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Synthesis of β-phenyl-δ,ε-unsaturated amino acids and stereoselective introduction of side chain groups into [4,3,0]-bicyclic β-turn dipeptides☆

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Abstract—(2*S*,3*S*)- and (2*R*,3*R*)-2-amino-3-phenyl-5-hexenoic acids have been synthesized in large scale by using Ni(II)-complexes as a template. The amino acids were used in the synthesis of [4,3,0]-bicyclic β-turn mimetics by a convergent methodology. The unique advantage of this strategy is the convenience of introducing side chain groups with predetermined chiralities on both the five- and six-membered heterocyclic rings.

The development of novel β-turn mimetics has drawn significant attention in peptidomimetic research.[1] A β-turn is defined as a tetrapeptide sequence in which the $C\alpha^{i}$-$C\alpha^{i+3}$ distance in a nonhelical region is less than 7 Å. In several versions it is stabilized by a 10 membered hydrogen-bonded ring (Fig. 1).[2] For many biologically active peptides, the β-turn is an important secondary structural element which is critical for their biological activities.[2] A number of bicyclic β-turn mimetics have been synthesized.[3] Among them, the [4,3,0]-bicyclic β-turn dipeptide (BTD) has been introduced as a β-turn mimetic by Nagai and co-workers,[4] and it has been used to study a number of bioactive peptides.[5] Despite the fact that the [4,3,0]-BTD induces a β-II′ turn conformation,[6] this simple β-turn dipeptide has not been very useful for improving the activity of small peptides in which the β-turn structure itself plays an important role in the interaction between peptide and receptor site.[7] This is primarily because individual side chain groups critical for bioactivity in the natural peptides were not present in the β-turn mimetic.[8]

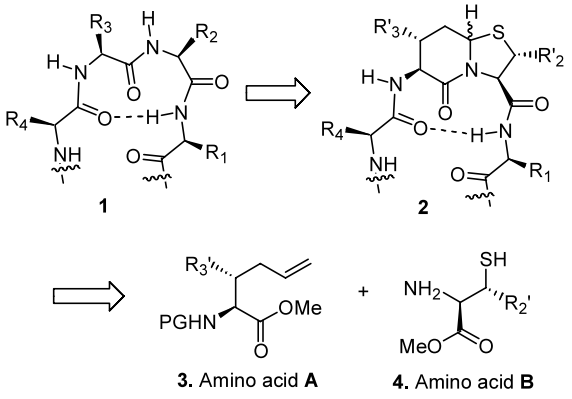

Figure 1. β-Turn in peptide, bicyclic design and its retrosynthetic analysis.[9]

We have succeeded in the development of a new methodology for the [4,3,0]-bicyclic scaffold from δ,ε-unsaturated amino acids.[10] Retrosynthetic analysis shows that the five chiral centers involved in the β-turn mimetics can be synthesized from two stereochemically defined amino acid derivatives (Fig. 1). While the asymmetric syntheses of β-aromatic and β-aliphatic substituted cysteines **4** have been developed in our group,[11] the synthesis of β-substituted δ,ε-unsaturated amino acids **3** has not been reported. ω-Unsaturated amino acids are of value in terms of their biological importance and their utility as asymmetric synthetic building blocks.[12] The terminal double bond is a precursor in organic synthesis which can be converted to the ω-hydroxy, ω-oxo, ω-carboxy, ω-epoxy, and ω-amino α-amino acids.[13] They also have been used in cyclization of peptides for secondary structures which were built

Keywords: Ni(II)-complex; δ,ε-unsaturated amino acid; β-side chain; β-turn mimetic; bicyclic dipeptide.

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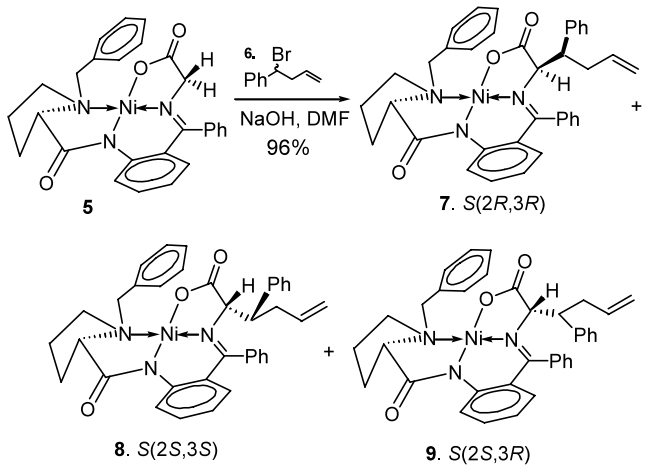


Scheme 1. The alkylation of (*S*)-BPB-Ni(II)Gly-complex.

Table 1. The alkylation of Ni(II)Gly-complex[a]

Entry	*T* (°C)	Time (min)	Yield[b]	Ratio(**7**/**8**/**9**)[c]
1	25	<5	98	11/85/4
2	0	15	96	12/85/3
3	−30	45	96	7/90/3
4	50	<5	<80	inconclusive

[a] All the reactions were preformed under argon. Decomposition of the Ni(II)-complex was observed when a prolonged reaction time was used.

[b] Combined yield of all diastereomeric products.

[c] Products ratios were determined on the crude products mixture by ^{1}H NMR. In particular, the most downfield aromatic signal in the region of 8.0–8.5 ppm were used for the determination.[21]

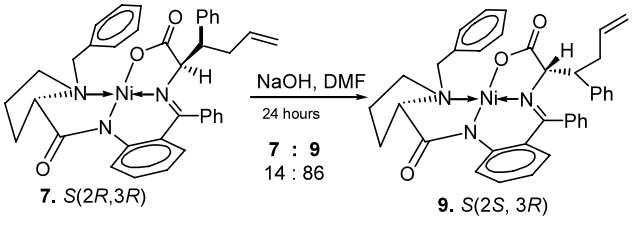
up by ring closing metathesis.[14] This paper reports the successful implementation of large scale synthesis of (2*S*,3*S*)- and (2*R*,3*R*)-2-amino-3-phenyl-5-hexenoic acids and their application in the synthesis of [4,3,0]-bicyclic dipeptides as β-turn mimetics.

The synthesis of enantiopure amino acids using a glycine equivalent in a Ni(II)-complex was first developed by Belokon et al.,[15] and the synthesis of ω-unsaturated amino acids has been reported via Ni(II)-complexes, though in low yield.[16] This reaction has been modified and the purification procedure has been improved recently (Scheme 1).[10,17] The alkylation of a secondary bromide[18] using the Ni(II)-complex generated a mixture of three diastereomers. Their relative stereochemistries were assigned according to our previous work[19] and finally confirmed by X-ray crystallography.[20] We have found that the reactivities of the two bromide enantiomers are very different, and high diastereoselectivity can be reached by using the racemic bromide in threefold excess (Table 1).

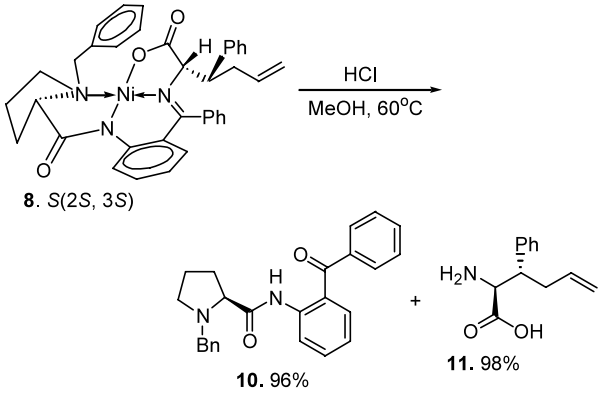
The diastereomeric ratio of these alkylated products changed as the temperature was changed. The ratio of the major isomer **8**[*S*(2*S*,3*S*)] to the minor isomer **7**[*S*(2*R*,3*R*)] was increased to 12:1 when the temperature was decreased to −30°C (Table 1). The minor product, **9**[*S*(2*S*,3*R*)], was always present at about 3% under our optimal reaction conditions. A higher temperature (50°C) not only gave both minor products in higher ratio, but also led to significant decomposition of the Ni(II)-complex. The stereoisomeric relationship of **7** and **9** was further confirmed by epimerization studies. The assigned minor product **7**[*S*(2*S*,3*R*)] was subjected to the reaction conditions of alkylation, but at room temperature for 24 h. Based on the ^{1}H NMR, the epimerization gives a mixture of **7**[*S*(2*R*,3*R*)]:**9**[*S*(2*S*,3*R*)] = 16:84 (Scheme 2). In this way, **9**[*S*(2*S*,3*R*)] was isolated by liquid chromatography and the sample was ready for characterization.

The major product **8** was purified by fractional recrystallization.[22] It was then hydrolysized to give a quantitative yield of the free amino acid **11** (Scheme 3). The organic chiral auxiliary, (*S*)-BPB **10**, was isolated by extraction with 96% recovery. It can be reused in the synthesis of the Ni(II)-complex **5** as starting material.[15] The separation of free amino acid from the Ni^{2+} salt was accomplished on an ion exchange column loaded in the H^+ form of the resin (Aldrich, Dowex® 50WX2-100 ion-exchange resin). (2*R*,3*R*)-2-Amino-3-phenyl-5-hexenoic acid also was synthesized from the (*R*)-Ni(II)-complex. Both free amino acids were isolated and dried by lyophilization. By using this modified method, the alkylation product could be synthesized on a 10-gram scale, and the free amino acid can be obtained on a 3-gram scale.

The α-amino functional group of the amino acid **11** was protected using CF_3CO_2Et, and the carboxyl group was converted to its methyl ester (Scheme 4). The unique advantage of using N^{α}-TFA protection is that it allows the aldehyde presented in an equilibrium between open



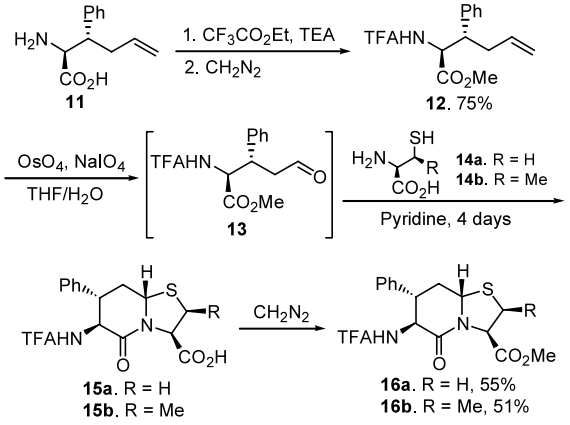
Scheme 2. Epimerization equilibrium of **7**[*S*(2*R*,3*R*)] and **9**[*S*(2*S*,3*R*)].



Scheme 3. Hydrolysis of the (*S*)-BPB-Ni(II)-complex.

chain and hemiaminal formation as discussed in our previous paper.[10] Osmylation and diol oxidation can be completed in 2 h in THF/H_2O, and without further purification, thiazolidine formation was accomplished in 6 h at room temperature using pyridine (Scheme 4). The bicyclic lactam formation was accomplished in tandem at 50°C in 4 days with no epimerization. The β-methyl-*L*-cysteine (**14b**) used was synthesized by modification of our recently reported method.[11,23] For purification and characterization, the bicyclic moieties were converted to the methylated products using diazomethane. The bicyclic products **16a** and **16b** with different side chain groups can be synthesized in about 50% yield in three steps from the starting material **12**. The bicyclic dipeptide with different chiralities at the 3 and 4 positions (Scheme 4) also was synthesized in comparable yield by using the (2*R*,3*R*)-amino acid as starting material.

The ^{1}H NMR spectra of the bicyclic structures were assigned by DQF-COSY. The ^3J coupling constants of H^3 and H^4 in **16a** and **b** are 9.2 Hz, which indicates an *anti*-relationship of these two hydrogens. This further confirmed the assigned stereochemistry of the major product **8** from the Ni(II)-alkylation. The bridge-head H was assigned as *S* in all the [4,3,0]-bicyclic dipeptides. NMR NOE studies also confirmed the bridge-head H configuration (Fig. 2). The 1,3-diaxial proton's NOE in the piperidine ring of **16b** indicated a *pseudo*-chair like conformation, and the large 1,4-diaxial proton's NOE in **16c** indicated a boat-like conformation which ensures both large substitutions Ph- and TFA-HN- are in equatorial positions. The bridge-head H configuration can be explained thermodynamically because the 2,5-*trans*-relationship is more stable than the 2,5-*cis* due to steric effects in thiazolidine formation.



Scheme 4. Synthesis of bicyclic dipeptides derivatives with side chain groups.

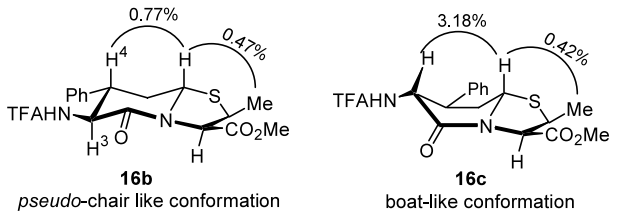


Figure 2. Proposed conformations and their transient NMR NOE of bicyclic dipeptides.

In summary, two enantiomers of β-substituted ω-unsaturated amino acids have been synthesized on a large scale. By using these novel amino acids, [4,3,0]-BTD with two β-side chain groups and five controlled chiral centers have been synthesized in five steps. This highly efficient strategy makes it possible to introduce chiral side chain functionalities in these β-turn mimetics, which in turn can be inserted into targeted peptides in a few steps.

Supporting information available

Experimental procedures and spectroscopic characterization ($[\alpha]_D$, ^{1}H NMR, ^{13}C NMR, HRMS) of all new compounds.

Acknowledgements

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17. General procedure for alkylation of the Ni(II)-complex: Ni(II)-complex **5** (1 equiv.) and ground NaOH (10 equiv.) were added to a flask which was purged two times with argon. Anhydrous DMF (4 mL/mmol) was added by syringe and the mixture was allowed to react for 5 min at room temperature. It was cooled down to −30°C before 1-bromo-but-3-enyl-benzene **6** (3 equiv.) was added in one portion. The reaction was kept at this temperature for 45 min. It was decanted into an aqueous solution (40 mL/mmol) containing 5% of HOAc. The suspended solution was extracted with benzene (3×20 mL/mmol) and the combined benzene extracts were washed with brine (4×10 mL/mmol). The emulsion was diminished by filtration through Celite. The solution was dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was first purified by fast liquid chromatograph, followed by fractional recrystallization in DCM/ether solution.[22]
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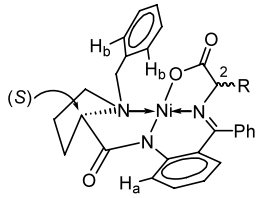
20. We have obtained X-ray structures of the diastereomeric cocrystal with 1/1 mixture of the *S*(2*S*,3*S*)/*S*(2*R*,3*R*) compounds, and the X-ray structure of the pure *S*(2*R*,3*R*)-compound which has two different conformers in the unit cell. These results will be published elsewhere.
21. The Ni(II)-complex products ^{1}H NMR structure were analyzed by COSY and 1D NOE. We found the two most downfield (~8.2 ppm) proton signals are the doublets of H_a and H_b in a ratio of 1 to 2 in all the spectra. In the *S*(2*R*) products, however, the H_a proton signal moves further downfield (~8.5 ppm), while the H_b proton signal moves toward highfield, and as a result, overlap with other aromatic proton signals.



22. The purity of the major products in the mother liquor was increased until no **7**[*S*(2*R*,3*R*)] could be detected by ^{1}H NMR. Nevertheless, the minor product **9**[*S*(2*S*,3*R*)], which had a similar R_f value to **8**[*S*(2*S*,3*S*)] (0.62 for **8**[*S*(2*S*,3*S*)] and 0.59 for **9**[*S*(2*S*,3*R*)] in 1/1 hexane/acetone solution), always coexisted in the mother liquor with the major product. A small amount of **7** and **8** were purified on an analytical HPLC column (IBM silica 2872053 column with a flow of 1 mL/min, gradient elute 2~4% isopropanol in DCM in 22 min) for characterization.
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