1,2-Carbonyl Transposition of a Protected Rubanone: Stereoselective Synthesis of Bicyclic and Tricyclic Lactams Derived from Quinidine

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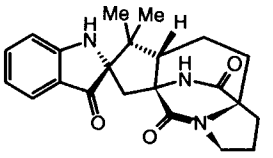
α-Bromination of 9-acetoxy rubanone **2** and subsequent reaction with secondary amines gave bicyclic α-amino ketones as a kinetic product and a 4-oxa-1-azatwistan-2-one **6** under thermodynamic conditions. This two-step procedure represents a concise 1,2-carbonyl transposition and provides a short route to lactam alkaloids.

Introduction. – Despite the central role of the carbonyl (CO) group in organic chemistry, CO transpositions have not been extensively exploited in organic synthesis in recent years since the review by *Morris* [1]. To our knowledge, only a few of the methods developed have been applied to natural-product chemistry. Selected examples are the 1,3-carbonyl transposition in the course of the synthesis of (+)-ceroplastol I [2a] and stemodin [2b], and the 1,2-CO transposition of *Robinson* annulation products[1]). The resulting 1,4-diketones have served as precursors of strained polycyclic frameworks such as ylangene [2c]. *Woodward et al.* have described a detailed procedure for converting cyclohexanone into 2,2-(trimethylenedithio)cyclohexanone [2d]. Carbonyl-conjugated vinylic selenides undergo 1,3- and 1,5-CO transposition sequences mediated by addition of *Grignard* or organolithium reagents and subsequent acid hydrolysis [2e].

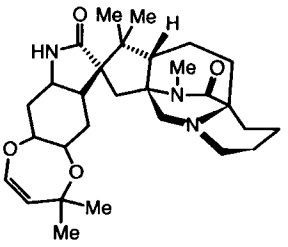
The 1,2-CO transposition of an α-brominated 9-acetoxyrubanone **3** with cyclic amines and subsequent cyclization described herein provides a short route to novel bi- and tricyclic lactam alkaloids derived from quinidine. Lactam alkaloids occur in a large number of fungi [3]. The culture extracts of *Penicillium brevicompactum* were observed to produce several highly colored, neutral toxic metabolites, the brevianamides A–D [4]. These complex alkaloids are part of a small class of natural products that have recently been joined by the mycotoxins marcfortine and paraherquamide.

Marcfortine A has been isolated from *Penicillium roqueforti* which is the essential fungus used in the production of many varieties of blue cheese containing internal mould [5]. Chaenorhine is a member of the family of polyamine alkaloids. Incorporating units corresponding to spermine and *p*-hydroxycinnamic acid, it is related to other naturally occurring macrocyclic polyamine lactams such as the hypotensive agent ephedradine A [6]. Due to the intrinsic interest in lactam alkaloids, we investigated the possibility of a direct α-functionalization of 9-acetoxyrubanones at C(2) and a suitable 1,2-CO transposition to have short access to lactam derivatives of *Cinchona* alkaloids.

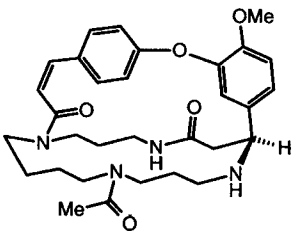
[1]) In this work, the usual 1,5-functionality distance of *Robinson* annulation products was transformed into the required 1,4-dicarbonyl distance.



Brevianamide B



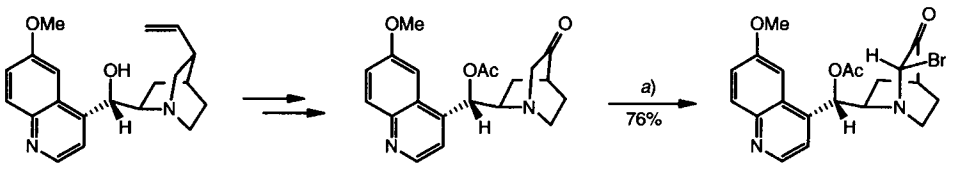
Marcfortine



(+)-Chaenorhine

9-Acetoxyrubanone **2** has recently been prepared from quinidine (**1**) by a reliable five-step reaction sequence in high yield [7]. The α-bromination of **2** is feasible and proceeds under optimized conditions in satisfactory yield (72%) and with complete diastereoselectivity (*Scheme 1*). The configuration of the α-brominated 9-acetoxyrubanone **3** at C(2) was established by a strong NOE H–C(2) and H–C(9)[2] (11.6%). Diastereoselectivity is assumed to be sterically controlled.

Scheme 1



1 **2** **3**

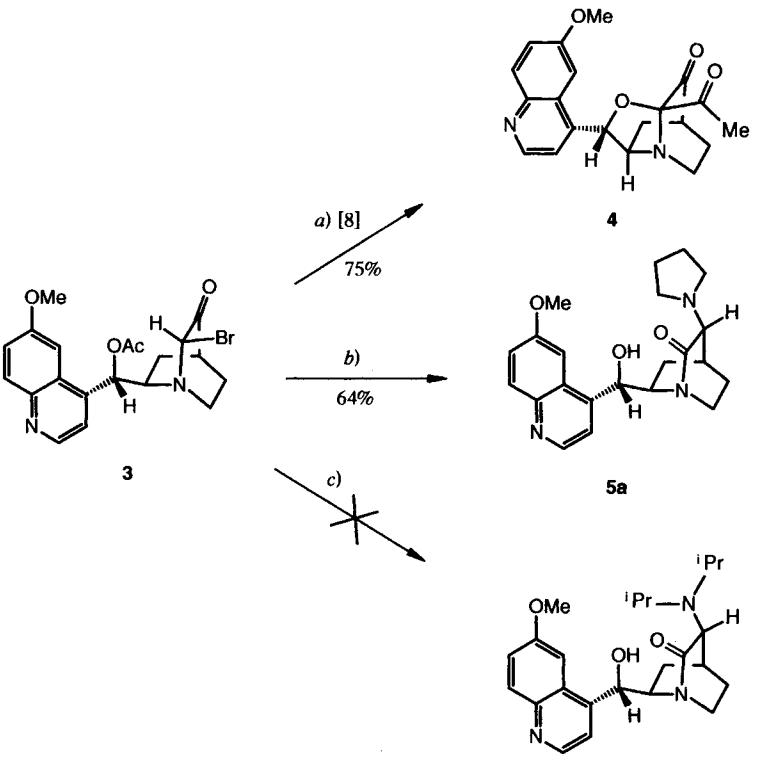
a) 3.0 equiv. Br_2, 1.2 equiv. Br_3P, AcOH, r.t., 6 h, 76%.

The reaction of **3** with NaN_3 and NaI in DMF furnished the tricyclic *Cinchona* cage compound **4**, containing a 1,3-dicarbonyl-2-N,O functionality, in good yield (75%; *Scheme 2*). The one-pot cyclization involves a reduction-oxidation sequence and an intramolecular acyl transfer, and has been applied to various acyl protecting groups [8].

Results and Discussion. – Based on the results obtained with NaN_3 and NaI, we examined the reaction of α-brominated 9-acetoxyrubanone **3** with various cyclic and acyclic amines. In view of the different electrophilic centres in **3**, simple nucleophilic

[2]) The C-atom numbering corresponds to the cinchonan numbering (see *Fig. 2*).

Scheme 2

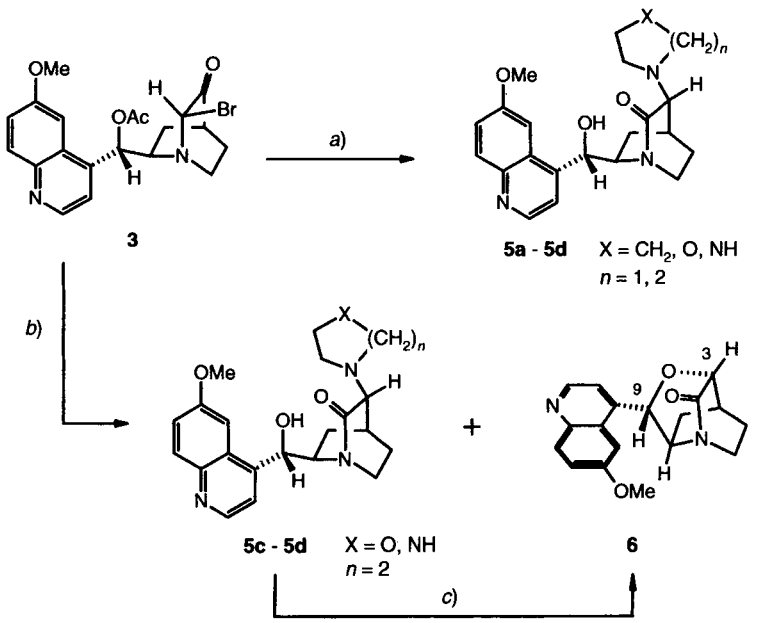


a) NaN_3 (excess), 1.0 equiv. NaI, DMF, 115°, 10 h. *b*) 10 equiv. pyrrolidine, CH_2Cl_2, r.t., 10 h. *c*) 10 equiv. $(i\text{-}Pr)_2NH$, CH_2Cl_2, r.t., 10 h.

substitution or other reactions could be expected. While acyclic amines such as $(i\text{-}Pr)_2NH$, Et_2NH, or Et_3N failed to react; pyrrolidine, a secondary cyclic amine, in CH_2Cl_2 furnished rearranged deprotected lactam **5a** in 64% yield (*Schemes 2* and *3*). Similarly, piperidine, morpholine, and piperazine also induced the 1,2-CO transposition and provided the corresponding rearranged lactams **5b–d** in fair yields (51–58%; *Table*, *Entries 1–3* and *7*). CH_2Cl_2 proved to be a suitable solvent for the 1,2-CO transposition with cyclic secondary amines. In other chlorinated and non-chlorinated solvents ($CHCl_3$, toluene, THF, MeCN), the rearranged lactams **5b–d** were formed in lower yields. As long as the reaction time did not exceed 10 h, by-products could not be discerned, and the resulting rearranged lactams were epimerically pure. Longer reaction times caused epimerization at C(3) and furnished a second product with high polarity, tricyclic cage compound **6** (*Scheme 3*). Subsequent addition of KOH, Bu_4NI, and H_2O, and stirring at elevated temperature provided the 4-oxa-1-azatwistan-2-one (= 4-oxa-1-azatricyclo[4.4.0.$0^{3,8}$]decan-2-one) **6** exclusively (*Table*, *Entries 6* and *8*).

The 1,2-CO transposition of α-brominated 9-acetoxyrubanone **3** into rearranged lactams **5a–d** was analyzed by IR, ^1H- and ^{13}C-NMR spectroscopy. FAB-MS of **5a–d** gave molecular-ion peaks. In addition to strong amide-absorption bands at 1670–

Scheme 3



a) 10 equiv. *sec*-amine, CH_2Cl_2, r.t., 10 h. *b*) 10 equiv. *sec*-amine, CH_2Cl_2, r.t., 72 h. *c*) KOH, H_2O, Bu_4NI, 40°, 1 h.

Table. *Reaction of 9-Acetoxyrubanone* **3** *with Secondary Amines*

Entry	Secondary amine	X	*n*	Reaction conditions	Rearranged lactam, yield [%]	4-Oxa-1-aza twistan-2-one **6**, yield [%]
1	Pyrrolidine	CH_2	1	10 h, r.t.	**5a** (64)	–
2	Piperidine	CH_2	2	10 h, r.t.	**5b** (58)	–
3	Morpholine	O	2	10 h, r.t.	**5c** (56)	–
4	Morpholine	O	2	48 h, r.t.	**5c** (35)	**6** (10)
5	Morpholine	O	2	72 h, 40°	**5c** (21)	**6** (18)
6	Morpholine	O	2	72 h, r.t.[a])	**5c** (0)	**6** (41)
7	Piperazine	NH	2	10 h, r.t.	**5d** (51)	–
8	Piperazine	NH	2	72 h, r.t.[a])	**5d** (0)	**6** (53)

[a]) Followed by addition of KOH, Bu_4NI, and H_2O, and stirring for 1 h at 40°.

1630 cm^{-1} in the IR spectra, ^{13}C-NMR spectra only showed one characteristic new C=O peak (C(2)) at 169.0–169.6 ppm. The C(3)=O peak (210.74 ppm) of the rubanone moiety, the peaks of the Ac group and of C(2) in ^{13}C- and ^1H-NMR spectra, respectively, had disappeared, whereas a new CH peak (C(3)) could be observed (^{13}C-NMR: 73.5–70.0, ^1H-NMR: 3.35–3.01 ppm). The signal and coupling pattern of H–C(9) (*dd*, $^3J = 6.5$, 10 Hz) in the ^1H-NMR spectrum ((D_6)DMSO) of **5a** underline that the O–C(9) is deprotected in rearranged lactams **5a–d**. This is also shown by a significant

upfield shift of the resonance (5.00–5.20 ppm) of H–C(9) relative to **3** (6.73 ppm). Furthermore, a rearrangement of the 1-azabicyclo[2.2.2]octane moiety was not observed in C,H-COSY spectra (*Fig. 1*). Therefore, treatment of α-bromorubanone **3** leads to deprotected α-amino lactams **5a–d**. In contrast to rearranged lactams **5a–d**, MS of 4-oxa-1-azatwistanone **6** shows a strong molecular-ion peak (100%). The resonance of C(9) in **6** (79.96 ppm) is shifted downfield by *ca.* 6–9 ppm relative to lactams **5a–d**, being characteristic for twisted tricyclic *Cinchona* cage structures.

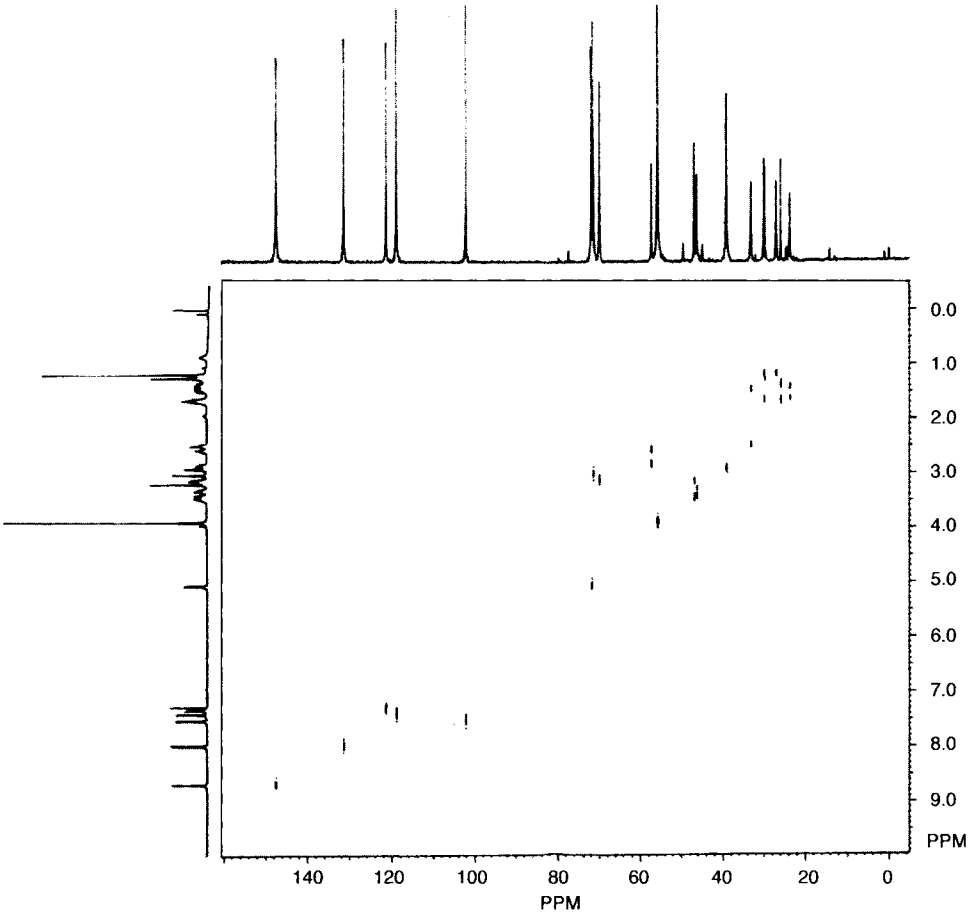
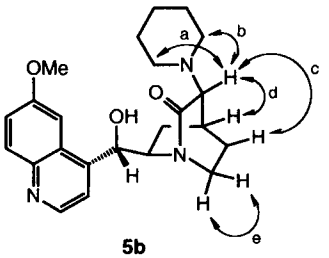


Fig. 1. *C,H-COSY Spectrum of the rearranged lactam* **5a**

Conformational analysis of *Cinchona* alkaloids was undertaken to elucidate their catalytic and chemical properties [9]. In our studies, configuration and conformation of rearranged bicyclic and tricyclic lactams were determined by NOE, ^{1}H- and ^{13}C-NMR spectroscopy. The $^3J(8,9)$ value is an indicator of the open-closed conformation equilibrium in *Cinchona* alkaloids. The small $^3J(8,9)$ value of 3 Hz suggested a staggered (open) conformation for **5b**. Moreover, the $^3J(8,9)$ coupling cannot be observed in the rigid

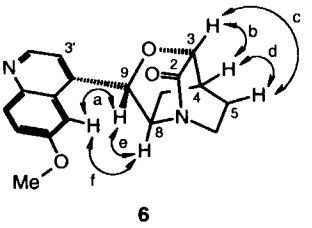
4-oxa-1-azatwistan-2-one (**6**) [10], and H–C(9) only shows a broad *singlet*. In contrast, the acetate precursor **3** showed a ^3J coupling constant of 8 Hz, due to a change in conformation from '*anti*'-open to '*anti*'-closed. Note that the '*anti*'-closed ⇌ '*anti*'-open conformational equilibrium changes on protection of the H–C(9) group. In addition, the rearranged lactams feature strong NOEs of H–C(5') with H–C(9) (15.1–21.8%).

In the case of **6** a strong NOE between H–C(5') and H–C(8) (6.4%) was also observed (*Fig. 2*). Both NOEs indicate the horizontal position of the 6-methoxyquinoline group showing the '*anti*'-open conformation. The horizontal conformation can be explained by reduced rotational mobility about the C(4')–C(9) bond, due to the sterically demanding 6'-substituted quinoline group attached to the bicyclic or tricyclic moiety. Because of the proximity of the C(9)–*OH* group and C(3) in the '*anti*'-open conformation, *exo*-**5c** is well set up for the observed cyclization leading to the tricyclic lactam **6**. Confirming evidence for the configuration at C(3) in the rearranged lactam **5b** was provided by a comparison of NOEs between H–C(3) and H–C(4), and H–C(3) and H_{exo}–C(5) in **5b** (6.0 and 2.1%, resp.) and in **6** (5.2 and 2.3%, resp.) with a defined configuration at C(3). The fact that both NOEs can be observed in **6** and **5b** with a similar intensity indicates that the amino substituent adopts the same orientation as the vinyl group in quinidine (**1**). Furthermore, this configuration is in agreement with the proposed mechanism for the CO transposition outlined in *Scheme 4*.



5b

a: 5.0%, b: 3.0%, c: 2.1%, d: 6.0%, e: 5.0%



6

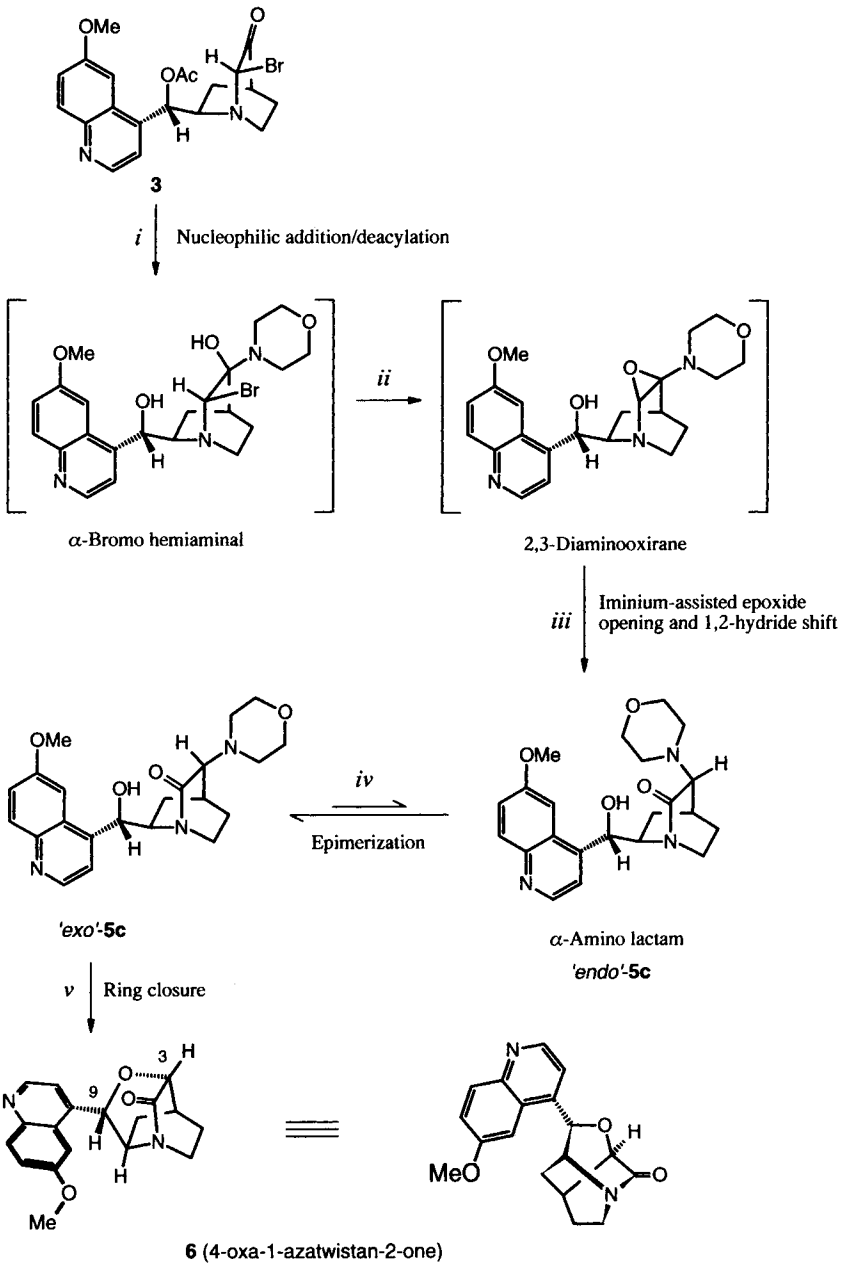
a: 21.6%, b: 5.2%, c: 2.3%, d: 2.6%, e: 4.9%, f: 6.4%

Fig. 2. *NOE Analysis of rearranged* Cinchona *alkaloids* **5** *and* **6**

A well-documented reaction pathway for a 1,2-CO transposition involves initial formation of an α-bromo ketone. This pathway has been applied to the transformation of cholestan-3-one into the corresponding cholestan-2-one, mediated by a nitrone [10]. Furthermore, the transformation of hecogenin acetate into 11-oxotigogenin acetate proceeds *via* α-bromination, subsequent epoxide generation, nucleophilic ring opening, and oxidation [11]. This 1,2-CO-transposition sequence established by *Cornforth et al.* leads us to propose the mechanism for the base-mediated CO transposition of α-bromorubanone **3** outlined in *Scheme 4*.

The secondary amine is assumed to attack the CO atom C(3) in the first step (step *i*), rather than brominated C-atom C(2). Subsequent intramolecular displacement of Br^- under the basic conditions is stereoelectronically favorable (step *ii*), giving a 2,3-diaminooxirane. The epoxide opening is accompanied by a [1,2]-H shift and oxidation at C(2) with formation of an α-amino lactam (step *iii*). The kinetic product of the rearrange-

Scheme 4



ment turned out to be the C(3)-*endo*-configurated α-amino lactam *endo*-**5c**. Extended reaction times or base treatment at elevated temperature (40°) gave rise to *exo*-**5c** epimer (step *iv*), which was not stable, but cyclized to 4-oxa-1-azatwistane **6** (step *v*). Previously, the steroidal hecogenin acetate with its CO group at C(10) was converted into 11-oxoti-

gogenin acetate in six steps [11], *via i*) α-bromination, *ii*) $NaBH_4$-mediated reduction of the CO group, *iii*) base-induced 3-*exo-tet* closure to the epoxide, *iv*) HBr-promoted additive opening, *v*) OH to CO oxidation, and *vi*) reductive removal of Br^-. In contrast, the 1,2-CO transposition of the 9-acetoxyrubanone **2** into rearranged lactam *endo*-**5c** requires only two steps.

Conclusion. – We have functionalized C(2) of 9-acetoxy-6′-methoxyruban-3-one by bromination under carefully controlled conditions and carried out a secondary-amine-mediated O migration. As a consequence, the rubanone moiety is transformed into α-amino lactams **5a–d** and into 4-oxa-1-azatwistanone **6**. To our knowledge, the direct 1,2-CO transposition in *Cinchona* alkaloids to lactam alkaloids has not been previously observed.

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Experimental Part

General. THF was distilled over Na and benzophenone before use. AcOEt and *t*-BuOMe were distilled before use. Anal. TLC: on Al-backed 0.2-mm silica gel *60* F_{254} plates (*E. Merck*). Prep. column chromatography (CC): on *J. T. Baker* silica gel (particle size 30–60 mm). M.p.: on a *Büchi* apparatus, uncorrected. IR: on a *Perkin-Elmer 1710* spectrometer. ^{1}H- and ^{13}C-NMR: on a *Bruker AM 400* spectrometer, in $CDCl_3$ unless otherwise stated, δ in ppm rel. to TMS; *J* in Hz. ^{13}C-NMR Assignments for each signal were established by DEPT measurements. MS: on a *Finnigan MAT 312* (70 eV) or a *VG Autospec* spectrometer. The *Chemical Abstracts* name of **2** is *{1R-[1α,4α,6β(S*)]}-6-[hydroxy-(6-methoxy-4-quinolinyl)methyl]-1-azabicyclo[2.2.2]octan-3-one*. Our C-atom numbering corresponds to the numbering of cinchonan (*cf. Fig. 2*). Rubanone **2** has been described previously [7].

(2S,8R,9S)-9-Acetoxy-2-bromo-6′-methoxyruban-3-one (**3**). *Optimized Procedure*: Br_2 (0.16 ml, 3 mmol, 3 equiv.) and Br_3P (0.11 ml, 1.2 mmol, 1.2 equiv.) were added dropwise within 15 min to a soln. of **2** (1 mmol, 1 equiv.) at 0° under Ar. After stirring for 4 h at r.t., the mixture was treated with sat. aq. $NaHCO_3$ and sat. aq. NaCl, and extracted with $CHCl_3$. The combined org. layer was dried ($MgSO_4$), evaporated, and purified by CC (AcOEt/MeOH 20:1) to afford **3** (335 mg, 76%). IR ($CHCl_3$): 2944, 2872, 1736, 1714, 1620, 1592, 1508, 1472, 1432, 1372, 1308, 1228, 1132, 1080, 1028. ^{1}H-NMR ($CDCl_3$): 8.89 (*d*, *J* = 4, H–C(2′)); 8.22 (*d*, *J* = 9, H–C(8′)); 7.51 (*dd*, *J* = 2, 9, H–C(7′)); 7.47 (*d*, *J* = 4, H–C(3′)); 7.39 (*d*, *J* = 2, H–C(5′)); 6.75 (*d*, *J* = 6, H–C(9)); 6.02 (*s*, H–C(2)); 4.04 (*s*, MeO); 3.73 (*m*, H–C(8)); 3.45 (*m*, H–C(6)); 2.93 (*m*, H–C(6)); 2.74 (*m*, H–C(4)); 2.24 (*s*, Ac); 2.15–2.03 (*m*, 2 H–C(7)); 1.98–1.82 (*m*, 2 H–C(5)). ^{13}C-NMR ($CDCl_3$): 210.73 (C(3)); 169.11 (C(12)); 158.89 (C(6′)); 147.41 (C(2′)), 145.61 (C(10′)), 143.17 (C(4′)), 130.49 (C(8′)), 126.72 (C(9′)); 120.81 (C(7′)); 117.86 (C(3′)); 100.90 (C(5′)); 72.89 (C(9)), 68.10 (C(2)); 59.76 (C(8)); 56.08 (MeO), 44.68 (C(6)); 40.27 (C(4)); 25.99 (C(5)); 25.61 (C(7)); 20.91 (*Me*COO). MS (230°): 434 (6, M^+), 432 (6, M^+), 407 (23), 405 (22), 390 (11), 345 (14), 325 (65), 311 (5), 283 (27), 265 (92), 254 (16), 224 (12), 212 (15), 198 (19), 184 (13), 172 (100), 159 (9), 141 (8). HR-MS: 432.0661 ($C_{20}H_{21}BrN_2O_4$; calc. 432.0685).

Preparation of Rearranged Lactam Alkaloids **5a**, **5b**, *and* **5d**. Pure α-brominated rubanone **3** is essential for the 1,2-CO transposition with cyclic *sec*-amines. Rubanone **3** (434 mg, 1 mmol) was added to a soln. of the *sec*-amine (10 mmol, 10 equiv.) in abs. CH_2Cl_2 (5 ml). The mixture was stirred for 10 h at r.t. under Ar. After removing solvent and *sec*-amine under reduced pressure, the resulting product was purified by CC.

(3R,8R,9S)-9-Hydroxy-6′-methoxy-3-(pyrrolidin-1-yl)ruban-2-one (**5a**). Pyrrolidine (710 mg, 10 mmol, 10 equiv.) afforded, after CC (*t*-BuOME/MeOH 20:1), **5a** (241 mg, 64%). Waxy, slightly yellow solid. IR ($CHCl_3$): 2976, 2956, 2880, 1620, 1508, 1456, 1432, 1348, 1240, 1172, 1084. ^{1}H-NMR ($CDCl_3$): 8.69 (*d*, *J* = 4, H–C(2′)); 7.98 (*d*, *J* = 10, H–C(8′)); 7.53 (*d*, *J* = 2.5, H–C(5′)); 7.39 (*d*, *J* = 4, H–C(3′)); 7.32 (*dd*, *J* = 2.5, 10, H–C(7)); 5.06 (*d*, *J* = 8, H–C(9)); 3.88 (*s*, MeO); 3.45, 3.15 (*m*, 2 H–C(6)); 3.41, 3.30 (*m*, CH_2N); 3.11 (*m*, H–C(8)); 3.01 (*m*, H–C(3)); 2.92 (*m*, H–C(4)); 2.85, 2.55 (*m*, CH_2N), 2.50, 1.70–1.15 (*m*, 2 H–C(5), 2 H–C(7), CH_2CH_2). ^{1}H-NMR ((D_6)DMSO): 5.71 (*d*, *J* = 6.5, OH); 4.58 (*dd*, *J* = 6.5, 10, H–C(9)). ^{13}C-NMR ($CDCl_3$): 169.38 (C(2)); 157.72 (C(6′)); 147.70 (C(2′)); 147.45 (C(10′)); 144.63 (C(4′)); 131.56 (C(8′)); 127.60 (C(9′)); 121.26 (C(7′));

118.98 (C(3')); 102.41 (C(5')); 72.03 (C(9)); 71.40 (C(3)); 69.98 (C(8)); 57.25 (C(6)); 55.75 (MeO); 46.80 (CH_2N); 46.18 (CH_2N); 39.15 (C(4)); 33.25, 29.89 (CH_2CH_2); 25.81 (C(7)); 23.70 (C(5)). MS (180°): 381 (3, M^+), 380 (6, $[M-1]^+$), 379 (15), 337 (5), 308 (58), 282 (69), 265 (16), 214 (64), 96 (77). FAB-MS: 382 (100, $[M+1]^+$).

(3R,8R,9S)-9-Hydroxy-6'-methoxy-3-(piperidin-1-yl)ruban-2-one (**5b**). Piperidine (850 mg, 10 mmol, 10 equiv.) afforded, after CC (*t*-BuOMe/MeOH 20:1), **5b** (227 mg, 58%). Waxy, yellow solid. IR ($CHCl_3$): 3388, 3072, 2940, 2880, 2856, 1668, 1620, 1508, 1472, 1444, 1368, 1240, 1132, 1088. ^{1}H-NMR ($CDCl_3$): 8.72 (*d*, J = 4, H–C(2')); 8.01 (*d*, J = 10, H–C(8)); 7.56 (*d*, J = 2.5, H–C(5)); 7.47 (*d*, J = 4, H–C(3')); 7.35 (*dd*, J = 2.5, 10, H–C(7')); 5.18 (*d*, J = 8, H–C(9)); 3.95 (*s*, MeO); 3.48, 3.35 (*m*, CH_2N); 3.16 (*m*, H–C(3)); 3.10 (*m*, H–C(8)); 2.92, 2.62 (*m*, 2 H–C(6)); 2.91 (*m*, H–C(4)); 2.60, 2.57 (*m*, CH_2N); 1.70–1.20 (*m*, CH_2CH_2). NOE: H–C(3) irradiated: H–C(4) (6.0), H_{exo}–C(7) (3.0), H_{exo}–C(5)); H–C(4) irradiated: H–C(3) (3.4); CH_2N (3.33 ppm) irradiated: H–C(3) (5.0); CH_2N (3.47 ppm) irradiated: H–C(3) (3.0). ^{13}C-NMR ($CDCl_3$): 169.18 (C(2)); 157.55 (C(6')); 147.59 (C(2')); 147.30 (C(10')); 144.51 (C(4')); 131.58 (C(8')); 127.36 (C(9')); 121.39 (C(7')); 118.70 (C(3')); 102.28 (C(5')); 71.92 (C(9)); 70.43 (C(3)); 70.31 (C(8)); 57.18 (C(6)); 55.62 (MeO); 46.78 (CH_2N); 42.89 (CH_2N); 39.72 (C(4)); 33.59, 29.73, 26.05 ($CH_2CH_2CH_2$); 25.40 (C(7)); 24.19 (C(5)). MS (110°): 309 (2), 283 (3), 98 (100). FAB-MS: 396 (46, $[M+1]^+$), 281 (71), 221 (86), 147 (100).

(3R,8R,9S)-9-Hydroxy-6'-methoxy-3-(piperazin-1-yl)ruban-2-one (**5d**). Piperazine (860 mg, 10 mmol, 10 equiv.) afforded, after CC (AcOEt/MeOH 20:1), **5d** (201 mg, 51%). Waxy, colorless solid. IR ($CHCl_3$): 3604, 3440, 3072, 3000, 2972, 2860, 1624, 1508, 1472, 1432, 1368, 1300, 1240, 1172, 1144, 1116, 1084, 1032, 1008. ^{1}H-NMR ($CDCl_3$): 8.71 (*d*, J = 4, H–C(2')); 8.03 (*d*, J = 9, H–C(8')); 7.46 (*d*, J = 4, H–C(3')); 7.44 (*d*, J = 2, H–C(5')); 7.37 (*dd*, J = 2, 9, H–C(7')); 5.05 (*d*, J = 5, H–C(9)); 3.90 (*s*, MeO); 3.68 (*m*, H–C(8)); 3.54 (*m*, 2 H–C(6) of piperazine); 3.44 (*m*, 2 H–C(2) of piperazine); 3.35 (*m*, H–C(3)); 3.22–3.15 (*m*, 2 H–C(6)); 3.07 (*s*, NH); 2.96–2.85 (*m*, 2 H–C(3), 2 H–C(5) of piperazine); 2.68 (*m*, 2 H–C(7)); 2.51 (*m*, H–C(4)); 1.69–1.51 (*m*, 2 H–C(5)). ^{13}C-NMR ($CDCl_3$): 169.57 (C(2)); 157.83 (C(6')); 147.47 (C(2')); 146.48 (C(10')); 144.49 (C(4')); 131.56 (C(8')); 127.71 (C(9')); 121.42 (C(7')); 119.04 (C(3')); 102.22 (C(5')); 73.72 (C(9)); 70.41 (C(3)); 69.28 (C(8)); 57.26 (C(6)); 55.79 (MeO); 53.51 (C(5) of piperazine); 51.99 (C(3) of piperazine); 46.01 (C(6) of piperazine); 41.93 (C(2) of piperazine); 39.37 (C(4)); 33.60 (C(7)); 28.44 (C(5)). MS (180°): 396 (15, M^+), 354 (5), 310 (100), 283 (21), 269 (20), 251 (15), 237 (11), 225 (15), 213 (83), 188 (25), 172 (17), 159 (25), 155 (22), 140 (16), 128 (11), 116 (23), 114 (22), 100 (17), 96 (9), 91 (14), 86 (8). FAB-MS: 397 (48, $[M+1]^+$)

(3R,8R,9S)-9-Hydroxy-6'-methoxy-3-morpholinoruban-2-one (**5c**). Rubanone **3** (434 mg, 1 mmol, 1 equiv.) was added to a soln. of morpholine (880 mg, 10 mmol, 10 equiv.) in abs. CH_2Cl_2 (5 ml). The mixture was stirred for 10 h at r.t. under Ar. After removing solvent and morpholine under reduced pressure, the residue was purified by CC (AcOEt/MeOH 20:1) to yield epimerically pure '*endo*'-**5c** (223 mg, 56%). Longer reaction times at 40° (48 and 72 h) furnished an epimeric mixture of '*endo*'-**5c** and '*exo*'-**5c** (5:1) together with tricyclic lactam **6**.

Data for endo-**5c**: IR ($CHCl_3$): 3436, 3080, 3000, 2972, 2860, 1636, 1508, 1460, 1432, 1392, 1360, 1300, 1268, 1248, 1180, 1144, 1112, 1068, 1038, 1008, 832, 580. ^{1}H-NMR ($CDCl_3$): 8.85 (*d*, J = 4, H–C(2')); 8.14 (*d*, J = 9, H–C(8')); 7.53 (*d*, J = 4, H–C(3')); 7.49 (*dd*, J = 2, 9, H–C(7')); 7.16 (*d*, J = 2, H–C(5')); 5.06 (*s*, H–C(9)); 4.02 (*s*, MeO), 3.77 (*m*, 2 H–C(2), 2 H–C(6) of morpholine); 3.67 (*m*, 2 H–C(5) of morpholine); 3.52 (*m*, 2 H–C(3) of morpholine); 3.23 (*m*, H–C(3)); 3.15 (*m*, H–C(8)); 2.79 (*m*, 2 H–C(6)); 2.28 (*m*, H–C(4)); 1.85 (*m*, 2 H–C(7)); 1.35 (*m*, 2 H–C(5)). ^{13}C-NMR ($CDCl_3$): 169.36 (C(2)); 158.43 (C(6')); 147.26 (C(2')); 144.57 (C(10')); 142.49 (C(4')); 131.98 (C(8')); 126.29 (C(9')); 122.16 (C(7')); 117.75 (C(3')); 102.39 (C(5')); 74.71 (C(9)); 73.19 (C(3)); 68.22 (C(8)); 67.59 (C(6) of morpholine); 66.83 (C(2) of morpholine); 57.34 (C(6)); 55.79 (MeO); 46.67 (C(5) of morpholine); 44.71 (C(3) of morpholine); 40.35 (C(4)); 25.81 (C(7)); 25.34 (C(5)). MS (180°): 397 (37, M^+), 382 (29) 366 (3), 356 (5), 310 (100), 295 (11), 283 (99.8), 265 (51), 251 (17), 237 (13), 225 (15), 214 (82), 189 (25), 172 (18), 160 (31), 154 (31), 140 (14), 129 (30), 117 (24), 114 (20), 100 (33), 96 (19), 86 (39). FAB-MS: 398 (37, $[M+1]^+$). HR-MS: 397.0121 ($C_{22}H_{27}N_3O_4$; calc. 397.0341).

Data for exo-**5c**: ^{1}H-NMR ($CDCl_3$): 8.77 (*d*, J = 4, H–C(2')); 8.08 (*d*, J = 9, H–C(8')); 7.46 (*m*, H–C(3'), H–C(5')); 7.38 (*dd*, J = 2, 9, H–C(7')); 5.18 (*s*, H–C(9')); 3.95 (*s*, MeO); 3.61 (*m*, H–C(8)); 3.56 (*m*, 2 H–C(2), 2 H–C(6) of morpholine); 3.33 (*m*, 2 H–C(5)); 3.27 (*m*, 2 H–C(3)); 3.23 (*s*, H–C(3)); 2.82 (*m*, 2 H–C(6)); 2.49 (*m*, H–C(4)); 2.45–2.39 (*m*, 2 H–C(5)); 1.72–1.51 (*m*, 2 H–C(7)). ^{13}C-NMR ($CDCl_3$): 169.12 (C(2)); 158.27 (C(6')); 147.41 (C(2')); 145.34 (C(10')); 144.49 (C(4')); 132.08 (C(8')); 127.18 (C(9')); 121.44 (C(7')); 118.65 (C(3')); 100.99 (C(5')); 71.49 (C(9)); 69.19 (C(3)); 67.52 (C(8)); 66.83 (C(6) of morpholine); 66.02 (C(2) of morpholine); 57.36 (C(6)); 55.85 (MeO); 45.52 (C(5) of morpholine); 42.01 (C(3) of morpholine); 39.92 (C(4)); 29.33 (C(5)); 25.31 (C(7)).

(3R,8R,9S)-3,9-Epoxy-6'-methoxyruban-2-one (**6**). Rubanone **3** (217 mg, 1 mmol, 1 equiv.) was added to a soln. of piperazine (430 mg, 5 mmol, 5 equiv.) in abs. CH_2Cl_2 (5 ml). The mixture was stirred for 72 h at r.t. under Ar. After partially removing the solvent under reduced pressure, KOH (280 mg, 5 mmol, 10 equiv.), Bu_4NI

(10 mg), and H_2O (2 ml) were added, and stirring was continued for 1 h at 40°. The soln. was diluted with $CHCl_3$ and extracted with H_2O and sat. aq. $NaHCO_3$. The org. layer was separated, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by CC (AcOEt/MeOH 6:1) afforded **6** (82 mg, 53%). Slightly yellow, waxy solid. IR ($CHCl_3$): 2960, 2880, 1744, 1668, 1620, 1596, 1508, 1472, 1432, 1360, 1344, 1264, 1232, 1180, 1108, 1084, 1028, 1004, 908. ^{1}H-NMR ($CDCl_3$): 8.85 (*d*, *J* = 4, H–C(2')); 8.14 (*d*, *J* = 9, H–C(8')); 7.52 (*d*, *J* = 4, H–C(3')); 7.48 (*dd*, *J* = 3, 9, H–C(7')); 7.16 (*d*, *J* = 3, H–C(5')); 6.43 (*s*, H–C(9)); 4.02 (*s*, MeO); 3.61 (*m*, H–C(8)); 3.49 (*s*, H–C(3)); 3.22 (*m*, H–C(6)); 3.05 (*t*, *J* = 4, H–C(4)); 2.79 (*m*, H–C(6)); 1.84 (*m*, 2 H–C(7)); 1.35 (*m*, H–C(5)); 0.96 (*m*, H–C(5)). NOE: H–C(9) irradiated: H–C(8) (4.9), H–C(5') (21.6); H–C(3) irradiated: H–C(6) (2.5), H–C(5) (2.6), H–C(4) (4.4), H–C(3') (2.3), H–C(9) (0.7); H–C(4) irradiated: H–C(3) (5.2), H_{endo}–C(7) (6.6), H–C(5) (2.6), H–C(3') (1.7); H–C(5') irradiated: H–C(9) (20.5), H–C(8) (6.4), MeO (7.1), H–C(6) (0.7). ^{13}C-NMR ($CDCl_3$): 169.23 (C(2)); 158.43 (C(6')); 147.70 (C(2')); 144.42 (C(10')); 139.29 (C(4')); 132.41 (C(8')); 125.77 (C(9')); 121.64 (C(7')); 118.79 (C(3')); 100.96 (C(5')); 79.96 (C(9)); 68.69 (C(3)); 62.23 (C(8)); 56.00 (MeO), 52.39 (C(6)); 43.55 (C(4)); 31.18 (C(7)); 27.39 (C(5)). MS (108°): 310 (100, M^+), 295 (12), 281 (10), 269 (21), 265 (31), 251 (15), 241 (10), 223 (14), 210 (21), 201 (15), 184 (12), 172 (9), 159 (8), 141 (8), 116 (10), 96 (14). FAB-MS: 310 (100, M^+), 265 (56), 210 (24), 197 (36). HR-MS: 310.0967 ($C_{18}H_{18}N_2O_3$; calc. 310.1049).

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