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# New Strategy for the Synthesis of 3-Substituted Prolines

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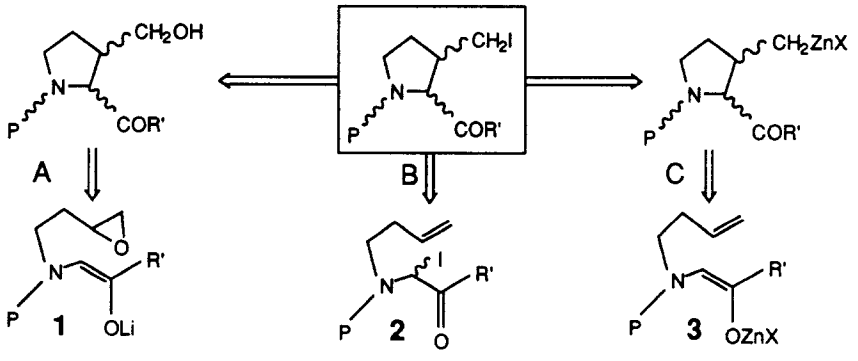
**Abstract** : Ring formation involving a 5-exo trig cyclization between a zinc enolate and a non activated double bond led to cis diastereoisomer of 3-substituted prolines. This cyclization was achieved with transfer of chirality onto the C-2 carbon when nitrogen was protected by an α-methylbenzyl group. Reprotonation of the lithium enolate of cis derivative yielded the trans diastereoisomer.


The introduction of conformational constraints into peptides has led to major breakthroughs in the analysis of bioactive conformation of peptides. Replacements of a native residue by a proline is sometimes associated with a reduction of the biological activity. However, it is not always clear whether this decreased potency is related either to conformational and steric considerations or to the loss of determinant interactions of the side chain of the original amino acid. Therefore, we have undertaken the synthesis of proline derivatives that incorporate in β-position the side-chain functionality of the original amino acid. We report here a new approach for the synthesis of 3-substituted proline starting from an iodo precursor. The synthesis of the key precursor involves a 5-exo trig cyclization. The potentiality of this strategy was demonstrated by the synthesis of proline analogues of methionine and valine.

Three different pathways for the cyclizations have been investigated which are summarized below.

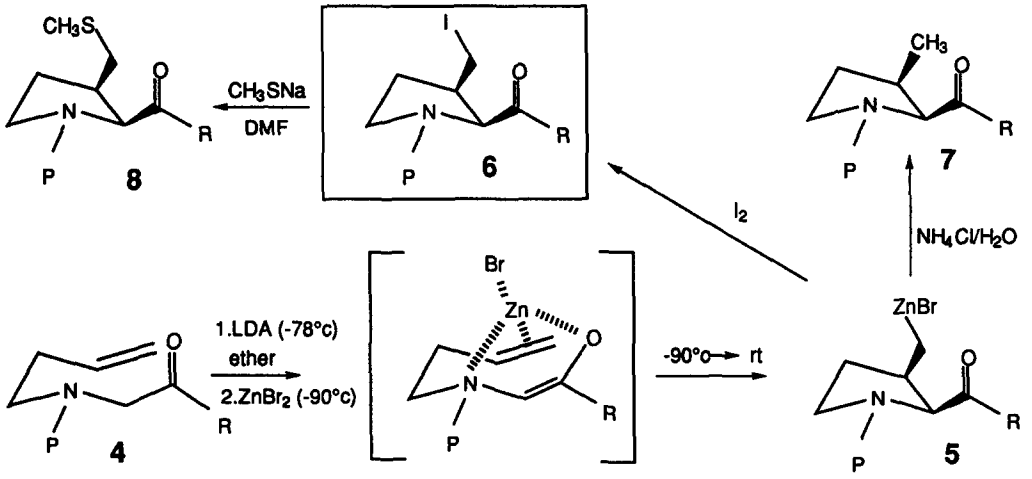



P= 2-mesitylene sulfonyl, 2,4,6 triisopropylbenzene sulfonyl, tert-butyloxycarbonyl, trityl, benzyl, α -methylbenzyl, acetyl, and R'= ethoxy, menthyloxy, phenylmenthyloxy, camphor sultam.

In pathway **A**, the ring opening of epoxide **1** by lithium enolate, a strategy previously used in the construction of polysubstituted cycloalkanes,[1] failed whatever the protecting group "P" on the nitrogen. The iodo compound **2** generated in pathway **B** was too unstable to be used in a radical atom transfer cyclization.[2,3] Pathway **C** is based on an intramolecular zinc enolate addition on non-activated alkene. Carbocyclizations of ε-ethylenic secondary organozinc iodide and metallo-ene-allene have been previously reported.[4,5] In this note, we

show for the first time, that cyclization between a zinc enolate and a non-activated double bond occurs cleanly. Furthermore, these cyclizations are regiospecific and stereospecific.

The different starting materials **4a-e** were prepared according to two methodologies. Ethyl-N-benzylglycinate **4a** and ethyl-N-(α–methylbenzyl)glycinate **4e** were obtained by reacting ethyl bromoacetate on benzylamine and (-) α-methylbenzylamine (DMSO, $NEt_3$, 1 equiv, rt, 10min, 90%), respectively and subsequent alkylation by 4-bromobutene (DMSO, $NEt_3$, 2.5 equiv, 50°C, 8 days, 95%). Derivatives **4b** and **4c** were obtained respectively by transesterification of compound **4a** with either the lithium salt of (-)menthol (THF, BuLi, rt, 1equiv, overnight, 85%) or the lithium salt of (-) phenylmenthol (THF, BuLi, rt, 1 equiv, overnight, 95%).[6] Alkylation of camphor sultam glycinate[7] with 4-bromobutene (DMSO, rt , 24 hrs, 74%), followed by benzylation with benzyl bromide ($CH_2Cl_2$, $NEt_3$, 1equiv, rt, 24 hrs, 96%) led to compound **4d**. Deprotonation of derivative **4a** with LDA in diethyl ether at low temperature (-78°C) yielded the lithium enolate which was transmetalated with 3 equiv of dried $ZnBr_2$ at -90°C. A transition state with the zinc interacting with the non activated double bound, the enolate oxygen and the nitrogen atom may be postulated (scheme I). Warming to room temperature led to a highly diastereoselective cyclization (compound **5**) with the carbanionic center localized on the methylenic group of position 3.[8]




P= benzyl with R= ethoxy (**4a**), menthoxy (**4b**), phenylmenthoxy (**4c**) and camphor sultam (**4d**).
P= (-) α methylbenzyl with R= ethoxy (**4e**).

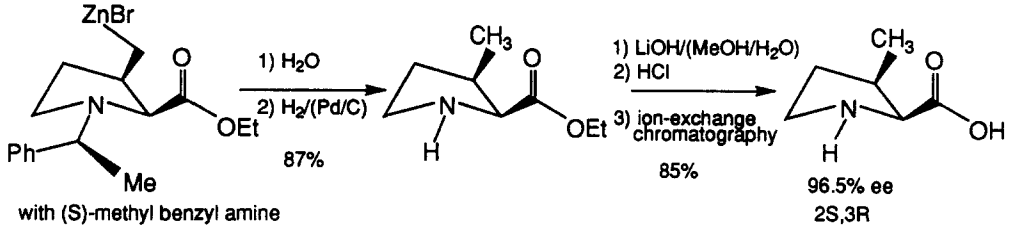
Scheme I: Synthesis of 3-substituted proline

This postulated structure was indirectly characterized by quenching the reaction with an aqueous solution of ammonium chloride, giving ethyl cis-3 methyl-N-benzylprolinate **7**. In the absence of $ZnBr_2$, quenching the lithium enolate yielded starting material **4a**. Nuclear Overhauser effects allowed us to assign a cis orientation for the 3-methyl and 2-carboxylate groups in compound **7**. The ring formation is totally regiospecific with a 5-exo trig cyclization as expected, but surprisingly this cyclization is also highly stereoselective (100% cis). The cis stereoselectivity is better than those observed for the carbocyclization of ε–ethylenic secondary organozinc iodides[4] and similar to that obtained in the metallo-ene allene reactions.[5] The driving force of this stereoselectivity may be attributed to a π/π interaction between two double bonds in the transition state.

In order to introduce a functionality in position 3 the reactivity of this carbanionic compound **5** was examined. It is well established that organozinc derivatives are poor nucleophilic. However, they react generally with iodine leading to stable electrophilic precursors such as **6a**, ethyl cis-3-iodomethyl-N-benzylprolinate, as a single diastereoisomer (2S,3S/2R,3R).[9] The versality of this precursor **6a** was demonstrated by the alkylation of the sodium salt of methanethiol leading to ethyl-cis-3(2-thiapropyl)-N-benzylprolinate **8**.[10] An elimination product, ethyl 3-methylene-N-benzylprolinate, was also isolated as a minor side-product (5%).

The transformation of the cis diastereoisomer in the thermodynamically more stable trans diastereoisomer by epimerization at the C-2 center was completed in the conditions reported for ethyl-N-acetyl-3-n-propylprolinate and ethyl-N-acetyl-3-phenylprolinate.[11] In this equilibrating conditions (1M EtONa/EtOH, 4 equiv, ethyl trifluoroacetate, 3 equiv, reflux, 2hrs), the major product was the trans product (55/45, trans/cis). Whereas, quenching at room temperature the lithium enolate with ethanol (THF, LDA, 1 equiv, -78°C→rt, EtOH, 10 equiv, rt) led to a ratio of 77:23 for the trans/cis diastereoisomers which were separated by chromatography.[12] This stereochemistry implies that in the enolate the benzyl and the methyl group adopt a trans orientation and that the reprotonation occurs on the same side of the methyl group.

For the preparation of optically active derivatives, the ethoxy group has been substituted by either menthyloxy, phenylmenthyloxy or camphor sultam groups. With the camphor sultam derivative **4d**, cyclization does not occur even in presence of 3 to 10 equivalents of $ZnBr_2$ probably due to a strong chelation of $ZnBr_2$ with the oxygen of the $SO_2$ function. Weak asymmetric induction on the α center was observed with the menthyl ester (55/45), the induction increased to 75:25 with the phenylmenthyl ester. However, changing the chiral center from the ester fonction to the amine fonction (compound **4e**) led to a high asymmetric induction at the C-2 carbon of 7 (97:3).




Scheme II: Determination of absolute configuration of ß-methyl proline

(S)-methyl benzyl amine led to (2S,3R)-ß-methyl proline (scheme II)[13].The absolute configuration was assigned by comparing its optical rotation with (2R,3S)-ß-methyl proline, previously reported.[14] This enantiomeric excess (96.5%) similar to the diastereoisomeric excess of **4e** (94%) showed that the deprotecting steps (hydrogenolysis and saponification) did not affect the chiral centers. The ß-methyl proline can be considered as a constrained analogue of valine with a carbon bridge linking the γ carbon to the nitrogen.

In conclusion, both cis and trans diastereoisomers of 3-substituted optically active prolines can be selectively prepared by this strategy and their absolute configurations can be predicted from the absolute configuration of methyl benzyl amine.

ACKNOWLEDGEMENTS

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8. Compound **4a** (500 mg, 2 mmoles) was dissolved in dry ether (5 ml), under argon, and cooled at -78°C. LDA (2.2 ml, 2.2 mmoles) was added and the reaction stirred for five minutes at -78°C. $ZnBr_2$ (6 ml, 6 mmoles) was added at -90°C, and the temperature was slightly increased to rt. After 20 min stirring, the reaction was quenched with aqueous saturated $NH_4Cl$, diluted with ether and washed with aqueous $NH_4Cl$ (1x). The aqueous layers were then extracted with $CH_2Cl_2$ (1x). The combined organic layers were dried ($MgSO_4$) and concentrated to give 480 mg (96%) of a pale yellow liquid as a single product.
9. Instead of quenching with aqueous $NH_4Cl$, iodine (565 mg, 2.2 mmoles) was added at 0°C. After stirring (20 min, rt), the reaction was diluted with ether. The organic layer was washed with aqueous saturated $Na_2S_2O_3$ (1x), with aqueous saturated $NH_4Cl$ (1x). The combined aqueous layers were extracted with $CH_2Cl_2$ (1x), dried ($MgSO_4$), and concentrated to give an oil as a pure product in quantitative yield.
10. The iodo compound (750 mg, 2 mmoles) was dissolved in dry DMF (5 ml) under argon. $CH_3SNa$ (221 mg, 3 mmoles) was added and the reaction was stirred overnight at room temperature. The solution was diluted with $CH_2Cl_2$ (50 ml), washed with aqueous saturated $NH_4Cl$ (1x), dried ($MgSO_4$) and concentrated. The recovered orange oil was purified by flash chromatography (cyclohexane/AcOEt: 95/5) to give 430 mg (73%) of a pale yellow liquid.
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12. Column chromatography: $SiO_2$, cyclohexane/AcOEt: 91/9. $^1$H-NMR; **7a-cis**: (200 MHz, $CDCl_3$): δ (ppm): 0.94–0.97 (d, 3H, $CH_3\beta$), 1.18–1.24 (tr, 3H, $CH_3$ ester), 1.51–1.66 (m, 1H, $H\gamma_2$), 1.92–2.1 (m, 1H, $H\gamma_1$) 2.44–2.59 (m, 2H, $H\beta+H\delta_2$), 3.00-3.09 (m, 1H, $H\delta_1$), 3.32-3.37 (d, $J\alpha\beta$=10Hz, 1H, $H\alpha$), 3.59-3.82 (AB, 2H, $CH_2\beta$· $J_{AB}$=12Hz), 4.05-4.16 (q, 2H,$CH_2$ ester), 7.20-7.30 (m, 5H, arom.) and **7a-trans**: (400 MHz, $CDCl_3$): δ (ppm): 1.12–1.18 (d, 3H, $CH_3\beta$) 1.23–1.28 (tr, 3H, $CH_3$ ester), 1.33–1.44 (m, 1H, $H\gamma_2$), 2.09–2.17 (m, 1H, $H\gamma_1$), 2.34-2.38 (m, 1H, $H\beta$), 2.39-2.46 (m, 1H,$H\delta_1$), 2.78-2.80(d, $J\alpha\beta$=6Hz, 1H, $H\alpha$), 3.02-3.08 (m, 1H, $H\delta_2$), , 3.48-3.90 (AB, 2H, $CH_2\beta$· $J_{AB}$=12Hz), 4.10-4.18 (m, 2H, $CH_2$ ester), 7.28-7.40 (m, 5H, arom.).
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14. (2S,3R)-ß-methyl proline; $[\alpha]_D^{25}$-65 (*c* 1, $H_2O$), mp 232°C,.(2R,3S)-ß-methyl proline $[\alpha]_D^{25}$+69.8 (*c* 1, $H_2O$).[13]

All isolated compounds have satisfactory analytical and spectroscopic data.


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