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Highly Stereoselective Synthesis of cis-*(2R,3S)*-3-Hydroxyproline

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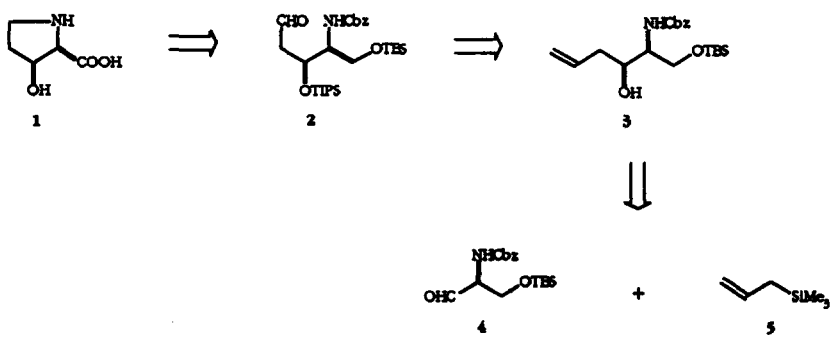
Abstract: Allyltrimethylsilane (**5**) reacted with *N*-carbobenzoxy-*O*-*tert*-butyldimethylsilyl-L-serinal (**4**) to give with high diastereoselectivity *syn*-adduct **3** which was subsequently transformed into *cis-(2R,3S)*-3-hydroxyproline (**1**).

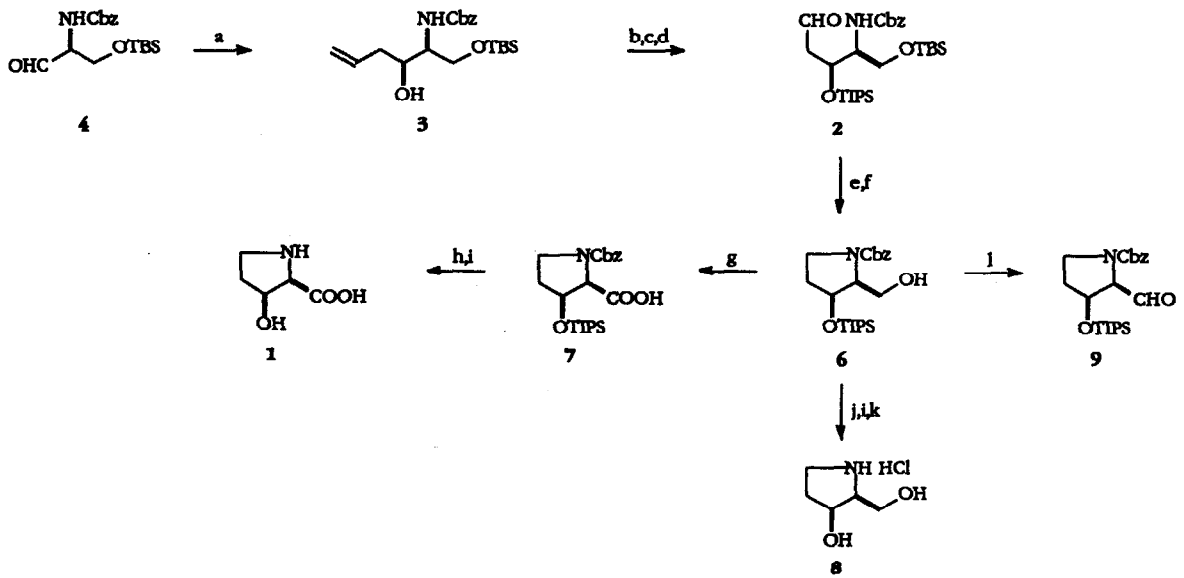
The synthesis of optically active α-amino acids has long been of great interest owing to their use as components of biologically active molecules.[1] Further interest has followed their application as convenient chiral building blocks for stereoselective synthesis of various natural products.[2-5] In our recent studies involving the synthesis of antibiotic amino sugars,[3,5,6] we have found that suitably protected α-amino aldehydes are very convenient and versatile chirons. For example, addition of 2-furyllithium to *N,N*-diprotected α-amino aldehydes offers an easy access to almost enantiomerically pure *anti*-adducts which are readily transformed into natural products.[5-7]

Now we report a new application of our methodology to the highly stereoselective synthesis of *cis-(2R,3S)*-3-hydroxyproline (**1**), a structural unit present in some biologically important compounds, such as slaframine,[8] castanospermine,[9] and detoxinine.[10] Retrosynthetic analysis, shown in Scheme 1, suggested that *N*-carbobenzoxy-*O*-*tert*-butyldimethylsilyl-L-serinal (**4**)[11] and allyltrimethylsilane (**5**) could serve as starting materials.

Scheme 1



Scheme 2



Reaction conditions: a) 5, $SnCl_4$, CH_2Cl_2, -78°C; b) TIPS-Tf, 2,6-lutidine, CH_2Cl_2, 0°C; c) OsO_4, NMO, Me_2CO-H_2O, r.t.; d) $NaIO_4$, silica gel, CH_2Cl_2, r.t.; e) $NaBH_3CN$, AcOH-MeOH, r.t.; f) AcOH-MeOH, reflux, 1h; g) NaOCl, TEMPO, KBr, $NaHCO_3$, Et_2O-H_2O, 0°C, then Me_2CO, $NaIO_4$, $RuCl_3$ (cat.), r.t.; h) H_2SiF_6, MeCN-H_2O, 55°C, 50 min; i) H_2, Pd/C, MeOH, r.t.; j) *n*-Bu_4NF, THF, r.t.; k) HCl, MeOH, r.t.; l) NaOCl, TEMPO, KBr, $NaHCO_3$, EtOAc-PhMe-H_2O, 0°C.

Addition of **5** to aldehyde **4** in the presence of 1 equiv. of $SnCl_4$ at -78°C, afforded with very high diastereoselectivity (>95:5)[13] *syn*-adduct **3** in 60% yield[14,15] (Scheme 2). Protection of the hydroxy group with triisopropylsilyl (TIPS) triflate, followed by *cis*-hydroxylation and sodium periodate - silica gel oxidative cleavage,[16] led to aldehyde **2** in 81% yield. Treatment of **2** with $NaBH_3CN$, followed by selective deprotection of the primary hydroxy group, afforded the pyrrolidine derivative **6** in 91% yield. Two-step oxidation[17] of **6** gave acid **7** which upon treatment with H_2SiF_6,[18] followed by reductive cleavage of the Cbz group afforded *cis-(2R,3S)*-3-hydroxyproline (**1**)[19] in 86% yield.

For independent verification of the *cis*-relation of the substituents in the product **1**, compound **6** was transformed into the known *cis*-2-hydroxymethylene-3-hydroxypyrrolidine hydrochloride **8**.[21]

The presented synthesis of *cis-(2R,3S)*-3-hydroxyproline proves to be a practical alternative to the known procedures.[20,22] Moreover, it allows for simple synthesis of optically active aldehyde **9** which can serve as starting material in our intended synthesis of castanospermine.

References and Notes:

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11. The serinal derivative **4** was obtained as follows: *N*-Cbz-L-serine methyl ester was treated with *tert*-butyldimethylsilyl chloride in the presence of imidazole in DMF, affording *N*-Cbz-*O*-TBS-L-serine methyl ester (90% yield), which was then reduced with $NaBH_4$ in MeOH at 50° C to give the corresponding alcohol (95% yield). Oxidation of the alcohol using the TEMPO-NaOCl procedure[12] afforded aldehyde **4** (95% yield), which did not require further purification.
12. Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029.
13. *anti*-Diastereoisomer was not detected in ^1H, ^{13}C NMR, and chromatography experiments.
14. Satisfactory analyses and spectral data were obtained for all new compounds.

15. The stereochemical results can be rationalized by transition-state models **A** and **B**, as shown in Scheme 3. In the case of the Lewis acid-catalyzed reaction leading to *syn*-adduct **3**, the chelation-controlled model **A** is preferred. To achieve *anti* diastereoselection, the Felkin-Anh model **B** should operate.

Scheme 3

A B

16. Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Le Goffic, F. *Synthesis* **1989**, 64.
17. Compound **6** was first treated according to the TEMPO-NaOCl procedure,[12] and then the aldehyde formed was oxidized with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$.
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19. Selected data: mp. 225-235°C, decomp. [Lit.[20] m.p. 220-230°C, decomp.]; $[\alpha]_D$ +89.0° (*c* 0.7, H_2O) [Lit.[20] $[\alpha]_D$ -101° (*c* 1.0, H_2O) for enantiomer]; HRMS calcd for $C_5H_9NO_3$ (M^+) 131.0582, found 131.0583; ^1H NMR (500 MHz, D_2O): 2.02-2.11 (m, 1H), 2.14-2.23 (m, 1H), 3.33 (dt, J=11.7, 2.8 Hz, 1H), 3.49 (dt, J=10.8, 7.7 Hz, 1H), 3.99 (d, J=4 Hz, 1H), 4.63 (m, 1H); ^{13}C NMR (50 MHz, H_2O): 36.37, 46.55, 70.53, 74.39.
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