

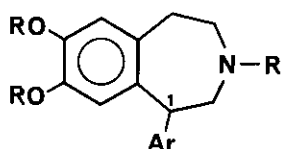
SYNTHESIS OF THE ENANTIOMERS OF 7,8-DIMETHOXY-2-PHENYL-
1,2,4,5-TETRAHYDRO-3-BENZAZEPINE¹

Jürg R. Pfister

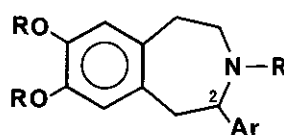
Institute of Organic Chemistry, Syntex Research
Palo Alto, California 94304, U.S.A.

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 fenoldopam² and the tranquilizer trepipam³ (former USAN name: trimopam) are representatives of the well documented⁴ 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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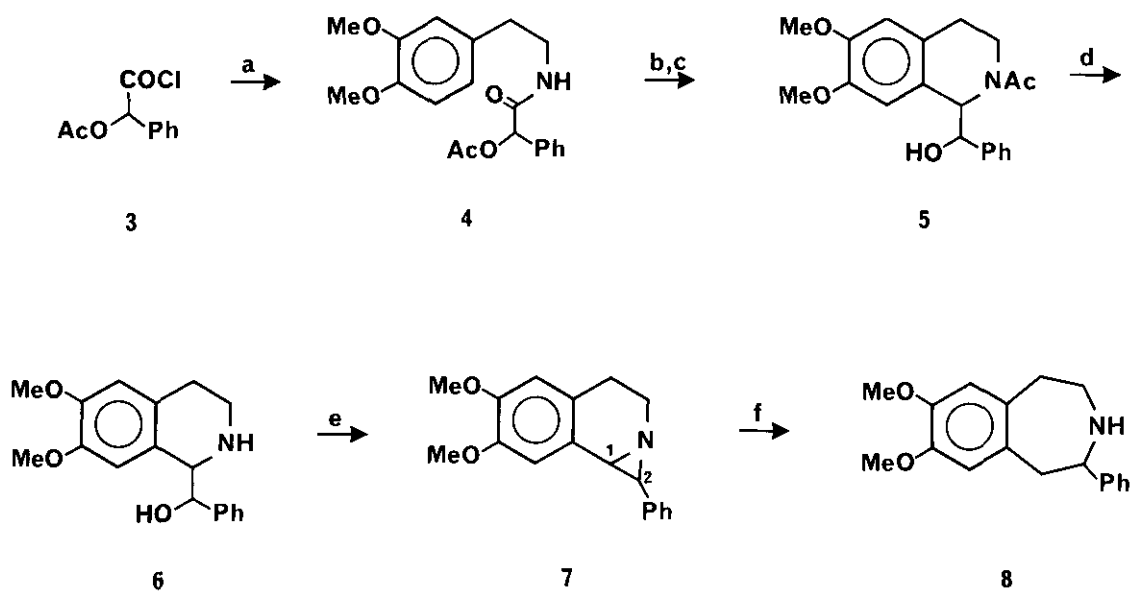
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tion, we wanted to develop a fairly general synthetic approach to these compounds. Since, as is the case for fenoldopam⁵, the individual isomers of chiral pharmacological agents often display diverse activity profiles, a particular goal of this endeavor 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. NaHCO₃, 0 °C → R.T., 2 h) produced the acetoxamide 4 (mp 102-103°C, 82%

yield)⁷. This compound was subjected to a Bischler-Napieralski cyclization using conditions originally reported by Schöpf⁸ (2.5 equiv. PCl_5 , CH_2Cl_2 , 0°C , 3 h). Reduction of the resulting crude imine with NaBH_4

Scheme I

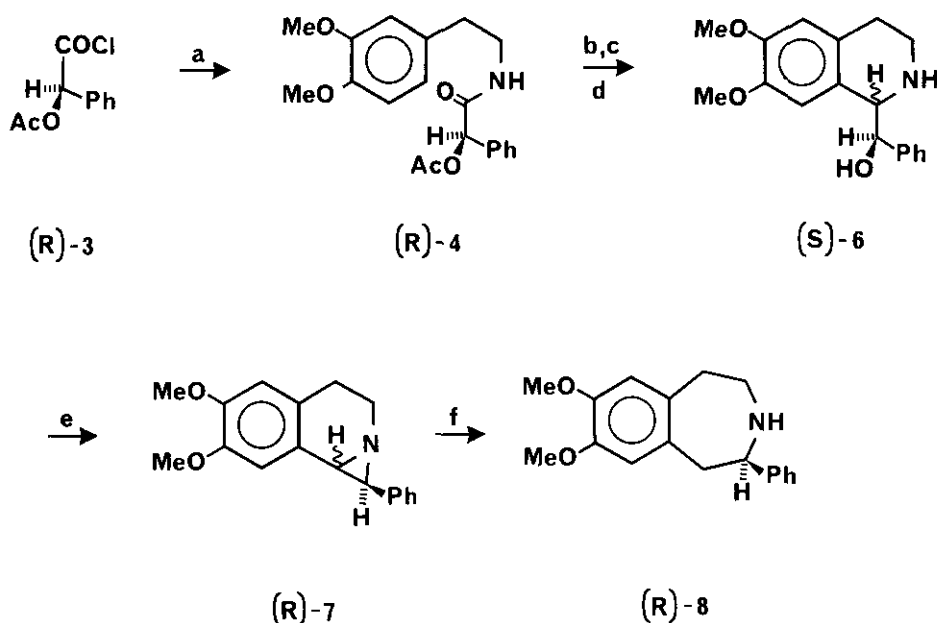


Reagents: a) homoveratrylamine, NaHCO_3 b) PCl_5 c) NaBH_4
 d) KOH e) Ph_3P , DEAD f) H_2 , RaNi

(EtOH, 18 h) directly produced amide **5** (mp $139\text{--}140^\circ\text{C}$, 88% yield) as a result of $\text{O} \rightarrow \text{N}$ acyl migration⁹. Alkaline hydrolysis of **5** (KOH , EtOH, reflux, 6 h) gave the amino alcohol **6** (mp $131\text{--}134^\circ\text{C}$, 60% yield), which formed aziridine **7** (mp $94\text{--}95^\circ\text{C}$, 72% yield) under Mitsunobu conditions¹⁰ with concomitant inversion¹¹ of stereochemistry at C_2 . Selective hydrolysis of the more activated $\text{C}_1\text{-N}$ bond (H_2 , RaNi , MeOH, 1 atm.) provided the racemic target compound **8** (HCl salt, hemihydrate, mp $172\text{--}174^\circ\text{C}$, 82% yield).

Application of this methodology to the chiral case (Scheme II) started with (*R*)-*O*-acetylmandoyl chloride¹², which was converted into acetoxo amide

Scheme II



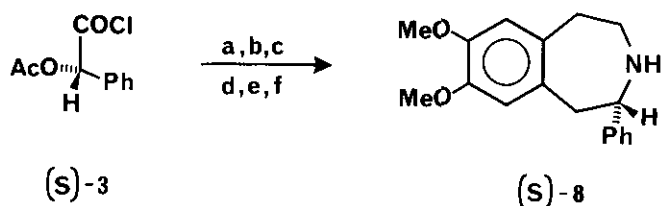
Reagents: see Scheme I

(R)-4 (mp 98-99°C, $[\alpha]_D^{25} -64.7^\circ$) 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, $[\alpha]_D^{25} +51.4^\circ$, 80% yield for the combined steps) was then cyclized to the aziridine (R)-7 (mp 93-96°C, $[\alpha]_D^{25} -26.4^\circ$), which gave the chiral benzazepine (R)-8 (HCl salt, mp 188-192°C, $[\alpha]_D^{25} -25.4^\circ$) 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 chloride¹² was converted into the benzazepine (S)-8 (HCl salt, mp 183-190°C, $[\alpha]_D^{25} +26.2^\circ$) via the intermediates (S)-4 (mp 99-100°C, $[\alpha]_D^{25} +67.4^\circ$), (R)-6 (mp 120-122°C, $[\alpha]_D^{25} -49.8^\circ$), and (S)-7 (mp 88-89°C, $[\alpha]_D^{25} +27.0^\circ$) (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



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 cyanohydrins derived from aldehydes, the methodology described herein should provide access to a wide variety of chiral 2-substituted tetrahydro-3-benzazepines.

REFERENCES AND NOTES

1. Contribution No. 714 from the Institute of Organic Chemistry.
2. F.R. Pfeiffer, J.W. Wilson, J. Weinstock, G.Y. Kuo, P.A. Chambers, K.G. Holden, R.A. Hahn, J.R. Wardell, Jr., A.J. Tobia, P.E. Setler, and H.M. Sarau, J. Med. Chem., 1982, 25, 352.
3. A. Barnett, R.I. Taber, and S.S. Steiner, Psychopharmacologia, 1974, 36, 281.
4. S. Kasparek, Adv. Heterocycl. Chem., 1974, 17, 45.
5. D.M. Ackerman, A.L. Blumberg, J.P. McCafferty, S.S. Sherman, J. Weinstock, C. Kaiser, and B. Berkowitz, Fed. Proc., 1983, 42, 186.

6. H. Schmidhammer, R. Eigenmann, and W. Klötzler, Eur. J. Med. Chem. - Chim. Ther., 1980, 15, 151; S. Smith, Jr., V. Elango, and M. Shamma, J. Org. Chem., 1984, 49, 581.
7. Yields refer to recrystallized compounds which exhibited satisfactory spectral and elemental analyses.
8. C. Schöpf, H. Perrey and I. Jäckh, Liebig's Ann. Chem., 1932, 497, 47.
9. J. Bäckvall and S.E. Byström, J. Org. Chem., 1982, 47, 1126 and references cited therein.
10. J.R. Pfister, Synthesis, 1984, 969; C.R. Hall and N.E. Williams, J. Chem. Soc. Perkin Trans. I, 1981, 2746.
11. O. Mitsunobu, M. Wada, and T. Sano, J. Am. Chem. Soc., 1972, 94, 679.
12. E.G. Breitholle and C.H. Stammer, J. Org. Chem., 1974, 39, 1311.
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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