Total Synthesis and Structural Refinement of the Cyclic Tripyrrole Pigment Nonylprodigiosin

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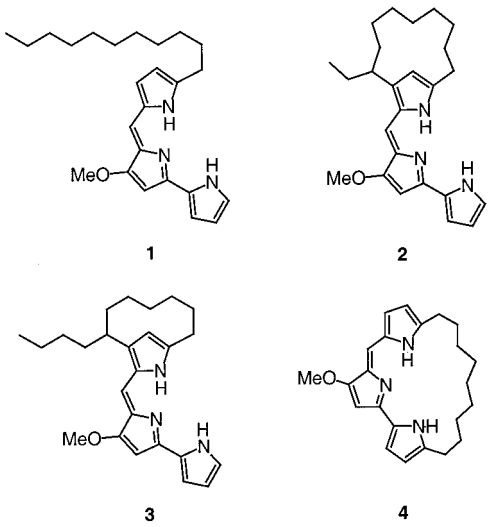
Received June 25, 1999

The first total synthesis of the cyclic prodigiosin derivative **4** is described, which constitutes a potential lead compound for the development of immunosuppressive agents. The key steps of this approach comprise a palladium-catalyzed Suzuki cross coupling reaction of the rather unstable pyrrole boronic acid derivative **17** with the electron rich pyrrolyl triflate **15** followed by a ring-closing metathesis reaction (RCM) of the resulting diene to form the macrocyclic ring of the target molecule. This transformation is best achieved by using the ruthenium indenylidene complex **21** as precatalyst. X-ray data of product **18**·HCl thus formed suggest that the tautomeric form **B** properly describes the electron distribution within the heteroaromatic segment of this alkaloid, in which the central ring constitutes the azafulvene unit of the pyrrolylpyrromethene chromophore.

Introduction

The deeply red colored prodigiosin alkaloids produced by a restricted group of actinomycetes are endowed with potent antibacterial, cytotoxic, and antimalaria properties.[1−3] In addition to this spectrum of biological effects discovered early on, a series of recent reports claims that this family of natural products also displays a significant immunosuppressive activity at doses which are not cytotoxic.[4,5] This finding is particularly noteworthy since the mechanism of action seems to be distinctly different from that of cyclosporin and FK-506 which set the standards in this field.[6,7] Although the actual therapeutic window may be too narrow for direct clinical applications of the naturally occurring prodigiosins,[8] these alkaloids serve as lead structures in the search for new drugs to prevent allograft rejection and have already inspired the development of synthetic analogues with more favorable pharmacological properties.[9]

Most pharmacological studies on the prodigiosins have focused on undecylprodigiosin (**1**) as the most abundant



member of this family,[4,5] although some preliminary data indicate significant immunosuppressive activity for its cyclic analogues such as metacycloprodigiosin (**2**) and streptorubin B (**3**) as well.[10,11] Compounds **1**−**3** and analogues thereof exist as two stable isomers **I** and **II** in

(1) For a review of the early studies on prodigiosins see the following for leading references: (a) Castro, A. J. *Nature* **1967**, *213*, 903. (b) Gerber, N. N. *Crit. Rev. Microbiol.* **1974**, *3*, 469 and references therein.

(2) For previous synthetic studies on various prodigiosins, see inter alia (a) Hearn, W. R.; Elson, M. K.; Williams, R. H.; Medina-Castro, J. *J. Org. Chem.* **1970**, *35*, 142. (b) Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, 1725. (c) Rapoport, H.; Holden, K. G. *J. Am. Chem. Soc.* **1962**, *84*, 635. (d) Boger, D. L.; Patel, M. *Tetrahedron Lett.* **1987**, *28*, 2499. (e) Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405. (f) Wasserman, H. H.; Rodgers, G. C.; Keith, D. D. *J. Am. Chem. Soc.* **1969**, *91*, 1263. (g) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *J. Am. Chem. Soc.* **1969**, *91*, 1264. (h) Wasserman, H. H.; Keith, D. D.; Rodgers, G. C. *Tetrahedron* **1976**, *32*, 1855. (i) Wasserman, H. H.; Gosselink, E.; Keith, D. D.; Nadelson, J.; Sykes, R. J. *Tetrahedron* **1976**, *32*, 1863. (j) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *Tetrahedron* **1976**, *32*, 1867.

(3) For preparation and the biological evaluation of prodigiosin analogues, see ref 1 and the following for leading references: (a) Brown, D.; Griffiths, D.; Rider, M. E.; Smith, R. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 455. (b) Blake, A. J.; Hunter, G. A.; McNab, H. *J. Chem. Soc., Chem. Commun.* **1990**, 734. (c) Berner, H.; Schulz, G.; Reinshagen, H. *Monatsh. Chem.* **1977**, *108*, 233. (d) Berner, H.; Schulz, G.; Reinshagen, H. *Monatsh. Chem.* **1978**, *109*, 137. (e) Berner, H.; Schulz, G.; Reinshagen, H. *Monatsh. Chem.* **1977**, *108*, 285. (f) Berner, H.; Schulz, G.; Fischer, G.; Reinshagen, H. *Monatsh. Chem.* **1978**, *109*, 557. (g) Castro, A. J.; Gale, G. R.; Means, G. E.; Tertzakian, G. *J. Med. Chem.* **1967**, *10*, 29. (h) D'Auria, M.; De Luca, E.; Mauriello, G.; Racioppi, R. *Synth. Commun.* **1999**, *29*, 35.

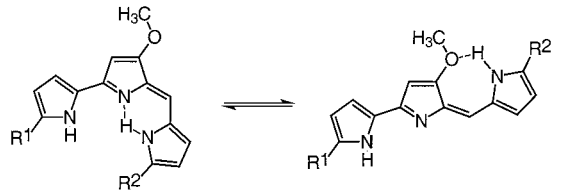
(4) (a) Lin, J. *Immunol. Today* **1993**, *14*, 290. (b) Nakamura, A.; Nagai, K.; Ando, K.; Tamura, G. *J. Antibiot.* **1986**, *39*, 1155. (c) Tsuji, R. F.; Yamamoto, M.; Nakamura, A.; Kataoka, T.; Magae, J.; Nagai, K.; Yamasaki, M. *J. Antibiot.* **1990**, *43*, 1293. (d) Kataoka, T.; Magae, J.; Nariuchi, H.; Yamasaki, M.; Nagai, K. *J. Antibiot.* **1992**, *45*, 1303. (e) Tsuji, R. F.; Magae, J.; Yamashita, M.; Nagai, K.; Yamasaki, M. *J. Antibiot.* **1992**, *45*, 1295. (f) Kataoka, T.; Magae, J.; Kasamo, K.; Yamanishi, H.; Endo, A.; Yamasaki, M.; Nagai, K. *J. Antibiot.* **1992**, *45*, 1618. (g) Kataoka, T.; Muroi, M.; Ohkuma, S.; Waritani, T.; Magae, J.; Takatsuki, A.; Kondo, S.; Yamasaki, M.; Nagai, K. *FEBS Lett.* **1995**, *359*, 53. (h) Lee, M.-H.; Yamashita, M.; Tsuji, R. F.; Yamasaki, M.; Kataoka, T.; Magae, J.; Nagai, K. *J. Antibiot.* **1998**, *51*, 92. (i) Han, S. B.; Kim, H. M.; Kim, Y. H.; Lee, C. W.; Jang, E.-S.; Son, K. H.; Kim, S. U.; Kim, Y. K. *Int. J. Immunopharmacol.* **1998**, *20*, 1. (j) Sato, T.; Konno, H.; Tanaka, Y.; Kataoka, T.; Nagai, K.; Wasserman, H. H.; Ohkuma, S. *J. Biol. Chem.* **1998**, *273*, 21455. (k) Nakamura, A.; Magae, J.; Tsuji, R. F., Yamasaki, M.; Nagai, K. *Transplantation* **1989**, *47*, 1013.

(5) Songia, S.; Mortellaro, A.; Taverna, S.; Fornasiero, C.; Schreiber, E. A.; Erba, E.; Colotta, F.; Mantovani, A.; Isetta, A.-M.; Golay, J. *J. Immunol.* **1997**, *158*, 3987.

(6) Undecylprodigiosin **1** has been shown to inhibit T cell activation in the mid to late G_1 phase, mostly downstream from the interaction of IL-2 with its receptor, cf. ref 5.

10.1021/jo991021i CCC: $18.00
Published on Web 10/29/1999

solution, with the interconversion and equilibrium distribution being strongly dependent on the pH of the medium, i.e., on the degree of protonation of the basic nitrogen atom.[9] Because it is unlikely that both conformers show the same affinity to the (yet unknown) biological receptor, prodigiosin derivatives with a *defined configuration* may be of significant interest for more detailed biochemical and pharmaceutical investigations.



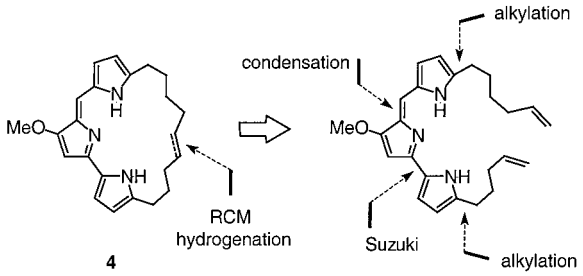
I II

Therefore we reasoned that the naturally occurring macrocyclic nonylprodigiosin **4**, isolated in 1970 by Gerber from *Actinomadura madurae*,[12] may constitute an attractive biochemical tool since its alkyl chain spans all three heterocyclic rings and therefore makes isomer **II** energetically highly unfavorable. We now describe the first total synthesis of this particular natural product based on a ring-closing metathesis (RCM) reaction as the key step which is effected by a recently devised metathesis catalyst.

Results and Discussion

Synthesis. Systematic investigations on RCM have revealed the truly remarkable scope of this transformation for the synthesis of macrocycles.[13−15] During these studies it was possible to spell out rules for retrosynthetic analysis which help to identify those sites within a given target where productive formation of a large ring can be expected. According to this rationale,[13d] a properly balanced interaction of Lewis-basic heteroatoms in the diene substrate with the emerging Lewis-acidic carbene (and/or metallacyclobutane) species involved in the catalytic cycle is necessary in order to achieve an efficient macrocylization event. If such a chelation becomes too strong,

Scheme 1



however, the activity of the metal carbene is attenuated and RCM is likely to cease. Therefore, it is of utmost importance in retrosynthetic planning to assess the *distance* as well as the *affinity* of the polar groups toward the catalytically active metal species. A suitably biased ground state conformation of the substrate is not required for productive RCM, although conformational predisposition toward ring closure will certainly facilitate matters.

When applied to nonylprodigiosin **4**, this "relay model" suggests to close the macrocyclic ring at (or near) the site indicated in Scheme 1. In this particular case, however, a certain risk remains as the required precursor **5** already contains the intact pyrrolylpyrromethene chromophore of the target which is known for its good chelating properties toward metals and may therefore interfere with or even quench the activity of the metathesis catalyst.

The initial steps en route to the required cyclization precursor, i.e., diene **5**, adapt a sequence previously outlined by D'Alessio for the synthesis of the acyclic parent compound **1**.[16] The necessary building blocks are obtained in excellent yields on a multigram scale by acylation of the magnesium salt of pyrrole with the 2-pyridylthioesters derived from 4-pentenoic acid or 5-hexenoic acid, respectively (Scheme 2).[17] The resulting ketones **8** and **9** are smoothly reduced by excess $NaBH_4$ in 2-propanol,[18] giving rise to the rather unstable alkylpyrroles **10** and **11**. Standard formylation of **11** by means of $POCl_3$ and DMF, followed by condensation of the resulting aldehyde **12** with commercially available lactam

(7) These different mechanisms of action also suggest that a combined use of these drugs may be possible, permitting the use of relatively low concentrations of each drug and thereby potentially reducing toxicity, cf. ref 5.

(8) A report in the recent literature shows that the dose−response curve of **1** on T and B lymphocytes is rather steep, with a maximal inhibition of proliferation at 40 ng/mL and an IC_{50} of 3−8 ng/mL (7−20 M) for both cell types. In mice, the ED_{50} of **1** was reported to be 1.5 mg/kg i.p. for 6 days, while toxic signs are appreciable from a dose of 4 mg/kg, cf. ref 5.

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(10) (a) Magae, J.; Miller, M.; Nagai, K.; Shearer, G. M. *J. Antibiot.* **1996**, *49*, 86. (b) Abe, F.; Morimoto, M.; Shibuya, K.; Yamazaki, M.; Nishigori, T.; Saito, S.; Shimada, N. Jpn. Kokai Tokkyo Koho JP 02, 250, 828 [90, 250, 828], 08 Oct 1990. *Chem. Abstr.* **1990**, *114*, 108967g.

(11) For recent syntheses of these compounds from our laboratory see: Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. (b) For a synthesis of the structurally related alkaloid roseophilin see: Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817.

(12) (a) Gerber, N. N. *Tetrahedron Lett.* **1970**, 809. (b) Gerber, N. N. *J. Antibiot.* **1971**, *24*, 636. (c) Gerber, N. N. *J. Heterocycl. Chem.* **1973**, *10*, 925.

(13) For recent reviews on RCM see the following for leading references: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Top. Catal.* **1997**, *4*, 285. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37.

(14) For RCM-based macrocycle syntheses from our laboratory see: (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (c) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005. (d) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746. (e) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010. (f) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (g) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.*, **1999**, *64*, 2361. (h) Fürstner, A.; Müller, T. *J. Org. Chem.* **1998**, *63*, 424. (i) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron*, **1999**, *55*, 8215. (j) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814.

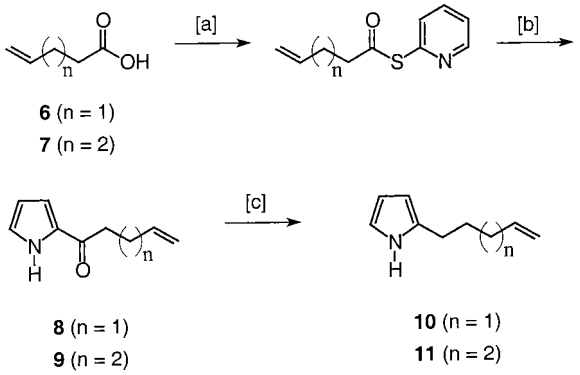
(15) For RCM-based total syntheses of natural products from other groups see the following for leading references: (a) Nicolaou, K. C.; King, N. B.; He, Y. *Top. Organomet. Chem.* **1998**, *1*, 73. (b) Hoveyda, A. H. *Top. Organomet. Chem.* **1998**, *1*, 105. (c) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. (d) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000. (e) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (f) Magnier, E.; Langlois, Y. *Tetrahedron Lett.* **1998**, 837. (g) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601. (h) Irie, O.; Samizu, K.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 587. (i) Arakawa, K.; Eguchi, T.; Kakinuma, K. *J. Org. Chem.* **1998**, *63*, 4741. (j) May, S. A.; Grieco, P. A. *Chem. Commun.* **1998**, 1597.

(16) D'Alessio, R.; Rossi, A. *Synlett* **1996**, 513.

(17) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, *22*, 4647.

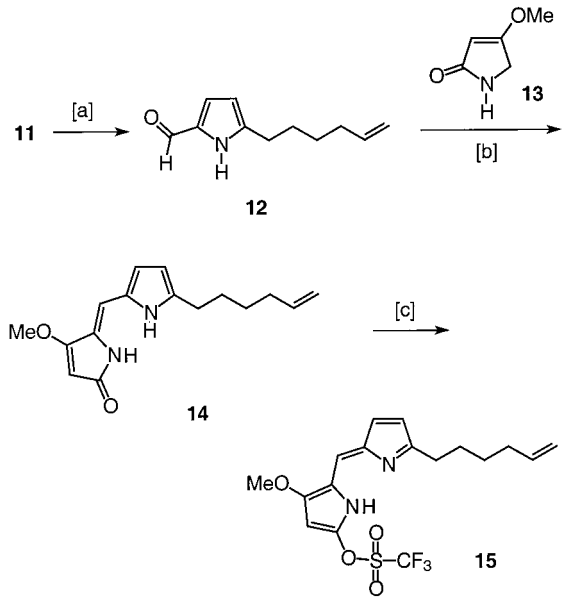
(18) Greenhouse, R.; Ramirez, C.; Muchowski, J. M. *J. Org. Chem.* **1985**, *50*, 2961.

Scheme 2[a]



[a] (a) Bis(2-pyridyl) disulfide, PPh_3, toluene; (b) pyrrolylmagnesium chloride, toluene, 97% ($n = 1, 2$); (c) $NaBH_4$ (excess), i-PrOH, 63% ($n = 1$), 65% ($n = 2$).

Scheme 3[a]

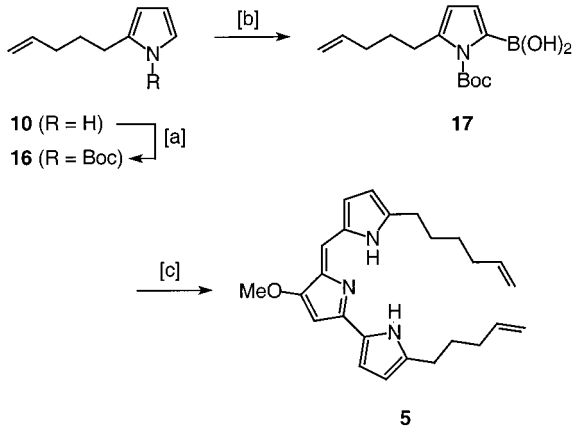


[a] (a) $POCl_3$, DMF, $C_2H_4Cl_2$, 80%; (b) NaOH, DMSO, 60 °C, 94%; (c) triflic anhydride, CH_2Cl_2, 0 °C → rt, 93%.

13 in the presence of NaOH in DMSO, delivers product **14** in excellent yield, which is converted into the corresponding pyrrolyl triflate derivative **15** on exposure to Tf_2O in CH_2Cl_2 (Scheme 3). No base must be added, since the emerging azafulvene itself traps the equivalent of F_3CSO_3H liberated in this step.

In contrast to this very productive and uneventful sequence, the formation of the boronic acid derivative **17** and its subsequent Suzuki cross-coupling with triflate **15** turned out to be rather delicate due to the inherent lability of **17** (Scheme 4). Its synthesis is best achieved by directed *ortho*-metalation of the N-Boc protected substrate **16** using lithium tetramethylpiperidinide as the base and quenching of the lithiated pyrrole derivative thus formed with an excess of $B(OMe)_3$ followed by hydrolysis of the resulting adduct with dilute HCl.[19] This delivers boronic acid **17** in 58% yield which must be used

Scheme 4[a]



[a] (a) Boc_2O, DMAP, CH_2Cl_2, rt, 92%; (b) (i) lithium 2,2,6,6-tetramethylpiperidinide, −78 °C, THF; (ii) $B(OMe)_3$; (iii) aq HCl, 58%; (c) **15**, $Pd(PPh_3)_4$ cat., aq Na_2CO_3, LiCl, DME, 85 °C, 57%.

immediately in the subsequent Suzuki reaction.[20] Despite considerable experimentation, however, its cross-coupling with triflate **15** gave only 57% yield of the desired, N-unprotected pyrrolylpyrromethane derivative **5**. This rather moderate yield is mainly ascribed to concomitant proto-deborylation of **17** which could not be avoided even under nonaqueous reaction conditions. Attempts to replace the labile boronic acid **17** by zincated **16** as the nucleophile for the palladium-catalyzed cross-coupling reaction met with failure.[21]

Because free amines are generally incompatible with metathesis reactions mediated by ruthenium carbene complexes of the Grubbs type,[13] we performed the crucial RCM step with the hydrochloride salt of substrate **5**. Protonation of pyrrolylpyrromethane derivatives bearing an oxygen substituent at the 4-position of the B-ring, however, has been shown to favor isomer **II** over **I** due to the formation of a hydrogen bond as indicated in Scheme 5.[9] Although **II** itself is hardly amenable to ring closure, cyclization of the minor isomer **I** in solution may occur which will then constantly shift the equilibrium between **II** and **I** and hence still allow productive RCM. In fact, treatment of the deeply red colored diene **5**·HCl with catalytic amounts of the Grubbs carbene $(PCy_3)_2Cl_2Ru{=}CHCH{=}CPh_2$[22] in refluxing CH_2Cl_2 solution leads to the formation of the desired macrocycle **18**·HCl in 42% yield. This results was improved by using a previously introduced variant **21** of the catalyst which is formed upon reaction of $(PPh_3)_3RuCl_2$ with diphenyl propargyl alcohol, followed by exchange of the PPh_3 ligands for PCy_3 (Scheme 6).[23] In line with our previous experiences on

(19) (a) For the borylation of N-Boc-pyrrole see: Martina, S.; Enkelmann, V.; Wegner, G.; Schlüter, A.-D. *Synthesis* **1991**, 613. (b) For a recent report on Pd(0)-catalyzed cross-coupling reactions of (N−Boc-pyrrol-2-yl)boronic acid see: Johnson, C. N.; Stemp, G.; Anand, N., Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025.

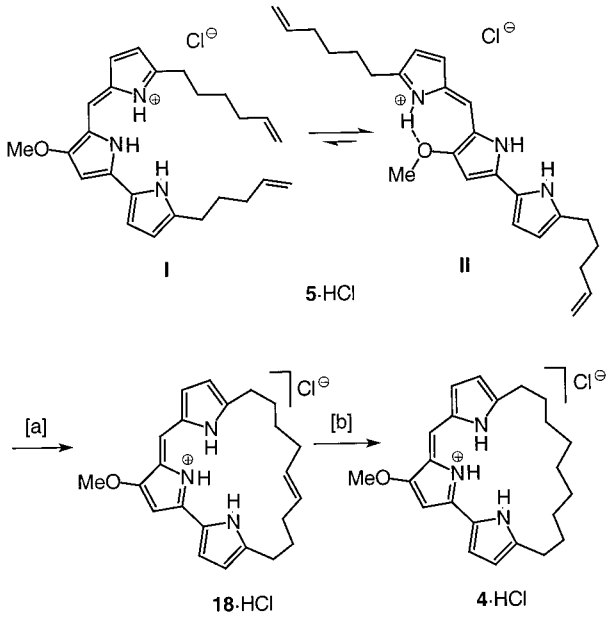
(20) Review: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. For recent applications of Suzuki reactions from our laboratory see: (b) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165. (c) Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107. (d) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072.

(21) For a report on cross-coupling reactions using zincated 1-methylpyrrole, see: Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 5319.

(22) (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) See also: Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem.* **1995**, *107*, 2179.

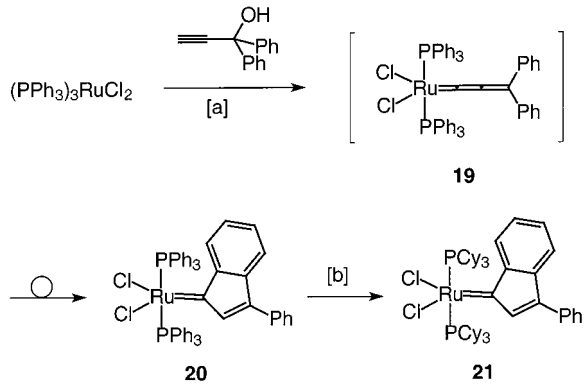
(23) Originally it has been believed that the species formed from $(PPh_3)_3RuCl_2$ and $HC{\equiv}CPh_2OH$ is the diphenylallenylidene complex **19**, cf. Harlow, K. J.; Hill, A. F.; Winton-Ely, J. D. E. T. *J. Chem. Soc., Dalton Trans.* **1999**, 285. More detailed studies, however, have shown that the stable product formed is the rearranged product, i.e., the indenylidene ruthenium complex **20**, cf. Hill, A. F.; Fürstner, A.; Liebl, M.; Mynott, R.; Gabor, B., Nolan, S. P. Manuscript in preparation.

Scheme 5[a]



[a] (a) **21** cat., CH_2Cl_2, reflux, 16 h, 65%; (b) $RhCl(PPh_3)_3$ cat., H_2 (1 atm), EtOH, rt, 90%.

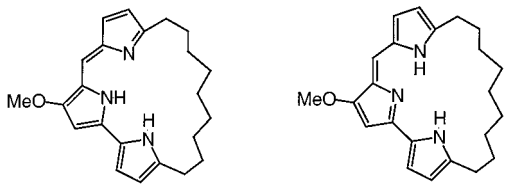
Scheme 6[a]



[a] (a) THF, reflux, 2 h; (b) PCy_3, CH_2Cl_2, rt, 30 min.

the excellent catalytic performance of this particular complex,[23,24] exposure of diene **5**·HCl to **21**[23] in refluxing CH_2Cl_2 indeed effects a smooth cyclization reaction, giving rise to the desired cycloalkene product **18**·HCl in 65% isolated yield ($E:Z \geq 10:1$).[25] Attempted hydrogenation of the disubstituted double bond over Pd on charcoal led to the destruction of the molecule. The use of Wilkinson's catalyst, however, opened a viable alternative, although rather high catalyst loadings are necessary in order to achieve quantitative conversion. Under these conditions, nonylprodigiosin is obtained in excellent yield as a deeply red colored crystalline material. This completes the first total synthesis of this interesting alkaloid and highlights once again the remarkable scope of ring-closing metathesis which rapidly evolves into a mature tool for advanced natural product synthesis.

Structural Aspects. A survey of the literature on prodigiosins reveals some conflicting assumptions as to the best description of the extended π-electron system of their heterocyclic part. Whereas recent NMR studies on rotamer interconversions indicate that protonation occurs at the nitrogen atom of the C-ring and hence tautomer **A** dominates the chemical behavior of the prodigiosins in solution, the older literature uniformly favors tautomer **B** in which the basic site resides in the central ring. Theoretical calculations on the parent pyrrolylpyrromethene system lacking the 4-OMe substituent at the B-ring show that the energy difference between these two possible tautomers is low, and no definite conclusions have therefore been drawn.[26]



Because we were able to obtain the metathesis product **18** and the final target **4** as crystalline solids, an X-ray study has been carried out in order to clarify this point. The molecular structure of **18**·HCl in the crystal is depicted in Figure 1.[27] The analysis of the relevant bond length within the heterocyclic perimeter shows beyond doubt that the structure is best represented by tautomer **B** in which the central ring constitutes the azafulvene entity. Although the crystal structure of nonylprodigiosin **4** itself suffers from substantial disorder,[28] there is no doubt that the tripyrrole chromophore of this product is also best described by tautomer **B**.

For further studies on the preparation of prodigiosin alkaloids and functionalized derivatives thereof which may allow a synthesis driven mapping of the immunosuppressive properties of this family of natural products, see the accompanying paper in this issue.

Experimental Section

General. All reactions were carried out under Ar in predried glassware using Schlenk techniques. The solvents were dried by distillation over the drying agents indicated and were stored and transferred under Ar: CH_2Cl_2 (P_4O_{10}), toluene (Na/K), THF (magnesium/anthracene), DMF (Desmodur, Bayer AG; dibutyltin dilaurate), pyridine (KOH), EtOH (Mg), MeOH (Mg). Flash chromatography: Merck silica gel (230−400 mesh) or activated aluminum oxide (Aldrich, neutral, Brockmann I, STD grade, ≈ 150 mesh) using hexane/ethyl acetate in various proportions as eluent. For the instrumenta-

(24) (a) Fürstner, A.; Hill, A.; Liebl, M.; Winton-Ely, J. *Chem. Commun*. **1999**, 601. For other studies on metathesis catalysts from our laboratory see: (b) Fürstner, A.; Ackermann, L. *Chem. Commun*. **1999**, 95. (c) Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun*. **1998**, 1315. (d) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J., Herrmann, W. A. *Tetrahedron Lett*. **1999**, *40*, 4787.

(25) One recrystallization provides pure (*E*)-**18** which was used for the X-ray analysis.

(26) Falk, H.; Stressler, G.; Müller, N. *Monatsh. Chem*. **1988**, *119*, 505.

(27) Crystal structure analysis of compound (*E*)-**18**: dark red crystals grown from CH_2Cl_2; $C_{24}H_{30}Cl_3N_3O$; M_r = 482.86 g·mol^{-1}; crystal size 0.67 × 0.21 × 0.08 mm; a = 26.091(5), b = 8.3912(17), c = 22.571(5) Å; V = 4773.4(17) Å^3; β = 104.99(3)°; T = 100 K; d_{calcd} = 1.344 Mg·m^{-3}, Z = 8; space group: monoclinic, $C2/c$ (no. 15); θ range for data collection: 1.62 to 27.80°; 21146 collected reflections, 5173 unique reflections; refinement method: full-matrix least squares on F^2; final R indices: $R(F) = 0.082$, $wR^2 = 0.234$. For further information, see the Supporting Information. The complete set of data has been deposited at the Cambridge Crystallographic Data Center, Cambridge, UK, under the deposition number CCDC 121761.

(28) The disorder originates from a 2-fold rotation of the macrocycle around an axis passing through the N-atom of the central pyrrole ring.

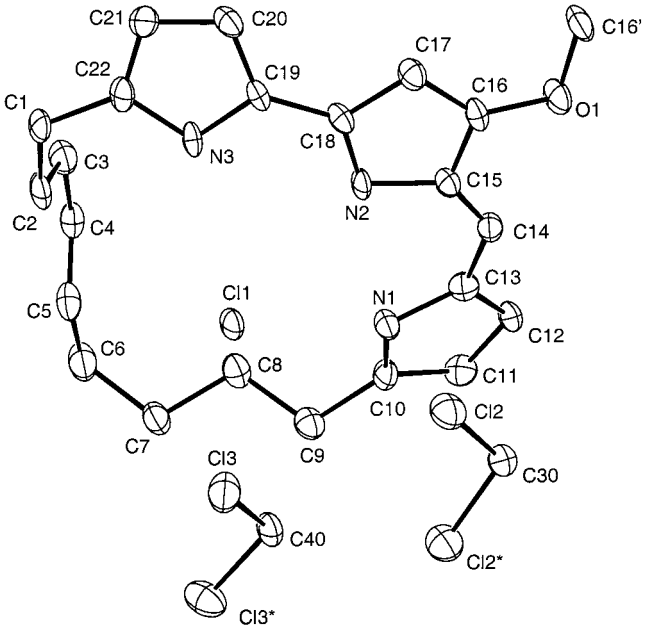


Figure 1. Structure of compound (*E*)-**18**·HCl·CH_2Cl_2 in the crystal. Selected bond lengths (Å): N1−C10 1.362(7), C10−C11 1.388(7), C11−C12 1.396(7), C12−C13 1.401(7), C13−N1 1.402(7), C13−C14 1.420(7), C14−C15 1.355(7), C15−N2 1.429(6), C15−C16 1.435(7), C16−C17 1.369(7), C17−C18 1.414(7), C18−N2 1.363(7), C18−C19 1.429(7), C19−N3 1.396(6), C19−C20 1.384(7), C20−C21 1.397(7), C21−C22 1.383(7), C22−N3 1.375(7).

tion used and the spectra formats, see the Supporting Information. Mp: Gallenkamp apparatus (uncorrected). Elemental analyses: Dornis & Kolbe, Mülheim. Commercially available reagents (Aldrich, Fluka) were used as received.

Hex-5-enoic acid (7). To a suspension of Mg-turnings (3.43 g, 141 mmol) in Et_2O (60 mL) is added 5-bromo-1-pentene (19.84 g, 133 mmol) in Et_2O (60 mL) at room temperature. The reaction mixture is stirred at 34 °C for 6 h. Residual Mg is filtered off, and the filtrate containing the Grignard reagent is added dropwise over a period of 2 h to a saturated solution of CO_2 in Et_2O at −20 °C, while passing through the solution a stream of CO_2. The resulting mixture is allowed to warm to ambient temperature and is quenched by addition of aqueous HCl (v/v, 1:1, concentrated HCl/water; 100 mL). The organic phase is dried (Na_2SO_4), the solvent is evaporated, and the crude product is distilled (52 °C/10^{-2} mbar) to give acid **7** (10.32 g, 68%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.57 (bs, 1H), 5.75 (ddt, J = 17.1, 10.3, 6.6 Hz, 1H), 5.04−4.95 (m, 2H), 2.34 (t, J = 7.6 Hz, 2H), 2.12−2.05 (m, 2H), 1.76−1.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.3, 137.4, 115.5, 33.3, 32.9, 23.7.

1-(1*H*-Pyrrol-2-yl)hex-5-en-1-one (9). A solution of 5-hexenoic acid (4.78 g, 41.87 mmol), 2,2′-dipyridyl disulfide (12.0 g, 54.47 mmol), and triphenylphosphine (14.28 g, 54.47 mmol) in toluene (60 mL) is stirred at rt for 4 h. The reaction mixture is then cooled to −78 °C and a solution of pyrrolylmagnesium chloride [formed by deprotonation of pyrrole (11.7 mL, 168.46 mmol) with methylmagnesium chloride (3 M in THF, 42 mL, 126.0 mmol) in toluene (270 mL) at −40 °C)] is introduced. After stirring for 1 h, the reaction is quenched with saturated aqueous ammonium chloride at −78 °C, and the aqueous layer is repeatedly extracted with *tert*-butyl methyl ether. The organic phase is successively washed with aq potassium carbonate (5%), water, and brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue (hexane/ethyl acetate, 6:1) affords compound **9** (6.67 g, 97.5%) as a colorless syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.89 (bs, 1H), 7.03−7.00 (m, 1H), 6.92−6.88 (m, 1H), 6.27−6.23 (m, 1H), 5.80 (ddt, J = 17.1, 10.3, 6.6 Hz, 1H), 5.07−4.94 (m, 2H), 2.77 (t, J = 7.5 Hz, 2H), 2.18−2.07 (m, 2H), 1.89−1.74 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.9, 138.0, 132.1, 124.6, 116.2, 115.2, 110.5, 37.1, 33.3, 24.3. Anal. Calcd for $C_{10}H_{13}NO$ (163.22): C 73.59, H 8.03, N 8.58. Found: C 73.34, H 7.95, N 8.62.

1-(1*H*-Pyrrol-2-yl)pent-4-en-1-one (8). Compound **8** is obtained as a colorless syrup (5.93 g, 95%) according to the procedure described above using 4-pentenoic acid (4.20 g, 41.9 mmol) as the starting material. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (bs, 1H), 7.03−7.01 (m, 1H), 6.92−6.90 (m, 1H), 6.27−6.24 (m, 1H), 5.86 (ddt, J = 17.0, 10.3, 6.5 Hz, 1H), 5.10−4.95 (m, 2H), 2.86 (t, J = 7.2 Hz, 2H), 2.50−2.42 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0, 137.3, 131.9, 124.6, 116.2, 115.2, 110.6, 37.0, 28.9. Anal. Calcd for $C_9H_{11}NO$ (149.19): C 72.46, H 7.43, N 9.39. Found: C 72.43, H 7.47, N 9.31.

2-Hex-5-enyl-1*H*-pyrrole (11). A solution of compound **9** (4.58 g, 28.1 mmol) in 2-propanol (150 mL) is added dropwise to a suspension of $NaBH_4$ (2.95 g, 78.0 mmol) in 2-propanol (100 mL), and the resulting mixture is refluxed for 24 h. Standard extractive workup followed by flash chromatography on neutral alumina using hexane/ethyl acetate (20:1) as the eluent affords compound **11** (2.73 g, 65%) as a colorless syrup. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.97 (bs, 1H), 6.65−6.62 (m, 1H), 6.07 (dd, J = 5.6, 2.7 Hz, 1H), 5.92−5.78 (m, 2H), 5.07−4.95 (m, 2H), 2.61 (t, J = 7.4 Hz, 2H), 2.15−2.07 (m, 2H), 1.69−1.41 (m, 4H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 139.0, 132.6, 115.9, 114.2, 108.1, 104.9, 33.6, 29.3, 28.7, 27.5. Anal. Calcd for $C_{10}H_{15}N$ (149.24): C 80.48, H 10.13, N 9.39. Found: C 80.29, H 10.06, N 9.42.

2-Pent-4-enyl-1*H*-pyrrole (10). Compound **10** is obtained as a colorless syrup (3.43 g, 63%) according to the procedure described above using ketone **8** (5.95 g, 39.9 mmol) as the starting material. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.98 (bs, 1H), 6.65−6.62 (m, 1H), 6.08−6.06 (m, 1H), 5.93−5.79 (m, 2H), 5.08−4.97 (m, 2H), 2.61 (t, J = 7.7 Hz, 2H), 2.16−2.08 (m, 2H), 1.76−1.66 (m, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 138.6, 132.3, 116.0, 114.6, 108.1, 105.0, 33.4, 29.1, 27.0. Anal. Calcd for $C_9H_{13}N$ (135.21): C 79.95, H 9.69, N 10.36. Found: C 79.73, H 9.62, N 10.40.

5-(Hex-5-enyl)-1*H*-pyrrole-2-carbaldehyde (12). Phosphorus oxychloride (2.91 g, 19.0 mmol) is added dropwise to DMF (1.39 g, 19.0 mmol) at 0 °C. The mixture is diluted with 1,2-dichloroethane (5 mL), and a solution of compound **11** (2.58 g, 17.3 mmol) in 1,2-dichloroethane (10 mL) is slowly introduced at 0 °C (30 min). After the addition is complete, the solution is refluxed for 20 min. After cooling to 30 °C, a solution of sodium acetate (8.2 g, 10 mmol) in water (25 mL) is added, and the resulting mixture is refluxed for another 15 min. Standard extractive workup followed by flash chromatography on silica using hexane/ethyl acetate (6:1) as the eluent gives compound **12** (2.45 g, 80%) as a colorless solid. mp = 37−38 °C. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 10.61 (bs, 1H), 9.36 (s, 1H), 6.94 (dd, J = 3.7, 2.5 Hz, 1H), 6.12−6.10 (m, 1H), 5.81 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.04−4.92 (m, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.12−2.04 (m, 2H), 1.74−1.64 (m, 2H), 1.50−1.39 (m, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 178.2, 144.1, 138.8, 132.0, 123.2, 114.4, 109.5, 33.5, 28.6, 28.5, 27.6. Anal. Calcd for $C_{11}H_{15}NO$ (177.25): C 74.54, H 8.53, N 7.90. Found: C 74.51, H 8.48, N 7.85.

5-[5-(Hex-5-enyl)-1*H*-pyrrol-2-ylmethylene]-4-methoxy-1,5-dihydropyrrol-2-one (14). Aqueous NaOH (2 N, 32 mL) is added to a solution of compound **12** (2.03 g, 11.4 mmol) and 4-methoxy-3-pyrrolin-2-one **13** (2.59 g, 22.8 mmol) in DMSO (40 mL), and the resulting mixture is stirred at 60 °C for 24 h. After dilution with EtOAc (140 mL), the yellow suspension is extracted with water and brine, and the organic layers are dried (Na_2SO_4) and evaporated. The crude material is rinsed with hexane affording pure **14** (2.92 g, 94%) as a yellow crystalline solid. mp = 139−140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.99 (bs, 1H), 10.43 (bs, 1H), 6.36−6.34 (m, 1H), 6.31 (s, 1H), 5.96−5.95 (m, 1H), 5.80 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.05 (s, 1H), 5.02−4.90 (m, 2H), 3.86 (s, 3H), 2.74 (t, J = 7.6 Hz, 2H), 2.13−2.06 (m, 2H), 1.79−1.69 (m, 2H) 1.52−1.42 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 168.0, 140.7, 138.2, 125.5, 122.7, 117.7, 114.4, 107.7, 102.9, 89.9, 58.1, 33.6, 29.2, 28.7, 28.0. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.35): C 70.56, H 7.40, N 10.29. Found: C 70.66, H 7.43, N 10.19.

Trifluoromethanesulfonic Acid 5-[5-(Hex-5-enyl)-pyrrol-2-ylidenmethyl]-4-methoxy-1*H*-pyrrol-2-yl Ester (15). Trifluoromethanesulfonic anhydride (0.5 mL, 3.05 mmol) is added dropwise to a solution of compound **14** (700 mg, 2.57 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After stirring at this temperature for 1 h, the reaction mixture is poured into aq 2% $NaHCO_3$ solution, and the aqueous phase is repeatedly extracted with ethyl acetate. The combined organic layers are washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the crude material on neutral alumina using hexane/ethyl acetate (6:1) as the eluent provides triflate **15** (972 mg, 93%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.87 (bs, 1H), 7.02 (s, 1H), 6.66 (d, J = 3.7 Hz, 1H), 6.05 (d, J = 3.7 Hz, 1H), 5.79 (ddt, J = 17.1, 10.3, 6.6 Hz), 5.41 (s, 1H), 5.03−4.90 (m, 2H), 2.68 (t, J = 7.6 Hz, 2H), 2.12−2.04 (m, 2H), 1.74−1.63 (m, 2H), 1.51−1.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 160.9, 145.3, 138.4, 128.4, 123.1, 122.0, 118.6, 114.7, 110.3, 110.2, 87.1, 58.7, 33.4, 28.4, 28.2, 28.2. Anal. Calcd for $C_{17}H_{19}F_3N_2O_4S$ (404.41): C 50.49, H 4.74, N 6.93. Found: C 50.26, H 4.73, N 7.06.

2-(Pent-4-enyl)pyrrole-1-carboxylic Acid *tert*-Butyl Ester (16). To a solution of compound **10** (546 mg, 4.04 mmol) and DMAP (50 mg, 0.40 mmol) in CH_2Cl_2 (3 mL) is added a solution of Boc_2O (1.057 g, 4.84 mmol) in CH_2Cl_2 (4 mL) at ambient temperature. The mixture is stirred for 4 h, the solvent is evaporated, and the residue is purified by flash chromatography on silica with hexane/*tert*-butyl methyl ether (50:1) as the eluent affording compound **16** (875 mg, 92%) as a colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamer): δ 7.18 (dd, J = 3.3, 1.8 Hz, 1H), 6.06 (t, J = 3.3 Hz, 1H), 5.95−5.93 (m, 1H), 5.83 (ddt, J = 17.0, 10.2, 6.6, 1H), 5.06−4.94 (m, 2H), 2.84 (t, J = 7.6, 2H), 2.17−2.09 (m, 2H), 1.79−1.65 (m, 2H), 1.58 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.5, 138.6, 136.0, 120.8, 114.6, 110.9, 109.8, 83.2, 33.4, 28.3, 28.1, 28.0. Anal. Calcd for $C_{14}H_{21}NO_2$ (235.33): C 71.46, H 8.99, N 5.95. Found: C 71.26, H 9.12, N 6.02.

Dimethyl [5-(Pent-4-enyl)-1-*tert*-butoxycarbonylpyrrol-2-yl]boronate (17). n-BuLi (1.6 M in hexane, 1.84 mL, 2.95 mmol) is slowly added to a solution of 2,2,6,6-tetramethylpiperidine (434 μL, 2.57 mmol) in THF (10 mL) at −78 °C under Ar. After stirring for 15 min at that temperature, the mixture is allowed to warm to 0 °C within 30 min. After cooling again to −78 °C, a solution of pyrrole **16** (561 mg, 2.38 mmol) in THF (10 mL) is added at such a rate that the temperature remains below −65 °C. The reaction mixture is stirred for 2 h at −78 °C prior to the addition of trimethyl borate (1.24 g, 11.9 mmol). The solution is allowed to warm to ambient temperature overnight. For workup, aq HCl (0.25 N, 15 mL, 3.75 mmol) is added, the solvent is evaporated, the residue is extracted with Et_2O, and the combined organic phases are washed with water and dried (Na_2SO_4). The solution is slowly concentrated until a solid starts to precipitate. The mixture is then cooled to 0 °C, and the precipitated product is filtered off. Tituration with cold Et_2O and drying of the residue in vacuo affords boronic acid **17** (386 mg, 58%) as a rather unstable pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (d, J = 3.4 Hz, 1H), 6.79 (bs, 2H), 6.03 (d, J = 3.4 Hz, 1H), 5.87−5.73 (m, 1H), 5.05−4.92 (m, 2H), 2.85−2.76 (m, 2H), 2.15−2.08 (m, 2H), 1.74−1.63 (m, 2H), 1.61 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2, 142.0, 138.2, 127.3, 115.0, 112.6, 85.8, 33.4, 30.1, 28.3, 28.0. ^{11}B NMR (64 MHz, $CDCl_3$): δ 26.0.

5-[5-(Hex-5-enyl)pyrrol-2-ylidenemethyl]-4-methoxy-5′-pent-4-enyl-1*H*,1′*H*-[2,2′] bipyrrolyl Hydrochloride (5·HCl). A solution of triflate **15** (268 mg, 0.66 mmol), LiCl (85 mg, 1.98 mmol), $Pd(PPh_3)_4$ (38 mg, 0.033 mmol), boronic acid **17** (370 mg, 1.32 mmol) in DME (20 mL) is treated with aq Na_2CO_3 (2 M, 1.3 mL, 2.6 mmol) and the resulting mixture is stirred at 85 °C for 15 h under Ar. A standard extractive workup followed by flash chromatography on neutral alumina using hexane/ethyl acetate (15:1 → 2:1) as the eluent provides diene **5**; treatment of the free base thus formed with a solution of HCl in Et_2O and evaporation of the solvent provides **5**·HCl (159 mg, 56%) as a dark-red solid. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 12.81 (bs, 1H), 12.70 (bs, 2H), 6.97−6.95 (m, 2H), 6.82−6.80 (m, 1H), 6.20 (dd, J = 3.8, 1.8 Hz, 1H), 6.16 (dd, J = 3.9, 2.3 Hz, 1H), 6.10 (d, J = 1.9 Hz, 1H), 5.94−5.77 (m, 2H), 5.10−4.91 (m, 4H), 4.00 (s, 3H), 2.91 (t, J = 7.5 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 2.18−2.07 (m, 4H), 1.92−1.72 (m, 4H), 1.56−1.46 (m, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 166.4, 151.0, 148.9, 145.0, 139.0, 138.3, 127.7, 125.9, 122.2, 121.0, 119.6, 114.9, 114.7, 114.2, 11.8, 111.0, 110.3, 92.9, 59.0, 33.6, 33.3, 28.9, 28.6, 28.2, 28.1, 27.6. UV (CH_2Cl_2): λ_{max} = 539, 392, 374, 297 nm. MS (ESI pos): m/z (rel intensity) 390 ([M − Cl)$^+$], 100). Anal. Calcd for $C_{25}H_{31}N_3O$·HCl (426.01): C 70.49, H 7.57, N 9.86. Found: C 70.28, H 7.69, N 9.95.

Macrocycle 18·HCl. A solution diene **5**·HCl (58 mg, 0.136 mmol) in CH_2Cl_2 (100 mL) is slowly added to a solution of the ruthenium indenylidene complex **21** (13.4 mg, 0.014 mmol)[23,24] in CH_2Cl_2 (50 mL), and the resulting mixture is refluxed for 16 h. For workup, the reaction mixture is washed with saturated aqueous Na_2CO_3, the organic layer is dried (Na_2SO_4) and evaporated, and the residue is subjected to flash chromatography on neutral alumina using hexane/ethyl acetate (6:1) as the eluent. The combined fractions of compound **18** are concentrated to a small volume, treated with a solution of HCl in Et_2O and evaporated in vacuo. This affords macrocycle **18**·HCl (35 mg, 65%)[27] as a deeply red solid. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 12.85 (bs, 1H), 12.70 (bs, 1H), 12.58 (bs, 1H), 6.96−6.93 (m, 2H), 6.75 (dd, J = 3.6, 2.6 Hz, 1H), 6.15−6.12 (m, 2H), 6.07 (d, J = 1.9 Hz, 1H), 5.57 (dt, J = 15.3, 5.6 Hz, 1H), 5.45 (dt, J = 15.3, 6.5 Hz, 1H), 3.99 (s, 3H), 2.96−2.80 (m, 4H), 2.25−2.03 (m, 4 H), 1.93−1.77 (m, 4H), 1.56−1.44 (m, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 167.2, 160.3, 150.9, 149.5, 144.8, 131.2, 129.1, 127.2, 126.6, 123.1, 121.1, 119.8, 115.3, 112.1, 111.6, 92.7, 59.1, 32.1, 30.5, 29.6, 28.9, 28.3, 26.7, 25.9. HRMS ($C_{23}H_{29}N_3O$): calcd 361.215412; found 361.217201.

Nonylprodigiosine Hydrochloride (4·HCl). A solution of compound **18** (81 mg, 0.203 mmol) and $RhCl(PPh_3)_3$ (97 mg, 0.105 mmol) in EtOH (30 mL) is stirred under H_2 (1 atm) at ambient temperature for 6 h. The reaction mixture is washed with saturated aqueous Na_2CO_3, the aq layer is extracted with CH_2Cl_2, the combined organic phases are dried (Na_2SO_4) and evaporated, and the residue is purified by flash chromatography on neutral alumina using hexane/ethyl acetate (10:1 → 6:1). The combined fractions containing compound **4** are concentrated to a small volume, treated with a solution of HCl in Et_2O, and evaporated. This affords compound **4**·HCl (73 mg, 90%) as a deeply red solid. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 12.85 (bs, 1H), 12.65 (bs, 2H), 6.96−6.94 (m, 2H), 6.79 (dd, J = 3.8, 2.5 Hz, 1H), 6.15 (dd, J = 3.8, 1.9 Hz, 1H), 6.13 (dd, J = 3.8, 2.3 Hz, 1H), 6.08 (d, J = 1.9 Hz, 1H), 4.00 (s, 3H), 2.92 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 6.4 Hz, 2H), 1.86−1.72 (m, 4H), 1.55−1.13 (m, 10 H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 167.1, 151.3, 149.4, 145.2, 127.1, 126.7, 123.0, 121.0, 119.7, 115.2, 111.9, 111.2, 92.7, 59.1, 30.2, 29.5, 28.3, 28.2, 27.9, 27.8, 27.7, 27.3, 26.6. HRMS ($C_{23}H_{31}N_3O$): calcd 363.231062; found 363.229082.

Acknowledgment. Generous financial support by the Deutsche Forschungsgemeinschaft (Leibniz Program) and by the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Details concerning the X-ray structure of compound **18**·HCl, listing of the IR and MS data, compilation of the instrumentation used, copies of the ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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