CNS AGENTS: OPTICAL RESOLUTION WITH BAKER'S YEAST AS KEY STEP IN THE SYNTHESIS OF OPTICALLY ACTIVE TRICYCLIC AMINES[#)]

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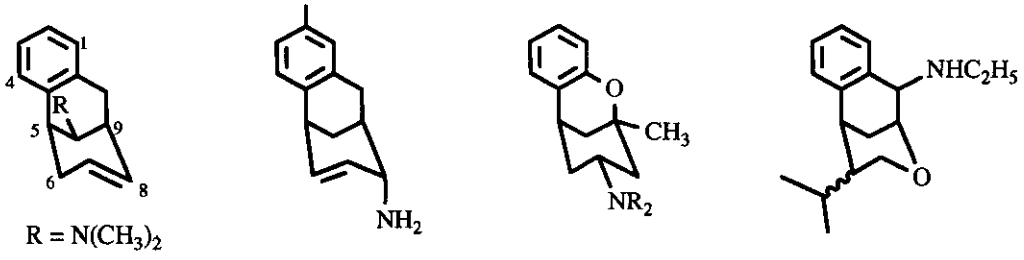
Abstract - The synthesis of the optically active 1,5-epoxy-3,4,5,6-tetrahydro-*N*-methyl-1*H*-2-benzoxocin-6-amines ((-)-**10**) and ((+)-**10**) is achieved by optical resolution of the racemic 1,5-epoxy-4,5-dihydro-1*H*-2-benzoxocin-6(3*H*)-one ((±)-**8**) with baker's yeast as the key step. (+)-**10** can also be prepared starting with the homochiral α-hydroxy-γ-butyrolactone ((-)-**6a**), which is easily obtained from (S)-(-)-malic acid.

5,9-Methanobenzocyclooctene derivatives bearing an amino group in different ring positions show considerable effects on the central nervous system (CNS). Thus, ORG 6370 ((±)-**1**) with the amino group at the methano bridge has a profile of activity similar to phenytoin and is, therefore, investigated as an

Scheme 1



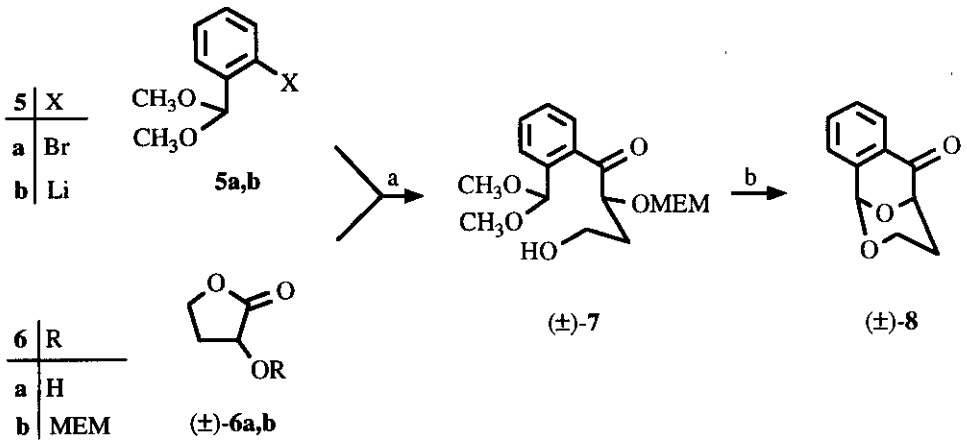
(±)-**1**: ORG 6370 (±)-**2** (±)-**3** (±)-**4**

#) Dedicated to Prof. Dr. B. Unterhalt on the occasion of his 60th birthday.

antiepileptic in phase 2 of clinical trials.[1] Because of its antidepressant activity a patent was taken out for the methanobenzocyclooctenamine ((±)-**2**).[2] Replacing the C-8 carbon atom of the 5,9-methanobenzocyclooctene ring system by a nitrogen atom leads to the strong analgesic benzomorphanes.[3] But, also tricycles with oxygen atoms in different ring positions can display strong CNS effects, if an amino group is attached to the ring system. Thus, anxiolytic and anticonvulsant activity as well as analgesic and sedative effects were found for the methanobenzoxocinamines ((±)-**3**)[4] and ((±)-**4**),[5] respectively.

In this communication we describe the stereoselective synthesis of the enantiomeric 1,5-epoxy-2-benzoxocin-6-amines ((-)-**10**) and ((+)-**10**) which are related to the tricyclic amines ((±)-**1** - (±)-**4**). Key step in the preparation of (-)-**10** and (+)-**10** was the optical resolution of the racemic ketone ((±)-**8**) by baker's yeast. Alternatively, (+)-**10** could be obtained starting with the chiral building block (S)-(-)-malic acid.

Scheme 2



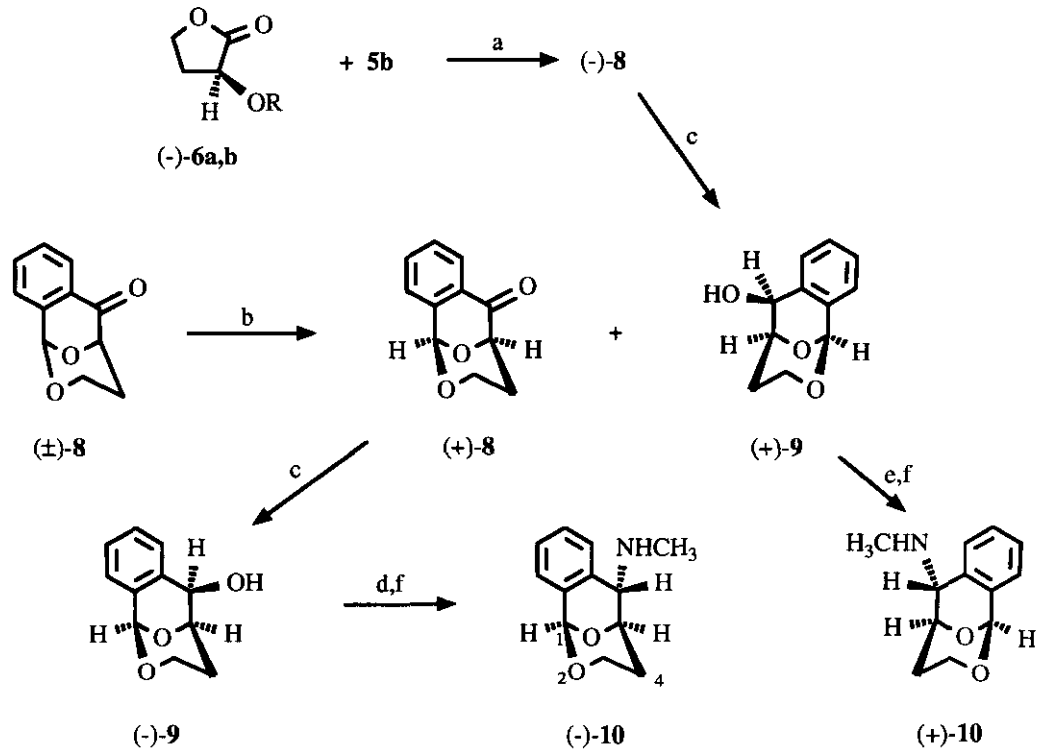
(a) n-C_4H_9Li, THF, -78°C, 1 h. - (b) *p*-Toluenesulfonic acid, toluene, 8 h, 110°C, 42 %.

Alkylation of the hydroxy group of the α-hydrox-γ-butyrolactone ((±)-**6a**) with MEM-Cl (2-methoxethoxymethyl chloride) and Hünig's base afforded the protected γ-butyrolactone ((±)-**6b**). The reaction of (±)-**6b** with the aryllithium compound (**5b**) obtained from the aryl bromide (**5a**) by bromine/lithium exchange led to the addition product ((±)-**7**). Whithout purification (±)-**7** was heated with *p*-toluenesulfonic acid to yield the tricyclic ketone ((±)-**8**).[6]

With baker's yeast[7] only the laevorotatory enantiomer ((-)-**8**) was reduced to give the alcohol ((+)-**9**), while the dextrorotatory enantiomer ((+)-**8**) remained unchanged. Thus, the ketone ((+)-**8**) ($[\alpha]_D^{20}$ =

+107.0, c = 1.4 in $CHCl_3$) was prepared in a 40 % yield and with an optical purity of 86 % ee, determined with the lanthanide shift reagent $Eu(hfc)_3$. The yield of the alcohol ((+)-**9**) ($[\alpha]_D^{20}$ = +1.9, c = 0.77 in $CHCl_3$) was only 9 %, probably because of further reactions of (+)-**9** with baker's yeast enzymes.

Scheme 3



(a) see Scheme 2. - (b) Baker's yeast, H_2O, 48 h, 37°C. - (c) $NaBH_4$, CH_3OH, 1 h, 20°C, 62 % (-)-**9**, 59 % (+)-**9**. - (d) CH_3SO_2Cl, $N(C_2H_5)_3$, CH_2Cl_2, 8 h, 20°C. - (e) $C_6H_5SO_2Cl$, pyridine, 72 h, 5°C. - (f) CH_3NH_2, C_2H_5OH, 8 h, 20°C, 41 % (-)-**10**, 39 % (+)-**10**.

This disadvantage was overcome by starting the reaction sequence with the homochiral α-hydroxy-γ-butyrolactone ((-)-**6a**) which was easily obtained from (S)-(-)-malic acid.[8] Like the racemic lactone ((±)-**6a**) the laevorotatory lactone ((-)-**6a**) reacted with **5b** to yield the enantiomerically pure tricyclic ketone ((-)-**8**) ($[\alpha]_D^{20}$ = -124.8, c = 1.25 in $CHCl_3$). The known absolute configuration of the α-hydroxy-γ-lactone ((-)-**6a**) allows the determination of the absolute configurations of the tricyclic ketones ((-)-**8**) and ((+)-**8**) to be (1S,5S) and (1R,5R), respectively. $NaBH_4$ reduction from the "backside"

stereoselectively transformed the enantiomeric ketones ((+)-**8**) (*si* attack) and ((-)-**8**) (*re* attack) to give the alcohols ((-)-**9**) ($[\alpha]_D^{20}$ = -1.6, c = 1.1 in $CHCl_3$) and ((+)-**9**), respectively. Activation of the hydroxy group of (-)-**9** and (+)-**9** with methanesulfonyl chloride or benzenesulfonyl chloride followed by S_N2 substitution with methylamine led to the tricyclic amines ((-)-**10**) ($[\alpha]_D^{20}$ = -10.9, c = 0.8 in $CHCl_3$) and ((+)-**10**) ($[\alpha]_D^{20}$ = +12.5, c = 1.2 in $CHCl_3$), respectively.

Thus, we demonstrated a procedure for the selective preparation of both the enantiomers of the 1,5-epoxy-2-benzoxocin-6-amines (**10**). Now we are going to prepare further examples of tricyclic amines like **10** which will be tested for their psychopharmacological properties.

ACKNOWLEDGEMENT

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