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# A Diastereoselective Radical Cyclisation Approach to Pyroglutamates

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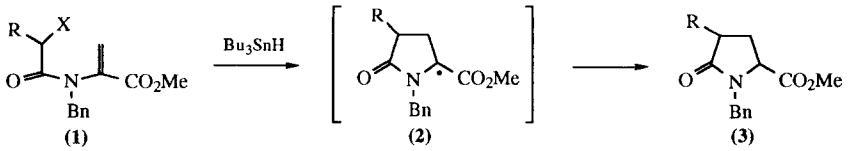
***Abstract:*** *The 5-endo radical cyclisation of pyruvic acid derived dehydroalanines which contain chiral ester auxiliaries is reported. Cyclisation of the menthol ester derivative using $Bu_3SnH$ at 80°C proceeded with low diastereoselectivity (1.75:1) but the selectivity could be increased to 6:1 on cyclisation of the corresponding 8-phenylmenthyl ester at 20°C.* Copyright © 1996 Elsevier Science Ltd

The control of stereochemistry in free radical reactions has attracted considerable recent interest.[1] Examples of diastereoselective radical cyclisations,[2] reactions of cyclic radicals[3] and acyclic diastereocontrol[4] have all been reported in recent years. One method for achieving stereocontrol involves the use of chiral auxiliaries which can differentially shield the diastereotopic faces of the prostereogenic radical centre. This is only possible when the orientation of the resident chiral group is fixed relative to the prostereogenic centre. Amide and imide auxiliaries are thus commonly employed where conformational control is achieved through either $C_2$ symmetry, chelation, dipole-dipole repulsion, H-bonding or steric considerations.[1,2] The application of ester-based auxiliaries is less commmon because of the difficulty in controlling the ester conformation and early studies gave poor to modest levels of asymmetric induction.[5] However, substantially better selectivities have recently been reported for both inter-[6] and intramolecular[2,7] radical reactions using predominantly 8-phenylmenthyl esters. We now wish to describe the novel application of chiral ester auxiliaries in the asymmetric synthesis of pyroglutamates formed on *endo* radical cyclisation of *N*-acyl dehydroalanine derivatives.[8]

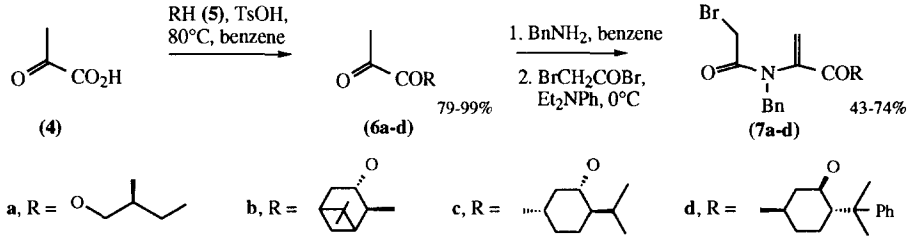
Recently, we reported[9] the regioselective 5-*endo-trig* radical cyclisation of dehydroalanines of type **(1)** to racemic pyroglutamates **(3)** mediated by $Bu_3SnH$ (scheme 1). We envisaged that this methodology could be extended to the preparation of chiral pyroglutamates using an ester auxiliary to control the delivery of the hydrogen atom (from $Bu_3SnH$) to the intermediate captodatively stabilised radical **(2)**.



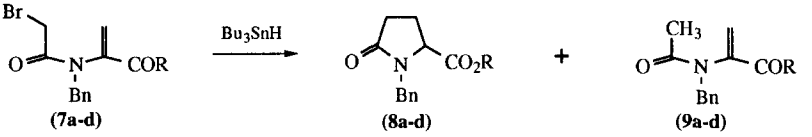

**SCHEME 1**

Initial studies concentrated on the development of a new and quick approach to the chiral ester precursors **(7a-d)** from pyruvic acid **(4)** (scheme 2). This involved the acid catalysed esterification[10] of **(4)** using

commercially available alcohols **(5a-d)**[11] to afford pyruvates **(6a-d)**.[12] Reaction of **(6a-d)** with benzylamine (under anhydrous conditions using a Dean and Stark trap) was immediately followed by *N*-acylation of the resultant enamine, using bromoacetyl bromide[13] and *N,N*-diethylaniline[14] at 0°C, to give the desired dehydroalanines **(7a-d)** in 43-74% yield.




**SCHEME 2**




| Entry | Bromide (7) | Reaction Conditions | Products (yield %) | Pyroglutamate (8) diastereomer ratio* |
|---|---|---|---|---|
| 1 | **a** | AIBN, Benzene, 80°C | **8a** (52) + **9a** (22) | 1:1 |
| 2 | **b** | AIBN, Benzene, 80°C | **8b** (47) + **9b** (21) | 1:1 |
| 3 | **c** | AIBN, Benzene, 80°C | **8c** (62) + **9c** (21) | 1.75:1 |
| 4 | **c** | $Et_3B$, Toluene, 60°C | **8c** (52) + **9c** (22) | 1.5:1 |
| 5 | **c** | $Et_3B$, Toluene, 40°C | **8c** (36) + **9c** (31) | 1.5:1 |
| 6 | **c** | $Et_3B$, Toluene, 20°C | **8c** (21) + **9c** (34) | 1.5:1 |
| 7 | **c** | $Et_3B$, Toluene, 0°C | **8c** (16) + **9c** (21) | 1.5:1 |
| 8 | **d** | AIBN, Benzene, 80°C | **8d** (69) + **9d** (15) | 4:1 |
| 9 | **d** | $Et_3B$, Benzene, 20°C | **8d** (22) + **9d** (9) + **13** (32)‡ | 6:1 |
| 10 | **d** | $Et_3B$, Toluene, 20°C | **8d** (25) + **9d** (9) + **13** (31)‡ | 6:1 |

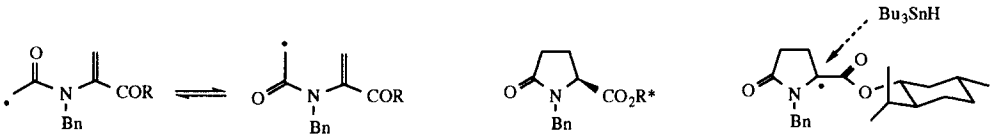
*Isomer ratio determined from the NMR spectra. ‡Isolated as a 2:1 mixture of diastereomers.

**TABLE**

Reaction of the butanoate **(7a)** with $Bu_3SnH$ (1.1eq) and AIBN (0.1eq) in boiling benzene gave the *N*-acetyl derivative **(9a)** (resulting from simple bromoamide reduction), and the desired pyroglutamate **(8a)**, in 22 and 52% yield respectively (table, entry 1). However, analysis of the $^1H$ NMR spectrum of **(8a)** clearly showed the formation of both diastereomers of **(8a)** (which were inseparable by column chromatography) in equal amounts. A similar result was realised on cyclisation of the isopinocampheol derived precursor **(7b)** which gave the pyroglutamate **(8b)** in 47% yield as a 1:1 mixture of diastereomers (entry 2). More promising results were obtained using the menthol ester precursor **(7c)** (entries 3-7) and reaction at 80°C gave **(8c)** as a 1.75:1 mixture of diastereomers (28% d.e.) in 62% yield. Changing the reaction temperature to 60°C (and using $Et_3B$ as the initiator) led to a slight decrease in the diastereoselectivity to 1.5:1 and no improvement was

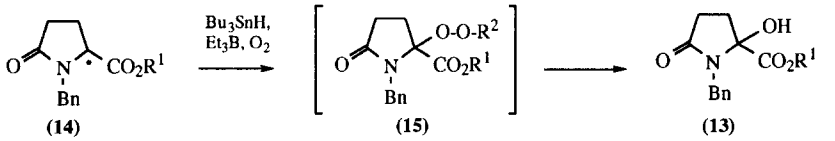
observed when lowering the temperature further (to 0°C). The efficiency of the cyclisation was shown to be strongly dependant on the reaction temperature and this was thought to be the result of the change in amide conformer population of intermediate carbamoylmethyl radical **(10c)** derived from precursor **(7c)**.[15] At 80°C free rotation about the amide bond of **(10c)** is possible [and observed in the $^1$H NMR spectrum for **(7c)**] and the pyroglutamate **(8c)** can be isolated in good yield (62%). Lowering the reaction temperature will lead to a decrease in the rate of rotation and the population of the *syn* rotamer **(10c)-*syn***, which cannot cyclise, is expected[15] to increase. The fact that cyclisation can occur at low temperature can be attributed to the presence of a bulky *N*-benzyl group which gives rise to a higher proportion of the the *anti* rotamer **(10c)-*anti*** than would be expected with smaller protecting groups.

Comparison of the $^1$H and $^{13}$C NMR spectra of **(8c)** with an authentic sample of menthol (2*S*)-*N*-benzylpyroglutamate **(11)** (prepared by esterification[16] and *N*-benzylation[17] of L-pyroglutamic acid) showed that this was the major diastereomer formed. This could be explained by preferential approach of tributyltin hydride to transition-state **(12)**, the conformation of which is controlled by dipole-dipole repulsion.[18]




**(10c)-*syn*** **(10c)-*anti*** **(11)** R*= (+)-menthyl **(12)**

Cyclisation of the 8-phenylmenthyl ester **(7d)** gave rise to more pronounced diastereoselectivities. Reaction at 80°C afforded the cyclised product **(8d)** in 69% yield as a 4:1 mixture of diastereomers which were inseparable on column chromatography (entry 8). The *N*-acetyl by-product **(9d)** was also formed in 15% yield. The diastereoselectivity of the process could be improved even further to 6:1 (71% d.e.) by lowering the reaction temperature to 20°C (entries 9-10). Cyclisation in toluene or benzene gave rise to **(8d)** in 22-25% yield while **(9d)** was only isolated in 9% yield. Both reactions also gave rise to the formation of an additional and unexpected product which on spectroscopic analysis was assigned the structure **(13)**. The surprising formation of this α-hydroxypyroglutamate[19] in 31-32% yield (as a 2:1 mixture of diastereomers) could result from reaction of intermediate radical **(14)** with molecular $O_2$[20] (which is essential for initiation) or with $Et_2BO_2^{\bullet}$ (derived from $Et_3B$ and $O_2$[21]) followed by $Bu_3SnH$ reduction of the resultant peroxide **(15)** (scheme 3).




**(14)** **(15)** **(13)**

$R^1$= (-)-8-phenylmenthyl; $R^2$= $BEt_2$ or H

**SCHEME 3**

This work has demonstrated the potential use of chiral ester auxiliaries for the stereocontrol of radical cyclisation reactions[22] leading to pyroglutamates. We are currently investigating further applications of this methodology and exploring the synthetic utility of captodative radicals of type **(2)**.

### Typical Cyclisation Procedure

*Initiation using $Et_3B/O_2$*: To a stirred 0.024 mol dm$^{-1}$ solution of the alkene **(7c-d)** (0.09-0.30 mmol) in toluene or benzene at 60-0°C was added a 0.014 mol dm$^{-1}$ solution of $Bu_3SnH$ (1.1eq.) and $Et_3B$ (0.1eq, 0.1M solution

in THF) *via* a syringe pump over 1h. After 3-48h, TLC analysis showed disappearance of starting material and the solvent was removed *in vacuo*. Diethyl ether (10ml) and aqueous KF (8%, 10ml) was added to the residue and the mixture was stirred for 2 h. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford crude product which was purified by flash column chromatography (silica).

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11. (*S*)-(-)-2-Methyl-1-butanol, (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheol and (1*S*,2*R*,5*S*)-(+)-menthol were purchased from Fluka Chemicals. (+)-8-Phenylmenthyl chloroacetate, which was hydrolysed (KOH, EtOH, reflux) to (-)-8-phenylmenthol, was purchased from the Aldrich Chemical Company.
12. All new compounds exhibited satisfactory spectral and analytical (high resolution mass) data.
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