New Functional Derivatives of 9-Phenylquinine

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Abstract: A rapid synthesis of various 9-aryl derivatives of quinine is presented. They are obtained via coupling reactions of functionalized arylmagnesium halides and 9-chloroquinine.

Key words: cinchona alkaloid, Grignard reaction, chiral pool, coupling reaction, quinine

Enantioselective bifunctional organocatalysts have attracted much interest over the last decade.[1] Most notably they concern the derivatives of cinchona alkaloids.[2] These compounds, apart from the native basic and nucleophilic center of the quinuclidine moiety, may contain a hydrogen bond donor such as a phenolic group (cupreines)[3] or thiourea[4] (Figure 1). Although new catalytic applications of these types of compounds continue to evolve rapidly, the number of possible derivatizations is still very limited.

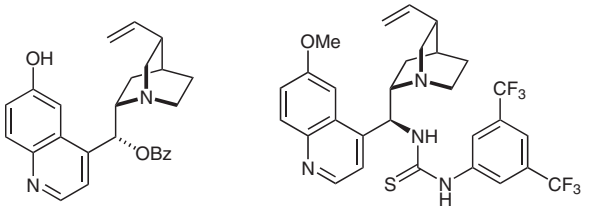


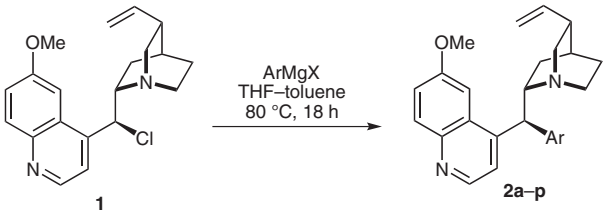
Figure 1 Selected bifunctional cinchona alkaloid derivatives[3,4]

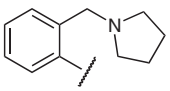
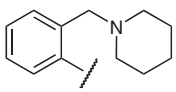
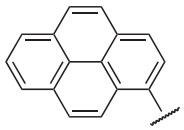
There is a single, dated report of a coupling reaction between 9-chloroquinine **1** and phenylmagnesium bromide to afford 9-phenylquinine of unspecified configuration.[5] In our preliminary study we discovered that this reaction proceeds with surprisingly high stereoselectivity towards the 8,9-*like* isomer.[6] This approach seemed to provide a new way to introduce additional functionalities to the cinchona alkaloid framework. So far, however, only one such substituted compound has been obtained.[6] Later we utilized the same approach to obtain a dimeric cinchona alkaloid derivative.[7]

In this paper we present the syntheses of a series of substituted 9-arylquinine derivatives, bearing various heteroatoms. We also further investigate the scope of the coupling reaction between 9-chloroquinine and various Grignard reagents.

In the initial experiments we separately reacted the Grignard reagents obtained from magnesium turnings and 2-iodo- and 4-iodotoluene with (9*S*)-9-chloroquinine (**1**). The respective (9*S*)-9-tolylquinines **2a** and **2b** were obtained in fair yields. The higher was achieved for the *ortho*-product, indicating that the presence of a substituent at this position has no unfavorable effect on the reaction outcome (Table 1). The stereochemical course of the reaction with phenylmagnesium bromide has previously been established by X-ray crystallography,[6] and this time the

Table 1 Synthesis of 9-Aryl Derivatives of Quinine



Entry	Ar	Product	Yield (%)
1	2-MeC_6H_4	**2a**	54
2	4-MeC_6H_4	**2b**	38
3	2-MOMOC_6H_4	**2c**	74
4	3-MOMOC_6H_4	**2d**	43
5	4-MOMOC_6H_4	**2e**	45[6]
6	2-(MOMOCH$_2$)C_6H_4	**2f**	62
7	3-(MOMOCH$_2$)C_6H_4	**2g**	67
8	3-$Bn_2NC_6H_4$	**2h**	61
9	4-$Bn_2NC_6H_4$	**2i**	45
10		**2j**	31
11		**2k**	40
12	3-IC_6H_4	**2l**	23
13	4-IC_6H_4	**2m**	80
14	3-BrC_6H_4	**2n**	49
15	4-BrC_6H_4	**2o**	70
16		**2p**	47

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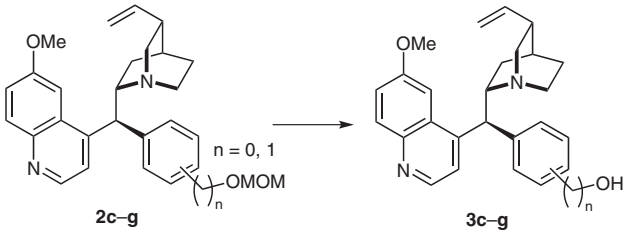
same configuration of products were confirmed by NOESY NMR experiments.

The organomagnesium compounds obtained from methoxymethoxy (MOM)-protected 2- and 3-iodophenol were added to a solution of (9*S*)-9-chloroquinine (**1**); the reaction afforded the respective protected phenolic derivatives of quinine **2c** and **2d**. These experiments concluded the series with the known 4-isomer **2e**.[6] The yields were exceptionally good for the 2-MOM ether **2c**. Similarly 2- and 3-iodobenzyl alcohols were protected as their MOM ethers which, unlike THP protection, proved appropriate for their transformation to Grignard reagents. The reaction of these compounds with **1** afforded **2f** and **2g** in good yields. The deprotection step, uncovering the hydroxy functionality was carried out by the treatment of the phenol ethers with 95% trifluoroacetic acid for two hours. While quantitative transformation was observed for **2d** and **2e**, 2-MOM-phenyl **2c** remained unchanged. An application of slightly harsher conditions (4 M HCl in MeOH, 48 h) allowed for the quantitative removal of the MOM group from **2c** as well. The same conditions were used to cleave the MOM groups from the primary alcohols **2f** and **2g** (Table 2).

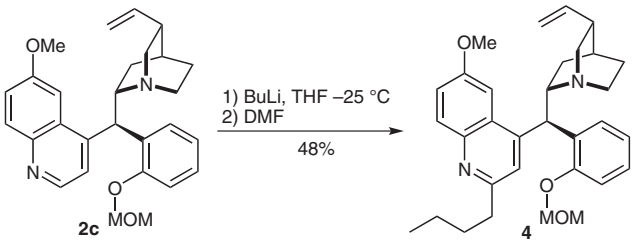
Table 2 Removal of MOM group from **2c–g**



Entry	Substrate	Conditions	Product	Yield (%)
1	**2c**	TFA–H_2O (20:1), 2 h	**3c**	0
2	**2c**	4 M HCl in MeOH, 48 h	**3c**	98
3	**2d**	TFA–H_2O (20:1), 2 h	**3d**	93
4	**2e**	TFA–H_2O (15:1), 2 h	**3e**	99
5	**2f**	4 M HCl, MeOH, 48 h	**3f**	98
6	**2g**	TFA–H_2O (20:1), 2 h	**3g**	96

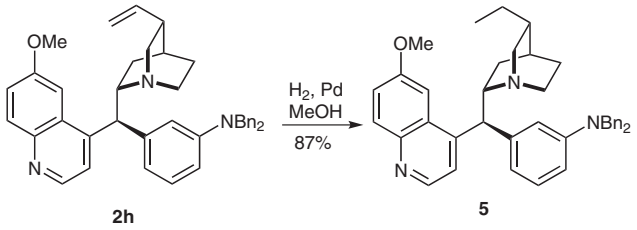
In order to functionalize the introduced aromatic ring further, **2c** was treated of with butyllithium at –25 °C, aiming at a lithiation (hydrogen–metal exchange) at a site adjacent to the MOM group. However, this reaction resulted in butylation at the C2′ atom only to give **4** (Scheme 1), analogous to the reaction of native quinine.[8] The ^{1}H NMR spectrum of phenol **3c**, in which the hydroxy group is in the 2-position, showed two sets of signals that exhibited coalescence at 40 °C ($\Delta G^{\ddagger}$ ~14.5 kcal/mol).

Having successfully introduced both aromatic and aliphatic hydroxy functionalities, we attempted the same with amino groups. First we obtained and *N*,*N*-dibenzyl-3- and -4-iodoaniline by the reaction of benzyl chloride



Scheme 1 Reactivity of **2c** with butyllithium

with the respective iodoaniline. The reaction of the derived Grignard reagents with **1** produced the coupling products **2h** and **2i** in fair to good yields. However, the corresponding synthesis of the 2-(dibenzylamino)phenyl isomer was unsuccessful. An attempted cleavage of the benzyl groups in **2h**,**i** under hydrogenation conditions failed and only the vinyl group reacted affording **5** from **2h** (Scheme 2).

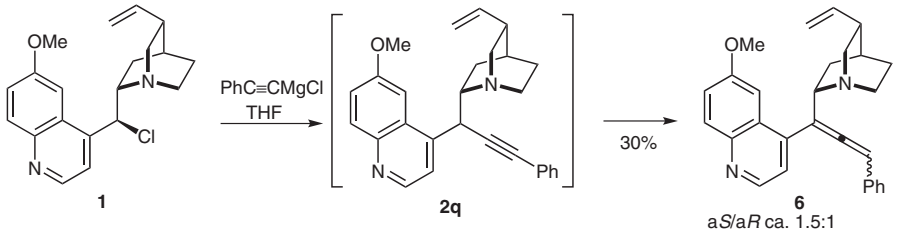


Scheme 2 Catalytic hydrogenation of **2h**

The Grignard reagents bearing tertiary aliphatic amino groups were also coupled with 9-chloroquinine **1**. The reaction of either 2-(pyrrolidin-1-ylmethyl)phenylmagnesium iodide and 2-(piperidin-1-ylmethyl)phenylmagnesium iodide resulted in the respective products **2j** and **2k** in 31% and 40% yields.

The presence of an additional halogen atom at the new benzene ring makes the product suitable for further couplings. Thus we obtained mono-Grignard reagents from 1,3- and 1,4-isomers of diiodobenzene and dibromobenzene. The coupling reaction was very effective, however the crude products contained also (9*S*)-9-phenylquinine. This problem particularly concerned the syntheses of 3-substituted products **2l** and **2n** and caused their yields to be much lower (23% and 49%). On the other hand, 4-substituted products **2m** and **2o** were obtained in very good yields.

The substitution of **1** proceeded well with most of the sp^2-Grignard reagents and even very bulky ones like pyren-1-ylmagnesium bromide affording coupling product **2p** in modest yields. However, the synthesis was ineffective with sp^3-type Grignard reagents. No coupling product was isolated with either ethyl,[6] cyclohexyl, or allyl reagents. Yet, when we reacted the sp-organomagnesium compound derived from phenylacetylene with (9*S*)-9-chloroquinine (**1**), the alkyne-substitution product **2q** spontaneously rearranged to the respective allene **6** (Scheme 3). The diastereoselectivity of the overall pro-



Scheme 3 Reaction of phenylethynylmagnesium chloride with (9*S*)-9-chloroquinine (**1**)

cess was poor, which is likely to be associated with a rearrangement step lacking stereoselectivity. The final yellow product **6** was isolated as a mixture of axial isomers. Both infrared (1938 cm^{-1}) and ^{13}C NMR (δ = 206.6/206.2) spectra confirmed their structure.

In summary, we have demonstrated that various functionalities can be introduced to the cinchona alkaloid scaffolds by a coupling reaction of properly substituted arylmagnesium iodides with 9-chloroquinine. The products were formed in fair to very good yields. The syntheses were at most two steps and the final deprotection usually proceeded quantitatively.

The iodoaryls were protected with methoxymethoxy or benzyl groups according to known procedures[9] using commercially available materials. **1** was most conveniently prepared by treatment of quinine with $SOCl_2$.[10] ^1H NMR samples in $CDCl_3$ (TMS as internal standard) were recorded on a Brucker DRX 300 spectrometer (300 MHz). IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrophotometer. Observed rotations at 589 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. HRMS were recorded on a Waters LCT Premier XE (oa-TOF/ESI) apparatus. Silica gel (60–120 mesh) was used for chromatographic separation.

9-Substituted 6′-Methoxycinchonans 2a–p; General Procedure

A clean and dry 25-mL 2-necked flask containing a magnetic stirrer bar, equipped with a reflux condenser and a septum, kept under argon was charged with Mg (52 mg, 2.17 mmol), THF (8 mL), aryl halide (2.1 mmol), and 1,2-dibromoethane (0.01 mL). The mixture was stirred under reflux until most of the Mg dissolved (1–2 h). A soln of (9*S*)-9-chloroquinine (**1**, 377 mg, 1.1 mmol) in toluene (10 mL)[11] was added with a syringe. The mixture was heated in an oil bath at 80 °C for 18 h. Then it was allowed to attain r.t. and 3.0 M aq NH_4Cl was added (5 mL). The mixture was extracted with $CHCl_3$ (3 × 15 mL), dried (Na_2SO_4), and purified by column chromatography (silica gel, $CHCl_3$–MeOH, 25:1 to 15:1).

(8*S*,9*S*)-6′-Methoxy-9-(2-methylphenyl)cinchonan (2a)

R_f = 0.25 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –183.5 (*c* 1.36, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 4.7 Hz, 1 H), 7.95 (d, *J* = 9.2 Hz, 1 H), 7.59 (d, *J* = 2.7 Hz, 1 H), 7.54 (d, *J* = 7.7 Hz, 1 H), 7.32 (dd, *J* = 9.2, 2.6 Hz, 1 H), 7.18–7.24 (m, 1 H), 7.19 (d, *J* = 4.7 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 6.97 (dd, *J* = 7.7, 1.1 Hz, 1 H), 5.80 (ddd, *J* = 17.3, 10.4, 7.5 Hz, 1 H), 4.90–5.00 (m, 3 H), 3.90 (s, 3 H), 3.61 (q, *J* = 9.5 Hz, 1 H), 3.15 (dd, *J* = 13.8, 10.1 Hz, 1 H), 3.09 (m, 1 H), 2.63–2.79 (m, 2 H), 2.13–2.23 (m, 1 H), 2.17 (s, 3 H), 1.38–1.64 (m, 4 H), 0.99 (dd, *J* = 13.6, 7.4 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.8, 147.7, 147.0, 144.6, 142.0, 140.4, 136.5, 132.1, 130.7, 129.1, 127.3, 126.5, 126.2, 121.8, 121.1, 114.3, 101.9, 59.8, 26.1, 55.5, 43.7, 41.3, 39.7, 28.3, 27.8, 26.9, 20.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{31}N_2O$: 399.2431; found: 399.2434.

(8*S*,9*S*)-6′-Methoxy-9-(4-methylphenyl)cinchonan (2b)

R_f = 0.31 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{28}$ –112 (*c* 1, CH_2Cl_2).

IR (KBr): 2936, 2860, 1620, 1586, 1508, 1471, 1430, 1258, 1230, 1031, 841, 826, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 4.7 Hz, 1 H), 7.91 (d, *J* = 9.2 Hz, 1 H), 7.43 (br, 1 H), 7.32 (d, *J* = 4.7 Hz, 1 H), 7.26 (dd, *J* = 9.2, 2.6 Hz, 1 H), 7.18 (d, *J* = 7.7 Hz, 2 H), 6.97 (d, *J* = 7.7 Hz, 2 H), 5.87 (ddd, *J* = 17.4, 9.9, 7.3 Hz, 1 H), 4.95–5.03 (m, 2 H), 4.64 (d, *J* = 11.2 Hz, 1 H), 3.89 (s, 3 H), 3.63 (m, 1 H), 3.23 (m, 1 H), 3.16 (dd, *J* = 14.1, 10.1 Hz, 1 H), 2.60–2.73 (m, 2 H), 2.21 (m, 1 H), 2.15 (s, 3 H), 1.84 (m, 1 H), 1.45–1.66 (m, 3 H), 0.75 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.7, 147.6, 147.0, 144.7, 142.0, 139.1, 136.2, 131.8, 129.3, 128.7, 127.7, 120.9, 119.5, 114.3, 102.1, 59.6, 56.6, 55.5, 49.3, 40.9, 39.6, 28.9, 28.1, 28.0, 21.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{31}N_2O$: 399.2431; found: 399.2428.

Anal. Calcd for $C_{27}H_{30}N_2O{\cdot}0.5\ H_2O$: C, 79.57; H, 7.67; N, 6.87. Found: C, 79.54; H, 7.67; N, 6.98.

(8*S*,9*R*)-6′-Methoxy-9-[2-(methoxymethoxy)phenyl]cinchonan (2c)

Thiocyanate salt of **2c** (NH_4SCN and **2c** dissolved in boiling MeOH, precipitated on cooling); mp 204–206 °C (dec.).

R_f = 0.25 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{18}$ –34.5 (*c* 0.99, CH_2Cl_2).

IR (KBr): 3431 (H_2O), 2932, 2859, 1621, 1586, 1508, 1489, 1472, 1454, 1230, 1151, 1078, 1032, 993, 919, 850, 752 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 4.6 Hz, 1 H), 7.90 (d, *J* = 9.3 Hz, 1 H), 7.71 (d, *J* = 2.8 Hz, 1 H), 7.35 (dd, *J* = 7.7, 0.9 Hz, 1 H), 7.28 (dd, *J* = 9.3, 2.8 Hz, 1 H), 7.26 (d, *J* = 4.8 Hz, 1 H), 7.04 (td, *J* = 7.7, 1.8 Hz, 1 H), 6.93 (d, *J* = 8.2 Hz, 1 H), 6.89 (td, *J* = 7.3, 1.5 Hz, 1 H), 5.86 (m, 1 H), 5.23 (d, *J* = 11.5 Hz, 1 H), 5.10 (d, *J* = 6.6 Hz, 1 H), 4.95–5.03 (m, 3 H), 3.91 (s, 3 H), 3.60 (m, 1 H), 3.29 (m, 1 H), 3.13 (m, 1 H), 3.12 (s, 3 H), 2.59–2.73 (m, 2 H), 2.20 (m, 1 H), 1.41–1.58 (m, 4 H), 0.81 (dd, *J* = 13.4, 7.5 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.6, 154.7, 147.7, 147.5, 144.5, 142.1, 131.6, 131.0, 129.4, 128.1, 127.6, 121.9, 120.7, 120.5, 114.2, 113.7, 102.9, 94.5, 59.6, 56.4, 55.9, 55.5, 41.3, 41.2, 39.7, 28.2, 28.1, 27.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{33}N_2O_3$: 445.2486; found: 445.2491.

(8*S*,9*S*)-6′-Methoxy-9-[3-(methoxymethoxy)phenyl]cinchonan (2d)

R_f = 0.29 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –72.5 (*c* 1, CH_2Cl_2).

IR (film): 2938, 2861, 1621, 1585, 1506, 1487, 1471, 1229, 1150, 1079, 1023, 995, 921, 851, 829, 714, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 4.8 Hz, 1 H), 7.92 (d, *J* = 9.3 Hz, 1 H), 7.43 (br, 1 H), 7.31 (d, *J* = 4.8 Hz, 1 H), 7.27 (dd,

J = 9.3, 2.8 Hz, 1 H), 7.09 (t, J = 8.1 Hz, 1 H), 6.92–6.97 (m, 2 H), 6.76 (m, 1 H), 5.87 (m, 1 H), 5.02 (s, 1 H), 5.03 (s, 1 H), 4.96–5.05 (m, 2 H), 4.65 (d, J = 10.8 Hz, 1 H), 3.89 (s, 3 H), 3.64 (m, 1 H), 3.35 (s, 3 H), 3.24 (m, 1 H), 3.16 (dd, J = 13.9, 10.1 Hz, 1 H), 2.62–2.74 (m, 2 H), 2.20 (m, 1 H), 1.82 (m, 1 H), 1.63 (m, 1 H), 1.46–1.59 (m, 2 H), 0.74 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.7, 157.3, 147.6, 146.5, 144.7, 143.8, 142.0, 131.9, 129.4, 128.8, 121.4, 121.1, 119.5, 116.3, 114.3, 113.9, 101.9, 94.4, 59.5, 56.5, 55.9, 55.5, 49.5, 40.9, 39.5, 28.8, 28.0 (2 overlapping signals).

HRMS: m/z [M + H]$^+$ calcd for $C_{28}H_{33}N_2O_3$: 445.2486; found: 445.2491.

(8*S*,9*R*)-6′-Methoxy-9-[2-(methoxymethoxymethyl)phenyl]cinchonan (2f)

R_f = 0.26 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –179.5 (c 1.036, CH_2Cl_2).

IR (film): 2939, 2884, 1622, 1507, 1472, 1247, 1228, 1148, 1097, 1032, 919, 849, 747 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, J = 4.8 Hz, 1 H), 7.98 (d, J = 9.3 Hz, 1 H), 7.86 (d, J = 2.6 Hz, 1 H), 7.72 (d, J = 7.9 Hz, 1 H), 7.42 (m, 1 H), 7.38 (dd, J = 9.2, 2.6 Hz, 1 H), 7.18 (d, J = 4.7 Hz, 1 H), 7.12–7.17 (m, 2 H), 5.81 (ddd, J = 17.4, 10.3, 7.4 Hz, 1 H), 5.51 (d, J = 11.4 Hz, 1 H), 4.98 (dt, J = 11.4, 1.5 Hz, 1 H), 4.95 (dt, J = 10.3, 1.4 Hz, 1 H), 4.58 (d, J = 6.6 Hz, 1 H), 4.57 (d, J = 12.5 Hz, 1 H), 4.53 (d, J = 6.6 Hz, 1 H), 4.23 (d, J = 12.5 Hz, 1 H), 4.03 (s, 3 H), 3.64 (m, 1 H), 3.31 (s, 3 H), 3.21 (dd, J = 13.8, 10.0 Hz, 1 H), 3.19 (m, 1 H), 2.77 (ddd, J = 13.8, 4.8, 2.3 Hz, 1 H), 2.66 (m, 1 H), 2.24 (m, 1 H), 1.47–1.71 (m, 3 H), 1.36 (m, 1 H), 0.81 (ddt J = 13.5, 7.0, 1.8 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.1, 147.7, 147.5, 144.7, 141.9, 141.7, 135.7, 131.8, 130.9, 129.3, 128.6, 127.7, 126.4, 121.8, 121.6, 114.2, 101.6, 94.3, 66.9, 59.5, 56.1, 55.4, 55.3, 42.2, 40.7, 39.6, 28.2, 27.8, 26.3.

HRMS: m/z [M + H]$^+$ calcd for $C_{29}H_{35}N_2O_3$: 459.2642; found: 459.2648.

(8*S*,9*S*)-6′-Methoxy-9-[3-(methoxymethoxymethyl)phenyl]cinchonan (2g)

$[\alpha]_D^{20}$ –48 (c 1.01, CH_2Cl_2).

IR (KBr): 3375 (H_2O), 2932, 2861, 1621, 1586, 1509, 1471, 1454, 1240, 1230, 1029, 828, 715 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (d, J = 4.5 Hz, 1 H), 7.92 (d, J = 9.2 Hz, 1 H), 7.43 (br, 1 H), 7.32 (d, J = 4.5 Hz, 1 H), 7.25 (s, 1 H), 7.20–7.30 (m, 2 H), 7.16 (t, J = 7.6 Hz, 1 H), 7.04 (d, J = 7.5 Hz, 1 H), 5.84 (ddd, J = 17.4, 9.7, 7.5 Hz, 1 H), 4.95–5.04 (m, 2 H), 4.69 (d, J = 10.0 Hz, 1 H), 4.56 (s, 2 H), 4.44 (s, 2 H), 3.89 (s, 3 H), 3.64 (m, 1 H), 3.26 (s, 3 H), 3.19–3.30 (m, 1 H), 3.15 (dd, J = 13.9, 10.0 Hz, 1 H), 2.60–2.73 (m, 2 H), 2.22 (m, 1 H), 1.83 (m, 1 H), 1.63 (m, 1 H), 1.44–1.58 (m, 2 H), 0.77 (dd J = 13.5, 6.7 Hz, 1 H).

(8*S*,9*S*)-9-[3-(Dibenzylamino)phenyl]-6′-methoxycinchonan (2h)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, J = 4.8 Hz, 1 H), 7.90 (d, J = 9.1 Hz, 1 H), 7.40 (br, 1 H), 7.07–7–32 (m, 12 H), 6.96 (t, J = 7.7 Hz, 1 H), 6.66 (d, J = 7.5 Hz, 1 H), 6.58 (s, 1 H), 6.46 (dd, J = 8.4, 2.5 Hz, 1 H), 5.80 (m, 1 H), 4.90–4.99 (m, 2 H), 4.41–4.62 (m, 1 H), 4.50 (s, 4 H), 3.81 (s, 3 H), 3.41 (m, 1 H), 3.01–3.18 (m, 2 H), 2.49–2.66 (m, 2 H), 2.16 (m, 1 H), 1.34–1.77 (m, 4 H), 0.62 (m, 1 H).

(8*S*,9*S*)-9-[4-(Dibenzylamino)phenyl]-6′-methoxycinchonan (2i)

R_f = 0.24 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{22}$ –154.1 (c 1.28, CH_2Cl_2); $[\alpha]_D^{22}$ –176.5 (c 1.15, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, J = 4.7 Hz, 1 H), 7.97 (d, J = 9.1 Hz, 1 H), 7.50 (br, 1 H), 7.10–7.33 (m, 14 H), 6.59 (d, J = 8.7 Hz, 2 H), 5.89 (m, 1 H), 4.96–5.06 (m, 2 H), 4.65 (d, J = 10.4 Hz, 1 H), 4.51 (s, 4 H), 3.87 (s, 3 H), 3.65 (m, 1 H), 3.29 (m, 1 H), 3.24 (dd, J = 13.8, 10.2 Hz, 1 H), 2.68–2.80 (m, 2 H), 2.25 (m, 1 H), 1.82 (m, 1 H), 1.63 (m, 1 H), 1.53–1.58 (m, 2 H), 0.77 (dd, J = 12.9, 6.4 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.7, 147.9, 147.7, 147.6, 144.8, 142.0, 138.7, 131.9, 130.0, 128.8, 128.6, 128.6, 126.8, 126.7, 120.9, 119.6, 114.3, 112.6, 102.2, 59.5, 56.5, 55.5, 54.2, 48.4, 40.9, 39.6, 28.9, 28.1, 28.0.

HRMS: m/z [M + H]$^+$ calcd for $C_{40}H_{42}N_3O$: 580.3322; found: 580.3328.

(8*S*,9*S*)-6′-Methoxy-9-[2-(pyrrolidin-1-ylmethyl)phenyl]cinchonan (2j)

R_f = 0.10 ($CHCl_3$–MeOH, 10:1).

IR (KBr): 2935, 2874, 1673, 1620, 1587, 1508, 1471, 1456, 1431, 1238, 1031, 849, 829 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, J = 4.7 Hz, 1 H), 7.95 (d, J = 9.2 Hz, 1 H), 7.81 (d, J = 2.3 Hz, 1 H), 7.65 (d, J = 7.8 Hz, 1 H), 7.29–7.38 (m, 2 H), 6.96–7.12 (m, 3 H), 5.96 (d, J = 11.6 Hz, 1 H), 5.75 (ddd, J = 17.4, 10.3, 7.5 Hz, 1 H), 4.85–4.96 (m, 2 H), 3.96 (s, 3 H), 3.67 (d, J = 12.2 Hz, 1 H), 3.54 (m, 1 H), 3.28 (m, 1 H), 3.17 (dd, J = 13.7, 10.0 Hz, 1 H), 2.72 (d, J = 12.2 Hz, 1 H), 2.51–2.71 (m, 2 H), 2.12–2.44 (m, 5 H), 1.08–1.79 (m, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.8, 147.8, 146.7, 141.8, 141.6, 137.8, 131.8, 131.5, 131.1, 129.7, 127.7, 127.6, 126.3, 122.1, 120.5, 114.2, 103.7, 59.7, 55.9, 55.6, 54.2, 41.6, 40.2, 40.6, 39.6, 28.2, 27.9, 25.9, 23.4.

HRMS: m/z [M + H]$^+$ calcd for $C_{31}H_{38}N_3O$: 468.3009; found: 468.3015.

(8*S*,9*S*)-6′-Methoxy-9-[2-(piperidin-1-ylmethyl)phenyl]cinchonan (2k)

R_f = 0.16 ($CHCl_3$–MeOH, 10:1).

$[\alpha]_D^{18}$ –193 (c 1, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, J = 4.8 Hz, 1 H), 7.95 (d, J = 9.2 Hz, 1 H), 7.78 (d, J = 2.6 Hz, 1 H), 7.66 (d, J = 7.7 Hz, 1 H), 7.35 (dd, J = 9.2, 2.6 Hz, 1 H), 7.30–7.36 (m, 1 H), 7.09 (d, J = 4.7 Hz, 1 H), 7.06 (td, J = 7.3, 1.1 Hz, 1 H), 6.94 (dd, J = 7.6, 1.5 Hz, 1 H), 5.86 (d, J = 11.6 Hz, 1 H), 5.74 (ddd, J = 17.6, 10.3, 7.6 Hz, 1 H), 4.84–4.96 (m, 2 H), 3.96 (s, 3 H), 3.52 (m, 1 H), 3.43 (d, J = 12.3 Hz, 1 H), 3.34–3.43 (m, 1 H), 3.18 (dd, J = 13.7, 10.1 Hz, 1 H), 2.71 (ddd, J = 13.7, 5.1, 2.1 Hz, 1 H), 2.62 (d, J = 12.3 Hz, 1 H), 2.52–2.63 (m, 1 H), 2.12–2.34 (m, 4 H), 1.19–1.75 (m, 12 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.9, 148.3, 147.9, 144.6, 142.1, 142.0, 136.7, 132.2, 132.0, 129.8, 128.1, 127.7, 126.1, 122.3, 120.5, 114.2, 103.8, 63.0, 59.8, 56.0, 55.7, 55.1, 41.8, 40.9, 39.8, 28.2, 28.0, 26.3, 36.0, 24.7.

HRMS: m/z [M + H]$^+$ calcd for $C_{32}H_{40}N_3O$: 482.3166; found: 482.3171.

(8*S*,9*S*)-9-(3-Iodophenyl)-6′-methoxycinchonan (2l)

R_f = 0.43 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –27.5 (c 1, CH_2Cl_2).

IR (KBr): 2932, 2859, 1620, 1585, 1561, 1507, 1452, 1470, 1260, 1228, 1030, 922, 825, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, J = 4.7 Hz, 1 H), 7.94 (d, J = 9.2 Hz, 1 H), 7.61 (s, 1 H), 7.21–7.49 (m, 5 H), 6.91 (t, J = 7.7 Hz, 1 H), 5.87 (m, 1 H), 4.95–5.06 (m, 2 H), 4.59 (d, J = 11.0 Hz, 1 H), 3.90 (s, 3 H), 3.63 (m, 1 H), 3.19 (m, 1 H), 3.16 (dd, J = 13.9, 9.9 Hz, 1 H), 2.62–2.76 (m, 2 H), 2.24 (m, 1 H), 1.42–1.94 (m, 4 H), 0.75 (dd, J = 13.4, 7.0 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.9, 147.6, 145.7, 144.8, 141.8, 137.0, 135.7, 132.0, 130.2, 128.6, 127.3, 127.1, 121.1, 119.8, 114.4, 101.8, 94.6, 59.3, 56.5, 55.5, 49.2, 40.9, 39.5, 28.7, 28.00, 27.96.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{28}IN_2O$: 511.1241; found: 511.1246.

(8*S*,9*S*)-9-(4-Iodophenyl)-6′-methoxycinchonan (2m)
R_f = 0.26 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –138.5 (*c* 1.2, CH_2Cl_2).

IR (KBr): 3435 (H_2O), 2926, 2906, 2861, 1620, 1505, 1484, 1470, 1427, 1244, 1225, 1027, 1007, 834, 841, 719, 624 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 4.7 Hz, 1 H), 7.94 (d, *J* = 9.1 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.35 (br, 1 H), 7.29 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.27 (d, *J* = 4.7 Hz, 1 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 5.86 (ddd, *J* = 17.4, 10.1, 7.4 Hz, 1 H), 4.95–5.03 (m, 2 H), 4.62 (d, *J* = 11.0 Hz, 1 H), 3.88 (s, 3 H), 3.57 (m, 1 H), 3.18 (m, 1 H), 3.16 (dd, *J* = 14.0, 10.0 Hz, 1 H), 2.61–2.73 (m, 2 H), 2.23 (m, 1 H), 1.82 (m, 1 H), 1.63 (m, 1 H, H4), 1.46–1.58 (m, 2 H), 0.75 (ddt, *J* = 13.5, 7.1, 1.6 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.8, 147.6, 146.1, 144.7, 142.0, 141.9, 139.2, 137.5, 132.0, 129.9, 120.9, 119.7, 114.4, 102.0, 92.2, 59.4, 56.5, 55.5, 48.9, 41.0, 39.4, 28.7, 28.02, 27.96.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{28}IN_2O$: 511.1241; found: 511.1246.

(8*S*,9*S*)-9-(3-Bromophenyl)-6′-methoxycinchonan (2n)
R_f = 0.35 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –72 (*c* 0.974, CH_2Cl_2).

IR (film): 3058, 3021, 2947, 2864, 1618, 1587, 1561, 1508, 1428, 1359, 1224, 1132, 1088, 1074, 1033, 907, 845, 828, 771, 754, 436 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.70 (d, *J* = 4.7 Hz, 1 H), 7.95 (d, *J* = 9.1 Hz, 1 H), 7.61 (s, 1 H), 7.01–7.42 (m, 6 H), 5.86 (ddd, *J* = 17.6, 10.0, 7.6 Hz, 1 H), 4.96–5.04 (m, 2 H), 4.63 (d, *J* = 10.9 Hz, 1 H), 3.89 (s, 3 H), 3.85 (m, 1 H), 3.19 (m, 1 H), 3.16 (dd, *J* = 13.9, 10.2 Hz, 1 H), 2.62–2.75 (m, 2 H), 2.23 (m, 1 H), 1.83 (m, 1 H), 1.64 (m, 1 H), 1.45–1.58 (m, 2 H), 0.75 (dd, *J* = 13.5, 7.0 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.8, 147.6, 145.9, 144.7, 144.5, 141.9, 132.0, 131.0, 130.0, 129.8, 126.6, 123.0, 122.5, 121.1, 119.7, 114.4, 101.8, 59.4, 56.5, 55.5, 49.2, 41.0, 39.5, 28.7, 28.01, 27.96.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{28}BrN_2O$: 463.1379; found: 463.1385.

(8*S*,9*S*)-9-(4-Bromophenyl)-6′-methoxycinchonan (2o)
R_f = 0.36 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{25}$ –79 (*c* 1, CH_2Cl_2).

IR (film): 2938, 2861, 1622, 1588, 1507, 1488, 1469, 1260, 1230, 1069, 1032, 1005, 836, 810 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 4.6 Hz, 1 H), 7.94 (d, *J* = 9.1 Hz, 1 H), 7.35 (br, 1 H), 7.25–7.32 (m, 3 H), 7.08–7.21 (m, 3 H), 5.86 (ddd, *J* = 17.3, 10.0, 7.4 Hz, 1 H), 4.95–5.05 (m, 2 H), 4.64 (d, *J* = 11.4 Hz, 1 H), 3.87 (s, 3 H), 3.58 (m, 1 H), 3.13–3.26 (m, 1 H), 3.16 (dd, *J* = 13.9, 10.0 Hz, 1 H), 2.61–2.76 (m, 2 H), 2.23 (m, 1 H), 1.64 (m, 1 H), 1.83 (m, 1 H), 1.44–1.58 (m, 2 H), 0.75 (dd, *J* = 13.7, 6.8 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.9, 147.5, 146.1, 144.7, 141.9, 141.2, 132.0, 131.6, 129.6, 128.8, 120.9, 120.5, 119.7, 114.4, 102.0, 59.4, 56.5, 55.5, 48.9, 41.0, 39.5, 28.7, 28.05, 27.96.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{28}BrN_2O$: 463.1379; found: 463.1385.

(8*S*,9*S*)-6′-Methoxy-9-pyren-1-ylcinchonan (2p)
R_f = 0.30 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ +62 (*c* 1, CH_2Cl_2).

IR (KBr): 2938, 2917, 2857, 1620, 1579, 1505, 1471, 1429, 1240, 1226, 1220, 1034, 845, 836, 712 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 4.7 Hz, 1 H), 8.57 (d, *J* = 9.5 Hz, 1 H), 7.86–8.14 (m, 9 H), 7.67 (d, *J* = 2.6 Hz, 1 H), 7.45 (d, *J* = 4.5 Hz, 1 H), 7.23 (dd, *J* = 9.2, 2.6 Hz, 1 H), 5.94 (ddd, *J* = 17.2, 9.8, 7.3 Hz, 1 H), 5.77 (d, *J* = 10.6 Hz, 1 H), 5.00–5.07 (m, 2 H), 3.95 (m, 1 H), 3.78 (s, 3 H), 3.32 (m, 1 H), 3.06 (dd, *J* = 13.9, 10.1 Hz, 1 H), 2.75 (m, 1 H), 2.59 (ddd, *J* = 14.4, 10.4, 4.3 Hz, 1 H), 2.23 (m, 1 H), 1.92 (m, 1 H), 1.44–1.78 (m, 3 H), 1.19 (dd, *J* = 13.7, 7.7 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.9, 147.6, 147.4, 144.7, 142.1, 136.4, 132.0, 131.4, 130.4, 130.0, 129.0, 128.9, 127.7, 127.5, 127.0, 125.8, 125.5, 125.28, 125.25, 125.17, 125.1, 124.7, 122.6, 121.4, 120.9, 114.4, 101.9, 60.9, 56.5, 56.7, 44.3, 41.7, 39.7, 28.3, 28.2, 28.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{33}N_2O$: 509.2587; found: 509.2593.

9-(Hydroxyphenyl)-6′-methoxycinchonans 3c–g; General Procedure
A 25-mL flask was charged with the MOM derivative **2c**–**g** (1 mmol) and either TFA [8 mL, containing H_2O (0.4 mL)] or 4 M HCl in MeOH (8 mL). The mixture was stirred at r.t. for the specified time (Table 2), then the solvent was removed in vacuo. The residue was suspended in 5% aq NH_3 (10 mL) and extracted with $CHCl_3$. The extracts were dried (anhyd Na_2SO_4). Removal of solvents in vacuo afforded products that did not require further purification.

(8*S*,9*R*)-9-(2-Hydroxyphenyl)-6′-methoxycinchonan (3c)
Mp 181–184 °C (CH_2Cl_2); R_f = 0.15 ($CHCl_3$–MeOH, 10:1).

Perchlorate salt of **3c** (NH_4ClO_4 and **3c** were dissolved in hot EtOH, precipitated on cooling); mp 259–261 °C (dec.).

$[\alpha]_D^{20}$ –47 (*c* 0.5, EtOH).

IR (KBr): 3427, 3068, 1932, 1862, 1621, 1586, 1509, 1473, 1454, 1433, 1272, 1241, 1030, 846, 751 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 313 K): δ = 8.66 (d, *J* = 4.4 Hz, 1 H), 7.94 (d, *J* = 9.2 Hz, 1 H), 7.29 (d, *J* = 2.6 Hz, 1 H), 7.24 (dd, *J* = 9.2, 2.6 Hz, 1 H), 7.20 (d *J* = 4.4 Hz, 1 H), 6.95 (td, *J* = 7.6, 1.5 Hz, 1 H), 6.83 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.60 (dd, *J* = 8.0, 1.4 Hz, 1 H), 6.43 (td, *J* = 7.6, 1.4 Hz, 1 H), 5.72 (ddd, *J* = 17.8, 10.8, 7.2 Hz, 1 H), 4.98 (d, *J* = 17.8 Hz, 1 H) 4.97 (d, *J* = 10.8 Hz, 1 H), 4.74 (br, 1 H), 3.77 (s, 3 H), 3.69 (q, *J* = 8.5 Hz, 1 H), 3.33 (m, 1 H), 3.21 (dd, *J* = 13.8, 10.3 Hz, 1 H), 2.79–2.94 (m, 2 H), 2.33 (m, 1 H), 1.71 (m, 1 H), 1.52–1.67 (m, 3 H), 0.91 (dd, *J* = 13.6, 7.9 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$, 313 K): δ = 157.8, 156.6, 147.1, 146.3, 145.2, 140.5, 131.7, 130.4, 128.5, 128.2, 127.7, 123.0, 121.7, 119.2, 118.9, 115.1, 102.7, 59 (br), 55.5, 54.3, 40.6, 38.7, 28.8, 27.7, 27.2 (1 signal not observed due to coalescence).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{29}N_2O_2$: 401.2223; found: 401.2229.

Anal. Calcd for $C_{26}H_{28}N_2O_2 \cdot 0.5\ H_2O$: C, 74.25; H, 7.13; N, 6.84. Found: C, 76.33; H, 7.13; N, 6.80.

(8*S*,9*S*)-9-(3-Hydroxyphenyl)-6′-methoxycinchonan (3d)
Mp 165–172 °C (CH_2Cl_2–hexane); R_f = 0.09 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –102 (*c* 0.764, EtOH).

IR (KBr): 3634, 3077, 2941, 2862, 1621, 1586, 1507, 1482, 1472, 1455, 1364, 1259, 1243, 1226, 1027, 831, 715 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 4.7 Hz, 1 H), 7.91 (d, *J* = 9.2 Hz, 1 H), 7.45 (d, *J* = 2.3 Hz, 1 H), 7.37 (d, *J* = 4.7 Hz, 1 H),

7.24 (dd, *J* = 9.2, 2.6 Hz, 1 H), 6.95 (t, *J* = 7.8 Hz, 1 H), 6.81 (d, *J* = 7.7 Hz, 1 H), 6.44 (s, 1 H), 6.21 (d, *J* = 7.8 Hz, 1 H), 5.89 (ddd, *J* = 17.3, 10.3, 7.3 Hz, 1 H), 5.08 (d, *J* = 10.3 Hz, 1 H), 5.00 (d, *J* = 17.3 Hz, 1 H), 4.62 (d *J* = 11.2 Hz, 1 H), 3.85 (s, 3 H), 3.78 (m, 1 H), 3.89 (m, 1 H), 3.09 (dd, *J* = 13.8, 10.3 Hz, 1 H), 2.72 (m, 1 H), 2.56–2.72 (m, 2 H), 2.02 (t, *J* = 11.2 Hz, 1 H), 1.71 (m, 1 H), 1.52–1.69 (m, 2 H), 0.86 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.1, 157.9, 147.2, 146.4, 144.5, 141.7, 140.7, 131.6, 129.5, 128.8, 121.3, 119.1, 118.6, 115.2, 115.0, 114.9, 102.1, 59.9, 56.4, 55.5, 50.5, 40.5, 38.6, 28.9, 27.7, 27.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{29}N_2O_2$: 401.2223; found: 401.2228.

Anal. Calcd for $C_{26}H_{28}N_2O_2{\cdot}H_2O$: C, 74.65; H, 7.22; N, 6.69. Found: C, 73.52; H, 7.29; N 6.71.

(8*S*,9*S*)-9-[2-(Hydroxymethyl)phenyl]-6′-methoxycinchonan (3f)

R_f = 0.21 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –179.5 (*c* 0.86, EtOH).

IR (KBr): 3385, 3163, 2936, 2860, 1622, 1587, 1510, 1472, 1432, 1252, 1240, 1229, 1023, 851, 748, 726 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 4.7 Hz, 1 H), 7.87 (d, *J* = 9.2 Hz, 1 H), 7.45–7.48 (m, 2 H), 7.13–7.26 (m, 4 H), 7.06 (t, *J* = 7.3 Hz, 1 H), 5.82 (m, 1 H), 5.32 (d, *J* = 10.7 Hz, 1 H), 4.93–5.00 (m, 2 H), 4.81 (d, *J* = 12.0 Hz, 1 H), 4.53 (br, 1 H), 4.34 (d, *J* = 12.0 Hz, 1 H), 3.87 (s, 3 H), 3.50 (m, 1 H), 3.24 (m, 1 H), 3.02 (dd, *J* = 13.8, 10.1 Hz, 1 H), 2.60–2.71 (m, 2 H), 2.20 (m, 1 H), 1.75 (m, 1 H), 1.67 (m, 1 H), 1.55 (m, 1 H), 1.44 (m, 1 H), 0.92 (dd, *J* = 13.5, 8.5 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.1, 147.1, 146.6, 144.6, 141.7, 140.7, 139.7, 131.7, 130.3, 129.0, 128.4, 128.2, 127.0, 121.7, 121.7, 114.7, 101.3, 63.5, 60.9, 55.6, 55.5, 42.8, 41.2, 39.4, 27.9, 27.8, 27.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{31}N_2O_2$: 415.2380; found: 415.2383.

(8*S*,9*R*)-9-[3-(Hydroxymethyl)phenyl]-6′-methoxycinchonan (3g)

R_f = 0.08 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{20}$ –67.7 (*c* 1.167, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 4.7 Hz, 1 H), 7.85 (d, *J* = 9.2 Hz, 1 H), 7.43 (br, 1 H), 7.32 (s, 1 H), 7.28 (d, *J* = 4.7 Hz, 1 H), 7.21 (dd, *J* = 9.2, 2.6 Hz, 1 H), 7.20 (m, 1 H), 7.13 (t, *J* = 7.4 Hz, 1 H), 7.01 (d, *J* = 7.4 Hz, 1 H), 5.84 (ddd, *J* = 17.4, 9.9, 7.4 Hz, 1 H), 4.94–5.02 (m, 2 H), 4.67 (d, *J* = 11.3 Hz, 1 H), 4.47 (s, 2 H), 3.87 (s, 3 H), 3.62 (m, 1 H), 3.21 (m, 1 H), 3.07 (dd, *J* = 13.8, 10.2 Hz, 1 H), 2.52–2.67 (m, 2 H), 2.20 (m, 1 H), 2.0 (br, 1 H), 1.82 (m, 1 H), 1.62 (m, 1 H), 1.36–1.57 (m, 2 H), 0.74 (dd, *J* = 13.7, 7.0 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.7, 147.5, 146.6, 144.6, 142.3, 141.8, 141.5, 131.8, 128.7, 128.5, 127.0, 126.5, 125.5, 120.9, 119.6, 114.4, 102.0, 65.0, 59.6, 56.4, 55.5, 49.6, 40.8, 39.4, 28.7, 27.98, 27.91.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{31}N_2O_2$: 415.2380; found: 415.2384.

(8*S*,9*R*)-2′-Butyl-6′-methoxy-9-[2-(methoxymethoxy)phenyl]cinchonan (4)

A dry 10-mL 2 neck flask with an argon atmosphere was charged with **2c** (312 mg, 0.7 mmol), THF (6 mL), TMEDA (0.1 mL, 0.7 mmol), and cooled to –25 °C. 2.5 M BuLi in hexanes (0.3 mL, 0.75 mmol) was added. The mixture was stirred for 0.25 h and DMF (0.1 mL, 1.4 mmol) was added and the stirring continued for an additional 18 h. The reaction was quenched with sat. aq NH_4Cl. The product extracted with $CHCl_3$, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified (silica gel, $CHCl_3$–MeOH, 25:1) to afford **4** (167 mg, 48%) as an oil.

R_f = 0.29 ($CHCl_3$–MeOH, 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 9.2 Hz, 1 H), 7.69 (d, *J* = 2.3 Hz, 1 H), 7.36 (d, *J* = 7.4 Hz, 1 H), 7.23 (dd, *J* = 9.2, 2.8 Hz, 1 H), 7.19 (s, 1 H), 6.85–7.05 (m, 3 H), 5.87 (ddd, *J* = 17.8, 10.6, 7.3 Hz, 1 H), 5.22 (d, *J* = 11.3 Hz, 1 H), 5.11 (d, *J* = 6.6 Hz, 1 H), 5.04 (d, *J* = 6.6 Hz, 1 H), 4.95–5.02 (m, 2 H), 3.87 (s, 3 H), 3.60 (m, 1 H), 3.31 (m, 1 H), 3.16 (s, 3 H), 3.13 (dd, *J* = 14.3 10.1 Hz, 1 H), 2.86 (t, *J* = 7.7 Hz, 2 H), 2.69 (m, 1 H), 2.62 (m, 1 H), 2.19 (m, 1 H), 1.40–1.77 (m, 6 H), 1.34 (sext, *J* = 7.5 Hz, 2 H), 0.88 (t, *J* = 7.4 Hz, 3 H), 0.82 (dd, *J* = 13.2, 7.2 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.9, 157.0, 154.8, 147.8, 144.3, 142.2, 131.2, 131.0, 128.1, 127.8, 127.6, 122.0, 120.6, 120.3, 114.2, 113.8, 103.2, 94.6, 59.9, 56.6, 56.0, 55.6, 41.3, 41.2, 39.8, 38.9, 32.3, 28.3, 28.2, 28.0, 22.6, 14.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{41}N_2O_3$: 501.3112; found: 501.3117.

(8*S*,9*S*)-9-[3-(Dibenzylamino)phenyl]-10,11-dihydro-6′-methoxycinchonan (5)

A 25-mL flask was charged with **2h** (347 mg, 0.6 mmol), MeOH (10 mL), EtOAc (5 mL), and 10% Pd–C (60 mg). A thin stream of H_2 was passed through the suspension for 90 h. Then, the mixture was filtered through Cellite and washed with MeOH. The solvents were removed in vacuo to afford **5** (301 mg, 87%).

R_f = 0.24 ($CHCl_3$–MeOH, 10:1); $[\alpha]_D^{18}$ –101 (*c* 0.443, CH_2Cl_2).

IR (KBr): 2929, 2858, 1620, 1599, 1507, 1495, 1451, 1360, 1230, 1028, 729, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 4.6 Hz, 1 H), 7.91 (d, *J* = 9.3 Hz, 1 H), 7.39 (br, 1 H), 7.08–7.33 (m, 12 H), 6.98 (t, *J* = 7.7 Hz, 1 H), 6.66 (d, *J* = 7.3 Hz, 1 H), 6.54 (s, 1 H), 6.49 (m, 1 H), 4.46–4.63 (m, 5 H), 3.82 (s, 3 H), 3.11–3.65 (m, 3 H), 2.74 (m, 1 H), 2.39 (m, 1 H), 1.48–1.79 (m, 7 H), 0.81 (t, *J* = 7.2 Hz, 3 H), 0.76–0.82 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.8, 149.3, 147.4, 145.9, 144.6, 141.9, 138.5, 131.7, 129.5, 128.64, 128.59, 126.8, 126.5, 121.2, 119.1, 116.7, 112.2, 111.6, 101.8, 59.8, 57.7, 55.6, 54.8, 49.4, 40.9, 36.4, 27.9, 27.4, 27.3, 25.5, 11.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{40}H_{44}N_3O$: 582.3479; found: 582.3484.

(8*S*)-6′-Methoxy-9-(phenylvinylidene)cinchonan (6)

A dry 25-mL 2-neck flask containing a magnetic stirrer bar, equipped with a reflux condenser and a septum, kept under argon was charged with phenylacetylene (0.22 mL, 2 mmol), THF (4 mL), and 2 M *i*-PrMgBr in THF (1 mL). The mixture was stirred at r.t. for 1 h and a soln of (9*S*)-9-chloroquinine (**1**, 498 mg, 1.46 mmol) in toluene (5 mL) was added.[11] The mixture was initially stirred at r.t. for 0.5 h then heated under reflux 2 h. Then it was allowed to attain r.t. and sat. aq NH_4Cl was added (15 mL). The mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and purified by column chromatography (silica gel, $CHCl_3$–MeOH, 20:1) to afford **6** (180 mg, 30%) as an yellow oil as an *aS*/*aR* isomer mixture.

R_f = 0.26 and 0.23 ($CHCl_3$–MeOH, 10:1).

IR (film): 3064, 2936, 2867, 1938, 1668, 1620, 1580, 1505, 1470, 1454, 1429, 1361, 1225, 1030, 848, 753, 695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.652/8.648 (2 d, *J* = 4.6 Hz, 1 H), 7.909/7.903 (2 d, *J* = 9.3 Hz, 1 H), 7.54 (d, *J* = 4.6 Hz, 3/5 H), 7.13–7.41 (m, 7 2/5 H), 6.546/6.539 (2 s, 1 H), 5.79–5.94 (m, 1 H), 4.94–5.05 (m, 2 H), 3.69–4.00 (m, 1 H) 3.56/3.48 (2 s, 3 H), 3.09–3.28

(m, 2 H), 2.56–2.77 (m, 2 H), 2.18–2.29 (m, 1 H), 1.96–2.08 (m, 1 H), 1.37–1.80 (m, 4 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 206.6/206.2, 157.8/157.7, 147.5/147.3, 144.8/144.7, 142.3/142.2, 141.6/141.5, 133.3/133.1, 131.4, 129.5/129.3, 129.00, 129.97, 128.89, 128.4, 127.8, 127.7, 127.6, 127.5, 127.2/127.1, 121.9/121.8, 120.4/120.2, 114.63/114.61, 108.7/108.2, 102.9/102.8, 98.8/98.7, 59.3/58.2, 55.4, 55.33, 55.31, 55.28, 41.5/41.3, 39.4/39.3, 28.0/27.9, 27.7/27.4, 26.5/26.3.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O$: 409.2274; found: 409.2284.

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(11) (9*S*)-9-Chloroquinine (**1**) is not very soluble in toluene at r.t.; more concentrated solutions can be obtained by dissolving **1** in toluene at 100 °C then cooling.