Simple Enantiospecific Synthesis of Sulfides of *Cinchona* Alkaloids

Mariola Zielińska-Błajet, Małgorzata Kucharska, Jacek Skarżewski*

Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Technology, 50-370 Wrocław, Poland
Fax +48(71)3284064; E-mail: jacek.skarzewski@pwr.wroc.pl

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Abstract: The native and *epi*-*Cinchona* alkaloids were reacted with $(ArS)_2/Bu_3P$ in toluene at 65 °C to give the corresponding arylsulfanyl derivatives (15 examples, 31–75%) with complete inversion of configuration at 9-C stereogenic centers. Similar products were also obtained in the enantiospecific nucleophilic substitution of the 9-mesylates of alkaloids with sodium thiolates (4 examples, 73–84%) and no cinchona rearrangement was observed. The chiral thioethers obtained were preliminarily tested as N(sp^3), S-donating chiral ligands in the Pd-catalyzed allylic alkylation of dimethyl malonate with *rac*-1,3-diphenylprop-2-enyl acetate and gave the product with up to 78% ee.

Key words: asymmetric synthesis, chiral pool, ligands, stereoselectivity, sulfur

For the last two decades, *Cinchona* alkaloids have been regarded as powerful chiral auxiliaries and catalysts.[1] Their applications in the Sharpless asymmetric dihydroxylation[2] as well as asymmetric phase-transfer reactions and enantioselective *meso*-anhydride methanolysis[3] portray the most outstanding examples. *Cinchona* alkaloids have also been used effectively in the asymmetric reactions catalyzed by chiral nucleophiles.[4] Finally, it has recently been suggested that *Cinchona* alkaloids belong to a *privileged catalyst* class. These most valuable chiral auxiliaries are highly successful in enantioselective reactions of different types.[5]

On the other hand, the possibilities for the selective synthetic transformation of *Cinchona* alkaloids are rather limited. Essentially, excluding splitting and skeleton rearrangements,[6] their structure can be modified at the C-9 hydroxy group and at the quinuclidine nitrogen. The first type of modification has led to ethers, esters, and C-9 nitrogen derivatives.[1b] Recently, much attention has been paid to the N,S-donating chiral ligands, which induce high enantioselectivity in Pd-catalyzed asymmetric allylic substitution.[7] Our interest in this field[7h,i] turned our attention to the preparation of aryl sulfides of *Cinchona* alkaloids. To the best of our knowledge, their C-9 sulfur derivatives have not been reported as yet.

The *Cinchona* alkaloid family consists of two pairs of diastereomers, namely, cinchonidine (CD)/cinchonine (CN) and quinine (QN)/quinidine (QD) (Figure 1). Their dihydro derivatives (DH-alkaloids) are also available. Moreover, preparation of the respective C-9-*epi*-configured alkaloids adds another set of compounds accessible for further elaboration.[8] We were interested in the transformation of all these secondary alcohols into a library of corresponding new sulfur compounds, and prospective catalytic chiral ligands with the nitrogen/sulfur-donating functions. In this paper we describe a simple stereospecific transformation of the native and C-9-*epi*-alkaloids to the respective sulfanyl derivatives.

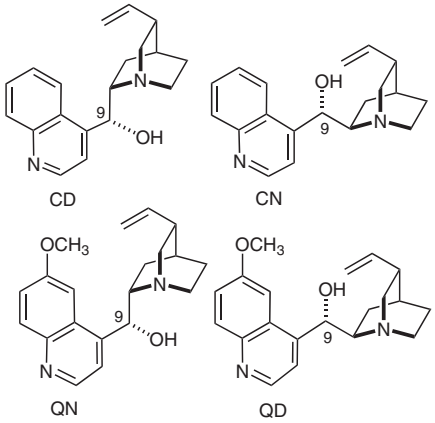
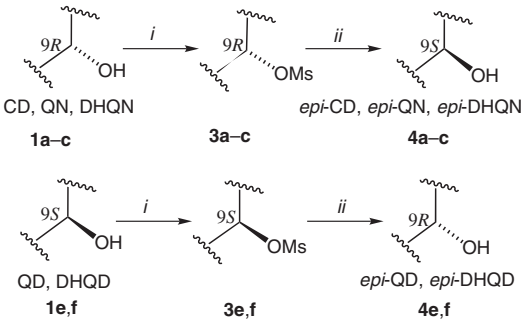


Figure 1 *Cinchona* alkaloids

Firstly, the native alkaloids were converted into their mesylate esters[8b] in 83–95% yields. These products were hydrolyzed in the presence of (+)-tartaric acid[8] and gave the respective *epi*-alkaloids in 70–78% yields (Scheme 1, Table 1).



Scheme 1 *Reagents and conditions*: *i*) MsCl/Et_3N, toluene, 0 °C, 24 h; *ii*) (+)-tartaric acid/H_2O, reflux, 3 h.

In spite of the limited stability, we fully characterized the mesylates spectroscopically. If the freshly prepared 9-MsO-QN (**3b**) was reacted with sodium thiophenoxide in DMF–toluene, the desired nucleophilic substitution took

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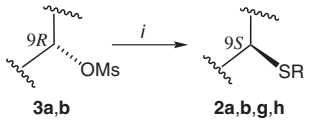
Table 1 Synthesis of Mesylates **3** and *epi*-Alkaloids **4**

Entry	Mesylate **3**	$[\alpha]_D^{25}$ (CH_2Cl_2)	Config.	Yield (%)	*epi*-Alkaloid **4**	$[\alpha]_D^{25}$ (EtOH)	Config.	Yield (%)
1	9-MsO-CD (**3a**)	−70.5	8*S*,9*R*	94	*epi*-CD (**4a**)	+55.6	8*S*,9*S*	70
2	9-MsO-QN (**3b**)	−71.9	8*S*,9*R*	95	*epi*-QN (**4b**)	+39.5	8*S*,9*S*	78
3	9-MsO-DHQN (**3c**)	−55.4	8*S*,9*R*	87	*epi*-DHQN (**4c**)	+30.6	8*S*,9*S*	76
4	9-MsO-QD (**3e**)	+125.4	8*R*,9*S*	90	*epi*-QD (**4e**)	+96.9	8*R*,9*R*	75
5	9-MsO-DHQD (**3f**)	+126.3	8*R*,9*S*	83	*epi*-DHQD (**4f**)	+73.0	8*R*,9*R*	78

place and *epi*-9-PhS-QN (**2b**) was isolated in 73% yield. Moreover, under the same reaction conditions 9-MsO-CD (**3a**) also gave *epi*-9-PhS-CD (**2a**) in 84% yield as the only product. The last result differs from the observed tendency of 9-MsO-CD to undergo the second cinchona rearrangement.[6] The corresponding successful nucleophilic substitutions were also carried out with ethyl ester of sodium thioglycololate (79%) and sodium benzyl mercaptide (75%), respectively. Only when bulky sodium 2-methyl-2-propanethiolate was used as a nucleophile, the substitution could not be attained. Thus, it seems that the two-step conversion of the alkaloids into their 9-sulfides offers a quite practicable method for the title transformation (Scheme 2, Table 2).



3a,**b** **2a**,**b**,**g**,**h**

Scheme 2 *Reagents and conditions*: *i*) PhSNa for **2a**,**b**; $NaSCH_2CO_2Et$ for **2g**; BnSNa for **2h**, toluene–DMF, 20 °C, 24 h.

Table 2 Nucleophilic Substitution of **3** to *epi*-Sulfides **2**

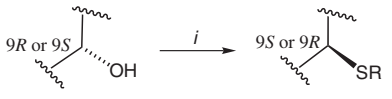
Entry	Sulfide **2**	$[\alpha]_D^{25}$ (CH_2Cl_2)	Yield (%)
1	*epi*-9-PhS-CD (**2a**)	+83.7	84
2	*epi*-9-PhS-QN (**2b**)	+15.1	73
3	*epi*-9-(EtO_2CCH_2S)-QN (**2g**)	+184.5	79
4	*epi*-9-BnS-QN (**2h**)	+134.3	75

However, because of the observed instability of the mesylates, we decided to examine the direct transformation of the alcohols into the sulfides by using the Hata reaction.[9] In this process diaryl disulfide is reduced by tributylphosphine to the thiophosphonium salt that activates an alcohol by formation of oxophosphonium salt. The salt undergoes S_N2 reaction giving the arylsulfanyl derivative as follows:

$ArSSAr + Bu_3P \rightarrow Bu_3P^+SPAr + ArS^-$
$Bu_3P^+SAr + ROH \rightarrow Bu_3P^+OR + ArSH$
$Bu_3P^+OR + ArS^- \rightarrow RSAr + Bu_3PO$ (S_N2)

Secondary alcohols are much less reactive than primary alcohols and the application of the Hata reaction to the highly hindered secondary benzylic-type alcohol has not been explored.

Thus, for the purpose of direct activation and substitution of C-9 hydroxy groups we applied our version of the Hata reaction,[10] i.e. treatment of the alkaloids with diaryl disulfide and tributylphosphine in toluene solution under argon atmosphere in a sealed tube at 65 °C, typically for 5 days. The reaction went smoothly and the products were obtained in 60–70% yields. The native alkaloids **1** were converted into the respective *epi*-arylsulfanyl derivatives **2** (Scheme 3, Table 3) and the *epi*-alkaloids **4** gave the corresponding phenyl sulfides **5** (Scheme 3, Table 4). All the products were obtained as a single diastereomer and no trace of the rearrangement products could be detected. The reaction yield decreased somewhat for bulky nucleophiles (cf. Table 3, entries 7 and 9).



1a–d; **4a–c**,**e**,**f** **2a–f**, **i–l**; **5a–c**,**e**,**f**

Scheme 3 *Reagents and conditions*: *i*) Bu_3P and $(PhS)_2$ for **2a–f** and **4**; Bu_3P and $(ArS)_2$ for **2i–l** toluene, 65 °C, 5 d. For clarity, only 9*R*-epimers of **1** are shown.

The phenylsulfanyl derivatives obtained were tested in the Pd-catalyzed allylic alkylation of dimethyl malonate with *rac*-1,3-diphenylprop-2-enyl acetate using *N*,*O*-bis(trimethylsilyl)acetamide/potassium acetate (3 mol%) as a base, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) as palladium pre-catalyst and the respective sulfide as a chiral ligand (10 mol%). The reaction was carried out in dichloromethane at 25 °C for 3–10 days as reported before.[11]

The examined derivatives showed relatively low to moderate activity (20 to 46% chemical yield). However, in the absence of ligand no product could be detected. Enantioselectivity varied from 12 and 16% ee for PhS-QD (**5e**) and PhS-CD (**5a**) to 76 and 78% ee for *epi*-PhS-CN (**2d**) and *epi*-PhS-QD (**2e**), respectively. It seems, that in this reaction the ligands of *like* configurations, e.g. (8*R*,9*R*)-**2** demonstrated much better fit than those of *unlike* configurations **5**. Further studies on the catalytic applications of the prepared *Cinchona* alkaloid derivatives are underway.

Table 3 Direct Substitution of Native Alkaloids **1** to *epi*-Sulfides **2**

Entry	Sulfide **2**	$[\alpha]_D^{25}$ (CH_2Cl_2)	Yield (%)
1	*epi*-9-PhS-CD (**2a**)	+84.3	66
2	*epi*-9-PhS-QN (**2b**)	+15.8	68
3	*epi*-9-PhS-DHQN (**2c**)	−17.0	68
4	*epi*-9-PhS-CN (**2d**)	+79.6	66
5	*epi*-9-PhS-QD (**2e**)	+177.0	72
6	*epi*-9-PhS-DHQD (**2f**)	+156.0	69
7	*epi*-9-(2-NaphthS)-QD (**2i**)	+211.7	53
8	*epi*-9-(4-$MeOC_6H_4S$)-QD (**2j**)	+154.2	66
9	*epi*-9-(2-$MeOC_6H_4S$)-QD (**2k**)	+73.7	31
10	*epi*-9-(2-$BuO_2CC_6H_4S$)-QD (**2l**)	+159.1	67

Table 4 Direct Substitution of *epi*-Alkaloids **4** to Phenyl Sulfides **5**

Entry	Sulfide **5**	$[\alpha]_D^{25}$ (CH_2Cl_2)	Yield (%)
1	9-PhS-CD (**5a**)	+19.0	75
2	9-PhS-QN (**5b**)	+62.5	65
3	9-PhS-DHQN (**5c**)	+105.3	68
4	9-PhS-QD (**5e**)	−22.5	63
5	9-PhS-DHQD (**5f**)	−15.9	70

In conclusion, the developed stereospecific substitution reaction of C-9 hydroxy group of the native- and *epi-Cinchona* alkaloids offers simple synthetic way to the corresponding diastereomeric alkyl- and arylsulfanyl derivatives, promising chiral N,S-donating ligands for asymmetric synthesis.

All procedures with ArSSAr and RSH were carried out under dry argon. All solvents were purified and dried by standard methods. The starting *Cinchona* alkaloids were commercially available and used after drying by azeotropic distillation with toluene. Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker CPX (^{1}H, 300 MHz) spectrometer using TMS as an internal standard. GC/MS spectra were determined on a Hewlett-Packard 5890 II gas chromatograph (25 m capillary column) with a Hewlett-Packard mass spectrometer 5971A operating on the electron impact mode (70 eV). Optical rotations at 578 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. Separations of products by chromatography were performed on silica gel 60 (230–400 mesh) purchased from Merck. TLC was performed using silica gel 60 pre-coated plates (Merck).

Mesylates 3; General Procedure

A solution of *Cinchona* alkaloid **1a–c**, **1e**, or **1f** (2 mmol), Et_3N (1.62 g, 2.23 mL, 16 mmol) in toluene (40 mL) was cooled to –15 °C and then $MeSO_2Cl$ (298 mg, 0.202 mL, 2.6 mmol) was added dropwise. The mixture was stirred at 0 °C overnight. The reaction was quenched with H_2O (10 mL), the product was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with H_2O (3 × 10 mL), brine (10 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude product was purified by column chromatography ($CHCl_3$–MeOH, 40:3) to furnish O-mesylated alkaloids **3a–c**, **3e** and **3f**.

9-Mesyloxycinchonidine (9-MsO-CD, 3a)

Yield: 94%; yellow solid; mp 133–134.5 °C $[\alpha]_D$ –70.5 (*c* 1.02, CH_2Cl_2); R_f = 0.47 ($CHCl_3$–MeOH, 40:3).

IR (KBr): 3003, 2944, 2871, 1594, 1511, 1365, 1164, 982, 933, 875, 528, 505 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45–1.72 (m, 3 H), 1.84 (d, *J* = 2.4 Hz, 1 H), 2.97–2.10 (m, 1 H), 2.17–2.30 (m, 1 H), 2.42–2.58 (m, 4 H), 2.88 (dd, *J* = 13.8, 3.7 Hz, 1 H), 2.99–3.04 (m, 1 H), 3.36 (br s, 1 H), 4.91–4.97 (m, 2 H, CH_2=), 5.71–5.83 (m, 1 H, CH=), 6.13 (br s, 1 H, H-9), 7.42 (d, *J* = 4.4 Hz, 1 H, ArH), 7.57 (dt, *J* = 7.6, 1.2 Hz, 1 H, ArH), 7.69 (dt, *J* = 7.6, 1.2 Hz, 1 H, ArH), 8.10 (dd, *J* = 8.5, 1.2 Hz, 2 H, ArH), 8.89 (d, *J* = 4.4 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4, 27.4, 27.7, 39.2, 39.6,[12] 42.2, 56.6, 60.3, 114.6, 119.7, 122.9, 125.5, 127.5, 129.6, 130.9, 141.6, 143.2, 148.9, 150.1.

9-Mesyloxyquinine (9-MsO-QN, 3b)

Yield: 95%; yellow solid; mp 114–116.5 °C $[\alpha]_D$ –71.9 (*c* 0.92, CH_2Cl_2); R_f = 0.48 ($CHCl_3$–MeOH, 40:3).

IR (KBr): 3028, 2944, 2869, 1620, 1507, 1476, 1353, 1221, 1180, 1027, 924, 866, 533, 504, 505 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51–1.82 (m, 3 H), 1.87–1.95 (m, 1 H), 2.05–2.15 (m, 1 H), 2.25–2.34 (m, 1 H), 2.53–2.68 (m, 5 H), 2.98 (dd, *J* = 13.7, 3.4 Hz, 1 H), 3.06–3.15 (m, 1 H), 3.42 (br s, 1 H), 3.97 (s, 3 H, OCH_3), 4.99–5.05 (m, 2 H, CH_2=), 5.79–5.91 (m, 1 H, CH=), 6.14 (br s, 1 H, H-9), 7.37–7.46 (m, 3 H, ArH), 8.06 (d, *J* = 9.2 Hz, 1 H, ArH), 8.81 (d, *J* = 4.5 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3, 27.4, 27.8, 39.2, 39.6,[12] 42.3, 55.7, 56.6, 59.9, 101.0, 114.6, 119.7, 122.2, 126.6, 132.2, 141.6, 143.0, 145.1, 147.5, 158.4.

9-Mesyloxydihydroquinine (9-MsO-DHQN, 3c)

Yield: 87%; yellow solid; mp 105–108 °C $[\alpha]_D$ –55.4 (*c* 0.94, CH_2Cl_2); R_f = 0.42 ($CHCl_3$–MeOH, 40:3).

IR (KBr): 3026, 2939, 2865, 1620, 1506, 1475, 1353, 1223, 1179, 1025, 937, 868, 533 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.23–1.41 (m, 4 H), 1.52–1.60 (m, 1 H), 1.63–1.75 (m, 1 H), 1.78–1.83 (m, 1 H), 1.90–1.98 (m, 1 H), 2.18 (d, *J* = 13.3 Hz, 1 H), 2.49–2.59 (m, 1 H), 2.52 (s, 3 H, OSO_2CH_3), 2.89 (dd, *J* = 13.5, 4.2 Hz, 1 H), 2.97–3.08 (m, 1 H), 3.34 (br s, 1 H), 3.89 (s, 3 H, OCH_3), 6.07 (br s, 1 H, H-9), 7.31–7.39 (m, 3 H, ArH), 7.98 (d, *J* = 9.2 Hz, 1 H, ArH), 8.73 (d, *J* = 4.5 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9, 24.9, 26.5, 27.3, 27.5, 36.8, 39.3, 39.4, 42.7, 56.2, 58.1, 59.5, 100.6, 119.5, 122.7, 127.7, 132.1, 140.7, 144.9, 147.3, 158.8.

9-Mesyloxyquinidine (9-MsO-QD, 3e)

Yield: 90%; yellow solid; mp 125–126.5 °C $[\alpha]_D$ +125.4 (*c* 0.94, CH_2Cl_2); R_f = 0.49 ($CHCl_3$–MeOH, 40:3).

IR (KBr): 3002, 2938, 2872, 1620, 1508, 1475, 1356, 1224, 1175, 1027, 942, 878, 850, 823, 532, 501 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53–1.59 (m, 2 H), 1.68–1.75 (m, 1 H), 1.86–1.88 (m, 1 H), 1.93–2.00 (m, 1 H), 2.24–2.32 (m, 1 H),

2.64 (s, 3 H, OSO_2CH_3), 2.67–2.72 (m, 2 H), 2.88 (d, *J* = 8.9 Hz, 2 H), 3.31–3.37 (m, 1 H), 3.96 (s, 3 H, OCH_3), 5.08–5.16 (m, 2 H, CH_2=), 5.98–6.10 (m, 1 H, CH=), 6.18 (br s, 1 H, H-9), 7.35 (br s, 1 H, ArH), 7.41 (dd, *J* = 9.2, 2.7 Hz, 1 H, ArH), 7.45 (d, *J* = 4.4 Hz, 1 H, ArH), 8.05 (d, *J* = 9.2 Hz, 1 H), 8.80 (d, *J* = 4.4 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 26.3, 27.8, 38.8, 39.1, 39.7, 49.0, 49.9, 55.7, 60.0, 101.1, 115.2, 119.5, 122.2, 126.6, 132.2, 140.0, 141.8, 145.0, 147.5, 158.4.

9-Mesyloxydihydroquinidine (9-MsO-DHQD, 3f)

Yield: 83%; yellow solid; mp 139–141.5 °C $[\alpha]_D$ +126.3 (*c* 0.92, CH_2Cl_2); R_f = 0.46 ($CHCl_3$–MeOH, 40:3).

IR (KBr): 3002, 2932, 2873, 1620, 1507, 1474, 1355, 1223, 1175, 1029, 981, 939, 850, 824, 532, 501 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.35–1.53 (m, 5 H), 1.55–1.65 (m, 1 H), 1.70–1.75 (m, 1 H), 1.79–1.86 (m, 1 H), 2.49–2.62 (m, 6 H), 2.77–2.84 (m, 1 H), 3.23–3.28 (m, 1 H), 3.89 (s, 3 H, OCH_3), 6.08 (br s, 1 H, H-9), 7.28 (br s, 1 H, ArH), 7.34 (dd, *J* = 9.2, 2.7 Hz, 1 H, ArH), 7.37 (d, *J* = 4.4 Hz, 1 H, ArH), 7.98 (d, *J* = 9.2 Hz, 1 H, ArH), 8.73 (d, *J* = 4.4 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 24.2, 25.5, 25.9, 27.1, 37.4, 39.1, 39.4, 50.0, 50.7, 55.7, 60.2, 101.2, 119.3, 122.2, 126.6, 132.2, 141.9, 145.0, 147.5, 158.3.

***epi*-Alkaloids 4a–c, 4e and 4f; General Procedure**

O-Mesylated alkaloids **3a**–**c**,**e**,**f** (1.5 mmol) were allowed to react according to a general procedure described in reference 8a (for O-tosylated alkaloids) and reference 8b with (+)-tartaric acid (234 mg, 1.56 mmol), in distilled H_2O (20 mL) for 3 h. The crude products were purified by column chromatography on silica gel using $CHCl_3$–MeOH (4:1) as eluent.

***epi*-Cinchonidine (*epi*-CD, 4a)**

Yield: 70%; oil; $[\alpha]_D$ +55.6 (*c* 0.80, EtOH) {Lit.[8a] $[\alpha]_D$ +56.9 (*c* 1.29, EtOH)}.

The spectral data were in accordance with literature values.[8b]

***epi*-Quinine (*epi*-QN, 4b)**

Yield: 78%; oil; $[\alpha]_D$ +39.5 (*c* 0.96, EtOH) {Lit.[8a] $[\alpha]_D$ +39.9 (*c* 1.13, EtOH)}.

The spectral data were in accordance with literature values.[8a,13]

***epi*-Dihydroquinine (*epi*-DHQN, 4c)**

Yield: 76%; oil; $[\alpha]_D$ +30.6 (*c* 0.84, EtOH) {Lit.[14] $[\alpha]_D$ +32.5 (*c* 0.97, EtOH)}.

IR (film): 3336, 2932, 1621, 1591, 1508, 1456, 1359, 1241, 1082, 1033, 855, 736 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.92–0.99 (m, 1 H), 1.23–1.32 (m, 2 H), 1.37–1.69 (m, 6 H), 2.46–2.53 (m, 1 H), 2.73–2.82 (m, 1 H), 3.03–3.29 (m, 3 H), 3.95 (s, 3 H, OCH_3), 5.01 (d, *J* = 10.0 Hz, 1 H, H-9), 7.38 (dd, *J* = 9.2, 2.7 Hz, 1 H, ArH), 7.42 (d, *J* = 4.5 Hz, 1 H, ArH), 7.67 (d, *J* = 2.7 Hz, 1 H, ArH), 8.04 (d, *J* = 9.2 Hz, 1 H, ArH), 8.75 (d, *J* = 4.5 Hz, 1 H, ArH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 11.8, 24.4, 24.7, 27.3, 27.5, 36.9, 41.0, 55.8, 57.0, 61.6, 70.6, 102.5, 120.2, 121.6, 128.1, 131.6, 144.1, 144.8, 147.6, 157.7.

***epi*-Quinidine (*epi*-QD, 4e)**

Yield: 75%; oil; $[\alpha]_D$ +96.9 (*c* 1.12, EtOH) {Lit.[8a] $[\alpha]_D$ +96.3 (*c* 1.15, EtOH)}.

The spectral data were in accord with literature values.[8a,13]

***epi*-Dihydroquinidine (*epi*-DHQD, 4f)**

Yield: 78%; oil; $[\alpha]_D$ +73.0 (*c* 0.96, EtOH) {Lit.[14] $[\alpha]_D$ +73.7 (*c* 0.33, EtOH)}.

The spectral data were in accord with literature values.[13,15]

Sulfanyl Derivatives of *Cinchona* Alkaloids 2 and 5; General Procedure

A solution of alkaloid **1** or **4** (1 mmol), ArSSAr (3 mmol), and Bu_3P (585 mg, 0.713 mL, 4 mmol) in anhyd toluene (8 mL) was placed under argon in an ampoule. The sealed tube was heated at 65 °C for 5 d. Thereafter, the cooled mixture was diluted with Et_2O (5 mL) and washed with aq 5% NaOH (5 mL). The organic phase was washed with H_2O (2 × 5 mL) and then with 1 M HCl (3 × 5 mL). The combined acid layers were basified to pH 12 with aq 10% NaOH and extracted with Et_2O (3 × 5 mL). The Et_2O solution was washed with H_2O, brine, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography on silica gel ($CHCl_3$–*t*-BuOMe, 1:1) and recrystallized from CH_2Cl_2–hexane.

(1*S*,3*R*,4*S*,8*S*,9*S*)-9-Phenylsulfanylcinchonan (9-Phenylsulfanyl-*epi*-cinchonidine, 9-PhS-*epi*-CD, 2a)

Yield: 66%; white crystals; mp 86.5–87.5 °C; $[\alpha]_D$ +84.3 (*c* 0.94, CH_2Cl_2).

IR (KBr): 2920, 2863, 1585, 1506, 1472, 1049, 917, 765, 695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75–0.79 (m, 1 H), 1.51–1.64 (m, 4 H), 2.27–2.36 (m, 1 H), 2.85–2.99 (m, 2 H), 3.31–3.45 (m, 3 H), 4.98–5.04 (m, 2 H, CH_2=), 5.18 (d, *J* = 11.0 Hz, 1 H, H-9), 5.75–5.86 (m, 1 H, CH=), 6.93–7.08 (m, 5 H, SC_6H_5), 7.40 (d, *J* = 4.2 Hz, 1 H, ArH), 7.47 (t, *J* = 7.4 Hz, 1 H, ArH), 7.64 (t, *J* = 7.4 Hz, 1 H, ArH), 7.93 (d, *J* = 8.5 Hz, 1 H, ArH), 8.04 (d, *J* = 8.5 Hz, 1 H, ArH), 8.81 (d, *J* = 4.2 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 27.9, 28.0, 39.3, 41.0, 49.6, 56.3, 60.1, 114.5, 120.2, 122.3, 126.6, 127.8, 127.9, 128.4, 129.0, 130.4, 132.9, 134.4, 141.6, 146.4, 148.2, 150.0.

MS (EI, 70 eV): *m*/*z* = 386 (1, [M$^+$]), 277 (18), 181 (7), 167 (19), 136 (100), 109 (7), 42 (8).

Anal. Calcd for $C_{25}H_{26}N_2OS$: C, 77.68; H, 6.78; N, 7.24; S, 8.30. Found: C, 77.45; H, 6.79; N, 7.22; S, 8.34.

(1*S*,3*R*,4*S*,8*S*,9*S*)-6′-Methoxy-9-phenylsulfanylcinchonan (9-Phenylsulfanyl-*epi*-quinine, 9-PhS-*epi*-QN, 2b)

Yield: 68%; white crystals; mp 85.5–87.0 °C; $[\alpha]_D$ +15.8 (*c* 0.98, CH_2Cl_2).

IR (KBr): 2939, 2853, 1617, 1508, 1454, 1254, 1166, 1087, 1036, 917, 844, 739, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.73–0.77 (m, 1 H), 1.59–1.65 (m, 4 H), 2.28–2.35 (m, 1 H), 2.84–2.99 (m, 2 H), 3.34–3.41 (m, 3 H), 3.88 (s, 3 H, OCH_3), 4.99–5.05 (m, 3 H, CH_2=, H-9), 5.76–5.87 (m, 1 H, CH=), 6.94–7.10 (m, 6 H, SC_6H_5 + ArH), 7.30–7.40 (m, 2 H, ArH), 7.95 (d, *J* = 9.2 Hz, 1 H, ArH), 8.67 (d, *J* = 4.3 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 28.1, 28.2, 39.3, 41.0, 49.9, 55.5, 56.3, 60.0, 101.0, 114.5, 120.3, 121.1, 127.8, 128.4, 128.9, 131.9, 133.1, 134.4, 141.6, 144.5, 144.8, 147.6, 157.8.

Anal. Calcd for $C_{26}H_{28}N_2OS$: C, 74.96; H, 6.78; N, 6.72; S, 7.70. Found: C, 75.08; H, 6.75; N, 6.70; S, 7.66.

(1*S*,3*R*,4*S*,8*S*,9*S*)-10,11-Dihydro-6′-methoxy-9-phenylsulfanylcinchonan (9-Phenylsulfanyl-*epi*-dihydroquinine, 9-PhS-*epi*-DHQN, 2c)

Yield: 68%; colorless oil; $[\alpha]_D$ –17.0 (*c* 0.94, CH_2Cl_2); R_f = 0.26 ($CHCl_3$–*t*-BuOMe, 1:1).

IR (film): 2932, 2862, 1620, 1585, 1508, 1438, 1239, 1033, 912, 833, 733, 693, 627 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.26–1.33 (m, 2 H), 1.46–1.60 (m, 6 H), 2.55–2.60 (m, 1 H), 2.89–2.96 (m, 1 H), 3.31–3.42 (m, 3 H,), 3.88 (s, 3 H, OCH_3), 5.04 (d, *J* = 10.9 Hz, 1 H, H-9), 6.95–7.10 (m, 6 H, SC_6H_5 + ArH), 7.30–7.39 (m, 2 H, ArH), 7.95 (d, *J* = 9.2 Hz, 1 H, ArH), 8.67 (d, *J* = 3.4 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 25.7, 27.6, 27.8, 28.8, 37.0, 41.1, 50.0, 55.5, 58.0, 60.1, 101.0, 120.4, 121.2, 127.7, 128.4, 128.9, 131.8, 133.3, 134.3, 144.4, 145.1, 147.6, 157.7.

Anal. Calcd for $C_{26}H_{30}N_2OS$: C, 74.60; H, 7.23; N, 6.69; S, 7.66. Found: C, 74.42; H, 7.21; N, 6.71; S, 7.69

(1*S*,3*R*,4*S*,8*R*,9*R*)-9-Phenylsulfanylcinchonan (9-Phenylsulfanyl-*epi*-cinchonine, 9-PhS-*epi*-CN, 2d)
Yield: 66%; white crystals; mp 73.5–74.5 °C; $[\alpha]_D$ +79.6 (*c* 1.02, CH_2Cl_2).

IR (KBr): 3073, 2936, 2870, 1587, 1508, 1453, 1056, 915, 770, 739, 693, 622 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 8.5 Hz, 2 H), 1.51–1.64 (m, 3 H), 2.29–2.36 (m, 1 H), 3.02–3.32 (m, 5 H), 5.05–5.11 (m, 2 H, CH_2=), 5.25 (d, *J* = 10.9 Hz, 1 H, H-9), 5.79–5.90 (m, 1 H, CH=), 6.92–7.09 (m, 5 H, SC_6H_5), 7.44 (d, *J* = 4.6 Hz, 1 H, ArH), 7.49 (t, *J* = 7.6 Hz, 1 H, ArH), 7.66 (t, *J* = 7.6 Hz, 1 H, ArH), 7.95 (d, *J* = 8.5 Hz, 1 H, ArH), 8.05 (d, *J* = 8.5 Hz, 1 H, ArH), 8.81 (d, *J* = 4.6 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5, 27.2, 27.8, 39.6, 47.5, 48.8, 49.6, 60.4, 114.7, 120.1, 122.3, 126.6, 127.6, 128.0, 128.4, 129.0, 130.4, 133.2, 134.0, 140.7, 146.6, 148.2, 149.9.

Anal. Calcd for $C_{25}H_{26}N_2OS$: C, 77.68; H, 6.78; N, 7.24; S, 8.30. Found: C, 77.41; H, 6.81; N, 7.26; S, 8.33.

(1*S*,3*R*,4*S*,8*R*,9*R*)-6′-Methoxy-9-phenylsulfanylcinchonan (9-Phenylsulfanyl-*epi*-quinidine, 9-PhS-*epi*-QD, 2e)
Yield: 72%; white crystals; mp 153–153.5 °C; $[\alpha]_D$ +177 (*c* 0.98, CH_2Cl_2).

IR (KBr): 3059, 2934, 1665, 1603, 1494, 1447, 1048, 897, 751, 693 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 7.7 Hz, 2 H), 1.47–1.58 (m, 3 H), 2.23–2.27 (m, 1 H), 2.97–3.24 (m, 5 H), 3.80 (s, 3 H, OCH_3), 4.98–5.05 (m, 3 H, CH_2=, H-9), 5.75–5.86 (m, 1 H, CH=), 6.88–7.04 (m, 6 H, SC_6H_5 + ArH), 7.22–7.24 (m, 1 H, ArH), 7.36 (d, *J* = 4.4 Hz, 1 H, ArH), 7.86 (d, *J* = 9.2 Hz, 1 H, ArH), 8.59 (d, *J* = 4.4 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.9, 27.7, 28.1, 39.8, 47.8, 49.6, 50.0, 55.8, 60.8, 100.7, 115.0, 120.7, 122.0, 128.0, 128.8, 128.9, 132.2, 133.9, 134.2, 141.4, 144.8, 145.5, 147.9, 158.2.

MS (EI, 70 eV): *m*/*z* = 416 (5, [M^+]), 308 (23), 307 (100), 281 (8), 253 (10), 184 (11), 172 (12), 155 (16), 136 (39), 109 (14), 81 (12), 42 (11).

Anal. Calcd for $C_{26}H_{28}N_2OS$: C, 74.96; H, 6.78; N, 6.72; S, 7.70. Found: C, 74.84; H, 6.81; N, 6.66; S, 7.74.

(1*S*,3*R*,4*S*,8*R*,9*R*)-10,11-Dihydro-6′-methoxy-9-phenylsulfanylcinchonan (9-Phenylsulfanyl-*epi*-dihydroquinidine, 9-PhS-*epi*-DHQD, 2f)
Yield: 69%; white crystals; mp 150–151 °C; $[\alpha]_D$ +156 (*c* 0.94, CH_2Cl_2).

IR (KBr): 2866, 2830, 1619, 1586, 1505, 1479, 1237, 1214, 1028, 846, 822, 743, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.97–1.05 (m, 2 H), 1.19–1.33 (m, 2 H), 1.35–1.53 (m, 4 H), 2.62–2.67 (m, 1 H), 2.93–3.02 (m, 2 H), 3.07–3.22 (m, 2 H), 3.80 (s, 3 H, OCH_3), 5.05 (d, *J* = 11.0 Hz, 1 H, H-9), 6.85–6.94 (m, 3 H, SC_6H_5), 7.00–7.05 (m, 3 H, SC_6H_5, ArH), 7.24 (dd, *J* = 9.2, 2.3 Hz, 1 H, ArH), 7.34 (d, *J* = 4.6 Hz, 1 H, ArH), 7.87 (d, *J* = 9.2 Hz, 1 H, ArH), 8.59 (d, *J* = 4.6 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 26.0, 26.2, 27.0, 27.2, 37.6, 49.1, 49.6, 49.7, 55.4, 60.5, 100.4, 120.4, 121.5, 123.8, 127.5, 128.4, 129.0, 131.9, 133.8, 144.4, 145.1, 147.6, 157.8.

Anal. Calcd for $C_{26}H_{30}N_2OS$: C, 74.60; H, 7.23; N, 6.69; S, 7.66. Found: C, 74.26; H, 7.19; N, 6.55; S, 8.00.

9-(2-Naphthylsulfanyl)-*epi*-quinidine [9-(2-NaphthS)-*epi*-QD, 2i]
Yield: 53%; light yellow oil; $[\alpha]_D$ +211.7 (*c* 0.80, CH_2Cl_2); R_f = 0.25 ($CHCl_3$–*t*-BuOMe, 1:1).

IR (film): 3056, 2938, 1622, 1505, 1462, 1237, 1081, 1032, 913, 848, 751 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 7.7 Hz, 2 H), 1.58–1.66 (m, 3 H), 2.32–2.38 (m, 1 H), 3.11–3.35 (m, 5 H), 3.84 (s, 3 H, OCH_3), 5.06–5.14 (m, 2 H, CH_2=), 5.23 (d, *J* = 10.9 Hz, 1 H, H-9), 5.84–5.95 (m, 1 H, CH=), 7.16–7.63 (m, 10 H, ArH), 7.92 (d, *J* = 9.2 Hz, 1 H, ArH), 8.64 (d, *J* = 4.4 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.5, 27.3, 27.8, 39.4, 47.5, 49.0, 49.6, 55.4, 60.5, 100.4, 114.6, 120.3, 121.6, 126.2, 126.3, 127.2, 127.5, 127.9, 128.9, 130.4, 131.2, 131.9, 132.3, 132.4, 133.3, 140.9, 144.5, 145.1, 147.6, 157.9.

Anal. Calcd for $C_{30}H_{30}N_2OS$: C, 77.22; H, 6.48; N, 6.00; S, 7.87. Found: C, 77.23; H, 6.48; N, 5.64; S, 7.50.

9-(4-Methoxyphenylsulfanyl)-*epi*-quinidine [9-(4-$MeOC_6H_4S$)-*epi*-QD, 2j]
Yield: 66%; colorless oil; $[\alpha]_D$ +154.2 (*c* 0.88, CH_2Cl_2); R_f = 0.18 ($CHCl_3$–*t*-BuOMe, 1:1).

IR (film): 3073, 2944, 1621, 1590, 1505, 1468, 1361, 1243, 1176, 1087, 916, 829, 753 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.95–1.09 (m, 1 H), 1.16–1.24 (m, 1 H), 1.56–1.64 (m, 3 H), 2.27–2.35 (m, 1 H), 3.03–3.31 (m, 5 H), 3.64 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.94–5.11 (m, 3 H, CH_2=, H-9), 5.79–5.90 (m, 1 H, CH=), 6.50 (d, *J* = 8.6 Hz, 2 H, SC_6H_5), 6.98–7.04 (m, 3 H, SC_6H_5), 7.25–7.31 (m, 2 H, ArH), 7.93 (d, *J* = 9.2 Hz, 1 H, ArH), 8.65 (d, *J* = 4.6 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.6, 27.5, 27.8, 39.5, 47.4, 49.6, 49.9, 55.2, 55.4, 59.4, 100.6, 114.0, 114.5, 120.2, 121.5, 123.4, 128.9, 131.7, 136.9, 141.0, 144.5, 145.0, 147.4, 157.8, 159.9.

Anal. Calcd for $C_{27}H_{30}N_2O_2S$: C, 72.61; H, 6.77; N, 6.27; S, 7.18. Found: C, 72.32; H, 6.80; N, 6.23; S, 7.22.

9-(2-Methoxyphenylsulfanyl)-*epi*-quinidine [9-(2-$MeOC_6H_4S$)-*epi*-QD, 2k]
Yield: 31%; white crystals; mp 168.5–171 °C; $[\alpha]_D$ +73.7 (*c* 1.00, CH_2Cl_2).

IR (KBr): 3068, 2933, 2868, 1618, 1584, 1505, 1474, 1430, 1242, 1026, 825, 749 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.07–1.26 (m, 2 H), 1.56–1.65 (m, 3 H), 2.30–2.36 (m, 1 H), 3.02–3.33 (m, 5 H), 3.64 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.07–5.19 (m, 2 H, CH_2=), 5.45 (d, *J* = 11.0 Hz, 1 H, H-9), 5.89–6.01 (m, 1 H, CH=), 6.48–6.56 (m, 2 H, SC_6H_5), 6.94–6.99 (m, 2 H, SC_6H_5), 7.10 (d, *J* = 6.9 Hz, 1 H, SC_6H_5), 7.21–7.29 (m, 1 H, ArH), 7.55 (d, *J* = 4.6 Hz, 1 H, ArH), 7.88 (d, *J* = 9.1 Hz, 1 H, ArH), 8.64 (d, *J* = 4.6 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.6, 27.2, 27.7, 39.4, 47.3, 47.5, 49.3, 55.3, 55.7, 61.4, 100.8, 110.5, 114.4, 120.6, 120.9, 121.4, 123.5, 129.2, 129.5, 131.6, 136.0, 141.4, 144.3, 145.7, 147.5, 157.5, 159.5.

Anal. Calcd for $C_{27}H_{30}N_2O_2S$: C, 72.61; H, 6.77; N, 6.27; S, 7.18. Found: C, 72.46; H, 6.79; N, 6.25; S, 7.21

9-(2-Butoxycarbonylphenylsulfanyl)-*epi*-quinidine [9-(2-BuO$_2$CC$_6$H$_4$S)-*epi*-QD, 2l]

Yield: 67%; yellow oil, which solidified later; $[\alpha]_D$ +159.1 (*c* 0.90, CH_2Cl_2); R_f = 0.26 (EtOAc–hexane, 9:1).

IR (KBr): 3071, 2934, 1717, 1618, 1582, 1506, 1463, 1359, 1246, 1111, 1056, 912, 848, 748 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.09–1.20 (m, 2 H), 1.40–1.62 (m, 5 H), 1.69–1.76 (m, 2 H), 2.29–2.33 (m, 1 H), 2.97–3.13 (m, 3 H), 3.26–3.33 (m, 2 H), 3.88 (s, 3 H, OCH_3), 4.33 (t, *J* = 6.3 Hz, 2 H, OCH_2), 5.10 (d, *J* = 10.5 Hz, 1 H, CH_2=), 5.23 (d, *J* = 17.2 Hz, 1 H, CH_2=), 5.62 (d, *J* = 10.8 Hz, 1 H, H-9), 5.87–5.98 (m, 1 H, CH=), 6.76–6.97 (m, 3 H, SC_6H_5), 7.20–7.26 (m, 1 H, ArH), 7.35 (s, 1 H, ArH), 7.42 (d, *J* = 7.6 Hz, 1 H, SC_6H_5), 7.70 (d, *J* = 4.3 Hz, 1 H, ArH), 7.85 (d, *J* = 9.1 Hz, 1 H, ArH), 8.71 (d, *J* = 4.3 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.3, 26.6, 27.0, 27.8, 30.7, 39.4, 46.9, 49.2, 49.6, 55.4, 61.3, 65.2, 100.5, 114.4, 120.6, 121.9, 127.1, 128.9, 129.6, 130.3, 131.4, 134.0, 135.3, 136.2, 141.0, 144.4, 145.6, 147.6, 157.7, 167.7.

Anal. Calcd for $C_{31}H_{36}N_2O_3S$: C, 72.06; H, 7.02; N, 5.42; S, 6.21. Found: C, 71.85; H, 6.99; N, 5.38; S, 6.24.

(1*S*,3*R*,4*S*,8*S*,9*R*)-9-Phenylsulfanylcinchonan (9-Phenylsulfanylcinchonidine, 9-PhS-CD, 5a)

Yield: 75%; oil; $[\alpha]_D$ +19.0 (*c* 0.84, CH_2Cl_2); R_f = 0.24 ($CHCl_3$–*t*-BuOMe, 1:1).

IR (film): 2938, 2862, 1636, 1588, 1508, 1470, 1263, 1025, 913, 766, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51–1.62 (m, 3 H), 1.85 (s, 1 H), 2.17–2.21 (m, 1 H), 2.32–2.40 (m, 2 H), 2.52–2.57 (m, 1 H), 2.66–2.78 (m, 1 H), 2.90–2.98 (m, 1 H), 3.16–3.21 (m, 1 H), 4.78 (d, *J* = 9.2 Hz, 1 H, H-9), 4.98–5.04 (m, 2 H, CH_2=), 5.85–5.90 (m, 1 H, CH=), 6.81–7.19 (m, 6 H, SC_6H_5 + ArH), 7.39–7.48 (m, 1 H, ArH), 7.58 (t, *J* = 7.4 Hz, 1 H, ArH), 7.89–7.91 (m, 1 H, ArH), 8.01 (d, *J* = 8.4 Hz, 1 H, ArH), 8.63 (d, *J* = 3.6 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9, 27.3, 28.1, 38.6, 40.3, 50.6, 55.0, 56.7, 113.4, 118.6, 121.3, 125.2, 125.6, 127.5, 127.6, 129.5, 129.8, 130.5, 134.6, 140.9, 145.3, 147.1, 148.6.

Anal. Calcd for $C_{25}H_{26}N_2OS$: C, 77.68; H, 6.78; N, 7.24; S, 8.30. Found: C, 77.40; H, 6.81; N, 7.21; S, 8.33.

(1*S*,3*R*,4*S*,8*S*,9*R*)-6′-Methoxy-9-phenylsulfanylcinchonan (9-Phenylsulfanylquinine, 9-PhS-QN, 5b)

Yield: 65%; oil, which solidified later; $[\alpha]_D$ +62.5 (*c* 0.32, CH_2Cl_2); R_f = 0.23 ($CHCl_3$–*t*-BuOMe, 1:1).

IR (film): 2936, 1621, 1586, 1505, 1471, 1360, 1224, 1086, 1026, 911, 833, 748, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.69 (m, 4 H), 1.87 (s, 1 H), 2.22 (s, 1 H), 2.35–2.39 (m, 2 H), 2.57–2.60 (m, 1 H), 2.74 (br s, 1 H), 2.88–2.98 (m, 1 H), 3.19–3.26 (m, 1 H), 3.82 (s, 3 H, OCH_3), 4.99–5.05 (m, 3 H, CH_2=, H-9), 5.83–5.94 (m, 1 H, CH=), 6.83–7.28 (m, 8 H, SC_6H_5, ArH), 7.91 (d, *J* = 9.2 Hz, 1 H, ArH), 8.50 (d, *J* = 3.4 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9, 28.3, 28.8, 39.5, 41.4, 51.8, 55.6, 56.0, 57.7, 101.0, 114.6, 120.0, 121.0, 127.2, 127.6, 128.6, 128.7, 131.9, 135.4, 141.8, 144.8, 147.2, 151.4, 157.7.

Anal. Calcd for $C_{26}H_{28}N_2S$: C, 74.96; H, 6.78; N, 6.72; S, 7.70. Found: C, 75.10; H, 6.72; N, 6.69; S, 7.67.

(1*S*,3*R*,4*S*,8*S*,9*R*)-10,11-Dihydro-6′-methoxy-9-phenylsulfanylcinchonan (9-Phenylsulfanyldihydroquinine, 9-PhS-DHQN, 5c)

Yield: 68%; oil; $[\alpha]_D$ +105.3 (*c* 0.98, CH_2Cl_2); R_f = 0.20 ($CHCl_3$–*t*-BuOMe, 1:1).

IR (film): 2932, 1621, 1587, 1508, 1472, 1260, 1088, 1033, 834, 751, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.34–1.50 (m, 4 H), 1.62–1.70 (m, 2 H), 1.87 (s, 1 H), 2.31–2.46 (m, 3 H), 2.72–2.83 (m, 1 H), 2.93–3.04 (m, 1 H), 3.20–3.26 (m, 1 H), 3.86 (s, 3 H, OCH_3), 4.69 (d, *J* = 9.2, 1 H, H-9), 7.01–7.32 (m, 8 H, SC_6H_5 + ArH), 7.97 (d, *J* = 9.2 Hz, 1 H, ArH), 8.56 (s, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2, 26.1, 27.8, 28.7, 28.8, 37.3, 41.5, 52.1, 55.5, 57.8, 59.9, 101.0, 119.9, 120.9, 127.6, 128.6, 128.7, 131.5, 131.9, 135.3, 144.8, 145.0, 147.3, 157.6.

Anal. Calcd for $C_{26}H_{30}N_2OS$: C, 74.60; H, 7.23; N, 6.69; S, 7.66. Found: C, 74.27; H, 6.91; N, 6.58; S, 7.65.

(1*S*,3*R*,4*S*,8*R*,9*S*)-6′-Methoxy-9-phenylsulfanylcinchonan (9-Phenylsulfanylquinidine, 9-PhS-QD, 5e)

Yield: 63%; oil; $[\alpha]_D$ –22.5 (*c* 0.94, CH_2Cl_2); R_f = 0.19 ($CHCl_3$–*t*-BuOMe, 1:1).

IR (film): 2935, 1621, 1587, 1508, 1472, 1432, 1244, 1032, 913, 831, 750, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.71 (m, 3 H), 1.94–2.11 (m, 1 H), 2.16–2.26 (m, 1 H), 2.61–2.81 (m, 5 H), 3.22–3.31 (m, 1 H), 3.85 (s, 3 H, OCH_3), 4.78 (d, *J* = 9.2 Hz, 1 H, H-9), 5.00–5.14 (m, 2 H, CH_2=), 5.94–6.05 (m, 1 H, CH=), 6.90–7.21 (m, 7 H, SC_6H_5 + ArH), 7.30 (dd, *J* = 9.2, 2.4 Hz, 1 H, ArH), 7.97 (d, *J* = 9.2 Hz, 1 H, ArH), 8.58 (s, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.6, 27.3, 28.3, 39.6, 47.9, 49.4, 51.3, 55.4, 58.1, 100.9, 114.6, 119.7, 121.1, 127.8, 128.4, 128.7, 131.5, 131.9, 134.7, 140.8, 144.8, 145.4, 147.3, 157.6.

MS (EI, 70 eV): *m*/*z* = 416 (14, [M$^+$]), 337 (12), 307 (100), 306 (16), 274 (12), 196 (34), 186 (21), 154 (22), 108 (17), 81 (22), 55 (21).

Anal. Calcd for $C_{26}H_{28}N_2S$: C, 74.96; H, 6.78; N, 6.72; S, 7.70. Found: C, 74.72; H, 6.81; N, 6.69; S, 7.73.

(1*S*,3*R*,4*S*,8*R*,9*S*)-10,11-Dihydro-6′-methoxy-9-phenylsulfanylcinchonan (9-Phenylsulfanyldihydroquinidine, 9-PhS-DHQD, 5f)

Yield: 70%; oil; $[\alpha]_D$ –15.9 (*c* 0.88, CH_2Cl_2); R_f = 0.19 ($CHCl_3$–*t*-BuOMe, 1:1).

IR (film): 2931, 2869, 1621, 1587, 1507, 1472, 1227, 1086, 1033, 846, 830, 747, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.32–1.50 (m, 4 H), 1.55–1.70 (m, 1 H), 1.80 (s, 1 H), 1.89–1.92 (m, 1 H), 2.00–2.08 (m, 1 H), 2.33–2.39 (m, 1 H), 2.66–2.77 (m, 3 H), 3.20–3.25 (m, 1 H), 3.87 (s, 3 H, OCH_3), 4.79 (d, *J* = 8.0 Hz, 1 H, H-9), 6.98–7.20 (m, 7 H, SC_6H_5 + ArH), 7.30 (dd, *J* = 9.2, 2.6 Hz, 1 H, ArH), 7.96 (d, *J* = 9.2 Hz, 1 H, ArH), 8.57 (s, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 25.8, 26.7, 27.4, 28.2, 37.6, 49.5, 49.9, 51.3, 55.5, 58.3, 101.1, 119.7, 120.9, 127.8, 128.3, 128.7, 131.5, 131.9, 134.6, 144.8, 145.6, 147.4, 157.5.

Anal. Calcd for $C_{26}H_{30}N_2OS$: C, 74.60; H, 7.23; N, 6.69; S, 7.66. Found: C, 74.26; H, 7.30; N, 6.71; S, 7.50.

Sulfanyl Derivatives of *Cinchona* Alkaloids 2 from Mesylates 3; General Procedure

A solution of thiophenol (110 mg, 0.104 mL, 1 mmol) for the preparation of **2a** and **2b** or ethyl thioglycolate (120 mg, 0.112 mL, 1 mmol) for **2g** or benzyl mercaptan (124 mg, 0.117 mL, 1 mmol) for **2h** in anhyd toluene (2 mL) was added to a stirred solution of NaOH (0.048 g, 1.2 mmol) in absolute EtOH (5 mL) at r.t. under argon. Stirring was continued for 5 min and then the solvents were removed under reduced pressure. The residue was dissolved in anhyd DMF (4 mL) and the appropriate mesylate (**9**-MsO-CD or **9**-MsO-QN, 1 mmol) in anhyd toluene (5 mL) was added. The resulting mixture was kept for 2–3 days at r.t. under argon and then most of the solvents were evaporated. The reaction residue was dissolved in Et_2O (10 mL), diluted with aq 5% NaOH (3 mL) and the organic phase was washed with H_2O (2 × 3 mL), brine and dried (Na_2SO_4). After removal of solvent, the crude product was purified by chromatography on silica gel (EtOAc–hexane, 9:1).

9-PhS-*epi*-CD (2a)

Yield: 84%; $[\alpha]_D$ +83.7 (*c* 0.90, CH_2Cl_2); >97% pure (by GC). GC retention time: 34.3 min (from 130 to 280 °C, 6 °C/min).

9-PhS-*epi*-QN (2b)

Yield: 73%; $[\alpha]_D$ +15.1 (*c* 0.96, CH_2Cl_2); >97% pure (by GC). GC retention time: 39.1 min (from 130 to 290 °C, 6 °C/min).

IR and NMR spectra for **2a** and **2b** are identical with those described above for the respective Hata reaction products.

9-(Ethoxycarbonylmethylsulfanyl)-*epi*-quinine [9-(EtO_2CCH_2S)-*epi*-QN, 2g]

Yield: 79%; light yellow oil; $[\alpha]_D$ +184.5 (*c* 0.90, CH_2Cl_2); R_f = 0.32 (EtOAc–hexane, 9:1).

IR (film): 3074, 2941, 1731, 1621, 1586, 1508, 1473, 1363, 1287, 1240, 1151, 1030, 918, 842, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.70–0.77 (m, 1 H), 1.15 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.47–1.63 (m, 4 H), 2.25–2.33 (m, 1H), 2.74–2.88 (m, 3 H), 3.21–3.44 (m, 4 H), 4.00 (s, 3 H, OCH_3), 4.05–4.09 (m, 2 H, OCH_2), 4.97–5.03 (m, 2 H, CH_2=), 5.29 (d, *J* = 11.2 Hz, 1 H, H-9), 5.73–5.85 (m, 1 H, CH=), 7.39 (dd, *J* = 9.2, 2.5 Hz, 1 H, ArH), 7.56 (d, *J* = 2.5 Hz, 1 H, ArH), 7.58 (d, *J* = 4.6 Hz, 1 H, ArH), 8.04 (d, *J* = 9.2 Hz, 1 H, ArH), 8.78 (d, *J* = 4.6 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 27.6, 27.8, 28.0, 32.2, 39.3, 40.8, 45.1, 55.6, 56.2, 61.1, 62.0, 101.2, 114.4, 120.6, 121.9, 129.4, 131.9, 141.5, 144.6, 144.9, 147.9, 158.3, 171.1.

Anal. Calcd for $C_{24}H_{30}N_2O_3S$: C, 67.57; H, 7.09; N, 6.57; S, 7.52. Found: C, 67.35; H, 7.12; N, 6.53; S, 7.56.

9-(Benzylsulfanyl)-*epi*-quinine [9-(BnS)-*epi*-QN, 2h]

Yield: 75%; light yellow oil; $[\alpha]_D$ +134.3 (*c* 0.96, CH_2Cl_2); R_f = 0.26 (EtOAc–hexane, 9:1).

IR (film): 3064, 2943, 1621, 1586, 1507, 1472, 1453, 1360, 1240, 1031, 915, 833, 732 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.71–0.76 (m, 1 H), 1.34–1.55 (m, 4 H), 2.22–2.24 (m, 1 H), 2.74–2.84 (m, 2 H), 3.12–3.35 (m, 4 H), 3.45–3.51 (m, 1 H), 3.72 (s, 3 H, OCH_3), 4.63 (d, *J* = 11.0 Hz, 1 H, H-9), 4.92–4.99 (m, 2 H, CH_2=), 5.67–5.76 (m, 1 H, CH=), 6.80 (d, *J* = 2.4 Hz, 1 H, C_6H_5), 6.95–6.97 (m, 2 H, C_6H_5), 7.12–7.21 (m, 3 H, C_6H_5 + ArH), 7.36 (dd, *J* = 9.2, 2.5 Hz, 1 H, ArH), 7.76 (d, *J* = 4.6 Hz, 1 H, ArH), 8.03 (d, *J* = 9.2 Hz, 1 H, ArH), 8.81 (d, *J* = 4.6 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.2, 27.6, 28.1, 34.8, 39.3, 40.9, 44.7, 55.2, 56.2, 62.0, 100.7, 114.4, 120.9, 121.7, 126.8, 128.2, 128.9, 129.2, 131.9, 138.1, 141.5, 144.6, 145.2, 148.0, 157.7.

Anal. Calcd for $C_{27}H_{30}N_2OS$: C, 75.31; H, 7.02; N, 6.50; S, 7.45. Found: C, 75.03; H, 6.98; N, 6.43; S, 7.40.

References

(1) (a) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87. (b) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961.

(2) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Dihydroxylation,* In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, **2000**, 357–398. (c) Bolm, C.; Hildebrand, J. P.; Muniz, K. *Recent Advances in Asymmetric Dihydroxylation and Aminohydroxylation,* In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, **2000**, 398–428.

(3) (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (c) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (d) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (e) Corey, E. J.; Zhang, F.-Y. *Angew. Chem.* **1999**, *111*, 2057. (f) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 1097. (g) O'Donnell, M. J. *Asymmetric Phase-Transfer Reactions,* In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, **2000**, 727–755. (h) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195. (i) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542.

(4) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.

(5) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

(6) Hoffmann, H. M. R.; Frackenpohl, J. *Eur. J. Org. Chem.* **2004**, 4293; and references cited therein.

(7) (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Tsuji, J. *Pure Appl. Chem.* **1999**, *71*, 1539. (c) Lubbers, T.; Metz, P. In *Houben–Weyl, Methods of Organic Chemistry, Stereoselective Synthesis*, Vol. E21c; Thieme Verlag: Stuttgart, **1995**, 2371–2473. (d) *Comprehensive Asymmetric Catalysis*, Vol. 1-3; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**. (e) Adams, H.; Anderson, J. C.; Cubbon, R.; James, D. S.; Mathias, J. P. *J. Org. Chem.* **1999**, *64*, 8256. (f) Hiroi, K.; Suzuki, Y. *Polyhedron* **2000**, *19*, 525. (g) Bayon, J. C.; Claver, C.; Masdeu-Bulto, A. M. *Coord. Chem. Rev.* **1999**, *193-195*, 73. (h) Skarżewski, J.; Gupta, A.; Wojaczyńska, E.; Siedlecka, R. *Synlett* **2003**, 1615. (i) Siedlecka, R.; Wojaczyńska, E.; Skarżewski, J. *Tetrahedron: Asymmetry* **2004**, *15*, 1437.

(8) (a) Hiratake, I.; Inagaki, M.; Yamamoto, Y.; Oda, I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1053. (b) Franz, M. H.; Röper, S.; Wartchow, R.; Hoffmann, H. M. R. *J. Org. Chem.* **2004**, *69*, 2983.

(9) (a) Hata, T.; Sekine, M. *Chem. Lett.* **1974**, *15*, 837. (b) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409. (c) Nakagawa, I.; Aki, K.; Hata, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1315. (d) For a review, see: Valentine, D. H.; Hillhouse, J. H. *Synthesis* **2003**, 317.

(10) Siedlecka, R.; Skarżewski, J. *Synlett* **1996**, 757.

(11) For experimental details, see reference 7i.

(12) Resonances for the allylic and C-8 carbons coincide at this signal.

(13) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069.

(14) Rabe, P. *Liebigs Ann. Chem.* **1932**, *492*, 242.

(15) Moreland, C. M.; Philip, A.; Carroll, F. I. *J. Org. Chem.* **1974**, *39*, 2413.