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Asymmetric Synthesis of 2,4-Disubstituted Pyrrolidines

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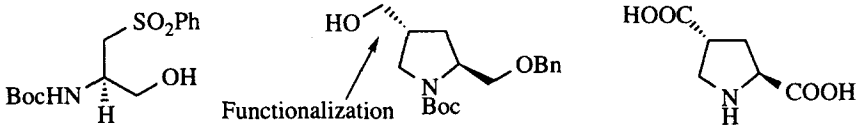
Abstract: A new strategy for asymmetric synthesis of 2,4-disubstituted pyrrolidines is described, starting from readily available chiral building blocks **1** and (2*R*)-2,3-*O*-isopropylideneglycealdehyde (**6**) .

The conformational study of a flexible peptide must consider torsional movement within the backbone and side chaines, the influence of the side chains on the preferred backbone conformations and cooperative effects between multiple side chains.[1] It has been now well established that the optimal orientation of side chain functional groups of amino acids is often responsible for the observed biological activity of peptides or peptidomimetics.[2,3] As such, conformationally constrained peptides are emerged as powerful tools in developing peptide-derived pharmaceutical agents. Among numerous possibilities to reach conformational rigidity, incorporation of proline-amino acid chimeras[3] into peptides or peptidomimetics are particularly interesting for the following reasons. Firstly, the side chain of the original amino acid was preserved in such chimeras. Secondly, the pyrrolidine residue can reduce considerably the conformational mobility of the side chain by limiting the torsion angles ϕ, ψ and χ.[4] As a consequence of these two characteristics, only the conformational effects will be responsible for the activity variation of the peptidomimetics resulting from the incorporation of proline-amino acid chimeras. This can simplify enormously the structure-activity relationship (SAR) studies. Indeed, synthesis of biologically potent peptidomimetics has recently been reported based on this approach.[5]



1 **2** **3**

Figure 1

To fully develop this conceptually novel approach, an efficient enantiospecific synthesis of all diastereomers of substituted prolines is a prerequisite. Although a significant effort has been directed toward the development of asymmetric methods for the synthesis of chiral pyrrolidines because of their presence in many natural and unnatural bioactive products, general and effective strategies for the enantiospecific synthesis of these species are noticeably rare and are thus highly demanding. Recent reports from this laboratory described asymmetric synthesis of 2,3- and 2,5-disubstituted pyrrolidines from readily available chiral synthon **1**.[6] In

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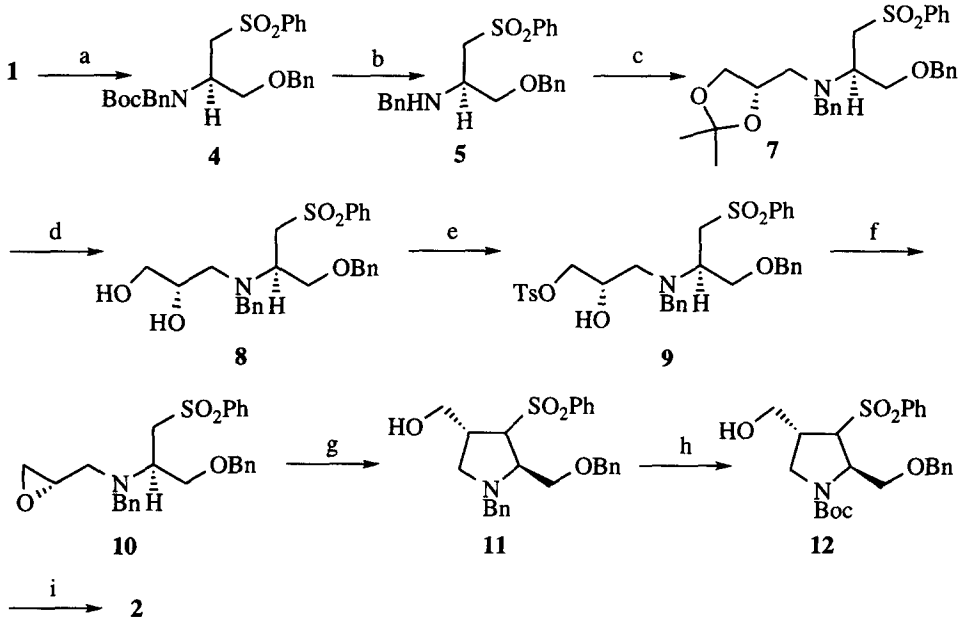
conjunction with our ongoing studies, we were interested in the use of 4-substituted prolines[7] as conformationally restricted analogues of naturally occurring amino acids. Keeping in mind the molecular diversity, compound **2** (Figure 1) with two discernible hydroxy groups was selected as our primary synthetic target. Homologation of the unprotected hydroxy function should, *a priori*, allow us to prepare a range of proline-amino acid chimeras increasing thus the divergency of our approach. We describe herein an efficient synthesis of compound **2** as well as a natural product (2*S*,4*R*)-L-proline-4-carboxylic acid (**3**).



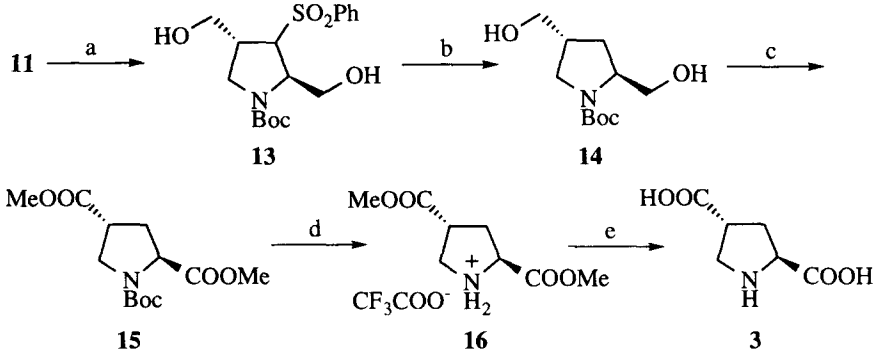
Reagents and conditions: a) NaH, THF, 0°C, 30 min; then BnBr, $^{n}Bu_4NI$, 0°C, 24 h, 86%; b) 3M HCl-EtOAc, rt, 1 h, 95%; c) (2*R*)-2,3-*O*-isopropylideneglycealdehyde (**6**), $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, overnight, 97%; d) 4M HCl-THF, rt, 3 h, 94%; e) TsCl, Py, 0°C, 24 h, 85%; f) K_2CO_3, wet DMF, rt, 24 h, 99%; g) $Ti(O^{i}Pr)_4$, THF, -78°C, 10 min, then KHMDS, -70°C, 2 h, 73%; h) 10% Pd/C, H_2 (1 atm), Boc_2O, MeOH, rt, overnight, 95%; i) 6% Na-Hg, Na_2HPO_4, MeOH, 0°C, 2 h, 96%.

Scheme 1

Synthesis of (2*S*,4*R*)-*N*-Boc-*trans*-2-benzyloxymethyl-4-hydroxymethyl pyrrolidine (**2**) was shown in Scheme 1. The *N,O*-bisbenzylation of (*R*)-**1** (NaH, $^{n}Bu_4NI$, BnBr, THF) followed by the removal of *N*-Boc function provided the secondary amine **5**. Reductive alkylation of **5** with (2*R*)-2,3-*O*-isopropylideneglycealdehyde (**6**) using sodium triacetoxyborohydride as reductant in 1,2-dichloroethane at room temperature afforded tertiary amine **7** in 97% yield.[8] Hydrolysis of acetonide under mild acidic conditions furnished diol **8** (94%) which was then converted to the epoxide **10** by a straightforward two-step sequence *via* monotosylate **9** in excellent overall yield.[9] Cyclization of the epoxy sulfone **10** was found to be more difficult than expected. After much experimentations varying the base, the Lewis acid additive, the solvent and the reaction temperature, the optimal conditions found in our hands involved the treatment of compound **10** in THF with potassium bis(trimethylsilyl)amide (KHMDS) in the presence of 2 equiv of $Ti(O^{i}Pr)_4$ at -70°C. Under these conditions, pyrrolidine **11** was isolated in 73% yield as a single diastereomer.[10] The exclusive 5-*exo* cyclization

mode was in accord with the literature precedent.[11] The stereochemistry of **11** was deduced from the ^{1}H NMR studies. While the stereochemistry of C-3 was of no consequence as it will be destroyed at the late stage, that of C-4 (inversion) was confirmed by the synthesis of natural product **3** (*vide supra*). It is worthy noting that the issue of the stereochemistry of C-4 was uncertain at the outset of this work due to the possible participation of nitrogen atom leading to a double S_N2 process (retention at C-4).[12] We hypothesized that the coordination of Lewis acid to the nitrogen atom decreased significantly its nucleophilicity favoring thus the direct attack of carbanion onto the epoxide.

One pot deprotection-protection of compound **11** (10% Pd/C, H_2, 1atm, MeOH, Boc_2O)[13] afforded compound **12** in excellent yield. It is interesting to note that the *N*-benzyl group was selectively removed without affecting the *O*-benzyl function. Treatment of compound **12** with 6% Na-Hg in the presence of 3 equiv of Na_2HPO_4 in MeOH at 0°C gave the desired (2*S*,4*R*) *N*-Boc-*trans*-2-benzyloxymethyl-4-hydroxymethyl pyrrolidine (**2**) in 96% yield.



Reagents and conditions: a) H_2 (60 psi), 10% Pd/C, MeOH, rt, overnight, 89%; b) 6% Na-Hg, Na_2HPO_4, MeOH; 0°C, 2h, 96%; c) i) TEMPO, NaOCl, KBr, 5% $NaHCO_3$, acetone, 0°C, 2 h; ii) CH_2N_2, 84%; d) CH_2Cl_2-TFA, rt, 1 h, 100%; e) i) 1M HCl, rfx, 3 h; ii) EtOH, propylene oxide, heat, 100%

Scheme 2

The synthesis of natural product (2*S*,4*R*)-L-proline-4-carboxylic acid (**3**), a potent competitive glutamate transport inhibitor,[7b] was accomplished as shown in Scheme 2. Simultaneous removal of *N*- and *O*-benzyl groups from **11** and *in situ* derivatization of the secondary amine was realized by hydrogenolysis at 60 psi in the presence of 10% Pd/C and Boc_2O. Desulfonylation of **13** under standard conditions gave the diol **14** in 96% yield. Jones oxidation (0°C, 1 h) followed by treatment with diazomethane gave the dicarboxylic ester **15** in low yield (23%). However, when TEMPO catalyzed NaOCl oxidation[14] was employed, the diester **15** was isolated in 84% yield as a mixture of two rotamers. Removal of *N*-Boc group (CH_2Cl_2-TFA, rt, 1 h, 100%) provided **16** as a single diastereoisomer based on the ^{1}H and ^{13}C NMR spectra. Finally sequential treatment of **16** with HCl followed by propylene oxide gave the (2*S*,4*R*)-L-proline-4-carboxylic acid (**3**)[15] whose physical data including the optical rotation were in good agreement with those reported in the literature.[7b,7c,16]

In summary, we have developed a new efficient method for the synthesis of 2,4-disubstituted pyrrolidines. The synthesis is highly flexible and can be stereodivergent. In fact, the (2*S*,4*S*) diastereomers of **2** and **3** were readily accessible by manipulating the diol function of intermediate **8**. We are currently exploring variants of this new methodology by functionalization at C-4 hydroxymethyl group which should allow the

preparation of other 4-substituted prolines as conformationally constrained amino acid analogues. Results will be reported in due course.

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10. Compound **11**: $[\alpha]_D^{25}$ = -92 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3536, 3072, 2952, 2896, 2861, 2404, 1497, 1455, 1448, 1303, 1293, 1234, 1198, 1142, 1084, 1028 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.83-7.79 (m, 2H), 7.59-7.52 (m, 1H), 7.47-7.40 (m, 2H), 7.33-7.23 (m, 10H), 4.35 (dd, *J* = 12.5, 9.9 Hz, 1H), 4.17 (d, *J* = 12.0 Hz, 1H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.95 (d, *J* = 12.8 Hz, 1H), 3.85 (dd, *J* = 12.5, 4.7 Hz, 1H), 3.80 (dd, *J* = 8.0, 3.1 Hz, 1H), 3.66 (d, *J* = 12.8 Hz, 1H), 3.17-3.11 (m, 1H), 3.03-2.93 (m, 3H), 2.79 (dd, *J* = 9.9, 4.3 Hz, 1H), 2.73 (dd, *J* = 11.6, 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 138.3, 137.7, 133.7, 129.0, 128.8, 128.6, 128.2, 127.6, 127.2, 72.8, 70.8, 66.6, 65.4, 60.1, 59.5, 55.5, 45.7; MS (CI) 452 $[M+H]^+$, 143, 107; HRMS *m/z* 452.1889 ($C_{26}H_{30}NO_4S$ (M+H) requires 452.1896).
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15. Compound **3**: $[\alpha]_D^{25}$ = -52 (*c* 0.9, H_2O) {lit.: $[\alpha]_D^{20}$ -46 (*c* 1, H_2O);[16] $[\alpha]_D^{25}$ -54 (*c* 1.04, H_2O);[7b] $[\alpha]_D^{20}$ = -46.6 (*c* 0.09, H_2O)[7c]}; IR (KBr) 3419, 2925, 1719, 1619, 1413, 1388, 1363, 1338, 1288, 1225 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 4.29 (t, *J* = 7.9 Hz, 1H), 3.65-3.62 (m, 2H), 3.34 (quintet, *J* = 7 Hz, 1H), 2.60 (ddd, *J* = 14.2, 8.2, 5.9 Hz, 1H), 2.43 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 177.8, 175.1, 62.7, 49.3, 44.2, 34.2; MS (CI) *m/z* 160 $[M+H]^+$, 114.
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