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The First and Second *Cinchona* Rearrangement. Two Fundamental Transformations of Alkaloid Chemistry

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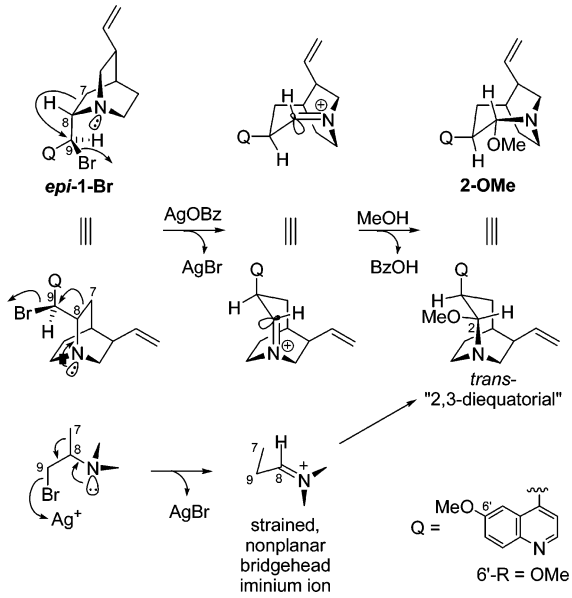
Stereochemistry, products, and driving forces of the "first and second *Cinchona* rearrangement" have been investigated and a unified theory is presented. The first cage expansion affords [3.2.2]-azabicyclic α-amino ether and is formulated via a configurationally stable bridgehead iminium ion and quasiequatorial nucleophilic attack. The second cage expansion affords *β*-functionalized [3.2.2]-azabicycles. In this case a nonclassical nitrogen-bridged cation is postulated to account for retention of configuration and potential reversibility of the cage expansion. The second rearrangement is favored for the so-called *cinch* bases (6′-R = H) in trifluoroethanol. Stereoelectronic factors, electron demand at C9, ground state conformation, and solvent type are crucial in all cases. A two-step protocol for preparing 9-*epi*-configured *Cinchona* alkaloids from 9-*nat* precursors is described.

Introduction

Solvolysis and nucleophilic displacement reactions at saturated carbon are among the most studied and best known reactions of organic chemistry.[1] Although *Cinchona* alkaloids are very useful templates in asymmetric synthesis,[2,3] chemical transformations of these natural products have been little studied. For solvolyses of *Cinchona* alkaloids with a C9-leaving group not only the basic amino nitrogen but also the 6′-substituent (R′ = H, OMe) and stereochemistry add further complexity. We have earlier reported on the silver benzoate assisted reaction of 9-*epi*-quinine with bromide as the leaving group (*epi*-**1**-Br) in methanol to afford cage-expanded 1-azabicyclo[3.2.2]nonane with a methoxy group α to the bridgehead nitrogen (cf. **2**-OMe, Scheme 1). The rearrangement was shown to be stereoelectronically favorable, involving shift of the (nonprotonated) nitrogen lone pair, nucleophilic shift of carbon C7 to C9, and stereocontrolled external capture of a strained, nonplanar bridgehead iminium ion intermediate. In the observed product **2**-OMe the quinolyl and methoxy groups adopt a quasi *trans*-2,3-diequatorial orientation. In an analogous sequence quinidine with a C9-*epi*-configured chloride leaving group provided the pseudoenantiomeric[4] α-methoxy amine.[5]

SCHEME 1. "First *Cinchona* Rearrangement" of 9-*epi*-Configured Bromoquinine (*epi*-1-Br) Mediated by Silver Ion and Driven by Formation of Iminium Ion



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(1) For the solvolysis of *Cinchona* alkaloids see: Rabe, P. *Liebigs Ann. Chem.* **1949**, *561*, 132. Rabe, P. *Chem. Ber.* **1941**, *74*, 725 and references therein. For general reviews of solvolytic displacements see: Streitwieser, A. *Chem. Rev.* **1956**, *56*, 71. Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1969; Chapter VII. March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 292−307. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 4th ed.; Plenum Press: New York, 1993.

(2) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, Germany, 1993.

(3) Nelson, A. *Angew. Chem.* **1999**, *111*, 1685. Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000. Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403 and references therein.

(4) Replacement of a vinyl group by hydrogen generates enantiomers.

(5) Braje, W.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 2540.

10.1021/jo030363s CCC: $27.50
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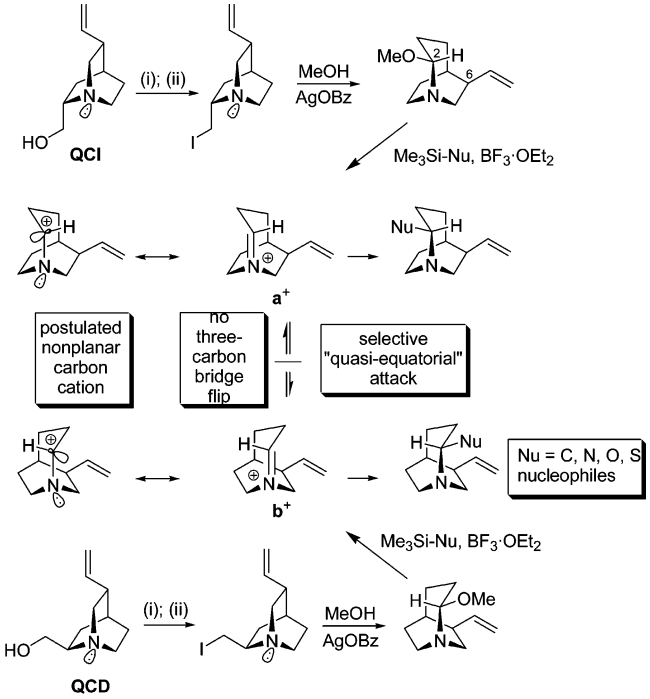
SCHEME 2. First Rearrangement of QCI and QCD Iodinated at C9: Distinct Pseudoenantiomeric[4] Bridgehead Iminium Ions a^+ and b^+ and Their Stereospecific Nucleophilic Capture[6]



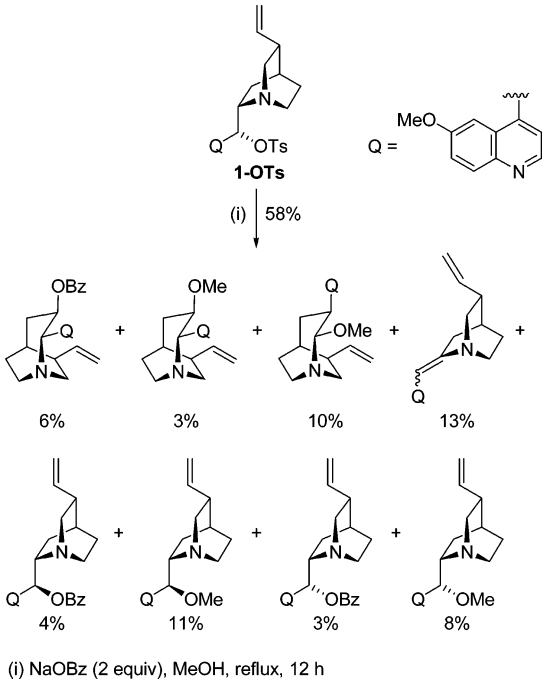
The first rearrangement was also realized for Quincorine QCI and Quincoridine QCD,[6] after the introduction of iodide as the leaving group (Scheme 2).

By comparison to the Ag^+ ion mediated rearrangement of *epi*-**1**-Br in Scheme 1, the methanolysis of *O*-tosylquinine **1**-OTs with natural configuration at C9 appears hopelessly complex (Scheme 3).

Remarkably, the change of solvent to the more ionizing trifluoroethanol and the change of substrate to *O*-mesylated cinchonidine **3**-OMs and cinchonine **4**-OMs have simplified the product spectrum and brought to light a "second *Cinchona* rearrangement" giving 1-azabicyclo-[3.2.2]nonanes functionalized at carbon C3 rather than C2 (Scheme 4). Nitrogen-bridged cation ***i*** (and the pseudoenantiomeric species) is formulated as the reactive intermediate: Four ligands around the bridging nitrogen are constrained in one hemisphere. The nitrogen lone pair is equivalent to a fifth valence and in the second imaginary hemisphere. The intermediacy of cation ***i*** accounts for retention of configuration via double inversion on nucleophilic attack of carbon C9.[7] Once generated the cation of the "second rearrangement" manifold is capable of sustaining both cage expansion and cage conservation.

A major goal of our work is the synthesis of a variety of functionalized 1-azabicyclo[3.2.2]nonanes with control over the two cage-expansion routes and stereochemistry. Added nucleophiles are expected to afford new functionality and new homologues. An understanding of the baffling molecular rearrangements is essential for further work.

SCHEME 3. Methanolysis of *O*-Tosylated 1-OTs



Results

Cage expansion and introduction of the 3-hydroxy group were accomplished as follows: The *cinch* bases (6′-R = H) with C9-*nat* configuration were mesylated and submitted to trifluoroethanolysis in the presence of added nucleophile. With added NaOBz the benzoic esters **5**-OBz (43%) and **6**-OBz (56%) were formed, isolated, and hydrolyzed to the alcohol (see Scheme 4 above). Alternatively, **6**-OH was prepared in a single flask by nucleophilic displacement with *n*-Bu_4NONO and acidic hydrolysis (Table 1, entry 1). Furthermore, *β*-amino alcohols **5**-OH and **6**-OH were prepared directly in pure water (see Scheme 10 below).

Of the various nucleophiles investigated in solvent trifluoroethanol thiocyanate ion was found to be most effective for capturing and "freezing out" the cage-expanded structure giving covalent thiocyanate **6**-SCN (89%, entry 2).

Azide ions in the trifluoroethanol furnished cage conserved [2.2.2]- and [3.2.2]azabicycles **3**-N_3 and **5**-N_3 side-by-side (entry 3). Covalent azide **3**-N_3 was formed with retention at C9 consistent with azabridged intermediate ***i*** (Scheme 4).[8] (In contrast, *O*-mesylated cinchonine **4**-OMs and NaN_3 in trifluoroethanol enter into cascade reactions involving intramolecular 1,3-dipolar cycloaddition with formation of triazolines.[8])

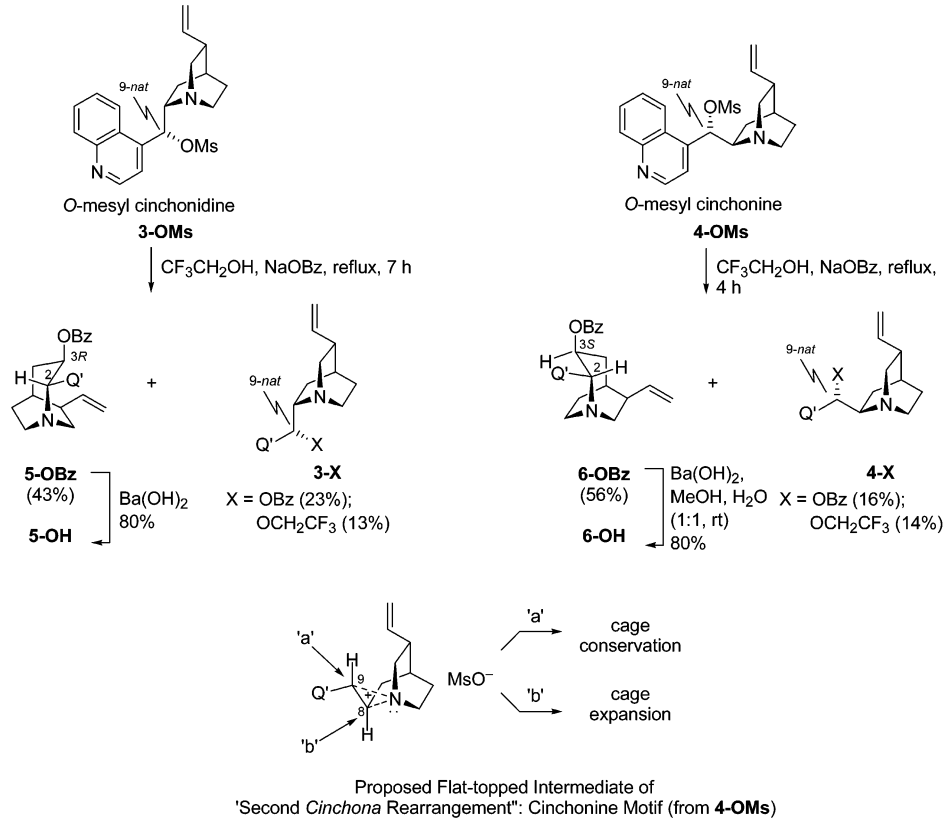
In the reaction with KCN/CF_3CH_2OH (entry 4) we isolated four different products (76%). The displacement allows the one-carbon homologation to *β*-amino nitrile **5**-CN (40%). The two products **3**-CN and **3**-OCH_2CF_3 with intact azabicyclic cage were formed with retention at C9. Ring-expanded trifluoroethyl ether **5**-OCH_2CF_3 was also

(6) (a) Röper, S.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 1661. (b) Röper, S.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2002**, *4*, 3179.

(7) Röper, S.; Franz, M. H.; Wartchow, R.; Hoffmann, H. M. R. *J. Org. Chem.* **2003**, *68*, 4944.

(8) See also: Röper, S.; Franz, M. H.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2003**, *5*, 2773.

SCHEME 4. "Second *Cinchona* Rearrangement" of C9-Activated, So-Called *Cinch* Bases (6′=R = H) in Trifluoroethanol: Cage Expansion to *β*-Amino Benzoates 5-OBz and 6-OBz Is Accompanied by Stereoretentive Solvolysis at C9 with Intact Azabicyclic Cage[a]



[a] Q′ = 4′-quinolyl; 'a' and 'b' indicate nucleophilic trajectories.

formed, although in only 5%.[9] For comparison trifluoroethanolysis of **3**-OMs in the presence of NaOBz instead of KCN provided benzoate **5**-OBz as the only cage-expanded product (see Scheme 4).

Attempted preparation of tosylated quinine (6′-R = OMe; C9-*nat* configuration) at elevated temperature furnished a minor amount of cage-expanded chloride **5a**-Cl (see the Supporting Information), which was isolated as beautiful crystals (4%). The structure and 3*R* configuration were confirmed by X-ray crystallography.[10] Introduction of chloride was more efficient starting with activated *cinch* base **3**-OMs (6′-R = H) and *n*-Bu_4NCl in trifluoroethanol. Cage-expanded chloride **5**-Cl with 3*R* configuration was isolated (46%), and both unrearranged **3**-Cl and **3**-OCH_3CF_3 were formed with retention at C9 (entry 6).

Similar to the reaction with nitrite ion (entry 1) the hard fluoride ion was introduced via highly hygroscopic *n*-$Bu_4N^+F^-$ (4 equiv of *n*-Bu_4NF, entries 7 and 8).

Surprisingly, treatment of **3**-OMs or **4**-OMs with $Et_4N^+Br^-$ in trifluoroethanol furnished only cage conserved [2.2.2]azabicyclic bromides **3**-Br and **4**-Br with *retention* of configuration! This efficient conversion of cinchonine and cinchonidine into the C9-*nat*-configured bromides in *only two steps* is currently without precedent (Scheme 5). We suggest that in trifluoroethanol both *O*-mesylated cinchonidine **3**-OMs and cinchonine **4**-OMs enter the second rearrangement manifold (Scheme 4) with generation of bridged ion **i** as an intermediate. In the presence of chloride and fluoride ion cage expanded **5**-Cl an **5**-F could, however, be isolated. The two bromides **3**-Br and **4**-Br with intact [2.2.2]azabicyclic moiety (Scheme 5) appear to be favored over their ring-expanded isomers under the experimental conditions. In principle, the second rearrangement is reversible as we demonstrated in another reaction (see guideline 4 below).[8]

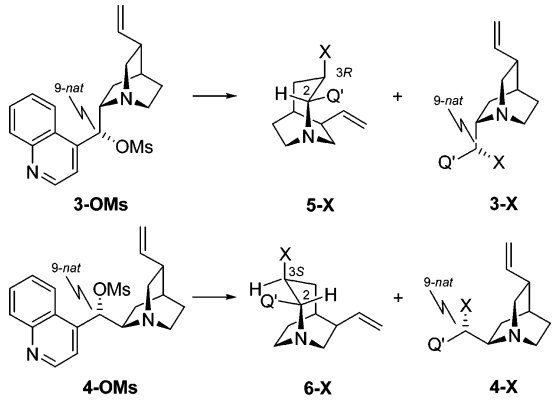
Silver Ion Mediated "Second *Cinchona* Rearrangement". As shown 9-*epi*-configured bromide *epi*-**1**-Br and AgOBz undergo the first *Cinchona* rearrangement (Scheme 1). Therefore, the behavior of C9-*nat*-configured substrates was of interest. An X-ray crystal study and NOE showed that in **3**-Br (C9-*nat* configuration) the C9−Br and N−C8 *σ*-bonds are antiperiplanar. In fact, silver ion assisted heterolysis in methanol (Scheme 6) provided both **5**-OMe (16%) and **5**-OBz (21%) with a change of product type and mechanism, although the reaction was sluggish (complete after 3 d).

Both **3**-OMe and **3**-OBz were formed with retention of configuration. We were pleased to find that a solvent change to trifluoroethanol provided just two products

(9) For examples of the ionizing and solvating power of trifluoroethanol see: Mayr, H.; Minegishi, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 4493. McClelland, R. A. *Tetrahedron* **1996**, *52*, 6823. Presumably, trifluoroethanol is partially deprotonated in the presence of KCN: $CF_3CH_2OH + KCN \rightarrow CF_3CH_2OK + HCN$. For the effect of trifluoroethanol on protein folding (TFE effect) see: Díaz, M. D.; Fiorini, M.; Burger, K.; Berger, S. *Chem. Eur. J.* **2002**, *8*, 1663 and references therein.

(10) Thus, even quinine (6′-R = OMe) undergoes the second rearrangement, although in much lower yield. See also Scheme 3.

TABLE 1. Trifluoroethanolysis in the Presence of Added Nucleophile

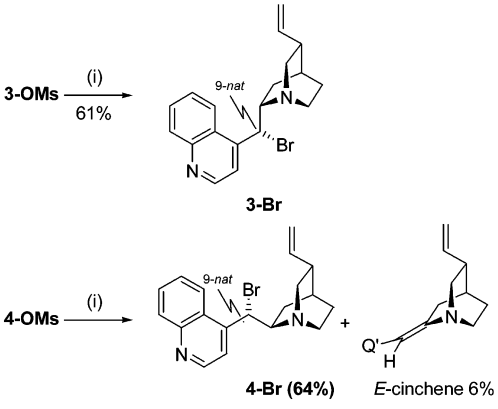


X = OH, SCN, N_3, CN, OCH_2CF_3, Cl, F (see Table)

		conditions[a]		products	
entry	substrate	added nucleophile (equiv)	solvent trifluoroethanol	cage expansion	cage conservation
1	4-OMs	*n*-$Bu_4N^+ONO^-$ (2); then 2 N HCl	reflux, 6 h	**6**-OH (41%)[b]	
2	4-OMs	*n*-Bu_4NSCN (2)	reflux, 4 h	**6**-SCN (89%)	
3	3-OMs	NaN_3 (2)	reflux, 18 h	**5**-N_3 (53%)	**3**-N_3 (44%)
4	3-OMs	KCN (4)	reflux, 9 h	**5**-CN (40%) **5**-OCH_2CF_3 (5%)	**3**-CN (11%) **3**-OCH_2CF_3 (20%)
5	4-OMs	KCN (3)	reflux, 5.5 h	**6**-CN (56%)[c] **6**-OCH_2CF_3 (9%)	
6	3-OMs	*n*-Bu_4NCl (1.6)	reflux, 6.5 h	**5**-Cl (46%)	**3**-Cl (28%) **3**-OCH_2CF_3 (2%)
7	4-OMs	*n*-Bu_4NF[d] (4)	reflux, 6 h	**6-F** (64%) **6**-OCH_2CF_3 (traces) **6**-OH (traces)	**4**-F (16%) **4**-OCH_2CF_3 (6%)
8	3-OMs	*n*-Bu_4NF[d] (4)	reflux, 24 h	**5**-F (61%) **5**-OH (3%)	**3**-F (18%) **3**-OCH_2CF_3 (5%) **3**-OMs (11%)

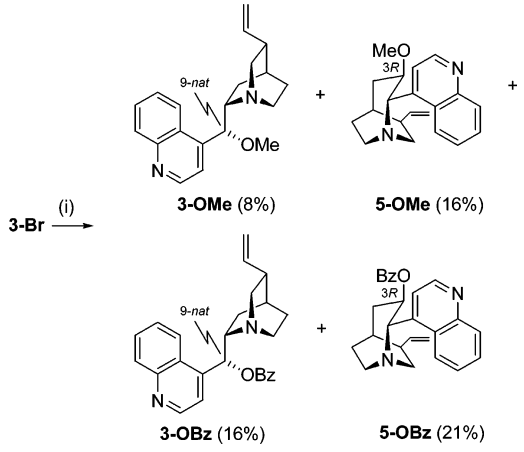
[a] *O*-Mesylated cinchonine **4**-OMs reacted faster than *O*-mesylated cinchonidine **3**-OMs. [b] See Scheme 4: hydrolysis of the resulting benzoic acid ester with $Ba(OH)_2$ afforded **3**-OH and **4**-OH, respectively (80%); see ref 7. [c] The products with an intact [2.2.2]azabicyclic cage were not isolated in this case. [d] 1 M in THF, contains water (5%).

SCHEME 5. Preparation of Unrearranged 3-Br and 4-Br from 3-OMs and 4-OMs, Respectively, by *Retentive* Substitution



(i) Et_4NBr (3 equiv), CF_3CH_2OH, reflux, 5 h.

SCHEME 6. Solvolysis of C9-*nat* Configured 3-Br (6′-R = H) with AgOBz in Methanol: "Second *Cinchona* Rearrangement"

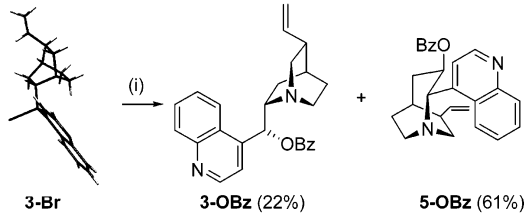


(i) AgOBz (1.1 equiv), MeOH, 65 °C, 3 d.

with an increase in cage expansion from 37% to 61% (Scheme 7)! Retentive solvolysis is favored on stereoelectronic grounds.

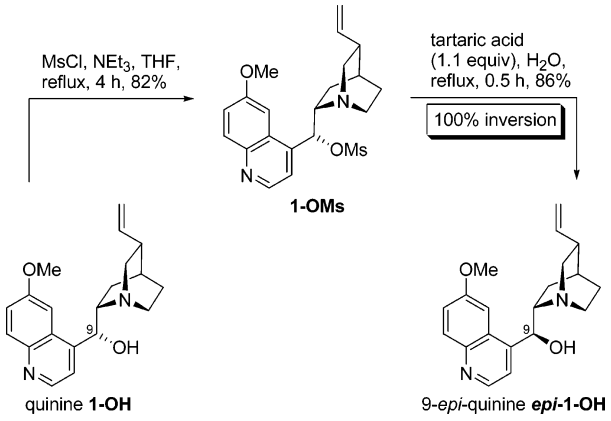
The Preparation of 9-*epi*-Configured *Cinchona* Alkaloids: Aqueous Hydrolysis in the Presence of Tartaric Acid as a Proton Donor. Hydrolysis of 9-*nat*-configured quinine and quinidine mesylates in water in the presence of tartaric acid has opened an efficient route to 9-*epi*-quinine *epi*-**1**-OH and 9-*epi*-quinidine, respectively, in a clean reaction. The azabicyclic skeleton remains intact in this case and hydrolysis entails nucleophilic attack at carbon C9 with complete *inversion* of configuration (Scheme 8). In the presence of tartaric acid the bridgehead nitrogen is at least partially protonated, so the possibility of the first rearrangement diminishes (cf. ref 19 below). Further hydrogen-bonding

SCHEME 7. Solvolysis of 3-Br with AgOBz in CF_3CH_2OH[11]



(i) AgOBz (1.1 equiv), CF_3CH_2OH, 75 °C, 2.5 d.

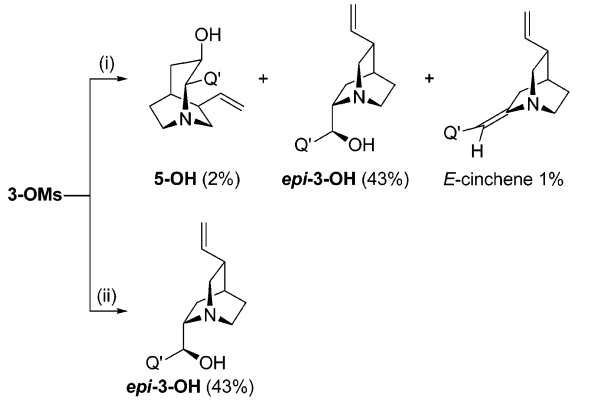
SCHEME 8. Hydrolysis of 9-*nat*-Quinine Mesylate in the Presence of Tartaric Acid[12]



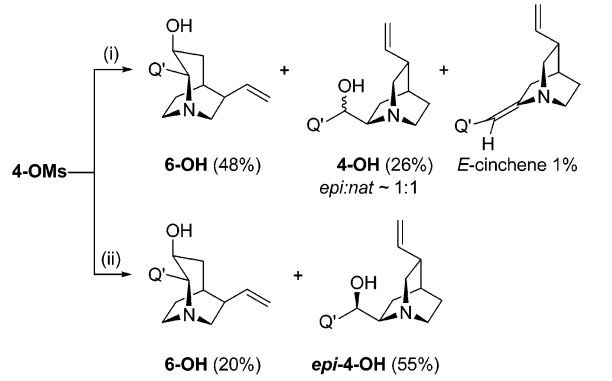
contacts between tartaric acid and the alkaloid are feasible and should help to dissolve the alkaloid in water.[12]

The hydrolysis has been extended to the C9-activated cinchonine and cinchonidine (6′-R = H). Although the parent alkaloids are "practically insoluble in water"[13] we observed that *O*-mesylated cinchonidine **3**-OMs first melts, then dissolves and hydrolyzes on heating in water. Unlike 9-mesylated quinine **1**-OMs (Scheme 8) the analogous cinchonidine substrate **3**-OMs furnished a minor new cage-expanded product **5**-OH (2%), which was detectable even in the *presence* of tartaric acid (1.1 equiv; Scheme 9, top entry). After an increase of added tartaric acid to 4.7 equiv, cage expansion was suppressed and [3.2.2]azabicycle **5**-OH was no longer discernible. Complete inversion of configuration to 9-*epi*-cinchonidine *epi*-**3**-OH was observed (43%), but with diminished conversion. On the other hand, after refluxing in pure water[14] (no tartaric acid) the amount of cage-expanded 1,2-amino alcohol **5**-OH rose to 35% (not shown in Scheme 9, see also Scheme 10 and ref 19 below).

SCHEME 9. Hydrolysis of 3-OMs and 4-OMs in Water/Tartaric Acid[a]



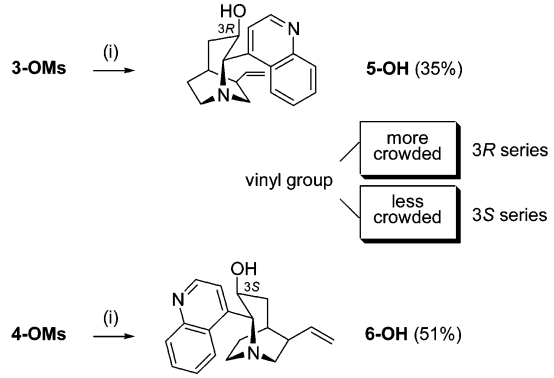
(i) tartaric acid (1.1 equiv), H_2O, reflux; (ii) tartaric acid (4.7 equiv), H_2O, reflux



(i) tartaric acid (0.1 equiv), H_2O, reflux; (ii) tartaric acid (1.1 equiv), H_2O, reflux

[a] *O*-Mesylated cinch bases (C9-*nat* configuration) undergo "second *Cinchona* expansion" *even* in the presence of tartaric acid. Traces of cinchene are formed (for X-ray crystal structure, see the Supporting Information).

SCHEME 10. Hydrolysis of 3-OMs and 4-OMs in Pure Water: "Second *Cinchona* Rearrangement"



(i) H_2O, reflux, 4.5 h.

Hydrolysis of pseudoenantiomeric *O*-mesylated cinchonine **4**-OMs furnished up to 20% of cage-expanded 1,2-amino alcohol **6**-OH, *even* in the *presence* of tartaric acid (1.1 equiv)! The inverted product with *intact* azabicyclic cage (*epi*-**4**-OH, 55%) was also formed under these conditions.[15] This is in agreement with earlier work on the hydrolysis (1.1 equiv of tartaric acid) of *O*-mesylated quinine (C9-*nat* configuration), which was shown to

(11) Reaction rates in MeOH and CF_3CH_2OH were roughly equal (Schemes 6 and 7). Inspection of the X-ray crystal structure suggests that generation of a silver dication is feasible from **3**-Br. Complexation of the bridgehead nitrogen is expected to slow migration of nitrogen.

(12) X-ray crystal structure of quininium hydrogen (*S*,*S*)-tartrate hemihydrate: Ryttersgard, C.; Larsen, S. *Acta Crystallogr. Sect. C* **1998**, *C54*, 1701. Quinine has three hydrogen bond acceptors excluding the quinoline nitrogen. Tartaric acid is present in an extended chain configuration and has four hydrogen bond donor and six potential acceptor atoms. Cooperative binding seems feasible, in the presence of 6′-R = OMe more so than in 6′-R = H.

(13) *Merck Index*, 11th ed.; Merck & Co, Inc.: Rahway, NJ, 1989.

(14) For reactivity in an aqueous environment see: Candler, D. *Nature* **2002**, *417*, 491. Ball, P. *Nature* **2003**, *423*, 25. See also: Grieco, P. A. O*rganic Synthesis in Water*; Blackie Academic; London, UK, 1998. Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. Breslow, R. *Acc. Chem. Res.* **1991**, *6*, 159.

FIGURE 1. Stabilization versus eclipsing strain in a C9 *Cinchona* cation (6′-R = OMe).

deliver 9-*epi*-quinine with 100% *inversion* (see Scheme 8).

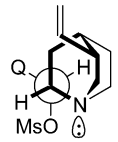
In pure water (no tartaric acid) the yield of cage-expanded 1,2-amino alcohol **6**-OH from *O*-mesyl cinchonine **4**-OMs rose to 51% (Scheme 10). The structure of 3*S*-configured **6**-OH was confirmed by single-crystal X-ray diffraction (Supporting Information). The preparation of **5**-OH and **6**-OH in water[14] represents green chemistry. Methanesulfonic acid is inexpensive, biodegradable, and toxicologically harmless.

The vinyl and quinolyl group in major 3-hydroxyamine **6**-OH are opposite to each other and less crowded than in minor pseudoenantiomeric **5**-OH (cf. also X-ray crystal structure). The mesylates of the *cinch* bases (6′-R = H) are readily soluble in CF_3CH_2OH while pure **3**-OMs and **4**-OMs, without additives, only melt in water. In $H_2O-CF_3CH_2OH$ (1:1) the yield of cage-expansion rose to 68% (**6**-OH, 59%; **6**-OCH_2CF_3 as byproduct, 9%). At higher temperature (ca. 110 °C) elimination to cinchene was facilitated (Scheme 9).[16,17]

Clearly, the second cage expansion (and neighboring nitrogen participation) is favored for *cinch* bases (6′-R = H). In contrast, for quinine and quinidine the C9 cation is stabilized by the remote methoxy group (***ii*** ↔ ***iii***), despite eclipsing strain along the quinoline perimeter. Electron demand at C9 and participation by nitrogen recede (Figure 1).

"First *Cinchona* Rearrangement" *without* Ag^+ Is Also Feasible: Stringent Stereochemical and Experimental Conditions. Previous studies (conformational analysis by NOE) showed that the antiperiplanar requirement of the first rearrangement is fulfilled in *epi*-**1**-Br, which was rearranged in the presence of Ag^+ (Scheme 1). Generally 9-*epi*-quinidine and 9-*epi*-cinchonidine are tosylated reluctantly, the desired sulfonate *epi*-**7**-OTs and *epi*-**3**-OTs being formed with an excess of TsCl (5 equiv) under forcing conditions. However, tosylation under modified conditions (addition of DMAP) and especially mesylation with $MeSO_2Cl/NEt_3$ proceed under mild conditions at room temperature.[18] Mesylates were used preferentially because they can be handled more readily and are also more soluble than tosylates in solvents such as methanol.

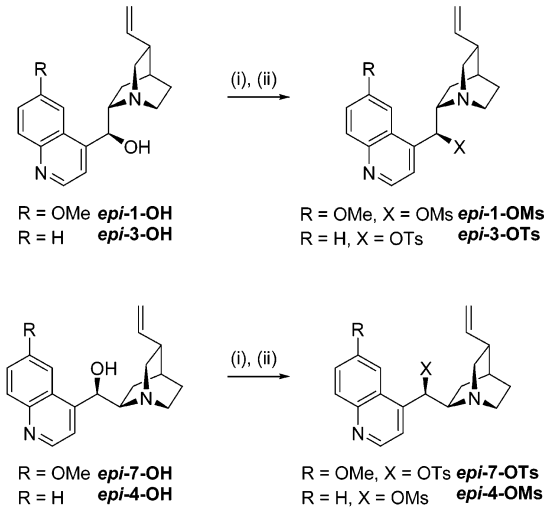
Antiperiplanarity of the C9−OMs bond and migrating C7−C8 σ-bond is not only encountered in *epi*-**1**-Br, but also in *epi*-configured *O*-mesyl quinine *epi*-**1**-OMs. In the conformation shown (Figure 2) the bulky 1-azabicyclo-



***epi*-1-OMs**

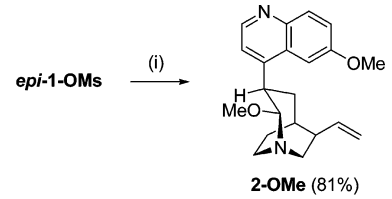
FIGURE 2. Preferred conformation of *epi*-**1**-OMs.

SCHEME 11. Preparation of *epi*-Sulfonates



(i)MsCl, Et_3N, THF, rt, 1-4 h; (ii) TsCl, Et_3N, DMAP, THF, reflux

SCHEME 12. Preparation of α-Amino Ether 2-OMe: "First Rearrangement"



2-OMe (81%)

(i) NaOBz (2 equiv), MeOH, reflux, 2 h

TABLE 2

entry	NaOBz [equiv]	*t* [h]	*T*	yield [%]	yield[a] [%]
1	0	1	reflux	30	50
2	0.1	4	reflux	55	68
3	2	3	reflux	84	84

[a] Based on recovered starting material.

[2.2.2]octyl moiety faces the simple hydrogen atom attached to neighboring C9.

We were pleased to find that methanolysis was complete after 2 h at reflux and provided α-amino ether **2**-OMe (81% yield, Scheme 12).

O-Mesylated *epi*-quinidine *epi*-**7**-OMs furnished **8**-OMe. Ring expansion was optimized to 84% (see Table 2). These experiments also demonstrate the beneficial effect of added NaOBz, which acts inter alia as a buffer for liberated methanesulfonic acid.

Under optimized conditions (Table 2, entry 3, OTs and OMs leaving groups) *epi*-configured *cinch* bases were also ring expanded to **9**-OMe and **10**-OMe in respectable yield (Scheme 14).

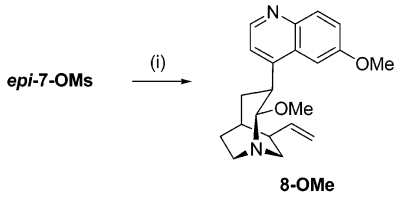
(15) As another route to 9-*epi* configured *cinch* bases with intact cage the Mitsunobu reaction can be used with moderate success (ca. 50% by standard protocol). See: Hughes, D. L. *Org. React.* **1992**, *42*, 335−656. Castro, B. R. *Org. React.* **1983**, *29*, 1−162.

(16) Königs, W. A. *Chem. Ber.* **1881**, *28*, 1854.

(17) See the X-ray crystal structure.

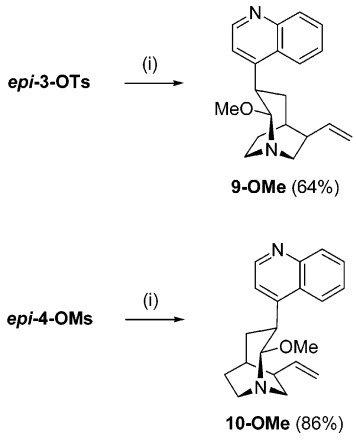
(18) Mesylation with $MeSO_2Cl/NEt_3$ involves the sterically less encumbered sulfene $CH_2{=}SO_2$ as intermediate; see: King, J. F. *Acc. Chem. Res.* **1975**, *8*, 10 and references therein.

SCHEME 13. Preparation of α-Amino Ether 8-OMe



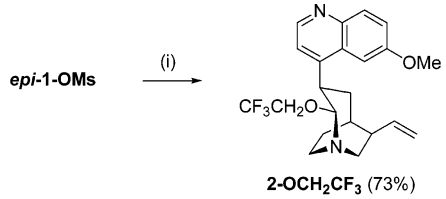
(i) conditions see Table 2

SCHEME 14. Preparation of α-Amino Ethers 9-OMe and 10-OMe from Cinch Bases: "First *Cinchona* Rearrangement"



(i) NaOBz (2 equiv), MeOH, reflux, 12-16 h.
NB. ***epi*-4-OMs** is more soluble than ***epi*-3-OTs**.

SCHEME 15. Preparation of 2-OCH_2CF_3



(i) NaOBz (2 equiv), CF_3CH_2OH, reflux, 2 h

In an attempt to prepare α-amino benzoate **2**-OBz we used the solvent trifluoroethanol instead of methanol. Only the more stable α-amino ether **2**-OCH_2CF_3 was isolated (73%, Scheme 15).

We propose to rationalize the experimental facts and previous experience[7,8] along a set of general guidelines.

1. In the solvent water with added tartaric acid the solubility of quinine and quinidine mesylates is enhanced due to protonation of the bridgehead nitrogen. Further supramolecular contacts with tartaric acid and water involving 6′-OMe oxygen and the C9 leaving group as hydrogen bond donors seem feasible. Simultaneously, *N*-protonation (which is not necessarily complete) blocks cage expansion by the *first* and perhaps somewhat less so by the *second* rearrangement: The [2.2.2]azabicyclic skeleton stays intact (for *cinch* bases see guideline 6). Aqueous hydrolysis of 9-*epi*-quinine substrates in the presence of tartaric acid entails 100% retention of configuration.[5,19]

2. Under neutral or weakly acidic conditions two different *Cinchona* rearrangements have been established. Overall, the "first cage expansion" to [3.2.2]-azabicycle is irreversible and driven by bridgehead iminium resonance en route to α-amino ethers. The "*first* rearrangement" has been realized for the near-prototype of quincorine (QCI) and quincoridine (QCD) with iodide as the leaving group and on treatment with silver benzoate. The nucleophile is introduced quasiequatorially. The "*second* rearrangement" is currently unknown in the QCI-QCD area.

3. The (nonplanar) cationic intermediate of the first *Cinchona* expansion shows a substantial barrier to flipping of the three-carbon bridge, in a formal violation of Bredt's rule. Usually there is no crossover or leakage between pseudoenantiomeric systems during the discrete QCI-QCD expansion (Scheme 2).

4. The second rearrangement can be reversed (e.g. Scheme 5 and text). For example, we have ring contracted a 1-azabicyclo[3.2.2]nonane with a quasiequatorial C3 mesyloxy leaving group to the 1-azabicyclo[2.2.2]octane derivative, as shown by azide trapping.[8]

5. In general, the "second cage expansion" of C9-*nat*-configured substrates is more favorable for cinchonine than for cinchonidine (e.g. Schemes 4 and 10). Relief of nonbonded repulsion in the initial state and product is thought to contribute (see also Table 1 and X-ray crystal structures).

6. *O*-Mesylated *cinch* bases undergo the "second cage expansion" in water *even* in the *presence* of tartaric acid (1.1 equiv, Scheme 9). Overall, the second cage expansion has the greater driving force for the two *O*-mesylated *cinch* bases (C9-*nat* and 6′-R = H) than for quinine and quinidine substrates (6′-R = OMe) (see Figure 1). There is increased electron demand at carbon C9 of cinch bases in the transition state.

7. Complete retention of configuration for nucleophilic attack on the *O*-mesylated *cinch* bases **3**-OMs and **4**-OMs (C9-*nat* configuration, 6′-R = H) is formulated via double inversion involving *N*-bridged cation ***i***. Currently, this retentive solvolysis is unique among C9-activated *cinch* bases under neutral conditions (cf. Schemes 4 and 5).

8. Solvolysis of *Cinchona* substrates with the 6′-methoxy donor is faster and more prone to E1-like enamine formation than that of the methoxy-free substrates from *cinch* bases. On steric grounds a 9-*epi*-configured leaving group facilitates formation of enamine.[7,8] The second rearrangement of *O*-mesylated *cinch* bases (C9-*nat*, 6′-R = H) is faster in CF_3CH_2OH than in EtOH (4 h vs 3.5 d).

9. Addition of a salt such as NaOBz is helpful for intercepting product cations and to buffer liberated sulfonic acid with partial precipitation of NaOMs.

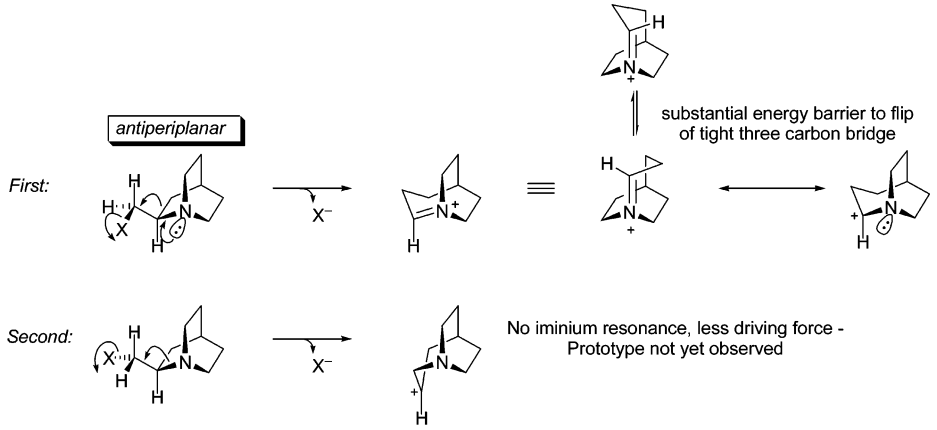
In conclusion, the set of *four* activated *Cinchona* substrates and the further preparation of the four *epi* compounds (C9-*nat*, C9-*epi*, 6′-R = H, OMe) have enabled us to investigate the product spectrum of nucleophilic displacement and solvolysis. The unified theory developed is in excellent agreement with experience accumulated so far.

(19) Protonation of bridgehead nitrogen and molecular recognition of tartaric acid by further hydrogen bonding contacts are considered to generate a *hydrophilic pocket* guiding attack of C9 by water molecule(s). The pocket is open for retentive hydrolysis in the 9-*epi*-quinine series (see Chart 1), but not so in the 9-*nat* series: In this case preorientation favors an S_N2-like attack by water; see: Braje, W. M.; Holzgrefe, J.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2085.

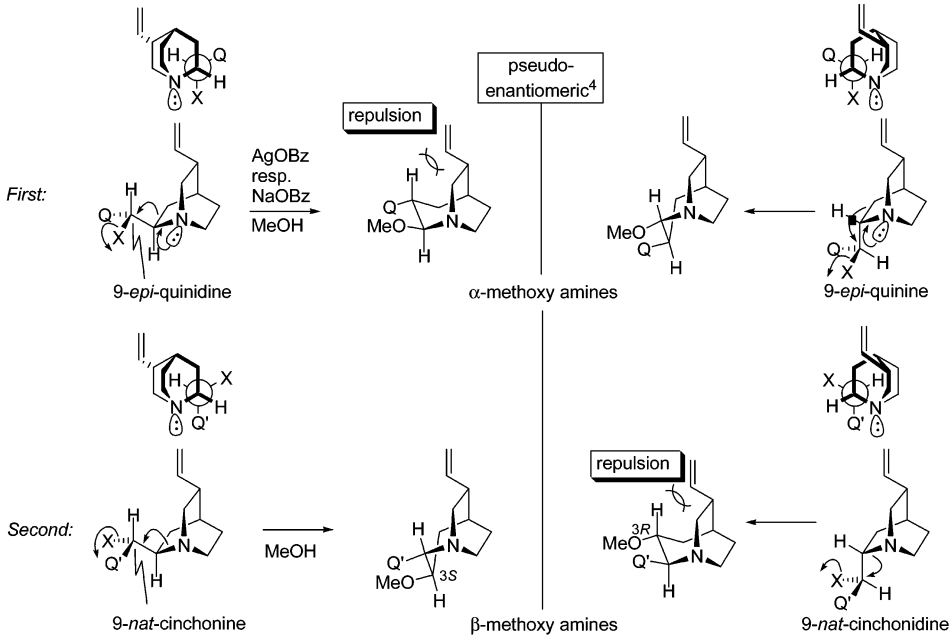
CHART 1. General *Cinchona* Cage Expansion and Solvolysis Scheme

Summary:

Prototype (1-azabicyclo[2.2.2]oct-2-yl)methyl-X rearrangement (X = leaving group)



Cinchona rearrangements illustrated for Q (6'-R = OMe) and Q' (6'-R = H). In rotamer shown the bulky azabicyclic moiety faces single H (C9).



Migratory aptitude depends on configuration at C9, conformation, stereoelectronic factors, leaving group ability, solvation and acidity (protonation of bridgehead nitrogen).
In H_2O + *tartaric acid* the [2.2.2]azabicyclic cage is completely preserved (6'-R = OMe):

9-*epi* quinine-X —100% retention→ 9-*epi*-quinine: Pseudo-enantiomeric quinidines react analogously.
9-*nat* quinine-X —100% inversion→ 9-*epi*-quinine: Pseudo-enantiomeric quinidines react analogously.

Extension to *cinch* bases feasible, although there is leakage into second rearrangement, depending on concentration of tartaric acid.
Stereoretentive hydrolysis with cage conservation occurs with C9 *epi*-configured substrates: In the preferred conformation and in the presence of tartaric acid the (protonated) amino group and the hydrophilic leaving group X are exposed to water on the same face of the molecule (see projection formulae).

Regarding the accessibility of the various reaction channels one must bear in mind that *Cinchona* alkaloids, unlike traditional organic substrates, generally have well-developed conformational minima with comparatively high energy barriers. Diastereomeric transition states are evidently very different. Even pseudoenantiomeric reaction paths can be distinguished when reactions at carbon C9 are involved. Some remarkable solvent effects have also come to light. It is obvious that a host of new molecular scaffolds with multiple diversity connectors are now accessible from *Cinchona* alkaloids via the "first cage expansion" and the "second cage expansion" and their variants. The two rearrangements and the solvolysis are much more than mechanistic curiosities. The enantiopure materials are of interest for asymmetric syntheses and combinatorial and medicinal chemistry and set the stage for a fruitful development of the *Cinchona* alkaloid area.

Experimental Section

General. The atom numbering follows the *Cinchona* alkaloid convention. The new ring expanded *Cinchona* alkaloids are numbered according to the Beilstein AutoNom.

^{1}H NMR and ^{13}C NMR spectra (peaks assigned by DEPT, HMQC, HMBC, H, H-COSY) were recorded at 400 and 500 MHz in deuterated chloroform unless otherwise stated, with tetramethylsilane as internal standard. Mass spectra were recorded at 70 eV. Preparative column chromatography was performed on silica gel (particle size 30−60 μm). Analytical TLC was carried out on aluminum-backed 0.2-mm silica gel 60 F254 plates. Petrol ether (PE) and methyl *tert*-butyl ether (MTBE) were distilled before use. Methanol was dried over calcium hydride and citric acid and distilled over magnesium before use. The quality of the *Cinchona* alkaloids may vary from batch to batch. Usually, the *cinch* bases (6′-R = H) are accompanied by 10,11-dihydro and 6′-OMe derivatives (<10%).

General Procedure A for Preparation of Ring-Expanded 1-Azabicyclo[3.2.2]nonanes with C3 Substituents. To a solution of *O*-mesylated cinchonine or cinchonidine in trifluoroethanol (5 mL/mmol) was added the nucleophile (2−3 equiv) and the reaction mixture was refluxed at 80−90 °C for 4−8 h. Progress of the reaction was monitored by thin-layer chromatography (TLC). Saturated aq $NaHCO_3$ was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by column chromatography (MTBE-MTBE/MeOH 5:1) to furnish the ring-expanded products and products with intact cage.

Illustrative Solvolysis with Thiocyanate as Nucleophile: (1*S*,2*R*,3*S*,5*S*,6*R*)-2-Quinolin-4-yl-3-thiocyanato-6-vinyl-1-aza-bicyclo[3.2.2]nonane 6-SCN. *O*-Mesylated cinchonine **4**-OMs (437 mg, 1.17 mmol) was allowed to react according to general procedure **A** with *n*-Bu_4NSCN (706 mg, 2.35 mmol) to afford **6**-SCN (342 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (d, J = 4.5 Hz, H-2′), 8.20−8.06 (m, H-8′, H-5′), 7.77−7.69 (m, H-7′), 7.68−7.60 (m, H-6′), 7.31 (d, J = 4.6 Hz, H-3′), 5.99 (ddd, J = 6.9, 10.4, 17.2 Hz, H-10), 5.23−5.01 (m, H-11, H-11), 4.71 (d, J = 11.4 Hz, H-2), 4.08−3.98 (m, H-3), 3.65 (dd, J = 9.6, 15.0 Hz, H-7), 3.27−3.20 (m, H-8), 2.93−2.83 (m, H-7), 2.63−2.41 (m, H-8. H-4, H-4), 2.33−2.26 (m, H-6), 1.98−1.88 (m, H-5, H-9), 1.82−1.71 (m, H-9). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3 (CH, C-2′), 149.2 (C, C-10′), 144.4 (C, C-4′), 139.5 (CH, C-10), 130.5 (CH, C-8′), 129.3 (CH, C-7′), 127.4 (C, C-9′), 127.2 (CH, C-5′), 123.6 (CH, C-6′), 116.8 (CH, C-3′), 115.9 (CH_2, C-11), 110.4 (C, C-12, SCN), 69.6 (CH, C-3), 56.5 (CH_2, C-7), 44.5 (CH, C-2), 42.9 (CH, C-6), 39.1 (CH_2, C-8), 34.1 (CH_2, C-4), 32.2 (CH, C-5), 27.8 (CH_2, C-9). IR (Golden Gate ATR) υ 2961 m, 2873 m, 2147 w, 2052 s, 1593 w, 1507 w, 1464 m, 1381 m, 1162 w, 995 w, 881 w, 733 m. MS-MAT (160 °C): m/z 337 (M^+ + 2, 11.86), 335 (M^+, 38), 309 (6), 302 (100), 295 (47), 278 (66), 250 (19), 236 (17), 222 (24), 210 (11), 195 (24), 183 (33), 167 (42), 155 (20), 136 (24), 115 (15), 108 (8), 95 (6), 81 (19), 67 (11). HRMS ($C_{20}H_{21}N_3S$) calcd 335.1456, found 335.1454.

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Supporting Information Available: General procedures and spectroscopic data for 23 azabicycles with expanded and intact cage; crystallographic data for **3**-Br, **5a**-Cl, **6**-OH, and *E*-cinchene as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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