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# Preparation and Evaluation of 1,3-Diaminocyclopentane-Linked Dihydropyrimidinone Derivatives as Selective $\alpha_{1a}$-Receptor Antagonists

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**Abstract**—Several 1,3-diaminocyclopentane linked $\alpha_{1a}$-receptor antagonists were prepared using a divergent chemical strategy that allows for rapid analysis of all stereochemical permutations for their effect on $\alpha_1$-receptor binding. © 2000 Published by Elsevier Science Ltd.

Recently, dihydropyrimidinone/piperidines such as **1**[1] (Fig. 1) have been disclosed as selective $\alpha_{1a}$-receptor antagonists, and these compounds have the potential to be effective therapy for treatment of benign prostatic hyperplasia.[2] As part of a strategy to design potent and selective antagonists of the $\alpha_{1a}$-receptor, constraints in the flexible linker between the piperidine and dihydropyrimidinone heterocycle of **1** were examined. Constraining a flexible section of an enzyme inhibitor or receptor antagonist often results in enhanced binding affinity due to reduced entropic penalties on binding when the constraint mimics the bioactive conformation.[3] While there are several conceivable ways to constrain the 3-carbon chain of **1**, 1,3-substituted cyclopentanes such as **2** were chosen for this study. It was hoped that, in addition to improving the potency at the $\alpha_{1a}$-receptor, the four stereochemical permutations of this cyclopentane system might reveal new strategies for gaining selectivity among the $\alpha_{1a}$-, $\alpha_{1b}$-, and $\alpha_{1d}$-receptor subtypes.[4] Below is described a novel method for synthesis of stereochemically defined 1,3-diaminocyclopentanes and evaluation of each configuration at the three $\alpha_1$-receptor subtypes.

The most rapid and convergent method for construction of each possible stereoisomer of **2** would be a non-selective reductive alkylation of a piperidine with enantiopure ketone **3**. At the outset of these studies, the only preparation of optically active analogues of **3** was the chiral auxillary-based approach of Miller.[5] A more flexible approach that would provide entry into all stereochemical permutations involves resolution of a 3-amino cyclopentanol derivative **5**[6] in analogy to the known desymmetrization of **4a**.[7]

Deardorff has reported the palladium catalyzed opening of epoxide **6** (Scheme 1) with several oxygen nucleophiles[8] as well as displacement of **4b**[9] with $NaN_3$ which afforded azide (+)**8** in 44% yield as a 4:1 mixture with the *trans*-isomer.[10] It is possible to combine these two procedures so that **6** can be opened with azide under Pd(0) catalysis to give **8**. Further, it was found that replacing $NaN_3$ with $TMSN_3$ improved the yield and selectivity of this reaction, most likely because the steric bulk of the TMS group helps direct attack of azide toward the distal end of the Pd-allyl system. Furthermore, the large TMS group stabilizes the allylic azide **7** from decomposition via sigmatropic rearrangements.[11] Removal of the silyl protecting group from **7** (1 M aq HCl/EtOAc, 15 min) afforded the more labile allylic azide **8** in racemic form. To minimize the number of operations involving these somewhat unstable allylic azide intermediates, a resolution procedure based on a selective enzyme catalyzed acylation was chosen rather than an acylation followed by selective hydrolysis. In analogy to the work of Theil[7] we employed the convenient pancreatin/vinyl acetate system in THF.[12] Using 10 equiv of vinyl acetate and 0.5 g of pancreatin/mmol of substrate, the selective acylation of **8** proceeded to

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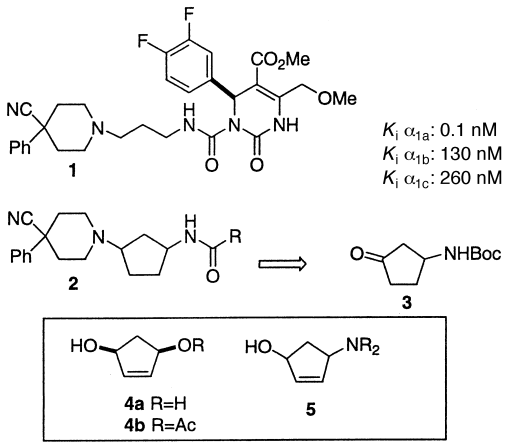



Figure 1.

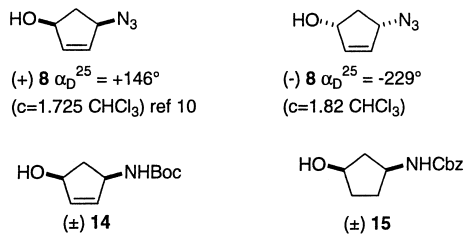



Figure 2.

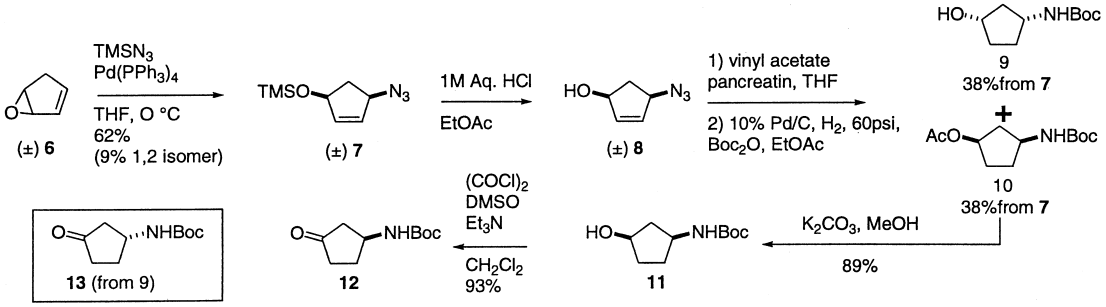
50% conversion in 3–4 h (as monitored by $^1$H NMR analysis of aliquots) and the product was isolated by filtration through Celite followed by removal of the solvent in vacuo. The unpurified reaction mixture was immediately subjected to reduction by 60 psi $H_2$ over 10% palladium on carbon with in situ protection with Boc anhydride.[13] This procedure afforded the stable and easily separable acetate **10** and alcohol **9** in 88–92% ee[14] at 50% conversion. The optical purity of either product could be increased (at the expense of the other) by modulating the resolution reaction conversion.

Despite the sensitivity of some of the intermediates, the overall yield of the four-step process was good (38% of **9**, 30% of **10**)[15] due to rapid reactions and simple work up procedures. Alcohol **9** could be oxidized directly to the desired ketone **13** ($COCl_2$, DMSO, $Et_3N$), while acetate **10** was first hydrolyzed ($K_2CO_3$, MeOH) then oxidized (Scheme 1). The stereochemical course of the resolution was confirmed by comparison of optical rotation of unreacted (−)**8** with that reported for (+)**8** by Deardorff, and this is consistent with the analogous diol resolution.[7] Interestingly, compounds (±)**11**, (±)**14**, and (±)**15** were not good substrates for the pancreatin enzyme[16] and were recovered unchanged when subjected to the standard reaction conditions.

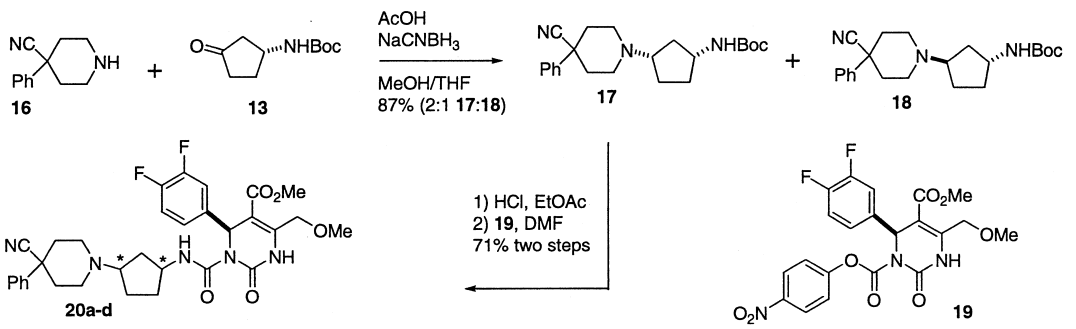
With the resolved ketones **12** and **13** in hand, the attachment of the piperidine or piperazine segment was examined (Scheme 2). Treatment of the free base of piperidine **16** and the ketone **13** with acetic acid followed by slow addition of $NaCNBH_3$ afforded excellent yields of the alkylated products with a 2:1 ratio of *cis* to *trans* isomers.[17] Chromatographic separation followed by removal of the Boc group (HCl, EtOAc) afforded the corresponding amines which could be coupled to the resolved dihydropyrimidinone **19** under the previously reported conditions.[1] This process allowed for several piperidines and a piperazine to be coupled with ketones **12** and **13** to give the set of products arrayed in Table 1.

Each of the compounds prepared was screened for binding affinity toward the human cloned $\alpha_{1a}$-, $\alpha_{1b}$- and $\alpha_{1d}$-receptors stably expressed in CHO, LM and HEK cells, respectively.[18] Interestingly, few distinct trends emerge from Table 1 as there appears to be interplay between the cyclopentane stereochemistry and the nature of the piperidine or piperazine substituents. The most potent compounds at the $\alpha_{1a}$-receptor subtype have similar potency to the open chain variant **1** (Fig. 1) with several of the stereochemical permutations. The best configuration for overall potency and $\alpha_{1a}$- subtype selectivity is the (*R,R*) stereochemistry of **20c**, **21c** and **22c**. The $\alpha_{1b}$- and $\alpha_{1d}$-receptor subtypes favor the (*S,S*) cyclopentane configuration (**20d**, **21d**, **22d** and **23d**), but these compounds were still somewhat $\alpha_{1a}$ selective. The piperazines **23a–d** were quite potent but displayed low subtype selectivity compared to the piperidines. Also notable is the complementarity between the *ortho*-cyanophenyl substituent on the piperidine and piperazine with the (*R,S*) cyclopentane configuration (**22b, 23b**). That these compounds have sub-nanomolar potency and good subtype selectivity for the $\alpha_{1a}$-receptor would not have been predicted by consideration of the data for **20a–d** and **21a–d** alone.

The strategy of constraining the flexible linker of $\alpha_{1a}$-receptor antagonists such as **1** into a 1,3-diaminocyclopentane has resulted in the preparation of several potent and receptor subtype selective antagonists, indicating

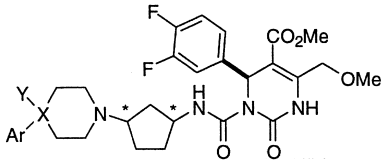



Scheme 1.




**Scheme 2.**

**Table 1.** Comparison of in vitro binding $K_i$ (nM) versus human cloned $\alpha_{1a}$-, $\alpha_{1b}$-, and $\alpha_{1d}$-receptors[a]



| | | 20 | | | 21 | | | 22 | | | 23 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $\alpha_{1a}$ | $\alpha_{1b}$ | $\alpha_{1d}$ | $\alpha_{1a}$ | $\alpha_{1b}$ | $\alpha_{1d}$ | $\alpha_{1a}$ | $\alpha_{1b}$ | $\alpha_{1d}$ | $\alpha_{1a}$ | $\alpha_{1b}$ | $\alpha_{1d}$ |
| A |  | 1.0±0.15 | 1900±240 | 620±170 | 0.40±0.15 | 1300±680 | 320±60 | 0.24±0.10 | 130±31 | 16±5.4 | 1.6±0.45 | 28±1.5 | 7.5±3.6 |
| B |  | 2.4±0.45 | 730±380 | 660±400 | 4.7±1.2 | 290±95 | 550±65 | 0.60±0.35 | 70±19 | 97±5.8 | 0.44±0.09 | 51±10 | 39±20 |
| C |  | 0.37±0.12 | 210±75 | 660±330 | 0.38±0.01 | 350±110 | 500±20 | 0.46±0.18 | 91±20 | 31±6.4 | 0.90±0.21 | 14±1.5 | 5.4±3.3 |
| D |  | 2.3±0.25 | 120±2.5 | 95±20 | 8.3±2.8 | 130±5 | 170±10 | 2.4±0.90 | 36±16 | 11±3.8 | 4.8±0.50 | 15±1.5 | 9.0±3.0 |

[a]Values represent the mean ± SEM (nM) for displacement of $^{125}$I-HEAT from the human cloned receptor subtypes.

that this particular constraint mimics the bioactive conformation of **1**. Surprisingly, many of the stereochemical permutations were tolerated indicating some receptor flexibility. The divergent chemical strategy utilized to prepare these compounds allowed for expedient preparation of all possible isomers from the common starting material (±)**8** and uses low-cost, readily available reagents. This process is quite general and flexible, and should prove useful in other contexts as 4-aryl piperidines and piparazines are common units in bioactive molecules.

## Acknowledgements

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## References and Notes

1. Dhar, T. G. M.; Nagarathnam, D.; Marzabadi, M. R.; Lagu, B.; Wong, W. C.; Chiu, G.; Tyagrajan, M. R.; Miao, S. W.; Zhang, F.; Sun, W.; Tian, D.; Shen, Q.; Zhang, J.; Wetzel, J. M.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Schorn, T. W.; Chen, T. B.; O'Malley, S.; Ransom, R.; Schneck, K.; Bendesky, R.; Harrell, C. M.; Vyas, K.; Zhang, K.; Gilbert, J.; Pettibone, D. J.; Pantane, M. A.; Bock, M. G.; Freidinger, R. M.; Gluchowski, C. M. *J. Med. Chem.* **1999**, *42*, 4778.
2. Chapple, C. R. *Eur. Urol.* **1996**, *29*, 129.
3. Khan, A. R.; Parrish, J. C.; Fraser, M. E.; Smith, W. W.; Bartlett, P. A.; James, M. N. G. *Biochemistry* **1998**, *37*, 16839.
4. De Benedetti, P. G.; Fanelli, F.; Menziani, M. C.; Cocchi, M.; Testa, R.; Leonardi, A. *Bioorg. Med. Chem.* **1997**, *5*, 809.
5. Ghosh, A.; Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1995**, *60,* 5808. See also Ramesh, N. G.; Kiunder, A. J. H.; Zwanenburg, B. *J. Org. Chem.* **1999**, *64,* 3635.
6. Since completion of this work, a similar enzymatic resolution was reported: Mulvihill, M. J.; Gage, J. L.; Miller, M. J. *J. Org. Chem.* **1998**, *63,* 3357.
7. Theil, F.; Schick, H.; Lapitskaya, M. A.; Pivnitsky, K. K. *Liebigs Ann. Chem.* **1991**, 195.
8. Deardorff, D. R.; Myles, D. C. *Tetrahedron Lett.* **1985**, *26*, 5615.
9. Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Org. Synth.* **1995**, *73*, 25.
10. Deardorff, D. R.; Linde, R. G.; Martin, A. M.; Shulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759.
11. Compound **7** can be stored for at least 3 months at 0 °C without significant decomposition.
12. Pancreatin is exceptionally cheap ($36.40/kg Aldrich) and the reaction does not require aqueous conditions.
13. Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837.
14. The ee was determined after conversion to ketones **12** and **13** by HPLC analysis on a 4.6×250 mm Chiracel™ AD chiral column, 10% EtOH/Hexane 1.5 mL/min, detected by UV absorbance at 200 nM.
15. The lower yield of the acetylated product is probably due to Pd catalyzed decomposition of the allylic acetate

during the reduction step. When lower $H_2$ pressures were used (resulting in longer reaction times), the yield of **10** was even lower.

16. Compound (±)**14** was shown by Miller to be a substrate for several other enzymes. See ref 6.

17. 2D-COSY and 1-D NOE $^1$H NMR experiments on **17** and **18** confirmed the stereochemical assignment. The other compounds were assigned by analogy (ratio of products, TLC $R_f$, $^1$H NMR). We thank Dr. S. Varga for performing the NMR analysis.

18. O'Malley, S. S.; Chen, T. B.; Francis, B. E.; Gibson, R. E.; Burns, H. D.; DiSalvo, J.; Bayne, M. L.; Wetzel, J. M.; Nagarathnam, D.; Marzabadi, M.; Gluchowski, C.; Chang, R. S. L. *Eur. J. Pharm.* **1988**, *348*, 287.