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From Macrocycle Dipeptide Lactams To Azabicyclo[X.Y.0]alkanone Amino Acids: A Transannular Cyclization Route for Peptide Mimic Synthesis

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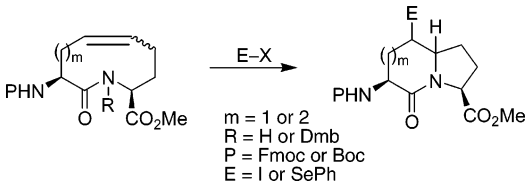
ABSTRACT



Macrocyclic and fused bicyclic dipeptides are complementary motifs for mimicry of different types of β-turn geometry. Macrocyclic dipeptide mimics have served as precursors for the synthesis of their bicyclic counterparts using electrophilic transannular cyclizations of 9- and 10-membered ring lactams 9–12 to form azabicyclo[4.3.0]- and -[5.3.0]alkanone amino esters 13–16.

Peptides are important endogenous molecules responsible for a multitude of roles in human physiology; however, their therapeutic potential is often limited because of their poor bioavailability, rapid metabolism, and short duration of action. Peptide mimics have thus been developed to retain the desired biological effects of the parent peptide and to remove such undesirable characteristics.[1] In this respect, azabicyclo[X.Y.0]alkanone amino acids have proven to be effective dipeptide mimics because their fused bicyclic ring system can constrain the backbone dihedral angle geometry to induce secondary structures such as β-turns. Although many approaches have been conceived for making azabicycloalkanone amino acids,[2] few examples have made practical use of common precursors for making a set of ring systems.

The introduction of a set of dipeptide mimics is often desired to provide detailed information about the conformation specifically required by the peptide to effectively bind and activate the receptor. The acquisition of a set of azabicycloalkanone amino acids requires, however, performing a series of multistep syntheses because few dipeptide mimics are commercially available. For example, to study opioid receptor-like 1 (ORL1) receptor antagonists,[3] replacement of the commercially available fused-6,5 thiaindolizidinone amino acid with fused-6,5, -5,6, and -6,6 azabicycloalkanone amino acids required syntheses of seven, seven, and five steps, respectively, from suitably protected amino dicarboxylic acids in overall yields ranging from 45% to 61%.[4] The use of such a tour de force of peptide scaffolds

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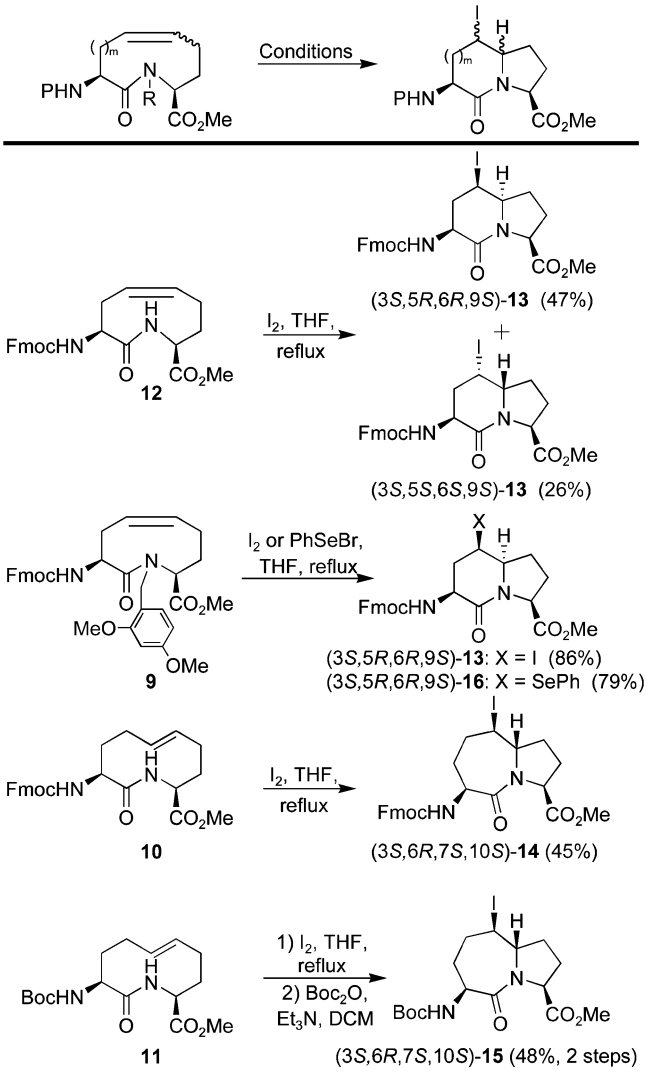
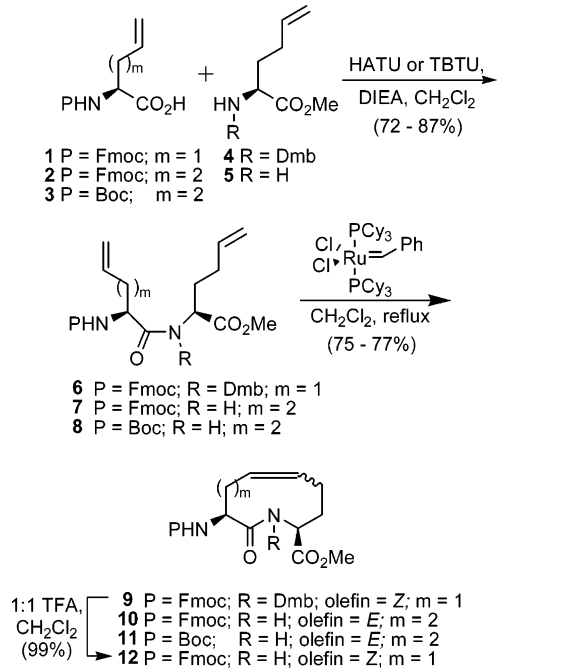
Scheme 1. Conversion of Macrocyclic Dipeptides into Bicyclic Dipeptides by Electrophilic Transannular Cyclization



Scheme 2. Unsaturated Macrocyclic Dipeptide Lactam Synthesis[a]



[a] Dmb = 2,4-dimethoxybenzyl.

did deliver analogues with remarkable potency and selectivity for the ORL1 receptor over the other opioid receptor subtypes. For such structure−activity studies to become more practical, however, a more efficient methodology is needed for making such mimics.

Considering that electrophilic transannular cyclization of unsaturated macrocyclic lactams of 9- and 10-membered rings has been previously used to prepare indolizidinone and quinolizidinone ring systems,[5] we have pursued this approach for converting macrocyclic dipeptide surrogates into their azabicycloalkanone amino acid counterparts (Scheme 1).

The set of 9- and 10-membered unsaturated macrocyclic dipeptides **9**−**12** was synthesized using our recently described protocol[6] (Scheme 2). Briefly, suitably Fmoc- and Boc-protected allyl- and homoallylglycines **1**−**3** were coupled to homoallylglycine methyl ester **5** using TBTU and DIEA and to *N*-(Dmb)homoallylglycine methyl ester **4** using HATU and DIEA in yields varying between 75% and 87% (Dmb = 2,4-dimethoxybenzyl). Annulation of the dipeptides **6**−**8** bearing two olefinic side chains was achieved using the first generation of Grubbs catalyst to afford the macrocyclic unsaturated lactams **9**−**11** in yields between 71% and 77%. Finally, the Dmb group, which was essential for the annulation of the nine-membered lactams, was removed by treatment with 50% TFA in CH_2Cl_2 to afford quantitatively the secondary amide **12**.

The electrophilic transannular cyclization was initially performed on 9- and 10-membered lactams **9**−**12** using iodine as the source of electrophile (Scheme 1). Treatment of the Fmoc-protected, nine-membered lactam **12** with 4 equiv of I_2 in THF at reflux gave two isomeric bicyclic products (3*S*,5*R*,6*R*,9*S*)- and (3*S*,5*S*,6*S*,9*S*)-**13** in 46% and 27% respective yields (see below for stereochemical assignments). On the other hand, treatment of the corresponding tertiary Dmb-amide **9** under similar conditions afforded bicycle (3*S*,5*R*,6*R*,9*S*)-**13** as a single product in 86% yield.

(3*S*,6*R*,7*S*,10*S*)-Azabicyclo[5.3.0]alkanone **14** was similarly prepared in 45% yield by treating Fmoc-protected secondary lactam **10**, bearing the trans double bond, with iodine in THF at reflux. Loss of the Boc group was observed

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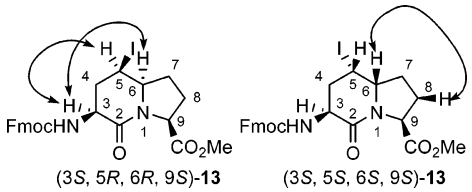

Figure 1. NOESY correlations observed for compounds (3*S*,5*R*,-6*R*,9*S*)-**13** and (3*S*,5*S*,6*S*,9*S*)-**13**.

in the reaction of the corresponding Boc-protected 10-membered macrocycle **11** with iodine in THF; however, pyrroloazepinone **14** with the same stereochemistry as its Fmoc counterpart could be isolated in 48% overall yield after reprotection using Boc_2O and triethylamine in CH_2Cl_2.

In light of the effective transannular cyclizations using iodine, a cursory investigation of alternative electrophiles was performed using macrocycle **9** to examine effects on reaction stereochemistry and product structure. Treatment of **9** with bromine or *N*-bromosuccinimide did not afford a bicycle; instead, bromination of the aromatic ring was observed by LC/MS. Also, treatment of **9** with mercuric acetate did not lead to bicyclic products. Alternatively, exposure of dipeptide **9** to 4 equiv of phenylselenium bromide in THF at reflux provided bicyclic amino ester **16** in 79% yield (Scheme 1).

The assignment of the structures and stereochemistry of the different azabicyclo[X.Y.0]alkanone amino acids was performed using NMR spectroscopy and X-ray crystallography (Supporting Information). For bicycle **13**, the ring protons came at distinct chemical shifts and their sequential order was assigned using a COSY experiment. Coupling between the downfield carbamate proton and the proton of the adjacent backbone carbon was used as the starting point for tracing the through-bond connectivities of the various protons around the bicycle. With the through-bond connectivities ascertained, the through-space connectivities observed in the NOESY spectra were used to assign relative stereochemistry. In the NOESY spectrum of indolizidinone (5*R*,6*R*)-**13**, long-distance transfer of magnetization between the C3 proton and the iodinated C5 and ring-fusion C6 protons, respectively, confirmed the concave bicycle structure and the trans relation between the ring-fusion proton and the iodide (Figure 1). In (5*S*,6*S*)-**13**, the bridgehead stereochemistry was assigned on the basis of NOE with the C8 β-proton which came downfield relative to its α-proton counterpart due to the anisotropic effect of the C9 carboxylate (β is on the same face as the C3 amine).[7] In the cases of fused-7,5 systems **14** and **15**, the relative stereochemistry of the newly formed centers was confirmed by X-ray crystallographic analysis of crystals from acetone/hexanes and ethyl acetate/hexanes, respectively (Figure 2).[8] The *cis* relationship among

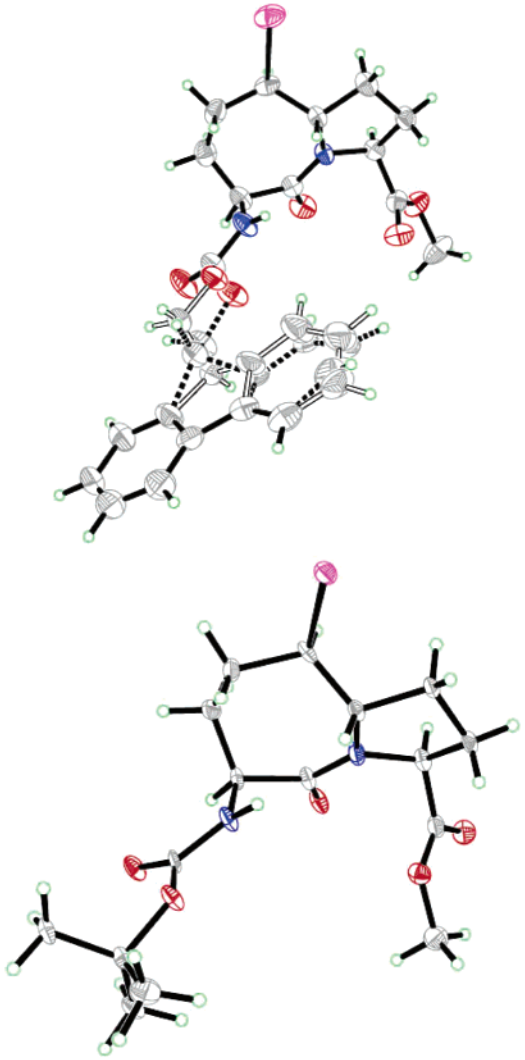

Figure 2. X-ray crystal structures of **14** (top) and **15** (bottom).

the iodide and the bridgehead proton and the convex bicycle was observed in both structures.

In concurrence with an earlier computational study of the parent pyrroloazepinone,[9] in their respective X-ray structures, the ψ and φ dihedral angles within bicycles **14** (−64.1°; −49.4°) and **15** (−63.5°; −46.6°) were similar to ideal values for the central residues in a type I β-turn (−30°; −90°);[10] however, they were less similar than the dihedral

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(8) (a) Crystallographic data for **14**: $C_{26}H_{27}IN_2O_5$; M_w = 574.40; orthorhombic crystals; space group *P*212121; unit cell dimensions, a = 5.7630(2) Å, b = 17.0035(8) Å, c = 25.3668(11) Å; volume of unit cell, 2485.72(18) Å^3; Z = 4; d = 1.535 g/cm^3; R_f = 0.0354, R_w = 0.0565 for all data; GOF = 1.005. (b) Crystallographic data for **15**: $C_{16}H_{25}IN_2O_5$; M_w = 452.28; monoclinic crystals; space group *P*21; unit cell dimensions, a = 11.6497(11) Å, b = 5.8377(6) Å, c = 13.4469(14) Å, β = 100.394(5) Å; volume of unit cell, 899.48(16) Å^3; Z = 2; d = 1.670 g/cm^3; R_f = 0.0998, R_w = 0.2443 for all data; GOF = 1.005. The author has deposited the atomic coordinates for the structures of **14** and **15** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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angles of the parent macrocyclic dipeptide, which exhibited $\psi = -20°$ and $\varphi = -107°$ in the X-ray structure of a model peptide.[11] Moreover, the φ dihedral angle was consistent with an inverse γ-turn ($\varphi = -70$ to $-85°$).[12] The power to pass from macrocycle- to bicycle-constrained dipeptide surrogates provides the opportunity to explore different turn geometries with mimics derived from a common reaction sequence.

A novel effective approach for the synthesis of azabicyclo-[4.3.0]- and -[5.3.0]alkanone amino esters has been developed featuring the electrophilic transannular cyclization of 9- and 10-membered macrocyclic dipeptides. This approach offers potential for converting one turn mimic into another. Furthermore, the resulting iodide provides the opportunity for the introduction of side chains onto the heterocycle ring. We are now developing these avenues for peptide mimicry.

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Supporting Information Available: Experimental procedures and spectral data for compounds **13**−**16**. Copies of ^{1}H and ^{13}C NMR, DEPT 135, COSY, and HMQC spectra for compounds **13**−**16**, and X-ray data for compounds **14** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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