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Synthesis of Enantiopure 1-Azabicyclo[3.2.2]nonanes via Stereoselective Capture of Chiral Carbocations

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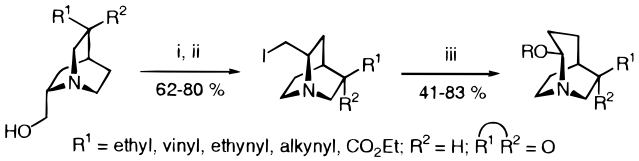
ABSTRACT



i) MsCl, Et_3N, DCM, 0 °C; ii) LiI, dioxane, reflux; iii) AgOX (X = CF_3SO_2, Ac, Bz), MeOH or Me_2CO, 50 °C or 0 °C, ultrasound.

A new class of doubly functionalized and enantiomerically pure 1-azabicyclo[3.2.2]nonanes derived from quincorine and quincoridine is described. 2,5-Disubstituted quinuclidines with a C9-mesyloxy group were easily transformed into the corresponding halides upon treatment with lithium salts. Subsequent silver salt-mediated ring expansion stereoselectively furnished the title azabicyclics. Chiral carbocations which are configurationally stable and nonplanar are postulated to account for the striking stereoselectivity of the capture of external nucleophile. 5-Ethynyl-2-iodomethylquinuclidines afford the α-benzoyloxy amines rather than α-methoxy amines, even in MeOH.

Azabicyclic systems[1] are common building blocks in medicinal chemistry and are structural motifs in natural products, especially alkaloids including *Cinchona* species. Monosubstituted 1-azabicyclo[2.2.2]octanes play an important role in modern medicinal chemistry as the quinuclidine nucleus has been found to be a good mimic for the quaternary nitrogen in acetylcholine.[2] Quinuclidine derivatives are able to block 5-HT_3[3] and NK_1 receptors[4] and to act as squalene synthase inhibitors.[5] Tropane alkaloids with an 8-azabicyclo[3.2.1]-octane moiety are classified as anticholinergics as they compete with acetylcholine for the muscarinic site of the parasympathetic nervous system, thus preventing the passage of nerve impulses.[6] Anatoxin-*a* with a 9-azabicyclo[4.2.1]-nonane ring system acts as a potent agonist for the nicotinic acetylcholine receptor.[7] Substituted 1-azabicyclo[3.2.2]-

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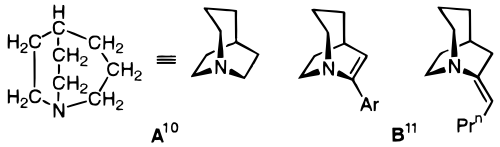
nonanes are already used as precursors for the synthesis of rigid substance P antagonists.[8] Consequently, general synthetic routes to these azabicycles are of considerable interest. Although the lower azabicyclics have been studied extensively, much less is known about the higher [3.2.2]-homologues.[9] Before the advent of conformational analysis, Prelog reported the preparation of parent 1-azabicyclo[3.2.2]-nonane **A** by double intramolecular cyclization under forcing conditions (Scheme 1).[10] More recently, Pearson described

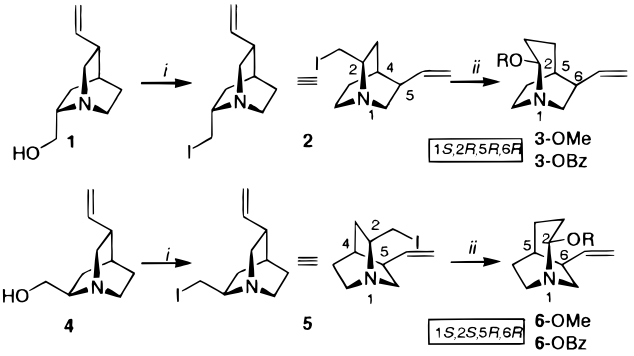
Scheme 1. Selected 1-Azabicyclo[3.2.2]nonanes Described in the Literature



another route to these amines **B** via an intramolecular Schmidt reaction involving carbocation chemistry.[11] To our knowledge most of the [3.2.2]-azabicycles reported in the literature were either achiral or racemic mixtures.

Results and Discussion. We report herein the efficient three-step synthesis of a variety of rearranged bridgehead amines from functionalized 2-hydroxymethyl quinuclidines. O-Mesylation of quincorine **1** (QCI) and quincoridine **4** (QCD) proceeds smoothly and is followed by lithium halide-promoted S_N2 displacement. The use of lithium salts in dioxane is crucial for C9-halogenation, presumably because the lithium cation is chelated by the β-amino mesylate moiety exposing the rear side of CH_2-OMs to external nucleophilic attack.[12] The resulting β-amino iodides were treated with a reactive silver salt in MeOH as polar protic solvent and also in anhydrous acetone. Reaction of β-amino iodide **2** with AgOTf in MeOH at 22 °C provided rearranged α-amino ether **3**-OMe in 19−30% yield (Table 1). Similarly, pseudoenantiomeric[13] QCD-based β-amino iodide **5** diastereoselectively afforded α-amino ether **6**-OMe. Longer reaction times did not increase the yield significantly. The silver salt-mediated synthesis of 1-azabicyclo[3.2.2]octane **3**-OMe was optimized

Table 1. Ring Expansion of 2-Iodomethyl-2-azabicyclo[2.2.2]octane **2** to 3-OMe under Various Conditions



entry	solvent	silver salt, equiv	time [h]	temp [°C]	yield [%]
1	MeOH	AgOTf, 1.0	1	22	19
2	MeOH	AgOTf, 1.0	3	22	30
3	MeOH	AgOTf, 1.5	1	22	28[a]
4	MeOH	AgOTf, 1.1	20	22	39[a]
5	MeOH	AgOTf, 1.0	6	22	28
6	MeOH/pyr	AgOTf, 1.0	16	22	21
7	MeOH/pyr	AgOTf, 1.0	4	110	25[a]
8	MeOH	AgOAc, 1.5	8	22	10
9	Me_2CO	AgOBz, 1.1	18	50	76[b]
10	MeOH	AgOBz, 1.0	4	22	39
11	MeOH	AgOBz, 1.2	6	50	68
12	MeOH	AgOBz, 1.2	20	50	86
13	MeOH	AgOBz, 1.1	2.5[c]	0	68

[a] Epimeric mixture with respect to carbon C2. [b] **3**-OBz was obtained instead of **3**-OMe. [c] The reaction mixture was sonicated for 2.5 h.

with respect to solvent, silver counterion, and temperature. Use of an excess of AgOTf promoted the epimerization of **3**-OMe at carbon C2 without leading to higher yields (Table 1, entries 3 and 4).

Ring expansion with AgOTf in the presence of external base at 22 °C was less efficient (Table 1, entries 6 and 7). Therefore, silver salts with less reactive counterions were examined next. While AgOAc provided only traces of product, **3**-OMe was obtained diastereoselectively in high yield upon treatment with AgOBz in MeOH after extended reaction times or with ultrasound at 0 °C. A change of solvent from methanol to anhydrous acetone furnished the corresponding benzoate **3**-OBz (entry 9). The stereochemical outcome of the rearrangement was not affected by this variation of solvent.

1. Tolerance to Additional Functionality. To evaluate the scope of this novel route to 1-azabicyclo[3.2.2]nonanes, various functionalized 2-iodomethylquinuclidines were prepared.[14] Ethyl-substituted quinuclidines **7** and **9** were submitted to the optimized rearrangement conditions and gave α-amino ethers **8** and **10** in fair yield (up to 78%). Iodo ester **11** was more polar than parent β-amino iodides **2** and **5**,

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(13) Replacement of the vinyl group by hydrogen generates enantiomeric pairs with the 2*S* and 2*R* configurations, respectively.

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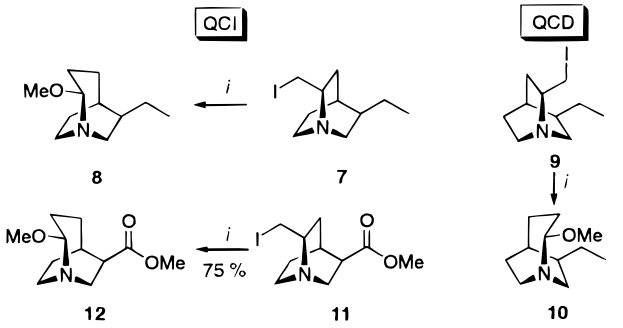
and the ester group appeared to slow the S_N1 like ring expansion as full conversion was only observed after 40 h. Nonetheless, the yield of the desired diastereomerically and enantiomerically pure ester **12** remained high (75%) (Scheme 2).

Scheme 2. Ring Expansion of C9-Iodinated Alkyl-Substituted Quinuclidines and Quinuclidine Esters[a]

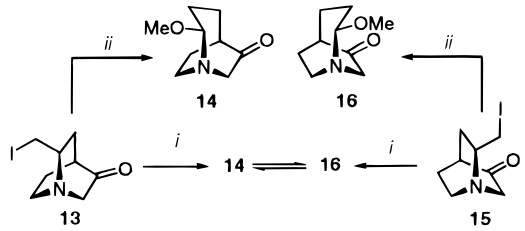


[a] (*i*) AgOBz, MeOH, 50 °C, 20 h.

We were pleased to find that even 2-iodomethyl ketones **13** and **15** afforded 1-azabicyclo[3.2.2]nonan-6-ones **14** and **16**, respectively, although in a more sluggish reaction.

Surprisingly, given the high stereoselectivity exhibited by the other silver triflate-mediated ring expansions, partial epimerization was observed upon treatment of iodo ketones **13** and **15** with AgOTf at 22 °C (**14** → 80:20 and **16** → 68:32) (Table 2). AgOBz-promoted rearrangement of

Table 2. Ring Expansion of 2-Iodomethylquinuclidin-5-ones

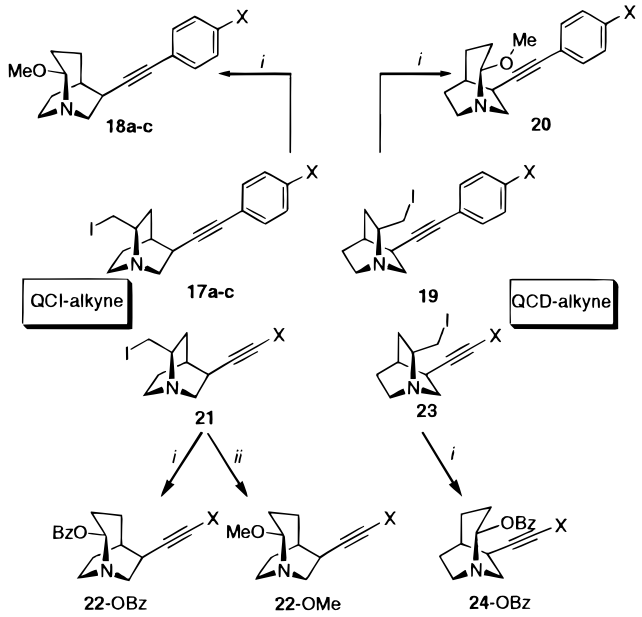


entry	iodo ketone	silver salt (1.1 equiv, 50 °C)	yield [%]	ratio of epimers **14** [%]	**16** [%]
1	13	AgOTf (*i*)	47	80	20
2	13	AgOBz (*ii*)	76	100	
3	15	AgOTf (*i*)	41	32	68
4	15	AgOBz (*ii*)	72		100
5	15	1. AgOTf (*i*), 2. HCl	32	48	52

β-amino keto iodides **13** and **15** gave epimerically pure (GC, NMR) ketones **14** and **16**, respectively.

2. Interception of Silver Counterion in Solvent MeOH. Arylated alkynes **17a**−**c** and **19** were readily available from parent terminal alkynes[15] by Sonogashira coupling[16] and subsequent C9-iodination. AgOBz-mediated ring expansions proceeded spot-to-spot, affording diastereomerically pure rearranged alkynes **18a**−**c** and **20** in respectable yields (70−82%) (Scheme 3, Table 3). Thus, substituents **X** in the *p*-position of the phenylethynyl side chain affected neither rate nor yield.

Scheme 3. Rearrangement of 10,11-Didehydroquincorine and 10,11-Didehydroquincoridine Iodides



Reagents and conditions: *i*, AgOBz, MeOH, 50 °C; *ii*, $AgNO_3$, MeOH, 50 °C.

The terminal iodo alkynes **21** and **23**, however, confounded expectations by yielding, on reaction with AgOBz in MeOH, benzoates **22**-OBz and **24**-OBz rather than the anticipated α-methoxy amines **22**-OMe and **24**-OMe. The desired hemiaminal **22**-OMe could only be prepared upon treatment of iodide precursors with $AgNO_3$ in MeOH (Scheme 3). Iodo alkynes **21** and **23** proved to be more polar than vinylic (**2**, **5**) and ethyl analogues (**7**, **9**): preassociation with AgOBz seems to influence capture of the external nucleophile (OBz versus MeOH).

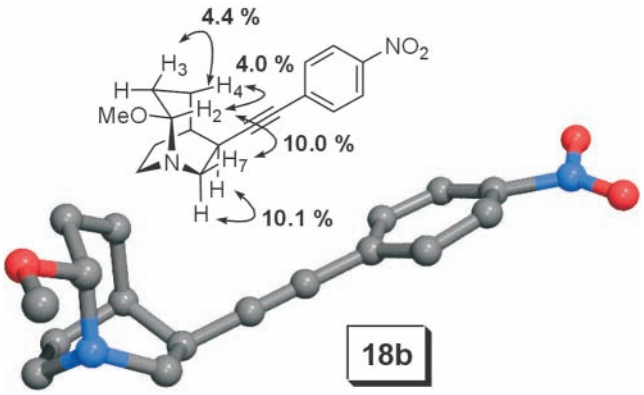
3. Spectroscopic, Conformational and Mechanistic Considerations. In our studies, configuration and conformation of rearranged 1-azabicyclo[3.2.2]nonanes and their

Table 3. Ring Expansion of 2-Iodomethylalkynes

entry	2-iodo-methylalkyne	X	1-azabicyclo-[3.2.2]nonane	yield [%]
1	**17a**	H	**18a**	82
2	**17b**	NO_2	**18b**	77
3	**17c**	CO_2Et	**18c**	74
4	**19**	H	**20**	70
5	**21**	H	**22-OBz**	48
6	**21**	H	**22-OMe**	61
7	**23**	H	**24-OBz**	43

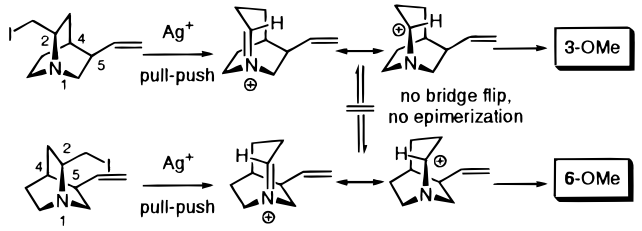
azabicyclo[2.2.2]octane precursors were determined by NMR spectroscopy and by X-ray analysis. The stereochemical outcome of ring expansion reactions and the configuration at carbon C2 could easily be assigned by NOE interactions of protons H2, $H7_{endo}$, and $H8_{endo}$. QCI-based 2R-configured [3.2.2]-azabicyclic **18b** showed strong interactions between H2 and $H7_{endo}$, H3 and H4 (4 → 10%). Further evidence for the equatorial position of the methoxy group was provided by X-ray analysis of alkyne **18b** (Scheme 4).[17]

Scheme 4. NOE and X-ray Analysis of **18b**



Throughout our experiments QCI consistently gave higher yields of ring-expanded azabicycles than the corresponding QCD derivatives. We attribute this to interference of the C5-side chain with the emerging ring-expanded system. The mechanism of the silver salt-mediated rearrangement is assumed to involve a nucleophilic shift of C3 from C2 to C9 to generate a strained, nonplanar iminium ion instead of an aziridinium ion which is reported to be the key intermediate in various rearrangements of β-amino alcohols such as the ring enlargement of an L-proline derivative in the synthesis of (−)-pseudoconhydrine.[18] Bicyclic systems with strained bridgehead imine double bonds (*E* and *Z* isomers) have been obtained in a matrix in the dark at low temperature.[19] The double stereochemical label facilitates evaluation of both leakage from QCI to pseudoenantiomeric QCD and stereoselectivity of nucleophilic attack of the cation. It is striking that although a carbocation is involved in our rearrangement, the configuration at carbon C2 is retained throughout the reaction, and equilibration between the postulated QCI and QCD cations is not observed (Scheme 5). We suggest that iminium resonance of the cation is

Scheme 5. Mechanism of Silver-Mediated Ring Expansion via Pseudoenantiomeric[13] Carbocations



accompanied by some pyramidalization of the carbocation. This has the effect of directing external capture of the nucleophile to one π-face only. The carbocation of the quinuclidin-5-one system is more prone to bridge flipping (weaker C−N iminium bond) than the system with vinyl side chain (stronger C−N iminium bond). The nucleophilic shift of C3 from C2 to C9 is stereoelectronically favored if the migrating C2−C3 bond is antiperiplanar to the C9-X bond as well as to the nitrogen lone pair. The crystal structure of a C9-brominated QCD analogue which is similar to iodomethyl precursor **15** fulfills the criterion of antiperiplanarity, with torsion angle Φ (C3−C2−C9−X) = 166.5°.[20]

Conclusion. A simple stereoselective one-pot synthesis of a new class of azabicycles has been accomplished. Currently, more than a dozen of the title azabicyclics have been prepared. They are of potential therapeutic and pharmaceutical interest. In addition, functionalized and substituted forms of these compounds should be useful as building blocks for asymmetric synthesis. The rearrangement proceeds under mild S_N1-like conditions and tolerates additional functionalities such as carbonyl and ester groups and alkynes. After optimization, no crossover from the QCI into the QCD series and vice versa occurs. Preliminary evaluation of biological activity suggests that our [3.2.2]-azabicyclics are nontoxic,[21] unlike quinidine and anatoxin-*a*.

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Supporting Information Available: X-ray data for **18b** and spectroscopic data for each new compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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