**Homo-Freidinger Lactams: Stereoselective Synthesis of 4-Aminopiperidin-2-one Derivatives from Aspartic Acid**

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Received 20 April 1998-06-23

Abstract: Starting from aspartic acid a stereoselective synthesis of enantiomerically pure 4-aminopiperidin-2-ones which can serve as conformationally restrained β-amino acid equivalents in peptidomimetics is described. The synthesis is based on the regioselective functionalization of the 1,4-bis-electrophile 2b and a diastereoselective introduction of various side chain equivalents into the lactam α-position of 4b,c.

Conformationally locked peptide surrogates have been utilized extensively in the design and development of enzyme inhibitors or neuroreceptor ligands.14 This strategy afforded valuable information regarding the elucidation of the biologically active conformation of peptides and led to drug candidates with remarkable affinity, selectivity and metabolic stability.5 Among the numerous developments in this field, incorporating the α-amino carboxamide moiety of a peptide backbone into a Freidinger lactam (I) has proven very successful.6-10 On the other hand, β-amino acid derived substructures and the investigation of β-peptides led to interesting peptidomimetics.11-13 As far as we know, a combination of these two strategies was not reported yet.

As part of our efforts on the synthesis of enantiopure β-amino acid derivatives,14,15 here we report the first stereoselective synthesis of 4-aminopiperidin-2-ones as lactam-bridged analogs with a β-amino carboxamide substructure (Homo-Freidinger lactams, II). Applying this approach, our initial results on lactam-constrained mimetics of the dopamine receptor modulating peptide Pro-Leu-Gly-NH216 are presented.

![Diagram of lactam synthesis](https://via.placeholder.com/150)

The synthesis of a N-protected 4-aminopiperidine in enantiomerically pure form was planned starting from natural aspartic acid (I). Taking advantage of our recently described methodology we were able to functionalize regioselectively the dibenzyl protected aminobutanediol 2a.17-20 Thus, activation of 2a by MesCl gave the bis-electrophile 2b which could be transformed into the azido nitrile 3a by subsequent substitution with LiCN and NaN₃. Due to an activating anhemic participation of the dibenzylamino group the leaving group in position 1 is exclusively displaced by the nucleophile which is added first. The formation of regioisomers was not observed. Chemoselective reduction of the azide functionality in the presence of the nitrile group was accomplished under Staudinger conditions 21 giving the amino nitrile 3b in 81 % yield. Alternatively, a more direct preparation of 3b is possible when liquid NH₃ is used as the "second nucleophile" instead of NaN₃.22 Lactamization of the amino nitrile 3b was induced by HCl/MeOH. The reaction sequence is highly practical and efficient providing the amino lactam 4a in 58 % overall yield, based on (S)-aspartic acid (I), as well as the (R)-configured enantiomer of 4a (ent-4a) when commercially available (R)-aspartic acid (ent-1) is used as the starting material.

Since 4a should serve as a versatile building block, introduction of substituents representing β-amino acid side chains was envisioned. This should be done by N-protection, deprotonation of the lactam α-position and subsequent reaction with representing electrophiles. We evaluated Boc and, alternatively, benzyl as protecting groups for the lactam function. Thus, deprotonation of the lactam 4 followed by addition of Boc₂O or BnBr afforded 4b 23 and 4c, respectively. For the introduction of the Boc group reaction of 4a with Boc₂O in the presence of DMAP 24 turned out to be the more convenient and higher yielding alternative. C-alkylation in position 3 was accomplished by deprotonation of 4b with LDA and subsequent reaction with representing electrophiles. We evaluated Boc and, alternatively, benzyl as protecting groups for the lactam function. Thus, deprotonation of the lactam 4 followed by addition of Boc₂O or BnBr afforded 4b 23 and 4c, respectively. For the introduction of the Boc group reaction of 4a with Boc₂O in the presence of DMAP 24 turned out to be the more convenient and higher yielding alternative. C-alkylation in position 3 was accomplished by deprotonation of 4b with LDA and subsequent trapping with MeI at -78°C. The reaction proceeded with high diastereoselectivity. Only the trans isomer 5a could be detected by NMR spectroscopy of the crude reaction product 25. After purification by flash chromatography the methylation product 5a, which represents a conformatively restricted equivalent for β²-homoalanine,26 was isolated in 75 % yield. Analogously, deprotonation and methylation of the N-benzyl protected lactam 4c resulted in exclusive formation of trans configured isomer 5b. Since the methylation of 4b proceeded in higher yield and enabled the performance of a selective cleavage of either N-substituents we chose the orthogonally protected lactam 4b for further alklylation reactions. Thus, the lactam bridged β²-homo phenylalanine derivative 5c could be obtained from 4b in diastereomerically pure form when benzyl bromide was used as an...
electrophile (yield: 85%). Furthermore, highly diastereoselective introduction of an allyl, propynyl or TMS-propynyl substituent could be accomplished. Thus, deprotonation of 4b and subsequent reaction with allyl iodide, propynyl bromide as well as TMS-propynyl bromide resulted in formation of the products 5d, 5e and 5f, respectively. Electrophilic fluorination employing NFSI (N-fluorobenzene sulfonimide) afforded the α-fluoro lactam 5g. In all cases, the electrophilic attack at the enolate occurs exclusively from the bottom side (re). Obviously, the si-face is strongly shielded by the sterically demanding dibenzylamine substituent. Structural analysis of the alkylation products was performed by 1H NMR spectroscopy when diagnostic coupling constants and NOEs indicate a half-chair conformation and an equatorial disposition for both the dibenzylamine and the introduced substituents.

The incorporation of the described Homo-Freidinger lactams into conformationally restricted mimetics of the dopamine receptor modulating peptide Pro-Leu-Gly-NH₂ and their investigation for biological activity are currently investigated in our laboratories. Using the (S)-configured building block 4a as an representative example the preparation of such a tripeptide surrogate is reported. Thus, N-deprotonation of the aminopiperidinone 4a by KH and subsequent reaction with ethyl bromoacetate led to formation of the N-alkylation product 6a incorporating a Gly subunit. Coupling of the amino function with Pro was accomplished by hydrogenolytic N-debenzylation and subsequent DCC/HOBt induced acylation of the primary amine 6b with Cbz-Pro. Finally, aminolysis of the ester functionality of the coupling product 7a afforded 7b which could be readily N-deprotected to give the lactam-restricted Pro-Leu-Gly-NH₂ analog 7c in good overall yield.

In conclusion, an efficient and practical approach to enantiomerically pure 4-aminopiperidin-2-ones including 3-substituted derivatives and their application as peptidomimetics with Homo-Freidinger lactam substructure is presented. Further investigations on structure activity relationship studies of conformationally restrained dopamine receptor modulating peptide mimetics will be reported shortly.

Acknowledgments: This work was supported by the Deutsche Forschungsgemeinschait and the Fonds der Chemischen Industrie. Dr. R. Waibel is acknowledged for NMR studies and helpful discussions. Tanks are also due to Mrs. E. Tigla for skillful technical assistance.

References and Notes
(22) Preparation of 3b from 2a: To a solution of 2a (5.76 g, 20.2 mmol) in THF (100 ml) was added Et3N (6.13 g, 60.6 mmol) and MesCl (4.74 g, 41.4 mmol) at -23°C. After stirring for 30 min the cooled mixture was filtered into a precooled solution of LiCN (48 ml, 0.5 M in DMF). Then stirring was continued for further 3 h at RT. After addition of sat. aq. NaHCO3 and Et2O the org. layer was dried (MgSO4) and evaporated. The residue was dissolved in MeOH (200 ml) and cooled to -30°C. After addition of liquid NH3 (100 ml) the mixture was stirred for 4 d at RT. Then sat. aq. NaHCO3 and Et2O was added and the org. layer was dried (MgSO4) and evaporated. The residue was purified by flash chromatography (petroleum ether / acetone 1:4) to give pure 3b.
(23) 4b: [α]20^21 = -31.3°, (c = 0.9, CHCl3); 1H NMR (CDCl3): δ (ppm) = 1.46 - 1.63 (m, 1H, 4-Ha), 1.83 - 2.01 (m, 1H, 4-Hb), 2.41 (dd, J = 16.8, 6.8 Hz, 1H, 2-Ha), 2.58 (dd, J = 16.8, 6.3 Hz, 1H 2-Hb), 2.74 - 2.81 (m, 2H, 5-H), 3.07 - 3.20 (m, 1H, 3-H), 3.47 (d, J = 13.6 Hz, 2H, NCH3Ph), 3.77 (d, J = 13.6 Hz, 2H, NCH3Ph), 7.24 - 7.38 (m, 10H, Ar).
(25) 5a: [α]20^20 = +37.1°, (c = 5.5, CHCl3); 1H NMR (CDCl3): δ (ppm) = 1.31 (d, J = 6.5 Hz, 3H, CH3), 1.50 (s, 9H, Boc-CH3), 1.82 (dddd, J = 14.3, 9.6, 9.5, 4.8 Hz, 1H, 5-Hax), 2.08 (m, 1H, 5-Heq), 2.59 (m, 1H, 3-H), 2.65 (m, 1H, 4-H), 3.38 (d, J = 13.8 Hz, 2H, NCH2Ph), 3.53 (dd, J = 13.0, 9.6, 4.7 Hz, 1H, 6-Hax), 3.72 (dd, J = 13.0, 5.3, 4.8 Hz, 1H, 6-Heq), 3.83 (d, J = 13.8 Hz, 2H, NCH2Ph), 7.24 - 7.38 (m, 10H, Ar).
(27) General Procedure for the Reaction of 4b,c with Electrophiles to give 5a-g: To a solution of 4b (1 mmol) in THF (30 ml) was added LDA (2 ml, 1M in THF) at -78°C. After being stirred for 1 h at -78°C the electrophile (2.5 mmol) was added. The reaction was kept at -78°C for 1 h. Then, it was allowed to warm up to RT. After 12 h, the mixture was treated with saturated aqueous NaHCO3 and extracted with ether. The organic layer was dried (MgSO4) and evaporated and the residue purified by flash chromatography (petroleum ether / ethyl acetate 4:1) to give 5a-g in analytically pure form.
(29) The diastereomeric purity was determined by 1H NMR spectroscopy (360 MHz) of the crude material. At a signal to noise ratio > 4:1 for the 13C satellites of the N-benzyl resonances, no signal of any impurity exceeded the intensity of the 13C satellites, indicating a diastereoselectivity > 99 %.