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Asymmetric Synthesis of β-Alkoxy Substituted Phenethylamine Analogs

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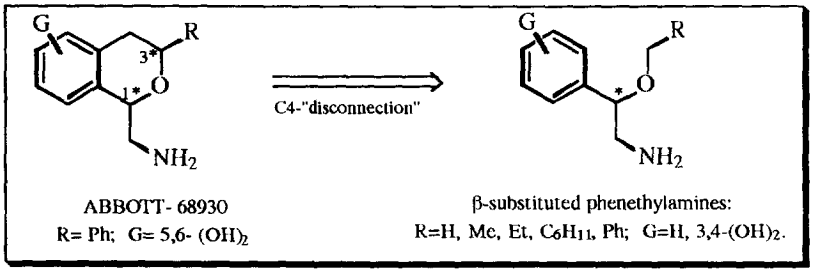
Abstract: The enantioselective synthesis of beta-alkoxy substituted phenethylamines is described. The enantiomeric excess of the products ranges from 77 to 87 %. Copyright © 1996 Elsevier Science Ltd

We have recently synthesized a series of β-alkoxy substituted phenethylamines and tested them for activity at the dopamine receptors and alpha-adrenoceptors.[1] These structures could be considered as deriving from the "disconnection" of the C-4 methylene of the isochroman moiety in a number of isochroman-type dopamine analogs, such as the ABBOT-68930. The isochroman analogs exhibit very high selectivity towards the D_1 receptor with the [1R,3S] enantiomers being always the active ones, as reported by DeNinno et al.[2-4] Such disconnection could provide us with substantial information on the mode of interaction of substituted phenethylamines with the D_1 receptor as chirality at C-3 is abolished and the interaction depends only on the stereochemistry at C-1. This allows for a direct evaluation of the effect that this chiral center has on the compounds' selectivity. Moreover the conformational restrictions imposed by the isochroman ring have been cancelled.



Although most of the compounds were readily resolved in the form of diastereomeric tartarate salts, we experienced insuperable difficulties to resolve the bis benzyloxy precursors (G=3,4- $(OBn)_2$, R= Ph or C_6H_{11}) to their enantiomers. All attempts were totally fruitless regardless of chiral reagents and reaction conditions used. HPLC experiments using various chiral columns also failed to give a satisfactory separation of the enantiomeric pairs.

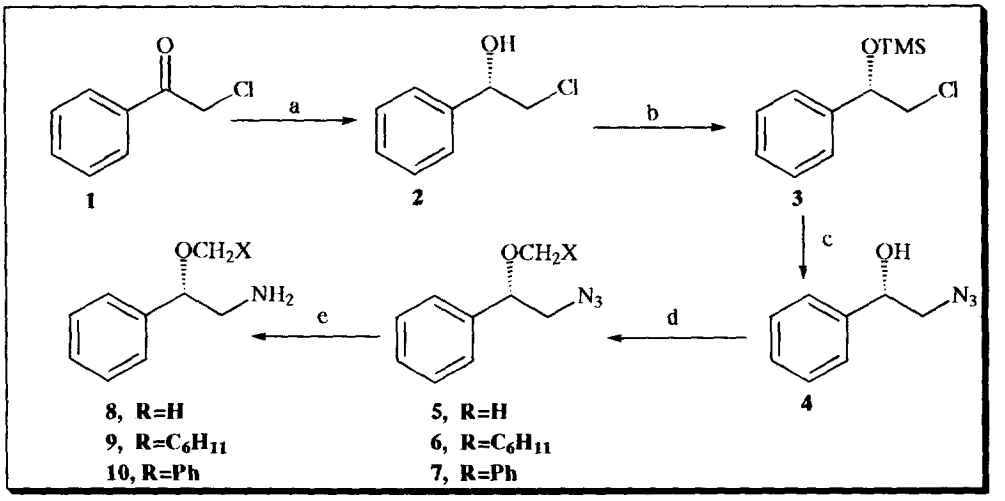
We were therefore prompted to explore the alternative of an enantioselective synthesis of these Dopamine congeners. The best approach to this synthetic problem appeared to be the introduction of the chiral center by an enantioselective reduction of an intermediate ketone with either isomer of diisopinocamphenylchloroborane (Ipc_2BCl).[5-7] Thus, 2-chloroacetophenone was reduced with (+)-Ipc_2BCl in THF to give (S)-2-chloro-1-phenyl ethanol **2** which was converted to its TMS ether (Scheme 1). Reaction of this chloride in DMSO with sodium azide in the presence of tetrabutyl ammonium iodide[8] yielded azide **4**, which upon treatment with 1N HCl solution yielded the azido alcohol **5** in 68% yield from **2**. Subsequent alkylation of the alcohol (DMF, sodium hydride, alkylating agent), and catalytic hydrogenation furnished the desired amines. Ring bis-benzyloxy substituted analogs syntheses included α-chlorination of 3′,4′-dibenzyloxyacetophenone[9] using benzyltrimethyl ammonium dichloroiodate[10] in 1, 2-dichloroethane/methanol, reduction of **12** with (-)-Ipc_2BCl, to the (R)-enantiomer of **13** according to the theory[5] and essentially the same trend of reactions to the desired (R)- amines.

Table 1. Enantiomeric Excess of β-Alkoxy Substituted Phenethylamines.

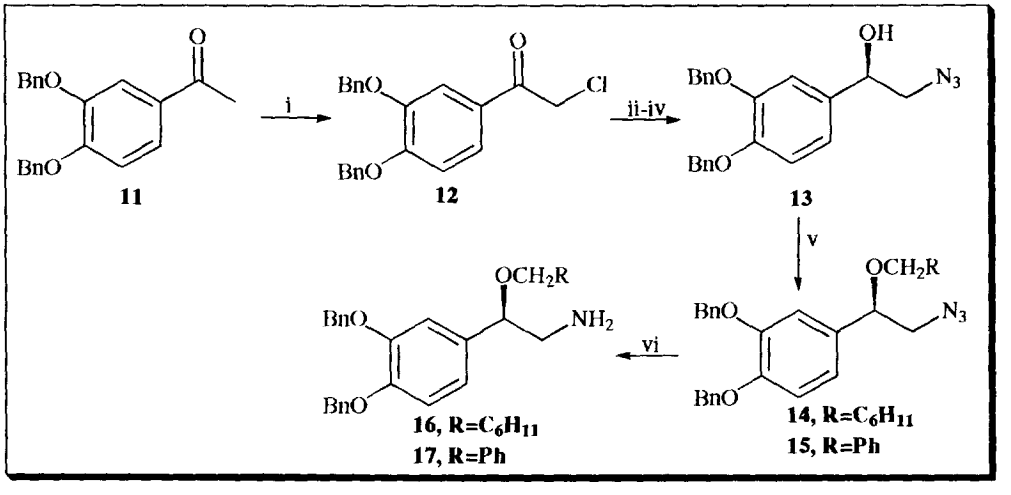
Compound	Optical Rotation[a]	% ee
(S)-8	$[\alpha]_D$ =+90.0° (c=1.0, EtOH) *$[\alpha]_D$ =+46 .0° (c=1.0, EtOH)*	87
(S)-9	$[\alpha]_D$ =+53.1° (c=4.6, EtOH) *$[\alpha]_D$ =+41 .2° (c=0.5, EtOH)*	87
(S)-10	$[\alpha]_D$ =+82.4° (c=1.0, EtOH) *$[\alpha]_D$ =+63 .2° (c=1.0, EtOH)*	87
(R)-16	$[\alpha]_D$ =-15.3° (c=1.0, EtOH)	77
(R)-17	$[\alpha]_D$ =-37.0° (c=1.0, EtOH)	77

[a]Values in italics from ref. 1.

The enantiomeric excess (ee) of the ring-unsubstituted congeners (Table 1) was calculated by comparison of the optical rotation of the known intermediate **4** with the literature value.[11] In the case of the bis benzyloxy derivatives, ee was calculated directly by NMR study of **13**, using optically active NMR shift reagents, with tris(trifluoroacetyl-d-camphorato)europium(III) giving the best results on the methine hydrogen differentiation.[12]



Scheme 1: Reagents and conditions: a) (+)-Ipc_2BCl, THF, 0°C, 24 h, 55%; b) TMSCl, imidazole, DMAP, DMF, 0°C, 1h, 90%; c) NaN_3, DMSO, $Bu_4N^+I^-$, 80°, 12 h, then 3% HCl, 75%; d) NaH, DMF, and MeI (90%), $C_6H_{11}CH_2OTs$ (31%) or $PhCH_2Br$, (95%); e) H_2, 10% Pt/C, EtOH, 15h, 94-95%.



Scheme 2: Reagents and conditions: i) $BnMe_3N^+Cl_2I^-$, 2 eq, $ClCH_2CH_2Cl$ / MeOH 2.5:1, 80°C, 3 hr, 91% ii) (-)-Ipc_2BCl, THF, 0°C, 24 h, 55%; iii) TMSCl, imidazole, DMAP, DMF, 0°C, 1h, 90%; iv) NaN_3, DMSO, $Bu_4N^+I^-$, 80°C, 12 h, then 3% HCl, 76%; v) NaH, DMF, and $C_6H_{11}CH_2OTs$ (31%) or $PhCH_2Br$, 90-95%; vi) H_2, 10% Pt/C, EtOH, 15h, 94-95%.

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