JOC*Note*

Preparation of Enantiopure 1-Azabicyclo[3.2.2]nonanes Functionalized at Carbon C3, from Cinchonine and Cinchonidine. Stereoselective Solvolysis and an Easily Enolizable Ketone

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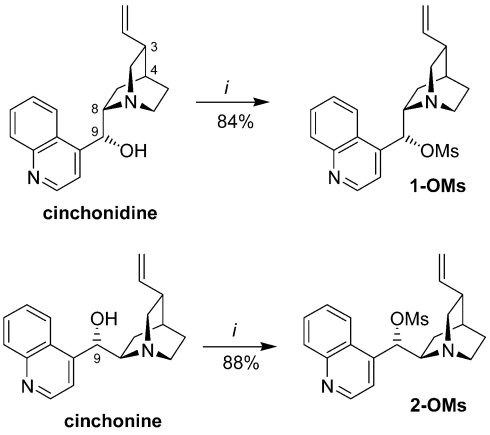
Abstract: Solvolysis of C9 mesylated cinchonidine **1-OMs** and cinchonine **2-OMs** in solvent MeOH, EtOH, and CF_3CH_2OH affords ring-expanded 1-azabicyclo[3.2.2]nonanes oxygenated at carbon C3 ("second *Cinchona* rearrangement"). The newly introduced substituents at C3 and the neighboring quinolyl group Q′ at C2 adopt quasiequatorial positions. The derived 1-azabicyclo[3.2.2]nonan-3-ones **5** and **6** are easily equilibrated. On contact with MeOD uptake of deuterium takes place at room temperature.

Cinchona alkaloids are indispensable auxiliaries in enantioselective reactions such as the AD reaction.[1] A further important application of quaternized *Cinchona* salts is in asymmetric phase transfer reactions.[2]

In contrast to these many applications the general chemistry of *Cinchona* alkaloids has been studied much less over the years.[3] We report the preparation of enantiopure 1-azabicyclo[3.2.2]nonanes oxygenated at C3 from so-called cinch bases cinchonine and cinchonidine and ancillary reactions.

Mesylation at C9 under standard conditions afforded the *O*-mesylated derivatives **1-OMs** and **2-OMs** in excellent yield. Heating of the *pseudo-enantiomeric*[4] mesylates **1-OMs** and **2-OMs** in ethanol (solvent polarity index, $E_T(30) = 51.9$)[5] at reflux provided the new cage expanded azabicyclics **3-OEt** and **4-OEt**, respectively, as major products. Addition of NaOBz is helpful for intercepting the product cations giving the benzoyloxy derivatives **3-OBz** and **4-OBz**. Sodium benzoate also buffers methanesulfonic acid, which is liberated on solvolysis (NaOBz + MsOH → NaOMs + HOBz). On changing the solvent to methanol ($E_T(30) = 55.5$) the reaction proceeded with an increase of 1-azabicyclo[3.2.2]nonane products **4-OMe** and **4-OBz** (55% vs 31% in ethanol).

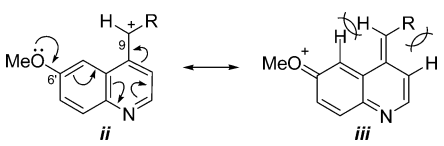
SCHEME 1. Preparation of C9 Mesylates of Cinchonidine and Cinchonine[a]



[a] Reagents and conditions: (i) MsCl, NEt_3, THF, rt, 3−16 h.

In even more polar 2,2,2-trifluoroethanol ($E_T(30) = 59.5$) solvolysis was most selective. The only cage expanded product was benzoyloxy derivative **3-OBz**. The cage-expanded trifluoroethyl ether **3-OCH$_2$CF$_3$** was not detected, unlike ethyl ether **3-OEt** and methyl ether **3-OMe** obtained in EtOH and MeOH, respectively (Scheme 2). Unrearranged benzoic esters **1-OBz** and **2-OBz** may be recycled.

The structure of the new [3.2.2]azabicyclics was established by NMR spectroscopy, including NOE experiments, and corroborated by single-crystal X-ray analysis (Supporting Information). Ring-expanded **3-X** and **4-X** were formed with complete inversion of configuration at C3 (previously C8) resulting in a quasiequatorial arrangement of substituents at C3 and C2. Unrearranged solvolysis products **1-OEt**, **1-OMe**, **1-OBz**, and also **1-OCH$_2$CF$_3$** were formed with clean *retention* of configuration at C9. Similarly, pseudoenantiomeric products **2-X** were formed with complete retention under these conditions.[6]



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(1) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024.

(2) (a) O'Donnell, M. J. Asymmetric Phase Transfer Reactions. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 1993. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (c) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931. (d) Nelson, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1583. (e) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599. (f) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375.

(3) The solvolysis of C9 halogenated quinine and quinidine has been studied in the last century before the advent of modern spectroscopic and separation techniques: (a) Rabe, P. *Liebigs Ann. Chem.* **1949**, *561*, 132−158. (b) Rabe, P. *Chem. Ber.* **1941**, *74*, 725−728.

(4) Replacement of the vinyl group by hydrogen creates enantiomers. The term *pseudo-enantiomer* is used routinely for related pairs of *Cinchona* alkaloids, e.g. quinine and quinidine.

(5) Reichardt, C. *Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, Germany, 1988.

(6) The solvolysis of C9 mesylated quinine and quinidine (6′-R = OMe instead of 6′-R = H) was faster than that of **1-OMs** and **2-OMs** (4−12 h vs 3−4 d for the cinch bases). Cage expansion was less developed (9% for quinine and 36% for quinidine in MeOH). In methanol the products with *intact* [2.2.2]azabicyclic cage were formed with *epimerization* at C9 (C9-*nat*:C9-*epi* ∼ 1:1). For C9 carbocations derived from quinine and quinidine an open classical cation rather than a nitrogen-bridged species becomes more favorable because of extended conjugation with the 6′-OMe donor ***ii*** ↔ ***iii***.

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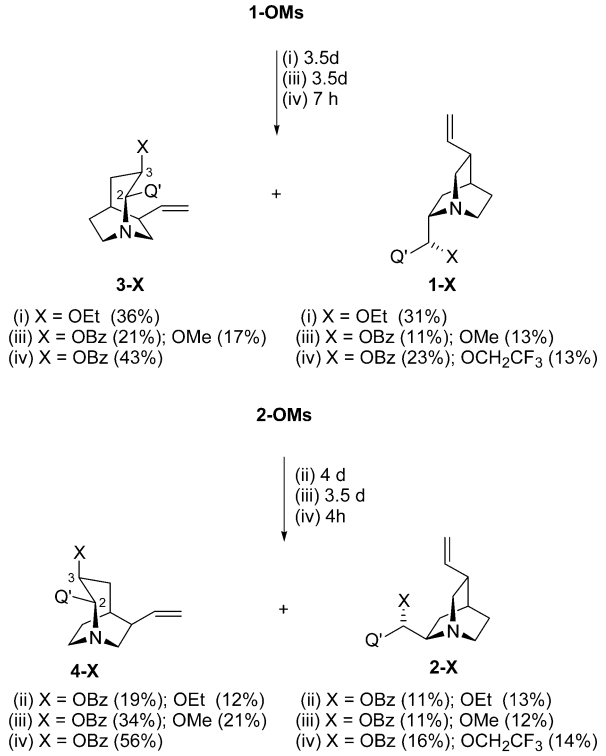
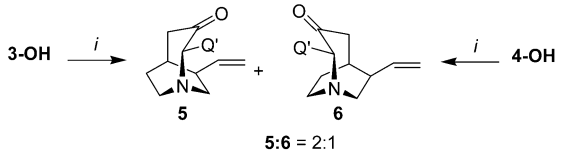
SCHEME 2. Cage Expansion and Stereoretentive Solvolysis of C9 Mesylates of Cinchonine and Cinchonidine[a]



[a] Key: (i) EtOH, rf; (ii) EtOH, NaOBz, rf; (iii) MeOH, NaOBz, rf; (iv) CF_3CH_2OH, NaOBz, rf.

SCHEME 3. Swern Oxidation[a]

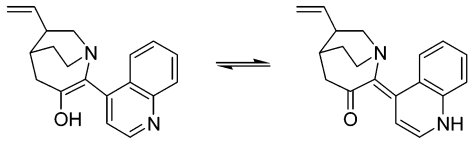


[a] Reagents and conditions: (i) CH_2Cl_2, DMSO, $(COCl)_2$, NEt_3, −78 °C-rt, 90%.

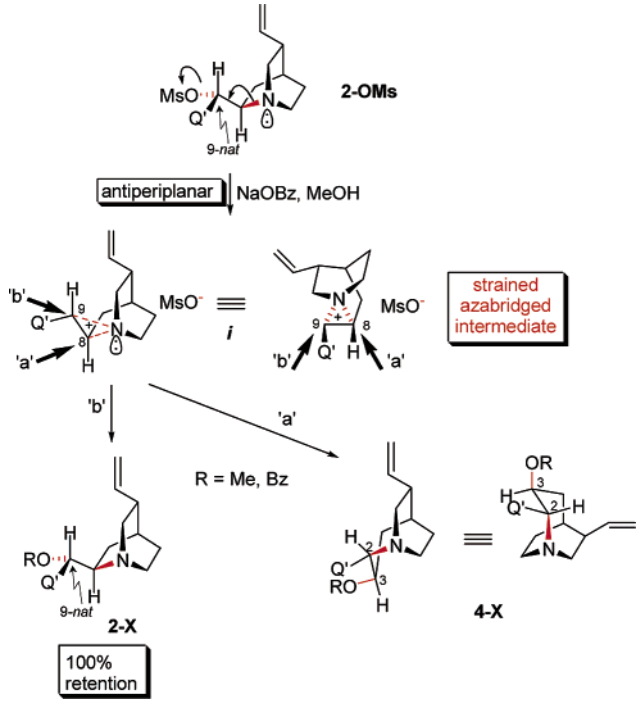
Swern oxidation of the *β*-amino alcohol[7] **3-OH** afforded not only the expected azabicyclic α-amino ketone[8] **5**, but also its epimer **6** (ratio **5**:**6** 2:1).[9]

As a test of the extent of kinetic[10] versus thermodynamic control of the oxidation procedure, alcohol **4-OH** derived from pseudoenantiomeric cinchonine was oxidized. Again, an epimeric mixture of α-amino ketones (**5**:**6** 2:1) was obtained, indicating substantially complete equilibration of **5** and **6**. On contact with MeOD freshly prepared ketones **5** and **6** smoothly took up deuterium at C2, exchange being complete after 2 days at room temperature. A number of factors clearly facilitate enolization and tautomerization of ketones **5** and **6**, including extended conjugation (Scheme 4).

SCHEME 4. Tautomers of Ketones 5 and 6



SCHEME 5. Postulated Mechanism: Solvolysis of 2-OMs via Azabridged Cation *i*[a]



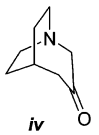
[a] Key: 'a' and 'b' indicate trajectories of attack by external nucleophile.

We formulate stereochemistry and product type via intermediate ***i*** to account for 100% inversion (trajectory 'a') and 100% retention (trajectory 'b') (Scheme 5). Cation ***i*** is a nitrogen-bridged species. In general, the extent of bridging depends on conformation, electron demand at carbon C9 (Q′ versus Q), solvent ionizing power, and pH.[11,12]

In conclusion a variety of cage expanded and enantiopure 1-azabicyclo[3.2.2]nonanes are accessible, both as α-amino ethers by the "first *Cinchona* rearrangement"[13] and now also as *β*-amino ethers and their derivatives by a second *Cinchona* rearrangement.

(7) Illustrative route to *β*-amino alcohol 4-OH: To a solution of 4-OBz in MeOH/H_2O (**5**:**1**) was added $Ba(OH)_2 \cdot 8H_2O$. The reaction mixture was stirred for 16 h. After workup with H_2O and extraction with CH_2Cl_2 the crude product was purified by column chromatography to furnish 4-OH (82%).

(8) The synthesis of parent 1-azabicyclo[3.2.2]nonan-3-one (***iv***) has very recently been put forward as InnoCentive Challenge 260715, $70 000 USD. See www.innocentive.com.



(9) The ratio of **5**:**6** was determined by ^1H NMR and NOESY.

(10) Review of kinetic enantioselective protonation of enolates: Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566. See also: (b) Zimmerman, H. E.; Wang, P. *Org. Lett.* **2002**, *4*, 2593.

(11) The structure of the nitrogen-bridged intermediate remains open to discussion. While we prefer a flat-topped *σ*-bridged species, a referee has suggested that the limiting case of the highly electrophilic, parent model cation (Q′ = H and vinyl group replaced by H) in the gas phase can be described as a conventional aziridinium ion (B3LYP/6-31G* calculations).

These new substances and their derivatives are of interest as ligands in asymmetric syntheses and in pharmacology.

(12) Cf. also reviews on structural studies of the 2-norbornyl cation: (a) Olah, G. A.; Prakash, G. K. S.; Saunders, M. *Acc. Chem. Res.* **1983**, *16*, 440. (b) *Methoden der Organischen Chemie, Houben-Weyl*; Hanack, M., Ed.; Thieme: Stuttgart, Germany, 1990; Vol. E19c. (c) Saunders, M.; Jiménez-Vazquez, H. A. *Chem. Rev.* **1991**, *91*, 375. (d) X-ray crystal structures: Laube, T. *Acc. Chem. Res.* **1995**, *28*, 339. (e) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1993.

(13) (a) Röper, S.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2002**, *4*, 3179. (b) Röper, S.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 1661. (c) Braje, W. M.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 2540.

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Supporting Information Available: Experimental preparations and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data of **4-OBz** (CCDC-188973) can be obtained free of charge on application to CCDC (e-mail: deposit@ccdc.cam.ac.uk).

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