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ENANTIOSPECIFIC SYNTHESIS OF R- AND S-5,6-DIHYDROXY-2-(N,N-DI-*n*-PROPYLAMINO)TETRALINS FROM SERINE.

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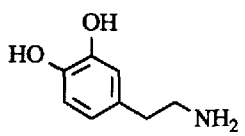
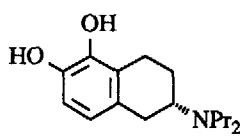
Abstract: The first enantiospecific synthesis of 5,6-dihydroxy-2-(N,N-di-*n*-propylamino)tetralin [5,6-$(HO)_2$DPAT] is reported. Starting from D- or L-serine either enantiomer is readily available in high optical purity.

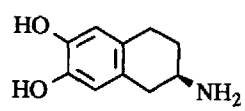
Drugs acting on central dopamine D_2 receptors are known to be of clinical interest in the treatment of schizophrenia and Parkinson's disease.[1] 5,6-Dihydroxy-2-(N,N-di-*n*-propylamino)tetralin (S-5,6-$(HO)_2$DPAT) (**1**) is a potent D_2 receptor agonist and hence an important pharmacological tool. 5,6-$(HO)_2$DPAT (**1**) has been prepared in racemic form[2] and subsequently resolved using (+)- and (-)-dibenzoyltartaric acid.[3]



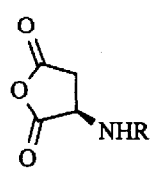
DOPAMINE



(**1**)

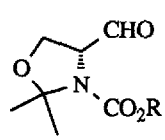


(**4**)



(**2**); R = $COCF_3$

(**3**); R = CO_2Me



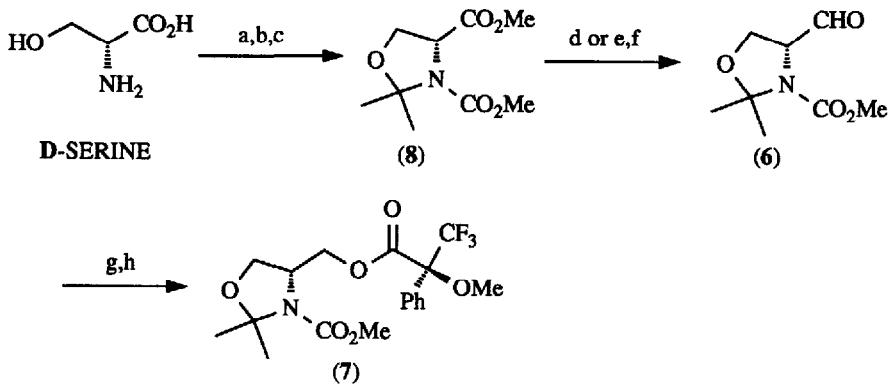
(**5**); R = t-Bu

(**6**); R = Me

Previous enantiospecific syntheses of aminotetralins have been achieved from the aspartic anhydride derivatives (**2**)[4] and (**3**)[5] by means of a Friedel-Crafts acylation procedure. Acylation of catechol with the aspartic anhydride derivative (**3**) occurs in the 4-position and ultimately leads to a synthesis of the regioisomeric 6,7-$(HO)_2$DPAT (**4**). This reagent is therefore unsuitable for the preparation of (**1**). We report here an alternative general strategy for the enantiospecific synthesis of aminotetralins starting from serine. This procedure also provides an efficient method for the preparation of *homo*-phenylalanine derivatives.

The aldehyde (**5**) is configurationally stable[6] and has been widely used in synthesis.[7] We now report the first synthesis and use of the more robust aldehyde (**6**) which is compatible with all the conditions employed in our synthesis of 5,6-$(HO)_2$DPAT. Thus the aldehyde derivative (**6**) was prepared from **D**-serine (scheme1) and has been shown to be configurationally stable by hplc analysis of the Mosher's ester derivative (**7**).[8] The most convenient preparation of (**6**) proved to be lithium borohydride reduction of the ester (**8**) followed by Swern oxidation. DIBAL reduction of (**8**), although more direct, proceeded in low yield.

Scheme 1



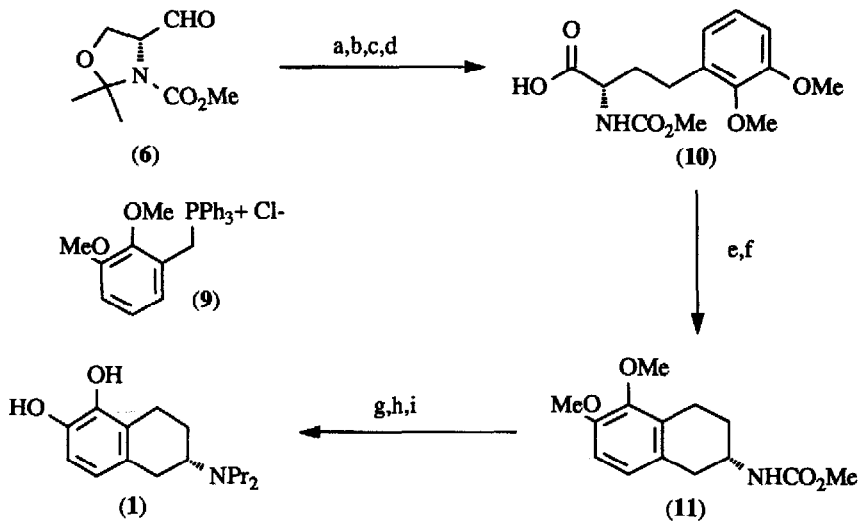
Reagents and conditions:

a) MeOH, HCl, reflux, 18h, 100%. b) $ClCO_2Me$, $NaHCO_3$, H_2O, 5°C, 1h, 80%. c) 2,2-Dimethoxypropane, TsOH, toluene, reflux, 2h, 75%. d) DIBAL, toluene, -78°C, 1h, 20%. e) $LiBH_4$, THF, room temperature, 18h, 80%. f) $(COCl)_2$, DMSO, CH_2Cl_2, -65°C; N-methylmorpholine, 70%. g) $NaBH_4$, THF, *i*-PrOH, 0°C, 2h, 90%. h) (S)-MTPA, DCC, DMAP, CH_2Cl_2, room temperature, 6h, 92%.

Wittig reaction of (**6**) with the known phosphonium salt (**9**)[9] produced a mixture of olefins (E:Z, *ca.* 60:40), which were hydrogenated. Hydrolysis of the acetonide, followed by PDC oxidation of the resulting alcohol then provided the *homo*-phenylalanine derivative (**10**) in good yield.

Acid chloride formation under mild conditions, followed by intramolecular Friedel-Crafts acylation using titanium tetrachloride as the catalyst, produced a stable ketone which was deoxygenated with triethylsilane to the carbamate (**11**) (>98% e.e. by hplc analysis).[8]

Scheme 2



Reagents and conditions:

a) (**9**), *t*-BuOK, THF, 0°C, 2h, 100%. b) H_2, Pd-C, EtOAc, 2h, 100%. c) TsOH, MeOH, room temperature, 18h, 84%. d) PDC, DMF, room temperature, 6h, 56%. e) $(COCl)_2$, cat. DMF, CH_2Cl_2, 0°C; $TiCl_4$, CH_2Cl_2, 0°C - room temperature, 2h, 80%. f) Et_3SiH, $BF_3.OEt_2$, room temperature, 18h, 59%. g) KOH, MeOH, H_2O, reflux, 18h, 86%. h) $NaBH(OAc)_3$, EtCHO, HOAc, $ClCH_2CH_2Cl$, room temperature, 2h, 92%. i) BBr_3, CH_2Cl_2, room temperature, 18h, 89%.

Hydrolysis of the carbamate protecting group, followed by reductive dialkylation using sodium triacetoxyborohydride and propionaldehyde, then finally boron tribromide deprotection of the methyl ether groups furnished **S**-(-)-5,6-$(HO)_2$DPAT (**1**) in 5% overall yield from serine. [Mp of hydrochloride salt, 168-171°C; Lit.[3] mp 170-171°C. $[\alpha]^{20}_D$ -54.7° (c = 0.3, H_2O); Lit.[3] $[\alpha]^{20}_D$ -51.7° (c = 0.15, H_2O)].
In a similar procedure **L**-serine was converted to the isomerically pure **R**-(+)-5,6-$(HO)_2$DPAT. [Mp of hydrochloride salt, 168-172°C. $[\alpha]^{20}_D$ +48.4° (c = 0.8, H_2O); Lit.[3] $[\alpha]^{20}_D$ +48.8° (c = 0.15, H_2O)].

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8. For hplc analyses of (7) and (**11**), the authors are indebted to Mr R. J. Boughtflower and his colleagues in the Structural Chemistry Department at Glaxo Group Research, Ware.

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