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THE LIBRARY OF CINCHONA ALKALOIDS-1,2,3-TRIAZOLE DERIVATIVES: STRUCTURE AND FACILE ACCESS BY "CLICK CHEMISTRY"

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Abstract – New Cinchona alkaloids-1,2,3-triazole derivatives library was prepared readily and efficiently using Huisgen 1,3-dipolar cycloaddition of 9-azido substituted Cinchona alkaloids and various terminal and disubstituted alkynes (click chemistry). Spectroscopic, X-Ray, and molecular modelling data show that these derivatives maintain the conformation of the parent alkaloids.

INTRODUCTION

1,3-Dipolar cycloaddition of azides and alkynes (Huisgen cycloaddition) which leads to 1,2,3-triazoles is a long known reaction[1] which has been recently rediscovered by Sharpless[2,4-7] as a powerful tool for modification (derivatives synthesis) or linking various molecules. This reaction is modular and of wide scope, it shows also perfect atom economy and provides products with high yield after usually simple workup. Moreover, due to the stability of organic azides toward many organic reactions conditions, including oxygen and water, this cycloaddition can be carried out in water[2,3] or even in biological fluids.[4] It thus meets all of the criteria for "click chemistry"[2] and is ideally suited for combinatorial synthesis.

The utility of this cycloaddition has been recently demonstrated in the field of medicinal chemistry in finding enzyme inhibitors for acetylcholinesterase,[5] 1,3-fucosyl transferase VI[6] and HIV protease[7] and in biochemistry and molecular biology for bioconjugation and labeling.[8] Surprisingly, until now relatively few reports appeared on the synthesis 1,2,3-triazole derivatives of more complex, chiral organic compounds and low weight natural products and these are largely restricted to the sugars and their derivatives,[9] proteins[10] and vitamin D analogues.[11]

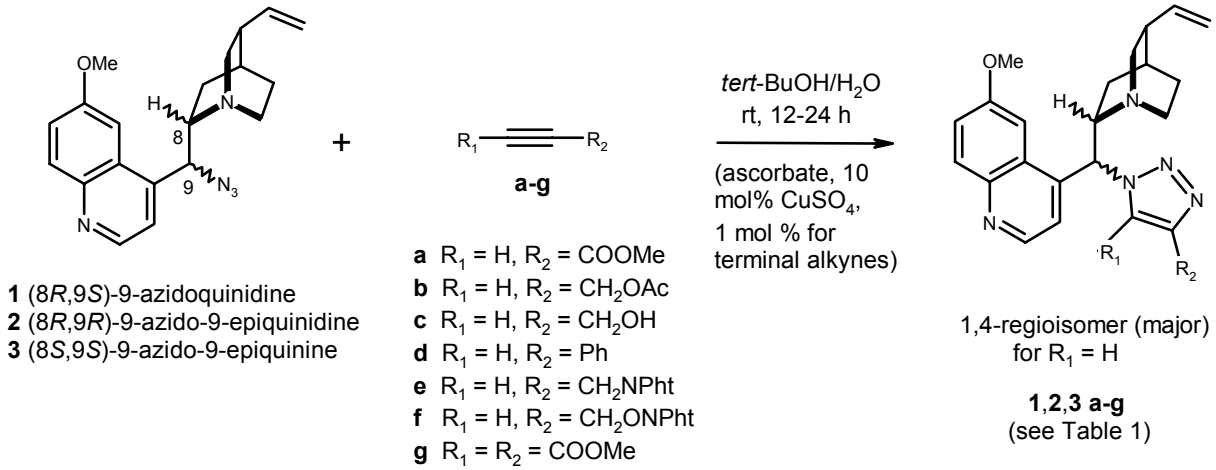
Although Cinchona alkaloids and their derivatives attracted much attention as chiral organocatalysts, selectors, resolving agents and pharmaceuticals,[12] their reactivity toward formation of 1,2,3-triazole

derivatives is unknown. Only recently Hoffmann demonstrated intramolecular 1,3-dipolar cycloadditon of *in situ* prepared 9-azido-10,11-didehydro Cinchona alkaloids, the direction of which depends on the configuration at C9 and polarity of solvents and leads to the mixtures of fused 1,2,3-triazoles.[13]

In the course of our studies on Cinchona alkaloid receptors and selectors we were interested in finding a robust and general method for easy synthesis of diverse Cinchona alkaloids derivatives as well as anchoring the alkaloids to the solid support. 1,3-Dipolar cycloaddition of 9-azido alkaloids was selected as a promising method and the goal of this work was to check the utility and scope of this reaction and to determine the structure and conformation of 1,2,3-triazole-Cinchona alkaloid derivatives.

RESULTS AND DISCUSSION

The reactions of 9-azido Cinchona alkaloids (**1-3**)[14] with various terminal and disubstituted alkynes (**a-g**) in *tert*-butanol/water mixtures were carried out at room temperature within 12-24 h (Scheme 1, Table 1).



Scheme 1. Synthesis of 1,2,3-Triazole-Cinchona Alkaloids Library

Table 1. 1,2,3-triazole synthesis by 1,3-dipolar cycloaddition (Scheme 1).

Product	1				2					3						
	a	**b**	**d**	**e**	**a**	**b**	**d**	**e**	**g**	**a**	**b**	**c**	**d**	**e**	**f**	**g**
Isolated yield (%)	20	40	86	49	96	82	67	52	62	92	76	63	65	70	57	60
Workup[a]	A	B	A	A+B	A	B	A	A	B	A	B	A	A	A+B	A	B

[a]A – product precipitation by dilution with water and filtration; B – product extracted with dichloromethane and purified by flash chromatography on silica gel (eluent 5% MeOH in dichloromethane)

The terminal alkynes (**a-f**) and highly activated dimethyl acetylenedicarboxylate (**g**) reacted cleanly and TLC analysis usually showed one main spot of product after the reaction was complete. On the other hand, the reaction with diphenylacetylene at room temperature gave only trace amount of the corresponding

triazole (~1%), probably due to steric hindrance of the alkyne, and the use of microwave radiation resulted in only small increase of the yield (to 10%). For terminal alkynes 1,4-regioselectivity was succesfully controlled by the catalysis with *in situ* generated Cu(I) salts (Sharpless protocol).[15] Thus, 1,4-regioisomers were the main products and 1,5-regioisomers were only detected by ^{1}H NMR spectroscopy for **2a** and **2b** in quantities below ~5%. Protons of triazole of 1,4- and 1,5-regioisomers (**2a**) appeared as singlets at 8.10 and 7.86 ppm, respectively. The products were isolated either by simple filtration (if precipitated from the reaction mixture, method A) or by extraction with dichloromethane followed by flash chromatography purification (method B), with yields 20-96% (Table 1). In a few cases precipitation and extractive workup of a filtrate (A+B) increased the total yield of the products.

STRUCTURE AND CONFORMATION

Conformational behaviour of parent Cinchona alkaloids is well recognized[16] and it was found that the alkaloids with natural configuration at C9 prefer compact, *closed* conformation where the lone electron pair of the quinuclidine nitrogen points over the quinoline ring, whereas the 9-epimers prefer *open* structure with quinuclidine nitrogen oriented away from the quinoline ring (see structure of **3a** in Figure 1).[17] As these preferences are responsible for the pharmacological and catalytic behaviour of Cinchona alkaloids and their derivatives (9-epi-derivatives usually are less active than these of natural configuration)[12] it was of interest to investigate the conformation and the structure of newly synthetized Cinchona-alkaloid 1,2,3-triazoles. For these studies ^{1}H NMR spectroscopy, X-Ray diffraction and molecular modelling were selected. The coupling constant of the ^{1}H NMR doublet of H9 is a sensitive measure of the conformation of Cinchona alkaloids. Independently of the configuration at C9, large $J_{H9\text{-}H8}$ values indicate *anti* arrangement of these protons and in consequence *closed* conformation for naturally configured and *open* for *epi*-configured alkaloids and their derivatives. In all of our derivatives the doublet of H9 is located in the 6.42 - 7.06 ppm range, with the coupling constant 10.5 to 11.5 Hz ($CDCl_3$). These large values confirm the *anti* orientation between H9 and H8 protons.

Crystal structure of **3a**[18] (Figure 1a) shows the *syn, open* conformation of 9-epi-quinine fragment, and *synperiplanar* orientation of N-N(triazole) and C9-H9 bonds. Selected torsion angles determining the conformation are as follows: H8-C8-C9-H9 (T1) = 175°, C3'-C4'-C9-H9 (T2) = –133° and C10'C4'C9N2 (T3) = –71°. Molecular modelling studies were carried out for a molecule (**3a**) (8*S*,9*S*-*epi* configuration) and its analog (**4a**) of natural 8*S*,9*R* configuration. Generation of conformers was performed by rotating all the torsion angles which contribute to the conformation, using molecular mechanics method (MM+), whereas semiempirical AM1 hamiltonian was used for final geometry optimisation.[19] Figure 1b presents the lowest energy conformer of **4a** together with description of the three torsions (T1-T3) of primary importance for the conformation of these compounds. Preferred conformation for **4a** is *anti*, *closed*, where

the protons of torsion angle T1 are nearly antiperiplanar (170.2°) and 1,2,3-triazole ring is almost coplanar with H9-C9 bond (Figure 1b). *Syn*, *closed* conformer which differs from the *anti*,*closed* one by the orientation of the quinoline ring (T2) is of 1.8 kcal/mol higher energy.

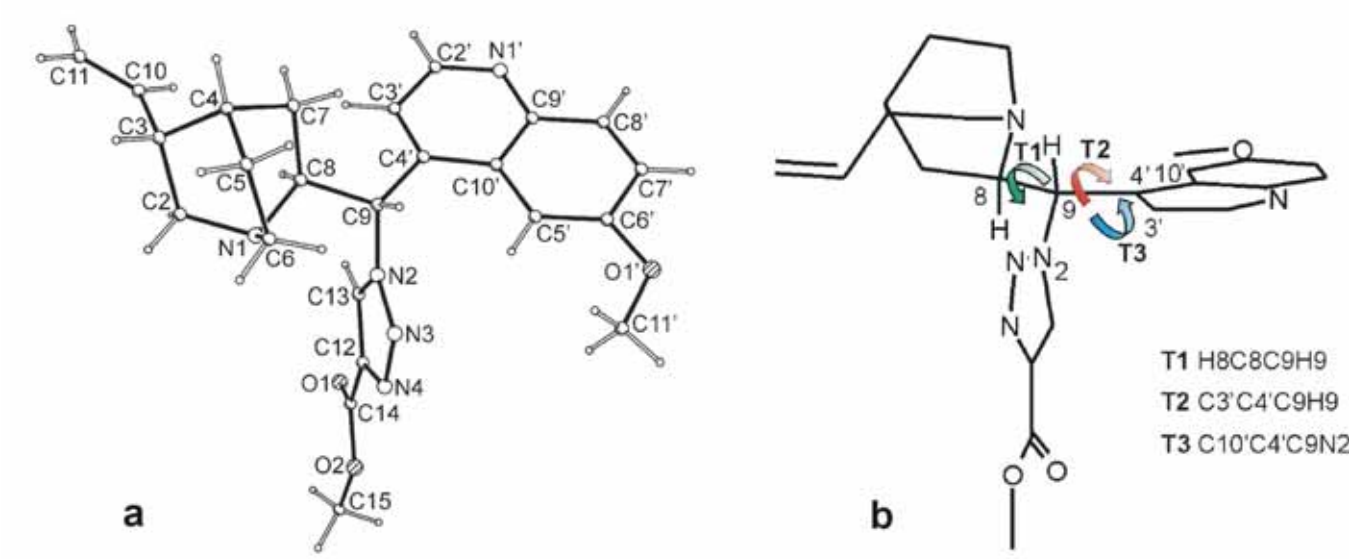


Figure 1. X-Ray crystal structure of **3a** (a), a*nti*, *closed* lowest energy conformer of **4a** and labeling of torsion angles (see text for details, b).

The energy of the less favored *anti*, *open* conformer with a *gauche* arrangement of H8, H9 protons is 2.6 kcal/mol higher. For the *epi*-configured compound (**3a**), *anti*, *open* conformer was found to be of the lowest energy and again the H8, H9 protons were found antiperiplanar (T1 = 176°) whereas 1,2,3-triazole ring was found nearly coplanar with H9-C9 bond. *Syn*, *open* conformer of **3a**, similar to that found in the crystal of **3a** (Figure 1), is of about 0.5 kcal/mol higher energy. Again the change of the conformation towards *anti, closed* (disfavoured in this configuration series) results in a significant increase of steric energy by about 4.9 kcal/mol. Selected data characterizing the conformers are summarised in Table 2.

Table 2. Selected data for conformers of **3a** and **4a** (AM1).

Conformation of alkaloid moiety	Heat of formation kcal/mol	T1	T2	T3
		degree		
3a				
anti, *open*	56.05	175.9	175.8	-123.6
syn, *open*	56.40	-178.8	-152.9	-89.0
anti, *closed*	60.95	81.9	-173.9	-110.3
4a				
anti, *closed*	57.13	170.2	149.2	87.0
syn, *closed*	58.91	172.1	4.0	-62.9
anti, *open*	59.70	-78.1	-179.7	115.4

These studies indicate that the conformational preferences of Cinchona alkaloid moiety in the newly prepared 1,2,3-triazole derivatives are convergent with the conformational behaviour of the parent Cinchona bases of the same configuration. Thus it can be expected that naturally configured Cinchona-1,2,3-triazole derivatives with similar conformation of alkaloidal moiety are likely to maintain some activity (eg. biological) of parent alkaloids. We believe that the combination of Cinchona alkaloids with 1,2,3-triazoles which exihibit wide array of activities[20] will result in an interesting class of bioactive compounds for further screening. We have demonstrated that such derivatives are readily available by the protocol reported in communication. Screeninig of new catalytic and recognition properties of these and similar derivatives is currently in progress in our laboratory.

EXPERIMENTAL

General: All reagents including alkyenes were purchased from Aldrich and Fluka and used as received. *N*-propargylphthalimid was obtained by the reaction of phthalimide-DBU salt with propargyl bromide (71%).

^{1}H NMR spectra were recorded on a Varian EM-360 or AC-200 spectrometers (300 MHz) in $CDCl_3$, with TMS as an internal standard. Mass spectra were recored on a AMD 604/402, IR spectra (KBr pellets) were recorded on a Brucker ITS 113v spectrometer and elemental analysis on Vario ELIII Elementar CHN analyser. Melting points were determined by using Boetius instrument and are not corrected.

The structure of all newly synthetised compounds was confirmed by ^{1}H NMR and MS spectra.

Representative Procedure: To a vigorously stirred solution of 140 mg of 9-azido-9-epi-quinine (0.4 mmol) in 1-2 mL of *tert*-BuOH/H_2O (1:2 or 1:1 for more nonpolar alkynes eg. phenylacetylene), 36 μL of methyl propiolate (0.4 mmol) was added followed by 8 mg of sodium ascorbate and 5 μL of 1M $CuSO_4$ The flask was capped and stirred until the reaction was complete (TLC monitoring), usually within 12-24 h. To the solution cold water was slowly added and the white solid was collected by filtration and dried in air. Yield 160 mg, 92 %. Note: if precipitation is too oily for the filtration, agitation with water (or very small amount of methanol) was continued for several hours. Such a precipitated products are of high purity and there is no need for further purification. For the products which do not precipitate extractive workup was employed followed by column chromatography purification (see Table 1).

Product (**3a**): white powder, mp. 239-241 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, J = 4.6 Hz, 1H), 8.06 (s, 1H), 8.03 (d, J = 4.6 Hz, 1H), 7.49 (d, J = 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.41 (dd, J = 2.7, 9,2 Hz, 1H), 6.49 (d, J = 11.5 Hz, 1H), 5.99 (m, 1H), 5.14 (dt, J = 18.0, 1.1 Hz, 1H), 5,11 (dt, J = 10.3, 1.3 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.44 (m, 1H), 3.22 (dd, J = 10.1, 3.8 Hz, 1H), 2.77 (m, 2H), 2.35 (m, 1H), 2.00 (t, J = 11.1 Hz, 1H), 1.82 (m, 1H), 1.65 (m, 3H), 0.98 (m, 1H); HRMS (EI) calcd for $C_{24}H_{27}N_5O_3$ 433.2114, found 433.2110, IR (KBr) ν (cm^{-1}) 3104, 3070, 2937, 2862, 2099, 1712, 1620,

1592, 1547, 1506, 1475, 1435, 1359, 1323, 1307, 1245, 1156, 1085, 1045. Anal. Calcd for $C_{24}H_{27}N_5O_3$: C, 66.54; H, 6.23; N, 16.16, found: C, 66.26; H, 6.53; N, 15.91.

(**1d**) white powder, yield 90 mg (86%), mp. 192-195 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 9.1, 1H), 7.73 (m, 2H), 7.50 (s, 1H), 7.42-7.23 (m, 6H), 6.47 (d, J = 11.0 Hz, 1H), 6.11 (m, 1H), 5.17 (m, 2H), 3.93 (s, 3H), 3.15 (m, 1H), 2.94 (m, 2H), 2.77 (dd, J = 5.8, 7.7 Hz, 1H), 2.36 (q, J = 6.9, 8.5 Hz, 1 H), 1.84-1.66 (m, 6H), $C_{28}H_{29}N_5O$ 451.2372, found 451.2356, IR (KBr) ν (cm^{-1}) 2936, 2870, 1621, 1544, 1509, 1473, 1433, 1361, 1230, 1028, 913, 836. Anal. Calcd for $C_{28}H_{29}N_5O$: C, 74.46; H, 6.43; N, 15.51, found: C, 74.32; H, 6.70; N, 15.30.

(**2a**) white powder, yield 180 mg (97%), mp. 143-147 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, J = 4.7 Hz, 1H), 8.10 (s, 1H), 8.07 (m, 1H), 7.51 (d, J = 4.7 Hz, 1H), 7.46 (dd, J = 2.5, 9.7 Hz, 1H), 7.40 (m, 1H), 6.52 (d, J = 11.0 Hz, 1H), 5.14 (m, 1H), 5.17 (m, 2H), 3.97 (s, 3H), 3.87 (s, 3H), 3.11-2.85 (m, 3H), 2.44 (m, 1H), 1.87-1.51 (m, 5H), 1.49 (m, 1H), 1.28 (m, 1H); HRMS (EI) calcd for $C_{24}H_{27}N_5O_3$ 433.2114, found 433.2118, IR (KBr) ν (cm^{-1}) 3103, 3070, 2934, 2877, 2100, 1711, 1621, 1544, 1507, 1474, 1435, 1360, 1233, 1043. Anal. Calcd for $C_{24}H_{27}N_5O_3$: C, 66.54; H, 6.23; N, 16.16, found: C, 66.27 ; H, 6.26; N, 15.22.

(**2d**) white powder, yield 130 mg (67%), mp. 224-226 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, J = 4.7 Hz, 1H), 8.06 (d, J = 9.4 Hz, 1H), 7.77 (m, 2H), 7.70 (s, 1H), 7.60 (d, J = 4.7 Hz, 1H), 7.53 (d, J = 2.7 Hz, 1H), 7.42-7.27 (m, 4H), 6.50 (d, J = 11.1 Hz, 1H), 5.94 (m, 1H), 5.18 (m, 2H), 3.98 (s, 3H), 3.16-2.87 (m, 4H), 2.36 (q, J = 8.12, 7.7 Hz, 1H), 1.79-1.30 (m, 6H), HRMS (EI) calcd for $C_{28}H_{29}N_5O$ 451.2372, found 451.2364, IR (KBr) ν (cm^{-1}) 3141, 3074, 2947, 2873, 2833, 1620, 1592, 1502, 1474, 1432, 1356, 1256, 1227, 1169, 1132, 1081, 1033, 974, 913, 765. Anal. Calcd for $C_{28}H_{29}N_5O$: C, 74.46; H, 6.43; N, 15.51, found: C, 74.18 ; H, 6.58; N, 15.13.

(**3c**) white powder, yield 80 mg (63%), mp. 229-232 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, J = 4.7 Hz, 1H), 8.04 (d, J = 9.1 Hz, 1H), 7.53 (d, J = 2.5 Hz, 1H), 7.48 (s, 1H), 7.46 (d, J = 3.3 Hz, 1H), 7.40 (dd, J = 2.7, 9.3 Hz, 1H), 6.44 (d, J = 11.0 Hz, 1H), 5.98 (m, 1H), 5.13 (m, 2H), 4.67 (s, 2H), 3.96 (s, 3H), 3.48 (m, 1H), 3.23 (dd, J = 10.2, 3.8 Hz, 1H), 2.76 (m, 2H), 2.34 (m, 2H), 1.96 (t, J = 11.0 Hz, 1H), 1.79 (d, J = 2.5 Hz, 1H), 1.64 (t, J = 6.7 Hz, 2H), 0.94 (dd, J = 6.7, 6.2 Hz, 1H); HRMS (EI) calcd for $C_{23}H_{27}N_5O_2$ 405.2164, found 405.2137, IR (KBr) ν (cm^{-1}) 3125, 2917, 2856, 1621, 1590, 1511, 1476, 1444, 1362, 1319, 1250, 1230, 1141, 1093, 1042, 1023, 930. Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.11; H, 6.66; N, 17.27, found: C, 67.85 ; H, 6.82; N, 16.92.

(**3d**) white powder, yield 100 mg (65%), mp. 115-120 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (d, J = 4.4 Hz, 1H), 8.05 (d, J = 9.1 Hz, 1H), 7.75 (m, 2H), 7.63 (s, 1H), 7.58 (d, J = 2.7 Hz, 1H), 7.54 (d, J = 4.4 Hz, 1H), 7.40-7.22 (m, 4H), 6.48 (d, J = 11.5 Hz, 1H), 6.00 (m, 1H), 5.14 (m, 2H), 3.97 (s, 3H), 3.54 (m, 1H), 3.26 (dd, J = 10.2, 3.8 Hz, 1H), 2.79 (m, 2H), 2.36 (s, 1H), 2.01 (t, J = 9.9 Hz, 1H), 1.82-1.64 (m, 4H),

1.07 (m, 1H); HRMS (EI) calcd for $C_{28}H_{29}N_5O$ 451.2372, found 451.2340, IR (KBr) ν (cm^{-1}) 3125, 3079, 2934, 2862, 1621, 1592, 1510, 1476, 1457, 1434, 1358, 1322, 1266, 1231, 1080, 1046, 1028, 918, 833, 764. Anal. Calcd for $C_{28}H_{29}N_5O$: C, 74.46; H, 6.43; N, 15.51, found: C, 74.25; H, 6.84; N, 15.29.
All other compounds showed good ^1H NMR, MS and IR spectra.

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17. Due to the limited space, conformations of Cinchona alkaloids are not presented here, see ref. 16. *Open/closed* is widley accepted nomenclature of this class of compounds. *Syn/anti* specify the orientation of the methoxy grup and the substituent at C9 (the same side = *syn*, opposite side = *anti*).
18. X-Ray crystal structure data for **3a** (crystallization from MeOH): 295K; λ=1.54178Å. Crystal system: monoclinic. Space group: $P2_1$. Unit cell dimensions: a=10.550(2); b=8.053(2); c=13.709(3)Å; β=104.32(3)°; V=1128.5(4) $Å^3$; Z=2; density (calcd) 1.276 Mg/m^3; F(000): 460. Crystal size: 0.60 x 0.20 x 0.08mm^3. Final R indices [$I>2sigma(I)$]: R_1=0.0573, wR_2=0.1091 (for 1411 refl.); R indices (all data 2137 refl.): R_1=0.1035, wR_2=0.1335. Largest diff. peak and hole: 0.270 and –0.331e$Å^{-3}$. The absolute structure of the crystal was assumed from the known absolute configuration (8*S*,9*S*) of the 9-azido-9-epiquinine used as a starting material. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center, CCDC reference number 251443. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033; e-mail deposit@ccdc.cam.ac.uk or Web http://www.ccdc.cam.ac.uk).
19. Cache Worksystem Pro 5 (Fujitsu) was used for the calculations.
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