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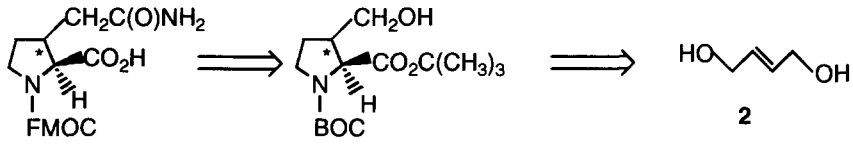
Constrained Amino Acids. The Synthesis of Glutamine Mimetics

Jeffrey S. Sabol*, Gary A. Flynn#, Dirk Friedrich, Edward W. Huber

Hoechst Marion Roussel Inc., 2110 East Galbraith Rd., Cincinnati, OH 45215
Selectide Corporation, 1580 East Hanley Blvd., Tucson, AZ 85737

Abstract: The preparation and utility of conformationally constrained homoserines *trans*- **8a** and *cis*-**8b** as intermediates for the synthesis of constrained glutamine mimetics *trans*-**1a** and *cis*-**1b** is presented. © 1997 Elsevier Science Ltd.

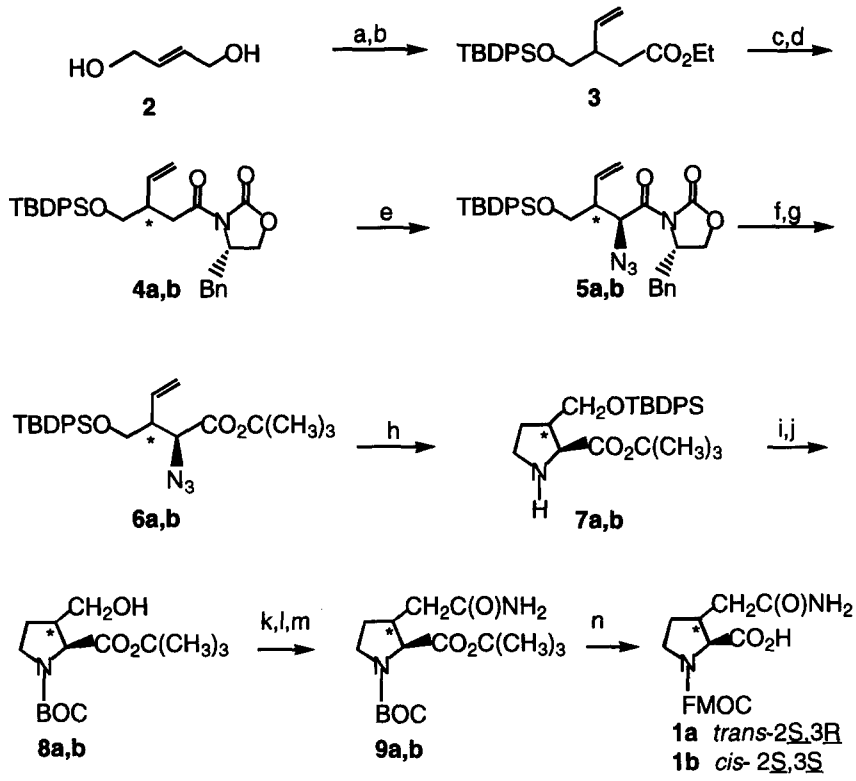
The use of proline as a template for inducing conformational constraints in amino acids is well documented. For example, we recently reported an approach to the synthesis of 3-substituted prolines, and prepared tyrosine derivatives that were suitable for incorporation into peptides.[1] As a continuation of this effort, we desired to demonstrate the applicability of this approach to the synthesis of more complex constrained amino acids. Our reported preparation of chiral β-substituted-β-vinyl-α-azido esters, and their facile cyclization to 3-substituted prolinates mediated by hydroboration with dicyclohexylborane (DCB), appeared attractive to us as a general entry to more complex targets. Herein we describe the preparation of constrained homoserines **8a,b**, and report their utility as intermediates in the synthesis of glutamine analogs **1a,b**.



1a,b **8a,b** **2**

The synthesis commences with protection of 2-butene-1,4-diol **2** as a mono-*t*-butyldiphenylsilyl (TBDPS) ether (Scheme I). Johnson ortho ester Claisen rearrangement[2] of the resulting allylic alcohol afforded ester **3** in 90% yield for the two steps in a preparatively useful fashion. Saponification of this ester, and treatment of the intermediate acid with pivaloyl chloride then afforded a mixed anhydride which was reacted with lithiated (S)-4-benzyl-2-oxazolidinone to afford a chromatographically separable mixture of diastereomeric N-acyloxazolidinones **4a** and **4b** in 70% yield in a 1:1 ratio. At this point, individual diastereomers **4a** and **4b** were separated and used in subsequent transformations.[3] The potassium enolates of chiral diastereomeric imides **4a** or **4b** were generated using potassium bistrimethylsilyl amide as the base, and electrophilic azide

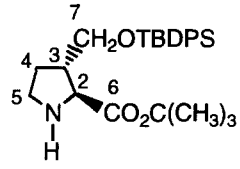
Scheme I



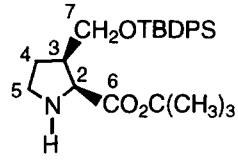
Conditions: a) n-BuLi, THF, TBDPS-Cl, 0°C, (Quant.); b) $CH_3C(OEt)_3$ (3.5 eq.), $(CH_3)_3CCO_2H$ (5%), o-xylene, 140°C(3h), (90%); c) 1:1:1-1N NaOH(1.5 eq.)/CH_3OH/THF, rt(18h), (78%); d) $(CH_3)_3CC(O)Cl$, Et_3N, THF, then N-lithio-(4S)-benzyl-2-oxazolidinone, -78°C-rt, (90%); e) $(TMS)_2NK$, THF, -78°C(0.5h), Trisyl-N_3(2 min.), then HOAc, rt, (**a**-80%, **b**-86%); f) LiO_2H, THF-H_2O, (**a**-88%, **b**-97%); g) $CCl_3C(=NH)OC(CH_3)_3$, BF_3OEt_2, CH_2Cl_2, (**a**-89%, **b**-94%); h) $(c\text{-}C_6H_{11})_2BH$, CH_2Cl_2, rt, (**a**=48%, **b**=64%); i) $(BOC)_2O$ Et_3N, CH_2Cl_2, (**a**=95%, **b**=93%); j) 1M TBAF/THF, (**a**=92%, **b**=95%); k) MsCl, CH_2Cl_2, $(i\text{-}Pr)_2NEt$, (**a,b**=Quant.); l) NaCN, DMSO, 80°C(1h), (**a**=84%, **b**=74%); m) 30% H_2O_2, CH_2Cl_2,5N NaOH, $(Bu)_4NHSO_4$, (**a**=82%, **b**=73%); n) 50% CF_3CO_2H/CH_2Cl_2, then FMOC-Cl, 1:1 10% aq. Na_2CO_3/dioxane, (**a**=63%, **b**=62%).

transfer[4] with triisopropylbenzenesulfonyl azide afforded diastereomeric azides **5a** ($\alpha^{20}D$ = +43.3 (c=0.86, $CHCl_3$)) and **5b** ($\alpha^{20}D$ = +26.5 (c = 0.515, $CHCl_3$)) in 80% and 86% yield respectively. Removal of the chiral auxiliary with $LiOH\text{-}H_2O_2$ followed by esterification with *t*-butyl 2,2,2-trichloroacetimidate[5] then afforded diastereomeric α-azido-*t*-butyl esters **6a** and **6b** in 78% and 91% yield respectively. The choice of a *t*-butyl ester as a base stable carboxylate protecting group was judged to be critical for compatibility with subsequent synthetic transformations, and to allow for the differentiation and manipulation of the carboxylate functionalities of the target mimetics **1a,b**. The procedure to this point is easily scaleable to give multigram quantities of **6a** and **6b**.

The intramolecular dicyclohexylborane (DCB)-mediated cyclizations following the Evans protocol[6] were next investigated. Hydroboration of **6a** or **6b** with dicyclohexylborane was accompanied by the evolution



7a



7b

of nitrogen gas. The expected 3-substituted prolinates **7a** ($\alpha^{20}D$ = +19.7 (c = 0.86, $CHCl_3$)), and **7b** ($\alpha^{20}D$ = +2.44 (c = 0.858, $CHCl_3$)) were obtained in 48% and 64% yields respectively, and assignment of *trans* and *cis* relative stereochemistry to **7a** and **7b**, respectively, was unambiguously made from ^1H NMR NOESY and NOE difference data. In particular, for **7a**, pre-irradiation of H-4β resulted in strong NOE's at H-3 (9%) and H-5β (6%), while pre-irradiation of H-4α resulted in weak NOE's at H-2 (1%), H-3 (0.5%), and H-5β (0.5%) in addition to a stronger NOE at H-5α and NOE's at H-7 (1.5%) and H-7' (1.5%). Further diagnostic NOE's included those at H-2 (2%), H-4α (0.5%), and H-5α (0.5%) upon pre-irradiation of $SiC(CH_3)_3$, and at H-3 (1.5%) and H-5β (0.5%) upon pre-irradiation of $CO_2C(CH_3)_3$.. For **7b**, the *cis* relative stereochemistry of H-2 and H-3 is supported by the strong NOE observed at H-3 (7%) upon pre-irradiation of H-2; no NOE to H-7 was observed in this experiment.[7]

To complete the synthesis, individual prolinates **7a** and **7b** were first protected as BOC derivatives, and the TBDPS protecting groups were then removed to afford homoserines **8a** ($\alpha^{20}D$ = -40.0 (c = 0.958, $CHCl_3$)), and **8b** (m.p. = 88-90°C, $\alpha^{20}D$ = +0.35 (c = 1.21, $CHCl_3$)) in 87% and 88% yields respectively for the two steps. Homologation of **8a** or **8b** was accomplished by mesylate formation, cyanide displacement, and phase

transfer hydrolysis[8] to give amides **9a** (m.p.=118-119°C, $\alpha^{20}D$ = -16.3 (c = 0.867, $CHCl_3$)) and **9b** (m.p.=174-176°C, $\alpha^{20}D$ = +5.8 (c = 0.827, $CHCl_3$)) in 69% and 54% overall yields. BOC removal and ester cleavage of **9a** or **9b** was accomplished in a one pot sequence with 50% CF_3CO_2H/CH_2Cl_2. FMOC protection then yielded the desired protected glutamines **1a** ($\alpha^{20}D$ = -28.2 (c = 1.03, $CHCl_3$)) and **1b** ($\alpha^{20}D$ = +30.1 (c = 0.60, $CHCl_3$)) suitably derivatized for incorporation into peptides.

In conclusion, constrained glutamine mimetics **1a** and **1b** have been prepared from homoserines **8a** and **8b**, which are readily available in multigram quantities using the Johnson orthoester Claisen rearrangement and Evans chemistry as key components of this approach. The utility of **8a** and **8b** as useful conformationally constrained building blocks has been demonstrated in our laboratory. Further applications of this general approach to 3-substituted prolines may be envisioned.

References and Notes

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3. The faster eluting **4a** (R_f = 0.40, silica gel, 15% ethyl acetate/hexane; **4b**, R_f = 0.35) gives rise to the faster eluting *trans* **7a** (R_f = 0.21, silica gel, 3% methanol/methylene chloride; **7b**, R_f = 0.17).
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6. Evans, D.A.; Webber, A.E. *J. Am. Chem. Soc.* **1987**, *109*, 7151-7157.
7. **7a**: ^1H NMR, 400 MHz, $CDCl_3$ [DMSO-d_6] δ 7.69-7.65 [7.64-7.60] (m, 4H, $SiPh_2$-H^{ortho}), 7.45-7.35 [7.50-7.40] (m, 6H, $SiPh_2$-H^{meta}/H^{para}), 3.78 [3.69] (dd, 1H, J=10,5.5 Hz, H-7), 3.68 [3.63] (dd, 1H, J=10, 6.5Hz, H-7'), 3.50 [3.37] (d, 1H, J=6 Hz, H-2), 3.06 [2.89] (ddd, 1H, J=10, 7, 7 Hz, H-5β), 2.94 [2.77] (ddd, 1H, J=10, 7.5, 5.5 Hz, H-5α), 2.34 [2.27] (ddddd, 1H, J=8, 6.5, 6.5, 6, 5.5 Hz, H-3), 1.93 [1.82] (dddd, 1H, J=12.5, 8, 7, 5.5 Hz, H-4β), 1.88 [2.60] (br, 1H, H-1), 1.74 [1.52] (dddd, 1H, J=12.5, 7.5, 7, 6.5Hz, H-4α), 1.40 [1.34] (s, 9H, $OC(CH_3)_3$), 1.06 [1.00] (s, 9H, $SiC(CH_3)_3$). Reported NOE's were observed in DMSO-d_6 (6 sec pre-irradiation, field strength $\gamma B_1/2\pi \cong 5$Hz); **7b**: 1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.61 (4H, m, $SiPh_2$-H^{ortho}), 7.45-7.32 (6H, m, $SiPh_2$-H^{meta}/H^{para}), 3.75 (dd, 1H, J=10, 5 Hz, H-7), 3.64 (d, 1H, J=8 Hz, H-2), 3.39 (t, 1H, J=10 Hz, H-7), 3.18 (m, 1H, H-5), 2.88 (dt, 1H, J=10.5, 7.5 Hz, H-5), 2.58 (m, 1H, H-3), 2.03 (m, 1H, H-4α), 1.94-1.68 (m, 7H, H-4β overlapped with H_2O from the NMR solvent), 1.24 (s, 9H, $OC(CH_3)_3$), 1.04 (s, 9H, $Si(C(CH_3)_3)_3$). Reported NOE's were observed in $CDCl_3$ (7 sec pre-irradiation).
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