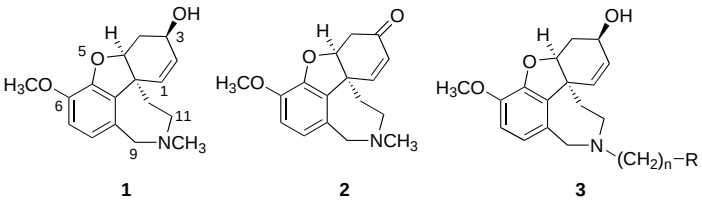
An Efficient Enantioselective Synthesis of (−)-Galanthamine**

Barry M. Trost* and Weiping Tang

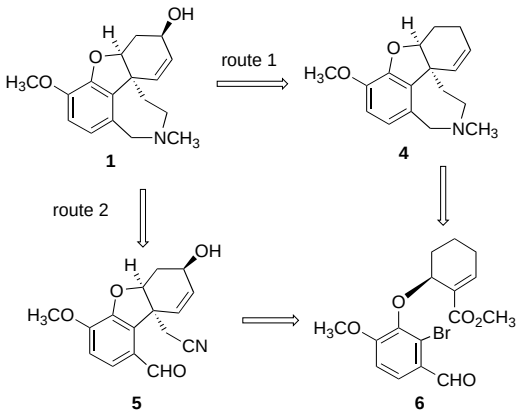
Galanthamine (**1**),[1] the parent member of the galanthamine-type *Amaryllidaceae* alkaloids, is a centrally acting competitive and reversible inhibitor of acetylcholinesterase (Ache), which significantly enhances cognitive functions of patients suffering from Alzheimer's disease.[2] It was first approved in Austria and most recently in the rest of Europe and in the United States for the treatment of Alzheimer's disease.

Because of the limited supplies and the high cost of its isolation from natural sources,[3, 4] several syntheses have been reported which use biomimetic oxidative bisphenol coupling[4, 5] to create the critical spiro quaternary carbon center of narwedine (**2**), which is converted into **1** by diastereoselective reduction.[3] We[6] disclosed the first enantioselective synthesis of (−)-**1** in 2000 in which a sequential palladium-catalyzed asymmetric allylic alkylation (AAA)[7] and intramolecular Heck cyclization were used. At the same time, several other groups utilized similar Heck cyclizations to construct the quaternary carbon center of (±)-3-deoxygalanthamine[8, 9] and(±)-**1**.[10]



In the endeavor to search for more potent inhibitors of Ache, there is considerable interest in derivatives that are based on (−)-galanthamine as a lead structure,[11, 12] since (−)-galanthamine is less toxic than other Ache inhibitors such as physostigmine and tacrine.[11, 13, 14] Among them, galanthamine derivatives **3**[14, 15] or their iminium salts, synthesized by selective N-demethylation followed by N-alkylation of galanthamine,[16] were found to be more potent (up to 70-fold) than galanthamine in inhibiting Ache. To date, syntheses that employ the oxidative phenol coupling step have not been used for direct access to these derivatives.

Our previous approach to **1** relied on a direct allylic oxidation of deoxygalanthamine **4** (Scheme 1, route 1) based on the success in the synthesis of the related *Amaryllidaceae* alkaloids. Attempts to directly oxidize **4** to **1** failed. Therefore, a four-step protocol was developed to introduce the C3 oxygen group stereoselectively. It appeared that the benzylic position is more labile towards oxidation than the allylic position.[9]



Scheme 1. Retrosynthetic analysis of (−)-galanthamine (**1**).

We envisioned a second-generation strategy, which had two goals: 1) realization of an effective general strategy for this family of alkaloids by total synthesis of galanthamine, and 2) development of a flexible strategy to provide ready access to galanthamine analogues by simple modification of the synthetic scheme. Scheme 1 (route 2) illustrates the key feature of this new strategy, which envisions closing the hydrobenzazepine ring after the introduction of the C3 allylic hydroxy group. Direct allylic oxidation is proposed to set the C3 OH group for intermediate **5**, whose benzylic position was already at the oxidation state of an aldehyde.

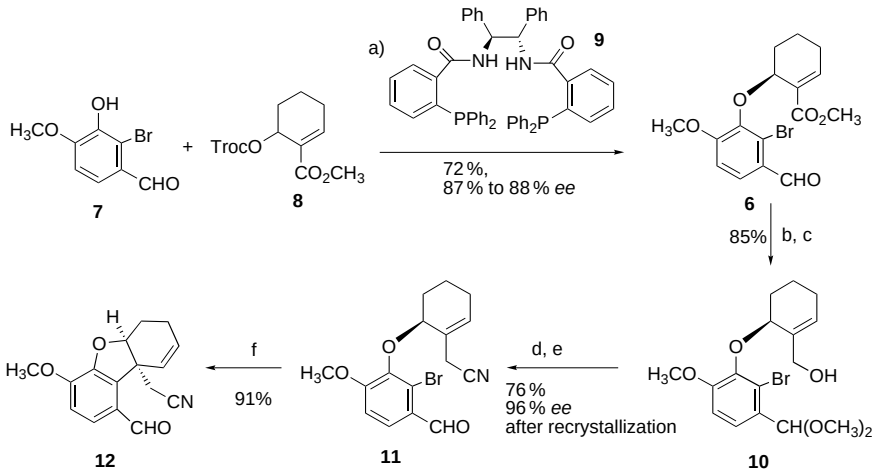
As in the first-generation synthesis, aryl ether **6**[6] was prepared in good yield (72%) and with high enantiomeric excess (87% to 88% *ee*) by palladium-catalyzed reaction of 2-bromovanillin (**7**)[17] with carbonate **8** (available in two steps from glutaraldehyde and the Emmons–Wadsworth–Horner reagent)[18] in the presence of chiral ligand **9** (Scheme 2). All attempts to effect the intramolecular Heck reaction of aryl ether **6** failed in our previous synthesis, resulting primarily in ionized product phenol **7**. Early results[19] suggested that the presence of electron-withdrawing substituents on the phenol ring favored the palladium-catalyzed ionization over the intramolecular Heck reaction. Therefore, in our earlier work **6** was reduced with DIBAL-H and the resulting diol was protected as the bis-silyl ether for the Heck reaction. Recent reports[8, 9] showed that the Heck cyclization worked smoothly in similar systems in the presence of an aldehyde on the phenol ring. This observation suggested that the electron-withdrawing group on the olefin favored the ionization, whereas the electron-withdrawing group on the phenol ring facilitated oxidative addition of the palladium to both the C–O and C–Br bonds. We decided to keep the aldehyde functionality while removing the electron-withdrawing substituent on the olefin by homologation of the α,β-unsaturated ester to a β,γ-unsaturated nitrile.

To this end, aldehyde **6** was protected as its dimethylacetal by treatment with trimethyl orthoformate and catalytic

[*] Prof. B. M. Trost, W. Tang
Department of Chemistry, Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0259
E-mail: bmtrost@stanford.edu

[**] We thank the National Science Foundation and the National Institute of Health, General Medical Sciences (GM13598), for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Facility of the University of California, San Francisco, supported by the NIH Division of Research Resources.

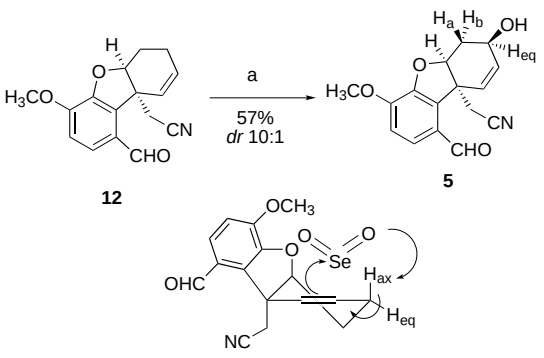
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Convergent synthesis of the carbon skeleton of galanthamine. a) 3 % **9**, $\{[\eta^3\text{-}C_3H_3PdCl]_2\}$ (1 %), Et_3N, CH_2Cl_2, room temperature, b) TsOH (5 %), $CH(OMe)_3$, MeOH; c) DIBAL-H/toluene, $-78\,^\circ C$; d) Ph_3P, acetonecyanohydrin, DIAD, Et_2O; e) TsOH (20 %), THF, H_2O; f) $Pd(OAc)_2$ (15 %), dppp (15 %), Ag_2CO_3, $PhCH_3$, 107 °C, 24 h. Troc = 2,2,2-trichloroethoxycarbonyl, DIAD = diisopropyl azodicarboxylate, TsOH = *p*-toluenesulfonic acid, DIBAL-H = diisobutylaluminum hydride, dppp = bis(diphenylphosphanyl)propane.

p-toluenesulfonic acid. Selective reduction of the α,β-unsaturated ester with DIBAL-H at $-78\,^\circ C$ afforded allylic alcohol **10**. The β,γ-unsaturated nitrile **11** was prepared in 84 % yield by using a modified Mitsunobu protocol[20] followed by acid hydrolysis. The enantiomeric excess of **11** was improved to 96 % *ee* by recrystallization from diethyl ether and petroleum ether with 90 % mass recovery.

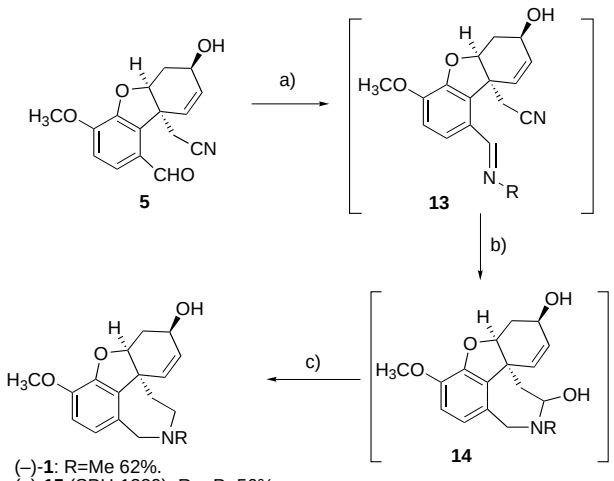
We examined the Heck reaction of the acetonitrile-substituted cyclohexene **11** (Scheme 2). The Heck product **12** was obtained in high yield (91 %) by using a catalytic amount of dppp and $[Pd(OAc)_2]$ in refluxing toluene in the presence of excess silver carbonate. Other solvent (DMF) or ligands (dppe, dppf) gave lower yields. Once we had established the core structure of the galanthamine, we turned our attention to the introduction of the C3 allylic hydroxy group. This can be realized by oxidation of the olefin to enone followed by known diastereoselective 1,2-reduction or more efficiently, direct oxidation to the allylic alcohol, which raises the question regarding the diastereoselectivity. Usually, the electrophile would approach the olefin from the less hindered convex face. We envisioned that SeO_2 would react with the olefin from the more hindered concave face through an ene mechanism[21] (Scheme 3), because the axial proton H_{ax} is



Scheme 3. Diastereoselective allylic oxidation. a) SeO_2, NaH_2PO_4, dioxane, 150 °C 3 h, 64 % based on recovered starting material.

perfectly aligned with the π system. Gratifyingly, treatment of olefin **12** with SeO_2 in dioxane at 150 °C in the presence of NaH_2PO_4 and quartz sand in a sealed tube provided alcohol **5** in 57 % yield (64 % based on recovered starting material; *dr* 10:1) with 7 % recovered starting material.[22] Other additives, such as HCO_2H,[23] $InCl_3$, $YbCl_3$ and Na_2HPO_4, gave less of the desired product. Attempts to fully convert all the starting material by extending the reaction time or increasing the temperature resulted in more decomposition. Only trace amounts of product was found after 8 h when the reaction was carried out in refluxing dioxane (110 °C). This represents the first successful allylic oxidation[6, 9] of the galanthamine skeleton. The stereochemistry of **5** was tentatively assigned based on the coupling constants of H_a/H_{eq} and H_b/H_{eq} ($J < 5$ Hz). The high diastereoselectivity reflects the stereoelectronic requirement for the ene reaction.

Allylic alcohol **5** together with its epimer (10:1) was then converted into the natural product in a one-pot process (Scheme 4). Aldehyde **5** was treated with methylamine in



Scheme 4. Completion of the synthesis by a one-pot procedure. a) RNH_2, MeOH; b) DIBAL-H (4 equiv), then aqueous NaH_2PO_4; c) $NaCNBH_3$. R = Me: 62 % of **1** and 6 % of *epi*-**1**; R = *n*Pr: 56 % of **15**.

methanol solution. Excess methylamine and methanol was removed in vacuo. Concomitant reduction of the imine and nitrile by DIBAL-H followed by acid quenching presumably gave the seven-membered ring of hemiaminal **14**. The resulting solution was treated directly with sodium cyanoborohydride, and (–)-galanthamine (**1**) and *epi*-**1** were isolated in 62 % and 6 % yields, respectively. All spectral data (^{1}H NMR, ^{13}C NMR, IR) are identical to those of a sample of the natural product and to data from previous synthesis, $[\alpha]_D = -123.1$ ($c = 0.4$, EtOH), lit[11]: $[\alpha]_D = -131.4$ ($c = 0.6$, EtOH), lit[6]:

  0044-8249/02/11415-2920 $ 20.00+.50/0 *Angew. Chem.* **2002**, *114*, Nr. 15

$[\alpha]_D = -112.8$ (88% *ee*, $c = 0.5$, EtOH). SPH-1339 (**15**),[15] a slightly more potent inhibitor of Ache than (−)-galanthamine **1**, was prepared in 56% yield by this one-pot process, by using propylamine instead of methylamine.

This new synthesis of galanthamine (8 steps, 96% *ee*, 14.8% overall yield from **7** and **8**) is a significant improvement over and successfully addresses many of the shortcomings of the previous synthesis (14 steps, 88% *ee*, 1.5% overall yield). Furthermore, by exchanging methylamine for other alkyl amines in the last step various galanthamine derivatives are easily accessible, as demonstrated by the synthesis of **15**. This is the shortest and most efficient nonbiomimetic total synthesis of (−)-galanthamine to date. The sequential palladium-catalyzed AAA and intramolecular Heck reaction followed by a diastereoselective allylic oxidation provided the key intermediate **5** with all the functionality installed, except the hydrobenzazepine ring. The one-pot reductive cyclization represents a simple and efficient strategy to form the latter and to access many galanthamine analogues. All the stereochemistry emanates from the palladium-catalyzed AAA. This strategy should allow for entry into a variety of *Amaryllidaceae* alkaloids related to galanthamine.

Received: April 4, 2002 [Z19040]

[1] For reviews see: O. Hoshino in *The Alkaloids*, *Vol. 51* (Ed.: G. A. Cordell), Academic Press, New York, **1998**, pp. 323 – 424; S. F. Martin in *The Alkaloids*, *Vol. 30* (Ed.: A. Brossi), Academic Press, New York, **1987**, pp. 251 – 376.

[2] M. Weinstock, *CNS Drugs* **1999**, *12*, 307 – 323; U. Thatte, *Curr. Opin. Cent. Peripher. Nerv. Syst. Invest. Drugs* **1999**, *1*, 357 – 372; K. Unni, *CNS Drugs* **1998**, *10*, 447 – 460; A. Nordberg, A.-L. Svensson, *Drug Saf.* **1998**, *19*, 465 – 480; M. Rainer, *Drugs Today* **1997**, *33*, 273 – 279; H. A. M. Mucke, *Drugs Today* **1997**, *33*, 251 – 257.

[3] W.-C. Shieh, J. A. Carlson, *J. Org. Chem.* **1994**, *59*, 5463 – 5465.

[4] B. Küenburg, L. Czollner, J. Fröhlich, U. Jordis, *Org. Process Res. Dev.* **1999**, *3*, 425 – 431.

[5] D. H. R. Barton, G. W. Kirby, *J. Chem. Soc.* **1962**, 806; T. Kametani, K. Yamaki, H. Yagi, K. Fukumoto, *J. Chem. Soc. D* **1969**, 425 – 426; T. Kametani, K. Yamaki, H. Yagi, K. Fukumoto, *J. Chem. Soc. C* **1969**, 2602 – 2605; T. Kametani, K. Yamaki, T. Terui, *J. Heterocycl. Chem.* **1973**, *10*, 35; K. Shimizu, K. Tomioka, S. Yamada, K. Koga, *Heterocycles* **1977**, *8*, 277 – 282; K. Shimizu, K. Tomioka, S. Yamada, K. Koga, *Chem. Pharm. Bull.* **1978**, *26*, 3765 – 3771; D. Krikorian, R. Vlahov, S. Parushev, M. Chinova, I. Vlahov, H. J. Schaefer, H. Duddeck, G. Snatzke, *Tetrahedron Lett.* **1984**, *25*, 2969 – 2972; R. Vlahov, D. Krikorian, G. Spassov, M. Chinova, I. Vlahov, S. Parushev, G. Snatzke, L. Ernst, K. Kieslich, W.-R. Abraham, W. S. Sheldrick, *Tetrahedron* **1989**, *45*, 3329 – 3345; J. Szewczyk, J. W. Wilson, A. H. Lewin, F. I. Carroll, *J. Heterocycl. Chem.* **1995**, *32*, 195 – 199; D. A. Chaplin, N. Fraser, P. D. Tiffin, *Tetrahedron Lett.* **1997**, 7931; L. Czollner, W. Frantsits, B. Küenburg, U. Hedenig, J. Fröhlich, U. Jordis, *Tetrahedron Lett.* **1998**, *39*, 2087 – 2088; Y. Kita, M. Arisawa, M. Gyoten, M. Nakajima, R. Hamada, H. Tohma, T. Takada, *J. Org. Chem.* **1998**, *63*, 6625 – 6633; D. Krikorian, V. Tarpanov, S. Parushev, P. Mechkarova, *Synth. Commun.* **2000**, *30*, 2833 – 2846; M. Node, S. Kodama, Y. Hamashima, T. Baba, N. Hamamichi, K. Nishide, *Angew. Chem.* **2001**, *113*, 3150 – 3152; *Angew. Chem. Int. Ed.* **2001**, *40*, 3060 – 3062.

[6] B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 11262 – 11263.

[7] B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1998**, *120*, 815 – 816; B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1998**, *120*, 9074 – 9075; B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1999**, *121*, 3543 – 3544; B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1999**, *121*, 4545 – 4554; B. M. Trost, H. C. Tsui, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 3534 – 3535.

[8] C. Pilger, B. Westermann, U. Flörke, G. Fels, *Synlett* **2000**, 1163 – 1165.

[9] P. J. Parsons, M. D. Charles, D. M. Harvey, L. R. Sumoreeah, A. Shell, G. Spoors, A. L. Gill, S. Smith, *Tetrahedron Lett.* **2001**, *42*, 2209 – 2211.

[10] C. Guillou, J.-L. Beunard, E. Gras, C. Thal, *Angew. Chem.* **2001**, *113*, 4881 – 4882; *Angew. Chem. Int. Ed.* **2001**, *40*, 4745 – 4746.

[11] S. Y. Han, J. E. Sweeney, E. S. Bachman, E. J. Schweiger, G. Forloni, J. T. Coyle, B. M. Davis, M. M. Joullie, *Eur. J. Med. Chem.* **1992**, *27*, 673 – 687.

[12] G. M. Bores, R. W. Kosley, Jr., *Drugs Future* **1996**, *21*, 621 – 635.

[13] S. Y. Han, S. C. Mayer, E. J. Schweiger, B. M. Davis, M. M. Joullie, *Bioorg. Med. Chem. Lett.* **1991**, *1*, 579 – 580, and references therein.

[14] A. Mary, D. Z. Renko, C. Guillou, C. Thal, *Bioorg. Med. Chem.* **1998**, *6*, 1835 – 1850; C. Guillou, A. Mary, D. Z. Renko, E. Gras, C. Thal, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 637 – 639.

[15] U. Jordis, J. Fröhlich, M. Treu, M. Hirnschall, L. Czollner, B. Kälz, S. Welzig, PCT Int. Appl., WO 0174820, **2001**.

[16] A. Mary, D. Z. Renko, C. Guillou, C. Thal, *Tetrahedron Lett.* **1997**, *38*, 5151 – 5152.

[17] J. E. Toth, P. R. Hamann, P. L. Fuchs, *J. Org. Chem.* **1988**, *53*, 4694 – 4708.

[18] H. Amri, M. Rambaud, J. Villieras, *Tetrahedron* **1990**, *46*, 3535 – 3546.

[19] R. C. Larock, D. E. Stinn, *Tetrahedron Lett.* **1988**, *29*, 4687 – 4690.

[20] B. K. Wilk, *Synth. Commun.* **1993**, *23*, 2481 – 2484; M. C. Aesa, G. Baán, L. Novák, C. Szántay, *Synth. Commun.* **1995**, *25*, 1545 – 1550.

[21] K. C. Nicolaou, N. A. Petasis, *Selenium in Natural Products Synthesis*, CIS, Philadelphia, **1984**.

[22] B. M. Trost, D. L. Van Vranken, *J. Am. Chem. Soc.* **1993**, *115*, 444 – 458.

[23] K. Shibuya, *Synth. Commun.* **1994**, *24*, 2923 – 2941.

Monomeric Compounds Containing the *cis*-$[V(=O)(OH)]^+$ Core

Evangelos J. Tolis, Manolis J. Manos, Anastasios J. Tasiopoulos, Catherine P. Raptopoulou, Aris Terzis, Michael P. Sigalas,* Yiannis Deligiannakis,* and Themistoklis A. Kabanos*

Monomeric metal compounds with terminal hydroxy ligands are important functional units in metalloproteins.[1] Metal – OH (M–OH) units are proposed as the active species

[*] Dr. T. A. Kabanos, Dr. E. J. Tolis, M. J. Manos, Dr. A. J. Tasiopoulos
Department of Chemistry
Section of Inorganic and Analytical Chemistry
University of Ioannina
45110 Ioannina (Greece)
Fax: (+30) 6510-44831
E-mail: tkampano@cc.uoi.gr

Dr. Y. Deligiannakis
Department of Environmental and Natural Resources Management
Laboratory of Physical Chemistry
University of Ioannina
Seferi 2, 30100 Agrinio (Greece)
Fax: (+30) 6410-39576
E-mail: ideligia@cc.uoi.gr

Dr. M. P. Sigalas
Department of Chemistry
Laboratory of Applied Quantum Chemistry
Aristotle University of Thessaloniki
54124 Thessaloniki (Greece)
Fax: (+30) 310-99-7739
E-mail: sigalas@chem.auth.gr

Dr. C. P. Raptopoulou, Prof. A. Terzis
NRCPS Demokritos
Institute of Materials Science
15310 Agia Paraskevi Attikis (Greece)