Articles

New Rearrangement of an *Aspidosperma* Alkaloid. The First Biomimetic Entry in the Goniomitine Skeleton

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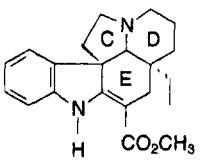
The first biomimetic approach to the skeleton of goniomitine (**12**) from an *Aspidosperma* alkaloid is described. With 16-chloro-1-dehydro-5-methoxyvincadifformine (**4**) (easily available from vincadifformine (**1**) as starting material, the rearrangement is performed in two steps: (a) Oxidation of **4** by *m*-CPBA followed by methanolysis affords the hemiketal **10** with a tetrahydro-1,2-oxazine structure for ring C, and (b) acid-catalyzed reaction on **10** provides either a mixture of both rearranged compounds **15** and **16** or **15** alone according to reaction time. Mechanisms of formation of **10**, **15**, and **16** are discussed.

Introduction

The *Aspidosperma* alkaloids constitute a large family of natural products in which biologically active structures account for the continuing interest in these compounds. The pivotal position of the largely available vincadifformine (**1**) in the biosynthesis of various structural types of indole alkaloids has already elicited study of several biomimetic in vitro rearrangements[1] from **1** derivatives (especially 16-chloro-1-dehydrovincadifformine (**2**)[2]) and from their 14,15-dehydro analogs.[3]

In a previous publication,[4] we reported on a new method of functionalization of the tryptamine chain by a Polonovski–Potier reaction from **2**.[5] Two different compounds were obtained according to the final treatment of the mixture: The addition of KCN before the extraction step gave the α-amino nitrile **3**,[6] while a standard workup (washing with aqueous NaOH) afforded by crystallization in MeOH the carbinolamine ether **4**.[4] The behaviors of **3** and **4**, two 4,5-iminium equivalents, toward an electrophilic reagent such as BrCN displayed great differences. Compound **3** was unreactive, whereas the carbinolamine ether **4** led very easily to the epimers on C-5 of **5** and **6**. Comparison of **3** and **4** was then carried on with *m*-chloroperoxybenzoic acid (*m*-CPBA), another electrophilic reagent.



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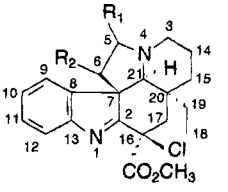

R_1 = H	R_2 = H	**2**
R_1 = CN(α)	R_2 = H	**3**
R_1 = OMe(α)	R_2 = H	**4**
R_1 = CN(α)	R_2 = Br(α)	**5**
R_1 = CN(β)	R_2 = Br(α)	**6**

In this article, we report on the reactivity of the carbinolamine ether **4** with *m*-CPBA and its application to the discovery of a new biomimetic in vitro rearrangement.

Results and Discussion

The previously reported oxidation of **3** with *m*-CPBA (dichloromethane, room temperature) provided the desired N-4-oxide.[6] Under the same conditions, **4** led to compound **7** (Scheme 1) in 82% yield. The structure of **7** was supported by spectroscopic data. Compared with that of **4**, the UV spectrum of **7** was very similar while the EI mass spectrum showed dichlorinated molecular ions at *m*/*z* 542, 544, and 546 and a base peak at *m*/*z* 139 (*m*-$ClC_6H_4C{\equiv}O^+$) consistent with loss of a methoxy group and addition of the elements of *m*-chlorobenzoate. Compound **7** was homogeneous in TLC (silica gel, dichloromethane), but its ^1H NMR displayed a splitting of some signals in a 3:1 ratio, especially at δ 6.87 (d, J = 5.6 Hz) and 7.00 (t, J = 7.5 Hz) ppm for H-5. On the basis of

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(1) For a general review of the rearrangements of the *Aspidosperma* alkaloids, see: Cordell, G. A. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. 17, p 267–296. For more recent studies on *Aspidosperma* alkaloid rearrangements, see: (a) Hugel, G.; Massiot, G.; Lévy, J.; Le Men, J. *Tetrahedron* **1981**, *37*, 1369–1375. (b) Lewin, G.; Poisson, J.; Lamotte Brasseur, J. *Tetrahedron* **1982**, *38*, 3291–3298. (c) Hugel, G.; Lévy, J. *Tetrahedron* **1983**, *39*, 1539–1542. (d) Hugel, G.; Lévy, J. *Tetrahedron* **1984**, *40*, 1067–1073. (e) Hugel, G.; Lévy, J. *J. Org. Chem.* **1984**, *49*, 3275–3277. (f) Palmisano, G.; Danieli, B.; Lesma, G.; Riva, R.; Riva, S.; Demartin, F.; Masciocchi, N. *J. Org. Chem.* **1984**, *49*, 4138–4143. (g) Lewin, G.; Poisson, J. *Tetrahedron Lett.* **1984**, *25*, 3813–3814. (h) Lewin, G.; Poisson, J.; Toffoli, P. *Tetrahedron* **1987**, *43*, 493–500. ((i) Palmisano, G.; Danieli, B.; Lesma, G.; Trupiano, F.; Pilati, T. *J. Org. Chem.* **1988**, *53*, 1056–1064. (j) Lewin, G.; Poisson, J.; Schaeffer, C.; Volland, J. P. *Tetrahedron* **1990**, *46*, 7775–7786. (k) Hugel, G.; Royer, D.; Sigaut, F.; Lévy, J. *J. Org. Chem.* **1991**, *56*, 4631–4636.

(2) Pierron, C.; Garnier, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1971**, 1007–1010.

(3) Numbering system proposed by: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508–510.

(4) Lewin, G.; Poisson, J. *Tetrahedron Lett.* **1994**, *35*, 8153–8156.

(5) Ahond, A.; Cavé, Ad.; Kan-Fan, C.; Husson, H.-P.; de Rostolan, J.; Potier, J. *J. Am. Chem. Soc.* **1968**, *90*, 5622–5623.

(6) Lewin, G.; Poisson, J.; Schaeffer, C.; Volland, J. P. *Tetrahedron* **1990**, *46*, 7775–7786.

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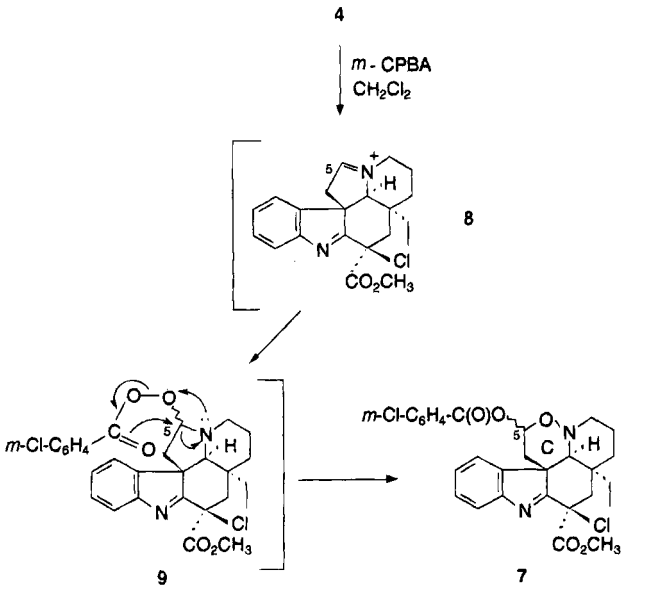
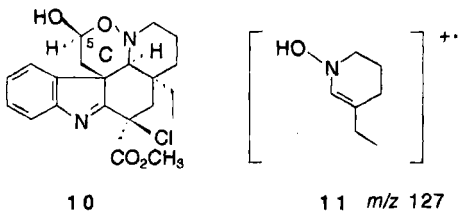
Scheme 1



these results, the formation of a N-4-oxide could certainly be excluded and **7** identified as the 3:1 mixture of two *m*-chlorobenzoate ester epimers at C-5 with a tetrahydro-1,2-oxazine structure for ring C. This ring expansion (pyrrolidine → tetrahydro-1,2-oxazine) is similar to the oxidation of physostigmine into geneserine[7] and has been recently described in a synthesis of FR 900482, an antitumor compound related to mitomycins.[8] The mechanism of this ring expansion is closely dependent on the already-observed great nucleofugal character of the methoxy group in **4**. The arising iminium ion **8** may then initially undergo a nucleophilic addition of the peracid, leading to the intermediate **9**, which evolves to **7** according to Scheme 1.[9] The assigned structure **7** has been confirmed and the stereochemistry at C-5 of the two epimers established after methanolysis of **7** by a careful spectral analysis of the hemiketal **10**.

Methanolysis of **7** in 0.2 M methanolic NaOH at room temperature afforded, besides methyl *m*-chlorobenzoate, the hemiketal **10** isolated in 71% yield as the main product by column chromatography. Compound **10** showed in the EI mass spectrum a chlorinated molecular ion at *m*/*z* 404–406 (404.1497, calcd for $C_{21}H_{25}{}^{35}ClN_2O_4$ 404.1502) and a base peak at *m*/*z* 127 consistent with the formula of **11**. Furthermore, the hemiketal function



10 **11** *m*/*z* 127

of the tetrahydro-1,2-oxazine ring was supported by the presence of significant signals for C-5 at δ 93.6 ppm and H-5 (dd, J = 5.6 and 8.7 Hz) at δ 5.30 ppm in the ^{13}C and ^1H NMR spectra, respectively. Unlike **7**, the hemiketal **10** appeared to be a single epimer, and its stereochemistry was settled by a thorough ^1H NMR study. First of all, 1D and 2D ^1H NMR correlation experiments (COSY) allowed for all the proton assignments (Table 1) and confirmed the structure of **10**. Then, owing to the cleavage of the N-4–C-5 bond during the ring expansion step, the stereochemistry at these two centers had to be fixed. With the known configuration at C-21 (unmodified during the ring expansion and the methanolysis) as the starting point, the stereochemistry at N-4 and C-5 was unambiguously inferred from rotating Overhauser spectroscopy (ROESY) experiments. Namely, significant ROE were observed between H-21 and H-3α_{ax}, H-5, H-9, H-15α_{ax}, and both H-19 and between H-5 and H-9 as well as between H-6β and H-17β. These observed ROE were fully in agreement with a *trans* junction of rings C and D [e.g. the lone pair of N-4 as in (−)-vincadifformine] and a 5*S* stereochemistry (H-5α), while conformations of rings C and E corresponded to a boat form and conformation of ring D to a chair form. Furthermore, a modeling study with free energy calculations confirmed the greatest stability of the *trans* C/D junction stereochemistry. Isolation of a single epimer by chromatography could not be explained by an opening–recyclization process of the ring C via the intermediate aldehyde–hydroxylamine. Indeed, a modeling study on this intermediate did not support a favored stereospecific recyclization; furthermore, attempts to quench such an intermediate by methanolysis of the analog **13** in the presence of $NaBH_4$ were unsuccessful (the same hemiketal compound was recovered with or without $NaBH_4$). At last and by analogy with **10**, an ROE experiment on the mixture **7** (especially between H-5 and H-21) clearly indicated the same *trans* junction of rings C and D, a 5S stereochemistry (as in **10**) for the most abundant epimer, and a 5*R* stereochemistry for the other one.

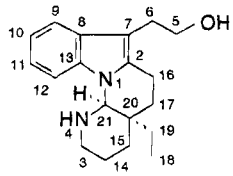
Now that the conditions of an easy cleavage of the N-4–C-5 bond in the *Aspidosperma* system were found, we then considered the feasibility of a biomimetic entry into the skeleton of (−)-goniomitine (**12**) from **7** or **10**. (−)-Goniomitine is an indole alkaloid of an unusual structural type, isolated from the root bark of *Gonioma malagasy* (Apocynaceae) by Husson and co-workers, who proposed a biogenetic scheme to account for the formation

Table 1. ^1H NMR (500 MHz) Data of Compound 10 in $CDCl_3$

proton no.	δ (ppm)	J (Hz)
3α_{ax}	2.60	14.0, 9.5, 2.5
3β_{eq}	3.45	*a*
5	5.30	8.7, 5.6
6$\alpha_{pseudo\ eq}$	1.45	14.3, 5.6
6$\beta_{pseudo\ ax}$	3.30	14.3, 8.7
9	7.45	7.5
10	7.25	7.5, 1.25
11	7.35	7.5, 1.25
12	7.65	7.5
14α_{eq}	1.70	*a*
14β_{ax}	1.90	14.0, 13.7, 9.5, 3.7
15α_{ax}	1.30	*a*
15β_{eq}	1.45	13.7, 3.7, 2.0
17$\alpha_{pseudo\ eq}$	2.90	15.0, 1.9
17$\beta_{pseudo\ ax}$	3.10	15.0
18	0.75	7.5
19	0.65 and 0.95	14.3, 7.5
21	2.95	1.9
CO_2CH_3	4.00	
OH	3.40	

[a] br m (J not measured).

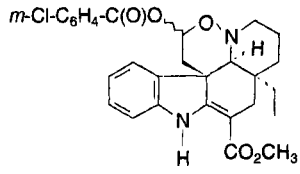
(7) Hootelé, C. *Tetrahedron Lett.* **1969**, 2713–2716.
(8) Dmitrienko, G. I.; Denhart, D.; Mithani, S.; Prasad, G. K. B.; Taylor, N. J. *Tetrahedron Lett.* **1992**, *33*, 5705–5708.
(9) For peracidic oxygenation of an iminium salt, see: Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron* **1993**, *49*, 423–438.



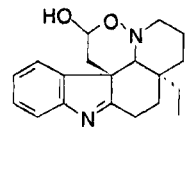
12

of **12** from vincadifformine (**1**).[10] A total synthesis of (−)-goniomitine (**12**) has been completed by Takano and coworkers, who established the absolute stereochemistry of this alkaloid.[11] However, no biomimetic in vitro conversion of the *Aspidosperma* skeleton to the goniomitine system has been described up to now.

The lack of the C-16-methoxycarbonyl group in goniomitine prompted us to remove, in a first approach, this group before the rearrangement. The direct decarbomethoxylation of **10** was unsuccessful but could be carried out by a two-step process. First, treatment of **7** by sodium iodide in acetic acid[12] allowed for recovery of the anilinoacrylate ester chromophore and afforded the compound **13** in a quantitative yield. The EI mass spectrum of **13** displayed the molecular ions at m/z 508–510 with a base peak at m/z 139, while UV and IR spectra exhibited the characteristic data of the chromophore of vincadifformine (**1**). Then, heating **13** in 11 N HCl for 10 min at 105 °C[13] provided the expected indolenine **14** by a simultaneous decarbomethoxylation and *m*-chlorobenzoate ester hydrolysis. The EI mass



13

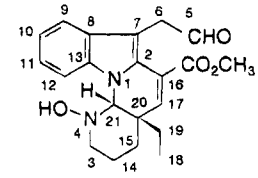


14

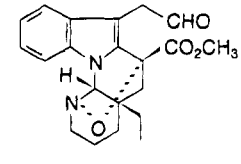
spectrum of **14** showed a parent ion at m/z 312 and the same base peak at m/z 127 as the hemiketal **10**. The indolenine chromophore was supported by a typical UV spectrum (λ_{max} at 221 and 262 nm) and by the lack of the carbonyl band in the IR spectrum. In the ^{1}H NMR spectrum, the significant signal of H-5 at δ 5.25 ppm (dd, J = 6 and 8 Hz) confirmed the tetrahydro-1,2-oxazine structure and the hemiketal function. Though our purpose was reached when we isolated the indolenine **14**, the low yield (18%) of the decarbomethoxylation led us to renounce this strategy.

In a second approach, we turned our attention to mild conditions for the opening of the tetrahydro-1,2-oxazine ring. In our opinion, such an opening could allow by a retro-Mannich mechanism for the cleavage of the C-7–C-21 bond and then the rearrangement to the skeleton of goniomitine according to Husson's group hypothesis. This key step was found to take place very easily, since treatment of **10** in the mixture dichloromethane–trifluoroacetic acid (99:1, v/v) for 20 min at room temperature afforded the two rearranged compounds **15** and **16** in 42 and 11% yields, respectively.

The structure of the main compound **15** was suggested by the presence in the EI mass spectrum of a molecular



15



16

ion at m/z 368 (368.1732, calcd for $C_{21}H_{24}N_2O_4$ 368.1735) and the presence in the ^{1}H NMR spectrum of three significant signals at δ 4.60 (s, H-21), 6.80 (s, H-17), and 9.74 ppm (t, J = 1.9 Hz, H-5). The IR spectrum showed a strong absorption at 1720 cm^{-1} consistent with aldehyde and α,β-unsaturated ester groups and a hydroxyl band at about 3400 cm^{-1}, while the observed UV spectrum was indicative of a chromophore [λ_{max} (log ϵ) 222 (4.23), 255 sh (3.63), 279 sh (3.49), and 327 (3.88)] more conjugated than the starting compound **10**. Furthermore, the EI mass spectrum exhibited a base peak at m/z 266 and a significant rearrangement giving the radical cations at m/z 241 and 127, fully in agreement with the structure **15** (Scheme 2). Lastly, 2D homo- and heteronuclear experiments unambiguously confirmed the structure **15**. A COSY experiment, on the one hand, and HMQC (heteronuclear multiple quantum coherence) and HMBC (heteronuclear multiple bond coherence) experiments on the other hand allowed for identification of most of the hydrogens and carbons (Table 2). The HMBC experiment was particularly useful for assigning all quaternary carbons (except C-16 not surely located); for instance, they clearly exhibited characteristic $^3J(^1H-^{13}C)$ values between C-2 and H-6, H-17, and H-21. As a last point for discussion about structure **15**, the C-20–C-21 ring junction was proved to be a *cis* junction according to ROE experiments. This stereochemistry was indeed inferred from the significant ROE observed between H-21 and H-18 and H-19, only consistent with a *cis* junction.

The second compound of the reaction of **16** revealed some spectral data in common with **15**: The EI mass spectrum showed the same molecular ion at m/z 368 (368.1731, calcd for $C_{21}H_{24}N_2O_4$ 368.1735) and the same fragmentation pattern as **15** (probably owing to a thermic evolution of **16** into **15**), while the ^{1}H NMR spectrum displayed the significant signals of H-21, slightly deshielded at δ 5.00 ppm, and of the aldehyde proton H-5 at δ 9.60 ppm (t, J = 1.9 Hz). On the other hand, **16** was different from **15** in the following points: The olefinic signal was lacking in the ^{1}H NMR spectrum, while the IR spectrum was devoid of the hydroxyl band but displayed two carbonyl absorptions at 1720 (aldehyde) and 1740 (saturated ester) cm^{-1}. Moreover, the observed UV spectrum was indicative of a typical indole chromophore. These considerations enabled us to assign the hydroxylamine ether structure **16** to this compound. The structure **16** was unambiguously confirmed by the same 2D NMR and ROE experiments as described for **15** (Table 2). Moreover, according to the inspection of molecular models, the structure **16** could only be consistent with a *cis* C-20–C-21 ring junction.

The formation of **15** and **16** is related to Husson's biogenetic proposal for goniomitine. However, it requires participation of the C-16-chlorine for activating the indole

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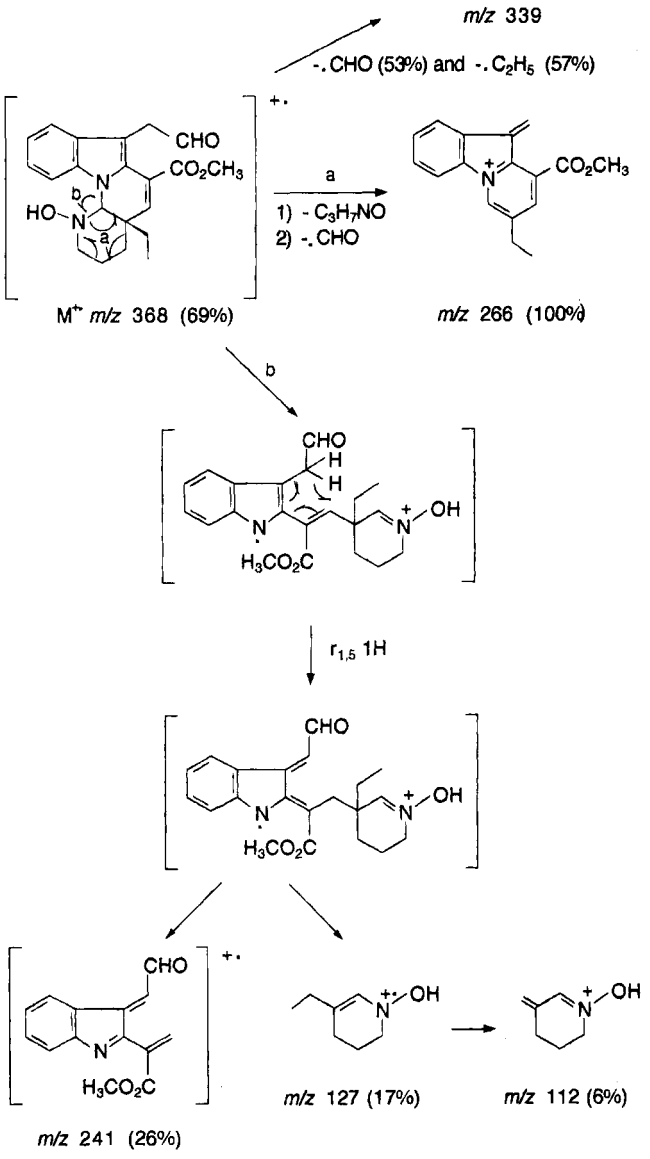
(11) (a) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1991**, 462–464. (b) Takano, S.; Ogasawara, K. Jpn. Patent 05,271,231; *Chem. Abstr.* **1994**, *120*, 299062q.

(12) Tamura, Y.; Chun, M. W.; Nishida, H.; Ikeda, M. *Heterocycles* **1977**, *8*, 313–318.

(13) Henriques, A.; Husson, H.-P. *Tetrahedron Lett.* **1981**, *22*, 567–570.

Scheme 2



ring for nucleophilic attack on the intermediate nitrone. Cyclization of N-1–C-21 by attack on the less hindered face of the nitrone provides the intermediate zwitterion **17**, leading either to the unsaturated ester **15** or to the hydroxylamine ether **16** (Scheme 3). Knowledge of the stereochemistry of C-20 in **10** allows us to assign the absolute configuration (20*S*,21*S*) to **15** and **16**.

Treatment of **16** in trifluoroacetic acid for 4 h at 20 °C mainly transformed **16** into **15** (Scheme 3). This observation suggested to us that **16** could be the kinetically favored product and **15** the thermodynamic compound of the rearrangement. In order to avoid the undesirable separation step of **15** and **16**, we then decided to prolong the reaction time of the rearrangement. Then, treatment of **10** in dichloromethane–trifluoroacetic acid (99:1) for 15 h at room temperature afforded a product almost exempt of **16** and allowed for easier isolation of **15** in 52% yield. Lastly, the rearrangement pathway was still more simplified, when the skeleton conversion was carried out from the mixture of ester epimers **7**. In the same acid medium, compound **15** was then isolated, after 2 days, in 48% yield.

Table 2. ^{1}H and ^{13}C NMR Chemical Shift Values of Compounds 15 and 16 in $CDCl_3$[a]

	15		16	
atom no.	δ_H	δ_C	δ_H	δ_C
2		127.7		128.4
3	2.75/3.33	56.6	3.00/3.66	53.4
5	9.74	200.7	9.60	199.6
6	3.87	40.1	3.62	38.6
7		105.5		*b*
8		129.1		134.5
9	7.51	119.0	7.37	119.5
10	7.13	120.4	7.17	120.6
11	7.27	123.6	7.28	122.9
12	7.56	110.6	7.57	108.8
13		138.4		139.4
14	1.53/2.02	21.6	1.53/1.87	32.9
15	1.81	33.8	1.62/2.29	32.0
16		*b*		98.0
17	6.80	144.9	2.05/2.49	41.8
18	0.78	8.0	0.80	6.9
19	1.20/1.30	29.8	1.06/1.17	36.1
20		43.8		*b*
21	4.60	78.5	5.00	72.9
CO_2CH_3	3.84	52.6	3.94	53.3
CO_2CH_3		166.1		168.6

[a] 500 MHz for ^{1}H and 125.8 MHz for ^{13}C. [b] Signals not detected.

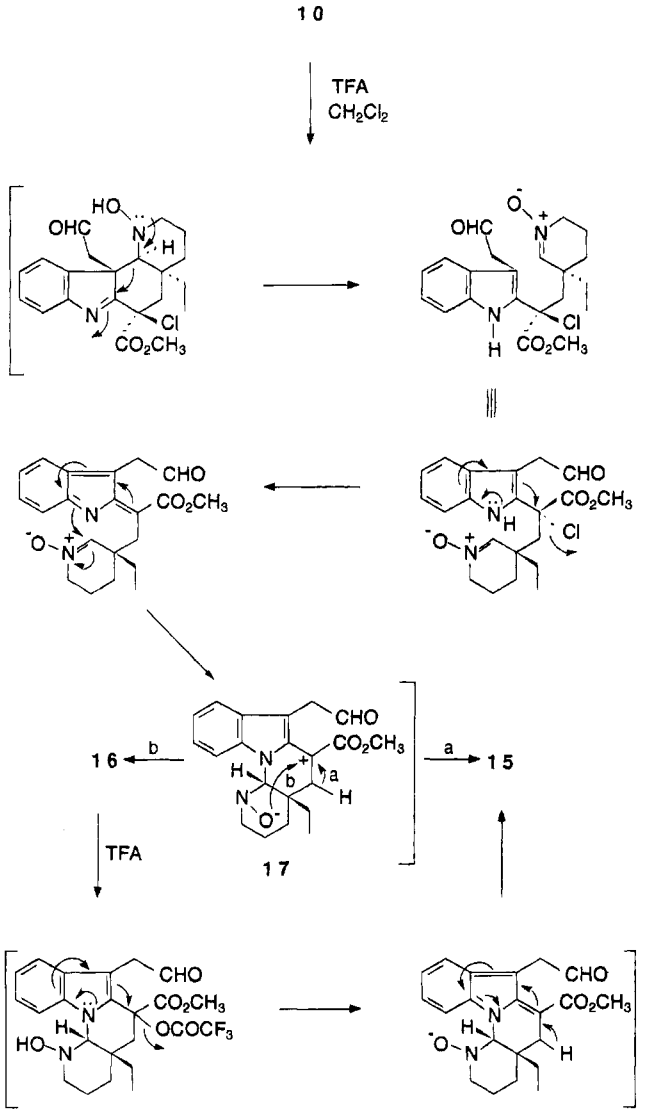
Conclusion

The rearrangement developed herein is noteworthy in that it represents the first biomimetic in vitro access to the skeleton of goniomitine. Correlation with goniomitine itself from **15** still requires several reductions (aldehyde and hydroxylamine groups, 16–17 double bond) and elimination of the methoxycarbonyl group by reduction–deformylation or saponification–decarboxylation. Another method would consist of the loss of the methoxycarbonyl group before the rearrangement step. Both strategies are currently under investigation and will be the subject of a further report.

Experimental Section

UV spectra were acquired on a Unicam SP 1800 instrument, IR spectra on a Perkin-Elmer 457 spectrophotometer, and optical rotations on a Schmidt–Haensch polarimeter. EI (70 eV) direct introduction mass spectra were obtained on a Finnigan MAT 95Q (BEqQ geometry) apparatus. Mass assignments and molecular formulas were confirmed by "peak matching" measurements using a high resolution of ca. 10 000 (10% valley). MS/MS spectra were recorded in order to establish the fragmentation pattern shown in Scheme 2. NMR spectra of **10** (^{13}C) and **13** and **14** (^{1}H) were carried out in $CDCl_3$ on a Bruker AC-200 (200 MHz for ^{1}H, 50.3 MHz for ^{13}C) instrument. All other NMR experiments were performed at 300 K for solutions of ca. 2–3 mg of compounds dissolved in 0.5 mL of $CDCl_3$ on a Bruker AMX-500 instrument equipped with a 5 mm QNP probe and a X32 computer, operating at 500.13 and 125.77 MHz for ^{1}H and ^{13}C, respectively. The homonuclear ^{1}H–^{1}H and heteronuclear ^{1}H–^{13}C chemical shift-correlated 2D diagrams were obtained using the standard COSY 90 and HMQC and HMBC pulse sequences, respectively. Homonuclear correlation: 1024 × 512 data set, delay = 1 s, 16 scans. Heteronuclear correlations: 1024 × 256 or 1024 × 512 data set, HMQC [delay = 1 s, $(2 \times {}^1J_{CH})^{-1} = 3.8$ ms], 32 scans, TPPI mode and GARP decoupling during acquisition; HMBC spectroscopy [delay = 1 s, $(2 \times {}^1J_{CH})^{-1} = 3.8$ ms], $(2 \times {}^nJ_{CH})^{-1} = 70$ ms, 32 scans. Finally, 2D rotating frame Overhauser spectroscopy (ROESY) spectra were recorded in the phase sensitive mode TPPI. A mixing time of 800 ms was used. A 1024 × 256 data set was collected, 32 scans each. *J* values are given in hertz. TLC data were obtained with Merck 60 F 254 silica gel and Merck 60 F 254

Scheme 3



aluminum oxide neutral (Type E) precoated on aluminum sheets. Compounds were visualized with a 10% solution of ceric ammonium sulfate (CAS) in phosphoric acid as a spray reagent.

Peracid Oxidation of 4 to the Tetrahydro-1,2-oxazine 7. To a solution of the carbinolamine ether **4** (804 mg, 2 mmol) in CH_2Cl_2 (75 mL) was added *m*-CPBA (2.2 mmol), and the solution was kept at room temperature for 3 h. The organic layer was washed with 10% aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated. The dried residue was purified by flash chromatography on silica gel (CH_2Cl_2) to yield **7** as an amorphous compound (890 mg, 82%).

7: amorphous solid; TLC (SiO_2, CH_2Cl_2) R_f 0.16 (CAS, light gray); two epimers [major/minor (3:1)]; UV (EtOH) λ_{max} (log ϵ) 233 (4.41), 285 (3.96) nm; IR (CCl_4) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) significant splitting in a ratio of 3:1 of the following signals δ 7.80 (d, J = 7.5) H-9 major and 7.50 (d, J = 7.5) H-9 minor, 7.00 (t, J = 7.5) H-5 minor and 6.87 (d, J = 5.6) H-5 major, 3.83 (dd, J = 14.0, 5.6), 1.40 (d, J = 14.0) H-6 major and 2.64, 1.98 (2 dd, J = 14.0, 7.5) H-6 minor, 3.59, 2.95 (2 m) H-3 minor and 3.54, 2.55 (2 m) H-3 major, 3.36 (s) H-21 major and 3.12 (s) H-21 minor, 3.34, 2.81 (2 d, J = 15.0) H-17 minor and 3.10, 2.83 (2 d, J = 15.0) H-17 major, other characteristic signals at δ 8.10–7.30 (8H, aromatic), 3.98 (s, 3H, CO_2CH_3), 0.53 (t, J = 7.5, H-18); EIMS m/z (relative intensity) 546 [1, $M^{\bullet+}$ (2 ^{37}Cl)], 544 [6, $M^{\bullet+}$ (^{35}Cl ^{37}Cl)], 542 [8, $M^{\bullet+}$ (2 ^{35}Cl)], 141 [32 (^{37}Cl)], 139 [100 (^{35}Cl)], 113 [32 (^{37}Cl)], 111 [100 (^{35}Cl)]. Anal. Calcd for $C_{28}H_{28}Cl_2N_2O_5$: C, 61.88; H, 5.19; N, 5.16; Cl, 13.05. Found: C, 62.16; H, 5.30; N, 5.02; Cl, 12.98.

Methanolysis of 7 to the Hemiketal 10. Compound **7** (759 mg, 1.4 mmol) was dissolved in 0.2 M methanolic NaOH (20 mL). After 5 min at room temperature, the mixture was diluted with water and extracted with CH_2Cl_2. Standard workup of the organic layer provided a dry residue (713 mg). This residue was purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 99:1) and afforded **10** as a pure amorphous compound (400 mg, 71%).

10: mp 139–141 °C (acetone); TLC (SiO_2, CH_2Cl_2–MeOH, 98:2) R_f 0.35 (CAS, grey); $[\alpha]_D$ −77.5 (c = 0.8, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 230 (4.17), 284 (3.91) nm; IR ($CHCl_3$) 3580, 3360, 1740 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 181.0 (C-2), 169.7 (CO_2CH_3), 152.7 (C-13), 145.7 (C-8), 128.3 and 127.2 (C-9, C-10), 123.0 and 122.3 (C-11, C-12), 93.6 (C-5), 73.8 (C-21), 63.6 (C-16), 57.3 (C-7), 55.4 (C-3), 54.0 (CO_2CH_3), 42.9 (C-17), 39.7 (C-20), 38.6 (C-6), 32.7 (C-15), 29.8 (C-19), 21.4 (C-14), 7.5 (C-18); EIMS m/z (relative intensity) 406 [1, $M^{\bullet+}$ (^{37}Cl)], 404 [2, $M^{\bullet+}$ (^{35}Cl)], 370 (6), 339 (4), 309 (3), 266 (4), 244 (18), 214 (10), 127 (100); HRMS calcd for $C_{21}H_{25}{}^{35}ClN_2O_4$ 404.1502, found 404.1497. Anal. Calcd for $C_{21}H_{25}ClN_2O_4$: C, 62.29; H, 6.22; N, 6.92; Cl, 8.76. Found: C, 62.15; H, 6.35; N, 6.80; Cl, 8.85.

Reaction of 7 with Sodium Iodide. To a solution of **7** (108 mg, 0.2 mmol) in AcOH (10 mL) was added a solution of sodium iodide (90 mg, 0.6 mmol) in AcOH (2 mL), and the mixture was kept at room temperature for 1.5 h. The solution was diluted with iced water neutralized with 2 N aqueous NaOH and extracted with CH_2Cl_2. The dark red organic layer was washed twice with 1 N aqueous $Na_2S_2O_3$ and with water to provide, after standard treatment, the compound **13** as a pure amorphous residue (100 mg, quantitative yield).

13: amorphous solid; TLC (SiO_2, CH_2Cl_2) R_f 0.21 (CAS, blue); UV (EtOH) λ_{max} (log ϵ) 232 (4.17), 299 (3.97), 330 (4.16) nm; IR (CH_2Cl_2) 3360, 1735, 1680, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (br s, 1H, N-H), 7.80–6.70 (9H, aromatic and H-5), 3.80 (s, 3H, CO_2CH_3), 0.57 (t, J = 7.0, H-18); EIMS m/z (relative intensity) 510 [1, $M^{\bullet+}$ (^{37}Cl)], 508 [3, $M^{\bullet+}$ (^{35}Cl)], 141 [34 (^{37}Cl)], 139 [100 (^{35}Cl)]. Anal. Calcd for $C_{28}H_{29}ClN_2O_5$: C, 66.07; H, 5.74; N, 5.50; Cl, 6.97. Found: C, 65.88; H, 5.91; N, 5.39; Cl, 7.11.

Decarbomethoxylation and Ester Hydrolysis of 13 to the Indolenine 14. A solution of **13** (50 mg, 0.1 mmol) in 11 N HCl (5 mL) was heated under nitrogen for 10 min at 110 °C. The mixture was diluted with iced water neutralized with 5 N aqueous NaOH and extracted with CH_2Cl_2. After the usual workup, the dry residue (15 mg) was purified by TLC on silica gel (CH_2Cl_2–MeOH, 97:3) to yield the indolenine **14** as a pure amorphous compound (5 mg, 18%).

14: amorphous solid; UV (EtOH) λ_{max} 221, 262 nm; IR (CH_2Cl_2) 3400–3150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65–7.10 (4H, aromatic), 5.25 (dd, J = 8.0, 6.0, H-5), 0.68 (t, J = 7.0, H-18); EIMS m/z (relative intensity) 312 (69, $M^{\bullet+}$), 127 (100); HRMS calcd for $C_{19}H_{24}N_2O_2$ 312.1839, found 312.1836.

Acid-Catalyzed Rearrangement of 10 to 15 and 16. To a solution of **10** (101 mg, 0.25 mmol) in CH_2Cl_2 (30 mL) was added trifluoroacetic acid (0.3 mL). The pale yellow mixture turned orange and reverted to the starting color within 20 min at room temperature. The solution was then evaporated under vacuum at 35 °C. The dry residue (92 mg) was purified by TLC on alumina (CH_2Cl_2–MeOH, 99.5:0.5) to provide **15** (39 mg, 42%) and the less polar **16** (10 mg, 11%) as amorphous compounds. When this reaction was kept at room temperature for 15 h, the same workup afforded only the compound **15** in 52% yield.

15: amorphous solid; TLC (alumina, CH_2Cl_2–MeOH, 99:1) R_f 0.36 (CAS, light yellow-grey); $[\alpha]_D$ −94 (c = 1, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 222 (4.23), 255 sh (3.63), 279 sh (3.49), 327 (3.88) nm; IR (CH_2Cl_2) 3400, 1720 cm^{-1}; HRMS calcd for $C_{21}H_{24}N_2O_4$ 368.1735, found 368.1732.

16: amorphous solid; TLC (alumina, CH_2Cl_2–MeOH, 99:1) R_f 0.45 (CAS, light grey); $[\alpha]_D$ −90.5 (c = 0.6, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 226 (4.43), 276 sh (3.95), 284 sh (3.93), 294 sh (3.81) nm; IR (CH_2Cl_2) 1740, 1720 cm^{-1}; HRMS calcd for $C_{21}H_{24}N_2O_4$ 368.1735, found 368.1731.

Acid Isomerization of 16 to 15. Compound **16** (5 mg) was dissolved in trifluoroacetic acid (2 mL), and the mixture was left at room temperature for 4 h. The solution was then

evaporated under vacuum at room temperature. TLC of the dry residue (alumina, CH_2Cl_2–MeOH, 99:1) did not display any more starting compound and only provided **15** (2 mg).

Acid-Catalyzed Rearrangement of 7 to 15. Compound **7** (2.33 g, 4.3 mmol) was dissolved in CH_2Cl_2 (400 mL), and trifluoroacetic acid (4 mL) was added. The reaction was kept at room temperature and monitored by TLC (SiO_2, CH_2Cl_2–MeOH, 98:2). Starting compound **7** and the intermediate **10** fully disappeared within 45 h. The mixture was then evaporated to dryness under vacuum at 35°C. Flash chromatography of the residue on alumina (CH_2Cl_2–MeOH, 99.5:0.5) only yielded **15** (754 mg, 48%), while compound **16** was not recovered.

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Supplementary Material Available: ^1H NMR spectra of compounds **15** and **16** for which combustion analytical data are not available (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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