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Atropselective Halogenation

Exploration of the Bis(thio)urea-Catalyzed Atropselective Synthesis of Marinopyrrole A

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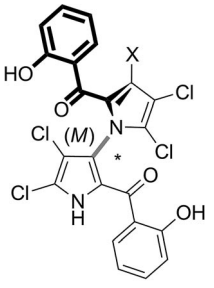
Abstract: The marinopyrroles are a new class of natural products with highly interesting biomedical and structural features. We herein provide a concise, nitrogen-protective-group-free synthesis of marinopyrrole A, constituting the as yet most efficient route. The presented studies elaborate a straightforward and mild chlorination protocol. Moreover, the first study towards the atropselective synthesis of marinopyrrole A, using chiral, C_2-symmetric bisthiourea catalysts, is presented.

Introduction

The halogenated bipyrroles are a recently discovered class of antimicrobial natural products, exemplified by (–)-marinopyrrole A (**1**) and B (**2**) (Figure 1).[1] These two compounds were isolated from the marine *Streptomyces* strain CNQ-418 by Fenical et al. in 2008,[2] and they show highly potent in vitro activities. Their pronounced activity, especially against MRSA strains and a colon cancer cell line, makes them promising lead structures for the development of new drugs.[3] In addition, these compounds have an unprecedented structural core with an axially chiral *N*,*C*-linkage connecting the two densely chlorinated pyrrole portions. The formation of this very rare heterobiaryl axis follows an unexpected biosynthetic pathway catalyzed by an $FADH_2$-dependent halogenase.[4] The involvement of the flavoenzyme suggests an electrophilic aromatic substitution as the biosynthetic mechanism for the homocoupling. Such a biosynthesis is in clear contrast to the phenol oxidative coupling usually observed for *C*,*C*-coupled biaryls.[5] Rotation around the heterobiaryl axis in **1** and **2** is hampered at ambient temperatures, leading to separable enantiomers, of which only the (*M*) isomer has been found in the bacterial producer. Their interesting antibiotic and anticancer properties, together with their remarkable structural features, make the marinopyrroles attractive targets not only for biological and medicinal studies, but also for natural product synthesis. This attention has resulted in four approaches to **1** and **2**, to date; however, these have only been racemic syntheses, involving a Paal–Knorr condensation or a copper-mediated *N*-arylation as the key step.[6]

In this paper, we describe the most efficient route to date to the antibiotic marinopyrrole A (**1**), featuring a mild, organocatalytic tetrachlorination step. By this approach, the dechloromarinopyrrole analog **8**, the key intermediate for an atropselective preparation of **1**, is easily available in multigram quantities. This set the scene for an intensive exploration of the structural properties of **8** and its interaction with thioureas, which were used as chiral catalysts. These molecules can, in principle, act as chiral molecular tweezers giving the opportunity to envisage an atropselective chlorination using the concept of dynamic kinetic resolution.[7]



X = H: (–)-marinopyrrole A [(*M*)-**1**]
X = Br: (–)-marinopyrrole B [(*M*)-**2**]

Figure 1. Marinopyrroles A [(*M*)-**1**] and B [(*M*)-**2**].

Results and Discussion

Our synthesis of racemic marinopyrrole A (**1**) began with the formation of bipyrrole **5** (Scheme 1). This was achieved by condensation of aminopyrrole **3**[8] and α-keto ester **4**[9] in 75 % yield. After conversion of both ester groups into the corresponding Weinreb amides (91 %), diamide **6** was treated with *o*-lithiated anisole **7** to give ketone **8** in one step in 86 % yield. It is worth mentioning that the use of organolithium reagent **7** was crucial for the success of this transformation. Other metalated anisoles resulted in either no or only a sluggish reaction. For example, when the corresponding Grignard reagent (not shown) was used, a complex reaction mixture was obtained, with the monoaddition products being the major products. That the addition of organometallic species to C-3-substituted

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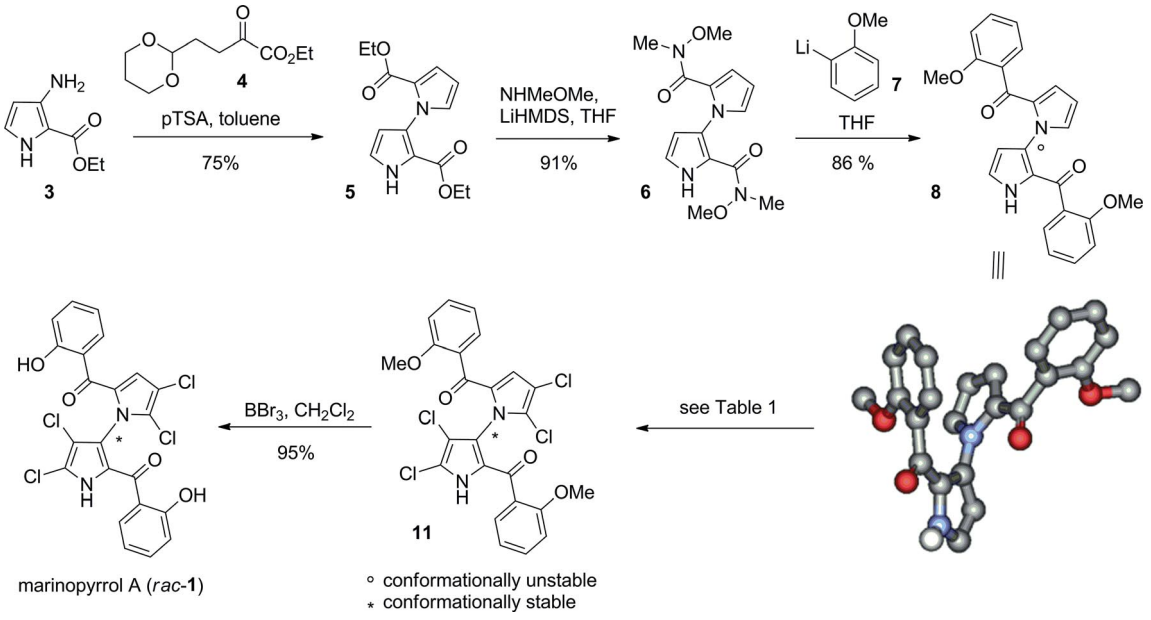


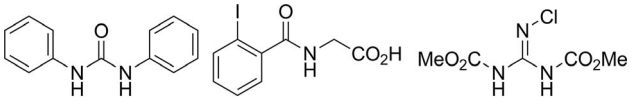
Scheme 1. Highly efficient route to racemic marinopyrrole A (**1**). pTSA = 4-toluenesulfonic acid; LiHMDS = lithium hexamethyldisilazide.

and thus sterically demanding pyrroles tends to be very sensitive was already observed by Sarli et al.[6c] when they tried to transform 3-bromopyrrole derivatives by treatment with aryl Grignard reagents. Using our conditions, this crucial step was carried out on a gram scale, allowing the generation of large quantities of key intermediate **8**, thus providing the bipyrrole in sufficient quantities to facilitate studies on the asymmetric synthesis of **1**.

In the next step, optimum conditions for a mild aromatic tetrachlorination were evaluated (Table 1). Treatment of **8** with NCS (*N*-chlorosuccinimide) in CH_2Cl_2 under standard conditions at room temperature gave **11**, but the yield was only 35 % after 2 d (Table 1, Entry 1). Changing the solvent did not lead to an improvement of the conversion (Table 1, Entries 2–4). The only exception was the use of MeCN (Table 1, Entry 5). This rate enhancement was not surprising, as Lewis-basic solvents are prone to activate electrophilic halogenating reagents, such as NCS. A similar, but more pronounced effect was observed by using 10 mol-% of the Lewis base PPh_3, which provided **11** in 58 % yield overnight (Table 1, Entry 9). The best results were obtained by the addition of catalytic amounts of either thiocarbanilide **9** (10 mol-%) or iodobenzamide **10** (10 mol-%).[10] Both of these additives significantly accelerated the electrophilic chlorination, giving *O,O'*-dimethylmarinopyrrole (**11**) in 76 and 84 % yields, respectively (Table 1, Entries 10 and 11). When **10** is used as an additive (Table 1, Entry 11), the electrophilic chlorination most probably proceeds via a cyclic iodane-chloro species, which is formed by the oxidation of **10** by NCS, and should be significantly more reactive than NCS. Another hint towards an actual hypervalent iodine(III)-triggered chlorination came from the use of the preformed iodine(III) reagent $PhICl_2$ (Table 1, Entry 12). Here, product **11** was produced in comparable yields (78 %), albeit after extended reaction times. Other conditions for the tetrachlorination step, e.g., using more reactive chlorination reagents such as Palau'chlor[11] or $SOCl_2$ (Table 1, Entries 13 and 14), or activating NCS with a Brønsted[12] (Table 1, Entries 6 and 7) or Lewis acid (Table 1, Entry 8) resulted in lower yields of **11** together with the formation of side-products. Cleavage of the *O*-methyl groups under standard Lewis-acidic conditions[6d] completed the formation of **1** in only five steps in an excellent 42 % overall yield, and without the need for protection of the pyrrole nitrogen atom.

Table 1. Optimization of the tetrachlorination of **8** (NCS = *N*-chlorosuccinimide).

Entry	Cl^+	Additive	Solvent	Time	Conversion [%]
1	NCS	–	CH_2Cl_2	2 d	42 (35)[a]
2	NCS	–	EtOAc	1 d	<10
3	NCS	–	THF	1 d	15
4	NCS	–	toluene	1 d	<10
5	NCS	–	MeCN	1 d	34
6	NCS	HCl[b]	CH_2Cl_2	0.5 h	>99 (40)[a]
7	NCS	TsOH[b]	CH_2Cl_2	0.5 h	>99 (63)[a]
8	NCS	$Zn(OAc)_2$[b]	CH_2Cl_2	1 d	<10
9	NCS	PPh_3[b]	CH_2Cl_2	16 h	>99 (58)[a]
10	NCS	**9**[b]	CH_2Cl_2	16 h	>99 (76)[a]
11	NCS	**10**[b]	CH_2Cl_2	5 h	>99 (84)[a]
12	$PhICl_2$	–	CH_2Cl_2	10 h	>99 (78)[a]
13	Palau'chlor	–	CH_2Cl_2	8 h	>99 (20)[a]
14	$SOCl_2$	–	CH_2Cl_2	1 h	>99 (53)[a]



9 **10** Palau'chlor

[a] Isolated yield. [b] 10 mol-% of additive was used.

In contrast to the large repertoire available for the stereoselective formation of *C,C*-axes,[13] optically pure *N,C*-coupled compounds are mostly obtained by chiral resolution[6d,14] due to the lack of suitable procedures for establishing *N,C*-biaryl connectivities in a stereochemically controlled fashion. To date,

only an auxiliary-based method using a nucleophilic aromatic substitution of planar-chiral arylchromium complexes,[15] and two transition-metal-catalyzed cyclization reactions have been reported.[16] Our efforts to close this methodological gap, and, in particular, to gain stereoselective access to marinopyrrole **1** involve an enantiotopos-differentiating electrophilic chlorination of **8**, applying a dynamic kinetic resolution. We speculated that C_2-symmetric compounds possessing two hydrogen-bond-donor entities (cf. Figure 2) could simultaneously coordinate both of the carbonyl groups in **8**. In the resulting diastereomeric complexes, one axial configuration is thermodynamically favored. At the same time, the rotational barrier of the axis in the complexed biaryls should be increased, decreasing the interconversion of the atropepimers, and thus locking bipyrrole **8** as a single atropisomer. A now diastereomer-differentiating chlorination terminates the reaction by introducing two further substituents adjacent to the *N*,*C*-connection. This conversion fixes the absolute configuration, and results in the formation of only one specific enantiomer of **11**. Based on our experience in the mild tetrachlorination of **8** (cf. Table 1) and the application of (thio)ureas as powerful catalysts in numerous asymmetric reactions in general,[17] the use of such chiral hydrogen-bond donors seemed to be very promising. The catalysts would play a double role: coordination to the carbonyl groups, thus preventing rotation around the bipyrrole axis, and activation of the electrophilic chlorination reagent for the aromatic halogenation. This hypothesis was further corroborated by the X-ray structure analysis of compound **8** (cf. Scheme 1).[18] There, both carbonyl groups are pointing in one direction, separated by a distance of 4.5 Å. These properties make them perfectly suited as anchor points.

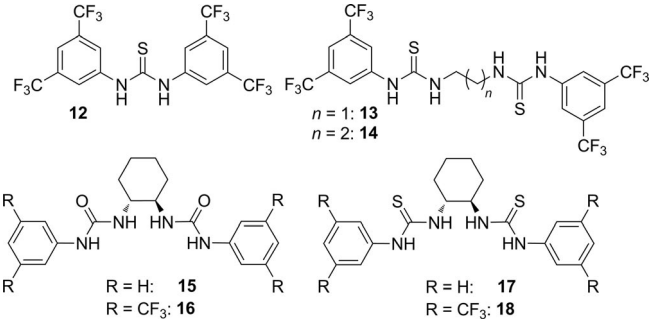


Figure 2. Studied (thio)urea catalysts.

Based on this structural information, we selected (thio)urea compounds **12**–**18**,[19] which differ in their aryl substitution patterns and in the number of carbon atoms linking the hydrogen-bond-donor entities. An examination of their binding ability towards the two carbonyl groups in **8** by ^{13}C NMR spectroscopy revealed that CF_3 substituents on the *N*-phenyl rings as well as thiourea groups are necessary for the formation of noncovalent interactions between **8** and the N–H moieties in the putative catalysts (see Supporting Information).

This observation is completely consistent with the noncovalent binding of **8** with our organocatalysts through hydrogen

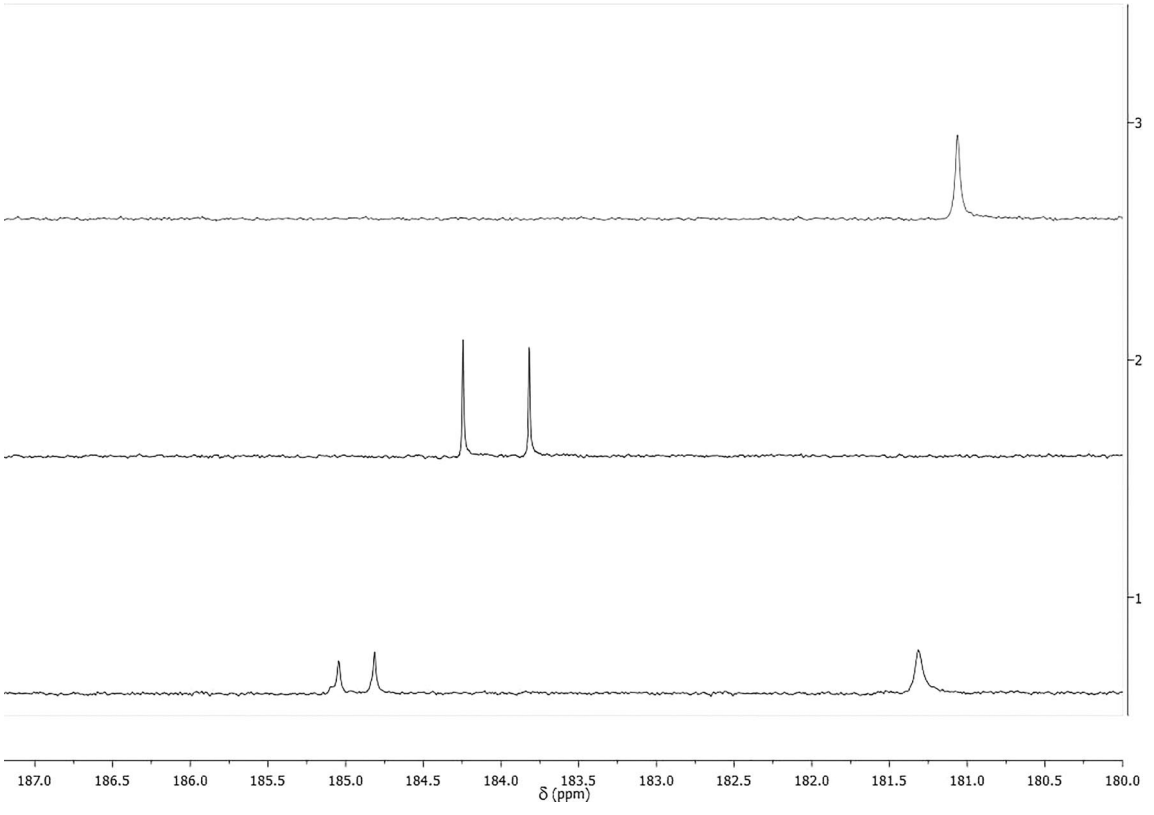


Figure 3. Comparison of the ^{13}C NMR signals of the carbonyl and thiocarbonyl groups in (1) a 1:1 mixture of **8** and (*R*,*R*)-**18**, (2) bipyrrole **8**, and (3) bisthiourea (*R*,*R*)-**18**.

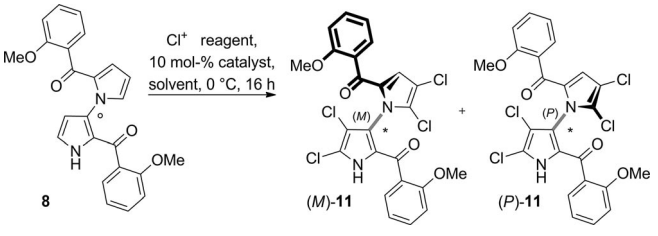
bonding. Earlier studies by Schreiner showed that the presence of CF_3 groups had a dramatic impact on the hydrogen-bond-donor abilities of such systems.[20] The coordination of bipyrrole **8** to **12** or **14** was clearly visible by the downfield shift of the C=O signals in the ^{13}C NMR spectra, although the interaction with one of the carbonyl groups was stronger (see Supporting Information). A rather equal shift of the ketone signals was observed using **13**, in which two methylene groups are located between the thiourea fragments, apparently reaching an optimal tether length. Similar shifts of the diagnostic NMR signals were observed (Figure 3) when the ethyldiamine chain was replaced by (*R*,*R*)-cyclohexyl-1,2-diamine, thus making **18** perfectly suited as the catalyst scaffold for the enantiotopos-differentiating chlorination.

Next, chiral (thio)urea compounds **15**–**18** were tested as catalysts (10 mol-%) in the asymmetric halogenation (Table 2). Using the optimized conditions for the nonstereoselective tetrachlorination corroborated the results obtained in the NMR spectroscopic studies. A significantly hampered reactivity or only the formation of racemic product **11** was observed when poorly binding catalysts **15**–**17** were used (Table 2, Entries 1–3). The most promising catalyst [i.e., (*R*,*R*)-**18**] together with NCS in CH_2Cl_2 at 0 °C overnight gave *O*,*O*′-dimethylmarinopyrrole A (**11**) in an excellent 74 % yield and 8 % *ee* in favor of the (*M*) atropisomer (Table 2, Entry 4). Raising the amount of **18** to 100 mol-% did not improve the optical purity, but gave **11** in a lower yield (ca. 50 %, 8 % *ee*, not shown). Variation of the reaction conditions (Table 2, Entries 5–10) revealed that to obtain a high yield, it was necessary to run the reaction at a temperature not lower than 0 °C, using a polar aprotic solvent, such as CH_2Cl_2, chloroform, or MeCN. An increase in the *ee*, however, was not achieved. Neither did changing the electrophilic halogenation reagent from NCS to NCP, or the, in principle, more reactive Palau'chlor, result in the desired improvement of the enantiomeric excess (Table 2, Entries 11 and 12).

The low *ee* values obtained could be explained by the ability of ureas to coordinate imides and imidate anions through hydrogen bonding.[21] Such noncovalent interactions would block the hydrogen-bond-donor entities in **18**, and thus severely change the envisaged binding of bipyrrole **8** to the thiourea catalyst. In order to shed light on this hypothesis, electrophilic chlorine reagents without hydrogen-bond-acceptor properties were tested. Only hypervalent iodine(III) chlorination agents, such as $PhICl_2$, gave (*M*)-**11** in similar yields but with slightly higher *ee* (11 %) compared to NCS (Table 2, Entry 13). Notably, by switching catalyst (*R*,*R*)-**18** to its antipode (*S*,*S*)-**18** (Table 2, Entry 14), the corresponding unnatural atropisomer [i.e., (*P*)-**11**] was predominantly obtained with the same enantiomeric excess (11 %). This clearly indicates that the observed enantioselectivity is not an artefact. Increasing the amount of **18** from 10 mol-% to 100 mol-% similarly did not give **11** with a higher *ee*.

As both types of chlorination reagents gave **11** with the same unsatisfactory *ee*, a common mechanism might be involved that does not solely rely on hydrogen bonding. A nucleophilic activation of NBS (*N*-bromosuccinimide) or DIH (1,3-diiodo-5,5-dimethylhydantoin) by the Lewis-basic sulfur in thiourea **12** was recently reported for the oxidation of alcohols[22] and the iodination of aromatic compounds.[23] Bearing in mind the high affinity of sulfur-derived Lewis bases for halogen atoms,[21a,24,25] a plausible explanation of the poor stereoinduction in the synthesis of *O*,*O*′-dimethylmarinopyrrole (**11**) might be the formation of the Lewis-base–Cl^+ complex, intermediate **19** (Scheme 2). Here, the chlorine atom is activated towards nucleophilic attack by the bipyrrole system, which could lead to the observed increase in chlorination reactivity.

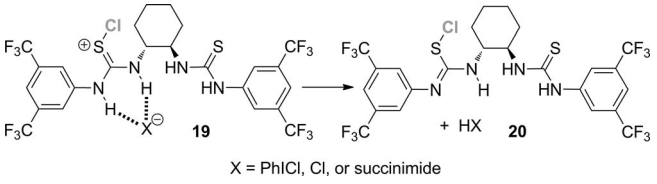
Table 2. Attempted atropselective transformation of **8** (NCS = *N*-chlorosuccinimide; NCP = *N*-chlorophthalimide).



Entry	Cl^+	Catalyst	Solvent	Yield [%][a]	*ee* [%][b]
1	NCS	(*R*,*R*)-**15**	CH_2Cl_2	–	–
2	NCS	(*R*,*R*)-**16**	CH_2Cl_2	12	–
3	NCS	(*R*,*R*)-**17**	CH_2Cl_2	76	–
4	NCS	(*R*,*R*)-**18**	CH_2Cl_2	74	8 (*M*)
5[c]	NCS	(*R*,*R*)-**18**	CH_2Cl_2	–	–
6	NCS	(*R*,*R*)-**18**	$CHCl_3$	72	2 (*M*)
7	NCS	(*R*,*R*)-**18**	toluene	39	4 (*M*)
8	NCS	(*R*,*R*)-**18**	MeCN	63	–
9	NCS	(*R*,*R*)-**18**	EtOAc	54	4 (*M*)
10	NCS	(*R*,*R*)-**18**	THF	43	4 (*M*)
11	NCP	(*R*,*R*)-**18**	CH_2Cl_2	41	–
12	Palau'chlor	(*R*,*R*)-**18**	CH_2Cl_2	54	4 (*M*)
13	$PhICl_2$	(*R*,*R*)-**18**	CH_2Cl_2	68	11 (*M*)
14	$PhICl_2$	(*S*,*S*)-**18**	CH_2Cl_2	70	11 (*P*)

[a] Isolated yield. [b] *ee* was determined by HPLC using a chiral stationary phase. [c] Reaction was carried out at –35 °C.

Such Cl^+ activation is also in agreement with the aforementioned structural requirements of the catalysts. After deprotonation, thiochloro imine species **20** is generated, in which the hydrogen-bond-donor ability is clearly decreased. NMR spectroscopic measurements of **18** with and without NCS showed the formation of a new unsymmetrical species bearing an imine structural motif, as indicated by the signal at δ = 155 ppm in the ^{13}C NMR spectrum (see Supporting Information), thus supporting our mechanistic assumption.



Scheme 2. Proposed intermediates in the catalytic electrophilic chlorination.

In intermediate **20**, the envisaged fixation of the axial conformation in **8** by C_2-symmetric molecular tweezers is no longer possible, as one of the thiourea moieties is blocked. Nevertheless, **20** is still able to act as an in-situ-formed chiral chlorination reagent coordinating to one of the carbonyl groups in **8**. This will lead to a hampered, but not abolished rotation around the *N*,*C*-biaryl axis, thus giving stereochemically enriched tetrachlorinated **11**.

Conclusions

We have developed an efficient, *N*-protecting-group-free synthesis of the structurally and biologically intriguing natural product marinopyrrole A (**1**) involving a mild, Lewis-base- or iodine(III)-catalyzed tetrachlorination step. This strategy for the synthesis of racemic **1**, combined with structural analysis of configurationally labile bipyrrole **8**, and NMR binding studies of C_2-symmetric bis(thio)urea catalysts **13**–**18**, paved the way for the first attempts at the asymmetric generation of **1** using an atropselective chlorination. Although all the bis(thio)ureas tested had an impact on the chlorination rate, their stereoinduction did not exceed 11 %. Nevertheless, these experiments provide an explicit proof-of-principle, and show that such a strategy is, in general, feasible. Preliminary investigations into the interactions of the electrophilic chloro reagents and catalyst **18** revealed the importance of the Lewis-basic sulfur atom for enhancing the reaction rate. Unfortunately, this Cl^+ activation is also responsible for breaking the hydrogen bonds to at least one of the carbonyl groups in bipyrrole **8**. Based on the mechanistic information obtained here, a more streamlined and rational catalyst design becomes possible, and this is currently underway in our laboratory.

Experimental Section

General Information: Solvents used in reactions were p.a. grade. Solvents for chromatography were technical grade, distilled before use. Anhydrous dichloromethane and THF were obtained from an MBraun MB-SPS 800 solvent purification system. Reagents were purchased at the highest commercial quality, and were used without further purification. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC), carried out on Merck silica gel aluminium plates with F-254 indicator using UV light as the visualizing agent, and an acidic solution of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate and heat as developing agents. Merck silica gel 60 (particle size 0.63–0.2 mm) was used for flash column chromatography. Solvent mixtures are understood as volume/volume. NMR spectra were recorded with Varian Mercury 300, V NMR 400, or Bruker AV500-cryo spectrometers. The spectra were calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$: δ = 7.26 ppm, CH_2Cl_2: δ = 5.32 ppm for ^1H NMR; $CHCl_3$: δ = 77.00 ppm, CH_2Cl_2: δ = 54.00 ppm for ^{13}C NMR). The following abbreviations (or combinations thereof) are used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet, br. = broad. Melting points were determined with a Büchi M-560 melting-point apparatus. IR spectra were recorded with a JASCO FTIR 4100 (ATR) instrument or a Perkin–Elmer Spectrum 100 spectrometer, and are reported in wavenumbers (cm^{-1}). Mass spectra were recorded with Finnigan MAT SSQ 7000 (MS-EI, 70 eV; CI, 100 eV), ThermoFinnigan LCQ Deca XP plus (ESI MS), and ThermoFisher Scientific LTQ Orbitrap XL (ESI HRMS) spectrometers.

Synthesis of Racemic Marinopyrrole (1)

Diethyl *N*′,3-Bipyrrole-2,2′-dicarboxylate (5):[6a] Ethyl 3-aminopyrrole-2-carboxylate hydrochloride[8] (**3**; 1.91 g, 10.0 mmol, 1.0 equiv.) was dissolved in toluene (25 mL, 0.4 M), and keto ester **4**[9] (2.59 g, 12.00 mmol, 1.2 equiv.) and *p*-toluenesulfonic acid monohydrate (17.0 mg, 0.10 mmol, 0.01 equiv.) were added at room temperature. The mixture was heated at reflux for 10 h, and then stirred at room temperature for additional 12 h. The mixture was then washed with satd. aq. $NaHCO_3$ solution (3 × 30 mL). The aqueous layer was reextracted with CH_2Cl_2 (3 × 30 mL), and the combined organic phases were dried with anhydrous $MgSO_4$. The solvent was evaporated, and the brown slurry was purified by column chromatography (SiO_2; hexane/EtOAc, 7:3) to give diester **5** (2.07 g, 7.50 mmol, 75 %) as colorless crystals; m.p. 75 °C (hexane/EtOAc). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.12 (br., 1 H, NH), 7.06 (dd, *J* = 3.9, 1.8 Hz, 1 H, CH_{ar}), 6.91 (dd, *J* = 3.3, 2.8 Hz, 1 H, CH_{ar}), 6.88 (dd, *J* = 2.7, 1.8 Hz, 1 H, CH_{ar}), 6.31 (t, *J* = 2.9 Hz, 1 H, CH_{ar}), 6.25 (dd, *J* = 3.9, 2.7 Hz, 1 H, CH_{ar}), 4.22–4.07 (m, 4 H, OCH_2), 1.22 (t, *J* = 7.1 Hz, 3 H, Me), 1.11 (t, *J* = 7.1 Hz, 3 H, Me) ppm. MS (ESI): *m*/*z* = 277.4 [M + H]$^+$. The obtained physical and spectroscopic data of **5** were in agreement with those published in the literature.[6a]

***N*′,3-Bipyrrole-2,2′-bis(*N*″-methoxy-*N*″-methylamide) (6):** A stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.82 g, 29.0 mmol, 4.0 equiv.) and diester **5** (2.00 g, 7.24 mmol, 1.0 equiv.) in dry THF (60 mL, 0.5 M) was treated with LiHMDS (1 M solution in THF; 36.2 mL, 36.2 mmol, 5.0 equiv.) at –78 °C. After 1 h, the mixture was warmed to room temperature and stirred for 6 h. After this time, it was recooled to 0 °C, and further LiHMDS (1 M solution in THF; 36.2 mL, 36.2 mmol, 5.0 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (2.82 g, 29.0 mmol, 4.0 equiv.) were added. The reaction mixture was stirred at room temperature for further 16 h. The latter procedure [addition of LiHMDS (36.2 mL, 36.2 mmol, 5.0 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (2.82 g, 29.0 mmol, 4.0 equiv.)] was repeated once again. Then, the reaction mixture was treated with satd. aq. NH_4Cl solution (100 mL), followed by the addition of water (100 mL). The THF was removed, and the aqueous residue was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude

product was purified by column chromatography on silica gel using a solvent gradient (hexane/EtOAc, 3:7, to EtOAc) to give compound **6** (2.02 g, 6.59 mmol, 91 %) as a white solid; m.p. 146 °C (hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (br., 1 H, NH), 6.92 (dd, J = 3.9, 1.7 Hz, 1 H, CH_{ar}), 6.87–6.85 (m, 2 H, CH_{ar}), 6.25 (dd, J = 3.9, 2.7 Hz, 1 H, CH_{ar}), 6.22 (t, J = 2.9 Hz, 1 H, CH_{ar}), 3.70 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 3.25 (s, 3 H, NMe), 3.13 (s, 3 H, NMe) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.1 (C=O), 160.4 (C=O), 129.4 (C_{ar}), 128.2 (C_{ar}), 124.8 (C_{ar}), 120.0 (C_{ar}), 119.8 (C_{ar}), 116.7 (C_{ar}), 115.8 (C_{ar}), 108.4 (C_{ar}), 61.32 (OMe), 61.06 (OMe), 34.09 (NMe), 33.96 (NMe) ppm. IR (film): $\tilde{\nu}$ = 3224, 1623, 1429, 1374, 1071, 852, 732 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{18}N_4O_4Na$ $[M + Na]^+$ 329.1223; found 329.1220.

Dechloro-*O,O′*-dimethylmarinopyrrole A (8): A solution of 2-bromoanisole (12.2 g, 65.3 mmol, 10.0 equiv.) in THF (25 mL, 2.9 M) was cooled to −78 °C, and *t*BuLi (1.6 M in pentane; 40.8 mL, 65.3 mmol, 10.0 equiv.) was added dropwise. The mixture was stirred at 0 °C for 1 h, then it was added to a solution of Weinreb amide **6** (2.00 g, 6.53 mmol, 1.0 equiv.) in dry THF (22.5 mL, 0.29 M) by cannula. The reaction mixture was stirred at −78 °C for 1 h and then warmed to 0 °C overnight. After this time, satd. aq. NH_4Cl solution (60 mL) was added slowly at 0 °C, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried with $MgSO_4$, and the solvent was evaporated. The residue was purified by column chromatography (SiO_2; hexane/EtOAc, 4:6) to give **8** (5.62 mmol, 86 %) as slightly yellow crystals; m.p. 177 °C (hexane/EtOAc). ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 9.72 (s, 1 H, NH), 7.39 (ddd, J = 8.4, 7.4, 1.8 Hz, 1 H, CH_{ar}), 7.21 (ddd, J = 8.4, 7.4, 1.8 Hz, 1 H, CH_{ar}), 7.16 (dd, J = 7.5, 1.7 Hz, 1 H, CH_{ar}), 7.13 (dd, J = 7.6, 1.8 Hz, 1 H, CH_{ar}), 7.08 (dd, J = 3.3, 2.7 Hz, 1 H, CH_{ar}), 6.98–6.93 (m, 2 H, CH_{ar}), 6.78–6.73 (m, 1 H, CH_{ar}), 6.70 (d, J = 8.9 Hz, 1 H, CH_{ar}), 6.69–6.67 (m, 1 H, CH_{ar}), 6.29 (t, J = 2.8 Hz, 1 H, CH_{ar}), 6.26 (dd, J = 4.0, 1.8 Hz, 1 H, CH_{ar}), 5.85 (dd, J = 4.0, 2.6 Hz, 1 H, CH_{ar}), 3.77 (s, 3 H, OMe), 3.67 (s, 3 H, OMe) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 184.3 (C=O), 183.8 (C=O), 157.40 (O C_{ar}), 156.9 (OC_{ar}), 133.0 (C_{ar}), 132.8 (C_{ar}), 131.6 (C_{ar}), 131.5 (C_{ar}), 131.3 (C_{ar}), 130.4 (C_{ar}), 129.5 (C_{ar}), 129.1 (C_{ar}), 128.7 (C_{ar}), 126.7 (C_{ar}), 123.7 (C_{ar}), 123.2 (C_{ar}), 120.5 (C_{ar}), 120.1 (C_{ar}), 111.9 (C_{ar}), 111.11 (C_{ar}), 111.07 (C_{ar}), 109.1 (C_{ar}), 56.08 (OMe), 55.80 (OMe) ppm. MS (ESI): m/z = 423.4 $[M + Na]^+$. The obtained physical and spectroscopic data of **8** are in agreement with those published in the literature.[6d]

***O,O′*-Dimethylmarinopyrrole A (11). Method A:** Bipyrrole **8** (100 mg, 0.25 mmol, 1.0 equiv.), thiocarbanilide **9** (6.00 mg, 0.025 mmol, 0.1 equiv.), and NCS (144 mg, 1.08 mmol, 4.3 equiv.) were stirred in CH_2Cl_2 (2.5 mL, 0.1 M) at room temperature for 16 h. The reaction mixture was directly submitted to column chromatography on silica gel (hexane/EtOAc, 7:3) to give **11** (103 mg, 0.19 mmol, 76 %) as slightly yellow crystals. **Method B:** Bipyrrole **8** (100 mg, 0.25 mmol, 1.0 equiv.), iodobenzamide **10** (7.63 mg, 0.025 mmol, 0.1 equiv.), and NCS (144 mg, 1.08 mmol, 4.3 equiv.) were stirred in CH_2Cl_2 (2.5 mL, 0.1 M) at room temperature for 5 h. The reaction mixture was directly submitted to column chromatography on silica gel (hexane/EtOAc, 7:3) to give **11** (113 mg, 0.21 mmol, 84 %) as slightly yellow crystals; m.p. 193 °C (hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.1 (br. s, 1 H, NH), 7.42 (t, J = 7.7 Hz, 1 H, CH_{ar}), 7.30–7.21 (m, 3 H, CH_{ar}), 6.97 (t, J = 7.2 Hz, 2 H, CH_{ar}), 6.77 (d, J = 8.7 Hz, 1 H, CH_{ar}), 6.65 (t, J = 7.4 Hz, 1 H, CH_{ar}), 6.40 (s, 1 H, CH_{ar}), 3.81 (s, 3 H, OMe), 3.75 (s, 3 H, OMe) ppm. MS (ESI): m/z = 561.1 $[M + Na]^+$. The obtained physical and spectroscopic data of **8** are in agreement with those published in the literature.[6d]

Marinopyrrole A (1):[6d] Compound **11** (140 mg, 0.26 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2 mL, 0.13 M), and the solution was cooled to 0 °C. BBr_3 (1 M solution in CH_2Cl_2; 1.0 mL, 1.04 mmol, 4.0 equiv.) was added dropwise, and the mixture was stirred at 0 °C for 1 h. Saturated aqueous $NaHCO_3$ solution (10 mL) was then added, and the biphasic mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (SiO_2; hexane/EtOAc, 4:1) to give marinopyrrole (**1**) (126 mg, 0.25 mmol, 95 %) as a yellow solid; m.p. 201 °C (hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.18 (s, 1 H, OH), 10.41 (s, 1 H, OH), 9.79 (br., 1 H, NH), 7.58 (dd, J = 8.0, 1.7 Hz, 1 H, CH_{ar}), 7.55–7.44 (m, 2 H, CH_{ar}), 7.35 (ddd, J = 8.6, 7.2, 1.7 Hz, 1 H, CH_{ar}), 7.02 (dd, J = 8.5, 1.1 Hz, 1 H, CH_{ar}), 6.95–6.86 (m, 2 H, CH_{ar}), 6.72 (s, 1 H, CH_{ar}), 6.52 (ddd, J = 8.2, 7.2, 1.1 Hz, 1 H, CH_{ar}) ppm. The obtained physical and spectroscopic data of **1** are in agreement with those published in the literature.[2b]

Atropselective Chlorination of 8

***O,O′*-Dimethylmarinopyrrole A (11). Method A:** Bipyrrole **8** (100 mg, 0.25 mmol, 1.0 equiv.), bisthiourea **18** (16.4 mg, 0.025 mmol, 0.1 equiv.), and NCS (144 mg, 1.08 mmol, 4.3 equiv.) were stirred in CH_2Cl_2 (2.5 mL, 0.1 M) at 0 °C for 16 h. The reaction mixture was directly submitted to column chromatography on silica gel (hexane/EtOAc, 7:3) to give **11** (99.6 mg, 0.19 mmol, 74 %) as slightly yellow crystals. The enantiomeric excess of *O,O′*-dimethylmarinopyrrole (**11**) was determined by HPLC using a Daicel Chiracel OD-RH column (4.6 × 250 mm, 5 µm), hexane/*i*PrOH, 75:25, 1 mL/min. **Method B:** Bipyrrole **8** (100 mg, 0.25 mmol, 1.0 equiv.), bisthiourea **18** (16.4 mg, 0.025 mmol, 0.1 equiv.), and NCS (297 mg, 1.08 mmol, 4.3 equiv.) were stirred in CH_2Cl_2 (2.5 mL, 0.1 M) at 0 °C for 16 h. The reaction mixture was directly submitted to column chromatography on silica gel (hexane/EtOAc, 7:3) to give **11** (91.5 mg, 0.17 mmol, 68 %) as slightly yellow crystals. The enantiomeric excess of *O,O′*-dimethylmarinopyrrole (**11**) was determined by HPLC on an analytical scale using a Phenomenex Lux Cellulose-1 column (4.6 × 250 mm, 5 µm), hexane/*i*PrOH, 75:25, 1 mL/min.

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Keywords: Atropisomerism · Asymmetric synthesis · Natural products · Total synthesis · Biaryls · Chlorine

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