Flexible Synthesis of Metacycloprodigiosin and Functional Derivatives Thereof

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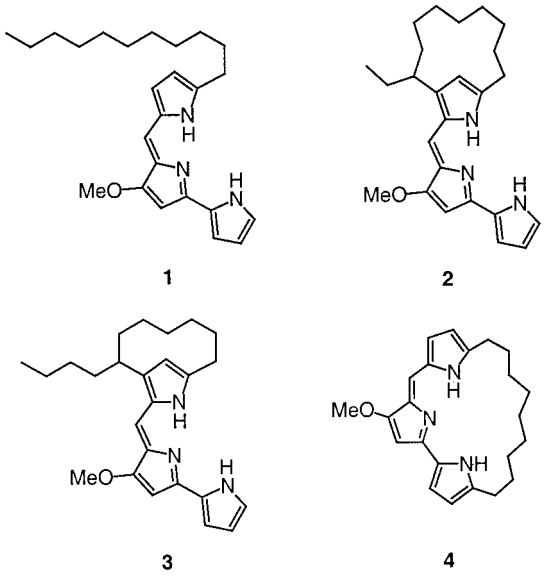
A conceptually new approach to *m*-pyrrolophane derivatives is outlined providing ready access to compound **23** which can be elaborated into the immunosuppressive alkaloid metacycloprodigiosin **2** according to literature procedures. The key steps of this sequence involve a palladium-catalyzed macrocyclization reaction of vinyl epoxide **10**, the conversion of the α-pyrone derivative **14** into the pyrrole targets, and the attachment of the side chain via a Wittig (or Peterson) olefination followed by hydrogenation of the alkene formed over Crabtree's catalyst. The flexibility of this route is demonstrated by the synthesis of several analogues of the parent compound **23** which may help to assess the structure/activity profile of the prodigiosin family of natural products in more detail. The unusual pyrone structure **14** used to encode the *meta*-bridged pyrrolophane units was characterized by X-ray crystallography.

Introduction

Recent reports on the pronounced immunosuppressive activity of prodigiosin alkaloids have led to strongly renewed interest in this well-known class of natural products, particularly because their biochemical mechanism of action is distinctly different from that of cyclosporin A and FK 506.[1,2] Most studies are dealing with undecylprodigiosin (prodigiosin 25-C) **1** as the most accessible member of this family,[3,4] although preliminary data indicate that its cyclic analogues metacycloprodigiosin **2** and streptorubin B **3** show similar potency.[5]

Intrigued by this pharmacological perspective, we have embarked in a detailed study of compounds of this type. As part of this program, the first total synthesis of the macrocyclic derivative nonylprodigiosin **4** via an intrinsically modular metathesis approach was reported,[6] as well as a convenient approach to compounds **2** and **3** based on a conceptually new, $PtCl_2$-catalyzed pyrrole synthesis.[7,8] Although the latter method is highly optimized, delivering the natural products in excellent overall yield in a few steps only, it is less adequate for the formation of functionalized analogues thereof. We now describe a complementary approach to metacycloprodigisin **2** which forms its core **5** by a palladium-catalyzed macrocylization reaction and encodes the pyrrole ring in a keto-pyrone entity. This unusual strategy can be used for a synthesis-driven mapping of the structure/activity relationship of **2** because it provides access to various metacycloprodigiosin analogues bearing polar substituents on the macrocyclic part and allows systematic variations of the side chain.



Results and Discussion

It is well established in the literature that prodigiosin derivatives can be conveniently formed by condensation

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

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

(3) Compound **1** is available e. g. by fermentation of *Streptomyces hiroshimensis*, cf. Harashima, K.; Tsuchida, N.; Tanaka, T.; Nagatsu, J. *Agric. Biol. Chem.* **1967**, *31*, 481.

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

(5) (a) Magae, J.; Miller, M.; Nagai, K.; Shearer, G. M. *J. Antibiot.* **1996**, *49*, 86. (b) Abe, F.; Morimoto, M.; Shibuya, K.; Yamazaki, M.; Nishigori, T.; Saito, S.; Shimada, N. Jpn. Kokai Tokkyo Koho JP 02,250,828 [90,250,828], Oct 8, 1990. *Chem. Abstr.* **1990**, *114*: 108967g.

(6) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275.

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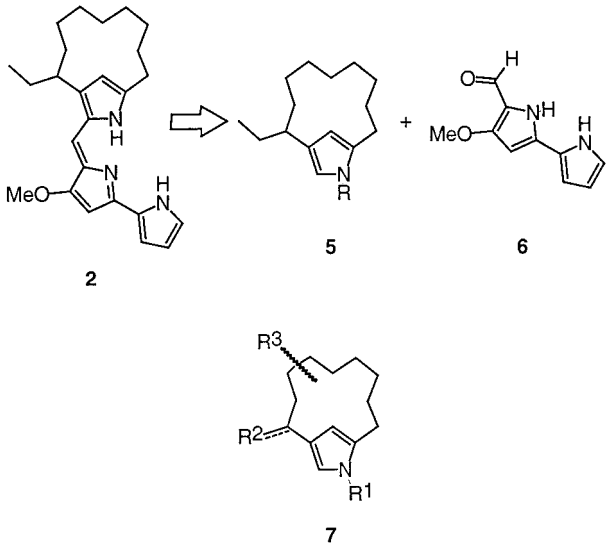
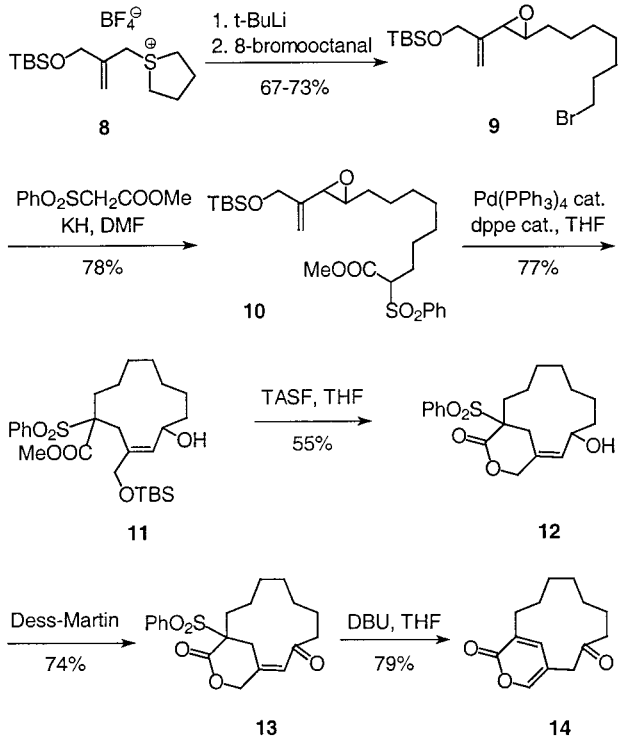
Scheme 1



Scheme 2



of an appropriate pyrrole segment (i.e., **5** for metacycloprodigiosin) with aldehyde **6** or analogues thereof (Scheme 1).[8,9] Early studies have outlined productive routes to the latter and have described numerous modifications of the parent pyrrolylpyrromethene chromophore by introducing different N-substituents, by replacing the pyrrole units with other heterocycles, or by changing the substitution pattern on the individual aromatic rings.[10] In contrast, however, variations of the macrocyclic core are scarce since a general entry into compounds of this type is missing.

Summarized in the following is a flexible approach to *meta*-pyrrolophane derivatives of type **7** bearing substituents of different polarity on the macrocyclic perimeter. The initial steps (Scheme 2) closely follow our route to the antitumor alkaloid roseophilin outlined recently.[11] In this study, we have identified sulfonium salt **8**[12] as a valuable building block for heterocycle synthesis via transition metal-catalyzed C−C-bond formations.[11,13] Specifically, deprotonation of **8** with *tert*-BuLi followed by trapping of the sulfur ylide[14] thus formed with 8-bromooctanal affords vinylepoxide **9**, which can be alkylated at its bromine terminus with the potassium salt of methyl (phenylsulfonyl)acetate. Exposure of the resulting product **10** to catalytic amounts of $Pd(PPh_3)_4$ and dppe (dppe = bis(diphenylphosphino)ethane) under high dilution conditions delivers the desired 12-membered ring **11** via a π-allylpalladium intermediate formed upon regioselective activation of the vinylepoxide group.[15] Compound **11** is obtained as a mixture of diastereoisomers;[16] however, it is not necessary to separate the individual compounds since all of them converge into the final *meta*-pyrrolophane target. Cleavage of the silyl ether then effects a lactonization of the primary hydroxyl group with the adjacent ester. This seemingly trivial step turned out to be somewhat delicate and was best achieved by using TASF (= tris(dimethylamino)sulfonium difluorotrimethylsilicate) in dilute THF solution. Subsequent oxidation of the secondary OH group of **12** by means of Dess−Martin periodinane as the preferred reagent provides ketone **13** in 74% isolated yield.[17]

Exposure of compound **13** to DBU in refluxing THF converts the saturated lactone into α-pyrone **14** by elimination of the sulfone moiety and concomitant shift of the exocyclic double bond into the ring. The outcome

(7) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305.

(8) For previous synthetic studies on metacycloprodigiosin, see: (a) Wasserman, H. H.; Rodgers, G. C.; Keith, D. D. *J. Am. Chem. Soc.* **1969**, *91*, 1263. (b) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *J. Am. Chem. Soc.* **1969**, *91*, 1264. (c) Wasserman, H. H.; Keith, D. D.; Rodgers, G. C. *Tetrahedron* **1976**, *32*, 1855. (d) Wasserman, H. H.; Gosselink, E.; Keith, D. D.; Nadelson, J.; Sykes, R. J. *Tetrahedron* **1976**, *32*, 1863. (e) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *Tetrahedron* **1976**, *32*, 1867.

(9) For previous syntheses of other prodigiosins derivatives, see inter alia: (a) Hearn, W. R.; Elson, M. K.; Williams, R. H.; Medina-Castro, J. *J. Org. Chem.* **1970**, *35*, 142. (b) Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, 1725. (c) Rapoport, H.; Holden, K. G. *J. Am. Chem. Soc.* **1962**, *84*, 635. (d) Boger, D. L.; Patel, M. *Tetrahedron Lett.* **1987**, *28*, 2499. (e) Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405.

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

(11) (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1997**, *119*, 2944. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (c) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361.

(12) A large scale preparation is described in the Supporting Information.

(13) For an application of this building block to a furan synthesis, see: Fürstner, A.; Gastner, T. *Synlett* **1999**, 29.

(14) (a) *tert*-BuLi was recommended as the deprotonating agent of choice, cf.: LaRochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem.* **1971**, *36*, 1126. (b) Review: Trost, B. M.; Melvin, L. S. *Sulfur Ylides*; Organic Chemistry Series; Academic Press: New York, 1975; Vol. 31.

(15) For pertinent reviews on Pd(0)-catalyzed reactions of vinyl epoxides, see: (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995. (b) Trost, B. M. *Angew. Chem.* **1989**, *101*, 1199.

(16) The same is true for compounds **9**−**13** in Scheme 2.

(17) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

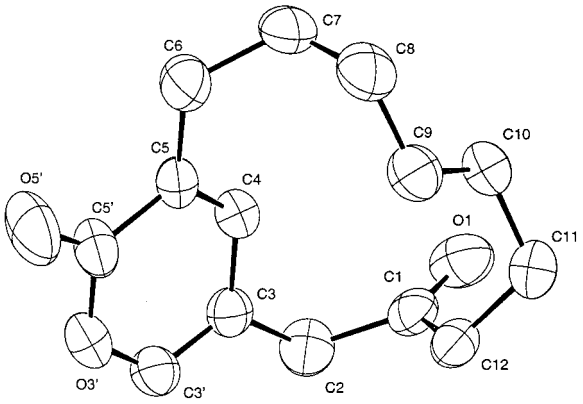
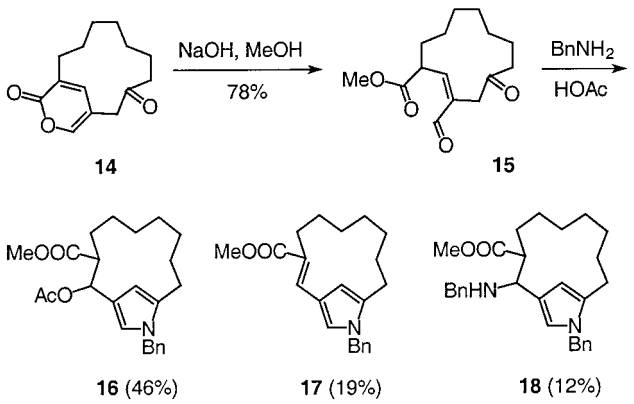


Figure 1. ORTEP diagram of the molecular structure of compound **14**. Anisotropic displacement parameter ellipsoids are drawn at 50% probability, hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and torsion angles (deg): O3′−C3′ 1.358(1), O3′−C5′ 1.372(2), O5′−C5′ 1.212(2), C3−C3′ 1.337(2), C3−C4 1.429(2), C4−C5 1.346(2), C5−C5′ 1.448(2); C5−C6−C7−C8 −77.2(2), C6−C7−C8−C9 72.8(2), C7−C8−C9−C10 70.1(2), C8−C9−C10−C11 −176.80(13), C9−C10−C11−C12 68.33(18), C10−C11−C12−C1 68.57(18), C12−C1−C2−C3 58.32(17).

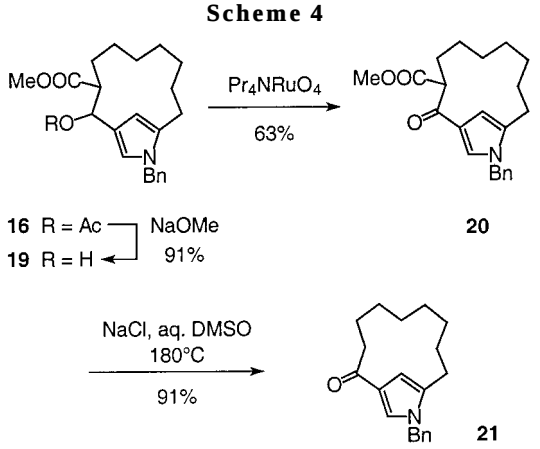
Scheme 3



of this unusual transformation was corroborated by the X-ray structure of the meta-bridged α-pyrone **14** depicted in Figure 1.[18] Note that this rearrangement advantageously adjusts the oxidation pattern of the former primary OH group, because **14** mimics a masked 1,4-dicarbonyl compound encoding the targeted pyrrole ring. The enol lactone character of **14** is reflected in the alternating C−C-bond length of the fully planar six-membered ring (mean deviation from least squares plane is 0.018 Å), with the formal single bonds being somewhat shortened via conjugation. The macrocyclic ring of **14** adopts a conformation which involves only gauche interactions (except for the anti arrangement of C8−C9−C10−C11) forcing the carbonyl group into an axial position.

Solvolysis of pyrone **14** with NaOMe in MeOH unravels tricarbonyl compound **15**, in which the residual double bond appears in conjugation to the aldehyde group as unequivocally deduced from its NMR spectra (Scheme 3).[19] This Michael acceptor system, however, renders the subsequent Paal−Knorr pyrrole synthesis somewhat

Scheme 4



delicate.[20] Specifically, treatment of compound **15** with benzylamine in the presence of HOAc in THF leads to a mixture of pyrroles **16**−**18**. Despite considerable experimentation (solvent, temperature, acid, amine) we were unable to change this distribution pattern to a significant extent.

Fortunately, however, the prevailing product of this step, i.e., compound **16** formed by concomitant 1,4-addition of an acetate during the pyrrole condensation reaction, lends itself very well for the purpose of this study (Scheme 4). Cleavage of the acetoxy group with NaOMe in MeOH delivers aldol **19** in 91% yield which can be oxidized to the β-ketoester derivative **20** by using tetra-*n*-propylammonium perruthenate.[21] This smooth transformation is in stark contrast to attempted oxidations with PDC or under Swern conditions, which destroy the rather sensitive pyrrole ring. Decarboxylation of ketoester **20** according to Krapcho's protocol [22] in the presence of NaCl in hot aq DMSO forms ketone **21** in excellent yield which serves as a convenient platform for a systematic variation of the side chain. To demonstrate this aspect, compound **21** was converted into alkene **22** on exposure to freshly prepared ethylidenetriphenylphosphorane. **22** is then reduced in the presence of Crabtree's catalyst[23] to product **23** which can be elaborated into metacycloprodigiosin **2** according to literature procedures by condensation with the known aldehyde **6**.[8,9] The more lipophilic analogue **24** is analogously obtained upon reaction with undecylidenetriphenyl-phoshorane. Likewise, ketone **21** allows the formation of functionalized core compounds as demonstrated by the preparation of ester **25** via a Peterson olefination with the lithium enolate of ethyl trimethylsilyl acetate as the reagent.[24]

In summary, we have outlined a conceptually novel route to *meta*-pyrrolophane derivatives based on a palladium-catalyzed macrocyclization of a vinyl epoxide precursor followed by an unprecedented transformation of a keto-pyrone derivative into a 2,4-disubstituted pyrrole ring. This methodology gives ready access to compound **23** which constitutes a key intermediate en route

(18) Full information on the X-ray structure of compound **14** is given in the Supporting Information. The complete set of data has been deposited at the Cambridge Crystallographic Data Center, Cambridge, UK, under the deposition number CCDC 127650.

(19) For details, see the Supporting Information.

(20) For a timely and comprehensive review on the Paal-Knorr and related pyrrole syntheses, see: Gossauer, A. In *Houben-Weyl, Methoden der Organischen Chemie*; Kreher, R. R., Ed.; Thieme: Stuttgart, 1994; Vol. E 6a, Part 1, pp 556−798.

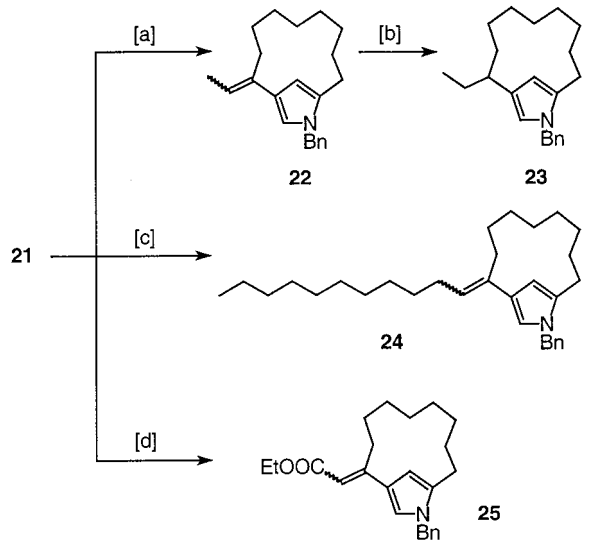
(21) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(22) Krapcho, P. A. *Synthesis* **1982**, 893.

(23) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem*. **1979**, *168*, 183.

(24) For a review on the Peterson olefination, see: Ager, D. J. *Org. React*. **1990**, *38*, 1.

Scheme 5[a]



[a] Key: (a) $Ph_3P{=}CH_2$, DMSO, rt, 73%; (b) H_2 (1 atm), [Ir(COD)(PCy_3)(pyridine)] (10 mol %), rt, 88%; (c) $Ph_3P{=}CH(CH_2)_9CH_3$, DMSO, rt, 51%; (d) Me_3SiCH_2COOEt, LDA, THF, −78 °C → rt, 78%.

to metacycloprodigiosin **2**. Moreover, we have obtained a panel of functional analogues thereof (i.e., compounds **16**−**21**, **24**, and **25**) which allow investigation of the biological response to structural variations within the macrocyclic ring of this lead structure. Studies along these lines are underway and will be described in due course.

Experimental Section

General. The setup of the reactions and the purification of chemicals was carried out as described in the preceding paper of this issue. For the instrumentation used and the spectral formats see the Supporting Information.

{2-[(7-Bromoheptyl)oxiran-3-yl]propenyl-1-oxy}-*tert*-butyldimethylsilane (9). A solution of *tert*-BuLi (1.5 M in pentane, 21 mL, 31 mmol) is slowly added to a solution of the sulfonium salt **8** (10.8 g, 30.0 mmol) in THF (350 mL) at −78 °C under Ar. After stirring for 30 min at that temperature, a solution of 8-bromooctanal (5.4 g, 26.0 mmol) in THF (20 mL) is added, and the mixture is stirred for another 30 min at −78 °C and then slowly warmed to ambient temperature. Standard extractive workup with EtOAc and water followed by flash chromatography of the crude product (hexane/ethyl acetate, 50/1) provides compound **9** as a colorless syrup (6.86 g, 67%, mixture of diastereoisomers). Experiments on a smaller scale (2.51 g of the sulfonium salt) lead to slighly better yields of **9** (1.71 g, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.15−5.10 (m, 1.5H), 4.93 (m, 0.5H), 4.10 (s, 1H), 4.02−4.04 (m, 1H), 3.37 (m, 0.5H), 3.30 (t, 1.5H), 2.80−3.09 (m, 2H), 1.75−1.80 (m, 2H), 1.26−1.35 (m, 10H), 0.84 (s, 4.5H), 0.83 (s, 4.5H), 0.019 (s, 3H), 0.010 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 144.8, 142.2, 111.9, 111.1, 64.4, 62.7, 60.0, 58.6, 58.3, 56.2, 33.8, 32.7, 32.2, 29.2, 29.1, 28.6, 28.3, 26.5, 26.1, 25.8, 18.3, 18.2, −4.5, −4.6. Anal. Calcd for $C_{18}H_{35}BrO_2Si$ (391.46): C 55.2, H 9.0, Br 20.4. Found: C 55.34, H 9.12, Br 20.16.

2-(Benzenesulfonyl)-9-{3-[1-(((*tert*-butyldimethylsilanyl)oxy)methyl)vinyl]oxiran-2-yl}nonanoic Acid Methyl Ester (10). KH (197 mg, 4.92 mmol) is added to a solution of methyl (phenylsulfonyl)acetate (922 mg, 4.29 mmol) in DMF (50 mL). After stirring for 15 min at ambient temperature, a solution of bromide **9** (1.50 g, 3.83 mmol) in DMF (15 mL) is added, and the resulting mixture is stirred at ambient temperature for 24 h. Standard extractive workup followed by flash chromatography with hexane/ethyl acetate (6/1) as the eluent affords the title compound as a colorless syrup (1.57 g, 78%, mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53−7.91 (m, 5H), 5.17−5.22 (m, 1.5H), 5.00 (m, 0.5H), 4.09−4.17 (m, 2H), 3.93 (dd, J = 10.3, 4.7 Hz, 1H), 3.61 (s, 3H), 3.36−3.45 (m, 0.5H), 3.14 (d, J = 2.2 Hz, 0.5H), 3.04 (m, 0.5H), 2.82−2.89 (m, 0.5H), 1.94−1.99 (m, 2H), 1.22−1.49 (m, 12H), 0.91 (s, 4.5H), 0.90 (s, 4.5H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.4, 144.7, 142.1, 137.0, 134.1, 130.0, 129.2, 128.9, 128.5, 111.8, 111.1, 70.8, 64.4, 62.6, 59.9, 58.6, 58.2, 56.2, 52.8, 32.1, 29.6, 29.1, 29.0, 28.9, 28.8, 26.8, 26.6, 26.5, 26.1, 26.0, 25.8, 25.7, 18.3, 18.2, −5.40, −5.44. Anal. Calcd for $C_{27}H_{44}O_6SSi$ (524.78): C 61.8, H 8.5, S 6.1. Found: C 61.66, H 8.41, S 6.01.

Macrocycle 11. A solution of compound **10** (2.43 g, 4.63 mmol) in THF (150 mL) is added over a period of 2 h to a refluxing solution of $Pd(PPh_3)_4$ (538 mg, 0.465 mmol) and dppe (368 mg, 0.924 mmol) in THF (300 mL). Once the addition is complete, the reaction is worked up by evaporation of the solvents. The remaining residue is purified by flash chromatography (hexane/ethyl acetate, 3/1) affording macrocycle **11** as a pale yellow syrup (1.68 g, 68%, mixture of diastereoisomers). Careful chromatography allows enrichment of two individual isomers for analytical purposes. Diastereoisomer **11a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50−7.78 (m, 5H), 5.78 (d, J = 8.8 Hz, 1H), 4.54 (dt, J = 8.8, 2.7 Hz, 1H), 4.01 (AB, J = 11.6 Hz, 2H), 3.59 (s, 3H), 2.98 and 3.16 (AB, J = 13.9 Hz, 2H), 2.07−2.24 (m, 2H), 1.20−1.86 (m, 14H), 0.82 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.1, 140.1, 136.5, 134.5, 134.1, 134.0, 133.4, 130.0, 129.9, 128.7, 76.5, 68.1, 60.7, 52.8, 38.0, 34.4, 29.4, 27.0, 25.9, 25.8, 25.6, 23.6, 22.6, 19.9, 18.1, −5.5. Diastereoisomer **11b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50−7.79 (m, 5H), 5.17 (d, J = 8.6 Hz, 1H), 4.35 (dt, J = 8.0, 4.5 Hz, 1H), 4.29 and 4.15 (AB, J = 11.9 Hz, 2H), 3.60 (s, 3H), 3.11 and 2.98 (dAB, J = 16.9, 1.1 Hz, 2H), 2.14−2.25 (m, 2H), 1.92 (br. s, 1H, OH), 1.05−1.72 (m, 13H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.1, 136.0, 134.8, 134.2, 134.1, 130.2, 128.7, 75.9, 69.1, 62.0, 53.0, 33.8, 33.3, 26.7, 26.2, 25.8, 24.5, 24.0, 21.9, 19.3, 18.1, −5.4, −5.5.

Lactone 12. A solution of silyl ether **11** (1.43 g, 2.72 mmol) in THF (200 mL) is treated with TASF (= tris(dimethylamino)-sulfonium difluorotrimethylsilicate) (1.00 g, 3.65 mmol). After stirring for 20 min at ambient temperature, the reaction mixture is partitioned between ethyl acetate and brine, the organic layer is dried over Na_2SO_4, the solvent is evaporated, and the crude product is purified by flash chromatography (hexanes/ethyl acetate, 2/1), affording lactone **12** as a colorless foam (562 mg, 55%, mixture of diastereoisomers). mp = 70−72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51−7.90 (m, 5H), 5.62 (d, J = 10.4 Hz, 1H), 5.09 (dd, J = 12.5, 2.7 Hz, 0.5H); 4.83 (dt, J = 12.5, 1.2 Hz, 0.5H), 4.51−4.65 (m, 0.5H), 4.31−4.41 (m, 0.5H), 3.73 (s), 3.72 (s), 3.71 (s), 3.70 (s) [0.5H], 3.54 (ddd, J = 14.8, 2.1, 1.1 Hz, 0.5H), 3.40 (ddd, J = 16.0, 2.5, 1.1 Hz, 0.5H), 3.15 (dd, J = 16.0, 2.9 Hz, 0.5H), 2.77 (dd, J = 14.9, 2.8 Hz, 0.5H), 2.01−2.10 (m, 1.5H), 0.80−1.70 (m, 14H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.0, 134.6, 134.5, 134.4, 133.5, 133.0, 131.4, 131.2, 129.9, 128.6, 128.5, 128.3, 74.6, 72.6, 71.9, 68.6, 68.1, 65.8, 36.2, 35.9, 35.4, 34.9, 34.5, 27.5, 26.4, 26.3, 25.6, 24.5, 23.5, 23.1, 22.7, 21.9, 20.5. Anal. Calcd for $C_{20}H_{26}O_5S$ (378.48): C 63.5, H 6.9, S 8.5. Found: C 63.52, H 7.04, S 8.32.

Ketone 13. Dess−Martin periodinane (1.575 g, 3.71 mmol) is added to a solution of alcohol **12** (562 mg, 1.48 mmol) in CH_2Cl_2 (125 mL), and the resulting mixture is stirred for 3 h. For workup, the reaction is diluted with ethyl acetate and successively extracted with aq sat. $NaHCO_3$ and aq sat. $Na_2S_2O_3$, the organic layer is dried over Na_2SO_4, the solvent is evaporated, and the residue is purified by flash chromatography (hexanes/ethyl acetate, 3/1), affording ketone **13** as a colorless foam (414 mg, 74%, mixture of diastereoisomers). mp = 71−73 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50−8.03 (m, 5H), 6.40−6.51 (m, 1H), 5.09 (d, J = 12 Hz, 0.5H), 4.52 (dd, H = 12.2, 2.8 Hz, 0.5H), 3.76 (dd, J = 16.4, 2.8 Hz, 0.5H), 3.39 (ddd, J = 16.5, 2.8, 1.2 Hz, 0.5H), 3.16 (d, J = 12.5 Hz, 1H), 2.75−3.06 (m, 1.5H), 2.63−2.70 (m, 0.5H), 2.15−2.27 (m, 1H), 0.90−2.05 (m, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 206.4,

202.6, 166.0, 163.8, 141.6, 138.2, 136.0, 134.5, 134.3, 131.6, 131.3, 129.2, 129.0, 128.7, 128.6, 110.9, 73.5, 73.1, 68.9, 46.2, 43.5, 36.7, 35.1, 30.2, 27.9, 26.1, 26.0, 25.9, 25.1, 23.6, 23.3, 23.2, 22.3, 21.9, 21.0, 20.1, 19.5. HRMS ($C_{20}H_{24}O_5S$): calcd 376.134445; found 376.134468.

Pyrone 14.[18] A solution of ketone **13** (410 mg, 1.08 mmol) and DBU (186 mg, 1.22 mmol) in THF (50 mL) is refluxed for 17 h. Standard extractive workup followed by flash chromatography of the crude product with hexanes/ethyl acetate (3/1) as the eluent affords α-pyrone **14** as colorless crystals (200 mg, 79%). mp = 74−75 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34 (d, J = 2.5 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 3.27 (s, 2H), 2.55 (t, J = 6.0 Hz, 2H), 2.35 (t, J = 7.0 Hz, 2H), 1.66 (m, 2H), 1.55 (m, 2H), 1.33 (m, 2H), 1.22 (m, 2H), 1.03 (quint, J = 7.4, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 208.6, 162.1, 147.2, 139.3, 130.4, 113.6, 45.4, 36.5, 30.3, 28.0, 26.0, 24.8, 22.8, 22.3. Anal. Calcd for $C_{14}H_{18}O_3$ (234.29): C 71.8, H 7.7. Found: C 71.91, H 7.76.

Macrocycle 15. NaOH (ca. 20 mg) is dissolved in MeOH (1 mL), pyrone **14** (70 mg, 0.298 mmol) is added, and the resulting mixture is stirred for 2.5 h at ambient temperature. For workup, aq sat. NH_4Cl is added until the mixture reaches a pH of 4−5, the aqueous phase is extracted with *tert*-butylmethyl ether, and the organic layer is dried over Na_2SO_4. Evaporation of the solvent followed by flash chromatography (hexanes/ethyl acetate, 10/1) provides product **15** as a colorless syrup (62 mg, 78%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 6.67 (d, J = 10.8, 1H), 3.70 (s, 3H), 3.53 (s, 2H), 3.52 (ddd, J = 10.7, 8.4, 5.6 Hz, 1H), 2.62 (ddd, J = 14.7, 8.4, 2.9 Hz, 1H), 2.32 (ddd, J = 14.6, 10.2, 3.2 Hz, 1H), 1.69−1.88 (m, 4H), 1.23−1.44 (m, 6H), 1.07−1.19 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 206.6, 193.4, 172.9, 150.7, 138.9, 52.4, 43.4, 42.7, 37.5, 31.2, 26.1, 25.9, 25.0, 24.3, 22.2. HRMS ($C_{15}H_{22}O_4$): calcd 266.151809; found 266.151928.

Paal−Knorr Pyrrole Formation. A solution of benzylamine (102 mg, 0.95 mmol) and HOAc (158 mg, 2.63 mmol) in THF (4 mL) is added via a syringe pump over a period of 1 h to a solution of substrate **15** (115 mg, 0.43 mmol) in THF (5 mL) at 65 °C. After the addition is complete, the solvent is removed in vacuo and residual HOAc is coevaporated with toluene. Flash chromatography (hexanes/ethyl acetate, 10/1) of the remaining residue provides pyrroles **16** (78 mg, 46%), **17** (28 mg, 19%), and **18** (22 mg, 12%) each as a colorless syrup.

Analytical data of pyrrole **16**: ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.04−7.28 (m, 5H), 6.69 (d, J = 1.9 Hz, 1H), 6.06 (d, J = 1.9 Hz, 1H), 5.64 (d, J = 11.0 Hz, 1H), 4.97 (s, 2H), 3.66 (s, 3H), 2.73 (ddd, J = 11.0, 7.0, 1.5 Hz, 1H), 2.62 (dt, J = 14.7, 3.8 Hz, 1H), 2.49 (ddd, J = 14.9, 10.6, 4.3 Hz, 1H), 1.94 (s, 3H), 1.60−1.66 (m, 1H), 1.40−1.48 (m, 2H), 1.13−1.29 (m, 6H), 0.97−1.01 (m, 1H), 0.59−0.71 (m, 1H), −0.20 (m, 1H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 175.6, 170.0, 138.5, 134.4, 129.0, 127.9, 127.4, 122.2, 120.1, 107.6, 71.7, 51.9, 51.8, 50.6, 49.3, 28.5, 27.3, 26.8, 26.1, 26.0, 25.9, 25.4, 21.3. HRMS ($C_{24}H_{31}NO_4$): calcd 397.225308; found 397.225501.

Analytical data of compound **17**: ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 7.58 (s, 1H), 7.32 (t, J = 6.2 Hz, 2H), 7.27 (t, J = 7.3 Hz, 1H), 7.11 (d, J = 7.3 Hz, 1H), 6.65 (d, J = 1.5 Hz, 1H), 6.28 (d, J = 1.5 Hz, 1H), 4.99 (s, 2H), 3.71 (s, 3H), 2.56 (t, J = 6.5 Hz, 2H), 2.52 (m, 2H), 1.60 (m, 2H), 1.25−1.28 (m, 4H), 1.12 (m, 2H), 1.02 (m, 2H). ^{13}C NMR (CD_2Cl_2, 150 MHz): δ = 169.6, 138.6, 134.9, 133.8, 130.7, 129.1, 127.9, 127.1, 122.3, 119.5, 112.1, 51.8, 50.8, 30.0, 27.5, 26.2, 25.9, 25.8, 25.5, 24.5, 23.8. HRMS ($C_{22}H_{27}NO_2$): calcd 337.204179; found 337.204202.

Analytical data of compound **18**: ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.11−7.36 (m, 10H), 6.52 (d, J = 1.9 Hz, 1H), 6.01 (d, J = 1.9 Hz, 1H), 5.00 (AB, J = 16 Hz, 2H), 3.82 and 3.61 (AB, J = 13.3 Hz, 1H), 3.67 (s, 3H), 3.50 (d, J = 10.8 Hz, 1H), 2.66 (dt, J = 14.7, 4.3 Hz, 1H), 2.39−2.51 (m, 2H), 0.88−1.66 (m, 11H), 0.64 (m, 1H), −0.19 (m, 1H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 177.4, 141.6, 139.3, 134.2, 128.9, 128.5, 128.4, 127.7, 127.0, 126.8, 123.1, 122.3, 107.0, 58.0, 51.6, 50.4, 30.0, 28.8, 27.6, 27.0, 26.8, 26.3, 25.5. HRMS ($C_{29}H_{36}N_2O_2$): calcd 444.277678; found 444.277692.

Pyrrole 19. A solution of acetate **16** (82.5 mg, 0.207 mmol) and NaOMe (179 mg, 3.32 mmol) in MeOH (8 mL) is stirred at ambient temperature for 1.5 h. The solvent is evaporated and the residue purified by flash chromatography (hexanes/ethyl acetate, gradient: 6/1 → 4/1 → 1/1), providing product **19** as a colorless syrup (67 mg, 91%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.01−7.25 (m, 5H), 6.52 (d, J = 1.9 Hz, 1H), 6.05 (d, J = 1.9 Hz, 1H), 4.90 (AB, J = 16 Hz, 2H), 4.47 (d, J = 10.3 Hz, 1H), 3.61 (s, 3H), 2.55 (dt, J = 14.8, 4.2 Hz, 1H), 2.30−2.47 (m, 3H), 0.79−1.62 (m, 10H), 0.58 (m, 1H), −0.32 (m, 1H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 177.2, 138.9, 134.4, 128.9, 127.7, 127.0, 123.8, 121.0, 107.2, 70.2, 51.8, 51.7, 50.4, 28.5, 27.4, 26.9, 26.4, 26.2, 26.1, 25.4. HRMS ($C_{22}H_{29}NO_3$): calcd 355.214744; found 355.214716.

Ketoester 20. To a slurry of compound **19** (67 mg, 0.188 mmol) and powdered molecular sieves (4 Å) in CH_2Cl_2 (10 mL) is added tetra-*n*-propylammonium perruthenate (79.3 mg, 0.225 mmol), and the resulting mixture is stirred for 1.5 h at ambient temperature. Insoluble residues are filtered off, and the crude product is purified by flash chromatography (hexanes/ethyl acetate, 5/1), providing ketoester **20** as a colorless syrup (42 mg, 63%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.33−7.36 (m, 3H), 7.23 (d, J = 2.0 Hz, 1H), 7.14−7.16 (m, 2H), 6.56 (d, J = 2.0 Hz, 1H), 5.06 (s, 2H), 4.07 (dd, J = 9.3, 4.7 Hz, 1H), 3.72 (s, 3H), 2.59 (A part of dddAB, J = 15.1, 7.0, 4.3, 0.9 Hz, 1H), 2.44 (B part of ddAB, J = 15.1, 9.1, 3.8 Hz, 1H), 1.87−1.97 (m, 1H), 1.60−1.77 (m, 2H), 1.43−1.49 (m, 2H), 0.96−1.25 (m, 6H), 0.56−0.58 (m, 1H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 193.9, 171.9, 137.2, 135.9, 129.1, 128.2, 127.3, 124.8, 124.4, 111.7, 54.1, 52.1, 51.3, 29.2, 27.4, 27.1, 26.0, 25.5, 24.9. HRMS ($C_{22}H_{27}NO_3$): calcd 353.199093; found 353.199114.

Ketopyrrole 21. A solution of compound **20** (30.9 mg, 0.087 mmol) and NaCl (10 mg) in DMSO (3 mL) and water (50 μL) is kept at 180−190 °C for 1.5 h. The reaction mixture is then adsorbed on silica and purified by flash chromatography (hexanes/ethyl acetate, 4/1), thus leading to product **21** as a colorless solid (23.4 mg, 91%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.32−7.35 (m, 3H), 7.14−7.17 (m, 3H), 6.58 (d, J = 1.8 Hz, 1H), 5.04 (s, 2H), 2.63 (t, J = 6.3 Hz, 2H), 2.49 (t, J = 6.2 Hz, 2H), 1.57−1.65 (m, 4H), 1.30−1.39 (m, 2H), 0.90−1.10 (m, 6H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 199.2, 137.5, 135.0, 129.1, 128.1, 127.3, 126.1, 123.4, 112.3, 51.2, 39.1, 27.9, 27.3, 26.9, 25.8, 25.3, 25.0, 24.7. HRMS ($C_{20}H_{25}NO$): calcd 295.193614; found 295.193599.

Pyrrole 22. $[Ph_3PCH_2CH_3]^+$ I^- (56 mg, 0.135 mmol) dissolved in DMSO (1.5 mL) is deprotonated with KH (5.4 mg, 0.135 mmol), and a solution of ketone **21** (25 mg, 0.08 mmol) in DMSO (1.1 mL) is then introduced into the ylide thus formed. After stirring the mixture for 20 min at ambient temperature, the reaction is quenched with water (5 mL), the aqueous layer is extracted with CH_2Cl_2 (20 mL in several portions), the organic phase is dried over Na_2SO_4, the solvent is evaporated, and the residue is purified by flash chromatography (hexanes/ethyl acetate, 6/1) affording alkene **22** as a pale yellow oil (18 mg, 73%, (*E*,*Z*)-mixture, ratio of isomers ≈ 3:1). ^{1}H NMR (300 MHz, CD_2Cl_2) [minor isomer in brackets, where resolved]: δ = 7.03−7.25 (m, 5H), 6.42 (d, J = 1.9 Hz) [6.41, (d, J = 1.9 Hz)] [1H], [5.96 (d, J = 1.9 Hz)], 5.94 (d, J = 1.9 Hz) [1H], [5.40 (q, J = 6.8)], 5.25 (q, J = 6.7) [1H], 4.92 (s), [4.87 (s)] [2H], 2.38−2.47 (m, 2H), [2.24 (t, J = 6.3 Hz)], 2.14 (t, J = 6.3) [2H], 1.65 (d, J = 6.7), [1.58 (d, J = 6.8)] [3H], 1.32−1.39 (m, 2H), 0.95−1.26 (m, 8H), 0.48 (m, 2H). ^{13}C NMR (CD_2Cl_2, 75 MHz) [minor isomer in brackets, where resolved]: δ = 139.3, [139.2], 137.9, [137.6], 132.8, 128.9, 127.6, 127.4, 127.2, 127.1, 127.0, [121.6], 120.7, [118.3], 117.1, [115.9], 110.2, [109.4], 50.4, [50.3], 36.5, 27.5, 27.3, 27.1, 26.9, 26.8, 26.7, 26.5, 26.4, 26.0, 25.9, 15.0, [13.4]. HRMS ($C_{22}H_{29}N$): calcd 307.230000; found 307.232011.

Pyrrole 24. Prepared as described above using $[Ph_3P(CH_2)_{10}CH_3]^+$ Br^- (56 mg, 0.11 mmol), KH (4.4 mg, 0.11 mmol), and ketone **21** (20 mg, 0.067 mmol). Alkene **24** was obtained as a pale yellow syrup (14.7 mg, 51%, (*E*,*Z*)-mixture, ratio of isomers ≈ 1.5:1). ^{1}H NMR (300 MHz, CD_2Cl_2) [minor isomer in brackets, where resolved]: δ = 7.14−7.36 (m, 5H), [6.52 (d, J = 1.9 Hz)], 6.50 (d, J = 1.9 Hz), [6.36 (d, J = 1.9 Hz)], [6.07 (d, J = 1.9 Hz)], 6.03 (d, J = 1.9 Hz), 5.83 (d, J = 1.9 Hz), 5.45 (t, J = 7.6 Hz), 5.28 (t, J = 7.6 Hz), 4.98−5.03 (m, 2H), 2.49−

2.60 (m, 2H), 1.83−2.35 (m, 6H), 1.05−1.49 (m, 23H), 0.89 (t, J = 6.8 Hz, 3H), 0.54−0.63 (m, 2H), 0.33 (m, 1H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 139.6, 139.4, 139.3, 136.8, 136.7, 132.9, 132.8, 131.4, 128.9, 127.7, 127.6, 127.5, 127.2, 127.1, 127.0, 126.8, 123.9, 122.6, 122.0, 120.6, 118.7, 118.4, 112.6, 110.6, 110.3, 109.4, 50.4, 50.3, 39.3, 36.6, 32.3, 30.8, 30.6, 30.0, 29.9 (2×), 29.8 (2×), 29.7, 29.6, 28.2, 27.7, 27.6, 27.5, 27.1, 27.0, 26.9, 26.8, 26.5, 26.4, 26.2, 26.0 (2×), 23.0, 14.2. HRMS ($C_{31}H_{47}N$): calcd 433.370850; found 433.370644.

Pyrrole 25. Ethyl trimethylsilyl acetate (18.5 mg, 0.115 mmol) is added to a solution of LDA (12.4 mg, 0.115 mmol) in THF at −78 °C. After stirring for 10 min, a solution of ketone **21** (18.0 mg, 0.061 mmol) in THF (1 mL) is introduced and the mixture is stirred for another 10 min at −78 °C and then allowed to warm to ambient temperature. A standard extractive workup followed by flash chromatography of the crude product (hexanes/ethyl acetate, 4/1) provides ester **25** as a pale yellow syrup (17.5 mg, 78%) (*E*:*Z* mixture, ratio of isomers ≈ 1.2:1). ^{1}H NMR (300 MHz, CD_2Cl_2) [minor isomer in brackets, where resolved]: δ = 7.14−7.37 (m, 6H), 6.79 (d, J = 1.9), [6.31 (d, J = 1.9 Hz)], 6.20 (d, J = 1.9 Hz), [5.90 (s)], 5.60 (s), 5.04 (s), [5.02 (s)], [4.13 (q, J = 7.1 Hz)], 4.06 (q, J = 7.1 Hz, 2H), [2.99 (t, J = 6.3 Hz)], 2.41 (t, J = 6.3 Hz), 2.51 (dd, J = 5.8, 6.0 Hz, 2H), 1.06−1.58 (m, 10 H), [1.27 (t, J = 7.1 Hz)], 1.20 (t, J = 7.1 Hz), 0.66−0.76 (m, 2H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 167.2, 166.9, 158.3, 155.7, 138.7, 138.3, 134.6, 132.9, 129.0, 128.9, 127.8, 127.7, 127.2, 127.0, 126.2, 124.3, 119.9, 119.6, 111.8, 110.4, 109.8, 109.7, 59.5, 59.4, 50.8, 50.7, 38.0, 28.5, 27.7, 27.5, 27.4, 27.2, 27.1, 26.7, 26.5 (2x), 26.4, 26.2, 26.1, 25.6, 25.5, 14.5, 14.4. HRMS ($C_{24}H_{31}NO_2$): calcd 365.235479; found 365.235483.

Pyrrole 23. A solution of alkene **22** (17 mg, 0.055 mmol) and [Ir(COD)(Cy_3P)pyridine] PF_6 (4.4 mg, 10 mol %)[23] in CH_2Cl_2 (3.5 mL) is stirred under an atmosphere of H_2 (1 atm) for 10 min. The solvent is evaporated and the residue purified by flash chromatography (hexanes/ethyl acetate, 6/1), affording product **23** as a pale yellow oil (15 mg, 88%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.11−7.32 (m, 5H), 6.39 (d, J = 1.9 Hz, 1H), 5.90 (d, J = 1.9 Hz, 1H), 4.98 (s, 2H), 2.58 (A part of ddAB, J = 14.6, 6.1, 4.0 Hz, 1H), 2.47 (B part of ddAB, J = 14.6, 9.4, 4.0 Hz, 1H), 2.22 (m, 1H), 1.48−1.58 (m, 4H), 1.10−1.39 (m, 10H), 0.91 (t, J = 7.3 Hz, 3H), 0.47−0.52 (m, 1H), 0.07−0.11 (m, 1H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 139.7, 133.1, 128.8, 127.4, 127.2, 127.0, 120.2, 110.6, 107.7, 50.2, 40.8, 33.2, 29.0, 28.7, 27.5, 27.2, 27.1, 26.2, 25.6, 21.6, 12.8. HRMS ($C_{22}H_{31}N$): calcd 309.245650; found 309.245737.

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Supporting Information Available: Details concerning the X-ray structure of compound **14**, complete listing of the MS (EI) and IR data, copies of the NMR spectra of all new compounds, full assignment of the NMR data of compounds **14**, **15**, and **17**, procedure for the large scale preparation of sulfonium salt **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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