Tetrahedron Letters, Vol 32, No 42, pp 5927-5930, 1991
Printed in Great Britain

0040-4039/91 $3 00 + 00
Pergamon Press plc

Efficient Methodology for the Preparation of ß-Aminotetralin Derivatives via Electrophilic Amination

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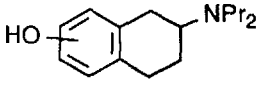
Key Words Electrophilic amination, stereoselective reduction, α-amino ketones;

Abstract A mild and efficient method for the construction of ß-aryl amines from the corresponding α-aryl ketones is presented The key steps of the synthesis involve an electrophilic amination by dibenzyl azodicarboxylate followed by a stereoselective $LiHBEt_3$ reduction The reaction sequence is applied to the synthesis of the tricyclic ergoline analogue **4**

Among the conformationally restricted analogues of the neurotransmitters dopamine and serotonin, bi- and tricyclic ß-aminotetralin derivatives are a widely studied family of compounds with excellent pharmacological properties Thus the hydroxydipropylaminotetralins **1** show strong affinity to the dopamine (D) or serotonin (5-HT) binding sites [1,2] The 8-hydroxy isomer (8-OH DPAT) turned out to be the first selective $5\text{-}HT_{1A}$ agonist [3] On the other hand the aminobenzindole derivative **2** with tricyclic partial ergoline structure reveals remarkable dopaminergic activity [4]



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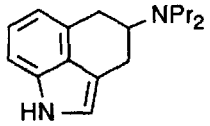

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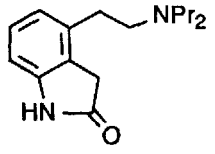

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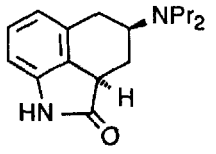


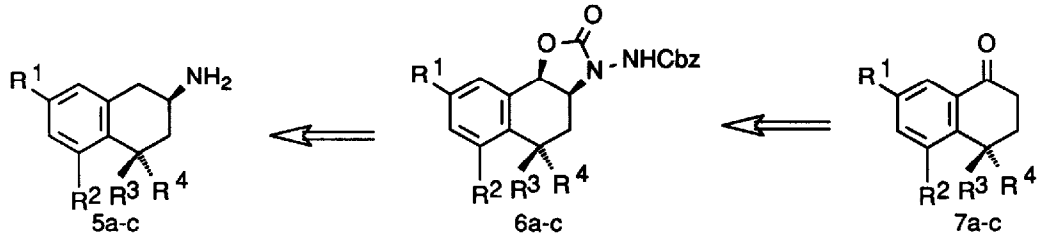
4

As an extension of our structure activity relationship studies with bi- and tricyclic ergoline analogues[5] we attempted to approach the aminobenzindolone **4** as a conformationally restricted variant of ropinirole ^{R} (**3**), which is known to be a strong and selective D_2 agonist.[6] Since we intended to synthesize our target molecule (**4**) starting from the acetal protected tetrahydrobenz[cd]indolone **7c** (Scheme 1), which is unstable towards acidic reaction conditions, a mild α-amination / reduction sequence had to be elaborated We anticipated that the established methods,[7] including fairly drastic reaction conditions, would not be suitable in our case Additionally the method was expected to facilitate a stereocontrolled amination

In this communication we report a new and efficient methodology for the preparation of ß-aminotetralins (**5a-c**) from the corresponding aromatic ketones (**7a-c**) as well as its application to the construction of the tricyclic ropinirole ^{R} analogue **4** The key intermediates of the synthesis are the

oxazolones **6a-c** which can be derived employing an electrophilic amination[8] with dibenzyl azodicarboxylate followed by stereoselective $LiHBEt_3$ reduction and transesterification **6a-c** can be readily transformed into the target amines **5a-c** by hydrogenolytic cleavage both, the benzylic C-O bonds and the hydrazine N-N bond

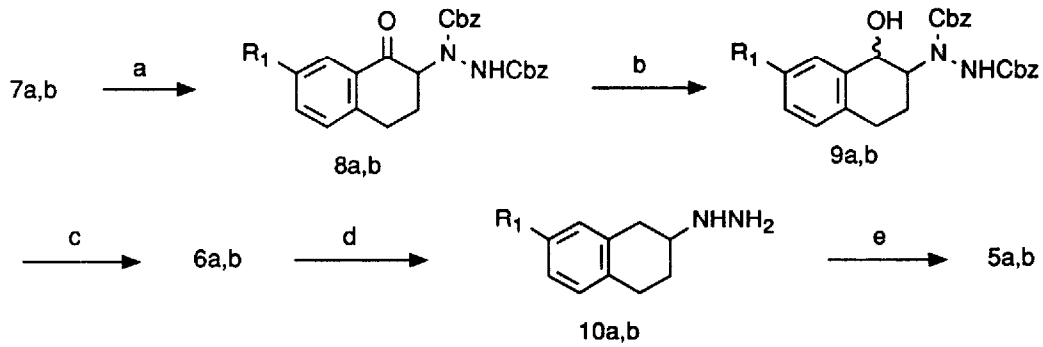
SCHEME 1



5a, 6a, 7a R^1, R^2, R^3, R^4 = H
5b, 6b, 7b R^1 = OCH_3, R^2, R^3, R^4 = H
5c, 6c, 7c R^1 = H, R^2-R^3 = $N[CH(OEt)_2]$-C(O), R^4 = $CH(OEt)_2$

Although electrophilic amination of ketene acetal derivatives with dialkyl azodicarboxylate is reported to be a very effective method for the construction of α-amino acids,[9] similar reactions with ketone enolates have not been described - as far as we know We chose dibenzyl azodicarboxylate (DBAD) as a suitable electrophile because the projected removal of the Cbz groups under neutral hydrogenolytic conditions was supposed to be the most convenient way of deprotection

SCHEME 2

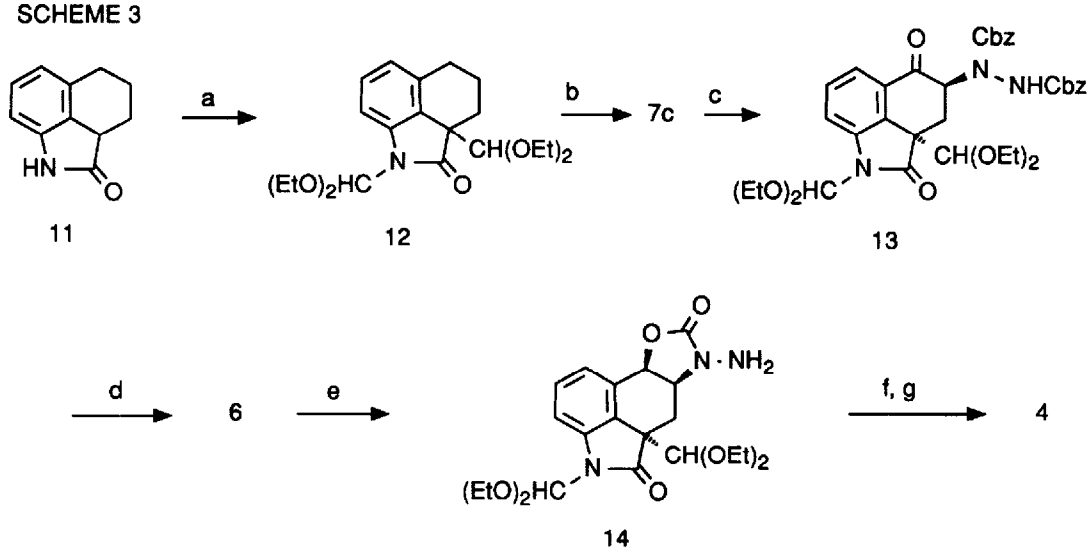


a) 1 1 1 eq LDA, THF, -78°, 2 1 1 eq DBAD (87, 57 %) b) 1 1 eq $LiBHEt_3$, THF, -78° c) RT (77, 72 %) d) Pd/C-H_2, MeOH, RT e) Ra-Ni, MeOH, RT, 50 bar (55, 50 % from **6a,b**)

Tetralone (**7a**) as well as 7-methoxytetralone (**7b**) were transformed into their lithio enolates with help of LDA in THF at -78° Subsequent addition of 1 1 equiv of DBAD gave the amination products **8a,b** (Scheme 2) The work up turned out to be very comfortable since pure **8a,b** crystallized completely from Et_2O or EtOH Transformation of **8a,b** into the oxazolone derivatives **6a,b** was planned to proceed by stereoselective reduction to yield the protected hydrazino alcohols **cis-9a,b**, followed by transesterification

Knowing that earlier reported reductions of α-aminotetralone derivatives by $NaBH_4$ lead to trans-configurated products[10] (*product development control*[11]) we planned to employ the sterically demanding $LiBHEt_3$ which should favor an approach from the less hindered ß-side (*steric approach control*[11]) In fact we observed a 6 1 diastereofacial selectivity in favor of cis-**9a,b**, which can be raised to 11·1, when the reaction is done at -100° [12] The diastereomers can be isolated by quenching the reaction mixture at dry ice temp , immediately followed by an aqueous extraction On the other hand complete oxazolone formation of the cis-isomers to give **6a,b** was observed, when the reaction mixture was allowed to warm up to room temp before hydrolysis with sat $NaHCO_3$ Subsequent treatment of **6a,b** with Pd/C-H_2 in MeOH resulted in complete hydrogenolysis of the 2 benzylic carbamates to give the 2-hydrazinotetralins **10a**[13] and **10b**, which underwent N,N bond cleavage with Ra-Ni / MeOH - H_2 to afford the target compounds **5a,b**[14]

SCHEME 3



a) $H(OEt)_3$, 160° (60 %) b) 1 NBS / dibenzoyl peroxide, CCl_4, reflux, 2 DMSO, Et_3N, CCl_4 (60 %) c) LDA, DBAD, THF, -78° (85 %) d) 1 $LiBHEt_3$, THF, -78°, 2 RT (80 %) e) Pd/C-H_2, EtOH, RT (81 %) f) Ra-Ni, MeOH, RT, 50 bar (74 %) g) 1 Pd/C-H_2, MeOH, 70°, 50 bar; 2 Propionic aldehyde, $Na(CN)BH_3$, MeOH, RT, 3 2N aqueous HCl, EtOH (35 %) or BBr_3 / CH_2Cl_2, RT (32 %)

The synthesis of the aminobenzindolone **4** with tricyclic ergoline partial structure was planned to proceed from the tetrahydrobenzindolone **11** as an inexpensive commercially available educt (Scheme 3) Since the benzylic CH_2-position should be oxidized regioselectively and without aromatisation as a possible side reaction the benzylic methine moiety had to be protected For this purpose introduction of a diethoxymethine group was envisaged Similarly to a procedure, which was established by Grob and coworkers,[15] **11** was treated with formic acid orthoester, when protection occurred on both acidic positions - the benzylic methine group and the NH of the lactam function to afford **12** Radically induced bromination at C-5 (NBS / dibenzoyl peroxide in CCl_4), followed by addition of DMSO and triethylamine gave access to the tricyclic ketone **7c** Electrophilic amination of **7c** with DBAD accomplished **13**, when LDA was employed to generate the enolate It is noteworthy that this reaction proceeded under total stereocontrol [16] Only the trans diastereomer could be isolated Subsequent cis-reduction with $LiHBEt_3$, followed by transesterification

accomplished oxazolone **6c** The observed diastereoselectivity was 36 1 In contrast to the examples described above hydrogenolysis with Pd/C-MeOH gave only cleavage of the exocyclic carbamate to yield the N-aminooxazolone **14** This reaction step, however, succeeded after cleavage of the hydrazine group with Raney-Ni Finally the primary amine **5c** was 'dialkylated' with propionic aldehyde / $NaCNBH_3$, followed by removal of the two diethoxymethine groups with aqueous HCl or BBr_3 / CH_2Cl_2 under complete retention at C-2a The configuration at C-2a is expected to be thermody namically controlled, because in this case the amine function is positioned equatorially

Further investigations on a stereocontrolled approach to cis- and trans-amino alcohols as well as an evaluation of an enantioselective amination process are in progress

Acknowledgments·

We wish to thank Prof F Eiden for stimulating discussions and generous support Thanks are also due to S Nerdinger for technical assistance This work is supported by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie*

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16 The trans- relationsship between the protected hydrazino group and the acetal function of **13** was established by ^{1}H-NMR spectroscopy, when a significant NOE between the proton of the acetal methine group and the axially positioned 4-H was observed

(Received in Germany 25 March 1991)