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A NOVEL APPROACH TO THE SYNTHESIS OF OPTICALLY PURE NON PROTEIN α-AMINO ACIDS IN BOTH L AND D CONFIGURATIONS FROM L-SERINE

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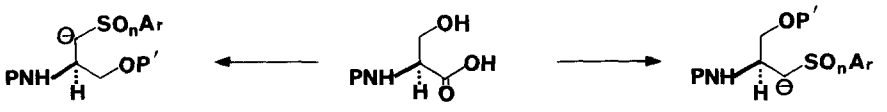
Summary: Efficient syntheses of (2R)-2-Boc-amino-3-phenylsulfonyl-1-propanol **3** and its enantiomer **9** from L-serine are described. The potential of these compounds in a novel general method for the synthesis of optically pure non protein α-amino acids in both the L and D configurations is exemplified by the preparation of N-Boc-L-and D-homophenylalanine, -norvaline and -norleucine.

Interest in non protein α-amino acids is growing because of their potential biological activity. This has prompted many groups in recent years to develop general methods for the synthesis of this class of compounds in optically pure form. One appropriate approach to this end is the transformation of common α-amino acids into new ones with retention of the original configuration (1). Another trend is the diastereoselective alkylation or amination of chiral auxiliaries on the potential α-carbon with enantiomeric excess in more than 95% (2).

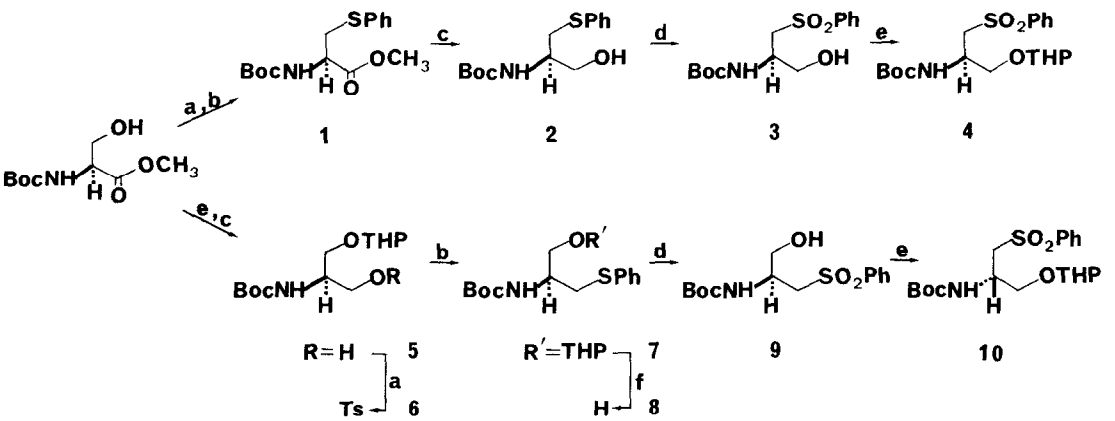
We have designed a new general synthetic methodology in this area by preparing novel chiral synthons which may serve as versatile intermediates in the synthesis of a variety of optically pure non protein α-amino acids in both the L and D configurations. Provided that the hydroxy and carboxylic groups of N-protected L-serine are transformed into an arylsulfonyl (or sulfoxy) group and a protected form of alcohol respectively, a reactive carbanion can be generated by treatment with a strong base. Adducts of the resulting carbanion with electrophiles may in turn be converted to a wide variety of non protein L-α-amino acids depending upon the mode of removal of the sulfonyl (or sulfoxy) group. Furthermore, since the hydroxy and carboxylic groups of this particular amino acid are **a priori** interconvertible to each other, we anticipated that the same approach might consequently lead to non protein α-amino acids in D configuration.



P,P' = protecting group, n = 1,2

In this preliminary report, we wish to describe efficient syntheses of chiral intermediates from L-serine and their facile transformation into N-protected optically pure non protein α-amino acids in both the L and D configurations.

Scheme I summarizes the preparation of the key intermediates **4** and **10** as the THP derivatives in good overall yield (68 - 70%) from L-serine derivative.

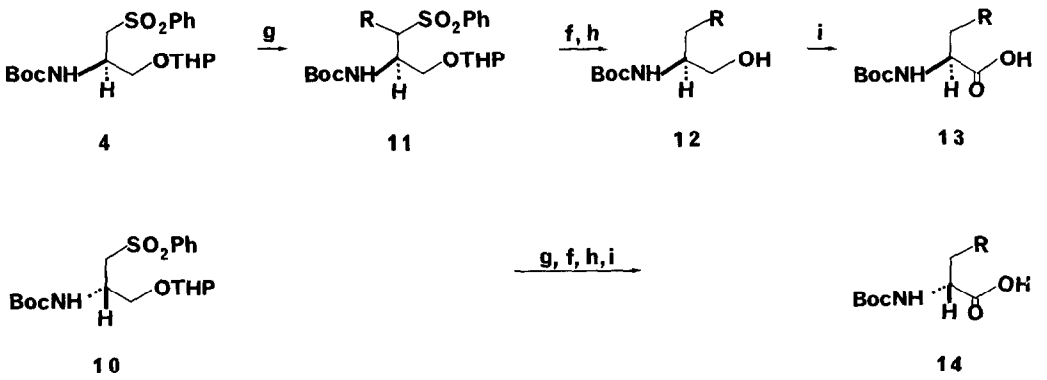


(a) TsCl/pyridine ; (b) NaSPh/DMF, 0°C, 1 h ; (c) 4 equiv $NaBH_4$/MeOH, 25°C, 1 h ; (d) mCPBA/CH_2Cl_2, 25°C, 1 h ; (e) DHP/CH_2Cl_2-PyH·OTs, 25°C, 24 h ; (f) EtOH-PyH·OTs, 60°C, 6 h.

Scheme I

Readily available N-Boc-L-serine methyl ester (3) was transformed into its tosylate (1b) in 90% yield which was then treated at 0°C with sodium thiophenolate prepared **in situ** in DMF to give the phenylsulfide ester **1** in essentially quantitative yield (viscous oil ; $[\alpha]^*_D$ - 19°). Reduction of this methyl ester with $NaBH_4$ resulted in 92% yield of the corresponding alcohol **2** (mp 59-60°C ; $[\alpha]_D$ - 55°). Treatment of the alcohol **2** with 2 equiv of mCPBA gave the sulfone **3** in 93% yield (mp 124-125°C ; $[\alpha]_D$ - 7°) (4). Protection of the hydroxy group of **3** with DHP afforded **4** in 95% yield (mp 103-108°C) (5). The same reaction conditions were applied to the preparation of compounds **5** (mp 85-93°C ; 91% yield in two steps) (6). **6** (mp 85-96°C, 97%) and **7** (mp 69-71°C, 88%). Since treatment of the sulfide **7** with 2 equiv of mCPBA gave only the corresponding sulfoxide in 90% yield, removal of the THP group was required prior to the oxidation to afford the alcohol **8** in a quantitative yield (mp 59-60°C ; $[\alpha]_D$ +57°). The preparation of the compounds **9** (mp 124-125°C ; $[\alpha]_D$ + 7°, 95%) and **10** (mp 102-108°C, 96%) was carried out in the same manner as their antipodes.

The use of the THP derivatives **4** and **10** of (2R)-2-Boc-amino-3-phenylsulfonyl-1-propanol **3** and its enantiomer **9** in the facile four-step synthesis of non protein α-amino acids in both the L and D configurations is illustrated in Scheme II.



(g) 2 equiv n-BuLi/THF, 5 equiv R-Br, -78°C, 2h ;
(h) 6% Na-Hg/MeOH, Na_2HPO_4, 25°C, 24h ;
(i) 5 equiv PDC/DMF, 25°C, 6 h.

Scheme II

In a typical example, a solution of **4** in dry THF was treated with 2 equiv of n-BuLi in hexane at -78°C. To the resulting solution of the dilithio derivative was added 5 equiv of benzyl bromide and the reaction mixture was stirred at -50°C for 2h. The usual work-up and the purification by flash chromatography resulted in 91% yield of the adduct **11** (R = CH_2Ph) (viscous oil). Removal of THP (93% yield) followed by reductive cleavage of the phenylsulfonyl group by 6% sodium amalgam afforded 2-Boc-amino-4-phenyl-1-butanol **12** (R = CH_2Ph) in 92% yield (mp 78-79°C ; $[\alpha]_D$ - 10°) (7). Oxidation of this alcohol by 5 equiv of pyridinium dichromate in DMF at 25°C gave N-Boc-L-homophenylalanine **13** (R = CH_2Ph) in 78% yield (viscous oil ; $[\alpha]_D$ + 6°, c 1, EtOH). N-Boc-D-Homophenylalanine **14** (R = CH_2Ph) was obtained from **10** (viscous oil ; $[\alpha]_D$ -6°, c 1, EtOH, lit(8). $[\alpha]_D$ - 5.6°, c 2, EtOH ; mp 153-154°C as dicyclohexylamine salt, lit(8). mp 153.5-154.5°C as DCHA salt) following exactly the same procedure.

The results of further examples summarized in Table 1 demonstrate the generality and efficient applicability of the method.

	% yield			$[\alpha]_D$		$[\alpha]_D$ of methyl ester	
R	11	12	13	13	14	13	14
C_2H_5	95	86[a]	87	-14	+15	-32(1b)	+32
n-C_3H_7	91	90[a]	81	- 9	+ 9	-25(1b)	+25

[a] Overall yield for two steps

Table 1

The optical purity of **13** (R = CH_2Ph, C_2H_5, n-C_3H_7) and **14** (R = CH_2Ph, C_2H_5, n-C_3H_7) was established as $\geq$ 98.5% by ^{19}F NMR analysis on (+)-α-methoxy-α-trifluoromethyl-phenylacetyl derivatives (9) of these non protein α-amino acids.

Further investigation in the scope and utility of this novel methodology for the synthesis of a variety of optically pure non protein α-amino acids is currently under way in this laboratory.

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3. Best prepared on a large scale from L-serine in 90% yield : (i) $SOCl_2$/MeOH, (ii) di-t-butyl dicarbonate/DMF-Et_3N according to L. Moroder, A. Hallett, E. Wünsch, O. Keller, G. Wersin, **Hoppe-Seylers Z. Physiol. Chem.**, 1976, 357, 1651.
4. IR($CHCl_3$) : 3430, 3400, 1700, 1495, 1365, 1305, 1150 cm^{-1}. ^1H NMR : δ(80 MHz, $CDCl_3$) 7.95 (2H, m, Ar), 7.55 (3H, m, Ar), 5.43 (1H, NH), 4.05 (1H, m, $C\underline{H}CH_2OH$), 3.80 (2H, m, $CHC\underline{H}_2OH$), 3.45 (2H, d, J = 6 Hz, $C\underline{H}_2SO_2Ph$), 1.42 (9H, s, Boc). EIMS : m/z 316.
5. IR($CHCl_3$) : 3440, 1700, 1500, 1365, 1310, 1150 cm^{-1}. ^1H NMR : δ (80 MHz, $CDCl_3$) 7.97 (2H, m, Ar), 7.56 (3H, m, Ar), 5.05 (1H, NH), 4.60-3.30 (8H, m), 1.90-1.20 (6H, m, THP), 1.40 (9H, s, Boc). EIMS : m/z 400.
6. The precursor of compound **5**, N-Boc-O-tetrahydropyranyl-L-serine methyl ester, is prepared in essentially quantitative yield, mp 82-91°C.
7. IR($CHCl_3$) 3400, 3380, 1680, 1480, 1350, 1150 cm^{-1}. ^1H NMR : δ (80 MHz, $CDCl_3$) 7.17 (5H, s, Ar), 4.75 (1H, NH), 3.80-3.37 (3H, m, $C\underline{H}C\underline{H}_2OH$), 2.78 (2H, t, J = 7 Hz, $C\underline{H}_2Ph$), 1.87 (2H, m, $CHC\underline{H}_2CH_2Ph$), 1.45 (9H, s, Boc). EIMS : m/z 265.
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* Unless otherwise mentioned, all $[\alpha]_D$ were measured in MeOH (c 1) at 20°C.

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