*Tetrahedron: Asymmetry* Vol. 3, No. 3, pp. 329-332, 1992
Printed in Great Britain

0957-4166/92 $3.00+.00
Pergamon Press plc

# NOVEL,ENANTIOSELECTIVE SYNTHESIS OF VICINAL CYCLOHEXANE-DIAMINES AS KEY-INTERMEDIATES FOR HIGHLY SELECTIVE OPIOID KAPPA AND SIGMA AGONISTS.

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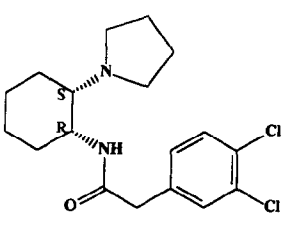
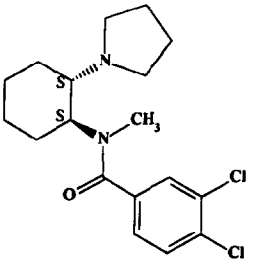
(*Received* 19 *December* 1991)

*Abstract :Enantiomers of Cyclohexane-1,2-diamines have been synthesized via two different synthetic approaches by asymmetric catalytic hydrogenation.*

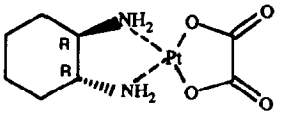
Cyclohexanediamines and their derivatives have received increasing attention in recent literature due to discoveries of their selective action at opioid κ- [1-7] and σ-receptor-sites [8-10,24].They are also used as chelating ligands in anti-tumor agents such as Oxaliplatin [11] and as chiral inductors in asymmetric synthesis [12,21-23] . In all medicinal applications they display highly enantioselective and diastereoselective pharmacologies with eudismic ratios up to 1500 :1. It is therefore highly desirable to apply the optically pure enantiomers ,especially in the case of the κ-opioid agonists, dealing with dysphoric side-effects in clinical tests [7] similar to those of racemic ketamine [13] .
Thus an asymmetric synthesis for cyclohexane-diamines was desirable in order to support further research work on their enantioselective pharmacology. Not many synthetic procedures exist for this class of compound, due to reactive precursors and the double reactivity of the product diamine functionality.To the best of our knowledge the few that are of practical importance are non-enantioselective in the the direct sense [1-6,24] .




σ-Agonist [24]




κ-Agonist [6]




Oxaliplatin [11]

Our first approach (fig.1) is an enantioselective synthesis of bifunctional enantiomers, which are stereoselectively transformed to the diamines and their derivatives respectively.

***In memoriam of Professor Alan Stuart Horn, University of Groningen,Netherlands***

This strategy is generally applicable either to various types of cycloaliphatic,vicinal aminoalcohols or to the corresponding diamino compounds of differing ring sizes. Its disadvantage is that asymmetry has to be established in an early stage of the synthesis with many consecutive steps to be conducted using precious optically pure material. Also this approach leads only to the trans-configurated diamine class.The initial asymmetric induction (I) was accomplished according to previous work of G.Lauktien and A.W.Frahm[20]. The catalytic hydrogenation of the intermediate imines yielded exclusively the cis-diastereomer and of the two possible cis-enantiomers selectively only the one with the absolute configuration "S " at C1 for the same configuration of the inducing agent.When using 1R-methyl-benzyl-amine the configuration at C1 was R (like-induction). Enantiomeric excess was always above 97% [20] as determined by HPLC-analysis of the Mosher amides prepared from the primary amines.

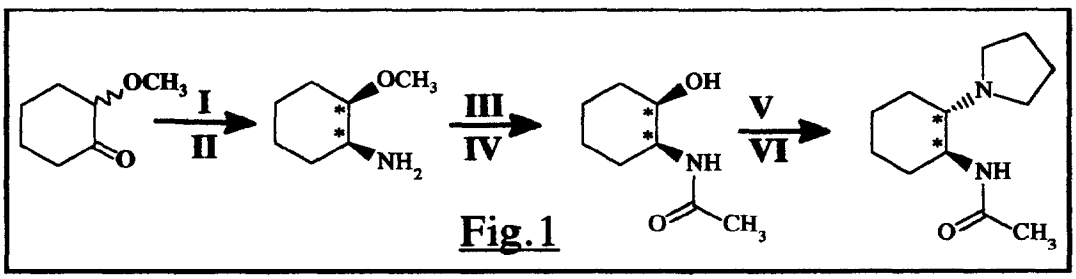



Fig.1

( **I**:1S-Methyl-benzyl-amine, reflux, asymm.hydrogenation :Raney-Nickel/EtOH, **II**: $H_2$,10% Pd /C,EtOH, **III** :$Ac_2O$, **IV**: BBr 3/ CH 2Cl 2/ -50°C, **V**: Mesyl-Cl/ NEt 3/ N 2/-10°C, **VI**: Pyrrolidine/ 100°C / 5h)

From the cis-enantiomer the target trans-diamine derivative was synthesized in 60% yield by the configuration conserving steps III-V and finally by substitution of the mesylate with pyrrolidine, a reaction that has been proven to proceed with complete inversion of the configuration at $C_2$.

In order to overcome the relative drawbacks of our first approach,we have been looking for an enantioselective synthetic pathway, that produces the diamino moiety and simultaneously induces asymmetry at both stereogenic centers .

We have tested different types of cyclohexanones substituted with a protected vicinal amino-function for their potential use in asymmetric, hydrogenating amination a technique well established [14-20] to yield various substituted cycloaliphatic amines and amino-acids respectively of high optical purity.

So far we've achieved the best results starting with the benzoyl-protected aminoketone (3)

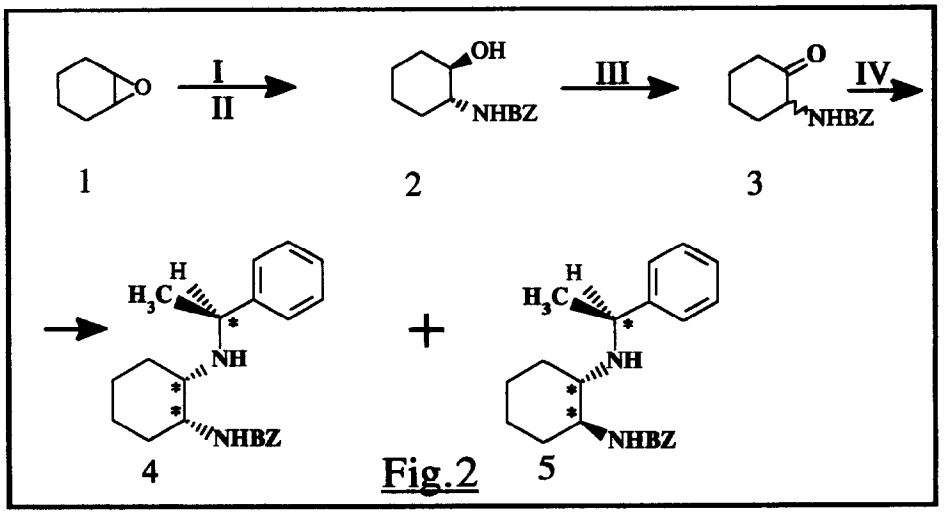



Fig.2

( I:25% $NH_3$/ 10°C/ 24h; II:Benzoylchloride/ NaOH/ 5°C; III:$CrO_3$/ Pyridine/ $Al_2O_3$/ Hexane IV:1S-Methyl-benzylamine,reflux, Asymm.Hydrogenation :Raney-Nickel/EtOH )

synthesized by standard methods (Fig.2).It readily leads to the cis and trans enantiomers 4 and 5 (ratio 2:1) in a high overall yield of 66% based on the epoxide (1).
The reduced diastereoselectivity, usually observed in most cycloaliphatic imine-hydrogenations, turns out to be advantageous,giving simultaneous access to the cis- and trans-diamines. The diastereomers can be easily seperated by column chromatography and subsequent crystallisation.
As observed previously [19],a drop in the diastereoselectivity of the imine hydrogenation didn't influence the level of enantioselectivity, which was clearly maintained. Both $^{13}C$ and $^{1}H$-NMR spectra of the crude product did not show a second set of signals either for the cis (4) or for the trans configurated amino-benzamide (5),which both represent a new and so far inaccessible class of diamino-compounds with a very high potential to have $\sigma$ [24] and $\kappa$-agonist [9] properties not yet tested pharmacologically. After hydrogenolysis

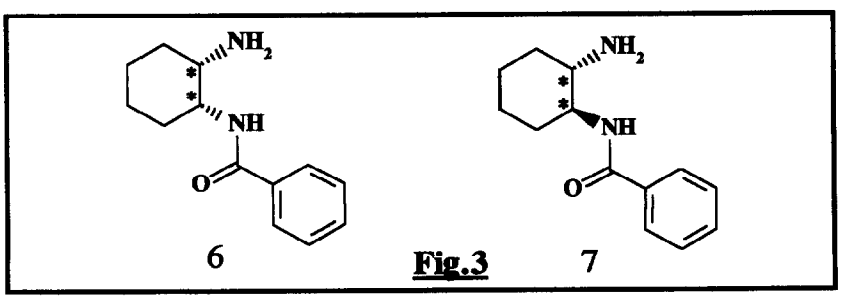
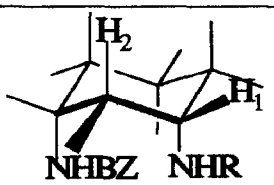
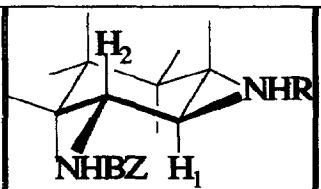
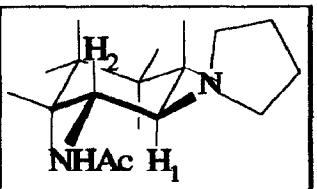



Fig.3

($NH_4$-formate/10% Pd/C) of the inducing 1-phenylethyl-group the primary amino-benzamides (6) and (7) are obtained in 82% yield respectively, allowing the synthesis of not only the "classical" pyrrolidino-agonists, but any other ring-size of the hetero-ring (fig.3).

Conclusion: In a one-pot synthesis the key intermediate enantiomers for two different opioid agonist-types can be synthesized starting from inexpensive ,racemic materials. Work to extend the application of this new synthesis to the 2-phenylacetamido-cyclohexanone has already proven to be successful. Extension of this method to other ring sizes and substituents is presently underway and will be reported in full.

| $^1$H-NMR-DATA $\delta$(TMS) in ppm ($CDCl_3$) BZ=Benzoyl Ac=Acetyl |  | |  | |  |
|---|---|---|---|---|---|
| R | 1-Phenyl-ethyl (inverted chair) | H | 1-Phenyl-ethyl | H | Pyrrolidinyl |
| $H_1$ | 2.80 m,b | 3.08 q | 2.41 dt | 2.50 dt | 2.54 dt |
| $H_2$ | 4.16 m,b | 4.04 tt | 3.70 dt | 3.7 m | 3.53 sept |
| $H_{3eq/ax}$ | 1.65/1.65m | 1.79/1.4 m | 2.22/1.2 m | 2.10/1.2 m | 2.46/1.07 m |
| $J_{12}$ | 6.0 Hz | 4.5 Hz | 10.0 Hz | 10.3 Hz | 11.0 Hz |
| $J_{23eq}$ | 4.0 Hz | 4.5 Hz | 4.0 Hz | 4.0 Hz | 4.0 Hz |
| $J_{23ax}$ | 6.0 Hz | 10.0 Hz | 10.5 Hz | 11.0 Hz | 10.0 Hz |

We gratefully acknowledge funds and substantial support received from the Degussa, Frankfurt a. Main, the BASF, Ludwigshafen and the Fonds der Chemischen Industrie. We also wish to thank Mr. V. Brecht for carefully performing detailled NMR-spectral analysis of all reported compounds.

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