Pergamon

Tetrahedron Letters 42 (2001) 3159–3161

TETRAHEDRON LETTERS

An efficient approach to asymmetric synthesis of dipeptide β-turn mimetics: indolizidinone amino acids

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Received 16 January 2001; revised 2 March 2001; accepted 5 March 2001

Abstract—Azabicyclo[*X.Y.0*] alkane amino acids are rigid dipeptide β-turn mimetics with great potential applications for drug discovery. The lack of efficient methods to synthesize these compounds is a major bottleneck in this field. Herein we report an efficient approach to the enantiopure synthesis of (3*S*,6*S*,9*S*) and (3*R*,6*R*,9*R*) methyl 2-oxo-3-[*N*-(Boc/Cbz)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylates **1**. In this approach, the key intermediates **5a** and **5b** with different stereochemical configurations were efficiently constructed from the same precursor in high stereoselectivity via asymmetric hydrogenations using (*S*,*S*) or (*R*,*R*) Et-DUPHOS, Rh(I)-based catalysts. The process, starting from inexpensive diethyl 1,3-acetonedicarboxylate **2**, can allow for the practical synthesis of this class of compounds.

One of the active peptide mimetic fields is the so-called 'rigid dipeptide β-turn mimetics' that have been proposed to mimic or induce β-turn secondary structural features for peptides and proteins that are thought to play important roles in molecular recognition and biological activity.[1,2] Several peptide mimetic systems have been designed to try and mimic different types of reverse-turns.[1,2] Azabicyclo[*X.Y.0*]-alkane amino acids are particularly attractive because of their ability to serve as conformationally fixed surrogates of peptide turn secondary structures (Fig. 1).[1,2] It has been demonstrated that incorporation of some of these scaffolds into biologically active peptides has led to peptide mimetic ligands with enhanced activities and metabolic stabilities.[1–3] As part of our α-MSH (melanocyte stimulating hormones) program, we have identified the core sequence of α-MSH peptides His-(D/L) Phe-Arg-Trp and found a β-turn which includes the Phe and Arg residues.[4] We propose that azabicyclo[*X.Y.0*]-alkane amino acids may be useful to mimic the β-turn in

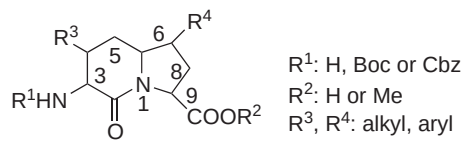

Figure 1. Indolizidinone amino acids **1**.

α-MSH peptides. This has created a need for efficient synthetic approaches toward such molecules. The synthesis of these molecules is very challenging because of many chiral centers. Though many methods have been developed for the synthesis of these compounds,[1a,b] most of these approaches require relatively long synthetic sequences, limiting practical syntheses. Here we report an efficient approach to synthesis of enantiopure indolizidinone-type 6,5-fused bicyclic lactams **1**.

Our group has been long interested in the design and synthesis of novel unnatural amino acids and peptide mimetics.[2,5] Recently we have developed a convenient method for the synthesis of (2*S*,6*S*)-diaminopimelic acid (DAP) and *meso*-(2*S*,6*R*)-diaminopimelic acid (*meso*-DAP), and aryl-substituted phenylalanine and tryptophan amino acids using asymmetric hydrogenation of didehydroamino acids with Burk's catalyst, Rh(I)(COD)-(*S*,*S*) or (*R*,*R*) Et-DUPHOS in high stereoselectivity (>95% ee). Herein we have employed these methods to synthesize the key intermediates 5-(1,3-dioxolane)-2,8-bis[*N*-benzyloxycarbonylamino]nonane-1,9-dioic acid dimethyl esters (**5**), which can be useful precursors of indolizidinone-type 6,5-fused bicyclic lactams **1** (Scheme 1).

The synthesis started from commercially available diethyl 1,3-acetonedicarboxylate (**2**) (Scheme 1). The functional carbonyl group in **2** was protected as a ketal by refluxing a mixture of **2** and ethylene glycol in the presence of catalytic amounts of $BF_3 \cdot OEt_2$ in benzene.[6]

Keywords: amino acids; β-turn mimetics; asymmetric hydrogenation.
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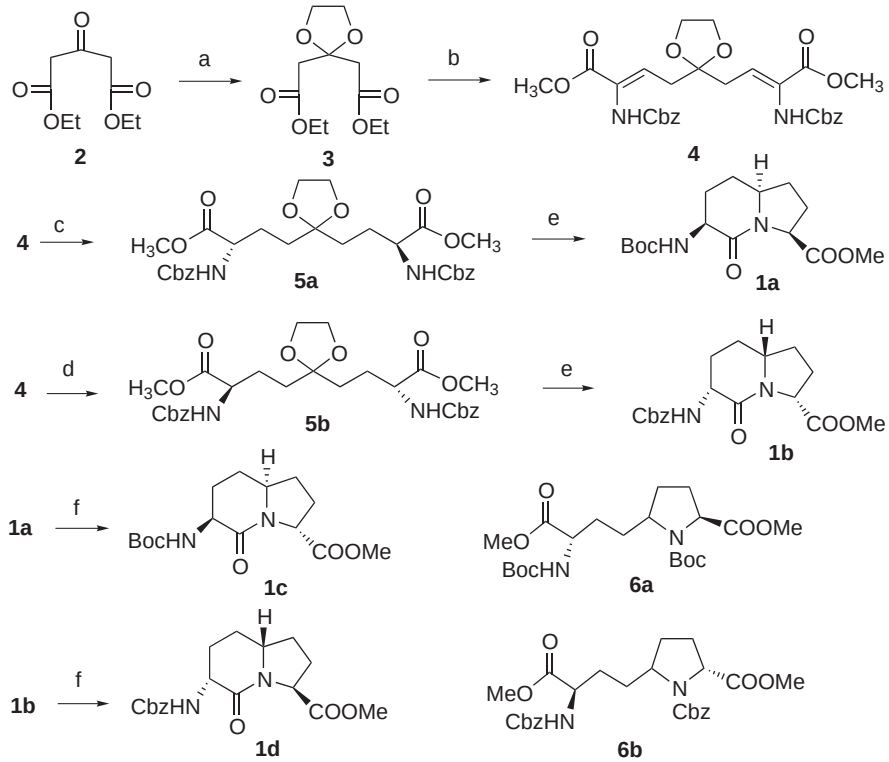
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00409-9



Scheme 1. Synthesis of indolizidinone amino acid **1**. (a) $HO(CH_2)_2OH$, $BF_3{\cdot}OEt_2$, benzene, reflux, 24 h, 76%; (b) (i) DIBAL, −78°C, toluene, 70 min, ca. 70%, (ii) $(MeO)_2P(O)CH(NHCbz)COOCH_3$, DBU, CH_2Cl_2, rt, 4 h, 72%; (c) Rh (I) (COD) (*S*,*S*) Et-DUPHOS, H_2 (70 psi), 24 h, MeOH, 97%; (d) Rh (I) (COD) (*R*,*R*) Et-DUPHOS, H_2 (70 psi), 24 h, MeOH, 95%;(e) (i) 10% Pd/C, H_2 (70 psi), MeOH/conc. HCl (1/4), 24 h, (ii) $NaHCO_3$, 1,4-dioxane, H_2O, 3–4 h, then $(Boc)_2O$ or Cbz-Cl, 3 h, 71–74%; (f) $NaN(SiMe_3)_2$, THF, −50°C, 1 h, then −20°C, 1 h, 70–74%.

The product **3** was obtained after work-up with high purity without further purification. The diethyl ester **3** was reduced to a dialdehyde using DIBAL (diisobutylaluminum hydride) in anhydrous toluene at −78°C for about 70 min. Approximately a 70% yield of the desired product was obtained as determined by ^{1}H NMR of the crude product mixture, with ca. 15% monoreduction product and 15% unreacted starting materials. Without purification of the crude product, the resulting mixture was subjected to the subsequent reaction (Scheme 1). The didehydroamino acid dimethyl ester **4** was obtained as the major product via the Horner–Emmons olefination[7] of the mixture with the phosphonate $(MeO)_2P(O)CH(NHCbz)COOMe$ and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as the base, in 72% yield. The ratio of (2*Z*,7*Z*) and (2*E*,7*Z*) was determined to be 95:5 by ^{1}H NMR.[8] Asymmetric hydrogenation of the mixture of the didehydroamino acids **4** using Burk's catalysts Rh (I) (COD) (*S*,*S*)-Et-DuPHOS or (*R*,*R*)-Et-DuPHOS afforded **5a** and **5b** in 97 and 95% yields, respectively, after column purification.[8–10] The two new absolute configurations were assigned as 2*S*,7*S* in **5a** and 2*R*,7*R* in **5b** based on the selectivity of the (*S*,*S*)-Et-DuPHOS and (*R*,*R*)-Et-DuPHOS ligands, respectively.[11] The key intermediates **5a** and **5b** then underwent deprotection, reductive amination, cyclization, and protection to provide the final molecules **1** (Scheme 1). We adapted a literature one-pot process of deprotection, reductive amination, and cyclization. Therefore, ketal hydrolysis and reductive amination followed by lactamization was accomplished in a mixture of methanol and concentrated hydrochloric acid (volume ratio 4/1) in the presence of 10% Pd/C under 70 psi of hydrogen for 24 h.[12,13] Without purification of the crude product, the free amino group was protected with Boc (*t*-butoxycarbonyl) or Cbz (benzoxycarbonyl). In fact, because of the incomplete lactamization reaction under acidic conditions, the reaction mixture was stirred for 3–4 h under basic conditions (pH 8–9) to render the lactamization complete followed by addition of $(Boc)_2O$ or Cbz-Cl.[13] The final product **1a** or **1b** was separated in 74 and 71% yields, respectively. Only one diastereomer (3*S*,6*S*,9*S*) **1a** or (3*R*,6*R*,9*R*) **1b** was isolated in each case. In contrast, previous literature results gave two isomers, (3*S*,6*S*,9*S*) **1a** or (3*R*,6*R*,9*R*) **1b** as the major products and (3*S*,6*R*,9*S*) or (3*R*,6*S*,9*R*) as the minor products.[13] Compounds **6a** and **6b** were also obtained in 8–12% yields due to incomplete lactamization, respectively.[13] The optical rotation $[\alpha]_D^{21}$ −17.4 (*c* 0.96, $CHCl_3$)], ^{1}H and ^{13}C NMR of (3*S*,6*S*,9*S*) **1a** was the same as reported in the literature[13] $[\alpha]_D^{20}$ −17.6 (*c* 1.0, $CHCl_3$)]. This result indicated that a >95% ee was achieved in the asymmetric hydrogenation reactions.[8] The epimerization of the C-9 center in **1a** or **1b** with $NaN(SiMe_3)_3$ in THF at −50°C for 1 h, then −20°C for 1 h, afforded the 9*R* or 9*S* diastereomer **1c** or **1d** as the major product in 70–74% yield following the literature procedure.[13]

In conclusion, we have developed an efficient approach to the synthesis of enantiopure indolizidinone amino acids **1**. In this approach, the key intermediates **5a** and **5b**, with different stereochemical configurations, were efficiently constructed from the same precursor via asymmetric hydrogenations using Burk's Rh(I)-based catalysts with different chrial ligands (*S*,*S*) or (*R*,*R*) Et-DUPHOS in high stereoselectivity. This method can be further exploited for the synthesis of alkyl-substituted indolizidinone amino acids **1** (Fig. 1).[14] The incorporation of these molecules into biologically active α-MSH peptides and the study of structure–activity relationships are in progress.

Acknowledgements

This work was supported by US Public Health Service (DK 17420) and the National Institute of Drug Abuse (DA 13449). We also thank Professor Dominic V. McGrath for using his group's polarimeter. The views are those of the authors and not necessarily the USPHS.

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10. Compound **5a**: $[\alpha]_D^{24}$ −11.8 (*c*1.01, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.59–1.69 (m, 6H), 1.88–1.93 (m, 2H), 3.74 (s, 6H), 3.89 (s, 4H), 4.36 (dd, $J_1=7.0$ Hz, $J_2=13.0$ Hz, 2H), 5.10 (s, 4H), 5.38 (d, $J=8.0$ Hz, 2H), 7.29–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.9, 32.9, 52.5, 53.9, 65.2, 67.1, 110.5, 128.2, 128.3, 128.6, 136.4, 156.1, 172.9. HRMS (FAB) calcd for $C_{29}H_{37}N_2O_{10}$ 573.2448. Found 573.2444. **5b**: $[\alpha]_D^{26}$ −12.1 (*c*1.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 159–1.69 (m, 6H), 1.88–1.93 (m, 2H), 3.73 (s, 6H), 3.89 (s, 4H), 4.36 (dd, $J_1=7.0$ Hz, $J_2=13.5$ Hz, 2H), 5.10 (s, 4H), 5.39 (d, $J=7.5$ Hz, 2H), 7.30–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.9, 32.9, 52.5, 53.9, 65.2, 67.1, 110.5, 128.2, 128.3, 128.6, 136.4, 156.1, 172.9; HRMS (FAB) calcd for $C_{29}H_{37}N_2O_{10}$ 573.2448. Found 573.2441.
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