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A Synthesis of (-)-Denopamine

Roger F.C.Brown, W. Roy Jackson and Tom D. McCarthy*

Department of Chemistry, Monash University, Wellington Road, Clayton, 3168, Victoria, Australia.

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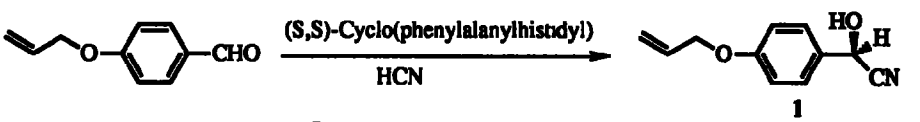
Abstract: The important cardiac drug, (-)-denopamine, has been synthesised in 68% overall yield from *para*-allyloxybenzaldehyde via (R)-2-hydroxy-2-[(2-propenyloxy)phenyl]acetonitrile

Denopamine (5) is a relatively new[1] β_1-receptor agonist.[2,3] It is effective in the treatment of congestive heart failure.[4] by increasing cardiac pumping function (positive inotropic activity) without a significant increase in heart rate.[4] An advantage of denopamine (5) over other drugs possessing positive inotropic activity is that it can be administered orally and has reduced toxicity.

The active form of denopamine is the (R)-enantiomer, (-)-denopamine (5). The Tanabe Seiyaku Co. Ltd, Japan holds two patents for the preparation of (-)-denopamine (5).[5,6] Other synthetic approachs to (-)-denopamine (5) have been based on asymmetric reduction of ketone precursors[7,8] or the chirality has been introduced by microbial reduction of alpha ketoesters.[9] We now report an asymmetric synthesis of (-)-denopamine (5) in high yield from *para*-allyloxybenzaldehyde.

When *para*-allyloxybenzaldehyde was treated with HCN in the presence of (S,S)-cyclo(phenylalanylhistidyl),the Inoue catalyst[10,11,12], under conditions described previously by us[13], using precipitated dipeptide[14], the cyanohydrin (1) was produced in 96% conversion and >98% enantiomeric excess. Recrystallisation of the crude reaction mixture (CH_2Cl_2/light petroleum) gave pure cyanohydrin (1) in 90% yield. The reaction was run several times and worked equally successfully on large (100 mmol) or small (10 mmol) scale. The optical purity of the cyanohydrin (1) is dependent on the reaction temperature. For example, when the reaction was carried out at -2° for 36h, the cyanohydrin (1) was obtained in 96% conversion but only 30% e.e..[15,16]



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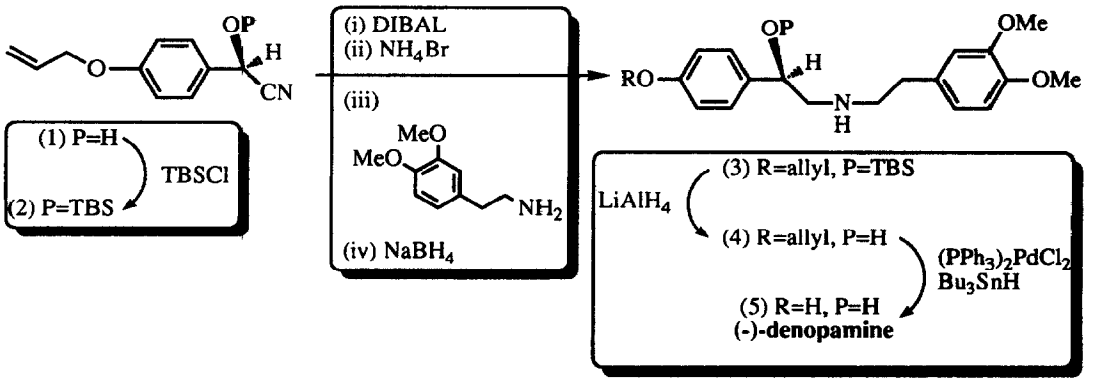
Conditions	Catalyst Activation	Conversion	E.e. %
36h, -15°	precipitated	96%	>98%
36h, -2°	precipitated	96%	30%

Brussee *et al* has shown that the protected cyanohydrins can be converted into a series of N-substituted β-ethanolamines.[17] Applying these conditions, the cyanohydrin (1) was treated with *tert*-butylchlorodimethylsilane (TBSCl) and imidazole to give the silylether (2) in 97% yield. The silylether (2) was then treated successively with DIBAL and quenched with ammonium bromide in methanol to give the primary imine. Addition of excess 3,4-dimethoxyphenylethylamine led to the more stable secondary imine[18] and $NaBH_4$ reduction gave the silyl protected aminoalcohol (3) in 90% yield in one pot from the silylether (2). There were two advantages in using

the TBS protected cyanohydrin (2) instead of the corresponding acetal or TMS protected cyanohydrin. The first is that the TBS group was stable to the aqueous acid quench used in the work up of the reaction. Secondly, the aminoalcohol (3) is essentially insoluble in aqueous acid. Excess 3,4-dimethoxyphenylethylamine can be extracted with aqueous HCl leaving the aminoalcohol (3) in the organic phase. The low solubility of TBS-protected ethanolamines in aqueous HCl has been noted previously.[19] The removal of silyl ethers by $LiAlH_4$, while not a usual reaction, has been applied by Brussee *et al* to the deprotection of the silylethers of aminoalcohols.[19] When the aminoalcohol (3) was treated with $LiAlH_4$ in refluxing THF the allyl ether (4) was obtained in 96% yield. The allyl ether (4) was then deprotected with $(PPh_3)_2PdCl_2$ and tributyltin hydride[20] to give the (-)-denopamine (5) in 88% yield after chromatography. The optical rotation and melting point of this sample were in good agreement with that reported in the literature ($[\alpha]_D$ -28.8, c=1.3, MeOH; m.p. 165-165.5°. Lit.[9] $[\alpha]_D$ -28.3, c=1.1, MeOH, Lit.[9] m.p. 164-165°).

In conclusion, the synthesis of homochiral (-)-denopamine (5) has been achieved in five steps from *para* -allyloxybenzaldehyde in 68% overall yield, with only the final step requiring chromatographic separation.



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14. The dipeptide was precipitated from methanol by the addition of ether; Danda, H., *Synlett*, 1991, 263.
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16. Compound (1) to (4) gave satisfactory ^1H n.m.r., i.r. mass spectra and combustion analysis
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