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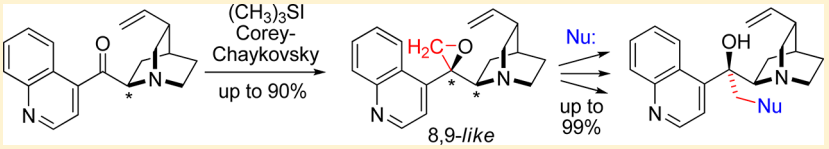
Diastereoselective Corey–Chaykovsky 9-Epoxymethylation of *Cinchona* Alkaloids: Access to Chiral Scaffolds with Diverse Functionalities

Przemysław J. Boratyński* and Jacek Skarżewski

Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Technology, 50-370 Wrocław, Poland

Supporting Information



ABSTRACT: Reaction of dimethylsulfonium methylide with *Cinchona* alkaloid ketones proceeds with complete diastereoselectivity to give epoxides of 8,9-*like* configuration. The reaction of dimethylsulfoxonium methylide gives different isomers, albeit with lower (4:1) selectivity. α-Epimerization of the alkaloid ketones resulted in formation of two separable diasteromeric products. The configurations of the epoxides were elucidated on the basis of NMR data combined with DFT calculations. Models explaining observed selectivity are discussed. The epoxides were efficiently transformed to a number of derivatives through selective S_N2-type ring-opening reactions with various nucleophiles, often without the need of additional purification steps.

1. INTRODUCTION

Cinchona alkaloids, privileged transition metal ligands and organocatalysts, enjoy continued interest for their numerous applications in asymmetric synthesis.[1] Nevertheless, there have been relatively few successful modifications to the alkaloid carbon skeleton at the C-9 center. Few examples include the introduction of additional CF_3,[2] simple alkyl, aryl and vinyl groups,[3] and the corresponding ring rearrangements.[4] An attractive approach to the extension of carbon framework is offered by the Corey–Chaykovsky reaction of sulfur ylides[5] with the respective 9-carbonyl compounds. Generally, the stereochemistry of epoxides resulting from the Corey–Chaykovsky reaction can be controlled by the use of stabilized chiral sulfur ylides[6] or chiral lithium–lanthanide complexes.[7] Highly diastereoselective reaction was also noted for the adequately substituted cyclic ketones.[8] However, in the case of acyclic ketones with a stereogenic center at the α-position, rather fair diastereoselectivities have been found.[9]

The feasibility of epoxides for further transformations makes them valuable synthetic intermediates. As a result, a library of multifunctional derivatives of *Cinchona* alkaloids relevant to organocatalysis[1,10] and metal–organic frameworks[11] can be envisaged.

2. RESULTS AND DISCUSSION

2.1. Synthesis of Epoxides. *Cinchona* alkaloids (quinine and cinchonine) were converted to the corresponding ketones **QD-1** and **CN-1** by Oppenauer oxidation and crystallization.[12] The ketones treated with trimethylsulfonium iodide and potassium hydroxide in DMSO were cleanly transformed to the epoxides **2** (Scheme 1).

Similar results were also obtained for other solvent and base combinations[13] (like potassium *tert*-butoxide in THF). After an aqueous workup, the epoxides were obtained as a mixture of two diastereomers in very high (80–90%) yield. No other isomeric products could be detected by NMR. However, when instead of trimethylsulfonium, respective sulfoxonium iodide was used, all of the four possible isomers were identified in the crude mixture (Scheme 2). This is in contrast to the usually observed higher selectivity of the sulfoxonium reagents.[14]

The epoxides from the reaction of trimethylsulfonium iodide were formed with essentially invariable diastereomeric ratio of 7:6, regardless of the base, solvent, and addition sequence. Chromatography of the initial mixtures on silica gel did not separate the isomers; however, fractional crystallization allowed for isolation of pure diastereomers. Crystallization from *tert*-butyl methyl ether was particularly efficient for cinchonine-derived epoxides **CN-2** and **CD-2** (Scheme 1). In the first crop pure **CN-2** was isolated in 30% yield. Pure **CD-2** was obtained by sequential crystallization or a chromatography of the enriched mother liquor followed by recrystallization from diethyl ether. Unfortunately this separation procedure did not translate well to the quinidine-series epoxides. There, only **QD-2** could be isolated in high diastereomeric purity by crystallization from diethyl ether. However, each of the two additional isomers (**QD-3** and **QN-3**) formed in the reaction of trimethylsulfoxonium iodide (Scheme 2) was separated by chromatography.

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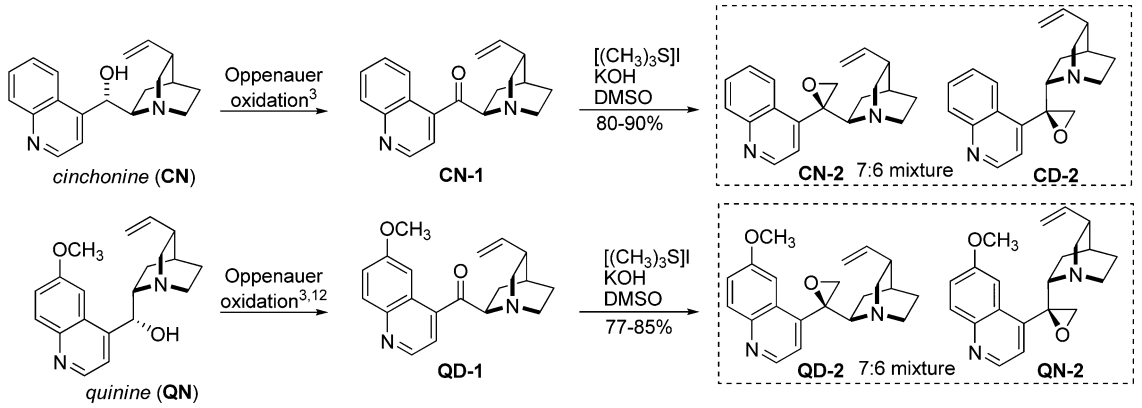
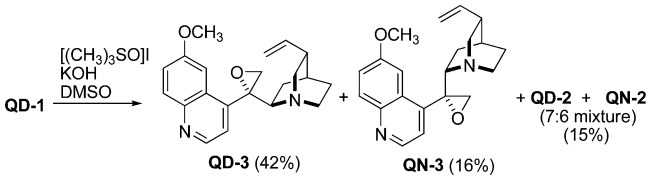
Scheme 1. Synthesis of Epoxides 2



Scheme 2. Reaction of Dimethylsulfoxonium Methylide



2.2. Configuration of Epoxides. Investigation of the NOESY spectra of the separated **CN-2** and **CD-2** allowed for the unequivocal assignment of the configuration at the C-8 stereogenic center. The correlation of H-8 with H-6 for **CN-2** identifies 8*R* configuration. For **CD-2** the correlation of H-8 with H-2 confirms its 8*S* configuration (Figure 1). The overall patterns of the correlations suggest 8,9-*like* configuration.

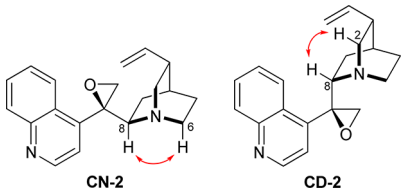


Figure 1. Nuclear Overhauser effect experiments for **CN-2** and **CD-2**.

A molecular model (Figure 2) was used to verify the configuration at C-9. The lowest energy conformers for both **CN-2** and **CD-2** and their 9-epimers were determined at the DFT/B3LYP/6-31G(d,p) level of theory. The essential pattern of the observed NOESY correlations, involving quinoline's H-5′ and H-3′ atoms as well as the epoxide CH_2 group are much better explained assuming 9*R* configuration for **CN-2** and 9*S* for **CD-2** (Figure 2). In the molecular models of **CN-2** and **CD-2**, but not of their 9-epimers, the interatomic distances corresponding to the observed NOESY cross-peaks were relatively short (2.2−3.7 Å) and exhibited good correlation with the measured signal intensities (see Section S3.3, Supporting Information). The assignment of configuration was further augmented by comparison of the experimental and calculated (GIAO/B3LYP/6-31G(d,p)) chemical shifts. Both the calculated ^{1}H and ^{13}C NMR shifts are in consistently better correlation with the experimental data for the assigned 8,9-*like* configuration (see Section S3.4, Supporting Information).

2.3. Stereochemistry of Corey−Chaykovsky Reaction. Identification of (8*R*,9*R*)-**CN-2** and (8*S*,9*S*)-**CD-2** as diastereomeric pair differing in configuration at both C-8 and C-9 stereocenters indicates that the Corey−Chaykovsky reaction using the sulfonium ylide is diastereoselective. The compositions of the obtained **CN-2**/**CD-2** and **QD-2**/**QN-2** product mixtures correspond to the compositions of the respective ketone mixtures equilibrated in the presence of base. Furthermore, identical product mixtures were obtained both from crystalline **QD-1** and the previously equilibrated mixture of **QD-1** and **QN-1**. The isomerization of the ketones (**QD-1** and **CN-1**) in solution is long documented,[15] and here it appears to be much faster than the nucleophilic addition of the ylide (Scheme 3).

The observed addition of the sulfonium ylide occurred from the *Re* face of cinchoninone (**CN-1**) and quinidinone (**QD-1**)

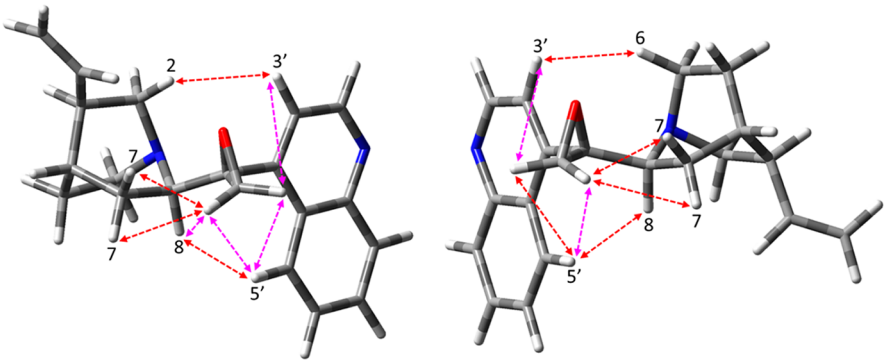


Figure 2. DFT/B3LYP/6-31G(d,p) optimized structures and selected NOESY interactions (dashed lines) for **CN-2** (left) and **CD-2** (right). Strong interactions are marked in red, weak in magenta (for details, see Section S3.3, Supporting Information).

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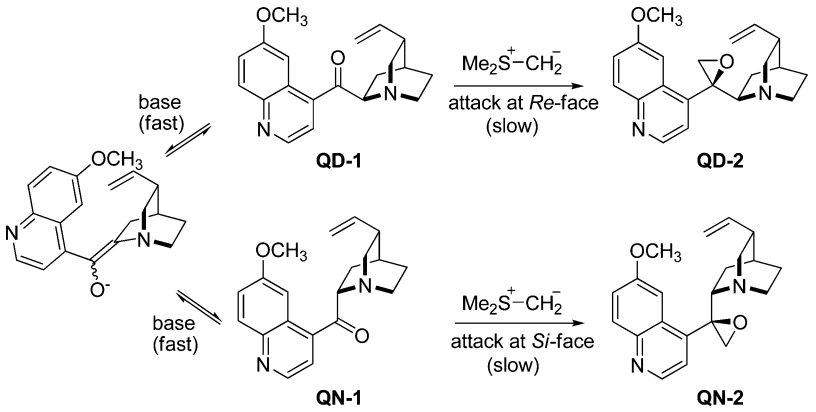
Scheme 3. Stereochemistry of Corey–Chaykovsky Reaction of Dimethylsulfonium Methylide



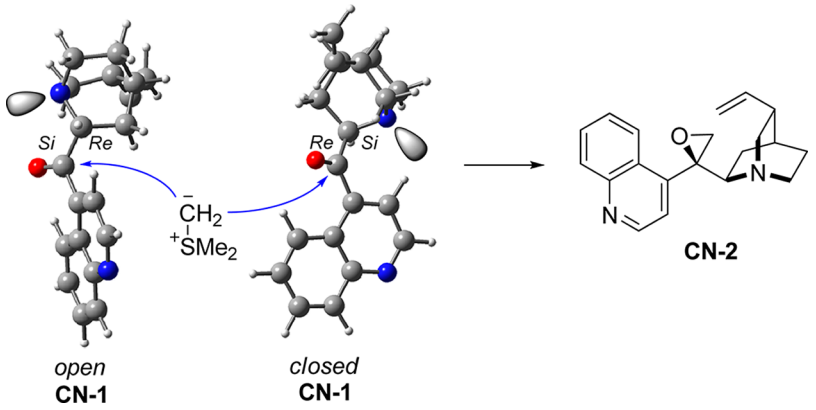


Figure 3. DFT/B3LYP/6-31G(d,p) low energy conformations and reactivity of **CN-1**. *Re* and *Si* faces of carbonyl group are marked.

and *Si* face for cinchonidinone and quininone (**QN-1**) (Scheme 3). Similar facial selectivity was previously reported for the addition of TMS-CF_3 to qunidinone.[2] Conversely, addition at the opposite face occurred in cases where metal chelates were involved, like in the addition of Grignard reagents,[3] and lithium aluminum hydride reduction.[16]

We hypothesized that the conformation of the starting material determines the outcome of the reaction. The optimization of **CN-1** in vacuum at the DFT/B3LYP/6-31G(d,p) level of theory indicates two low energy conformations (Figure 3). They differ in the $O-C^9-C^8-N^1$ dihedral angle of +103° and +10° for the *closed* and *open* conformers, respectively. The *closed* conformer is lowest in energy and is similar to the observed in the crystal structure of **QD-1**.[2] In this conformation the *Re* face is exposed, while the quinuclidine ring sterically hinders the nucleophilic attack from the *Si*-face (Figure 3). Nevertheless, the calculated energy difference between the conformers is rather small (3 and 1 kcal/mol for calculations in vacuum and DMSO (PCM), respectively). Thus, the steric factors alone cannot be responsible for the observed selectivity in the nucleophilic additions. In both conformations the nitrogen lone pair is directed from the *Si* face. It is more pronounced for the *open* conformer, where the lone electron pair is nearly perpendicular to the plane of the carbonyl group. The overlap of the filled orbital at the nitrogen atom with the orbitals of the carbonyl group causes a stereoelectronic effect that prevents the approach of the reacting nucleophile from the side of the overlap[17] (see Section S3.1, Supporting Information). Similarly, in the recently reported Corey–Chaykovsky reaction of heterocyclic ketone with dimethylsulfonium methylide,[18] the face of the nucleophilic attack was opposite to the heteroatom lone pair. Thus, in our case the electrostatic and stereoelectronic effects appear to be dominant and result in the formation of the observed kinetic products from either of the two lowest energy conformers of the starting material.

In the case of reaction of dimethylsulfoxonium methylide, a different set of isomers ((8*R*,9*S*)-**QD-3** and (8*S*,9*R*)-**QN-3**) was dominant (Scheme 2). There, unlike in the reactions of dimethylsulfonium methylide, the addition step to form intermediate betaines is known to be reversible.[19] Our preliminary calculations indicate that the betaines leading to the epoxides of 8,9-*unlike* configuration are of lower energy (see Section S3.2, Supporting Information). Thus thermodynamic equilibration of the betaines seems to define the stereochemical outcome.

2.4. Epoxide Ring-Opening. In order to examine possible applications of the epoxides as synthetic intermediates, several ring-opening reactions with various nucleophiles were studied. Hydrolysis of the epoxide **CN-2** under mildly acidic conditions (tartaric acid) delivered a single diol **CN-4**. The reaction of epoxide **CN-2** with thiophenolates under ambient conditions gave the respective phenylsulfanyl derivatives **CN-5** and **CN-6** with excellent yields (Scheme 4).

On the other hand the reaction of **CN-2** with ammonium thiocyanate resulted predominantly in deoxygenation.[20] The most likely course of the reaction involves thiirane[21] that undergoes spontaneous desulfurization[22] to give the 9-methylidene derivative **CN-7**. The reaction of epoxide **CN-2** with NaN_3 in the presence of NH_4Cl in MeOH gave the

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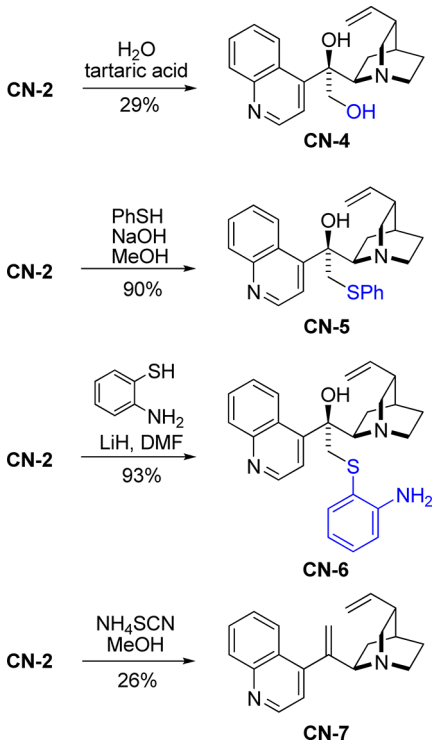
Scheme 4. Reaction of Epoxide CN-2 with Chalcogen Nucleophiles



respective azide **CN-8**. In this case the crude product did not require further purification, and the yield was nearly quantitative (Scheme 5).

The azide **CN-8** reacted with phenylacetylene in the copper(I)-catalyzed 1,3-dipolar cycloaddition "*click* reaction" giving the corresponding triazole **CN-9**. Also, the azide **CN-8** was reduced to the corresponding amine **CN-10** with $LiAlH_4$.[23] Although the isolation of pure aminoalcohol **CN-10** was ineffective, the crude product was used for further transformations. Alternatively, the azide **CN-8** was first converted to the corresponding silyl ether **CN-11**, which was reduced under the Staudinger conditions to the more tangible aminoether **CN-12**. The reaction of crude **CN-10** with 3,5-bis(trifluoromethyl)-phenyl isothiocyanate gave the corresponding thiourea **CN-13**. Apart from the desired thiourea, also oxazolidinethione **CN-14** was isolated from the reaction mixture. Oxazolidinethione **CN-14** was independently obtained in the reaction of **CN-10** and carbon disulfide. It was also found to form in the heated sample of **CN-13** in DMSO. However, under similar conditions thiourea with silyl ether group **CN-15** was stable. Amine **CN-10** was also converted to the amide **CN-16** with acetic anhydride.

The epoxide **CN-2** reacted with benzylamine in the presence of lithium perchlorate at 100 °C, giving the corresponding secondary amine **CN-17**. Treatment of the aminoalcohol **CN-17** with an excess of acetic anhydride gave the *N*-acetylated product **CN-18** with unmodified 9-hydroxyl group.

Hydrogenation of **CN-2** on 10% Pd/C occurred solely at the vinyl group of the alkaloid. The product **DHCN-2** was identical to one of the isomers obtained in the epoxidation of 10,11-dihydrocinchoninone (**DHCN-1**, Scheme 6). The epoxides could not be efficiently opened by Grignard reagents or by $LiAlH_4$.

In all the described epoxide ring-openings only one isomer of product was formed from a single isomer of the epoxide. Likewise in both the hydrolysis and azidolysis the use of **CD-2** instead of **CN-2** led to the single diol **CD-4** and azide **CD-8**, respectively (Scheme 7).

All the compounds with free hydroxyl group exhibit quaternary ^{13}C NMR signals at 79–83 ppm attributed to the C-9 of tertiary alcohols. As expected, these signals are affected only to a little extent by the nucleophiles attached at the neighboring CH_2 group. The structures of the products were additionally confirmed by further NMR experiments. In the HMBC spectrum of **CN-18**, the introduced CH_2 group (but not the quaternary C-9) correlates with the atoms of benzyl and acetyl groups (Figure 4). Additionally, the ^{13}C NMR shifts observed for **CN-14** also agree with those observed for 5,5-disubstituted oxazolidinethiones and not for the 4,4-disubstituted derivatives (for the details see Figure S5, Supporting Information). Thus the ring-opening reaction must have occurred at the less substituted carbon atom through the S_N2 mechanism. The unlikely S_N1-type reaction at the more substituted carbon would not lead to a clean conversion observed in most of the reactions here. Involvement of a carbocation at C-9 had previously resulted in two diastereomers of the products and a series of rearranged compounds (cf. *Cinchona* rearrangements).[4]

3. CONCLUSIONS

The diastereoselective Corey–Chaykovsky reaction of the *Cinchona* alkaloid ketones led to the corresponding 9-epoxymethyl derivatives in good yields. The reaction with dimethylsulfonium methylide occurred at the face opposite to the nitrogen lone pair, resulting exclusively in the 8,9-*like* configuration. Particularly, (9*R*)-9-epoxymethyl-cinchonine (**CN-2**) was easily prepared from the commercially available alkaloids, without the use of chromatography. The reaction of dimethylsulfoxonium methylide gave predominantly the epoxides of 8,9-*unlike* configuration. The selective S_N2 ring-opening of epoxides with various oxygen, sulfur, and nitrogen nucleophiles gave multifunctional aminoalcohols, chiral building blocks for prospective catalysts.

4. EXPERIMENTAL SECTION

NMR spectra were internally referenced to solvent signals: ^1H 7.26 for $CHCl_3$, 2.50 for DMSO-d_5, and ^{13}C 77.16 for $CDCl_3$, 39.52 for DMSO-d_6. High resolution mass spectra (TOF) were obtained in electrospray ionization mode. All reagents were purchased from commercial suppliers and used as received, **CN-1**, and **QD-1** were prepared according to literature procedures.[3,13] **DHCN-1** was prepared following the literature procedure used for **CN-1**[3b] from 10,11-dihydrocinchonidine and recrystallized from Et_2O in 62% yield.

10,11-Dihydrocinchonanone (DHCN-1). Yellow crystalline solid: mp 121–124 °C (Et_2O), 122–125 °C (EtOH) (lit.[15] mp 138 °C (EtOH)); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.97 (d, J = 4.4 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.72 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.64 (d, J = 4.4 Hz, 1H), 7.58 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 4.16 (m, 1H), 3.12 (dd, J = 13.6, 9.2 Hz, 1H), 2.77 (m, 1H), 2.50–2.74 (m, 2H), 2.07 (m, 1H), 1.83 (m, 1H), 1.77 (m, 1H), 1.63 (m, 1H), 1.33–1.51 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 203.2, 149.8, 149.2, 143.4, 130.2, 129.7, 128.0, 125.1, 124.6, 119.5, 63.4, 57.4, 43.5, 37.4, 28.0, 27.6, 25.2, 21.6, 12.2.

Corey–Chaykovsky Reaction of CN-1 and Dimethylsulfonium Methylide. In a 100 mL round-bottom flask were placed recrystallized cinchoninone[3] (11.9g, 40.8 mmol), trimethylsulfonium iodide (8.67 g, 42.4 mmol, 1.04 equiv), and DMSO (64 g). The suspension was stirred for 5 min, and potassium hydroxide (flakes

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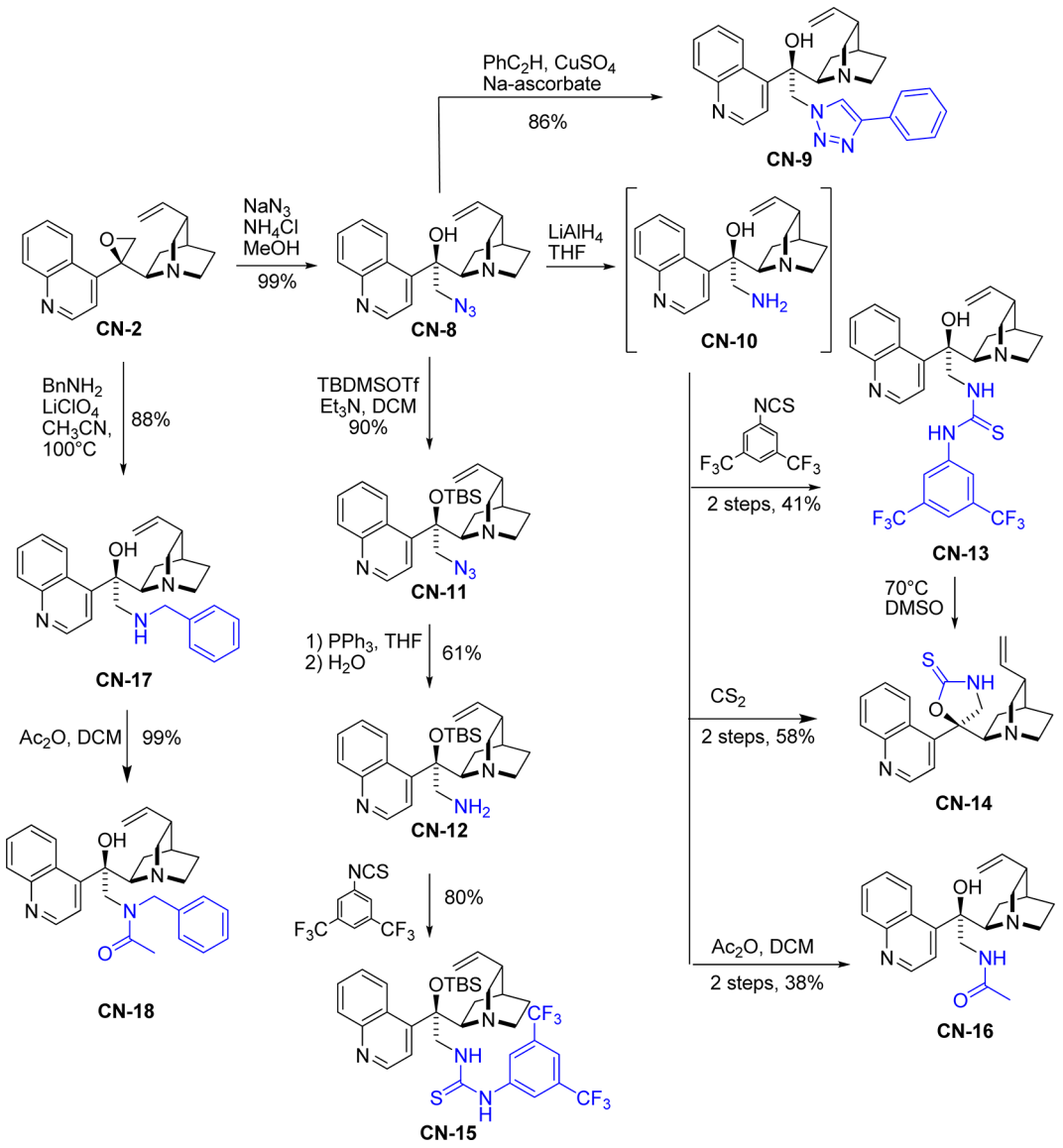
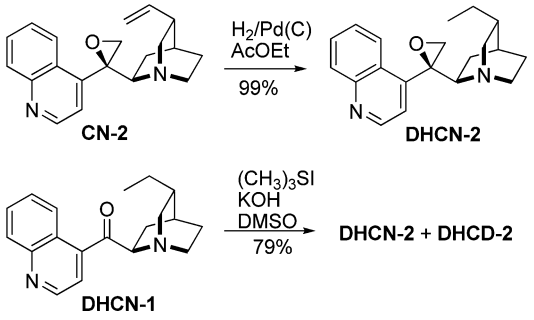
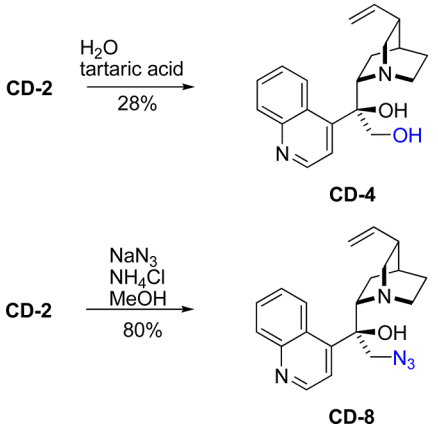
Scheme 5. Synthesis of Nitrogen Derivatives



Scheme 6. Synthesis of 10,11-Dihydroepoxides



Scheme 7. Selected Reactions of Epoxide CD-2



90%, 2.65 g, 41.8 mmol, 1.03 equiv) was added. Within a few minutes the mixture turned deep red and became temporarily homogeneous. After a few hours a precipitate formed and the mixture turned light orange. The mixture was stirred for a total of 52 h, and then it was diluted with diethyl ether (450 mL),[24] washed with brine (8 × 50 mL), and dried over Na_2SO_4. On evaporation, a mixture of **CN-2** and **CD-2** (11.1 g, 90%) was obtained. Repeated procedures on 0.1−32 g scale gave 80−90% yields.

The mixture of isomers was recrystallized from *tert*-butyl methyl ether giving 4.17 g of pure **CN-2** (33%). On slow evaporation of solvent from the mother liquor crystalline material containing mostly **CD-2** was obtained. Chromatography of **CD-2**-enriched fractions on

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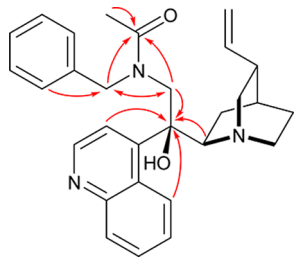

Figure 4. Selected ^{1}H, ^{13}C HMBC correlations for **CN-18**.

silica gel with ethyl acetate followed by crystallization from diethyl ether gave pure **CD-2**. Two additional crops of crystallizations yielded pure **CN-2** (total 5.68 g, 45%) and pure **CD-2** (2.52 g, 20%).

9*R*-Epoxymethylcinchonine (CN-2). White crystalline solid: mp 173−177 °C (MTBE); $[\alpha]_D^{24}$= +92.5 (*c* 1, EtOH 96%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80 (d, *J* = 4.4 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.94 (br., 1H), 7.69 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.55 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.51 (br., 1H), 6.04 (m, 1H), 5.03−5.10 (m, 2H), 3.63 (t, *J* = 8.9 Hz, 1H), 3.07 (d, *J* = 4.8 Hz, 1H), 2.96−3.05 (m, 1H), 2.78 (dd, *J* = 13.4, 10.2 Hz, 1H), 2.67 (d, *J* = 4.7 Hz, 1H), 2.52−2.64 (m, 2H), 2.18 (q, *J* =8.4 Hz, 1H), 1.77 (m, 1H), 1.66 (m, 1H), 1.47−1.57 (m, 2H), 1.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 150.3, 148.1, 146.4, 140.9, 130.6, 129.0, 126.6, 125.9, 123.4, 120.1, 114.7, 59.5, 58.1, 49.5, 49.1, 47.6, 40.3, 28.5, 26.7, 20.2; IR (KBr) 2925, 2865, 1633, 1597, 1569, 1507, 1448, 1297, 1223, 937, 914, 844, 802, 764; HRMS (ESI) calcd. for $[C_{20}H_{22}N_2O + H]^+$ 307.1805, found 307.1806.

9*S*-Epoxymethylcinchonidne (CD-2). Large transparent crystals: mp 124−127 °C (Et_2O); $[\alpha]_D^{24}$= −35.6 (*c* 1, EtOH 96%); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.88 (d, *J* = 4.5 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.93 (br. d, *J* = 8.1 Hz, 1H), 7.70 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.56 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.52 (br.d, *J* = 4.5 Hz, 1H), 5.88 (ddd, *J* = 17.2, 10.6, 7.3 Hz 1H), 5.01 (d, *J* = 10.6 Hz, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 3.70 (t, *J* = 8.5 Hz, 1H), 3.27 (m, 1H), 3.06 (d, *J* = 4.9 Hz, 1H), 2.90 (d, *J* = 13.4, 10.5 Hz, 1H), 2.64 (d, *J* = 4.5 Hz, 1H), 2.55 (m, 1H), 2.41 (m, 1H), 2.20 (m, 1H), 1.83 (m, 1H), 1.65−1.75 (m, 2H), 1.44 (m, 1H), 1.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 150.3, 148.1, 146.4, 142.2, 130.7, 129.0, 126.6, 125.9, 123.3, 119.7, 114.4, 59.3, 58.2, 56.4, 47.3, 42.5, 39.6, 27.9, 27.5, 20.3; IR (KBr) 2932, 2860, 1636, 1593, 1567, 1507, 1445, 1307, 1215, 1002, 938, 914, 850, 825, 769 cm^{-1}; HRMS (ESI) calcd. for $[C_{20}H_{22}N_2O + H]^+$ 307.1805, found 307.1796.

9*R*-Epoxymethyl-10,11-dihydrocinchonine (DHCN-2). *Method A*: Epoxide **CN-2** (144 mg, 0.47 mmol) was dissolved in AcOEt (10 mL) and palladium on activated charcoal (10%, 11.6 mg, 2.5 mol %) was added. Hydrogen was passed through the stirred suspension for 18 h, and the catalyst was filtered off. On evaporation, 145 mg (99%) of **DHCN-2** was obtained. *Method B*: **DHCN-1** (1.17 g, 4.00 mmol) and trimethylsulfonium idodide (821 mg, 4.02 mmol, 1.01 equiv) were dissolved in DMSO (7.5 mL), and KOH was added (flakes, 90%, 0.29 g, 4.6 mmol, 1.1 equiv). The mixture was stirred at room temperature for 80 h and diluted with diethyl ether (50 mL), washed with brine (5 × 20 mL), dried over Na_2SO_4, and evaporated giving 0.993 g (81%) of a 1:1 mixture of **DHCN-2**/**DHCD-2**. Crystallization from *tert*-butyl methyl ether at 0 °C gave **DHCN-2** as yellowish crystals: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.88 (d, *J* = 4.5 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.93 (br. d, *J* = 8 Hz, 1H), 7.68 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.54 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.51 (br., 1H), 3.60 (t, *J* = 9.2 Hz, 1H), 3.06 (d, *J* = 4.9 Hz, 1H), 2.67−2.80 (m, 1H), 2.62 (d, *J* = 4.9 Hz, 1H), 2.46−2.64 (m, 2H), 1.70 (m, 1H), 1.22−1.63 (m, 7H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.3, 148.1, 146.5, 130.6, 129.0, 126.5, 125.9, 123.4, 120.2, 59.3, 58.2, 50.7, 49.6, 47.5, 37.4, 27.5, 26.4, 25.4, 20.0, 12.2; IR (KBr) 2957, 2932, 2864, 1597, 1509, 1451, 1298, 936, 844, 762 cm^{-1}; HRMS (ESI) calcd. for $[C_{20}H_{24}N_2O + H]^+$ 309.1961, found 309.1960.

Corey−Chaykovsky Reaction of QN-1 and Dimethylsulfonium Methylide. Reaction was performed analogously to the reaction of **CN-1**. Starting from **QN-1** (5.56 g, 17.2 mmol), trimethylsulfonium iodide (3.62 g, 17.7 mmol, 1.03 equiv) and KOH (flakes 90%, 2.16 g, 34.1 mmol, 1.98 equiv) in DMSO (25 mL), 4.50 g (78%) of **QN-2**/**QD-2** mixture was obtained. Repeated procedures on 0.05−3 g scale gave 77−85% yields: HRMS (ESI) calcd. for $[C_{21}H_{24}N_2O_2 + H]^+$ 337.1911, found 337.1918. A sample was recrystallized in diethyl ether at 0 °C to give pure **QD-2**.

9*R*-Epoxymethylquinidine (QD-2). White crystalline solid: mp 102−106 °C (Et_2O); $[\alpha]_D^{21}$= +59.6 (*c* 0.78, EtOH 96%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.74 (d, *J* = 4.3 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.47 (br., 1H), 7.37 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.16 (br., 1H), 6.03 (m, 1H), 5.056 (d, *J* = 16.5 Hz, 1H), 5.047 (d, *J* = 11.0 Hz, 1H), 3.94 (s, 3H), 3.59 (t, *J* = 8.9 Hz, 1H), 3.08 (d, *J* = 4.9 Hz, 1H), 3.01 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.80 (m, 1H), 2.53−2.74 (m, 3H), 2.18 (q, *J* = 8.6 Hz, 1H), 1.85 (m, 1H), 1.77 (m, 1H), 1.66 (m, 1H), 1.48−1.57 (m, 2H), 1.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 157.6, 147.9, 144.8, 144.3, 140.9, 132.1, 126.8, 120.6, 120.4, 114.7, 102.6, 59.4, 57.7, 55.7, 49.6, 49.2, 47.7, 40.2, 28.5, 26.7, 20.3; IR (KBr) 2928, 2869, 1621, 1506, 1430, 1251, 1229, 1028, 903, 845, 827, 720 cm^{-1}.

Corey−Chaykovsky Reaction of QD-1 and Dimethylsulfoxonium Methylide. In a 50 mL round-bottom flask were placed recrystallized quinidinone (1.05 g, 3.26 mmol) and trimethylsulfoxonium iodide (0.746 g, 3.39 mmol, 1.04 equiv) and DMSO (9 mL). Potassium hydroxide (90%, 0.233 g, 3.73 mmol, 1.15 equiv) was added. Within a few minutes an orange solution was obtained. The mixture was stirred for 24 h. Then it was diluted with ethyl acetate (40 mL), washed with brine (5 × 15 mL), dried over Na_2SO_4, and evaporated. Chromatography on silica gel (EtOAc/Et_3N 25:1) gave 162 mg (15%) of 7:6 **QD-2**/**QN-2** mixture, 459 mg (42%) of **QD-3**, and 177 mg (15%) of **QN-3**.

9*S*-Epoxymethylquinidine (QD-3). White solid: mp 107−111 °C (CH_2Cl_2), $[\alpha]_D^{24}$= +114.5 (*c* 1.1, EtOH 96%); ^{1}H NMR ($CDCl_3$, 300 MHz, 318 K) δ 8.69 (d, *J* = 4.4 Hz, 1H), 8.00 (d, *J* = 9.3 Hz, 1H), 7.38 (d, *J* = 4.4 Hz, 1H), 7.33 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.30 (br., 1H), 5.95 (ddd, *J* = 17.4, 10.0, 7.0 Hz, 1H), 5.00−5.08 (m, 2H), 3.90 (s, 3H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.32 (t, *J* = 9.5 Hz, 1H), 3.01 (ddd, *J* = 13.7, 8.0, 2.2 Hz, 1H), 2.67−2.92 (m, 3H), 2.77 (d, *J* = 5.8 Hz, 1H), 2.16 (m, 1H), 1.84 (m, 1H), 1.70 (m, 1H), 1.40−1.52 (m, 2H), 1.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 318 K) δ 158.1, 147.5, 144.7, 143.9, 140.5, 131.9, 127.0, 121.7, 120.2, 114.5, 102.6, 63.1, 56.2, 55.6, 51.8, 50.5, 49.3, 39.8, 28.5, 26.6, 23.5; IR (KBr) 2930, 2869, 1619, 1504, 1475, 1429, 1229, 1023, 913, 904, 850, 828, 719 cm^{-1}; HRMS (ESI) calcd. for $[C_{21}H_{24}N_2O_2 + H]^+$ 337.1911, found 337.1918.

9*R*-Epoxymethylquinine (QN-3). Light brown oil: $[\alpha]_D^{24}$= −6.7 (*c* 1.1, EtOH 96%); ^{1}H NMR ($CDCl_3$, 300 MHz, 318 K) δ 8.70 (d, *J* = 4.5 Hz, 1H), 8.01 (d, *J* = 9.1 Hz, 1H), 7.37 (d, *J* = 4.4 Hz, 1H), 7.35 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.32 (d, *J* = 2.6 Hz, 1H), 5.68 (ddd, *J* = 17.4, 10.4, 7.3 Hz, 1H), 4.91 (dt, *J* = 17.4, 1.5 Hz, 1H), 4.86 (dt, *J* = 10.4, 1.5 Hz, 1H), 3.92 (s, 3H), 3.63 (d, *J* = 5.6 Hz, 1H), 3.44 (t, *J* = 9.2 Hz, 1H), 3.21 (m, 1H), 3.06 (dd, *J* = 13.8, 10.1 Hz, 1H), 2.81 (d, *J* = 5.6 Hz, 1H), 2.69 (m, 1H), 2.61 (m, 1H), 2.23 (m, 1H), 1.78 (m, 1H), 1.39−1.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 318 K) δ 158.2, 147.5, 144.8, 143.9, 142.0, 131.9, 127.0, 121.8, 120.3, 114.4, 102.5, 62.8, 57.6, 56.4, 55.8, 51.4, 42.9, 40.0, 28.07, 28.04, 24.1; IR (KBr) 2938, 2867, 1620, 1507, 1475, 1432, 1230, 1030, 915, 853, 832 cm^{-1}; HRMS (ESI) calcd. for $[C_{21}H_{24}N_2O_2 + H]^+$ 337.1911, found 337.1916.

9*R*-Hydroxymethyl-cinchonine (CN-4). Epoxide **CN-2** (800 mg, 2.61 mmol) and L-tartaric acid (610 mg, 4.06 mmol, 1.56 equiv) were suspended in water (40 mL) and heated under reflux for 4 h. Then the mixture was cooled to room temperature and alkalized with solid $NaHCO_3$, extracted with $CHCl_3$ (7 × 10 mL), and dried over Na_2SO_4. Column chromatography on silica gel ($CHCl_3$/MeOH/Et_3N 40:1:4) gave unreacted starting material and 239 mg of **CN-4** (29%) as white crystalline solid: mp 168−171 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 313 K) δ 8.54 (d, *J* = 4.4 Hz, 1H), 8.46 (br. d, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.51−7.62 (m, 2H), 7.44 (m, 1H), 5.98 (ddd, *J* = 17.2, 10.7, 7.3 Hz, 1H), 5.03 (dt, *J* = 10.7, 1.5 Hz, 1H), 5.01 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.32 (d, *J* = 11.1 Hz, 1H), 4.00 (d, *J* = 11.1 Hz, 1H), ∼4.0 (br. ∼2H), 3.45 (t, *J* = 9.7 Hz, 1H), 2.98 (ddd, *J* = 13.8, 8.0, 2.2 Hz, 1H),

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2.55−2.82 (m, 3H), 2.10−2.25 (m, 2H), 1.34−1.64 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 151.8 (br.), 149.4, 148.2, 140.9, 130.0, 128.6, 126.4, 125.8, 125.4, 120.3, 114.5, 80.4, 66.2, 61.8, 50.4, 49.7, 40.2, 29.0, 26.6, 22.4; IR (KBr) 3452, 3254, 3101, 2916, 2865, 1579, 1513, 1454, 1110, 1070, 1050, 909, 826, 770 cm^{-1}; HRMS calcd. for $[C_{20}H_{24}N_2O_2 + H]^+$ 325.1911, found 325.1905.

9*S*-Hydroxymethyl-cinchonidine (CD-4). Compound was obtained analogously to **CN-4**. Starting from 625 mg (2.04 mmol) of **CD-2**, 189 mg (28%) of **CD-4** was obtained as white solid: mp 150−156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 313 K) δ 8.34 (m, 1H), 8.26 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 4.7 Hz, 1H), 7.34−7.48 (m, 2H), 5.89 (ddd, J = 17.4, 9.8, 7.3 Hz, 1H), 4.96−5.05 (m, 2H), ∼4.35 (br., 2H), 4.32 (d, J = 11.1 Hz, 1H), 3.81 (d, J = 11.1 Hz, 1H), 3.53 (t, J = 8.9 Hz, 1H), 3.16 (m, 1H), 2.84 (dd, J = 13.6, 10.4 Hz, 1H), 2.52 (m, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 2.03 (m, 1H), 1.86 (m, 1H), 1.66−1.84 (m, 2H), 1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 313 K) δ 152.0, 149.4, 148.4, 142.4, 130.2, 128.5, 126.7, 125.8, 125.3, 120.3 114.2, 80.5, 66.5, 62.0, 57.6, 43.4, 40.0, 28.6, 27.7, 22.9; IR (KBr) 3465, 3102, 2934, 2872, 1583, 1512, 1386, 1070, 921, 820, 767 cm^{-1}; HRMS calcd. for $[C_{20}H_{24}N_2O_2 + H]^+$ 325.1911, found 325.1907.

9*R*-Phenylsulfanylmethyl-cinchonine (CN-5). Epoxide **CN-2** (110 mg, 0.36 mmol) and thiophenol (0.10 mL, 0.96 mmol, 2.7 equiv) were dissolved in ethanol (96%, 5 mL), and sodium hydroxide (12.5 mg, 0.31 mmol, 0.86 equiv) was added. The mixture was stirred for 18 h at room temperature and diluted with diethyl ether (35 mL), washed with 10% aqueous NaOH (2 × 20 mL), and extracted with 2 M HCl (30 mL). Acidic extracts were treated with excess Na_2CO_3 and extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated to give 136 mg (90%) of **CN-5** as amorphous solid: ^{1}H NMR ($CDCl_3$, 300 MHz, 318 K) δ 8.76 (d, J = 4.7 Hz, 1H), 8.38 (br, 1H), 8.06 (dd, J = 8.4, 1.3 Hz, 1H), 7.72 (br. 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.63 (br. 1H), 7.57 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.42 (ddd, J = 8.7, 6.9, 1.5 Hz, 1H), 7.01−7.06 (m, 2H), 6.94−7.00 (m, 3H), 5.99 (ddd, J = 17.2, 10.6, 7.3 Hz, 1H), 5.01 (ddd, J = 10.6, 1.6, 1.3 Hz), 4.98 (ddd, J = 17.2, 1.6, 1.4 Hz, 1H), ∼4.1 (br., 1H), 4.09 (d, J = 13.4 Hz, 1H), 3.55 (t, J = 9.4 Hz, 1H), 3.48 (d, J = 13.4 Hz, 1H), 3.04 (ddd, J = 13.9, 7.9, 2.2 Hz, 1H), 2.46−2.71 (m, 3H), 2.27 (t, J = 10.8 Hz, 1H), 2.11 (q, J = 8.3 Hz, 1H), 1.82 (m, 1H), 1.41−1.63 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 318 K) δ 150.6, 149.5, 149.3, 140.8, 134.9, 131.1, 130.7, 128.6, 128.0, 126.8, 125.62, 125.58, 125.3, 120.2, 114.2, 79.9, 63.4, 50.8, 49.7, 45.8, 40.1, 29.2, 26.7, 22.3; IR (KBr) 3434, 3071, 2933, 2869, 1582, 1510, 1439, 1301, 1103, 1089, 759, 741, 690 cm^{-1}; HRMS (ESI) calcd. for $[C_{26}H_{28}N_2OS + H]^+$ 417.1995, found 417.1985.

9*R*-(2-Aminophenyl)-sulfanylmethyl-cinchonine (CN-6). Lithium hydride (26 mg, 2.6 mmol, 2.3 equiv) was suspended in a solution of 2-aminothiophenol (0.26 mL, 2.43 mmol, 2.2 equiv) in DMF (1 mL), and stirred until a clear solution was obtained (ca. 15 min). Then epoxide **CN-2** (356 mg, 1.11 mmol) was added, the suspension was stirred for 5 min, and additional DMF (1 mL) was added. The mixture was stirred for 18 h at room temperature, evaporated in vacuo (50 °C), and dried in a vacuum desiccator over H_2SO_4. The residue was dissolved in ethyl acetate (50 mL) and washed with brine (3 × 10 mL), dried over Na_2SO_4 and evaporated. Chromatography on silica gel ($CHCl_3$/MeOH 10:1) gave 442 mg (93%) of **CN-6** as a yellowish amorphous solid: ^{1}H NMR ($CDCl_3$, 300 MHz, 313 K) δ 8.79 (d, J = 4.8 Hz, 1H), ∼8.39 (br., 1H), 8.08 (dd, J = 8.5, 1.3 Hz, 1H), 7.65 (br. 1H), 7.58 (ddd, J = 8.5, 7.0, 1.1 Hz, 1H), 7.41 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.90 (t, J = 7.6 Hz, 1H), 6.44 (d, J = 7.7 Hz, 1H), 6.41 (t, J = 7.5 Hz, 1H), 5.94 (m, 1H), 4.98 (dt, J = 10.2, 1.3 Hz, 1H), 4.95 (dd, J = 17.3, 1.2 Hz, 1H), ∼4.1 (br., 2H), 4.04 (d, J = 13.1 Hz, 1H), 3.44 (t, J = 8.3 Hz, 1H), 3.24 (d, J = 13.1 Hz, 1H), 3.00 (m, 1H), 2.45−2.70 (m, 3H), 2.04−2.24 (m, 2H), 1.78 (m, 1H), 1.37−1.58 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 318 K) δ 149.7, 149.4, 148.0, 142.4, 140.8, 135.7, 131.1, 130.0, 128.2, 127.0, 125.7 (2C overlap), 120.4, 119.0, 117.8, 115.2, 114.4, 80.6, 63.9, 51.0, 49.9, 46.1, 40.2, 29.3, 26.7, 22.5; IR (KBr) 3434, 3302, 3175, 3066, 2934, 2870, 1609, 1581, 1479, 1449, 1303, 910, 752 cm^{-1}; HRMS (ESI) calcd. for $[C_{26}H_{29}N_3OS + H]^+$ 432.2104, found 432.2097.

9-Deoxy-9-methylidene-cinchonine (CN-7). In a resealable tube epoxide **CN-2** (434 mg, 1.42 mmol) and ammonium thiocyanate (470 mg, 6.17 mmol, 4.3 equiv) were suspended in methanol (6 mL). The mixture was heated at 50−60 °C for 144 h. Then the mixture was cooled to room temperature, NaOH (10 mL, 10% aqueous) was added, and the mixture was extracted with CH_2Cl_2 and evaporated. Chromatography on silica gel ($CHCl_3$/MeOH 20:1) gave 109 mg (26%) of **CN-7** as solidifying oil: mp 84−87 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.84 (d, J = 4.4 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.69 (ddd, J = 8.3, 7.0, 1.4 Hz, 1H), 7.52 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.21 (d, J = 4.4 Hz, 1H), 5.84 (ddd, J = 17.1, 9.9, 7.0, 1H), 5.74 (dd, J = 2.0, 1.3 Hz, 1H), 5.30 (dd, J = 2.0, 1.3 Hz, 1H), 5.00−5.07 (m, 2H), 3.82 (t, J = 9.4 Hz, 1H), 2.74−3.09 (m, 4H), 2.26 (q, J = 8.0 Hz, 1H), 1.72 (m, 1H), 1.54−1.65 (m, 3H), 1.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 149.8, 149.1, 148.7, 145.6, 140.3, 130.0, 129.3, 127.3, 126.5, 125.5, 120.1, 117.2, 114.7, 59.2, 49.0, 48.1, 40.1, 28.2, 26.6, 25.8; IR (KBr) 3064, 2922, 2862, 1637, 1583, 1504, 1018, 909, 830, 763 cm^{-1}; HRMS calcd. for $[C_{20}H_{22}N_2 + H]^+$ 291.1856, found 291.1852.

9*S*-Azidomethyl-cinchonine (CN-8). Epoxide **CN-2** (1.31 g, 4.28 mmol), sodium azide (1.05 g, 16.2 mmol, 3.8 equiv) and ammonium chloride (0.537 g, 10.0 mmol, 2.34 equiv) were suspended in methanol (10 mL) in a resealable tube and stirred vigorously for 3 days at 60−65 °C. The solvent was removed in vacuo, and the residue was treated with aqueous NaOH (2%, 5 mL), extracted with $CHCl_3$ and dried over Na_2SO_4. After evaporation 1.49 g (99%) of **CN-8** was obtained as slowly crystallizing oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 (d, J = 4.7 Hz, 1H), ∼8.59 (br. 1H), 8.15 (dd, J = 8.4, 1.3 Hz, 1H), 7.69 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.53 (ddd, J = 8.6, 6.9, 1.5 Hz, 1H), ∼7.50 (br. 1H), 5.92 (ddd, J = 17.3, 10.4, 7.0 Hz, 1H), 5.07 (dt, J = 10.4, 1.4 Hz, 1H), 5.03 (dt, J = 17.2, 1.5 Hz, 1H), 4.07 (d, J = 12.6 Hz, 1H), 3.88 (d, J = 12.6 Hz, 1H), 3.40 (t, J = 9.8 Hz, 1H), 2.65−2.95 (m, 4H), 2.21 (q, J = 8.3 Hz, 1H), 2.00 (br. 1H), 1.84 (m, 1H), 1.50−1.59 (m, 2H), 1.43 (br. 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 149.6, ∼149.5 (br.), 149.4, 140.0, 130.9, 128.6, 126.5, 126.1, 125.8 (br.), 119,9, 114.8, 80.2, 62.6, 57.6, 50.8, 49.9, 39.5, 28.7, 26.0, 22.3; IR (KBr) 3196, 3076, 2939, 2872, 2103, 1582, 1510, 1454, 1302, 1284, 911, 763, 733 cm^{-1}; HRMS (ESI) calcd. for $[C_{20}H_{23}N_5O + H]^+$ 350.1975, found 350.1971.

9*R*-Azidomethyl-cinchonidine (CD-8). Compound was prepared analogously to **CN-8**. Starting from **CD-2** (324 mg, 1.06 mmol) after chromatography on silica gel ($CHCl_3$/MeOH 20:1) 278 mg of **CD-8** (80%) was obtained: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (d, J = 4.7 Hz, 1H), ∼8.44 (br. 1H), 8.16 (dd, J = 8.5, 1.2 Hz, 1H), 7.68 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), ∼7.57 (br. 1H), 7.53 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 5.79 (ddd, J = 17.2, 10.3, 7.2 Hz, 1H), 4.99 (dt, J = 17.2, 1.4 Hz, 1H), 5.97 (d, J = 10.3 Hz, 1H), ∼4.2 (br. ∼1H), 4.11 (d, J = 12.4 Hz, 1H), 3.81 (d, J = 12.4 Hz, 1H), 3.55 (t, J = 9.3 Hz, 1H), 3.16 (m, 1H), 2,98 (m, 1H), 2.48−2.72 (m, 2H), 2.26 (m, 1H), 1.91 (m, 1H), 1.75−1.88 (m, 2H), 1.69 (m, 1H), 1.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 149.7, 149.6 (br.), 149.2, 141.8, 131.0, 128.6, 126.4, 126.1, 125.2 (br.), 119.9, 114.5, 80.1, 62.2, 57.8, 57.6, 43.4, 39.6, 28.3, 27.5, 23.2; IR (neat) 3393, 2935, 2864, 2102, 1582, 1509, 1284, 912, 761 cm^{-1}; HRMS (ESI) calcd. for $[C_{20}H_{23}N_5O + H]^+$ 350.1975, found 350.1961.

9*S*-(4-Phenyl-1,2,3-triazol-1-yl-methyl)-cinchonine (CN-9). Azide **CN-8** (74.2 mg, 0.214 mmol) and phenylacetylene (45 μL, 0.41 mmol, 1.9 equiv) were dissolved in THF (2 mL), and a solution of sodium ascorbate (45 mg, 0.23 mmol, 106 mol %) in water (0.6 mL) was added, followed by aqueous $CuSO_4$ (18 μL, 0.78 M, 0.014 mmol, 6 mol %). The mixture was stirred for 24 h at room temperature. Pyridine (0.07 mL) was added, and the mixture was filtered through a pad of silica gel, washed with $CHCl_3$/MeOH 5:1, and evaporated. Purification on silica gel ($CHCl_3$/MeOH 20:1) afforded 82.6 mg of **CN-9** (86%) as amorphous solid: ^{1}H NMR (DMSO-d_6, 300 MHz, 343 K) δ 8.75 (br., 1H), 8.73 (d, J = 4.7 Hz, 1H), 8.03 (s, 1H), 8.01 (dd, J = 8.5, 1.4 Hz, 1H), 7.61−7.70 (m, 4H), 7.56 (ddd, J = 8.7, 6.8, 1.5 Hz, 1H), 7.34−7.41 (m, 2H), 7.28 (m, 1H), 5.90 (m, 1H), 5.74 (br., ∼1H), 5.17 (d, J = 14.4 Hz, 1H), 5.03 (d, J = 14.4 Hz, 1H), 4.83−4.94 (m, 2H), 3.72 (m, 1H), 2.84 (m, 1H), 2.68 (m, 1H), 2.32−2.48 (m, 2H), 2.17 (m, 1H), 2.06 (m, 1H), 1.73 (m,

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1H), 1.62 (m, 1H), 1.38−1.51 (m, 2H); ^{1}H NMR ($CDCl_3$, 600 MHz, 273K, mixture of conformers ~1:1) δ 9.06 (d, J = 8.8 Hz, 1H), 8.68 (d, J = 4.7 Hz, 1H), 8.67 (d, J = 4.7 Hz, 1H), 8.58 (br. m, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 8.06 (br., 1H), 8.04 (d, J = 8.3 Hz, 1), 7.72 (t, J = 7.4 Hz, 1H), 7.70 (d, J = 4.7 Hz, 1H), 7.62−7.68 (m, 4H), 7.50 (t, J = 7.7 Hz, 1H), 7.45 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 4.7 Hz, 1H), 7.26−7.32 (m, 4H), 7.21−7.24 (m, 1H), 6.07 (ddd, J = 17.6, 10.0, 7.6 Hz, 1H), ~6.0 (br, ~1H), 5.85 (ddd, J = 17.3, 10.5, 6.6 Hz, 1H),), 5.10 (d, J = 10.5 Hz, 1H), 5.00−5.07 (m, 3H), 4.98 (d, J = 14.2 Hz, 1H), 3.77 (t, J = 9.0 Hz, 1H), 3.34 (t, J = 9.9 Hz, 1H), 2.99−3.09 (m, 3H), 2.87 (m, 1H), 2.64−2.74 (m, 2H), 2.52−2.62 (m, 2H), 2.45−2.50 (m, 1H), 2.27 (q, J = 8.0 Hz, 1H), 2.15 (q, J = 8.1 Hz, 1H), 1.78−1.90 (m, 3H), 1.47−1.66 (m, 5H), 1.30 (m, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz, 333 K) δ 149.1, 148.9, 148.2, 145.2, 140.7, 130.4, 129.8, 128.3, 127.5, 127.2, ~126 (br.), 125.9, 125.1, 124.7, 121.9, 119.7, 113.5, 80.3, 60.5, 57.0, 49.3, 48.4, 39.2, 28.2, 25.7, 20.7; IR (KBr) 3408, 2934, 2871, 1581, 1510, 1456, 1232, 1201, 1047, 764, 695 cm^{-1}; HRMS calcd. for $[C_{28}H_{29}N_5O + H]^+$ 452.2445, found 452.2434.

9*S*-Aminomethyl-cinchonine (CN-10). Azide **CN-8** (1.42 g, 4.07 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. $LiAlH_4$ (159 mg, 4.18 mmol, 1.03 equiv) was added, the mixture was stirred for 15 min at 0 °C followed by another portion of $LiAlH_4$ (15.4 mg, 0.40 mmol, 0.10 equiv), and the mixture was stirred for additional 10 min. The reaction was quenched by addition of brine, extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated. The crude mixture was used without further purification. A sample was purified on silica gel with $CHCl_3$/MeOH (5:1) followed by MeOH: ^{1}H NMR ($CDCl_3$, 300 MHz, 313 K) δ 8.85 (d, J = 4.6 Hz, 1H), ~8.39 (br., 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.78 (br., 1H), 7.64 (m, 1H), 7.48 (m, 1H), 6.06 (m, 1H), 4.97−5.05 (m, 2H), 3.61 (d, J = 12.4 Hz, 1H), 3.55 (m, 1H), 3.13 (m, 1H), 3.00 (d, J = 12.4 Hz, 1H), 1.97−2.90 (m, 7H), 1.82 (m, 1H), 1.40−1.67 (m, 3H); HRMS (ESI) calcd. for $[C_{20}H_{25}N_3O + H]^+$ 324.2072, found 324.2082.

***O*-*tert*-Butyldimethylsilyl-9*S*-azidomethyl-cinchonine (CN-11).** Azide **CN-8** (544 mg, 1.56 mmol) was dissolved in dichloromethane (9 mL), and triethylamine (0.25 mL, 1.79 mmol, 1.15 equiv) was added. The mixture was cooled to 0 °C, a first portion of TBDMS triflate (0.50 mL) was added, and then the mixture was allowed to attain room temperature, and after 2.5 h another portion of TBDMS was added (0.25 mL; total 3.27 mmol, 2.1 equiv). The mixture was stirred at room temperature for 18 h, and filtered through a pad of silica gel with $CHCl_3$/MeOH 10:1. After evaporation, the residue (1.40 g) was triturated with 10% aqueous NaOH, extracted with CH_2Cl_2, dried over Na_2SO_4, evaporated, and washed with 0.3 mL of hexane to give 656 mg (90%) of product as off-white crystalline solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (d, J = 4.8 Hz, 1H), 8.72 (d, J = 8.8 Hz, 1H), 8.12 (dd, J = 8.4, 1.1 Hz, 1H), 7.66 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 7.58 (br., 1H), 7.50 (ddd, J = 8.3, 6.8, 1.2 Hz, 1H), 5.31 (ddd, J = 17.0, 10.4, 6.2 Hz, 1H), 4.72 (d, J = 13.4 Hz, 1H), 4.68 (d, J = 10.5 Hz, 1H), 4.44 (d, J = 17.1 Hz, 1H), 4.06 (d, J = 13.4 Hz, 1H), 3.21 (t, J = 9.5 Hz, 1H), 2.96 (m, 1H), 2.68 (dt, J = 13.1, 8.8 Hz, 1H), 2.42 (m, 1H), 1.88−2.00 (m, 2H), 1.52−1.76 (m, 3H), 1.39−1.52 (m, 2H), 0.99 (s, 9H), 0.28 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 149.3, 149.2, 147.6, 139.4, 130.6, 128.7, 127.6, 127.4, 125.9, 122.1, 114.4, 84.0, 64.5, 58.9, 51.5, 49.6, 39.5, 28.9, 26.5, 26.0, 22.5, 19.4, −1.8, −2.2; IR (KBr) 3065, 2955, 2860, 2108, 1512, 1472, 1259, 1160, 1030, 838, 779, 638 cm^{-1}; HRMS (ESI) calcd. for $[C_{26}H_{37}N_5OSi + H]^+$ 464.2840, found 464.2837.

***O*-*tert*-Butyldimethylsilyl-9*S*-aminomethyl-cinchonine (CN-12).** Azide **CN-11** (80.6 mg, 0.173 mmol) was dissolved in THF (4 mL), and triphenylphosphine (69.9 mg, 0.267 mmmol, 1.54 equiv) was added. The mixture was stirred at 45 °C for 18 h and then allowed to attain room temperature. Water (0.5 mL) was added, and the mixture was stirred for additional 24 h, and extracted with $CHCl_3$, dried over Na_2SO_4, and evaporated. Chromatography on silica gel ($CHCl_3$/MeOH 10:1) gave 46 mg (61%) of **CN-12** as colorless oil: R_f 0.38 ($CHCl_3$/MeOH, 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 (d, J = 4.6 Hz, 1H), 8.79 (d, J = 8.7 Hz, 1H), 8.10 (dd, J = 8.3, 1.2 Hz, 1H), 7.64 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.58 (br., 1H), 7.48 (ddd, J = 8.7, 6.8, 1.5 Hz, 1H), 5.44 (ddd, J = 17.2, 10.5, 7.1 Hz, 1H), 4.75 (d, J = 10.5 Hz, 1H), 4.55 (d, J = 17.2 Hz, 1H), 4.04 (br. m, 1H), 3.15−3.29 (m, 2H), 2.94 (m, 1H), 2.66 (ddd, J = 13.2, 8.8, 8.6 Hz, 1H), 2.48 (m, 1H), 2.13 (m, 1H), 1.96 (q, J = 7.9 Hz, 1H), 1.64 (m, 1H), 1.11−1.62 (m, 6H), 0.95 (s, 9H), 0.32 (s, 3H), 0.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 149.5, 149.4, 149.3, 139.8, 132.1, 130.6, 128.6, 127.2, 126.0, 122.2, 114.2, 87.1, 64.3, 51.5, 49.9, 49.2, 39.5, 28.9, 26.7, 26.0, 22.9, 19.6, −1.9, −2.1; IR (neat) 3394, 3299, 2930, 2857, 2576, 1508, 1472, 1249, 1120, 1093, 1055, 982, 834, 776 cm^{-1}; HRMS (ESI) calcd. for $[C_{26}H_{39}N_3OSi + H]^+$ 438.2935, found 438.2949.

***N*-3,5-Bis(trifluoromethyl)phenyl-*N*′-(8*R*,9*S*-9-hydroxy-cinchonan-9-yl-methyl)-thiourea (CN-13).** Crude mixture containing **CN-10** (1.12 g) was dissolved in DCM (20 mL), and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (934 mg, 3.44 mmol) was added. The mixture was stirred for 18 h, concentrated to about 10 mL, and subjected to chromatography on silica gel ($CHCl_3$/MeOH 10:1 to 5:1). Obtained was 800 mg (41% over 2 steps) of **CN-13**. Additionally 30 mg (3%) of **CN-14** was isolated. **CN-13**: mp 120−128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 313 K) δ ~9.5 (br., 1H), ~8.5 (br. 1H), 8.25 (br. 1H), 7.87 (s, 2H), 7.52−7.76 (br. m, 3H), 7.55 (s, 1H), 7.40−7.49 (m, 2H), 6.00 (ddd, J = 17.1, 10.5, 7.0 Hz 1H), 5.10 (d, J = 10.5 Hz, 1H), 5.07 (d, J = 17.1 Hz, 1H), 4.74 (br. 1H), 4.39 (br. d, J = ~13 Hz, 1H), 3.48 (br., 1H), 3.03 (dd, J = 13.0, 7.9 Hz, 1H), 2.55−3.81 (br. m, 3H), 2.15−2.29 (m, 2H), 1.89 (m, 1H), 1.47−1.66 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 313 K) δ 183.6, ~151 (br.), 149.0, 148.3 (br.), 140.4, 139.6, 132.2 (q J_{C-F} = 34 Hz), 129.3, 129.2, 126.7, ~126 (br.), 123.7, 123.1 (q J_{C-F} = 273 Hz), 118.6 (*sept* J = 4 Hz), 115.1, 81.5, 62.8, 51.7, 50.9, 49.8, 39.7, 28.9, 26.3, 22.4 (2 sp^2 C missing due to coalescence and overlaps); IR (KBr) 3366, 2940, 1576, 1513, 1471, 1381, 1279, 1177, 1133, 759 cm^{-1}; HRMS (ESI) calcd. for $[C_{29}H_{28}F_6N_4OS + H]^+$ 595.1961, found 595.1946.

5*S*-5-(Quinolin-4-yl)-5-((1*S*,2*R*,5*R*)-5-vinyl-quinuclidin-2-yl)-oxazolidine-2-thione (CN-14). Crude mixture containing **CN-10** (28 mg) was dissolved in THF (1.5 mL). Triethylamine (0.11 mL, 0.79 mmol) and carbon disulfide (0.06 mL, 0.99 mmol) were added, and the mixture was stirred at 50−60 °C for 20 h. The mixture was briefly evaporated and purified on silica gel ($CHCl_3$/MeOH, 10:1) giving 18.6 mg (58% over 2 steps) of white crystalline solid After chromatography the sample became insoluble in $CHCl_3$: mp 273−275 °C (dec); ^{1}H NMR (DMSO-d_6/H_2O, 600 MHz) δ 10.26 (br, 1H), 8.88 (d, J = 4.6 Hz, 1H), 8.08 (dd, J = 8.4, 0.9 Hz, 1H), 7.96 (br. d, J = ~8.4 Hz, 1H), 7.77 (ddd, J = 6.7, 8.1, 0.9 Hz, 1H), 7.59−7.62 (m, 2H), 6.19 (ddd, J = 17.0, 10.4, 8.2 Hz, 1H), 5.06 (dd, J = 17.0, 1.9 Hz, 1H), 4.99 (dd, J = 10.4, 1.9 Hz, 1H), 4.35 (d, J =10.8 Hz, 1H), 3.93 (d, J =10.8 Hz, 1H), 3.83 (t, J = 8.2 Hz, 1H), 2.89 (dd, J = 12.9, 7.4 Hz, 1H), 2.45 (t, J = 12.0 Hz, 1H), 2.23−2.31 (m, 2H), 2.09 (q, J = 8.6 Hz, 1H), 1.83 (m, 1H), 1.72−1.78 (m, 2H), 1.56 (q, J = 10.6 Hz, 1H), 1.41 (m, 1H); ^{13}C NMR (DMSO-d_6/H_2O, 151 MHz) δ 186.1, 150.0, 148.8, 148.4, 141.0, 130.5, 129.0, 126.7, 123.5, 124.2, 117.2, 115.0, 93.9, 62.0, 53.2, 49.6, 48.4, 40.1, 28.7, 25.8, 20.4; IR (KBr) 2942, 2872, 1547, 1511, 1317, 1277, 1173, 1132, 912, 776, 759 cm^{-1}; HRMS (ESI) calcd. for $[C_{21}H_{23}N_3OS + H]^+$ 366.1636, found 366.1651.

***N*-((8*R*,9*S*)-9-(*tert*-Butyldimethylsilyloxy)-cinchonan-9-yl-methyl)-*N*′-3,5-bis(trifluoromethyl)phenyl-thiourea (CN-15).** Amine **CN-12** (44.0 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (4 mL), and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (19 μL, 0.10 mmol, 1.0 equiv) was added. The mixture was stirred for 28 h and then chromatographed on silica gel ($CHCl_3$/MeOH 20:1) to give 56.5 mg (80%) of product as solidifying oil: ^{1}H NMR ($CDCl_3$, 300 MHz, 318 K) δ 8.79 (d, J = 8.8 Hz, 1H), ~8.72 (br., 1H), 8.62 (br., 1H), 7.90 (br., 1H), 7.70 (s, 2H), 7.69 (m, 1H), ~7.5 (br. 1H), 7.57 (s, 1H), 7.50 (m, 1H), 7.47 (br. 1H), 5.36 (m, 1H), 4.72−4.83 (m, 2H), 4.59 (d, J = 17.2 Hz, 1H), 4.33 (d, J = 14.4 Hz, 1H), 3.45 (t, J = 9.6 Hz, 1H), 2.94 (t, J = 11.0 Hz, 1H), 2.31−2.59 (m, 2H), 1.89−2.07 (m, 2H), 1.63 (m, 1H), 1.38−1.59 (m, 3H), 1.06 (m, 1H), 0.86 (s, 9H), 0.34 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 318 K) δ 181.6, 149.1, 148.1 (br.), 140.0, 139.2, 132.9 (q, J = 32 Hz), 129.7, 128.7 (br.), 127.7, 127.2, 126.4, 123.3, 123.0 (q, J = 273 Hz), 121.0 (br.), 118.7, 114.6 (br.), 83.1 (br.), 65.3, 55.0 (br.), 51.5, 49.6, 39.1, 29.0, 26.5, 25.9, 23.4, 19.3, −1.9, −2.5 (1 sp^2 C missing due to

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coalescence and overlaps); IR (KBr) 3384, 3337, 2933, 2860, 1514, 1472, 1385, 1279, 1180, 1136, 838, 778 cm^{-1}; HRMS (ESI) calcd. for $[C_{35}H_{42}N_4OF_6SSi + H]^+$ 709.2826, found 709.2827.

9*S*-(*N*-Acetylaminomethyl)-cinchonine (CN-16). Crude mixture containing **CN-10** (88.5 mg) was dissolved in dichloromethane (3 mL), and acetic anhydride (0.040 mL, 0.42 mmol) was added. The mixture was stirred at room temperature for 24 h, and saturated aqueous $NaHCO_3$ was added, extracted with dichloromethane, and dried over Na_2SO_4. The mixture was applied to silica gel column with $CHCl_3$/MeOH 10:1 and then eluted from with methanol providing 40 mg (38% over 2 steps) of white amorphous solid: ^1H NMR ($CDCl_3$, 300 MHz, 313 K) δ 8.73 (d, J = 4.6 Hz, 1H), ~8.56 (br., 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.61 (m, 1H), 7.46 (ddd, J = 8.6, 6.9, 1.4 Hz, 1H), ~7.64 (br., 1H), 6.08 (br., 1H), 5.94 (ddd, J = 17.5, 10.4, 7.6 Hz, 1H), 5.04 (dt, J = 10.4, 1.2 Hz, 1H), 5.00 (dt, J = 17.4, 1.5 Hz, 1H), ~7.57 (br., 1H), 4.19 (br., 1H), 3.85 (br. 1H), 3.48 (t, J = 9.2 Hz, 1H), 2.94 (m, 1H), 2.59−2.89 (m, 3H), 2.04−2.25 (m, 2H), 1.83 (m, 1H), 1.73 (s, 3H), 1.35−1.64 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 313 K) δ 171.9, 150.0, 149.7, 139.9, 131.2, 128.6, 126.2, ~126 (br.), 120.6, 115.1, 81.1, 63.1, 51.1, 50.1, 47.5, 39.8, 29.0, 26.3, 22.9, 22.2 (2 sp^2 C missing due to coalescence and overlaps); IR (KBr) 3261, 3069, 2934, 2670, 1637, 1570, 1510, 1376, 1302, 1116, 761; HRMS (ESI) calcd. for $[C_{22}H_{27}N_3O_2 + H]^+$ 366.2176, found 366.2192.

9*S*-(*N*-Benzyl-aminomethyl)-cinchonine (CN-17). Epoxide **CN-2** (219 mg, 0.72 mmol) and benzylamine (0.25 mL, 2.29 mmol, 3.2 equiv) were placed in a sealable tube and suspended in acetonitrile (1.5 mL), and a solution of $LiClO_4$ (0.15 mL, 4 M in Et_2O, 0.60 mmol, 0.83 equiv) was added. The tube was sealed and stirred for 5 days at 105 °C. Then the mixture was diluted with CH_2Cl_2, washed with 10% NaOH, dried over Na_2SO_4, and evaporated. Residual benzylamine was removed in a vacuum desiccator over H_2SO_4 to give 262 mg (88%) of yellow amorphous solid: ^1H NMR ($CDCl_3$, 300 MHz, 323 K) δ 8.83 (d, J = 4.7 Hz, 1H), 8.33 (br., 1H), 8.14 (dd, J = 8.5, 1.5 Hz, 1H), 7.81 (br., 1H), 7.63 (ddd, J = 8.5, 6.8, 1.5 Hz, 1H), 7.45 (ddd, J = 8.7, 6.8, 1.5 Hz, 1H), 7.18−7.30 (m, 3H), 7.02−7.07 (m, 2H), 6.08 (ddd, J = 17.8, 9.5, 7.6, 1H), 4.97−5.04 (m, 2H), 3.45−3.64 (m, 4H), 3.12 (ddd, J = 13.8, 7.7, 2.3 Hz, 1H), 2.92 (d, J = 12.0 Hz, 1H), 2.43−2.67 (m, 3H), 2.34 (t, J = 10.6 Hz, 1H), 2.10 (q, J = 8.5 Hz, 1H), 1.80 (m, 1H), 1.37−1.64 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 318 K) δ 152.7, 150.2, 149.4, 141.6, 139.6, 131.3, 128.6, 128.2, 128.0, 127.9 (br.), 127.3, 125.5, 125.4 (br.), 120.3, 114.0, 79.3, 64.5, 55.1, 54.0, 50.5, 49.7, 40.7, 29.4, 27.2, 22.2; IR (KBr) 3259, 2932, 2868, 1580, 1509, 1457, 1300, 1110, 909, 760, 699 cm^{-1}; HRMS (ESI) calcd. for $[C_{27}H_{31}N_3O + H]^+$ 414.2540, found 414.2548.

9*S*-(*N*-Acetyl-*N*-benzyl-aminomethyl)-cinchonine (CN-18). Amine **CN-17** (76.7 mg, 0.18 mmol) was dissolved in CH_2Cl_2, then triethylamine (0.15 mL, 1.1 mmol, 6 equiv) and acetic anhydride (70 μL, 0.74 mmol, 4.1 equiv) were added, and the mixture was stirred at room temperature for 20 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered through silica gel ($CHCl_3$/MeOH, 10:1) to give 85 mg (99%) of **CN-18** as brown oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 8.90 (d, J = 4.7 Hz, 1H), 8.19 (dd, J = 8.4, 0.8 Hz, 1H), 8.15 (d, J = 4.7 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.67 (dd, J = 8.4, 6.9 Hz, 1H), 7.43 (ddd, J = 8.6, 6.9, 0.8 Hz, 1H), 7.18−7.22 (m, 3H), 6.54−6.56 (m, 2H), 6.31 (br, ~0.7 H), 6.16 (ddd, J = 16.9, 10.5, 8.2 Hz, 1H), 5.00 (d, J = 16.9 Hz, 1H), 4.99 (d, J = 10.5 Hz, 1H), 4.45 (d, J = 14.6 Hz, 1H), 3.98 (d, J = 16.9 Hz, 1H), 3.65 (t, J = 8.9 Hz, 1H), 3.50 (d, J = 14.7 Hz, 1H), 3.17 (ddd, J = 13.6, 7.5, 1.9 Hz, 1H), 2.92 (d, J = 16.9 Hz, 1H), 2.56 (m, 1H), 2.52 (m, 1H), ~2.5 (br. ~0.3H), 2.36−2.43 (m, 2H), 2.06 (q, J = 8.2 Hz, 1H), 1.99 (s, 3H), 1.80 (m, 1H), 1.50−1.55 (m, 2H), 1.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 175.5, 151.5, 150.8, 148.6, 141.4, 135.1, 131.6, 128.9, 128.2, 127.9, 126.4, 126.14, 126.05, 124.2, 121.3, 114.1, 82.8, 61.7, 54.3, 53.4, 50.2, 48.9, 40.6, 29.0, 26.9, 22.4, 21.5; IR (neat) 3271, 2935, 2871, 1622, 1454, 1419, 1363, 1112, 911, 762, 734, 699 cm^{-1}; HRMS (ESI) calcd. for $[C_{29}H_{33}N_3O_2 + H]^+$ 456.2646, found 456.2666.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Supporting tables and figures. Additional spectral and computational details including tables of atom coordinates and absolute energies. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: przemyslaw.boratynski@pwr.wroc.pl.

Notes

The authors declare no competing financial interest.

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