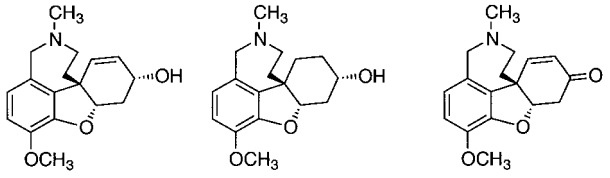
used for C,H,N, and Cl atoms and the SDD pseudopotential and basis was used for Te atoms in the program Gaussian 98. (Gaussian 98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.)

[9] A tridentate porphyrin bonding mode in which the fourth porphyrin nitrogen atom is protonated was proposed for [Re(HTPP)(CO)$_3$] on the basis of its ^{1}H NMR spectrum, but no X-ray crystal structure was obtained: M. Tsutsui, C. P. Hrung, D. Ostfeld, T. S. Srivastava, D. L. Cullen, E. F. Meyer, Jr., *J. Am. Chem. Soc.* **1975**, *97*, 3952.

An Efficient Total Synthesis of (±)-Galanthamine**

Catherine Guillou,* Jean-Luc Beunard, Emmanuel Gras, and Claude Thal*

(−)-Galanthamine (**1**),[1] a tertiary alkaloid isolated from *Amaryllidaceae*, is a centrally acting, competitive, and reversible inhibitor of acetylcholinesterase which enhances cognitive functions in Alzheimer's patients.[2] This drug is available



1 (−)-galanthamine **2** (−)-lycoramine **3** (−)-narwedine

in Austria, and is the most recently approved acetylcholinesterase inhibitor for use in the United States and Europe. However, the botanical supplies of **1** are insufficient for its clinical uses.[3] Galanthamine (**1**) has a spiro quaternary carbon atom. Establishment of this quaternary center is the critical element in the total synthesis of galanthamine-type alkaloids. Most of the reported syntheses of **1** are based on a biomimetic intramolecular phenolic oxidative coupling.[4]

[*] Dr. C. Guillou, Dr. C. Thal, J.-L. Beunard, Dr. E. Gras
Institut de Chimie des Substances Naturelles, CNRS
Avenue de la Terrasse, Gif-sur-Yvette (France)
Fax: (+33) 1-69-07-72-47
E-mail: guillou@icsn.cnrs-gif.fr

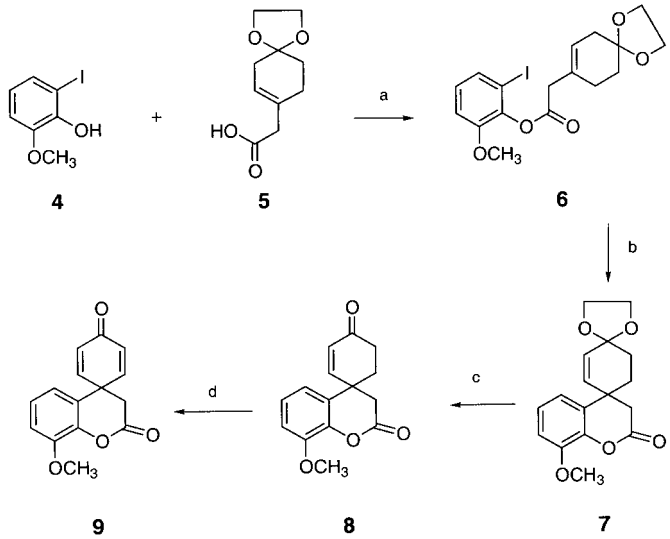
[**] We are grateful to the CNRS for financial support, and the French Ministry of Education and Research for Ph.D grants to J.L.B. and E.G. Professor P. Potier is gratefully acknowledged for his interest in our work.

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

We previously reported the use of an intramolecular Heck reaction as an alternative for creating the spiro quaternary carbon atom of galanthamine-type alkaloids. A formal synthesis of lycoramine (1,2-dihydrogalanthamine; **2**) was thus achieved.[5] Since then, the Heck reaction has been used to access 3-deoxygalanthamine.[6] However, many chemical transformations were required to introduce the allylic alcohol group,[6b] which is essential for anticholinesterase activity. The best total synthesis of galanthamine was achieved in 15 steps with an overall yield of only 1 %.[6b]

An efficient synthesis of (−)-galanthamine (**1**) could be facilitated by a short and efficient synthesis of (±)-narwedine (**3**) or derivatives thereof (e.g., (±)-oxonarwedine (**11**), Scheme 2), since the transformation of (±)-narwedine into its (−) enantiomer has been shown to proceed in high yield.[7] Moreover, (±)-narwedine may be resolved by means of dynamic diastereoisomeric salt formation with di-*p*-toluoyl-D-tartaric acid.[8]

Here we report on an efficient route to (±)-galanthamine (**1**) based on the synthesis of (±)-oxonarwedine (**11**). Our strategy was to form the C12a–C12b bond by an intramolecular Heck reaction to access the spiro tricyclic dienone **9**, which could then be used as a valuable synthetic precursor of **1** and eventually narwedine (**3**). A short synthesis of **9** is summarized in Scheme 1. Esterification of acid **5** with 2-iodo-6-methoxyphenol (**4**)[9] furnished the ester **6** in 80 % yield.



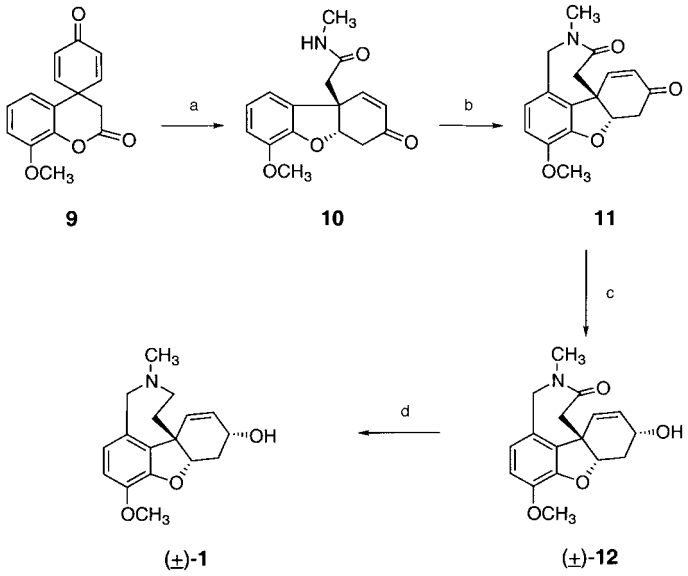
Scheme 1. a) EDCI, DMAP, CH_2Cl_2, 0 → 20 °C, 5 h, 80 %; b) [$Pd_2(dba)_3$], dppe, TlOAC, CH_3CN, reflux, 3 d, 67 %; c) Ph_3CBF_4, CH_2Cl_2, 20 °C, 1 h, 100 %; d) 4 Å molecular sieves, $(PhSeO)_2O$, CH_2Cl_2, reflux, 20 h, 50 %. dba = *trans,trans*-dibenzylideneacetone, DMAP = 4-dimethylaminopyridine, dppe = 1,2-bis(diphenylphosphanyl)ethane, EDCI = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide.

Heck cyclization of **6** was accomplished in 65 % yield in the presence of 10 % [$Pd_2(dba)_3$], 20 % dppe, and thallium acetate (1.2 equiv) in acetonitrile. The dioxolane group of **7** was deprotected with triphenylcarbenium tetrafluoroborate to give **8** in quantitative yield. The oxidation of the α,β-unsaturated ketone **8** to the corresponding dienone **9** proved difficult. Previous attempts to achieve this transformation

  1433-7851/01/4024-4745 $ 17.50+.50/0

with an excess of $(PhSeO)_2O$ or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone were unsuccessful.[10] Moreover, it was not possible to introduce a halogen atom α to the ketone group or to prepare the corresponding enol ether in order to obtain the required dienone **9**. We found that the transformation of **8** to **9** can be accomplished by nonclassical oxidation. The dienone **9** was obtained in 50% yield by using $(PhSeO)_2O$ in the presence of 4 Å molecular sieves. A 1/1 mixture of alumina and silica could also be used instead of the molecular sieves. These oxidative systems have not been previously described.

The reaction of **9** with 40% aqueous methylamine at room temperature resulted in the spontaneous Michael addition of the resulting phenol to cyclohexadienone to afford amide **10** in quantitative yield. Compound **10** was cyclized by the action of paraformaldehyde and trifluoroacetic acid to give **11** in 63% yield. Enone **11** was reduced with L-Selectride to give alcohol **12** in 93% yield. Finally, reduction of **12** with $LiAlH_4$ in DME afforded (±)-galanthamine (**1**) in 80% yield (Scheme 2).



Scheme 2. a) 40% $MeNH_2$, THF, 20 °C, 20 min, 100%; b) $(CH_2O)_n$, TFA, $Cl(CH_2)_2Cl$, 60 °C, 20 h, 63%; c) L-Selectride, THF, −78 °C, 1 h, 93%; d) $LiAlH_4$, DME, 50 °C, 12 h, 80%. DME = 1,2-dimethoxyethane, TFA = trifluoroacetic acid.

Thus, (±)-galanthamine was synthesized in eight steps with an overall yield of 12%. This is the shortest and most efficient nonbiomimetic total synthesis of (±)-galanthamine to date. An intramolecular Heck reaction followed by a nonclassical dehydrogenation reaction provided the key intermediate spirocyclohexadienone **9**. Syntheses of compounds related to galanthamine and narwedine (**3**) are in progress.

Received: July 3, 2001 [Z17414]

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

[2] a) U. Thatte, *Curr. Opin. CPNS Invest. Drugs* **1999**, *1*, 357–372; b) M. Weinstock, *CNS Drugs* **1999**, *12*, 307–323; c) A. Nordberg, A. L. Svensson, *Drug Saf.* **1998**, *19*, 465–480; d) K. Unni, *CNS Drugs* **1998**, *10*, 447–460.

[3] a) V. V. Mikhno, *Farm. Zh. (Kiev)* **1966**, *21*, 28–29; b) J. Batisda, F. Viladomat, J. M. Llabres, S. Quiroga, C. Codina, M. Rubiralta, *Planta Med.* **1990**, *56*, 123–124; c) T. Hille, H. R. Hoffmann, M. Kreh, R. Matusch, DE 19,509,663 Lts, Lohmann Thérapie système; *Chem. Abstr.* **1996**, *125*, 230784.

[4] a) D. Krikorian, V. Tarpanov, S. Parushev, P. Mechkarova, *Synth. Commun.* **2000**, *30*, 2833–2846; b) B. Küenburg, L. Czollner, J. Fröhlich, *Org. Process Res. Dev.* **1999**, *3*, 425–431; c) Y. Kita, M. Arisawa, M. Gyoten, M. Nakajima, R. Hamada, H. Tohma, T. Takada, *J. Org. Chem.* **1998**, *63*, 6625–6633; d) L. Czollner, W. Frantsits, B. Küenberg, U. Hedenig, J. Fröhlich, U. Jordis, *Tetrahedron Lett.* **1998**, *39*, 2087–2088; e) D. A. Chaplin, N. Fraser, P. D. Tiffin, *Tetrahedron Lett.* **1997**, *38*, 7931–7932; f) J. Szewczyk, J. W. Wilson, A. H. Lewin, F. I. Caroll, *J. Heterocycl. Chem.* **1995**, *32*, 195–199; e) R. Vlahov, D. Krikorian, G. Spassov, M. Chinova, F. Vlahov, S. Parushev, G. Snatzke, L. Ernst, K. Klieslich, W. R. Abraham, W. S. Sheldrick, *Tetrahedron* **1989**, *45*, 3329–3345; f) K. Shimizu, K. Tomioka, S. I. Yamada, K. Koga, *Chem. Pharm. Bull.* **1978**, *26*, 3765–3771; g) K. Shimizu, K. Tomioka, S. I. Yamada, K. Koga, *Heterocycles* **1977**, *8*, 277–281; h) D. H. R. Barton, G. W. Kirby, *J. Chem. Soc.* **1962**, 806–817; i) 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.

[5] E. Gras, C. Guillou, C. Thal, *Tetrahedron Lett.* **1999**, *40*, 9243–9244.

[6] a) 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; b) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 11262–11263; c) C. Pilger, B. Westermann, U. Flörke, G. Fels, *Synlett* **2000**, *8*, 1163–1165.

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

[8] D. A. Chaplin, N. B. Johnson, J. M. Paul, G. A. Potter, *Tetrahedron Lett.* **1998**, *39*, 6777–6780.

[9] C. Y. Chen, J. P. Liou, M. J. Lee, *Tetrahedron Lett.* **1997**, *38*, 4571–4574.

[10] M. Ishizaki, K. Ozaki, A. Kanmatsu, T. Isoda, O. Hoshino, *J. Org. Chem.* **1993**, *58*, 3877–3885.

Trimerization of a Steroid Ketone To Form a Chiral Molecular Cleft**

Robert A. Pascal, Jr.,* Mary S. Mathai, Xianfeng Shen, and Douglas M. Ho

The acid-catalyzed trimerization of cyclic ketones to give hexasubstituted benzenes has long been known, and various acid catalysts have been employed for this transformation.[1] Unlike the trimerization of alkynes, this triple aldol condensation is inherently directional, and, if an enantiomerically pure starting ketone is used, then only a single, enantiomerically pure, C_3-symmetric product will be obtained. We now show that the trimerization of steroid ketones with *cis* A/B ring fusions yields a new class of chiral molecular bowls.

[*] Prof. R. A. Pascal, Jr., Dr. M. S. Mathai, X. Shen, Dr. D. M. Ho
Department of Chemistry
Princeton University
Princeton, NJ 08544 (USA)
Fax: (+1) 609-2586746
E-mail: snake@chemvax.princeton.edu

[**] This work was supported by a National Science Foundation Grant (CHE-0077990).

  1433-7851/01/4024-4746 $ 17.50+.50/0