Synthesis of 10,11-Didehydro *Cinchona* Alkaloids and Key Derivatives

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A series of 10,11-didehydro *Cinchona* alkaloids containing an ethynyl group at C(3) were prepared efficiently in two steps from the naturally occurring *Cinchona* alkaloids (*Scheme 1*). 10,11-Didehydroquinine (**4c**) and 10,11-didehydroquinidine (**4a**) belong to a significantly new class of semi-natural *Cinchona* alkaloids. They are more polar and basic than the natural compounds and serve as versatile building blocks for further functionalization; they were transformed into the corresponding 11-halo and 11-pseudohalo derivatives and (*Z*)-vinyl halides (*Schemes 2* and *3*). The conformation of the alkaloids was elucidated by NOE and X-ray crystal diffraction analysis of **4a** (*Fig.*), and the cytostatic activity of selected didehydroquinidine derivatives was evaluated (*Table 5*).

Introduction. – The *Cinchona* alkaloids are commercially the most important alkaloid family. They are used in various pharmaceuticals and soft drinks and are produced worldwide at an estimated 700 t *per annum*. They are also versatile chiral auxiliaries for the separation of enantiomers *via* formation of diastereoisomeric salts, for asymmetric syntheses, *e.g.* as chiral ligands in the *Sharpless* asymmetric dihydroxylation [1] or as chiral phase-transfer catalysts [2]. *Cinchona* alkaloids have been known and studied for over 350 years, and a great deal of literature in diverse scientific journals and also in numerous patents has appeared. *Christensen* has reported one of the title alkaloids (10,11-didehydroquinine (**4c**)) at the beginning of this century [3], but to our surprise, no further work on this potentially interesting and useful class of compounds has come forward since then. Substituted alkynes can be found in various pharmacologically interesting natural products and lead structures [4]. Enynes [5] (brasilenyne, gephyrotoxin, histrionicotoxin) and enediyne antibiotics [6] (dynemicin A, calicheamicin γ_1) are two prominent classes of natural products containing alkyne units. Moreover, halogenated acetylenes are crucial intermediates for the synthesis of increasingly complex structures, especially in total synthesis, as they can easily be subjected to Pd- and Ni-catalyzed cross-coupling reactions. Cyclic enediyne cores of enediyne antibiotics have been formed *via* intramolecular *Nozaki*-type coupling of an iodoalkyne moiety or directly *via* a terminal alkyne [7]. Iodoalkynes have also been hydrogenated to (*Z*)-vinyl iodides, which have been elaborated further, *e.g.*, to pheromones [8].

In the course of our work on acetylenic *Cinchona* alkaloids, we have now prepared the four alkyne derivatives **4a**–**d** and their 9-*O*-protected analogs **4e**–**g** (*Scheme 1*, *Tables 1* and *2*). Quinidine- and quinine-based alkynes **4a** and **4c** have also been transformed into key derivatives **5a**–**k** ad **6a**–**d** *via* halogenation, *cis*-hydrogenation, propynol formation, cyanation, and isomerization.

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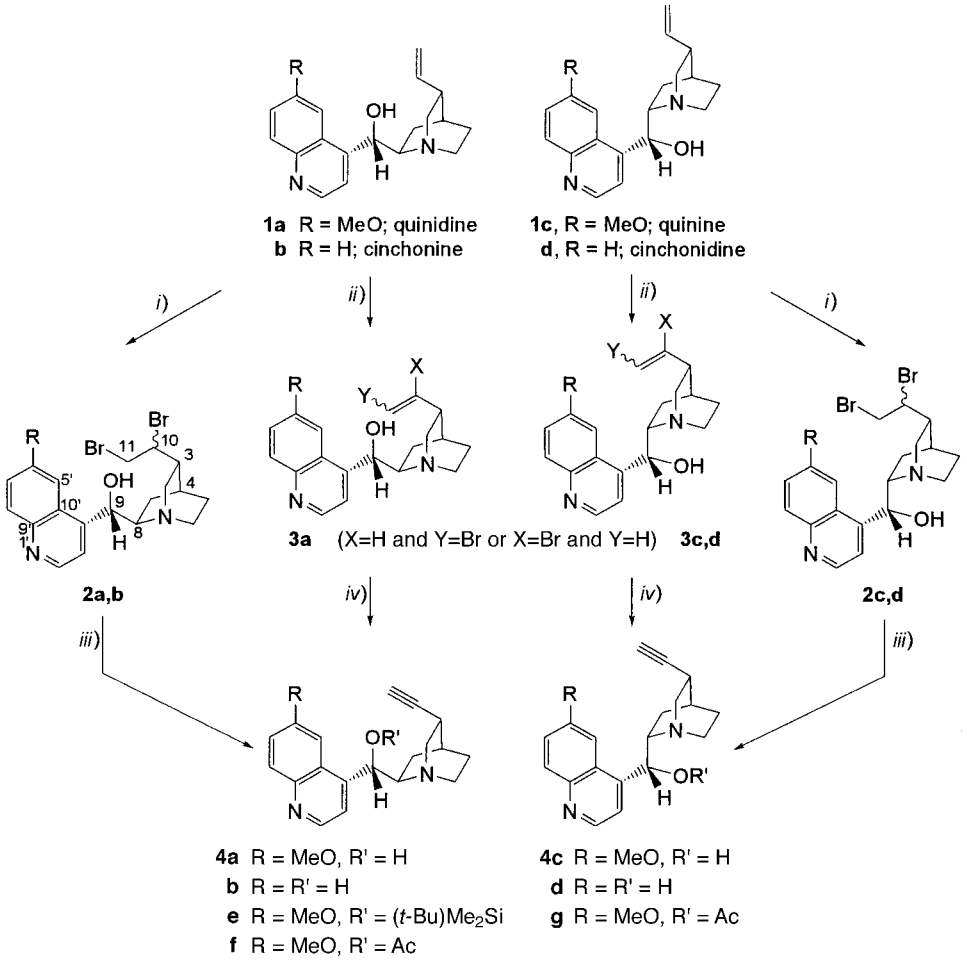
Results and Discussion. – Bromination of the natural products **1a**,**b**,**d** and the 9-*O*-acetyl-protected alkaloid **1f** in the solvent CCl_4 provided the corresponding 10,11-dibromo *Cinchona* alkaloids **2a**–**d**,**f** in quantitative yield as yellowish precipitate, which was filtered off, washed with $CCl_4/CHCl_3$ 5 : 1, and dried. The 10,11-dibromo derivatives were all obtained as a 1 : 1 mixture of diastereoisomers with respect to the configuration at C(10).

Scheme 1



i) Br_2, $CHCl_3$, CCl_4, 0°, 2 h. *ii*) 1. Br_2, $CHCl_3$, 0° → r.t., 4 h; 2. Et_3N, 2 h. *iii*) KOH, 1,2-dimethoxyethane, r.t., 4 h. *iv*) KOH, *Aliquat 336*, THF, r.t., 20 h.

The double dehydrobromination of the dibromides **2a**–**d**,**f** to alkynes **4a**–**d**,**f** was studied under a variety of conditions (*Table 1*) [9], but, ordinarily, the yields did not exceed 50%.

Table 1. *Synthesis of 10,11-Didehydro* Cinchona *Alkaloids: Double Dehydrobromination*

Alkaloid dibromide	Base (equiv.)		Solvent	T [°C]	t[h]	Didehydro alkaloid	Yield [%]
2a	*t*-BuOK	(6.0)	THF	20	14	**4a**	38
2a	KOH	(6.0)	THF	60	14	**4a**	34
2a	KOH	(8.0)	DME	90	3	**4a**	38
2a	KOH	(4.5)	DME	90	16	**4a**	32
2a	KOH	(4.5)	EtOH	80	12	**4a**	29
2a	KOH	(8.0)	DME	20	4	**4a**	45
2a	*t*-BuOK	(4.0)	*t*-BuOH	80	2	**4a**	48
2a	$NaNH_2$	(8.0)	DMSO	95	12	**4a**	40
2b	*t*-BuOK	(4.0)	*t*-BuOH	20	2	**4b**	67
2c	*t*-BuOK	(2.0)	*t*-BuOH	20	2	**4c**	49
2d	*t*-BuOK	(4.0)	*t*-BuOH	80	2.5	**4d**	67
2d	*t*-BuOK	(4.0)	*t*-BuOH	80	4	**4d**	46
2f	$NaNH_2$	(8.0)	DMSO	20	14	**4f**	41

Extended refluxing decreased the yield, due to product decomposition. We, therefore, decided to carry out the dehydrohalogenation in two steps. A change of solvent to $CHCl_3$ allowed the preparation of the intermediate vinyl bromides **3a**,**c**–**e** from **1a**,**c**–**e** in one pot, *i.e.* by subsequent addition of Et_3N, in quantitative yield[2]). It was then possible to dehydrobrominate **3a**,**c**–**e** under milder conditions with a concomitant increase in yield of **4a**,**c**–**e** (see *Table 2*). Initial experiments with *t*-BuOK provided the alkyne derivatives in moderate yields (56–61%, *Entries 1*, *2*, and *7*). The best conditions were room temperature and inexpensive anh. KOH (2 equiv.) in the presence of a catalytic amount of the highly lipophilic methyltrioctylammonium chloride (*Aliquat 336*) [10]. All alkyne derivatives prepared were more polar than the parent natural *Cinchona* alkaloids with the vinyl side chain. Thus, the remote substituent at C(3) has a significant impact on chemical properties [11].

Table 2. *Synthesis of 10,11-Didehydro* Cinchona *Alkaloids: Mono-dehydrobromination*

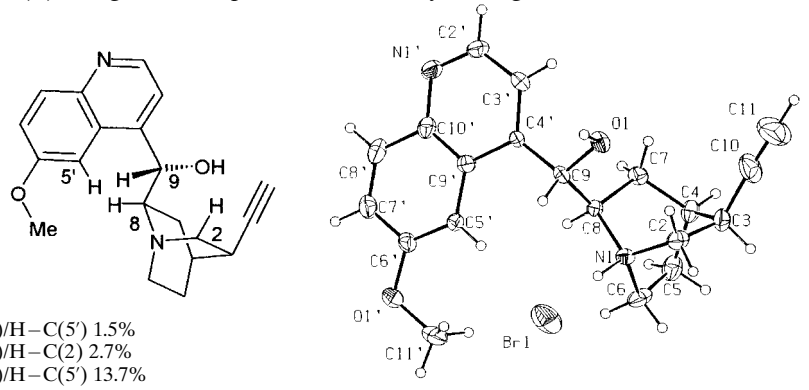
Entry	Alkaloid vinyl bromide	Base (equiv.)	Solvent	T [°]	t [h]	Didehydro alkaloid	Yield [%]
1	**3a**	*t*-BuOK (4.0)	*t*-BuOH	20	2	**4a**	61
2	**3a**	*t*-BuOK (2.0)	*t*-BuOH	20	2	**4a**	56
3	**3a**	KOH (2.0), *Aliquat 336*	THF	20	14	**4a**	79
4	**3a**	KOH (2.0), *Aliquat 336*	THF	20	20	**4a**	84
5	**3c**	KOH (2.0), *Aliquat 336*	THF	20	20	**4c**	81
6	**3d**	KOH (2.5), *Aliquat 336*	THF	20	16	**4d**	72
7	**3e**	*t*-BuOK (4.0)	*t*-BuOH	20	2	**4e**	59

Configuration and conformation of 10,11-didehydro *Cinchona* alkaloids were determined by NOE and ^{1}H-NMR spectroscopy. The $^3J(8,9)$ coupling constant is diagnostic for the 'open-closed' conformation equilibrium in *Cinchona* alkaloids [12]. All four unprotected alkyne derivatives **4a**–**d** feature small coupling constants $^3J(8,9)$ (3–4 Hz), suggesting a staggered ('open') conformation. Likewise, larger coupling constants $^3J(8,9)$ (up to 7.7 Hz) in the acetyl-protected alkyne derivatives **4f** and **4g**

[2]) Alternatively, the first dehydrobromination proceeds in the absence of external base, but requires a longer reaction time (1–5 d).

underline the influence of protecting groups as the conformation equilibrium is shifted towards the 'closed' conformation. In addition, a strong NOE of H–C(5′) with H–C(9) (13.7%) is observed in 10,11-didehydroquinidine (**4a**), consistent with the *anti*-'open' conformation and the resulting horizontal position of the 6′-methoxyquinoline moiety. Predominance of the horizontal conformation can be explained by reduced rotational mobility about the C(4′)–C(9) bond, due to the sterically demanding 6′-methoxyquinoline moiety attached to the bicyclic moiety.

Confirmatory evidence was provided by the X-ray analysis of 10,11-didehydroquinidine (**4a**) which showed the staggered conformation of H–C(8) and H–C(9) in the crystal (*Fig.*). This X-ray structure also demonstrates a clockwise twisting of the C(2)–C(3) bridge with respect to the azabicyclic cage.



H–C(8)/H–C(5′) 1.5%
H–C(9)/H–C(2) 2.7%
H–C(9)/H–C(5′) 13.7%

Figure. *NOE of 10,11-didehydroquinidine* (**4a**) *and X-ray crystal structure of* **4a** · *HBr*

By comparison, the distortion of the azabicyclic cage in the didehydro derivatives of quinine and quinidine is smaller than in dihydroquinine and dihydroquinidine (*Table 3*) [12]. As a result, the bicyclic moiety is forced towards the energetically disfavored eclipsed configuration. A similar effect is observed in the didehydro analogs of *Quincorine*® (QCI) and *Quincoridine*® (QCD), two homochiral 1,2-amino alcohols derived from quinine and quinidine [13]. Again, twisting of the azabicyclic core with the ethynyl side chain is smaller and the basicity is higher than in parent QCI and QCD with the vinyl side chain.

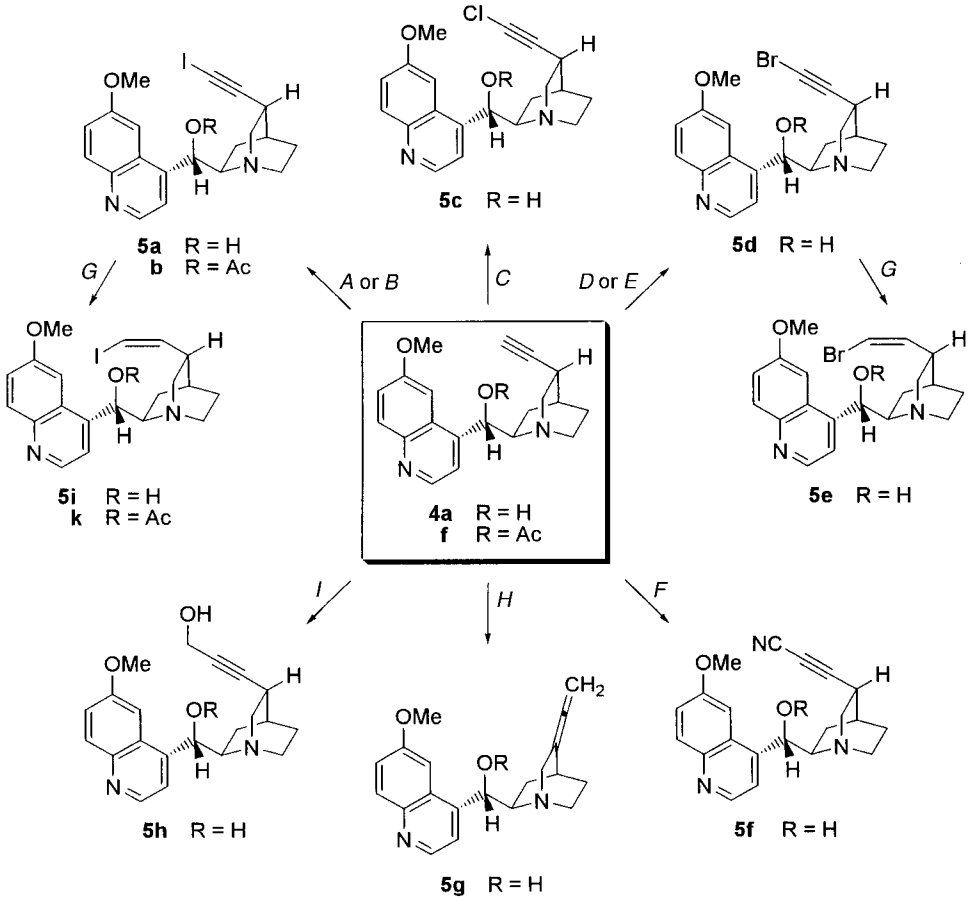
Table 3. *Clockwise Twisting of the 1-Azabicyclic Core in Quinidine Derivatives*

Bonds	Torsion angles	
	10,11-didehydroquinidine (**4a**)	10,11-dihydroquinidine [12]
N(1)–C(8)–C(7)–C(4)	11.4°	25°
N(1)–C(2)–C(3)–C(4)	13.2°	20°
N(1)–C(6)–C(5)–C(4)	12.3°	20°
Σ (twisting)	36.9°	65°

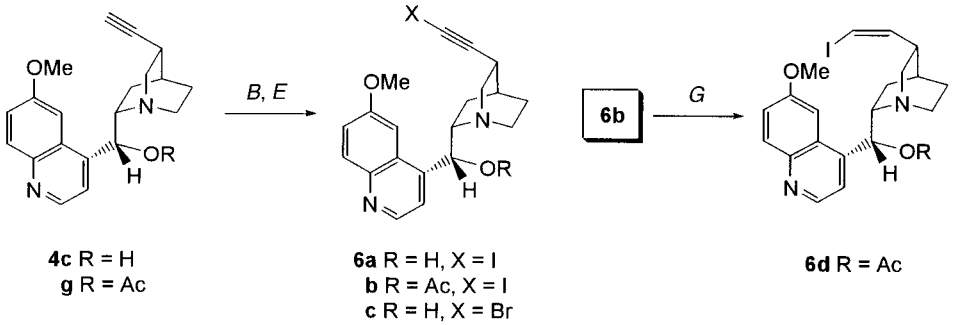
Didehydroquinidines **4a** and **4f** and didehydroquinines **4c** and **4g** could easily be transformed into the corresponding 11-haloalkynes (*Schemes 2* and *3*, *Table 4*). Reaction with the iodine-morpholine complex in toluene [8] at elevated temperature gave the iodinated alkynes **5a**,**b** and **6a**,**b**, respectively, in nearly quantitative yield.

Bromination at C(11) of **4a** and **4c** was achieved with Br_2 in aqueous KOH solution to provide substituted alkyne derivatives **5d** and **6c** in high yield (up to 93%). NaOCl-Mediated C(11)-chlorination of **4a**, however, was less effective (39%), and alternative methods based on alkyne lithiation did not increase the yield. Iodoalkyne derivatives **5a**,**b** and **6b** and bromo derivative **5d** were transformed into the corresponding (*Z*)-vinyl iodides **5i**,**k** and **6d** and (*Z*)-vinyl bromide **5e**, respectively, by *p*-toluenesulfonohydrazide-mediated diimide hydrogenation, but optimized yields did not exceed 65% [8][14]. Moreover, bromoalkyne derivative **5d** was a suitable intermediate for the synthesis of propynenitrile **5f** with CuCN in DMF [15]. The formation of propynol **5h** was feasible (87%) upon treatment of the unprotected **4a** with BuLi and paraformaldehyde in THF at gradually increased temperatures (−78 to +40°) [16]. To our surprise, isomerization of didehydroquinidine **4a** to the corresponding allene derivative **5g** was achieved without significant decomposition. Refluxing in toluene in the presence of powdered KOH/K_2CO_3 1:1 provided the desired allene in 68% yield (95% with respect to recovered starting material).

Scheme 2. *Reactions of 10,11-Didehydroquinidines* **4a**,**f** (for *A*–*I*, see *Table 4*)



Scheme 3. *Reactions of the Didehydroquinines* **4c**,**g** (for *B*, *E*, and *G*, see *Table 4*)



4c R = H
g R = Ac

6a R = H, X = I
b R = Ac, X = I
c R = H, X = Br

6d R = Ac

Table 4. *Functionalization of 10,11-Didehydro* Cinchona *Alkaloids*

Alkaloid	*Method*	Reagents and conditions	Product[a])	Yield [%]
4a	*A*	*N*-iodosuccinimide (NIS), $AgNO_3$, acetone, r.t.	**5a**	65
4a	*B*	I_2, morpholine, toluene, 55°	**5a**	91
4f	*B*	I_2, morpholine, toluene, 60°	**5b**	97
4c	*B*	I_2, morpholine, toluene, 55°	**6a**	95
4g	*B*	I_2, morpholine, toluene, 55°	**6b**	99
4a	*C*	KOH, NaOCl, H_2O, THF, r.t.	**5c**	39
4a	*D*	*N*-bromosuccinimide (NBS), $AgNO_3$, acetone, r.t.	**5d**	61
4a	*E*	Br_2, KOH, H_2O, THF, r.t.	**5d**	83
4c	*E*	Br_2, KOH, H_2O, THF, r.t.	**6c**	93
4a	*F*	1. Br_2, KOH, H_2O, THF, r.t.; 2. CuCN, DMF, 60°	**5f**	34
5a	*G*	$TsNHNH_2$, NaOAc, THF, H_2O, 55°	**5i**	59
5b	*G*	$TsNHNH_2$, NaOAc, THF, H_2O, 55°	**5k**	65
6b	*G*	$TsNHNH_2$, NaOAc, THF, H_2O, 55°	**6d**	63
5d	*G*	$TsNHNH_2$, NaOAc, THF, H_2O, 55°	**5e**	62
4a	*H*	KOH, K_2CO_3, toluene, reflux	**5g**	68
4a	*I*	BuLi, $(CH_2O)_n$, THF, $-78 \rightarrow 40°$	**5h**	87

[a]) Compounds **6a**–**d** are the quinine analogs (*cf. Scheme 3*).

The series of compounds **5a**–**k** derived from the didehydroquinidines **4a**,**f** is complemented by a corresponding series **6a**–**d** derived from the diastereoisomeric didehydroquinines **4c**,**g**, the yields being in the same range (see *Table 4*).

Halogenated alkynes or vinyl halides occur in various natural products with antitumor activity. As halogenation is often crucial for pharmacological activity (*cf.*, *e.g.*, vancomycin), the effect of 11-halogenation in didehydro *Cinchona* alkaloids on cytostatic activity was examined. Terminal-, bromo-, and iodoalkyne derivatives **4a**, **6c**, and **5a** were selected for *in vitro* tests with cell lines from gastric adenocarcinoma (HMO2) [17], colon carcinoma (KATO III), and human hepatocellular carcinoma (HEP G2)[3]).

[3]) The antitumor activity of the test compounds was determined according to the *NCI* guidelines [18]. Cells were grown in 96-well plates supplemented with 10% fetal calf serum at 37° in a humidified atmosphere of 5% CO_2 in air. After 24 h of incubation, the test compounds were added to the cells. Stock solutions of the test compounds were prepared in MeOH or H_2O. After a 48 h incubation period in the presence of the test drugs, the cells were fixed by addition of CCl_3COOH, and cell protein was assayed with sulforhodamin B.

It was found (*Tabe 5*) that iodoalkyne derivative **5a** exhibits the strongest and the terminal-alkyne derivative **4a** the weakest cytostatic activity (μmol/l range). All three alkaloid substrates show cytostatic activity in the HMO2 cell line, in the range of 5-fluorouracil, a well-known antimetabolite, capable of entering the synthesis and function of nucleic acids. Nonetheless, terminal-alkyne derivative **4a** shows cytostatic activity without significant cytotoxicity, whereas halogenoalkyne derivatives can also be cytotoxic (*Table 5*).

Table 5. *Antitumor Activity* (μmol/l) *of Selected Didehydro* Cinchona *Alkaloids*

	GI_{50}[a])			TGI[b])			LC_{50}[c])		
	HMO2	KATO III	HEP G2	HMO2	KATO III	HEP G2	HMO2	KATO III	HEP G2
4a ≡—H	6.5	1.3	12	8.5	28	50	50	> 50	> 50
6c ≡—Br	3.8	0.9	1.7	8.6	5.0	6.2	50	9.2	> 50
5a ≡—I	2.7	< 0.5	1.0	3.8	1.9	2.6	5.0	4.2	> 50
5-Fluorouracil	1.2	–	0.2	35	–	50	> 50	–	> 50
cis-Platinum	0.1	–	0.5	2.5	–	50	40	–	> 50

[a]) Drug concentration causing 50% growth inhibition. [b]) Drug concentration causing 100% growth inhibition. [c]) Drug concentration causing 50% reduction of the cells present at time point zero, *i.e.* at 24 h.

Conclusions. – The change of experimental conditions from double dehydrobromination to a stepwise dehydrobromination allowed the preparation of the title alkaloids in two steps in high yield. The first dibromination-monodehydrobromination proceeds in high yield in one pot. The second dehydrobromination affords the desired alkyne derivatives under mild conditions in more than 80% yield. All 10,11-didehydro *Cinchona* alkaloids represent a significantly new class of *Cinchona* alkaloids and show enhanced polarity and basicity. X-Ray data (twisting of the 1-azabicyclo[2.2.2]octane framework; see *Fig.*) and polarity tests indicate a reduced mobility (R_f values). Iodination, bromination, and subsequent *cis* hydrogenation of didehydroquinine and -quinidine proceed in satisfactory yield, furnishing further valuable precursors for *Heck*-type and other cross-coupling reactions.

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Experimental Part

General. THF was distilled over Na and benzophenone before use. AcOEt and *t*-BuOMe were distilled before use. (*t*-Bu)Me_2Si-Protected and Ac-protected quinidine **1e** and **1f**, resp., were prepared by standard procedures [19]. Only selected exper. data are given for the preparation of dibromides and vinyl bromides. Prep. column chromatography (CC): *J. T. Baker* silica gel (particle size 30–60 mm). Anal. TLC: Al-backed 0.2-mm silica gel *60* F_{254} plates (*E. Merck*). M.p.: *Büchi* apparatus; uncorrected. IR Spectra: *Perkin-Elmer-1710-IR* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-AM-400* spectrometer; in $CDCl_3$ unless otherwise stated, δ in ppm rel. to $SiMe_4$ as internal standard (= 0 ppm), coupling constants J in Hz; ^{13}C- assignments by DEPT measurements. Mass spectra: *Finnigan-MAT312* (70 eV) or *VG-Autospec* spectrometer.

Alkaloid Dibromides **2a**–**f**: *General Procedure I* (*G.P. I*). To a soln. of the *Cinchona* alkaloid (1 equiv.) in CCl_4 at 0°, a soln. of Br_2 (3 equiv.) in CCl_4 was added dropwise within 15 min. After stirring at r.t. for 2 h, the

resulting yellow precipitate was filtered off, washed with CCl_4, and dried. Further workup and purification was unnecessary in the case of unprotected alkaloid dibromides. The protected alkaloid dibromides were purified by CC (AcOEt/MeOH 20:1).

*(1*S*,3*R*,4*S*,8*R*,9*S*,10*R*)/(1*S*,3*R*,4*S*,8*R*,9*S*,10*S*)-10,11-Dibromo-10,11-dihydro-6′-methoxycinchonan-9-ol* (**2a**). According to the *G.P. I*, from quinidine (**1a**): **2a** (97%). IR (KBr): 3420, 3076, 2952, 2876, 2832, 1620, 1592, 1508, 1472, 1428, 1388, 1364, 1308, 1240, 1204, 1136, 1024, 992, 644. ^{1}H-NMR (CD_3OD): 8.95 (*d*, *J* = 4, H–C(2′)); 8.15 (*d*, *J* = 9, H–C(8′)); 7.74 (*d*, *J* = 4, H–C(3′)); 7.68 (*dd*, *J* = 2, 9, H–C(7′)); 6.82 (*d*, *J* = 2, H–C(5′)); 6.57, 6.52 (2*s*, H–C(9)); 5.62 (*dd*, *J* = 2, 8, 1 H–C(11)); 5.57 (*dd*, *J* = 2, 8, 1 H–C(11)); 4.76, 4.50 (2*dd*, *J* = 2, 7.5, H–C(10)); 4.29 (*m*, H–C(8)); 4.15 (*s*, MeO–C(5′)); 3.90–3.75 (*m*, 2 H–C(2)); 2.85–2.70 (*m*, H–C(3)); 2.60–2.30 (*m*, 2 H–C(6)); 2.10–1.85 (*m*, 2 H–C(7)); 1.70 (*m*, H–C(4)); 1.60–1.38 (*m*, 2 H–C(5)). ^{13}C-NMR (CD_3OD): 161.89, 159.55 (C(6′)); 149.75, 149.14 (CH(2′)); 144.02, 143.98 (C(10′)); 135.90, 135.61 (C(4′)); 131.28, 131.23 (CH(8′)); 128.61, 127.69 (C(9′)); 122.44, 122.38 (CH(7′)); 121.14, 121.09 (CH(3′)); 103.18, 100.08 (CH(5′)); 68.64, 67.66 (CH(9)); 60.74, 60.22 (CH(8)); 58.34, 54.43 (CH(10)); 55.56, 55.37 (*Me*O–C(6′)); 51.05, 50.85 (CH_2(11)); 50.44, 50.35 (CH_2(6)); 48.76, 48.63 (CH_2(2)); 40.98, 40.56 (CH(3)); 27.08, 25.96 (CH(4)); 24.18, 24.01 (CH_2(7)); 18.91, 18.06 (CH_2(5)). MS: 403 (7, $[M-Br]^+$), 323 (22), 308 (8), 295 (14), 240 (9), 216 (25), 214 (29), 201 (14), 189 (56), 173 (65), 160 (41), 158 (46), 136 (32), 130 (43), 117 (28), 108 (15), 95 (15), 91 (22), 81 (45), 80 (100), 79 (47), 77 (25). HR-MS: 403.1226 ($[C_{20}H_{24}BrN_2O_2]^+$; calc. 403.1220).

*(1*S*,3*R*,4*S*,8*R*,9*S*,10*R*)/(1*S*,3*R*,4*S*,8*R*,9*S*,10*S*)-9-{[(*tert*-Butyl)dimethylsilyl]oxy}-10,11-dibromo-10,11-dihydro-6′-methoxycinchonane* (**2e**). According to the *G.P. I*, from (*t*-Bu)Me_2Si-protected quinidine **1e**: **2e** (98%). IR (KBr): 3008, 2952, 2928, 2856, 1616, 1600, 1524, 1460, 1424, 1384, 1260, 1168, 1116, 1044, 996, 832, 780, 684. ^{1}H-NMR ($CDCl_3$): 8.92 (*d*, *J* = 4, H–C(2′)); 8.13 (*d*, *J* = 9, H–C(8′)); 7.69 (*d*, *J* = 4, H–C(3′)); 7.61 (*dd*, *J* = 2, 9, H–C(7′)); 6.97 (*d*, *J* = 2, H–C(5′)); 6.07, 6.04 (2*s*, H–C(9)); 4.34 (*dd*, *J* = 2, 8, 1 H–C(11)); 4.28 (*dd*, *J* = 2, 8, 1 H–C(11)); 4.04, 3.98 (2*dd*, *J* = 2, 7.5, H–C(10)); 3.96 (*s*, MeO–C(6′)); 3.83 (*m*, H–C(8)); 3.64–3.45 (*m*, 2 H–C(2)); 2.95–2.79 (*m*, H–C(3)); 2.60–2.42 (*m*, 2 H–C(6)); 2.30 (*m*, H–C(4)); 2.21–1.93 (*m*, 2 H–C(7)); 1.60–1.35 (*m*, 2 H–C(5)); 0.95 (*m*, Me_3CSi); 0.16 (*s*, MeSi); −0.21 (*s*, MeSi). ^{13}C-NMR ($CDCl_3$): 157.69, 157.50 (C(6′)); 147.18, 147.06 (CH(2′)); 146.04, 145.97 (C(10′)); 143.62, 143.55 (C(4′)); 131.29, 131.22 (CH(8′)); 128.62, 127.69 (C(9′)); 122.43, 122.38 (CH(7′)); 121.16, 121.00 (CH(3′)); 101.26, 100.98 (CH(5′)); 71.09, 70.88 (CH(9)); 60.74, 60.22 (CH(8)); 58.34, 57.24 (CH(10)); 55.56, 55.37 (*Me*O–C(6′)); 51.05, 50.85 (CH_2(11)); 50.44, 50.35 (CH_2(6)); 48.76, 48.63 (CH_2(2)); 40.98, 40.56 (CH(3)); 27.08, 25.96 (CH(4)); 24.18, 24.01 (CH_2(7)); 26.28 (*Me*$_3$CSi); 20.20, 19.98 (CH_2(5)); 14.21 (Me_3*C*Si); −3.91 (MeSi); −4.33 (MeSi). MS: 519 (2, $[M-Br]^+$), 517 (2, $[M-Br]^+$), 346 (21), 246 (81), 230 (17), 216 (23), 214 (13), 189 (21), 172 (100), 156 (23), 138 (72), 130 (27), 116 (21), 94 (40), 91 (13), 75 (88).

*(1*S*,3*R*,4*S*,8*R*,9*S*,10*R*)/(1*S*,3*R*,4*S*,8*R*,9*S*,10*S*)-9-Acetoxy-10,11-dibromo-10,11-dihydro-6′-methoxycinchonane*(**2f**). According to the *G.P. I*, from acetyl-protected quinidine **1f**: **2f** (95%). IR (KBr): 3068, 2940, 2922, 2872, 1744, 1620, 1598, 1508, 1472, 1432, 1368, 1304, 1228, 1132, 1084, 1028, 988, 834,786, 682. ^{1}H-NMR ($CDCl_3$): 8.79 (*d*, *J* = 4, H–C(2′)); 8.10 (*d*, *J* = 9, H–C(8′)); 7.49 (*d*, *J* = 4, H–C(3′)); 7.41 (*dd*, *J* = 2, 9, H–C(7′)); 7.35 (*d*, *J* = 2, H–C(5′)); 6.63, 6.52 (2*d*, *J* = 9, H–C(9)); 4.44 (*dd*, *J* = 2, 8, 1 H–C(11)); 4.35 (*dd*, *J* = 2, 8, 1 H–C(11)); 4.21, 4.08 (2*m*, H–C(10)); 4.02, 3.98 (2*s*, MeO–C(6′)); 3.78 (*m*, H–C(8)); 3.55–3.32 (*m*, 2 H–C(2)); 2.99–2.87 (*m*, H–C(3)); 2.71–2.51 (*m*, 2 H–C(6)); 2.33 (*m*, H–C(4)); 2.23, 2.19 (2*s*, AcO); 2.08–1.93 (*m*, 2 H–C(7)); 1.63–1.55 (*m*, 2 H–C(5)). ^{13}C-NMR ($CDCl_3$): 169.89, 169.87 (Me*C*O); 158.14, 158.07 (C(6′)); 147.33, 147.18 (CH(2′)); 144.68, 144.60 (C(10′)); 143.54, 143.18 (C(4′)); 131.84, 131.76 (CH(8′)); 126.81, 126.79 (C(9′)); 122.19, 121.82 (CH(7′)); 120.08, 119.64 (CH(3′)); 101.42, 101.04 (CH(5′)); 73.64, 73.06 (CH(9)); 58.79, 58.45 (CH(8)); 57.91, 57.03 (CH(10)); 55.70, 55.36 (*Me*O–C(6′)); 51.15, 50.92 (CH_2(11)); 50.81, 50.57 (CH_2(6)); 49.62, 49.49 (CH_2(2)); 40.34, 40.17 (CH(3)); 26.69, 26.31 (CH(4)); 25.75, 25.47 (CH_2(7)); 22.61, 22.39 (CH_2(5)); 21.22, 21.07 (*Me*CO). MS: 445 (4, $[M-Br]^+$), 443 (3, $[M-Br]^+$), 366 (46), 321 (27), 305 (76), 265 (12), 231 (15), 211 (10), 188 (69), 172 (22), 154 (14), 134 (100), 77 (57).

Vinyl Bromides **3a**–**f** *from the* Cinchona *Alkaloids* **1a**–**f**: *General Procedure II* (*G.P. II*). To a soln. of the *Cinchona* alkaloid in $CHCl_3$ at 0°, a soln. of Br_2 in $CHCl_3$ was added dropwise within 15 min. After stirring for 2 h under Ar at r.t., Et_3N (2 equiv.) was added to the yellow soln. Stirring at r.t. was continued for 4 h, and the mixture was treated with sat. aq. $NaHCO_3$ soln. and extracted with $CHCl_3$. The combined org. layer was dried ($MgSO_4$) and evaporated, and the residue purified by CC: vinyl bromide.

*(1*S*,3*R *and 3*S*,4*S*,8*R*,9*S*)-10 and 11-Bromo-6′-methoxycinchonan-9-ol* (**3a**). According to the *G.P. II*, from quinidine (**1a**): **3a** (89%) as a 1.2:1 mixture of vinyl bromides. IR ($CHCl_3$): 3604, 2945, 2875, 1622, 1592, 1509, 1471, 1431, 1365, 1307, 1241, 1136, 1100, 1032, 998, 863, 831. ^{1}H-NMR ($CDCl_3$): 8.49, 8.47 (2*d*, *J* = 4.6, H–C(2′)); 7.82, 7.81 (2*d*, *J* = 9.3, H–C(8′)); 7.55, 7.53 (2*d*, *J* = 4.3, H–C(3′)); 7.17, 7.16 (2*dd*, *J* = 9.2, 2.5, H–C(7′)); 6.93,

6.87 (2*d*, *J* = 2.5, H–C(5′)); 5.69, 5.64 (2*s*, H–C(9)); 4.84, 4.72 (2*m*, 1 H, H–C(11)); 3.88 (*m*, H–C(8)); 3.69, 3.66 (2*s*, MeO–C(6′)); 3.06–3.00 (*m*, 1 H–C(2)); 2.95–2.75 (*m*, 1 H–C(2), 2 H–C(6)); 2.24, 2.19 (2*m*, H–C(3)); 2.03 (*m*, H–C(4)); 1.95 (*m*, H–C(7)); 1.59–1.42 (*m*, 1 H–C(7), 1 H–C(5)); 0.95–0.85 (*m*, 1 H–C(5)). ^{13}C-NMR ($CDCl_3$): 157.84, 157.79 (C(6′)); 147.82, 125.64 (C(10) and CH(10)); 147.53, 147.08 (CH(2′)); 143.56, (C(10′)); 135.82, 116.42 (CH(11) and CH_2(11)); 133.02 (C(4′)); 130.99 (CH(8′)); 125.98, 125.87 (C(9′)); 121.78, 121.65 (CH(7′)); 118.08, 118.03 (CH(3′)); 100.69 (CH(5′)); 70.95, 70.73 (CH(9)); 59.12, 58.82 (CH(8)); 56.12, 55.64 (*Me*O–C(6′)); 50.74, 49.96 (CH_2(2)); 41.45, 41.29 (CH(3)); 38.53, 38.39 (CH_2(6)); 26.30, 26.19 (CH_2(7)); 25.13 (CH(4)); 18.76 (CH_2(5)). MS: 405 (88, $[M+H]^+$), 403 (84, $[M+H]^+$), 323 (30), 283 (6), 215 (17), 202 (16), 189 (25), 172 (23), 160 (12), 136 (100), 108 (9), 96 (23), 94 (23), 82 (49), 80 (47). HR-MS: 403.1023 ($[C_{20}H_{24}BrN_2O_2]^+$; calc. 403.1020).

(1S,3R and 3S,4S,8S,9R)-10 and 11-Bromo-6′-methoxycinchonan-9-ol (**3c**). According to the *G.P. II*, from quinine (**1c**): **3c** (86%) as a 1.3 : 1 mixture of vinyl bromides. IR ($CHCl_3$): 3606, 2946, 2835, 1622, 1591, 1509, 1472, 1431, 1373, 1309, 1241, 1135, 1097, 1033, 1001, 855, 832. ^{1}H-NMR ($CDCl_3$): 848, 8.46 (2*d*, *J* = 4.6, H–C(2′)); 7.88, 7.86 (2*d*, *J* = 9, H–C(8′)); 7.47, 7.46 (2*d*, *J* = 4, H–C(3′)); 7.26 (*m*, H–C(7′)); 7.19, 7.16 (2*d*, *J* = 2.6, H–C(5′)); 5.70, 5.60 (2*s*, H–C(9)); 4.61, 4.43 (2*m*, 1 H, H–C(11)); 3.98 (*m*, H–C(8)); 3.85, 3.68 (2*s*, MeO–C(6′)); 3.70 (*m*, 1 H–C(2)); 3.15–3.02 (*m*, 1 H–C(2), 1 H–C(6)); 2.73–2.58 (*m*, 1 H–C(6)); 2.31, 2.23 (2*m*, H–C(3)); 2.07–1.98 (*m*, H–C(4), 1 H–C(7)); 1.92–1.79 (*m*, 1 H–C(7), 1 H–C(5)); 1.57–1.42 (*m*, 1 H–C(5)). ^{13}C-NMR ($CDCl_3$): 157.96, 157.85 (C(6′)); 147.48, 125.36 (C(10) and CH(10)); 147.29, 147.21 (CH(2′)); 143.88 (C(10′)); 134.93, 117.59 (CH(11) and CH_2(11)); 134.32 (C(4′)); 131.26 (CH(8′)); 126.42, 126.29 (C(9′)); 121.66, 121.42 (CH(7′)); 118.58, 118.41 (CH(3′)); 101.46, 101.17 (CH(5′)); 70.86, 70.52 (CH(9)); 60.39, 59.98 (CH(8)); 56.08, 55.64 (*Me*O–C(6′)); 53.08, 52.79 (CH_2(2)); 41.34, 40.71 (CH(3)); 37.76/37.27 (CH_2(6)); 27.31, 27.08 (CH_2(7)); 26.22, 25.34 (CH(4)); 21.03, 20.38 (CH_2(5)). MS: 405 (17, $[M+H]^+$), 403 (14, $[M+H]^+$), 172 (15), 149 (17), 136 (100), 99 (27), 81 (24). HR-MS: 403.1026 ($[C_{20}H_{24}BrN_2O_2]^+$; calc. 403.1021).

*(1S,3R and 3S,4S,8R,9S)-10 and 11-Bromo-9-[[(*tert*-butyl)dimethylsilyl]oxy]-6′-methoxycinchonane* (**3e**). According to the *G.P. II*, from (*t*-Bu)Me_2Si-protected quinidine **1e**: **3e** (86%). IR ($CHCl_3$): 3008, 2952, 2928, 2896, 2856, 1620, 1600, 1496, 1460, 1428, 1384, 1260, 1216, 1116, 1048, 1016, 996, 832, 784. ^{1}H-NMR ($CDCl_3$/CD_3OD): 8.53 (*d*, *J* = 4, H–C(2′)); 8.11 (*d*, *J* = 9, H–C(8′)); 7.71 (*d*, *J* = 4, H–C(3′)); 7.33 (*d*, *J* = 2, H–C(5′)); 7.30 (*dd*, *J* = 2, 9, H–C(7′)); 5.92 (*s*, H–C(9)); 4.97 (*m*, 2 H, H–C(11)); 4.48 (*m*, H–C(8)); 4.28 (*s*, MeO–C(6′)); 3.89 (*m*, H_{endo}–C(2)); 3.82 (*m*, H_{exo}–C(2)); 3.46–3.25 (*m*, 2 H–C(6)); 2.68 (*m*, H–C(3)); 2.42 (*m*, H–C(4)); 2.04–1.90 (*m*, 2 H–C(7)); 1.79–1.60 (*m*, 2 H–C(5)); 1.02 (*m*, Me_3CSi); 0.49 (*s*, MeSi); –0.16 (*s*, MeSi). ^{13}C-NMR ($CDCl_3$/CD_3OD): 159.37 (C(6′)); 150.92 (CH(2′)); 146.57 (C(10′)); 143.29 (C(4′)); 138.65 (C(10)); 129.44 (CH(8′)); 123.12 (C(9′)); 120.19 (CH(7′)); 120.01 (CH_2(11)); 119.66 (CH(3′)); 102.08 (CH(5′)); 77.33 (CH(9)); 59.97 (CH(8)); 58.02 (*Me*O–C(6′)); 51.51 (CH_2(6)); 49.41 (CH_2(2)); 40.07 (CH(3)); 31.05 (CH(4)); 26.17 (CH_2(7)); 25.95 (Me_3CSi); 24.36 (CH_2(5)); 13.89 (Me_3CSi); –3.25 (MeSi); –4.83 (MeSi). MS: 518 (39, $[M+2]^+$), 516 (31, $[M+2]^+$), 461 (41), 438 (2), 397 (22), 302 (44), 246 (29), 198 (14), 186 (25), 172 (35), 149 (84), 83 (58), 73 (100).

Alkynes **4a**–**d** *from the Vinyl Bromides* **3a**–**d** *with KOH and* Aliquat 336: *General Procedure III* (*G.P. III*). KOH (2 equiv.) was added to a soln. of the vinyl bromide (1 equiv.) in THF. After stirring at r.t. for 10 min, *Aliquat 336* (0.1 equiv.) was added. The resulting homogenous soln. was stirred at r.t. for 20 h, diluted with H_2O and sat. aq. $NaHCO_3$ soln., and extracted with $CHCl_3$. The combined org. layer was dried ($MgSO_4$) and evaporated, and the residue purified by CC: alkyne.

Alkynes **4a**,**d**,**e** *from the Dibromides* **2a**,**d**,**e** *with* t-*BuOK in* t-*BuOH: General Procedure IV* (*G.P. IV*). *t*-BuOK (4 equiv.) was added to a soln. of the dibromide (1 equiv.) in *t*-BuOH. The resulting heterogeneous soln. was stirred at r.t. or at 80° for 2 h under Ar, diluted with H_2O and sat. aq. $NaHCO_3$ soln., and extracted with $CHCl_3$. The combined org. layer was dried ($MgSO_4$) and evaporated, and the residue purified by CC: alkyne.

(1S,3S,4S,8R,9S)-10,11-Didehydro-6′-methoxycinchonan-9-ol (**4a**). According to the *G.P. III*, with bromide **3a**: **4a** (84%). IR (KBr): 3304, 3244, 3080, 2944, 2876, 2836, 2225, 1620, 1592, 1508, 1472, 1432, 1360, 1228, 1172, 1136, 1092, 1032, 908, 828. ^{1}H-NMR ($CDCl_3$): 8.63 (*d*, *J* = 4, H–C(2′)); 7.98 (*d*, *J* = 9, H–C(8′)); 7.53 (*d*, *J* = 4, H–C(3′)); 7.33 (*dd*, *J* = 2, 9, H–C(7′)); 7.28 (*d*, *J* = 2, H–C(5′)); 5.65 (*d*, *J* = 4, H–C(9)); 3.89 (*s*, MeO–C(6′)); 3.45 (*m*, H–C(8)); 3.17 (*m*, H_{endo}–C(2)); 3.09 (*m*, H_{exo}–C(2)); 2.88 (*m*, H–C(3)); 2.74 (*m*, 1 H–C(6)); 2.53 (*m*, 1 H–C(6)); 2.36 (*m*, H–C(4)); 2.19 (*m*, 1 H–C(7)); 2.03 (*s*, H–C(11)); 1.54 (*m*, 1 H–C(7)); 1.45–1.28 (*m*, 2 H–C(5)). NOE ((D$_6$)DMSO): H–C(9) irradiated → H–C(5′) (10.2%), H–C(8) (1.5%), H_{endo}–C(2) (2.7%); H–C(5′) irradiated → H–C(9) (13.7%), H–C(11′) (4.6%), H–C(8) (1.4%), H_{endo}–C(2) (1.5%). ^{13}C-NMR ($CDCl_3$): 157.63 (C(6′)); 147.56 (CH(2′)); 144.23 (C(10′)); 143.82 (C(4′)); 131.48 (CH(8′)); 126.77 (C(9′)); 121.50 (CH(7′)); 118.68 (CH(3′)); 101.37 (CH(5′)); 87.26 (C(10)); 71.80 (CH(9)); 69.24 (CH(11)); 59.94 (CH(8)); 55.61 (*Me*O–C(6′)); 50.28 (CH_2(2)); 49.46 (CH_2(6)); 28.02 (CH(3)); 27.96 (CH(4)); 25.07 (CH_2(5));

22.64 (CH_2(7)). MS: 322 (62, M^+), 321 (18), 308 (17), 294 (11), 284 (22), 265 (13), 250 (21), 236 (8), 214 (12), 201 (12), 198 (13), 189 (91), 186 (21), 173 (82), 160 (38), 158 (26), 134 (100), 117 (41), 106 (29), 94 (13), 91 (18), 81 (16), 77 (63). HR-MS: 322.1686 ($[C_{20}H_{22}N_2O_2]^+$; calc. 322.1681). Anal. calc. for $C_{20}H_{22}N_2O_2$ (322.17): C 74.05, H 7.43, N 8.64; found: C 74.02, H 7.51, N 8.63.

Crystal Structure Analysis of **4a**·*HBr*[4]): $C_{20}H_{23}BrN_2O_2$, M 403.32, monoclinic, space group $P2_1$, a = 9.218(2), b = 11.508(2), c = 9.564(2) Å, α = 90, β = 104.93(2), γ = 90°; V = 980.3(4) Å^3, Z = 2, D_c = 1.366 g·cm^{-3}; F(000) = 416, crystal size 0.23 × 0.33 × 0.35 mm, T 300 K, μ(MoK_α) = 21.1 cm^{-1}. Data collection: diffractometer *Stoe IPDS* (imaging plate), graphite-monochromated MoK_α radiation (fine-focus sealed tube, λ 0.71073 Å), 2θ range = 4.4–48.5°; data set h, k, l − 10: 10; −12; 12; −10: 10; total data 10080, unique data 3056, observed data 1830 with $I > 2\sigma(I)$, R_{int} = 0.092. Structure solution by SHELXS-86 and refinement by SHELXL-93, 234 refined parameters, H-atoms in geometrically calculated positions, but H(1) (at N(1)) free and bond-length restraints for H(14) (at O(1), H(14) H-bonds to N(1′) of another molecule); $\Delta\rho_{max}$ = 0.21 eÅ^{-3}, $\Delta\rho_{min}$ = −0.24 eÅ^{-3}; R_1 = 0.0345, R_1 based on F of 1830 reflections with $F_o > 4\sigma(F_o)$, wR_2 = 0.0605, wR_2 based on F^2 of 3056 reflections, *Flack x* parameter −0.02(1).

(1S,3S,4S,8R,9S)-10,11-Didehydrocinchonan-9-ol (**4b**). According to the *G.P. III*, with vinyl bromide **3b**: **4b** (75%). IR (KBr): 3304, 2932, 2860, 1620, 1592, 1572, 1508, 1456, 1372, 1316, 1224, 1080, 1020, 804. ^{1}H-NMR (CD_3OD, 200 MHz): 8.78 (d, J = 4, H−C(2′)); 8.09 (dd, J = 8, 1, H−C(8′)); 8.02 (dd, J = 8, 1, H−C(3′)); 7.79–7.64 (m, H−C(3′), H−C(7′), H−C(5′)); 5.61 (d, J = 5, H−C(9)); 3.68–3.60 (m, H−C(8)); 3.31–3.12 (m, 2 H−C(2)); 2.80–2.68 (m, H−C(3)); 2.59–2.45 (m, 2 H−C(6)); 2.19 (d, J = 5.5, H−C(11)); 2.02–1.72 (m, 2 H−C(7), 1 H−C(5), H−C(4)); 1.59–1.46 (m, 1 H−C(5)). ^{13}C-NMR (CD_3OD, 50 MHz): 150.72 (C(6′)); 147.78 (C(2′)); 147.19 (C(10′)); 129.67 (C(4′)); 128.22 (C(8′)); 126.74 (C(9′)); 123.89 (C(7′)); 119.27 (C(3′)); 102.15 (C(5′)); 85.51 (C(10)); 72.34 (C(9)); 68.66 (C(11)); 59.82 (C(8)); 53.41 (C(2)); 49.67 (C(6)); 27.05 (C(3)); 26.52 (C(4)); 25.48 (C(7)); 21.13 (C(5)). MS: 292 (14, M^+), 216 (3), 195 (23), 184 (9), 168 (6), 159 (31), 143 (19), 134 (90), 106 (22), 91 (48), 75 (100), 67 (15). HR-MS: 292.1580 ($[C_{19}H_{20}NO]^+$; calc. 292.1578).

(1S,3S,4S,8S,9R)-10,11-Didehydro-6′-methoxycinchonan-9-ol (**4c**). According to the *G.P. III*, with vinyl bromide **3c**: **4c** (81%). IR ($CHCl_3$): 3607, 3305, 2943, 2835, 2109, 1622, 1591, 1509, 1472, 1454, 1431, 1364, 1323, 1283, 1241, 1094, 1032, 1001, 853. ^{1}H-NMR ($CDCl_3$): 8.47 (d, J = 4.5, H−C(2′)); 7.83 (d, J = 9.3, H−C(8′)); 7.49 (d, J = 4.5, H−C(3′)); 7.20 (dd, J = 9.2, 2.6, H−C(7′)); 7.11 (d, J = 2.5, H−C(5′)); 5.53 (d, J = 3.0, H−C(9)); 3.76 (s, MeO−C(6′)); 3.62–3.53 (m, H−C(8)); 3.14 (dd, J = 13.5, 10.1, 1 H−C(2)); 2.84–2.80 (m, 1 H−C(2)); 2.61–2.54 (m, 1 H−C(6)); 2.52–2.47 (m, 1 H−C(6)); 2.00 (s, H−C(11)); 1.97 (m, H−C(3)); 1.90 (m, H−C(4)); 1.85–1.83 (m, 1 H−C(5), 2 H−C(7)); 1.43–1.35 (m, 1 H−C(5)). ^{13}C-NMR ($CDCl_3$) 157.83 (C(6′)); 148.22 (C(10′)); 147.27 (CH(2′)); 143.85 (C(4′)); 131.05 (CH(8′)); 126.61 (C(9′)); 121.73 (CH(7′)); 118.61 (CH(3′)); 101.31 (CH(5′)); 87.53 (C(10)); 71.24 (CH(9)); 69.04 (CH(11)); 59.45 (CH(8)); 57.89 (CH_2(2)); 55.74 (*Me*O−C(6′)); 42.88 (CH_2(6)); 27.60 (CH(3)); 27.17 (CH(4)); 25.95 (CH_2(7)); 21.45 (CH_2(5)). MS: 322 (3, M^+), 261 (10), 230 (1), 211 (2), 173 (5), 155 (1), 136 (100), 107 (2), 83 (7). HR-MS: 322.1681 ($[C_{20}H_{22}N_2O_2]^+$; calc. 322.1681).

(1S,3S,4S,8S,9R)-10,11-Didehydrocinchonan-9-ol (**4d**). According to the *G.P. III*, with vinyl bromide **3d**: **4d** (72%). $[\alpha]_D$ = 154.4 (c = 1.075, CH_2Cl_2). IR (KBr): 3296, 2924, 2856, 1616, 1588, 1572, 1508, 1456, 1376, 1320, 1208, 1096, 1020, 804, 760, 636. ^{1}H-NMR (CD_3OD, 200 MHz): 8.81 (d, J = 4, H−C(2′)); 8.22 (dd, J = 8, 1, H−C(8′)); 8.08 (dd, J = 8, 1, H−C(3′)); 7.9–7.8 (m, H−C(6′), H−C(7′), H−C(5′)); 5.65 (d, J = 4, H−C(9)); 3.7–3.5 (m, H−C(8)); 3.34–3.09 (m, 2 H−C(2)); 2.82–2.72 (m, H−C(3)); 2.62–2.49 (m, 2 H−C(6)); 2.23 (d, J = 5.5, H−C(11)); 1.98–1.76 (m, 2 H−C(7), 1 H−C(5), H−C(4)); 1.55–1.35 (m, 1 H−C(5)). ^{13}C-NMR (CD_3OD, 50 MHz) 150.84 (C(6′)); 149.53 (C(2′)); 147.43 (C(10′)); 129.32 (C(4′)); 128.7 (C(8′)); 126.76 (C(9′)); 125.8 (C(7′)); 123.15 (C(3′)); 118.57 (C(5′)); 86.93 (C(10)); 70.9 (C(9)); 68.78 (C(11)); 59.85 (C(8)); 57.47 (C(2)); 42.14 (C(6)); 27.1 (C(3)); 27.02 (C(4)); 25.28 (C(5)); 21.42 (C(7)). MS: 292 (8, M^+), 216 (5), 195 (2), 184 (3), 168 (4), 159 (22), 143 (9), 134 (100), 115 (6), 106 (11), 91 (21), 77 (24), 67 (6). HR-MS: 292.1576 ($[C_{19}H_{20}N_2O]^+$; calc. 292.1578).

*(1S,3S,4S,8R,9S)-9-{[(*tert*-Butyl)dimethylsilyl]oxy}-10,11-didehydro-6′-methoxycinchonane* (**4e**). According to the *G.P. IV*, with dibromide **2e**: **4e** (49%). IR (KBr): 3304, 3080, 2944, 2876, 2310, 1620, 1592, 1508, 1472, 1456, 1372, 1236, 1084, 1068, 1032, 916, 844. ^{1}H-NMR ($CDCl_3$): 8.81 (d, J = 4, H−C(2′)); 8.09 (d, J = 9,

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[4]) Crystallographic data (excluding structure factors) for **4a**·HBr have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-141952. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

H–C(8′)); 7.63 (*d*, *J* = 4, H–C(3′)); 7.42 (*dd*, *J* = 2, 9, H–C(7′)); 7.29 (*d*, *J* = 2, H–C(5′)); 5.69 (*d*, *J* = 8, H–C(9)); 3.99 (*s*, MeO–C(6′)); 3.51 (*m*, H–C(8)); 3.07 (*m*, H_{endo}–C(2)); 2.99 (*m*, H_{exo}–C(2)); 2.85 (*m*, H–C(3)); 2.71 (*m*, 1 H–C(6)); 2.52 (*m*, 1 H–C(6)); 2.37 (*m*, H–C(4)); 2.19 (*m*, 1 H–C(7)); 2.00 (*s*, H–C(11)); 1.87 (*m*, 1 H–C(7)); 1.76 (*m*, 1 H–C(5)); 1.48 (*m*, 1 H–C(5)); 0.99 (*m*, Me_3CSi); 0.19 (*s*, MeSi); – 0.29 (*s*, MeSi). ^{13}C-NMR ($CDCl_3$): 157.88 (C(6′)); 147.55 (CH(2′)); 146.12 (C(10′)); 144.34 (C(4′)); 131.90 (CH(8′)); 126.35 (C(9′)); 121.56 (CH(7′)); 119.03 (CH(3′)); 100.52 (CH(5′)); 88.31 (C(10)); 72.28 (CH(9)); 69.22 (CH(11)); 61.36 (CH(8)); 55.69 (*Me*O–C(6′)); 50.37 (CH_2(2)); 49.75 (CH_2(6)); 28.23 (CH(3)); 27.02 (CH(4)); 25.99 (*Me*$_3$CSi); 25.75 (CH_2(5)); 25.00 (CH_2(7)); 18.04 (Me_3*C*Si); – 4.26 (MeSi); – 4.86 (MeSi). MS: 436 (81, M^+), 421 (9), 397 (16), 379 (85), 329 (4), 303 (55), 258 (7), 246 (7), 186 (9), 173 (16), 154 (9), 136 (48), 115 (11), 99 (21), 73 (100). HR-MS: 436.2539 ($[C_{26}H_{36}N_2O_2Si]^+$; calc. 436.2546).

(1S,3S,4S,8R,9S)-9-Acetoxy-10,11-didehydro-6′-methoxycinchonane (**4f**). To a soln. of Ac-protected dibromide **2f** (1 equiv.) in abs. DMSO, $NaNH_2$ (8 equiv.) was slowly added. The mixture was stirred for 14 h at r.t. under Ar, diluted with H_2O and sat. aq. $NaHCO_3$ soln., and extracted several times with $CHCl_3$. The combined org. layer was dried ($MgSO_4$) and evaporated, and the residue purified by CC: **4f** (41%). IR ($CHCl_3$): 3304, 3076, 2948, 2876, 2836, 2205, 1744, 1620, 1592, 1508, 1472, 1456, 1432, 1372, 1300, 1232, 1172, 1136, 1104, 1032, 988, 844. ^{1}H-NMR ($CDCl_3$): 8.79 (*d*, *J* = 4, H–C(2′)); 8.07 (*d*, *J* = 9, H–C(8′)); 7.49 (*d*, *J* = 4, H–C(3′)); 7.43 (*dd*, *J* = 2, 9, H–C(7′)); 7.32 (*d*, *J* = 2, H–C(5′)); 6.67 (*d*, *J* = 7, H–C(9)); 4.01 (*s*, MeO–C(6′)); 3.35 (*m*, H–C(8)); 3.18 (*m*, H_{endo}–C(2)); 3.11 (*m*, H_{exo}–C(2)); 2.84 (*m*, H–C(3)); 2.73 (*m*, 1 H–C(6)); 2.56 (*m*, 1 H–C(6)); 2.26 (*m*, H–C(4)); 2.19 (*s*, *Me*CO); 2.08 (*m*, 1 H–C(7)); 2.05 (*s*, H–C(11)); 1.59–1.50 (*m*, 2 H–C(5), 1 H–C(7)). ^{13}C-NMR ($CDCl_3$): 169.88 (Me*C*O); 158.02 (C(6′)); 147.34 (CH(2′)); 144.64 (C(10′)); 143.75 (C(4′)); 131.70 (CH(8′)); 126.91 (C(9′)); 122.01 (CH(7′)); 118.50 (CH(3′)); 101.36 (CH(5′)); 87.19 (C(10)); 71.82 (CH(9)); 69.40 (CH(11)); 59.07 (CH(8)); 55.67 (*Me*O–C(6′)); 50.15 (CH_2(2)); 49.37 (CH_2(6)); 27.97 (CH(3)); 27.68 (CH(4)); 24.99 (CH_2(5)); 23.75 (CH_2(7)); 21.12 (*Me*CO). MS: 364 (79, M^+), 321 (27), 305 (76), 294 (5), 281 (13), 265 (12), 231 (15), 211 (10), 201 (9), 188 (69), 186 (12), 172 (22), 160 (11), 158 (14), 134 (100), 106 (17), 91 (15), 77 (57). HR-MS: 364.1791 ($[C_{20}H_{24}N_2O_3]^+$; calc. 364.1787).

(1S,3S,4S,8S,9R)-9-Acetoxy-10,11-didehydro-6′-methoxycinchonane (**4g**). Acetyl chloride (0.40 ml, 5.59 mmol) and Et_3N (0.87 ml, 6.21 mmol) were added to a soln. of quinine-based alkyne **4c** (1.0 g, 3.10 mmol) in THF (10 ml) at 0°. The mixture was stirred for 12 h at r.t, sat. aq. $NaHCO_3$ soln. added, and the aq. layer extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$) and evaporated and the residue purified by CC (AcOEt/MeOH 10 : 1): **4g** (1.03 g, 91%). IR ($CHCl_3$): 3305, 2955, 2870, 1742, 1623, 1593, 1509, 1475, 1454, 1433, 1372, 1323, 1302, 1238, 1085, 1030, 851, 831. ^{1}H-NMR ($CDCl_3$): 8.75 (*d*, *J* = 4.4, H–C(2′)); 8.02 (*d*, *J* = 9.2, H–C(8′)); 7.45 (*d*, *J* = 2.8, H–C(5′)); 7.38 (*d*, *J* = 4.2, H–C(3′)); 7.37 (*dd*, *J* = 2.8, 9.3, H–C(7′)); 6.49 (*d*, *J* = 7.7, H–C(9)); 3.95 (*s*, MeO–C(6′)); 3.62–3.56 (*m*, H–C(8)); 3.13–3.05 (*m*, H_{endo}–C(6), H_{exo}–C(2)); 2.82–2.77 (*m*, H_{endo}–C(2)); 2.64–2.57 (*m*, H_{exo}–C(6)); 2.52–2.47 (*m*, H–C(3)); 2.24–2.15 (*m*, H_{exo}–C(7)); 2.13 (*s*, MeCO); 2.07 (*d*, *J* = 2.6, H–C(11)); 2.03 (br. *s*, H–C(4)); 1.75–1.67 (*m*, H_{endo}–C(5)); 1.58–1.51 (*m*, H_{endo}–C(7)); 1.48–1.39 (*m*, H_{exo}–C(5)). ^{13}C-NMR ($CDCl_3$): 170.06 (Me*C*O); 157.92 (C(6′)); 147.39 (CH(2′)); 144.73 (C(4′)); 143.56 (C(10′)); 131.71 (CH(8′)); 127.10 (C(9′)); 121.86 (CH(7′)); 119.08 (CH(3′)); 101.49 (CH(5′)); 87.67 (C(10)); 73.44 (CH(9)); 68.86 (CH(11)); 58.54 (CH(8)); 57.46 (CH_2(2)); 55.59 (*Me*O–C(6′)); 41.82 (CH_2(6)); 27.42 (CH(3)); 26.73 (CH(4)); 26.12 (CH_2(5)); 24.67 (CH_2(7)); 21.04 (*Me*CO). MS: 365 (4), 364 (14, M^+), 349 (2), 321 (3), 305 (14), 290 (2), 231 (6), 189 (20), 188 (21), 172 (8), 134 (100). HR-MS: 364.1784 ($[C_{22}H_{24}N_2O_3]^+$; calc. 364.1786).

(1S,3S,4S,8R,9S)-10,11-Didehydro-11-iodo-6′-methoxycinchonan-9-ol (**5a**). Morpholine (0.674 ml, 7.75 mmol, 6 equiv.) was added dropwise to a soln. of I_2 (984 mg, 3.88 mmol, 3 equiv.) in abs. toluene. After stirring at r.t. for 1 h, **4a** (416 mg, 1.29 mmol, 1 êquiv.) was added. The mixture was stirred at 60° for 10 h, sat. aq. $NaHCO_3$ soln. added, and the aq. layer extracted with CH_2Cl_2. The combined org. layer was dried ($MgSO_4$) and evaporated, and the residue purified by CC (AcOEt/MeOH 6 : 1): **5a** (527 mg, 91%). IR ($CHCl_3$): 3416, 2932, 2872, 1620, 1592, 1508, 1468, 1428, 1384, 1320, 1240, 1112, 1072, 1028, 828, 640, 620. ^{1}H-NMR ((D$_6$)DMSO): 8.69 (*d*, *J* = 4.6, H–C(2′)); 7.94 (*d*, *J* = 9.2, H–C(8′)); 7.71 (*d*, *J* = 4.9, H–C(3′)); 7.49 (*d*, *J* = 3, H–C(5′)); 7.41 (*dd*, *J* = 9.2, 2.6, H–C(7′)); 5.29 (*d*, *J* = 3.0, H–C(9)); 4.06–4.01 (*m*, H–C(8)); 3.92 (*s*, MeO–C(6′)); 3.12–3.04 (*m*, 2 H–C(2)); 2.89–2.82 (*m*, 1 H–C(6)); 2.68–2.59 (*m*, 1 H–C(6)); 1.99 (*m*, H–C(3)); 1.87 (*m*, H–C(4)); 1.60–1.42 (*m*, 1 H–C(7)); 1.41–1.20 (*m*, 2 H–C(5), 1 H–C(7)). ^{13}C-NMR ((D$_6$)DMSO): 156.85 (C(6′)); 147.98 (C(10′)); 147.58 (CH(2′)); 144.05 (C(4′)); 131.25 (CH(8′)); 128.73 (C(9′)); 121.06 (CH(7′)); 119.38 (CH(3′)); 102.40 (CH(5′)); 97.49 (C(10)); 70.63 (CH(9)); 60.27 (CH(8)); 55.65 (*Me*O–C(6′)); 49.34 (CH_2(2)); 48.47 (CH_2(6)); 38.16 (CH(3)); 31.37 (C(11)); 29.88 (CH_2(7)); 28.44 (CH(4)); 22.47 (CH_2(5)). MS: 448 (7, M^+), 433 (1), 322 (53), 307 (9), 283 (15), 265 (8), 254 (30), 236 (7), 214 (7), 189 (55), 173 (39), 160 (16), 134 (64), 117 (13), 106 (13), 91 (12), 75 (100). FAB-MS: 449 (100, $[M + H]^+$), 355 (24), 323 (59), 281 (52), 221 (68), 207

(53), 189 (32). HR-MS: 448.0648 ($[C_{20}H_{21}IN_2O_2]^+$; calc. 448.0647). Anal. calc. for $C_{20}H_{21}IN_2O_2$ (448.06): C 53.58, H 4.72, N 6.25; found: C 53.19, H 5.19, N 6.02.

*(1*S*,3*S*,4*S*,8*R*,9*S*)-9-Acetoxy-10,11-didehydro-11-iodo-6′-methoxycinchonane* (**5b**). As described for **5a**, with morpholine (3.12 ml, 36 mmol, 6 equiv.), I_2 (4.56 g, 18 mmol, 3 equiv.), toluene (20 ml), and **4f** (2.18 g, 6 mmol, 1 êquiv.) (at 60° for 16 h). CC (AcOEt/MeOH 20:1) afforded **5a** (2.85 g, 97%). IR ($CHCl_3$): 2956, 2868, 1740, 1624, 1592, 1508, 1472, 1452, 1432, 1372, 1324, 1300, 1232, 1112, 1084, 1032, 852, 83. ^{1}H-NMR ($CDCl_3$): 8.79 (*d*, *J* = 4.4, H–C(2′)); 8.08 (*d*, *J* = 9.2, H–C(8′)); 7.49 (*d*, *J* = 2.6, H–C(5′)); 7.43–7.40 (*m*, H–C(3′), H–C(7′)); 6.16 (*d*, *J* = 7.9, H–C(9)); 4.01 (*s*, *Me*O–C(6′)); 3.77–3.69 (*m*, H–C(8)); 3.65–3.58 (*m*, 1 H–C(2)); 3.13–3.07 (*dd*, *J* = 13.6, 9.9, 1 H–C(2)); 2.84–2.79 (*m*, 1 H–C(6)); 2.72–2.69 (*m*, 1 H–C(6)); 2.62–2.58 (*m*, H–C(3)); 2.19 (*s*, *Me*CO); 2.09–2.08 (*m*, H–C(4)); 1.77–1.69 (*m*, 1 H–C(7)); 1.59–1.53 (*m*, 1 H–C(5), 1 H–C(7)); 1.50–1.44 (*m*, 1 H–C(5)). ^{13}C-NMR ($CDCl_3$) 170.11 (Me*C*O); 157.93 (C(6′)); 147.43 (CH(2′)); 144.83 (C(10′)); 143.39 (C(4′)); 131.80 (CH(8′)); 127.08 (C(9′)); 121.86 (CH(7′)); 119.29 (CH(3′)); 101.59 (CH(5′)); 97.81 (C(10)); 73.63 (CH(9)); 58.57 (CH(8)); 57.41 (CH_2(2)); 55.71 (*Me*O–C(6′)); 41.80 (CH_2(6)); 30.08 (C(11)); 27.06 (CH(3)); 26.13 (CH_2(7)); 24.92 (CH(4)); 21.06 (CH_2(5)). MS: 490 (53, M^+), 475 (3), 447 (9), 431 (13), 415 (2), 389 (2), 364 (64), 349 (7), 321 (30), 303 (100), 283 (9), 260 (53), 254 (29), 231 (19), 200 (17), 188 (89), 172 (31), 154 (19), 134 (64), 114 (53), 106 (22), 86 (64), 78 (72). HR-MS: 490.0759 ($[C_{22}H_{23}N_2O_3I]^+$; calc. 490.0753). Anal. calc. for $C_{22}H_{23}IN_2O_3$ (490.08): C 53.89, H 4.73, N 5.71; found: C 53.54, H 4.93, N 5.89.

(*1*S*,3*S*,4*S*,8*S*,9*R)*-11-Iodo-10,11-didehydro-6′-methoxycinchonan-9-ol* (**6a**). Morpholine (0.67 ml, 7.75 mmol, 6 equiv.) was added dropwise to a soln. of I_2 (984 mg, 3.88 mmol, 3 equiv.) in abs. toluene. After stirring at r.t. for 1 h, **4c** (416 mg, 1.29 mmol, 1 equiv.) was added. The mixture was stirred at 55° for 10 h, sat. aq. $NaHCO_3$ soln. was added, and the aq. layer was extracted with CH_2Cl_2. The combined org. layer was dried ($MgSO_4$) and evaporated, and the residue was purified by CC (AcOEt/MeOH 6:1): **6a** (95%, 550 mg). IR ($CHCl_3$): 3414, 2926, 2876, 1620, 1592, 1508, 1468, 1380, 1320, 1236, 1110, 1068, 1020, 824. ^{1}H-NMR ((D$_6$)DMSO): 8.74 (*d*, *J* = 4.6, H–C(2′)); 7.90 (*d*, *J* = 9.2, H–C(8′)); 7.75 (*d*, *J* = 4.6, H–C(3′)); 7.46 (*d*, *J* = 2.6, H–C(5′)); 7.37 (*dd*, *J* = 9.2, 2.6, H–C(7′)); 5.25 (*d*, *J* = 3.2, H–C(9)); 3.92 (*s*, 3 H–C(11′)); 3.78–3.74 (*m*, H–C(8)); 3.09–2.98 (*m*, 2 H–C(2)); 2.86–2.79 (*m*, 1 H–C(6)); 2.62–2.54 (*m*, 1 H–C(6)); 2.10 (*m*, H–C(3)); 1.88–1.81 (*m*, H–C(4)); 1.68–1.55 (*m*, H–C(7)); 1.51–1.32 (*m*, 3 H, H–C(5), H–C(7)). ^{13}C-NMR ((D$_6$)DMSO): 156.64 (C(6′)); 150.61 (C(10′)); 147.22 (CH(2′)); 143.87 (C(4′)); 130.92 (CH(8′)); 128.36 (C(9′)); 121.59 (CH(7′)); 118.70 (CH(3′)); 101.49 (CH(5′)); 97.43 (C(10)); 72.03 (CH(9)); 60.52 (CH(8)); 57.32 (CH_2(2)); 55.79 (CH_3(11′)); 41.95 (CH_2(6)); 36.26 (CH(3)); 31.71 (C(11)); 28.82 (CH_2(7)); 27.65 (CH(4)); 22.31 (CH_2(5)). MS: 448 (12, M^+), 322 (64), 307 (14), 283 (13), 265 (17), 254 (48), 236 (5), 189 (100), 173 (23), 160 (12), 134 (72), 117 (18), 106 (9), 91 (26), 75 (82); HR-MS: 448.0645 ($[C_{20}H_{21}N_2O_2I]^+$; calc. 448.0647).

*(1*S*,3*S*,4*S*,8*S*,9*R)-9-Acetoxy-10,11-didehydro-11-iodo-6′-methoxycinchonane* (**6b**). As described for **5a**, with morpholine (0.78 ml, 9.02 mmol, 6 equiv.), I_2 (1.14 g, 4.51 mmol, 3 equiv.), toluene (5 ml), and **4g** (550 mg, 1.50 mmol, 1 equiv.) (at 55° for 14 h). After addition of sat. aq. $NaHCO_3$ soln. and sat. aq. $Na_2S_2O_3$ soln. were added, the aq. layer was extracted with $CHCl_3$. CC (AcOEt/MeOH 10:1) gave **6b** (730 mg, 99%). IR (KBr): 2936, 2868, 1744, 1620, 1592, 1508, 1472, 1432, 1304, 1228, 1084, 1028, 852. ^{1}H-NMR ($CDCl_3$): 8.74 (*d*, *J* = 4.4, H–C(2′)); 8.02 (*d*, *J* = 9.2, H–C(8′)); 7.45 (*d*, *J* = 2.8, H–C(5′)); 7.38 (*d*, *J* = 4.2, H–C(3′)); 7.37 (*dd*, *J* = 9.3, 2.8, H–C(7′)); 6.48 (*d*, *J* = 7.7, H–C(9)); 3.96 (*s*, MeO–C(6′)); 3.58–3.52 (*m*, H–C(8)); 3.10–3.01 (*m*, H_{endo}–C(6), H_{exo}–C(2)); 2.79–2.73 (*m*, H_{endo}–C(2)); 2.68–2.62 (*m*, H–C(3)); 2.61–2.53 (*m*, H_{exo}–C(6)); 2.13 (*s*, MeCO); 2.12–2.05 (*m*, H_{exo}–C(7)); 2.03 (br. *s*, H–C(4)); 1.72–1.64 (*m*, H_{endo}–C(5)); 1.56–1.49 (*m*, H_{endo}–C(7)); 1.46–1.36 (*m*, H_{exo}–C(5)). ^{13}C-NMR ($CDCl_3$): 170.06 (Me*C*O); 157.90 (C(6′)); 147.37 (CH(2′)); 144.72 (C(4′)); 143.43 (C(10′)); 131.72 (CH(8′)); 127.03 (C(9′)); 121.89 (CH(7′)); 119.22 (CH(3′)); 101.50 (CH(5′)); 97.58 (C(10)); 87.67 (C(11)); 73.58 (CH(9)); 58.51 (CH(8)); 57.40 (CH_2(2)); 55.73 (*Me*O–C(6′)); 41.81 (CH_2(6)); 29.92 (CH(3)); 27.03 (CH(4)); 26.07 (CH_2(5)); 24.80 (CH_2(7)); 21.05 (*Me*CO). MS: 491 (3, $[M+H]^+$), 490 (8, M^+), 447 (2), 431 (2), 363 (17), 321 (4), 303 (42), 260 (100), 188 (30), 172 (14), 134 (51), 132 (57), 78 (34). HR-MS: 490.0746 ($[C_{22}H_{23}IN_2O_3]^+$; calc. 490.0753).

*(1*S*,3*S*,4*S*,8*R*,9*S*)-11-Chloro-10,11-didehydro-6′-methoxycinchonan-9-ol* (**5c**). KOH (150 mg, 2.68 mmol, 8.6 equiv.) was dissolved in 10% aq. NaOCl soln. at 0° and stirred for 30 min at 0°. After portionwise addition of **4a** (100 mg, 0.31 mmol, 1 equiv.), the mixture was stirred for 72 h at r.t. and extracted (sat. aq. $NaHCO_3$ soln., CH_2Cl_2). The combined org. layer was dried ($MgSO_4$) and evaporated, and the residue purified by CC (AcOEt/MeOH 4:1): **5c** (43 mg, 39%). IR ($CHCl_3$): 2948, 2872, 1620, 1592, 1508, 1472, 1432, 1364, 1320, 1240, 1136, 1104, 1084, 1032, 908, 640. ^{1}H-NMR ($CDCl_3$): 8.59 (*d*, *J* = 4.6, H–C(2′)); 7.94 (*d*, *J* = 9.8, H–C(8′)); 7.56 (*d*, *J* = 4.6, H–C(3′)); 7.28–7.24 (*m*, H–C(5′), H–C(7′)); 5.78 (*d*, *J* = 4.2, H–C(9)); 3.85 (*s*, MeO–C(6′)); 3.70–3.62 (*m*, H–C(8)); 3.17–3.06 (*m*, 2 H–C(2)); 2.94–2.85 (*m*, 1 H–C(6)); 2.76–2.68 (*m*, 1 H–C(6)); 2.41–2.35 (*m*, H–C(3)); 2.03–1.99 (*m*, H–C(4)); 1.56–1.49 (*m*, 1 H–C(7)); 1.28–1.24 (*m*, 1 H–C(5), 1 H–C(7));

1.07–1.05 (*m*, 1 H–C(5)). ^{13}C-NMR ($CDCl_3$): 157.19 (C(6′)); 147.87 (C(10′)); 147.37 (CH(2′)); 144.03 (C(4′)); 131.29 (CH(8′)); 126.59 (C(9′)); 121.64 (CH(7′)); 118.76 (CH(3′)); 101.21 (CH(5′)); 86.53 (C(10)); 70.73 (CH(9)); 59.91 (CH(8)); 55.80 (*Me*O–C(6′)); 49.99 (CH_2(2)); 49.32 (CH_2(6)); 31.22 (CH(3)); 45.85 (C(11)); 27.94 (CH(4)); 24.67 (CH_2(7)); 21.91 (CH_2(5)). MS: 356 (5, M^+), 333 (2), 321 (72), 306 (13), 283 (12), 265 (7), 250 (2), 237 (5), 213 (33), 200 (10), 189 (64), 173 (51), 160 (24), 134 (100), 117 (32), 106 (27), 91 (22), 77 (64). FAB-MS: 357 (38, $[M+H]^+$), 323 (100), 189 (14), 149 (36).

(1S,3S,4S,8R,9S)-11-Bromo-10,11-didehydro-6′-methoxycinchonan-9-ol (**5d**). Br_2 (0.1 ml, 1.96 mmol, 6 equiv.) was added dropwise to a soln. of KOH (400 mg, 7.14 mmol, 22 equiv.) in H_2O (2 ml) at 0°. The homogeneous soln. was stirred for 20 min at 0°, **4a** (105 mg, 0.33 mmol, 1 equiv.) added, and the resulting yellow mixture stirred for 24 h at r.t. After addition of sat. aq. $NaHCO_3$ soln., the aq. layer was extracted with CH_2Cl_2. The combined org. layer was dried ($MgSO_4$) and evaporated, and the residue purified by CC (AcOEt/MeOH 6:1): **5d** (108 mg, 83%). IR ($CHCl_3$): 3416, 2948, 2876, 1620, 1592, 1508, 1472, 1432, 1364, 1320, 1260, 1240, 1136, 1104, 1032, 828, 640, 608. ^{1}H-NMR ((D$_6$)DMSO): 8.69 (*d*, *J* = 4.4, H–C(2′)); 7.94 (*d*, *J* = 9.2, H–C(8′)); 7.49 (*m*, H–C(3′), H–C(5′)); 7.41 (*dd*, *J* = 9.2, 2.8, H–C(7′)); 5.78 (*d*, *J* = 4.8, H–C(9)); 3.91 (*s*, Me–C(6′)); 3.47–3.36 (*m*, H–C(8)); 3.09–3.03 (*m*, 1 H–C(2)); 2.88–2.82 (*m*, 1 H–C(2)); 2.57–2.48 (*m*, 2 H–C(6)); 2.06–2.00 (*m*, H–C(3)); 1.89–1.86 (*m*, H–C(4)); 1.58–1.36 (*m*, 2 H–C(7), 1 H–C(5)); 1.15–1.04 (*m*, 1 H–C(5)). ^{13}C-NMR ((D$_6$)DMSO): 159.88 (C(6′)); 152.10 (C(10′)); 150.67 (CH(2′)); 147.12 (C(4′)); 134.32 (CH(8′)); 130.19 (C(9′)); 124.15 (CH(7′)); 122.46 (CH(3′)); 105.48 (CH(5′)); 86.94 (C(10)); 73.88 (CH(9)); 63.31 (CH(8)); 58.50 (*Me*O–C(6′)); 52.11 (CH_2(2)); 51.57 (CH_2(6)); 48.34 (C(11)); 34.46 (CH(3)); 31.86 (CH_2(7)); 30.70 (CH(4)); 27.84 (CH_2(5)). MS: 402 (24, M^+), 400 (20), 385 (5), 371 (3), 343 (4), 321 (41), 307 (6), 293 (11), 283 (14), 263 (6), 250 (9), 236 (7), 214 (41), 212 (37), 189 (100), 173 (39), 159 (27), 132 (53), 117 (38), 106 (20), 91 (20), 78 (65). HR-MS: 400.0796 ($[C_{20}H_{21}BrN_2O_2]^+$; calc. 400.0786).

(1S,3S,4S,8S,9R)-11-Bromo-10,11-didehydro-6′-methoxychinchonan-9-ol (**6c**). As described for **5d**, with Br_2 (0.1 ml, 1.96 mmol, 6 equiv.), KOH (400 mg, 7.14 mmol, 22 equiv.) in H_2O (2 ml), and **4c** (105 mg, 0.33 mmol, 1 equiv.) in THF (0.2 ml) (14 h at r.t.). Workup with $CHCl_3$. The crude product was recrystallized from $CHCl_3$: **6c** (119 mg, 93%). IR ($CHCl_3$): 3606, 2952, 1622, 1592, 1509, 1473, 1432, 1260, 1241, 1230, 1032. ^{1}H-NMR ($CDCl_3$): 8.58 (*d*, *J* = 4.6, H–C(2′)); 7.89 (*d*, *J* = 9.2, H–C(8′)); 7.58 (*d*, *J* = 4.8, H–C(3′)); 7.27 (*dd*, *J* = 9.2, 2.8, H–C(7′)); 7.15 (*d*, *J* = 2.6, H–C(5′)); 5.57 (*d*, *J* = 2.9, H–C(9)); 3.84 (*s*, MeO–C(6′)); 3.67–3.60 (*m*, H–C(8)); 3.25–3.16 (*m*, H_{endo}–C(6), H_{exo}–C(2)); 2.88–2.82 (*m*, H_{endo}–C(2)); 2.67–2.56 (*m*, H_{exo}–C(6), H–C(3)); 2.04 (br. *s*, H–C(4)); 1.92–1.88 (*m*, H_{endo}–C(5), H_{exo}–C(7)); 1.64–1.56 (*m*, H_{endo}–C(7)); 1.48–1.39 (*m*, H_{exo}–C(5)). ^{13}C-NMR ($CDCl_3$): 157.92 (C(6′)); 148.10 (C(4′)); 147.10 (CH(2′)); 143.67 (C(10′)); 130.85 (CH(8′)); 126.50 (C(9′)); 121.87 (CH(7′)); 118.62 (CH(3′)); 101.17 (CH(5′)); 82.90 (C(10)); 77.20 (C(11)); 70.68 (CH(9)); 59.29 (CH(8)); 57.27 (CH_2(2)); 55.70 (*Me*O–C(6′)); 42.74 (CH_2(6)); 28.82 (CH(3)); 27.15 (CH(4)); 25.57 (CH_2(5)); 21.08 (CH_2(7)). MS: 402 (6), 400 (5, M^+), 385 (2), 323 (47), 283 (3), 214 (100), 212 (88), 189 (46), 172 (19), 158 (12), 132 (81), 117 (22), 78 (40). HR-MS: 400.0786 ($[C_{20}H_{21}BrN_2O_2]^+$; calc. 400.0786).

(1S,3S,4S,8R,9S,10Z)-11-Bromo-6′-methoxycinchonan-9-ol (**5e**). To a vigorously stirred soln. of *p*-toluenesulfonohydrazide (175 mg, 0.94 mmol, 2.3 equiv.) and $NaOAc \cdot 3\,H_2O$ (195 mg, 1.43 mmol, 3.5 equiv.) in THF/H_2O 1:1 (8 ml), **5d** (164 mg, 0.41 mmol, 1 equiv.) was added. The homogeneous mixture was stirred at 55° for 10 h under Ar, followed by addition of sat. aq. $NaHCO_3$ soln. and extraction of the aq. layer with CH_2Cl_2. The combined org. layer was dried ($MgSO_4$) and evaporated and the residue purified by CC (AcOEt/MeOH 4:1): **5e** (102 mg, 62%). IR ($CHCl_3$): 3268, 2952, 2876, 2836, 1620, 1592, 1508, 1472, 1432, 1364, 1324, 1308, 1240, 1136, 1096, 1032, 864, 832, 608. ^{1}H-NMR ($CDCl_3$): 8.54 (*d*, *J* = 4.5, H–C(2′)); 7.84 (*d*, *J* = 9.2, H–C(8′)); 7.53 (*d*, *J* = 4.6, H–C(3′)); 7.19 (*dd*, *J* = 9.2, 2.6, H–C(7′)); 7.13 (*d*, *J* = 2.6, H–C(5′)); 6.55 (*dd*, *J* = 8.2, 7.1, H–C(10)); 6.29 (*d*, *J* = 7.1, H–C(11)); 5.75 (*d*, *J* = 3.9, H–C(9)); 3.76 (*s*, MeO–C(6′)); 3.27–3.19 (*m*, H–C(8)); 3.14–3.01 (*m*, 1 H–C(2)); 2.91–2.83 (*m*, 1 H–C(6)); 2.72–2.63 (*m*, 1 H–C(2)); 2.58–2.52 (*m*, 1 H–C(6)); 2.36–2.29 (*m*, H–C(3)); 2.01–1.96 (*m*, H–C(4)); 1.80–1.72 (*m*, 1 H–C(7)); 1.54–1.42 (*m*, 1 H–C(5), 1 H–C(7)); 1.24–1.17 (*m*, 1 H–C(5)). ^{13}C-NMR ($CDCl_3$): 157.98 (C(6′)); 147.27 (CH(2′)); 145.86 (C(10′)); 143.85 (C(4′)); 135.34 (CH(11)); 131.18 (CH(8′)); 126.37 (C(9′)); 125.67 (CH(10)); 121.91 (CH(7′)); 118.79 (CH(3′)); 100.98 (CH(5′)); 69.83 (CH(9)); 59.75 (CH(8)); 55.82 (*Me*O–C(6′)); 49.18 (CH_2(2)); 48.91 (CH_2(6)); 28.89 (CH(3)); 27.79 (CH(4)); 24.26 (CH_2(7)); 21.55 (CH_2(5)). MS: 404 (12, M^+), 402 (13), 368 (11), 343 (7), 323 (14), 321 (14), 309 (10), 291 (9), 284 (8), 263 (6), 245 (8), 214 (26), 212 (7), 203 (20), 189 (28), 173 (17), 159 (13), 134 (12), 117 (10), 103 (13), 99 (44), 83 (100). HR-MS: 402.0940 ($[C_{20}H_{23}BrN_2O_2]^+$; calc. 402.0943).

(1S,3S,4S,8R,9S)-10,11-Didehydro-9-hydroxy-6′-methoxycinchonane-10-carbonitrile (**5f**). CuCN (89 mg, 1.00 mmol, 2 equiv.) in abs. DMF was stirred for 20 min at 50°. After addition of **5d** (200 mg, 0.5 mmol, 1 equiv.), the mixture was stirred for 12 h at 60°. Sat. aq. $NaHCO_3$ soln. was added and the aq. layer extracted with CH_2Cl_2. The combined org. layer was dried ($MgSO_4$) and evaporated and the residue purified by CC

(AcOEt/MeOH 6:1): **5f** (59 mg, 34%). IR ($CHCl_3$): 2956, 2876, 2272, 1620, 1592, 1508, 1472, 1432, 1360, 1320, 1304, 1240, 1136, 1088, 1032, 864, 832. ^{1}H-NMR ($CDCl_3/CD_3OD$): 878 (*d*, *J* = 4.6, H–C(2′)); 8.08 (*d*, *J* = 9.0, H–C(8′)); 7.59 (*d*, *J* = 4.6, H–C(3′)); 7.42 (*dd*, *J* = 9.0, 2.4, H–C(7′)); 7.59 (*d*, *J* = 2.4, H–C(5′)); 5.68 (*d*, *J* = 3.8, H–C(9)); 3.96 (*s*, MeO–C(6′)); 3.71–3.59 (*m*, H–C(8)); 3.25–3.06 (*m*, 2 H–C(2)); 2.89–2.64 (*m*, 2 H–C(6)); 2.28–2.23 (*m*, H–C(3)); 2.19–2.12 (*m*, H–C(4)); 1.64–1.52 (*m*, 1 H–C(7)); 1.48–1.28 (*m*, 1 H–C(5), 1 H–C(7)); 0.99–0.92 (*m*, 1 H–C(5)). ^{13}C-NMR ($CDCl_3/CD_3OD$): 157.93 (C(6′)); 147.82 (C(10′)); 147.33 (CH(2′)); 143.81 (C(4′)); 131.29 (CH(8′)); 128.50 (C(9′)); 121.42 (CH(7′)); 118.73 (CH(3′)); 114.22 (CN); 101.04 (CH(5′)); 91.02 (C(10)); 82.38 (C(11)); 71.69 (CH(9)); 59.46 (CH(8)); 55.81 (*Me*O–C(6′)); 49.88 (CH_2(2)); 48.35 (CH_2(6)); 36.07 (CH(3)); 29.14 (CH_2(7)); 27.96 (CH(4)); 22.38 (CH_2(5)). MS: 347 (2, M^+), 322 (1), 279 (15), 261 (10), 189 (3), 167 (33), 158 (1), 149 (100.00), 132 (3), 113 (12), 104 (7), 83 (10), 71 (21). HR-MS: 347.1631 ($[C_{21}H_{21}N_3O_2]^+$); calc. 347.1634).

(1S,4S,8R,9S)-3,10-Didehydro-6′-methoxycinchonan-9-ol (**5g**). Powdered KOH (52 mg, 0.93 mmol, 2 equiv.) and K_2CO_3 (129 mg, 0.93 mmol, 2 equiv.) were added to a soln. of **4a** (150 mg, 0.47 mmol, 1 equiv.) in abs. toluene (5 ml). The mixture was refluxed for 8 h in a *Dean-Stark* apparatus, followed by addition of sat. aq. $NaHCO_3$ soln. The aq. layer was extracted with CH_2Cl_2, the combined org. layer dried ($MgSO_4$) and evaporated, and the residue purified by CC (AcOEt/MeOH 4:1): **5g** (82 mg, 55%). IR ($CHCl_3$): 2956, 2872, 1960, 1672, 1620, 1592, 1508, 1472, 1432, 1384, 1360, 1296, 1240, 1172, 1136, 1108, 1076, 1028, 1004, 848. ^{1}H-NMR ($CDCl_3$): 8.64 (*d*, *J* = 4.6, H–C(2′)); 7.98 (*d*, *J* = 9.2, H–C(8′)); 7.56 (*d*, *J* = 4.4, H–C(3′)); 7.33 (*dd*, *J* = 9.2, 2.7, H–C(7′)); 7.23 (*d*, *J* = 2.6, H–C(5′)); 5.79 (*d*, *J* = 3.2, H–C(9)); 4.80–4.76 (*m*, 1 H–C(11)); 3.89 (*s*, MeO–C(6′)); 3.53–3.46 (*m*, H–C(8)); 3.30–3.22 (*m*, 1 H–C(2)); 3.14–2.90 (*m*, 2 H–C(6)); 2.63–2.57 (*m*, 1 H–C(2)); 2.21–2.15 (*m*, H–C(4)); 1.71–1.59 (*m*, 1 H–C(7)); 1.51–1.42 (*m*, 1 H–C(7)); 1.40–1.29 (*m*, 1 H–C(5)); 0.98–0.92 (*m*, 1 H–C(5)). ^{13}C-NMR ($CDCl_3$): 199.07 (C(10)); 159.34 (C(3)); 157.85 (C(6′)); 147.48 (CH(2′)); 147.02 (C(10′)); 144.12 (C(4′)); 131.52 (CH(8′)); 126.19 (C(9′)); 121.66 (CH(7′)); 118.49 (CH(3′)); 101.06 (CH(5′)); 71.05 (CH(9)); 68.17 (CH_2(11)); 59.29 (CH(8)); 55.82 (*Me*O–C(6′)); 50.79 (CH_2(2)); 48.17 (CH_2(6)); 29.48 (CH(4)); 25.69 (CH_2(7)); 22.98 (CH_2(5)). MS: 322 (4, M^+), 292 (7), 273 (2), 263 (17), 250 (6), 238 (11), 210 (6), 198 (7), 189 (58), 173 (100), 167 (30), 158 (40), 149 (44), 134 (4), 106 (2), 82 (15), 70 (19). Anal. calc. for $C_{20}H_{22}N_2O_2$ (322.40): C 74.05, H 7.43, N 8.64; found: C 74.46, H 7.79, N 8.29.

(1S,3S,4S,8R,9S)-10,11-Didehydro-11-(hydroxymethyl)-6′-methoxycinchonan-9-ol (**5h**). Under Ar, 1.6M BuLi (0.43 ml, 0.68 mmol, 2.2 equiv.) in hexane was added dropwise to a soln. of **4a** (100 mg, 0.31 mmol, 1 equiv.) in abs. THF (5 ml) at −78°. The mixture was stirred at −78° for 15 min, warmed to 0°, and stirred for further 15 min. Dry paraformaldehyde (14 mg, 0.47 mmol, 1.5 equiv.) was added, and the homogeneous soln. was stirred for 1 h at 40°. Then, sat. aq. $NaHCO_3$ soln. was added, the aq. layer extracted with $CHCl_3$, the combined org. layer dried ($MgSO_4$) and evaporated, and the residue purified by CC (AcOEt/MeOH 4:1): **5h** (95 mg, 87%). IR ($CHCl_3$): 3388, 3000, 2944, 2872, 1672, 1620, 1592, 1508, 1456, 1432, 1388, 1320, 1260, 1228, 1172, 1136, 1092, 1028, 832. ^{1}H-NMR (CD_3OD): 8.67 (*d*, *J* = 4.6, H–C(2′)); 7.95 (*d*, *J* = 9.2, H–C(8′)); 7.67 (*d*, *J* = 4.6, H–C(3′)); 7.48 (*d*, *J* = 2.6, H–C(5′)); 7.42 (*dd*, *J* = 9.2, 2.6, H–C(7′)); 5.63 (*d*, *J* = 5.0, H–C(9)); 4.27–4.24 (*m*, CH_2OH); 3.97 (*s*, MeO–C(6′)); 3.62–3.53 (*m*, H–C(8)); 3.22–3.14 (*m*, H–C(2)); 3.08–2.97 (*m*, 1 H–C(2)); 2.76–2.69 (*m*, 1 H–C(6)); 2.67–2.61 (*m*, 1 H–C(6)); 2.44–2.37 (*m*, H–C(3)); 1.96–1.92 (*m*, H–C(4)); 1.60–1.53 (*m*, 2 H–C(7)); 1.43–1.27 (*m*, 2 H–C(5)). ^{13}C-NMR (CD_3OD): 160.05 (C(6′)); 150.76 (C(10′)); 148.69 (CH(2′)); 145.36 (C(4′)); 131.84 (CH(8′)); 128.89 (C(9′)); 123.85 (CH(7′)); 120.83 (CH(3′)); 103.06 (CH(5′)); 88.68 (C(10)); 81.46 (C(11)); 72.74 (CH(9)); 69.31 (CH_2OH); 61.56 (CH(8)); 56.84 (*Me*O–C(6′)); 51.59 (CH_2(2)); 50.69 (CH_2(6)); 29.93 (CH(3)); 29.61 (CH(4)); 26.21 (CH_2(7)); 23.83 (CH_2(5)). MS: 352 (35, M^+), 335 (4), 323 (4), 307 (2), 283 (4), 244 (9), 230 (9), 214 (3), 202 (8), 189 (17), 172 (14), 164 (100), 160 (88), 133 (38), 117 (1), 91 (2). FAB-MS: 353 (79, $M+H]^+$), 189 (9), 167 (16), 149 (100), 136 (26).

(1S,3S,4S,8R,9S,10Z)-11-Iodo-6′-methoxycinchonan-9-ol (**5i**). As described for **5e**, with **5a** (209 mg, 0.47 mmol, 1 equiv.), *p*-toluenesulfonohydrazide (182 mg, 0.98 mmol, 2.1 equiv.), $NaOAc \cdot 3\,H_2O$ (200 mg, 1.47 mmol, 3.2 equiv.), and THF/H_2O 1:1 (6 ml) (at 60° for 6 h). Extraction with $CHCl_3$ and CC (AcOEt/MeOH 6:1) gave **5i** (124 mg, 59%). IR ($CHCl_3$): 3008, 2952, 2872, 1672, 1620, 1592, 1508, 1472, 1432, 1392, 1364, 1300, 1260, 1240, 1112, 1080, 1032, 1008, 864, 832. ^{1}H-NMR ($CDCl_3$): 8.68 (*d*, *J* = 4.6, H–C(2′)); 7.93 (*d*, *J* = 9.2, H–C(8′)); 7.63 (*d*, *J* = 4.6, H–C(3′)); 7.25 (*dd*, *J* = 9.2, 2.6, H–C(7′)); 7.11 (*d*, *J* = 2.7, H–C(5′)); 6.68–6.64 (*dd*, *J* = 7.9, 6.7, H–C(10)); 6.40–6.38 (*dd*, *J* = 7.7, 1.3, H–C(11)); 6.08 (*s*, H–C(9)); 3.91–3.84 (*m*, H–C(8)); 3.73 (*s*, MeO–C(6′)); 3.29–3.20 (*m*, 1 H–C(2)); 3.17–3.09 (*m*, 1 H–C(6)); 3.07–2.99 (*m*, 1 H–C(6)); 2.75–2.66 (*m*, 1 H–C(2)); 2.35–2.31 (*m*, H–C(3)); 2.27–2.20 (*m*, H–C(4)); 1.97–1.93 (*m*, 1 H–C(7)); 1.89–1.74 (*m*, 1 H–C(7)); 1.64–1.53 (*m*, 1 H–C(5)); 1.16–1.08 (*m*, 1 H–C(5)). ^{13}C-NMR ($CDCl_3$): 157.88 (C(6′)); 147.92 (C(10′)); 147.26 (CH(2′)); 143.85 (C(4′)); 131.35 (CH(8′)); 128.72 (C(9′)); 125.67 (CH(10)); 121.68 (CH(7′)); 118.38 (CH(3′)); 100.50 (CH(5′)); 83.66 (CH(11)); 69.19 (CH(9)); 59.48 (CH(8)); 55.82

(MeO–C(6′)); 49.59 (CH_2(2)); 48.40 (CH_2(6)); 40.34 (CH(3)); 26.85 (CH(4)); 24.61 (CH_2(7)); 21.21 (CH_2(5)). MS: 450 (39, M^+), 433 (6), 323 (54), 295 (8), 283 (10), 262 (100), 254 (19), 226 (6), 214 (10), 189 (42), 172 (30), 160 (14), 149 (17), 135 (50), 117 (21), 107 (13), 91 (20), 80 (41), 70 (16). HR-MS: 450.0807 ($[C_{20}H_{23}IN_2O_2]^+$; calc. 450.0804).

*(1*S*,3*S*,4*S*,8*R*,9*S*,10*Z*)-9-Acetoxy-11-iodo-6′-methoxycinchonane* (**5k**) *and (1*S*,3*R*,4*S*,8*R*,9*S*)-9-Acetoxy-10,11-dihydro-11-iodo-6′-methoxycinchonane* (**5l**). As described for **5e**, with **5b** (980 mg, 2.00 mmol, 1 equiv.), *p*-toluenesulfonohydrazide (856 mg, 4.6 mmol, 2.3 equiv.), NaOAc · 3H_2O (952 mg, 7.0 mmol, 3.5 equiv.), and THF/H_2O 1:1 (20 ml) (at 65° for 4 h). Extraction with $CHCl_3$ and CC (AcOEt/MeOH 20:1) yielded **5k** (640 mg, 65%) and **5l** (79 mg, 8%) as by-product.

Data for **5k**: IR ($CHCl_3$): 3002, 2944, 2876, 2836, 1744, 1660, 1620, 1592, 1508, 1472, 1456, 1432, 1372, 1304, 1264, 1236, 1184, 1084, 1068, 1032, 988, 844. ^{1}H-NMR ($CDCl_3$): 8.78 (*d*, *J* = 4.6, H–C(2′)); 8.07 (*d*, *J* = 9.9, H–C(8′)); 7.44–7.40 (*m*, H–C(7′), H–C(5′)); 7.37 (*d*, *J* = 4.6, H–C(3′)); 6.64–6.61 (*d*, *J* = 6.6, H–C(9)); 6.61–6.57 (*dd*, *J* = 7.9, 7.3, H–C(10)); 6.40–6.38 (*dd*, *J* = 7.4, 0.9, H–C(11)); 3.99 (*s*, MeO–C(6′)); 3.79–3.70 (*m*, H–C(8)); 3.42-3.35 (*m*, 1 H–C(2)); 3.20–3.14 (*dd*, *J* = 13.8, 10.3, H–C(2)); 2.97–2.81 (*m*, 2 H–C(6)); 2.67–2.60 (*m*, H–C(3)); 2.19 (*s*, MeCO); 1.94–1.86 (*m*, H–C(4), 2 H–C(7)); 1.69–1.56 (*m*, 2 H–C(5)). ^{13}C-NMR ($CDCl_3$): 169.82 (Me*C*O); 158.04 (C(6′)); 147.37 (CH(2′)); 144.73 (C(10′)); 143.32 (C(4′)); 131.84 (CH(8′)); 128.91 (CH(10)); 126.88 (C(9′)); 121.94 (CH(7′)); 118.43 (CH(3′)); 101.32 (CH(5′)); 82.92 (CH(11)); 73.28 (CH(9)); 58.68 (CH(8)); 55.74 (*Me*O–C(6′)); 49.78 (CH_2(2)); 48.63 (CH_2(6)); 41.16 (CH(3)); 26.99 (CH(4)); 25.76 (CH_2(7)); 23.80 (CH_2(5)); 21.16 (*Me*CO). MS: 492 (24, M^+), 477 (1), 449 (2), 433 (5), 365 (11), 339 (2), 325 (7), 305 (6), 284 (2), 262 (41), 233 (13), 218 (6), 198 (49), 188 (15), 172 (8), 150 (19), 135 (18), 106 (9), 91 (100), 80 (14). HR-MS: 492.0913 ($[C_{22}H_{25}IN_2O_3]^+$; calc. 492.0909.

Data for **5l**: IR ($CHCl_3$): 2944, 2868, 1744, 1672, 1624, 1592, 1508, 1472, 1456, 1432, 1372, 1304, 1232, 1112, 1084, 1068, 1032, 844. ^{1}H-NMR ($CDCl_3$): 8.75 (*d*, *J* = 4.4, H–C(2′)); 8.04 (*d*, *J* = 9.2, H–C(8′)); 7.44 (*d*, *J* = 2.6, H–C(5′)); 7.41–7.37 (*m*, H–C(7′), H–C(3′)); 6.61 (*d*, *J* = 5.9, H–C(9)); 3.99 (*s*, MeO–C(6′)); 3.70–3.64 (*m*, 2 H–C(11)); 3.62–3.55 (*dd*, *J* = 14.2, 5.5, 1 H–C(2)); 3.46–3.37 (*ddd*, *J* = 14.8, 5.0, 3.8, 1 H–C(2)); 3.35–3.26 (*m*, H–C(8)); 2.85–2.76 (*m*, 1 H–C(6), 1 H–C(2)); 2.72–2.64 (*m*, 1 H–C(6)); 2.21 (*s*, MeCO); 2.19–2.16 (*m*, H–C(3)); 2.04–2.01 (*m*, H–C(4)); 1.90–1.79 (*m*, 1 H–C(7)); 1.62–1.43 (*m*, 2 H–C(5), 1 H–C(7), 2 H–C(10)). ^{13}C-NMR ($CDCl_3$): 169.82 (MeCO); 158.17 (C(6′)); 147.37 (CH(2′)); 144.27 (C(10′)); 143.70 (C(4′)); 131.78 (CH(8′)); 126.73 (C(9′)); 121.94 (CH(7′)); 118.29 (CH(3′)); 101.36 (CH(5′)); 73.76 (CH(9)); 58.95 (CH(8)); 55.83 (*Me*O–C(6′)); 49.50 (CH_2(2)); 46.64 (CH_2(6)); 41.73 (CH_2(10)); 30.40 (CH(3)); 27.93 (CH(4)); 25.46 (CH_2(7)); 23.54 (CH_2(5)); 21.30 (*Me*CO); 3.82 (CH_2(11)). MS: 494 (10, M^+), 452 (2), 435 (9), 412 (1), 390 (1), 365 (58), 350 (8), 326 (20), 305 (48), 280 (14), 254 (33), 231 (12), 211 (8), 188 (56), 167 (30), 149 (76), 134 (61), 115 (67), 86 (100), 70 (44).

*(1*S*,3*S*,4*S*,8*S*,9*R*,10*Z*)-9-Acetoxy-11-iodo-6′-methoxycinchonane* (**6d**). As described for **5e**, with **6b** (240 mg, 0.49 mmol, 1 equiv.), *p*-toluenesulfonohydrazide (182 mg, 0.98 mmol, 2.3 equiv.), and NaOAc · 3 H_2O (200 mg, 1.47 mmol, 3.5 equiv.) in THF/H_2O 1:1 (6 ml) (reflux for 4 h). Extraction with $CHCl_3$ and CC (AcOEt/MeOH 20:1) yielded **6d** (151 mg, 63%). IR ($CHCl_3$): 2952, 2868, 1744, 1620, 1592, 1508, 1472, 1432, 1372, 1300, 1276, 1236, 1084, 1032, 908. ^{1}H-NMR ($CDCl_3$): 8.75 (*d*, *J* = 4.4, H–C(2′)); 8.02 (*d*, *J* = 9.2, H–C(8′)); 7.45 (*d*, *J* = 2.6, H–C(5′)); 7.38 (*dd*, *J* = 9.3, 2.6, H–C(7′)); 7.35 (*d*, *J* = 4.6, H–C(3′)); 6.52 (*d*, *J* = 6.8, H–C(9)); 6.27 (*dd*, *J* = 7.6, 7.4, H–C(10)); 6.22 (*d*, *J* = 7.4, H–C(11)); 3.96 (*s*, MeO–C(6′)); 3.39–3.31 (*m*, H–C(8)); 3.20 (*dd*, *J* = 13.1, 9.2, H_{exo}–C(2)); 3.16–3.07 (*m*, H_{endo}–C(6)); 2.74–2.65 (*m*, H_{endo}–C(2)); 2.62–2.50 (*m*, H_{exo}–C(6), H–C(3)); 2.14 (*s*, MeCO); 1.93 (br. *s*, H–C(4)); 1.85–1.57 (*m*, 2 H–C(7), 2 H–C(5)). ^{13}C-NMR ($CDCl_3$): 169.97 (Me*C*O); 157.99 (C(6′)); 147.42 (CH(2′)); 144.75 (C(4′)); 144.25 (CH(10)); 143.50 (C(10′)); 131.83 (CH(8′)); 126.97 (C(9′)); 121.81 (CH(7′)); 118.66 (CH(3′)); 101.43 (CH(5′)); 82.54 (CH(11)); 73.60 (CH(9)); 59.41 (CH(8)); 56.84 (CH_2(2)); 55.70 (*Me*O–C(6′)); 42.38 (CH_2(6)); 41.23 (CH(3)); 27.23 (CH_2(5)); 26.22 (CH(4)); 24.62 (CH_2(7)); 21.08 (*Me*CO). MS: 492 (3, M^+), 433 (3), 325 (2), 305 (4), 262 (100), 211 (4), 188 (11), 172 (8), 135 (41). HR-MS: 492.0908 ($[C_{22}H_{25}IN_2O_3]^+$; calc. 492.0909).

REFERENCES

[1] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

[2] A. Nelson, *Angew. Chem.* **1999**, *111*, 1685; E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414; E. J. Corey, Y. Bo, J. Busch-Petersen, *J. Am. Chem. Soc.* **1998**, *120*, 13000.

[3] B. Christensen, *J. Prakt. Chem.* **1904**, 217.

[4] G. W. Gribble, *Acc. Chem. Res.* **1998**, *31*, 141.

[5] L. E. Overman, D. Lesuisse, M. Hashimoto, *J. Am. Chem. Soc.* **1983**, *105*, 5373; S. C. Carey, M. Aratani, Y. Kishi, *Tetrahedron Lett.* **1985**, *26*, 5887.
[6] M. P. Cabal, R. S. Coleman, S. J. Danishefsky, *J. Am. Chem. Soc.* **1990**, *112*, 3253; J. N. Haseltine, S. J. Danishefsky, *J. Org. Chem.* **1990**, *55*, 2576; A. L. Smith, E. N. Pitsinos, C.-K. Hwang, Y. Mizuno, H. Saimoto, G. R. Scarlato, T. Suzuki, K. C. Nicolaou, *J. Am. Chem. Soc.* **1993**, *115*, 7612; R. D. Groneberg, T. Miyazaki, N. A. Stylianides, T. J. Schulze, W. Stahl, E. P. Schreiner, T. Suzuki, Y. Iwabuchi, A. L. Smith, K. C. Nicolaou, *J. Am. Chem. Soc.* **1993**, *115*, 7593.
[7] K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto, H. Nozaki, *J. Am. Chem. Soc.* **1986**, *108*, 6048; C. Crevisy, J. M. Beau, *Tetrahedron Lett.* **1991**, *32*, 3171; A. G. Myers, P. M. Harrington, E. Y. Kuo, *J. Am. Chem. Soc.* **1991**, *113*, 694.
[8] D. Michelot, *Synthesis*, **1983**, 130; F. Björkling, T. Norin, R. Unelius, *Synth. Commun.* **1985**, *15*, 463.
[9] F. X. Erben, E. Philippi, N. Schniderschitz, *Chem. Ber.* **1925**, *58*, 2854; H. C. Kretschmar, W. F. Erman, *Tetrahedron Lett.* **1970**, *11*, 41; A. A. Schriesheim, C. A. Rowe, *J. Am. Chem. Soc.* **1962**, *84*, 3160.
[10] E. V. Dehmlow, M. Lissel, *Tetrahedron* **1981**, *37*, 1653.
[11] H. Wynberg, A. Smaardijk, *J. Org. Chem.* **1987**, *52*, 135.
[12] G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Marko, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 8069; G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, *J. Org. Chem.* **1990**, *55*, 6121; P. Norrby, H. C. Kolb, K. B. Sharpless, *J. Am. Chem. Soc.* **1994**, *116*, 8470.
[13] O. Schrake, W. M. Braje, H. M. R. Hoffmann, R. Wartchow, *Tetrahedron Asymm.* **1998**, *9*, 3717.
[14] J. A. Berson, M. S. Poonian, W. J. Libbey, *J. Am. Chem. Soc.* **1969**, *91*, 5567; H. A. Dieck, R. F. Heck, *J. Org. Chem.* **1975**, *40*, 1083.
[15] S. R. Landor, P. Forche Asobo, Z. Tanee Fomum, R. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1991**, 1201.
[16] J. Pohlmann, C. Sabater, H. M. R. Hoffmann, *Angew. Chem.* **1998**, *110*, 656; *Angew. Chem., Int. Ed.* **1998**, *37*, 633.
[17] S. Wagner, W. Beil, U. E. H. Mai, C. Bokemeyer, H. J. Meyer, M. P. Manns, *Pharmacology* **1994**, *49*, 226.
[18] M. R. Grever, S. A. Schepartz, B. A. Chabner, *Semin. Oncol.* **1992**, *19*, 622.
[19] P. Langer, J. Frackenpohl, H. M. R. Hoffmann, *J. Chem. Soc., Perkin Trans. 1* **1998**, 801; W. M. Braje, J. Frackenpohl, P. Langer, H. M. R. Hoffmann, *Tetrahedron* **1998**, *54*, 3495.

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