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Synthetic approaches to 9-arylated *Cinchona* alkaloids: stereoselective addition of Grignard reagents to cinchonanones and hydroxylation of 9-phenylcinchonanes

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ABSTRACT

All 8,9-isomers of the 9-phenyl *Cinchona* alkaloids were obtained by autoxidation of 9-deoxy-9-phenyl-alkaloids and by the addition of Grignard reagents to the respective ketones. The diastereoselective addition of phenyl-, methyl-, and vinylmagnesium reagents to quinidinone and cinchoninone gave the corresponding (8*R*,9*S*)-products with acceptable yields and starting material recovery. The configurations of the compounds obtained were established by chemical correlations, NMR experiments, and were supported by DFT calculations and X-ray structures. Stereochemical models for both reactions were also devised and discussed.

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1. Introduction

Easily available, *pseudoenantiomeric* natural *Cinchona* alkaloids, such as quinine (QN) and quinidine (QD) have gained much interest for their use in asymmetric synthesis.[1] Despite significant achievements in the catalytic applications, their derivatives are only easily accessible in relatively limited numbers.[2] In particular, those with the extended molecular frameworks remain rather scarcely available. We have previously reported a series of stereospecific carbon–carbon bond forming reactions leading to the corresponding 9-deoxy-9-aryl-alkaloids.[3] Recently, Connon et al. prepared a library of the corresponding compounds and evaluated their effectiveness as chiral bifunctional organocatalysts.[4] However, all of these products lack the 9-hydroxy functionality, which is essential in many catalytic applications.

Herein we report two synthetic approaches to the derivatives with the 9-OH group and additional carbon substituents present at the same position (Fig. 1).

2. Results and discussion

2.1. Synthesis

One straightforward approach to the desired 9-aryl-alkaloids is the addition of a Grignard reagent to the corresponding ketone.[5,6] The overall sequence of the transformations (Scheme 1) starts with an alkaloid of any configuration at both the C-8 and C-9 stereogenic centers. The Oppenauer oxidation[5,7] deprives the compound of chirality at the C-9 center and allows for easy epimerization at the adjacent center, while crystallization of the ketone gives the

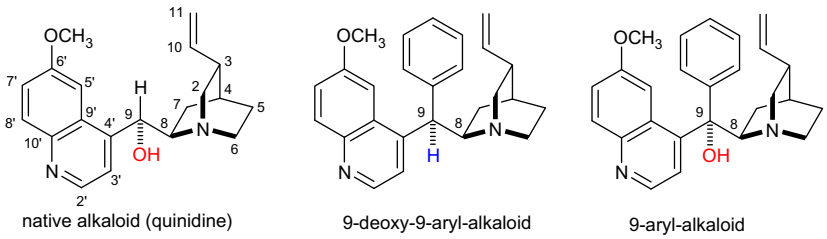

Figure 1.

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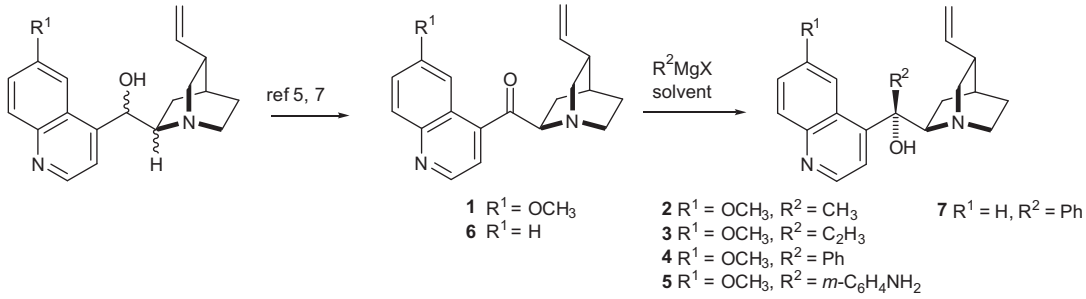


Scheme 1.

Table 1
Addition of Grignard reagents to quinidinone **1** and cinchoninone **6**

Entry	R^2MgX	Solvent	Product	Yield[a] %
1	CH_3MgCl	THF/toluene	**2**	55 (71)
2	PhMgCl	THF/toluene	**4**	25 (30)
3	PhMgBr	CH_2Cl_2	**4**	48 (50)
4	C_2H_3MgBr	CH_2Cl_2	**3**	37 (50)
5	3-$(TMS)_2NC_6H_4MgCl$	CH_2Cl_2	**5**	61 (65)
6	PhMgBr	CH_2Cl_2	**7**	30 (40)

[a] Yields are preparative, content of product in crude reaction mixtures given in parentheses is estimated by NMR integration.

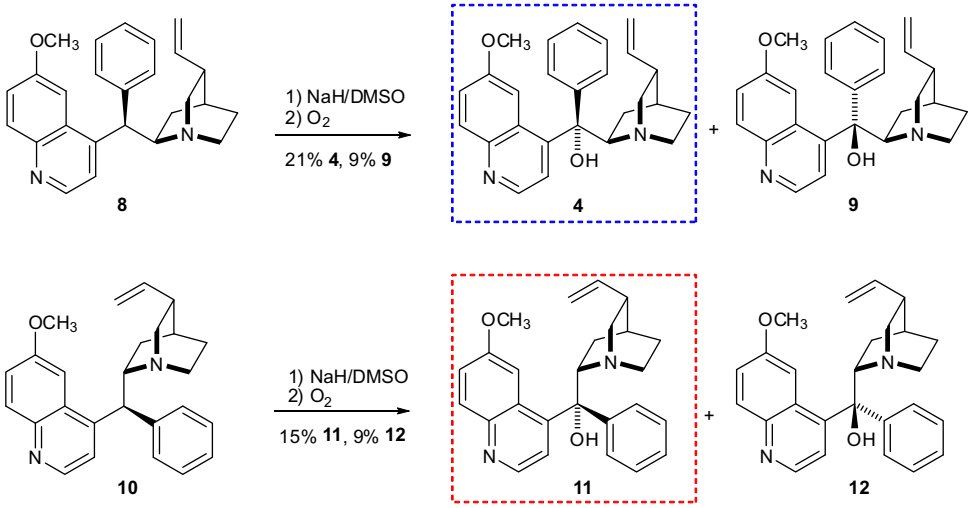
(8*R*)-isomer **1**.[8,9] The reaction of **1** with methylmagnesium halide has already been carried out by Woodward et al., however no convincing evidence for the stereochemistry of the transformation could be given at that time.[5] Thus, we repeated the addition of methylmagnesium chloride to quinidinone **1** in a THF/toluene mixture and we obtained a single addition product **2** (Scheme 1).

Similarly, the reactions of vinylmagnesium and phenylmagnesium halides gave a single isomer of the corresponding addition products **3** and **4**. Each crude mixture obtained after aqueous work-up contained the respective, easily separable, single diastereomeric addition product (within the ^1H NMR detection limit) and the starting material only. The ketone was recovered as a mixture of (8*R*)- and (8*S*)-epimers. The initial yields of the addition were rather poor (Table 1, entry 2). After several attempts, the yield was improved by changing the solvent from THF or diethyl ether to methylene chloride, and the desired product **4** was obtained in 48% yield (entry 3). The initial low yields of the Grignard additions, as well as the unsuccessful reaction with phenyllithium, were most likely the result of concurrent enolate formation. In addition to simple Grignards, heteroatom-containing reagents were also added as exemplified by the reaction of 3-*N*,*N*-bis(trimethylsilyl)aminophenylmagnesium chloride (entry 5). In a similar reaction, cinchoninone **6** and phenylmagnesium bromide also gave the single addition product **7**.

In another approach, the sequence of the formation of the carbon–carbon and carbon–oxygen bonds was inverted. Thus, we subjected the previously obtained 9-deoxy-9-aryl alkaloids[3] (Fig. 1) to 9-hydroxylation. (9*R*)-Deoxy-9-phenyl-quinidine **8** was deprotonated in DMSO and the corresponding carbanion solution was saturated with dry oxygen. The oxidation resulted in the formation of two separable isomeric products **4** and **9**, as confirmed by ESI-MS (Scheme 2). One of them was identical to product **4**, obtained in the addition of the Grignard reagent to ketone **1**. Similarly, (9*S*)-deoxy-9-phenyl-quinine **10** was oxidized to two distinct isomeric products **11** and **12**. Both autoxidation reactions proceeded with moderate diastereoselectivity (dr ca. 2:1) and the more polar products **4** and **11** were favored over the less polar **9** and **12**.

2.2. Configuration of the products

In the Grignard addition, the stereogenic center at C-9 is newly formed. Furthermore, the adjacent center at C-8 in the starting ketone is configurationally labile.[9] It was previously speculated (on the basis of the specific rotation) that the product **2** formed from



Scheme 2. Synthesis of 9-phenyl-alkaloids.

quinidinone **1** and methylmagnesium iodide was of the same configuration as that of native quinidine.[5] We have investigated the NOE interactions for **2** (Fig. 2). The newly introduced 9-CH_3 group shows cross correlations to 8-CH and one of the hydrogen atoms of

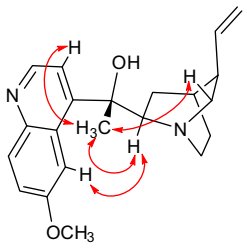


Figure 2. NOE interactions for 9-methylquinidine **2** in $CDCl_3$.

the 2-CH_2 group, while the latter two groups do not correlate with each other. These unequivocally confirm the (8*R*)-configuration. Correlations of 3′-CH with 9-CH_3 as well as correlations of 5′-CH with 8-CH are better explained by assuming the (9*S*)-configuration.

Finally, we unambiguously proved the configuration of the product (8*R*,9*S*)-**2** with an X-ray crystal structure (Fig. 3A). The same stereochemical outcome was expected for the reaction of other Grignard reagents, where a high stereoselectivity was also achieved. The absolute configuration of **4** was also proven to be (8*R*,9*S*) by the X-ray crystal structure (Fig. 3B).

Product **4** and starting materials **1** and **8** share the same configuration at the C-8 center. As one can expect, autoxidation did not cause epimerization at the C-8 atom (cf. Scheme 2). Consequently, the diastereomer (8*R*,9*S*)-**4** must differ from **9** in the configuration at C-9 only. An analogous stereochemical outcome was expected for the autoxidation of (8*S*,9*S*)-**10**,[3a] where we also obtained two C-9 epimers, respectively, **11** and **12**.

In another experiment, prior to the addition of phenylmagnesium chloride, ketone **1** was allowed to isomerize for a few days in solution, giving a mixture of C-8 epimers **1** and **1a** (Scheme 3), as was earlier documented by NMR.[8] This time both diastereomers **4** and **11** were observed as the reaction products. Phenylalkaloid **11** was identical to that previously isolated from the autoxidation of deoxy-phenyl-quinine **10**. Thus it could be anticipated that epimers **1** and **1a** gave compounds **4** and **11** of the same relative (*unlike*) configuration at the C-8 and C-9 stereogenic centers.

Additionally, it is known that the native alkaloids [*unlike*, i.e., (8*R*,9*S*) and (8*S*,9*R*)] are more polar than their 9-*epi* counterparts [*like*, i.e., (8*R*,9*R*) and (8*S*,9*S*)];[10] the same regularities were observed here, when comparing the corresponding R_f values (see Section 4).

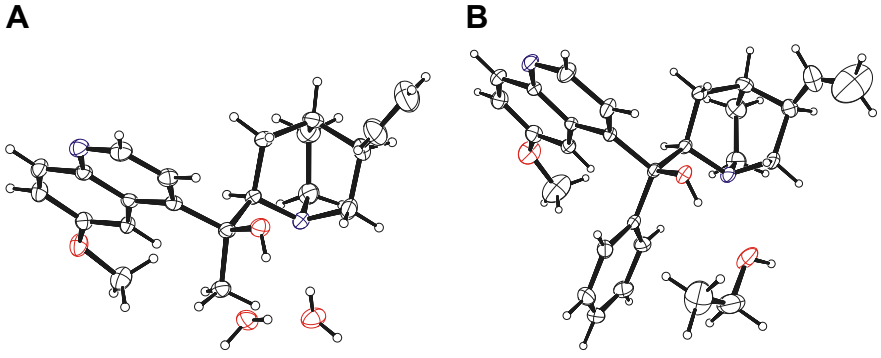
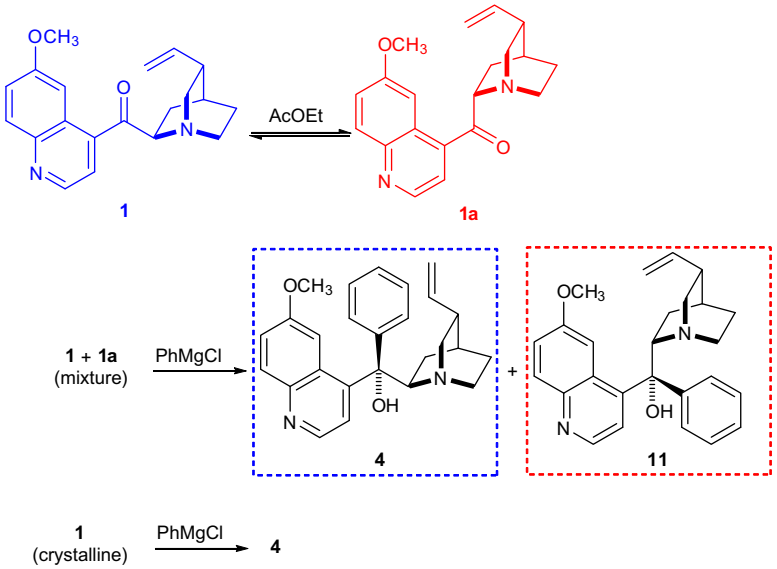


Figure 3. Crystal structures of (A) 9-methylquinidine (**2**·$2H_2O$) and (B) 9-phenylquinidine (**4**·EtOH).



Scheme 3. Addition of phenylmagnesium chloride to ketones **1** and **1a**.

In the solid state both **2** and **4** adopt very similar conformations, herein referred to as *anti-open*[11] (Fig. 3). The same type of conformation was observed in the nuclear Overhauser effect experiments for **2** in $CDCl_3$ suggesting that the *open* conformation is prevalent in solution as well (Fig. 2). Optimization of the geometries at the DFT/B3LYP/6-31G(d,p) level of theory[12] in vacuum also indicated that the *anti-open* conformation was the most energetically favored for both **9** and **12** (by ca. 5 kcal/mol) as well as for **4** and **11** (by ca. 2 kcal/mol).

The tentative assignment of configuration for phenylalkaloids **9**, **11**, and **12** (isomers of **4**) was augmented by comparison of the experimental and theoretical (GIAO-DFT/B3LYP/6-31G(d,p)) ^{13}C chemical shifts.[12,13] The correlations of DFT and experimental data were very good for all compounds (R^2 = 0.998). In order to emphasize the differences in the ^{13}C chemical shifts between the isomers and compensate for the systematic errors of a DFT calculation,[13] a statistical approach was adopted. For each carbon atom we defined a deviation from an averaged chemical shift taken for all four diastereomers **4**, **9**, **11**, and **12**. The patterns of these deviations for the experimental and DFT data were in good agreement for all isomers (Fig. 4); RMS error was in the 0.58–0.77 ppm range, while the assignments of inappropriate configurations gave 1.26–2.65 ppm RMS error. The configuration at the C-8 center was assigned on the basis of the deviations of the C-2 and C-6 chemical shifts. The patterns observed for the 9-aryl alkaloids were similar to those observed for 9-unsubstituted alkaloids[14] and were very well matched by the DFT calculation. The relative configuration at the C-8 and C-9 stereogenic centers was distinguished by observing deviations in the C-8 and C-9 chemical shifts that was in qualitative agreement with the computational data.

2.3. Stereochemical models

The addition of the Grignard reagents to (8*R*)-**1** only provided (8*R*,9*S*)-products **2**, **3**, **4**, and **5**. As we had proved, the configuration at the C-8 center of the products is the same as in the crystalline starting material.[8] An isomerization at this center would require a proton to be transferred from the 8-CH group and back. However, under the Grignard reaction conditions, protonation of the enolate is prevented until the reaction is quenched with water (Scheme 4). Only on the addition of Grignard reagents to the mixture of **1** and **1a**, were both products **4** and **11** obtained (Scheme 3).

The diastereoselectivity of the reaction at the C-9 center is in agreement with the previous findings by Hintermann[15] and by us[3] in that the complexation of magnesium to the quinuclidine nitrogen atom determines the stereochemical outcome. It has been demonstrated that in the addition and substitution reactions, the carbon nucleophile always approached the reaction center from the side of the quinuclidine nitrogen. The observed stereoselectivity of the reduction of ketone **1** was attributed to the *Re* attack of hydride from the complexed aluminum species, resulting exclusively in the native alkaloids.[16]

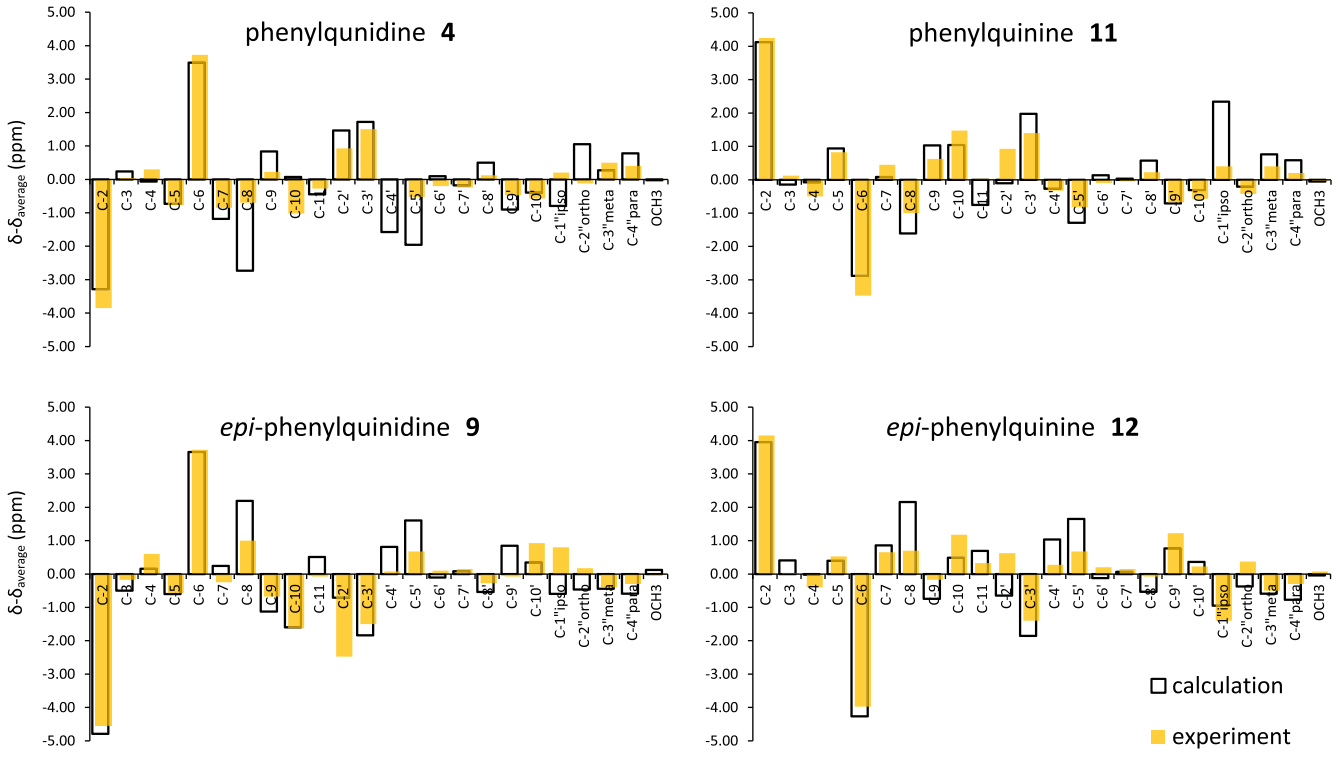
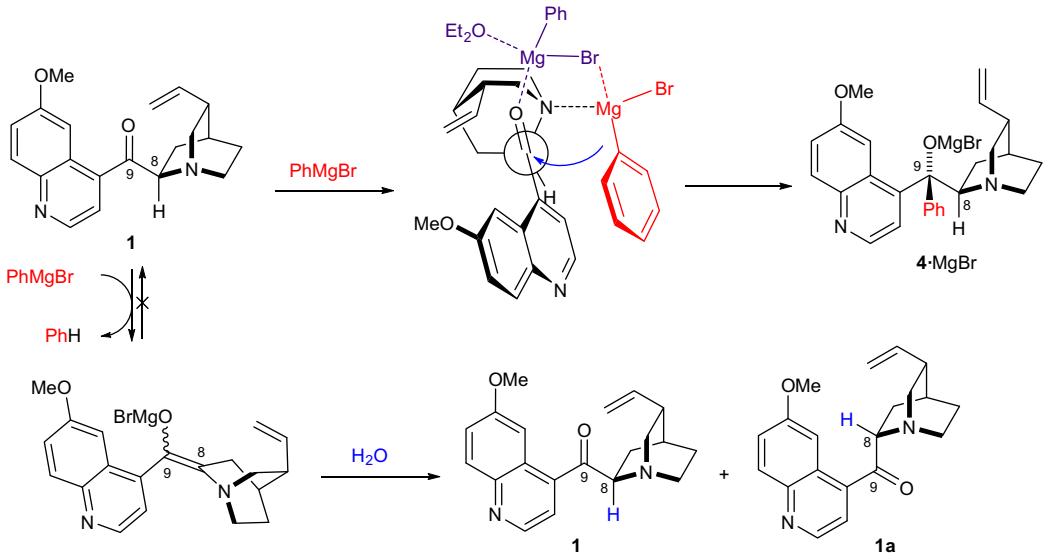


Figure 4. ^{13}C NMR patterns: experimental and calculated (GIAO DFT/B3LYP/6-31G(d,p)) differences of the ^{13}C chemical shifts from the mean chemical shifts for a set of four isomeric phenyl-alkaloids **4**, **9**, **11** and **12**.

Here, the complexation of magnesium species to quinidinone **1** most likely involved two metal atoms (Scheme 4) that would enforce the *syn*-orientation of the ketone oxygen and the quinuclidine nitrogen atoms. This conformation is distinct from that observed in solid quinidinone.[8] In such an orientation, the attack of the carbon nucleophile would occur from the *Re* face. The product formed would have a (9*S*)-configuration, following the substituent priority rules. Once the complex is formed, the alternative approach from the *Si* face becomes very unlikely because of steric



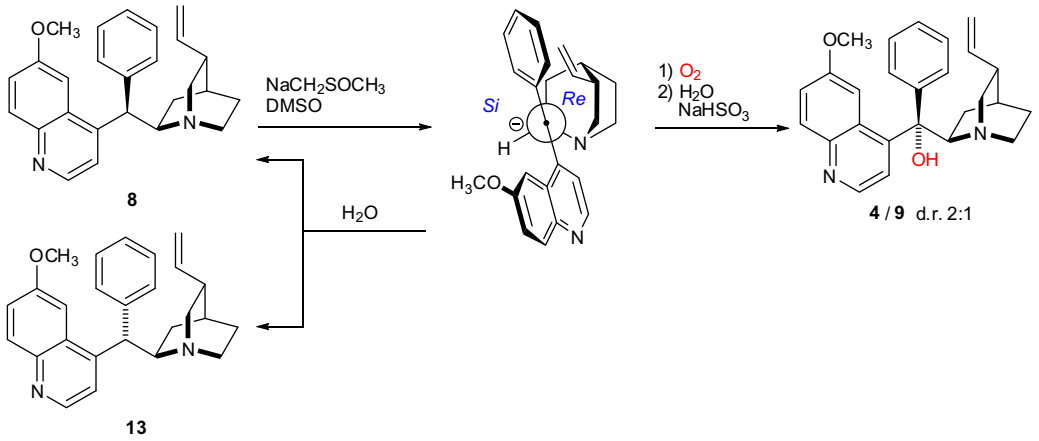
Scheme 4. Suggested intermediates in the synthesis of **4**.

hindrance. Thus, the neighboring group (quinuclidine) guides reactions at the 9-carbon stereocenter, whenever metal chelates could be formed and leads to a highly stereoselective transformation. These findings are in contrast to the additions that do not involve metal bidentate complexes, such as the addition of TMS–CF_3 reagent, which results in the addition from the *Si* face.[8]

In the case of the hydroxylation reaction, it was anticipated that the intermediate anion (or a relatively short-lived radical) would be nearly flat. Deprotonation of **8** was evidenced by small quantities of (9*S*)-deoxy-9-phenylquinidine **13**, an epimer of **8**, found in the reaction mixture after aqueous workup (Scheme 5). The preferred approach of the reacting species was from the side opposite to the quinuclidine moiety, that is, *Si* for quinidine and *Re* for quinine. This stereochemical behavior has already been observed for the 9-cinchonanyl radical coupling reaction.[17] However, here the low steric demands of the reacting species (O_2) preclude high stereoselectivities.

3. Conclusion

In conclusion, a combination of the addition of Grignard reagents to cinchonanones and the autoxidation of 9-phenyl-cinchonanes gave all of the 8,9-stereoisomers of 9-phenyl-substituted *Cinchona* alkaloids. The 9-substituted *Cinchona* alkaloids prepared had all of their original functionalities, while offering an increased rigidity that could be important for their catalytic applications.



Scheme 5. Intermediate anion in the autoxidation of **8**.

4. Experimental

4.1. General

IR spectra were recorded on a Perkin Elmer System 2000 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured

on a Bruker Avance DRX 300 (^{1}H, 300 MHz) or a Bruker Avance 600 (^{1}H, 600 MHz) spectrometer using a solvent residual peak as a reference. Optical rotations were measured using an Optical Activity Ltd Model AA-5 automatic polarimeter. High resolution mass spectra were recorded using a Waters LCT Premier XE instrument in electrospray ionization mode. Separation of products by chromatography was performed on silica gel 60 (230–400 mesh) purchased from Merck. Thin layer chromatography was carried out using silica gel 60 precoated plates (Fluka). X-ray data were collected at 299 K using a KM4CCD diffractometer. Crystallographic data for the structures **2** and **4** herein have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 872905 and CCDC 872904, respectively.

4.1.1. Quinidinone 1

This compound was obtained according to a literature procedure[7] on a 130 mmol scale and was recrystallized from diethyl ether.

4.1.2. Cinchoninone 6

This compound was obtained according to a modified procedure[7] starting from cinchonine (34.6 g, 117 mmol). Precipitated crude product (28.6 g) was continuously extracted with 300 mL of diethyl ether using a Soxhlet apparatus. The extract was then cooled and the crystalline precipitate collected. The mother liquor was dried, evaporated and the residue was submitted to two consecutive recrystallizations from diethyl ether. Overall, 25.0 g of yellowish crystalline cinchoninone **6** were obtained (73% yield). Mp 121–123 °C, lit.[18] mp 125–125.5 °C. NMR (300 MHz, $CDCl_3$): δ 9.01 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.75 (m, 1H), 7.68 (d, J = 4.4 Hz, 1H), 7.61 (m, 1H), 5.95 (ddd, J = 17.5, 10.5, 7.2 Hz, 1H), 5.06–5.14 (m, 2H), 4.12–4.24 (m, 1H), 3.17 (dd, J = 17.8, 10.2 Hz, 1H), 2.73–2.95 (m, 2H), 2.54–2.69 (m, 1H), 2.34 (m, 1H), 2.09–2.20 (m, 1H), 1.80–1.96 (s, 2H), 1.61–1.73 (m, 1H), 1.39–1.58 (m, 1H).

4.2. Procedure for addition of Grignard reagents

A solution of Grignard reagent was obtained from magnesium (240 mg, 9.9 mmol) and bromobenzene (1.1 mL, 10 mmol) in diethyl ether (16 mL) and it was evaporated in vacuo. The residue was cooled to 0 °C and within 2 min a freshly prepared solution of crystalline quinidinone **1** (378 mg, 1.17 mmol) in CH_2Cl_2 (10 mL) was added and the mixture was allowed to return to room temperature. After 24 h, the reaction was quenched with a saturated NH_4Cl solution. The product was extracted with dichloromethane, dried over Na_2SO_4 and evaporated. The residue was purified on silica gel with $CHCl_3$/MeOH 10:1 to afford a mixture of quinidinone/quininone followed by 9-phenylquinidine **4** 223 mg, 48%.

4.2.1. 9-Phenylquinidine, (8*R*,9*S*)-6′-methoxy-9-phenyl-9-cinchonanol 4

White crystalline solid. Mp 182–186 °C (CH_2Cl_2/hexane). R_f ($CHCl_3$/MeOH, 4:1) 0.246. $[\alpha]_D^{26} = +127$ (c 0.7 EtOH, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (d, J = 4.7 Hz, 1H), 8.02 (br, 1H), 7.88 (d, J = 9.3 Hz, 1H), 7.46 (dt, J = 6.6, 1.8 Hz, 2H), 7.19–7.31 (m, 3H), 7.13 (dd, J = 9.2, 2.7 Hz, 1H), 6.82 (br, 1H), 5.43 (ddd, J = 17.3, 10.3, 7.0 Hz, 1H), 4.76 (dt, J = 10.4, 1.4 Hz, 1H), 4.62 (dt, J = 17.3, 1.4 Hz, 1H), 4.3 (br, 1H, exchangeable with D_2O), 3.96 (t, J = 10.2 Hz, 1H), 3.42 (s, 3H), 3.22 (m, 1H), 2.80–2.91 (m, 1H), 2.63–2.75 (m, 2H), 2.08 (m, 1H), 1.52–1.79 (m, 4H), 1.18–1.32 (br, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 156.4, 149.7, 147.4, 145.5, 145.3, 139.7, 131.4, 128.6, 127.7, 127.2, 127.1, 121.1, 120.5, 114.4, 105.1, 79.3, 61.4, 55.3, 50.8, 49.5, 39.8, 29.1, 26.2, 23.8. IR (KBr): 3143, 2932, 2870, 1622, 1509, 1449, 1432, 1357, 1242, 1229, 1028, 1018, 857, 702 cm^{-1}. HR-MS (ESI): calcd for $[C_{26}H_{28}N_2O_2+H]^+$ 401.2224, found: 401.2238.

4.2.2. 9-Vinylquinidine, (8*R*,9*S*)-6′-methoxy-9-vinyl-9-cinchonanol 3

According to the procedure for the addition of Grignard reagents, a solution of vinylmagnesium bromide (10 mL, 1 M in THF, 10 mmol, 4.4 equiv) was evaporated and a solution of quinidinone **1** (733 mg, 2.27 mmol) in dry CH_2Cl_2 (17 mL) was added to the residue. The reaction gave 297 mg of **3** (37%) as a yellowish amorphous solid after chromatography on silica gel ($CHCl_3$/MeOH, 10:1). R_f ($CHCl_3$/MeOH, 10:1) 0.25. $[\alpha]_D^{21} = +97$ (c 0.92, EtOH, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, J = 4.7 Hz, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.84 (d, J = 4.7 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 9.1, 2.4 Hz, 1H), 6.89 (dd, J = 17.7, 11.1 Hz, 1H), 5.84 (ddd, J = 17.0, 10.1, 7.7 Hz, 1H), 5.25 (d, J = 10.9 Hz, 1H), 5.03 (d, J = 17.7 Hz, 1H), 4.88 (d, J = 11.1 Hz, 1H), 4.87 (d, J = 17.0 Hz, 1H), ~4 (br, 1H), 3.80 (s, 3H), 3.35–3.62 (m, 2H), 3.00 (m, 1H), 2.76–2.90 (m, 2H), 2.13 (q, J = 8.4 Hz, 1H), 1.73 (m, 1H), 1.59 (m, 1H), 1.40–1.53 (m, 2H), 0.69 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 156.4, 148.7, 147.4, 144.8, 141.6, 140.1, 131.5, 126.5, 120.8, 120.4, 117.4, 114.5, 105.7, 78.7, 61.4, 55.4, 50.9, 49.9, 39.9, 28.6, 26.0, 21.7. IR (KBr): 3235, 2935, 2869, 1621, 1509, 1240, 1228, 1031, 861, 831 cm^{-1}. HR-MS (ESI): calcd for $[C_{22}H_{26}N_2O_2+H]^+$ 351.2067, found: 351.2083.

4.2.3. 9-(3-Aminophenyl)quinidine, (8*R*,9*S*)-6′-methoxy-9-(3-aminophenyl)-9-cinchonanol 5

According to the procedure for addition of Grignard reagents, a solution of 3-bis(trimethylsilyl)aminophenylmagnesium chloride (10 mL, 1 M in THF, 10 mmol, 3.2 equiv) was evaporated and a solution of quinidinone **1** (1023 mg, 3.17 mmol) in dry CH_2Cl_2 (15 mL) was added to the residue at 0 °C. After 26 h at room temperature, a saturated NH_4Cl solution was added and the mixture was stirred for 30 min. The mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4. Chromatography on silica gel ($CHCl_3$/MeOH, 10:1 to 5:1) afforded 804 mg of **5** (61%) as yellowish amorphous solid. R_f ($CHCl_3$/MeOH, 10:1) 0.06. $[\alpha]_D^{23} = +104$ (c 0.80, EtOH, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, J = 4.5 Hz, 1H), 7.94 (br, 1H), 7.83 (d, J = 9.1 Hz, 1H), 7.11 (dd, J = 9.1, 2.9 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.87–7.16 (br, 1H), 6.58 (s, 1H), 6.49 (dd, J = 7.8, 1.3 Hz, 1H), 5.43 (ddd, J = 17.3, 10.2, 7.2 Hz, 1H), 4.73 (d, J = 10.2 Hz, 1H), 4.61 (d, J = 17.2 Hz, 1H), 3.5–5.0 (br, 3H), 3.82 (t, J = 9.8 Hz, 1H), 3.49–3.62 (m, 1H), 3.46 (s, 3H), 3.15 (m, 1H), 2.72–2.85 (m, 1H), 2.63 (br, 1H), 2.02 (m, 1H), 1.47–1.76 (m, 4H), 1.10–1.30 (br, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 156.3, 150.1, 147.1, 146.8, 146.5, 144.9, 139.8, 131.0, 129.1, 127.2, 121.1, 120.2, 116.6, 114.7, 114.5, 114.3, 105.2, 79.1, 61.2, 55.2, 50.6, 49.3, 39.7, 29.0, 26.1, 23.7. IR (KBr): 3335, 3211, 2935, 2868, 1621, 1605, 1508, 1453, 1240, 1226, 1029, 761 cm^{-1}. HR-MS (ESI): calcd for $[C_{26}H_{29}N_3O_2+H]^+$ 416.2333, found: 416.2333.

4.2.4. 9-Phenylcinchonine, (8*R*,9*S*)-9-phenyl-9-cinchonanol 7

According to a general procedure, an evaporated solution of phenylmagnesium bromide (16 mL in Et_2O, 10 mmol, 7.7 equiv) and a freshly prepared solution of cinchoninone **6** (384 mg, 1.31 mmol) in dry CH_2Cl_2 (17 mL) gave after chromatography on silicagel ($CHCl_3$/MeOH 20:1 to 20:3) 140 mg (30%) of **7**. Recrystallization from ethanol provided white crystals. Mp 225–233 °C (EtOH). $[\alpha]_D^{25} = +11$ (c 0.45, EtOH, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91 (d, J = 4.7 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 8.04 (br, 1H), 7.60 (br, 1H), 7.48–7.55 (m, 1H), 7.43–7.48 (m, 2H), 7.15–7.30 (m, 4H), 5.88 (ddd, J = 17.2, 10.3, 7.0 Hz, 1H), 5.07 (dt J = 17.2, 1.6 Hz, 1H), 5.02 (dt, J = 10.4, 1.4 Hz, 1H), 4.2 (br, ~1H), 4.00 (t, J = 9.8 Hz, 1H), 3.01–3.18 (m, 3H), 2.55 (m, 1H), 2.30 (m, 1H), 1.76 (m, 1H),

1.24–1.56 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 151.0, 149.9, 149.1, 145.7, 142.2, 130.3, 128.6, 128.4, 127.7, 127.1, 126.4, 126.2, 125.7, 120.1, 114.6, 80.0, 61.2, 57.6, 43.7, 40.1, 28.3, 27.9, 24.9. HR-MS (ESI): calcd for $[C_{25}H_{26}N_2O+H]^+$ 371.2118, found: 371.2124.

4.2.5. 9-Methylquinidine, (8*R*,9*S*)-6′-methoxy-9-methyl-9-cinchonanol 2

The reaction was carried out according to Woodward's procedure.[5] From quinidinone **1** (440 mg, 1.37 mmol) and methylmagnesium chloride (3.0 mL, 3 M in Et_2O, 9.0 mmol, 6.5 equiv) 280 mg (55%) of **2** were obtained.

Dihydrate $[\alpha]_D^{23} = +151$ (*c* 0.49, EtOH, 96%); anhydrous lit.[5] $[\alpha]_D$ = +168, = +170 (*c* 0.5, EtOH, 96%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.70 (d, *J* = 4.7 Hz, 1H), 8.03 (d, *J* = 9.3 Hz, 1H), 7.71 (br, 1H), 7.67 (br, 1H), 7.34 (dd, *J* = 9.3, 2.5 Hz, 1H), 5.73 (ddd, *J* = 17.3, 10.5, 7.7 Hz, 1H), 4.87 (d, *J* = 10.5 Hz, 1H), 4.79 (d, *J* = 17.3 Hz, 1H), 3.92 (s, 3H), ~3.4 (br, 1H), 3.28 (t, *J* = 9.1 Hz, 1H), 3.09 (m, 1H), 3.01 (m, 1H), 2.79–2.90 (m, 2H), 2.13 (m, 1H), 1.95 (s, 3H), 1.78 (m, 1H), 1.67 (m, 1H), 1.51–1.56 (m, 2H), 1.01 (m, 1H). ^{1}H NMR (600 MHz, C_6D_6): δ 8.74 (d, *J* = 4.6 Hz, 1H), 8.33 (d, *J* = 9.1 Hz, 1H), 7.87 (br, 1H), 7.47 (br, 1H), 7.22 (dd, *J* = 9.1, 2.7 Hz, 1H), 5.92 (m, 1H), 4.95 (d, *J* = 10.5 Hz, 1H), 4.91 (d, *J* = 17.4 Hz, 1H), 3.45 (s, 3H), 3.36 (m, 1H), 3.18 (br, 1H), ~3.0 (br, 1H), 2.79 (m, 1H), 2.74 (dd, *J* = 13.6, 10.3 Hz, 1H), 2.60 (m, 1H), 1.92 (m, 1H), 1.81–1.88 (m, 1H) 1.86 (s, 3H), 1.42 (m, 1H), 1.12–1.16 (m, 2H), 0.71 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 156.8, 150.9, 147.5, 145.3, 140.3, 132.1, 127.0, 120.6, 119.9, 114.3, 104.3, ~77.3, 63.4, 55.4, 51.2, 41.8, 39.9, 29.6, 28.8, 26.3, 22.1.

4.3. Autoxidation of 9-deoxy-9-phenyl-quinidine 8

Sodium hydride (60% dispersion in oil, 137 mg, 3.45 mmol, 8.8 equiv) was washed with hexane in an N_2-filled glovebag, suspended in dry DMSO (1.5 mL), stirred at 75 °C for 1.5 h, and cooled to room temperature. Then a solution of (9*R*)-deoxy-9-phenylalkaloid[3] **7** (151.6 mg, 0.39 mmol) in DMSO (1.5 mL) was added and the mixture turned dark red. After stirring for 20 min, dry oxygen was slowly passed through a solution for 48 h. The mixture initially warmed up and a gradual discoloration occurred. Then a solution of sodium hydrogen sulfite in water (1 mL, 40%) was added and the mixture was agitated for 30 min, and then alkalized with aqueous sodium hydroxide (10%) solution. The mixture was then extracted with ethyl acetate (6 × 15 mL). The combined organic phases were washed with brine and dried over Na_2SO_4 giving after evaporation approximately 100 mg of residue. Column chromatography on silica gel with $CHCl_3$/MeOH 10:1 afforded a mixture containing 9-*epi*-phenyl-alkaloid **9**, followed by pure (9*S*)-phenyl-quinidine **4** (32.2 mg, 21%). The *epi*-alkaloid fraction (~60 mg) was again chromatographed on silica gel with $CHCl_3$/MeOH 20:1 and gave pure (9*R*)-phenyl-quinidine **9** (14.5 mg, 9%) and (9*S*)-9-deoxy-9-phenylquinidine **13** (18.4 mg, 12%).

4.3.1. *epi*-9-Phenylquinidine, (8*R*,9*R*)-6′-methoxy-9-phenyl-9-cinchonanol 9

White crystalline solid. R_f ($CHCl_3$/MeOH, 4:1) 0.309. $[\alpha]_D^{24} = +110$ (*c* 0.3 EtOH, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76 (d, *J* = 4.7 Hz, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 2.8 Hz, 1H), 7.46 (d, *J* = 4.6 Hz, 1H), 7.42 (br d, *J* = ~6.9 Hz, 2H), 7.17–7.27 (m, 3H), 7.15 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.18 (ddd, *J* = 17.3, 10.4, 7.0, 1H), 4.71 (d, *J* = 10.4 Hz, 1H), 4.49 (d, *J* = 17.3 Hz, 1H), 3.68 (m, 1H), 3.61 (s, 3H), 3.08 (m, 1H), 2.78–2.91 (m, 1H), 2.67 (dd, *J* = 13.6, 9.8 Hz, 1H), 2.50–2.60 (m, 1H), 2.09 (q, *J* = 8.2 Hz, 1H) 1.59–2.01 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 156.7, 149.8, 146.8, 146.1, 144.0, 139.1, 131.0, 127.64, 127.59, 127.52, 127.0, 121.5, 117.5, 114.6, 106.3, 78.4, 63.1, 55.3, 50.8, 48.8, 39.6, 29.4, 26.4, 24.4. IR (KBr): 3302, 2916, 2867, 1623, 1509, 1449, 1240, 1228, 1034, 998, 912, 841, 709 cm^{-1}. HR-MS (ESI): calcd for $[C_{26}H_{28}N_2O_2+H]^+$ 401.2224, found: 401.2235.

4.3.2. (9*S*)-Deoxy-9-phenylquinidine, (8*R*,9*S*)-6′-methoxy-9-phenyl-cinchonane 13

Off-white solidified oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.79 (d, *J* = 4.7 Hz, 1H), 7.94 (d, *J* = 9.3 Hz, 1H), 7.51 (d, *J* = 4.7 Hz, 1H), 7.38 (d, *J* = 2.6 Hz, 1H), 7.18–7.35 (m, 5H), 7.10–7.17 (m, 1H), 6.01 (ddd, *J* = 17.3, 10.6, 17.8 Hz, 1H), 5.06–5.16 (m, 2H), 4.65 (d, *J* = 11.2 Hz, 1H), 3.89 (s, 3H), 3.64 (m, 1H), 2.75–3.13 (m, 4H), 2.25 (m, 1H), 1.76 (m, 1H), 1.48–1.70 (m, 3H), 1.13–1.28 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.5, 147.8, 147.2, 144.9, 140.83, 140.75, 131.9, 129.0, 128.69, 128.66, 127.0, 120.7, 119.5, 114.6, 102.2, 58.1, 55.5, 49.35, 49.34, 47.6, 39.8, 28.1, 27.2, 26.6. HR-MS (ESI): calcd for $[C_{26}H_{28}N_2O+H]^+$ 385.2274 found 385.2281.

4.4. Autoxidation of 9-deoxy-9-phenyl-quinine

According to the procedure for autoxidation of **8**, (9*S*)-phenyl-9-deoxy-quinine[3] **10** (52.5 mg, 0.13 mmol) and sodium dimsylate obtained from 63 mg of sodium hydride (1.6 mmol, 12 equiv) gave (9*R*)-phenyl-quinine **11** (7.2 mg, 13%) and (9*S*)-phenyl-quinine **12** (4.5 mg, 9%).

4.4.1. 9-Phenylquinine, (8*S*,9*R*)-6′-methoxy-9-phenyl-9-cinchonanol 11

White crystalline solid. R_f ($CHCl_3$/MeOH, 4:1) 0.377, $[\alpha]_D^{26} = -27$ (*c* 0.4 EtOH, 96%), $[\alpha]_D^{20} = -9.1$ (*c* 1 CH_2Cl_2), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, *J* = 4.7 Hz, 1H), 8.02 (br, 1H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.44–7.48 (m, 2H), 7.19–7.33 (m, 3H), 7.16 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.81 (br, 1H), 5.92 (ddd, *J* = 17.2, 10.5, 6.5 Hz, 1H), 5.11 (dt, *J* = 17.2, 1.8 Hz, 1H), 5.08 (dt, *J* = 10.5, 1.8 Hz, 1H), 4.04 (m, 1H), 3.48 (s, 3H), 3.10–3.24 (m, 3H), 2.55–2.68 (m, 1H), 2.35 (m, 1H), 2.1–3.8 (br, 1H), 1.82 (m, 1H), 1.19–1.67 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.5, 149.4, 147.4, 145.7, 145.3, 142.2, 131.5, 128.5, 127.5, 126.9, 121.3, 120.4, 114.7, 104.8, 79.7, 61.1, 57.6, 55.3, 43.6, 39.9, 28.3, 27.8, 25.1, (1 signal overlap). IR (KBr): 3138, 2920, 2859, 1621, 1509, 1449, 1244, 1229, 1032, 837, 707 cm^{-1}. HR-MS (ESI): calcd for $[C_{26}H_{28}N_2O_2+H]^+$ 401.2224, found: 401.2234.

4.4.2. *epi*-9-Phenylquinine, (8*S*,9*S*)-6′-methoxy-9-phenyl-9-cinchonanol 12

White crystalline solid. R_f ($CHCl_3$/MeOH, 4:1) 0.450. $[\alpha]_D^{23} = +13$ (*c* 0.2 EtOH, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.77 (d, *J* = 4.7 Hz, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.55 (d, *J* = 2.8 Hz, 1H), 7.31–7.43 (m, 3H), 7.10–7.26 (m, 4H), 6.08 (ddd, *J* = 17.2, 10.6, 6.6 Hz, 1H), 5.19 (dt, *J* = 10.6, 1.5 Hz, 1H), 5.17 (dt, *J* = 17.2, 1.5 Hz, 1H), 3.73 (t, *J* = 9.4 Hz, 1H), 3.61 (s, 3H), 3.13 (dd, *J* = 13.5, 9.9 Hz, 1H), 2.96–3.04 (m, 1H), 2.81–2.93 (m, 1H), 2.37 (m, 1H), 2.02–2.14 (m, 1H) 1.93 (m, 1H) 1.63–1.73 (m, 1H), 1.13–1.37 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 156.8, 150.0, 147.1, 146.1, 143.9, 141.9, 131.2, 128.8, 127.7, 127.6, 127.0, 121.5, 117.6, 115.0, 106.3, 78.9, 62.8, 57.5, 55.4, 43.1, 39.8, 28.4, 27.5, 25.3. IR (KBr): 3296, 2922, 2861, 1621, 1508, 1240, 1224, 1035, 839, 709, 701 cm^{-1}. HR-MS (ESI): calcd for $[C_{26}H_{28}N_2O_2+H]^+$ 401.2224, found: 401.2233.

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