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TETRAHEDRON

Synthesis of Oxazatwistanes and their Homo- and Bishomo-Analogues from Quinidine – Medium Ring Systems Derived from Cinchona Alkaloids

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Dedicated to Professor Peter Welzel on the occasion of his 60th birthday

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Abstract: Suitable functionalization of the vinyl group of quinidine (**1a**) allows cyclization involving the C9 hydroxyl group, giving novel 6-, 7- and 8-membered rings containing a distorted 1-azabicyclo-[2.2.2]octane framework. TIPS-triflate mediated cyclization of hydroxyaldehydes **13a** and **15b** to silylated tricyclic hemiacetals **14** and **16** is superior to an intramolecular S_N2-approach, especially for the formation of 7- and 8-membered rings.

Introduction. *Cinchona* alkaloids and their derivatives are used for ligand accelerated catalysis (LAC) in a variety of enantioselective reactions, as in the asymmetric dihydroxylation (AD) or asymmetric aminohydroxylation (AA) of olefins.[1,2] One aspect of their utility is their bidentate nature which allows optimal binding to transition metals.[3] Twisting of the azabicyclo[2.2.2]octane moiety is known to influence binding of the basic bridgehead nitrogen to metal d^0 oxo species such as OsO_4.[4] We have therefore synthesized a series of oxazatwistanes and higher twistanes of the monohomo and bishomo type. These compounds are diastereomerically pure and conformationally and configurationally defined. They also contain a strained medium ring ether subunit, which we introduced in the final step of the synthesis.

Results. A useful first step in the preparation of metabolites of quinidine turned out to be the reaction of quinidine with fuming (62%) HBr.[5] The secondary epimeric bromides **2a** and **2b** are the major products. To our surprise, an inseparable mixture of tricyclic ethers **3a** and **3b** was formed also, but in low yield (< 10%). The ethers proved to be very polar and were easy to overlook, since on chromatography they hardly moved from the

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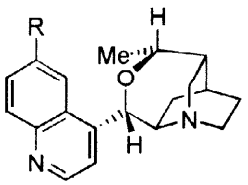
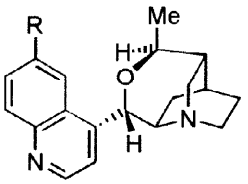
baseline. We thought it desirable to develop a more rational and efficient route to these ring ethers with a view to studying their conformation and configuration.



3a R = OMe
3c R = OH
3e R = H



3b R = OMe
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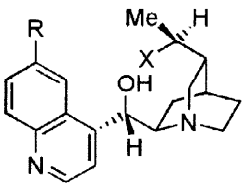
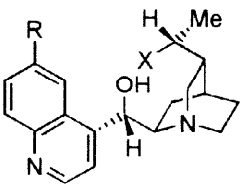


2a R = OMe, X = Br
2c R = OH, X = I
2e R = H, X = I

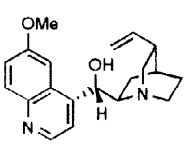
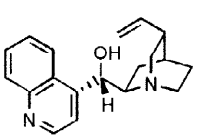
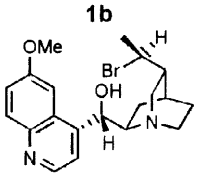


2b R = OMe, X = Br
2d R = OH, X = I
2f R = H, X = I

Scheme 1. Quinoline substituted homo-oxazatwistanes and halogen derivatives of quinidine

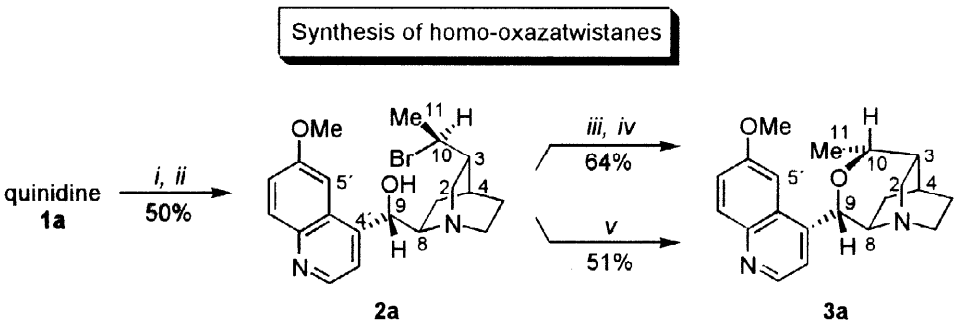
Exploratory work on quinidine **1a** with HBr generated *in situ* gave the tricyclic ethers **3a** (47%) and **3b** (10%) under optimized conditions (Table 1, entry 7). A change to HI (Table 1, entry 8) provided a complex reaction mixture containing not only the desired ethers **3a** and **3b**, but also the C6′- hydroxy quinolines **3c** and **3d** and the secondary epimeric iodides **2c** and **2d**.

Table 1. Synthesis of Quinoline Substituted Homo-oxazatwistanes

Alkaloid	Entry	Reaction Conditions	Homotwistanes **3a-f** (Yield [%])	Halogenated Alkaloids **2a-f** (Yield [%])
 **1a**	1	HCl (37%), 25 °C, 3 d	–	–
	2	H_2SO_4 (98%), 25 °C, 3 d	**3a**, **3b** (14)	–
	3	HBr (48%), 25 °C, 4 d	–	**2a**, **2b** (18)
	4	HBr (55%), 25 °C, 3 d	–	**2a**, **2b** (34)
	5	HBr (62%), 25 °C, 4 d	**3a** (10), **3b** (2)	**3a** (50), **3b** (31)
	6	HI (57%), 25 °C, 3 d	–	**2c**, **2d** (13)
	7	KBr, H_3PO_4, 100 °C, 3 d	**3a** (47), **3b** (10)	–
	8	KI, H_3PO_4, 100 °C, 3 d	**3a**, **3b** (32); **3c**, **3d** (15)	**2c**, **2d** (15)
	9	NaI, TMSCl, H_2O, 25 °C, 6 h	–	–
	10	$Pd(OAc)_2$, $Cu(OAc)_2$, O_2, MeOH, 25 °C, 4 d	–	–
	11	$Hg(OAc)_2$, HOAc, $NaBH_4$, NaOH, 25 °C, 3 d	–	–
 **1b**	12	KI, H_3PO_4, 100 °C, 24 h		**2e**, **2f** (29)
 **2a**	13	NaH, THF, 0 °C → r.t., 2 d; $NaHCO_3$, H_2O	**3a** (51)	–
	14	$AgBF_4$, THF, 0 °C → r.t., 4 h; Et_3N, KI, MeOH	**3a** (64)	–

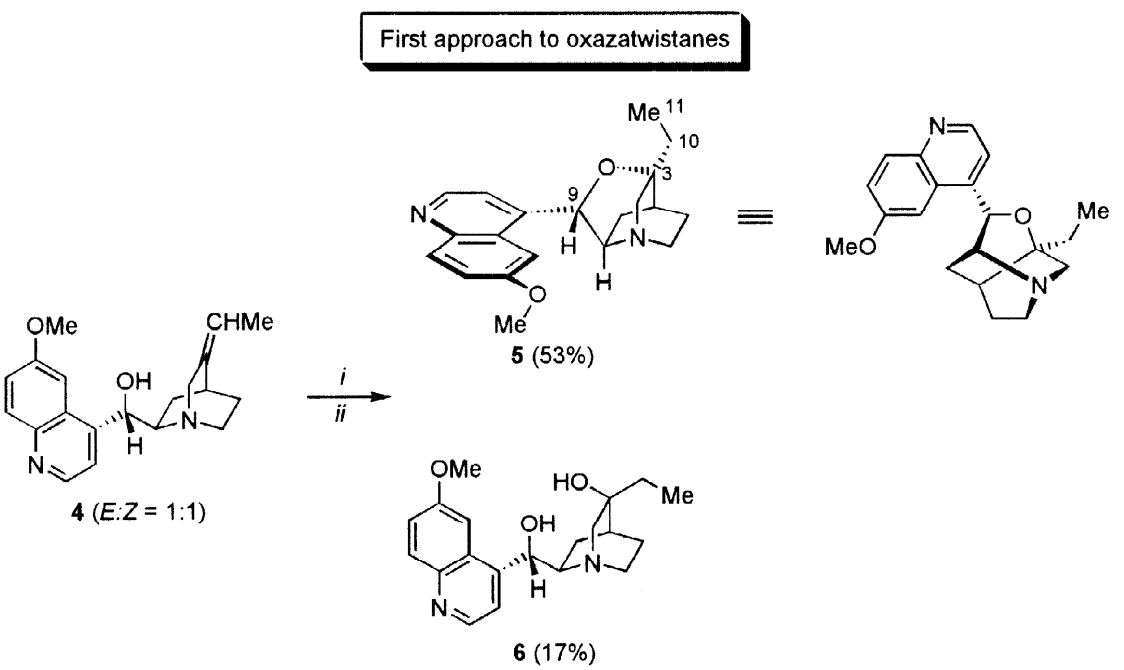
We were pleased to find that the NaH-assisted cyclization of hydroxy bromide **2a** proved to be stereospecific, affording just one diastereomerically pure tricyclic ether **3a** in satisfactory yield (51%) (entry 13).

Due to a stronger activation of secondary bromide **2a**, a change of reaction conditions ($AgBF_4$, THF, entry 14) provided even higher yields (64%) of **3a**, although the reaction was more difficult to carry out. Interestingly, the conversion of **2a** into **3a** was again stereospecific, S_N2 like (Scheme 2). Leakage into epimeric ether **3b** was not observed. Furthermore, although conformationally constrained γ-aminobromide **2a** has been reported to undergo the Grob fragmentation with opening of the azabicyclic cage,[6] this reaction did not occur under our conditions.



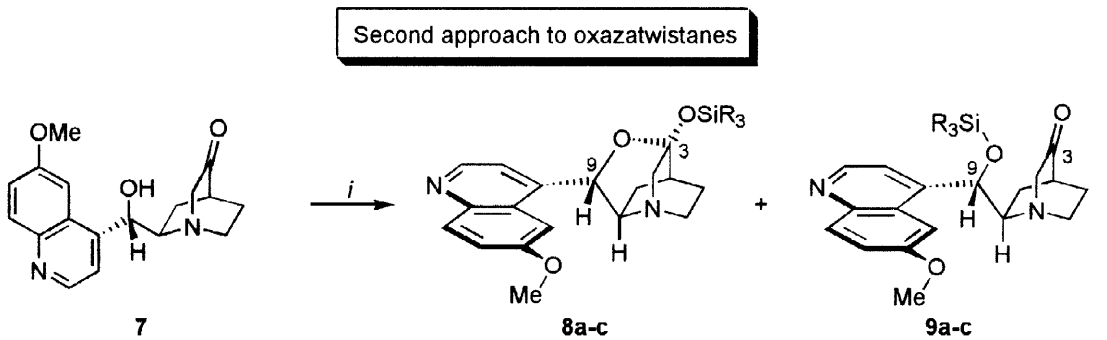
Scheme 2. Reagents and conditions: *i*, HBr (62%), 3 d, r.t.; *ii*, KOH (25%), $NaHCO_3$; *iii*, $AgBF_4$, THF, 0 °C → r.t., 4 h; *iv*, Et_3N, KI, MeOH; *v*, NaH, THF, 0 °C → r.t., 2 d.

In order to prepare the lower homologue, i.e. the oxazatwistane system **5** itself, we treated the readily accessible isoquinidines[5] *E*-**4** and *Z*-**4** with HBr generated *in situ*, obtaining **5** as a major product (53%). Diol **6** was a byproduct, which was probably formed on aqueous workup (Scheme 3). The 7-membered ring **3a** was not discerned.



Scheme 3. Reagents and conditions: *i*, KBr, H_3PO_4, 3 d, 100 °C; *ii*, KOH (25%), $NaHCO_3$

In a completely different approach we investigated the protection of rubanone **7** with silylating agents.[7] Treatment with TBDS-chloride afforded the expected O-protected rubanone **9b**, and TMS-triflate gave the corresponding trimethylsilylated rubanone **9a**. However, a change of silylating agent from Me_3SiOTf to sterically more hindered Me_2Bu^tSiOTf gave O-silylated rubanone **9b** as a minor product only (14%). The major product was, in fact, the oxazatwistane **8b** (68%), which can also be regarded as an azaglycoside (Scheme 4). The sterically even more hindered Pr^i_3SiOTf (TIPS-triflate) gave no silylated product at all, but tricycle **8c** in 88% yield (Table 2).



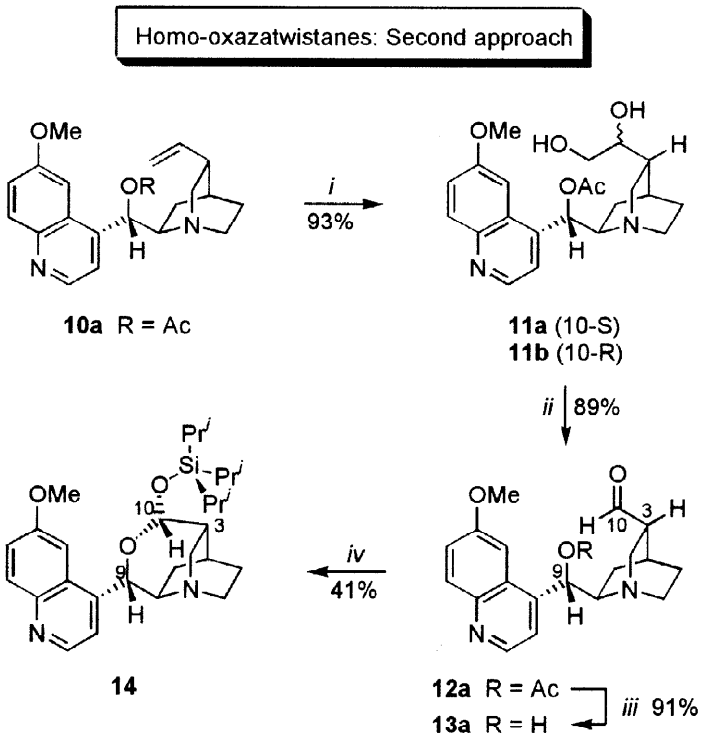
Scheme 4. Reagents and conditions: *i*, R_3SiOTf (1.3 eq), 2,6-lutidine (2.0 eq), CH_2Cl_2, 0 °C

Both the silicon counterion (chloride vs. triflate) and the nature of the trialkylsilyl group influence the position of ring-chain tautomerism of rubanone **7** and its azaglycosidic subunit, as it appears in **8b** and **8c**. A sterically demanding trialkylsilyl triflate as well as high *Lewis* acidity are mandatory for generating the oxazatricyclic cage. The very bulky triisopropylsilyl group is forced onto the periphery of the molecule, giving oxazatwistane **8c** in excellent yield.

Table 2. Reaction of Unprotected Rubanone **7** with Silylating Agents

SiR_3	Oxazatwistane	Yield [%]	Protected Rubanone	Yield [%]
$SiMe_3$	**8a**	0	**9a**	72
$SiMe_2Bu^t$	**8b**	68	**9b**	14
$SiPr^i_3$	**8c**	88	**9c**	0

In the course of the synthesis of Brevetoxin B Nicolaou has constructed 7-ring ethers from ε-hydroxy ketones by ionic hydrogenation under aprotic conditions.[8] In this case simple Me_3SiOTf, in the presence of Et_3SiH as hydride ion donor was successful. By comparison, bicyclic δ-hydroxy ketone **7**, on treatment with Me_3SiOTf and Et_3SiH, provided bicyclic TMS-protected rubanone **9a** rather than a *tricyclic* oxazatwistane. In any case, expulsion of silanoxide from azaglycoside **8b** and **8c** would have to generate a bridgehead carbocation which is assumed to be unstable.



Scheme 5. Reagents and conditions: *i*, OsO_4 (cat.), K_2CO_3, $K_3[Fe(CN)_6]$, ^tBuOH / H_2O (1:1), RT, 4 h; *ii*, $NaIO_4$, CH_2Cl_2, SiO_2, H_2O, RT, 1 h; *iii*, K_2CO_3, MeOH, 20 min, RT; *iv*, $^iPr_3SiOTf$ (1.3 eq), 2,6-lutidine (2.0 eq), CH_2Cl_2, 0 °C → 25 °C, 14 h.

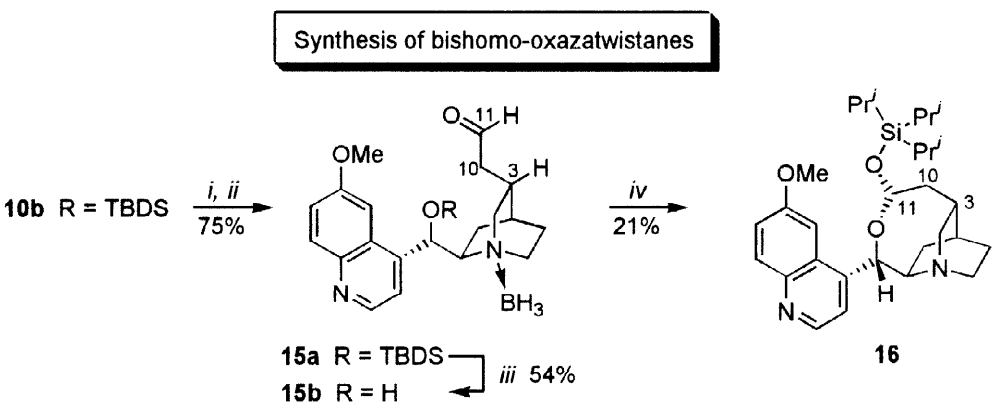
We extended the approach outlined in Scheme 4 to the synthesis of homo-oxazatwistanes (Scheme 5). The required aldehyde **13a** had to be epimerically pure with respect to carbon C3. It was eventually obtained by an optimized two-step route from acetylated quinidine **10a**.

Table 3. Optimized Conditions for Preparation of Rubane Carbaldehyde **12a**

Entry	Reaction Conditions[a]	Yield [%]	Ratio of **12a** and **epi-12b** [%]
1	MnO_2, CH_2Cl_2, r.t.	0	–
2	$Pb(OAc)_4$, xylene, r.t.	58	50 : 50
3	H_5IO_6, H_2O, 0 °C	0	–
4	OsO_4, $NaIO_4$, THF, H_2O, r.t.[b]	74	50 : 50
5	$(^nBu)_4NIO_4$, CH_2Cl_2, r.t.	78	80 : 20
6	$NaIO_4$, HOAc, r.t.	80	55 : 45
7	$NaIO_4$, H_2O, CH_2Cl_2, r.t.[c]	85	50 : 50
8	$NaIO_4$, SiO_2, CH_2Cl_2, r.t.	81	88 : 12
9	$NaIO_4$, SiO_2, H_2O, CH_2Cl_2, r.t.	89	>95 : 5

[a]Reaction time: 30 min; starting material: 1:1 mixture of diastereomeric diols **11a** and **11b**.
[b]Starting material: Acetylated quinidine **10a**. [c]Starting material: deprotected triol **11-OH**

Dihydroxylation of **10a** under two-phase conditions[9] furnished a 1:1 mixture of epimeric diols **11a** and **11b**. Periodate cleavage under standard and other conditions invariably provided an epimeric mixture of rubane carbaldehydes **12a** and **12b** (Table 3, entries 1 - 7).[10] For the preparation of epimerically pure acetylated aldehyde **12a** it was crucial to first coat wet silica gel with $NaIO_4$ and then add the diol at room temperature.[11] In this fashion, the yield of aldehyde was improved also (Table 3, entries 8 - 9). Deacetylation of **12a** with methanolic K_2CO_3 provided ε-hydroxyaldehyde **13a**. TIPS triflate promoted cyclisation furnished the desired silylated hemiacetal **14** with defined configuration of carbon C-10 (41% yield). As shown in Scheme 7 the bulky silyloxy group adopts the exocyclic position, away from the tricyclic cage.

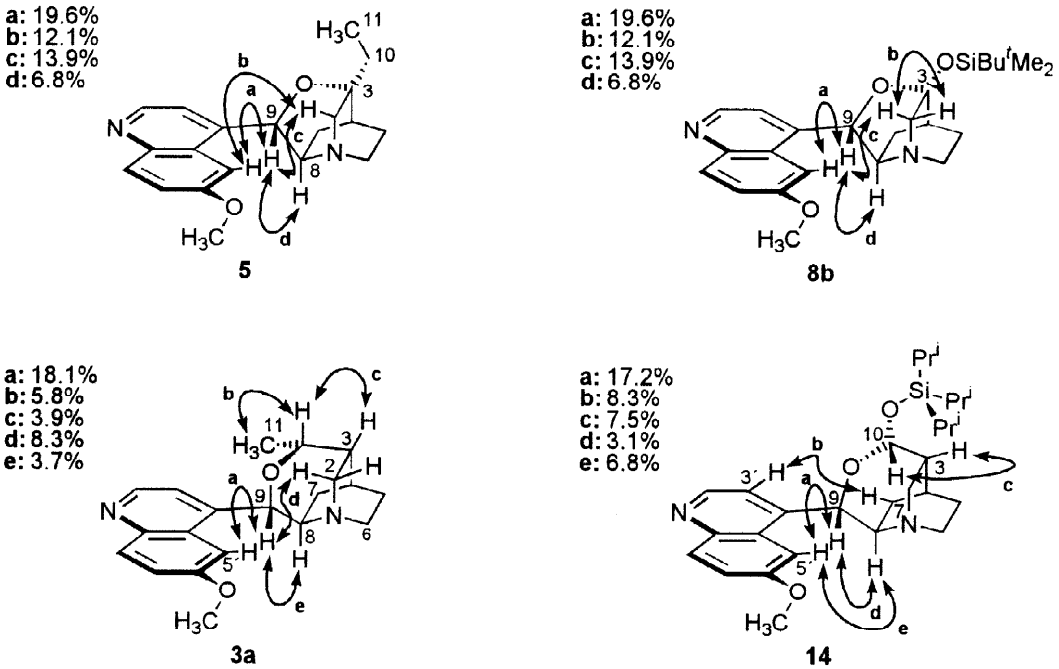


Scheme 6. Reagents and conditions: *i*, BH_3 (4.0 eq), THF, 0 °C, 6 h (97%); *ii*, PCC/SiO_2, CH_2Cl_2, 0 °C → 25 °C, 5 h (76%); *iii*, TBAF, THF, 10 h, RT; *iv*, $^iPr_3SiOTf$ (1.3 eq), 2,6-lutidine (2.0 eq), CH_2Cl_2, 0 °C → 25 °C, 14 h.

In order to test our cyclization methodology we converted TBDS-protected quinidine **10b** *via* hydroboration and PCC/SiO_2-mediated oxidation[12] into the homologous aldehyde **15a** followed by a TBAF deprotection. Even in this case the eight-membered hemiacetal **16** was formed (21%). The conventional S_N2-approach to the corresponding eight membered ring, analogous to the preparation of seven-membered system (**2a** → **3a**) was not successful.

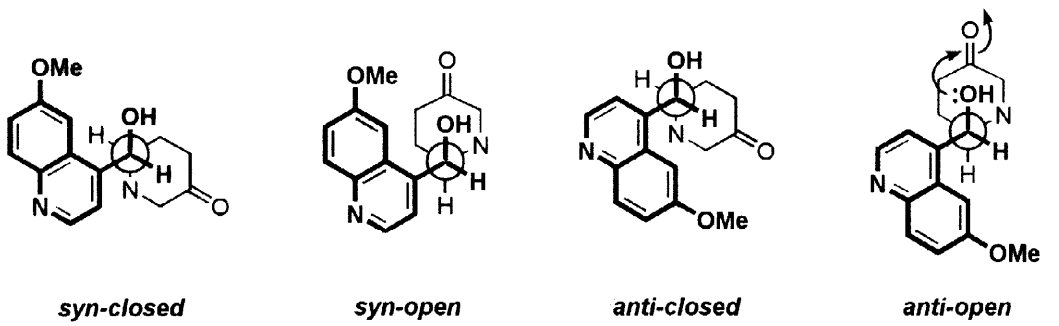
Spectroscopic investigation of oxazatwistanes and their homo-analogues. Conformational analysis of *Cinchona* alkaloids has been undertaken to elucidate their catalytic and chemical properties.[13] In our studies, configuration and conformation of tricyclic cages were determined by NOE, ^1H NMR and ^{13}C NMR spectroscopy. The configuration at carbon C10 in monohomotwistane **3a** was established by NOEs H10-H3 (3.9%) and H10-H11 (5.8%). Confirmatory evidence was provided by ^3J (H3-H10) coupling (2 Hz). In epimer **3b** a corresponding coupling could not be discerned. Furthermore, in **3a** H10 appeared as a double quartet, whereas in **3b** a simple quartet was observed. The calculated coupling constants ^3J (H3-H10) (4 Hz) and ^3J (H3-H11) (6 Hz) in **3a** were in agreement with the obtained coupling constants. In homotwistane **14** the

configuration at C10 was established similarly. NOEs of H10 with $H2_{endo}$ (5.4%), H9 (4.7%) and H3 (7.5%) show that H10 points to the inside of the tricyclic cage (Scheme 7).



Scheme 7. NOE analysis of tricyclic *Cinchona* alkaloids

In addition, all four cage compounds **5**, **8b**, **3a** and **14** feature strong NOEs of H5′ with H9 (15.8 to 19.6%). In the case of homotwistane **14** a strong NOE between H3′and H7 (8.3%) was observed, too. Both NOEs elucidate the horizontal position of the 6′-methoxyquinoline qroup (Scheme 7) resulting in an *anti* conformation. Necessarily, the conformation in the rigid oxazatwistane system is *open*. The horizontal position can be explained by reduced rotational mobility about the C4′-C9 single bond, due to the sterically demanding 6′-substituted quinoline qroup attached to the tricyclic moiety. Because of the proximity of C9-alcohol and C3-carbonyl functionality in the *anti-open* conformation (Scheme 8), precursor **13a** (Scheme 5) is well set up for the observed cyclization. Therefore, the *anti-open* conformation of carbonyl precursor **13a** is frozen in the tricyclic cage.



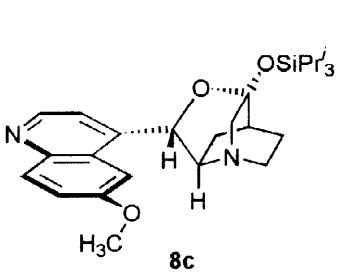
Scheme 8. The four major conformations of *Cinchona* alkaloids (rubanone 7)

As a supplement to the NOE analysis we present diagnostic spectroscopic data of our *Cinchona* twistanes in Table 4.

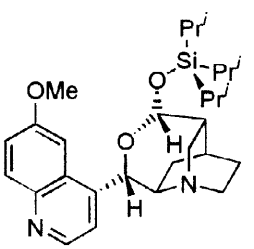
Table 4. Characteristic Spectroscopic Data of *Cinchona* Twistanes

Cinchona Twistane	δ H-9	δ C-9	δ C-O-C9	M^+ [%]
3a	6.05	79.08	72.54	100.0
5	6.03	72.87	78.27	77.4
8b	5.98	74.45	102.21	66.6
8c	6.08	74.03	99.18	71.5
14	6.12	73.66	99.47	17.8
16	6.59	70.27	90.33	1.4

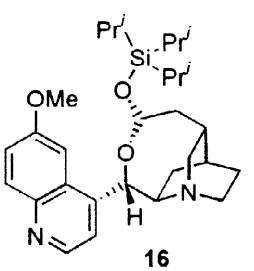
Of the various oxazatricyclic cages we have prepared the parent oxazatwistane **8c** was formed in the highest yield. MM2 calculations suggest that the increase in strain on going from **8c** to homologous 7-membered system **14** is moderate [ΔE(**14**) - ΔE(**8c**) = 5.6 kJ/mol]. Accordingly, the homotwistane system **14** was accessible in good yield (28% from quinidine over 5 steps; Scheme 9). However, formation of the 8-membered ring **16** is accompanied by a significantly higher ΔE(**16**) - ΔE(**14**) = 13.8 kJ/mol and is also entropically unfavourable. Whereas the classical S_N2 approach to the bishomotwistane system **16** failed, TIPS-OTf mediated cyclization (cf. also ref. 8) appears to be of general preparative utility (21% in the final step).



8c



14



16

ΔE(**14**) - ΔE(**8c**) = 5.6 kJ/mol[14] ΔE(**16**) - ΔE(**14**) = 13.8 kJ/mol[14]

Tricyclic Hemiketal	Steps from Quinidine	Total Yield [%]
8c	7	47
14	5	28
16	5	8

Scheme 9. Synthesis of *Cinchona* twistanes from quinidine

EXPERIMENTAL

General. Melting points were determined on a Büchi apparatus and are uncorrected. – Infrared spectra were recorded on a Perkin-Elmer 1710 infrared spectrometer. – ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer in deuterated chloroform unless otherwise stated, with tetramethylsilane as internal standard. – Mass spectra were recorded on a Finnigan MAT 312 (70 eV) or a VG Autospec spectrometer. – Microanalyses were performed in the Department of Organic Chemistry of the University of Hannover. – Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30 - 60 µm). – Analytical TLC was carried out on aluminum-backed 0.2-mm silica gel 60 F_{254} plates (E. Merck). – DMF was dried over BaO, distilled over calcium hydride under reduced pressure and stored over 4Å molecular sieves. THF was distilled over sodium and benzophenone before use. Ethyl acetate (EA), methanol and methyl *t*-butyl ether (MTBE) were distilled before use. – Compounds **4** and **7** were prepared as described previously.[5,15,16]

Preparation of Halogenated Alkaloids **2a-d** *and Homotwistanes* **3a-d**. *Method A.* To conc. HBr (62%, 5 ml) was added quinidine (1.0 g, 3.1 mmol) portionwise at 0 °C. When quinidine had been dissolved completely the cooling bath was removed and the reaction mixture was stirred for 4 d at r.t.. Then water (5 ml) was added and the mixture was neutralized with aq. KOH solution (25%, perfusor, 30 ml/h). The aqueous phase was extracted with $CHCl_3$, the organic layer dried ($MgSO_4$) and coated on silica gel. Chromatography (EA/MeOH, 6:1) afforded the ring ethers **3a** and **3b** (119 mg altogether, 12%) [the ratio of **3a/3b** was determined by ^{1}H NMR spectroscopy] and the bromides **2a** (625 mg, 50%) and **2b** (373mg, 30%). Scale-up (31 mmol) afforded **2a** (6.27 g, 51%), **2b** (3.69 g, 30%) and **3a/3b** (5:1) (1.22 g, 12%). *Method B.* Quinidine (324 mg, 1.00 mmol) was added to HBr (48%, 5 ml) at 0 °C. After removal of the cooling bath the mixture was stirred for 3 d at r.t., then water was added (5 ml). Aqueous KOH solution (25%) was added until pH 10 was reached. The aqueous phase was extracted with $CHCl_3$, the organic layer dried ($MgSO_4$) and purified by chromatography (MTBE/MeOH, 5:1) to give the bromo derivative **2a** and **2b** in low yield (74 mg, 18%). *Method C.* Quinidine (324 mg, 1.0 mmol) was added portionwise to a solution of KI (498 mg, 3.00 mmol) in H_3PO_4 (85%, 5 ml) at 0 °C. The mixture was stirred for 30 min at r.t. and then for 3 d at 100 °C. After being cooled to r.t. the mixture was treated with aqueous KOH (25) until pH 10 was reached. The aqueous layer was extracted with $CHCl_3$ and the combined organic layers were washed with sat. aq. $NaHCO_3$ solution, dried ($MgSO_4$) and chromatographed (MTBE/MeOH, 5:1) to afford **2c** and **2d** (68 mg, 15%), **3a/3b** (4:1) 104 mg, 32%) and **3c** (46 mg, 15%). *Method D.* Quinidine (324 mg, 1.0 mmol) was added portionwise to a solution of KBr (354 mg, 3.00 mmol) in conc. H_3PO_4 (85%, 5 ml) at 0 °C. The mixture was stirred for 3 d at 100 °C. After being cooled to r.t. the mixture was treated with aqueous KOH (25%) until pH 11 was reached. The aqueous layer was extracted with $CHCl_3$ and the combined organic phase was washed with sat. aq. $NaHCO_3$ solution, dried ($MgSO_4$) and chromatographed (EA/MeOH, 6:1) to afford **3a** (152 mg, 47%) and **3b** (33 mg, 10%). *Method E.* To a solution of quinidine (324 mg, 1.00 mmol) in CH_2Cl_2 (5 ml) was added H_2SO_4 (98%, 2 ml) slowly at 0 °C. The homogeneous mixture was stirred for 3 d at r.t. and then neutralized with aq. KOH solution (25%, perfusor, 30 ml/h). The aqueous phase was extracted with $CHCl_3$, the organic layer dried ($MgSO_4$) and chromatographed to afford **3a/3b** (45 mg, 14%). *Method F.* To a suspension of dry, fine-powdered $AgBF_4$ (194 mg, 1.0 mmol) in THF (3 ml) was added **2a** (202 mg, 0.5 mmol) in THF (2 ml) under argon at 0 °C. The mixture was stirred for 4 h at r.t. under exclusion of light. The excess HBF_4 was destroyed with Et_3N (0.13 ml, 1.0 mmol) and Ag^+ was precipitated with KI (200 mg, 1.2 mmol). The salts were filtered off, the residue washed with EA and MeOH and the combined organic layer was dried ($MgSO_4$). Chromatography (EA/MeOH, 7:1) yielded **3a** (103 mg, 64%). *Method G.* To a suspension of NaH (24 mg, 1.0 mmol) in THF (3 ml) was added **2a** (202 mg, 0.5 mmol) in THF (2 ml) at 0 °C. The reaction mixture was stirred for 2 d at r.t.. Water was added and stirring continued

for 30 min. The aqueous phase was extracted with $CHCl_3$, the organic layer dried ($MgSO_4$) and purified by chromatography to give **3a** (83 mg, 51%) as a colourless solid. *Method H.* Quinidine (324 mg, 1.00 mmol) was added to HI (57%, 5 ml) at 0 °C. After removal of the cooling bath the mixture was stirred for 3 d at r.t., then water was added (5 ml). Aqueous KOH solution (25%) was added until pH 10 was reached. The aqueous phase was extracted with $CHCl_3$, the organic layer dried ($MgSO_4$) and purified by chromatography (MTBE/MeOH, 5:1) to give the iodo derivative **2c/2d** in low yield (59 mg, 13%).

(8R,9S,10S)-10-Bromo-10,11-dihydro-6′-methoxy-cinchonan-9-ol (**2a**) and *(8R,9S,10R)-10-Bromo-10, 11-dihydro-6′-methoxy-cinchonan-9-ol* (**2b**). Data for **2a**, $[\alpha_D]^{20}$ = + 223.75° (*c* 1.12, $CHCl_3$). IR (KBr) ν 3420, 2928, 2852, 2544, 1620, 1592, 1508, 1460, 1432, 1392, 1328, 1240, 1132, 1100, 1024, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, CD_3OD) δ 8.62 (d, *J* = 4 Hz, H-2′), 7.91 (d, *J* = 9 Hz, H-8′), 7.60 (d, *J* = 4 Hz, H-3′), 7.21 (dd, *J* = 2, 9 Hz, H-7′), 6.89 (d, *J* = 2 Hz, H-5′), 6.43 (s, H-9), 4.53 (m, H-10), 4.33 (m, H-8), 3.62 (s, 3 H-11′), 3.50-2.90 (m, H-2_{endo}, H-2_{exo}, 2 H-6), 2.30-2.06 (m, 2 H-7, H-4), 2.01 (d, *J* = 6 Hz, 3 H-11), 1.80-1.60 (m, 2 H-5), 0.99 (m, H-3); ^{13}C NMR (100 MHz, $CDCl_3$, CD_3OD) δ 158.09 (C, C-6′), 147.18 (CH, C-2′), 146.93 (C, C-10′), 143.90 (C, C-4′), 131.40 (CH, C-8′), 126.18 (C, C-9′), 122.46 (CH, C-7′), 118.69 (CH, C-3′), 100.77 (CH, C-5′), 70.16 (CH, C-9), 59.81 (CH, C-8), 56.52 (CH_3, C-11′), 54.40 (CH, C-10), 50.64 (CH_2, C-6), 49.71 (CH_2, C-2), 45.72 (CH, C-3), 25.65 (CH, C-4), 25.42 (CH_3, C-11), 25.29 (CH_2, C-7), 18.78 (CH_2, C-5); MS (200°C) *m/z* 406 (M^+, 1), 404 (1), 326 (3), 325 (9), 324 (25), 283 (5), 201 (3), 189 (23), 174 (6), 173 (14), 172 (9), 160 (8), 137 (17), 136 (100), 117 (9), 95 (7), 82 (11), 81 (19); HRMS calcd. for $C_{20}H_{25}N_2O_2Br$: 406.1079, found 406.1095. Anal. Calcd. for $C_{20}H_{25}N_2O_2Br$: C 59.39, H 6.23, N 6.93; found C 59.40, H 6.11, N 6.86. Data for **2b**, mp 102 °C (decomp.), $[\alpha_D]^{20}$ = + 118.34° (*c* 0.545, $CHCl_3$). IR (KBr) ν 3420, 2928, 2852, 2544, 1620, 1592, 1508, 1460, 1432, 1392, 1328, 1240, 1132, 1100, 1024, 716 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.59 (d, *J* = 4 Hz, H-2′), 7.90 (d, *J* = 9 Hz, H-8′), 7.65 (d, *J* = 4 Hz, H-3′), 7.30 (dd, *J* = 2, 9 Hz, H-7′), 6.98 (d, *J* = 2 Hz, H-5′), 6.41 (s, H-9), 4.63 (dt, *J* = 1, 6 Hz, H-10), 4.15 (m, H-8), 3.51 (s, 3 H-11′), 3.45-2.95 (m, H-2_{endo}, H-2_{exo}, 2 H-6), 2.57 (m, H-4), 2.30-2.00 (m, 2 H-7), 1.80-1.60 (m, 2 H-5), 1.62 (d, *J* = 6 Hz, 3 H-11), 1.02 (m, H-3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.42 (C, C-6′), 147.36 (CH, C-2′), 147.18 (C, C-10′), 143.93 (C, C-4′), 131.40 (CH, C-8′), 126.18 (C, C-9′), 122.09 (CH, C-7′), 118.34 (CH, C-3′), 100.61 (CH, C-5′), 70.16 (CH, C-9), 59.73 (CH, C-8), 56.52 (CH_3, C-11′), 51.03 (CH, C-10), 50.34 (CH_2, C-6), 49.71 (CH_2, C-2), 45.72 (CH, C-3), 25.65 (CH, C-4), 25.42 (CH_3, C-11), 25.29 (CH_2, C-7), 18.78 (CH_2, C-5); MS (200°C) *m/z* 406 (M^+, 1), 404 (1), 326 (3), 325 (9), 324 (25), 283 (5), 201 (3), 189 (23), 174 (5), 173 (14), 172 (9), 160 (8), 137 (17), 136 (100), 117 (9), 95 (7), 82 (11), 81 (19).

(8R,9S,10R)-10,11-Dihydro-9,10-epoxy-6′-methoxy-cinchonane (**3a**) *and (8R,9S,10S)-10,11-Dihydro-9,10-epoxy-6′-methoxy-cinchonane* (**3b**). Data for **3a**, mp 118 °C (decomp.). IR (KBr) ν 3072, 2932, 2876, 2544, 1620, 1592, 1508, 1475, 1380, 1232, 1192, 1168, 1132, 1100, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4 Hz, H-2′), 8.05 (d, *J* = 9 Hz, H-8′), 7.65 (d, *J* = 4 Hz, H-3′), 7.39 (dd, *J* = 2, 9 Hz, H-7′), 7.36 (d, *J* = 2 Hz, H-5′), 5.95 (s, H-9), 4.26 (dq, *J* = 2, 6 Hz, H-10), 3.97 (s, 3 H-11′), 3.74 (d, *J* = 15 Hz, H-2_{endo}), 3.42 (d, *J* = 9 Hz, H-8), 3.19 (m, 2 H-6), 2.84 (m, H-2_{exo}), 2.43 (m, H-3), 2.38 (m, H-4), 1.85 (m, H-7), 1.71 (m, 2 H-5), 1.51 (d, *J* = 6 Hz, 3 H-11), 1.29 (m, H-7); NOE H-10 irradiated: H-9 (0.5), H-11 (5.8), H-3 (3.9), H-2_{endo} (2.8); H-9 irradiated: H-10 (3.3), H-8 (3.7), H-2_{endo} (8.3), H-5′ (18.1); H-11 irradiated: H-10 (3.8), H-7 (2.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.89 (C, C-6′), 147.60 (CH, C-2′), 146.05 (C, C-10′), 144.10 (C, C-4′), 131.61 (CH, C-8′), 126.03 (C, C-9′), 120.93 (CH, C-7′), 117.55 (CH, C-3′), 102.12 (CH, C-5′), 79.18 (CH, C-9), 72.62 (CH, C-10), 62.16 (CH, C-8), 55.94 (CH_3, C-11′), 51.36 (CH_2, C-2), 46.93 (CH_2, C-6), 39.07 (CH, C-3), 25.54 (CH_2, C-7), 23.11 (CH, C-4), 22.45 (CH_2, C-5), 20.96 (CH_3, C-11); MS (120°C) *m/z* 324 (M^+, 100), 309 (M^+-Me, 25), 295 (31), 281 (11), 265 (11), 241 (12), 214 (6), 187 (13), 173 (9), 159 (13), 138 (32), 136 (10), 122 (19), 111 (21), 109 (11), 95 (15), 84 (26), 77 (5), 69 (25); FAB-MS *m/z* 324 (M^+, 100), 309

(M^+-Me, 29), 295 (30); HRMS calcd. for $C_{20}H_{24}N_2O_2$: 324.1838, found 324.1835. Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C 74.05, H 7.46, N 8.46; found C 74.02, H 7.51, N 8.63. Data for **3b**, mp 118 °C. IR (KBr) ν 3072, 2932, 2876, 2544, 1620, 1592, 1508, 1475, 1308, 1232, 1192, 1168, 1132, 1100, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, J = 4 Hz, H-2′), 8.07 (d, J = 9 Hz, H-8′), 7.79 (d, J = 4 Hz, H-3′), 7.40 (dd, J = 2, 9 Hz, H-7′), 7.36 (d, J = 2 Hz, H-5′), 6.05 (s, H-9), 4.20 (q, J = 6 Hz, H-10), 3.98 (s, 3 H-11′), 3.69 (m, H-2_{endo}), 3.42 (d, J = 9 Hz, H-8), 3.20-3.00 (m, 2 H-6), 2.84 (m, H-2_{exo}), 2.40 (m, H-3), 2.32 (m, H-4), 1.62 (m, H-7), 1.55 (m, 2 H-5), 1.48 (d, J = 6 Hz, 3 H-11), 1.37 (m, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.68 (C, C-6′), 147.67 (CH, C-2′), 144.03 (C, C-10′), 143.28 (C, C-4′), 131.80 (CH, C-8′), 126.13 (C, C-9′), 121.69 (CH, C-7′), 117.26 (CH, C-3′), 102.07 (CH, C-5′), 79.08 (CH, C-9), 72.50 (CH, C-10), 62.39 (CH, C-8), 55.88 (CH_3, C-11′), 51.06 (CH_2, C-6), 47.33 (CH_2, C-2), 39.43 (CH, C-3), 23.54 (CH_2, C-7), 22.19 (CH, C-4), 21.07 (CH_2, C-5), 21.07 (CH_3, C-11); MS (120°C) *m/z* 324 (M^+, 100), 309 (M^+-Me, 25), 295 (31), 281 (11), 265 (11), 241 (12), 214 (6), 187 (13), 173 (9), 159 (13), 138 (32), 136 (10), 122 (19), 111 (21), 109 (11), 95 (15), 84 (26), 77 (5), 69 (25). Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C 74.05, H 7.46, N 8.46; found C 73.89, H 7.62, N 8.59.

(8R,9S,10R)-10,11-Dihydro-10-iodo-6′-methoxy-cinchonan-9-ol (**2c**), *(8R,9S,10S)-10,11-Dihydro-10-iodo-6′-methoxy-cinchonan-9-ol* (**2d**). IR (KBr) ν 3392, 2932, 2876, 2544, 1620, 1592, 1508, 1468, 1432, 1328, 1232, 1132, 1100, 1032, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 4 Hz, H-2′), 7.97 (d, J = 9 Hz, H-8′), 7.59 (d, J = 4 Hz, H-3′), 7.22 (dd, J = 2, 9 Hz, H-7′), 7.17 (d, J = 2 Hz, H-5′), 6.43 (s, H-9), 6.02 (s, OH), 4.63 (m, H-10), 4.15 (m, H-8), 3.90 (s, 3 H-11′), 3.40-2.98 (m, H-2_{endo}, H-2_{exo}, 2 H-6), 2.57 (m, H-4), 2.30-2.00 (m, 2 H-7), 1.80-1.60 (m, 2 H-5), 1.56 (d, J = 6 Hz, 3 H-11), 0.95 (m, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.09 (C-6′), 147.18 (C-2′), 147.93 (C-10′), 143.90 (C-4′), 131.40 (C-8′), 125.96 (C-9′), 122.44 (C-7′), 118.69 (C-3′), 100.80 (C-5′), 70.16 (C-9), 60.00 (C-8), 57.45 (C-11′), 50.64 (C-6), 49.97 (C-2), 45.72 (C-3), 32.39 (C-10), 25.65 (C-4), 25.42 (C-11), 25.29 (C-5), 18.79 (C-7); MS (200°C) *m/z* 323 (M^+- I, 26), 283 (5), 202 (2), 189 (23), 173 (12), 158 (6), 136 (100), 129 (19), 116 (9), 95 (7), 81 (19).

(8R,9S,10R)-10,11-Dihydro-9,10-epoxy-6′-hydroxy-cinchonane (**3c**) *and (8R,9S,10S)-10,11-Dihydro-9,10-epoxy-6′-hydroxy-cinchonane* (**3d**). IR (KBr) ν 3264, 2932, 2876, 1620, 1592, 1508, 1468, 1432, 1316, 1232, 1192, 1168, 1132, 1100, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 4 Hz, H-2′), 8.08 (d, J = 9 Hz, H-8′), 7.79 (d, J = 4 Hz, H-3′), 7.38 (dd, J = 2, 9 Hz, H-7′), 7.21 (d, J = 2 Hz, H-5′), 6.04/5.95 (s, H-9), 4.26 (dq, J = 1, 6 Hz, H-10)/4.20 (q, J = 6 Hz, H-10), 3.98/3.95 (s, 3 H-11′), 3.69 (m, H-2_{endo}), 3.42 (d, J = 9 Hz, H-8), 3.20-3.05 (m, 2 H-6, H-2_{endo}), 2.84 (m, H-3), 2.35 (m, 2 H-7), 1.87-1.52 (m, 2 H-5, H-4), 1.51 (d, J = 6 Hz, 3 H-11) sowie 1.48 (d, J = 6 Hz, 3 H-11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.68 (C-6′), 146.78 (C-2′), 144.03 (C-10′), 143.28 (C-4′), 131.58 (C-8′), 126.13 (C-9′), 120.83 (C-7′), 117.30 (C-3′), 102.07 (C-5′), 79.08 (C-9), 73.04 (C-10), 62.39 (C-8), 51.06 (C-6), 47.33 (C-2), 39.43 (C-3), 23.54 (C-7), 22.19 (C-4), 21.07 (C-5), 20.95 (C-11); MS (120°C) *m/z* 309 (M^+, 100), 295 (3), 267 (8), 238 (3), 173 (3), 159 (3), 138 (4), 122 (3), 111 (5), 95 (4), 81 (5).

(8R,9S,10S)-10,11-Dihydro-10-iodo-cinchonan-9-ol (**2e**), *(8R,9S,10R)-10,11-Dihydro-10-iodo-cinchonan-9-ol* (**2f**), *(8R,9S,10R)-10,11-Dihydro-9,10-epoxy-cinchonane* (**3e**) *and (8R,9S,10S)-10,11-Dihydro-9,10-epoxy-cinchonane* (**3f**). Cinchonine (294 mg, 1.00 mmol) was allowed to react according to *method C* to afford after chromatography (EA/MeOH, 3:1) **2e** and **2f** (212 mg, 50%) and **3e** and **3f** (85 mg, 29%). Data for **2e**, **f**. IR (KBr) ν 3384, 2936, 2868, 1616, 1588, 1508, 1452, 1420, 1376, 1328, 1236, 1140, 1112, 1048, 760, 528 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.64/8.58 (d, J = 4 Hz, H-2′), 7.91/7.82 (d, J = 9 Hz, H-8′), 7.66/7.59 (d, J = 4 Hz, H-3′), 7.41/7.38 (ddd, J = 2, 4, 9 Hz, H-6′), 7.30/7.25 (ddd, J = 2, 4, 9 Hz, H-7′), 7.02/6.88 (dd, J = 2, 4 Hz, H-5′), 6.43/6.38 (s, H-9), 4.42/4.30 (m, H-10), 4.28/4.17 (m, H-8), 3.50-2.93 (m, H-2_{endo}, H-2_{exo}, 2 H-6), 2.30-2.06 (m, 2 H-7, H-4), 2.01/1.93 (d, J = 6 Hz, 3 H-11), 1.80-1.60 (m, 2 H-5), 0.99 (m, H-3); ^{13}C NMR (100 MHz, CD_3OD) δ 147.44/147.18 (CH, C-2′), 147.05/146.93 (C, C-10′), 143.93/143.90 (C, C-4′),

131.41/131.40 (CH, C-8′), 129.79/129.71 (CH, C-5′), 125.96/125.88 (C, C-9′), 122.44/122.42 (CH, C-7′), 121.09/120.96 (CH, C-6′), 118.69/118.46 (CH, C-3′), 70.17/69.89 (CH, C-9), 60.01/60.01 (CH, C-8), 50.64/50.60 (CH_2, C-6), 49.97/49.94 (CH_2, C-2), 45.72/45.40 (CH, C-3), 32.39/30.51 (CH, C-10), 25.67/25.62 (CH, C-4), 25.42/25.40 (CH_3, C-11), 25.29/25.27 (CH_2, C-7), 18.79/18.68 (CH_2, C-5); MS (160°C) *m/z* 424 (M^+, 2), 295 (63), 294 (11), 277 (3), 213 (7), 181 (6), 167 (12), 159 (11), 143 (11), 137 (100), 129 (19), 122 (22), 95 (14). Data for **3e**, **f**. IR (KBr) ν 3060, 2936, 2868, 2760, 1616, 1588, 1508, 1452, 1376, 1208, 1160, 1132, 1100, 1032 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.64/8.58 (d, *J* = 4 Hz, H-2′), 8.14/8.05 (d, *J* = 9 Hz, H-8′), 7.85/7.76 (d, *J* = 4 Hz, H-3′), 7.69/7.67 (ddd, *J* = 2, 4, 9 Hz, H-6′), 7.65/7.45 (ddd, *J* = 2, 4, 9 Hz, H- 7′), 7.31/7.21 (dd, *J* = 2, 4 Hz, H-5′), 6.02/5.93 (s, H-9), 4.75/4.24 (m, H-10), 3.74 (m, H-2_{endo}), 3.62 (d, *J* = 9 Hz, H-8), 3.40-3.07 (m, 2 H-6, H-2_{exo}), 2.90 (m, H-3), 2.30-2.10 (m, 2 H-7), 1.90-1.50 (m, 2 H-5, H-4), 1.52/1.45 (d, *J* = 6 Hz, 3 H-11); ^{13}C NMR (100 MHz, CD_3OD) δ 151.01/150.97 (CH, C-2′), 148.57/148.19 (C, C-10′), 141.38/140.03 (C, C-4′), 131.58/130.92 (CH, C-8′), 127.40/127.36 (CH, C-5′), 126.82/126.60 (C, C-9′), 124.47/124.08 (CH, C-7′), 120.49/120.09 (CH, C-6′), 119.86/119.76 (CH, C-3′), 78.46/78.33 (CH, C-9), 74.92/73.65 (CH, C-10), 61.52/61.20 (CH, C-8), 50.70/49.76 (CH_2, C-6), 47.97/47.26 (CH_2, C-2), 39.90/39.39 (CH, C-3), 25.64/25.40 (CH, C-7), 23.71/23.41 (CH_2, C-4), 21.08/21.04 (CH_2, C-5), 20.51/19.59 (CH_3, C-11); MS (150°C) *m/z* 294 (M^+, 37), 279 (M^+-Me, 7), 267 (10), 237 (34), 195 (10), 181 (11), 172 (10), 159 (62), 138 (61), 136 (100), 122 (16), 111 (20), 95 (18), 82 (29), 77 (24), 69 (30).

*(3*R*,8*R*,9*S*)-10,11-Dihydro-3,9-epoxy-6′-methoxy-cinchonane* (**5**) *and (3*R*,8*R*,9*S*)-10,11-Dihydro-3-hydroxy-6′-methoxy-cinchonan-9-ol* (**6**). A mixture of diastereomeric *iso*-quinidines *E*-**4** and *Z*-**4** (324 mg, 1.0 mmol) was allowed to react according to *method D* to afford after chromatography (EA/MeOH, 4:1) 4-oxa-1-azatwistane **5** (172 mg, 53%) and diol **6** (58 mg, 17%). Data for **5**. IR (KBr) ν 3068, 2960, 2936, 2880, 1620, 1592, 1508, 1472, 1432, 1376, 1352, 1296, 1232, 1132, 1100, 1080, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 4 Hz, H-2′), 8.07 (d, *J* = 9 Hz, H-8′), 7.77 (d, *J* = 4 Hz, H-3′), 7.39 (dd, *J* = 2, 9 Hz, H-7′), 7.21 (d, *J* = 2 Hz, H-5′), 6.03 (s, H-9), 3.96 (s, 3 H-11′), 3.71 (d, *J* = 13 Hz, H-2_{endo}), 3.63 (d, *J* = 6 Hz, H-8), 3.15-2.90 (m, 2 H-6), 2.83 (d, *J* = 13 Hz, H-2_{exo}), 2.23 (m, H-4), 1.87 (m, H-7), 1.80-1.70 (m, 2 H-5), 1.64 (m, H-7), 1.37-1.23 (m, 2 H-10), 1.09 (dd, *J* = 6, 7 Hz, 3 H-11); NOE H-5′ irradiated: H-9 (11.3), H-2_{endo} (12.1), H-11′ (6.3), H-10 (5.6), H-11 (6.1); H-9 irradiated: H-10 (4.8), H-8 (6.8), H-2_{endo} (3.9), H-5′ (19.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.07 (C, C-6′), 147.57 (CH, C-2′), 144.07 (C, C-10′), 143.13 (C, C-4′), 131.75 (CH, C-8′), 126.95 (C, C-9′), 121.81 (CH, C-7′), 119.39 (CH, C-3′), 100.49 (CH, C-5′), 78.27 (C, C-3), 72.87 (CH, C-9), 56.40 (CH, C-8), 55.97 (CH_3, C-11′), 54.31 (CH_2, C-2), 46.38 (CH_2, C-6), 32.94 (CH, C-4), 27.37 (CH_2, C-10), 23.95 (CH_2, C-7), 23.11 (CH_2, C-5), 7.34 (CH_3, C-11); MS (200°C) *m/z* 324 (M^+, 8), 323 (38), 309 (21), 295 (4), 267 (100), 253 (50), 238 (10), 211 (8), 198 (6), 184 (8), 173 (9), 159 (6), 136 (2), 115 (3), 95 (2), 81 (3). Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C 74.05, H 7.46, N 8.64, found C 74.02, H 7.51, N 8.63. Data for **6**. IR ($CHCl_3$) ν 3596, 3324, 3052, 2972, 2788, 2732, 1620, 1592, 1508, 1468, 1432, 1384, 1368, 1300, 1228, 1132, 1064, 996 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.69 (d, *J* = 4 Hz, H-2′), 7.97 (d, *J* = 9 Hz, H-8′), 7.65 (d, *J* = 4 Hz, H-3′), 7.39 (dd, *J* = 2, 9 Hz, H-7′), 7.20 (d, *J* = 2 Hz, H-5′), 6.37 (s, H-9), 4.07 (s, 3 H-11′), 3.85 (d, *J* = 14 Hz, H-2_{endo}), 3.58 (m, H-8), 3.00-2.85 (m, 2 H-6), 2.65 (d, *J* = 14 Hz, H-2_{exo}), 2.36-2.26 (m, H-4), 2.00-1.80 (m, 2 H-7), 1.80-1.65 (m, 2 H-5), 1.64 (q, *J* = 7 Hz, 2 H-10), 1.13 (t, *J* = 7 Hz, 3 H-11); ^{13}C NMR (100 MHz, CD_3OD) δ 158.11 (C, C-6′), 148.18 (CH, C-2′), 147.65 (C, C-10′), 144.80 (C, C-4′), 131.72 (CH, C-8′), 127.54 (C, C-9′), 120.80 (CH, C-7′), 119.25 (CH, C-3′), 102.26 (CH, C-5′), 70.03 (C, C-3), 68.37 (CH, C-9), 61.15 (CH_2, C-2), 57.54 (CH, C-8), 57.29 (CH_3, C-11′), 51.60 (CH_2, C-6), 33.02 (CH, C-4), 31.17 (CH_2, C-10), 25.01 (CH_2, C-7), 24.67 (CH_2, C-5), 7.11 (CH_3, C-11); MS (120°C) *m/z* 342 (M^+, 8), 323 (61), 309 (21), 308 (27), 295 (9), 277 (18), 267 (11), 228 (7), 214 (9), 201 (27), 189 (82), 173 (36), 159 (27), 154 (39), 136 (100), 124 (39), 117 (31), 108 (40), 95 (15), 81 (25), 79 (26), 77 (24).

(3S,8R,9S)-3-tert.-Butyldimethylsilyloxy-3,9-epoxy-6′-methoxy-10,11-dinor-cinchonane (**8b**) *and (8R, 9S)-9-tert.-Butyldimethylsilyloxy-6′-methoxy-ruban-3-one* (**9b**). To a solution of rubanone **7** (400 mg, 1.28 mmol) in CH_2Cl_2 (10 ml) were added 2,6-lutidine (0.3 ml, 2 eq) and the corresponding silyl triflate (1.3 eq) at 0 °C under argon. After 5 min the cooling bath was removed and the mixture stirred for 2 h at r.t.. Water was added and the aqueous layer extracted with $CHCl_3$. The combined organic phases were dried ($MgSO_4$), evaporated and purified by chromatography (MTBE/MeOH, 20:1) to give **8b** (371 mg, 68%) as light-yellow waxy solid and **9b** (14%) as byproduct. Data for **8b**. IR (KBr) ν 3072, 2952, 2928, 2884, 1620, 1592, 1508, 1472, 1348, 1248, 1228, 1180, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4 Hz, H-2′), 7.99 (d, *J* = 9 Hz, H-8′), 7.72 (d, *J* = 4 Hz, H-3′), 7.38 (d, *J* = 1.5 Hz, H-5′), 7.31 (dd, *J* = 2, 9 Hz, H-7′), 5.98 (s, H-9), 3.90 (s, 3 H-11′), 3.56 (d, *J* = 13 Hz, H-2_{endo}), 3.38 (d, *J* = 6 Hz, H-8), 2.95 (m, 2 H-6), 2.72 (d, *J* = 13 Hz, H-2_{exo}), 2.15 (m, H-4), 1.84, 1.55, 1.21 (m, 2 H-5, 2 H-7), 0.88 (s, 9 H, SiC(CH_3)$_3$), 0.22, 0.13 (s, 6 H, Si(CH_3)$_2$); NOE H-9 irradiated: H-5′ (15.7), H-2_{endo} (10.1); H-2_{endo} irradiated: H-2_{exo} (19.1), H-9 (13.8); H-7_{endo} irradiated: H-3′(1.0), H-4 (1.5), H-8 (1.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.90 (C, C-6′), 147.78 (CH, C-2′), 144.01, 142.26 (C, C-4′, C-10′), 131.89 (CH, C-8′), 126.17 (C, C-9′), 121.21 (CH, C-7′), 119.02 (CH, C-3′), 102.32 (CH, C-5′), 102.21 (C, C-3), 74.45 (CH, C-9), 57.02 (CH_2, C-2), 56.11 (CH, C-8), 55.85 (CH_3, C-11′), 46.68 (CH_2, C-6), 37.66 (CH, C-4), 25.73 (CH_3, SiC(CH_3)$_3$), 25.78, 23.21 (CH_2, C-5, C-7), 17.82 (C, SiC(CH_3)$_3$), −2.42 (CH_3, SiCH_3), −2.55 (CH_3, SiCH_3); MS (120°C) *m/z* 426 (M^+, 67), 411 (56), 396 (18), 384 (55), 369 (71), 341 (39), 294 (78), 267 (92), 252 (66); HRMS calcd. for $C_{24}H_{34}N_2O_3Si$: 426.2339, found 426.2343. Data for **9b**. IR (KBr) ν 3164, 3072, 2936, 1712, 1620, 1592, 1508, 1472, 1368, 1308, 1228, 1084, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4 Hz, H-2′), 8.07 (d, *J* = 10 Hz, H-8′), 7.49 (d, *J* = 4 Hz, H-3′), 7.41 (dd, *J* = 2, 10 Hz, H-7′), 7.17 (s, H-5′), 5.68 (d, *J* = 3 Hz, H-9), 4.04 (d, *J* = 20 Hz, H-2_{endo}), 3.98 (s, 3 H-11′), 3.15 (d, *J* = 20 Hz, H-2_{exo}; m, H-8), 3.03, 2.82 (m, 2 H-6), 2.49 (m, H-4), 2.38, 1.99, 1.59 (m, 2 H-5, 2 H-7), 0.96 (s, 9 H, SiC(CH_3)$_3$), 0.15, −0.33 (s, 6 H, Si(CH_3)$_2$); NOE H-9 irradiated: H-5′(18.4), H-8 (3.8), H-2_{endo} (2.9); H-2_{endo} irradiated: H-2_{exo} (18.3), H-7_{endo} (4.5), H-9 (3.8); H-7_{endo} irradiated: H-3′(4.8), H-7_{exo} (15.6); H-8 irradiated: H-9 (2.7), H-3′(5.8); H-7_{exo} irradiated: H-7_{endo} (25.2), H-4 (6.1), H-8 (8.5); H-5′irradiated: H-9 (18.7), H-11′(10.2), H-8 (4.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.12 (C, C-3), 158.02 (C, C-6′), 147.43 (CH, C-2′), 146.85, 144.21 (C, C-4′, C-10′), 132.18 (CH, C-8′), 125.82 (C, C-9′), 122.52 (CH, C-7′), 118.31 (CH, C-3′), 102.10 (CH, C-5′), 72.82 (CH, C-9), 59.65 (CH_2, C-2), 59.20 (CH, C-8), 55.58 (CH_3, C-11′), 50.96 (CH_2, C-6), 40.80 (CH, C-4), 26.02 (CH_3, SiC(CH_3)$_3$), 25.17, 24.02 (CH_2, C-5, C-7), 17.98 (C, SiC(CH_3)$_3$), −0.40 (CH_3, SiCH_3), −0.51 (CH_3, SiCH_3); MS (130°C) *m/z* 426 (M^+, 13), 398 (15), 369 (21), 357 (18), 341 (44), 301 (16), 172 (37); HRMS calcd. for $C_{24}H_{34}N_2O_3Si$: 426.2339, found 426.2337.

(3S,8R,9S)-3-Triisopropylsilyloxy-3,9-epoxy-6′-methoxy-10,11-dinor-cinchonane (**8c**). Rubanone **7** (400 mg, 1.28 mmol) was allowed to react as described for **8b** to afford **8c** (527 mg, 88%) as a waxy solid. IR (KBr) ν 3196, 3068, 2944, 2888, 2864, 1620, 1592, 1508, 1472, 1348, 1248, 1228, 1188, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 4 Hz, H-2′), 8.06 (d, *J* = 9 Hz, H-8′), 7.74 (d, *J* = 4 Hz, H-3′), 7.39 (dd, *J* = 2, 9 Hz, H-7′), 7.10 (d, *J* = 1.5 Hz, H-5′), 6.08 (s, H-9), 4.00 (s, 3 H-11′), 3.86 (d, *J* = 13 Hz, H-2_{endo}), 3.69 (d, *J* = 7 Hz, H-8), 3.28-3.10 (m, 2 H-6), 2.98 (d, *J* = 13 Hz, H-2_{exo}), 2.41 (m, H-4), 2.04, 1.73, 1.40 (m, 2 H-5, 2 H-7), 1.20-1.10 (m, 21 H, SiCH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.28 (C, C-6′), 147.69 (CH, C-2′), 144.20, 140.91 (C, C-4′, C-10′), 131.95 (CH, C-8′), 126.19 (C, C-9′), 121.10 (CH, C-7′), 119.19 (CH, C-3′), 100.11 (CH, C-5′), 99.18 (C, C-3), 74.03 (CH, C-9), 56.72 (CH_2, C-2), 56.90 (CH, C-8), 56.09 (CH_3, C-11′), 46.62 (CH_2, C-6), 37.02 (CH, C-4), 24.82, 22.72 (CH_2, C-5, C-7), 18.20, 18.11 (CH_3, SiCH(CH_3)$_2$), 13.08 (CH, SiCH(CH_3)$_2$); MS (160°C) *m/z* 468 (M^+, 72), 453 (37), 425 (76), 412 (50), 396 (29), 294 (83), 267 (100), 252 (70), 210 (67), 198 (73); HRMS calcd. for $C_{26}H_{37}N_2O_3Si$ (M^+-CH_3): 453.2573, found 453.2559.

(8R,9S)-6′-Methoxy-9-trimethylsilyloxy-ruban-3-one (**9a**). Rubanone **7** (400 mg, 1.28 mmol) was allowed to react as described for **8b** and **9b** to afford **9a** (354 mg, 84%) as a light-yellow, highly viscous oil. IR ($CHCl_3$) ν 3080, 2960, 2884, 2836, 1728, 1668, 1620, 1592, 1508, 1472, 1432, 1364, 1304, 1228, 1124, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 4 Hz, H-2′), 7.90 (d, J = 10 Hz, H-8′), 7.30 (br. s, H-3′), 7.24 (dd, J = 2, 10 Hz, H-7′), 7.01 (s, H-5′), 5.62 (s, H-9), 3.95 (d, J = 17 Hz, H-2_{endo}), 3.80 (s, 3 H-11′), 3.00-2.85 (d, J = 17 Hz, H-2_{exo}; m, H-8), 2.90, 2.70 (m, 2 H-6), 2.32 (m, H-4), 2.21, 1.75, 1.35 (m, 2 H-5, 2 H-7), –0.80 (s, 9 H, Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.07 (C, C-3), 158.08 (C, C-6′), 147.38 (CH, C-2′), 146.32, 144.15 (C, C-4′, C-10′), 132.05 (CH, C-8′), 125.82 (C, C-9′), 121.70 (CH, C-7′), 118.26 (CH, C-3′), 101.25 (CH, C-5′), 72.65 (CH, C-9), 58.92 (CH_2, C-2), 59.20 (CH, C-8), 55.69 (CH_3, C-11′), 50.79 (CH_2, C-6), 40.71 (CH, C-4), 24.91, 23.79 (CH_2, C-5, C-7), 0.10 (CH_3, Si(CH_3)$_3$); MS (80°C) *m/z* 384 (M^+, 6), 369 (4), 356 (28), 341 (9), 314 (8), 260 (12), 210 (8), 172 (18), 83 (100); HRMS calcd. for $C_{21}H_{28}N_2O_3Si$: 384.1869, found 384.1870.

(8R,9S)-9-tert.-Butyldimethylsilyloxy-6′-methoxy-cinchonane (**10b**). To a solution of quinidine (2.00 g, 6.17 mmol) in CH_2Cl_2 (20 ml) were added TBDMSCl (1.02 g, 6.78 mmol, 1.1 eq), DMAP (75 mg, 0.61 mmol, 0.1 eq) and Et_3N (0.95 ml, 7.40 mmol, 1.3 eq) under argon and the mixture was stirred for 18 h at r.t.. Water was added, the aqueous phase extracted with $CHCl_3$, the combined organic layer was washed with sat. aq. $NaHCO_3$ solution and dried ($MgSO_4$). Purification by chromatography (EA/MeOH, 6:1) gave **10b** (2.378 g, 88%) as a light-yellow, highly viscous oil. IR (KBr) ν 3116, 3088, 2952, 2932, 2880, 2860, 1620, 1592, 1508, 1472, 1432, 1360, 1256, 1196, 1116, 1064, 1032, 1004, 880, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 4 Hz, H-2′), 8.09 (d, J = 9 Hz, H-8′), 7.61 (d, J = 4 Hz, H-3′), 7.43 (dd, J = 2, 9 Hz, H-7′), 7.16 (d, J = 2 Hz, H-5′), 6.15 (ddd, J = 8, 9, 15 Hz, H-10), 5.68 (s, H-9), 5.17 (d, J = 9 Hz, H-11_{cis}), 5.12 (d, J = 15 Hz, H-11_{trans}), 3.99 (s, 3 H-11′), 3.31 (m, H-8), 2.99 (m, H-2_{endo}), 2.87 (m, H-2_{exo}), 2.65 (m, H-3), 2.28 (m, H-4), 1.87-1.80 (m, 2 H-6), 1.61-1.45 (m, 2 H-7, 2 H-5), 0.98 (m, 9 H, SiC(CH_3)$_3$), 0.13 (s, 3 H, SiCH_3), –0.26 (s, 3 H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.86 (C, C-6′), 147.42 (CH, C-2′), 144.35 (C, C-10′), 143.52 (C, C-4′), 140.67 (CH, C-10), 131.90 (CH, C-8′), 126.38 (C, C-9′), 121.30 (CH, C-7′), 118.89 (CH, C-3′), 114.54 (CH_2, C-11), 100.59 (CH, C-5′), 72.92 (CH, C-9), 60.95 (CH, C-8), 55.42 (CH_3, C-11′), 50.06 (CH_2, C-2), 47.98 (CH_2, C-6), 39.87 (CH, C-3), 28.09 (CH, C-4), 26.68 (CH_2, C-7), 26.36 (CH_3, SiC(CH_3)$_3$), 21.07 (CH_2, C-5), 14.22 (C, SiC(CH_3)$_3$), –3.42 (CH_3, SiCH_3), –4.55 (CH_3, SiCH_3); MS (90°C) *m/z* 438 (M^+, 4), 381 (3), 303 (2), 302 (2), 173 (2), 137 (18), 136 (100), 95 (1), 81 (2), 77 (4); HRMS calcd. for $C_{26}H_{38}N_2O_2Si$: 438.2703, found 438.2705.

(3R,8R,9S,10R)-9-Acetoxy-10,11-dihydro-10,11-dihydroxy-6′-methoxy-cinchonane (**11a**) *and (3R,8R,9S,10S)-9-Acetoxy-10,11-dihydro-10,11-dihydroxy-6′-methoxy-cinchonane* (**11b**). To a solution of acetylated quinidine (**10a**) (876 mg, 2.39 mmol, 1 eq), K_2CO_3 (940 mg, 6.81 mmol, 2.8 eq), $K_3[Fe(CN)_6]$, (2.24 g, 6.81 mmol, 2.8 eq) in *tert.*BuOH/H_2O (20 ml, 1:1) was added OsO_4 (0.24 ml, 0.1M solution in *tert.*BuOH, 0.01 eq) under argon. The mixture was stirred for 4 h at r.t., then $CHCl_3$ was added. The organic layer was washed with aq. sat. $NaHSO_3$/NaCl solution (1:1), $NaHCO_3$ was added and the aqueous layer was reextracted with $CHCl_3$. The combined organic layer was dried ($MgSO_4$) and purified by chromatography (EA/MeOH, 4:1) to afford diols **11a** and **11b** (diastereomeric mixture, 1.5:1) (890 mg, 93%), mp 194 °C. IR (KBr) ν 3408, 3076, 2936, 2872, 1744, 1620, 1592, 1508, 1472, 1432, 1372, 1304, 1228, 1204, 1132, 1028 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.66 (d, J = 4 Hz, H-2′), 7.97 (d, J = 9 Hz, H-8′), 7.53 (d, J = 2 Hz, H-5′), 7.51 (d, J = 4 Hz, H-3′), 7.45 (dd, J = 2, 9 Hz, H-7′), 6.66/6.58 (d, J = 5 Hz, H-9), 3.99/3.89 (s, 3 H-11′), 3.92/3.79 (m, H-8), 3.66 (dd, J = 2, 8 Hz, H-11), 3.62 (dd, J = 2, 8 Hz, H-11), 3.49 (m, H-10), 2.95-2.80 (m, H-2_{endo}, H-2_{exo}), 2.78 (m, H-4), 2.20/2.19 (s, 3 H-13), 2.09-2.00 (m, 2 H-6), 1.84/1.46 (m, H-3), 1.80-1.55 (m, 2 H-7), 1.35-1.18 (m, 2 H-5); ^{13}C NMR (100 MHz, CD_3OD) δ 171.67/171.55 (C, C-12), 159.98/159.97 (C, C-6′),

148.19/148.16 (CH, C-2′), 146.01/145.97 (C, C-10′), 145.09/145.06 (C, C-4′), 131.60/131.56 (CH, C-8′), 128.33/128.22 (C, C-9′), 123.85/123.81 (CH, C-7′), 119.81/119.67 (CH, C-3′), 102.44/102.38 (CH, C-5′), 74.94/74.70 (CH, C-9), 73.58/73.51 (CH, C-10), 66.27/66.04 (CH_2, C-11), 59.90/59.77 (CH, C-8), 56.51/56.48 (CH_3, C-11′), 50.96/50.90 (CH_2, C-2), 48.83/48.11 (CH_2, C-6), 39.25/38.74 (CH, C-3), 27.54/25.12 (CH_2, C-7), 25.70/23.52 (CH, C-4), 24.10/23.28 (CH_2, C-5), 21.10/21.03 (CH_3, C-13); MS (180°C) *m/z* 400 (M^+, 39), 383 (10), 369 (11), 341 (48), 322 (9), 309 (11), 281 (10), 243 (6), 211 (6), 201 (10), 189 (29), 170 (100), 160 (7), 152 (9), 138 (9), 111 (7), 91 (6), 82 (8), 77 (3), 70 (13); HRMS calcd. for $C_{22}H_{28}N_2O_5$: 400.1998, found 400.1992.

*(3*R*,8*R*,9*S*)-9-Acetoxy-6′-methoxy-rubane-3-carbaldehyde* (**12a**). To a vigorously stirred suspension of silica gel (4.0 g), $NaIO_4$ (556 mg, 2.60 mmol, 1.3 eq) in CH_2Cl_2 (32ml) and H_2O (4 ml) was added a solution of diastereomeric diols **11a** and **11b** (800 mg, 2.00 mmol, 1 eq) in CH_2Cl_2 (4 ml). The mixture was stirred for 1 h at r.t., the silica gel was filtered off and the resulting residue was washed with CH_2Cl_2. The phases were separated, the organic layer dried ($MgSO_4$) and evaporated. Purification by chromatography (EA/MeOH, 6:1) gave aldehyde **12a** (655 mg, 89%) as a colourless solid. IR (KBr) ν 2940, 2872, 1744, 1716, 1620, 1592, 1508, 1472, 1456, 1432, 1372, 1304, 1228, 1132, 1084, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, H-10), 8.79 (d, *J* = 4 Hz, H-2′), 8.06 (d, *J* = 9 Hz, H-8′), 7.55 (d, *J* = 2 Hz, H-5′), 7.43 (dd, *J* = 2, 9 Hz, H-7′), 7.33 (d, *J* = 4 Hz, H-3′), 6.63 (d, *J* = 6 Hz, H-9), 4.03 (s, 3 H-11′), 3.75 (ddd, *J* = 2, 6, 7 Hz, H-8), 3.31 (m, H-2_{endo}), 2.97 (m, H-2_{exo}), 2.85-2.76 (m, H-3, H-4), 2.55-2.51 (m, 2 H-6), 2.20 (s, 3 H-13), 1.75-1.63 (m, 2 H-7), 1.61-1.54 (m, 2 H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.14 (CH, C-10), 171.64 (C, C-12), 157.85 (C, C-6′), 147.40 (CH, C-2′), 144.02 (C, C-10′), 143.78 (C, C-4′), 131.44 (CH, C-8′), 126.23 (C, C-9′), 121.69 (CH, C-7′), 118.58 (CH, C-3′), 101.16 (CH, C-5′), 73.35 (CH, C-9), 58.59 (CH, C-8), 55.81 (CH_3, C-11′), 50.02 (CH_2, C-2), 48.92 (CH, C-3), 42.26 (CH_2, C-6), 25.95 (CH_2, C-7), 24.14 (CH_2, C-5), 23.35 (CH, C-4), 21.03 (CH_3, C-13) ; MS (150°C) *m/z* 368 (M^+, 100), 353 (18), 339 (16), 324 (30), 309 (54), 298 (29), 285 (23), 281 (21), 231 (17), 214 (11), 201 (11), 198 (14), 188 (82), 168 (47), 159 (17), 138 (98), 126 (29), 95 (10), 82 (20), 70 (15); HRMS calcd. for $C_{21}H_{24}N_2O_4$: 368.1736, found 368.1744.

*(3*R*,8*R*,9*S*)-9-Hydroxy-6′-methoxy-rubane-3-carbaldehyde* (**13a**) *and (3*S*,8*R*,9*S*)-9-Hydroxy-6′-methoxy-rubane-3-carbaldehyde* (**13b**). To a solution of aldehyde **12a** (368 mg, 1 mmol, 1 eq) in MeOH (10 ml) was added finely powdered K_2CO_3 (1106 mg, 8 mmol, 8 eq). The mixture was stirred vigorously for 20 min at r.t., was then filtrated and concentrated. The residue was dissolved in $CHCl_3$ and washed with water and sat. aq. $NaHCO_3$ solution. The combined organic layer was dried ($MgSO_4$), evaporated and purified by chromatography (EA/MeOH, 6:1) to afford the desired aldehyde **13a** and the epimerized aldehyde **13b** (ratio 9:1) (303 mg, 93%). IR (KBr) ν 3400, 3072, 2940, 2872, 2832, 2716, 1716, 1620, 1588, 1508, 1472, 1432, 1360, 1304, 1240, 1132, 1108, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.89/9.80 (s, H-10), 8.58 (d, *J* = 4 Hz, H-2′), 7.96 (d, *J* = 9 Hz, H-8′), 7.47 (d, *J* = 4 Hz, H-3′), 7.34 (d, *J* = 2 Hz, H-5′), 7.32 (dd, *J* = 2, 9 Hz, H-7′), 5.64/5.58 (d, *J* = 4 Hz, H-9), 3.92/3.89 (s, 3 H-11′), 3.67 (m, H-8), 3.15 (m, H-2_{endo}), 2.93 (m, H-2_{exo}), 2.82-2.74 (m, H-3, 2 H-6), 2.45-2.41 (m, 2 H-7), 1.88 (m, H-4), 1.63-1.47 (m, 2 H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.76/204.34 (CH, C-10), 157.82/157.71 (C, C-6′), 147.79/147.43 (CH, C-2′), 144.10 (C, C-10′), 143.96 (C, C-4′), 131.42/131.38 (CH, C-8′), 126.66/126.27 (C, C-9′), 121.57/121.52 (CH, C-7′), 118.41/118.16 (CH, C-3′), 101.24/101.14 (CH, C-5′), 71.75/71.69 (CH, C-9), 59.72/59.36 (CH, C-8), 55.69/55.61 (CH_3, C-11′), 50.47/50.40 (CH_2, C-2), 48.90/48.88 (CH, C-3), 43.22/43.13 (CH_2, C-6), 26.08/26.00 (CH_2, C-7), 23.79/23.13 (CH, C-4), 21.66/21.06 (CH_2, C-5); MS (180°C) *m/z* 426 (M^+, 100), 311 (15), 297 (26), 283 (14), 269 (8), 241 (10), 214 (16), 201 (10), 198 (13), 189 (91), 173 (80), 160 (36), 145 (17), 138 (91), 126 (29), 117 (33), 110 (34), 95 (11), 81 (33), 70 (22). HRMS calcd. for $C_{21}H_{24}N_2O_4$: 368.1736, found 368.1744.

(3R,8R,9S,10R)-10-Triisopropylsilyloxy-9,10-epoxy-6′-methoxy-11-nor-cinchonane (**14**). To a solution of aldehyde **13a/b** (9:1) (89 mg, 0.27 mmol, 1 eq) in THF (2 ml) was added 2,6-lutidine (0.07 ml, 0.54 mmol, 2 eq) at 0 °C and the mixture was stirred for 15 min under argon. Then triisopropylsilyl triflate (0.11 ml, 0.38 mmol, 1.4 eq) was added, the cooling bath removed after 5 min, the mixture stirred for 16 h at r.t. and then treated with water and sat. aq. $NaHCO_3$ solution. The aqueous phase was extracted with $CHCl_3$, the combined organic layer dried ($MgSO_4$), evaporated and chromatographed (EA/MeOH, 6:1) to yield aldehyde **13b** (31 mg) and tricyclic aza-homoglycoside **14** (53 mg, 41%). IR ($CHCl_3$) ν 3068, 2928, 2868, 1620, 1592, 1508, 1472, 1348, 1252, 1228, 1176, 1132, 1088, 1048, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 4 Hz, H-2′), 8.08 (d, J = 9 Hz, H-8′), 7.78 (d, J = 4 Hz, H-3′), 7.41 (dd, J = 2, 9 Hz, H-7′), 7.36 (d, J = 2 Hz, H-5′), 6.12 (s, H-9), 5.61 (d, J = 3 Hz, H-10), 4.03 (s, 3 H-11′), 3.74 (d, J = 14 Hz, H-2_{endo}), 3.51 (d, J = 8 Hz, H-8), 3.25 (m, H-6), 3.09 (m, H-6), 2.88 (m, H-2_{exo}), 2.53 (m, H-3, H-7), 2.19 (m, H-7), 1.74 (m, 2 H-5, H-4), 1.35 (m, 21 H, Si(C*H*(CH_3)$_2$)$_3$); NOE H-10 irradiated: H-9 (1.2), H-11′ (2.5), H-3 (7.5), H-2_{endo} (4.3), Si(C*H*(CH_3)$_2$ (17.1); H-9 irradiated: H-10 (2.4), H-8 (3.1), H-2_{endo} (7.6), H-5′ (17.2); H-5′ irradiated: H-9 (14.9), H-11′ (11.9), H-2_{endo} (4.1), H-8 (6.8); H-3′ irradiated: H-2′ (10.7), H-9 (3.8), H-8 (3.1), H-3 (2.4), H-7_{endo} (8.3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.13 (C, C-6′), 147.43 (CH, C-2′), 145.24 (C, C-10′), 144.22 (C, C-4′), 131.72 (CH, C-8′), 126.01 (C, C-9′), 121.37 (CH, C-7′), 118.66 (CH, C-3′), 101.57 (CH, C-5′), 99.45 (CH, C-10), 73.66 (CH, C-9), 61.18 (CH, C-8), 56.07 (CH_3, C-11′), 56.02 (CH_2, C-2), 45.97 (CH_2, C-6), 40.27 (CH, C-3), 24.24 (CH_2, C-7), 23.48 (CH, C-4), 22.42 (CH_2, C-5), 17.92, 17.81, 17.74 (CH_3, Si(CH(*C*H_3)$_2$)$_3$), 12.11 (CH, Si(*C*H(CH_3)$_2$)$_3$); MS (140°C) *m/z* 482 (M^+, 18), 454 (2), 439 (M^+-Pr^i, 100), 397 (3), 358 (1), 344 (7), 301 (4), 279 (4), 265 (9), 241 (22), 228 (17), 172 (13), 149 (13); HRMS calcd. for $C_{28}H_{42}N_2O_3Si$: 482.2965, found 482.2970.

(3R,8R,9S)-9-tert.-Butyldimethylsilyloxy-3-formylmethylene-6′-methoxy-rubane (**15a**). To a solution of **10b** (876 mg, 2.00 mmol) in THF (10 ml) was added BH_3·THF (8.0 ml, 8.0 mmol, 1.0 M solution in THF) at 0 °C. The mixture was stirred for 30 min at 0 °C and then for 16 h at r.t.. The excess of borane was destroyed by dropwise addition of water. The solvent was removed to afford the BH_3 adduct (877 mg, 97%) as a light-yellow solid. To a solution of this borane (603 mg, 1.33 mmol) in CH_2Cl_2 (10 ml) was added pyridinium chlorochromate on silica gel (1.72 g, 3.99 mmol, 50%) in several portions at 0 °C. The mixture was stirred for 5 h at r.t., filtered through silica gel and the residue washed with $CHCl_3$ and EA. The combined organic layer was dried ($MgSO_4$) and the solvent was removed. The crude product was purified by chromatography (EA) to yield aldehyde **15a** (459 mg, 76%) as a colourless solid. IR (KBr) ν 3076, 2956, 2932, 2856, 2372, 2328, 1720, 1620, 1592, 1508, 1472, 1432, 1364, 1256, 1228, 1168, 1116, 1048, 1028, 872, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, H-11), 8.81 (d, J = 4 Hz, H-2′), 8.12 (d, J = 9 Hz, H-8′), 7.68 (d, J = 2 Hz, H-5′), 7.64 (d, J = 4 Hz, H-3′), 7.46 (dd, J = 2, 9 Hz, H-7′), 6.80 (d, J = 6 Hz, H-9), 4.06 (s, 3 H-11′), 3.75 (m, H-8), 3.30 (m, H-2_{endo}), 3.16 (m, H-2_{exo}), 3.11 (m, 2 H-10), 2.87 (m, H-3), 2.78 (m, H-4), 2.54-2.44 (m, 2 H-6), 1.86-1.70 (m, 2 H-7), 1.63-1.56 (m, 2 H-5), 1.03-0.94 (m, 9 H, SiC(C*H*$_3$)$_3$), 0.32 (m, 3 H, SiC*H*$_3$), -0.21 (m, 3 H, SiC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.09 (CH, C-11), 158.73 (C, C-6′), 146.20 (CH, C-2′), 145.96 (C, C-10′), 143.56 (C, C-4′), 131.10 (CH, C-8′), 126.00 (C, C-9′), 122.99 (CH, C-7′), 119.87 (CH, C-3′), 100.96 (CH, C-5′), 68.93 (CH, C-9), 63.94 (CH, C-8), 57.79 (CH_2, C-10), 56.52 (CH_3, C-11′), 56.23 (CH_2, C-2), 46.84 (CH_2, C-6), 36.86 (CH, C-3), 26.37 (CH_3, SiC(*C*H$_3$)$_3$), 25.68 (CH_2, C-7), 21.12 (CH, C-4), 19.19 (CH_2, C-5), 18.26 (C, Si*C*(CH_3)$_3$), –3.44 (CH_3, Si*C*H$_3$), –4.08 (CH_3, Si*C*H$_3$); MS (150°C) *m/z* 468 (BH_3M^+, 13), 454 (M^+, 56), 440 (44), 426 (9), 412 (35), 398 (100), 384 (22), 352 (16), 338 (20), 303 (73), 282 (10), 258 (14), 238 (6), 186 (14), 173 (21), 160 (12), 138 (9), 110 (11), 73 (79); HRMS calcd. for $C_{26}H_{38}N_2O_3Si$: 454.2652, found 454.2650.

(3R,8R,9S)-3-Formylmethylene-6′-methoxy-ruban-9-ol (**15b**). To a solution of aldehyde **15a** (241 mg, 0.531 mmol) in THF (5 ml) was added tetrabutylammonium fluoride (0.69 ml, 0.69 mmol, 1.0 M solution in THF). The mixture was stirred for 10 h at r.t., then water and sat. aq. $NaHCO_3$ solution was added and the aqueous phase was extracted with $CHCl_3$. The combined organic layer was dried ($MgSO_4$) and evaporated. Purification by chromatography (EA) afforded unprotected aldehyde **15b** (97 mg, 54%) as a colourless solid. IR (KBr) ν 3372, 2956, 2932, 2876, 2372, 2324, 1708, 1620, 1592, 1508, 1472, 1432, 1364, 1308, 1240, 1164, 1048, 1028, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, H-11), 8.65 (d, J = 4 Hz, H-2′), 7.98 (d, J = 9 Hz, H-8′), 7.64 (d, J = 4 Hz, H-3′), 7.36 (d, J = 2 Hz, H-5′), 7.33 (dd, J = 2, 9 Hz, H-7′), 6.63 (d, J = 3 Hz, H-9), 3.95 (s, 3 H-11′), 3.76 (m, H-8), 3.20-3.08 (m, $H\text{-}2_{endo}$, $H\text{-}2_{exo}$), 2.98 (m, 2 H-10), 2.27 (m, H-3), 2.08 (m, H-4), 2.03 (m, H-6), 1.91 (m, H-6), 1.71 (m, H-7), 1.59 (m, H-7), 1.31-1.26 (m, 2 H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.62 (CH, C-11), 158.25 (C, C-6′), 147.14 (CH, C-2′), 146.50 (C, C-10′), 143.52 (C, C-4′), 130.97 (CH, C-8′), 125.93 (C, C-9′), 122.59 (CH, C-7′), 118.92 (CH, C-3′), 101.02 (CH, C-5′), 67.52 (CH, C-9), 63.20 (CH, C-8), 60.45 (CH_2, C-10), 58.00 (CH_2, C-2), 57.75 (CH_2, C-6), 56.33 (CH_3, C-11′), 36.73 (CH, C-3), 26.29 (CH_2, C-7), 25.96 (CH, C-4), 19.18 (CH_2, C-5); MS (190°C) *m/z* 353 (BH_3M^+-1, 12), 340 (M^+, 15), 338 (22), 326 (18), 311 (18), 297 (17), 283 (14), 279 (12), 253 (11), 238 (10), 225 (14), 202 (21), 186 (37), 173 (62), 160 (100), 138 (53), 110 (61), 101 (13), 91 (39), 82 (45); HRMS calcd. for $C_{20}H_{24}N_2O_3$-BH_3 adduct: 354.2096, found 354.2095.

(3R,8R,9S,11R)-11-Triisopropylsilyloxy-10,11-dihydro-9,11-epoxy-6′-methoxy-cinchonane (**16**). 2,6-Lutidine (0.07 ml, 0.54 mmol), aldehyde **15b** (91 mg, 0.27 mmol) and triisopropylsilyl triflate (0.11 ml, 0.38 mmol) were allowed to react as described for compound **14** to afford after chromatography (EA/MeOH, 6:1) tricyclic oxazatwistane **16** (28 mg, 21%). IR ($CHCl_3$) ν 3078, 2932, 2883, 1620, 1592, 1508, 1472, 1364, 1256, 1232, 1148, 1132, 1100, 1088, 1028, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 4 Hz, H-2′), 8.02 (d, J = 9 Hz, H-8′), 7.61 (d, J = 4 Hz, H-3′), 7.35 (dd, J = 2, 9 Hz, H-7′), 7.31 (d, J = 2 Hz, H-5′), 6.59 (s, H-9), 4.92 (m, H-11), 3.98 (s, 3 H-11′), 3.80 (d, J = 8 Hz, H-8), 3.76 (m, $H\text{-}2_{endo}$), 3.08 (m, 2 H-6), 2.96 (m, $H\text{-}2_{exo}$), 2.28 (m, 2 H-10, H-3), 2.04 (m, H-4), 1.87-1.75 (m, 2 H-7), 1.69-1.56 (m, 2 H-5), 1.19-1.03 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.89 (C, C-6′), 146.69 (CH, C-2′), 146.55 (C, C-10′), 143.27 (C, C-4′), 131.98 (CH, C-8′), 125.73 (C, C-9′), 122.40 (CH, C-7′), 118.72 (CH, C-3′), 100.88 (CH, C-5′), 90.33 (CH, C-11), 70.27 (CH, C-9), 63.02 (CH, C-8), 61.06 (CH_2, C-10), 57.89 (CH_2, C-2), 57.67 (CH_2, C-6), 56.12 (CH_3, C-11′), 31.42 (CH, C-3), 25.96 (CH_2, C-7), 23.87 (CH, C-4), 19.03 (CH_2, C-5), 17.92 (CH_3, $Si(CH(CH_3)_2)_3$), 17.65 (CH_3, $Si(CH(CH_3)_2)_3$), 17.58 (CH_3, $Si(CH(CH_3)_2)_3$), 13.25 (CH, $Si(CH(CH_3)_2)_3$), 12.20 (CH, $Si(CH(CH_3)_2)_3$), 11.82 (CH, $Si(CH(CH_3)_2)_3$); MS (130°C) *m/z* 496 (M^+, 1), 487 (6), 467 (32), 417 (3), 375 (2), 357 (1), 331 (4), 288 (5), 277 (13), 245 (5), 199 (4), 171 (5), 160 (30), 149 (3), 131 (100), 107 (57), 89 (14), 76 (79); HRMS calcd. for $C_{29}H_{44}N_2O_3Si$: 496.3153, found 496.3153.

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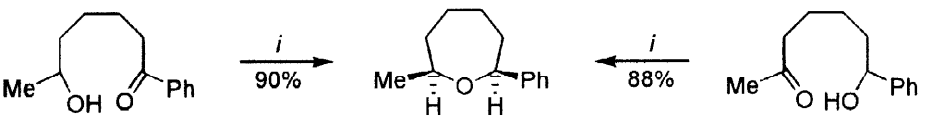
REFERENCES AND NOTES

1. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451.
2. Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem.* **1996**, *108*, 449-452.

3. Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*,1278-1291.
4. Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 8470.
5. von Riesen, C.; Jones, P. G.; Hoffmann, H. M. R. *Chem. Eur. J.* **1995**, *2*, 673. For the synthesis of further tricyclic *Cinchona* alkaloids containing a 1,3-diketo-2-N,O-acetal functionality see Langer, P.; Frackenpohl, J.; Hoffmann, H. M. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, in press.
6. Prelog, V.; Häfliger, O. *Helv. Chim. Acta* **1950**, *33*, 2021; Prelog, V.; Zalán, E. *Helv. Chim. Acta* **1944**, *27*, 535.
7. Langer, P.; Hoffmann, H. M. R. *Tetrahedron* **1997**, *53*, 9145-9158; see also Rowan, S. J.; Brady, P. A.; Sanders, J. K. M. *Angew. Chem.* **1996**, *108*, 2283; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2143.
8. Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136. For a survey see Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953-1980; see also Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, VCH, Weinheim, **1996**, 743-745.



i, 10 eq Et_3SiH, 1.0 eq TMSOTf, CH_2Cl_2, 0 °C, 15 min

9. Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.
10. Waddell, T. G., Rambalakos, T.; Christie, K. R. *J. Org. Chem.* **1990**, *55*, 4765.
11. Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Le Goffic, F. *Synthesis* **1989**, 64.
12. Brown, H. C.; Kulkarni, S. U.; Rao, C. G. *Synthesis* **1980**, 151.
13. Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.;. Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069; Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *J. Org. Chem.* **1990**, *55*, 6121.
14. The energies of the tricyclic compounds were sequentially minimized using a MM2 force field (see Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127).
15. 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; von Riesen, C.; Hoffmann, H. M. R. *Chem. Eur. J.* **1996**, *2*, 680.
16. Chemical Abstracts name of rubanone **7**: {1*R*-[-(1α,4α,6β(*S**)]}-6-[Hydroxy-(6-methoxy-4-quinolinyl)methyl]-1-azabicyclo[2.2.2]octan-3-one. Our numbering of *Cinchona* alkaloids follows the *Cinchona* convention as indicated in Scheme 2.