Chiroptical Analysis of Marine Sponge Alkaloids Sharing the Pyrrolopyrazinone Core

Delphine E. N. Jacquot, Peter Mayer, and Thomas Lindel*[a]

Dedicated to Professor Ingo-Peter Lorenz on the occasion of his 60th birthday

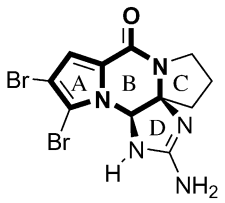
Abstract: A systematic experimental study has been conducted on the chiroptical properties of bi- and tricyclic pyrrolopyrazinones, which occur as the core in a variety of marine pyrrole–imidazole alkaloids, such as the immunosuppressive palau'amine. On the basis of the chiral-pool synthesis of conformationally fixed dipyrrolopyrazinones, it was possible to predict the CD spectrum of (−)-dibromophakellin above 240 nm. 2,2,2-Trifluoroethanol was identified as a superior solvent for this analysis. Positive Cotton effects at 250 nm can be used to determine the helicity of dibrominated pyrrolopyrazinones, while the intensity of the Cotton effect at 285 nm is governed by the relative stereochemistry. The influence of bromination of the pyrrole ring also becomes predictable. One of the tricycles can be considered as "conformationally frozen longamide A". Our study also gives the first comparative Röntgen analyses of diastereomeric Mosher esters of *N*,*O*-hemiacetals, with the results underlining the fact that caution is advised in the application of the advanced Mosher method.

Keywords: circular dichroism · heterocycles · natural products · pyrrole–imidazole alkaloids · structure elucidation

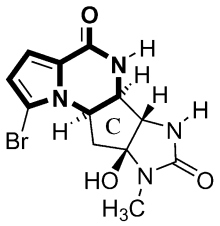
Introduction

Pyrrole–imidazole alkaloids are exclusively found in marine sponges, mainly of the families Agelasidae, Axinellidae, and Halichondridae. Novel examples with unprecedented molecular architecture and biological activities are constantly being discovered.[1] A pyrrolopyrazinone bicyclic system forms the AB core of several of the cyclized pyrrole–imidazole alkaloids (Scheme 1).

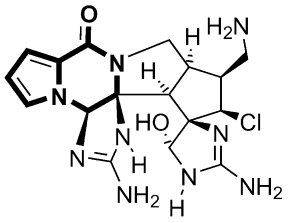
Sharma and co-workers reported the isolation of the ABCD tetracycle (−)-dibromophakellin (**1**) from *Phakellia flabellata*.[2] Ahond, Poupat, and co-workers discovered that **1** may occur in both enantiomeric forms.[3] The cytotoxic agelastatin A (**2**) from *Agelas dendromorpha* shows a different anellation of ring C to the pyrrolopyrazinone bicyclic system.[4] Kinnel, Scheuer, and co-workers elucidated the structure of the immunosuppressive natural product palau'amine (**3**) from *Stylotella aurantium*.[5] CD spectra of **3** were measured, but the absolute stereochemistry of the nonbrominated (−)-palau′amine (**3**) is still unknown. The bicyclic pyrrololactal longamide A (**4**) from *Agelas longissima* repre-



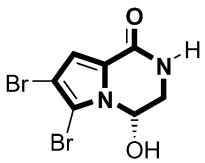
1: (–)-dibromophakellin



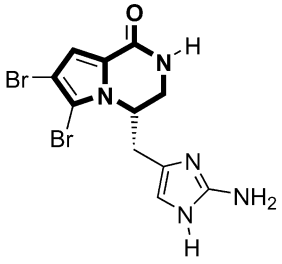
2: agelastatin A



3: palau'amine



4: longamide A



5: cyclooroidin

Scheme 1. Marine sponge alkaloids sharing the pyrrolopyrazinone partial structure.

[a] Dr. D. E. N. Jacquot, Dr. P. Mayer, Prof. Dr. T. Lindel
Department of Chemistry
Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13, 81377 Munich (Germany)
Fax: (+49) 89-2180-77734
E-mail: thomas.lindel@cup.uni-muenchen.de

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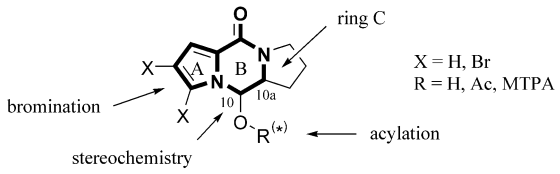
sents the most simple alkaloid with a pyrrolopyrazinone partial structure and has been described as optically active[6a] and as a racemate.[6b] Racemic longamide A (*rac*-**4**) was separated into the enantiomers by use of chiral HPLC.[7a] Although the configuration of the lactal center of **4** is labile, recent results by Evans et al.[8] regarding the remarkably stable configuration even of open-chain pyrrolyl carbinols support the possibility of **4** being isolable as an optically active compound. Cyclooroidin (**5**) is the latest member of the family.[9]

Our program on the total synthesis of the pyrrole–imidazole alkaloids from marine sponges gave us the opportunity to study stereochemically defined, bi- and tricyclic lactals containing pyrrolyl carbinol partial structures by chemical derivatization and by CD spectroscopy. Despite the use of CD spectra for the assignment of the absolute configuration of the pyrrole–imidazole alkaloids, there has been no systematic investigation based on chiral-pool syntheses. In the light of the efforts on the total synthesis of (−)-palau'amine (**3**),[10] an experimental study may be helpful.

Scheme 2 outlines the structural variations chosen in our study. Pyrrole bromination is of relevance due to the occurrence of variously brominated pyrrole–imidazole alkaloids in marine sponges. Ring C is present in phakellin- and palau'amine-type pyrrole–imidazole alkaloids but absent in longamide A (**4**). Throughout this article, the stereogenic centers of the ABC systems will be referred to as C-10 and C-10a.

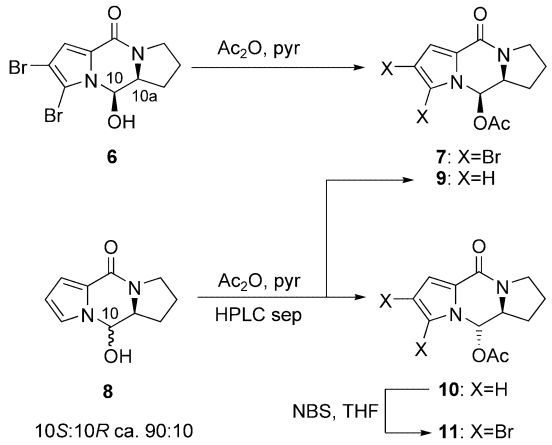


Scheme 2. Structural variations chosen in our study. The partial structure drawn in bold is shared by all the investigated compounds. MTPA = (*R*)- or (*S*)-2-methoxy-2-trifluoromethyl-2-phenylacetyl.

Abstract in French: *Les propriétés chiroptiques de pyrazinones bi- et tricycliques, structures appartenant au squelette d'alcaloïdes pyrrolo-imidazoliques d'origine marine comme l'immunosuppresseur palau'amine, ont été étudiées de façon expérimentale et systématique. La synthèse à partir du pool chiral d'une série de pyrazinones dipyrroliques conformationnellement fixées a rendu possible la prédiction précise du spectre de dichroïsme circulaire de la (−)-dibromophakelline dans le domaine de longueur d'onde supérieur à 230 nm. Dans cette étude, le 2,2,2-trifluoroethanol s'est révélé être le meilleur solvant. Les effets Cotton positifs autour de 251 nm ont été utilisés pour la détermination de l'hélicité des pyrazinones dipyrroliques bromées. L'intensité de l'effet Cotton à 285 nm semble être dirigée par la stéréochimie relative des substituants sur la pyrazinone. L'influence du degré de bromation du pyrrole a aussi été étudiée et quantifiée. Comme une des pyrazinones peut être considérée comme une longamide A "conformationnellement gelée", l'attribution de la stéréochimie absolue du produit naturel a été possible. Notre étude présente également la première analyse cristallographique des deux esters de Mosher diastéréomériques obtenus à partir d'un* N,O*-hemiacétal. Dans ce cas, la méthode de Mosher modifiée doit être appliquée avec la plus grande attention.*

Results

Synthesis of bi- and tricyclic pyrrolyl carbinols: Racemic longamide A (*rac*-**4**) and the dibrominated (10*R*,10a*S*)-dipyrrolopyrazinone **6** were synthesized by cyclization of the corresponding aldehyde precursors.[7,11] The tricycle **6**, obtained as a single stereoisomer, was acetylated to form **7** (Scheme 3), or converted into the diastereomeric MTPA



Scheme 3. Synthesis of all diastereomers (L-prolinol series) of the 10-*O*-acetylated, non- and dibrominated dipyrrolopyrazinone model compounds. NBS = *N*-bromosuccinimide, pyr = pyridine, sep = separation, THF = tetrahydrofuran.

esters **12** and **13** (see Figure 1 below). The diastereomeric 10*S*,10a*S* tricycle **8** was prepared as the major anomer (9:1) in three steps by oxidation/lactalization of a nonbrominated precursor obtained by condensation of L-prolinol with pyrrolyl trichloromethyl methanone. A mixture of the diastereomers **9** and **10** was then obtained by acetylation and separated by preparative HPLC (Scheme 3). Acylation of the carbinol hydroxy group was expected to be necessary to prevent anomerization. Dibromination of **10** to form **11** occurred readily on treatment with NBS.

Free longamide A (**4**) is known to racemize within minutes.[7a] In order to be able to analyze the CD spectra of stereochemically pure longamide derivatives, both diastereomeric (*R*)-MTPA esters **14** and **15** (see Figure 3 below) were prepared[12] by treatment of racemic longamide A (*rac*-**4**) with (*S*)-MTPA-Cl and separation by HPLC.

Mosher analysis: The diastereomeric (*R*)-MTPA esters **14** (4*R*) and **15** (4*S*) of racemic longamide A (*rac*-**4**) show the very small shift difference of −0.01 ppm ($\delta_{(S)\text{-MTPA}} - \delta_{(R)\text{-MTPA}}$) for the pyrrole proton 8-H, which is the only proton situated

on the "left side" of the Mosher ester plane. However, for an unambiguous assignment of the relative stereochemistries, significant chemical-shift differences have to be observed for the protons on *both* sides of the plane defined by the carbinol proton and the CF_3 group in synperiplanar positions (Figure 1). We decided to analyze the tricycle **6** as an independent example with a defined absolute stereochemistry. The diastereomeric (*R*)- and (*S*)-MTPA esters **12** and **13** of the ABC tricycle **6** also showed a shift difference of only −0.04 ppm ($\delta_{(S)\text{-MTPA}}-\delta_{(R)\text{-MTPA}}$) for the pyrrole proton 6-H. On further comparison with **12** and **13**, the relative configurations of the Mosher esters **14** and **15** of longamide A (**4**) can be assigned as depicted in Figure 3 (given below).

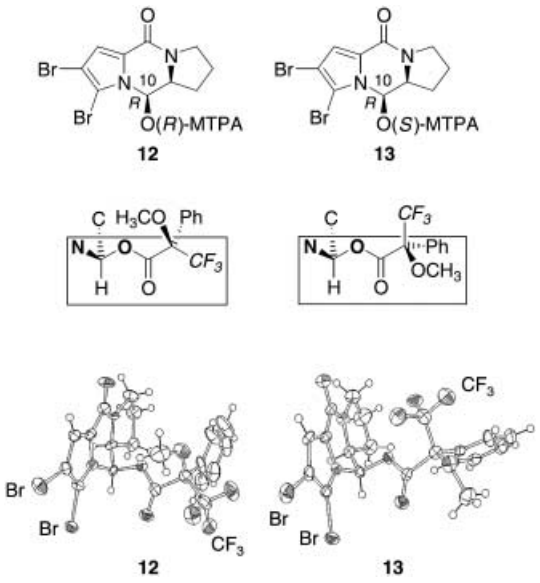


Figure 1. Mosher esters **12** and **13** of the (10*R*,10a*S*)-dipyrrolopyrazinone **6**. The ORTEP plots show syn- (**12**) and antiperiplanar (**13**) conformations of the diastereomers in the crystal.

Mosher esters prefer three almost equally populated conformations.[13] We were able to obtain crystals of both diastereomers **12** and **13** and it was found that, in the crystal, the expected conformation with the synperiplanar position of the CF_3 group and the carbinol proton 10-H is only obtained by the (*R*)-MTPA ester **12**. For the (*S*)-MTPA ester **13**, the antiperiplanar orientation was observed in the crystal. As a consequence, the chemical environment of the pyrrole protons is very similar for both diastereomers. Apparently, repulsing interaction between the pyrrole and the phenyl rings is responsible for the preference of the *anti* conformation of **13**. To our knowledge, the dipyrrolopyrazinones **12** and **13** represent the first pair of diastereomeric MTPA esters of *N*,*O*-hemiacetals for each of which X-ray structure analyses were performed. Our finding underlines the fact that caution is advised when applying the Mosher method to stereochemical analysis of natural products, in particular when steric hindrance can be expected.

CD spectra: The CD extrema of our compounds are summarized in Table 1. Importantly, 2,2,2-trifluoroethanol (TFE) proved to be the solvent leading to the most pronounced CD spectral characteristics. For example, the acetylated tricycle **7** exhibits an additional shoulder at about 255 nm that neighbors the most intense peak at 285 nm in TFE, while in acetonitrile one contourless peak at 274 nm is observed.

Figure 2 compares the CD spectra (in TFE) of all five ABC ring systems **6**, **7**, **9**, **12**, and **13** with 10*R*,10a*S* absolute configurations. In comparison with the dibrominated compounds, a hypsochromic shift of almost the entire CD spectrum by about 12 nm is observed for the nonbrominated ABC tricycle **9**, with the most intense peak now at 273 nm, the shoulder at 246 nm, and the trough at 220 nm. The CD spectra of the pyrrolyl carbinols appear to be only weakly dependant on the acetylation of the hydroxy group, since the *O*-free compound **6** shows a spectrum very similar to **7**. Even for the diastereomeric (*R*)- and (*S*)-MTPA esters **12** and **13**, the CD spectra are superposable above 245 nm. The troughs at 234 nm and 237 nm for **12** and **13**, respectively, occur at greater wavelengths than the trough in the case of the acetylated ABC tricycle **7** (226 nm).

Figure 3 gives the CD spectra of the (*R*)-MTPA esters **14** and **15** of the bicyclic racemic longamide A (*rac*-**4**), which lacks the second stereogenic center next to the amide nitrogen atom. The CD spectrum of the 4*R* derivative **14** is strikingly similar to the spectra of the conformationally fixed ABC systems (Figure 2). Although **14** and **15** are diastereomers, their CD spectra appear mirror-like, a result that in-

Table 1. CD spectral data for our series of pyrrolyl carbinols in TFE. Three wavelength zones were defined (pk = peak, tr = trough, sh = shoulder).

	System	Configuration at:		R	X	Wavelengths[a] (absorption maxima[a], zone)		
		C-10	C-10a			$\lambda < 240$ nm	$240 < \lambda < 260$ nm	$\lambda > 260$ nm
1[b]	ABCD	*S*	*R*	NHC(=NH)NH	Br	226 (−0.8, pk)	251 (−4.6, tr)	286 (−1.9, sh)
6	ABC	*R*	*S*	OH	Br	219 (−4.5, sh)	256 (+2.5, sh)	285 (+4.9, pk)
7	ABC	*R*	*S*	OAc	Br	226 (−4.4, tr)	253 (+3.2, sh)	284 (+7.4, pk)
9	ABC	*R*	*S*	OAc	H	220 (−3.5, tr)	246 (+3.9, sh)	273 (+7.8, pk)
10	ABC	*S*	*S*	OAc	H	218 (−5.4, sh)	245 (+6.3, pk)	270 (+1.8, sh)
11	ABC	*S*	*S*	OAc	Br	226 (−4.1, tr)	252 (+4.9, pk)	280 (+1.0, sh)
12	ABC	*R*	*S*	O((*R*)-MTPA)	Br	234 (−12.6, tr), 219 (−8.0, sh)	256 (+3.0, sh)	285 (+9.8, pk)
13	ABC	*R*	*S*	O((*S*)-MTPA)	Br	237 (−6.1, tr), 224 (−1.5, pk)	260 (+4.0, sh)	284 (+9.7, pk)
14	AB	*R*	–	O((*R*)-MTPA)	Br	234 (−5.5, tr)	257 (+1.8, sh)	284 (+3.6, pk)
15	AB	*S*	–	O((*R*)-MTPA)	Br	234 (+4.5, pk), 219 (+2.3, tr)	260 (−3.2, sh)	284 (−5.8, tr)

[a] Wavelengths are given in nm, $\Delta\varepsilon$ values are given in $L\,mol^{-1}\,cm^{-1}$. [b] The enantiomeric excess has not been determined. Both enantiomers occur as natural products.

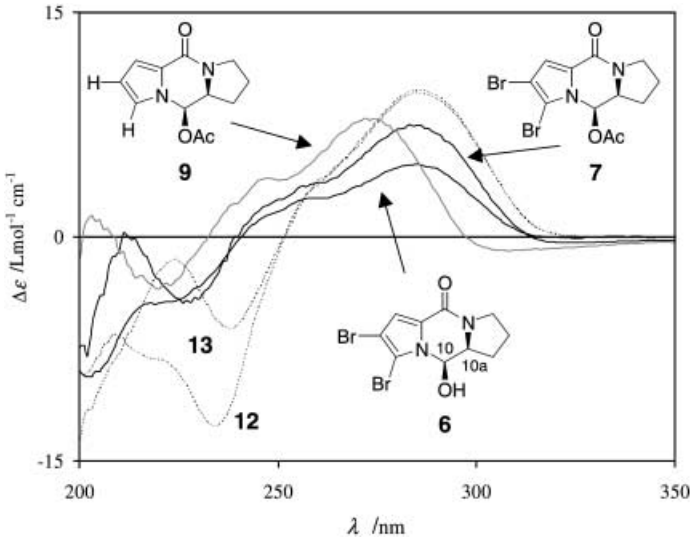


Figure 2. CD spectra (in TFE) of the five ABC systems with identical 10*R*,10a*S* absolute stereochemistry. For the structures of the Mosher esters **12** and **13**, see Figure 1.

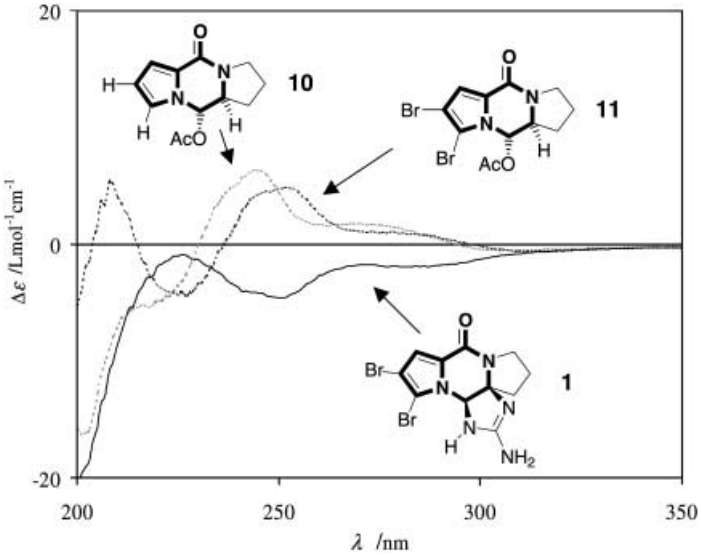


Figure 4. CD spectra (in TFE) of (−)-dibromophakellin (**1**) and of the ABC ring systems **10** and **11** with inverted stereochemistry at both stereogenic centers.

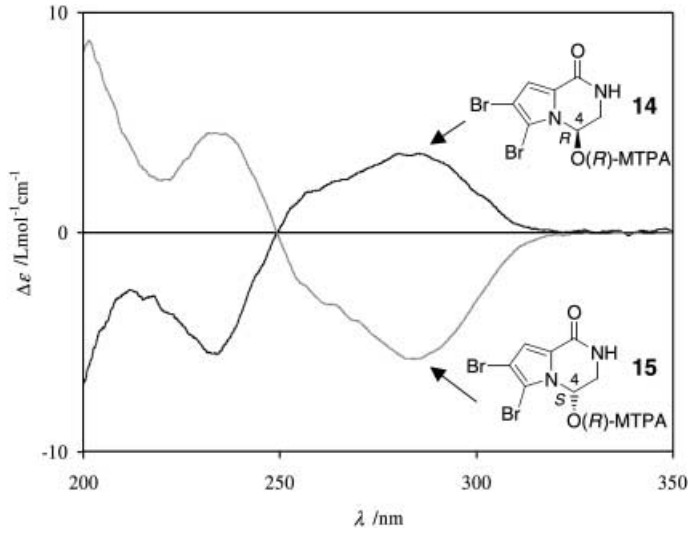


Figure 3. CD spectra (in TFE) of the diastereomeric (*R*)-MTPA esters **14** and **15** of racemic longamide A (*rac*-**4**) in TFE.

dicates the overwhelming influence of the pyrrolopyrazinone part on the optical properties.

For the epimeric 10*S* ABC systems, the band at 285 nm (dibrominated examples) is depleted to a shoulder (Figure 4) while the absorption at 252 nm, which appeared as a shoulder in the CD spectra of the 10*R* ABC epimers (Figure 2), is still present at an unchanged intensity but is now the most intense band. Again, debromination causes a hypsochromic shift of the CD spectrum. Figure 4 also compares the CD spectra of the di- and nonbrominated ABC tricycles **10** and **11** with the data for the tetracyclic natural product (−)-dibromophakellin (**1**). The CD spectrum of the pyrrole–imidazole alkaloid **1** shows very similar patterns, but, as expected, of opposite sign. Only below 235 nm do substantial differences in the CD spectra of the tri- and tetracycles occur.

The bi- and tricyclic systems have the advantage of obtaining rigid conformations. From our data, we can conclude that a positive peak at about 250 nm reflects the *S* configuration of the bridgehead C-10a. While high intensity of the band at about 285 nm indicates *R* configuration of the carbinol center, a shoulder-like appearance is observed for the diastereomeric *S* epimers. The nonbrominated compounds show very similar behavior with bands shifted to shorter wavelengths by about 12 nm.

It has been shown that in nonplanar bi- and tricyclic systems positive helicity leads to dominant positive Cotton effects (CEs), as observed for all of our compounds with the 10a*S* configuration.[14,15] Molecular modeling shows that for the tricyclic ABC systems derived from L-prolinol torsion of the amide against the pyrrole chromophore, and thereby the helicity of the fused ring system, is always positive, independant from the configuration at C-10.[16] The pyrrolopyrazinone partial structure of the bicyclic (4*R*)-longamide (*R*)-MTPA ester **14** achieves a conformation with positive helicity that is very similar to the AB partial structure of the 10*R*,10a*S* ABC systems **6**, **7**, **9**, **12**, and **13**. This is also reflected by the high similarity of the CD spectra over the entire wavelength range (Figures 2 and 3). Correspondingly, (4*S*)-longamide (*R*)-MTPA ester **15** exhibits negative helicity and negative CEs above 250 nm.

The tricycles **6**, **7**, **9**, **12**, and **13** differ from **10** and **11** with regard to the pseudoaxial (rather than pseudoequatorial) positions of the oxy substituents at C-10. The much weaker CE at 285 nm observed for the 10*S*,10a*S* diastereomers as compared to the 10*R*,10a*S* compounds is in agreement with findings by Hagishita and Kuriyama[15d] who studied octahydroanthracenes. Among nitrogen-containing ring frameworks, only isoquinoline derivatives have been investigated experimentally,[17] while rigid bicyclic perhydrobenzocycloal-

kenes and octahydroanthracenes have been studied more extensively.

The basis of the effect of TFE remains unclear. Despite detailed studies on the effect of TFE on the CD spectra of peptides,[18] DNA,[19] oligosaccharides,[20] and other macromolecular structures, only a few small molecules have been analyzed in this respect. The similarity of the CD curves of the nonacetylated ABC system **6** and those of the acyl derivatives suggests that hydrogen bonding[21] does not play a significant role. There is also hardly any difference between the CD spectra of the acetylated compounds and the fluorinated Mosher derivatives in TFE.[22]

Absolute configuration of the pyrrole–imidazole alkaloids: The absolute configuration of the pyrrolopyrazinone partial structure dominates the CD spectra of the pyrrole–imidazole alkaloids. Acetylation of the exocyclic amino group at ring D of (−)-dibromophakellin (**1**) or conversion to form the hydrochloride have no significant influence on the reported CEs.[2] CD spectra of the agelastatins A, C, and D were reported to be almost superposable, despite varying substitutions.[4c]

Table 2 summarizes the reported CD data of pyrrole–imidazole alkaloids with pyrrolopyrazinone partial structures. The weak influence of the MTPA groups on the overall CD spectra of our compounds may be explained by the CD

Table 2. Reported CD spectral data for selected pyrrole–imidazole alkaloids (**1**–**5**, see Figure 1) isolated from marine sponges, given for two wavelength areas.[a]

	Wavelengths[b] ($\Delta\varepsilon$[b])		ref.
	$\lambda < 260$ nm	$\lambda > 260$ nm	
1	210 (+26.2), 239 (−12.4)	285 (−4.6)	[2]
1·HCl	210 (+16.1), 239 (−8.0)	283 (−3.6)	[2]
Ac-**1**	210 (−11.7), 240 (−13.0)	285 (−4.2)	[2]
ent-**1**	241 (+10.2)	285 (+4.9)	[3]
2	219 (−7.2), 246 (+6.6)	n.r.[c]	[4]
3	208 (−9.1), 228 (−4.5, sh)	267 (+2.9)	[5b]
4	207 (−18), 233 (−4.1)	n.r.[c]	[6]
5	208 (−15.5), 238 (−6.2)	n.r.[c]	[9]

[a] Data have been obtained in methanol or acetonitrile. [b] Wavelengths are given in nm, $\Delta\varepsilon$ values are given in $L\,mol^{-1}\,cm^{-1}$. [c] n.r. = nothing reported.

bands of (*S*)-(−)-MTPA acid methyl ester (λ_{max} ($\Delta\varepsilon$) = 233 (−1.9), 261 (+0.4))[23] being much less intense than those observed for the pyrrolyl carbinol partial structure. Above 240 nm, the curves of the diastereomeric MTPA esters **14** and **15** should closely resemble those of enantiomerically pure longamides A. Longamide A (**4**) from *Agelas longissima* showed a negative CD band at 233 nm in acetonitrile, a solvent in which the conformationally very similar 10*R*,10a*S* ABC tricycle **6** shows a negative trough at 235 nm. This suggests that the absolute stereochemistry of longamide A (**4**) should be revised to 4*R*.

Originally, it was concluded that the helicities of naturally occurring longamide A (**4**) and (−)-dibromophakellin (**1**) should be identical, due to negative CD bands at 233 nm and 239 nm, respectively.[6a] If this were the case, longamide A (**4**) would indeed have 4*S* configuration, because the hydroxy substituent of longamide A (**4**) prefers the quasiaxial position, while in (−)-dibromophakellin (**1**) the nitrogen substituent is forced into the quasiequatorial position. However, it is probably not possible to conclude that the compared molecules have an identical helicity. In TFE, the region between 220 and 235 nm is the least interpretable (see Figure 4).[6b]

Based on our experimental study, the CD spectrum of (−)-dibromophakellin (**1**; Figure 4) can be understood. The small influence of the amino imidazoline ring D on the CD spectrum of **1** is no surprise because the key partial structure influencing the chiroptical properties obtains almost the same enantiomeric conformation as in our 10*S*,10a*S* ABC tricycles **10** and **11**. In particular, the helicities of the pyrrolopyrazinone partial structures are of opposite sign. As predicted, the CD spectrum of **1** with *R* configuration at C-10a appears to mirror the spectrum of the 10*R*,10a*S* diastereomer **11** above 240 nm. In turn, the negative CD band of the natural product **1** at 251 nm predicts a 10a*R* configuration, and the weak intensity of the band at 285 nm indicates that the nitrogen substituents forming ring D must be on the same side of the ABC system.

In one of the most complex pyrrole–imidazole alkaloids known to date, the immunosuppressive (−)-palau'amine (**3**), an additional cyclopentane ring is anellated to ring C of the dibromophakellin ABCD system. This leads to an almost planar conformation of the AB partial structure. Therefore, predictions on the CD spectrum of (−)-palau'amine (**3**) are more difficult to make on the basis of our study. The more significant band would be expected at about 270 nm, while the CE should be close to zero at 250 nm. We are currently investigating this in more detail.

Conclusions

In summary, we have shown how the CD spectra of pyrrole–imidazole alkaloids sharing a pyrrolopyrazinone partial structure reflect the helicity and the relative stereochemistry of ring substitution. Positive Cotton effects at about 250 nm can be used to determine the helicity of dibrominated pyrrolopyrazinones, while the intensity of the Cotton effect at 285 nm is governed by the relative stereochemistry of the pyrrolopyrazinone ring substitution. In particular, the CD spectrum of (−)-dibromophakellin (**1**) is now understood. The influence of bromination of the pyrrole ring is predictable. This is an important step towards the determination of the still-open absolute configuration of the immunosuppressive (−)-palau'amine (**3**). Our ABC tricycle **6** can be considered as "conformationally frozen longamide A", thereby allowing the assignment of the absolute configuration of the natural product. 2,2,2-Trifluoroethanol was identified as a superior solvent for the unprecedented analysis of bi-, tri-, and tetracyclic pyrrolopyrazinone systems. This study also gives the first comparative Röntgen analyses of diastereomeric MTPA esters of *N*,*O*-acetals, with the results underlining the fact that caution is advised in the application of the advanced Mosher method.

Experimental Section

General: Melting points were determined with Reichert hotstage and Electrothermal IA 9100 instruments and are uncorrected. NMR spectra were measured with Bruker WM-250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C), Bruker WM-360 (360 MHz for ^{1}H and 90.5 MHz for ^{13}C), and Varian VRX 400S (400 MHz for ^{1}H and 100 MHz for ^{13}C) instruments. All measurements were carried out at 300 K. Mass spectra were obtained with Varian MAT-311 A and Finnigan MAT95Q spectrometers. IR spectra were recorded with Perkin–Elmer PE 1600 FT-IR and Spectrum-1000 FT-IR spectrometers. UV/Vis spectra were measured with Hewlett-Packard HP-8452A and Perkin–Elmer Lambda-16 UV spectrometers. Optical rotations were determined with a Perkin–Elmer PE-241 polarimeter. Elemental analyses were performed with a Foss–Heraeus Vario EL apparatus. CD spectra were recorded with an ISA Jobin–Yvon CD 6 dichrometer (data listed in Table 1). All mesurements were carried out at 300 K. Silica gel 60 (230–400 mesh, Merck) was used for flash chromatography.

Acetic acid (5*R*,5a*S*)-2,3-dibromo-10-oxo-5a,6,7,8-tetrahydro-5*H*,10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-yl ester (7): Acetyl chloride (0.33 mL, 4.63 mmol) was added to a solution of the alcohol **6**[11] (324 mg, 0.93 mmol) in dry pyridine (3 mL) under argon. After 12 h, the solution was diluted with 6 N HCl (20 mL) and extracted three times with CH_2Cl_2 (30 mL). The organic layer was then washed with brine and dried over $MgSO_4$. The solution was evaporated to dryness and the residue was purified by flash chromatography (EtOAc). The acetate **7** (208 mg, 57 %) was obtained as a colorless solid. R_f (silica gel, EtOAc) = 0.32; m.p. 58–59 °C; $[\alpha]_D^{23} = +71$ ($c = 1.3$ in MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 1.63–1.75 (m, 1H; NCH_2CH_2CHH), 1.86–1.99 (m, 1H; NCH_2CHHCH_2), 2.09 (s, 3H; CH_3), 2.06–2.15 (m, 1H; NCH_2CHHCH_2), 2.23 (dtd, ^2J(H,H) = 12.8 Hz, ^3J(H,H) = 6.4, 2.4 Hz, 1H; NCH_2CH_2CHH), 3.56 (ddd, ^2J(H,H) = 11.6 Hz, ^3J(H,H) = 9.6, 7.2 Hz, 1H; NC*H*H), 3.77 (ddd, ^2J(H,H) = 11.6 Hz, ^3J(H,H) = 8.8, 2.8 Hz, 1H; NCH*H*), 4.15 (ddd, ^3J(H,H) = 10.0, 6.4, 2.8 Hz, 1H; 5a-H), 6.93 (d, ^3J(H,H) = 2.8 Hz, 1H; 5-H), 7.00 (s, 1H; HC=C) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 20.5$ (CH_3), 23.0 ($NCH_2CH_2CH_2$), 27.7 ($NCH_2CH_2CH_2$), 44.2 (NCH_2), 59.4 (C-5a), 74.1 (C-5), 102.8 (Br*C*–CH), 106.3 (Br*C*–CBr), 116.0 (H*C*=C), 127.1 (HC=*C*–N), 155.3 (CO), 168.9 (COO) ppm; IR (KBr): $\tilde{\nu} = 3436$, 1755, 1655, 1556, 1444, 1357, 1213, 1018, 942, 742, 616 cm^{-1}; UV/Vis (CH_3OH): λ_{max} (ε) = 282 (10715), 235 nm (11749 mol^{-1} dm^3 cm^{-1}); MS (EI, 70 eV): *m/z* (%): 390/392/394 (16/36/16) [M^+], 330/332/334 (6/12/6), 319/321/323 (10/20/10), 269/271 (22/22), 70 (100), 43 (29); HRMS (EI): calcd for $C_{12}H_{12}Br_2N_2O_3$: 389.9215, found: 389.9199.

(10*R*,10a*S*)- and (10*S*,10a*S*)-10-Hydroxy-2,3,10,10a-tetrahydro-1*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-one (8): *o*-Iodoxybenzoic acid (5.80 g, 20.6 mmol) was suspended in dimethylsulfoxide (DMSO; 15 mL). After 20 min, the solution became clear and ((2*S*)-2-hydroxymethyl-pyrrolidin-1-yl)-(1*H*-pyrrol-2-yl)-methanone[11] (2.00 g, 10.3 mmol) was added. After 12 h, the solution was diluted with water (200 mL). The precipitate was filtered off, dried, and extracted three times with CH_2Cl_2 (300 mL). Evaporation to dryness yielded a mixture of anomers of **8** as a colorless solid (875 mg, 39 % of (10*S*,10a*S*)-**8**, 5 % of (10*R*,10a*S*)-**8**). R_f (silica gel, acetone/CH_2Cl_2 (4:5)) = 0.32; $[\alpha]_D^{23} = +110$ ($c = 5.2$ in MeOH); (10*S*,10a*S*)-**8**: ^{1}H NMR ([D$_6$]DMSO, 400 MHz): $\delta = 1.76$–2.26 (m, 4H; $NCH_2CH_2CH_2$), 3.30–3.44 (m, 1H; NC*H*H), 3.50–3.58 (m, 1H; NCH*H*), 3.70 (ddd, ^3J(H,H) = 9.3, 9.2, 6.0 Hz, 1H; 10a-H), 5.31 (dd, ^3J(H,H) = 9.4, 8.0 Hz, 1H; 10-H), 6.18–6.20 (m, 1H; HC–C*H*=CH), 6.61–6.63 (dd, ^3J(H,H) = 3.4, 1.5 Hz, 1H; HC=C), 7.01–7.05 (m, 1H; HC=C*H*–N), 7.43 (d, ^3J(H,H) = 8.0 Hz, 1H; OH) ppm; ^{13}C NMR ([D$_6$]DMSO, 100 MHz): $\delta =$ 22.4 ($NCH_2CH_2CH_2$), 29.1 ($NCH_2CH_2CH_2$), 44.2 (NCH_2), 62.1 (C-10a), 81.5 (C-10), 109.3 (HC–*C*H=CH), 111.7 (H*C*=C), 119.5 (HC=*C*H–N), 124.2 (HC=*C*), 156.7 (CO) ppm; (10*R*,10a*S*)-**8**: ^{1}H NMR ([D$_6$]DMSO, 400 MHz): $\delta = 1.76$–2.26 (m, 4H; $NCH_2CH_2CH_2$), 3.30–3.44 (m, 1H; NC*H*H), 3.50–3.58 (m, 1H; NCH*H*), 3.98 (ddd, ^3J(H,H) = 9.0, 6.6, 2.8 Hz, 1H; 10a-H), 5.56 (dd, ^3J(H,H) = 6.8, 2.8 Hz, 1H; 10-H), 6.13–6.15 (m, 1H; HC–C*H*=CH), 6.58–6.60 (dd, ^3J(H,H) = 3.4, 1.5 Hz, 1H; HC=C), 6.64 (d, ^3J(H,H) = 7.2 Hz, 1H; OH), 7.01–7.05 (m, 1H; HC=C*H*–N) ppm; ^{13}C NMR ([D$_6$]DMSO, 100 MHz): $\delta = 22.6$ ($NCH_2CH_2CH_2$), 26.7 ($NCH_2CH_2CH_2$), 43.8 (NCH_2), 60.4 (C-10a), 75.4 (C-10), 109.1 (HC–*C*H=CH), 110.9 (H*C*=C), 122.7 (HC=*C*H–N), 124.1 (HC=*C*), 156.5 (CO) ppm; both anomers: IR (KBr): $\tilde{\nu} = 3125$, 2967, 2887, 1610, 1547, 1446, 1368, 1329, 1269, 1220, 1155, 1112, 1061, 1026, 963, 874, 790, 744, 727, 653 cm^{-1}; UV/Vis (CF_3CH_2OH): λ_{max} (ε) = 278 (9550), 230 (8318), 198 nm (7943 mol^{-1} dm^3 cm^{-1}); MS (EI, 70 eV): *m/z* (%): 192 (56) [M^+], 95 (14), 94 (47), 70 (100); HRMS (EI): calcd for $C_{10}H_{12}N_2O_2$: 192.0899, found: 192.0904.

5*R*,5a*S* and 5*S*,5a*S* diastereomers of acetic acid (5*R*,5a*S*)-10-oxo-5a,6,7,8-tetrahydro-5*H*,10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-yl ester (9, 10): Acetyl chloride (1.00 mL, 14.03 mmol) was added to a solution of the lactal **8** (500 mg, 2.64 mmol, 9:1 mixture of diastereomers) in dry pyridine (5 mL) under argon. After 5 min, the precipitate was filtered off and the solution was dried in vacuo. Flash chromatography (CH_2Cl_2/MeOH (95:5)) yielded the acetylation products **9** (44 mg, 7 %) and **10** (402 mg, 65 %) as yellowish solids which were separated by preparative HPLC (RP-18, MeOH/H_2O (1:1)). **9:** R_f (RP-18, MeOH/H_2O (1:1)) = 0.18; m.p. 96 °C; $[\alpha]_D^{23} = +9$ ($c = 6.25$ in MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 1.84–1.97 (m, 2H; $NCH_2CHHCHH$), 2.06–2.16 (m, 1H; NCH_2CHHCH_2), 2.21–2.26 (m, 1H; NCH_2CH_2CHH), 2.27 (s, 3H; CH_3), 3.54–3.62 (m, 1H; NCH*H*), 3.77 (ddd, ^2J(H,H) = 11.6 Hz, ^3J(H,H) = 8.4, 3.0 Hz, 1H; NCH*H*), 3.95 (td, ^3J(H,H) = 9.4, 6.0 Hz, 1H; 5a-H), 6.27 (dd, ^3J(H,H) = 3.6, 2.7 Hz, 1H; 2-H), 6.47 (d, ^3J(H,H) = 9.4 Hz, 1H; 5-H), 6.68 (dd, ^3J(H,H) = 2.7, 1.8 Hz, 1H; 3-H), 6.94 (dd, ^3J(H,H) = 3.6, 1.8 Hz, 1H; 1-H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 20.8$ (CH_3), 23.0 ($NCH_2CH_2CH_2$), 29.7 ($NCH_2CH_2CH_2$), 44.4 (NCH_2), 60.6 (C-5a), 80.8 (C-5), 111.1 (C-2), 113.0 (C-1), 120.0 (C-3), 125.0 (C-10a), 157.6 (CO), 169.4 (COO) ppm; IR (KBr): $\tilde{\nu} = 3436$, 2968, 1765, 1646, 1549, 1433, 1370, 1215, 1079, 1050, 753, 509 cm^{-1}; UV/Vis (CH_3OH): λ_{max} (ε) = 272 (10471), 230 nm (10965 mol^{-1}dm^{3}cm^{-1}); MS (EI, 70 eV): *m/z* (%): 234 (14) [M^+], 191 (3), 174 (100), 122 (41), 94 (26), 70 (34), 66 (13), 43 (25); HRMS (EI): calcd for $C_{12}H_{14}N_2O_3$: 234.1004, found: 234.1015. **10**: R_f (RP-18, MeOH/H_2O (1:1)) = 0.32; m.p. 136 °C; $[\alpha]_D^{23} = +132$ ($c = 2.2$ in MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.87$–2.00 (m, 2H; $NCH_2CH_2CH_2$), 2.04 (s, 3H; CH_3), 2.08–2.20 (m, 2H; $NCH_2CH_2CH_2$), 3.58–3.66 (m, 1H; NCH*H*), 3.73–3.79 (m, 1H; NCH*H*), 4.20 (ddd, ^3J(H,H) = 9.0, 6.0, 3.0 Hz, 1H; 5a-H), 6.22 (dd, ^3J(H,H) = 3.6, 2.8 Hz, 1H; 2-H), 6.64 (d, ^3J(H,H) = 2.8 Hz, 1H; 5-H), 6.92 (dd, ^3J(H,H) = 3.6, 1.6 Hz, 1H; 1-H), 6.95 (dd, ^3J(H,H) = 2.8, 1.6 Hz, 1H; 3-H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 20.8$ (CH_3), 23.3 ($NCH_2CH_2CH_2$), 27.3 ($NCH_2CH_2CH_2$), 44.1 (NCH_2), 59.4 (C-5a), 74.6 (C-5), 110.9 (C-2), 113.6 (C-1), 123.8 (C-3), 124.9 (C-10a), 157.3 (CO), 170.1 (COO) ppm; IR (KBr): $\tilde{\nu} = 3436$, 2982, 1748, 1641, 1556, 1433, 1356, 1215, 1072, 753, 586 cm^{-1}; UV/Vis (CH_3OH): λ_{max} (ε) = 270 (10233), 231 nm (10233 mol^{-1} dm^3 cm^{-1}); MS (EI, 70 eV): *m/z* (%): 234 (78) [M^+], 191 (9), 174 (87), 147 (22), 122 (84), 94 (49), 70 (100), 66 (26), 43 (63); HRMS (EI): calcd for $C_{12}H_{14}N_2O_3$: 234.1004, found: 234.1014.

Acetic acid (5*S*,5a*S*)-2,3-dibromo-10-oxo-5a,6,7,8-tetrahydro-5*H*,10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-yl ester (11): The acetate **10** (112 mg, 0.48 mmol) in dry THF (10 mL) was treated with NBS (175 mg, 0.81 mmol) under argon in the dark. After 1 h, the solution was evaporated in vacuo and the residue was suspended in CH_2Cl_2. The organic layer was then washed with water, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by flash chromatography (EtOAc) to yield **11** (100 mg, 55 %) as a colorless solid. R_f (silica gel, EtOAc) = 0.35; m.p. 108 °C; $[\alpha]_D^{23} = +46$ ($c = 5.9$ in MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 1.85–1.95 (m, 2H; $NCH_2CH_2CH_2$), 2.05–2.15 (m, 1H; NCH_2CH_2CHH), 2.19–2.30 (m, 2H; NCH_2CH_2CHH), 2.24 (s, 3H; CH_3), 3.60–3.75 (m, 2H; NCH_2), 3.91 (ddd, ^3J(H,H) = 9.8, 8.2, 5.6 Hz, 1H; 5a-H), 6.71 (d, ^3J(H,H) = 8.2 Hz, 1H; 5-H), 7.04 (s, 1H; 1-H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 21.0$ (CH_3), 22.6 ($NCH_2CH_2CH_2$), 29.6 ($NCH_2CH_2CH_2$), 44.3 (NCH_2), 61.1 (C-5a), 80.3 (C-5), 103.9 (Br*C*–CH), 104.9 (Br*C*–CBr), 116.7 (H*C*=C), 127.2 (HC=*C*H–N), 155.9 (CO), 169.1 (COO) ppm; IR (KBr): $\tilde{\nu} = 3436$, 2884, 1763, 1660, 1550, 1439, 1386, 1206, 1046, 738 cm^{-1}; UV/Vis (CH_3OH): λ_{max} (ε) = 280 (13183), 232 nm (7943 mol^{-1} dm^3 cm^{-1}); MS (EI, 70 eV): *m/z* (%): 390/392/394 (0.4/0.8/0.4) [M^+], 330/332/334 (50/100/50), 251/253 (26/24), 172 (9); HRMS (EI): calcd for $C_{12}H_{12}Br_2N_2O_3$: 389.9215, found: 389.9242.

(2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (5*R*,5a*S*)-2,3-dibromo-10-oxo-5a,6,7,8-tetrahydro-5*H*-10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-yl ester (13): Lactal **6**[11] (168 mg, 0.48 mmol) in dry pyridine (3 mL) was added to (*R*)-MTPA-Cl (250 mg, 1.00 mmol) under argon. After 15 h, 3-dimethylaminopropylamine (125 μL, 1.00 mmol) was added to the solution. After filtration and evaporation to dryness, the residue was extracted three times with Et_2O (15 mL). The organic layer was evaporated

to dryness and the residue was purified by flash chromatography (EtOAc/2,2,6,6-tetramethylpiperidine (TMP) (8:2)) to afford **13** (221 mg, 81%) as a colorless oil which crystallized at 4°C. R_f (silica gel, EtOAc/TMP (8:2)) = 0.34; m.p. 101°C; $[\alpha]_D^{23} = +202$ ($c = 3.6$ in MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.64$–1.78 (m, 1H; NCH_2CH_2CHH), 1.87–1.94 (m, 1H; NCH_2CHHCH_2), 2.00–2.09 (m, 1H; NCH_2CHHCH_2), 2.20–2.34 (m, 1H; NCH_2CH_2CHH), 3.33 (s, 3H; OCH_3), 3.40–3.55 (m, 1H; $NCHH$), 3.77 (ddd, ^2J(H,H) = 11.6 Hz, ^3J(H,H) = 8.6, 2.4 Hz, 1H; $NCHH$), 4.24 (ddd, ^3J(H,H) = 9.8, 6.6, 2.4 Hz, 1H; 5a-H), 6.99 (s, 1H; HC=C), 7.08 (dd, ^3J(H,H) = 2.4 Hz, 1H; 5-H), 7.36–7.51 (m, 5H; Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 90.6 MHz): $\delta = 22.9$ ($NCH_2CH_2CH_2$), 27.4 ($NCH_2CH_2CH_2$), 44.2 (NCH_2), 55.3 (OCH_3), 59.5 (C-5a), 75.7 (C-5), 84.9 (q, ^2J(C,F) = 28 Hz, CCF_3), 103.3 (HC=CBr), 106.2 (BrC=CBr), 116.5 (HC=CBr), 125.5 (q, ^1J(C,F) = 288 Hz, CF_3), 127.0 (C=CH), 127.6 (C-Ar), 128.6(C-Ar), 123.0 (C-Ar), 130.1 (C-Ar), 154.6 (CO), 165.0 (COO) ppm; IR (KBr): $\tilde{\nu} = 2983$, 2361, 1759, 1713, 1653, 1558, 1444, 1423, 1389, 1356, 1267, 1228, 1171, 1121, 1082, 993, 900, 829, 770, 741, 713 cm^{-1}; UV/Vis (CF_3CH_2OH): λ_{max} (ε) = 288 (9120), 234 (11749), 202 nm (20893 mol^{-1} dm^3 cm^{-1}); MS (EI, 70 eV): *m/z* (%): 565/567/569 (4/8/4) [M^++H], 564/566/568 (18/36/18) [M^+], 332/334/336 (6/12/6), 331/333/335 (50/100/50), 303/305/307 (3/6/3), 251/253 (18/20), 223/225 (7/7), 189 (60), 119 (13), 105 (29), 91 (9), 77 (13), 70 (12), 69 (12), 55 (7), 54 (7), 42 (12); elemental analysis: calcd (%) for $C_{20}H_{17}Br_2F_3N_2O_4$ (566.2): C 42.43, H 3.03, N 4.95; found: C 42.69, H 3.38, N 4.69.

(2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (5*R*,5a*S*)-2,3-dibromo-10-oxo-5a,6,7,8-tetrahydro-5*H*-10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-yl ester (12): In an analogous process to the synthesis of **13**, **6**[11] was treated with (*S*)-MTPA-Cl to yield **12** (188 mg, 69%) as a colorless solid. R_f (silica gel, EtOAc/TMP (8:2)) = 0.34; m.p. 178–180°C; $[\alpha]_D^{23} = +79$ ($c = 2.9$ in MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.40$–1.50 (m, 1H; NCH_2CH_2CHH), 1.65–1.80 (m, 2H; $NCH_2CH_2CH_2$), 2.08–2.21 (m, 1H; NCH_2CH_2CHH), 3.24–3.36 (m, 1H; $NCHH$), 3.40 (q, ^5J(H,F) = 1.4 Hz, 3H; OCH_3), 3.58–3.68 (m, 1H; $NCHH$), 4.20 (ddd, ^3J(H,H) = 9.5, 6.8, 2.4 Hz, 1H; 5a-H), 7.03 (s, 1H; HC=C), 7.08 (d, ^3J(H,H) = 2.4 Hz, 1H; 5-H), 7.33–7.44 (m, 5H; Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 90.6 MHz): $\delta = 22.7$ ($NCH_2CH_2CH_2$), 26.8 ($NCH_2CH_2CH_2$), 44.2 (NCH_2), 55.5 (OCH_3), 59.3 (C-5a), 75.2 (C-5), 84.1 (q, ^2J(C,F) = 28 Hz, CCF_3), 103.4 (HC=CBr), 106.1 (BrC=CBr), 116.6 (HC=CBr), 123.0 (q, ^1J(C,F) = 288 Hz, CF_3), 126.9 (C-Ar), 127.2 (C=CH), 128.5 (C-Ar), 129.9 (C-Ar), 131.1 (C-Ar), 154.8 (CO), 164.9 (COO) ppm; IR (KBr): $\tilde{\nu} = 3421$, 3157, 2972, 1768, 1652, 1569, 1442, 1420, 1348, 1280, 1232, 1168, 1027, 989, 767, 715 cm^{-1}; UV/Vis (CF_3CH_2OH): λ_{max} (ε) = 288 (8318), 234 (10233), 202 nm (19055 mol^{-1} dm^3 cm^{-1}); MS (EI, 70 eV): *m/z* (%): 565/567/569 (5/10/5) [M^++H], 564/566/568 (20/40/20) [M^+], 332/334/336 (6/12/6), 331/333/335 (50/100/50), 303/305/307 (3/6/3), 251/253 (22/23), 223/225 (9/9), 189 (56), 119 (16), 105 (28), 91 (10), 77 (13), 70 (13), 69 (14), 55 (7), 54 (6), 41 (5); elemental analysis: calcd for (%) $C_{20}H_{17}Br_2F_3N_2O_4$ (566.2): C 42.43, H 3.03, N 4.95; found: C 42.38, H 3.28, N 4.80.

MTPA esters 14 and 15 of racemic longamide A: A dried solution (4-Å molecular sieves) of racemic longamide A (*rac*-**4**, 150 mg, 0.48 mmol)[7c] in pyridine (3 mL) was added to neat (*S*)-(+)-MTPA-Cl (252 mg, 1.00 mmol). After 15 h at room temperature, 3-(dimethylaminopropyl)amine (102 mg, 125 µL, 1.00 mmol) was added. After 30 min, the solution was filtered and the evaporated filtrate was extracted with diethyl ether (2×15 mL). After evaporation this gave the crude product mixture. Purification by column chromatography (silica gel, EtOAc/TMP (gradient from 1:2 to 2:1)) yielded a mixture of **14** (4*R*) and **15** (4*S*) which was subjected to semipreparative HPLC (Merck LiChrospher Si60, length 250 mm, diameter 1 cm, flow rate 6 mL min^{-1}, eluent EtOAc/*n*-hexane (3:1)) to give **14** (67 mg, 26%, 9.46 min) and **15** (63 mg, 24%, 10.63 min) as colorless oils. **14**: $[\alpha]_D^{20} = -20$ ($c = 4$ in MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.45$ (s, 3H; OCH_3), 3.78 (dd, ^2J(H,H) = 14.7 Hz, ^3J(H,H) = 4.9 Hz, 1H; CHH), 4.00 (dd, ^2J(H,H) = 14.7 Hz, ^3J(H,H) = 2.9 Hz, 1H; CHH), 6.94 (m, 1H; 4-H), 6.99 (m, 1H; NH), 7.04 (s, 1H; pyrrole-CH), 7.30–7.50 (m, 5H; Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 63 MHz): $\delta = 44.3$ (CH_2), 55.5 (OCH_3), 74.6 (C-4), 84.9 (C), 103.6 (CBr), 107.1 (CBr), 117.7 (pyrrole-CH), 122.9 (q, CF_3), 126.0 (C), 127.1 (C-Ar), 128.6 (C-Ar), 130.0 (C-Ar), 131.1 (C), 157.9 (C=O), 165.4 (C=O) ppm; UV/Vis (CF_3CH_2OH): λ_{max} (ε) = 286 (7750), 234 (8350), 205 nm (16700 mol^{-1} dm^3 cm^{-1}); MS (FAB+): *m/z* (%): 529/527/525 (50/100/51) [M^++H]; HRMS (FAB): calcd for $C_{17}H_{14}{}^{79}Br^{81}BrF_3N_2O_4$: 526.9249, found: 526.9265. **15**: $[\alpha]_D^{20} = +6.8$ ($c = 7$ in MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 3.47$ (s, 3H; OCH_3), 3.92 (dd, ^2J(H,H) = 14.6 Hz, ^3J(H,H) = 4.8 Hz, 1H; CHH), 4.05 (dd, ^2J(H,H) = 14.6 Hz, ^3J(H,H) = 2.7 Hz, 1H; CHH), 6.89 (m, 1H; 4-H), 7.03 (s, 1H; pyrrole-CH), 7.25 (m, 1H; NH), 7.30–7.50 (m, 5H; Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 63 MHz): $\delta = 44.5$ (CH_2), 55.5 (OCH_3), 75.0 (C-4), 84.9 (C), 103.5 (CBr), 107.4 (CBr), 117.7 (pyrrole-CH), 122.9 (q, CF_3), 125.8 (C), 127.2 (C-Ar), 128.6 (C-Ar), 130.0 (C-Ar), 130.9 (C), 158.3 (C=O), 165.4 (C=O); UV (CF_3CH_2OH): λ_{max} (ε) = 286 (8560), 234 (8170), 205 nm (14250 mol^{-1} dm^3 cm^{-1}); MS (FAB+): *m/z* (%): 529/527/525 (53/100/53) [M^++H]; HRMS (FAB): calcd for $C_{17}H_{14}{}^{79}Br^{81}BrF_3N_2O_4$: 526.9249, found: 526.9230.

CCDC-220663 and CCDC-220664 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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