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A NEW SYNTHESIS OF 2-AMINO-6-7-DIHYDROXY TETRAHYDRONAPHTHALENE (ADTN) VIA FUNCTIONALIZED ARYL-LITHIUM REAGENTS AND METHYL 2-TRIMETHYLSILYLACRYLATE - A NEW ANNULATION SEQUENCE

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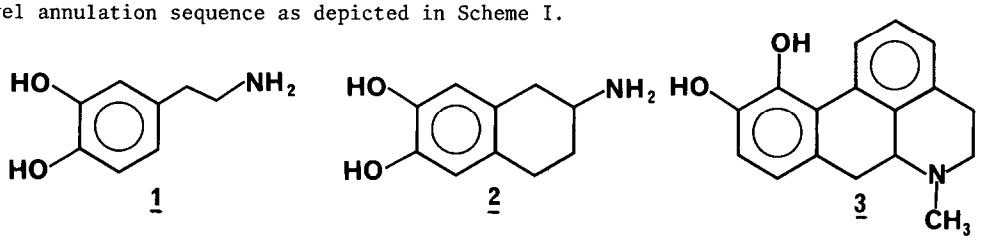
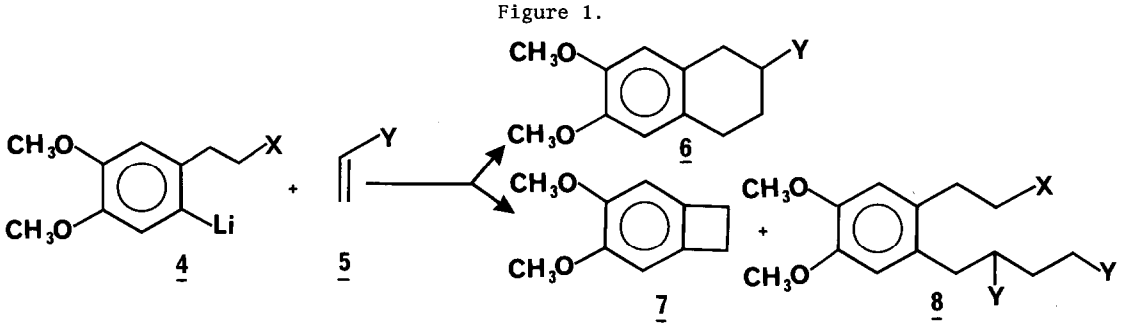
Abstract: A new high yield synthesis of a potent dopamine agonist, 2-amino-6-7-dihydroxytetrahydronaphthalene, is described utilizing a new annulation sequence.

Chemical imbalance in the levels and neuronal activity of dopamine (DA, 1), a CNS neurotransmitter, has been implicated in the aetiology and pathogenesis of the syndromes of schizophrenia and Parkinson's disease.[1] In order to understand the molecular geometry of DA as recognized at its receptor sites in the brain, a considerable effort has been expended to synthesize conformationally rigid analogues of DA. Two such potent DA agonists are ADTN (2)[2] and apomorphine (3). We now wish to report yet another expeditious synthesis[3] of ADTN via a novel annulation sequence as depicted in Scheme I.

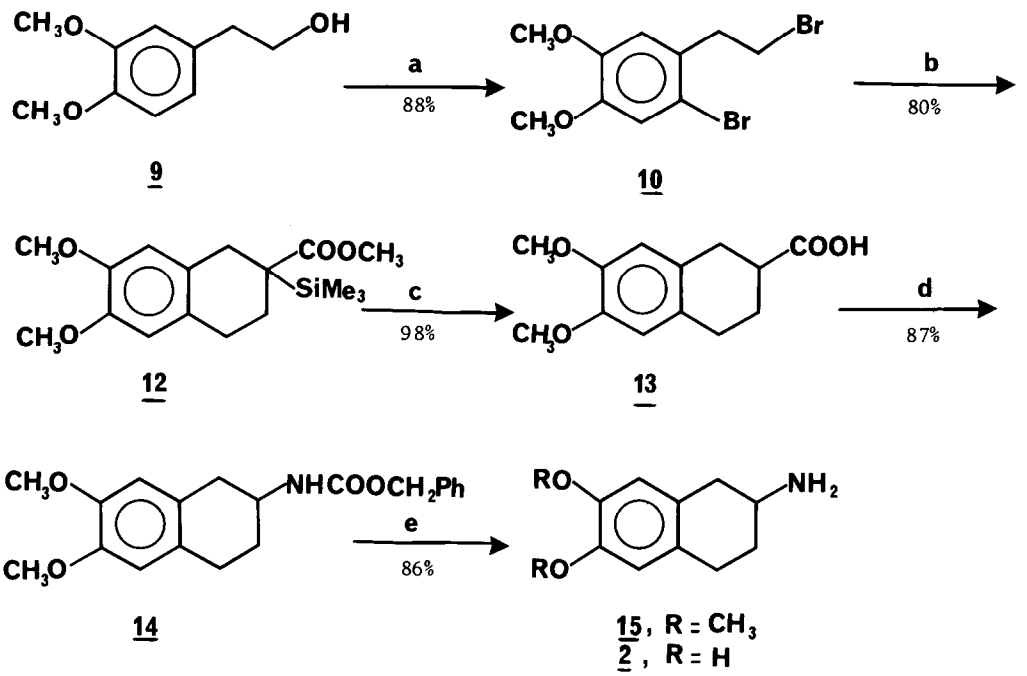


Our strategy envisioned Michael addition of functionalized aryl-lithium (4) to a suitable Michael acceptor (5), followed by concomitant cyclization to give the desired product (6, Figure 1). This would be feasible provided one could prevent the formation of two possible side products: (i) intramolecular decomposition of 4 to 4,5-dimethoxybenzocyclobutene (7);[4] (ii) anionic polymerization of the initial Michael adduct.

Figure 1.



Scheme 1.



Reagents:

a. 1. Br_2/AcOH. 2. NBS/Ph_3P/C_6H_6, refluxed 1.5h.

b. 1. n-BuLi/THF, ≤ -100°C, 1h, followed by addition of CH_2 = C($SiMe_3$)COOMe (11) at -100°C, 1h and then warm up to RT.

c. 20% aqueous NaOH/MeOH, refluxed 5h.

d. 1. $(PhO)_2P(O)N_3$/Et_3N/C_6H_6, refluxed, 2h. 2.$C_6H_5CH_2OH$, refluxed, 24h.

e. 1. 5%Pd/ Charcoal, H_2/MeOH. 2. 48%HBr, reflux under N_2.

Hence we explored the chemistry of (2-bromo-4,5-dimethoxyphenyl)ethyl bromide (10)[4,5] which was prepared from the commercially available 4,5-dimethoxyphenylethyl alcohol (9). Chemoselective halogen-metal exchange of the arylbromine atom of the dibromo compound (10) occurred readily with n-BuLi in THF (N_2) at temperature[6] $\lesssim$-100° to give 4 which on addition to nitroethylene[7] (5,Y=NO_2) gave mixtures and polymeric products. Next we carried out the addition of 4 to 2-chloroacrylonitrile which also furnished a mixture of products. In contrast, addition of 4 to methyl acrylate at $\lesssim$-100° in THF yielded only 25% of the desired compound (6, Y=COOMe)[8] together with 8 (Y=COOMe) as the major side product. In order to obviate the formation of 8, it was envisaged that an anion stablizing substituent α-to the COOMe group in methyl acrylate might prevent or retard anionic polymerization of the initial Michael adduct and thus promote cyclization to the desired product. Hence, we prepared methyl 2-trimethylsilylacrylate (11) as the Michael acceptor[9].

As anticipated, addition of 4 to 11 at $\lesssim$-100° in THF furnished the cyclized product (12) in 80% isolated yield after flash chromatography of the crude product over SiO_2-gel. It is not clear whether electronic or steric factors, or both, play the predominant role in suppressing anionic polymerizations when α-trimethylsilyl-substituted Michael acceptors[10] are used in Michael additions. Desilylation of 12 with 20% aq. NaOH in MeOH gave the known acid 13 (m.p.141.5-142.5°C, lit.[11] m.p. 136.5-137.5°C), thus corroborating the structure of the cyclized compound.

The next state of the synthesis was the conversion of the COOH to an NH_2 group which was realized by a two step sequence. Modified Curtius reaction of 13 with diphenylphosphorazidate[12] gave the benzyloxycarbamate 14 (m.p. 122-123°) which on hydrogenolysis with 5% Pd/charcoal in MeOH containing one equivalent of HCl furnished 15 as the HCl salt (m.p. 227-229°, lit. m.p. 223-224° [3b]/228-230° [3c]). Demethylation of 15 by refluxing with 48% HBr gave ADTN·HBr (m.p. 267-268°C, Lit[3c] m.p. 267-269°). This synthetic ADTN was found to be identical with an authentic sample on comparison of spectroscopic (NMR, IR, MS) & TLC data. The overall yield from 9 to 2 was 52%.

In conclusion, our synthesis offers a new annulation sequence and may find general use in the synthesis of polycyclic compounds as well as recently reported DA agonists such as 5,6-dihydroxy-[13a], and 5,7-dihydroxy -[13b] 2-aminotetralins.

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