Synthesis of ^{15}N-Labelled Chiral Boc-Amino Acids from Triflates: Enantiomers of Leucine and Phenylalanine

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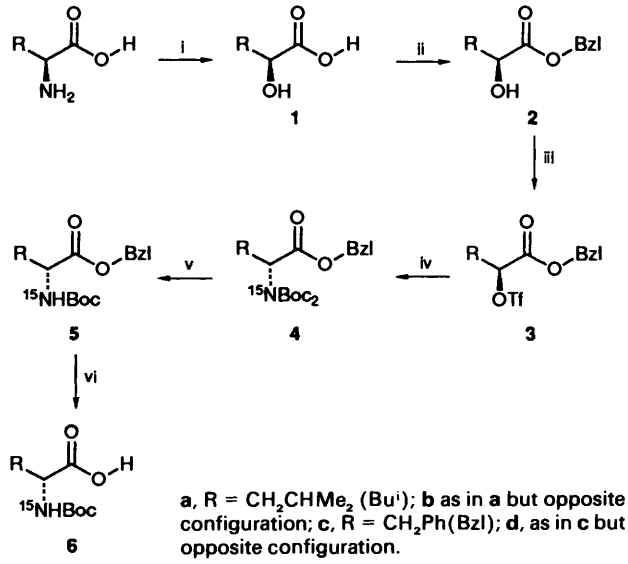
An efficient synthesis of ^{15}N-labelled chiral Boc-amino acids by triflate alkylation of di-*tert*-butyl [^{15}N]imidodicarbonate is reported. Both enantiomers of Boc-leucine and -phenylalanine were synthesized from commercial α-amino acids of opposite configuration *via* α-hydroxy carboxylic acids provided by diazotization, thus extending the scope of an earlier exploratory study. The high chiral purity of the final products was confirmed by HPLC. These labelled amino acid derivatives are suitable for direct application to the synthesis of labelled peptides.

Recently we reported[1] two different approaches to the synthesis of ^{15}N-labelled N-protected chiral alanines. Selected imidodicarbonates were used as amine synthons in both and they were alkylated by lactic acid esters—either directly, in accordance with Mitsunobu,[2] or after conversion into triflate[3]—in excellent enantiomeric excess. In the Mitsunobu experiments, we observed a strong dependence of the yield on the pK_a of the imidodicarbonate[4] and Boc-alanine could not be synthesized readily by this method. On the other hand, this derivative could easily be obtained by selective deprotection of the product made from the triflate.

Since Boc-derivatives are important precursors in peptide synthesis we decided to further explore the applicability of the triflate method to direct preparation of other Boc-amino acids. In this paper we describe the synthesis of ^{15}N-labelled Boc-(*R*)- and -(*S*)-leucine and -phenylalanine by a convenient procedure starting from the corresponding commercial α-amino acid of opposite configuration. These novel, specifically labelled compounds will be useful for the preparation of peptides suitable for various structural investigations by spectroscopic methods.



a, R = CH_2CHMe_2 (Bu^i); **b** as in **a** but opposite configuration; **c**, R = CH_2Ph(Bzl); **d**, as in **c** but opposite configuration.

Scheme 1 *Reagents:* i, $NaNO_2$, H_2SO_4; ii, Cs_2CO_3, DMF, BzlBr; iii, Tf_2O, lutidine, CH_2Cl_2; iv, $^{15}NHBoc_2$, BuLi, THF (cooling); v, TFA (1.5 mol equiv.), CH_2Cl_2; vi, H_2/Pd, MeOH

Results and Discussion

The syntheses of the new labelled compounds **6a–d** were accomplished by the multi-step route outlined in Scheme 1.

In the first step, the appropriate α-hydroxy carboxylic acids **1a–d** were obtained in satisfactory yields by diazotization of the corresponding amino acids. This reaction is claimed to occur with retention of configuration,[5] although the formation of trace amounts of racemate cannot be excluded. From a practical point of view, it is therefore important to remove impurities from the crude intermediates **1** by repeated recrystallizations followed by careful control of their physical properties.

The benzylation of the cesium salts of **1a–d** was readily accomplished using benzyl bromide in accordance with an earlier procedure.[6] The resulting benzyl esters **2a–d** were activated by conversion into the appropriate triflates **3a–d** with triflic anhydride in the presence of lutidine under anhydrous conditions.[3,7]

The generation of the Li-salt of $Boc_2{}^{15}NH$ was conducted at −78 °C using a slight deficiency of BuLi. The triflate **3** was then allowed to react with this salt with efficient cooling to suppress side reactions. Further investigations have revealed that quenching temperatures in the range −30 to +20 °C have little effect on the stereochemical outcome of the reaction. In this context we should mention that an excess of BuLi in this step apparently can cause considerable transesterification, significant amounts of the butyl ester of **6** being occasionally detected in the crude final products.

Selective removal of one Boc-group in Boc_2-derivative **4** was smoothly achieved by only a slight excess of TFA. The final catalytic hydrogenolysis of the resulting ester **5** furnished the desired ^{15}N-labelled Boc-amino acids **6a–d** in high overall yields from $Boc_2{}^{15}NH$.

The optical purity of compound **6**, after deblocking and subsequent derivatization with the proper chiral Flec-Cl, was assessed by HPLC of the resulting diastereoisomeric Flec-amino acids. The final products were generally obtained in an enantiomeric excess exceeding 98%, thus confirming that the displacement of the triflate moiety in **3** proceeds by complete inversion of the configuration at the α-carbon.

In conclusion, this work demonstrates that the triflate procedure offers an efficient direct route to ^{15}N-labelled Boc-amino acids of high optical purity. The fact that inexpensive commercial amino acids can serve as precursors is a further attractive feature of the method.

Experimental

General Methods.—For particular procedures, see ref. 1. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JNM-EX 270 instrument at 270 and 67.9 MHz, respectively, at 19 ± 1 °C and ^{15}N NMR spectra with a JEOL FX 90Q at 9.03 MHz, at

Table 1 Properties of unlabelled precursors **1–3**

	R (config.)	Yield (%)	M.p. (°C) [lit.]	$[\alpha]_D^{25}$ (c^b) [lit.]	^{1}H NMR (δ_H, $CDCl_3$, J/Hz)[a]
1a	Bu^i (*S*)	75	79–80 [80–81][8]	−27.4 (1.50$^\alpha$) [−26.9^c (1.55$^\alpha$)][8]	0.97 (6 H, d, Me), 1.63 (2 H, pert dd, CH_2), 1.91 (1 H, m, Pr^i), 4.30 (1 H, pert dd, CH-O)
1b	Bu^i (*R*)	55	78.5–79.5 [79–80][8]	+27.1 (1.50$^\alpha$) [+26.5^c (1.52$^\alpha$)][8]	
1c	Bzl (*S*)	60	123–124 [126–127][9]	−26.3 (3.80$^\beta$) [−27.8 (3.78$^\beta$)][9]	3.01, 3.22 (2 H, ABq coupled to CH, J_{gem} 14, J_α 4.3, J_β 7.2, CH_2), 4.53 (1 H, dd, CH), 7.25–7.37 (5 H, cpl sign, Ar)
1d	Bzl (*R*)	70	123–124 —	+26.7 (3.80$^\beta$) —	
2a	Bu^i (*S*)	98	Oil	−15.2 (2.96$^\gamma$) [−15.8^c (3.09$^\gamma$)][10]	0.93 (6 H, dd, Me), 1.57 (2 H, pert m, CH_2), 1.89 (1 H, m, Pr^i), 2.68 (1 H, d, OH), 4.24 (1 H, pert m, CH), 5.21 (2 H, s, Bzl), 7.36 (5 H, s, Ar)
2b	Bu^i (*R*)	93	Oil	+14.4 (2.98$^\gamma$) —	
2c	Bzl (*S*)	98	Oil	−55.4 (1.78$^\delta$) —	2.79 (1 H, d, OH), 2.97, 3.11 (2 H, ABq coupled to CH, J_{gem} 13.9, J_α 4.6, J_β 6.5, CH_2), 4.48 (1 H, pert m, CH), 5.17 (2 H, s, Bzl), 7.12–7.39 (10 H, cpl sign, Ar)
2d	Bzl (*R*)	97	Oil	+55.2 (1.88$^\delta$) —	
3a	Bu^i (*S*)	97	Oil	−44.7 (1.94$^\delta$) —	0.96 (6 H, dd, Me), 1.75 (2 H, cpl sign, CH_2), 1.95 (1 H, m, Pr^i), 5.18 (1 H, dd, J_α 3.5, J_β 9.3, CH), 5.25 (2 H, s, Bzl), 7.38 (5 H, s, Ar)
3b	Bu^i (*R*)	98	Oil	+43.8 (1.80$^\delta$) —	
3c	Bzl (*S*)	98	Oil	−34.7 (1.60$^\delta$) —	3.20, 3.33 (2 H, ABq coupled to CH, J_{gem} 14.6, J_α 4.4, J_β 8.4, CH_2), 5.24 (2 H, s, Bzl), 5.27 (1 H, dd, CH), 7.14–7.39 (10 H, cpl sign, Ar)
3d	Bzl (*R*)	98	Oil	+34.1 (1.60$^\delta$) —	

[a] All enantiomers gave identical spectra; cpl sign (complex signal); pert (perturbed). [b] The following solvents were used in polarimetry: 1 mol dm^{-3} NaOH$^\alpha$, acetone$^\beta$, $CHCl_3$$^\gamma$ and $CH_2Cl_2$$^\delta$. [c] Measured at 20–24 °C.

22 ± 1 °C, all in $CDCl_3$. All shifts are given in ppm, the ^{15}N ones using $HCO^{15}NH_2$ as reference [$\delta(HCO^{15}NH_2)$ = 113.2 ppm].

General Procedure for the Synthesis of α-Hydroxy Carboxylic Acids **1**.—To a stirred solution of the appropriate amino acid (75.0 mmol) in 0.5 mol dm^{-3} H_2SO_4 (300 cm^3) was added dropwise a solution of $NaNO_2$ (31 g, 0.45 mol) in water (100 cm^3) over a period of 3 h at 0 °C, after which it was left for 24 h at room temp. before extraction with ether (300 and 2 × 150 cm^3). The combined extracts were washed with saturated brine (2 × 40 cm^3), dried (Na_2SO_4) and evaporated. The sticky solid residue was recrystallized repeatedly from ether–light petroleum to constant optical rotation. (*S*)- **1a** and (*R*)-2-hydroxy-4-methylpentanoic acid **1b** and (*S*)- **1c** and (*R*)-2-hydroxy-3-phenylpropanoic acid **1d** were obtained as white needles. Data on **1a–d** are given in Table 1.

General Procedure for the Synthesis of α-Hydroxy Carboxylic Acid Benzyl Esters **2**.—A solution of **1** in MeOH–water (9:1, 2 cm^3 $mmol^{-1}$) was titrated to pH 7 with 20% aqueous Cs_2CO_3. The solvent was removed under reduced pressure, DMF added to the residue and the mixture again evaporated to afford the Cs salt. For the reaction, the latter was again suspended in DMF (1cm^3 $mmol^{-1}$) and benzyl bromide (0.9 equiv.) was added dropwise under nitrogen at 0 °C. After 2 h in ice-bath and overnight at room temp., the turbid mixture was evaporated to dryness and the residue partitioned between ether and water (15 cm^3 $mmol^{-1}$ each). The organic extract was successively washed with 1 mol dm^{-3} aqueous $NaHCO_3$ (3 × 5 cm^3 $mmol^{-1}$) and saturated brine (3 × 5 cm^3 $mmol^{-1}$), dried (Na_2SO_4), filtered and evaporated to afford essentially pure products: benzyl (*S*)-**2a** and (*R*)-2-hydroxy-4-methylpentanoate **2b** and benzyl (*S*)-**2c** and (*R*)-2-hydroxy-3-phenylpropanoate **2d** were obtained as pale yellow oils; for data on **2a–d** see Table 1.

General Procedure for the Synthesis of 2-Trifluoromethylsulfonyloxy Carboxylic Acid Benzyl Esters **3**.—Compound **2** was treated with triflic anhydride (1.15 equiv.) in dry CH_2Cl_2 (2 cm^3 $mmol^{-1}$) in the presence of lutidine (1.30 equiv.) with stirring under argon at −78 °C. After 30 min, the mixture was gradually (1 h) brought to room temp. and then after a further 30 min the pink solution was partitioned between CH_2Cl_2 (20 cm^3 $mmol^{-1}$) and water (15 cm^3 $mmol^{-1}$). The aq. phase was further extracted with CH_2Cl_2 (2 × 5 cm^3 $mmol^{-1}$) and the combined extracts were dried (Na_2SO_4) and evaporated to dryness. The crude product (in CH_2Cl_2–hexane, 1:1) was filtered through silica, furnishing, after evaporation, the pure title compounds: benzyl (*S*)- **3a** and (*R*)-2-trifluoromethylsulfonyloxy-4-methylpentanoate **3b** and benzyl (*S*)- **3c** and (*R*)-2-trifluoromethylsulfonyloxy-3-phenylpropanoate **3d** were all pink oils, relevant data for which are given in Table 1.

General Procedure for the Synthesis of N,N-*Bis*-(tert-*Butoxycarbonyl*)[^{15}N]*Amino Acid Benzyl Esters* **4** *and* N-(tert-*Butoxycarbonyl*)[^{15}N]*Amino Acid Benzyl Esters* **5**.—Finely ground dried $^{15}NHBoc_2$ (1.09 g, 5.00 mmol) was dissolved in dry THF (10 cm^3). The subsequent additions of reagent took place with a syringe at −78 °C with rapid stirring under argon. BuLi (1.6 mol dm^{-3} in hexane; 3.00 cm^3, 4.80 mmol) was introduced (30 min) and, after 30 min, the triflate **3** (5.5 mmol) was added slowly to give a pale yellow suspension. When the addition was completed, the temperature was gradually allowed to rise to a predetermined value (in most cases −30 °C, in the case of **4d** also 0 °C) to complete the reaction (at −30 °C, 2–4 h were required to obtain a clear solution, whereas at 0 °C all solid material dissolved immediately). The resulting pale yellow solution was quenched (after 16 h at −30 °C, 2 h at 0 °C) in an ice-cold mixture of ether and 0.2 mol dm^{-3} citric acid (200 and 100 cm^3, respectively). The ethereal extract was washed successively with 0.2 mol dm^{-3} citric acid, 1 mol dm^{-3} $NaHCO_3$ and saturated brine (3 × 50 cm^3 each), dried (Na_2SO_4) and evaporated. The crude product **4** was obtained as a yellow oil and used in the next step without further purification.

Crude **4** from above was dissolved in CH_2Cl_2 (50 cm^3) and

Table 2 Properties of ^{15}N-labelled Boc-amino acids **6** and benzyl esters **5**

	R (config.)	Yield /e.e. (%)	M.p. (°C) [lit.][c]	$[\alpha]_D^{25}$ (c[a]) [lit.][c]	^1H NMR (δ_H, $CDCl_3$, J/Hz) [^{13}C NMR (δ_C, $CDCl_3$, J/Hz)][b]	^{15}N NMR (δ_N, $CDCl_3$)
5a	Bu^i (*R*)	91/—	Oil	+14.3 (1.51[α])	0.92 (6 H, dd, Me), 1.43 (9 H, s, Boc Me), 1.49 (1 H, m, Pr^i), 1.66 (2 H, m, CHCH_2), 4.36 (1 H, pert m, NCH), 4.99 (1 H, dd, $J_{^1H,^1H}$ 8.8, $J^1{}_{^{15}N,^1H}$ 90, NH), 5.13 and 5.18 (2 H, ABq, J_{gem} 12.3, Bzl), 7.34 (5 H, s, Ar) [21.8, 22.7 Me), 24.6 (Pr^i), 28.2 (Boc Me), 41.5 (Bu^i), 52.1 (d, $J^1{}_{^{13}C,^{15}N}$ 13.5, NCH), 66.7 (Bzl), 79.7 (Bu^t), 128.1, 128.2, 128.4, 135.4 (Ar), 155.3 (d, $J^1{}_{^{13}C,^{15}N}$ 25.6, Boc*C*O), 173.3 (ester CO)]	88.8
5b	Bu^i (*S*)	88/—	Oil	−15.4 (1.45[α])		
5c	Bzl (*R*)	85/—	66.5–67.5	+11.9 (1.35[β])	1.41 (9 H, s, Boc Me), 3.08 (2 H, pert t, Bzl), 4.63 (1 H, pert q, CHCO), 5.01 (1 H, dd, $J_{^1H,^1H}$ 8.3, $J^1{}_{^{15}N,^1H}$ 90.9, NH), 5.09 and 5.11 (2 H, ABq, J_{gem} 12.3, Bzl), 7.03–7.37 (10 H, cpl sign Ar) [28.2 (Boc Me), 38.2 (*C*HCH$_2$), 54.4 (d, $J^1{}_{^{13}C,^{15}N}$ 13.4, NCH), 67.0 (CH_2O), 79.8 (Bu^t), 126.9, 128.4, 128.5, 129.3, 135.1, 135.8 (Ar), 155.0 (d, $J^1{}_{^{13}C,^{15}N}$ 25.6, Boc CO), 171.6 (ester CO)]	86.2
5d	Bzl (*S*)	92/—	66–67	−12.1 (1.34[β])		
			[64–65][11]	[−12.8, 2.0[β]][c]		
6a	Bu^i (*R*)	81[d]/99.7	68–72[e]	+24.0 (1.99[γ])	0.96 (6 H, d, Me), 1.45 (9 H, s, Boc Me), 1.56–1.75 (3 H, cpl sign, CHCH_2), 4.13 and 4.32 (1 H, 2 pert q, ~1:2, *Z* and *E* conf'r NCH), 5.01 and 6.35 (1 H, 2 dd, *E* and *Z* conf'r $J^1{}_{^{15}N,^1H}$ 91.7 (*E*), $J^1{}_{^{15}N,^1H}$ 92.1 (*Z*), $J_{^1H,^1H}$ 8.6 (*E*), $J_{^1H,^1H}$ 7.3 (*Z*), NH), ~10.1 (~1 H, br s, CO_2H) [21.7, 22.8 (Me), 24.5, 24.7 (2 s, Pr^i, *Z* and *E* conf'r), 28.3 (Boc Me), 41.4 (Bu^i), 52.0, 53.1 (2 d, *E* and *Z* conf'r, $J^1{}_{^{13}C,^{15}N}$ 12.2 (*E*), $J^1{}_{^{13}C,^{15}N}$ 11.0 (*Z*), NCH), 80.1, 81.6 (2 s, *E* and *Z* conf'r, Bu^t), 155.6, 156.8 (2 d, *E* and *Z* conf'r, $J^1{}_{^{15}N,^1H}$ 25.7, Boc CO), 177.9, 178.2 (*Z* and *E* conf'r, CO_2H)]	89.0 (*E*) 92.3 (*Z*)
6b	Bu^i (*S*)	84[d]/98.7	69–71[e]	−24.1 (1.97[γ])		
			[67–72][12]	[−24, 2.0[γ]][12]		
6c	Bzl (*R*)	80[d]/99.7	211–212[f]	−28.5 (1.0[β])[f]	1.27, 1.41 (9 H, 2 s, *Z* and *E* conf'r, Boc Me), 2.81–3.21 (2 H, cpl sign, Bzl), 4.39, 4.62 (2 pert q, ~2:3, *Z* and *E* conf'r, NCH), 5.08, 6.70 (1 H, 2 dd, *E* and *Z* conf'r, $J^1{}_{^{15}N,^1H}$ 91.4 (*E*), $J^1{}_{^{15}N,^1H}$ 92.5 (*Z*), $J_{^1H,^1H}$ 8.1 (*E*), $J_{^1H,^1H}$ 7.8 (*Z*), NH), 7.17–7.32 (5 H, cpl sign, Ar), ~11.2 (~1 H, br s, CO_2H) [28.0, 28.3 (2 s, *Z* and *E* conf'r, Boc Me), 37.8, 39.1 (2 s, *E* and *Z* conf'r, (Bzl), 54.2, 56.1 (2 d, *E* and *Z* conf'r, $J^1{}_{^{13}C,^{15}N}$ 12.5 (*E*), $J^1{}_{^{13}C,^{15}N}$ 11.0 (*Z*), NCH), 80.2, 81.5 (2 s, *E* and *Z* conf'r, Bu^t), 127.0, 128.5, 128.8, 129.4, 135.9, 136.5 (Ar), 155.3, 156.5 (2 d, *E* and *Z* conf'r, $J^1{}_{^{15}N,^1H}$ 25.7, Boc CO), 176.0, 176.4 (2 s, *Z* and *E* conf'r, CO_2H)]	86.2 (*E*) 90.6 (*Z*)
6d	Bzl (*S*)	88[d]/99.5[g]	210–212[f]	+28.3 (1.0[β])[f]		
			[209–214][13]	[+29.2, 1.02[β]][13]		

[a] The following solvents were used in polarimetry: dichloromethane[α], MeOH[β] and HOAc[γ]. [b] All enantiomers gave identical spectra; br (broad); conf'r (conformer); cpl sign (complex signal); pert (perturbed). [c] Literature data refer to unlabelled compounds; some optical rotations measured at room temperature (in one case 27 °C). [d] Calculated over three steps from $^{15}NHBoc_2$. [e] Boc-Leu × 0.5 H_2O. [f] Dicyclohexylamine salt. [g] Triflate alkylation at 0 °C (quenching temperature) gave the same e.e.

cautiously treated with trifluoroacetic acid (820 mg, 7.20 mmol) in CH_2Cl_2 (5 cm^3) with stirring under nitrogen. After 3 h at room temp., the yellowish solution was partitioned between ether (200 cm^3) and 1 mol dm^{-3} $NaHCO_3$ (100 cm^3). The ether extract was washed in turn with 0.2 mol dm^{-3} citric acid (60 cm^3), 1 mol dm^{-3} $NaHCO_3$ and saturated brine (3 × 60 cm^3 each), dried and evaporated. The resulting yellow oil was chromatographed on silica using ether–light petroleum (1:6) as eluent. Benzyl (*R*)- **5a** and (*S*)-(*tert*-butoxycarbonyl)[^{15}N]leucinate **5b** were obtained as pale yellow oils and benzyl (*R*)-**5c** and (*S*)-(*tert*-butoxycarbonyl)-[^{15}N]phenylalaninate **5d** as white solids. Relevant data for **5a–d** are collected in Table 2.

General Procedure for the Synthesis of N-(tert-*Butoxycarbonyl*)[^{15}N]*Amino Acids* **6**.—Pure **5** from the previous paragraph was dissolved in MeOH (50 cm^3) and hydrogenated at 1 atm in the presence of 5% (w/w) Pd on C (5%). The reaction was carefully monitored by TLC and when it was complete (2–3 h) the catalyst was filtered off and the clear filtrate was taken to dryness. The residual pure oil was crystallized or converted into dicyclohexylamine (DCHA) salt. (*R*)- **6a** and (*S*)-(*tert*-butoxycarbonyl)[^{15}N]leucine **6b** were originally obtained as oils. Recrystallization from EtOH–H_2O (1:2) afforded white shiny flakes. (*R*)- **6c** and (*S*)-(*tert*-butoxycarbonyl)[^{15}N]phenylalanine DCHA-salt **6d** were obtained *via* crude oils. Data on **6a–d** are found in Table 2.

Assessment of Optical Purity of Products **6**.—All products **6**, after deprotection with TFA, were assayed for their optical purity by the Flec-method essentially as described earlier.[1] Although for both leucine and phenylalanine the chromatographic resolution of the pairs of diastereoisomers was much better than for alanine,[1] we preferred always to derivatize with the Flec-Cl enantiomer which ensured that the minor diastereoisomer was eluted before the major one. Peak areas were estimated with an integrator (Shimadzu C-R3A) and corrected using standard curves.

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References

1 F. Degerbeck, B. Fransson, L. Grehn and U. Ragnarsson, *J. Chem. Soc., Perkin Trans. 1*, 1992, 245 (and relevant references cited therein).
2 D. L. Hughes, *Org. React. N.Y.*, 1992, **42**, 335.
3 F. Effenberger, U. Burkard and J. Willfahrt, *Angew. Chem.*, 1983, **95**, 50; *Angew Chem., Int. Ed. Engl.*, 1983, **22**, 65.
4 I. Koppel, J. Koppel, F. Degerbeck, L. Grehn and U. Ragnarsson, *J. Org. Chem.*, 1991, **56**, 7172.

5 P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold and P. A. D. S. Rao, *Nature* (*London*), 1950, **166**, 179.
6 L. K. M. Chan, G. W. Gray, D. Lacey, R. M. Scrowston, I. G. Shenouda and K. J. Toyne, *Mol. Cryst. Liq. Cryst.*, 1989, **172**, 125.
7 T. P. Kogan, T. C. Somers and M. C. Venuti, *Tetrahedron*, 1990, **46**, 6623.
8 K. Mori, *Tetrahedron*, 1976, **32**, 1101.
9 S. G. Cohen and S. Y. Weinstein, *J. Am. Chem. Soc.*, 1964, **86**, 5326.
10 S. Terashima, C. C. Tseng and K. Koga, *Chem. Pharm. Bull.*, 1979, **27**, 747.
11 M. K. Dhaon, R. K. Olsen and K. Ramasamy, *J. Org. Chem.*, 1982, **47**, 1962.
12 G. W. Anderson and A. C. McGregor, *J. Am. Chem. Soc.*, 1957, **79**, 6180.
13 H. Otsuka and K. Inouye, *Bull. Chem. Soc. Jpn.*, 1964, **37**, 1465.

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