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Stereoselective Synthesis of New Conformationally Restricted Analogues of a Potent CGRP Receptor Antagonist

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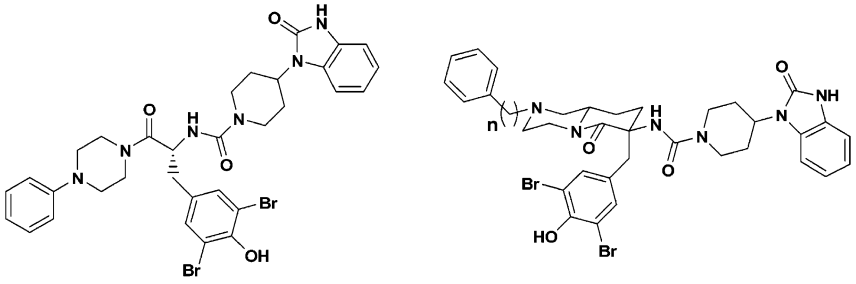
ABSTRACT



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2a n = 0
2b n = 1

A stereocontrolled racemic synthesis of conformationally restricted analogues 2a and 2b of a potent CGRP receptor antagonist 1 by novel functionalization of 2-substituted octahydropyrido[1,2-*a*]pyrazin-6-ones is described. The new diastereoselective LDA-promoted α-nitration of intermediate lactams established the required *trans*-configuration in the desired products.

Conformational restriction of biologically active molecules has significant importance in medicinal chemistry.[1] When the pharmacophore of the molecule of interest is locked into its binding conformation, the result is greater affinity to the complementary receptor site, resulting in increased binding potency. Among the other anticipated benefits are increased receptor selectivity and metabolic stability of the new molecule. Moreover, innovative chemistry efforts may culminate in the identification of original compounds, which reward a research chemist with a novel chemotype of interest. It is for these reasons that the strategy of conformational restriction has attracted widespread attention.[2]

For a few years, we have been interested in the discovery of new calcitonin gene-related peptide (CGRP) receptor antagonists as potential drug candidates for treatment of migraine.[3] In the course of our exploration program we proposed structures **2a** and **2b** as constrained analogues of a potent CGRP receptor antagonist **1** (Compound 1) (Figure 1), reported by Merck scientists.[4]

Initial molecular modeling results (not shown) suggested that compound **2a** should be a reasonable mimic of compound **1**. A subsequent, more sophisticated analysis, which is described below, supports the original conclusion.[5] Ten conformers of compound **1** predicted to be low in energy were superimposed with conformers of compound **2a** that

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(1) Mann, A. In *Practice of Medicinal Chemistry*, 2nd ed.; Wermuth, C. G., Ed.; Academic Press: San Diego, 2003; Chapter 15, p 233.

(2) Wermuth, C. G. In *Practice of Medicinal Chemistry*, 2nd ed.; Wermuth, C. G., Ed.; Academic Press: San Diego, 2003; Chapter 14, p 215.

(3) Calcitonin gene-related peptide (CGRP), a 37-amino acid peptide belonging to the calcitonine family of peptides, is believed to play an important role in the pathophysiology of migraine.[17,18] CGRP binds to a CGRP receptor, which is a G-protein coupled receptor, consisting of a classical 7-transmembrane component calcitonine receptor-like receptor (CRLR) and a receptor activity modifying protein (RAMP).[19,20]

(4) Edvinsson, L.; Sams, A.; Jansen-Olesen, I.; Tajti, J.; Kane, S. A.; Rutledge, R. Z.; Koblan, K. S.; Hill, R. G.; Longmore, J. *Eur. J. Pharmacol.* **2001**, *415*, 39.

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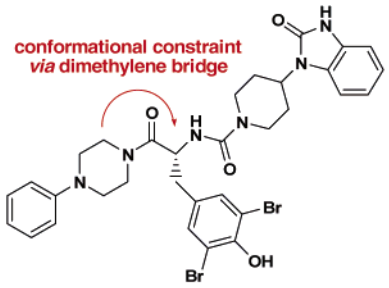
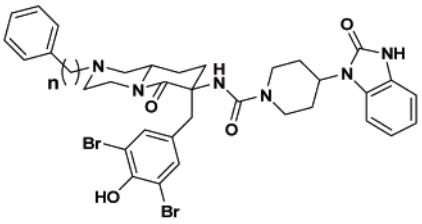


Compound 1 (Merck)

1



2a n = 0
2b n = 1

Figure 1. Conformationally restricted analogues **2a** and **2b** of potent CGRP receptor antagonist **1**.

were predicted to be within 5.0 kcal/mol of the lowest energy conformer identified. An in-house program that superimposes structures by matching classes of atoms in a reference structure to similar classes in a query structure and scores the alignment on the basis of the proximity of similar functional groups in the query and reference was used. The overlay of the best-fitting conformer of **2a** with a low energy conformer of **1** is shown in Figure 2. The energies of the conformers of compounds **1** and **2a** are 0.5 and 1.3 kcal/mol above those of the lowest energy conformers identified for **1** and **2a**, respectively. Although none of the conformers of **1** used as references necessarily represent its bioactive conformation, the ability of **2a** to adopt conformations similar

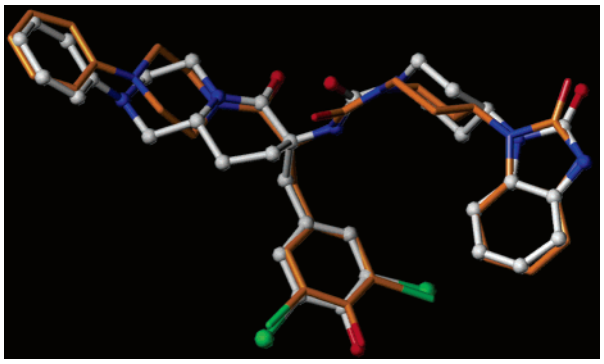
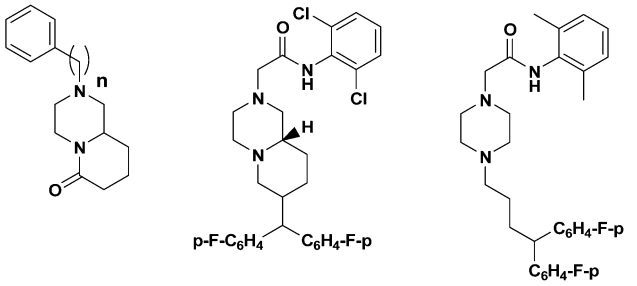


Figure 2. Overlay of predicted low energy conformations of potent CGRP antagonist **1** (stick rendering) and compound **2a** (ball-and-stick rendering).



3a n = 0
3b n = 1

4a (*cis*)
4b (*trans*)

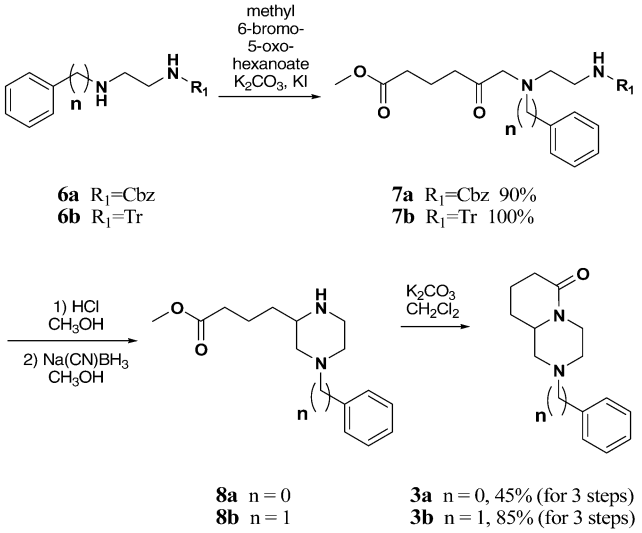
5

Figure 3. Conformationally restricted analogues **4a** and **4b** of lidoflazine **5**.

to several different low energy conformations of **1** suggested that **2a** should be a reasonable mimic of **1**. Encouraging molecular modeling results prompted us to accomplish the stereoselective synthesis of structurally complex molecule **2a** and its analogue **2b**, containing the previously unknown 2,6,6-trisubstituted octahydropyrido[1,2-*a*]pyrazin-6-one ring system.

A decade ago, Compernolle et al. reported a series of bicyclic lactams as useful scaffolds for the synthesis of conformationally restricted analogues of several piperazine-containing drugs.[6,7] As an example, lactam 2-benzyloctahydropyrido[1,2-*a*]pyrazin-6-one **3b** was used in the synthesis of analogues **4a** and **4b** of the coronary vasodilator lidoflazine **5** (Figure 3).[7] In the present publication we wish to report a novel stereoselective functionalization of bicyclic lactams **3a** and **3b** in the synthesis of proposed constrained analogues **2a** and **2b** of the CGRP receptor antagonist **1**.

Scheme 1. Synthesis of 2-Substituted Octahydropyrido[1,2-*a*]pyrazin-6-ones **3a** and **3b**



6a R_1=Cbz
6b R_1=Tr

7a R_1=Cbz 90%
7b R_1=Tr 100%

8a n = 0
8b n = 1

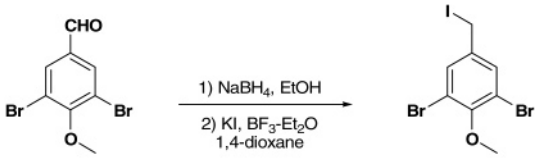
3a n = 0, 45% (for 3 steps)
3b n = 1, 85% (for 3 steps)

Synthesis of 2-phenyloctahydropyrido[1,2-*a*]pyrazin-6-one **3a** and 2-benzyloctahydropyrido[1,2-*a*]pyrazin-6-one **3b** was

performed by analogy with the previously described protocol (Scheme 1). With one of the amino functionalities blocked by an appropriately chosen protecting group, **6a**[8] and **6b** were alkylated regioselectively with methyl 6-chloro-5-oxohexanoate to give ketoesters **7a** and **7b**. Subsequent deprotection, followed by internal reductive amination with sodium cyanoborohydride in methanol at pH 5, yielded piperazinebutanoic esters **8a** and **8b**. Potassium carbonate induced cyclization of these compounds afforded the desired 2-substituted octahydropyrido[1,2-*a*]pyrazin-6-ones **3a** and **3b** in respective 45% and 85% yields for three steps.

Further novel elaboration of **3a** and **3b** involved treatment with LDA and 1,3-dibromo-5-iodomethyl-2-methoxybenzene **10** (prepared in 92% yield from 1,3-dibromo-4-methoxybenzaldehyde **9**,[9] according to Scheme 2) in THF to give

Scheme 2. Synthesis of 1,3-Dibromo-5-iodomethyl-2-methoxybenzene

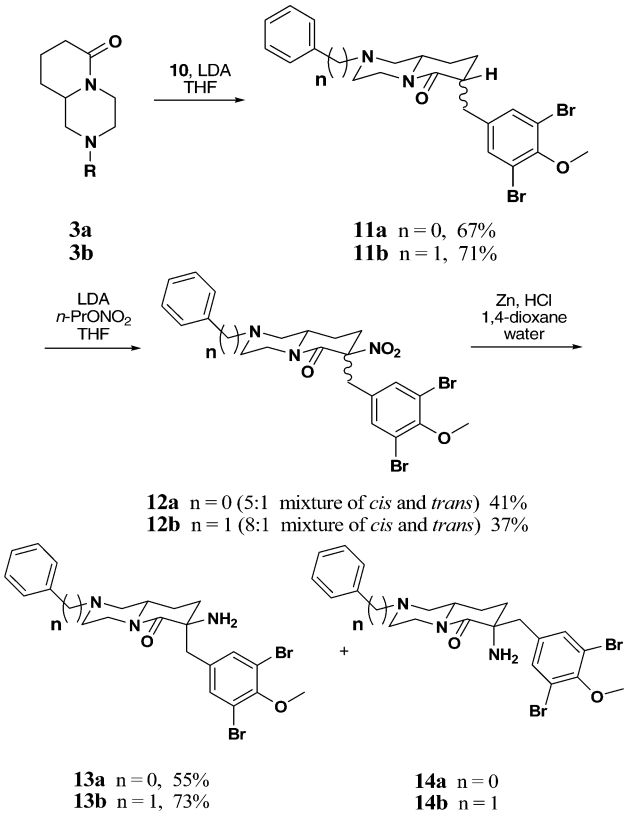


9 **10**

mixtures of diastereomeric lactams **11a** and **11b** in corresponding 67% and 71% combined yields (Scheme 3).[10] Although the LDA-promoted nitration of amide α-methylene groups has been previously established,[11] no examples of analogous α-methyne nitrations have been reported to date. Without separation, pairs of diastereomers **11a** and **11b** were deprotonated with LDA and quenched with *n*-propyl nitrate to afford a mixture of *trans*- and *cis*-nitro-derivatives **12a** and **12b** in 5:1 and 8:1 ratios. Despite the moderate yields (41% and 37%), these clean reactions allowed quantitative recovery of unreacted starting materials.

Mixtures of nitro-compounds **12a** and **12b** were carefully reduced to the corresponding amines with zinc in concentrated hydrochloric acid at room temperature to avoid potential problems of debenzylation and debromination, commonly observed with transition metal catalyzed reductions. The resulting major diastereomers **13a** and **13b** were

Scheme 3. Further Novel Elaboration of Lactams **3a** and **3b**



3a
3b

11a n = 0, 67%
11b n = 1, 71%

12a n = 0 (5:1 mixture of *cis* and *trans*) 41%
12b n = 1 (8:1 mixture of *cis* and *trans*) 37%

13a n = 0, 55%
13b n = 1, 73%

14a n = 0
14b n = 1

obtained in 55% and 73% yields, respectively, by separation from the minor isomers **14a** and **14b** using reverse phase preparative HPLC.[12]

X-ray crystallographic analysis of the monohydrate of the double TFA salt of major diastereomer **13b** (Figure 4)

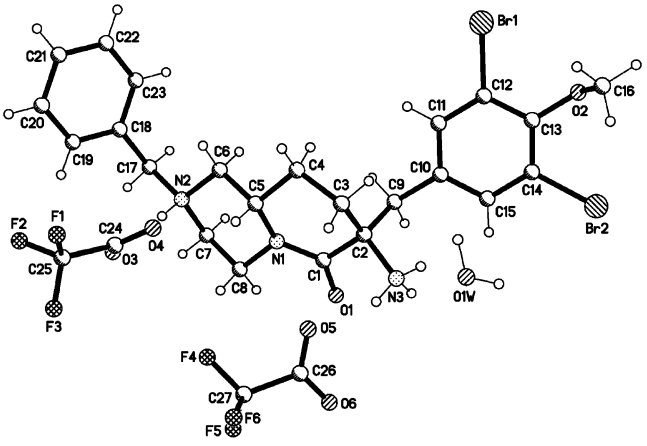
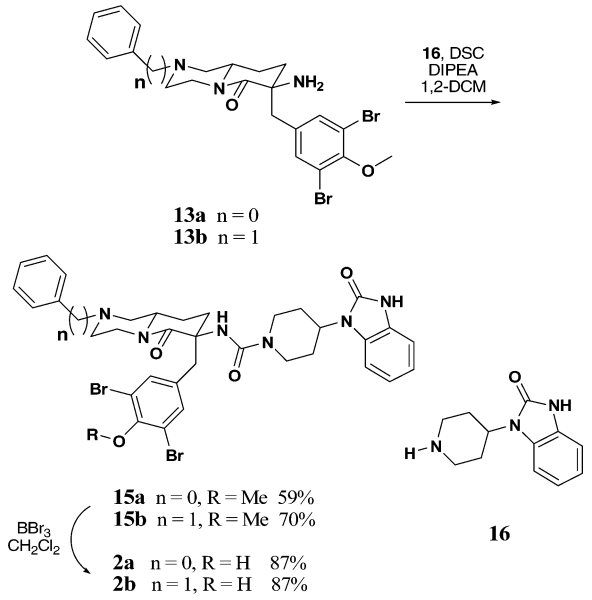


Figure 4. X-ray structure of amine **13b**.

revealed that the molecule has the *trans*-configuration at C2 and C5.[13] In the solid state, it exists in a double chair conformation with the 3,5-dibromo-4-methoxybenzyl group

(5) For a detailed description of the molecular modeling procedure, see Supporting Information.
(6) Van den Branden, S.; Compernolle, F.; Hoornaert, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1035.
(7) Saleh, M. A.; Compernolle, F.; Van den Branden, S.; De Buysser, W.; Hoornaert, G. *J. Org. Chem.* **1993**, *58*, 690.
(8) Nate, H. et al. *Chem. Pharm. Bull.* **1987**, *35*, 2825.
(9) Boukouvalas, J.; Lachance, N.; Ouellet, M.; Trudeau, M. *Tetrahedron Lett.* **1998**, *39*, 7665.
(10) Trost, B. M.; Kunz, R. A. *J. Org. Chem.* **1974**, *39*, 2475.
(11) Feuer H.; Panda, C. S.; Hou, L.; Bevinakatti, H. S. *Synthesis* **1983**, 187.
(12) Conditions for a reverse phase preparative HPLC separation of **13a** and **13b** included: column, XTERRA 30 mm × 150 mm S5; injection volume, 2000 μL; solvent A, CH_3OH (10%)/H_2O (90%)/TFA (0.1%); solvent B, CH_3OH (90%)/H_2O (10%)/TFA (0.1%); starting % B, 20; final % B, 80; gradient time, 20 min; end time, 25 min.

Scheme 4. Completion of the Synthesis of **2a** and **2b**



positioned axially and the amino group equatorially at C2. Based on the determined *trans* configuration of amine **13b**, we concluded that the attack of *n*-propyl nitrate on the enolate derived from mixtures **11a** and **11b** occurred predominantly from the equatorial direction.

Coupling of amines **13a** and **13b** to commercially available 1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one **16** in the presence of disuccinimidyl carbonate formed ureas **15a** and **15b** (Scheme 4).[14] Low-temperature O-demethylation promoted by boron tribromide[15] in dichloromethane cleanly afforded target molecules **2a** and **2b** in 87% yields.

Both conformationally restricted analogues were tested in a [^{125}I]CGRP binding assay,[16] where **2a** (K_i = 3.6 μM) was found to be only weakly active and activity for **2b** (K_i > 5 μM) could not be measured. The loss in binding affinity of **2a** compared to that of **1** (reported K_i = 16 nM)[4] clearly indicated a significant difference between the calculated low energy and binding conformations of the latter compound. Nonetheless, our chemistry efforts resulted in the preparation of structurally novel CGRP receptor binding agent **2a** and its binding affinity is the subject of further optimization.

In summary, we developed a racemic synthesis of conformationally restricted analogues **2a** and **2b** of potent CGRP receptor antagonist **1** by appropriate functionalization of 2-substituted octahydropyrido[1,2-*a*]pyrazin-6-ones **3a** and **3b**. The new stereocontrolled LDA-promoted nitration of lactams **13a** and **13b** established the required *trans*-configuration in the desired products.

Supporting Information Available: Full experimental procedures and spectral data for new compounds. Complete details of computational methods for **1** and **2a**. SK-N-MC cell membrane preparation and CGRP binding assay descriptions. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0510062

(13) Full crystallographic data for **13b** have been deposited to the Cambridge Crystallographic Data Center (CCDC reference number 238932).
(14) Takeda, K.; Ogura, H. *Synth. Commun.* **1980**, *10*, 373.
(15) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289.
(16) For a detailed description of the CGRP binding assay, see Supporting Information.
(17) Brain, S. D.; Cambridge, H. *Gen. Pharmacol.* **1996**, *27*, 607.
(18) Edvinsson, L. *CNS Drugs* **2001**, *15*, 745.
(19) Juaneda, C.; Dumont, Y.; Quirion, R. *Trends Pharmacol. Sci.* **2000**, *21*, 432.
(20) McLatchie, L. M.; Fraser, N. J.; Main, M. J.; Wise, A.; Brown, J.; Thompson, N.; Solari, R.; Lee, M. G.; Foord, S. M. *Nature* **1998**, *393*, 333.