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Asymmetric Synthesis from α-Amino Acids; Some Reactions of (S)-Pyroglutamate

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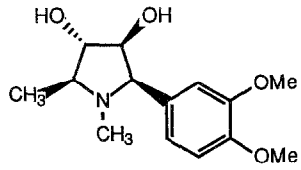
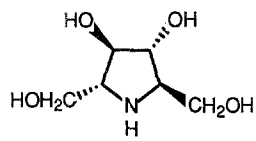
Key Words: amino acids; pyroglutamate; asymmetric synthesis.

Abstract: Reactions at C-3, C-4, and C-5 of pyroglutamate derivative (**10**) are presented.

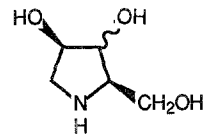
The use of α-amino acids as starting materials for the synthesis of enantiomerically-pure compounds has been well documented[1]. In comparison to carbohydrates which are generally overburdened with secondary alcohol chiral centres, the single chiral centre present in the naturally-occurring α-amino acids provides a more flexible starting point for asymmetric synthesis. Our interest in this area developed from a desire to synthesise biologically-active pyrrolidine derivatives such as codonopsine (**1**)[2], and the hydroxylated pyrrolidines (**2**), (**3a**) and (**3b**) which act as inhibitors of various glycosidases[3]. The outstanding work of Stork[4] and Hanessian[5] utilising stereocontrolled reactions of butenolide derivatives to control acyclic stereochemistry encouraged us to look at similar reactions on the pyroglutamate skeleton (**4**). Recent work on reactions of related pyroglutamate derivatives[6] prompts us to reveal our own results in this area.



(**1**)



(**2**)

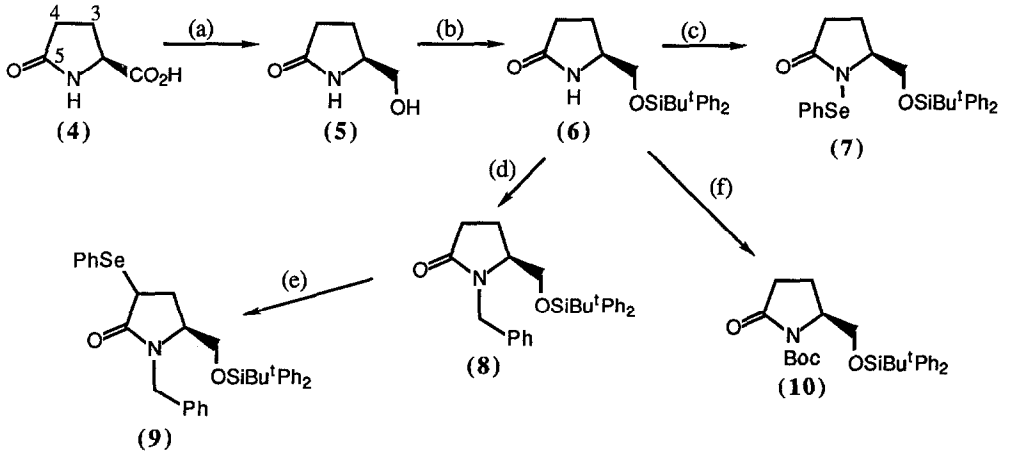


(**3**) a : α-OH
b : β-OH

Functionalisation at C-3 and C-4

In order to functionalise at C-3 and C-4 of the pyroglutamate skeleton, we decided to introduce a double bond at these positions. Starting with pyroglutamic acid (**4**), reaction with thionyl chloride and methanol gave the methyl ester which was reduced with sodium borohydride to give the alcohol (**5**)[7] in 98% yield (Scheme 1). The alcohol was protected with Bu^tPh_2SiCl to give the silyl ether (**6**) in 89% yield. Reaction of (**6**) with

two equivalents of lithium diisopropylamide (LDA) and phenylselenyl chloride in THF at low temperature[8] gave none of the desired C-4 phenylselenyl derivative but instead led to the unstable N-phenylselenyl derivative (**7**). Clearly protection of the lactam nitrogen is required and we turned firstly to the N-benzyl derivative (**8**) which was prepared in 86% yield by reaction of (**6**) with NaH and benzyl bromide in DMF. Treatment of benzyl lactam (**8**) with LDA and phenylselenyl chloride gave only a low yield of the C-4 selenated product (**9**). Model reactions using *N*-benzyl-2-pyrrolidone under similar conditions, led to the isolation of an unstable bis-phenylselenyl derivative carrying the phenylselenyl moieties at C-3 and on the benzylic carbon. This unusual product has precedent in the work of Meyers and Still[9] on medium ring lactams which undergo base-promoted alkylation on the N-benzyl group but, as far as we are aware, this behaviour is unknown in 5-membered ring lactams[10]. We believe that the problems associated with phenylselenylation of (**8**) under these conditions stem from competitive benzylic deprotonation. We finally turned to the *tert*-butoxycarbonyl (Boc) group for N-protection. Reaction of (**6**) with di-*t*-butyl dicarbonate in the presence of DMAP[11] gave the Boc-derivative (**10**) in 83% yield. The enolate chemistry of the Boc-derivative (**10**) proved to be much more predictable.

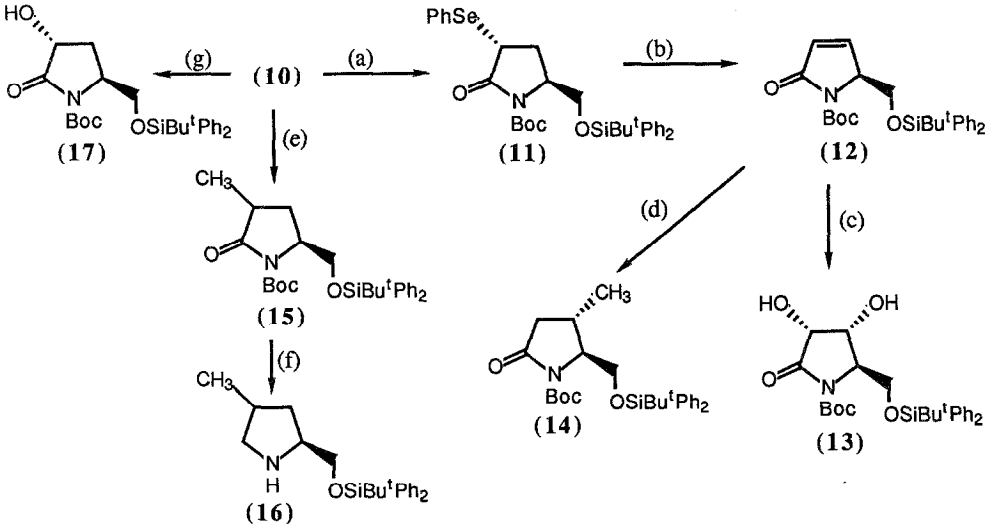


(a). 1. $SOCl_2$, MeOH; 2. $NaBH_4$ (98%). (b). Bu^tPh_2SiCl, imidazole, CH_2Cl_2 (89%). (c). 2LDA, PhSeCl, THF, -78°C (64%). (d). NaH, $PhCH_2Br$, DMF (86%). (e). LDA, PhSeCl, THF (23%). (f). $O[CO_2Bu^t]_2$, CH_2Cl_2, DMAP (83%).

SCHEME 1

Phenylselenation of (**10**) was achieved in high yield under standard conditions (LDA, PhSeCl, THF, -78°C) to give the 4R-enantiomer (**11**) in 74% yield along with 12% of the 4S-enantiomer [Scheme 2]. Treatment of (**11**) with hydrogen peroxide (-78°C to 0°C) gave the α,β-unsaturated lactam (**12**) via oxidation to the selenoxide followed by elimination. Osmylation of lactam (**12**) under catalytic conditions gave the *cis*-diol (**13**) as a single isomer in 57% yield. Epoxidation of (**12**) under a variety of conditions in an attempt to prepare the *trans*-diol proved unsuccessful. However, the unsaturated lactam (**12**) did undergo Michael addition with Me_2CuLi in high yield (84%) to give the 3S-enantiomer. Alkylation of the enolate of lactam (**10**) with methyl iodide gave the 4-methyl derivative (**15**) as a separable 6:1 (α:β) mixture. Removal of the Boc group from (**15**) using TFA followed by reduction of the lactam gave the pyrrolidine (**16**) in 55% yield.

The enolate of (**10**) could also be hydroxylated by reaction with MoOPH at -44°C to give the 4R-enantiomer (**17**) in 57% yield. These sequences demonstrate that functionalisation at C-3 and C-4 of pyroglutamate is feasible using the Boc protecting group on the nitrogen.



(a). LDA, PhSeCl, THF, -78°C (86% combined yield). (b). H_2O_2, Pyridine/CH_2Cl_2, -78 to 0°C (90%). (c). OsO_4, NMO, (57%). (d). Me_2CuLi, ether, -78°C (84%). (e). LDA, THF, -78°C then MeI (72%). (f). 1.TFA/CH_2Cl_2, RT. 2. BH_3DMS, THF, (55%). (g) LDA, THF, -78 to -44°C then MoOPH (57%).

SCHEME 2

Functionalisation at C-5

We next turned our attention to reactions at the lactam carbonyl (C-5). It has recently been reported that Grignard reagents react with N-Boc protected lactams to yield ring opened products which can be reductively recyclised to yield cyclic amines[12]. Treatment of (**10**) with MeMgBr gave the methyl ketone (**18**) in good yield. Reaction of (**18**) with TFA followed by $NaCNBH_3$ gave the 2,5-disubstituted pyrrolidine (**19**) in an overall yield of 60%. Under these conditions (**19**) was obtained as a 2:1 mixture of diastereomers. However reduction with Dibal following removal of the Boc-group gave a 10:1 mixture of diastereomers. We believe the major isomer obtained in these reductions is the 5S-enantiomer (i.e. 2,5-*cis* relative stereochemistry) based on analogy with recent reductions of related imines[13]. Reaction of (**10**) with vinyl magnesium bromide gave the α,β-unsaturated ketone (**20**) in 63% yield . Reduction to the allylic alcohol (**21**) was readily accomplished using $NaBH_4/CeCl_3$ in 90% yield. It is hoped that functionalisation of the double bond will allow recyclisation to give substituted piperidines. Finally, we reacted (**10**) with the anion derived from 1,3-dithiane. Again the reaction proceeded smoothly to give α-ketodithiane (**22**) in 89% yield. These reactions show clearly that functionalisation at C-5 of pyroglutamate is possible via this approach.

Acknowledgements

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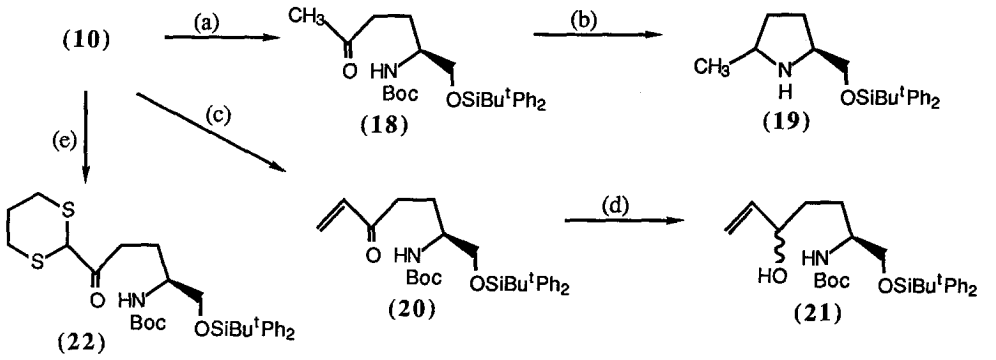

(a). MeMgBr, ether. (b). 1. TFA, RT. 2. NaOH (2M), stir 1hr (75% from (10)). 3. $NaCNBH_3$ (60%), or Bu^i_2AlH, toluene (56%). (c). VinylMgBr, THF (63%). (d). $NaBH_4$, $CeCl_3$, MeOH, 0°C (90%). (e). 2-lithio-1,3-dithiane, THF, -78°C (89%).

SCHEME 3

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