Recent Advances in *Cinchona* Alkaloid Chemistry

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Quinine has been among the best known alkaloids for over 300 years, thanks to its antimalarial activity. In the last two decades, *Cinchona* alkaloids have emerged as powerful chiral auxiliaries, resulting in some well known landmark developments in asymmetric synthesis, but more recently these alkaloids *themselves* have been shown to undergo some remarkable transformations and skeletal shifts that are rapidly widening perspectives in the chemistry of *Cinchona* bases, embracing both basic and applied science. The alkaloids enter into a series of fundamental transformations that have given rise to the industrial manufacture of a host of new enantiopure materials showing promise for asymmetric syntheses and combinatorial chemistry. Stereochemical diversity, well developed conformational minima not encountered in conventional organic substrates, hydrophilic pockets and stereoelectronics contribute subtle mechanistic features and structural complexity.

1. Introduction

The *Cinchona* alkaloids quinine, quinidine and the so-called *cinch* bases cinchonidine and cinchonine are produced on a commercial scale (approx. 700 t/year). They are extracted from the bark of the *Cinchona* tree, which is cultivated above 1400 m in equatorial climatic zones (Figure 1). Although three total syntheses of quinine have been achieved recently,[1] extraction remains the method of choice for commercial use. Over 30 alkaloids have been characterized in *Cinchona* bark, four of them − quinine (**1a-OH**), quinidine (**2a-OH**), cinchonidine (**1b-OH**) and cinchonine (**2b-OH**) (Figure 1) − accounting for over 50% of the alkaloid content. These alkaloids are all made up of a

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Hans Martin Rudolf Hoffmann was born in Ludwigshafen, studied chemistry in Braunschweig and Darmstadt and obtained his PhD at University College London with Sir Christopher Ingold and Edward David Hughes. He was a postdoctoral fellow at UCLA with Don Cram and Saul Winstein, and at Harvard with R. B. Woodward. Having been a Lecturer at University College he then moved to a Chair of Organic Chemistry at the University of Hannover. After a start in Physical Organic Chemistry his research has evolved to novel synthetic methodology, ene chemistry, and natural product synthesis (for recent articles see, Angew. Chem. Int. Ed. ***2003***, *42*, *2711 and, Angew. Chem. Int. Ed.* ***2004***, *43*, *1934). He resurrected the Baylis−Hillman reaction after it had lain dormant in the patent literature for more than a decade.*

Jens Frackenpohl was born in Bremerhaven in 1972. He studied chemistry at the Universities of Hannover and Cambridge (UK), obtaining his diploma in 1997 and his dissertation in 2000 from the University of Hannover working with Prof. H. M. R. Hoffmann on novel transformations of Cinchona alkaloids. He then spent one and a half years as a postdoctoral research fellow with Prof. D. Seebach at the ETH Zürich working on the synthesis of β-peptides and their biological properties. In 2001 he joined Bayer's Central Research unit in Leverkusen, and since 2003, he has worked in the chemical research division of Bayer CropScience in Frankfurt as team leader.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

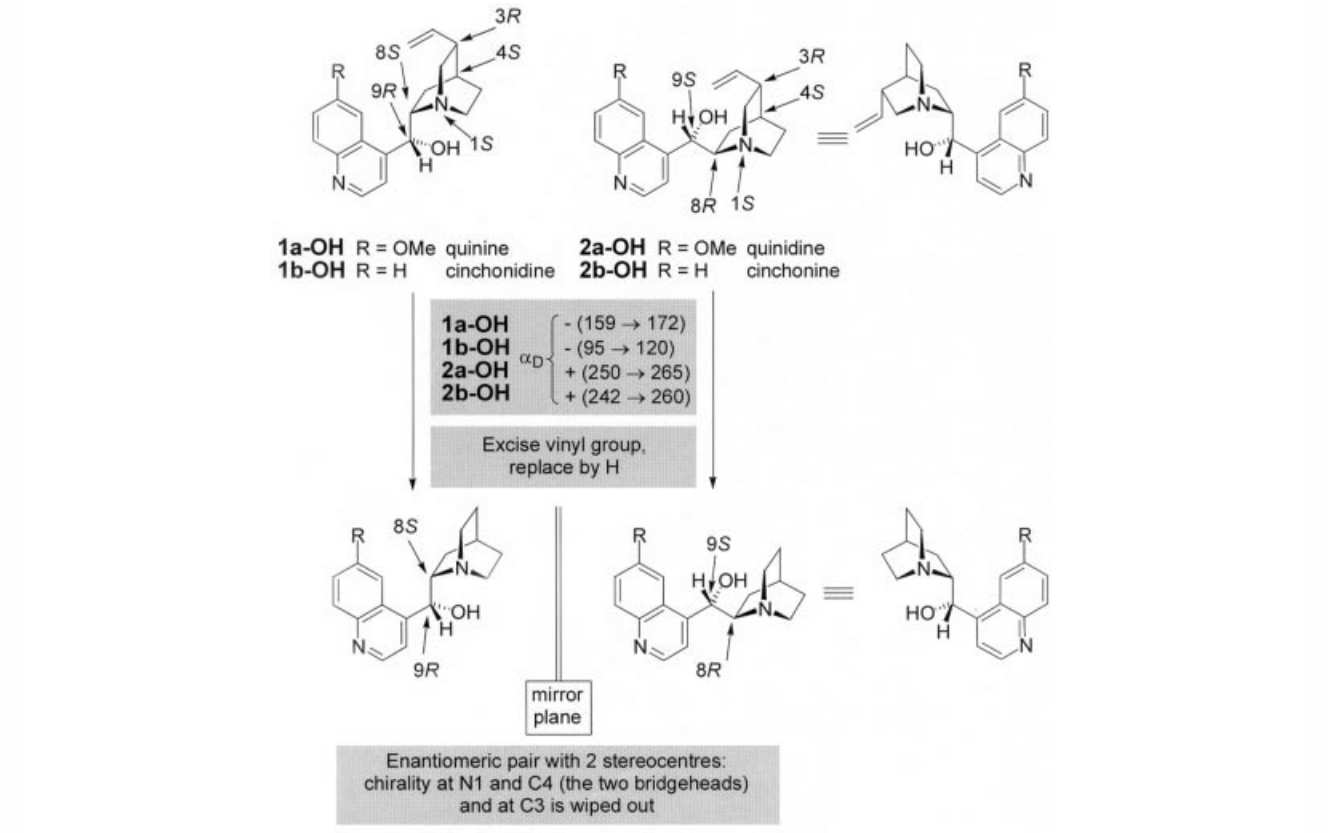


Figure 1. The four most common *Cinchona* alkaloids; *pseudo*-enantiomerism; the optical rotation was measured mainly in EtOH at various concentrations (except for cinchonine **2b-OH**, which was measured in aq. HCl)

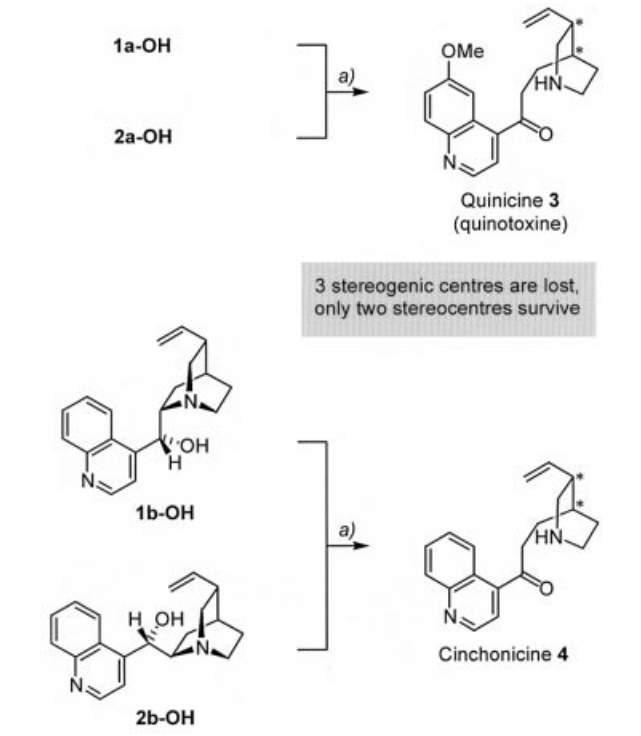
quinoline joined to a substituted chiral 1-azabicyclo[2.2.2]octane moiety through stereogenic carbon C9. Natural companions of the *Cinchona* alkaloids are always the 10,11-dihydro derivatives, in the ranges of 15−20% (cinchonine and quinidine) or 10−15% (cinchonidine and quinine). The components are separated by crystallization.

Cinchona alkaloids are widely used in the pharmaceutical and chemical industries. Quinine is a traditional antimalarial drug, while quinidine is prescribed for irregular heart beat therapy. A further major application of quinine is in soft drinks and tonic water.[2] As cinchonine and cinchonidine and their salts crystallize well, separation of racemates with the aid of their diastereomeric salts is a major and robust application.[3] Quinine and cinchonidine are used in, for example, the large-scale classical separation of racemic naproxene, of which only the (+)-(*S*) enantiomer is pharmacologically active as an anti-inflammatory drug. The pairs **1a-OH** and **2a-OH** (and **1b-OH** and **2b-OH**) are often termed *pseudo-enantiomeric*, because they are "almost enantiomeric pairs" as can be seen by a simple *gedanken-experiment* (Figure 1).[4]

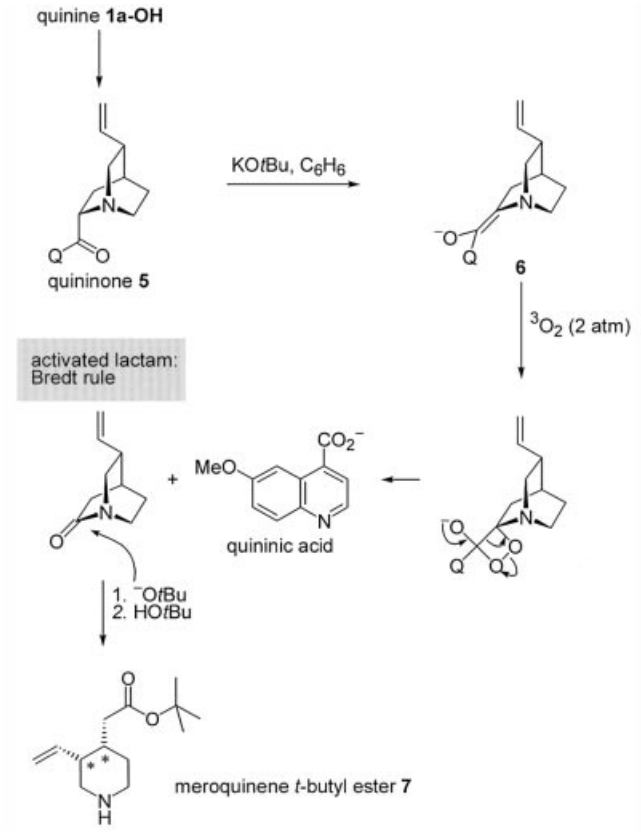
While the 6′-R = OMe substituent is remote from the C9−C8 region, *cinch* bases (6′-R = H) show some special properties. Apart from the obvious absence of fluorescence, which makes them "invisible" to UV detection (at 366 nm) on chromatography, "onium salts of cinch bases (e.g. protonated species) show marked differences from those of quinine and quinidine salts with respect to solubility, crystallizability (enhanced), HPLC and chromatography behaviour. *Cinch* bases are also prone to undergo the "second *Cinchona* rearrangement".

There are only a few general reactions of *Cinchona* alkaloids, among which the quinotoxine cleavage goes back to Pasteur (Scheme 1).[5] On treatment with strong acid, both the quinine/quinidine pair and the cinchonidine/cinchonine pair are cleaved to give quinicine (quinotoxine) **3** and cinchonicine **4** (cinchotoxine), respectively. Three stereocentres are lost and functionalized piperidines are formed. It is often stated that quinine (and quinidine) contain four stereocentres. In fact, the bridgehead nitrogen is an important fifth stereocentre, storing chirality information that can be transmitted directly to a complexed metal (Ni, Os, Ir; see below), thus maximizing stereoinduction (proximity rule). The Pasteur cleavage amounts to internal oxidation (at C9) and reduction (at C8).

Thanks to quinicine (**3**) and cinchonicine (**4**), Pasteur achieved the first separation of racemic tartaric acid, using diastereomeric salts. This resolution is considered a milestone in organic chemistry. Later on, the tartaric acids themselves became primary chiral standards. Meroquinene ester (**7**) is a 3,4-disubstituted piperidine formed from quininone (cinchoninone) and base in the presence of $^3O_2$: a key



Scheme 1. The quinotoxine cleavage (L. Pasteur, 1853)



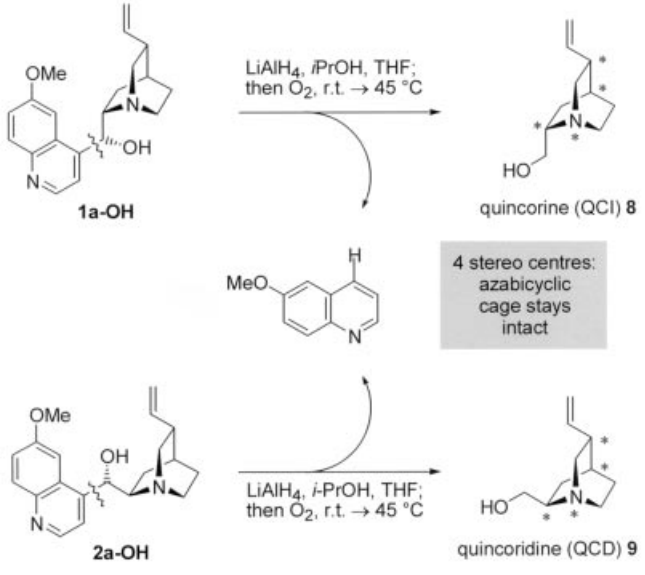
Scheme 2. Oxidative cleavage of quininone and synthesis of meroquinene ester (W. E. Doering, 1946)

intermediate in this reaction is an activated bridgehead lactam, which is opened by KOBu^t; three stereocentres are lost and only two survive in the course of this transformation (Scheme 2).[6]

It has been suggested that *Cinchona* bases, while most valuable chiral auxiliaries (e.g., the AD reaction[7] and asymmetric phase-transfer reactions[8]), "*... are very unlikely to find application as (chiral) building blocks*".[9] The recent developments here outlined should change this view.

2. Quincorine and Quincoridine: Synthesis and Basic Transformations − Nucleophilic Substitution at Carbon Atom C9

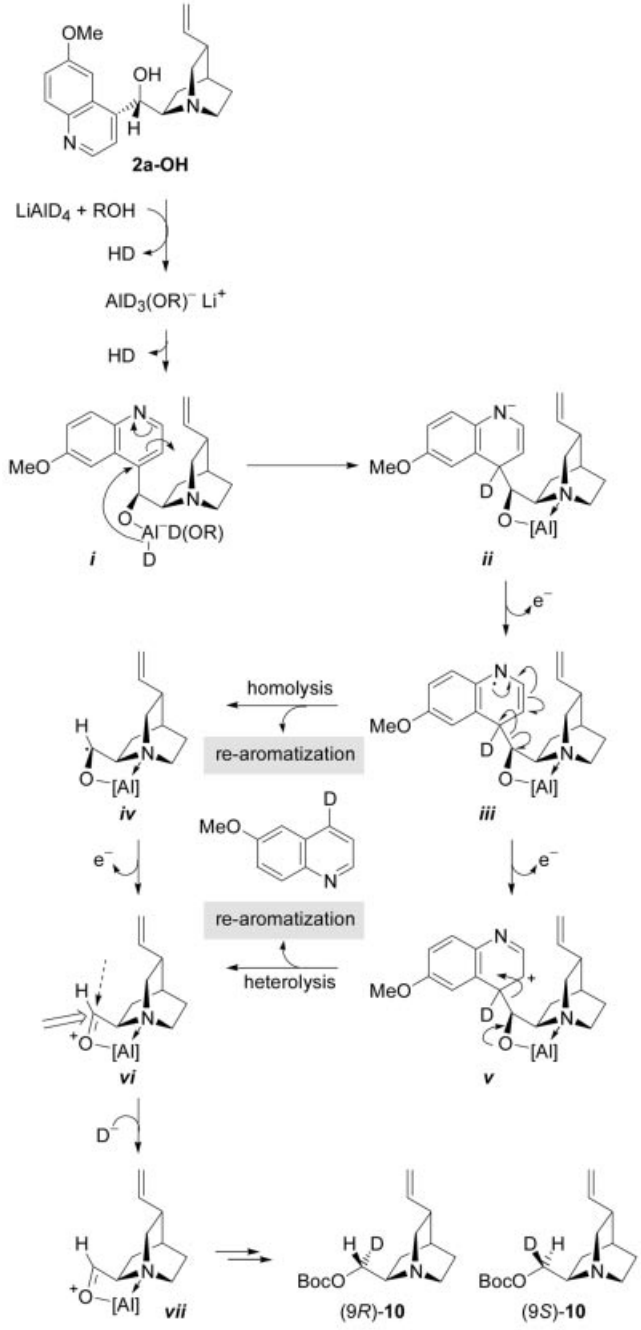
Quinine and quinidine have been transformed into quincorine (QCI) and quincoridine (QCD), respectively. These two bicyclic 1,2-amino alcohols, which can be regarded as truncated alkaloids, each contain four chiral centres including the 1*S*-configured bridgehead nitrogen. Like quinine and quinidine, they are available in enantiomerically pure forms, and like their parent precursors, they are "pseudo-enantiomeric": Replacement of the vinyl groups in QCI and QCD by hydrogen leaves only carbon C2 as a stereocentre. Our route to QCI and QCD is outlined in Scheme 3.[10] 6′-Methoxyquinoline is formed from both quinine and quinidine.



Scheme 3. Invention and innovation in natural product chemistry: quincorine and quincoridine from *Cinchona* alkaloids (H. M. R. Hoffmann, 1996)

Experiments with $LiAlD_4$ and other evidence suggest a fascinating sequence of elementary steps and reactivity, embracing transient carbanionic, radical ion, radical and electrophilic intermediates (Scheme 4).

$LiAlD_4$ and added secondary alcohol are thus believed to furnish an alkoxy aluminium deuteride, which docks onto the secondary hydroxy group of the alkaloid (**2a-OH**



Scheme 4. En route to quincoridine (QCD); proposed mechanism of the formation of QCD from quinidine

→ ***i***). Intramolecular attack by deuteride ion at C4′ generates an azaallyl anion (***i*** → ***ii***), which undergoes one-electron oxidation to afford an intermediate azaallylic radical (***ii*** → ***iii***). Homolysis of this radical affords neutral, deuterated 6-methoxyquinoline and aluminium-complexed ketyl radical ***iv***. A second one-electron oxidation is assumed to generate the electrophilic aldehyde (***iv*** → ***vi***). Alternatively, but considered less likely, azaallylic radical ***iii*** might undergo one-electron oxidation to provide the azaallylic cation ***v***, which would then have to experience a heterolytic fragmentation to give aldehyde ***vi*** and 6′-methoxyquinoline. Aldehyde ***vi*** undergoes diastereoselective deuteration through an ionic reaction (***vi*** → ***vii***). Intramolecular complexation of aluminium by the bridgehead nitrogen is thought to restrict rotation of the formyl group. After Boc-protection, deuterated diastereomer (9*R*)-**10** is isolated in excess, consistently with nucleophilic attack from the more accessible side.

Thus, in addition to the classical degradation of the *Cinchona* bases, there is scope for new reactivity and new selectivity involving radical, radical ion-SET and ionic chemistry with sequential oxidation *and also* hydrogenation steps, all in a single flask! The transformation takes place under mild conditions with high functional group selectivity; protecting and activating groups are not necessary. The process has been carried out on a 100-kg scale in a 5000-L vessel (see a in Figure 2). A potentially dangerous reaction is started and sustained by controlled access of oxygen (Scheme 4).

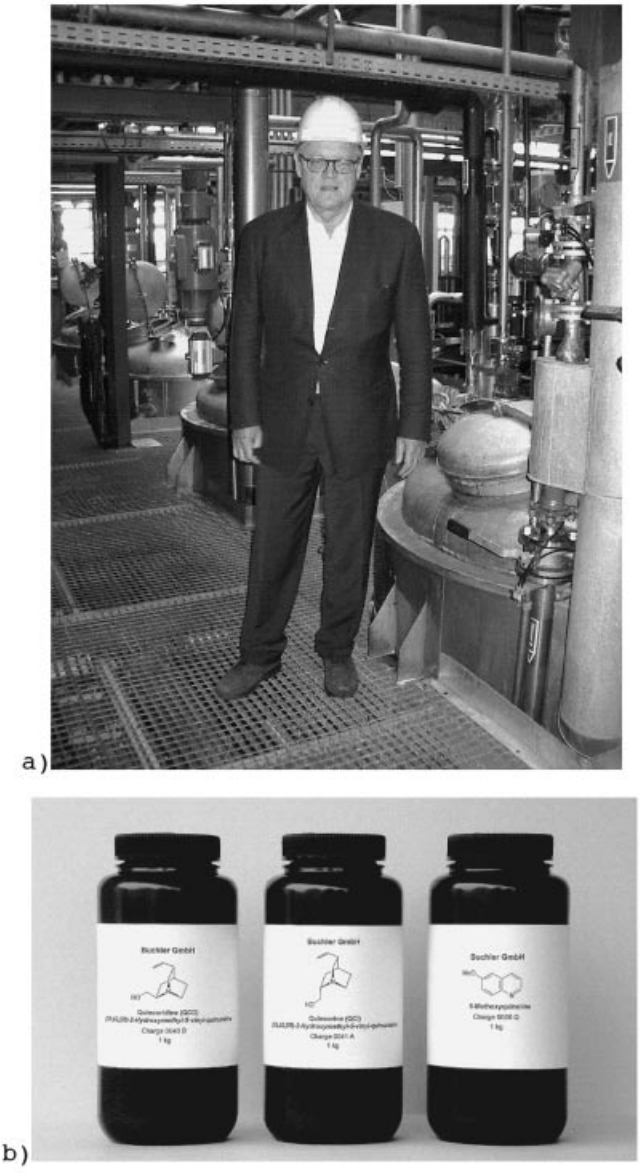


Figure 2. a) Manufacture of QCI and QCD on industrial scales, b) bottles of QCI, QCD, and 6′-methoxyquinoline prepared for shipment (both photographs were taken at Buchler GmbH's production site in Braunschweig)

The other product (see b in Figure 2) is 6′-methoxyquinoline, obtained in high purity as almost colourless crystals, with only a slight yellow tinge. Previously this heteroaromatic material was available commercially only as a brown mass. Derivatives with substituents at C2 and C4 have been prepared by nucleophilic addition to the pyridine nucleus (Figure 3).

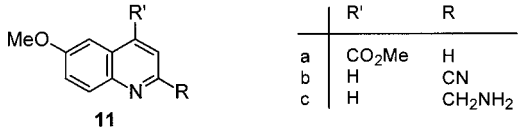
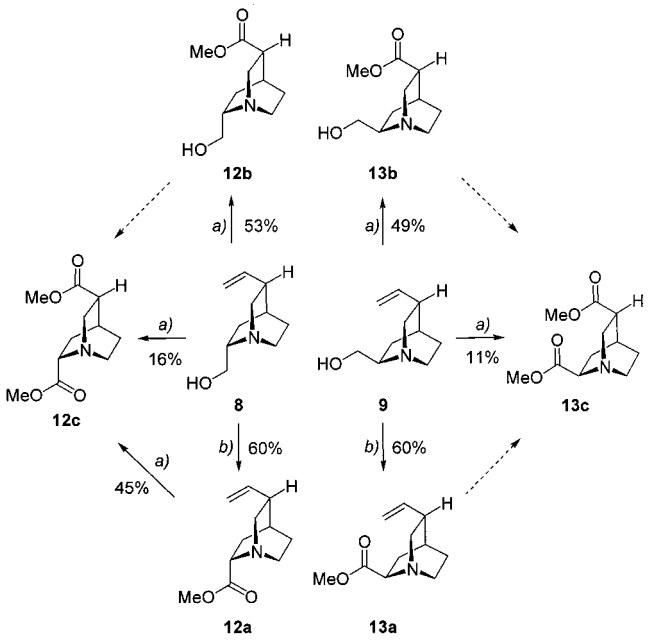


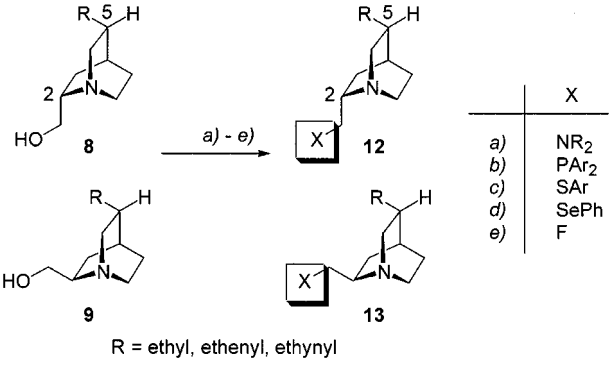
Figure 3. 6′-Methoxyquinoline and some derivatives

Oxidation At C9 and Oxidative Vinylic Side Chain Cleavage: Oxidation allows modification of the QCI and QCD side arms at C9, selectively affording C9-esters **12a** and **13a** (Scheme 5).[11] Furthermore, the desired products can be isolated in epimerically pure form (and also enantiopure). To our surprise, $KMnO_4$-mediated oxidation results in selective cleavage of the vinylic side chains of quincorine **8** and quincoridine **9**. The unprotected primary C9 alcohol function and the configuration at C5 are preserved. 1,6-Dicarboxylic esters **12c** and **13c**, which are potential linkers, were formed only as side products in variable yields (10−20%). The vinylic side chains of the natural products quinine and quinidine have also been cleaved oxidatively by Jones reagent[12] or by $KMnO_4$.[13] Because of their low molecular weights, their compact and rigid structures and their chemodifferentiated side arms, amino acid esters **12a**, **13a**, **12b** and **13b** are versatile chiral building blocks and novel acid-soluble spacers.



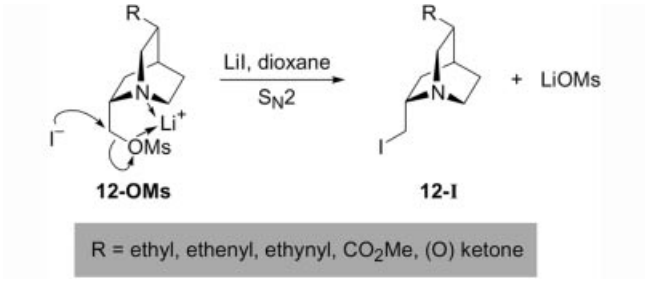
Scheme 5. Selective oxidation of the side arms of QCI and QCD; *reagents and conditions: a)* 1. $KMnO_4$ (2 equiv.), H_2SO_4, H_2O, 0 °C → room temp., 2. MeOH, cat. HCl, room temp., 3 d; *b)* 1. Jones reagent (3.6 equiv.), acetone, 0 °C → reflux, 3 d, 2. MeOH, cat. HCl, room temp., 3 d

Nucleophilic Substitution at C9: Introduction of a nucleophile at C9 may look simple, but often requires optimization. S, P and also Se have been introduced using their highly nucleophilic monoanions (Scheme 6).[14]



Scheme 6. S_N2 displacements in C9-activated QCI and QCD; *reagents and conditions: a)* R = H: PPh_3, DEAD, HN_3, THF, 0 °C → reflux, 2.5 h; R = Ar: 1. MsCl, Et_3N, DCM; 2. phosphide, THF, reflux; *b)* 1. MsCl, Et_3N, DCM; 2. phosphide, THF, reflux; *c)* 1. MsCl, Et_3N, DCM; 2. NaSAr, THF, reflux; *d)* 1. MsCl, Et_3N, DCM; 2. KSePh, THF, reflux; *e)* nBu_4NF (1 M soln. in THF)

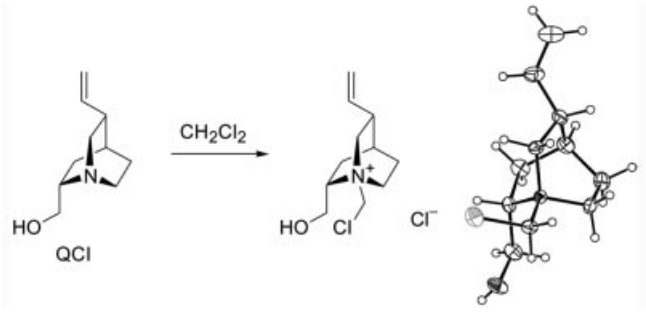
Preparation of the iodomethyl derivative **12-I**, which enters into the "first *Cinchona* rearrangement" (see below), proceeds from the derived mesylate by treatment with LiI (approx. 3 equiv.) in refluxing dioxane (Scheme 7).[15] The *N−C8−C9−O* backbone conformation allowing free access to C9 from the rear is usually only a minor rotamer, and S_N2 displacements may be sluggish. Bidentate interaction with excess Li^+ in solvent dioxane (but not in THF), however, is believed to change the rotameric equilibrium and to "open up" C9 to backside attack. The situation appears to parallel that in some carbohydrates, in which S_N2 displacements on 1,2-alkoxy halides can also be recalcitrant.[14,15] Fluorides **12-F** and **13-F** and corresponding amines have been prepared by standard methods.[14,16] Interestingly, fluorine derivative **12-F** is highly volatile and has a characteristic odour. The Staudinger procedure with triphenylphosphane and trifluoroacetic acid provided 1,2-diamines directly from the corresponding azides. A variant (PPh_3, 3-



Scheme 7. Synthesis of iodomethyl derivative **12-I**; Li^+-promoted chelation facilitates S_N2 displacement

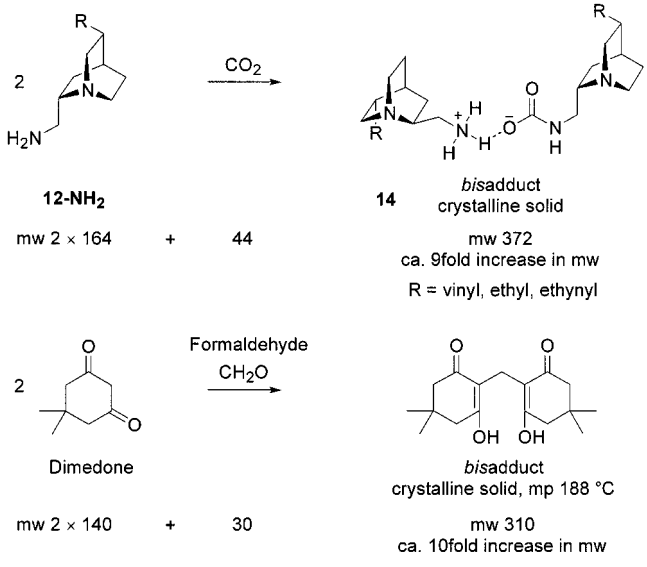
$ClC_6H_4CO_2H$) afforded a related *m*-chlorobenzamide that is less water-soluble and readily isolable.[14]

QCI reacts spontaneously with dichloromethane, the nucleophilic bridgehead nitrogen being quaternized, apparently with some assistance from the hydroxymethyl group, which enters into hydrogen bonding to the leaving group (Scheme 8).[17]



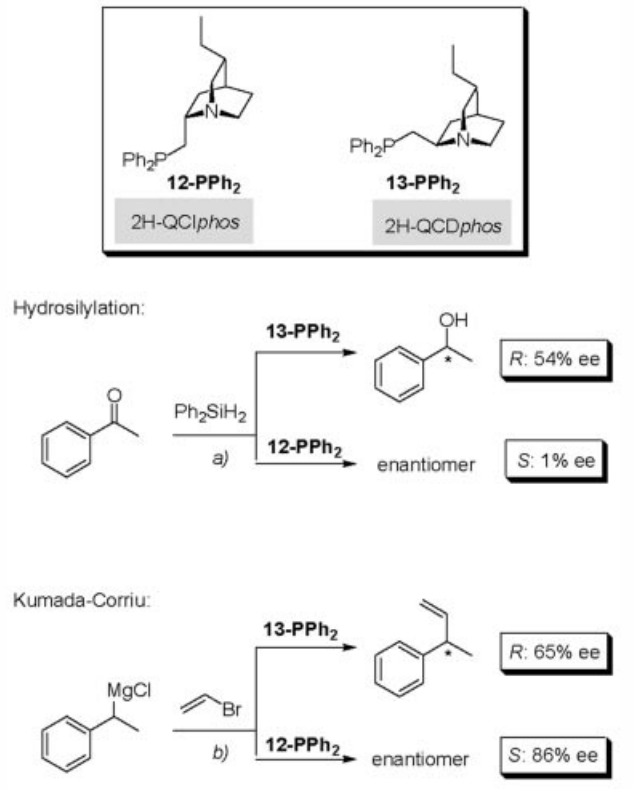
Scheme 8. Spontaneous quaternization of QCI in dichloromethane

In contrast, diamine **12-NH$_2$** can be stored in CH_2Cl_2. Neda et al. have shown that, on contact with CO_2 (from the air) or with CO_2 in ether, **12-NH$_2$** reacts spontaneously to form the primary ammonium carbamate salt **14** (2:1 adduct) as a colourless, crystalline solid. The neat salt is quite stable. When it is heated above 120 °C in vacuo, CO_2 is removed and pure 1,2-diamine **12-NH$_2$** can be recovered. In this simple fashion, even traces of QCI can be removed from **12-NH$_2$** without recourse to HPLC, distillation or other traditional separation and purification techniques (Scheme 9).[18] Conversely, the chemical fixation of CO_2 by **12-NH$_2$** can be used for gravimetric analysis.



Scheme 9. Ammonium carbamate **14**; a stable crystalline carbamate salt from 1,2-diamine **12-NH$_2$** (I. Neda, 2003)

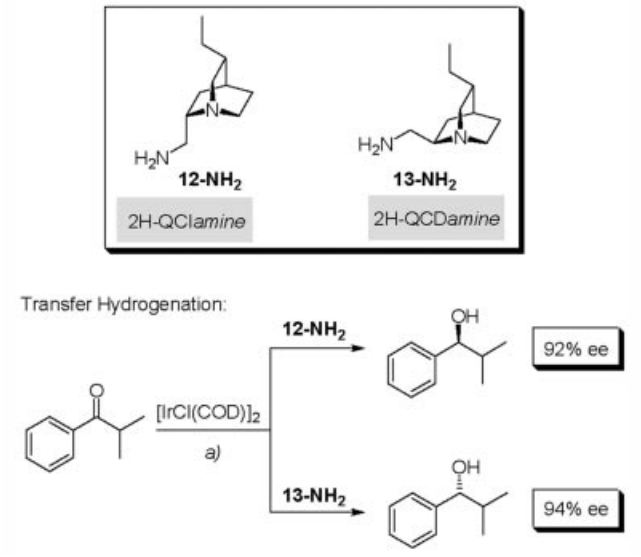
Further applications of QCD- and QCI-derived bidentate ligands are beginning to emerge. Although hydrosilylations with QCI- and QCD-derived phosphane ligands afford only low *ee*s (up to 54%), the asymmetric Kumada-Corriu coupling with 2H-QCI*phos* (**12-PPh$_2$**) proceeds in up to 85% *ee* (Scheme 10).[19] Interestingly, QCD-derived phosphane ligands afforded higher enantioselectivities in the hydrosilylation, whereas QCI-derived ligands proved to be more suitable for Ni-catalysed cross-coupling.



Scheme 10. Asymmetric catalysis with QCI- and QCD-derived phosphane ligands (M. Lemaire, 2001); *reagents and conditions: a)* Ph_2SiH_2, QCI/QCD-ligand, $[RhCl(COD)]_2$, toluene, 72 h, −10 °C; *b)* $NiCl_2$, QCI/QCD-ligands **12-PPh$_2$** or **13-PPh$_2$**, vinyl bromide, Et_2O, 12 h.

Recently, a collection of transition metals and QCI- and QCD-diamine ligands have been evaluated in the catalytic asymmetric transfer hydrogenation of aromatic ketones, a benchmark reaction in asymmetric catalysis. In the course of a catalyst screening, it was found that complexes of QCI- and QCD-diamines **12-NH$_2$** and **13-NH$_2$** with oxophilic $[IrCl(COD)_2]$ were the most active catalysts, capable of reducing a broad range of aromatic ketones with excellent levels of conversion and good enantioselectivities (up to 95% *ee*) (Scheme 11).[20] Either pseudo-enantiomeric diamine ligand was effective, providing ready access to either enantiomeric secondary alcohol. These are the best selectivities so far reported for QCI- or QCD-derived ligands in an asymmetric transformation. Their low molecular weights (*Mw* = 168) and their commercial availability, in both

pseudo-enantiomeric forms, suggest that these ligands with *N*-chiral bridgehead nitrogens will find further practical use in asymmetric syntheses. The Arvidsson procedure[20] complements other variants of the transfer hydrogenation of prochiral ketones by 2-propanol (MPV or Meerwein−Ponndorf−Verley reduction).[21]

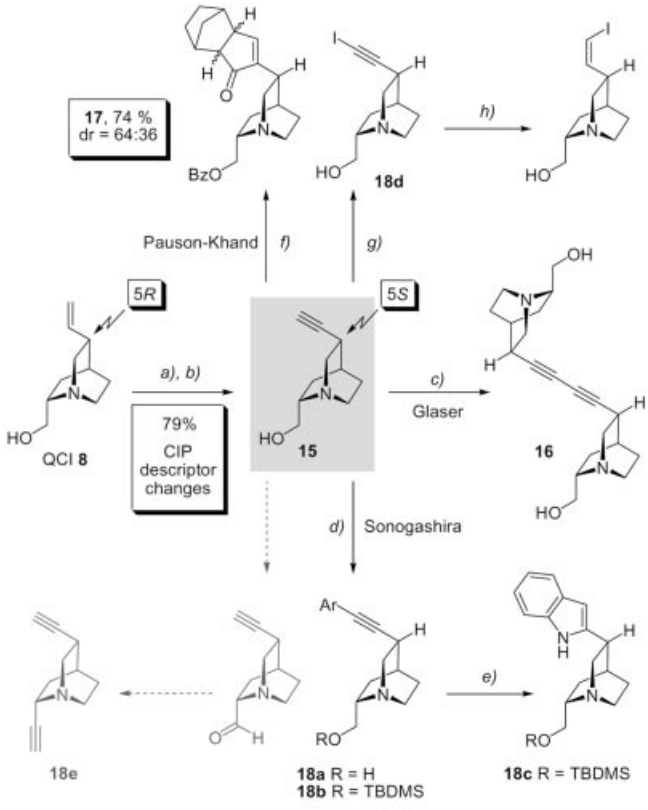


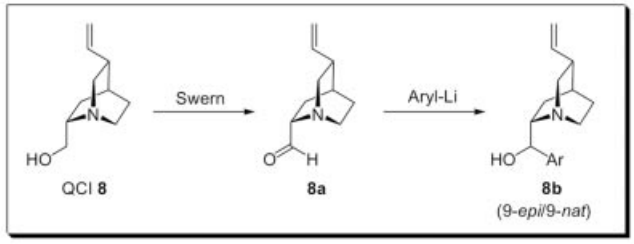
Scheme 11. Catalytic asymmetric transfer hydrogenation with QCI- and QCD-derived diamine ligands (P. I. Arvidsson, 2003); *reagents and conditions: a)* QCI/QCD-ligands **12-NH$_2$** or **13-NH$_2$**, [IrCl(COD)]$_2$, *i*PrOH, *i*PrOK, 10 h

3. *Cinchona*-Alkynes and Their Derivatives. Basic Transformations and Transition Metal-Mediated Reactions

We have recently converted the ethenyl group of the *Cinchona* alkaloid into an ethynyl group by a bromination-double dehydrobromination sequence.[22,23] Simple 10,11-didehydro QCD and 10,11-didehydro QCI are also accessible by this reliable two-step procedure. Thus, QCI (which solidifies at room temperature when pure) forms alkyne **15** with a change in chirality descriptor at C5. QCI-derived alkyne **15** crystallizes readily and also sublimes on warming, forming beautiful, colourless needles, reaching from wall to wall of the reaction vessel.[23]

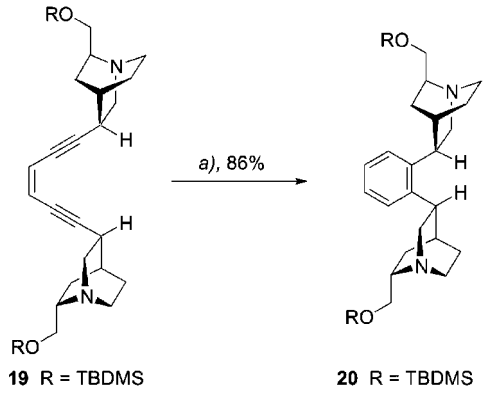
Thanks to the terminal alkyne function, a wide range of Pd-catalysed sp^2-sp cross-coupling reactions involving vinylic, aromatic and heteroaromatic centres are feasible.[22] Sonogashira coupling with aniline derivatives and subsequent cyclization affords conjugate *indole-Cinchona* alkaloids (**18c**).[24] Furthermore, cobalt-catalysed cycloadditions such as the Pauson−Khand reaction proceed with high yields and moderate diastereoselectivities (Scheme 12). Terminal alkyne **15** is easily transformed into its iodinated analogue **18d**,[23] which can be hydrogenated to afford a vinyl iodide, a further versatile building block for cross-coupling reactions. Oxidation of alkyne **15** and subsequent conversion of the intermediate aldehyde into an alkyne function would provide a short route to diterminal diyne **18e**. The alkyne derived from QCD should be accessible in analogous fashion. Additionally, reactions of sensitive aldehydes (e.g., **8a**) with aryllithium reagents at low temperatures allow the reconstitution of *Cinchona* alkaloids,[25] including analogues.[26] At the time of writing, no diterminal alkynes derived from QCI (**18e**) and QCD have yet been prepared − time for a change!





Scheme 12. Synthesis and transformations of QCI-alkyne **15**; *reagents and conditions: a)* 1. Br_2, CCl_4, 0 °C, 2 h; 2. Et_3N, $CHCl_3$, room temp., 14 h; *b)* KOH, aliquat 336, THF, reflux, 7 h; *c)* [$(Ph_3P)_2PdCl_2$], CuI, I_2, Et_3N, THF, 16 h; *d)* $(Ph_3P)_2PdCl_2$, CuI, aryl or vinyl halide, Et_3N, THF, 16 h; *e)* 1. TFAA (6 equiv.), Et_3N (3 equiv.), THF, −78 °C → 0 °C, 1 h; 2. imidazole (2.6 equiv.), LiCl (1.2 equiv.), $Pd(OAc)_2$ (5 mol %), DMF, 6 h, 35%; with 40 mol % of $Pd(OAc)_2$ the yield increases to 57%; *f)* 1. $Co_2(CO)_8$, CH_2Cl_2, room temp., 90 min; 2. NMO, alkene, CH_2Cl_2/THF (1:1), room temp., 5 h; *g)* I_2, morpholine, toluene, 70 °C, 5 h; *h) p*-TsNHNH$_2$, NaOAc, THF, H_2O, 65 °C, 4 h

Although enediyne **19** is not part of a strained ring it undergoes a cycloaromatization at moderately elevated temperatures (60−70 °C) in $CHCl_3$ (86%) (Scheme 13).[22,27]

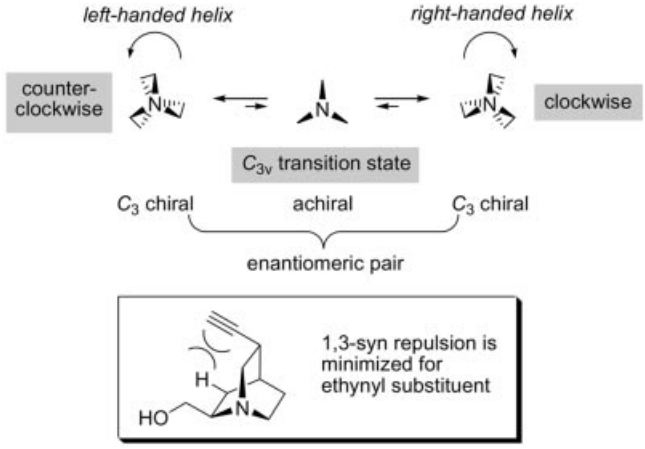


Scheme 13. Bergman cyclization of QCI-derived enediyne **19**

The Ethynyl Group is Anything But a Spectator Substituent: All alkyne-alkaloids prepared, including 10,11-didehydro-QCI and 10,11-didehydro-QCD, were found to be crystalline and more polar than the parent ethenyl (vinyl) alkaloids on chromatography.[23−24,28] Increased polarity/basicity is consistent with the observation that Os-mediated AD reactions proceed significantly more slowly with alkyne ligands.[29] The efficiency of alkyne-*Cinchona* alkaloids in AD reactions has been evaluated both with standard substrates and with challenging targets such as homoallylic alcohols and bryostatin C-ring lactol segments. In the case of substituted C-ring lactols, higher selectivity (although a lower rate) was observed with novel alkyne AD-ligands, thus overcoming selectivity problems inherent in the use of commercial AD-mixes.

A priori, the 1-azabicyclo[2.2.2]octane helix may be twisted clockwise or counterclockwise and may also adopt a higher energy C_{3v} conformation in which the three ethano bridges are fully eclipsed. Interaction of the nitrogen lone pair with the three *anti*-periplanar σ bonds would be expected to be maximized in the C_{3v} conformer (Scheme 14), which contains two fused boat (rather than twist) azacyclohexanes. The conformational energy (or A value) of the "slim" −C≡CH group is considerably less (1.71−2.18 kJ·mol^{-1}) than that of the sterically more demanding −CH=CH_2 (6.23−7.00 kJ·mol^{-1}) and −CH_2−CH_3 (7.49 kJ·mol^{-1}) groups.[30] As a result, 1,3-*syn* repulsion at C3 and C5 will be less in the alkyne bicyclics than in the ethyl and ethenyl analogues.

From a variety of X-ray crystal studies (e.g., didehydro-QCI/-QCD and didehydroquinidine) it has been established that alkyne-quinuclidines are *consistently less twisted* than their vinyl and ethyl analogues. Overall torsion angles (i.e., the sums of the three torsion angles) vary from 26° to 49°, in comparison with up to 65° for ethyl and 60° for ethenyl derivatives, respectively (Figure 4).



Scheme 14. Quinuclidines as simple helices; helicity of 1-azabicyclo[2.2.2]octane

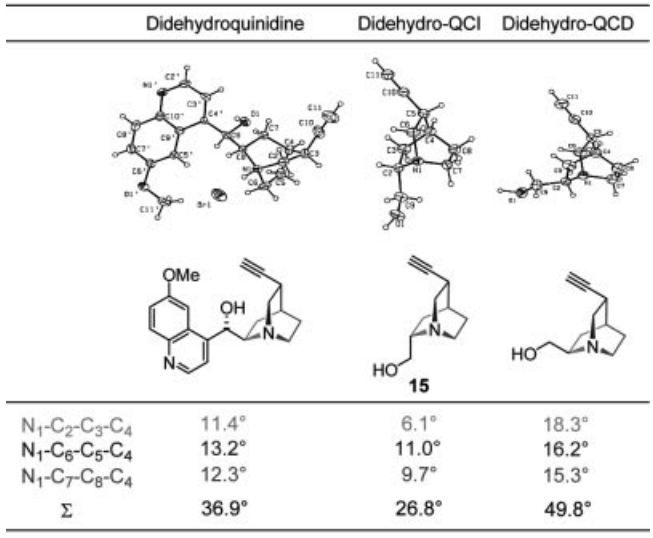


Figure 4. X-ray crystal structure of alkynes derived from *Cinchona* alkaloids; torsion angles defining twist-sense: cf. Scheme 14

Fine-tuning of nitrogen polarity (and basicity), which may be important for catalysis and perhaps pharmacological activity, is thus possible.[31] Furthermore, alkyne derivatives of *Cinchona* alkaloids are able to form interesting supramolecular arrays in the crystalline state (Figure 5).

The X-ray diffraction pattern of the quinine-derived bromoalkyne shown in Figure 5 reveals a highly organized supramolecular structure consisting of three polymeric chains orientated in the same direction. Each chain is held

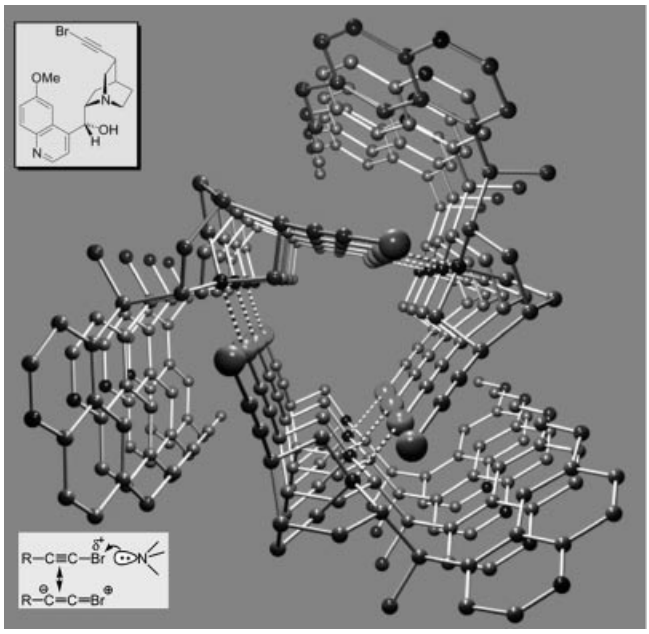


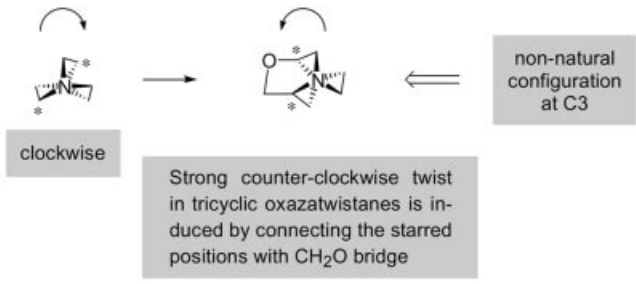
Figure 5. Supramolecular array of 11-bromo-didehydroquinidine in the crystal state; unusual donor-acceptor interactions and morphological triple helix; crystallographic data CCDC-246626 can be obtained from the Cambridge Crystallographic Data Centre, deposit@ccdc.com.ac.uk

together by short contacts (2.82 Å) between the nucleophilic amino nitrogen of one bromoethyne azabicycle and the electrophilic acetylenic bromine of another, and so on. The three strands follow left-handed helices, which are coiled around the same central C_3 axis being a helical or screw axis. The resulting triple helix has a narrow central channel. Unlike other quinine molecules that we have studied, the individual azabicyclic moiety of this quinine derivative traces out a right-handed helix rather than left-handed one.

4. Cage Helicity and Further Consequences. Nucleophilic Attack on Quinuclidin-3-ones

1-Azabicyclo[2.2.2]octane represents a simple helix, which can, a priori, be right-handed or left-handed (Scheme 14).

Unlike *Cinchona* alkaloids with ethyl or ethenyl side chains, in which pseudo-enantiomerism is often reflected by twist sense, the corresponding alkyne derivatives are predominantly twisted clockwise. Furthermore, both QCI-alkyne and QCD-alkyne form right-handed helices. However, a strong counterclockwise twist is enforced in a suitably bridged oxaza-twistane (Scheme 15) that has been used as an asymmetric catalyst in Baylis–Hillman reactions (Scheme 16, a).

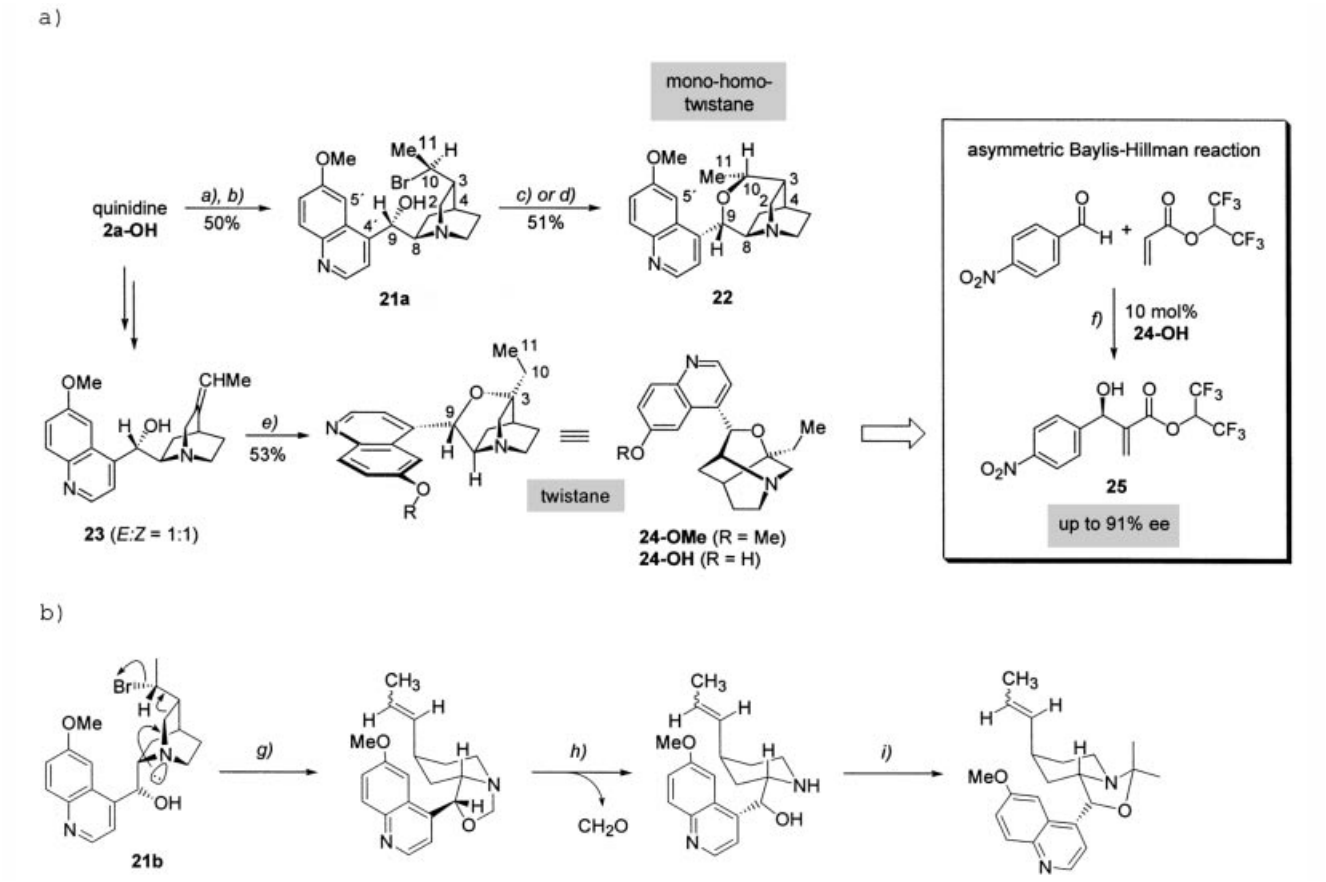


Scheme 15. Twist-sense of quinidine-derived oxaza-twistanes

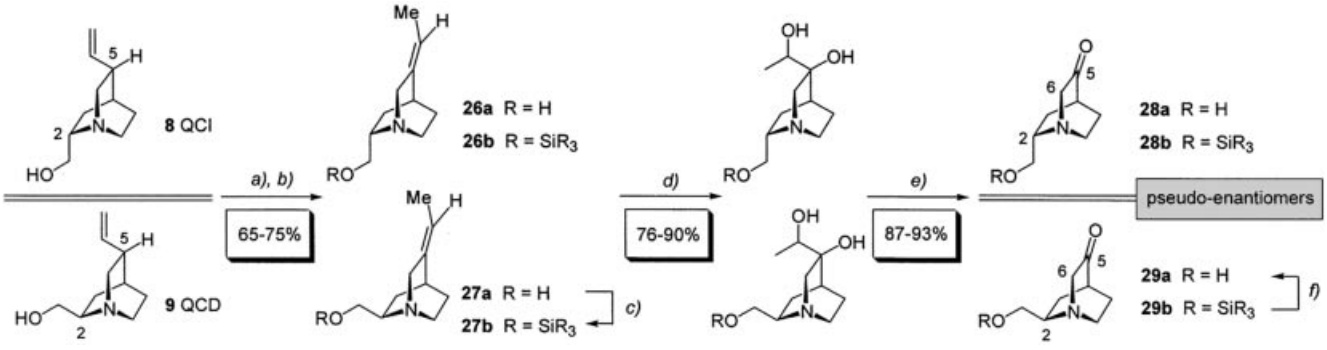
The use of semi-rigid chiral aminophenol **24-OH** as a catalyst in reactions between aldehydes and activated acrylates, affording *ee* values of over 90%, can be seen as a major step forward in the asymmetric Baylis–Hillman reaction.[32] A series of hydroxylated amines derived from *Cinchona* alkaloids has been surveyed, with only oxaza-twistane **24-OH**, in which the phenolic hydroxy group functions as a proton donor within the transition state aggregate, proving to be a suitable ligand.[33] The same twistane catalyst has recently been used for the catalytic asymmetric protonation of fluoro-enolic species derived from β-keto esters.[34] Like QCI- and QCD-based ligands, oxaza-twistanes are easily prepared in a few steps from readily available starting materials.[35] The active catalyst **24-OH** is obtained from isoquinidine in fair yield through acid-mediated cyclization. Nonetheless, even apparently simple transformations have to be monitored carefully: homo-twistane **22** was initially obtained as highly polar side-product in the course of the hydrobromination of quinidine.[36]

Grob fragmentation of precursor **21a** has been suppressed in favour of twistane and homotwistane formation by masking of the nitrogen lone pair (with Ag^+ or H^+). Under S_N1-like conditions and at elevated temperatures, *Cinchona*-derived γ-amino bromides (e.g., **21a** and its quinine analogue **21b**) undergo Grob fragmentation with intramolecular capture of the intermediate iminium ions by the C9-OH group to give oxazabicyclo[4.3.0]nonanes (Scheme 16, b).[37] Fragmentation is also a potential side reaction in the double dehydrobromination of 10,11-dibromo-1-azabicycles (cf. Scheme 12, **8** → **15**). Formation of the desired alkyne **15** is facilitated by the generation of the intermediate vinylic bromide under mild conditions and then by use of strong base (Aliquat 336, anhydrous KOH) to enforce the second, more difficult, dehydrobromination.

3-Quinuclidinone and derived 3-quinuclidinols represent fundamental pharmacophoric leads and are of longstanding interest in medicinal chemistry in the continued quest for selective high-affinity ligands for neuronal receptors.[38] Substituted chiral quinuclidin-3-ones have been prepared by oxidative degradation of the vinyl side chains of QCI and QCD, carried out by (i) double bond shift, and (ii) dihydroxylation and subsequent 1,2-diol cleavage (Scheme 17).[39] The transformation of QCI and QCD into their corresponding keto analogues has been optimized and



Scheme 16. a) Synthesis and application of quinidine-derived oxaza-twistanes in the asymmetric Baylis−Hillman coupling; b) Grob fragmentation of bromo-dihydroquinine **21b**; *reagents and conditions: a)* HBr (62%), 3 d, room temp., *b)* KOH (25%), $NaHCO_3$; *c)* 1. $AgBF_4$, THF, 0 °C → room temp., 4 h; 2. Et_3N, KI, MeOH; *d)* NaH, THF, 0 °C → room temp., 2 d; *e)* 1. KBr, H_3PO_4, 3 d, 100 °C; 2. KOH (25%), $NaHCO_3$; *f)* DMF, −55 °C; *g)* $NaHCO_3$, aq. EtOH, reflux, 11 h; *h)* $(CO_2H)_2$, aq. EtOH, reflux, 80 min; *i)* acetone, room temp., 8 weeks

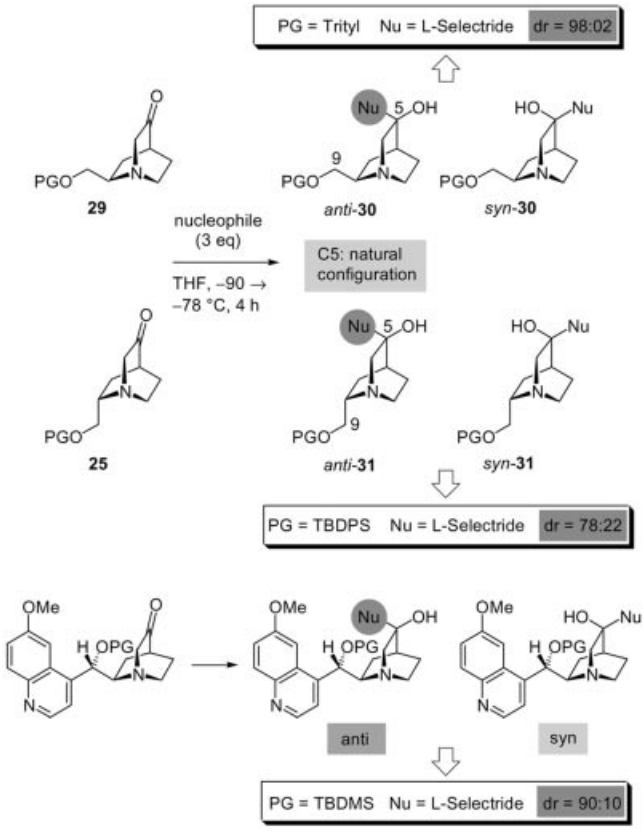


Scheme 17. Synthesis of QCI- and QCD-derived ketones; *reagents and conditions: a)* HBr (62%), 3 d, room temp.; *b)* DBU, DMF, 110 °C; *c)* R_3SiCl, Et_3N, DMAP, CH_2Cl_2, 0 °C → room temp., 10 h; *d)* K_2CO_3, $K_3[Fe(CN)_6]$, OsO_4, *t*BuOH/H_2O (1:1), 6 h, room temp.; *e)* $NaIO_4$, *t*BuOH/H_2O (1:1), 6 h, room temp.; *f)* TBAF, THF, 0 °C → room temp., 12 h.

carried out on a multigram scale in 30−35% overall yield, modelled on the earlier route to rubanone.[36] Shifting of the olefinic double bonds of the parent *Cinchona* alkaloids has recently attracted further interest, isomerization by treatment with rhodium on alumina having been reported.[40]

Because of their low-molecular weights (*mw* = 155) and their compact bicyclic structures, the diastereomeric quinuclidin-5-ones **28** and **29** are both attractive homochiral building blocks for asymmetric synthesis, pharmacology and combinatorial chemistry. Substrate control of stereochemistry in the reactions of ketones **28** and **29** with nucleophiles is a challenge greater than substrate control with the sterically more demanding parent *Cinchona* alkaloids. Nonetheless, face selectivity has been established, and nucleophilic attack has been directed preferentially toward the

supposedly more hindered *endo*-π-face of the carbonyl group, mainly giving the functionalized quinuclidinols ***anti*-30** and ***anti*-31** with natural configuration at C5 in diastereomeric excesses of up to 97% (Scheme 18).[39]

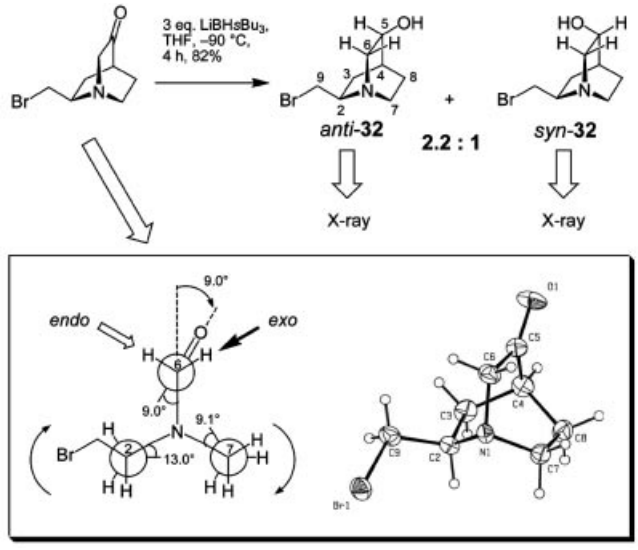


Scheme 18. Synthesis of substituted 2-(hydroxymethyl)quinuclidin-5-ols; masochistic nucleophilic attack on quinuclidinone helix

π-Face selectivity, especially in the QCD series, is unprecedented and strongly depends on the size of the remote *O*-protecting group: it is highest with bulky *O*-protecting groups, involving 1,7-stereoinduction (the bulk of the trityl group is evident from the fact that the dimeric hexaphenylethane does not exist). The origin of π-facial selectivity is believed to be due to helicity and torsional strain rather than electronic in nature. The X-ray crystal structure of 2-(bromomethyl)quinuclidin-5-one **29-Br** shows that its azabicyclic helix is twisted clockwise (Scheme 19).[41]

Thus, the "masochistic nucleophilic attack" from the sterically more demanding face is favoured, affording quinuclidinols with natural configuration at C5. The right-handed helicity is conserved during preferred nucleophilic addition from the *endo* face: the fully eclipsed high-energy C_{3v}-like conformation is bypassed en route to the major products ***anti*-30**, ***anti*-31** and ***anti*-32**. The stereochemical assignments at C5 have been confirmed by NOE experiments and by X-ray analyses of ***anti*-32** and ***syn*-32**.

Similarly, addition of vinylmagnesium bromide to the C3 carbonyl group of the quinidine-based rubanone directly provides the known major quinidine metabolite.[42] Again,



Scheme 19. Investigation of the origins of face selectivity (see also Figure 4): right-handed helicity

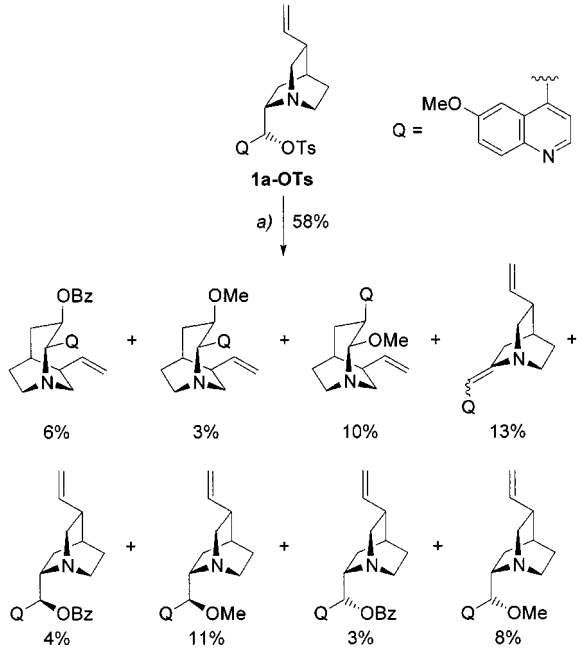
a surprising diastereoselectivity of up to 7:1 in favour of attack from the sterically more hindered π-face was observed (Scheme 18).[42] Similarly, the quinidine-derived ketone also traces out a right-handed helix.

5. Unusual Steric Course of Solvolysis of C9-Activated Alkaloids. Access to C9 *epi*-Configured Stereoisomers

Mapping the Hydrophilic Domain Through Aqueous Hydrolysis: Solvolytic displacements at saturated carbon are among the best known and most widely investigated reactions in organic chemistry. It is generally accepted that the steric course of solvolysis ranges from complete inversion of configuration to substantial and even complete racemization, depending on the stability and lifetime of any ion-pair and carbocation intermediates. In the past, hydrocarbons with tosyloxy leaving groups have usually been investigated in solvolyses. Substrates with a neighbouring basic amino function, as in *Cinchona* alkaloids, give rise to novel reactivity. The well defined conformations of *Cinchona* alkaloids and the presence or absence of the remote 6′-methoxy group also have to be considered (see "Second Cage Expansion" below).

Methanolysis of *O*-tosylated quinine **1a-OTs** may appear to be hopelessly complex (Scheme 20), and C9-functionalized *Cinchona* alkaloids were ignored completely even during the 1960s heyday of solvolytic work and controversy.

A change of leaving group (from **1a-OTs** to **1a-OMs**) gave a substrate that could be handled more easily and dissolved readily in water in the presence of tartaric acid (1 equivalent), which serves as proton donor and asymmetric catalyst. On heating to 100 °C, completely inverted 9-*epi*-

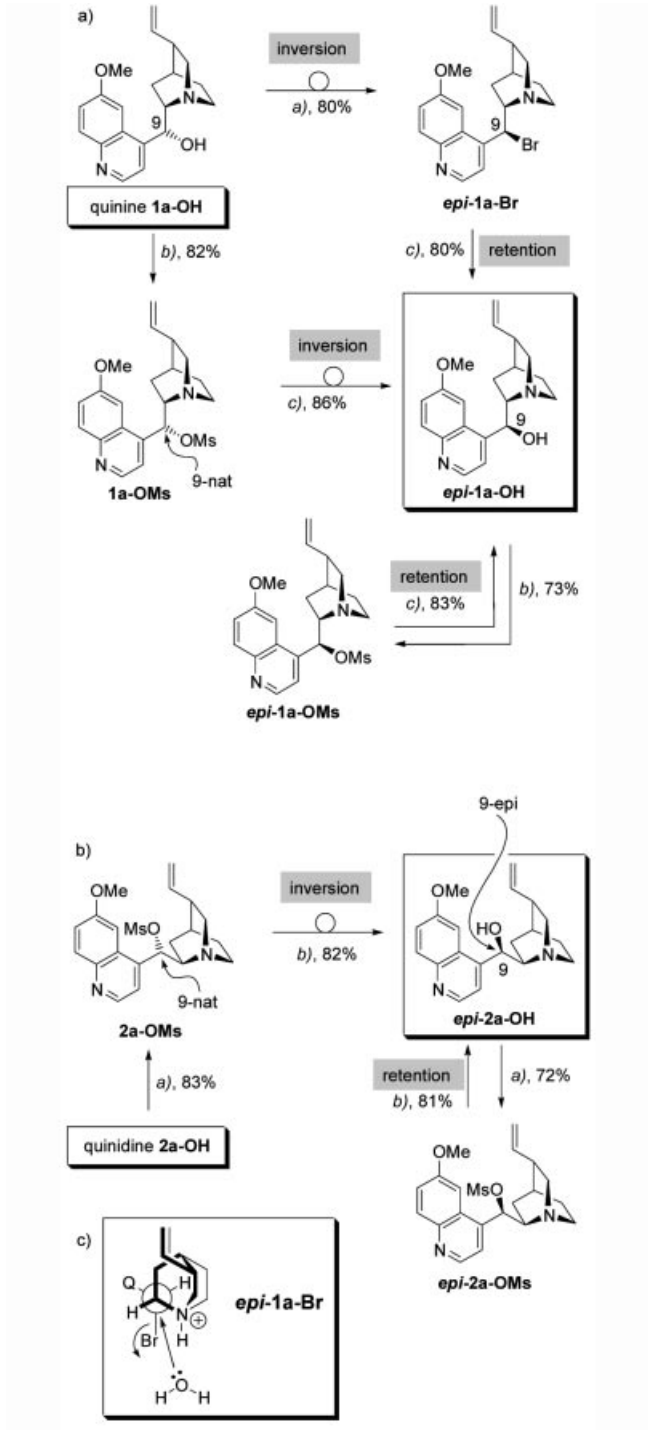


Scheme 20. Methanolysis of *O*-tosylated quinine **1a-OTs**; *reagents and conditions: a)* $C_6H_5CO_2Na$ (2 equiv.), MeOH, reflux, 12 h

quinine ***epi*-1a-OH** was obtained as the only product in a *spot-to-spot* reaction and in good yield (Scheme 21, a).[43]

Similarly, the 9-*epi*-quinine mesylate ***epi*-1a-OMs** was subjected to aqueous hydrolysis in the presence of tartaric acid at ca. 100 °C. In this case 9-*epi*-quinine ***epi*-1a-OH** was again formed, but with complete *retention* of configuration! In an analogous sequence, pseudo-enantiomeric quinidine **2a-OH** was converted into its mesylate and hydrolysed, furnishing 9-*epi*-quinidine ***epi*-2a-OH** with complete *inversion* of configuration. Hydrolysis of *O*-mesylated *epi*-quinidine ***epi*-2a-OMs** proceeded with complete *retention* of configuration. The results from the quinidine series (Scheme 21, b) support the quinine work (Scheme 21, a). A change in the leaving group made no difference: both C9-*epi*-bromides and C9-*epi*-mesylates gave the alcohol with *retention* of configuration, and quinine and quinidine, the products of inversion, were not formed. Put another way, 9-*epi*-quinine ***epi*-1a-OH** is formed ***both from*** 9-*nat* ***and from*** 9-*epi* precursors **1a-OMs** and ***epi*-1a-OMs**. Similarly, 9-*epi*-quinidine ***epi*-2a-OH** arises from both 9-*nat* and 9-*epi*-precursors **2a-OMs** and ***epi*-2a-OMs**.

We have suggested that this surprising finding is due to conformational control and to molecular recognition of solvent water through hydrogen bonding in the presence of tartaric acid. C9-*epi*-Quinine is believed to adopt a conformation containing a hydrophilic pocket with the leaving group and the (protonated) bridgehead nitrogen. This pocket is open to retentive solvolysis (Scheme 21, c).[43] The bonding motif in the *epi* series is reminiscent of the postulated chelation of **12-OMs** by excess Li^+ (Scheme 6). For the C9-*nat*-configured alkaloids, on the other hand, the leaving group X and the protonated amino nitrogen are on opposite faces (Scheme 31), and inversion of configuration is strongly favoured. We have applied the inversion procedure to prepare all four *epi*-configured *Cinchona* alkaloids: *epi*-quinine (***epi*-1a-OH**), *epi*-quinidine

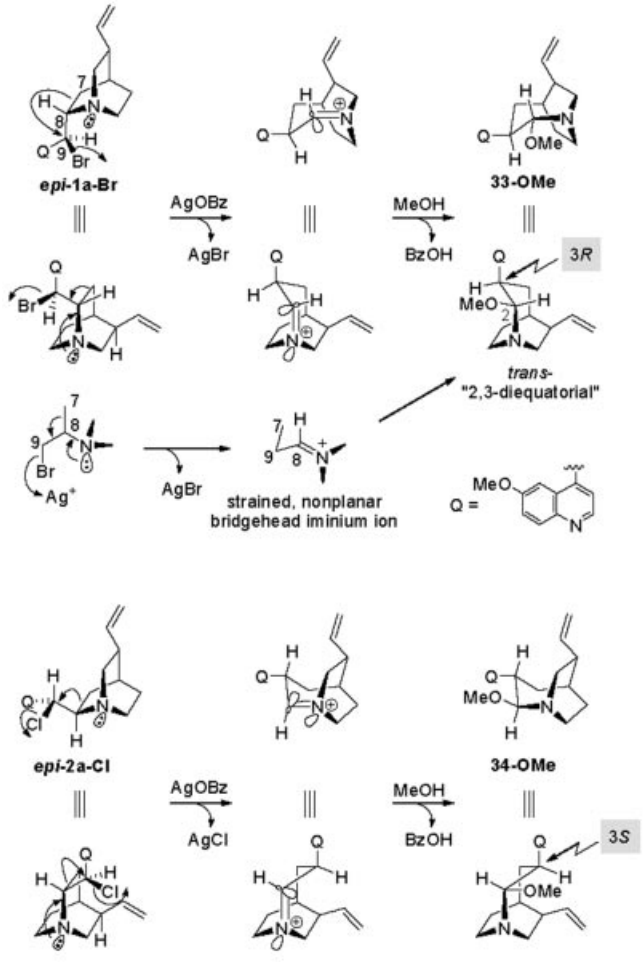


Scheme 21. Hydrolysis with complete inversion and complete retention of configuration (tartaric acid present); a) activated quinine; b) activated quinidine; c) in the rotamer shown in Scheme 21 (part c) the bulky 1-azabicyclo[2.2.2]octane moiety faces the single H(C9) hydrogen; *reagents and conditions*: *a)* PPh_3, CBr_4, toluene, 20 °C, 12 h; *b)* MsCl, Et_3N, THF, reflux, 4 h; *c)* tartaric acid, H_2O, ca. 100 °C, 0.5 h

(***epi*-2a-OH**), *epi*-cinchonidine (***epi*-1b-OH**) and*epi*-cinchonine (***epi*-2b-OH**).

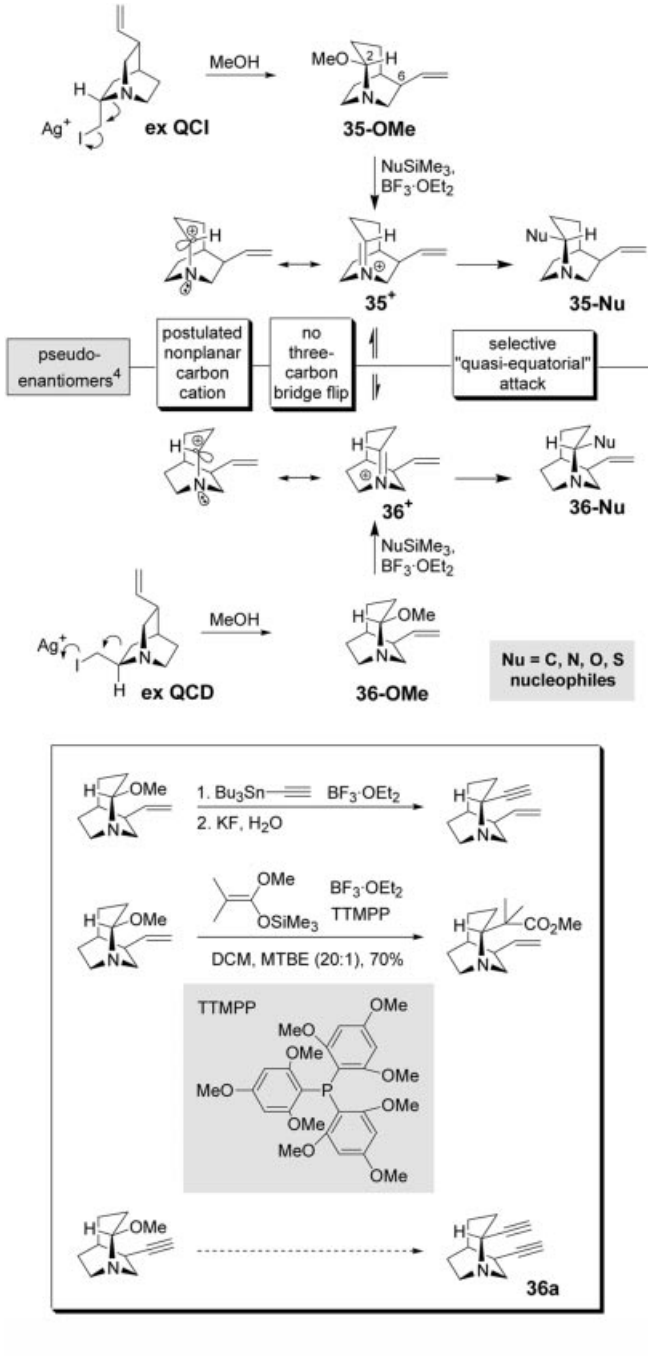
6. "First *Cinchona* Rearrangement"

The silver benzoate-assisted reaction of 9-*epi*-quinine with bromide as leaving group (***epi*-1a-Br**) in methanol furnishes a cage-expanded 1-azabicyclo[3.2.2]nonane with the methoxy group α to the bridgehead nitrogen. This rearrangement is stereoelectronically favourable, involving a shift of the (*non-protonated*) nitrogen lone pair, a nucleophilic shift of carbon C7 to C9, and stereocontrolled external capture of a strained, non-planar bridgehead iminium ion by the nucleophile. In the observed Braje products, the quinolyl and methoxy groups adopt a quasi *trans*-2,3-diequatorial orientation. In the analogous sequence, quinidine, with the C9-*epi*-configured chlorine leaving group, provides the pseudo-enantiomeric[4] α-methoxyamine (Scheme 22).[44] All five chirality centres in the starting materials ***epi*-1a-Br** and ***epi*-2a-Cl** are neatly transposed into the stereocentres of the cage-expanded product.



Scheme 22. "First *Cinchona* cage expansion" of 9-*epi*-configured bromoquinine ***epi*-1a-Br** and 9-*epi*-configured chloroquinidine ***epi*-2a-Cl** mediated by silver ion

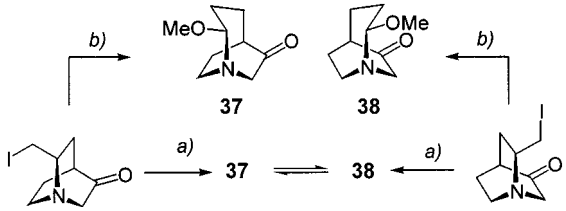
More recently, the "first *Cinchona* cage expansion" has also been accomplished for quincorine and quincoridine (Scheme 23).[15] There are substantial barriers to flipping of the tight 3-carbon bridges, with the limits of the Bredt rule being tested. The rearrangement proceeds stereoselectively under mild S_N1-like conditions and tolerates additional functionality such as carbonyl and ester groups, as well as terminal alkynes. Evidence of the stereochemical outcome was provided by NOE experiments and X-ray analysis.[45]



Scheme 23. First *Cinchona* cage expansion of quincorine and quincoridine; distinct bridgehead iminium ions **35**$^+$ and **36**$^+$ and their stereospecific capture by nucleophiles

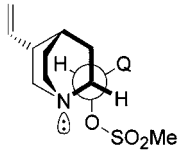
In the presence of nucleophiles, Lewis acid-mediated cleavage of α-amino ethers **35-OMe** and **36-OMe** affords a variety of enantiopure substituted 1-azabicyclo[3.2.2]nonanes, which are formed in S_N1-like reactions and with complete stereocontrol. There is no leakage into pseudo-enantiomeric **36-Nu** en route to product **35-Nu** or vice versa. The carbocation is pyramidalized with imperfect orbital overlap,[46] and model calculations suggest that the carbenium carbon is above the trigonal plane by ca. 36°. A variety of Lewis acids and nucleophiles were screened for the preparation of **35-Nu** and **36-Nu**. At first, simple alkylation, vinylation and ethynylation proved difficult. Use of Me_3SiCN provides new Strecker-type α-aminonitriles, whereas new β-amino acid esters can be prepared directly by two-carbon homologation with silylated ketene acetal (Nu = $Me_2C{=}CO_2SiR_3$) and $BF_3{\cdot}OEt_2$ as Lewis acid and TTMPP [tris(trimethoxyphenyl)phosphane] as co-catalyst.[15b] Dead-end complexation of the bridgehead amino nitrogen by the Lewis acid and a narrow trajectory of nucleophilic attack of the iminium ion probably impede some of the desired displacements. Diterminal enynes **35-C≡CH** and **36-C≡CH** are potential chiral spacers in supramolecular chemistry, possessing well defined geometries, whereas hydroxy esters and novel amino acids should be of use in combinatorial chemistry. The corresponding diynes, which are of interest for cyclooligomerization,[47] have not yet been prepared (cf. **36a** from QCD and also diyne **18e** from QCI in Scheme 12).

Even QCI- and QCD-derived 2-iodomethyl ketones afford ring-expanded 1-azabicyclo[3.2.2]nonan-6-ones **37** and **38**, respectively, although in a more sluggish reaction. Surprisingly, given the high stereoselectivity exhibited by the other silver triflate-mediated cage expansions, partial epimerization was observed upon treatment of iodo ketones with AgOTf (**37** → 80:20 and **38** → 68:32). Silver benzoate-promoted rearrangement of iodo ketones, however, gave epimerically pure ketones **37** and **38** (Scheme 24).



Scheme 24. Ring expansion of 2-iodomethylquinuclidin-5-ones: a further molecular diversity connector; *reagents and conditions: a)* AgOTf (1.1 equiv.), MeOH, 50 °C; *b)* AgOBz (1.1 equiv.), MeOH, 50 °C

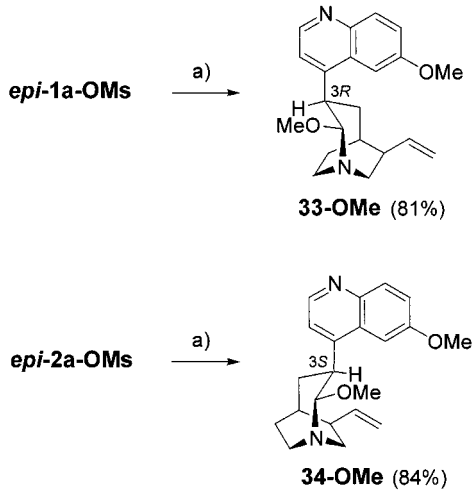
The "first *Cinchona* rearrangement" is also feasible without Ag^+, provided that stringent stereochemical and experimental conditions are fulfilled. In the preferred conformation of ***epi*-1a-OMs**, the C9-OMs leaving group and the migrating C7−C8 σ-bond are antiperiplanar (Schemes 21 and 25).



***epi*-2a-OMs**

Scheme 25. C9-*epi* configured quinidine mesylate: the conformer is set up for the "first *Cinchona* rearrangement" (see also Scheme 21, c)

Under optimized conditions with NaOBz as a buffer (for the liberated methanesulfonic acid), α-amino ether **33-OMe** was formed in 81% yield (Scheme 26), whereas *pseudo*-enantiomeric[4] α-amino ether **34-OMe** could be obtained in 84% yield.

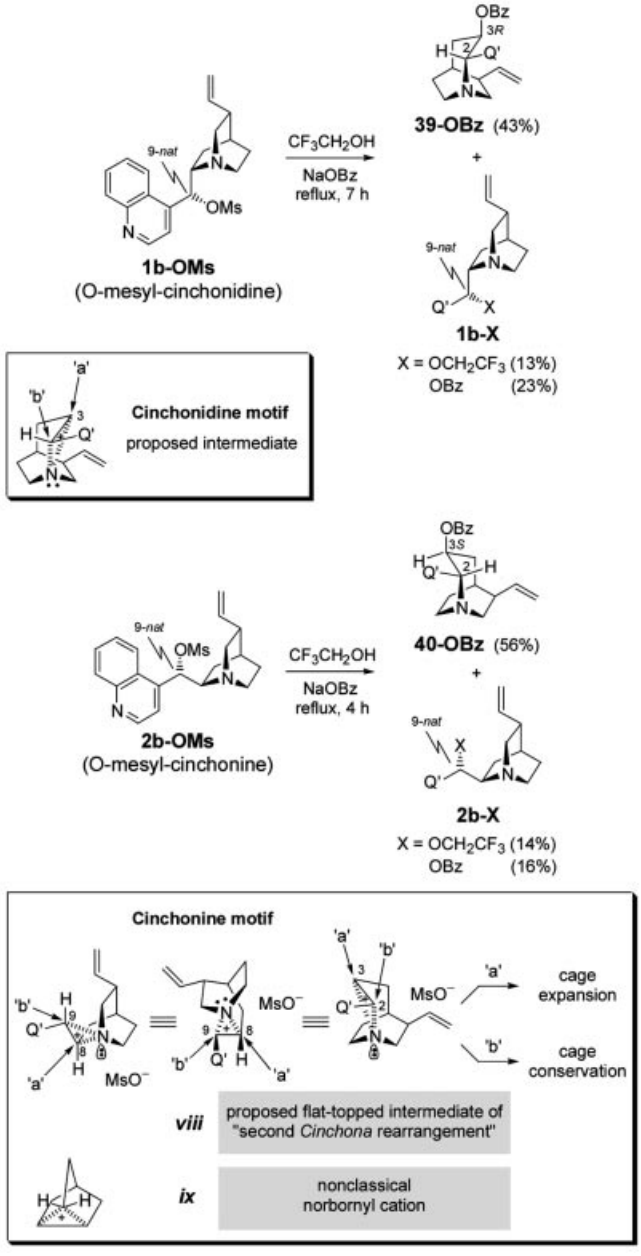


Scheme 26. First *Cinchona* cage-expansion of *epi*-configured *O*-mesylated quinine ***epi*-1a-OMs** and quinidine ***epi*-2a-OMs**; preparation of α-amino ethers **33-OMe** and **34-OMe**; *reagents and conditions: a)* NaOBz (2 equiv.), MeOH, reflux, 2 h

7. "Second *Cinchona* Rearrangement"

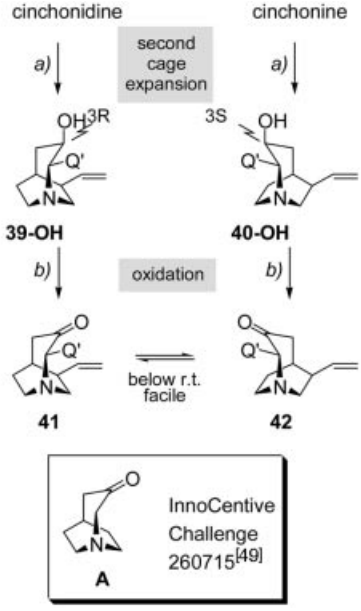
As shown in Scheme 20, methanolysis of *O*-tosylated quinine (**1a-OTs**) afforded a host of products that had to be carefully chromatographed and individually identified after separation. In fact, it would have been tempting to consign the reaction mixture to the dustbin at this stage of the investigation (Scheme 20). However, the *cinch* bases (6′-R = H) cinchonidine **1b-OH** and cinchonine **2b-OH** behave differently. Especially in trifluoroethanol as solvent, the C9 mesylates of *cinch* bases undergo cage expansion to give the Röper products **39-OBz** and **40-OBz**, β-functionalized amines that arise side-by-side with the products of stereoretentive, cage-conserving solvolysis (Scheme 27).

Alternatively, the cage-expanded alcohols **39-OH** (3*R* configuration) and **40-OH** (3*S* configuration) have been prepared in simple complementary fashion from the mesylates in pure water. The hydrolysis of the mesylates can be



Scheme 27. "Second *Cinchona* rearrangement"; effect of a change to *O*-mesylated *cinch* base (6′-R = H) and trifluoroethanol as solvent

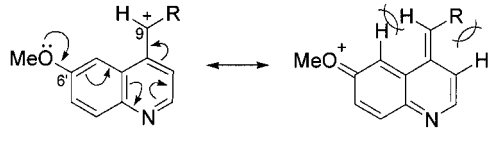
viewed as *green chemistry*, since methanesulfonic acid is inexpensive, biodegradable and toxicologically harmless. Oxidation provides the corresponding amino ketones **41** and **42**, which each have a relatively acidic α-proton and are equilibrated spontaneously below room temperature: enolization is a rational pathway and is also consistent with deuterium uptake at C2 when the ketones are dissolved in MeOD (Scheme 28).[48] The pseudo-enantiomeric[4] barrier between cage-expanded 1,2-amino alcohols **39-OH** and **40-OH** can thus easily be broken after oxidation to ketones. The synthesis of the deceptively simple 1-azabicyclo[3.2.2]nonan-3-one (**A**) was recently put forward as an InnoCentive challenge at US$ 70 000.[49] The offer was withdrawn while our work was being considered for publication.



Scheme 28. Preparation of bicyclic amino ketones **41** and **42**; oxidation breaks the *pseudo*-enantiomeric barrier

We have formulated the "second Cage Expansion" as proceeding via the nitrogen-bridged cation ***viii*** (Scheme 27) as an intermediate. Note that this is not a conventional tetrahedral ammonium ion. The two-electron, three-centre 9-*Cinchona* cation has a nonclassical character because four ligands around the bridging nitrogen are constrained in one hemisphere. The nitrogen lone pair is in the second imaginary hemisphere and represents a fifth valence (the bulky Q' moiety points away from the azabicyclic core and towards the observer). The delocalized 9-*Cinchona* cation ***viii*** (Scheme 27) can be compared with delocalized nonclassical 2-norbornyl cation ***ix***,[50] in which bridging of pentacoordinate carbon is constrained by the nortricyclic scaffold. Cation ***viii*** accounts for reversibility of the cage-expansion and retention of configuration (= double inversion) on nucleophilic attack of carbon C9 (Scheme 27, box).

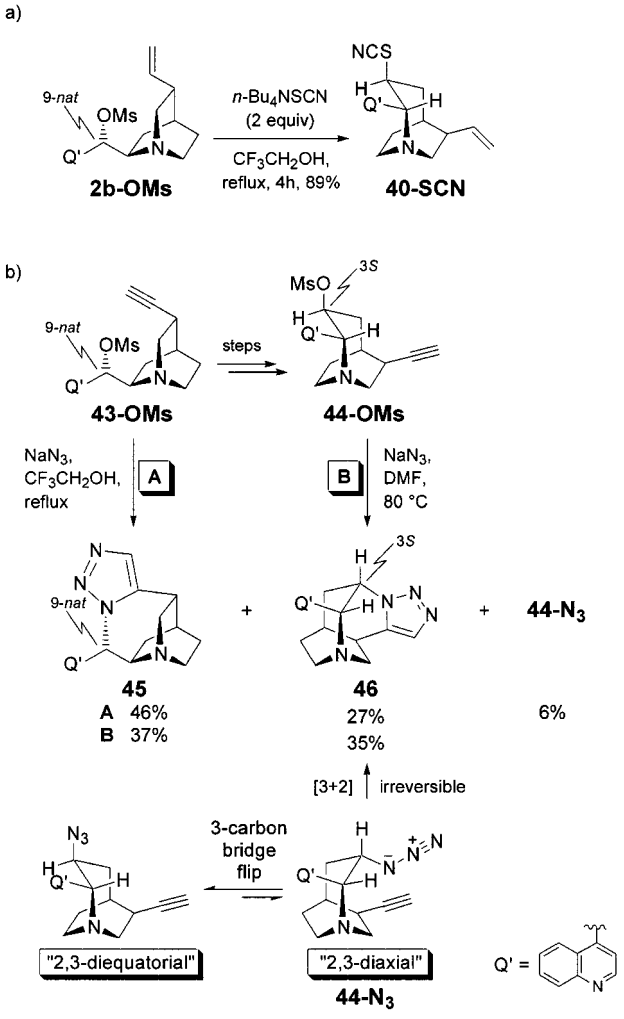
In general, cinch bases (6′-R = H) are more prone to bridging (cf. ***viii***) than quinine and quinidine (6′-R = OMe), in which the methoxy donor facilitates electron delocalization and reduces electron demand at C9 (Scheme 29). The migrating aptitude of the bridgehead nitrogen also depends



Scheme 29. Quinine/quinidine (6′-R = OMe) versus *cinch* bases (6′-R = H); oxonium resonance disfavours C−N bridging in planar 6′-methoxy-stabilized 9-*Cinchona* cation

on conformation, solvent ionizing power and pH (non-protonated bridgehead nitrogen).

The "second Cage Expansion" is open to many variations and has been carried out in the presence of added nucleophiles under S_N1-like conditions. With added thiocyanate ion, cage expansion is especially efficient (Scheme 30, a; see ref.[52]). With added azide ion (Scheme 30, b), a cascade reaction occurs, being terminated by 1,3-dipolar cycloaddition to give triazoles (**45** and **46**), which are of general interest as antifungals. The reversibility of the rearrangement has been clearly demonstrated (Scheme 30, a−b).[51] As an example, the cage-expanded 1,5-diazatricyclo[4.4.1.$0^{3,8}$]undecane derivative **46** is formed from **43-OMs** under S_N1-like conditions. Equally, isomeric mesylate **44-OMs**, which contains a quasi-equatorial and stereoelectronically favourable mesyloxy leaving group, forms both the tricyclic **46**, through cage conservation and also homo-twistane **45**, through cage-contraction. Thus, route **A** and route **B** are remarkably convergent with respect to their product spectra. The skeletons and stereochemistry of both **43-OMs** and **44-OMs** are linked by the second *Cinchona* rearrangement and an *N*-bridged cation such as ***viii*** (Scheme 27). Termination by *trans*-annular 1,3-dipolar cycloaddition is, of course, not feasible in the pseudo-enantiomeric cinchonidine (quinine) series. In this case the C9-azide moiety and the ethynyl (vinyl) acceptor are remote from each other.



Scheme 30. Cascade reactions of **43-OMs** and **44-OMs** with azide ion under strongly ionizing conditions

A general cage expansion and solvolysis scheme together with a set of general guidelines for both *Cinchona* rearrangements has recently been put forward and is in excellent agreement with the experimental evidence so far accumulated by us (Scheme 31).[52]

As yet, the 1-azabicyclo[3.2.2]nonane scaffold has been encountered in nature only rarely: in, for example, tronoharine **47**, vincathicine **48** and communesin B **49** (Scheme 32). Tronoharine **47**, obtained from the stem bark extract of the Malayan plant *Tabernaemontana corymbosa* and structurally assigned in 1999, represents a previously unencountered indole alkaloid bearing a hexacyclic carbon skeleton.[53] Vincathicine **48**, related to dimeric vinca alkaloids such as the cytostatic vinblastine and vincristine, was structurally elucidated by a Lilly group in 1976.[54] The communesins A−C, exhibiting cytotoxic activity, were isolated from the mycelium of strains of *Penicillium sp.* in the marine alga *Enteromorphia intestinalis*[55] or the sponge *Axinella verrucosa*.[56]

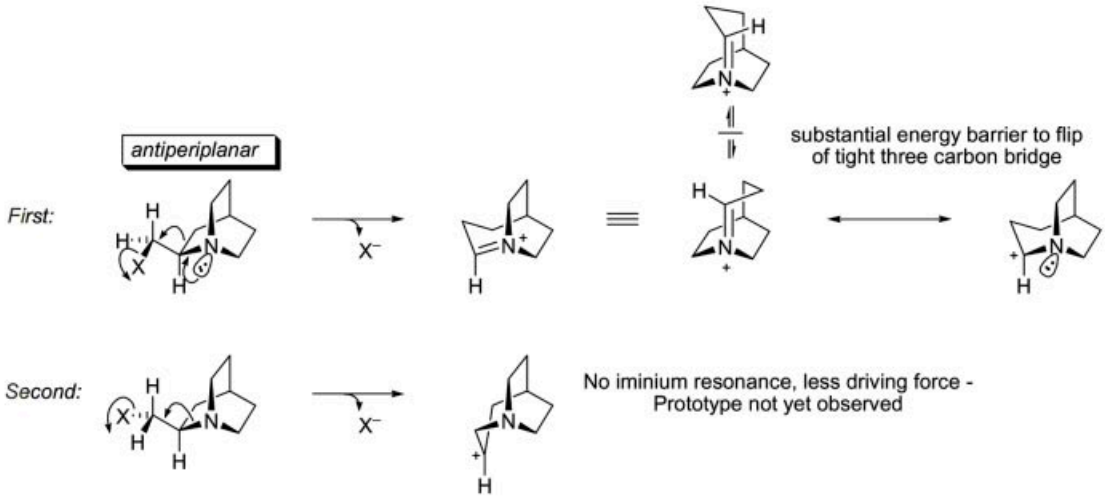
Communesin B **49** has a rigid heptacyclic framework, and only one synthetic approach toward its skeleton has been published.[57] The isolation and identification of "nomofungin" has been retracted recently.[58] The challenge of 1-azabicyclo[3.2.2]nonane scaffolds as synthetic targets, their biosynthesis and the intrinsic interest of polycyclic natural products as a source of new drug leads are obvious.

8. Conclusion

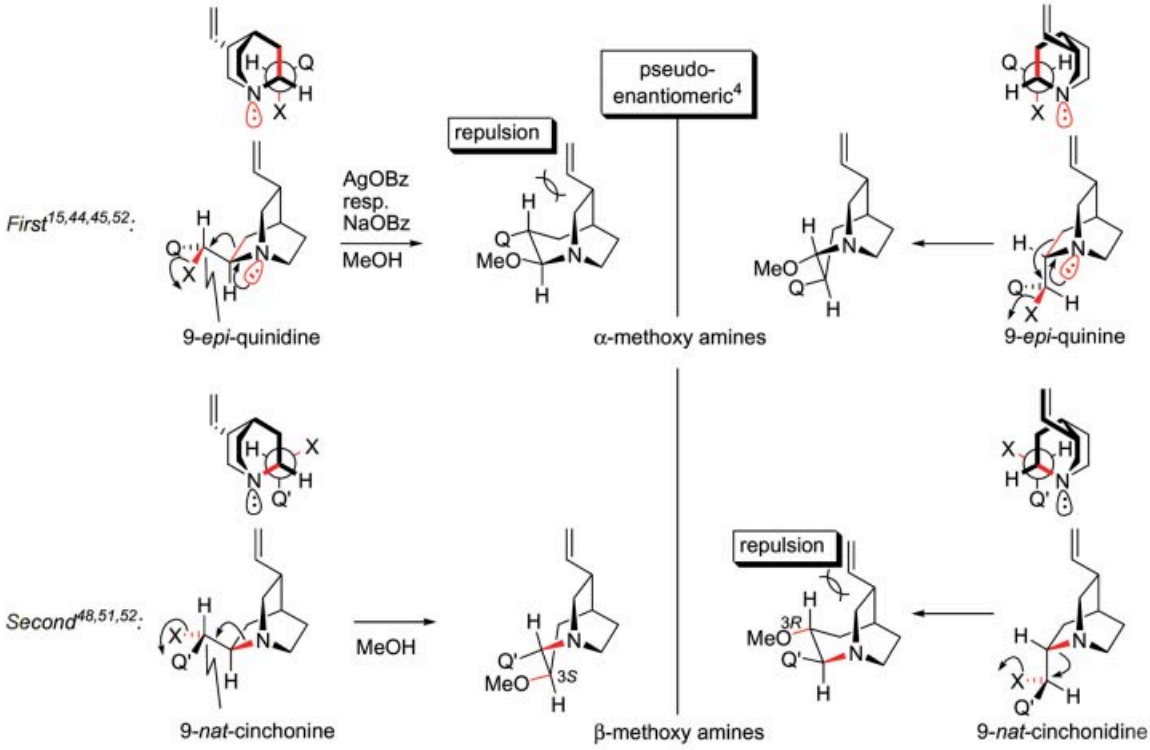
During the last seven years or so, *Cinchona* alkaloids have come of age. New enantiopure materials include the *Cinchona* alkyne family and also quincorine and quincoridine, which have given rise to novel classes of ligands ("the smaller the better") for catalytic asymmetric syntheses. In this context, pseudo-enantiomerism and azabicyclic helicity have served as a handrail for exploration of structure, reactivity, remote stereoinduction and mechanism. *Cinchona* alkaloids have been induced to undergo some baffling molecular reorganisations and solvolytic displacements. The preparation and availability of all four C9 *epi*-configured substrates from quinine, quinidine, cinchonidine and cinchonine have helped us to elucidate the various pathways. In depicting the molecules three-dimensionally we are reminded of the wrappings of Christo, the more familiar aspects of the molecular architecture, including the bulky quinoline moiety, being hidden and decisive stereoelectronic and other features being brought out from another perspective, such as in the projection formulae of Scheme 31. The "first and second *Cinchona* cage expansions" afford a range of functionalized 1-azabicyclo[3.2.2]nonanes with full trans-

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)

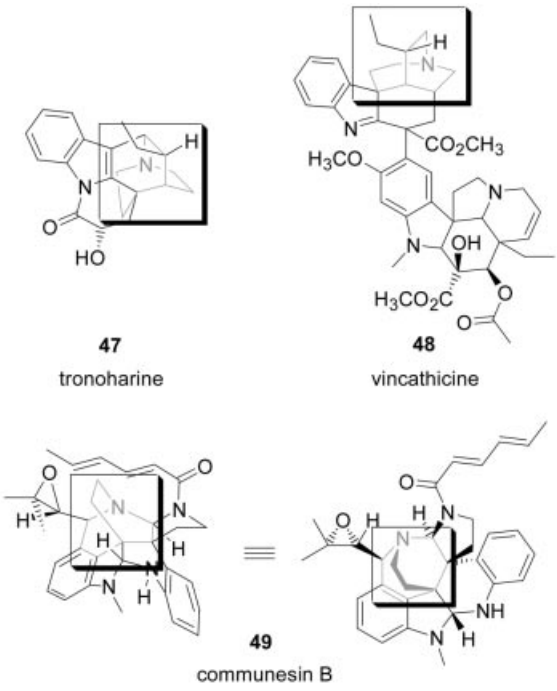


Migratory aptitude depends on configuration at C9, conformation, stereoelectronic factors, leaving group ability, solvation and acidity (protonation of bridgehead nitrogen).
In H_2O + *tartaric acid* the [2.2.2]azabicyclic cage is conserved (6'-R = OMe):

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

Extension to *cinch* bases feasible, although they are likely to undergo the second rearrangement, depending on concentration of tartaric acid.[52] 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).

Scheme 31. General *Cinchona* alkaloid cage expansion and solvolysis scheme



Scheme 32. Natural products with 1-azabicyclo[3.2.2]nonane nucleus, **47**−**49**

position of all five chiral centres and with multiple diversity connectors for combinatorial studies. These fundamental and innovative transformations and the cascade of ensuing products are expected to stimulate *Cinchona* alkaloid chemistry for years to come.

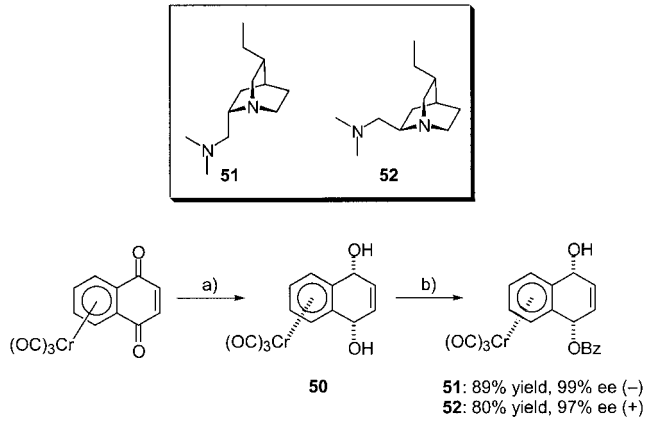
9. Notes Added on Revision

After the above had been written, Kündig et al. reported a highly stereoselective desymmetrization of a chromium *meso*-diol complex **50** through low-temperature acylation with the two quincorine- and quincoridine-derived diamines **51** and **52** as chiral catalysts (Scheme 33).[59] Either planar chromium complex is thus readily accessible with high enantioselectivity.

Furthermore, the reaction mediated by QCI and QCD derivatives stops after a first acyl transfer and no dibenzoyl complex is formed, whereas other diamine catalysts also afforded unstable dibenzoate complexes.

The synthesis and structures of Pd^{II} and Pt^{II} complexes of quincorine and quincoridine derivatives have also been studied.[60]

X-ray crystal structure analysis was performed on single crystals of QCI and QCD as their salts with tartaric and *p*-toluenesulfonate anions.[61] A comparison of the conformational features of QCI, QCD and the parent *Cinchona* alkaloids in the crystalline state shows that the molecular geometry of QCI and QCD is similar to that of *epi*-alkaloids rather than to that of quinine and quinidine.



Scheme 33. Desymmetrization of a *meso*-dihydronaphthalenediol complex through asymmetric acylation; *reagents and conditions: a)* $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 5 min, 82%; *b)* BzCl (1.5 equiv.), Et_3N (1.0 equiv.), 4-Å molecular sieves, CH_2Cl_2, diamine catalysts **51** and **52**

New chiral P,N-bidentate amino phosphoramidites have been prepared by one-step phosphorylation of QCI and QCD. These novel ligands proved to be effective in Pd-catalysed asymmetric allylic substitution.[62]

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[1] [1a] G. Stork, D. Niu, A. Fujimoto, E. R. Koft, J. M. Balkovec, J. R. Tata, G. R. Dake, *J. Am. Chem. Soc.* **2001**, *123*, 3239. [1b] I. T. Raheem, S. N. Goodman, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 706. [1c] J. Igarashi, M. Katsukawa, Y.-G. Wang, H. P. Acharya, Y. Kobayashi, *Tetrahedron Lett.* **2004**, *45*, 3783; see also ref.[25] and two accompanying papers.

[2] [2a] D. C. McHale, *The Biologist* **1986**, *33*, 45. [2b] F. Eiden, *Pharmazie in unserer Zeit* **1998**, *27*, 257. [2c] P. M. Dewick, *Medicinal Natural Products*, John Wiley & Sons, Chichester, New York, **1997**, 335−338. [2d] J. Herrmann, *Pharm. Ztg.* **2001**, *146*, 1486.

[3] [3a] *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2003**. [3b] C. von Riesen, personal communication. [3c] R. Dagani, *Chem. & Eng. News* **1995**, *73*, 33. [3d] S. C. Stinson, *Chem. & Eng. News* **1995**, *73*, 44. [3e] For a recent review see K. Kacprzak, J. Gawronski, *Synthesis* **2001**, 961. [3f] S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985.

[4] Replacement of the vinyl group by hydrogen generates enantiomers.

[5] [5a] L. Pasteur, *Compt. Rend. Acad. Sci.* **1853**, *37*, 113. [5b] W. v. Miller, G. Rohde, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1187. [5c] W. v. Miller, G. Rohde, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1279. [5d] W. v. Miller, G. Rohde, *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 1056. [5e] W. v. Miller, G. Rohde, *Ber. Dtsch. Chem. Ges.* **1901**, *33*, 3214. [5f] G. Rohde, G. Schwab, *Ber. Dtsch. Chem. Ges.* **1905**, *34*, 306.

[6] W. E. Doering, J. D. Chanley, *J. Am. Chem. Soc.* **1946**, *68*, 586.
[7] [7a] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483. [7b] R. A. Johnson, K. B. Sharpless, *Catalytic Asymmetric Dihydroxylation*, in *Catalytic Asymmetric Synthesis* (I. Ojima, Ed.), Wiley-VCH, Weinheim, **1993**. [7c] K. C. Nicolaou, E. Sorensen, *Classics in Total Synthesis*, Wiley-VCH, Weinheim, **1996**. [7d]E. J. Corey, M. C. Noe, M. J. Grogan, *Tetrahedron Lett.* **1994**, *35*, 6427.
[8] [8a] M. J. O′Donnell, Z. Fang, X. Ma, J. C. Huffman, *Heterocycles* **1997**, *46*, 617. [8b] M. J. O′Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353. [8c] B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595. [8d] E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414. [8e] E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347. [8f] E. J. Corey, F.-Y. Zhang, *Org. Lett.* **2000**, *2*, 1097. [8g] M. Horikawa, J. Busch-Petersen, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 3843. [8h] E. J. Corey, F.-Y. Zhang, *Org. Lett.* **1999**, *2*, 2057. [8I] E. J. Corey, F.-Y. Zhang, *Angew. Chem.* **1999**, *111*, 2057.
[9] J. Crosby, *Chirality in Industry* (A. N. Collins, G. N. Sheldrake, J. Crosby, Eds.), John Wiley & Sons, New York, **1992**, pp. 19−20.
[10] [10a] H. M. R. Hoffmann, T. Plessner, C. von Riesen, *Synlett* **1996**, 690. [10b] Quincorine and quincoridine represent the cores of quinine and quinidine. In German, ′cor′ can also stand for "*C ohne Rest*" (C without residue) as in ′nor′ "*N ohne Rest*" (N without residue, e.g. adrenaline and noradrenaline).
[11] O. Schrake, V. S. Rahn, J. Frackenpohl, W. M. Braje, H. M. R. Hoffmann, *Org. Lett.* **1999**, *1*, 1607.
[12] [12a] S. J. Rowan, J. K. M. Sanders, *J. Org. Chem.* **1998**, *63*, 1536. [12b] S. J. Rowan, D. J. Reynolds, J. K. M. Sanders, *J. Org. Chem.* **1999**, *64*, 5804.
[13] J. Frackenpohl, *PhD Thesis*, University of Hannover, **2000**.
[14] O. Schrake, M. H. Franz, H. M. R. Hoffmann, *Tetrahedron* **2000**, *56*, 4453.
[15] [15a] S. Röper, J. Frackenpohl, O. Schrake, R. Wartchow, H. M. R. Hoffmann, *Org. Lett.* **2000**, *2*, 1661. [15b] S. Röper, R. Wartchow, H. M. R. Hoffmann, *Org. Lett.* **2002**, *4*, 3179.
[16] I. Neda, T. Kaukorat, C. Hrib, *Tetrahedron: Asymmetry* **2002**, *13*, 1327.
[17] C. von Riesen, R. Wartchow, H. M. R. Hoffmann, *Z. Kristallogr. NCS* **1998**, *213*, 483.
[18] I. Neda, T. Kaukorat, A. Fischer, *Eur. J. Org. Chem.* **2003**, 3784.
[19] [19a] C. Saluzzo, J. Breuzard, S. Pellet-Rostaing, M. Vallet, F. Le Guyader, M. Lemaire, *J. Organomet. Chem.* **2002**, *643−644*, 98−104. [19b] M. Lemaire, S. Pellet-Rostaing, J. Breuzard, R. T. Halle, C. Saluzzo, M. Vallet, *Fr. Demande* **2001**, 2810666. [19c] S. Pellet-Rostaing, C. Saluzzo, R. T. Halle, J. Breuzard, L. Vial, F. L. Guyader, M. Lemaire, *Tetrahedron: Asymmetry* **2001**, *12*, 1983.
[20] A. Hartikka, S. A. Modin, P. G. Andersson, P. I. Arvidsson, *Org. Biomol. Chem.* **2003**, *1*, 2522.
[21] [21a] S. F. M. Nordin, P. Roth, T. Tarnai, D. A. Alonso, P. Brandt, P. G. Andersson, *Chem. Eur. J.* **2001**, *7*, 1431 and references cited therein. [21b] R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40; *Angew. Chem. Int. Ed.* **2001**, *40*, 40.
[22] J. Frackenpohl, W. Braje, H. M. R. Hoffmann, *J. Chem. Soc., Perkin Trans. 1* **2001**, 47.
[23] [23a] W. M. Braje, J. Frackenpohl, O. Schrake, R. Wartchow, W. Beil, H. M. R. Hoffmann, *Helv. Chim. Acta* **2000**, *83*, 777. [23b] O. Schrake, W. M. Braje, H. M. R. Hoffmann, R. Wartchow, *Tetrahedron: Asymmetry* **1998**, *9*, 3717.
[24] W. M. Adam, *PhD thesis*, University of Hannover, **2003**.
[25] G. Grethe, H. L. Lee, T. Mitt, M. R. Uskokovic, *J. Am. Chem. Soc.* **1978**, *100*, 581.
[26] [26a] V. S. Rahn, *Diploma thesis*, University of Hannover, **1999**. [26b]E. V. Dehmlow, S. Duttmann, B. Neumann, H.-G. Stammler, *Eur. J. Org. Chem.* **2002**, 2087; the X-ray crystal structure in Figure 5 of this paper belongs to the quinine series, but is not identical to either **5** or **6** (compound numbering of the Dehmlow publication), which belong to the quinidine series.
[27] The structure of enediyne was corroborated by X-ray crystal diffraction: I. Neda, personal communication.
[28] R. Wartchow, J. Frackenpohl, H. M. R. Hoffmann, *Z. Kristallogr. NCS* **2001**, *216*, 235.
[29] M. C. Seidel, R. Smits, C. B. W. Stark, O. Gaertzen, J. Frackenpohl, H. M. R. Hoffmann, *Synthesis* **2004**, 1391.
[30] E. L. Eliel, S. H. Wilen, M. P. Doyle, *Basic Organic Stereochemistry*, Wiley-Interscience, New York, **2001**.
[31] [31a] For further discussion of this multifactorial problem see: P. Rademacher, K. Kowski, H. M. R. Hoffmann, L. O. Haustedt, J. Holzgrefe, *ChemPhysChem* **2002**, *3*, 957. [31b] R. Wartchow, list of X-ray studies, personal communication.
[32] [32a] Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219. [32b] see also: P. Langer, *Angew. Chem.* **2000**, *112*, 4503; *Angew. Chem. Int. Ed.* **2000**, *39*, 3049.
[33] [33a] Y. Iwabuchi, T. Sugihara, T. Esumi, S. Hatakeyama, *Tetrahedron Lett.* **2001**, *42*, 7867. [33b] Y. Iwabuchi, M. Furukawa, T. Esumi, S. Hatakeyama, *Chem. Commun.* **2001**, 2030. [33c] M. Shi, J.-K. Jiang, *Tetrahedron: Asymmetry* **2002**, *13*, 1941. [33d] D. Balan, H. Adolfsson, *Tetrahedron Lett.* **2003**, *44*, 2521. [33e] For early work on the Baylis-Hillman reaction see: H. M. R. Hoffmann, J. Rabe, *Angew. Chem.* **1983**, *95*, 795, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 795; J. Rabe, H. M. R. Hoffmann, *Angew. Chem.* **1983**, *95*, 796, *Angew. Chem. Int Ed.* **1983**, *22*, 796.
[34] M. A. Baur, A. Riahi, F. Hénin, J. Muzart, *Tetrahedron: Asymmetry* **2003**, *14*, 2755.
[35] W. Braje, J. Frackenpohl, P. Langer, H. M. R. Hoffmann, *Tetrahedron* **1998**, *54*, 3495.
[36] [36a] C. von Riesen, P. G. Jones, H. M. R. Hoffmann, *Chem. Eur. J.* **1996**, *2*, 673. [36b] C. von Riesen, H. M. R. Hoffmann, *Chem. Eur. J.* **1996**, *2*, 680.
[37] [37a] J. Thiel, A. Katrusiak, *Tetrahedron: Asymmetry* **2002**, *13*, 47. [37b] J. Thiel, P. Fiedorow, *J. Mol. Struct.* **1998**, *440*, 203.
[38] [38a] G. Nordvall, S. Sundquist, L. Nilvebrant, U. Hacksell, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2837. [38b] G. Johansson, S. Sundquist, G. Nordvall, B. M. Nilsson, M. Brisander, L. Nilvebrant, U. Hacksell, *J. Med. Chem.* **1997**, *40*, 3804.
[39] J. Frackenpohl, H. M. R. Hoffmann, *J. Org. Chem.* **2000**, *65*, 3982.
[40] D. E. Portlock, D. Naskar, L. West, W. L. Seibel, T. Gu, H. J. Krauss, X. S. Peng, P. M. Dybas, E. G. Soyke, S. B. Ashton, J. Burton, *Tetrahedron Lett.* **2003**, *44*, 5365.
[41] R. Wartchow, J. Frackenpohl, H. M. R. Hoffmann, *Z. Kristallogr. NCS* **2000**, *215*, 435.
[42] [42a] P. Langer, H. M. R. Hoffmann, *Tetrahedron* **1997**, *53*, 9145. [42b] For the influence of helicity on stereoselectivity see also: A. M. Rouhi, *Chem. Eng. News* **2003**, Sept. 29, 34.
[43] W. Braje, J. Holzgrefe, R. Wartchow, H. M. R. Hoffmann, *Angew. Chem.* **2000**, *112*, 2165; *Angew. Chem. Int. Ed.* **2000**, *39*, 2085.
[44] W. M. Braje, R. Wartchow, H. M. R. Hoffmann, *Angew. Chem.* **1999**, *111*, 2698; *Angew. Chem. Int. Ed.* **1999**, *38*, 2540.
[45] R. Wartchow, J. Frackenpohl, S. Röper, H. M. R. Hoffmann, *Z. Kristallogr. NCS* **2000**, *215*, 437.
[46] See also: W. E. von Doering, L. Birladeanu, D. W. Andrews, M. Pagnotta, *J. Am. Chem. Soc.* **1985**, *107*, 428.
[47] See e.g. K. Stöckel, F. Sondheimer, *Org. Synth. Coll. Vol. VI,* John Wiley & Sons, New York, **1988**, 68.
[48] S. Röper, M. H. Franz, R. Wartchow, H. M. R. Hoffmann, *J. Org. Chem.* **2003**, *68*, 4944.
[49] www.innocentive.com, Challenge No. 260715.
[50] [50a] G. A. Olah, G. K. S. Prakash, M. Saunders, *Acc. Chem. Res.* **1983**, *16*, 440. [50b] G. A. Olah, *Angew. Chem.* **1995**, *107*, 1519; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1393. [50c] X-ray crystal structures: T. Laube, *Acc. Chem. Res.* **1995**, *28*, 339.
[51] S. Röper, M. H. Franz, R. Wartchow, H. M. R. Hoffmann, *Org. Lett.* **2003**, *5*, 2773.

[52] M. H. Franz, S. Röper, R. Wartchow, H. M. R. Hoffmann, *J. Org. Chem.* **2004**, *69*, 2983.
[53] T.-S. Kam, K.-M. Sim, T.-M. Lim, *Tetrahedron Lett.* **1999**, *40*, 5409.
[54] S. S. Tafur, J. L. Occolowitz, J. W. Paschal, D. E. Dorman, *J. Org. Chem.* **1976**, *41*, 1001.
[55] A. Numata, C. Takahashi, Y. Ito, T. Takada, K. Kawai, Y. Usami, E. Matsumura, M. Imachi, T. Ito, T. Hasegawa, *Tetrahedron Lett.* **1993**, *34*, 2355.
[56] R. Jadulco, R. A. Edrada, R. Ebel, A. Berg, K. Schaumann, V. Wray, K. Steube, P. Proksch, *J. Nat. Prod.* **2004**, *67*, 78.
[57] S. L. Crawley, R. L. Funk, *Org. Lett.* **2003**, *5*, 3169.
[58] [58a] A. S. Ratnayake, W. Y. Yoshida, S. L. Mooberry, T. K. Hemscheidt, *J. Org. Chem.* **2001**, *66*, 8717. [58b] Erratum: A. S. Ratnayake, W. Y. Yoshida, S. L. Mooberry, T. K. Hemscheidt, *J. Org. Chem.* **2003**, *68*, 1640.
[59] E. P. Kündig, T. Lomberget, R. Bragg, C. Poulard, G. Bernardinelli, *Chem. Commun.* **2004**, 1548.
[60] M. Fild, C. Thöne, S. Tötös, *Eur. J. Inorg. Chem.* **2004**, 749.
[61] I. Kania, K. Stadnicka, B. J. Oleksyn, *Chirality* **2004**, *16*, 180.
[62] K. N. Gavrilov, V. N. Tsarev, A. A. Shiryaev, O. G. Bondarev, S. E. Lyubimov, E. B. Benetsky, A. A. Korlyukov, M. Y. Antipin, V. A. Davankov, H.-J. Gais, *Eur. J. Inorg. Chem.* **2004**, 629.
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