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CONSTRAINED AMINO ACIDS. AN APPROACH TO THE SYNTHESIS OF 3-SUBSTITUTED PROLINES

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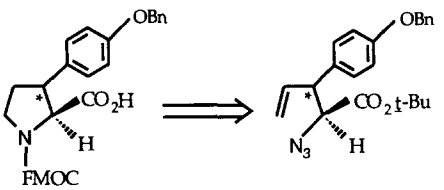
Abstract : The synthesis of diastereomeric substituted proline peptidomimetics as conformationally restricted tyrosine derivatives **1a,b** has been accomplished utilizing the intramolecular hydroboration-cycloalkylation of azido-olefins **7a,b** as the key step. Copyright © 1996 Elsevier Science Ltd

As part of our ongoing rational drug design program focused on developing a process for designing small molecule receptor antagonists as successors to peptide leads, we have been interested in the identification of highly populated low energy motifs for amino acids, and synthesizing constrained peptidomimetics that closely mimic these orientations.[1] When incorporated into peptides, constrained amino acid surrogates serve as useful ligands for probing receptor recognition. In addition to defining conformational parameters for a specified residue, often adjacent residues are also affected in a predictable manner. The use of proline as a template for inducing conformational constraints in amino acids is well documented.[2] We were interested in developing a versatile approach to 3-substituted prolines that would accommodate both natural and unnatural amino acid side chains, and provide access to all four possible diastereomers in a stereocontrolled manner. We wish to report an approach to 3-substituted prolines, demonstrated by the synthesis of diastereomeric tyrosine derivatives **1a,b**, which utilizes the intramolecular reductive-alkylation of azido-olefins **7a,b** as the key step.

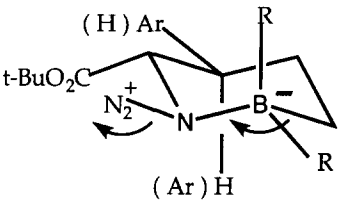


1a,b **7a,b**

In the following illustrative synthesis (Scheme I), commercially available 4-hydroxycinnamic acid **2** was converted to O-benzyl allylic alcohol **3** via a 2- step sequence in 85% overall yield. Subsequent Johnson ortho ester Claisen rearrangement[3] of allylic alcohol **3** cleanly gave an intermediate ester which was then saponified to acid **4** in 81% overall yield. Treatment of acid **4** with pivaloyl chloride and base, and reaction of the resulting mixed anhydride with lithiated *S*-4-benzyl-2-oxazolidinone afforded a chromatographically separable mixture of diastereomeric *N*-acyloxazolidinones **5a** and **5b** in 89% yield in a 1:1 ratio. After separation,[4] the individual diastereomers were transformed to key intermediates **7a** and **7b** without difficulty. The chiral imide potassium enolates of **5a** and **5b** were formed and quenched by electrophilic azide transfer[5] using 2,4,6 -triisopropylbenzenesulfonyl azide, and α-azido carboximides **6a** and **6b** were obtained as

single diastereomers after chromatography as indicated by ^{1}H NMR (300 MHz, $CDCl_3$) analysis, in yields of 84% and 92%, respectively. The chiral auxiliaries were removed and the α-azido acids were treated with *tert*-butyl 2,2,2-trichloroacetimidate[6] to afford diastereomerically pure *t*-butyl esters **7a** and **7b** in 78% and 82% yields, respectively. In this fashion, multigram quantities of **7a** and **7b** were obtained in a preparatively useful manner.

To complete the synthesis, we examined an approach to substituted prolines which utilizes the intramolecular hydroboration-cycloalkylation of an azido-olefin.[7] The reported procedure employs dicyclohexylborane for the hydroboration, and is suggested to proceed through cyclic



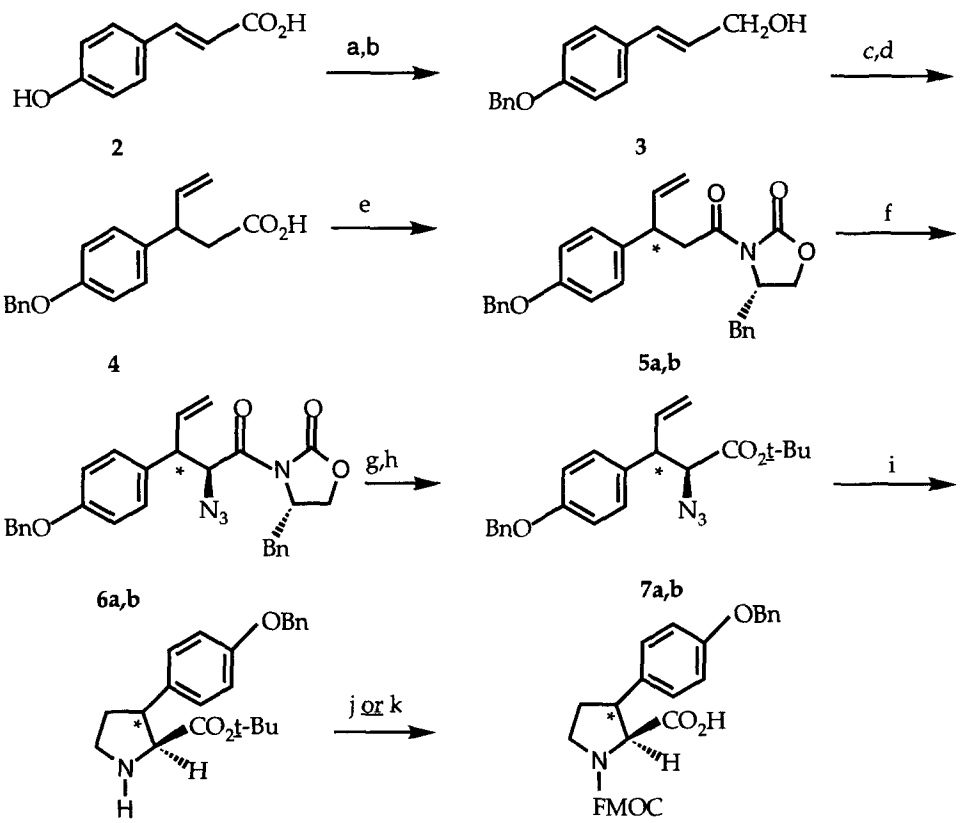
A (R = cyclohexyl)

transition state **A** with migration of the methylene group from an intermediate trialkylborane with concomitant loss of nitrogen. Hydroboration-cycloalkylation of azido-olefins **7a** and **7b** with dicyclohexylborane proceeded as expected, and furnished diastereomeric prolines **8a** and **8b** in 60% and 48% yields, respectively. The relative stereochemistries were assigned based on ^{1}H NMR NOE difference data. Thus for **8a**, irradiation of methine H-2 (δ 3.57, d, J=7.5 Hz) resulted in a large 9% enhancement of the ortho-aromatic protons, indicating a *cis* relationship between these protons. In addition, a small 2% enhancement was observed to methine H-3, consistent with the *trans* relative stereochemistry. By contrast for **8b**, irradiation of methine H-2 (δ 3.90, d, J=8.5 Hz) resulted in a 6% enhancement of H-3 and only a very small (<1%) enhancement of the ortho-aromatic protons, consistent with a *cis* relative stereochemistry at C-2 and C-3.

The conversion of **8a** and **8b** to tyrosine derivatives **1a** and **1b** suitable for incorporation into peptides, was next examined. Hydrolysis of *trans*-**8a** with trifluoroacetic acid followed by introduction of the FMOC protecting group provided *trans*-**1a** in 39% yield for the 2 steps. For *cis*-**8b**, it was convenient to first introduce the FMOC protecting group and then cleave the *tert*- butyl ester with dry HCl in ethyl acetate,[8] and in this way, *cis*-**1a** was prepared in 32% yield for the 2 steps.[9]

In summary, we have described a route to 3-substituted prolines that utilizes a relatively unexplored intramolecular cycloalkylation as the key step. A variety of substituents at C-3 may be envisioned with this route and further applications under study will be reported in subsequent publications.

Scheme I



8a trans-2S, 3R
8b cis-2S, 3S

1a trans-2S, 3R
1b cis-2S, 3S

Conditions : a) Cs_2CO_3, DMF, $PhCH_2Br$ (92%); b) DIBAL(2.5 eq.), toluene, 0°C (92%); c) $CH_3C(OEt)_3$ (3.5 eq.), $(CH_3)_3CCO_2H$ (5%), o-xylene, 3h, 140°C (90%); d) 1:1:5-3N NaOH(1.5 eq.)/CH_3OH/THF, 48h, rt (90%); e) $(CH_3)_3CCOCl$, Et_3N, THF, then N-lithio-(4S)-benzyl-2-oxazolidinone, -78°C-rt (89%); f) $(TMS)_2NK$, THF, -78°C(0.5h), Trisyl-N_3(2 min.), then HOAc, rt, (**a**-84%, **b**-92%); g) LiOH, THF-H_2O, (**a**-72%, **b**-75%); h) $CCl_3C(=NH)OC(CH_3)_3$, $BF_3.OEt_2$, CH_2Cl_2, (**a**-78%, **b**-84%); i) (**c**-$C_6H_{11})_2BH$, CH_2Cl_2, rt, (**a**-60%, **b**-48%); j) CF_3CO_2H, CH_2Cl_2, rt, then FMOC-Cl, 10% aq. Na_2CO_3-dioxane, (**a**-39%); k) FMOC-Cl, 10% aq. Na_2CO_3-dioxane, then AcCl-MeOH, EtOAc, (**b**-32%).

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4. Flash chromatography, silica gel, 20% ethyl acetate/hexane, R_f **5a** = 0.36, R_f **5b** = 0.30.

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9. All structural assignments in the text are consistent with spectral and analytical data.

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