Notes

Asymmetric Transformation of Either Enantiomer of Narwedine via Total Spontaneous Resolution Process, a Concise Solution to the Synthesis of (−)-Galanthamine†

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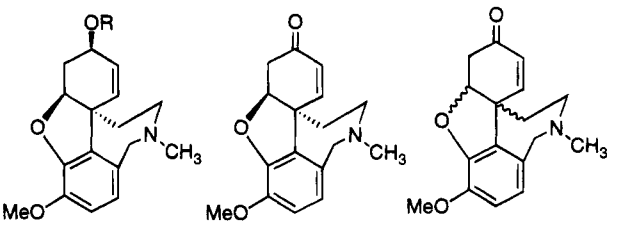
Introduction

(−)-Galanthamine (**1**), a tertiary *Amaryllidaceae* alkaloid, is a selective acetylcholinesterase inhibitor which enhances cholinergic function and is being considered for the treatment of Alzheimer's disease.[1] In patients diagnosed with Alzheimer's disease, (−)-galanthamine was well tolerated and produced significant improvement in performance and attention.[2] Interesting respiratory, cardiac, analgesic, and hypotensive activities have also been reported for (−)-narwedine (**3**),[3] the biogenetic precursor of **1**. Galanthamine is currently available from extraction of daffodils (*Narcissus Pseudonarcissus L.*) and is extremely expensive (~$50,000/kg) for clinical usage. The chemical synthesis of **1**, an alternative source of active ingredient which has been reported by several groups[4,5] in the past four decades, is still a prominent synthetic problem. A short and elegant synthesis of racemic narwedine (**4**) has been reported recently by Holton.[6] We report herein a new, simple, and practical approach to the preparation of (−)-narwedine. Also disclosed is a highly stereospecific conversion of **3** into (−)-galanthamine.

Results and Discussion

The first successful synthesis of (−)-galanthamine was reported in 1962 by Barton[4a] employing reduction of (−)-narwedine obtained by chemical resolution. The Barton process requires 0.5 equiv of (+)-galanthamine, the unnatural alkaloid, for the resolution. Preparation of quantities of (+)-galanthamine for large scale resolution is problematic. Conceptually, we considered the possibility that (±)-narwedine (**4**) is a racemic conglomerate, enabling the enantiomers to be separated directly by crystallization without making a diastereoisomeric derivative.[7] This concept would allow 100% of (±)-narwedine to be transformed into (−)-narwedine if racemization of narwedine in solution is facile. As described below, this concept has been confirmed experimentally.

Scheme 1



1, R = H
2, R = $COCH_3$ 3 4

(±)-Narwedine (**4**)[8] was dissolved into a solvent mixture (16 mL/g) of 95% ethanol–triethylamine (9:1) at 80 °C. To the supersaturated solution at 68 °C, (−)-narwedine seeds (2.5%) were added, and the suspension was cooled and held at 40 °C for 16 h. The crystalline precipitate obtained in 84% from **4** was isolated at 25 °C by filtration and shown to be highly enriched (−)-narwedine (**3**): $[\alpha]^{25}_D$ −408° (c = 1, $CHCl_3$) [lit.[4a] $[\alpha]^{25}_D$ −400° (c = 1, $CHCl_3$)]. A similar process was successfully used to prepare (+)-narwedine (**5**), $[\alpha]^{25}_D$ +412.9° (c = 1, $CHCl_3$) [lit.[4a] $[\alpha]^{25}_D$ +405° (c = 1, $CHCl_3$)], obtained from **4** in 85% yield, by seeding the supersaturated racemic solution with (+)-narwedine. A simple hydrogen–deuterium exchange experiment of (±)-narwedine with 2 equiv of triethylamine and 12 equiv of D_2O led to the formation of 80% trideuterated narwedine (**6**) and 20% mono deuterated narwedine (**7**). This result was consistent with formation of **8** by retro-Michael and subsequent reclosure reactions. Comparison of the IR spectra of **3** and **4** in the solid state (Nujol mull), which were superimposable, provided further indication that the racemate **4** is a conglomerate.[9] In view of the foregoing discussion, it is clear that the above process utilizes the unique *conglomerate nature of narwedine* and is a ***total*** *spontaneous resolution of enantiomers.*

We were able to extend the concept to achieve a *total*, spontaneous resolution of racemic narwedine using either enantiomer of galanthamine as "catalyst". In this alternative process, the enantiomerically pure narwedines were obtained depending on which enantiomeric galan-

†This paper is dedicated to Professor E. J. Corey on the occasion of his 66th birthday.

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(3) Bazhenova, E. D.; Aliev, Kh. U.; Zakirov, U. B. *Farmakol. Alkaloidov Ikh. Proizvod.* **1972**, 74; *Chem. Abstr.* **1974**, *80*, 103864r.

(4) (−)-**1**: (a) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806. (b) Shimizu, K.; Tomioka, K.; Yamada, S.; Koga, K. *Heterocycles* **1977**, *8*, 277. (c) Shimizu, K.; Tomioka, K.; Yamada, S.; Koga, K. *Chem. Pharm. Bull.* **1978**, *26*, 3765.

(5) (±)-**1**: (a) Szewczyk, J.; Lewin, A. H.; Carroll, F. I. *J. Heterocycl. Chem.* **1988**, 25, 1809. (b) Kametani, T.; Shishido, K.; Hayashi, E.; Seino, C.; Kohno, T.; Shibuya, S.; Fukumoto, K. *J. Org. Chem.* **1971**, *36*, 1295. (c) Kametani, T.; Yamaki, K; Terui, T.; Shibuya, S.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1513. (d) Kametani, T.; Yamaki, K; Terui, T. *J. Heterocycl. Chem.* **1973**, *10*, 35. (e) Vlahov, R.; Krikorian, D.; Spassov, G.; Chinova, M.; Vlahov, I.; Parushev, S.; Snatzke, G.; Ernst, L.; Kieslich, K.; Abraham, W.-R.; Sheldrick, W. S. *Tetrahedron* **1989**, *45*, 3329.

(6) Holton, R. A.; Sibi, M. P.; Murphy, W. S. *J. Am. Chem. Soc.* **1988**, *110*, 314.

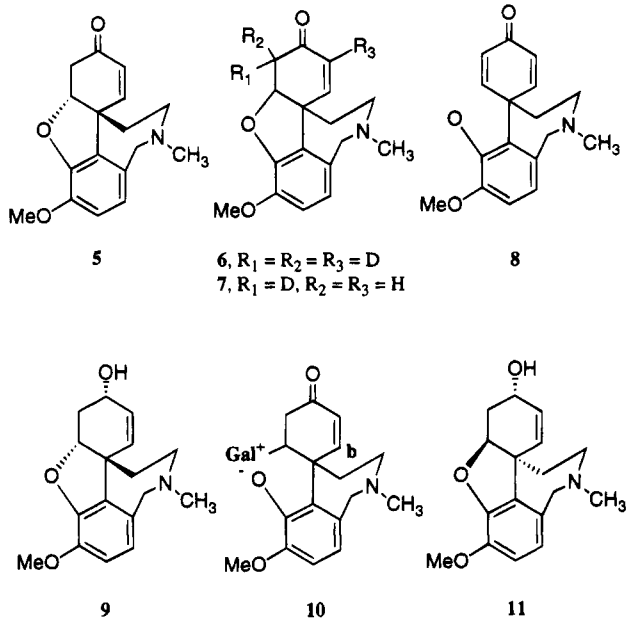
(7) For a summary of existing examples see: Jacques, J.; Collet, A.; Wilen, S. H. In *Enantiomers, Racemates, and Resolution*; Wiley-Interscience Publication: New York, 1981; pp 369–377.

(8) (±)-Narwedine with no optical rotation was obtained in our laboratory by Swern oxidation of natural (−)-galanthamine, which was purchased from MacfarlanSmith Ltd, Edinburgh, Scotland.

(9) For identification of a conglomerate racemate by IR spectroscopy, see: ref 7 pp 80, 81, and 138.

0022-3263/94/1959-5463$04.50/0

Scheme 2



5 6, $R_1 = R_2 = R_3 = D$ 7, $R_1 = D$, $R_2 = R_3 = H$ 8 9 10 11

thamine was involved.[10] (±)-Narwedine (**4**) was dissolved into a solvent mixture (16 mL/g) of 95% ethanol–triethylamine (9:1) at 80 °C in the presence of a catalytic (1%) amount of natural (−)-galanthamine.[8] The solution was cooled to 40 °C and held for 16 h to afford a white precipitate. The precipitate isolated at 25 °C by filtration proved, without further purification, to be enantiomerically pure (+)-narwedine obtained in 75% yield from **4**: $[\alpha]^{25}_D$ +416° (c = 1, $CHCl_3$). Similarly, optically pure (−)-narwedine: $[\alpha]^{25}_D$ −415° (c = 1, $CHCl_3$) was prepared from (±)-narwedine, using a catalytic amount (1%) of (+)-galanthamine (**9**),[11] in 76% isolated yield. It was also confirmed that the mother liquor from the above transformation can be recycled by adjusting the solvent volume, without adding fresh "catalyst", to isolate additional (−)-narwedine. This process is so efficient that we were able to convert 10 g of (±)-narwedine into 9.02 g of (−)-narwedine in two cycles (cycle 1, 7.62 g; cycle 2, 1.4 g). In theory, conversions approaching 100% may be achieved without much effort.

Three possible mechanisms were proposed to rationalize these remarkable phenomena: (i) (+)-Galanthamine functions as a reversible nucleophilic catalyst which stereospecifically interacts with (+)-narwedine in solution resulting in an intermediate such as **10**. Reclosure of **10** at site **b** via Michael addition followed by elimination of **9** would complete the racemization of **5** and enrich the formation of (−)-narwedine. (ii) Racemic narwedine forms a more soluble (+)-galanthamine/(+)-narwedine pair in solution. This preferred complexation, a molecular recognition of **9** by **5**, then allows the formation of (−)-narwedine crystal seeds which enable the accumulation of more crystalline **3** by a spontaneous crystallization process. This process and the accompanying racemization of (+)-narwedine in solution by triethylamine via **8** lead to a total transformation of racemic narwedine into a single enantiomer. (iii) Stereoselective adsorption of (+)-galanthamine onto the surface of (+)-narwedine inhibits the growth of the (+)-narwedine crystal and favors the crystallization of (−)-narwedine.[12] That complex **10** is unlikely to be the key transition-state assembly for resolution may be inferred from the ability of (+)-*O*-acetylgalanthamine (**2**) as the catalyst to promote the same resolution. Upon completion, optically pure **3** was isolated in 81% yield. Further evidence was provided by an NMR study where the spectra of a (−)-galanthamine/(−)-narwedine mixture and a (−)-galanthamine/(+)-narwedine mixture were examined carefully. It was found that neither ^1H nor ^{13}C NMR spectra of these two pairs showed any difference in chemical shift.[13] Besides, the fact that (−)-narwedine cannot be transformed into (+)-narwedine using (−)-galanthamine as the catalyst while (−)-narwedine was seeded at the saturation point was consistent with the same conclusion. The absence of (+)-galanthamine in the (−)-narwedine crystals produced was supported by careful analyses of ^1H NMR, ^{13}C NMR, and HPLC of **3** (Waters, μPorasil, silica gel, CH_2Cl_2–MeOH (85:15)). Furthermore, results from a study in which 1% of (+)-galanthamine was recycled for three different batches and achieved consistent, *total* resolutions in both yields and optical rotations were inconsistent with the hypothesis that (+)-galanthamine was adsorbed onto (−)-narwedine surface. These results suggest that the process described in the proceeding paragraph is a seeded (galanthamine-controlled), total, spontaneous resolution of enantiomers.

As reported seperately by Barton,[4a] Koga,[4b] Carroll,[5a] and Kametani,[5b] the problem associated with chemical reduction of narwedine to galanthamine is the facial selectivity of the hydride. In general, about 20–40% of epigalanthamine (**11**) is generated by either $LiAlH_4$ or $NaBH_4$ reduction of **3**. We report herein the first *completely* diastereoselective reduction of enantiomerically pure narwedine. The (−)-narwedine obtained from the above process can be reduced stereospecifically to afford (−)-galanthamine by L-Selectride[14] at −78 °C in 99% isolated yield, $[\alpha]^{25}_D$ −93.4° (c = 1, $CHCl_3$) [natural galanthamine, $[\alpha]^{25}_D$ −91.0° (c = 1, $CHCl_3$)], corresponding to 99% ee. The diastereomeric purity of synthetic galanthamine was established by HPLC analysis (Waters, μPorasil, silica gel, CH_2Cl_2–MeOH 85:15) which indicated the absence of epigalanthamine. Comparison of synthetic **1** with a sample from natural source by ^1H NMR , ^{13}C NMR, mp, and elemental analysis confirmed its high chemical purity.

In summary, we have demonstrated that a *total* spontaneous resolution process can be used effectively for the asymmetric transformation of narwedine into either of its enantiomers in high yields, depending on which enantiomer is used as the seeds. The same results can be achieved when either enantiomer of galanthamine is used as a "catalyst" in the process. This is the first example for the *total*, spontaneous resolution of a racemate induced by a small amount of foreign substance. Mechanisms for these remarkable transformations which utilized the conglomerate nature of narwedine were discussed. These effective processes and the new methodology for the stereospecific reduction of (−)-narwedine

(10) For studies of spontaneous resolution involving additives with similar configurations, see: Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Mil, J. V.; Shimon, L. J. W.; Lahav, M.; Leiserowitz, L. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 466.

(11) Optically pure (+)-galanthamine, $[\alpha]^{25}_D$ +90.9° (c = 1, $CHCl_3$), was prepared from (+)-narwedine according to Barton's procedure, see ref 4a.

(12) The adsorption hypothesis was invoked by both Barton and Lahav in their resolution studies, see refs 4a and 10.

(13) Diastereomeric interactions may be observed by NMR spectroscopy; see: (a) Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 5150. (b) Pirkle, W. H.; Burlingame, T. G. *ibid*, **1966**, *88*, 4294.

(14) Martin, S. F.; Garrison, P. J. *J. Org. Chem.* **1982**, *47*, 1513.

demonstrate an efficient and practical method of converting racemic narwedine into (−)-galanthamine in 90% overall yield.

Experimental Section

Proton and carbon magnetic resonance spectra were recorded on an FT-NMR spectrometer (^{1}H at 270 MHz, ^{13}C at 68 MHz). ^{1}H NMR chemical shifts are reported in ppm referenced to the residual $CHCl_3$ (7.24 ppm), and J values are reported in Hz. ^{13}C chemical shifts are reported in ppm referenced to the center peak of $CDCl_3$ (77.0 ppm). Microanalysis was performed by Robertson Laboratory Inc. of Madison, NJ. High-performance liquid chromatography was performed on a Waters system 600E equipped with a Waters μPorasil, silica gel, 300- × 3.9-mm column, eluted (1 mL/min) with CH_2Cl_2–methanol 85:15 and detected by a UV lamp at λ = 288 nm. Optical rotation was recorded at 25 °C. Concentration refers to removal of solvent under reduced pressure using a rotary evaporator. L-Selectride was purchased from Aldrich. Optically pure narwedine seeds used in the resolution were prepared according to Barton's procedure.[4a]

Total Spontaneous Resolution of Racemic Narwedine Using (−)-Narwedine as Seeds. A clear solution of racemic narwedine (200 mg) in 95% ethanol–Et_3N (9:1) (3.2 mL) at 80 °C was gradually cooled until a hazy solution was observed at 68 °C. To the supersaturated solution were added (−)-narwedine seeds (5 mg), and the suspension was continued to cool to 40 °C. The mixture was held at this temperature with stirring for an additional 16 h to give a precipitate, which was cooled further to 25 °C and stirred for 3 h. The solid was isolated by filtration and rinsed with 95% ethanol–Et_3N (9:1) (1 mL) to obtain 168 mg (84%) of (−)-narwedine **3** as a white solid: mp 189–192 °C (lit.[4a] 187–190 °C); $[\alpha]^{25}_D$ −408° (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.95 (d, 1H, J = 10.4), 6.67 (q, 2H, J = 8.2), 6.0 (d, 1H, J = 10.4), 4.72 (bs, 1H), 4.07 (d, 1H, J = 15.4), 3.81 (s, 3H), 3.74 (d, 1H, J = 15.4), 3.12 (m, 3H), 2.74 (dd, 1H, J = 18.0, 3.6), 2.42 (s, 3H), 2.27 (td, 1H, J = 13.4, 3.0), 1.85 (d, 1H, J = 13.8). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.50; H, 6.73; N, 4.84.

Total Spontaneous Resolution of Racemic Narwedine Using 1% (+)-Galanthamine as Catalyst. Racemic narwedine (10 g) and (+)-galanthamine[11] (100 mg) were heated in a solvent mixture of 95% ethanol–Et_3N (9:1) (160 mL) at 80 °C until a clear solution was obtained. This solution was cooled to 40 °C and held for 24 h with stirring to give a white suspension, which was furthur cooled to 25 °C and stirred for 2 h. The precipitate was isolated by filtration and rinsed with 95% ethanol–Et_3N (9:1) (50 mL) to yield 7.62 g (76%) of (−)-narwedine **3** as a white solid: mp 192–193 °C; $[\alpha]^{25}_D$ −415° (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) was identical to the reference standard. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.58; H, 6.62; N, 4.82. The mother liquors were concentrated to give a solid mixture (theoretically 2.4 g of narwedine and 100 mg of galanthamine remained), which was dissolved into 95% ethanol–Et_3N (9:1) (38 mL) at 80 °C. The clear solution was cooled to 40 °C and held for 16 h to obtain a white suspension. The mixture was cooled to 25 °C and held for 2 h. The solid was isolated by filtration and rinsed with the same solvent mixture (12.5 mL) to give 1.4 g of **3** as white solid: $[\alpha]^{25}_D$ −403° (c = 1, $CHCl_3$). A total conversion of 9.02 g (90.2%) was achieved.

Diastereoselective Reduction of (−)-Narwedine to (−)-Galanthamine. A solution of (−)-narwedine (285.4 mg, 1 mmol) in THF (50 mL) was added over a period of 30 min to a solution of L-Selectride (2 mL, 1 N in THF) in THF (8 mL) at -78 °C. After the addition, the mixture was stirred at −78 °C for 2 h. Methanol (0.4 mL) was added, and the mixture was warmed to 25 °C and held for 15 min. An aliquot analyzed by HPLC confirmed that the reduction was both complete and stereospecific: **1** (t_R 6.9 min, >99.4%), **11** (t_R 10.6 min, 0%). The solution was concentrated and the product was purified via flash chromatography (silica gel 60, 200–400 mesh, Aldrich) using CH_2Cl_2–methanol (6:1) as eluent to yield 286 mg (99.5%) of (−)-galanthamine as a white solid: mp 128–129 °C (natural galanthamine 126–127 °C); $[\alpha]^{25}_D$ −93.4° (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.67 (q, 2H, J = 8.2), 6.0 (m, 2H), 4.61 (bs, 1H), 4.14 (bs, 1H), 4.09 (d, 1H, J = 15.2), 3.83 (s, 3H), 3.69 (d, 1H, J = 15.2), 3.27 (t, 1H, J = 13.8), 3.05 (d, 1H, J = 14.4), 2.69 (dd, 1H, J = 15.8, 1.9), 2.47 (bs, 1H), 2.40 (s, 3H), 2.05 (m, 2H), 1.45 (dd, 1H, J = 13.8, 2.0); ^{13}C NMR ($CDCl_3$) 145.8, 144.1, 133.1, 129.3, 127.6, 126.9, 122.1, 111.2, 88.7, 62.1, 60.6, 55.9, 53.9, 48.2, 42.1, 33.8, 30.0. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.84; H, 7.36; N, 4.71.

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