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A Concise, Scaleable Synthesis of Narwedine

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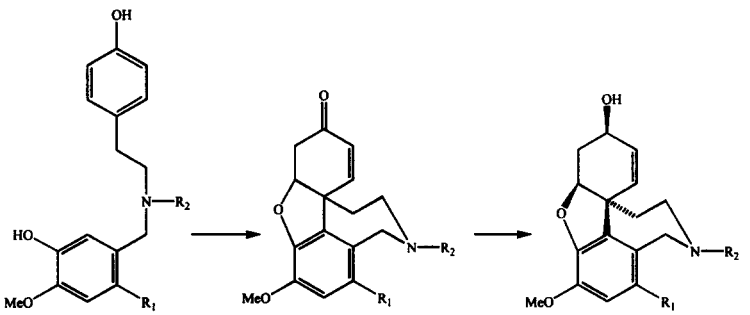
Abstract: A concise, scaleable synthesis of narwedine from 3,4-dimethoxybenzaldehyde is described. The procedure features a simple modification to the Barton phenolic coupling route.

(-)-Galanthamine (**1**), is a natural product currently under evaluation for the treatment of Alzheimer's disease.[1] Isolation by extraction from bulbs, such as daffodils or snowdrops, is low yielding resulting in high costs and limited supplies. The need for a synthetic process has long been recognised and was first addressed by Barton,[2] wherein the tertiary amine (**2a**) was converted into racemic narwedine (**3a**) (<2% yield) via a phenolic oxidative coupling reaction. These workers also identified a novel dynamic resolution procedure which gave (-)-narwedine in *ca.* 80% yield.[3] The synthesis of (-)-galanthamine (**1a**) was completed by reduction with lithium aluminium hydride (Scheme 1)



(2) (3) (1)

Scheme 1 a) R_1 = H, R_2 = Me; b) R_1 = Br, R_2 = CHO; c) R_1 = Br, R_2 = Me

Most practical syntheses of (-)-galanthamine (**1**) focus on the use of narwedine (**3a**) as a pivotal intermediate and consequently much effort has focused on improving the yield of the phenolic coupling step by acylation of the amine and blocking *para-para* coupling by bromination. However, products such as (**3b**) then require a two step conversion to narwedine.[4]

We report in this letter an improved process for the synthesis of racemic narwedine which is based on the phenolic coupling of the bromo amine (**2c**) followed by chemoselective reduction.[5] Tyramine was

converted to the tertiary amine (**2c**) in a "one-pot" procedure by sequential reductive amination with 6-bromoisovanillin and formaldehyde in 77% yield. 6-Bromoisovanillin was readily obtained by bromination of isovanillin (3-hydroxy-4-methoxy-benzaldehyde),[6] although the high cost of this material and the poor regioselectivity (*ca.* 3:1) of the reaction prompted us to investigate the use of 3,4-dimethoxybenzaldehyde for large scale work. The preparation of 6-bromisovanillin by bromination and subsequent demethylation with concentrated sulphuric acid has been described.[7] We have developed this process to provide a "one-pot" transformation by performing the bromination in acetic acid and using 48% aqueous hydrobromic acid for the demethylation step (63% unoptimised).

The preferred conditions for the phenolic coupling involved the use of potassium ferricyanide as oxidant in a dilute toluene/aqueous sodium bicarbonate mixture giving a 30% yield of the bromonarwedine (**3c**). In common with other workers we found that such reactions are greatly facilitated by the use of an in-line homogeniser. A further synthetic advantage of the amine (**3c**) over acylated variants, *eg* (**3b**), was that it had a basic handle which allowed it to be extracted from the dilute toluene solution with a much smaller volume of acid, thus providing a simple work-up which avoided the need for lengthy solvent evaporations. The synthesis of racemic narwedine was completed by a palladium catalysed [$Pd(OAc)_2/PPh_3/NaO_2CH$] debromination in 84% yield (on a 0.5 mol. scale).

In summary we have developed a short and scaleable route to racemic narwedine (**3a**) through a simple improvement to the Barton phenolic coupling procedure. The avoidance of low-temperature reactions and chromatographic purifications are noteworthy features of the process. The overall yield is 19% from 6-bromoisovanillin.

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