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Stereoselective Synthesis of Previously Unattainable Enantio(diastereo)enriched Bridged Tetrahydro-2-benzazepines.

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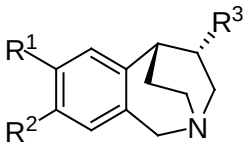
Abstract: A new and flexible route for the asymmetric synthesis of a variety of alkylated bridged tetrahydro-2-benzazepines has been developed. The key steps are the highly diastereoselective Michael addition of metalated SAMP-hydrazones to α,β-unsaturated esters combined with cyclomethylenation/Mitsunobu coupling reactions to secure the formation of the seven-membered azaheterocycle and of the bridged unit respectively.

Keywords: *SAMP-hydrazones, Michael addition, cyclization, Mitsunobu reaction.*

Introduction

Seven-membered nitrogen heterocycles are constituents of a great variety of poly and diversely substituted models endowed with profound chemotherapeutic properties and consequently, have attracted the particular attention of medicinal chemists. The benzoannulated systems such as 2-benzazepine derivatives fall into this category and display an impressive repertoire of biological activities [1]. Consequently the last decades have witnessed a strong incentive in the development of synthetic approaches to structurally sophisticated models and interest in the chemistry of 2-benzazepines continues unabated [2]. Paradoxycally the assembly of conformationally constrained models has not elicited interest of synthetic and pharmaceutical groups and benzofused bridged systems remain ignored by the scientific community in this series.

This is notably the case of the azabicyclo[3.2.2]nonane derivatives **1** despite the fact that the bicyclic bridged scaffold is a common structural feature of structurally constrained analogues of balanol endowed with promising protein kinase inhibitor properties [3] and of heteroaromatic olefinic compounds that have been recently used as inhibitors of nicotinic cholinergic receptors [4].



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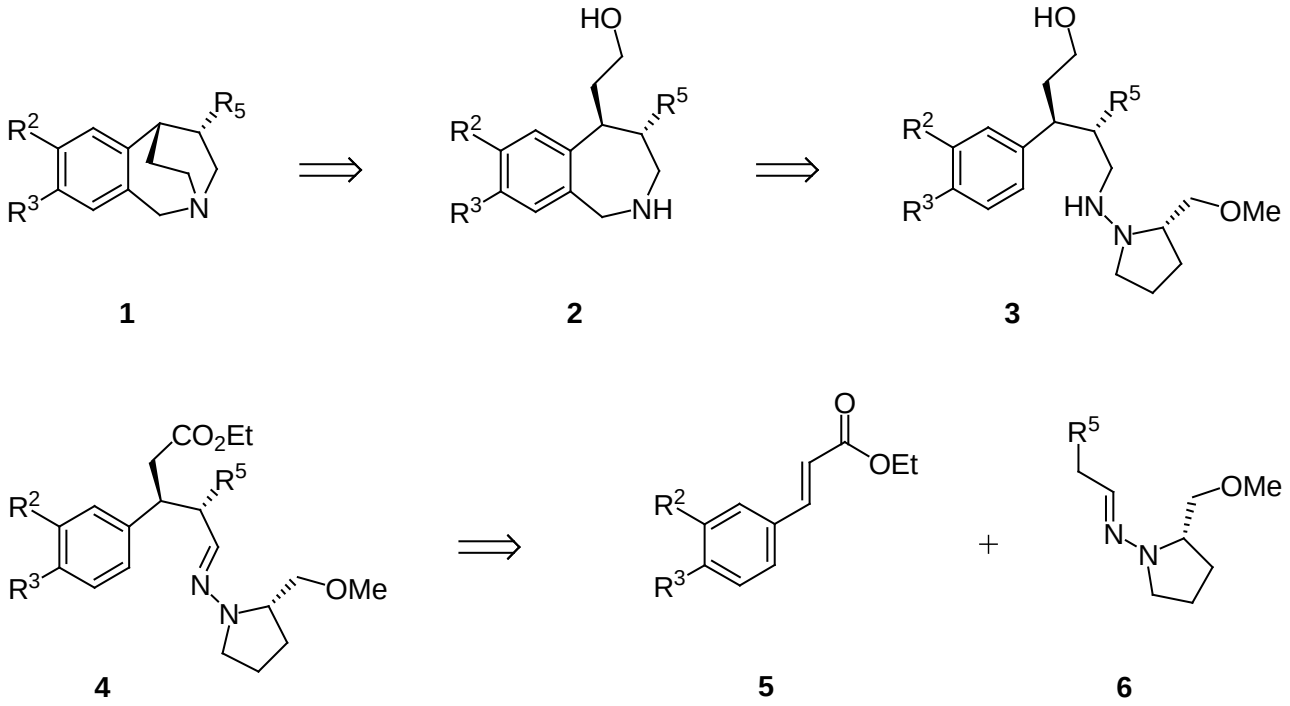
We delineate here a concise and conceptually new asymmetric approach to such a variety of diversely substituted bridged tetrahydro-2-benzazepines **1**.

Results and Discussion

1. The synthetic strategy

Our synthetic approach which is depicted in Retrosynthetic Scheme 1 is based upon strategic combinations of the highly diastereo and enantioselective addition of SAMP-hydrazones **6** to α,β-unsaturated esters **5** [5] followed by a sequence involving simultaneous reduction of ester and hydrazone functions of **4** / subsequent cyclomethylenation of **3** with an intramolecular Mitsunobu reaction to secure the ultimate formation of the bridged unit.



1 **2** **3**

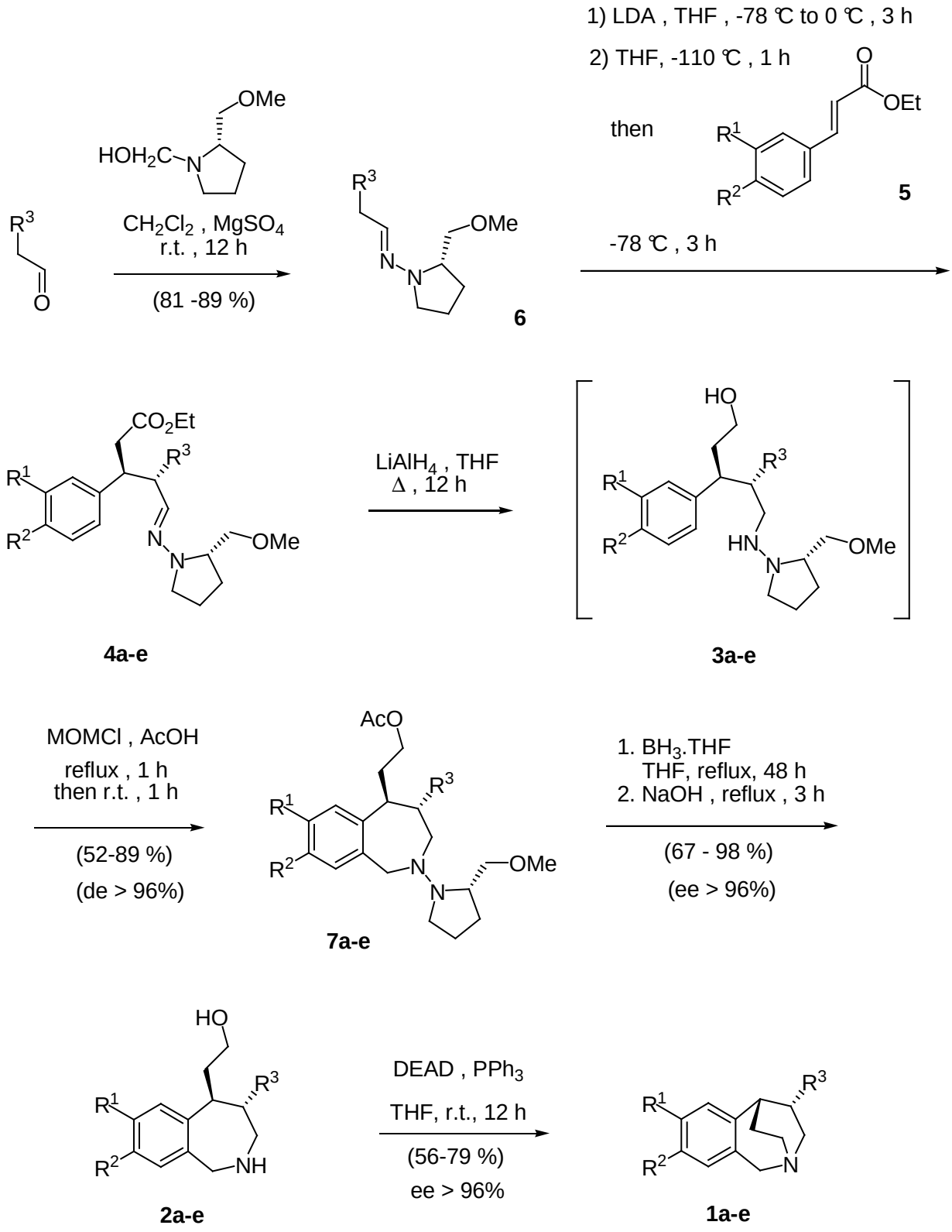
4 **5** **6**

Retrosynthetic Scheme 1.

2. Stereoselective synthesis of multifarious bridged tetrahydro-2-benzazepines **1.**

The first facet of the synthesis which is depicted in Scheme 2 was the elaboration of the Michael adducts **4a-e**. These ester-hydrazones were obtained in good yields and high diastereoselectivity (de ≥ 96%) by deprotonation of the parent hydrazones **6** followed by

reaction with the unsaturated esters **5** (Table 1). The Michael adducts, that is hydrazones **4**, were obtained as *E*-isomers exclusively based on the observed chemical shifts [6] and the *S,S*-configuration of the newly generated stereogenic center was assigned according to previously confirmed mechanism for the asymmetric 1,4-addition of metalated aldehyde SAMP-hydrazones to enoate Michael acceptors [6,7].



Scheme 2.

For the synthesis of hydrazines **3a-e**, hydrazones **4a-e** were subsequently reduced with $LiAlH_4$ but owing to the limited stability and sensitivity usually exhibited bu this type of NH-free hydrazines, cyclomethylenation accompanied with concomitant conversion of the hydroxyalkyl chain into the corresponding acetate was performed on crude products **3a-e**. This operation delivered satisfactory yields of the desired cyclic hydrazines (*R,S*)-**7a**, (*S,S,S*)-**7b-e** (Scheme 2, Table 1) as the sole diastereoisomer detectable by NMR upon flash column chromatographic treatment.

The reductive N–N bond cleavage by the BH_3·THF complex triggered off the release of the chiral appendage with simultaneous regeneration of the hydroxy functionality and completed the synthesis of the virtually enantio and diastereopure 5-hydroxyethyl NH free tetrahydrobenzazepines (*R*)-**2a** and (*S,S*)-**2b-e** respectively (Scheme 2). These amino-hydroxylated compounds were obtained in good yields with high enantio and diastereoisomeric excesses (ee ≥ 96%, de ≥ 96%; Table 1).

Compounds **2a-e** possess the requisite structure and functional group location to be easily converted into the bridged seven-membered models under the agency of the Mitsunobu reaction. Thus treatment of **2a-e** with diethyl azidodicarboxylate (DEAD) and triphenylphosphine delivered quite satisfactory yields of *meso* compound **1a** and of the virtually diastereopure benzofused bridged tetrahydroazepines (*S,S*)-**1b-e** (Scheme 2, Table 1).

Table 1. Benzazepines **7a-e, 2a-e** and **1a-e** Synthesized.

R^1	R^2	Michael adducts **4a-e** (Yield %)[a]	R^3	2-Benzazepine derivatives **7a-e** (Yield %)[a,b]	Hydroxyethyl-2-benzazepines **2a-e** (Yield %)[c]	Bridged 2-benzazepines **1a-e** (Yield %)[c]
OMe	OMe	(*R,S*)-**4a** (51)	H	(*R,S*)-**7a** (61)	(*R*)-**2a** (88)	**1a** (64)
OMe	OMe	(*S,S,S*)-**4b** (48)	Me	(*S,S,S*)-**7b** (89)	(*S,S*)-**2b** (67)	(*S,S*)-**1b** (79)
OMe	OMe	(*S,S,S*)-**4c** (47)	Et	(*S,S,S*)-**7c** (55)	(*S,S*)-**2c** (98)	(*S,S*)-**1c** (62)
OCH_2O		(*S,S,S*)-**4d** (53)	Et	(*S,S,S*)-**7d** (59)	(*S,S*)-**2d** (73)	(*S,S*)-**1d** (59)
OCH_2O		(*S,S,S*)-**4e** (47)	*n*-C_5H_{11}	(*S,S,S*)-**7e** (52)	(*S,S*)-**2e** (76)	(*S,S*)-**1e** (56)

[a]Yield of isolated diastereoisomer (de ≥ 96%).
[b]Over two steps.
[c]Yield of isolated virtually enantiopure isomer (ee ≥ 96%).

Conclusion

We have devised a new and flexible method for the diastereoselective synthesis of a variety of diversely substituted bridged tetrahydro-2-benzazepines. The key steps are the highly diastereoselective Michael addition of metalated aldehyde hydrazones to aromatic enoates followed by a double reduction process to generate hydroxy and hydrazine functionalities combined with a cyclomethylenation reaction to secure the formation of the benzazepine ring system.

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