.2 (SCH_2), 68.1 (Ph*C*H_2), 127.3, 128.5, 128.7, 129.1, 134.7 and 136.8 (aryl C), 151.3 (Z CO) and 169.4 (SCO) (Found: C, 63.6; H, 5.0; N, 4.7. $C_{16}H_{15}NO_3S$ requires C, 63.8; H, 5.0; N, 4.6%).

p-*Nitrobenzyl* N-(p-*Tolylsulfonyl*)*carbamate* **1n**.—Commercial toluene-*p*-sulfonyl isocyanate (1.52 cm^3, 10.0 mmol) was dissolved in dry CH_2Cl_2 (20 cm^3) and the solution was added dropwise to a rapidly stirred, ice-cooled suspension of *p*-nitrobenzyl alcohol (1.45 g, 9.5 mmol) in dry CH_2Cl_2 (20 cm^3) during 30 min. The resulting solution was stirred for 1 h at 0 °C and overnight at ambient temperature. After evaporation of the mixture, the solid residue was triturated with light petroleum. The insoluble product was chromatographed in CH_2Cl_2–Me_2CO (4:1) and the last traces of impurities were removed by repeated recrystallization from toluene–EtOAc. The yield of *purified compound* **1n** was 60%; m.p. 143–145 °C; δ_H 2.45 (3 H, s, Me), 5.19 (2 H, s, CH_2), 7.31 and 7.90 (~4 H, 2 × d, A_2B_2 q, *J* 8.5, Tos ArH), and 7.40 and 8.17 [~4 H, 2 × d, A_2B_2 q, *J* 8.8, Z(NO_2) ArH]; δ_C 21.7 (Me), 66.8 (CH_2), 123.8, 128.4, 129.7, 135.1, 141.6, 145.5 and 147.9 (aryl C) and 150.0 (CO) (Found: C, 51.4; H, 4.0; N, 7.9. $C_{15}H_{14}N_2O_6S$ requires C, 51.4; H, 4.0; N, 8.0%).

Benzyl N-(p-*Tolylsulfonyl*)*carbamate* **1o**.—This compound was obtained, by analogy with the preceding compound **1n**, from benzyl alcohol and toluene-*p*-sulfonyl isocyanate. The yield of crude but essentially pure title compound **1o** was 97%. Recrystallization from CH_2Cl_2–Et_2O (1:5; 20 cm^3 g^{-1}; decolourizing carbon) gave *crystals*, m.p. 103.5–104 °C; δ_H 2.42 (3 H, s, Me), 5.08 (2 H, s, CH_2), 7.23–7.37 (~8 H, complex, ArH + NH) and 7.88 (2 H, d, *J* 8.5, Tos ArH); δ_C 21.5 (Me), 68.4 (CH_2), 128.2, 128.4, 129.4, 134.3, 135.3 and 144.8 (aryl C) and 150.7 (CO) (Found: C, 59.1; H, 5.1; N, 4.6. $C_{15}H_{15}NO_4S$ requires C, 59.1; H, 5.0; N, 4.6%).

Preparation of Potassium Salt of Imidodicarbonates **1a**, **1c**, **1e**, **1f**, **1h** *and* **1l**: *General Procedure*.—A rapidly stirred solution of the appropriate imidodicarbonate (1.00 mmol) in dry ethanol (1.0 cm^3) was treated dropwise with a suspension of finely ground KOH (0.90 mmol) in dry ethanol (1.0 cm^3) at room temperature. After 10 min, the resulting mixture was diluted with cold, dry diethyl ether (5–10 cm^3) whereupon a thick voluminous solid appeared. The precipitation was completed overnight at −20 °C and the product was collected by filtration, rinsed with small portions of cold, dry diethyl ether, and dried in high vacuum overnight. The salts were obtained as fine powders: **2a**, yield 79%; δ_H[$(CD_3)_2SO$] 1.37 (9 H, s, Me), 4.99 (2 H, s, CH_2) and 7.33 (5 H, s, Ph); **2c**, yield 90%; δ_H[$(CD_3)SO$] 4.31 (2 H, m, CH_2O), 4.88 (2 H, s, PhCH_2), 5.02–5.28 (~2 H, complex, CH_2=CH), 5.68–6.06 (~1 H, complex, C*H*=CH_2) and 7.30 (5 H, s, Ph); **2e**, yield 84%; δ_H[$(CD_3)SO$] 4.60 (2 H, s, Troc CH_2), 4.89 (2 H, s, PhCH_2), and 7.31 (5 H, s, Ph); **2f**, yield 97%; δ_H[$(CD_3)_2SO$] 4.89 (4 H, s, CH_2) and 7.32 (10 H, s, Ph); **2h**, yield 97%; δ_H[$(CD_3)_2SO$] 4.88 (2 H, s, PhCH_2), 5.03 [2 H, s, Z(NO_2) CH_2], 7.30 (5 H, s, Ph), 7.57 and 8.20 [4 H, 2 × d, A_2B_2 q, *J* 8.8, Z(NO_2) ArH]; **2l**, yield 93%; δ_H[$(CD_3)_2SO$] 1.29 (18 H, s, Me).

Gabriel Reaction of Potassium Salts **2a**, **2c**, **2e**, **2f**, **2h** *and* **2l** *with Ethyl* (R,S)-2-*Bromopropionate: General Procedure*.—To a vigorously stirred slurry of well dried, finely ground potassium salt (1.00 mmol) in dry DMF (2.5 cm^3) was added dropwise, under dry nitrogen, ethyl (*R*,*S*)-2-bromopropionate (272 mg, 1.50 mmol) at room temperature during 5 min. The resulting mixture was stirred for 24 h and then partitioned between diethyl ether (80 cm^3) and 0.2 mol dm^{-3} aq. citric acid (60 cm^3). The organic phase was washed in turn with 0.2 mol dm^{-3} aq. citric acid, 1 mol dm^{-3} aq. $NaHCO_3$, and saturated aq. NaCl (3 × 30 cm^3 each), and then dried over Na_2SO_4. Evaporation afforded a pale yellow oil, which was chromatographed using light petroleum–diethyl ether as eluant. For further information see Tables 1 and 2.

Benzyl [^{15}N]*Carbamate*.—A solution of $^{15}NH_4Cl$ (5.46 g, 0.10 mol) in water (60 cm^3) was cooled in ice and cautiously treated with 2 mol dm^{-3} NaOH (200 cm^3). Benzyl chloroformate (90% w/w; 28.4 g, 0.15 mol) was added dropwise to the vigorously stirred mixture during 2 h. After a further 7 h in ice and 14 h at ambient temperature, the turbid mixture was extracted with EtOAc (3 × 200 cm^3). The combined extracts were repeatedly washed with saturated aq. NaCl, dried (Na_2SO_4), and evaporated. The sticky solid residue was thoroughly treated with cold light petroleum (100 cm^3) and the fine-grained powder was collected, rinsed with small portions of cold solvent, and dried *in vacuo*. The yield of crude, chromatographically pure product was 14.4 g (97%). Recrystallization from toluene (6 cm^3 g^{-1}; decolourizing carbon) furnished lustrous flakes, m.p. 88–88.5 °C; δ_H 5.04 [~1 H, br d, J^1(^{15}N,^{1}H) 88.9, NH], 5.08 (2 H, s, CH_2) and 7.34 (5 H, s, Ph); δ_C 66.8 (CH_2), 128.0, 128.2, 128.5, and 136.1 (aryl C) and 157.0 [d, J^1(^{15}N,^{13}C) 26.4, CO]; mass spectrum (EI; 70 eV) showed 99.0 ± 0.3% nitrogen-15.

Benzyl 2,2,2-*Trichloroethyl* [^{15}N]*Imidodicarbonate* ([^{15}N]-**1e**).—A slurry of ground benzyl [^{15}N]carbamate (4.56 g, 30.0 mmol) in rapidly stirred, dry CH_2Cl_2 (45 cm^3) was treated with a solution of oxalyl dichloride (5.71 g, 45 mmol) in CH_2Cl_2 (18 cm^3) under argon at 0 °C during 15 min. After being stirred in ice for 2 h, at room temperature for 6 h, and at reflux for 13 h, the turbid mixture was chilled in ice and the fine-grained precipitate was filtered off, and rinsed with CH_2Cl_2 under argon. Evaporation of the combined filtrate at 0 °C under dry conditions afforded an oil (5.03 g) consisting of benzyloxycarbonyl [^{15}N]isocyanate (~70%) and benzyl chloride (~30%, ^{1}H NMR). This was dissolved in dry CH_2Cl_2 (40 cm^3) and slowly added to a well stirred solution of 2,2,2-trichloroethanol (3.10 g, ~5% excess as calculated from crude isocyanate) at 0 °C under argon. After the mixture had been stirred for 1 h in ice and at ambient temperature for 2 h, the solvent was removed at reduced pressure and the oily residue was chromatographed on silica in CH_2Cl_2–Et_2O (20:1). The yield of pure title compound was 4.34 g (44%). Recrystallization from hexane–diethyl ether (6:1; 50 cm^3 g^{-1}) furnished shiny flakes, m.p. 86–86.5 °C; δ_H 4.79 (2 H, s, Troc CH_2), 5.23 (2 H, s, PhCH_2), 7.38 (5 H, s, Ph) and 7.40 [~1 H, br d, J^1(^{15}N,^{1}H) 92.1, NH]; δ_C 68.3 (Ph*C*H_2), 74.7 (Troc CH_2), 94.3 (CCl_3), 128.5, 128.7, and 134.6 (aryl C), 149.0 [d, J^1(^{15}N,^{13}C) 27.8, Troc CO] and 150.2 [d, J^1(^{15}N,^{13}C) 26.4, Z CO].

Mitsunobu Reaction of Imidodicarbonates **1a**–**p** *with Chiral Lactate Esters. Typical Procedure*.—*Preparation of ethyl* (R)-

N-*benzyloxycarbonyl*-N-(2,2,2-*trichloroethoxycarbonyl*)-[^{15}N]*alaninate* ([^{15}N]-**4e**). To an ice-cold solution of benzyl 2,2,2-trichloroethyl [15N]imidodicarbonate ([^{15}N]-**1e**) (1.64 g, 5.00 mmol) in dry THF (10 cm^3) containing triphenylphosphine (1.57 g, 6.00 mmol) under dry argon was added ethyl (*S*)-lactate (650 mg, 5.50 mmol). Subsequently, a solution of DEAD (1.13 g, 6.50 mmol) in dry THF (3 cm^3) was introduced dropwise to the rapidly stirred solution during 30 min and the mixture was then stirred overnight at room temperature. Removal of the solvent left a yellowish, viscous oil, which was chromatographed (silica) in light petroleum–diethyl ether (3:1) to give an essentially colourless, viscous liquid (1.93 g, 90%); $[\alpha]_D^{25}$ +13.2° (*c* 1, $CHCl_3$); δ_H 1.18 (3 H, t, *Me*CH_2), 1.59 [3 H, dd, $J(^1H,^1H)$ 7.0, $J^3(^{15}N,^1H)$ 2.6, *Me*CH], 4.11 (2 H, q, MeCH_2), 4.80 and 4.86 (2 H, ABq, *J* 11.9, Troc CH_2), 5.12 [1 H, dq, $J(^1H,^1H)$ 7.0, $J^2(^{15}N,^1H)$ 1.5, MeC*H*], 5.29 (2 H, s, PhCH_2) and 7.37 (5 H, s, Ph); δ_C 14.0 (*Me*CH_2), 15.4 (*Me*CH), 55.0 [d, $J^1(^{15}N,^{13}C)$ 9.8, Me*C*H], 61.5 (Me*C*H_2), 69.4 (Ph*C*H_2), 76.0 (Troc CH_2), 94.1 (CCl_3), 128.4, 128.5 and 134.7 (aryl C), 151.5 [d, $J^1(^{15}N,^{13}C)$ 27.8, Troc CO], 152.5 [d, $J^1(^{15}N,^{13}C)$ 26.4, Z CO] and 169.9 (ester CO).

Benzyl (*S*)-*N*-benzyloxycarbonyl-*N*-(2,2,2-trichloroethoxycarbonyl)[^{15}N]alaninate ([^{15}N]-**4r**) was obtained analogously from benzyl (*R*)-lactate in 68% yield after chromatography in light petroleum–diethyl ether (4:1); $[\alpha]_D^{25}$ −10.7° (*c* 1, $CHCl_3$); δ_H 1.61 [dd, $J(^1H,^1H)$ 7.0, $J^3(^{15}N,^1H)$ 2.6, *Me*CH], 4.58 and 4.79 (2 H, ABq, *J* 11.9, Troc CH_2), 5.07 and 5.13 (2 H, ABq, *J* 12.2, CH_2Ph), 5.18 [1 H, dq, $J(^1H,^1H)$ 7.0, $J^2(^{15}N,^1H)$ 1.8, MeC*H*], 5.22 (2 H, s, PhCH_2), 7.31 (5 H, s, Ph) and 7.35 (5 H, s, Ph); δ_C 15.6 (*Me*CH), 55.1 [d, $J^1(^{15}N,^{13}C)$ 9.8, Me*C*H], 67.2 (*C*H_2Ph), 69.5 (Ph*C*H_2OCON), 75.9 (Troc CH_2), 94.1 (CCl_3), 128.4, 128.6, 134.7 and 135.3 (aryl C), 151.4 [d, $J^1(^{15}N,^{13}C)$ 29.2, Troc CO], 152.5 [d, $J^1(^{15}N,^{13}C)$ 27.8, Z CO] and 169.8 (ester CO).

Similarly were prepared benzyl (*R*)-*N*-benzyloxycarbonyl-*N*-(2,2,2-trichloroethoxycarbonyl)alaninate **4q** and its corresponding (*S*)-enantiomer **4r** from the appropriate chiral benzyl lactates in 68% and 67% yield, respectively; $[\alpha]_D^{25}$ +10.6° (*R*), −10.6° (*S*) (*c* 1, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structures.

Assessment of Optical Purity of Mitsunobu Products.—Selected *N*,*N*-blocked ethyl alaninates **4** carrying acid-labile protective groups throughout (**4a**, **4b**, **4c**, **4f** and **4g**) were subjected to total acidolysis using 6 mol dm^{-3} aq. HCl (1 cm^3 mg^{-1} compound; 110 °C; sealed, evacuated tubes; agitation for 24 h). After evaporation at reduced pressure, the resulting hydrolysates were dissolved in 1.0 mol dm^{-3} borate buffer (pH 6.85) and converted into the corresponding (−)-Flec analogues by reaction with (−)-Flec-Cl (for the antipode (+)-Flec was used; both are commercially available from Fluka), essentially according to the published procedure.[26] Chromatographic analyses of the derivatized mixtures were accomplished similarly to the previously described conditions, except that UV (265 nm) was used instead of fluorescence for detection (Fig. 1). Integration revealed that the enantiomeric excess of the major component exceeded 95%. Analogous analyses of the corresponding crude reaction mixtures from the Mitsunobu conversions before chromatographic work-up gave roughly the same results. Furthermore, preliminary measurements have shown that the amounts of (*S*)-enantiomer in the crude products were virtually unaffected by the solvent used as reaction medium.

(R)-N-*Benzyloxycarbonyl*[^{15}N]*alanine* ([^{15}N]-**6e**).—A rapidly stirred solution of ethyl (*R*)-*N*-benzyloxycarbonyl-*N*-(2,2,2-trichloroethoxycarbonyl)[^{15}N]alaninate ([^{15}N]-**4e**) (1.71 g, 4.00 mmol) in THF (40 cm^3) was treated with activated Zn powder (4.0 g) followed by 1.0 mol dm^{-3} aq. NaH_2PO_4 (8.0 cm^3) dropwise under nitrogen. The reaction was monitored by TLC and after being vigorously stirred for 4 h the slurry was filtered and the filtrate was evaporated. The oily residue was partitioned between diethyl ether (200 cm^3) and 0.2 mol dm^{-3} aq. citric acid (100 cm^3) and the ethereal phase was washed successively and repeatedly with 0.2 mol dm^{-3} aq. citric acid, 1 mol dm^{-3} aq. $NaHCO_3$, and saturated aq. NaCl. After drying of the mixture over $MgSO_4$ the solvent was stripped off to leave an oil (1.0 g) consisting of essentially pure ethyl (*R*)-*N*-benzyloxycarbonyl-[^{15}N]alaninate ([^{15}N]-**5e**). This was dissolved in 1,4-dioxane (10 cm^3) and cautiously treated with 1.05 mol dm^{-3} aq. NaOH (4.10 cm^3, 4.30 mmol). After being stirred for 3 h at ambient temperature, diluted with water (150 cm^3), and evaporated to 100 cm^3, the turbid mixture was filtered, and then extracted with diethyl ether (50 cm^3). The aq. phase was acidified (to pH ~2.5, indicator paper) with dil. HCl and extracted with diethyl ether (3 × 50 cm^3). The combined extracts were washed with saturated aq. NaCl, dried over Na_2SO_4, and evaporated to furnish the title acid as an oil which soon solidified. The yield of chromatographically pure product was 852 mg (95%). Recrystallization from hexane–EtOAc (10:1) (100 cm^3 g^{-1}; decolourizing carbon) afforded crystals, m.p. 84–84.5 °C; $[\alpha]_D^{25}$ +14.0° (*c* 1.97, HOAc) {lit.,[36a] (^{14}N-analogue), m.p. 86–87 °C; lit.,[36b] $[\alpha]_D^{25}$ 13.9° (*c* 2, HOAc)}; δ_H(270 MHz) 1.45 [3 H, dd, $J(^1H,^1H)$ 7.2, $J^3(^{15}N,^1H)$ 3.0, *Me*CH] 4.29 and 4.42 (together 1 H, 2 × m, MeC*H*, two conformers, ratio ~1:2), 5.11 and 5.16 (together 2 H, 2 × s, PhCH_2, ratio 1:2), 5.43 and 7.07 [together 1 H, 2 × dd, $J(^1H,^1H)$ ~7, $J^1(^{15}N,^1H)$ 92.0, NH, ratio 1:2], 7.34 (5 H, s, Ph) and 11.50 (1 H, br s, CO_2H); δ_C(67.9 MHz) 18.3 and 18.7 (2 × s, *Me*CH), 49.4 and 49.9 [2 × d, $J^1(^{15}N,^{13}C)$ 12.2, Me*C*H], 67.1 and 67.6 (2 × s, Ph*C*H_2), 127.9, 128.1, 128.2, 128.5, 135.6 and 136.0 (aryl C), 155.8 and 157.0 [2 × d, $J^1(^{15}N,^{13}C)$ 26.9, Z CO), and 177.0 and 177.8 (2 × s, CO_2H). A small aliquot was deprotected [H_2(Pd/C); 80% aq. HOAc; 3 h] and analysed by HPLC as the (−)-Flec derivative. (*R*)-Ala was present in the crystallized product in 98.3% ee.

Benzyl (S)-N-(2,2,2-*Trichloroethoxycarbonyl*)[^{15}N]*alaninate* [(S)-*Troc*-[^{15}N]*Ala-OBzl*).—Chromatographed [^{15}N]-**4r** (1.71 g, 3.50 mmol) was suffused with TFA (20 cm^3) under nitrogen. After being stirred for 1 h the resulting pinkish solution was evaporated to dryness and the oily residue was partitioned between diethyl ether (175 cm^3) and 0.2 mol dm^{-3} aq. citric acid (75 cm^3). The ethereal phase was washed in turn with 0.2 mol dm^{-3} aq. citric acid, 1 mol dm^{-3} aq. $NaHCO_3$, and saturated aq. NaCl (3 × 50 cm^3 each) and dried over $MgSO_4$. Removal of the solvent left a crude oil, which was purified by column chromatography [light petroleum–diethyl ether (3:1)]. The yield of pure product obtained as a viscous oil, which slowly solidified, was 1.10 g (89%); $[\alpha]_D^{25}$ −4.2° (*c* 1, $CHCl_3$); δ_H 1.46 [3 H, dd, $J(^1H,^1H)$ 7.2, $J^3(^{15}N,^1H)$ 3.1, *Me*CH], 4.44 (1 H, m, MeC*H*), 4.67 and 4.75 (2 H, ABq, *J* 12.1, Troc CH_2), 5.19 (2 H, s, PhCH_2), 5.61 [1 H, dd, $J(^1H,^1H)$ 7.8, $J^1(^{15}N,^1H)$ 92.2, NH], and 7.36 (5 H, s, Ph); δ_C 18.5 (*Me*CH), 49.9 [d, $J^2(^{15}N,^{13}C)$ 12.5, Me*C*H], 67.3 (Ph*C*H_2), 74.6 (Troc CH_2), 95.3 (CCl_3), 128.2, 128.5, 128.7 and 135.1 (aryl C), 153.8 [d, $J^1(^{15}N,^{13}C)$ 29.2, Troc CO] and 172.3 (ester CO).

Benzyl (S)-[^{15}N]*Alaninate* {(S)-[^{15}N]*Ala-OBzl*}.—A stirred solution of benzyl (*S*)-Troc-[^{15}N]alaninate (889 mg, 2.50 mmol) in THF (50 cm^3) was treated with activated Zn powder (5 g) under argon and to this slurry was added dropwise during 5 min 1.0 mol dm^{-3} aq. KH_2PO_4 (10 cm^3). The reaction was monitored by TLC and, after 8 h, the unchanged Zn was filtered off and rinsed thoroughly and successively with THF (2 × 10 cm^3) and EtOH–0.1 mol dm^{-3} aq. HCl (1:1) (5 × 40 cm^3). The combined turbid filtrates were concentrated to 100 cm^3 at room

temperature and extracted with diethyl ether (2 × 25 cm^3). The aq. phase was made alkaline with $K_2CO_{3(s)}$ (30 g) and again extracted with diethyl ether (4 × 25 cm^3). After being washed with saturated aq. NaCl (2 × 25 cm^3) and dried over Na_2SO_4 the extract was evaporated. The yield of essentially pure product obtained as a viscous liquid was 260 mg (58%); δ_H 1.34 [3 H, dd, $J(^1H,^1H)$ 7.2, $J^3(^{15}N,^1H)$ 3.1, *Me*CH), 1.95 (2 H, br s, NH_2), 3.58 (1 H, complex, MeC*H*), 5.15 (2 H, s, CH_2), and 7.35 (5 H, s, Ph). After hydrogenolysis as described for [^{15}N]-**6e** the free alanine was analysed by HPLC as its (+)-Flec derivative, which demonstrated that (*S*)-Ala was present in 89% ee. The product was treated with anhydrous toluene-*p*-sulfonic acid (1.2 mol equiv.) in a small volume of dry benzene. Dilution with dry diethyl ether and cooling furnished a precipitate, which was recrystallized from Et_2O–EtOH (9:1; 40 cm^3 g^{-1}); m.p. 110–112 °C; $[\alpha]_D^{25}$ −5.2° (*c* 4, MeOH) {lit.,[37] (nitrogen-14 analogue): m.p. 116–118 °C; $[\alpha]_D^{25}$ −6.0° (*c* 4, MeOH)}; $\delta_H(CD_3OD)$ 1.51 [3 H, dd, $J^3(^{15}N,^1H)$ 2.8, $J(^1H,^1H)$ 7.2, *Me*CH], 2.36 (3 H, s, Tos Me), 4.12 (1 H, q, MeC*H*), 5.26 (2 H, s, CH_2Ph), 7.37 (5 H, s, Ph), and 7.22 and 7.70 (4 H, ABq, *J* 8.1, Tos ArH).

Benzyl (S)-O-(*Trifluoromethylsulfonyl*)*lactate* **7s**.—Benzyl (*S*)-lactate was treated with triflic anhydride in dichloromethane in the presence of pyridine under anhydrous conditions as previously described for the ethyl ester.[9,24] Filtration through silica and removal of solvent afforded the essentially pure title compound as a liquid in 85% yield: $[\alpha]_D^{25}$ −37.8° (*c* 1.81, CH_2Cl_2); δ_H 1.70 (3 H, d, Me), 5.26 (2 H, s, CH_2), 5.26 (1 H, q, CH), and 7.37 (5 H, s, Ph).

Benzyl (R)-O-(*Trifluoromethylsulfonyl*)*lactate* **7t**.—Synthesized from benzyl (*R*)-lactate according to the same procedure. The yield of pure product was 89%: $[\alpha]_D^{25}$ +37.2° (*c* 2.23, CH_2Cl_2). The ^{1}H NMR spectrum was identical with that of the (*S*)-enantiomer.

(S)-N-(t-*Butoxycarbonyl*)[^{15}N]*alanine* ([^{15}N]-**10t**).—A. *Benzyl* (S)-N,N-*Bis*(t-*butoxycarbonyl*)[^{15}N]*alaninate* ([^{15}N]-**8t**). Finely ground, well dried di-*t*-butyl [^{15}N]imidodicarbonate[21] (1.09 g, 5.00 mmol) was dissolved in dry THF (10 cm^3). The subsequent additions took place at −78 °C in rapidly stirred mixtures under dry argon. BuLi (1.65 mol dm^{-3} in hexane; 3.00 cm^3, 4.95 mmol) was introduced dropwise (30 min) and after another 30 min freshly prepared triflate **7t** (1.80 g, 5.75 mmol) was added similarly (30 min), giving a suspension. After the mixture had been stirred for a further 30 min the temperature was gradually brought to −28 °C during 30 min, then the mixture was stirred at −28 ±2 °C for 2 h, during which time the insoluble material slowly dissolved. The resulting pale yellow solution was quenched in a mixture of ice-cold diethyl ether and 0.2 mol dm^{-3} aq. citric acid (200 and 100 cm^3, respectively). The ethereal extract was washed successively with 0.2 mol dm^{-3} aq. citric acid, 1 mol dm^{-3} aq. $NaHCO_3$, and saturated aq. NaCl (3 × 50 cm^3 each), dried over $MgSO_4$, and evaporated. The yield of crude compound [^{15}N]-**8t** obtained as a pale yellow oil was 1.99 g (quant.) after drying in high vacuum. The product was essentially pure as indicated by ^{1}H NMR spectroscopy and TLC; δ_H 1.46 (18 H, s, Boc Me), 1.53 [3 H, dd, $J(^1H,^1H)$ 6.8, $J^3(^{15}N,^1H)$ 3.4, *Me*C*H*], 5.01 [1 H, dq, $J(^1H,^1H)$ 6.8, $J^2(^{15}N,^1H)$ 1.8, MeC*H*], 5.15 (2 H, s, PhCH_2), and 7.33 (5 H, s, Ph). This product was used without purification in the next step.

B. *Benzyl* (S)-N-(t-*Butoxycarbonyl*)[^{15}N]*alaninate* ([^{15}N]-**9t**). The above crude oil was dissolved in dry dichloromethane (40 cm^3) and the rapidly stirred mixture was cautiously treated with a solution of TFA (855 mg, 7.50 mmol) in dry dichloromethane (15 cm^3) under nitrogen. After 3 h the yellowish solution was evaporated and the residual brownish oil was partitioned between diethyl ether (200 cm^3) and 0.2 mol dm^{-3} aq. citric acid (100 cm^3). The ethereal phase was washed and dried as described above, and removal of the solvent left a yellow oil consisting of essentially pure title ester [^{15}N]-**9t** in quantitative yield; δ_H 1.38 [3 H, dd, $J(^1H,^1H)$ ~7, $J^3(^{15}N,^1H)$ ~3, *Me*CH], 1.43 (9 H, s, Boc Me), 4.21–4.69 (1 H, complex, MeC*H*), 5.08 [1 H, dd, $J(^1H,^1H)$ ~8, $J^1(^{15}N,^1H)$ ~92, NH], 5.17 (2 H, s, PhCH_2) and 7.35 (5 H, s, Ph). This crude product was suitable for the next step.

C. (S)-N-(t-*Butoxycarbonyl*)-[^{15}N]*alanine* ([^{15}N]-**10t**). The crude ester [^{15}N]-**9t** as obtained above was dissolved in methanol (50 cm^3) and hydrogenated at 1 atm in the presence of Pd (5% on C; 150 mg). The reaction was carefully monitored by TLC and when complete the catalyst was filtered off and the clear filtrate was taken to dryness. The residual oil was partitioned between diethyl ether (25 cm^3) and 1 mol dm^{-3} aq. $NaHCO_3$ (50 cm^3). The aq. phase was extracted with diethyl ether (25 cm^3) and then cautiously acidified to pH 2.5 (indicator paper) with $KHSO_{4(s)}$ while being vigorously stirred in the presence of diethyl ether (25 cm^3). The aq. phase was extracted with diethyl ether (2 × 25 cm^3) and the combined extracts were washed with saturated aq. NaCl (2 × 25 cm^3), dried over Na_2SO_4 and evaporated. The yield of chromatographically pure acid [^{15}N]-**10t** obtained as an oil, which slowly solidified, was 786 mg (83% over three steps from di-*t*-butyl [^{15}N]imidodicarbonate). Recrystallization was performed by dissolution of the crude product in diethyl ether (20 cm^3) and slow addition of the solution to refluxing light petroleum (150 cm^3). After concentration to ~100 cm^3 and chilling to −20 °C the crystals slowly precipitated after seeding: m.p. 79–80 °C; $[\alpha]_D^{25}$ −24.4° (*c* 1.97, HOAc) {lit.,[38] (nitrogen-14 analogue) m.p. 81–82 °C; $[\alpha]_D^{25}$ −24.0° (HOAc)}; δ_H(270 MHz) 1.44 [3 H, dd, $J(^1H,^1H)$ ~7, $J^3(^{15}N,^1H)$ 3.0, *Me*CH], 1.45 (9 H, s, Boc Me), 4.17 and 4.35 (together 1 H, 2 × m, MeC*H*), 5.13 [dd, $J(^1H,^1H)$ 7.6, $J^1(^{15}N,^1H)$ 91.1] and 6.96 [dd, $J(^1H,^1H)$ 5.7, $J^1(^{15}N,^1H)$ 92.9] (together 1 H, NH), and 11.98 (1 H, br s, CO_2H); δ_C(67.9 MHz) 18.4 (*Me*CH), 28.2 (Boc Me), 49.0 and 50.1 [2 × d, $J^1(^{15}N,^{13}C)$ 11.6, Me*C*H], 80.2 and 81.5 (*C*Me_3), 155.3 and 156.8 [2 × d, $J^1(^{15}N,^{13}C)$ 25.0, Z CO] and 177.3 and 178.1 (ester CO). A small sample was deprotected [CH_2Cl_2–TFA (2:1); 1 h; room temp.] and analysed by HPLC as the (+)-Flec derivative, showing (*S*)-Ala to be present in 96.4% ee.

(R)-N-t-*Butoxycarbonyl*[^{15}N]*alanine* ([^{15}N]-**10s**).—This compound was prepared by analogy with the above procedure for the (*S*)-analogue. The yield over three steps from di-*t*-butyl [^{15}N]imidodicarbonate and substrate **7s** was 68%; m.p. 80–81 °C; $[\alpha]_D^{25}$ +24.8° (*c* 1.87, HOAc) {lit.,[39] (nitrogen-14 analoque), m.p. 82.5–83.5 °C; $[\alpha]_D^{22}$ +23.7 (*c* 2 HOAc)}. The ^{1}H NMR spectra of the two intermediary, crude, protected derivatives as well as the ^{1}H and ^{13}C NMR spectra of the final purified product were in full agreement with those obtained for the (*S*)-enantiomer. According to the assay above, (*R*)-Ala was present in 99.8% ee.

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