Pergamon

Tetrahedron Letters 42 (2001) 8571–8573

TETRAHEDRON LETTERS

Enantioselective approach to 3-substituted prolines

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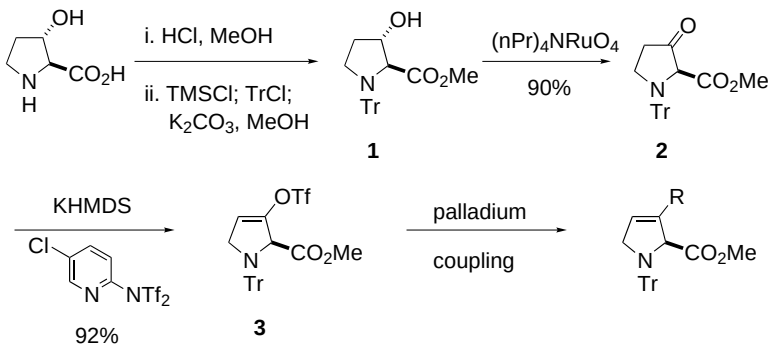
Received 17 August 2001; accepted 25 September 2001

Abstract—Enantioselective synthesis of 3-substituted prolines was achieved starting from commercially available 3-hydroxy-(*S*)-2-proline. Palladium-mediated couplings were used to introduce a variety of groups at C3 using the corresponding enol triflate derived from *N*-trityl 3-oxo-(*S*)-2-proline methyl ester. Cleavage of the trityl residue and hydrogenation provided final products with good to modest diastereoselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

Introduction of rigidity into bioactive peptides has been a useful tool to study the conformational requirements for biological activity.[1] Proline is well known for its ability to introduce conformational restrictions into bioactive peptides by forming *cis* peptide bonds which can induce the formation of β-turns as well as influence protein folding.[2,3] Replacement of proline with substituted analogs provides additional information about receptor recognition and affinity. Despite the growing interest in using substituted prolines as molecular probes, there are few practical methods to prepare them.

Recently, we had the need for a number of 3-substituted proline derivatives in enantiomerically pure form. Although there are several literature procedures for their synthesis, none of them proved optimal.[4a–f] Most approaches start with acyclic precursors and require several steps for each individual substrate. Furthermore, many of these routes provide racemic material that needs to be resolved at a later stage. We desired an approach which would provide rapid access to a variety of analogs from a common intermediate in enantiomerically pure form. Herein, we describe such a convergent approach starting from commercially available 3-(*R*)-hydroxy-2-(*S*)-proline (Scheme 1).

Esterification and trityl protection of 3-hydroxyproline afforded hydroxyester **1** uneventfully. Oxidation using catalytic TPAP provided ketone **2**. This β-ketoester was deprotonated with KHMDS and trapped as its enol triflate to give the Δ 3-olefin.[5] The regioselectivity of the triflate formation is surprising given the lower pK_a of the proton at C2, however, trityl protection of α-amino esters is known to shield the chiral center from deprotonation.[6a–c] This enol triflate smoothly participates in a number of palladium-mediated couplings as illustrated in Table 1.



Scheme 1.

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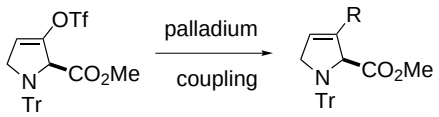
PII: S0040-4039(01)01869-X

Table 1.



3 **4a-j**

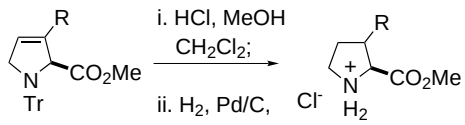
Reagent	Product	Yield[c] (%)
4-MeO_2CPh-X[a,b]	4-MeO_2CPh (**4a**)	84
Ph-X	Ph (**4b**)	74
4-Pyridyl-X	4-Pyridyl (**4c**)	44
trans-Hexenyl-X	1-*E*-Hexenyl (**4d**)	88
3-Thiophenyl-X	3-Thiophenyl (**4e**)	57
p-Tolyl-Y	*p*-Tolyl (**4f**)	70
Vinyl-Y	Vinyl (**4g**)	86
Me-Y	Me (**4h**)	65
Me_3Sn-Y	$SnMe_3$ (**4i**)	54
CO, MeOH	CO_2Me (**4j**)	67

[a] X = $B(OH)_2$, Y = $SnMe_3$.
[b] Proline benzyl ester was used in this case.
[c] Yields are unoptimized.

A variety of palladium mediated couplings were examined and gave good to modest yields of coupled products.[7,8] Suzuki couplings of aryl and vinyl boronic acids proceeded smoothly as did a number of Stille couplings of both aryl and alkyl stannanes.[9,10] Conversion of the enol triflate to the vinyl stannane **4i** was also feasible and may thereby expand the utility of this substrate in palladium mediated reactions. Lastly, standard carbonylation proved uneventful giving the diester **4j**. These examples attest to the versatility of **3** as a willing partner in palladium-catalyzed couplings.

Catalytic hydrogenation of the coupled products saturated the olefin and cleaved the trityl protecting group giving 3-substituted proline methyl esters in good yield (Table 2). Unexpectedly, varying degrees of diastereoselectivity were observed with several substrates with no clear trend.[11] To find a more general procedure, the trityl group was removed with HCl(g) in MeOH and the crude amine salts were subjected to hydrogenation. This procedure consistently provided the 2,3-*cis* product as the major diastereomer.[12] One possible

Table 2.



4 **5**

Structure	R	Product	*cis*/*trans*[a]
4b	Ph	**5b**	>15:1
4d	2-Hexenyl	**5d**[b]	4:1
4e	3-Thiophenyl	**5e**	13:1
4h	Me	**5h**	5:1
4j	CO_2Me	**5j**	2:5:1

[a] As determined by ^1H NMR.
[b] R = *n*-hexyl.

explanation for the good to excellent diastereoselectivity obtained by hydrogenating the amine salts comes from $A^{1,2}$ strain. As the C3 vinyl substituent gets larger, $A^{1,2}$ strain increases as does the preference for the C2 carboxylate to adopt an axial conformation. With the ester blocking the β-face, hydrogenation comes from below giving the 2,3-*cis* product.

To determine if any racemization had occurred during its synthesis, amine salt **5b** was converted to its *t*-butyl carbamate (**6b**) using di-*tert*-butyl dicarbonate and triethylamine. For comparison, racemic material was prepared following standard literature procedures.[4f] Compound **6b** was >98% enantiomerically pure as judged by chiral HPLC analysis indicating that no racemization occurred at the β-keto ester stage or during enol triflate formation.[13]

In summary, we have developed a convergent and efficient procedure for the synthesis of 3-substituted prolines in enantiomerically pure form. It has the advantage of proceeding through a common intermediate (enol triflate **3**) which is readily available in two steps from commercially available material. Palladium-mediated couplings proceed in good yield and modest to high diastereoselectivity can be achieved in the hydrogenation step. These methods should allow rapid access to analogs which were previously prepared by more laborious routes.

Acknowledgements

We wish to thank Mr. Henry Murillo and Dr. Nathan Yates for LC-MS measurements.

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5. The current method described is analogous to the strategy used by others for the preparation of 3- and 4-substituted prolines starting from 4-oxoproline.[4a,c,d]

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7. Representative procedure: To a solution of 1.0 g (1.93 mmol) of **3** and 0.60 g (3.9 mmol) of phenyl boronic acid in toluene:MeOH (10:1, v:v, 11 mL) was added 0.40 g (2.9 mmol) of K_2CO_3 and 79 mg (5 mol%) of $PdCl_2$(dppf). The reaction mixture was stirred at 85°C for 9 h, cooled and concentrated. Purification by silica-gel chromatography (3:1 hexanes:Et_2O) provided 0.62 g (72%) of **4b** as a colorless solid, homogeneous by TLC analysis.
8. (a) For the Stille couplings, the following conditions were used: 1 equiv. **3**, 2 equiv. Stannane, using (1) 10 mol% Pd_2dba_3, 20 mol% Ph_3As, in NMP at 50°C, or (2) 4 equiv. LiCl, 10 mol% $Pd(Ph_3P)_4$ in THF at 80°C; (b) conditions for the carbonylation were as follows: 1 equiv. **3**, 10 mol% $Pd(OAc)_2$, 20 mol% dppf, 2 equiv. TEA, 30 equiv. MeOH in DMF at 60°C for 18 h under a balloon of CO pressure.
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11. Direct hydrogenation of trityl protected derivatives **4a**–**4h**, **4j** gave *cis*/*trans* mixtures of deprotected products with the 2,3-*cis* predominating sometimes and other times, the 2,3-*trans* product was major.
12. As determined by ^1H NMR analysis. In the case of **5b** and **5h**, comparison to authentic material confirmed the assignments.
13. Chiral HPLC conditions: Chiralcel OJ 4.6×250 mm, 10 micron, 2% EtOH in hexane, isocratic at 0.75 mL/min. Racemic material appears as two peaks: peak 1 (retention time = 15.5 min), peak 2 (retention time = 23.6 min). Analysis of **6b** gave a single peak (retention time = 23.8 min).