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

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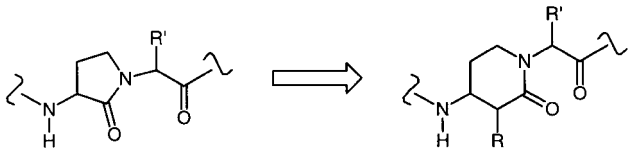
Abstract: Starting from aspartic acid a stereoselective synthesis of enantiomerically pure 4-aminopiperidin-2-ones which can serve as conformationally restrained ß-amino acid equivalents in peptidomimetics is described. The synthesis is based on the regioselective functionalization of the 1,4-bis-electrophile **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.[1-4] 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, ß-amino acid derived substructures and the investigation of ß-peptides led to interesting peptidomimetics.[11-13] As far as we know, a combination of these two strategies was not reported yet.

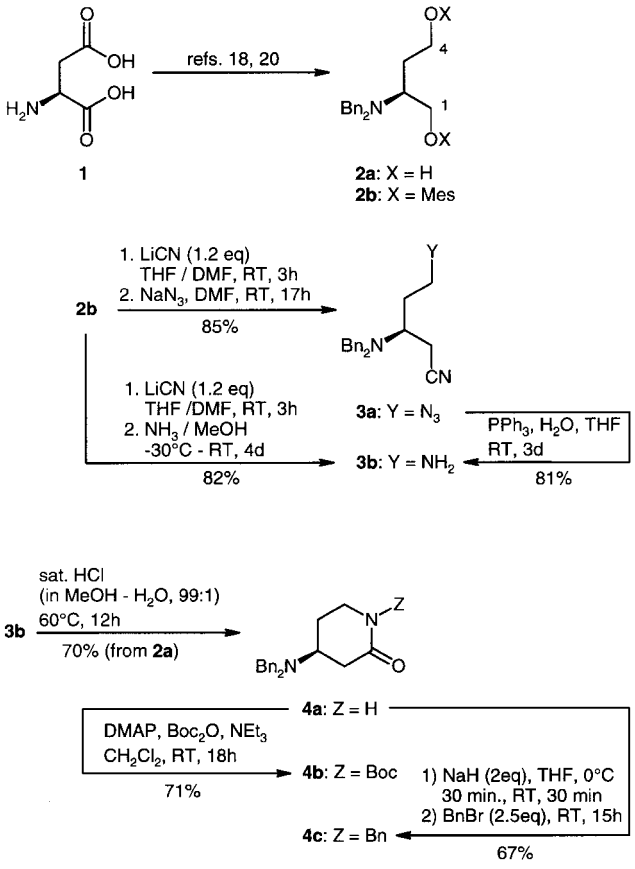
As part of our efforts on the synthesis of enantiopure ß-amino acid derivatives, [14,15] here we report the first stereoselective synthesis of 4-aminopiperidin-2-ones as lactam-bridged analogs with a ß-amino carboxamide substructure (*Homo-Freidinger* lactams, II). Applying this approach, our initial results on lactam-constrained mimetics of the dopamine receptor modulating peptide Pro-Leu-Gly-NH_2[16] are presented.



I II

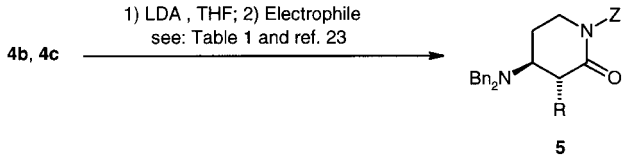
The synthesis of a *N*-protected 4-aminopiperidine in enantiomerically pure form was planned starting from natural aspartic acid (**1**). Taking advantage of our recently described methodology we were able to functionalize regioselectively the dibenzyl protected aminobutanediol **2a**.[17-20] Thus, activation of **2a** by MesCl gave the bis-electrophile **2b** which could be transformed into the azido nitrile **3a** by subsequent substitution with LiCN and NaN_3. Due to an activating anchimeric 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 NH_3 is used as the "second nucleophile" instead of NaN_3.[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 (**1**), 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.

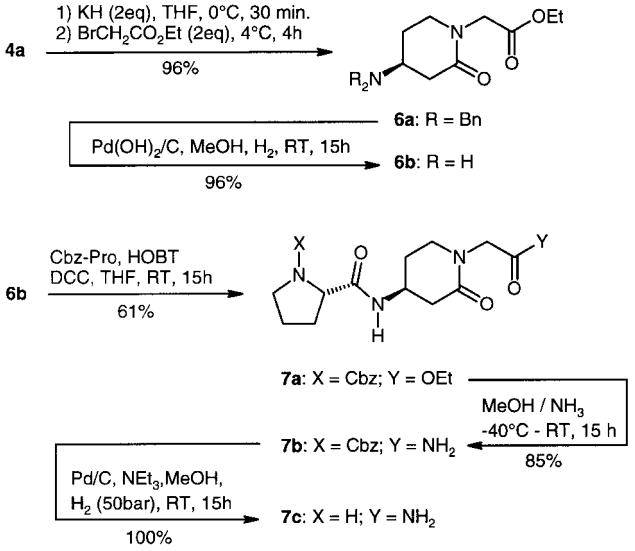


Since **4a** should serve as a versatile building block, introduction of substituents representing ß-amino acid side chains was envisioned. This should be done by *N*-protection, deprotonation of the lactam α-position and subsequent reaction with representing electrophiles. We evaluated Boc and, alternatively, benzyl as protecting groups for the lactam function. Thus, deprotonation of the lactam **4** followed by addition of Boc_2O or BnBr afforded **4b** [23] and **4c**, respectively. For the introduction of the Boc group reaction of **4a** with Boc_2O 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 ß^2-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 alkylation reactions. Thus, the lactam bridged ß^2-homophenylalanine 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.[27] Electrophilic fluorination employing NFSI (*N*-fluorobenzene sulfonimide)[28] afforded the α-fluoro lactam **5g**. In all cases, the electrophilic attack at the enolate occurs exclusively from the bottom side (*re*).[29] Obviously, the *si*-face is strongly shielded by the sterically demanding dibenzylamine substituent. Structural analysis of the alkylation products was performed by ^{1}H 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.

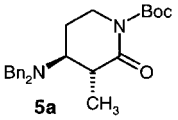
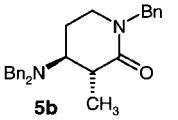
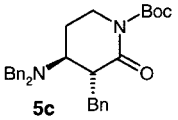
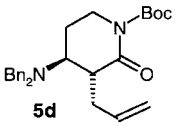
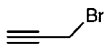
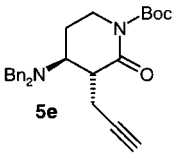
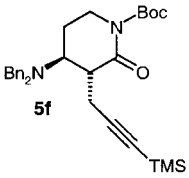
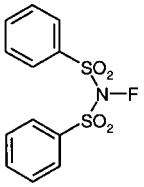
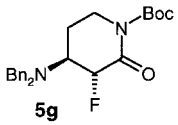


The incorporation of the described *Homo-Freidinger* lactams into conformationally restricted mimetics of the dopamine receptor modulating peptide Pro-Leu-Gly-NH_2 [16, 30] and their investigation for biological activity are currently investigated in our laboratories. Using the *(S)*-configured building 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-NH_2 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.

Table 1. Diastereoselective introduction of ß-amino acid side chain equivalents into position 3 of the lactams **4b,c**

Entry	Educt	Electrophile	Product	Yield [%]
1	**4b**	H_3C—I	 **5a**	75
2	**4c**	H_3C—I	 **5b**	53
3	**4b**	Bn—Br	 **5c**	85
4	**4b**		 **5d**	81
5	**4b**		 **5e**	55
6	**4b**	TMS—≡—Br	 **5f**	32
7	**4b**		 **5g**	78

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(22) Preparation of **3b** from **2a**: To a solution of **2a** (5.76 g, 20.2 mmol) in THF (100 ml) was added Et_3N (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. $NaHCO_3$ and Et_2O the org. layer was dried ($MgSO_4$) and evaporated. The residue was dissolved in MeOH (200 ml) and cooled to -30°C. After addition of liquid NH_3 (100 ml) the mixture was stirred for 4 d at RT. Then sat. aq. $NaHCO_3$ and Et_2O was added and the org. layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether - acetone 1:4) to give pure **3b**. $[\alpha]_D^{21}$ = -31.3°, (c = 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ(ppm) = 1.46 - 1.63 (m, 1H, 4-H_a), 1.83 - 2.01 (m, 1H, 4-H_b), 2.41 (dd, J = 16.8, 6.8 Hz, 1H, 2-H_a), 2.58 (dd, J = 16.8, 6.3 Hz, 1H 2-H_b), 2.74 - 2.81 (m, 2H, 5-H), 3.07 - 3.20 (m, 1H, 3-H), 3.47 (d, J = 13.6 Hz, 2H, NCH_2Ph), 3.77 (d, J = 13.6 Hz, 2H, NCH_2Ph), 7.24 - 7.38 (m, 10H, Ar).

(23) **4b**: $[\alpha]_D^{20}$ = -25.7°, (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ(ppm) = 1.5 (s, 9H, Boc-CH_3), 1.79 (dddd, J = 15.8, 11.1, 10.7, 4.8 Hz, 1H 5-H_{ax}), 2.10 (m, 1H, 5-H_{eq}), 2.63 (dd, J = 16.4, 9.8 Hz, 1H, 3-H_{ax}), 2.70 (ddd, J = 16.4, 6.3, 1.3 Hz, 1H 3-H_{eq}), 3.14 (m, 1H, 4-H), 3.35 (ddd, J = 13.0, 10.7, 4.3 Hz, 1H, 6-H_{ax}), 3.60 (d, J = 13.8 Hz, 2H, NCH_2Ph), 3.65 (d, J = 13.8 Hz, 2H, NCH_2Ph), 3.85 (ddd, J = 13.0, 4.8, 4.3 Hz, 1H, 6-H_{eq}), 7.20 - 7.40 (m, 10H, Ar).

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(25) **5a**: $[\alpha]_D^{20}$ = +37.1, (c = 5.5, $CHCl_3$) ^{1}H NMR ($CDCl_3$): δ(ppm) = 1.31 (d, J = 6.5 Hz, 3H, CH_3), 1.50 (s, 9H, Boc-CH_3), 1.82 (dddd, J = 14.3, 9.6, 9.5, 4.8 Hz, 1H, 5-H_{ax}), 2.08 (m, 1H, 5-H_{eq}), 2.59 (m, 1H, 3-H), 2.65 (m, 1H, 4-H), 3.38 (d, J = 13.8 Hz, 2H, NCH_2Ph), 3.53 (ddd, J = 13.0, 9.6, 4.7 Hz, 1H, 6-H_{ax}), 3.72 (ddd, J = 13.0, 5.3, 4.8 Hz, 1H, 6-H_{eq}), 3.83 (d, J = 13.8 Hz, 2H, NCH_2Ph), 7.24 - 7.38 (m, 10H, Ar).

(26) For an explanation of the term ß^2, see: Seebach, D.; Hintermann, T. *Synlett* **1997**, 437.

(27) **General Procedure for the Reaction of 4b,c with Electrophiles to give 5a-g**: To a solution of **4a,b** (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 slowly. 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 $NaHCO_3$ and extracted with ether. The organic layer was dried ($MgSO_4$**)** and evaporated and the residue purified by flash chromatography (petroleum ether / ethyl acetate 4:1) to give **5a-g** in analytically pure form.

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(29) The diastereomeric purity was determined by ^{1}H NMR spectroscopy (360 MHz) of the crude material. At a signal to noise ratio > 4:1 for the ^{13}C satellites of the *N*-benzyl resonances, no signal of any impurity exceeded the intensity of the ^{13}C satellites, indicating a diastereoselectivity > 99 %.

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