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A Simple Route To 4-Substituted-3,4-Didehydroprolines. Mechanistic Probes For The Inhibition of Prolyl-4-Hydroxylase.

Ari M.P. Koskinen*, Jörg Schwerdtfeger and Michael Edmonds

Department of Chemistry, University of Oulu, Linnanmaa, FIN-90570 Oulu, FINLAND

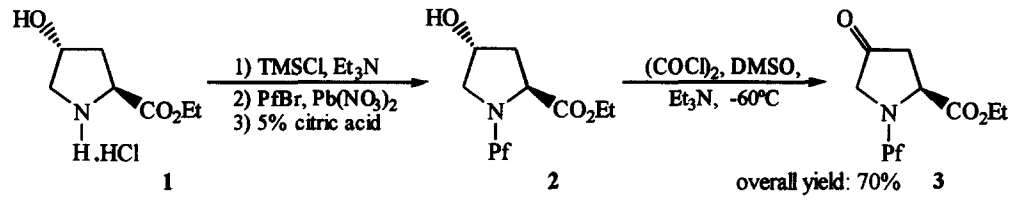
Abstract: Treatment of the 9-phenylfluoren-9-yl (Pf) protected 4-oxo-proline-ethyl ester (6) with NaHMDS and *N*-(5-chloro-2-pyridyl)triflimide gives the corresponding enoltriflate in good yield. Pd mediated coupling of the triflate with trimethylalkyltin, trimethylaryltin, trimethylalkenyltin and carbon monoxide proceeds to give the 4-substituted-3,4-didehydroprolines.

Proline is known to be unique among the natural amino acids in its abilities to induce β-turns and initiate the folding of an α-helix. Because of these structurally important properties, proline is often suggested as the primary contributor to the biological activity of several proteins, as well as having a key role in biological recognition phenomena.[1] Recently, several approaches have been described for the synthesis of 3,4-didehydroproline derivatives[2] and 4-alkylidene proline derivatives which have been implicated as possible mechanistic probes and drug design leads.[3] Didehydroproline derivatives have also found use as starting materials for kainic acid derivatives.[4]

Prolyl 4-hydroxylase plays a central role in collagen biosynthesis, as the 4-hydroxyproline residues it produces are an absolute requirement for the folding of the newly synthesised procollagen polypeptide chains into triple helical molecules.[5] Lack of hydroxylation leads to a non-functional protein that is rapidly degraded. This crucial role of 4-hydroxyproline in collagen synthesis makes prolyl 4-hydroxylase an interesting target for the study of its mechanism, as well as a potential target for pharmacological modulation of the excessive collagen formation symptomatic of a number of disease states (e.g. fibrosis of the liver, heart, kidneys and lungs, rheumatoid arthritis, scleroderma).[6] Prolyl 4-hydroxylase hydroxylates proline residues in fragments as small as tripeptides. This observation is particularly important in the context of synthesising peptide chains containing proline derivatives as mechanistic probes or inhibitors.

Trans-4-hydroxyproline derivatives have provided a convenient starting point for the synthesis of both unsubstituted and 3,4-disubstituted-3,4-didehydroproline derivatives.[7] However, the synthesis of 4-substituted-3,4-didehydroproline compounds has thus far been restricted to 4-aryl derivatives.[4] In this paper, we wish to report results which describe a general and efficient strategy for the synthesis of 4-substituted-3,4-didehydroproline derivatives in enantiopure form starting from trans-4-hydroxyproline.

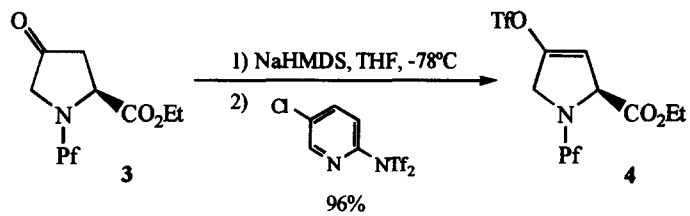
Central to our methodology is the formation of triflate **4** (Equation 1). In order to limit the possibility of non-regioselective enolisation and racemisation of the ester functionality under the basic reaction conditions required for triflate formation, the sterically demanding and highly efficient N-protecting 9-phenylfluoren-9-yl (Pf) group[8] was employed. Use of the Pf group to effect regioselective enolisation is supported by recent literature.[9]



Scheme 1

N-protection of the ethyl ester hydrochloride **1** with 9-bromo-9-phenylfluorene formed the *N*-9-phenylfluoren-9-yl protected alcohol **2** (94%, m.p. 128.5-129.5 °C, $[\alpha]_D^{20}$ = +141.5 (*c* = 2.3, $CHCl_3$).[10] Treatment of alcohol **2** with PCC[11] proved low yielding (21%), however, under Swern conditions[12] oxidation was achieved to afford ketone **3** in an overall yield of 70% (m.p. 170.5-171.5 °C, $[\alpha]_D^{20}$ = -35.4 (*c* = 2.8, $CHCl_3$). (Scheme 1).

The introduction of the Pf group has a twofold effect; protection of the hydrogens at positions 2 and 5 from attack by the base employed to enolise ketone **3**, thus assuring not only the regioselectivity of the ketone enolisation towards C-3, but also preservation of the chirality at C-2 as well.[9] Furthermore, we envisage that the presence of the Pf group would be beneficial in providing diastereofacial hydrogenation of the 3,4 double bond of compounds **5a-e**.[13]

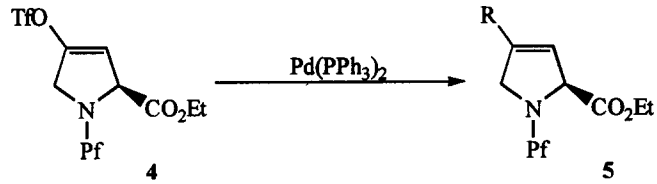


Equation 1

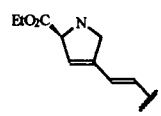
Treatment of ketone **3** with 1.2 eq. NaHMDS at -78°C, followed by addition of 5-chloropyridyltriflimide[14] gave the desired enoltriflate **4** as the only regioisomer in nearly quantitative yield after chromatography on silica gel (96%, mp 69.5-70.5 °C, $[\alpha]_D^{20}$ = +88.0 (*c* = 2.3, $CHCl_3$).

Triflimide **4** was then reacted with organotin compounds[15] or carbon monoxide in the presence of an appropriate nucleophile,[16] to afford the title compounds **5a-e** in adequate to excellent yields (Table 1). The synthesis of the 4-methyl-3,4-didehydro compound **5d** proved to be capricious on occasion affording yields between 5 and 10%.

Table 1: Synthesis of 4-Substituted-3,4-Didehydroprolines



4 5

Compound	R	Yield (%)	Reaction Conditions
5a	CO_2H	87	CO/KOAc, DMF, 66h, rt
5b	CO_2Me	81	CO/MeOH, DMF, 2h, reflux
5c	Ph	60	$PhSnMe_3$, THF, 16h, reflux
5d	Me	5-50	$SnMe_4$, THF, 48h, reflux
5e		40	$Bu_3SnCH{=}CHSnBu_3$, THF, 48h, reflux

In conclusion, a general and efficient strategy for the synthesis of enantiopure 4-substituted-3,4-didehydroproline derivatives from *trans*-4-hydroxyproline has been developed. Application of this methodology to the synthesis of potential inhibitors and mechanistic probes of prolyl-4-hydroxylase is now underway.

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