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Total Synthesis, Molecular Editing and Evaluation of a Tripyrrolic Natural Product: The Case of "Butylcycloheptylprodigiosin"

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Abstract: Conflicting reports are found in the literature on whether the *ortho*-pyrrolophane derivative **6**, which has been named "butylcycloheptylprodigiosin" even though it is a cyclononane derivative, is a natural product or merely a mis-assigned structure. This dispute has now been resolved by an unambiguous total synthesis of this complex alkaloid which confirms the initial structure assignment. The chosen approach is largely catalysis-based, featuring the first application of a "Narasaka–Heck" reaction in natural product chemistry. This palladium-catalyzed transformation allows the unsaturated oxime ester **26** to be converted into the bicyclic dihydropyrrole **27**. Other notable reactions of the reported approach to **6** are a regioselective Tsuji–Trost reaction of the doubly allylic acetate **21** with methyl acetoacetate, a base-induced aromatization of **27** to the corresponding pyrrole **28**, a chemoselective oxidation of the benzylic methyl group in **33** with cerium ammonium nitrate in a biphasic reaction medium that does not affect the labile pyrrole nucleus, and a Suzuki cross-coupling for the completion of the heterocyclic domain. Diversification in the latter step leads to a set of analogues that differ from the natural product in the terminal (hetero)arene ring. This structural modification results in complete loss of the very pronounced ability of the parent compound **6** to induce oxidative cleavage in double stranded DNA in the presence of Cu^{II}. Several cyclononane-, cyclononene- and cyclononadiene derivatives prepared en route to **6** have been characterized by crystal structure analysis, allowing the conformational behavior of nine-membered carbocycles to be studied.

Keywords: alkaloids · DNA cleavage · heterocycles · natural products · palladium · pyrroles

Introduction

The recent resurgence of interest in the prodigiosin alkaloids (**1**–**6**) arises from the attractive biological properties of these tripyrrolic pigments produced by various *Serratia* and *Streptomyces* strains.[1,2] Most notably, in vivo studies revealed their potential as immunosuppressive agents (e.g., PNU-156804, **7**) which act synergistically with the standard drugs for the prevention of allograft rejection in organ-transplanted mammals.[3,4] Moreover, some prodigiosin derivatives show promise as anticancer agents. Although various biochemical mechanisms had been invoked to explain their well documented cytotoxicity,[5] it was the discovery of their capacity to induce apoptotis which spurred in-depth investigations into heterocycles of this type.[6,7] Specifically, GX15-070 (**8**), a rather simple mono-indole analogue of prodigiosin **2**, was recently advanced into phase I/II clinical trials for the treatment of refractory chronic lymphoid leukaemia.[8,9]

As part of our investigations aiming at the total synthesis[10] and biological evaluation[11] of structurally diverse natural products, including various heterocyclic compounds,[12] we have devoted considerable effort towards the less abundant members of the prodigiosin family.[13–16] These rather unique metabolites,[17] in which the common tripyrrolic chromophore is embedded into a macrocyclic frame, are thought to derive biosynthetically from undecylprodigiosin **1** (or homologues thereof) by a formal two-electron oxidative cyclization effected by a non-heme iron dependent dioxygenase.[1,18]

While the *meta*-bridged compounds metacycloprodigiosin (**4**)[15,19] and streptorubin (**5**)[13,20] have a long history and are well characterized,[1] their *ortho*-annelated congener **6** ("butylcycloheptylprodigiosin")[21] was the subject of controversial claims. Originally isolated from *Streptomyces* sp. Y-42

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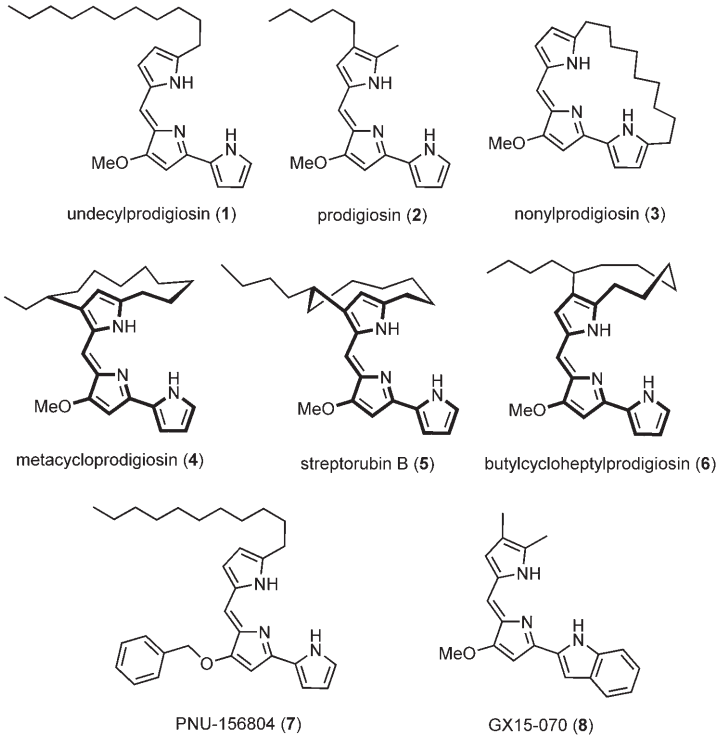
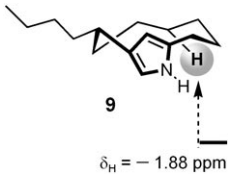


and *Streptomyces abikoensis* (formerly: *Streptoverticillium rubrireticuli*), Gerber assigned structure **6** to this then novel member of the prodigiosin family.[22] Later on, Floss et al. attributed the same structure to the "pink pigment" obtained from a culture broth of *Streptomyces coelicolor* mutants.[23] Subsequently, these assignments were questioned by Weyland et al. who showed that their sample isolated from the actinomycete strain B 4358 was the *meta*-bridged isomer streptorubin B (**5**) rather than the *ortho*-annelated compound **6**, which led them to suspect that the structure of the latter needed to be revised.[24] However, as these three groups were investigating samples derived from different bacterial strains, it appeared to us that Weyland's conclusion might have been premature and that the available data deserve more careful consideration.

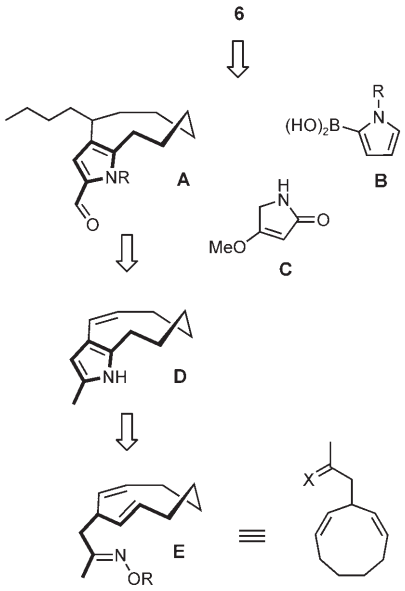
meta-Pyrrolophanes such as **5** show a very characteristic "finger print" in their ^{1}H NMR spectra. The rigidity of the ten-membered ring forces one of the protons of the *ansa*-chain to reside within the anisotropy cone of the pyrrole nucleus, thus causing a pronounced upfield-shift of the corresponding signal to $\delta = -1.55$ in **5** and -1.88 ppm in its core segment **9** (cf. Scheme 1).[13,20a] Although the reported spectral data of the "pink pigment" isolated by Gerber and by Floss are incomplete,[22,23] no such signal is documented. It appeared unlikely to us that such a conspicuous detail would have eluded both groups. Therefore we suspected that "butylcycloheptylprodigiosin" **6** does exist as a natural product on its own right, distinct from **5**. To answer this open question, we set out to prepare this structurally intriguing cyclononane derivative[21] by an unambiguous synthetic route. The results of this campaign together with the preparation of selected analogues and a preliminary biochemical evaluation of the resulting collection of prodigiosin-like molecules are summarized below.[25]



Scheme 1. High-field shift of an aliphatic proton as a characteristic signature of the ^{1}H NMR spectra of compounds with a rigid *meta*-pyrrolophane structure.

Results and Discussion

Retrosynthetic considerations: The pyrrolopyrromethane chromophore of **6** invites assembly via successive condensation/cross-coupling steps following previously established protocols.[14,26] Application of this logic unravels aldehyde **A** as the key building block (Scheme 2), the preparation of which, however, is non-trivial due to the strain inherent in this *ortho*-pyrrolophane derivative.

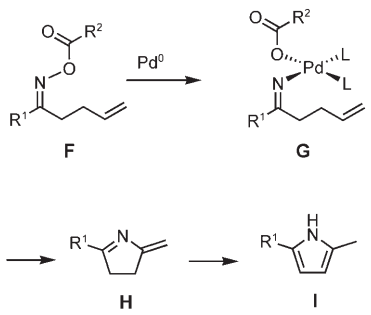


Scheme 2. Retrosynthetic analysis of "butylcycloheptylprodigiosin" **6** based upon a "Narasaka–Heck" transform to annulate the pyrrole ring to the pre-existing cyclononane skeleton.

While the formation of medium-sized rings in general is disfavored on thermodynamic as well as kinetic grounds, strain energy is known to reach a maximum with nine-membered cycles.[27] For this very reason, we preferred a strategy based upon the annulation of the pyrrole nucleus to a preexisting cyclononane over a late-stage cyclization of the medium-sized carbocycle. Specifically, it was assumed that the generation of the aromatic ring in **D** might be effected

with the aid of palladium catalysis by an intramolecular "aza-Heck" reaction of the type pioneered by Narasaka and co-workers.[28–30]

This intriguing transformation allows readily available oxime ester derivatives **F** bearing a lateral double bond to be converted into substituted pyrroles **I** in a single operation (Scheme 3).[28] It is believed that the reaction is triggered by



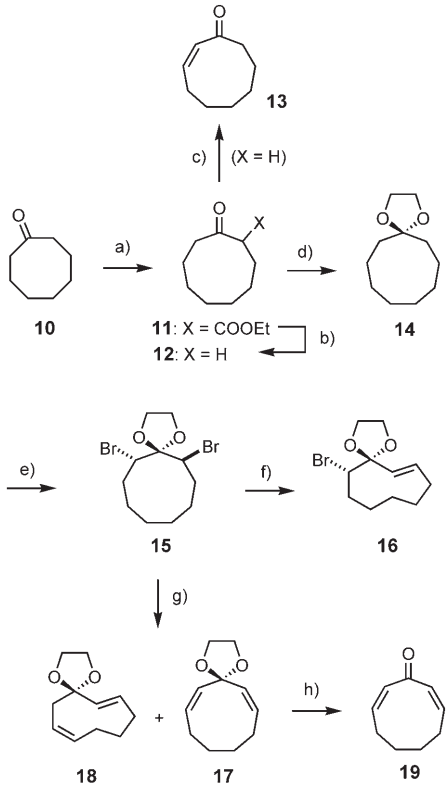
Scheme 3. Conversion of an unsaturated oxime ester into a substituted pyrrole derivative by a "Narasaka–Heck" reaction; L = ligand.

oxidative insertion of Pd^0 into the N–O bond of the oxime, giving rise to iminyl–palladium species of type **G**.[31] This reactive intermediate then attacks the suitably located olefin in a Heck-type manner to form methylenedihydropyrrole **H** as the primary product, which usually undergoes a spontaneous aromatization by sigmatropic H-shift. Although this transformation has been studied in great detail and considerable knowledge has been acquired as to various side reactions that might interfere (e. g. Beckmann rearrangements, fragmentation or hydrolysis of the reactive intermediates),[28] no application to natural product synthesis has been reported to date. Therefore, the projected route toward **6** provides an excellent opportunity to scrutinize the "Narasaka–Heck" process in a complex setting.

For this purpose, the oxime **E** derived from cyclononadienylacetone seemed highly appropriate. The presence of two synthetically equivalent double bonds in this substrate should increase the number of reactive encounters with the putative iminyl–palladium species and hence reduce the chance that this reactive intermediate would undergo the kind of unproductive degradation reactions known to plague Narasaka–Heck reactions in certain cases.[28] Furthermore, the remaining double bond in the expected product **D** provides a handle for the installation of the butyl side chain of the target. Finally, it was expected that the symmetrical structure of **E** would facilitate the large scale preparation of this rather strained compound.

Preparation of the starting materials: Although (*Z*,*Z*)-cyclononadienone (**19**) is a known compound whose photochemistry has been investigated in some detail,[32] its preparation has not been fully reported in the literature. However, it seemed that application of the Nicolaou method for the synthesis of alkadienones by *o*-iodoxybenzoic acid (IBX) oxidation of the parent saturated ketones would provide ready access to this compound.[33]

Cyclononanone **12**, as the required substrate, is commercially available; its prohibitively high price, however, forced us to develop a large-scale adaptable synthesis (Scheme 4) based upon ring expansion of cheap cyclooctanone **10** on treatment with ethyl diazoacetate in the presence of Meer-



Scheme 4. Large-scale adaptable synthesis of cyclononadienone **19**: a) ethyl diazoacetate, $Et_3O^+BF_4^-$, CH_2Cl_2, 0 °C, 64 %; b) aq. DMSO, 150 °C, 83–86 %; c) IBX, toluene/DMSO, 80 °C, 76 %; d) ethyleneglycol, catalytic pyridinium *p*-toluenesulfonate (PPTS), benzene, reflux, 75–92 %; e) Br_2, Et_2O, 0 °C → RT, 76–84 %; f) KOH, toluene, reflux, 64 %; g) *t*BuOK, DMSO, 85 °C, 96 % (purity: ≥80 % **17** + ≈11 % **18**, rest: other isomers); h) catalytic PPTS, aq. acetone, pyridine, 55 °C, 45–56 % (> 99 % pure).

wein salt ($Et_3O^+BF_4^-$) in dilute CH_2Cl_2 solution at 0 °C.[34] To ensure good yields, it is mandatory to employ freshly prepared, crystalline $Et_3O^+BF_4^-$;[35] the use of commercial samples resulted in highly variable rates, which make careful monitoring of the reaction necessary and may lead to erratic results. Under optimized conditions (cf. Experimental Section), however, ketoester **11** could be obtained in excess of 60 % isolated yield on a 20 gram scale with > 95 % purity. The subsequent Krapcho decarboxylation[36] could also be performed on a large scale, thus ensuring a good supply of cyclononanone **12**.

Unfortunately, however, attempted IBX oxidation[33] of this ketone did not afford the desired cyclononadienone **19** but rather stopped at the stage of the mono-unsaturated enone **13**; this failure is tentatively attributed to the high

strain imparted on the nine-membered ring upon incorporation of a second double bond. Therefore a stepwise synthesis of **19** was pursued by adaptation of a method developed by Garbisch.[32,37]

To this end, **12** was transformed into acetal **14**, which reacts with Br_2 at low temperature to give the *trans*-configured dibromide **15** as the major product. The highly crystalline nature of this compound greatly facilitates its isolation from the crude reaction mixture. The structures of the acetal **14** and the dibromide **15** in the solid state are shown in Figures 1 and 2.

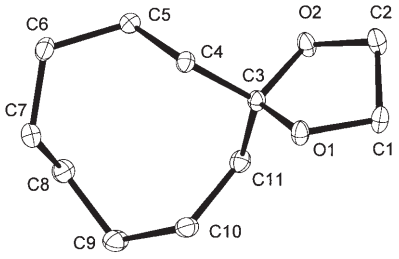


Figure 1. Molecular crystal structure of acetal **14** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level.

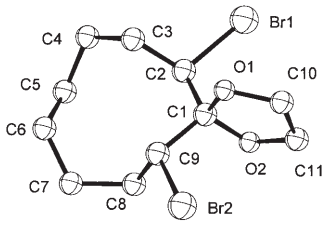


Figure 2. Molecular crystal structure of dibromide **15** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level.

With multigram amounts of **15** in hand, attempts were made to convert this dibromide into product **19** by a double elimination of HBr. However, neither the use of NaOH in MeOH[32,37] nor of KOH in boiling toluene, as previously recommended for related cases,[38] were anywhere close to being satisfactory. Rather, a complex mixture of products was obtained that contained compound **16** as one of its constituents; as evident from Figure 3, this by-product features an (*E*)-configured alkene in the nine-membered ring and hence shows that under the chosen conditions the elimination process is stereounselective.

In view of this unfavorable outcome, it was gratifying to find that the use of *t*BuOK as the base in DMSO resulted in much cleaner conversions. After careful optimization of the reaction conditions, we were able to transform dibromide **15** into the (*Z*,*Z*)-configured di-unsaturated ketal **17** in excellent yields on a multigram scale. Even though the material contains some isomeric compounds, including diene **18**,[39] it was used as such in the next step because the impurities could be conveniently removed by chromatography after the cleavage of the acetal.

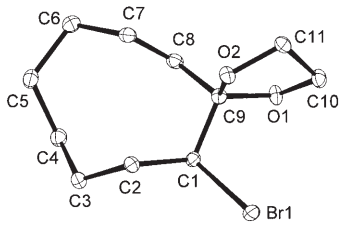
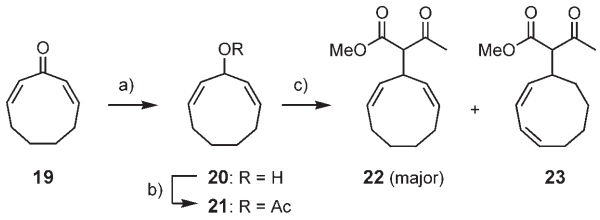


Figure 3. Molecular crystal structure of *E*-alkene **16** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level.

The seemingly trivial removal of the protecting group, however, was more difficult than anticipated. The standard conditions used in the literature for related cases (3% aq. H_2SO_4)[37] led to a morass of isomers. Only a transacetalization with acetone catalyzed by pyridinium *p*-toluenesulfonate afforded the desired (*Z*,*Z*)-cyclononadienone **19** in isomerically and analytically pure form. Because all steps of the newly developed route to **19** outlined above are scalable, this somewhat delicate compound could serve as an appropriate starting point for the envisaged total synthesis of "butylcycloheptylprodigiosin" **6**.

Elaboration of the *ortho*-pyrrolophane core: With a good supply of ketone **19** secured, the elaboration of this compound into a suitable substrate for the intramolecular Narasaka–Heck cyclization[28] was tackled. To this end, **19** was reduced with diisobutylaluminum hydride (Dibal-H) to the nicely crystalline doubly allylic alcohol **20** (Figure 4), which was then acetylated in excellent yield under standard conditions (Scheme 5).



Scheme 5. Elaboration of cyclononadienone by a Tsuji–Trost reaction: a) Dibal-H, CH_2Cl_2, 0°C, 98%; b) Ac_2O, Et_3N, catalytic DMAP, CH_2Cl_2, 97%; c) NaH, methyl acetoacetate, THF, $[Pd(PPh_3)_4]$ (5 mol%), 55°C, 74% (**22**/**23** ≥ 4:1).

Exposure of **21** to methyl acetoacetate in the presence of NaH and catalytic amounts of $[Pd(PPh_3)_4]$ afforded **22** as the major product. This outcome is remarkable for various reasons: Although one might expect that the oxidative insertion of Pd^0 into the bis-allylic acetate **21** engenders the formation of a pentadienyl–palladium intermediate which would react with the nucleophile to give a conjugated diene product preferentially,[40] the double bonds in **22** produced as the major isomer are site-isolated; only small amounts of a conjugated diene isomer **23** were detected. The structure of **22** in the solid state is shown in Figure 5. Moreover, it is

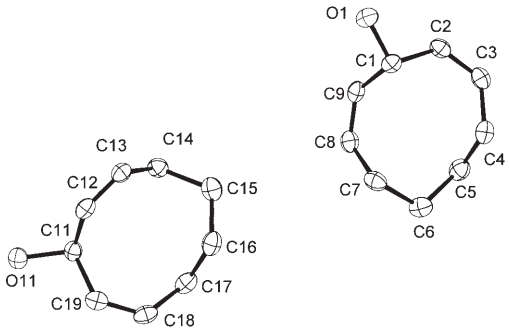


Figure 4. Molecular crystal structure of cyclononadienol **20** in the solid state (two independent molecules in the unit cell). Anisotropic displacement parameters are drawn at the 50% probability level.

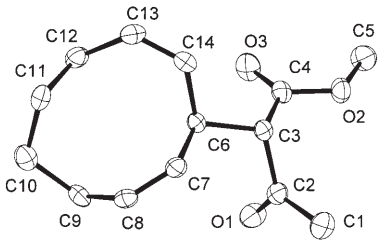
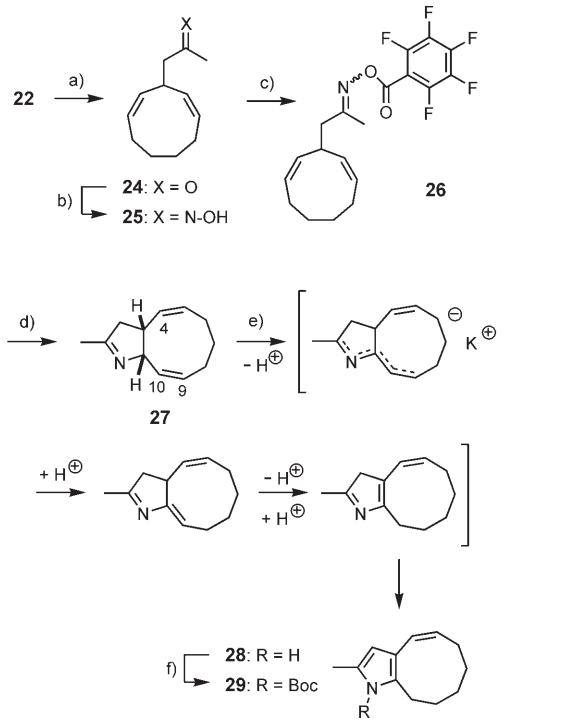


Figure 5. Molecular crystal structure of acetoacetate **22** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level.



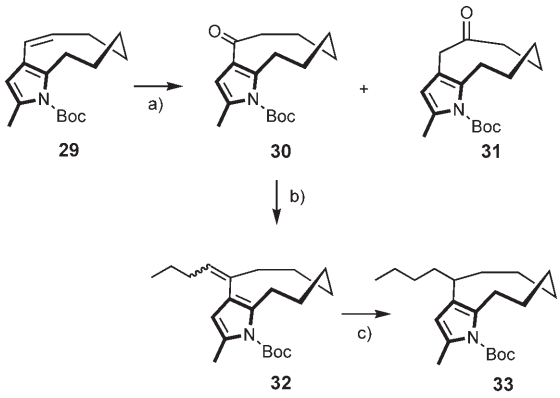
Scheme 6. a) Aq. DMSO, 180°C, 99%; b) $H_2NOH{\cdot}HCl$, NaOAc, aq. EtOH, 100°C, 97%; c) pentafluorobenzoylchloride, Et_3N, Et_2O, −78°C → RT, 97%; d) $Pd(OAc)_2$ (12 mol%), (*o*-tolyl)$_3$P (12 mol%), Et_3N, DMF, 110°C, 54%; e) KH, 1,3-diaminopropane, 65%; f) Boc_2O, DMAP (10 mol%), MeCN, 50°C, 69%.

noteworthy that both olefins in **22** are (*Z*)-configured, although nine-membered rings are large enough to embody (*E*)-alkenes without difficulty (see above) and palladium catalysis is known to isomerize allylic systems effectively.[41] This regio- and stereochemical outcome therefore suggests that during the course of the Tsuji–Trost reaction[41] the two "allylic" sites in substrate **21** remain uncoupled as a result of the conformational peculiarities of the medium-sized ring.[42]

Krapcho decarboxylation[36] of **22** followed by conversion of the resulting cyclononadienylacetone **24** into the pentafluorobenzoyl oxime ester **26** proceeded smoothly, thus setting the stage for the envisaged Narasaka–Heck cyclization (Scheme 6).[28] This key transformation was effected on a multigram scale by a catalyst formed in situ from $Pd(OAc)_2$ and P(*o*-tolyl)$_3$ in DMF at 110°C, delivering the unsaturated bicyclic imine **27** in 54% yield. Because of its quite exceptional sensitivity as well as unusual volatility,[43] this compound must be treated with greatest care and should be elaborated without unnecessary delay.

The formation of imine **27** came as a surprise since Narasaka-reactions usually deliver the corresponding pyrrole derivatives directly (cf. Scheme 3).[28] The reluctance of **27** to undergo spontaneous aromatization necessitated the development of an alternative procedure to obtain the required *ortho*-pyrrolophane structure (Scheme 6). Considering that deprotonation of this compound at the bridgehead position α to nitrogen creates a stabilized aza-pentadienyl anion that might be re-protonated to give the conjugated diene isomer preferentially, compound **27** was treated with KAPA (potassium 3-aminopropylamide)[44] in 1,3-diaminopropane as the reaction medium at ambient temperature. In line with our expectations, a series of "thermodynamic" deprotonation/reprotonation events ensued, resulting in the selective shift of the 9,10-double bond of **27**. The highly labile pyrrole **28** thus obtained was immediately *N*-protected to give compound **29**.[43,45] Although some isomeric by-products accompany the desired pyrrole at this stage (cf. Experimental Section), no further purification of this still rather sensitive material was performed because the impurities could be removed after the subsequent oxidation step.

The only remaining double bond in **29** is suitably located for the introduction of the butyl side chain of the final target. However, all attempts to manipulate this olefin by means of a Wacker oxidation,[41] a rhodium-catalyzed hydroboration, or an oxymercuration strategy were unsuccessful. Only the uncatalyzed hydroboration with $BH_3{\cdot}THF$ followed by stepwise oxidation with H_2O_2 (in the presence of excess Me_3N to protect the alkyl borane against proto-deborylation)[46] and Dess–Martin periodinane[47] allowed the alkene to be functionalized, furnishing ketone **30** and the unconjugated regioisomer **31** in a somewhat variable ratio (Scheme 7); the latter, as well as all impurities derived from isomeric olefins (see above) could be removed at that stage by routine flash chromatography. Thus, despite the lability and unusual volatility of its immediate precursors, ketone **30** was obtained in high purity and therefore qualified as the synthetic platform for the final stage of the projected total



Scheme 7. Elaboration of the core region: a) i) BH_3·THF, THF, −10 °C; ii) Me_3N/THF, aq. NaOH (3 M), H_2O_2, 0 °C; iii) Dess-Martin periodinane, 65 % (2–5:1 ratio); b) $Ph_3P{=}CHCH_2CH_2CH_3$, toluene, reflux, 75 %; c) H_2 (1 atm), [(cod)(pyridine)Ir(PCy_3)]PF_6 (10 mol %), CH_2Cl_2, 90 %.

synthesis. The structure of this key synthetic intermediate and its regioisomer **31** in the solid state are depicted in Figures 6 and 7.

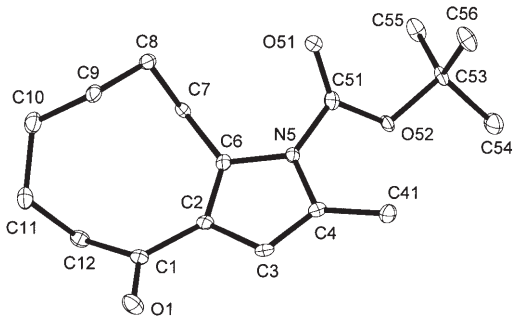


Figure 6. Molecular crystal structure of pyrrole **30** in the solid state. Anisotropic displacement parameters are drawn at the 50 % probability level.

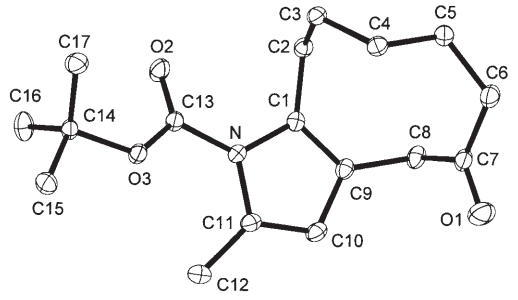


Figure 7. Molecular crystal structure of pyrrole **31** in the solid state. Anisotropic displacement parameters are drawn at the 50 % probability level.

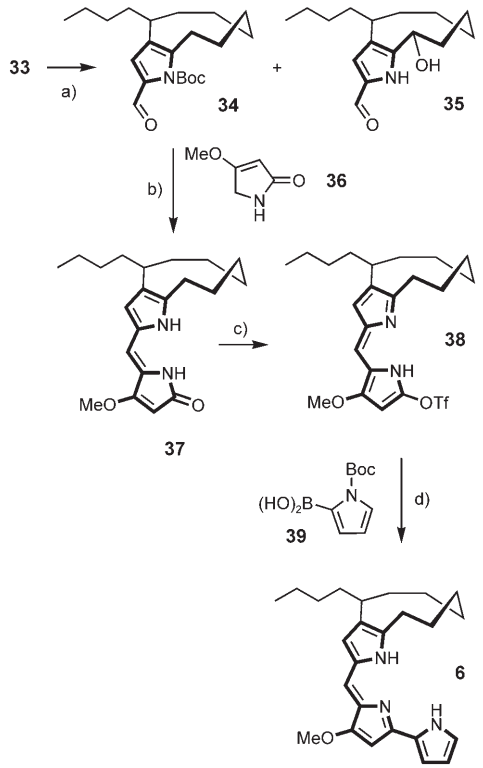
The steric shielding of the carbonyl group in **30**, apparent in the crystal structure, made itself felt in the subsequent Wittig olefination. This seemingly routine transformation proceeded only in boiling toluene but delivered the corresponding olefin **32** in good yield as a mixture of both stereoisomers. Its trisubstituted alkene could be hydrogenated over [(cod)(pyridine)Ir(PCy_3)]PF_6[48] as the catalyst to give the desired *ortho*-pyrrolophane **33** without reduction of the pyrrole ring interfering.

Completion of the total synthesis: The envisaged end game of the total synthesis required preparation of aldehyde **34** as the partner for the projected condensation/cross-coupling sequence to complete the heterocyclic rim of "butylcycloheptylprodigiosin" (**6**).[21] Pyrroles in general, however, are known to be sensitive to oxidizing agents.[49] Therefore, we were apprehensive that the conversion of the methyl branch in **33** to the corresponding aldehyde might be problematic. In fact, all the classical reagents known to affect such benzylic oxidations failed in the present case. Nevertheless, after some experimentation, a satisfactory solution was found using cerium ammonium nitrate (CAN).[50]

Success, however, did not come until a careful optimization of the reaction conditions had been carried out. While previous reports recommended the use of CAN in aq. THF/HOAc for similar purposes,[51] compound **33** was rapidly destroyed, probably due to uncontrolled over-oxidations. It seemed reasonable to remedy this by separating the reagent from the substrate and the products. Therefore, oxidations in various biphasic media were performed: While $CHCl_3$/H_2O furnished the desired aldehyde **34**,[52] the reaction was unacceptably slow; gratifyingly, however, the addition of dimethoxyethane (DME), which is thought to serve as a "phase-transfer" agent, led to a significant improvement. Under these conditions, the oxidation of **33** required only 30 min to go to completion and afforded the desired aldehyde **34** in well reproducible 60–65 % yield (Scheme 8). Small amounts of alcohol **35** were also formed but could be removed by flash chromatography.

Base-promoted condensation of **34** with commercial lactam **36** was accompanied by the cleavage of the *N*-Boc protecting group. As expected,[16,26] treatment of the resulting product **37** with Tf_2O induced a reorganization of the π-system and delivered triflate **38** as the substrate for the final Suzuki coupling.[53] Exposure of this compound to the boronic acid **39** in the presence of catalytic amounts of [Pd(PPh_3)$_4$] and LiCl (3 equiv) under previously optimized conditions[14] afforded prodigiosin **6** in 61 % yield as a deep red-pink colored solid.

No signal upfield of TMS was observed in the ^{1}H NMR spectrum of synthetic **6**. While its spectrum is therefore clearly different from that of the *meta*-bridged isomer streptorubin B **5**, the pattern signature is in accord with the reported but incomplete data of "butylcycloheptylprodigiosin".[22,23] A comparison of the spectrum with that of an authentic (though not entirely pure) sample of the "pink pigment" isolated by Floss showed an excellent match. Therefore, it must be concluded that "butylcycloheptylprodigiosin" **6** is a natural product on its own right, distinct from streptorubin B (**5**), as originally proposed by Gerber[22] and by Floss.[23] The analytical and spectroscopic data compiled in the Experimental section may serve as a reference



Scheme 8. Completion of the total synthesis: a) CAN, $CHCl_3$/DME/H_2O, 60–65% (**34**) + 25% (**35**); b) lactam **36**, aq. NaOH, DMSO, 60°C, 64–69%; c) Tf_2O, CH_2Cl_2, 0°C, 72–79%; d) boronic acid **39**, [$Pd(PPh_3)_4$] (8 mol%), LiCl, aq. Na_2CO_3, DME, 80°C, 61%.

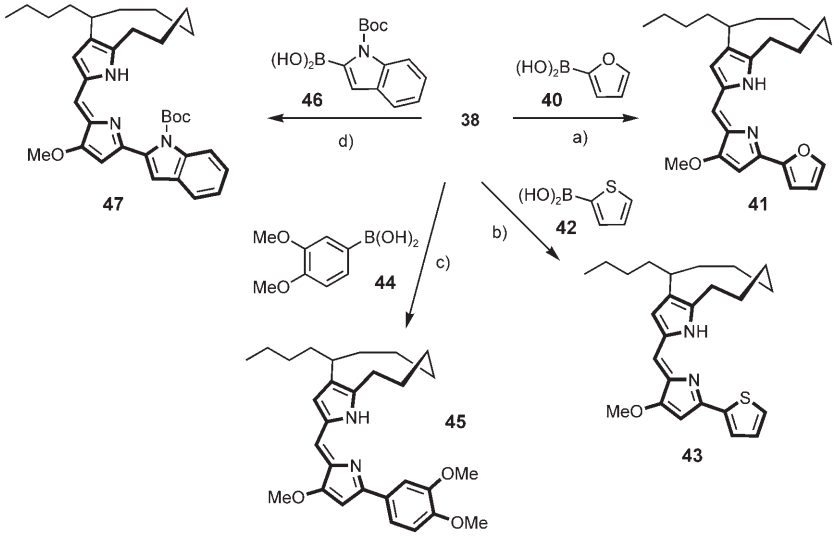
data set for this structurally rather unique tripyrrole derivative.

Analogues: As discussed in the Introduction, the simple prodigiosin analogue GX15-070 (**8**) is presently undergoing clinical trials as a drug candidate for the treatment of refractory chronic lymphoid leukaemia (CLL).[8] In this particular compound, one of the pyrrole units of the parent natural product **2** has been replaced by an indole moiety and the pentyl branch was formally cut back to a methyl substituent.

The favorable biological properties of **8** spurred the preparation of related derivatives of "butylcycloheptylprodigiosin" in which the terminal pyrrole entity is replaced by various other aromatic rings (Scheme 9). Exploiting the inherent flexibility in the late stages of the chosen synthesis route, this goal was readily attained. Thus, it sufficed to react triflate **38** with the boronic acid derivatives **40**, **42**, **44** or **46** under the standard cross-coupling conditions to gain access to four suitable analogues in good to excellent yields. These compounds should qualify for testing as apoptosis inducers, most notably for their ability to interfere with B-cell lymphoma-2 proteins (Bcl-2) as the immediate biological targets of the lead compound GX15–070.[8]

Structural aspects: As has already been outlined above, access to nine-membered rings still represents a synthetic challenge. Not surprisingly therefore, crystal structures of monocyclic nine-membered rings are rare; only 30 hits, excluding metal coordinating complexes, are found in the Cambridge Structure Database. 16 of these are cyclononanes, while the remaining 14 hits comprise cyclononenes, cyclononadienes, -trienes and one -tetraene. An even smaller subset of only five crystal structures is retrieved for bicyclic compounds such as **30** and **31**, where the nine-membered ring is annulated to a five-membered ring. No previous examples are found for bicyclic spiro-compounds,[54] for which we now present three representatives (**14**–**16**).

Nevertheless, the conformational details of nine-membered rings have been investigated in a number of experimental and theoretical studies, since rings of this size are sufficiently flexible to adopt various different conformations, which can be qualitatively described by a chair/boat nomenclature. Early work by Dunitz et al. did already highlight short intramolecular hydrogen contacts as well as extended endocyclic C-C-C angles in the crystal structure of cyclononylamine hydrobromide.[55] Later Hendrickson classified the conformations and energies of nine-membered rings;[56] this system was extended on the basis of improved computational methods.[57,58] With the introduction of the concept of ring puckering parameters, numerical descriptors are available for the conformational analysis of rings.[59] More recently



Scheme 9. Preparation of analogues: a) boronic acid **40**, catalytic [$Pd(PPh_3)_4$], LiCl, aq. Na_2CO_3, DME, 80°C, 81%; b) boronic acid **42**, catalytic [$Pd(PPh_3)_4$], LiCl, aq. Na_2CO_3, DME, 80°C, 81%; c) boronic acid **44**, catalytic [$Pd(PPh_3)_4$], LiCl, aq. Na_2CO_3, DME, 80°C, 44%; d) boronic acid **46**, catalytic [$Pd(PPh_3)_4$], LiCl, aq. Na_2CO_3, DME, 80°C, 72%.

Boyens et al. presented an in depths study of the conformations of nine-membered rings and the presentation of their six ring puckering parameters on the surface of a tubular helix wound into a torus.[60] For the present work the method developed by Zefirov et al. has been used, as implemented in the computer program RICON.[61] Table 1 summarizes the ring-puckering parameters for all nine-membered ring crystal structures reported in this paper. Table 2 gives the contributions of six basic nine-membered ring geometries to each of the molecular conformations found in the crystal structures reported herein.

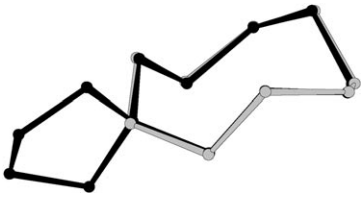


Figure 8. Overlap of the molecular crystal structure of compound **14** (black) and a calculated cyclononane (grey) in ideal twist boat–chair (TBC) conformation,[60] which show an excellent match (cf. Table 2).

Table 1. Puckering parameters of the nine-membered rings reported in this paper according to Zefirov et al.[61b] The total ring puckering or puckering amplitude S is the square root of $S(2)^2 + S(3)^2 + S(4)^2$. Atom labels refer to the chosen labels in each individual structure.

Compound	Sequence of atoms in cycle	S	$S(2)$	$S(3)$	$S(4)$	$\psi(2)$	$\psi(3)$	$\psi(4)$
14	C3-C11-C10-C9-C8-C7-C6-C5-C4	1.929	0.006	1.929	0.009	164.87	89.78	249.09
15	C1-C2-C3-C4-C5-C6-C7-C8-C9	1.943	0.023	1.942	0.047	321.89	270.42	304.31
16	C1-C9-C8-C7-C6-C5-C4-C3-C2	2.080	0.683	0.473	1.907	252.53	332.20	49.69
20	C1-C2-C3-C4-C5-C6-C7-C8-C9	1.814	0.276	1.745	0.409	279.97	11.34	270.88
	C10-C11-C12-C13-C14-C15-C16-C17-C18	1.810	0.283	1.742	0.401	264.18	169.01	266.64
22	C6-C7-C8-C9-C10-C11-C12-C13-C14	1.815	0.289	1.739	0.429	255.79	168.86	267.69
30	C1-C11-C10-C9-C8-C7-C6-C5-C2	1.771	0.812	0.707	1.406	56.88	165.77	24.50
31	C1-C2-C3-C4-C5-C6-C7-C8-C9	1.853	0.283	1.780	0.432	96.29	43.61	189.66

Table 2. Analysis of the nine-membered ring conformations for the molecular crystal structures reported in this paper in terms of linear combinations of basic symmetric nine-membered ring conformations.[a]

	BB [%]	TBB [%]	BC [%]	TBC [%]	CC [%]	TCC [%]
14			1	98		
15	1		1	95	1	1
16	6	17	1	14	2	60
20	11		45	28	1	15
	7	5	46	27	5	11
22	7	5	45	27	4	13
30	19	9	13	12	26	21
31	7	4	33	39	1	16

[a] Percentages don't add up to 100% due to rounding off to nearest integer. BB: "boat-boat"; TBB: "twist boat-boat"; BC: "boat–chair"; TBC: "twist-boat–chair"; CC: "chair–chair"; TCC: "twist-chair–chair" (BC corresponds to C_{3v} and TBC to D_3).

The molecular conformation of **14** (Figure 1) can be classified as twist-boat–chair (TBC) for the nine-membered ring and a distorted envelope (88% envelope, 12% twist) for the five-membered ring, with carbon atom C1 forming the flap of the envelope. Although the signs of the endocyclic dihedral angles in **14** follow the same pattern as for the idealised D_3 conformation, the maximum point group symmetry is C_2 due to the substituents in **14** (Figure 8).

The conformation of the nine-membered ring in **15** (Figure 2) is very similar to that of **14**. Overall, the introduction of the two bromine atoms has not altered any corresponding dihedral angles by more than six degrees. Surprisingly, the five-membered ring is essentially planar, a conformation which is probably governed by the two bromine substituents in the α-positions which are equatorially oriented on the medium ring.

The mono-bromo analogue **16** (Figure 3) has no longer a C_2-symmetric molecular geometry; however, the nine-membered ring, taken on its own, is still close to a C_2-symmetric conformation, with equivalent dihedral angles deviating by up to 19°. The C_2 axis does not bisect the five-membered ring but atom C3 and the mid-point of the bond between C7 and C8. As illustrated by Figure 9, the conformation is best described as a "twist-boat". The five-membered ring adopts an intermediate conformation between twist (41%) and envelope (59%).

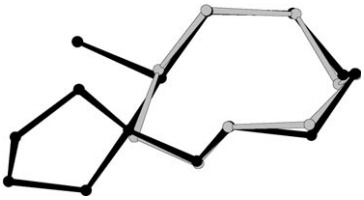


Figure 9. Overlap between the molecular crystal structure of compound **16** (black) and a calculated cyclononane (grey) adopting a "conventional" twist-boat (TB) conformation according to the conventions of Boyens et al.[60]

Dienol **20** (Figure 4) crystallizes with two independent molecules in the asymmetric unit which exhibit endocyclic dihedral angles within 2° of each other. The ring deviates substantially from any symmetric conformation, the mirror symmetric "boat–chair" conformation coming closest. The best fit has the pseudo-mirror plane not coinciding with the mirror plane imposed by the chemical structure but passing through the midpoint of the carbon–carbon double bond C2=C3 and carbon atom C7 in one of the two molecules and the corresponding atoms C18=C19 and C14 in the other molecule. Pairs of equivalent dihedral angles deviate from the mean between 2 and 57°, whereby the largest differences are associated with the dihedral angles involving the second double bond or being adjacent to this bond. The C–C=C bond angles are all enlarged and display values between 125 and 126°.

Acetoacetate **22** (Figure 5) adopts a very similar conformation to that of **20**. Again the "boat–chair" conformation is only approximate and there is again one choice for positioning the pseudo-mirror plane which is preferential and does not follow the chemical symmetry.

The two condensed bicyclic pyrrole compounds **30** and **31** adopt much less symmetric conformations. In particular **30** (Figure 6) is a linear combination of several of the basic shapes, none of which contributes more than about 25% (cf. Figure 10 and Table 2). Since the carbonyl group is in the α-

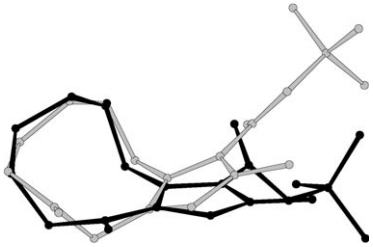


Figure 10. Overlap of the molecular crystal structures of the bicyclic derivatives **30** (black) and **31** (grey), featuring the low symmetry yet distinctly different shapes of their annulated nine-membered rings (compare Table 2).

position to the pyrrole ring, the two neighboring torsion angles are close to zero (C7-C6-C2-C1: 5.4° and C6-C2-C1-C12: 14°), thus reducing the flexibility of the entire system. Notably, this particular conformation forces the two methylene groups C7 and C12 to the same face of the nine-membered ring, reducing the distance between hydrogen atoms H7A and H12B. Based on a geometry with hydrogen atoms in idealised positions; this distance is only 1.94 Å.[62] Hydrogen atom H10B, which also points to the same face, does not come into such close contact (H···H distance 2.36 and 2.43 Å).

The less strained ring **31** (Figure 7, only one torsion angle is close to zero) also has three methylene hydrogen atoms in transannular proximity, but all of them are longer than 2.16 Å. Accordingly, the overall ring shape can be described as a linear combination of "boat–chair" and "twist-boat–chair", which account for 72% of the ring conformation (Figure 10 and Table 2).[63]

Evaluation of the DNA-damaging capacity of butylcycloheptylprodigiosin and analogues: The prodigiosins exhibit a broad range of biological activities elicited by various biochemical mechanisms.[1,2] Most characteristic are i) their capacity for H^+/Cl^- symport upon protonation of the basic azafulvene site which ultimately modulates the pH of cellular vacuoles,[16a,64] and ii) their ability to act as chelating ligands to various transition metal cations. If the latter are redox-active, coordination might be followed by single electron oxidation of the pyrrolylpyrromethene chromophore with formation of a π-radical cation, thus triggering a cascade leading to oxygen activation and ultimately DNA damage.[15,65,66] This nuclease-like activity is most prominent for the combination of prodigiosins and Cu^{II}, a cation known to be present in the nucleus of cells at relevant concentrations.[67] Importantly, certain cancer cells contain significantly more copper than non-malignant tissue.[68]

Therefore, it had been speculated that the cytotoxic activity of the prodigiosins might correlate with their ability to induce oxidative DNA cleavage.[69] A recent report, however, showed that DNA damage and cytotoxicity can be decoupled, in particular upon replacement of one of the pyrrole rings by an indole moiety.[9] For this very reason, it was of interest to investigate and compare the copper-mediated nuclease activity of the natural product "butylcycloheptylprodigiosin" (**6**) with that of its non-natural analogues **41**, **43**, **45** and **47** terminated by different aromatic entities.

As can be seen from the agarose gel depicted in Figure 11, the nuclease activities of these compounds are

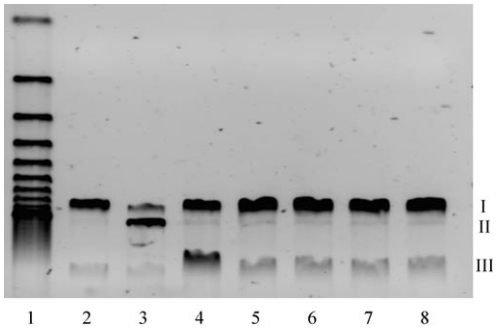
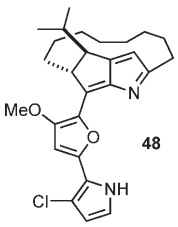


Figure 11. Agarose gel electrophoresis showing the extent of DNA cleavage caused by **6** and different analogues thereof in the presence of $Cu(OAc)_2$ after an incubation time of 1.5 h at 37°C. Lane 1: DNA marker (500 base pairs molecular weight difference); lane 2: DNA alone; lane 3: DNA enriched in linear form (II) by partial cleavage of the parent DNA by the restriction endonuclease *Xho I*; lane 4: DNA + compound **6** + Cu^{II}; lane 5: DNA + compound **41** + Cu^{II}; lane 6: DNA + compound **47** + Cu^{II}; lane 7: DNA + compound **43** + Cu^{II}; lane 8: DNA + compound **45** + Cu^{II}; band **I**: supercoiled double stranded plasmid DNA; band **II**: linear form of DNA; band **III**: nicked form of DNA.

distinctly different. In accord with previous investigations,[15,65] incubation of purified double-stranded plasmid DNA of the bacteriophage *Φ*X174 with the parent tripyrrolic prodigiosin **6** and $Cu(OAc)_2$ results in effective single-strand cleavage as evident from the intense band **III** corresponding to the nicked form of the DNA (lane 4). Double strand cleavage (producing the linear DNA leading to band **II**) is hardly visible under these conditions. Importantly, however, none of the synthetic analogues of **6**, irrespective of whether they incorporate a furan, indole, thiophene or dimethoxybenzene terminus, was able to induce significant strand cleavage (lanes 5–8). Therefore it must be concluded that the formal replacement of the terminal pyrrole by another electron rich arene results in more of less complete loss of nuclease activity, even though the electronic distribution within the heterocyclic perimeter should remain largely unchanged.

This striking observation is reminiscent of the behavior of roseophilin (**48**) as the closest naturally occurring analogue



48

of the prodigiosins,[1,17] which incorporates one furan moiety into an otherwise closely related heterocyclic domain. Much like the synthetic prodigiosins described herein, **48** is devoid of any significant capacity for damaging DNA in the presence of Cu^{II}.[15b,70]

Conclusion

The dispute whether "butylcycloheptylprodigiosin" (**6**) is a natural product or solely a mis-assigned structure has lasted for more than a decade. This open question has now been answered by the first total synthesis of this tripyrrole alkaloid, which makes explicit use of the peculiarities of its highly strained *ortho*-anellated nine-membered ring. After establishing a large-scale adaptable synthesis of cyclononadienone **19**, the *ortho*-pyrrolophane core of this target was formed by the first application of the "Narasaka–Heck" reaction to natural product synthesis. Specifically, oxime ester **26** was converted into the dihydropyrrole **27** by means of a palladium-catalyzed C–N bond formation. The total synthesis also features a noteworthy Tsuji–Trost reaction and a useful CAN-mediated oxidation of a benzylic methyl group to the corresponding aldehyde without damaging the labile pyrrole core. The flexibility inherent to the chosen approach enabled the preparation of a focused set of analogues of **6** in which one of the pyrrole rings of the heterocyclic domain has been replaced by other electron rich arene moieties. This structural change leads to a complete loss of the nuclease-like activity characteristic of the naturally occurring prodigiosins.

Experimental Section

General methods: All reactions were carried out in flame-dried glassware under Ar. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O, DME (Mg/anthracene), DMSO, CH_2Cl_2, MeCN, Et_3N, 1,3-diaminopropane (CaH_2), MeOH (Mg), DMF (Desmodur, dibutyltin dilaurate), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on Bruker DPX 300, AV 400, or DMX 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C \equiv 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.26$ ppm; CD_2Cl_2: $\delta_C \equiv 53.8$ ppm; residual CH_2Cl_2 in CD_2Cl_2: $\delta_H \equiv 5.32$ ppm). ^{15}N chemical shifts are given relative to neat external CH_3NO_2 ($\equiv 0$ ppm). Where indicated, the signal assignments are unambiguous; the numbering Scheme is arbitrary and is shown in the inserts. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (cosygs and cosydqtp); HSQC (invietgssi) optimized for $^1J(C,H) = 145$ Hz; HMBC (inv4gslplrnd) for correlations via $^nJ(C,H)$; HSQC-TOCSY (invietgsml) using an MLEV17 mixing time of 120 ms. ^{15}N was recorded indirectly using HMBC (inv4gslrnd) or HMQC (inv4gsnd) pulse sequences. IR: Nicolet FT-7199 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). Melting points: Büchi melting point apparatus B-540 (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Fluka, Lancaster, Aldrich) were used as received.

2-Oxocyclononancarboxylic acid ethyl ester (11): Freshly prepared Meerwein salt ($Et_3O^+BF_4^-$, 45.6 g, 240.0 mmol) was added in one portion to a cooled solution (0 °C) of cyclooctanone **10** (18.55 g, 147.0 mmol) in CH_2Cl_2 (420 mL). Ethyl diazoacetate (27.5 g, 241.0 mmol) was then added via a dropping funnel over a period of 8 min, causing a vigorous evolution of gas. The resulting solution was stirred for 4 h at 0 °C before the reaction was carefully quenched with aq. sat. $NaHCO_3$ (500 mL). The biphasic mixture was stirred for 45 min until the evolution of gas had ceased. The organic layer was successively washed with aq. HCl (10%, 3×10 mL), aq. sat. $NaHCO_3$ (60 mL) and brine (2×30 mL) before it was dried over Na_2SO_4 and carefully evaporated (≤ 40 °C bath temperature). The residue was purified by distillation (1×10^{-3} mbar, b.p. 85–90 °C) to give **11** as a pale yellow liquid (19.8 g, 64%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.14$ (2q, $J = 7.1$ Hz, 2H), 3.59 (2d, $J = 6.5$ Hz, 1H), 2.45 (m, 2H), 2.3 (m, 2H), 2.05 (m, 2H), 1.83 (m, 2H), 1.49 (m, 6H), 1.24 ppm (2t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 211.8$, 169.8, 61.2, 58.8, 42.3, 27.0, 25.8, 24.9, 24.4, 24.3, 23.9, 13.9 ppm; MS (EI): m/z (%): 212 (5) [M^+], 167 (21), 166 (16), 138 (46), 129 (14), 121 (14), 110 (27), 109 (15), 101 (33), 99 (10), 97 (25), 88 (19), 84 (64), 79 (10), 73 (50), 68 (21), 67 (20), 55 (100), 41 (58), 29 (45).

Cyclononanone (12): A degassed solution of compound **11** (35.5 g, 167.2 mmol) in DMSO (150 mL) and H_2O (8 mL) was stirred at 150 °C (bath temperature) for 16 h. After reaching ambient temperature, the mixture was partitioned between water (80 mL) and Et_2O (3×70 mL), the combined organic phases were dried (Na_2SO_4) and evaporated, and the residue purified by distillation under reduced pressure (1×10^{-3} mbar, b.p. 45–53 °C) to give ketone **12** as a colorless liquid (19.53 g, 83%). The analytical data are in accord with those reported in the literature.[34b] ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.41$ (m, 4H), 1.83 (m, 4H), 1.54 (m, 4H), 1.35 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 218.1$, 43.3, 26.7, 24.7, 24.0 ppm; MS (EI): m/z (%): 140 (16) [M^+], 111 (26), 98 (93), 97 (31), 82 (14), 81 (11), 71 (10), 67 (12), 58 (12), 55 (100), 54 (15), 43 (38), 42 (61), 41 (92), 39 (40), 29 (29).

1,4-Dioxaspiro[4.8]tridecane (14): A solution of ketone **12** (23.74 g, 169.29 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 4.29 g, 17.07 mmol) in ethylene glycol (45 mL) and benzene (300 mL) was heated under reflux in a Dean–Stark apparatus until the separation of water ceased (3–7 d). For work-up, the reaction mixture was partitioned between water and Et_2O, the combined organic phases were washed with brine, dried over Na_2SO_4, and evaporated, and the crude product was purified by distillation in high vacuum (1×10^{-3} mbar, b.p. 60–64 °C) to give ketal **14** as a colorless, low-melting solid (23.26 g, 75%). On smaller scale, yields of up to 92% were obtained. M.p. 35–36 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.88$ (s, 4H), 1.76 (m, 4H), 1.52 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 113.3$, 64.3, 32.1, 27.1, 23.6, 20.8 ppm; IR (KBr): $\tilde{\nu} = 2929$, 2897, 2877, 2844, 2678, 1485, 1450, 1329, 1176, 1114, 1093, 972, 838, 751, 705, 514 cm^{-1}; MS (EI): m/z (%): 184 (3) [M^+], 155 (11), 141 (14), 99 (100), 86 (26), 55 (20), 41 (17); HRMS (EI): m/z: calcd for $C_{11}H_{20}O_2$: 185.1542; found: 185.1540 [M^++H]; elemental analysis calcd (%) for $C_{11}H_{20}O_2$ (184.28): C 71.70, H 10.94; found: C 71.62, H 11.06.

6,13-Dibromo-1,4-dioxaspiro[4.8]tridecane (15): Br_2 (44.54 g, 278.7 mmol) was added via a dropping funnel over a period of 35 min to a vigorously stirred and cooled (0 °C) solution of acetal **14** (23.26 g, 126.2 mmol) in Et_2O (600 mL). Once the addition was completed, the reaction was allowed to reach ambient temperature and stirring was continued for 16 h. For work up, the mixture was slowly transferred into stirred sat. aq. $NaHCO_3$ (150 mL), the organic layer was separated and washed once more with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). After drying over Na_2SO_4 and evaporation of the solvent, the crude product was recrystallized from hexanes to give dibromide **15** as colorless crystals (36.10 g, 84%). M.p. 80–81 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.59$ (dd, $J = 5.9$, 4.3 Hz, 2H), 4.33 (s, 4H), 2.27 (m, 4H), 1.69 (m, 4H), 1.49 (m, 2H), 1.27 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 112.4$, 68.5, 56.6, 33.8, 26.3, 23.1 ppm; IR (KBr): $\tilde{\nu} = 2959$, 2927, 2873, 2850, 1477, 1453,

1440, 1377, 1188, 1056, 959, 778, 725, 572 cm^{-1}; MS (EI): *m/z* (%): 342 (1) [M^+], 261 (18), 177 (10), 99 (100), 55 (26), 41 (11); HRMS (EI): *m/z*: calcd for $C_{11}H_{18}Br_2O_2$: 339.9674; found: 339.9674 [M^+]; elemental analysis calcd (%) for $C_{11}H_{18}Br_2O_2$ (342.08): C 38.62, H 5.30; found: C 38.72, H 5.42.

(*Z*,*Z*)-1,4-Dioxaspiro[4.8]trideca-6,8-diene (17): *t*BuOK (10.63 g, 94.73 mmol) was added in portions to a solution of dibromide **15** (15.80 g, 46.19 mmol) in DMSO (320 mL) and the resulting solution was stirred at 85 °C for 15 min. After reaching ambient temperature, the mixture was partitioned between water (300 mL) and CH_2Cl_2 (7×50 mL) and the solvents were evaporated. To remove residual DMSO, the residue was diluted with water (150 mL) and the product re-extracted with CH_2Cl_2 (6×20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated, and the residue was purified by flash chromatography (pentanes/Et_2O 10:1) to give **17** as a colorless liquid (7.96 g, 96%). GC analysis showed that the product was ≥80% pure; the major impurity (ca. 10%) was diene **18**, the rest were traces of unidentified isomers. This material was used in the next step without further purification.

Compound **17**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.68 (dt, J=12.0, 8.8 Hz, 2H), 5.52 (d, J=12.0, 2H), 3.92 (s, 4H), 2.44 (m, 4H), 1.59 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=134.9, 130.0, 107.0, 63.8, 26.6, 23.5 ppm; IR (film): $\tilde{\nu}$=3016, 2928, 2884, 1643, 1472, 1450, 1406, 1195, 1161, 1108, 1026, 948, 715 cm^{-1}.

Characteristic data of compound **18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.47 (ddd, J=15.6, 11.4, 3.8 Hz, 1H), 5.44 (ddt, J=11.4, 5.2, 1.5 Hz, 1H), 5.24 (dtdd, J=11.6, 8.2, 1.6, 0.6 Hz, 1H), 5.14 (d, J=15.8 Hz, 1H), 3.95 (m, 1H), 3.91 (m, 2H), 3.82 (m, 1H), 2.41 (ddt, J=11.8, 4.0, 1.0 Hz, 1H), 2.34 (ddt, J=12.6, 8.8, 1.3 Hz, 1H), 2.20 (dd, J=12.6, 7.6 Hz, 1H), 1.97 (m, 1H), 1.90 (m, 1H), 1.84 (m, 1H), 1.76 (m, 1H), 1.55 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.3, 134.5, 128.6, 120.8, 109.3, 64.3, 64.0, 37.4, 33.9, 31.6, 26.4 ppm.

Compound 16: Formed as one of the constituents (ca. 25%) of a rather complex mixture generated on treatment of dibromide **15** with powdered KOH in refluxing toluene. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.91 (m, 1H), 5.23 (d, J=16 Hz, 1H), 4.10 (m, 2H), 3.95 (m, 2H), 2.35–1.03 (m, 10H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=136.2, 126.7, 108.7, 66.0, 65.7, 58.5, 34.4, 32.6, 31.2, 26.3, 23.2 ppm; IR (film): $\tilde{\nu}$=2931, 2859, 2690, 1707, 1660, 1472, 1450, 1234, 1176, 1057, 966, 771, 739, 616 cm^{-1}; MS (EI): *m/z* (%): 262 (0.95), 260 (0.86) [M^+], 181 (74), 137 (2), 125 (100), 112 (9), 99 (23), 91 (3), 86 (7), 81 (14), 79 (4), 77 (3), 68 (8), 66 (2), 55 (16), 51 (2), 41 (12), 39 (9); HRMS (EI): *m/z*: calcd for $C_{11}H_{17}BrO_2$: 260.0412; found: 260.0410 [M^+].

(*Z*,*Z*)-Cyclonona-2,8-dienone (19): A solution of acetal **17** (7.96 g, 44.16 mmol), PPTS (1.12 g, 4.46 mmol) and pyridine (180 μL) in acetone (90 mL) and H_2O (1.2 mL) was stirred for 18 h at 55 °C. For work up, H_2O (40 mL) and CH_2Cl_2 (40 mL) were added, the aqueous layer was extracted with CH_2Cl_2 (3×10 mL), and the combined organic phases were washed with brine before being dried over Na_2SO_4. Evaporation of the solvent followed by flash chromatography of the residue (pentanes/Et_2O 10:1 → 1:1) afforded ketone **19** as a colorless liquid (2.72 g, 45%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ=6.28 (dt, J=12.3, 9.2 Hz, 2H), 6.05 (d, J=12.2 Hz, 2H), 2.54 (m, 4H), 1.70 ppm (m, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=193.7, 146.2, 131.1, 26.3, 24.0 ppm; IR (film): $\tilde{\nu}$=3015, 2974, 2929, 2864, 1642, 1616, 1454, 1405, 1227, 840 cm^{-1}; MS (EI): *m/z* (%): 136 (25) [M^+], 121 (11), 107 (79), 93 (36), 81 (77), 79 (100), 77 (34), 68 (75), 55 (34), 53 (68), 41 (48), 39 (81), 27 (35); HRMS (EI): *m/z*: calcd for $C_9H_{12}O$: 136.0888; found: 136.0889 [M^+]; elemental analysis calcd (%) for $C_9H_{12}O$ (136.20): C 79.37, H 8.88; found: C 79.30, H 8.87.

(*Z*,*Z*)-Cyclonona-2,8-dienol (20): A solution of Dibal-H (0.9 M in CH_2Cl_2, 22.2 mL, 20.0 mmol) was added over a period of 45 min to a solution of ketone **19** (2.72 g, 19.97 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After stirring for 1 h at that temperature, the reaction was quenched by careful addition of MeOH (5 mL) and H_2O (40 mL). Conc. HCl was then added until the precipitate was dissolved (ca. 5 mL), the organic layer was separated and immediately neutralized by washing with aq. sat. $NaHCO_3$. The remaining aqueous phase was repeatedly extracted with Et_2O (4× 20 mL), the combined organic layers were washed with aq. sat. $NaHCO_3$ and brine before they were dried over Na_2SO_4. Careful evaporation of the solvent furnished alcohol **20** as colorless crystals (2.70 g, 98%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ=5.67–5.60 (m, 1H), 5.53–5.43 (m, 4H), 2.65–2.51 (m, 2H), 2.48 (br s, 1H), 1.97–1.85 (m, 2H), 1.77–1.65 (m, 2H), 1.52–1.40 ppm (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=134.4, 129.3, 65.9, 28.3, 23.2 ppm; IR (KBr): $\tilde{\nu}$=3407, 3015, 2935, 2911, 2864, 2852, 1651, 1466, 1299, 1255, 1028, 1020, 817, 760, 725 cm^{-1}; MS (EI): *m/z* (%): 138 (13) [M^+], 120 (20), 109 (20), 95 (100), 91 (41), 79 (83), 67 (55), 55 (51), 41 (59); HRMS (EI): *m/z*: calcd for $C_9H_{14}O$: 138.1045; found: 138.1044 [M^+]; elemental analysis calcd (%) for $C_9H_{14}O$ (138.21): C 78.21, H 10.21; found: C 78.35, H 10.16.

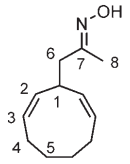
(*Z*,*Z*)-Cyclonona-2,8-dienyl acetate (21): Ac_2O (1.9 mL, 20.1 mmol) was added to a solution of alcohol **20** (2.70 g, 19.54 mmol) and DMAP (11.8 mg, 0.097 mmol) in CH_2Cl_2 (5 mL) and Et_3N (2.9 mL, 20.8 mmol). After stirring for 2 h, the reaction was quenched with MeOH (50 μL), diluted with Et_2O (50 mL), and successively washed with aq. $KHSO_4$ (10% w/w, 22 mL), aq. sat. $NaHCO_3$ (12 mL) and brine (6 mL). The organic phase was dried over Na_2SO_4 and carefully evaporated to give **21** in analytically pure form as a pale yellow liquid (3.40 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.60 (t, J=7.6 Hz, 1H), 5.57 (tdd, J=10.6, 7.1, 1.5 Hz, 2H), 5.46 (ddd, J=7.6, 3.8, 0.8 Hz, 2H), 2.70–2.61 (m, 2H), 2.06 (s, 3H), 2.01–1.93 (m, 2H), 1.79–1.69 (m, 2H), 1.53–1.43 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.3, 130.6, 129.6, 68.8, 27.7, 23.0, 21.3 ppm; IR (film): $\tilde{\nu}$=3022, 2938, 2869, 2854, 1737, 1644, 1471, 1368, 1231, 1024, 970, 818, 751, 711 cm^{-1}; MS (EI): *m/z* (%): 180 (5) [M^+], 138 (23), 120 (44), 105 (22), 92 (71), 79 (47), 67 (22), 55 (15), 43 (100); HRMS (EI): *m/z*: calcd for $C_{11}H_{16}O_2$: 180.1150; found: 180.1151 [M^+]; elemental analysis calcd (%) for $C_{11}H_{16}O_2$ (180.25): C 73.30, H 8.95; found: C 73.39, H 9.06.

Compound 22: Methyl acetoacetate (1.92 g, 16.54 mmol) was slowly added via syringe to a stirred suspension of NaH (60% in mineral oil, 640 mg, 16.0 mmol) in THF (140 mL) over a period of 10 min. Once the evolution of gas had ceased and a clear solution had formed, [$Pd(PPh_3)_4$] (768 mg, 0.67 mmol) and a solution of acetate **21** (2.35 g, 13.04 mmol) in THF (5 mL) were successively introduced and the resulting mixture stirred for 6 h at 55 °C. For work up, the reaction was carefully quenched with H_2O (70 mL) and the aqueous phase was repeatedly extracted with Et_2O (180 mL in several portions). The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (pentanes/Et_2O 10:1) to give **22** as a colorless syrup that solidified when kept in the freezer (2.28 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.60–5.42 (m), 5.35–5.14 (m), 4.44 (m), 3.70 (s), 3.53 (d, J= 10.5 Hz), 2.76–2.65 (m), 2.22 (s), 2.01–1.87 (m), 1.80–1.65 (m), 1.59–1.40 ppm (m); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.4, 169.1, 131.5, 131.4, 129.53, 129.46, 64.9, 52.4, 36.1, 28.8, 28.1, 27.9, 22.6, 22.5 ppm; IR (film): $\tilde{\nu}$=3008, 2935, 2866, 1742, 1714, 1636, 1471, 1435, 1357, 1155, 984, 818, 751, 715, 562 cm^{-1}; MS (EI): *m/z* (%): 236 (2) [M^+], 193 (43), 177 (21), 161 (19), 133 (18), 120 (60), 105 (20), 91 (64), 79 (41), 67 (22), 55 (15), 43 (100); HRMS (EI): *m/z*: calcd for $C_{14}H_{20}O_3$: 237.1491; found: 237.1489 [M^++H]; elemental analysis calcd (%) for $C_{14}H_{20}O_3$ (236.32): C 71.16, H 8.53; found: C 71.04, H 8.46. NMR analysis showed that the material contained 15–20% of the conjugated diene **23** in form of two atropisomers which show the following characteristic data: ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.98 (m), 5.90–5.70 (m), 3.71 (s), 3.68 (s), 3.42 (d, J=9.1 Hz), 3.35 (d, J=10.1 Hz), 3.34–3.22 (m), 2.20 (s), 2.14 (s), 1.38–1.16 ppm (m); ^{13}C NMR (100 MHz, $CDCl_3$, resolved signals): δ=203.0, 202.8, 169.5, 169.3, 134.2, 133.7, 132.8, 132.5, 129.9, 129.8, 127.3, 127.0, 66.7, 66.2, 52.3, 52.1, 39.5, 39.4, 31.9, 31.8, 30.4, 30.3, 29.2, 28.3, 25.2, 25.0 ppm.

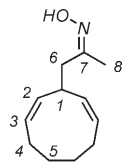
Cyclonona-(*Z*,*Z*)-2,8-dienylacetone (24): A degassed solution of compound **22** (7.08 g, 29.96 mmol) in DMSO (150 mL) and H_2O (1.5 mL) was stirred overnight at 180 °C (bath temperature). After reaching ambient temperature, the mixture was partitioned between H_2O (150 mL) and Et_2O (4×50 mL) and the combined organic phases were washed with brine (2×20 mL) before they were dried (Na_2SO_4) and evaporated to give **24** as a pale yellow liquid (5.28 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.48 (tdd, J=10.4, 7.1, 1.3 Hz, 2H), 5.21 (m, 2H), 4.20–4.09 (m, 1H), 2.75–2.61 (m, 2H), 2.53 (d, J=7.1, 2H), 2.13 (s, 3H), 1.95–1.84 (m, 2H), 1.79–1.66 (m, 2H), 1.52–1.40 ppm (m, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$): $\delta = 207.9$, 132.6, 130.0, 49.3, 31.7, 30.3, 28.0, 22.7 ppm; IR (film): $\tilde{\nu} = 3004$, 2931, 2866, 1713, 1636, 1470, 1359, 1231, 1155, 819, 751, 713, 563 cm^{-1}; MS (EI): *m/z* (%): 178 (5) [M^+], 135 (11), 120 (100), 105 (12), 91 (37), 79 (39), 67 (24), 55 (10), 43 (83); HRMS (EI): *m/z*: calcd for $C_{12}H_{18}O$: 178.1358; found: 178.1357 [M^+]; elemental analysis calcd (%) for $C_{12}H_{18}O$ (178.28): C 80.85, H 10.18; found: C 80.78, H 10.12; isomeric impurities formed by decarboxylation of the conjugated diene **23** showed the following characteristic signals: ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.5$, 135.8, 133.6, 128.0, 127.5, 51.4, 35.5, 34.4, 30.5, 30.1, 28.9, 25.2 ppm.

Oxime 25: A solution of ketone **24** (1.56 g, 8.75 mmol) in EtOH (11.5 mL) was added to a solution of hydroxylamine hydrochloride (727 mg, 10.46 mmol) and NaOAc (858 mg, 10.46 mmol) in H_2O (115 mL) and the resulting mixture was stirred for 4 h at 100 °C under Ar. For work up, MeOH (0.5 mL) was added and the resulting solution was stirred for 5 min before it was diluted with brine (55 mL) and extracted with Et_2O (5 × 30 mL). The combined organic layers were washed with brine (20 mL) before being dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (pentanes/Et_2O 10:1 → 5:1) to give oxime **25** as a colorless syrup (1.64 g, 97 %). For analytical purposes, the oxime isomers were separated by careful flash chromatography under the conditions mentioned above and were characterized separately.


(*E*)-**25**

(*E*)-**25**: ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.99$ (br s, 1H, OH), 5.46 (dtd, $J = 10.5$, 6.9, 1.2 Hz, 2H, H-3), 5.25 (dd, $J \approx 10$, ≈ 9 Hz, 2H, H-2), 3.94 (m, 1H, H-1), 2.61 (m, 2H, H-4a), 2.32 (d, $J = 7.4$ Hz, 2H, H-6), 1.87 (s, 3H, H-8), 1.87 (m, 2H, H-4b), 1.70 (m, 2H, H-5a), 1.46 ppm (m, 2H, H-5b); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 157.3$ (C-7), 133.1 (C-2), 129.6 (C-3), 41.2 (C-6), 32.6 (C-1), 28.1 (C-5), 22.7 (C-4), 13.4 ppm (C-8).

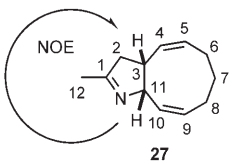

(*Z*)-**25**

(*Z*)-**25**: ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.04$ (br s, 1H, OH), 5.47 (dtd, $J = 10.5$, 6.9, 1 Hz, 2H, H-3), 5.30 (dtd, $J = 10.5$, 8.8, 1 Hz, 2H, H-2), 4.02 (m, 1H, H-1), 2.62 (m, 2H, H-4a), 2.54 (d, $J = 7.6$ Hz, 2H, H-6), 1.87 (m, 2H, H-4b), 1.86 (s, 3H, H-8), 1.71 (m, 2H, H-5a), 1.46 ppm (m, 2H, H-5b); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 157.7$ (C-7), 133.3 (C-2), 129.7 (C-3), 33.6 (C-6), 32.5 (C-1), 28.1 (C-5), 22.7 (C-4), 20.1 ppm (C-8); IR (KBr): $\tilde{\nu} = 3297$, 3005, 2931, 2866, 1664, 1636, 1469, 1444, 1367, 1062, 1034, 957, 752, 714, 650 cm^{-1}; MS (EI): *m/z* (%): 193 (16) [M^+], 176 (85), 148 (15), 135 (34), 121 (48), 105 (25), 98 (19), 91 (83), 79 (100), 73 (22), 67 (67), 55 (30), 41 (53); HRMS (EI): *m/z*: calcd for $C_{12}H_{19}NO$: 193.1467; found: 193.1466 [M^+]; elemental analysis calcd (%) for $C_{12}H_{19}NO$ (193.29): C 74.57, H 9.91, N 7.24; found: C 74.43, H 9.98, N 7.20; the oxime derived from the conjugated diene impurity in the starting material analyzed as follows: ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.2$ (br s, 1H), 5.89 (m, 1H), 5.85 (m, 1H), 5.72 (m, 1H), 5.32 (m, 1H), 2.73 (m, 1H), 2.19 (m, 1H), 2.15 (d, $^1/_2[J_{AX} + J_{BX}] = 7.4$ Hz, 2H), 2.01 (m, 1H), 1.81 (s, 3H), 1.73 (m, 1H), 1.71 (m, 1H), 1.55 (m, 1H), 1.44 (m, 1H), 1.33 (m, 1H), 1.19 ppm (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 158.0$, 136.5, 133.5, 127.6, 127.5, 43.0, 36.3, 34.1, 30.4, 29.0, 25.4, 13.2 ppm.

Oxime ester 26: Pentafluorobenzoyl chloride (1.80 g, 7.81 mmol) and Et_3N (915 mg, 9.04 mmol) were added to a solution of oxime **25** (1.50 g, 7.76 mmol) in Et_2O (20 mL) at −78 °C. The cooling bath was removed and the resulting mixture was stirred for 90 min while warming to ambient temperature. For work up, the precipitate formed was filtered off under Ar and the filtrate was evaporated to give **26** as a yellow-orange, somewhat air-sensitive syrup (2.91 g, 97 %). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.95$ (m), 5.88–5.64 (m), 5.51 (m), 5.42–5.33 (m), 5.33–5.20 (m), 4.01 (m), 3.18–3.04 (m), 2.95–2.76 (m), 2.67–2.51 (m), 2.62 (d, $J = 7.8$ Hz), 2.54 (d, $J = 7.8$ Hz), 2.38 (m), 2.26–2.15 (m), 2.12 (s), 2.10 (s), 2.03 (s), 1.97 (s), 1.95–1.84 (m), 1.81–1.65 (m), 1.60–1.37 (m), 1.29–1.08 ppm (m). For analytical purposes, an aliquot of this sample was subjected to rapid flash chromatography (pentanes/Et_2O 20:1) to give two fractions enriched in either isomer, which analyzed as compiled below: (*E*)-**26**: ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.3$, 132.0, 130.5, 36.0, 32.7, 27.9, 22.5, 20.2 ppm; (*Z*)-**26**: ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.8$, 132.1, 130.2, 40.5, 32.6, 28.0, 22.6, 15.7 ppm; IR (*E*/*Z* mixture, film): $\tilde{\nu} = 3009$, 2934, 2868, 1762, 1652, 1524, 1505, 1420, 1326, 1197, 1148, 1004, 869, 755, 715 cm^{-1}; MS (EI): *m/z* (%): 387 (7) [M^+], 195 (89), 176 (100), 167 (16), 135 (39), 91 (83), 79 (81), 67 (79), 55 (36), 41 (51); HRMS (EI): *m/z*: calcd for $C_{19}H_{18}F_5NO_2$: 387.1258; found: 387.1257 [M^+]; elemental analysis calcd (%) for $C_{19}H_{18}F_5NO_2$ (387.35): C 58.92, H 4.68, N 3.61; found: C 59.04, H 4.62, N 3.56.

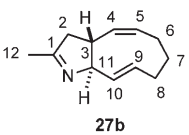
Narasaka–Heck reaction: **preparation of compound 27**: Ar was bubbled through a solution of $Pd(OAc)_2$ (225 mg, 1.00 mmol) and tris-*ortho*-tolylphosphine (304.3 mg, 1.00 mmol) in DMF (12 mL) for 15 min. An aliquot of this catalyst solution (5 mL) was added to a suspension of molecular sieves (4 Å, 500 mg) and Et_3N (5.8 mL, 41.6 mmol) in DMF (5 mL) and the resulting mixture was stirred for 30 min before a solution of compound **26** (3.23 g, 8.34 mmol) in DMF (160 mL) was added. The resulting mixture was stirred at 110 °C for 1.5 h before the remainder of the catalyst solution was introduced and stirring was continued for 3 h at that temperature. For work-up, the mixture was cooled to 0 °C before it was diluted with H_2O (180 mL) and the aqueous phase was quickly extracted with Et_2O (4 × 80 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried before the solvent was evaporated.

The residue was purified by short-path distillation in vacuo (1 × 10^{-3} mbar) to give **27** as a bright yellow liquid (b.p. 65–70 °C) (790 mg, 54 %). ^1H NMR (600 MHz, C_6D_6): $\delta = 5.99$ (ddt, $J = 10.8$, 7.2, 0.9 Hz, 1H, H-10), 5.36 (overlapping signals, 2H, H-4, H-9), 5.34 (ddd, $J = 10.8$, 5.4, 1.2 Hz, 1H, H-5), 4.46 (m, 1H, H-11), 2.68 (m, 1H, H-3), 2.33 (ddd, $J = 17.0$, 9.9, 1.8 Hz, 1H, H-2a), 2.01 (overlapping signals, 1H, H-8a), 2.00 (overlapping signals, 1H, H-6a), 1.93 (ddm, $J = 17.0$, 9.5, 2.3, 0.5 Hz, 1H, H-2b), 1.81 (overlapping signals, 1H, H-8b), 1.78 (overlapping signals, 1H, H-6b), 1.73 (m, 3H, H-12), 1.36–1.38 ppm (m, 2H, H-7); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 172.7$ (s, C-1), 136.0 (d, C-10), 134.4 (d, C-4), 130.2 (d, C-5), 127.8 (d, C-9), 78.2 (d, C-11), 47.0 (t, C-2), 45.6 (d, C-3), 28.7 (t, C-7), 25.4 (t, C-6), 25.3 (t, C-8), 19.4 ppm (q, C-12); ^{15}N NMR (60.8 MHz, C_6D_6): $\delta = -53$ ppm; IR (KBr): $\tilde{\nu} = 3004$, 2936, 2915, 2855, 1698, 1657, 1641, 1431, 1374, 1307, 1263, 1199, 999, 809, 742, 698, 571 cm^{-1}; MS (EI): *m/z* (%): 175 (75) [M^+], 174 (100), 160 (44), 146 (16), 132 (35), 119 (10), 108 (15), 94 (44), 91 (31), 79 (30), 67 (25), 53 (37), 41 (40); HRMS (EI): *m/z*: calcd for $C_{12}H_{17}N$: 175.1361; found: 175.1360 [M^+]; elemental analysis calcd (%) for $C_{12}H_{17}N$ (175.27): C 82.24, H 9.78, N 7.99; found: C 82.30, H 9.65, N 8.06.

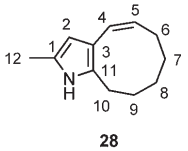


27

The major impurity in the sample (ca. 10 %) was identified as compound **27b**, the structure of which was unambiguously established: ^1H NMR (600 MHz, C_6D_6): $\delta = 5.36$ (overlapping signals, 1H, H-10), 5.30 (overlapping signals, 1H, H-5), 5.24 (overlapping signals, 1H, H-9), 4.97 (ddd, $J = 10.3$, 9.1, 1.7 Hz, 1H, H-4), 3.60 (m, 1H, H-11), 2.31 (overlapping signals, 1H, H-3), 2.25 (overlapping signals, 1H, H-8a), 2.12 (ddd, $J = 17.0$, 7.7, 0.5 Hz, 1H, H-2a), 1.79 (overlapping signals, 4H, H-2b, H-12), 1.74 (overlapping signals, 1H, H-7a), 1.73 (overlapping signals, 1H, H-8b), 1.70 (overlapping signals, 1H, H-6a), 1.59 (m, 1H, H-6b), 1.32 ppm (overlapping signals, 1H, H-7b); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 174.2$ (s, C-1), 134.9 (d, C-5), 131.5 (d, C-9), 131.4 (d, C-10), 125.9 (d, C-4), 81.6 (d, C-11), 50.2 (d, C-3), 43.2 (t, C-2), 34.6 (t, C-8), 33.5 (t, C-7), 26.7 (t, C-6), 20.2 ppm (q, C-12); ^{15}N NMR (60.8 MHz, C_6D_6): $\delta = -61$ ppm.

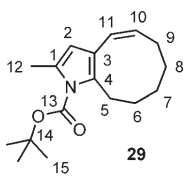

27b

Pyrrole 28: KH (360 mg, 8.98 mmol) was slowly added to 1,3-diaminopropane (22 mL) and the resulting mixture was stirred until the evolution of gas had ceased and a clear yellow solution had formed. A solution of compound **27**


28

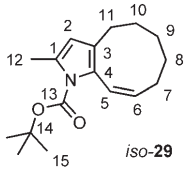
(790 mg, 4.51 mmol) in 1,3-diaminopropane (2 mL) was added and the resulting mixture was stirred at ambient temperature for 20 h. The mixture was then cooled to 0 °C before degassed H_2O (24 mL) was slowly introduced. Due to the exceptional sensitivity of the resulting pyrrole, a positive pressure of Ar was maintained during the extractive work up with Et_2O (5×15 mL) and brine (5 mL). The combined organic layers were dried (Na_2SO_4), the solvent was carefully evaporated, and the residue purified by short-path distillation (b.p. 60–65 °C, 1×10^{-3} mbar) to give pyrrole **28** as a pale yellow, highly air sensitive material which was used in the next step without unnecessary delay (510 mg, 65 %). ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 7.52 (br s, 1H, NH), 6.25 (d, J = 11.4 Hz, 1H, H-4), 5.62 (d, J = 2.6 Hz, 1H, H-2), 5.34 (dt, J = 11.4, 8.5 Hz, 1H, H-5), 2.82 (m, 2H, H-10), 2.33 (m, 2H, H-6), 2.16 (s, 3H, H-12), 1.71 (m, 2H, H-9), 1.63 (m, 2H, H-8), 1.61 ppm (m, 2H, H-7); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 127.8 (C-4), 127.0 (C-11), 126.2 (C-5), 124.6 (C-1), 118.3 (C-3), 110.7 (C-2), 30.4 (C-9), 30.0 (C-10), 29.1 (C-7), 28.7 (C-6), 24.3 (C-8), 12.6 ppm (C-12); IR (film): $\tilde{\nu}$ = 3460, 3370, 3004, 2923, 2849, 1640, 1592, 1504, 1475, 1452, 1388, 1267, 1116, 910, 805, 735, 646 cm^{-1}; MS (EI): m/z (%): 175 (100) [M^+], 160 (31), 146 (41), 132 (56), 120 (20), 107 (20), 94 (20); HRMS (EI): m/z: calcd for $C_{12}H_{17}N$: 175.1361; found: 175.1360 [M^+].

***N*-Boc-Pyrrole 29**: A suspension containing pyrrole **28** (510 mg, 2.91 mmol), molecular sieves (4 Å, 20 pellets), Boc_2O (1.27 g, 5.82 mmol) and DMAP (36 mg, 0.30 mmol) in MeCN (30 mL) was stirred at 50 °C for 5 h. The reaction was quenched at 0 °C with water (30 mL), the aqueous layer was extracted with Et_2O (4× 15 mL), and the combined organic phases were washed with brine before they were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue (pentanes/Et_2O 100:1) gave **29** as a pale yellow syrup (575 mg, 72 %). This product, which is ca. 80 % pure, was used as such in the next step, after which isomeric impurities could be conveniently separated. However, it is possible to obtain analytically pure samples by medium-pressure chromatography (Lobar) or preparative HPLC, which allowed **29** to be separated from compound *iso*-**29**, which constituted the major impurity.



29

Compound **29**: ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.22 (d, J = 10.9 Hz, 1H, H-11), 5.77 (dt, J = 10.9, 8.1 Hz, 1H, H-10), 5.65 (s, 1H, H-2), 2.73 (m, 2H, H-5), 2.36 (s, 3H, H-12), 2.08 (m, 2H, H-9), 1.66–1.47 (m, 6H), 1.60 ppm (s, 9H, H-15); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 150.8 (C-13), 134.8 (C-10), 132.7 (C-4), 130.6 (C-1), 125.1 (C-11), 121.6 (C-3), 111.6 (C-2), 83.6 (C-14), 29.93, 29.89, 28.3 (2×), 27.9, 27.2, 16.3 ppm (C-12); IR (film): $\tilde{\nu}$ = 3003, 2977, 2927, 2854, 1736, 1640, 1596, 1538, 1454, 1385, 1369, 1310, 1256, 1175, 1125, 1097, 852, 746 cm^{-1}; MS (EI): m/z (%): 275 (23) [M^+], 219 (76), 165 (13), 146 (11), 132 (15), 57 (100), 41 (18); HRMS (EI): m/z: calcd for $C_{17}H_{25}NO_2$: 275.1885; found: 275.1886 [M^+].

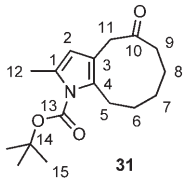


iso-**29**

iso-**29**: ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 6.34 (d, J = 10.5 Hz, 1H, H-5), 5.75 (s, 1H, H-2), 5.74 (dt, J = 10.5, 8.1 Hz, 1H, H-6), 2.36 (s, 3H, H-12), 2.35 (m, 2H, H-11), 2.01 (m, 2H, H-7), 1.58 (m, 2H, H-9), 1.54 (m, 2H, H-10), 1.54 (s, 9H, H-15), 1.45 ppm (m, 2H, H-8); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 150.5 (C-13), 134.0 (C-6), 131.0 (C-1), 127.6 (C-4), 125.8 (C-3), 124.7 (C-5), 113.7 (C-2), 83.3 (C-14), 29.8 (C-9), 29.2 (C-7), 28.7 (C-11), 28.2 (C-15), 27.5 (C-10), 27.0 (C-8), 16.2 ppm (C-12).

Ketones 30 and 31: A solution of BH_3 (1 M in THF, 4.15 mL, 4.15 mmol) was added to a cooled (−10 °C) solution of compound **29** (570 mg, 72 % pure, 2.07 mmol) in THF (23 mL) and the resulting mixture was stirred at that temperature for 4 h. Me_3N/THF (3 M in THF, 1.7 mL, 5.1 mmol), aq. NaOH (3 M, 1.7 mL, 5.1 mmol), H_2O_2 (27.8 % *w*/*w*, 1.35 mL, 12.25 mmol) were then successively added and stirring continued at 0 °C for 30 min. The reaction was quenched with aq. $Na_2S_2O_3$ (1 M, 3 mL), the THF was largely removed by distillation in vacuo (10 Torr), the remaining solution was diluted with water (20 mL), the aqueous phase was extracted with CH_2Cl_2 (4×15 mL), the combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated to a volume of ca. 30 mL total. Dess–Martin periodinane (860 mg, 2.03 mmol) was then added and the resulting mixture was stirred for 20 min at ambient temperature. For work up, the solution was successively washed with aq. $Na_2S_2O_3$ (1 M, 6 mL) and sat. aq. $NaHCO_3$ (2 mL), the aqueous layers were extracted with CH_2Cl_2 (4×10 mL), the combined organic phases were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (pentanes/Et_2O/Et_3N 100:10:1) to give ketone **30** as a colorless syrup (200 mg, 46 %) and ketone **31** as a colorless solid (80 mg, 18 %).

Ketone **30**: ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.26 (s, 1H), 3.26 (m, 2H), 2.78 (m, 2H), 2.31 (s, 3H), 1.79 (m, 2H), 1.67 (m, 2H), 1.63–1.55 (m, 2H), 1.61 (s, 9H), 1.42 ppm (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 199.8, 150.4, 139.0, 130.8, 127.2, 110.7, 85.3, 41.0, 30.9, 29.5, 28.1, 27.2, 25.4, 25.0, 15.7 ppm; IR (KBr): $\tilde{\nu}$ = 3122, 2975, 2937, 2859, 1744, 1640, 1525, 1469, 1388, 1371, 1290, 1134, 843, 816, 740, 583 cm^{-1}; MS (EI): m/z (%): 291 (18) [M^+], 235 (26), 191 (16), 179 (15), 57 (100), 41 (14); HRMS (EI): m/z: calcd for $C_{17}H_{25}NO_3$: 291.1834; found: 291.1838 [M^+].



31

Ketone **31**: ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 5.79 (q, J = 1 Hz, 1H, H-2), 3.36 (br s, 2H, H-11), 2.94 (t, J = 6.4 Hz, 2H, H-5), 2.39 (m, 2H, H-9), 2.33 (d, J = 1 Hz, 3H, H-12), 1.70 (m, 2H, H-8), 1.62 (m, 2H, H-6), 1.57 (s, 9H, H-15), 1.07 ppm (m, 2H, H-7); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 211.6 (C-10), 150.5 (C-13), 131.7 (C-1), 130.6 (C-4), 117.0 (C-3), 113.0 (C-2), 83.8 (C-14), 44.1 (C-9), 40.9 (C-11), 28.1 (C-15), 27.1 (C-6), 24.8 (C-7), 24.2 (C-5), 23.7 (C-8), 16.5 ppm (C-12)

Compound 32: Solid Ph_3P=$CHCH_2CH_2CH_3$ (590 mg, 1.85 mmol) was added to a solution of ketone **30** (265 mg, 0.91 mmol) in toluene (9.1 mL) and the resulting mixture was heated under reflux for 90 min. After reaching ambient temperature, the solvent was evaporated and the crude product was purified by flash chromatography (pentanes/Et_2O 50:1) to give **32** as a colorless syrup (226 mg, 75 %).

(*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (s, 1H), 5.36 (t, J = 7.1 Hz, 1H), 2.99 (t, J = 5.8 Hz, 2H), 2.35 (s, 3H), 2.38–2.33 (m, 2H), 2.10 (q, J = 7.3 Hz, 2H), 1.58 (s, 9H), [1.62–1.49 (m), 1.47–1.37 (m), 1.28–1.19 (m), 10H], 0.94 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 135.0, 130.3, 130.2, 129.8, 129.4, 111.9, 83.0, 30.4, 29.3, 28.1, 27.5, 26.7, 24.4, 23.9, 23.7, 22.9, 16.3, 14.0 ppm.

(*Z*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.58 (s, 1H), 5.44 (t, J = 7.1 Hz, 1H), 2.82 (t, J = 6.1 Hz, 2H), 2.37 (s, 3H), 2.22 (m, 2H), 1.88 (q, J = 7.3 Hz, 2H), 1.60 (s, 9H), [1.62–1.53 (m), 1.51–1.36 (m), 1.33 (q, J = 7.3 Hz, 2H), 1.29–1.20 (m), 8H], 0.85 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 135.8, 130.5, 130.1, 129.8, 124.7, 111.8, 82.9, 36.7, 31.3, 28.1, 27.0, 26.5, 24.7, 24.2, 24.1, 22.8, 16.5, 13.9 ppm; IR (*E*/*Z* mixture, film): $\tilde{\nu}$ = 3090, 2957, 2928, 2857, 1737, 1596, 1540, 1456, 1385, 1369, 1326, 1258, 1173, 1124, 852, 805, 772 cm^{-1}; MS (EI): m/z (%): 331 (40) [M^+], 275 (81), 246 (28), 232 (20), 218 (18), 202 (24), 188 (19), 174 (21), 159 (20), 134 (11), 57 (100), 41 (20); HRMS (EI): m/z: calcd for $C_{21}H_{33}NO_2$: 331.2511; found: 331.2514 [M^+].

Compound 33: A degassed solution of compound **32** (80 mg, 0.24 mmol) and [(cod)(pyridine)Ir(PCy_3)]PF_6 (19.4 mg, 0.024 mmol) in CH_2Cl_2 (5 mL) was stirred under an atmosphere of H_2 (1 bar) for 1 h. The mixture was then filtered through a short pad of silica gel which was carefully rinsed with CH_2Cl_2, the combined filtrates were evaporated and the residue was purified by flash chromatography (pentanes/Et_2O 50:1) to give **33** as a colorless oil (72 mg, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.66 (s, 1H), 3.18 (m, 1H), 2.69–2.51 (m, 2H), 2.36 (s, 3H), 1.82–1.70 (m, 1H), 1.59 (s, 9H), 1.62–1.17 (m, 14H), 1.13–1.10 (m, 1H), 0.87 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 131.5, 130.6, 126.8, 109.1, 82.7, 36.04, 36.03, 35.1, 30.4, 28.1, 27.5, 26.8, 25.8, 24.8, 24.3, 22.9, 16.7, 14.1 ppm; IR (film): $\tilde{\nu}$ = 2955, 2927, 2855, 1735, 1603, 1543, 1457, 1385, 1369, 1322, 1257, 1174, 1126, 853, 804, 772 cm^{-1}; MS (EI): m/z (%): 333 (22) [M^+], 277 (100), 233 (12), 193 (28), 178 (29), 134 (16), 120 (11), 57 (76), 41 (15); HRMS (EI): m/z: calcd for $C_{21}H_{35}NO_2$: 333.2668; found: 333.2663 [M^+].

Compound 34: A solution of cerium ammonium nitrate (CAN, 460 mg, 0.84 mmol) in degassed H_2O (2.1 mL) was added to a solution of compound **33** (70 mg, 0.21 mmol) in $CHCl_3$ (2.1 mL) and DME (2.1 mL) and the resulting mixture was vigorously stirred for 30 min. After separation of the two phases, the aqueous layer was extracted with Et_2O (3×2 mL), the combined organic phases were successively washed with sat. aq. $NaHCO_3$ (0.5 mL) and brine (3×1 mL) before they were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (pentanes/Et_2O 20:1) afforded aldehyde **34** (44 mg, 60%) and alcohol **35** (14 mg, 25%) as colorless syrups each.

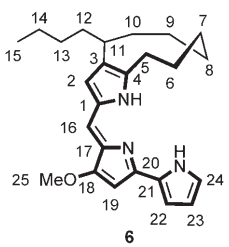
Compound **34**: ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.80 (s, 1H), 6.87 (s, 1H), 3.13 (m, 1H), 2.76–2.61 (m, 2H), 1.95–1.83 (m, 1H), 1.72–1.16 (m, 14H), 1.62 (s, 9H), 1.06–0.93 (m, 1H), 0.87 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 180.1, 149.9, 141.4, 134.3, 129.4, 120.1, 85.7, 36.8, 36.4, 35.5, 30.7, 28.0, 27.4, 27.2, 26.2, 25.0, 24.1, 23.2, 14.3 ppm; IR (film): $\tilde{\nu}$ = 2958, 2928, 2857, 2707, 1747, 1668, 1572, 1480, 1394, 1370, 1307, 1167, 1130, 848 cm^{-1}; MS (EI): m/z (%): 347 (9) [M^+], 247 (55), 218 (11), 190 (69), 162 (16), 57 (100), 41 (21); HRMS (EI): m/z: calcd for $C_{21}H_{33}NO_3$: 347.2460; found: 347.2466 [M^+].

Compound **35**: ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.90 (brs, 1H), 9.34 (s, 1H), 6.69 (d, J = 2.8 Hz, 1H), 5.07 (dt, J = 10.1, 3.5 Hz, 1H), 2.93 (d, J = 3.1 Hz, 1H), 2.78 (m, 1H), 2.03–1.85 (m, 2H), 1.76–1.64 (m, 2H), [1.63–1.48 (m), 1.48–1.36 (m), 1.36–1.16 (m), 1.11–0.99 (m) 12H], 0.87 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 178.7, 141.2, 131.1, 128.5, 123.1, 69.0, 39.2, 38.4, 37.7, 33.9, 30.4, 26.2, 26.1, 23.2, 22.9, 14.2 ppm; IR (film): $\tilde{\nu}$ = 3450, 3260, 2922, 2854, 1635, 1566, 1465, 1421, 1377, 1260, 1146, 1127, 1031, 836, 786 cm^{-1}; MS (EI): m/z (%): 263 (100) [M^+], 245 (15), 234 (26), 220 (26), 206 (100), 192 (21), 178 (16), 164 (24), 150 (27), 136 (27), 118 (22), 94 (14), 80 (27), 69 (17), 57 (31), 41 (29).

Compound 37: A solution containing aldehyde **34** (19 mg, 0.055 mmol) and lactam **36** (24.8 mg, 0.11 mmol) in DMSO (550 μL) was treated with degassed aq. NaOH (2 M, 200 μL) and the resulting solution was stirred overnight at 60 °C. For work up, the mixture was partitioned between water and CH_2Cl_2, the combined organic layers were washed with brine (1 mL), dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (pentanes/Et_2O 4:1 → 1:1 → 0:1) gave **37** as a yellow-brown solid (13 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.79 (brs, 1H), 10.16 (brs, 1H), 6.30 (s, 1H), 6.17 (d, J = 2.8 Hz, 1H), 5.06 (d, J = 1.5 Hz, 1H), 3.87 (s, 3H), 3.01–2.93 (m, 1H), 2.72–2.62 (m, 2H), 2.01–1.88 (m, 1H), [1.70–1.48 (m), 1.48–1.18 (m), 1.18–1.04 (m), 15H], 0.86 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 168.0, 138.5, 126.2, 124.7, 122.4, 115.6, 102.9, 89.8, 58.1, 37.0, 36.8, 35.9, 30.4, 27.7, 27.2, 26.6 (2C), 23.9, 22.9, 14.1 ppm; IR (KBr): $\tilde{\nu}$ = 3342, 2918, 2852, 1668, 1592, 1579, 1362, 1224, 782 cm^{-1}; MS (EI): m/z (%): 342 (100) [M^+], 299 (22), 285 (25), 243 (21), 229 (11).

Triflate 38: Triflic anhydride (60 μL, 0.357 mmol) was added to a solution of **37** (100 mg, 0.292 mmol) in CH_2Cl_2 (14.5 mL) at 0 °C and the resulting mixture was stirred at that temperature for 1 h. A standard extractive work up followed by flash chromatography (basic aluminium oxide, pentanes/Et_2O 10:1 → 0:1) gave triflate **38** as a yellow syrup (100 mg, 72%) which was immediately used in the next step without further characterization.

Butylcycloheptylprodigiosin 6: A degassed solution of triflate **38** (14.0 mg, 0.0295 mmol), boronic acid **39** (18.7 mg, 0.0886 mmol), [Pd(PPh$_3$)$_4$] (2.8 mg, 0.00242 mmol) and LiCl (3.8 mg, 0.0897 mmol) in DME (0.6 mL) was warmed to 80 °C before degassed aq. Na_2CO_3 (2 M, 88.5 μL) was added. After stirring at that temperature for 1 h, the mixture was partitioned between water and ethyl acetate, the combined organic layers were treated with aq. disodium ethylenediamine tetraacetate (Na_2·EDTA, 0.05 M, 50 μL) before they were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (basic aluminium oxide; pentanes/Et_2O 50:1 → 2:1) to give **6** as a dark red solid (7.0 mg, 61%). ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 6.82 (s, 1H, H-16), 6.72 (brs, 1H, H-24), 6.69 (dd, J = 3.6, 1.3 Hz, 1H, H-22), 6.34 (s, 1H, H-2), 6.20 (dd, J = 3.6, 2.6 Hz, 1H, H-23), 6.08 (s, 1H, H-19), 3.97 (s, 3H, H-25), 2.59 (m, 1H, H-11), 2.33 (br, 2H, H-5), 1.68 (m, 1H, H-6a), 1.62–1.50 (m, 4H, H-7a, 10a, 12), 1.41–1.15 (m, 9H, H-7b, 8, 9a, 10b, 13, 14), 1.00 (m, 1H, H-6b), 0.85 (t, J = 7.2 Hz, 3H, H-15), 0.83 ppm (m, 1H, H-9b); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 169.2 (s, C-18), 159.6 (s, C-20 or C-17), 142.9 (s, C-4), 139.2 (s, C-17 or C-20), 129.1 (s, C-21), 128.5 (s, C-1), 128.2 (s, C-3), 122.3 (d, C-24), 118.6 (d, C-2), 116.2 (d, C-16), 112.6 (d, C-22), 110.6 (d, C-23), 95.7 (d, C-19), 58.8 (q, C-25), 38.0 (t, C-10), 37.1 (t, C-12), 36.1 (d, C-11), 30.6 (t, C-13), 28.1 (t, C-8), 28.0 (t, C-7), 27.7 (t, C-6), 27.6 (t, C-5), 23.3 (t, C-9), 23.2 (t, C-14), 14.2 ppm (q, C-15); ^{15}N NMR (60.8 MHz, CD_2Cl_2): δ = −226.6, −153.4 ppm; IR (film): $\tilde{\nu}$ = 3322, 3103, 2921, 2852, 1618, 1577, 1552, 1449, 1333, 1285, 1148, 1116, 1057, 954, 890, 767, 728 cm^{-1}; MS (EI): m/z (%): 391 (100) [M^+], 334 (26); HRMS (EI): m/z: calcd for $C_{25}H_{33}N_3O$: 391.26236; found: 391.26242 [M^+]. Treatment of the product with sat. HCl in Et_2O followed by evaporation of the solvent afforded the corresponding hydrochloride (**6**·HCl) which showed the following spectral properties: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.76 (s, 1H), 12.57 (s, 1H), 12.56 (s, 1H), 7.19 (m, 1H), 6.95 (s, 1H), 6.89 (m, 1H), 6.60 (d, J = 2.6 Hz, 1H), 6.32 (dt, J = 3.8, 2.3 Hz, 1H), 6.06 (d, J = 1.9 Hz, 1H), 3.99 (s, 3H), 3.32 (ddd, J = 14.2, 8.2, 2.5 Hz, 1H), 2.74 (ddd, J = 14.2, 9.8, 2.6 Hz, 1H), 2.70 (m, 1H), 2.11 (m, 1H), 1.75–1.09 (m, 15H), 0.86 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 126.8, 126.5, 126.5, 116.8, 116.0, 92.6, 58.5, 36.8, 36.5, 35.8, 30.0, 27.1, 26.9, 26.7, 26.4, 23.6, 22.6, 14.0 ppm.



6

Compound 41: Prepared as described above from triflate **38** (18.0 mg, 0.0379 mmol) and boronic acid **40** (13.1 mg, 0.117 mmol); isolated in form of its hydrochloride salt as dark red solid (13.1 mg, 81%). ^{1}H NMR (600 MHz, [D$_8$]-THF): δ = 14.97 (brs, 1H), 14.53 (brs, 1H), 8.72 (d, J = 3.6 Hz, 1H), 7.77 (d, J = 1.4 Hz, 1H), 7.26 (s, 1H), 6.90 (s, 1H), 6.69 (dd, J = 3.6, 1.5 Hz, 1H), 6.47 (s, 1H), 4.06 (s, 3H), 3.45 (ddd, J = 13.8, 8.1, 2.5 Hz, 1H), 2.80 (m, 1H), 2.78 (m, 1H), 2.10 (m, 1H), 1.73 (m, 1H), 1.80–1.15 (m, 14H), 0.88 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, [D$_8$]-THF): δ = 166.8, 158.2, 147.2, 146.5, 145.1, 135.2, 129.9, 128.2, 121.3, 120.0, 118.9, 114.3, 94.1, 59.4, 37.8, 37.5, 37.0, 31.1, 28.2, 27.5, 27.4, 27.3, 24.8, 23.7, 14.4 ppm; IR (film): $\tilde{\nu}$ = 3255, 3090, 2920, 2851, 1620, 1571, 1542, 1417, 1334, 1283, 1231, 1156, 1089, 989, 944, 836, 775, 744 cm^{-1}; MS (EI): m/z (%): 392 (100) [M^+−HCl], 349 (13), 335 (42), 307 (9); HRMS of the free base (EI): m/z: calcd for $C_{25}H_{32}N_2O_2$: 392.24638; found: 392.24650 [M^+].

Compound 43: Prepared as described above from triflate **38** (10.0 mg, 0.0211 mmol) and boronic acid **42** (8.1 mg, 0.0633 mmol); dark red solid (7.0 mg, 81%). ^{1}H NMR (400 MHz, [D$_8$]-THF): δ = 7.51 (dd, J = 3.7, 1.1 Hz, 1H), 7.44 (dd, J = 5.1, 1.1 Hz, 1H), 7.07 (dd, J = 5.1, 3.7 Hz, 1H), 6.75 (s, 1H), 6.37 (brs, 1H), 6.07 (s, 1H), 3.87 (s, 3H), 2.84 (ddd, J = 14.8, 7.8, 2.7 Hz, 1H), 2.74 (m, 1H), 2.72 (m, 1H), 1.99 (m, 1H), 1.75–1.15 (m, 15H), 0.87 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, [D$_8$]-THF): δ = 169.2, 160.6, 142.3, 141.9, 141.8, 130.5, 128.5, 128.42, 128.38, 127.6, 118.3, 117.7, 95.2, 58.6, 38.3, 37.7, 37.1, 31.3, 28.5, 28.4, 28.2, 27.9, 24.7, 23.7, 14.5 ppm; IR (film): $\tilde{\nu}$ = 3279, 3010, 2921, 2851, 1613, 1547, 1405, 1365, 1330, 1274, 1203, 1144, 1107, 1013, 890, 703 cm^{-1}; MS (EI): m/z (%): 408 (100) [M^+], 365 (9), 351 (37); HRMS (EI): m/z: calcd for $C_{25}H_{32}N_2OS$: 408.22354; found: 408.22358 [M^+].

Compound 45: Prepared as described above from triflate **38** (12.0 mg, 0.0253 mmol) and boronic acid **44** (13.8 mg, 0.0758 mmol); dark red solid (5.1 mg, 44%). ^{1}H NMR (400 MHz, [D$_8$]-THF): δ = 7.67 (d, J = 1.8 Hz, 1H), 7.50 (dd, J = 8.3, 2.0 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.72 (s, 1H), 6.35 (brs, 1H), 6.14 (s, 1H), 3.88 (d, J = 5.3 Hz, 6H), 3.83 (s, 3H), 2.85 (m, 1H), 2.80–2.67 (m, 2H), 2.04–1.89 (m, 1H), 1.76–1.14 (m, 15H), 0.87 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, [D$_8$]-THF): δ = 169.3, 165.8, 152.3, 150.6, 142.3, 141.2, 130.7, 129.5, 128.1, 121.0, 117.6, 117.1, 112.3, 110.9, 95.0, 58.5, 56.1, 55.9, 38.2, 37.7, 37.1, 31.3, 28.5, 28.3, 28.2, 27.8, 24.7, 23.7, 14.5 ppm; IR (film): $\tilde{\nu}$ = 3311, 2919, 2849, 1619, 1585, 1567, 1551, 1515, 1252, 1234, 1141, 1107, 1021, 941, 813 cm^{-1}; MS (EI): m/z (%): 462 (100) [M^+], 405 (35); HRMS (EI): m/z: calcd for $C_{29}H_{38}N_2O_3$: 462.28824; found: 462.28828 [M^+].

Compound 47: Prepared as described above from triflate **38** (11.0 mg, 0.0232 mmol) and boronic acid **46** (18.2 mg, 0.0697 mmol); dark red solid

(9.0 mg, 72%). ^{1}H NMR (400 MHz, [D$_8$]-THF): δ = 8.07 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 8.3, 7.3 Hz, 1H), 7.18 (dd, J = 7.8, 7.3 Hz, 1H), 6.92 (d, J = 0.5 Hz, 1H), 6.85 (s, 1H), 6.42 (br s, 1H), 5.94 (s, 1H), 3.88 (s, 3H), 2.83 (ddd, J = 14.7, 7.8, 2.5 Hz, 1H), 2.73 (m, 1H), 2.66 (ddd, J = 14.7, 10.1, 2.5 Hz, 1H), 1.96 (m, 1H), 1.75–1.10 (m, 15H), 1.42 (s, 9H), 0.87 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, [D$_8$]-THF): δ = 168.0, 159.9, 151.2, 143.0, 141.1, 139.3, 138.0, 130.4, 130.0, 128.9, 125.5, 123.4, 121.7, 118.9 (2 C), 115.0, 111.2, 98.2, 84.0, 58.6, 38.4, 37.7, 37.1, 31.3, 28.32, 28.28, 28.25, 28.17, 27.9, 24.5, 23.7, 14.5 ppm; IR (film): $\tilde{\nu}$ = 3282, 2923, 2853, 1732, 1618, 1570, 1548, 1393, 1367, 1323, 1144, 959, 744 cm^{-1}; MS (EI): m/z (%): 541 (24) [M^+], 441 (100) [M^+ −Boc], 384 (19); HRMS (EI): m/z: calcd for $C_{34}H_{43}N_3O_3$: 541.33044; found: 541.33066 [M^+].

DNA-cleavage assay: Purified scDNA (ca. 300 ng) [ΦX174 RF1 DNA, purchased from MBI Fermentas GmbH, St. Leon-Rot, Germany; the EDTA contained in the commercial sample was removed according to the Qiaex II protocol for desalting and concentrating DNA by using a Qiaex II Gel Extraction Kit] was incubated at 37 °C with the respective alkaloid derivative (30 μM, final concentration) and Cu(OAc)$_2$ (30 μM) in a solution containing MOPS buffer (10 mM, pH 7.4), aq. NaCl (75 mM) and MeCN (10%, v/v) (total volume 20 μL) for 60 min. The mixture was quenched with loading buffer (BioRad laboratories) and the DNA resolved by electrophoresis (Powerpac 300, BioRad) (85 V, 1 h) on a 0.8% agarose gel (containing ethidium bromide) in boronic acid buffer (BioRad). The bands detected by UV were analyzed and processed using the Bio Doc II software (Biometra).

X-ray crystal structure analysis of acetal 14: $C_{11}H_{20}O_2$, M_r = 184.27 g mol^{-1}, colorless block, crystal size 0.43 × 0.17 × 0.10 mm^3, monoclinic, space group $P2_1/c$, a = 5.59620(10), b = 11.8764(2), c = 15.3886(3) Å, β = 94.0740(10)°, V = 1020.18(3) Å^3, T = 100 K, Z = 4, ρ_{calcd} = 1.200 g cm^3, λ = 0.71073 Å, $\mu(Mo_{K\alpha})$ = 0.080 mm^{-1}, multi-scan absorption correction, Nonius KappaCCD diffractometer, 4.16 < θ < 33.13, 21600 measured reflections, 3890 independent reflections, 3255 reflections with $I > 2\sigma(I)$. Structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.039 [$I > 2\sigma(I)$], wR_2 = 0.106, 118 parameters, H atoms riding, S = 0.966, residual electron density +0.5/−0.3 e Å^{-3}.

X-ray crystal structure analysis of dibromide 15: $C_{11}H_{18}Br_2O_2$, M_r = 342.07 g mol^{-1}, colorless plate, crystal size 0.20 × 0.12 × 0.03 mm^3, monoclinic, space group $C2/c$, a = 31.4053(4), b = 5.78380(10), c = 16.5219(3) Å, β = 118.9740(10)°, V = 2625.45(7) Å^3, T = 100 K, Z = 8, ρ_{calcd} = 1.731 g cm^3, λ = 0.71073 Å, $\mu(Mo_{K\alpha})$ = 6.156 mm^{-1}, Gaussian absorption correction (T_{min} = 0.29, T_{max} = 0.83), Nonius KappaCCD diffractometer, 2.47 < θ < 33.03, 9492 measured reflections, 4716 independent reflections, 2865 reflections with $I > 2\sigma(I)$, structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.070 [$I > 2\sigma(I)$], wR_2 = 0.252, 136 parameters, H atoms riding, S = 1.393, residual electron density +1.0/−1.4 e Å^{-3}.

X-ray crystal structure analysis of *E*-alkene 16: $C_{11}H_{17}BrO_2$, M_r = 261.16 g mol^{-1}, colorless plate, crystal size 0.20 × 0.20 × 0.10 mm^3, monoclinic, space group $P2_1/n$, a = 7.14430(10), b = 13.4880(2), c = 11.3576(2) Å, β = 96.7760(10)°, V = 1086.80(3) Å^3, T = 100 K, Z = 4, ρ_{calcd} = 1.596 g cm^3, λ = 0.71073 Å, $\mu(Mo_{K\alpha})$ = 3.755 mm^{-1}, Gaussian absorption correction (T_{min} = 0.52, T_{max} = 0.71), Nonius KappaCCD diffractometer, 2.35 < θ < 33.17, 11821 measured reflections, 4126 independent reflections, 3359 reflections with $I > 2\sigma(I)$, structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.035 [$I > 2\sigma(I)$], wR_2 = 0.089, 127 parameters, H atoms riding, S = 1.025, residual electron density +0.6/−1.0 e Å^{-3}.

X-ray crystal structure analysis of cyclononadienol 20: $C_9H_{14}O$, M_r = 138.20 g mol^{-1}, colorless plate, crystal size 0.32 × 0.20 × 0.02 mm^3, monoclinic, space group $P2_1/c$, a = 5.1770(3), b = 23.7974(12), c = 12.8564(7) Å, β = 90.638(2)°, V = 1583.80(15) Å^3, T = 100 K, Z = 8, ρ_{calcd} = 1.159 g cm^3, λ = 0.71073 Å, $\mu(Mo_{K\alpha})$ = 0.073 mm^{-1}, Gaussian absorption correction (T_{min} = 0.98, T_{max} = 1.00), Nonius KappaCCD diffractometer, 2.33 < θ < 22.49, 9672 measured reflections, 2068 independent reflections, 1512 reflections with $I > 2\sigma(I)$, structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.046 [$I > 2\sigma(I)$], wR_2 = 0.106, 189 parameters, H atoms riding, S = 1.101, residual electron density +0.2/−0.2 e Å^{-3}.

X-ray crystal structure analysis of acetoacetate 22: $C_{14}H_{20}O_3$, M_r = 236.30 g mol^{-1}, colorless plate, crystal size 0.28 × 0.07 × 0.01 mm^3, monoclinic, space group $C2/c$, a = 30.7682(8), b = 5.1307(2), c = 19.1813(9) Å, β = 119.021(2)°, V = 2647.81(18) Å^3, T = 100 K, Z = 8, ρ_{calcd} = 1.186 g cm^3, λ = 0.71073 Å, $\mu(Mo_{K\alpha})$ = 0.082 mm^{-1}, Nonius KappaCCD diffractometer, 1.51 < θ < 23.81, 4473 measured reflections, 2004 independent reflections, 1378 reflections with $I > 2\sigma(I)$, structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.064 [$I > 2\sigma(I)$], wR_2 = 0.222, 154 parameters, H atoms riding, S = 1.103, residual electron density +0.6/−0.8 e Å^{-3}.

X-ray crystal structure analysis of pyrrole 30: $C_{17}H_{25}NO_3$, M_r = 291.38 g mol^{-1}, colorless block, crystal size 0.22 × 0.04 × 0.04 mm^3, monoclinic, space group $P2_1/c$, a = 14.7000(3), b = 5.83620(10), c = 19.1666(4) Å, β = 107.0300(10)°, V = 1572.24(5) Å^3, T = 100 K, Z = 4, ρ_{calcd} = 1.231 g cm^3, λ = 0.71073 Å, $\mu(Mo_{K\alpha})$ = 0.083 mm^{-1}, Nonius KappaCCD diffractometer, 2.99 < θ < 30.03, 19542 measured reflections, 4593 independent reflections, 2970 reflections with $I > 2\sigma(I)$, structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.103 [$I > 2\sigma(I)$], wR_2 = 0.184, 194 parameters, H atoms riding, S = 1.106, residual electron density +0.6/−0.3 e Å^{-3}.

X-ray crystal structure analysis of the pyrrole 31: $C_{17}H_{25}NO_3$, M_r = 291.38 g mol^{-1}, colorless block, crystal size 0.11 × 0.07 × 0.04 mm^3, monoclinic, space group $P2_1/c$, a = 12.4758(3), b = 9.6933(2), c = 14.4196(3) Å, β = 113.032(1)°, V = 1604.78(6) Å^3, T = 100 K, Z = 4, ρ_{calcd} = 1.206 g cm^3, λ = 0.71073 Å, $\mu(Mo_{K\alpha})$ = 0.082 mm^{-1}, multi-scan absorption correction, Nonius KappaCCD diffractometer, 3.07 < θ < 31.50, 24306 measured reflections, 5334 independent reflections, 4388 reflections with $I > 2\sigma(I)$, structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.043 [$I > 2\sigma(I)$], wR_2 = 0.115, 202 parameters, H atoms riding, S = 1.020, residual electron density +0.4/−0.3 e Å^{-3}.

CCDC-617608–617615 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif/.

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