SYNTHESIS OF THE ENANTIOMERS OF 7,8-DIMETHOXY-2-PHENYL-1,2,4,5-TETRAHYDRO-3-BENZAZEPINE[1]

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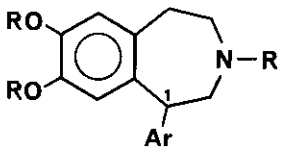
Abstract - The chiral 2-phenyltetrahydro-3-benzazepines (R)-8 and (S)-8 were prepared from optically active O-acetylmandeloyl chlorides utilizing a ring closure/ring opening strategy.

The antihypertensive agent fenoldopam[2] and the tranquilizer trepipam[3] (former USAN name: trimopam) are representatives of the well documented[4] class of compounds based on the readily accessible 7,8-dioxygenated 1-aryl-tetrahydrobenzazepine structure 1. Due to our interest in the biological activity of the corresponding 2-isomers 2, which have not received as much atten-



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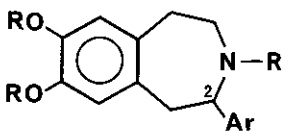


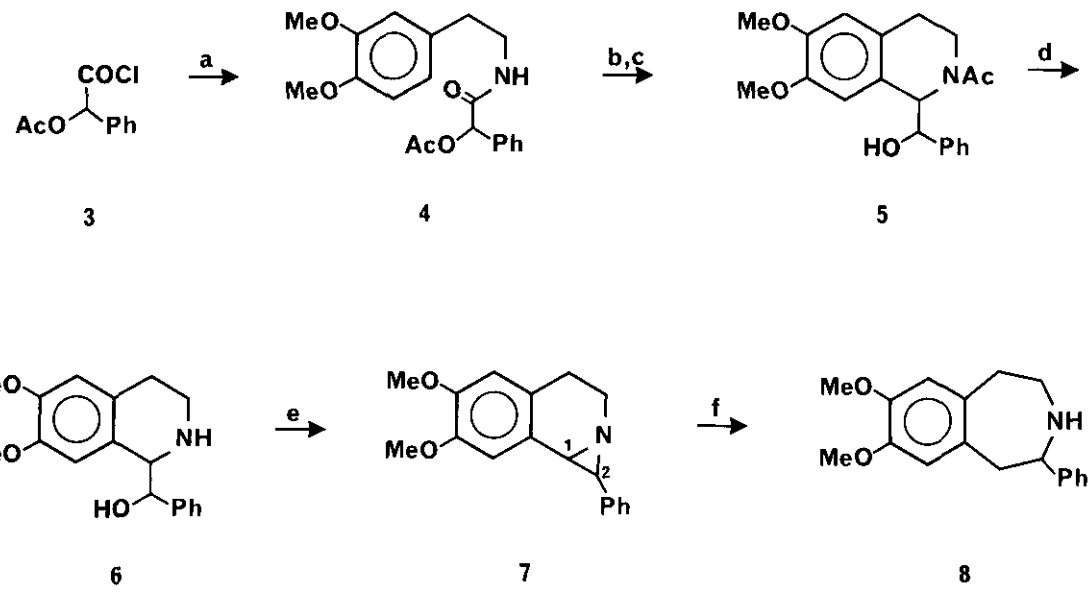
2

tion, we wanted to develop a fairly general synthetic approach to these compounds. Since, as is the case for fenoldopam[5], the individual isomers of chiral pharmacological agents often display diverse activity profiles, a particular goal of this endeavor had to be enantioselectivity. Approaches to 2 described in the literature[4,6] have invariably led to racemates.

The synthetic plan, for which the experimental details were first worked out in the racemic series, is depicted in Scheme I. Schotten-Baumann type acylation of homoveratrylamine with O-acetylmandeloyl chloride (two-phase system, AcOEt/aq. $NaHCO_3$, 0 °C → R.T., 2 h) produced the acetoxy amide 4 (mp 102-103°C, 82%

yield)[7]. This compound was subjected to a Bischler-Napieralski cyclization using conditions originally reported by Schöpf[8] (2.5 equiv. PCl_5, CH_2Cl_2, 0°C, 3 h). Reduction of the resulting crude imine with $NaBH_4$

Scheme I



3 4 5

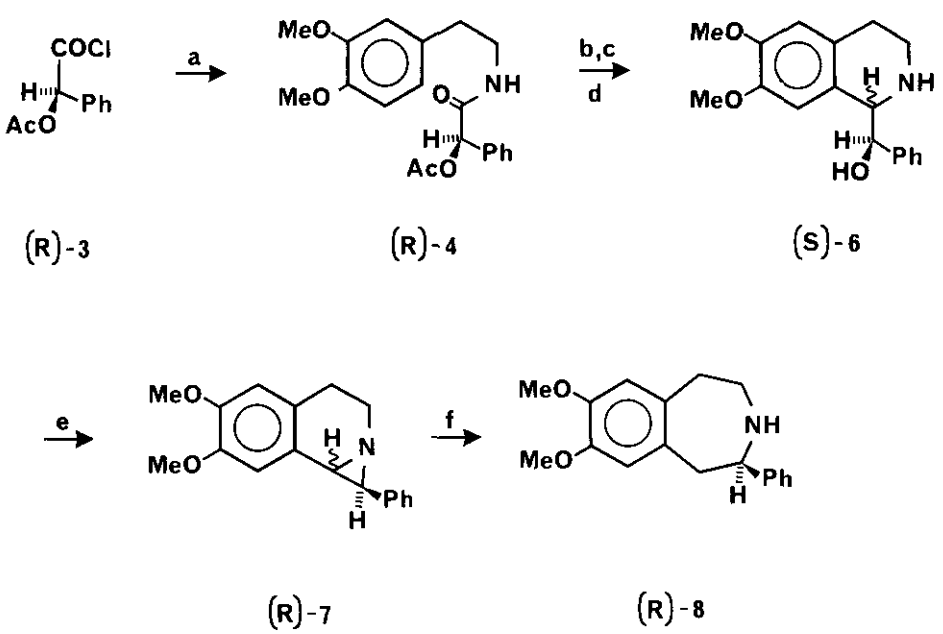
6 7 8

Reagents: a) homoveratrylamine, $NaHCO_3$ b) PCl_5 c) $NaBH_4$
d) KOH e) Ph_3P, DEAD f) H_2, RaNi

(EtOH, 18 h) directly produced amide 5 (mp 139-140°C, 88% yield) as a result of O → N acyl migration[9]. Alkaline hydrolysis of 5 (KOH, EtOH, reflux, 6 h) gave the amino alcohol 6 (mp 131-134°C, 60% yield), which formed aziridine 7 (mp 94-95°C, 72% yield) under Mitsunobu conditions[10] with concomitant inversion[11] of stereochemistry at C_2. Selective hydrolysis of the more activated C_1-N bond (H_2, RaNi, MeOH, 1 atm.) provided the racemic target compound 8 (HCl salt, hemihydrate, mp 172-174°C, 82% yield).

Application of this methodology to the chiral case (Scheme II) started with (R)-O-acetylmandeloyl chloride[12], which was converted into acetoxy amide

Scheme II



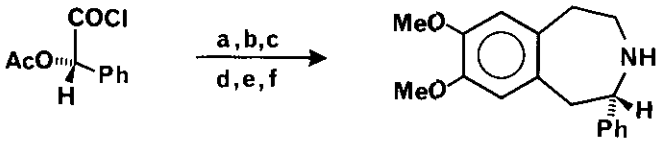
Reagents: see Scheme I

(R)-4 (mp 98-99°C, $[\alpha]_D$ -64.7° [13]) as described above. Bischler-Napieralski cyclization of (R)-4 was followed by treatment of the resulting imine with $NaBH_4$ and deacylation of the reduction product without isolating the latter by simply adding aqueous KOH to the reaction mixture. The resulting amino alcohol (S)-6 (mp 120-124°C, $[\alpha]_D$ +51.4°, 80% yield for the combined steps) was then cyclized to the aziridine (R)-7 (mp 93-96°C, $[\alpha]_D$ -26.4°), which gave the chiral benzazepine (R)-8 (HCl salt, mp 188-192°C, $[\alpha]_D$ -25.4°) on hydrogenolysis.[14] Assignment of the absolute configuration of (R)-7, and therefore of (R)-8, rests on the closely related conversion of (-)-erythro-ephedrine to the known (+)-trans-1,2-dimethyl-3-phenylaziridine.[10]

Conversely, (S)-O-acetylmandeloyl chloride[12] was converted into the benzazepine (S)-8 (HCl salt, mp 183-190°C, $[\alpha]_D$ +26.2°) via the intermediates (S)-4 (mp 99-100°C, $[\alpha]_D$ +67.4°), (R)-6 (mp 120-122°C, $[\alpha]_D$ -49.8°), and (S)-7 (mp 88-89°C, $[\alpha]_D$ +27.0°) (Scheme III). The rather high optical

rotations observed for (S)-6, (R)-7, (R)-6, and (S)-7 suggest that the borohydride reduction of the imine could have been subject to asymmetric induction via complexation of the reducing agent with the chiral α-hydroxybenzyl moiety.

Scheme III



(S)-3 (S)-8

Reagents: see Scheme I

with the result that these compounds could be single diastereomers.
Since resolvable α-hydroxy acids are readily obtained by hydrolysis of cyanohy- drins derived from aldehydes, the methodology described herein should provide access to a wide variety of chiral 2-substituted tetrahydro-3-benzazepines.

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7. Yields refer to recyrstallized compounds which exhibited satisfactory spectral and elemental analyses.

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13. All $[\alpha]_D$ values were determined in MeOH.

14. Unless indicated otherwise, yields in the chiral sequences were comparable to those in the racemic sequence.

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