Preparation of Optically Active Cyclic Ether Derivatives of Amino Acids and Peptides

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Treatment of *N*-tritylmethioninol (**1**) or peptides (**6**), incorporating methionyl and amino alcohol residues, with MeI, followed by base mediated cyclisation of the thus derived sulphonium salts, provides the title compounds in excellent yields.

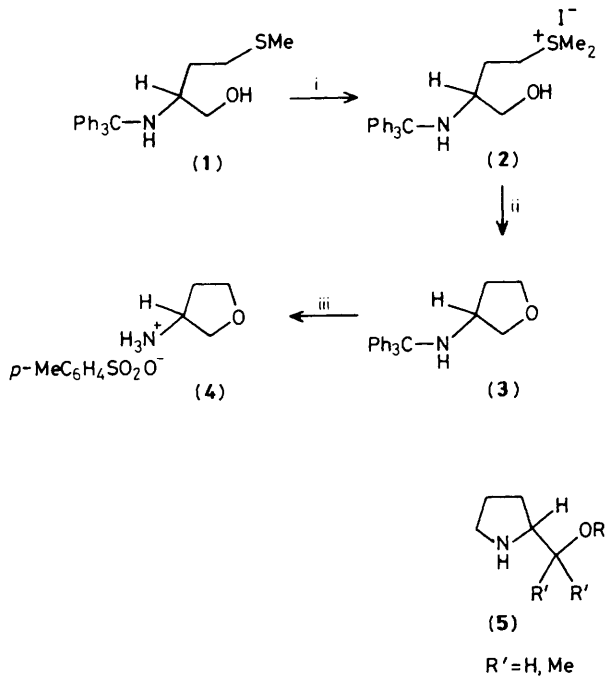
Modifications of naturally occurring amino acids and peptides often produce either a variety of biologically active derivatives or compounds useful in asymmetric synthesis.[1] In this communication we describe a methodology, similar to that used for the preparation of N-protected homoserine lactones,[2] which provides cyclic ethers of amino acids and can be applied to derivatives of methioninol and peptides containing both an amino alcohol at the carboxy terminus of their chain, and a methionyl residue. The significance of the described modification is exemplified by the simple preparation for the first time of the cyclic compounds 3-aminotetrahydrofurans (**3**) and 3-alkyl-6-tritylamino-1,4-oxazocanes (**7**) according to Schemes 1 and 2 respectively.†

For our initial studies *N*-tritylmethioninol[3] (**1**) and β-(*N*-tritylmethionyl)amino alcohols (**6a—c**), prepared in an analogous manner to that described for the synthesis of N-trityl protected peptides,[4] were employed as starting materials. Our cyclisation methodology includes methylation of (**1**) or (**6**) with an excess of MeI in refluxing ethyl acetate, thus producing the corresponding sulphonium salts, which in turn are cyclised upon treatment with NaH in dimethylformamide (DMF) at −10 °C or Bu^{t}OK in tetrahydrofuran (THF) at −15 °C to give the cyclic ethers (**3**) and (**7**). Detritylation of (**3**) and (**7**) affords the corresponding ammonium salts (**4**) and (**8**) in 90% and 63—80% overall yields respectively (Table 1).

A typical sequence of procedures for the synthesis of such compounds is exemplified by the preparation of (**4a**). Thus (**1a**) (6.8 g, 18 mmol) and MeI (5.6 ml, 90 mmol) were heated to reflux for 2 h in ethyl acetate (30 ml) to give (**2a**) {m.p. 138—139 °C, $[\alpha]_D^{25}$ +30.8° (*c* 2, DMF)} in 95% yield. Then (**2a**) (8.9 g, 17.10 mmol) was suspended in dry THF (30 ml) and treated with Bu^{t}OK (2.5 g, 22 mmol) for 20 min at −15 °C to afford (**3a**). Finally (**3a**) (5.5 g, 16.76 mmol) was treated with *p*-$MeC_6H_4SO_2OH \cdot H_2O$ (9.5 g, 50 mmol) in refluxing MeOH (100 ml) for 10 min. Concentration under reduced pressure and trituration with diethyl ether gave 4.0 g of (**4a**).

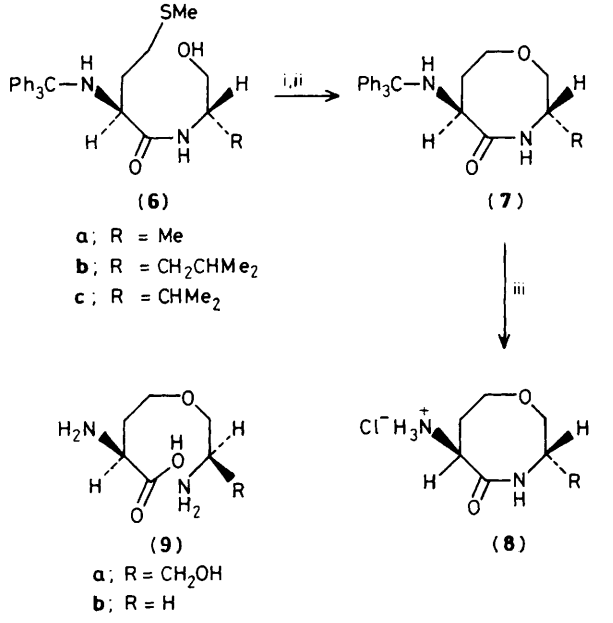
The cyclisation reactions proceed quantitatively, as shown by t.l.c. and h.p.l.c. analysis of the crude reaction products (**3**) and (**7**). In addition, h.p.l.c. analysis of the diastereoisomeric

† Unless otherwise indicated all optically active amino acids and derivatives referred in this communication are of the (*S*) configuration. New compounds gave analytical and spectral data in agreement with the proposed structures.



a; (*S*)-isomer
b; (*R*)-isomer

Scheme 1. *Reagents:* i, MeI; ii, NaH or Bu^{t}OK; iii, *p*-$MeC_6H_4SO_2OH \cdot H_2O$.



Scheme 2. *Reagents:* i, MeI; ii, NaH or Bu^{t}OK; iii, HCl–Et_2O.

amides (*S*)-*N*-tritylphenylalanyl-(*S*)-3-aminotetrahydrofuran, prepared by coupling[4] (*S*)-*N*-tritylphenylalanine benzotriazolyl ester with (**4a**) and (**4b**) respectively, clearly showed the excellent (≥99.9%) optical purity of (**4**).

Table 1. Yields, m.p.s, and optical rotations for compounds (**3**), (**4**), (**7**), and (**8**).

	% Yield	m.p./°C	$[\alpha]_D^{25}$
(**3a**)	98	132	+10.9(*c* 2, $CHCl_3$)
(**3b**)	97	103—131	−10.8 (*c* 2, $CHCl_3$)
(**4a**)	92	140	−4.4 (*c* 1, MeOH)
(**4b**)	90	137—138	+4.5(*c* 1, MeOH)
(**7a**)	70	85—87	−123.8 (*c* 1, MeOH)
(**7b**)	78	foam	—
(**7c**)	86	foam	—
(**8a**)	90	126	−47.1 (*c* 0.5, MeOH)
(**8b**)	95	181—183	−34.4 (*c* 1, MeOH)
(**8c**)	93	180	−55.1 (*c* 1, MeOH)

The structural analogy of (**4**) to the well known prolinol derivatives (**5**)‡ is promising for the application of (**4**) in asymmetric synthesis. Since the amino function can be stereoselectively transformed to hydroxy or halogen groups,[6] (**4**) can provide an entry to such 3-substituted chiral tetrahydrofurans. Hydrolysis of the lactams (**8**), expected to proceed readily, will give access to interesting homoserine derivatives bearing close resemblance to the naturally occurring amino acids dihydrorhizobitoxine[7] (**9a**) and *O*-aminoethyl-homoserine (**9b**). These compounds and other achiral derivatives of (**9b**) are of biological and economic importance, being useful in retarding the ripening of fruits, prolonging the life of cut flowers, and preventing or promoting bind break in fruit trees.[8]

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‡ Prolinol derivatives (**5**), have been extensively used in asymmetric synthesis. For some recent publications see ref. 5.