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Diastereocontrol of Nucleophilic Attack of the Rubanone Carbonyl Group *via* Remote Siloxy Tether. Establishing the Natural Configuration at Carbon C-3 of *Cinchona Alkaloids*

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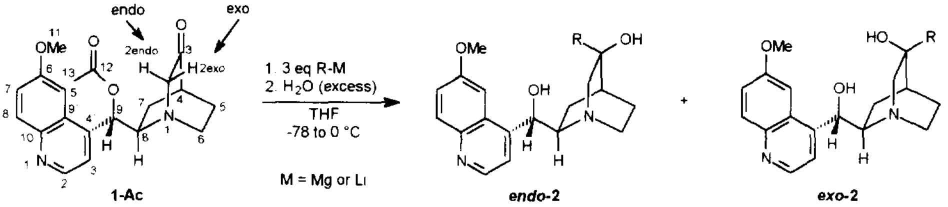
Abstract. *Cinchona* alkaloid derivatives with natural configuration at C-3 have been constructed by *Grignard* reaction of protected rubanone **1-TBDS**. The organomagnesium reagent attacks preferentially from the sterically more hindered *endo* face. Even L-Selectride® reacts *endo*-selectively (9 : 1). © 1997 Elsevier Science Ltd.

(8R,9S)-6'-Methoxyruban-3-on-9-ol (rubanone)[1] **1-H** is a stereodefined bicyclic α-amino-δ'-hydroxy ketone derivable from *cinchona alkaloid* quinidine.[2] We have recently developed a reliable procedure for the conversion of quinidine into **1-H** in five steps.[3] We now show that rubanone **1-H** is a promising intermediate for the synthesis of a variety of quinidine metabolites and their analogues, such as ***endo*-2b**, which has the natural configuration at C-3 and shows pharmacological activity.[4]

Results. Addition of a *Grignard* reagent such as methylmagnesium bromide to the carbonyl group of acetyl-protected rubanone **1-Ac** can, in principle, afford two diastereomeric tertiary alcohols: alcohol ***endo*-2a** with natural configuration at C-3 derived from *endo* attack and alcohol ***exo*-2a** with unnatural configuration from *exo* attack of the carbon nucleophile. When acetylated rubanone **1-Ac** was treated with methylmagnesium bromide an inseparable 1:1 mixture of the alcohols ***endo*-2a** and ***exo*-2a** was obtained. During the course of the reaction deacetylation occurred also. Vinylmagnesium bromide afforded the quinidine metabolites ***endo*-2b** and ***exo*-2b** which were separated by chromatography and isolated in 43% and 42% yield, respectively.[5] Furthermore, rubanone **1-Ac** and dilithiated propargyl alcohol $LiC{\equiv}CCH_2OLi$ yielded a 1.6:1 mixture of amino triols ***endo*-2c** and ***exo*-2c** which were inseparable. Similary disappointing results were obtained starting with unprotected rubanone **1-H**. In all reactions almost no diastereocontrol of addition to the carbonyl group was accomplished.

Interestingly, phenylmagnesium bromide and **1-Ac** gave a 7:1 diastereoselectivity in favor of the naturally-configurated tertiary alcohol ***endo*-2d**. Both major and minor alcohols were separated by chromatography and isolated in 70% and 8% yield, respectively. The configuration of ***endo*-2d** was in doubt for some time, but eventually secured by

X-ray crystallographic analysis (Fig. 1).[6] Inspection of the crystal lattice of aminodiol ***endo*-2d** shows π-stacking interaction of all 6'-methoxy-quinoline rings as predominant structural feature in the solid state (Fig. 2).

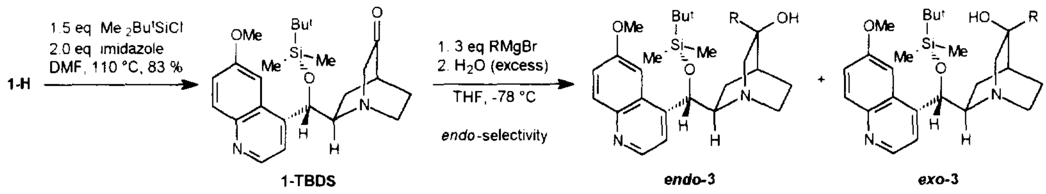


Product 2	R	endo : exo	Total Yield [%]
a	$-CH_3$	1 : 1	74[a]
b	$-CH=CH_2$	1 : 1	43 + 42 = 85
c	$-C{\equiv}CCH_2OH$	1.6 : 1	80[a]
d	$-C_6H_5$	7 : 1	70 + 8 = 78

[a] Inseparable mixture of diastereomers.

Scheme 1. Reaction of Acetyl-protected Rubanone **1-Ac** with *Grignard* Reagents.

Unlike acetyl protected **1-Ac** the corresponding TBDS derivative **1-TBDS**, which was prepared from unprotected rubanone **1-H** in 83% yield (with 5 mol/l of TBDS-chloride), was stable to base.[7] Addition of *Grignard* reagents to TBDS-protected rubanone **1-TBDS** showed significantly enhanced diastereoselectivity. For example, **1-TBDS** and vinylmagnesium bromide reacted in favor of ***endo*-3a** (4.5 : 1), whereas the corresponding reaction of **1-Ac** had been unselective. Phenylmagnesium bromide and *iso*propylmagnesium bromide gave still higher diastereoselectivities (6 : 1 and 7 : 1, respectively).



Product 3	R	endo : exo	Total Yield [%][a]
a	$-CH=CH_2$	4.5 : 1	85
b	$-C_6H_5$	6 : 1	86
c	$-CH(CH_3)_2$	7 : 1	70

[a] Mixture of diastereomers.

Scheme 2. Reaction of TBDS-protected Rubanone **1-TBDS** with *Grignard* Reagents

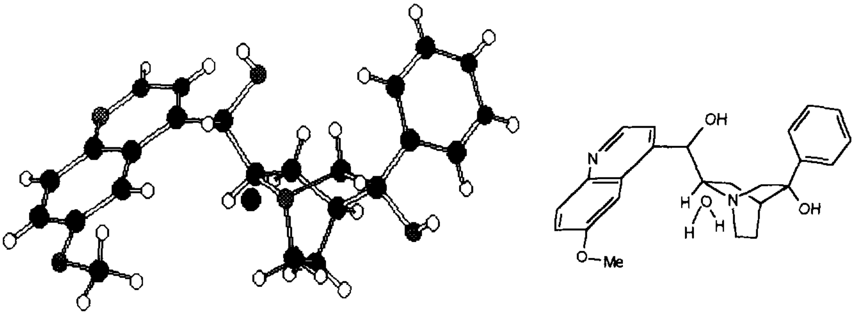


Fig. 1. Crystals Structure of ***endo*-2d** ($C_{24}H_{26}N_2O_3{\cdot}\frac{1}{2}H_2O$)

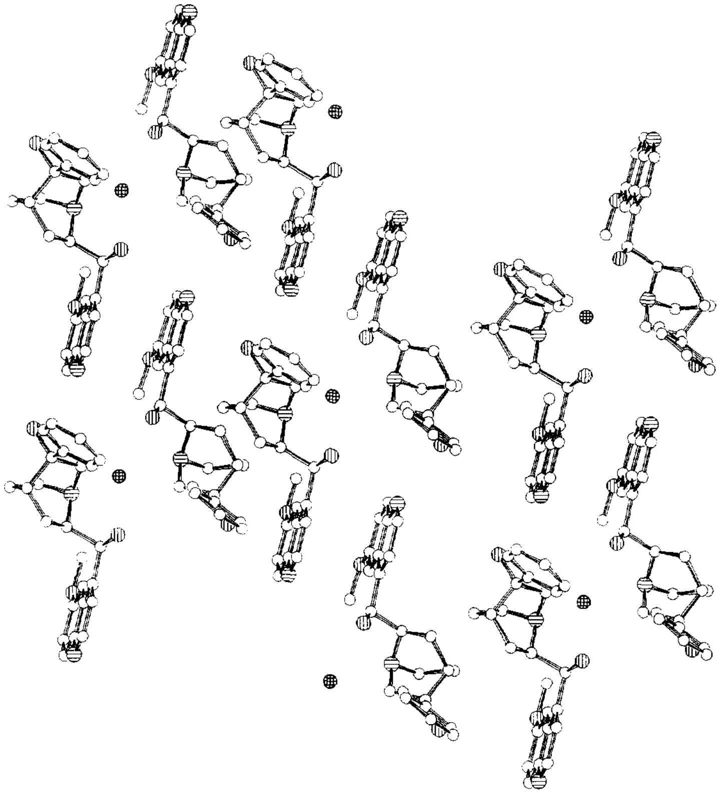
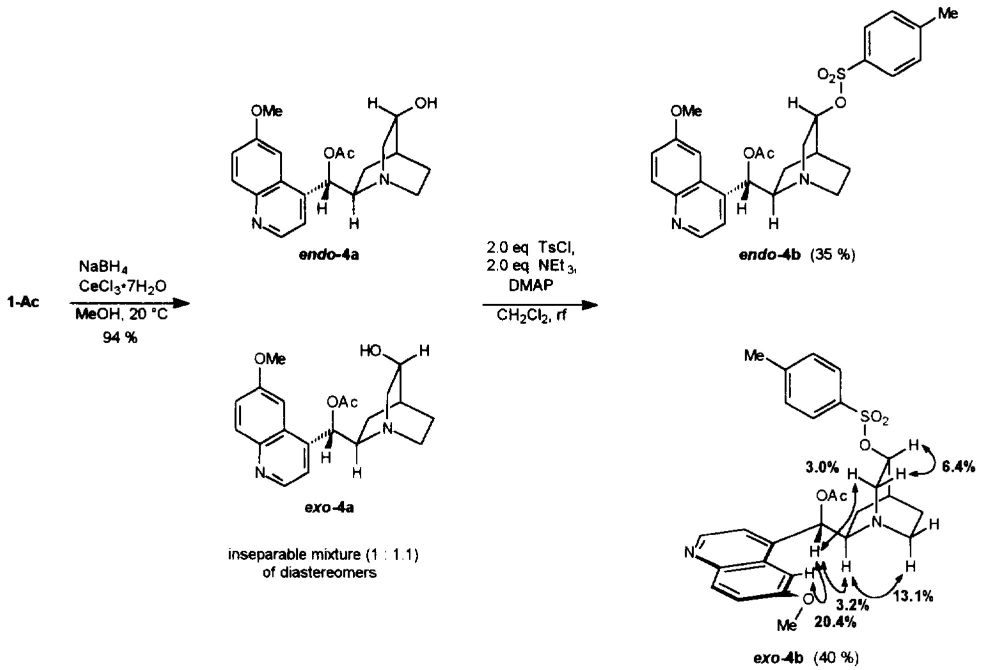


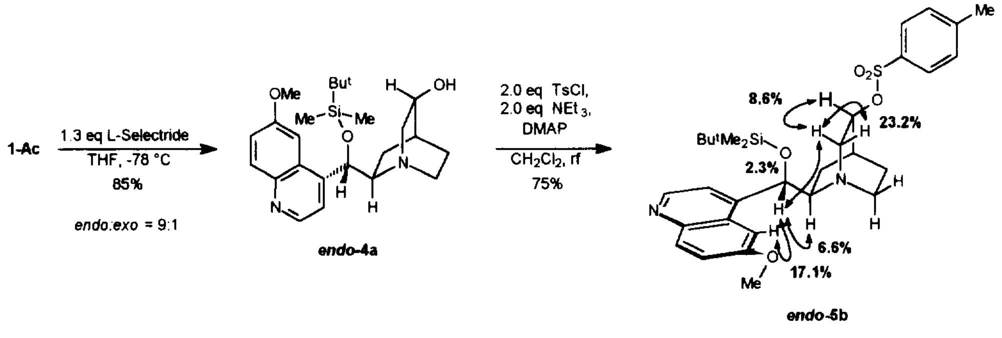
Fig. 2. Packing Mode of ***endo*-2d**

Sodium borohydride and acetylated rubanone **1-Ac** furnished a 1:1.1-mixture of diastereomeric alcohols ***endo*-4a** and ***exo*-4a**, which were not separable by chromatography (Scheme 3). After tosylation, the resulting diesters ***endo*-4b** and ***exo*-4b** were readily separated (35% and 40% yield, respectively). The configuration of ***exo*-4b** was established by NOE .



Scheme 3. Separation of Epimeric Rubanols *via* Tosylation. NOE analysis of *exo*-4b.

In contrast, TBDS-protected rubanone **1-TBDS** and L-Selectride® (LiBHBu$^s_3$) yielded rubanol ***endo*-5a** with high *endo* selectivity (9:1). Due to signal overlap NOE-measurements on alcohol ***endo*-5a** were not informative. However, treatment with tosyl chloride afforded tosylate ***endo*-5b** (75% yield), the configuration of which was readily determined by NOE (Scheme 4).



Scheme 4. Diastereoselective Reduction of **1-TBDS**. NOE Analysis of ***endo*-5b**.

Spectroscopic Assignments of Rubanols. The H-2$_{endo}$ signals (protons directed towards the 6'-methoxy-quinoline moiety and the C-9 alcohol) of all rubanols prepared are shifted downfield compared with the corresponding H-2$_{exo}$ signals. The H-2$_{endo}$ signals of the *endo* diastereomers are shifted downfield relative to those of the *exo* epimers. In contrast, the H-2$_{exo}$ signals of the *endo* diastereomers are shifted to higher field compared with those of the *exo* epimers. In case of C-3 hydrogen-substituted rubanols **4a**, **4b**, **5a** and **5b** the H-2$_{exo}$ signals are doublets for *endo*-diastereomers and multiplets for *exo*-diastereromers and *vice versa* for H-2$_{endo}$ signals. Based on these guidelines, one can distinguish diastereomeric rubanols without need for NOE investigations (which were found not to be informative for all rubanols).

Table 1. Structural Assignment of *endo*- and *exo*-Rubanols by H-2 Chemical Shifts.[a]

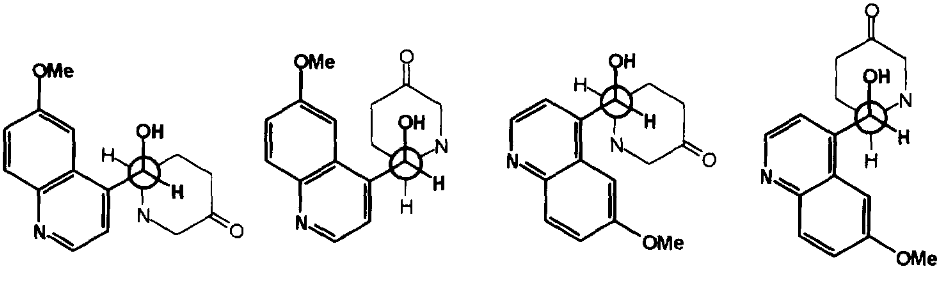
Rubanol	δH-2$_{endo}$ *endo*-diastereomer	δH-2$_{exo}$ *endo*-diastereomer	Δ	δH-2$_{endo}$ *exo*-diastereomer	δH-2$_{exo}$ *exo*-diastereomer	Δ
2a	4.20	3.18	1.02	3.08	2.78	0.30
2b	4.02	2.69	1.33	3.80	3.05	0.75
2c	3.65	3.05	0.60	–	–	–
2d	4.42	3.32	1.10	3.92	3.68	0.24
3a	3.62	2.65	0.97	3.16	2.44	0.72
3b	3.97	2.99	0.98	3.60	2.98	0.62
3c	3.96	2.80	1.16	–	–	–
4a	3.39 (dd)	2.53 (d)	0.86	–	–	–
4b	3.42 (m)	2.74 (d)	0.68	3.22 (d)	3.05 (m)	0.17
5a	3.88 (m)	2.75 (d)	1.13	–	–	–
5b	3.74 (m)	2.69 (d)	1.05	–	–	–

[a] δH-2$_{endo}$ and δH-2$_{exo}$ refer to the chemical shift of the respective C-2 proton; *endo*- and *exo*-diastereomer refer to the configuration at C-3 (see Scheme 1, **1-Ac**).

Conformational analysis of *Cinchona alkaloids* has been undertaken in order to elucidate their catalytic and chemical properties.[8] Four conformations of *Cinchona alkaloids* have been calculated as energy minima (Fig. 3). *Wynberg* has shown that the conformation strongly depends on C-9 substitution. Unprotected quinidine mainly populates an *anti-open* conformation, whereas acetyl-protected quinidine populates an *anti-closed* conformation.

Since conformational data on C-9 TBDS-protected *Cinchona alkaloids* had not been reported, we investigated **1-TBDS** which was shown to mainly populate an *anti-open* conformation in $CDCl_3$ (^3J(H-8)-(H-9),[9] NOE,[10] *vide infra*, Fig. 4, **ii**).

NOE measurements and the small ^3J(H-8)-(H-9) 3 Hz suggested that in analogy to quinidine unprotected rubanols ***endo*-2b** and ***endo*-2d** in methanol-d_4 mainly populate the *anti-open* conformation.[11] This conformation is, similarly to **1-TBDS**, also populated by TBDS-protected ***endo*-5a** and ***endo*-5b** (Scheme 4). The *anti-open* conformation is populated in the solid state as shown for alcohol ***endo*-2d** (Fig. 1). In contrast to acetylated quinidine (*anti-closed*), acetyl-protected tosylate ***exo*-4b** (Scheme 3) mainly populates the *anti-open* conformation, presumably due to steric encumbrance of tosyloxy group and methoxy-quinoline moiety in the *anti-closed* conformation.

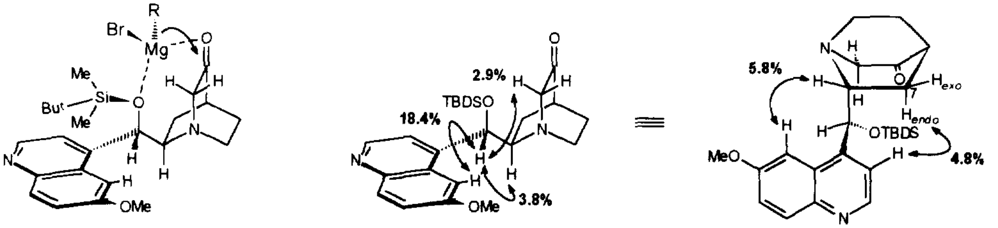


syn-closed *syn-open* *anti-closed* *anti-open*

Fig. 3. The Four Major Conformations of *Cinchona Alkaloids* (here Rubanone **1-H**)

Discussion. For the preparation of naturally configurated rubanols, reaction of TBDS-protected rubanone **1-TBDS** with *Grignard* reagents is currently the method of choice. Surprisingly, the bulky silyl group on the C-9 alcohol group does not block attack at the *endo* face, but appears to actually pull in the nucleophile towards the sterically more hindered carbonyl π-face. The *endo* selectivity is assumed to be due to chelation of the *Grignard* reagent by the C-9 oxygen lone-pair electrons. In the *anti-open* conformation, which has been established for TBDS-protected rubanone **1-TBDS**, this mode of attack is feasible (Fig. 4, **i**). Calculations suggest that TBDS-protected *endo*-**3b** is more stable, by ca. 1 kcal/mol, than the epimeric *exo*-**3b**.[12]

Acetylated rubanone **1-Ac** and parent rubanone **1-H** react unselectively (except for phenylmagnesium bromide as nucleophile). The *endo* selectivity observed for addition of the phenyl *Grignard* reagent *versus* non-phenyl *Grignard* reagents to the carbonyl group of acetylated rubanone **1-Ac** is assumed to be a consequence of a π-stacking interaction of phenylmagnesium bromide and methoxy-quinoline moiety.



i

anti-open conformation

ii

Fig. 4. (**i**) Diastereoselectivity of Nucleophilic Attack on the Carbonyl Group of Protected Rubanone **1-TBDS** and (**ii**) NOE Analysis of **1-TBDS**.

In summary, the $^{t}BuMe_2Si$ group in **1-TBDS** fulfills several functions. It eases handling, protects the C-9 alcohol group of rubanone **1-H**, while exerting little steric effect in reactions with organomagnesium reagents. In fact, thanks to the remote siloxy tether, attack is preferentially directed towards the more hindered *endo* π-face of the carbonyl group,[13] giving rubanols with natural configuration at carbon C-3.

EXPERIMENTAL

General Remarks. Melting points: Büchi apparatus. – Infrared spectra: Perkin-Elmer 1710 spectrometer. – ^{1}H NMR spectra and NOE's: Bruker AM 400 spectrometer. – ^{13}C NMR spectra: Bruker Bruker AM 400. –Low and High resolution and FAB mass spectra: Finnigan MAT 312 spectrometer, 70 eV at r.t. (unless otherwise stated) with relative intensities. – Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30 - 60 µm). – Analytical t.l.c. was carried out on aluminum-backed 0.2-mm silica gel 60 F_{254} plates (E. Merck). – MTBE (methyl *t*-butyl ether).

General Procedure for the Preparation of Rubanols **2a-2d**. Rubanone **1-Ac** (500 mg, 1.41 mmol) was dissolved in THF (2.5 ml) and a solution of the *Grignard* reagent (ca. 1.5 ml) (for **2a**, **2b** and **2d**) or a solution of bis-lithiated propargyl alcohol (3 equiv) was slowly added at −78 °C with stirring. The temperature was allowed to rise r.t. within 2h. After stirring for 3h at r. t. the reaction mixture was extracted (sat. aq. $NaHCO_3$ solution and $CHCl_3$). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude product was purified by chromatography (MTBE/MeOH, 20 : 1). In case of rubanols **2b** and **2d** the diastereomers were separated. In case of rubanols **2a** and **2c** a mixture of diastereomers was obtained.

(3S,8R,9S)-3-Hydroxy-3-methyl-6'-methoxy-ruban-9-ol ***endo*-2a** and *(3R,8R,9S)-3-Hydroxy-3-methyl-6'-methoxy-ruban-9-ol* ***exo*-2a**. Starting from **1-Ac** (500 mg) and a solution of methylmagnesium bromide in THF (3 equiv, prepared from methyl iodide and magnesium) ***endo*-2a** and ***exo*-2a** were obtained, 340 mg (74%) of a 1 : 1 mixture of diastereomers. The first of each pair signals can be assigned to ***endo*-2a.** ^{1}H NMR (400 MHz, d_4-MeOH) δ 1.50-2.20 (m, 4H, H-5, H-7), 1.50/1.28 (s, 3H, CH_3), 2.00/1.78 (m, 1H, H-4), 3.28/2.88, 3.12/2.72 (m, 2H, H-6), 3.12 (m, 1H, H-8), 3.18/2.78 (d, 1H, J = 15 Hz, H-2_{exo}), 3.96 (s, 3H, H-11'), 4.20/3.08 (d, 1H, J = 15 Hz, H-2_{endo}), 5.74 (d, J = 3 Hz, 1H, H-9), 7.40-7.80 (m, 3H, Ar), 7.98 (d, 1H, J = 9 Hz, H-8'), 8.73/8.68 (d, 1H, J = 4 Hz, H-2'); ^{13}C NMR (100 MHz, d_4-MeOH) δ 18.92/21.60, 23.81/24.22 (CH_2, C-5, C-7), 26.10/27.21 (CH_3), 33.82/34.22 (CH, C-4), 49.21/48.74 (CH_2, C-6), 56.81/55.80 (CH_3, C-11'), 58.91/57.40 (CH, C-8), 59.51/58.15 (CH_2, C-2), 72.91/66.13 (CH, C-9), 74.10 (C, C-3), 99.98/101.22 (CH, C-5'), 118.01/118.10 (CH, C-3'), 122.02/122.11 (CH, C-7'), 128.44 (C, C-9'), 131.80/131.87 (CH, C-8'), 146.91/147.00 (CH, C-2'), 145.11, 146.55 (C, C-4', C-10'), 158.92 (C, C-6'); MS (240°C) *m/z* 326 (M^+, 71), 310 (62), 297 (60), 285 (48), 267 (35), 201 (63), 189 (77).

(3S,8R,9S)-3-Hydroxy-quinidine ***endo*-2b** *and (3R,8R,9S)-3-Hydroxy-quinidine* ***exo*-2b**. Starting from **1-Ac** (500 mg) and vinylmagnesium bromide (4.2 ml, 1.0 M solution in THF) more polar diastereomer ***endo*-2b** (206 mg, 43%) and less polar diastereomer ***exo*-2b** (201 mg, 42%) were isolated. Data for ***endo*-2b**: IR (KBr) ν 3380, 3080, 3012, 2932, 2872, 1620, 1588, 1508, 1472, 1432, 1364, 1240, 1032 cm^{-1}; ^{1}H NMR (400 MHz,

d$_4$-MeOH) δ 1.19, 1.32, 2.04, 2.21 (m, 4H, H-5, H-7), 1.84 (m, 1H, H-4), 2.95-3.10 (m, 2H, H-6), 3.15 (m, 1H, H-8), 2.69 (d, 1H, *J* = 15 Hz, H-2$_{exo}$), 3.96 (s, 3H, H-11'), 4.02 (d, 1H, *J* = 15 Hz, H-2$_{endo}$), 5.20 (dd, 1H, *J* = 11, *J* = 2 Hz, CH=CH*H*$_{cis}$), 5.43 (dd, 1H, *J* = 17 Hz, *J* = 2 Hz, CH=CH*H*$_{trans}$), 5.74 (d, *J* = 3 Hz, 1H, H-9), 6.37 (dd, *J* = 11 Hz, *J* = 18 Hz, 1H, C*H*=CH$_2$), 7.36 (d, *J* = 2.5 Hz, 1H, H-5'), 7.40 (dd, 1H, *J* = 2.5 Hz, *J* = 9 Hz, H-7'), 7.69 (d, 1H, *J* = 4 Hz, H-3'), 7.93 (d, 1H, *J* = 9 Hz, H-8'), 8.65 (d, 1H, *J* = 4 Hz, H-2'); NOE: H-9 irradiated H-5' (13.8%), H-3' (2.4%); ^{13}C NMR (100 MHz, d$_4$-MeOH) δ 21.26, 22.77 (CH$_2$, C-5, C-7), 35.21 (CH, C-4), 50.86 (CH$_2$, C-6), 56.84 (CH$_3$, C-11'), 59.88 (CH, C-8), 58.48 (CH$_2$, C-2), 71.92 (CH, C-9), 72.82 (C, C-3), 102.40 (CH, C-5'), 113.90 (CH$_2$, CH=*C*H$_2$), 120.12 (CH, C-3'), 123.71 (CH, C-7'), 128.16 (C, C-9'), 131.75 (CH, C-8'), 144.97 (CH, *C*H=CH$_2$), 148.43 (CH, C-2'), 143.94, 150.33 (C, C-4', C-10'), 160.04 (C, C-6'); MS (120°C) *m/z* 340 (M$^+$, 17), 267 (12), 189 (44), 152 (100); HRMS calcd. for $C_{20}H_{24}N_2O_3$: 340.1781, found 340.1795. Data for ***exo*-2b**, mp. 214 °C: IR (KBr) ν 3380, 3080, 3012, 2932, 2872, 1620, 1588, 1508, 1472, 1432, 1364, 1240, 1032 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.08, 1.48, 1.72, 2.46 (m, 4H, H-5, H-7), 1.88 (m, 1H, H-4), 2.82, 3.17 (m, 3H, H-6, H-8), 3.05 (d, 2H, *J* = 15 Hz, C-9, H-2$_{exo}$), 3.78 (s, 3H, H-11'), 3.80 (d, 1H, *J* = 15 Hz, H-2$_{endo}$), 5.20 (d, 1H, *J* = 11, CH=CH*H*$_{cis}$), 5.35 (d, 1H, *J* = 17, CH=CH*H*$_{trans}$), 5.96 (br, 1H, H-9), 6.01 (dd, *J* = 11 Hz, *J* = 18 Hz, 1H, C*H*=CH$_2$), 7.08 (d, *J* = 2 Hz, 1H, H-5'), 7.24 (dd, 1H, *J* = 2.5 Hz, *J* = 9 Hz, H-7'), 7.54 (d, 1H, *J* = 5 Hz, H-3'), 7.89 (d, 1H, *J* = 9 Hz, H-8'), 8.56 (d, 1H, *J* = 5 Hz, H-2'); ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.23, 29.72 (CH$_2$, C-5, C-7), 34.18 (CH, C-4), 49.89 (CH$_2$, C-6), 55.91 (CH$_3$, C-11'), 58.96 (CH, C-8), 57.34 (CH$_2$, C-2), 70.78 (CH, C-9), 70.83 (C, C-3), 100.88 (CH, C-5'), 113.80 (CH$_2$, CH=*C*H$_2$), 118.09 (CH, C-3'), 121.81 (CH, C-7'), 125.92 (C, C-9'), 131.26 (CH, C-8'), 141.89 (CH, *C*H=CH$_2$), 147.26 (CH, C-2'), 143.84, 146.82 (C, C-4', C-10'), 157.91 (C, C-6'). MS (120°C) *m/z* 340 (M$^+$, 17), 267 (11), 189 (43), 152 (100).

(3S,8R,9S)-3-Hydroxy-3-(3''-hydroxy-1''-propynyl)-6'-methoxy-ruban-9-ol ***endo*-2c** and *(3R,8R,9S)-3-Hydroxy-3-(3''-hydroxy-1''-propynyl)-6'-methoxy-ruban-9-ol* ***exo*-2c**. Starting from **1-Ac** (500 mg) and a solution of bis-lithiated propargyl alcohol in THF (3 equiv, prepared from 3-propynol and *n*-BuLi) a mixture (1.6 : 1) of diastereomers ***endo*-2c** and ***exo*-2c** (416 mg, 80%) was isolated. IR (KBr) ν 3372, 2936, 2872, 2508, 2360, 1620, 1592, 1508, 1472, 1452, 1432, 1364, 1240, 1100, 1028 cm^{-1}; ^{1}H NMR (400 MHz, d$_4$-MeOH) δ 1.31, 1.58, 2.41/2.32 (m, 4H, H-5, H-7), 1.99/2.08 (m, 1H, H-4), 2.79 (m, 2H, H-6), 3.05 (d, 1H, *J* = 14 Hz, H-2$_{exo}$), 3.15 (m, 1H, H-8), 3.65 (d, 1H, *J* = 14 Hz, H-2$_{endo}$), 3.98 (s, 3H, H-11'), 4.22/4.32 (s, 2H, C*H*$_2$OH), 5.61/5.56 (d, *J* =5 Hz, 1H, H-9), 7.46 (d, *J* = 2.5 Hz, 1H, H-5'), 7.39 (dd, 1H, *J* = 2.5 Hz, *J* = 9 Hz, H-7'), 7.64 (d, 1H, *J* = 5 Hz, H-3'), 7.93 (d, 1H, *J* = 9 Hz, H-8'), 8.68 (d, 1H, *J* = 5 Hz, H-2'); ^{13}C NMR (100 MHz, d$_4$-MeOH) δ 21.59/20.29, 24.12/25.51 (CH$_2$, C-5, C-7), 36.26/36.18 (CH, C-4), 50.63/50.38 (CH$_2$, C-6), 51.08/51.22 (CH$_2$OH), 56.67/56.65 (CH$_3$, C-11'), 60.32/60.23 (CH, C-8), 61.28/61.02 (CH$_2$, C-2), 67.96/68.26 (C, C-3), 72.61 (CH, C-9), 83.62/83.22, 89.81/89.85 (C, C≡C), 102.87/102.86 (CH, C-5'), 120.53/120.56 (CH, C-3'), 123.64 (CH, C-7'), 128.69/128.64 (C, C-9'), 131.62 (CH, C-8'), 141.89 (CH, C-10), 148.48 (CH, C-2'), 145.14, 150.50/150.69 (C, C-4', C-10'), 159.89/159.85 (C, C-6'); MS (200°C) *m/z* 368 (M$^+$, 16), 351 (21), 325 (41), 284 (47), 267 (34), 214 (89), 202 (59), 189 (94); HRMS calcd. for $C_{21}H_{24}N_2O_4$: 368.1736, found 368.1730.

(3S,8R,9S)-3-Hydroxy-6'-methoxy-3-phenyl-ruban-9-ol ***endo*-2d** and *(3R,8R,9S)-3-Hydroxy-6'-methoxy-3-phenyl-ruban-9-ol* ***exo*-2d**. Starting from **1-Ac** (500 mg) and a solution of phenylmagnesium bromide in THF (3 equiv, prepared from bromobenzene and magnesium) the more polar diastereomer ***endo*-2d** (386 mg, 70%)

and the less polar diastereomer ***exo*-2d** (44 mg, 8%) were obtained. Data for ***endo*-2d**, mp. 188 °C. IR (KBr) ν 3412, 2932, 1620, 1592, 1508, 1472, 1432, 1364, 1240, 1108, 1028 cm^{-1}. ^{1}H NMR (400 MHz, d$_4$-MeOH) δ 1.18, 1.39, 1.92, 2.12 (m, 4H, H-5, H-7), 2.30 (m, 1H, H-4), 2.99, 3.12 (m, 2H, H-6), 3.10 (m, 1H, H-8), 3.32 (d, 1H, *J* = 15 Hz, H-2$_{exo}$), 3.95 (s, 3H, H-11'), 4.42 (d, 1H, *J* = 15 Hz, H-2$_{endo}$), 5.65 (d, *J* = 3 Hz, 1H, H-9), 7.25-7.40 (m, 5H, Ar), 7.55 (d, 1H, *J* = 5 Hz, H-3'), 7.68 (d, *J* = 9 Hz, 2H, Ph), 7.91 (d, 1H, *J* = 9 Hz, H-8'), 8.58 (d, 1H, *J* = 5 Hz, H-2'); NOE: H-9 irradiated H-2$_{endo}$ (2.7%), H-8 (3.0%), H-5' (16.1%), H-3' (3.4%); H-(Ph$_{ortho}$) irradiated H-2$_{endo}$ (2.9%), H-4 (3.3%), H-(Ph$_{meta}$) (13.0%); ^{13}C NMR (100 MHz, d$_4$-MeOH) δ 21.92, 23.58 (CH$_2$, C-5, C-7), 34.93 (CH, C-4), 51.03 (CH$_2$, C-6), 56.63 (CH$_3$, C-11'), 60.08 (CH, C-8), 59.34 (CH$_2$, C-2), 72.56 (CH, C-9), 74.02 (C, C-3), 102.61 (CH, C-5'), 120.27 (CH, C-3'), 123.62 (CH, C-7'), 128.42 (C, C-9'), 127.83, 128.38, 129.50 (CH, Ph), 131.67 (CH, C-8'), 141.89 (CH, C-10), 148.43 (CH, C-2'), 145.00, 147.59 (C, C-4', C-10'), 150.52 (C, Ph), 159.88 (C, C-6'); MS (170°C) *m/z* 390 (M$^+$, 19), 372 (11), 334 (13), 285 (29), 267 (28), 215 (51), 202 (100), 189 (56); HRMS calcd. for $C_{24}H_{26}N_2O_3$: 390.1943, found 390.1961. Data for ***exo*-2d**. IR (KBr) ν 3412, 2932, 1620, 1592, 1508, 1472, 1432, 1364, 1240, 1108, 1028 cm^{-1}; ^{1}H NMR (400 MHz, d$_4$-MeOH) δ 1.32, 1.46, 2.69 (m, 4H, H-5, H-7), 2.20 (m, 1H, H-4), 2.85 (m, 2H, H-6), 3.32 (m, 1H, H-8), 3.78 (d, 2H, *J* = 15 Hz, H-2$_{exo}$), 3.98 (s, 3H, H-11'), 3.92 (d, 1H, *J* = 15 Hz, H-2$_{endo}$), 5.92 (d, *J* = 3 Hz, 1H, H-9), 7.25-7.50 (m, 6H, Ar), 7.75 (d, 1H, *J* = 4 Hz, H-3'), 7.55 (d, *J* = 9 Hz, 1H, Ph), 7.91 (d, 1H, *J* = 9 Hz, H-8'), 8.58 (d, 1H, *J* = 4 Hz, H-2'); ^{13}C NMR (100 MHz, d$_4$-MeOH) δ 22.02, 22.84 (CH$_2$, C-5, C-7), 36.23 (CH, C-4), 50.61 (CH$_2$, C-6), 56.88 (CH$_3$, C-11'), 60.88 (CH, C-8), 58.18 (CH$_2$, C-2), 72.12 (CH, C-9), 73.28 (C, C-3), 102.82 (CH, C-5'), 120.42 (CH, C-3'), 123.71 (CH, C-7'), 128.45 (C, C-9'), 127.38, 128.62, 129.58 (CH, Ph), 131.77 (CH, C-8'), 141.89 (CH, C-10), 148.49 (CH, C-2'), 145.13, 146.41 (C, C-4', C-10'), 149.62 (C, Ph), 160.10 (C, C-6'); MS (200°C) *m/z* 390 (M$^+$, 25), 372 (23), 334 (14), 285 (29), 267 (31), 202 (100), 173 (35); HRMS calcd. for $C_{24}H_{26}N_2O_3$: 390.1943, found 390.1957.

(8R,9S)-9-tert.Butyldimethylsilyloxy-6'-methoxy-ruban-3-one **1-TBDS.** Rubanone **1-H** (1.18 g, 3.7 mmol), imidazole (0.51 g, 2.0 eq) and Me$_2$Bu^{t}SiCl (843 mg, 1.5 eq) were dissolved in dry DMF (1.1 ml) and stirred for 10 h at 100 °C. The cooled reaction mixture was extracted (sat. aq. NaHCO$_3$ solution and CHCl$_3$). The combined organic layers were dried (MgSO$_4$), filtered and the solvent was removed *in vacuo*. The crude product was purified by chromatography (MTBE/MeOH, 20 : 1) to obtain 1.31 g (83%) of **1-TBDS**, colorless solid, mp. 95 °C. IR (KBr) ν 3164, 3072, 2936, 1712, 1620, 1592, 1508, 1472, 1368, 1308, 1228, 1084, 1032 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ −0.33, 0.15 (s, Si(CH$_3$)$_2$, each 3H), 0.96 (s, 9H, C(C*H*$_3$)$_3$), 1.59, 1.99, 2.38 (m, 4H, H-5, H-7), 2.49 (m, 1H, H-4), 2.82, 3.03 (m, 2H, H-6), 3.15 (d, 2H, *J* = 20 Hz, H-2$_{exo}$ and m, 1H, H-8), 3.98 (s, 3H, H-11'), 4.04 (d, 1H, *J* = 20 Hz, H-2$_{endo}$), 5.68 (d, 1H, *J*= 3 Hz, H-9), 7.17 (s, 1H, H-5'), 7.41 (dd, 1H, *J* = 2 Hz, *J* = 10 Hz, H-7'), 7.49 (d, 1H, *J* = 4 Hz, H-3'), 8.07 (d, 1H, *J* = 10 Hz, H-8'), 8.76 (d, 1H, *J* = 4 Hz, H-2'); NOE: H-9 irradiated H-5' (18.4%), H-8 (3.8%), H-2$_{endo}$ (2.9%), H-3' (2.3%); H-2$_{endo}$ irradiated H-2$_{exo}$ (18.3%), H-7$_{endo}$ (4.5%), H-9 (3.8%); H-7$_{endo}$ (2.38 ppm) irradiated H-3' (4.8%), H-7$_{exo}$ (15.6%); H-8 irradiated H-9 (2.7%), H-3' (5.8%); H-7$_{exo}$ (1.58 ppm) 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 −0.51, −0.40 (Si(CH$_3$)$_2$), 17.98 (*C*(CH$_3$)$_3$), 24.02, 25.17 (CH$_2$, C-5, C-7), 26.02 (C(*C*H$_3$)$_3$), 40.80 (CH, C-4), 50.96 (CH$_2$, C-6), 55.58 (CH$_3$, C-11'), 59.20 (CH, C-8), 59.65 (CH$_2$, C-2), 72.82 (CH, C-9), 102.10 (CH, C-5'), 118.32 (CH, C-3'), 122.52 (CH, C-7'), 125.82 (C, C-9'), 132.18 (CH, C-8'), 147.43 (CH, C-2'), 144.21,

146.85 (C, C-4', C-10'), 158.02 (C, C-6'), 219.12 (C, C-3); MS (130°C) *m/z* 426 (M^+, 13), 398 (77), 383 (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.

General Procedure for the Preparation of Rubanols **3a-3c.** Rubanone **1-TBDS** (300 mg, 0.70 mmol) was dissolved in THF (2.5 ml). A solution of the *Grignard* reagent (ca. 1.5 ml) (for **2a**, **2b** and **2d**) or a solution of bis lithiated propargylic alcohol (3 equiv) was slowly added at −78 °C with stirring. The temperature was allowed to rise to r.t. within 2h. After stirring for 3 h at r. t. the reaction mixture was extracted (sat. aq. $NaHCO_3$ solution and $CHCl_3$). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude product was purified by chromatography (MTBE/MeOH, 20 : 1).

(3S,8R,9S)-9-tert.Butyldimethylsilyloxy-3-hydroxy-quinidine ***endo*-3a** and *(3R,8R,9S)-9-tert.Butyldimethylsilyloxy-3-hydroxy-quinidine* ***exo*-3a** Starting from **1-TBDS** (300 mg) and a solution of vinylmagnesium bromide (3 equiv, 1.0 M in THF) a mixture (4.5 : 1) of diastereomers ***endo*-3a** and ***exo*-3a** (270 mg, 85%) was isolated. The first of each pair of signals can be assigned to diastereomer ***endo*-3a**. IR (KBr) ν 3388, 2952, 2856, 1620, 1588, 1508, 1472, 1432, 1360, 1252, 1116, 1068, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.32/−0.47, 0.09/0.05 (s, $Si(CH_3)_2$, each 3H), 0.92/0.80 (s, 9H, $C(CH_3)_3$), 1.18, 1.93, 2.21 (m, 4H, H-5, H-7), 1.85 (m, 1H, H-4), 2.85, 2.92 (m, 2H, H-6), 2.96/3.43 (m, 1H, H-8), 2.65/2.44 (d, 2H, J = 15 Hz, H-2_{exo}), 3.93/3.90 (s, 3H, H-11'), 3.61/3.16 (d, 1H, J = 15 Hz, H-2_{endo}), 5.16/5.22 (dd, 1H, J = 11, J = 2 Hz, $CH=CHH_{cis}$), 5.64/5.35 (dd, 1H, J = 17 Hz, J = 2 Hz, $CH=CHH_{trans}$), 5.65/5.73 (br, 1H, H-9), 6.36/6.18 (dd, J = 11 Hz, J = 18 Hz, 1H, $CH=CH_2$), 7.16/7.21 (br, 1H, H-5'), 7.35/7.31 (dd, 1H, J = 2.5 Hz, J = 9 Hz, H-7'), 7.51/7.55 (d, 1H, J = 5 Hz, H-3'), 8.01/7.98 (d, 1H, J = 9 Hz, H-8'), 8.72/8.61 (d, 1H, J = 5 Hz, H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.81/−5.29, −4.60/−4.67 ($Si(CH_3)_2$), 18.07 ($C(CH_3)_3$), 20.52, 23.00 (CH_2, C-5, C-7), 26.03 ($C(CH_3)_3$), 33.68 (CH, C-4), 49.99/49.12 (CH_2, C-6), 55.73/56.11 (CH_3, C-11'), 59.35 (CH, C-8), 58.18 (CH_2, C-2), 72.32 (CH, C-9), 72.81 (C, C-3), 100.38/100.54 (CH, C-5'), 113.21, 112.50 (CH_2, $CH=CH_2$), 118.76/118.88 (CH, C-3'), 121.65/121.32 (CH, C-7'), 126.12 (C, C-9'), 131.81/131.47 (CH, C-8'), 144.29 (CH, $CH=CH_2$), 147.32 (CH, C-2'), 142.87, 147.28 (C, C-4', C-10'), 158.01 (C, C-6'); MS (120°C) *m/z* 454 (M^+, 8), 438 (3), 397 (6), 302 (29), 152 (100); HRMS calcd. for $C_{26}H_{38}N_2O_3Si$: 454.2652, found 454.2655.

(3S,8R,9S)-9-tert.Butyldimethylsilyloxy-3-hydroxy-6'-methoxy-3-phenyl-rubane ***endo*-3b** and *(3R,8R,9S)-9-tert.Butyldimethylsilyloxy-3-hydroxy-6'-methoxy-3-phenyl-rubane* ***exo*-3b**. Starting from **1-TBDS** (300 mg) and a solution of phenylmagnesium bromide (3 equiv) a mixture (6 : 1) of diastereomers ***endo*-3b** and ***exo*-3b** (303 mg, 86%) was isolated. The first of each pair of signals can be assigned to diastereomer ***endo*-3b**. IR (KBr) ν 3420, 2952, 2928, 1620, 1592, 1508, 1472, 1360, 1252, 1108, 1072, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.43/−0.59, 0.01 (s, $Si(CH_3)_2$, each 3H), 0.60/0.63 (s, 9H, $C(CH_3)_3$), 1.22, 1.33, 2.01, 2.13 (m, 4H, H-5, H-7), 2.47 (m, 1H, H-4), 2.95, 3.14 (br, 2H, H-6), 3.38/3.37 (m, 1H, H-8), 2.99/2.98 (m, H-2_{exo}), 3.96/3.84 (s, 3H, H-11'), 3.97/3.60 (d, 1H, J = 15 Hz, H-2_{endo}), 5.85 (br, 1H, H-9), 7.20-7.50 (m, 8H, Ar), 7.92/7.90 (d, 1H, J = 9 Hz, H-8'), 8.58/8.50 (d, 1H, J = 4 Hz, H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.82, −4.79 ($Si(CH_3)_2$), 17.78 ($C(CH_3)_3$), 20.38/20.96, 21.89/22.71 (CH_2, C-5, C-7), 25.61/25.58 ($C(CH_3)_3$), 31.72/29.63 (CH, C-4), 49.39/49.17 (CH_2, C-6), 56.12/56.38 (CH_3, C-11'), 59.13/59.88 (CH, C-8), 58.55/57.70 (CH_2, C-2), 79.69/77.38 (CH, C-9), 72.53/72.75 (C, C-3), 100.42/104.69 (CH, C-5'), 118.81 (CH, C-3'), 122.02 (CH, C-7'), 126.00 (C, C-9'), 125.81, 127.56, 128.59 (CH, Ph), 131.66/131.25 (CH, C-8'), 146.98/147.03 (CH, C-2'), 144.19, 145.25 (C, C-4', C-10'), 145.82 (C, Ph), 158.25 (C, C-6').

(3S,8R,9S)-9-tert.Butyldimethylsilyloxy-3-hydroxy-3-isopropyl-6'-methoxy-rubane ***endo*-3c** and *(3R,8R,9S)-9-tert.Butyldimethylsilyloxy-3-hydroxy-3-isopropyl-6'-methoxy-rubane* ***endo*-3c**. Starting from **1-TBDS** (300 mg) and a solution of *iso*propylmagnesium bromide (3 equiv) a mixture (7 : 1) of diastereomers ***endo*-3c** and ***exo*-3c** (230 mg, 70%) was isolated. The first of each pair of signals can be assigned to diastereomer ***endo*-3c**. IR ($CHCl_3$) ν 3372, 2936, 2872, 1620, 1592, 1508, 1472, 1452, 1432, 1364, 1240, 1100, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.34, 0.20 (s, $Si(CH_3)_2$, each 3H), 0.96 (m, 6H, $CH(CH_3)_2$), 0.98 (s, 9H, $C(CH_3)_3$), 1.30, 1.96 (m, 4H, H-5, H-7), 1.70 (m, 1H, $CH(CH_3)_2$), 2.05 (m, 1H, H-4), 2.90-3.10 (br, 2H, H-6), 3.00 (m, 1H, H-8), 2.80 (d, 1H, J = 15 Hz, C-9, H-2$_{exo}$), 4.01 (s, 3H, H-11'), 3.96 (d, 1H, J = 15 Hz, H-2$_{endo}$), 5.93 (br, 1H, H-9), 7.35 (s, 1H, H-5'), 7.39 (dd, 1H, J = 2.5 Hz, J = 9 Hz, H-7'), 7.50 (d, 1H, J = 4 Hz, H-3'), 8.04 (d, 1H, J = 9 Hz, H-8'), 8.74 (d, 1H, J = 4 Hz, H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.19, −4.34 ($Si(CH_3)_2$), 17.52 ($C(CH_3)_3$), 22.23/30.18 (CH_2, C-5, C-7), 25.72 ($CH(CH_3)_2$), 25.98 ($CH(CH_3)_2$, $C(CH_3)_3$), 28.93 (CH, C-4), 50.08 (CH_2, C-6), 56.12/56.21 (CH_3, C-11'), 58.90 (CH, C-8), 53.89 (CH_2, C-2), 71.00 (CH, C-9), 77.28 (C, C-3), 100.49 (CH, C-5'), 118.60 (CH, C-3'), 122.11 (CH, C-7'), 125.95 (C, C-9'), 131.88 (CH, C-8'), 147.06 (CH, C-2'), 144.30, 146.75 (C, C-4', C-10'), 158.38 (C, C-6'); MS (170°C) *m/z* 470 (M^+, 4), 428 (17), 414 (10), 372 (43), 301 (35), 73 (100).

(3S,8R,9S)-9-tert.Butyldimethylsilyloxy-3-hydroxy-6'-methoxy-rubane ***endo*-5a**. Rubanone **1-TBDS** (900 mg, 2.11 mmol) was dissolved in THF (3.5 ml) and L-Selectride (2.75 ml, 1.0 M solution in THF) was slowly added at −78 °C with stirring. The solution was stirred at −78 °C for 1h, the temperature was allowed to rise to r.t. within 3h. After stirring for 1 h at r. t. the reaction mixture was extracted (sat. aq. $NaHCO_3$ solution and $CHCl_3$). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude product was purified by chromatography (MTBE/MeOH, 20 : 1) to give a mixture (9 : 1) of rubanols ***endo*-5a** and ***exo*-5a** (769 mg, 85%), colorless solid, mp. 178 °C. IR (KBr) ν 3404, 3076, 2952, 2928, 2856, 1620, 1592, 1508, 1472, 1432, 1360, 1256, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.35, 0.19 (s, $Si(CH_3)_2$, each 3H), 0.99 (s, 9H, $C(CH_3)_3$), 1.29, 1.95 (m, 4H, H-5, H-7), 2.01 (m, 1H, H-4), 2.85-3.10 (m, 2H, H-6), 2.75 (d, 1H, J = 15 Hz, H-2$_{exo}$), 3.00 (m, 1H, H-8), 3.88 (dd, 1H, J = 15 Hz, J = 9 Hz, H-2$_{endo}$), 4.00 (s, 3H, H-11'), 4.02 (d, J = 9 Hz, H-3), 5.68 (d, 1H, J= 3 Hz, H-9), 7.32 (s, 1H, H-5'), 7.39 (dd, 1H, J = 2 Hz, J = 10 Hz, H-7'), 7.52 (d, 1H, J = 4 Hz, H-3'), 8.04 (d, 1H, J = 10 Hz, H-8'), 8.74 (d, 1H, J = 4 Hz, H-2'); NOE: H-9 irradiated H-5' (15.5%), H-8 (6.1%); H-2$_{exo}$ irradiated H-2$_{endo}$ (19.2%); H-2$_{endo}$ irradiated H-2$_{exo}$ (13.5%), H-9 (6.9%); H-3 irradiated H-4 (4.5%), H-5' irradiated H-9 (7.3%), H-11' (7.0%); H-3' irradiated H-2' (13.4%); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.18, −4.26 ($Si(CH_3)_2$), 17.78 ($C(CH_3)_3$), 18.03, 22.66 (CH_2, C-5, C-7), 25.98 ($C(CH_3)_3$), 29.13 (CH, C-4), 50.31 (CH_2, C-6), 56.11 (CH_3, C-11'), 59.02 (CH, C-8), 54.20 (CH_2, C-2), 67.22, 71.54 (CH, C-3, C-9), 101.17 (CH, C-5'), 118.61 (CH, C-3'), 122.09 (CH, C-7'), 126.07 (C, C-9'), 131.70 (CH, C-8'), 147.08 (CH, C-2'), 144.27, 147.11 (C, C-4', C-10'), 158.30 (C, C-6'); MS (110°C) *m/z* 428 (M^+, 19), 414 (4), 372 (45), 301 (37), 73 (100); HRMS calcd. for $C_{24}H_{36}N_2O_3Si$: 428.2495, found 428.2493.

General Procedure for the Preparation of Tosylates ***endo*-4b, *exo*-4b** and ***endo*-5b.** To a solution of rubanol ***endo*-5a** (450 mg) or a mixture (1 : 1.1) of rubanols **endo-4a** and **exo-4a** (391 mg, 1.1 mmol), tosyl chloride (440 mg, 2.0 eq) and DMAP (26 mg, 0.2 eq) in dry CH_2Cl_2 (3 ml) was added dry NEt_3 (0.29 ml, 2.0 eq). After refluxing for 6h the reaction mixture was extracted (sat. aq. $NaHCO_3$ solution and $CHCl_3$). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude product was purified by chromatography (MTBE/MeOH, 20 : 1). The tosylates ***endo*-4b** and ***exo*-4b** were separated by chromatography. Rubanol ***endo*-5a** (9 : 1 d. e.) gave tosylate ***endo*-5b** (9 : 1 d. e.).

(3S,8R,9S)-9-tert.Butyldimethylsilyloxy-6'-methoxy-3-tosyloxy-rubane ***endo*-5b**. Starting with ***endo*-5a** (450 mg) ***endo*-5b** was isolated (459 mg, 75%), slight yellow solid, mp. 164 °C. IR ($CHCl_3$) ν 2956, 2880, 1620, 1592, 1508, 1472, 1432, 1360, 1256, 1228, 1176, 1120, 1080, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.36, 0.09 (s, $Si(CH_3)_2$, each 3H), 0.95 (s, 9H, $C(CH_3)_3$), 1.22, 1.78 (m, 4H, H-5, H-7), 2.07 (m, 1H, H-4), 2.46 (s, 3H, $C_6H_4CH_3$), 2.69 (d, 1H, J = 15 Hz, H-2$_{exo}$), 2.86 (m, 2H, H-6), 3.00 (m, 1H, H-8), 3.74 (dd, 1H, J = 15 Hz, J = 8 Hz, H-2$_{endo}$), 43.93 (s, 3H, H-11'),.59 (m, H-3), 5.56 (s, 1H, H-9), 7.10 (d, J = 2 Hz, 1H, H-5'), 7.35 (d, J = 9 Hz, 2H, Tol), 7.37 (dd, 1H, J = 10 Hz, J = 2 Hz, H-7'), 7.45 (d, 1H, J = 4 Hz, H-3'), 7.80 (d, J = 9 Hz, 2H, Tol), 8.03 (d, 1H, J = 10 Hz, H-8'), 8.73 (d, 1H, J = 4 Hz, H-2'); NOE: H-3 irradiated H-2$_{endo}$ (5.4%), H-4 (6.4%), H-7$_{endo}$; H-2$_{endo}$ irradiated H-3 (8.6%), H-9 (2.3%), H-2$_{exo}$ (23.2%); H-2$_{exo}$ irradiated H-2$_{endo}$ (12.1%); H-9 irradiated H5' (17.1%), H-8 (6.6%), H-2$_{endo}$ (2.3%); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.28, −4.37 ($Si(CH_3)_2$), 17.91 ($C(CH_3)_3$), 17.85, 23.02 (CH_2, C-5, C-7), 21.56 ($C_6H_4CH_3$), 25.92 ($C(CH_3)_3$), 27.27 (CH, C-4), 50.51 (CH_2, C-6), 51.62 (CH_2, C-2), 55.69 (CH_3, C-11'), 58.82 (CH, C-8), 72.69, 79.61 (CH, C-3, C-9), 100.32 (CH, C-5'), 118.39 (CH, C-3'), 121.49 (CH, C-7'), 125.86 (C, C-9'), 127.59, 129.80 (CH, Tol), 131.97 (CH, C-8'), 134.25 (C, Tol with CH_3), 147.29 (CH, C-2'), 144.61 (C, Tol with S), 144.31, 147.12 (C, C-4', C-10'), 157.98 (C, C-6'); MS (180°C) *m z* 582 (M$^+$, 6), 567 (2), 525 (8), 427 (17), 410 (36), 353 (17), 302 (52), 74 (100).

(3S,8R,9S)-9-Acetoxy-6'-methoxy-3-tosyloxy-rubane ***endo*-4b** and *(RS,8R,9R)-9-Acetoxy-6'-methoxy-3-tosyloxy-rubane* ***exo*-4b**. Starting with a mixture (1 : 1.1) of rubanols ***endo*-4a** and ***exo*-4a** (391 mg) (which were prepared from rubanone **1-Ac**, $NaBH_4$ (1.5 equiv) and $CeCl_3 \cdot 7\,H_2O$)[3] the more polar tosylate ***exo*-4b** (215 mg, 40%) and the less polar tosylate ***endo*-4b** (188 mg, 35%) were isolated by chromatography. Data for ***endo*-4b**, mp. 180 °C. IR ($CHCl_3$) ν 2956, 2884, 1736, 1620, 1592, 1508, 1472, 1432, 1364, 1220, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30,1.60, 1.81 (m, 4H, H-5, H-7), 2.18 (m, 1H, H-4), 2.12 (s, 3H, C-13), 2.44 (s, 3H, $C_6H_4CH_3$), 2.65-2.85 (m, 2H, H-6), 2.74 (d, J = 15 Hz, 1H, H-2$_{exo}$), 3.28 (m, 1H, H-8), 3.93 (s, 3H, H-11'), 3.42 (dd, 1H, J = 15 Hz, J = 9 Hz, H-2$_{endo}$), 4.72 (m, H-3), 6.40 (d, J = 5 Hz, 1H, H-9), 7.25-7.40 (m, 5, Ar), 7.81 (d, J = 9 Hz, 2H, Tol), 8.02 (d, 1H, J = 9 Hz, H-8'), 8.72 (d, 1H, J = 4 Hz, H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.00 ($C_6H_4CH_3$), 21.67 (CH_3, C-13), 27.10 (CH, C-4), 26.19, 29.70 (CH_2, C-5, C-7), 49.98 (CH_2, C-6), 50.90 (CH_2, C-2), 55.72 (CH_3, C-11'), 57.31 (CH, C-8), 73.31, 78.74 (CH, C-3, C-9), 101.18 (CH, C-5'), 118.23 (CH, C-3'), 121.97 (CH, C-7'), 126.85 (C, C-9'), 127.61, 129.96 (CH, Tol), 131.02 (CH, C-8'), 134.12 (C, Tol with CH_3), 147.29 (CH, C-2'), 142.89 (C, Tol with S), 144.59, 144.94 (C, C-4', C-10'), 158.11 (C, C-6'), 169.57 (C, C-12); MS (160°C) *m/z* 510 (M$^+$, 5), 449 (3), 355 (30), 338 (46), 295 (71), 249 (51), 231 (92), 189 (83), 172 (81). FAB-MS *m/z* 511 (M$^+$ + 1, 100). Data for ***exo*-4b**, mp. 185 °C. IR ($CHCl_3$) ν 2956, 2884, 1736, 1620, 1592, 1508, 1472, 1432, 1364, 1220, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.65, 2.18 (m, 4H, H-5, H-7), 2.11 (m, 1H, H-4), 2.19 (s, 3H, C-13), 2.48 (s, 3H, $C_6H_4CH_3$), 2.60, 2.75 (m, 2H, H-6), 3.05 (m, 1H, H-2$_{exo}$), 3.22 (d, J = 14 Hz, 1H, H-2$_{endo}$), 3.25 (m, 1H, H-8), 3.97 (s, 3H, H-11'), 4.55 (m, H-3), 6.60 (d, J = 5 Hz, 1H, H-9), 7.31 (d, J = 4 Hz, 1H, H-3'), 7.39 (s, 1H, H-5'), 7.41 (m, 3H, Tol, H-7'), 7.82 (d, J = 9 Hz, 2H, Tol), 8.02 (d, 1H, J = 9 Hz, H-8'), 8.72 (d, 1H, J = 4 Hz, H-2'); NOE: H-3 irradiated H-2$_{exo}$ (6.4%), H-4 (5.0%); H-9 irradiated H-2$_{endo}$ (3.0%), H-8 (3.2%), H-5' (20.4%); H-6$_{endo}$ irradiated H-8 (13.1%), H-6$_{exo}$ (15.0%); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.38, 29.71 (CH_2, C-5, C-7), 21.04 ($C_6H_4CH_3$), 21.70 (CH_3,

C-13), 27.56 (CH, C-4), 49.42 (CH_2, C-6), 50.40 (CH_2, C-2), 55.91 (CH_3, C-11'), 58.53 (CH, C-8), 72.98, 78.03 (CH, C-3, C-9), 101.04 (CH, C-5'), 118.24 (CH, C-3'), 122.21 (CH, C-7'), 126.82 (C, C-9'), 127.69, 130.04 (CH, Tol), 131.69 (CH, C-8'), 134.21 (C, Tol with CH_3), 146.92 (CH, C-2'), 143.62 (C, Tol with S), 144.31, 144.97 (C, C-4', C-10'), 157.92 (C, C-6'), 169.91 (C, C-12); MS (120°C) *m/z* 510 (M^+, 1), 366 (9), 306 (11), 295 (3), 188 (11), 136 (17), 73 (100); FAB-MS *m/z* 511 ($M^+ + 1$, 100).

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REFERENCES AND NOTES

[1] Chemical Abstracts name of rubanone **1-H**: [1R-[1α,4α,6β(S*)]]-6-[Hydroxy(6-methoxy-4-quinolinyl)methyl]-1-azabicyclo[2.2.2]octane-3-one. Our numbering of *Cinchona alkaloids* follows the *cinchona* convention as indicated in Scheme 1.

[2] (a) Uskokovic, M. R.; Grethe, G. *The Alkaloids*, Academic Press, New York, **1973**, *Vol. 14*, 181; (b) Verpoorte, R.; Schripsema, J.; van der Leer, T. *The Alkaloids*, Academic Press, New York, **1988**, *Vol. 34*, 331; (c) Malcolm, A. D.; David, G. K. *Acta Leidensia* **1987**, *55*, 87.

[3] (a) von Riesen, C.; Jones, P. G.; Hoffmann, H. M. R. *Chem. Eur. J.* **1996**, *2*, 673; (b) von Riesen, C.; Hoffmann, H. M. R. *Chem. Eur. J.* **1996**, *2*, 680; (c) 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.

[4] D' Alonzo, A. J.; Butterfield, J. L.; Drexler, A. P.; Sergio S. L. *J. Cardiovascular Pharmacol.* **1990**, *16*, 506.

[5] Alcohol **2b** has also been prepared by Carroll et al., see reference 3(c).

[6] Crystal Data of ***endo*-2d**:
Crystal color, colorless; chemical formula, $C_{24}H_{26}N_2O_3 \cdot \frac{1}{2} H_2O$; molecular weight [g/mol], 399.15; temperature [°C], 27; crystal size [mm^3], 0.15 x 0.40 x 0.40; crystal system, monoclinic; space group, I2 no. 5; parameters, a [Å] = 11.108 (2), α [°] = 90.0, b = 10.057 (2), β = 104.29 (2), c = 19.187 (3), γ = 90.0; cell volumina [$Å^3$], 2077.1 (7); molecules per unit cell Z, 4; calculated density [g/cm^3], 1.278; F (000), 852; 2θ min-max [°], 4.8, 56.3; total number of reflections, 11112; number of independent reflections, 4946; number of refined parameters 281; goodness of fit, 1.17; R-values, R1 = 0.0316 wR2 = 0.0383; final difference Fourier min, max [$eÅ^{-3}$], 0.15, -0.13. The full crystallographic data are to be published as NCS in *Z. Kristallogr.* and may be obtained from the Fachinformationszentrum Karlsruhe, D-76344, Eggenstein-Leopoldshafen (Germany) on quoting the depository number CSD 409000.

[7] Langer, P. PhD thesis, University of Hannover **1997**; see also Rowan, S. J.; Brady, P. A.; Sanders, J. K. M. *Angew. Chem.* **1996**, *108*, 2283.

[8] (a) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. J.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069; (b) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. J. *J. Org. Chem.* **1990**, *55*, 6121.

[9] The ^{3}J(H-8)-(H-9) coupling constant is a sensitive indicator for the *open-closed* equilibria and can be calculated by a modified *Karplus* equation (see Colucci, W. J.; Gandour, R. D.; Mooberry, E. A. *J. Am. Chem. Soc.* **1986**, *108*, 7141). For **1-TBDS** the small ^{3}J(H-8)-(H-9) 3 Hz suggests an *open* conformation.

[10] The *anti-open* conformation for **1-TBDS** is indicated by the NOE's (H-9)-(H-5′) (18.4%), (H-9)-(H-8) (3.8%), (H-8)-(H-5′) (5.8%) and (H-7$_{endo}$)-(H-3′) (4.8%). A small amount of *anti-closed* conformation is indicated by NOE's (H-3′)-(H-8) (5.8%) and (H-2$_{endo}$)-(H-9) (3.8%). The weak NOE (H-3′)-(H-9) (2.3%) indicates that a *syn* conformation (*syn-open* or *syn-closed*) is also populated.

[11] Strong inter-ring NOE's (H-9)-(H-5′), significant NOE's ((H-8)-(H-9) and small ^{3}J(H-8)-(H-9) (ca. 3 Hz) suggest the *anti-open* conformation to be predominantly populated by all rubanols investigated herein. However, NOE (H-7$_{endo}$)-(H-3′) only was observed for rubanol ***endo*-5a**. A small amount of *closed* conformation (*syn* or *anti*) is indicated by weak NOE's (H-9)-(H-2$_{endo}$) for ***endo*-2d**, ***endo*-5b**, ***endo*-5b** and for ***exo*-4b**.

[12] The relative energies of the TBDS-protected rubanols ***endo*-3b** and ***exo*-3b** were calculated by MM2 (E(***endo*-3b**) - E(***exo*-3b**) = 0.95 kcal/mol). Thus, rubanol ***endo*-3b** is slightly more stable than epimeric ***exo*-3b**. The energies of the rubanols were sequentially minimized using a MM2 force field (see Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 27) working with the MacroModel© program. A systematic 2000 step Monte Carlo procedure was applied for conformational analysis.

[13] For stereocontrol of nucleophilic attack to a carbonyl group containing an α- and β-alkoxy substituent, see: Reetz, M. T. *Angew. Chem.* **1984**, *96*, 73. Review on complexation of α- and β-alkoxy carbonyls with Lewis acids, see: Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. See also: Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847; Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1995**, *117*, 5055; Martin, R.; Pascual, O., Romea, P.; Rovira, R.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1997**, *38*, 1633. See also: Coppola, G. M.; Schuster, H. F. in *α-Hydroxy Acids in Enantioselective Syntheses*, VCH, Weinheim, **1997**.

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