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Stereoselective C9 Carbon−Carbon Couplings of Quinine: Synthesis and Conformational Analysis of New C_2-Symmetric Dimers

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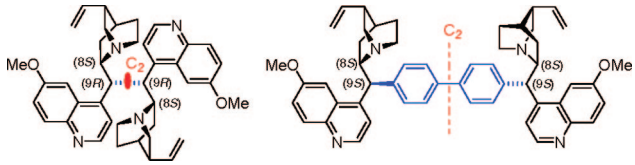
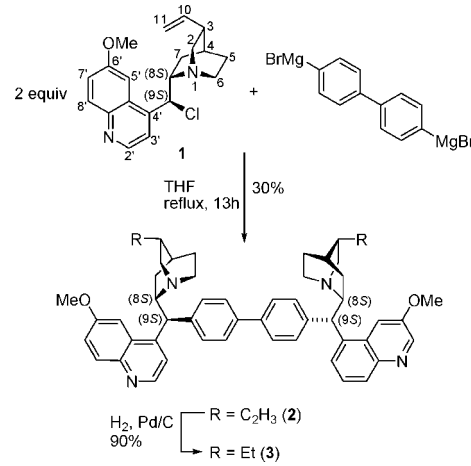


An unexpected stereoselective direct dimerization occurred when 9-quinine halide was treated with butyllithium. The reaction of either (9*S*)- or (9*R*)-chloroquinine gave the same C_2-symmetric dimer with 9*R* configuration (X-ray structure). A tentative mechanism involving radical recombination is discussed. This highly congested dimer forms two atropisomers, and their reversible interconversion was studied by NMR. Another C_2-symmetric (9*S*)-quinine dimer connected solely by carbon−carbon bonds was obtained by the stereoselective coupling of bis(arylbromomagnesium) derivative with (9*S*)-chloroquinine.

Cinchona alkaloids have found numerous applications in asymmetric synthesis.[1] The most impressive one, namely, asymmetric dihydroxylation, uses their dimeric C_2-symmetric derivatives.[2] These chiral ligands have been successfully used in other asymmetric processes as well.[3] The alkaloid units were linked at the C-9 position as ethers,[2] esters,[4] and 9-amino derivatives.[5] The only *Cinchona* alkaloid dimers, where the units are connected by carbon−carbon bonds, are those attached at the positions C-11[6] and C-4′.[7]

SCHEME 1. Synthesis of 9-Biphenyl Dimers 2 and 3



In this Note we describe an efficient and diastereoselective synthesis of new dimers, with a carbon−carbon bond formed between C-9 atoms of two alkaloid units, both with and without a linker.

Recently, we reported a highly diastereoselective carbon−carbon bond formation at the position C-9 of *Cinchona* alkaloids in the reaction of arylmagnesium compounds with the 9-chloro derivatives.[8] Now, we extended this approach for the synthesis of a C−C bonded dimeric *Cinchona* alkaloid derivative. Thus, we carried the reaction of bis-Grignard reagent obtained from 4,4′-dibromobiphenyl with 2 equiv of (9*S*)-chloroquinine. The bis-coupling gave the dimeric product **2** in moderate yield (30%) (Scheme 1) along with the monosubstituted biphenyl product (25%) and unreacted (9*S*)-chloroquinine. The best outcomes were obtained using active Rieke magnesium[9] for the preparation of Grignard reagent. The vinyl groups of **2** were hydrogenated giving **3** in 90% yield.

The dimeric product formed (**2**) was clearly C_2-symmetric, as was demonstrated by its NMR spectra, which closely resembled those of the corresponding monomeric derivative, namely, (9*S*)-phenyl quinine. Our previous studies revealed that in the coupling with Grignard reagents only the 8,9-*like* isomers were produced, as proved by X-ray.[8] Thus all of these findings imply that both quinine units in **2** are bound at their 9*S* stereogenic centers.

The attempted reaction of (9*S*)-chloroquinine (**1**) with phenyllithium used instead of the aryl Grignard reagent gave only 4% of (9*S*)-phenyl quinine. Nonetheless, we found that the reaction mixture contained also up to 11% of the new product of direct dimerization-dechlorination (as identified by ESI-MS). Additionally, we discovered small amounts (up to 4%) of this

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[‡] Institute of Physical and Theoretical Chemistry.

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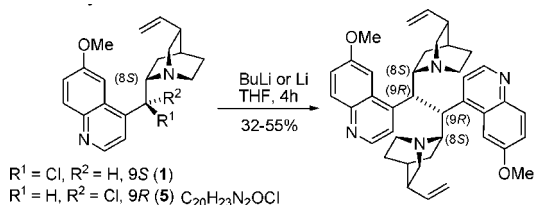
TABLE 1. Synthesis of Dimer 4



R^1 = Cl, R^2 = H, 9*S* (**1**)
R^1 = H, R^2 = Cl, 9*R* (**5**) $C_{20}H_{23}N_2OCl$
R^1 = Br, R^2 = H, 9*S* (**6**) $C_{20}H_{23}N_2OBr$
$C_{40}H_{46}N_4O_2$, $[M+H]^+$ 615.36, (**4**)

entry	reagents and conditions[a]	yield (%)
1	**1**, 1.4 equiv PhLi, 0 → 66 °C	~11[b]
2	**1**, 1.6 equiv PhMgBr, 66 °C	~4[b]
3	**1**, 1.3 equiv BuLi, −55 °C	44
4	**6**, 1.3 equiv BuLi, −55 °C	33
5	**1**, 1.3 equiv BuLi, −40 °C	32
6	**1**, 1.3 equiv BuLi, −90 °C	36
7	**1**, 1.3 equiv *t*-BuLi, −55 °C	34
8	**1**, 1.3 equiv BuLi, $CuCl_2$, −55 °C	41
9	**1**, 1.2 equiv Li, ultrasonic bath, 25 °C	36
10	**1**, 2.2 equiv BuLi, −55 °C	0
11	**1**, 1.3 equiv BuLi, −55 °C[c]	15
12	**5**, 1.3 equiv BuLi, −55 °C	55

[a] All reactions were carried out in dry THF for 4 h, organometallic reagent was added to the solution of quinine derivative, and the yields given refer to the isolated product. [b] Yield from the integration of NMR spectrum. [c] Reversed order of addition.

dimer in the reaction of **1** with phenylmagnesium bromide in boiling THF.

When a solution of (9*S*)-chloro- or (9*S*)-bromoquinine was treated with butyllithium at −55 °C, the same compound **4** was isolated by chromatography as the only dimeric product. The use of *t*-BuLi, BuLi/$CuCl_2$, or metallic lithium resulted in no apparent change in the reaction outcome (Table 1).

On the other hand, we noted that the yield of **4** depended on the rate of addition of butyllithium. When it was added within 3 min, the yield decreased to 18% compared to 44% for slow (90 min) addition. The use of 2-fold excess of butyllithium resulted in a complex mixture, from which the product could not be isolated. When the order of addition was reversed and **1** was slowly injected to the solution of butyllithium, the yield decreased substantially. In that case the major product was 9-deoxyquinine (up to 35%), apparently as result of quenching of a 9-lithiated intermediate. Under the favorable conditions for the synthesis of **4** (Table 1, entry 3) the lithiated product was formed in small amount or was immediately consumed. Moreover, when butyllithium was either added fast or in 2-fold excess or the addition order was reversed, the products of 2′-butylation of the quinoline ring[7,10] were observed.

As previously mentioned, the ESI-MS ($[M + H]^+$ 615.3) identified **4** as the dimer of 9-deoxyquinine. However, the NMR spectra of the same sample of **4** revealed the presence of two isomers (**4a**:**4b** ratio ca. 1:0.45). The NMR spectral pattern of the major one (**4a**) suggested that this dimer had an internal symmetry. Although chromatography failed to separate the mixture, treatment with diethyl ether resulted in the crystallization of **4a** as a highly pure material. Finally, a single crystal X-ray study proved its structure (Figure 1).

The configuration found at both C-9 stereogenic centers was *R* and the molecule in the crystal lattice had a distorted C_2 symmetry. The conformations of *Cinchona* alkaloids have been

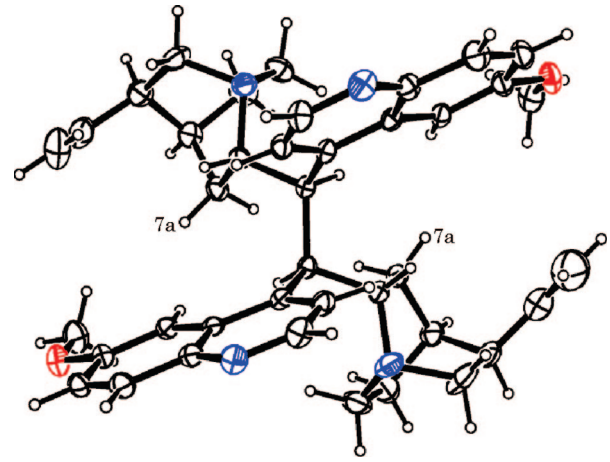


FIGURE 1. X-ray structure of **4a**.

studied in detail,[11] and the one we observed here for each quinine unit is referred to as *closed-2* (i.e., quinuclidine nitrogen points toward the quinoline ring and the C-3′ atom is *anti* vs H-9).[11] It should be noted that in the crystal of **4a** H-3′ atom of the quinoline of one unit is located directly above the quinoline ring of the second alkaloid unit. The ^{1}H NMR spectrum of the dissolved crystal of **4a** disclosed similar orientation,[12] and the signal of H-3′ was observed at an unusually high field (δ 5.5 and 5.8 ppm in $CDCl_3$ and C_6D_6, respectively). The NOESY experiment (correlations of H-5 with both H-7a and H-8 as well as the OCH_3 group with H-10) showed interactions between the alkaloid units. In the crystal structure the corresponding interatomic distances are between 2.21−3.21 Å.

It was found that a pure sample of **4a** dissolved in $CDCl_3$ underwent equilibration to a **4a**−**4b** mixture, reaching ca. 1:0.45 ratio within 1 day at room temperature.[13] On the other hand, after crystallization of **4a**, the mother liquor was enriched in **4b** up to 52% (1:1.01 **4a**:**4b** ratio). When this solution was stored at 25 °C for 2 days, it reached the same equilibrium ratio of 1:0.45 **4a**:**4b**. These experiments suggest that the observed reversible isomerization of **4a** to **4b** can be considered as a conformational change rather than a rearrangement involving the breakage of chemical bonds.

Although we failed to isolate pure **4b**, we deduced from its NMR spectral pattern that this isomer lacks C_2 symmetry. An inspection of a molecular model suggests that a hindered rotation along the C9−C4′ bond could be a cause for the observed atropisomerism of **4**. We believe that the transformation of **4a** to **4b** involves a flip of one of the quinoline rings. Thus the conformation we postulate for one quinine unit of **4b** (A) is that called *closed-1* (i.e., quinuclidine nitrogen points toward the quinoline ring and the C-3′ atom is *syn* vs H-9). The second quinine unit (B) still remains (as in **4a**) in the conformation *closed*-2[11] (Figure 2).

The NMR signals corresponding to **4b** are in good match with the presented structure. The signals of H-3′^{B} (δ 5.5 ppm) and H-5′^{A} (5.39 ppm) atoms and the $OCH_3{}^A$ group (2.66 ppm)

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(12) A similarity of the dominating conformation in a solution and that in the solid state was concluded: Carroll, F. I.; Abraham, P.; Gaetano, K.; Mascarella, S. W.; Wohl, R. A.; Lind, J.; Petzoldt, K *J. Chem. Soc., Perkin Trans. 1* **1991**, 3017.

(13) The rate constants for **4a** → **4b** at 25 °C correspond to $\Delta G^{\ddagger} = 98$ kJ/mol ($CDCl_3$) and 100 kJ/mol (DMSO-d_6); see Supporting Information.

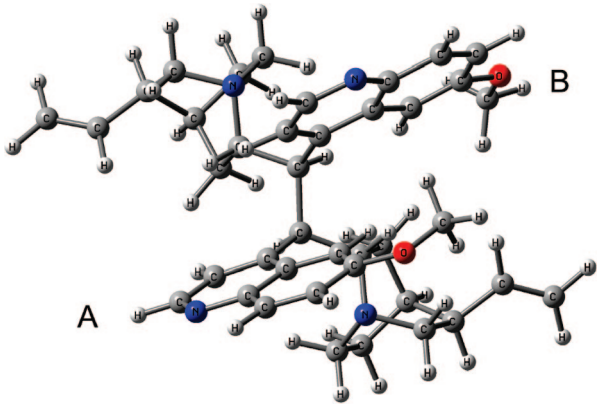


FIGURE 2. Molecular model of probable structure of **4b** (DFT-B3LYP/CC-pVDZ; for the details, see Supporting Information).

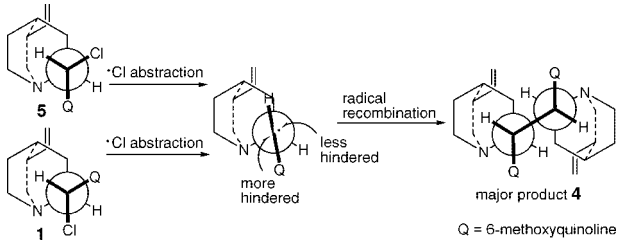


FIGURE 3. A radical mechanism: common flat or configurationally labile intermediate.

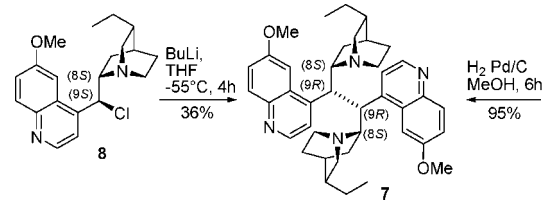
are located in the field of quinoline ring and thus are unusually shielded. In the NOESY spectrum only weak correlations were observed between the H-8 and H-9 atoms within each unit, which confirmed their *closed* conformation. Correlations of H-5′^{A} with H-8^{A} and H-3′^{A} with H-9^{A} atoms within quinine unit A indicated the changed orientation of the quinoline ring. In the quinine unit B an opposite pattern of correlations was observed: H-5′^{B} with H-9^{B} and H-3′^{B} with H-8^{B} indicated an orientation similar to that found in **4a**. Additionally, NOESY experiment revealed several interactions between the hydrogen atoms of the opposite units e.g. H-3′^{A} with H-8^{B}, H-8^{A} with both H5′^{B} and H-9^{B}, H-9^{A} with both H-9^{B} and H-8^{B} and weak but still notable of H-5′^{A} with H-2′^{B}, and OCH3^{A} with H-8′^{B}. These correlations are in agreement with the calculated geometry, where the distances between the mentioned nuclei are within 1.93−2.80 Å (strong correlations) and 3.02−4.3 Å (weak correlations).

We found that the use of either (9*S*)-chloroquinie (**1**), (9*S*)-bromoquinine (**6**), or (9*R*)-chloroquinine (**5**) resulted in the same product (9*R*)-**4**. Thus, **1** and **6** reacted with the inversion of configuration, whereas **5** gave retention of configuration at both C-9 centers. Previous studies on the nucleophilic substitution of 9-halides and mesylates of both (9*S*)- and (9*R*)-quinine demonstrated, unlike here, the formation of products having only a 9*S* configuration.[8,14] Involvement of quinuclidine's nitrogen and distinct reaction pathways for 9*S* and 9*R* substrates were postulated in those studies.[8]

Here, it seems that a common intermediate is formed from either **1**, **5**, or **6**. It is possible that in the first step a nearly flat 9-radical is generated. Two radicals can then recombine approaching each other from the less hindered face (Figure 3). The calculated molecular model (DFT-B3LYP/CC-pVDZ) for

(14) Braje, W. M.; Holzgrefe, J.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2085.

SCHEME 2. Synthesis of Dihydroquinine Dimer 7



the intermediate radical shows that its lowest energy conformer is more susceptible to the recombination from the *re* face (see Supporting Information). This result supports our hypothesis concerning diastereoselectivity of the coupling.

Essentially, the ionic mechanism could also be possible. Although the epimerization of benzyllithium species is known,[15] it does not explain why the following nucleophilic substitution of halide components **1** and **6** would occur with opposite stereoselectivities. Epimerization of 9-chloro alkaloids could not be excluded under the reaction conditions, but it seems very unlikely that such complex mechanism would provide the observed high diastereoselectivity.

Also the dihydroquinine dimer **7** was prepared by the analogous reaction of (9*S*)-chlorodihydroquinine (**8**) with butyllithium. Moreover, identical product **7** was obtained by the catalytic hydrogenation of pure **4a** using palladium catalyst. (Scheme 2). The ^{1}H NMR spectra showed that **7** also exhibits atropisomerism. At equilibrium in the chloroform solution C_2- (**7a**) and C_1-symmetric (**7b**) atropisomers were in 1:0.4 ratio.

In conclusion, we presented new diastereoselective C-9 carbon−carbon couplings of quinine derivatives to the respective C_2-symmetric dimers, prospective chiral ligands. Dimer **4** is perhaps the smallest possible and the most crowded dimeric derivative of *Cinchona* alkaloids and exhibits interesting conformational properties.

Experimental Section

4,4′-Bis((8*S*,9*S*)-6′-methoxycinchonan-9-yl)biphenyl (2). To a solution of Grignard reagent obtained from active magnesium (3.5 mmol) and 4,4′-dibromobiphenyl (0.32 g, 1.04 mmol) in THF (14 mL) was added a solution of (9*S*)-chloroquinine (**1**, 0.73 g, 2.1 mmol) in toluene (8 mL). The mixture was heated under reflux for 13 h, allowed to reach room temperature, and quenched with MeOH (1 mL) and after 0.5 h with saturated aqueous solution of NH_4Cl. The product was extracted with $CHCl_3$. The extracts were dried over Na_2SO_4 and evaporated. Purification on a silicagel column ($CHCl_3$/MeOH, 10:1) afforded 0.24 g of **2** (30%). ^{1}H NMR (300 MHz, $CDCl_3$, 318 K, ppm) 8.65 (d, J = 4.7 Hz, 2H), 7.93 (d, J = 9.2 Hz, 2H), 7.45 (br. s, 2H), 7.24−7.35 (m, 12H), 5.84 (ddd, J = 17.3, 10.1, 7.0 Hz, 2H), 4.98−5.05 (m, 4H), 4.81 (m, J = 10.0 Hz; 2H), 3.87 (s, 6H), 3.81 (m, 2H), 3.21−3.33 (m, 4H), 2.72−2.89 (m, 4H), 2.29 (m, 2H), 1.85 (m, 2H), 1.69 (m, 2H), 1.50−1.63 (m, 4H), 0.93 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 157.7, 147.6, 145.8, 144.7, 142.0, 141.0, 139.0, 131.9, 128.7, 128.1, 127.2, 120.9, 119.8, 114.3, 102.0, 59.5, 56.5, 55.5, 48.8, 40.9, 39.5, 28.7, 28.05, 28.00.

Bis((8*S*,9*R*)-6′-methoxycinchonan-9-yl) (4). (9*S*)-Chloroquinine (**1**, 1.03 g, 3 mmol) was dissolved in dry THF (12.5 mL) and cooled to −55 °C. A solution of BuLi (1.6 mL 2.5 M soln in hexane, 1.3 equiv) was added within 1.5 h. The mixture was stirred at −55 °C for additional 2.5 h and allowed to attain room temperature. Saturated aqueous NH_4Cl was added, and the

(15) Azzena, U.; Pilo, L.; Piras, E. *Tetrahedron Lett.* **2001**, *42*, 129.

mixture was extracted with $CHCl_3$. The extracts were dried over Na_2SO_4 and evaporated in vacuo. Purification on a silicagel column ($CHCl_3$/MeOH, 20:1) afforded 0.40 g of **4** (44%). This product was dissolved in Et_2O (5 mL) and within 5 min **4a** separated as colorless crystals. Mp 233.5−235.5 °C (dec). ^{1}H NMR (600 MHz, $CDCl_3$, ppm) 8.17 (d, J = 4.5 Hz, 2H), 8.01 (d, J = 9.1 Hz, 2H), 7.40 (d, J = 2.6 Hz, 2H), 7.35 (dd, J = 9.2, 2.6 Hz, 2H), 5.75 (ddd, J = 17.3, 10.5, 7.2 Hz, 2H), 5.51 (d, J = 4.5 Hz, 2H), 5.00 (d, J = 10.5 Hz, 2H), 4.92 (d, J = 17.2 Hz, 2H), 4.05 (d, J = 10.9 Hz, 2H), 3.96 (s, 6H), 2.89 (m, 2H), 2.77 (dd, J = 13.8, 9.9 Hz, 2H), 2.64 (m, 2H), 2.49 (m, 2H), 2.21 (m, 2H), 2.09−2.16 (m, 4H), 1.93 (m, 2H), 1.78 (m, 2H), 1.61 (m, 2H), 1.44 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) 157.8, 146.0, 144.6, 143.4, 141.7, 132.6, 129.7, 125.4, 120.2, 114.6, 100.9, 56.7, 55.6, 55.2, 45.7, 40.7, 39.2, 30.1, 28.9, 27.8.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds, a CIF file for **4a**, discussion of atropisomer structure, and DFT calculation results. This material is available free of charge via the Internet at http://pubs.acs.org.

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