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Dynamic Diastereomeric Salt Resolution of Narwedine and its Transformation to (-)-Galanthamine

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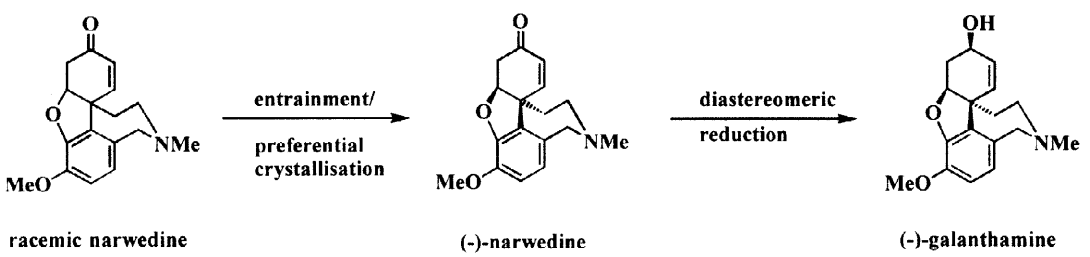
Abstract: Racemic narwedine may be resolved by means of *a dynamic diastereomeric salt formation* using di-*p*-toluoyl-D-tartaric acid. Both the 1:1 and 2:1 salts are formed in excellent yields and diastereomeric excesses. These salts are reduced in a highly diastereoselective and chemoselective manner to give (-)-galanthamine.

Dedicated to the memory of Sir Derek Barton who performed seminal work in this area.

(-)-Galanthamine, an Amaryllidacea alkaloid which is extracted from daffodil bulbs, is currently in clinical trials[2] for the treatment of Alzheimer's disease and hence an efficient means of preparation is of paramount importance. In the first reported synthesis of (-)-galanthamine, Barton *et al* showed that (-)-narwedine, a key intermediate in their sequence, crystallised from a racemic narwedine solution which was doped with (+)-galanthamine.[3,4] They obtained yields of enantiomerically pure narwedine crystals which were greater than 50% and deduced that narwedine was undergoing a facile racemisation by way of a prochiral di-enone intermediate. This work was extended by Sheih and Carlson who demonstrated that, due to the conglomerate nature of narwedine, dynamic entrainment of (-)-narwedine occured when a saturated racemic solution in ethanol/triethylamine was seeded with (-)-narwedine crystals.[5,6] (-)-Galanthamine was obtained by diastereoselective reduction of (-)-narwedine. (Scheme 1).



Scheme 1: Conversion of racemic narwedine to (-)-galanthamine

As part of our efforts to develop an industrially scaleable synthesis of (-)-galanthamine[7-11] we have examined other methods for the preparation of enantiomerically enriched narwedine.[8,10] The dynamic entrainment of narwedine is a kinetic process and so requires tightly controlled conditions to be effective. We therefore wished to devise an alternative method for the resolution of narwedine and believed that a process under thermodynamic control would be more reliable. Given the basic amine function of narwedine,

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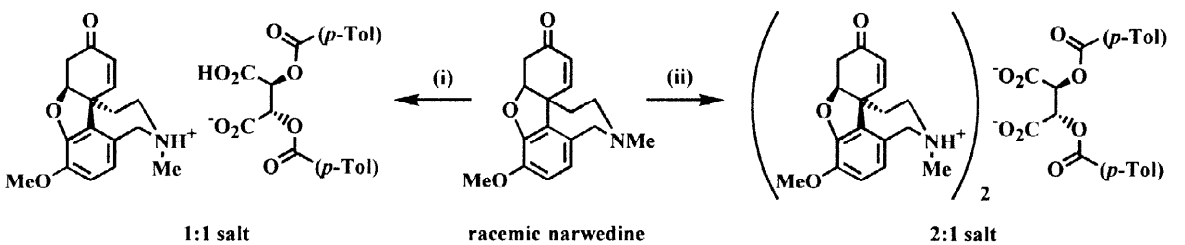
a thermodynamic classical resolution with a chiral acid was postulated. We conducted a screen of chiral acids against narwedine[12] and found that di-*p*-toluoyl tartaric acid was an effective resolving agent.

With 1.0 equivalent of di-*p*-toluoyl-D-tartaric acid per narwedine, a 1:1 (narwedine:acid) salt was isolated in 87% yield. This salt contained (-)-narwedine of 87% e.e..[13] Assuming a 'normal' classical resolution, the theoretical maximum yield of this 1:1 salt was only 53%. The initial experimental yield of 87% clearly indicated that narwedine was racemising under the 'neutral' reaction conditions, allowing material to be funnelled through into one diastereomeric salt in a *dynamic diastereomeric salt resolution.*

This dynamic diastereomeric salt resolution was optimised such that using 1.0 equivalent of di-*p*-toluoyl-D-tartaric acid provided a 1:1 salt in 92% yield containing (-)-narwedine of 97% e.e.[14] Furthermore, when 0.5 equivalent of acid was used, a 2:1 (narwedine:acid) salt was produced in 79% yield, containing (-)-narwedine of 98% e.e. (Scheme 2).[14] Conversely, use of di-*p*-toluoyl-L-tartaric acid allowed formation of the corresponding (+)-narwedine salts. The dynamic nature of these resolutions permits yields far in excess of those which would be obtained from a non-dynamic classical resolution. Moreover, their thermodynamic nature renders them reliable and scaleable, particularly in comparison to our experiences with the entrainment of narwedine.



Scheme 2: (i) 1.0 eq. di-*p*-toluoyl-D-tartaric acid (ii) 0.5 eq. di-*p*-toluoyl-D-tartaric acid

During the salt screen, it was noted that rather than forming salts with narwedine, some chiral acids promoted enantioenriched 'free' narwedine to crystallise. In particular, we found that (*S*)-pyrrolidone-5-carboxylic acid caused (-)-narwedine to crystallise in >99% e.e.. Conversely, addition of (*R*)-pyrrolidone-5-carboxylic acid resulted in (+)-narwedine crystallising in >99% e.e.. In neither case was the acid incorporated into the crystalline narwedine. Barton *et al*[4] showed that alkaloids, structurally similar to narwedine (e.g. galanthamine, epigalanthamine) interacted with the surface of growing narwedine crystals in a highly specific fashion, promoting the crystallisation of one enantiomer of narwedine.[15] In our case, however, a structurally dissimilar compound has produced the same effect.

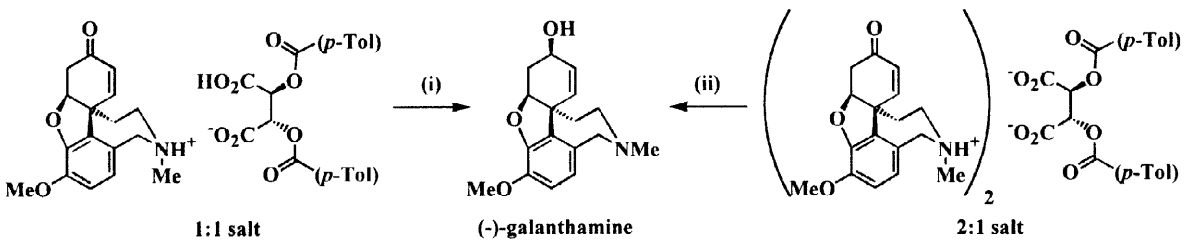
Having obtained the diastereomerically enriched 1:1 and 2:1 salts, we examined methods of converting them into (-)-galanthamine. Cracking the salts to provide free (-)-narwedine for reduction would

be difficult due to the base mediated racemisation of narwedine. As such, a method for the direct reduction of the (-)-narwedine within the matrix of the salt was essential. This reduction needed to be both regioselective for the carbonyl group over the conjugated olefin and diastereoselective to yield galanthamine rather than epigalanthamine.[16] Furthermore, it was not clear if the protonated amine of the salt (or the acid function of the 1:1 salt) would quench the reducing agent.

Experimentation revealed that both $LiAlH_4$ and L-Selectride® reduced narwedine within the 1:1 and 2:1 salt forms but sodium borohydride was ineffective. $LiAlH_4$ is known to reduce 'free' narwedine with low selectivity[17] (approximately 7:4 mixture of galanthamine to epigalanthamine along with minor amounts of dihydrogalanthamine from over reduction) and so we were surprised to find that reduction on the 1:1 and 2:1 narwedine salts was much more selective giving a 9:1 mixture of galanthamine to epigalanthamine with no other reduction products. L-Selectride®, however, proved superior and reduced the 1:1 and 2:1 narwedine salts with complete regio and diastereoselectivity to galanthamine, with no side products.

Reduction of the 1:1 salt required 2.0 equivalents of L-Selectride® per narwedine, one equivalent being consumed by the free carboxylic acid of the diacid resolving agent. (-)-Galanthamine was isolated in 76% yield with 82% e.e..[18] This e.e. was lower than anticipated as (-)-narwedine within the salt was racemising to some extent under the reduction conditions. The temperature of reaction and rate of addition of L-Selectride® were found to be critical to achieve the reduction of (-)-narwedine within the salt suspension without significant racemisation occurring.

Remarkably only 1.0 equivalent of L-Selectride® per narwedine was required to reduce (-)-narwedine within the 2:1 salt matrix to (-)-galanthamine in 91% yield, 94% e.e..[18] The hydride source was not quenched by the acidic NH^+ protons of the salt, so excess reagent was not required, nor was there any evidence of reduction of the carbonyl function of the resolving agent, which could be recovered in near quantitative yield.



Scheme 3: (i) L-Selectride® (2.0 eq. per narwedine) (ii) L-Selectride® (1.0 eq. per narwedine)

Finally, we found that galanthamine as its hydrobromide salt (the form in which it is generally supplied to the clinic) readily crystallises to optical purity. Conversion of (-)-galanthamine (94% e.e.) to its

hydrobromide salt and subsequent crystallisation from industrial methylated spirits provided chemically pure and enantiomerically pure (-)-galanthamine hydrobromide (95% yield, >99 % e.e.).

Herein we have described a novel dynamic diastereomeric salt resolution of the alkaloid narwedine with di-*p*-toluoyl-D-tartaric acid. This resolution is under thermodynamic control and is therefore reliable and scaleable. The resultant 1:1 and 2:1 (-)-narwedine salts are reduced with high diastereoselectivity and chemoselectively, to give (-)-galanthamine. Our general dynamic resolution process using a chiral acid should be amenable to analogues of narwedine. Unlike entrainment, it does not rely on the substrate being a conglomerate, therefore allowing easy access to enantiomerically pure galanthamine analogues for medicinal SAR programmes. Also described within this paper is an unusual example of the preferential crystallisation of one enantiomer of narwedine promoted by a structurally unrelated additive.

References and notes

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12. Narwedine was prepared synthetically by the process described in references 7 and 11.
13. Due to the base mediated racemisation of narwedine the salt was not cracked to liberate free narwedine for e.e. assay. A solution of the salt was directly injected onto the HPLC column where it dissociated *in-situ* and the e.e. of narwedine within the salt was obtained. Acetic acid was added to the to prevent racemisation of narwedine on the column. HPLC conditions: Chirocel OD. Size 25 cm x 4.6 mm. Particle size 10μm. 49.5% heptane, 49.5% ethanol and 1% acetic acid. 1 ml/min. 5 °C. 210 nm. (-)-Narwedine (6.20 minutes), (+)-narwedine (10.20 minutes).
14. General procedure for preparation of the 1:1 salt and 2:1 salt: Racemic narwedine was dissolved in ethanol (10 volumes) on warming. Di-*p*-toluoyl-D-tartaric acid (1.0 mol equivalent for the 1:1 salt and 0.5 mol equivalent for the 2:1 salt) was added to the hot solution. The mixture was heated at reflux for 1 h and then slowly cooled to 40 °C and maintained at this temperature for 16 hours. The mixture was then cooled to ambient temperature and the crystals were isolated by filtration and washed with ethanol and ether to afford the 1:1 salt or 2:1 salt respectively.
15. Eliel, E. L., Wilen, S. H. and Mander, L. N. 'Stereochemistry of Organic Compounds', John Wiley and Sons Inc., 1994, Chapter 7, pages 311-314 and references therein.
16. Epigalanthamine is the epimer at C-OH relative to galanthamine.
17. Szewczyk, J., Lewin, A. and Carrol, F. I. *J. Heterocyclic Chem.*, **1988**, *25*, 1809. This result was repeated in our labs.
18. General procedure for reduction of the 1:1 and 2:1 salts: The salt was suspended in THF (100 volumes) at 0 °C under a nitrogen atmosphere. L-Selectride® (2.0 mol equivalents per mol salt) was added dropwise and the mixture was stirred for 30 mins. Methanol was added to quench the reaction and the solvent evaporated. The white residue was partitioned between EtOAc and 2M NaOH. The aqueous phase was removed and acidified to give recovered di-p-toluoyl-D-tartaric acid. The organic phase was washed with water, brine, dried ($MgSO_4$), and evaporated to afford (-)-galanthamine. HPLC conditions: Chirocel OD. Size 25 cm x 4.6 mm. Particle size 10μm., 95:5 heptane:ethanol. 1 ml/min. 5 °C. 210 nm. (-)-Galanthamine (57.0 minutes), (+)-galanthamine (70.10 minutes).