Short and Efficient Synthesis of *Homo-Freidinger* Lactams: An Olefin Metathesis Approach Towards Conformationally Restricted β-Amino Acid Analogues

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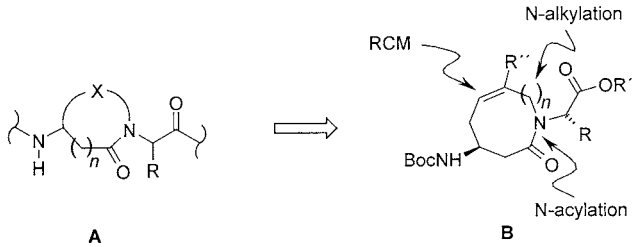
Abstract: Peptide coupling of the *N*-allyl or *N*-homoallyl α-amino acid esters **6a**–**d** with enantiomerically pure β-*C*-allylglycine gave access to the dienes **7a**–**d** which were subjected to an olefin metathesis reaction. Thus, the novel lactam bridged peptide mimics **8a**–**d** were obtained in good overall yield. Modifications in ring size and substitution pattern of the *Homo-Freidinger* lactams were demonstrated.

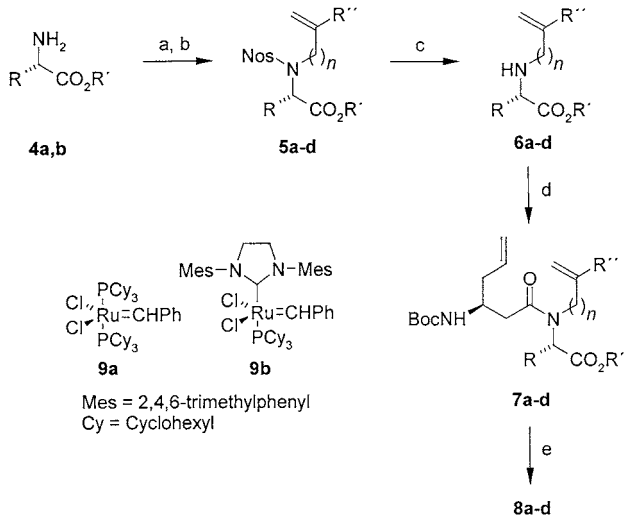
Key words: β-amino-acids, lactams, metathesis, peptide mimics, ruthenium

Constrained peptides offer a fascinating challenge to gain insight into molecular recognition processes between peptide ligands and bio-receptors. Thus, the incorporation of peptide backbones into cyclic structures has attracted tremendous efforts on the synthesis of enzyme inhibitors, peptide hormones and neuroreceptor ligands.[1,2] Among numerous examples, especially *Freidinger* lactams (Scheme 1, formula **A**, $n = 0$) were proven successful.[3,4] In addition, the application of the olefin metathesis reaction[5] to the synthesis of *Freidinger* lactams and other cyclic amino acid derivatives was recently demonstrated,[6] thus constraining the backbone of α-amino acids by an olefin linker.



Scheme 1

On the other hand, the remarkable metabolic stability and the interesting structural properties of β-amino acid derived peptide mimics are well-known.[7] Based on these findings, *Homo-Freidinger* lactams (formula **A**, $n = 1$) were developed, representing conformationally constrained β-amino acid equivalents.[8] As a part of our program established for the design of β-analogues[9] of the dopamine D2 receptor modulating peptide Pro-Leu-Gly-NH_2 (PLG),[10] *Homo-Freidinger* lactam derived tripeptide mimics were shown to adopt β-turn related structures and to induce an increase of affinity at the dopamine D2 receptor.[11] As an extension of our studies towards the synthesis of enantiopure β-amino acid derivatives and the design of secondary structure model systems,[12] we wish to present our results concerning the synthesis of unsaturated *Homo-Freidinger* lactams of type **B** (Scheme 1), when an olefin metathesis is employed as the key reaction step.



4a: R = H, R´=Et; **4b**: R = R´= Me; **5a, 6a, 7a**: R = R´´= H, R´= Et, $n = 1$; **5b, 6b, 7b**: R = R´= Me, R´´= H, $n = 1$; **5c, 6c, 7c**: R = H, R´= Et, R´´= Me, $n = 1$; **5d, 6d, 7d**: R = R´´= H, R´= Et, $n = 2$

Scheme 2 a) 4-nitrobenzenesulfonyl chloride, NEt_3, CH_2Cl_2, 0 °C (70–80%); b) allyl bromide, K_2CO_3, DMF for **5a** (92%) and for **5b** (95%), 3-bromo-2-methyl-1-propene, K_2CO_3, DMF for **5c** (94%), 3-butene-1-ol, DEAD, PPh_3, CH_2Cl_2 (76%) for **5d**; c) PhSH, K_2CO_3, DMF (50–80%); d) DCC, HOBt, (*S*)-*N*-Boc-3-amino-5-hexenoic acid, CH_2Cl_2 (40–94%); e) **9a** (10 mol%) or **9b** (5 mol%), see Table.

Following our plan of synthesis as indicated for **B**, the metathesis precursors **7a**–**d** were prepared by DCC–HOBt induced peptide coupling of (*S*)-*N*-Boc-3-amino-5-hexenoic acid[13] with the *N*-allyl and *N*-homoallyl amino acid esters **6a**–**c** and **6d**, (Scheme 2). In turn, the secondary amines **6a**–**d** were readily available from the natural

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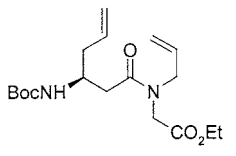
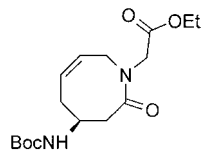
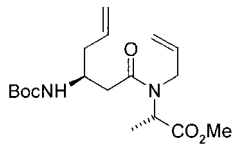
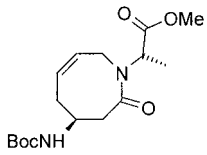
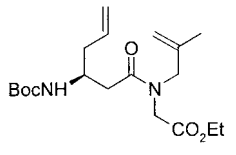
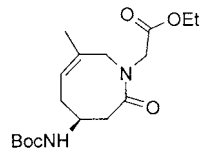
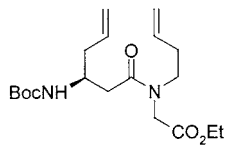
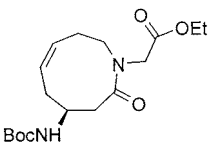
amino acid derivatives **4a,b** by sulfonylation, alkylation of the respective sulfonamides and subsequent thiol-assisted deprotection of the alkylation products **5a–d**. This strategy was first developed by Fukuyama[14] and recently applied by Reichwein and Liskamp.[15] Starting from the cyclization precursors **7**, we tried to prepare differently sized *Homo-Freidinger* lactams to evaluate the synthetic scope of our approach. The results of the RCM reaction of the dienes **7a–d** are summarized in the Table.

Table Results of the Metathesis Reaction of the Dienes **7a–d** (2 mM, Reflux, DCE)

Entry	Diene	Cycloolefin	Catalyst (yield)
1	 **7a**	 **8a**	**9a** (44%) **9b** (65%)
2	 **7b**	 **8b**	**9a** (61%)
3	 **7c**	 **8c**	**9b** (82%)
4	 **7d**	 **8d**	**9a** (47%) **9b** (64%)

The olefin metathesis experiments were performed employing the ruthenium-based catalysts **9a** or **9b**.[16] Since it is well known that elevated temperatures facilitate ring closure to medium sized rings,[17] 1,2-dichloro ethane (DCE) at reflux temperature (81 °C) was utilized for all metathesis reactions. In addition, we chose a substrate concentration of 2 mM since this concentration has proved to be sufficient to prevent possible oligomerization processes.[12] As a matter of fact, all cyclizations succeeded without any detectable by-products.[18] The synthesis of the azocinone **8a** from the diene **7a** proceeded with satisfying yield when promoted by Grubbs' catalyst **9a** (entry 1). Running the same reaction with the highly active ruthenium complex **9b** bearing a *N*-heterocyclic carbene ligand, an increase of the yield was observed. After this first encouraging results we were happy to obtain the alanine derived azacycle **8b** (entry 2), thus showing the possibility to introduce various side chains into the target dipeptidic structures which will be of interest for SAR studies in medicinal chemistry. The catalyst **9b** is known to tolerate different substitution patterns of the participating double bonds in metathesis reactions.[19] In fact, starting from the isopropenyl derivative **7c**, the cycloolefin **8c** could be obtained in 82% yield (entry 3). Variation of the ring size of lactam based templates is of particular interest for investigating the conformational behavior of peptide mimics.[12] Thus, we were happy to accomplish the synthesis of the 9-membered azoninone **8d** in 47% and 64% yield from the precursor **7d** renouncing any conformational predispositions which might have accelerating effects (entry 4). According to the NMR spectra, the endocyclic double bond of **8d** shows *cis*-geometry, exclusively. Oligomerization products were not observed.

In summary, we have developed a valuable and widely applicable synthetic procedure to lactam-bridged dipeptide mimics exploiting the combination of ex-chiral-pool synthesis and olefin metathesis reaction. The strategy enables the synthesis of the hitherto unknown unsaturated *Homo-Freidinger* lactams. Further investigations are ongoing in our laboratory.

Acknowledgement

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(18) **General Procedure for the Ring-Closing Olefin Metathesis Reaction:** Catalyst **9a** (10 mol%) or **9b** (5 mol%), was added to a 2 mM solution of the diene **8** in degassed 1,2-dichloro ethane under an atmosphere of dry nitrogen employing flame-dried glass ware. Subsequently, the mixture was heated to reflux until TLC indicated completion of the reaction. After evaporation of the solution the resulting residue was purified by column chromatography on Merck silica gel (230-400 mesh, ASTM) using freshly distilled solvents. All RCM-products were fully characterized by spectroscopic methods and microanalysis:
8a: colorless oil, $[\alpha]_D^{21}$ +5.3 (0.19, $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.43 (s, 9 H, *tert*-Bu), 2.35–2.46 (m, 3 H, H-5a,b/H-3a), 3.01 (dd, *J* = 12.4, 5.3 Hz, 1 H, H-3b), 3.78–3.89 (m, 1 H, H-8a), 4.00–4.10 (m, 1 H, H-4), 4.16 (d, *J* = 17.4 Hz, 1 H, α-C*H*$_2$), 4.20 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$), 4.24 (d, *J* = 17.4 Hz, 1 H, α-C*H*$_2$), 4.31–4.45 (m, 1 H, H-8b), 5.30 (d, *J* = 8.2 Hz, 1 H, N*H*), 5.48–5.66 (m, 1 H, C*H*=), 5.72–5.83 (m, 1 H, C*H*=). ^{13}C NMR ($CDCl_3$, 91 MHz): δ 14.1, 28.3, 29.8, 36.8, 48.9, 49.8, 52.6, 61.3, 79.2, 126.3, 128.5, 154.8, 169.2, 171.0. IR(film): 3324, 2977, 2931, 1747, 1712, 1700, 1643 cm^{-1}. MS (EI): *m/z* 326 [M$^+$]. Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 59.05; H, 8.21; N, 8.43. TLC: R_f 0.12 (ligroin–EtOAc, 6:4).
8b: colorless oil, $[\alpha]_D^{22}$ –25.7 (0.07, $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.39 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.44 (s, 9 H, *tert*-Bu), 2.35–2.47 (m, 3 H, H-5a,b/H-3a), 2.95 (dd, *J* = 12.2, 5.5 Hz, 1 H, H-3b), 3.69 (s, 3 H, OC*H*$_3$), 3.82–3.95 (m, 1 H, H-8a), 4.05–4.15 (m, 2 H, H-8b/H-4), 5.30 (d, *J* = 8.5 Hz, 1 H, N*H*), 5.36 (q, *J* = 7.1 Hz, 1 H, α-C*H*), 5.45–5.55 (m, 1 H, C*H*=), 5.70–5.80 (m, 1H, C*H*=). ^{13}C NMR ($CDCl_3$, 91 MHz): δ = 14.8, 28.6, 29.4, 36.9, 47.7, 49.4, 52.1, 60.4, 79.3, 126.1, 128.9, 154.9, 160.4, 172.0. IR(film): 3318, 2978, 1741, 1708, 1641, 1502, 1475 cm^{-1}. MS (EI): *m/z* 326 [M$^+$]. Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.73; H, 8.11; N, 8.31. TLC: R_f 0.11 (ligroin–EtOAc 6:4).
8c: colorless oil, $[\alpha]_D^{20}$ +31.6 (0.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.28 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.42 (s, 9 H, *tert*-Bu), 1.67 (s, 3 H, C*H*$_3$), 2.35–2.40 (m, 3 H, H-5a,b/H-3a), 2.98 (dd, *J* = 12.4, 5.3 Hz, 1 H, H-3b), 3.64 (d, *J* = 17.8 Hz, 1 H, α-C*H*$_2$), 4.20 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$), 4.28 (d, *J* = 17.5 Hz, 1 H, α-C*H*$_2$), 4.75–4.95 (m, 2 H, H-8a,b), 5.24 (d, *J* = 8.5 Hz, 1 H, N*H*), 5.48–5.55 (m, 1 H, H-4), 5.55–5.60 (m, 1 H, C*H*=). ^{13}C NMR ($CDCl_3$, 91 MHz): δ 14.1, 19.9, 23.3, 28.4, 29.7, 36.9, 50.0, 56.3, 61.3, 79.2, 121.9, 135.2, 154.9, 169.3, 173.1. IR(film): 3340, 2978, 2935, 1745, 1708, 1646, 1504 cm^{-1}. MS (EI): *m/z* 340 [M$^+$]. Anal. Calcd for $C_{17}H_{28}N_2O_5 \times {}^1/_4\ H_2O$: C, 58.94; H, 8.14; N, 8.09. Found: C 58.87; H, 8.56; N, 7.57. TLC: R_f 0.18 (ligroin–EtOAc 1:1).
8d: colorless oil, $[\alpha]_D^{22}$ +9.2 (0.13, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 360 MHz, 353 K): δ 1.20 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.40 (s, 9 H, *tert*-Bu), 2.15–2.25 (m, 2 H, C*H*$_2$), 2.28–2.39 (m, 2 H, C*H*$_2$), 2.40–2.50 (m, 2 H, C*H*$_2$), 3.45–3.60 (m, 2 H, H-9a,b), 3.70–3.85 (m, 1 H, H-4), 3.97 (d, *J* = 17.0 Hz, 1 H, α-C*H*$_2$), 4.07 (d, *J* = 17.0 Hz, 1 H, α-C*H*$_2$), 4.11 (q, *J* = 7.1 Hz, 2 H, OC*H*$_2$), 5.62 (ddd, *J* = 8.5, 10.6, 8.5 Hz, 1 H, C*H*=), 5.76 (ddd, *J* = 8.1, 10.6, 8.1 Hz, 1 H, C*H*=), 6.28 (br s, 1 H, N*H*). ^{13}C NMR (DMSO-d_6, 91 MHz): δ = 13.9, 26.0, 28.1, 31.3, 40.8, 49.6, 49.9, 50.3, 60.3, 79.1, 128.4, 130.2, 154.3, 169.3, 171.7. IR(film): 3385, 2979, 2933, 1747, 1706, 1630, 1487 cm^{-1}. MS (EI): *m/z* 340 [M$^+$]. Anal. Calcd for $C_{17}H_{28}N_2O_5$: C, 59.98; H, 8.29; N, 8.23. Found: C, 59.61; H, 8.48; N, 7.93. TLC: R_f 0.13 (ligroin/EtOAc 6:4).
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