A Second Generation Synthesis of Roseophilin and Chromophore Analogues

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Received October 16, 1998

A concise, flexible, and high-yielding synthesis of the macrocyclic compound **4** is outlined which served as a key intermediate in a previous total synthesis of the antitumor active alkaloid roseophilin **1**. The key steps of this approach consist of a Pd(0)-catalyzed reaction of vinyloxirane **6** with sulfone **7** and in a subsequent ring closing metathesis (RCM) reaction for the formation of the 13-membered ring catalyzed by the ruthenium carbene $Cl_2(PCy_3)_2Ru{=}CHCH{=}CPh_2$ introduced by Grubbs. Moreover, nitrile ylide cycloaddition reactions are used for the preparation of roseophilin side chain mimics. Finally, the synthesis of various chromophore analogues of **1** is reported, including deschlorodesmethoxyroseophilin **12** which is the most elaborate derivative of this complex target reported so far.

Introduction

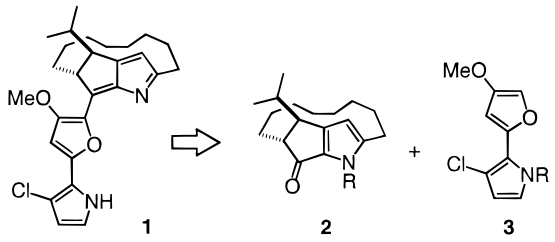
The intricate structure of roseophilin **1**, a macrocyclic pigment isolated from *Streptomyces griseoviridis*,[1] poses formidable challenges for a synthesis-driven mapping of the pharmacophore of this promising cytotoxic agent. Only recently, we have achieved the first total synthesis of this topologically unique alkaloid.[2,3] Our approach (Scheme 1) was based on a manifold of palladium-catalyzed reactions for the construction of the complex macro tricyclic core **2**, a cross coupling/dehydrative cyclization strategy delivering the labile pyrrolylfuran segment **3**, and a newly devised way of making azafulvenes which takes advantage of the high nucleophilicity of heteroarylcerium reagents.[2]

We now disclose further efforts meant to bring this demanding target into range of systematic biological evaluation. Specifically, a flexible "second generation" synthesis of its core segment **2** based on ring closing metathesis (RCM)[4] as well as the preparation of various elaborate chromophore analogues of roseophilin are outlined, including compound **12** which differs from the natural product **1** only by the missing chloro and methoxy substituents in the side chain.

Results and Discussion

RCM Approach to the Macrotricyclic Segment. In recent work we have gained insights into the basic requirements for successful macrocyclization reactions of appropriate dienes via RCM and have demonstrated the exceptional performance of this method by various natural product syntheses.[5−7] Compelling evidence has accumulated during these studies that polar functional groups of the substrate act as "relays" (e.g. via complexes of type **A** or similar, Scheme 2) which help to assemble the reacting sites within the coordination sphere of the metal and thus confer bias to cyclization over competing intermolecular metathesis events. However, if such a chelate becomes too stable, the catalyst will be sequestered in an unproductive form and RCM is likely to cease. This interpretation suggests that an adequate assessment of the *distance* between the alkenes and the polar groups as well as their relative *orientation* and *affinity* allows identification of the proper site for productive RCM within a given target. Although conformational predisposition of the substrate toward ring closure is a

Scheme 1



(1) Hayakawa, Y.; Kawakami, K.; Seto, H.; Furihata, K. *Tetrahedron Lett.* **1992**, *33*, 2701−2704.

(2) (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817−2825. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1997**, *119*, 2944−2945.

(3) For studies toward roseophilin see: (a) Nakatani, S.; Kirihara, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett.* **1995**, *36*, 8461−8464. (b) Mochizuki, T.; Itoh, E.; Shibata, N.; Nakatani, S.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1998**, *39*, 6911−6914. (c) Kim, S. H.; Fuchs, P. L. *Tetrahedron Lett.* **1996**, *37*, 2545−2548. (d) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601−2604. (e) Luker, T.; Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1998**, *63*, 220−221.

(4) For recent reviews on RCM see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Fürstner, A. *Top. Catal.* **1997**, *4*, 285−299. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2055.

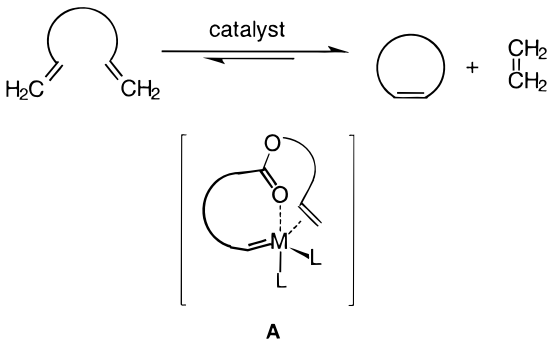
(5) (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942−3943. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792−803. (c) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005−7008. (d) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746−8749. (e) Fürstner, A.; Müller, Th. *Synlett* **1997**, 1010−1012. (f) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136. (g) Fürstner, A.; Müller, Th. *J. Org. Chem.* **1998**, *63*, 424−425.

(6) For methodological studies on metathesis reactions from this laboratory, see: (a) Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 1315−1316. (b) Fürstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, Ch. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2466−2469. (c) Fürstner, A.; Seidel, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1734−1736. (d) Fürstner, A.; Ackermann, L. *Chem. Commun.* **1999**, 95−96.

(7) For reviews on other RCM-based macrocycle syntheses, see: (a) Nicolaou, K. C. *Top. Organomet. Chem.* **1998**, *1*, 73−104. (b) Hoveyda, A. H. *Top. Organomet. Chem.* **1998**, *1*, 105−132. (c) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37−72 and literature cited.

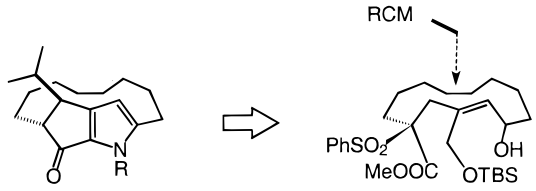
10.1021/jo982088t CCC: $18.00
Published on Web 03/12/1999

Scheme 2



A

Scheme 3



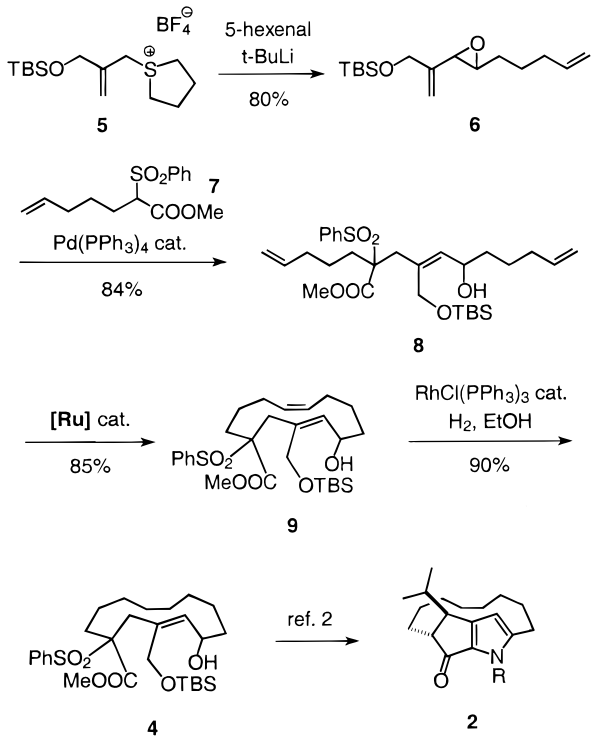
2 4

priori unnecessary, one has to keep in mind that macro cyclizations by RCM are essentially entropy driven and that the ability of this method to build up strain in the molecule is therefore rather limited.[5−7]

When applied to the tricyclic core **2** of roseophilin, this analysis suggests forging the macrocycle in an early stage and rigidifying the backbone of the target during subsequent, kinetically favorable cyclizations of the five-membered rings. This basic concept has already contributed to the success of our previous synthesis of this product, which involved compound **4** as a key precursor formed by a Pd(0)-catalyzed macrocyclization reaction.[2] We felt that this compound might also be accessible by RCM provided that the 13-membered ring is closed at (or near) the site indicated in Scheme 3.

This synthesis plan was reduced to practice as summarized in Scheme 4. Reaction of 5-hexenal with the sulfur ylide formed from sulfonium salt **5**[2,8] upon deprotonation with *tert*-BuLi at −78 °C provides epoxide **6** in 80% yield. Treatment of this product with catalytic amounts of $Pd(PPh_3)_4$ in the presence of methyl 2-(phenylsulfonyl)-6-heptenoate **7** as an external nucleophile readily delivers the desired triene **8**[9] as a mixture of isomers via the selective activation of the vinyloxirane entity of **6** without interference of its adjacent allyl ether site. In line with our expectations, exposure of **8** to the ruthenium carbene $Cl_2(PCy_3)_2Ru{=}CHCH{=}CPh_2$ [Ru] (10 mol %)[10] in refluxing CH_2Cl_2 under high dilution conditions effects a slow but smooth and high-yielding macrocyclization reaction.[11] This transformation features the excellent compatibility of the Grubbs catalyst [Ru] with various functional groups, including an unprotected OH

Scheme 4[9]



function, and shows that this catalyst rigorously distinguishes between terminal and trisubstituted alkenes.[4] Subsequent hydrogenation of **9** in the presence of $RhCl(PPh_3)_3$ cat. selectively saturates the disubstituted double bond formed by RCM without affecting the trisubstituted olefin. The resulting product **4** is identical to that obtained by our previous route in all respects and can be transformed into **2** in only five high-yielding steps as described in ref 2.

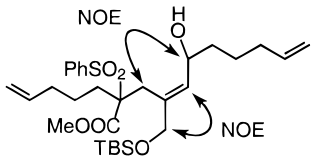
The following aspects of this "second generation" approach to **2** are noteworthy: although the metathesis route is one step longer than our previous palladium-based macrocyclization strategy,[2] the overall yield is in a comparable range (51% over four steps compared to 48% over three steps starting from **5** each). More important, however, is its flexible design. It is obvious that this sequence of reactions can be easily adapted to the synthesis of roseophilin analogues differing in the ring size of the macrocycle if 5-hexenal is replaced by other unsaturated aldehydes or if nucleophiles other than **7** are employed for the Pd(0)-catalyzed vinyl epoxide opening

(8) For an application of this building block to the synthesis of furans, see: Fürstner, A.; Gastner, T.; Rust, J. *Synlett* **1999**, 29−32.

(9) Products **4**, **6**, **8**, and **9** are obtained as mixtures of several stereoisomers. Because all of them converge into product **2**, the synthesis depicted in Scheme 4 was carried through with these mixtures, and no attempts were made to separate the individual compounds; see, however, ref 11.

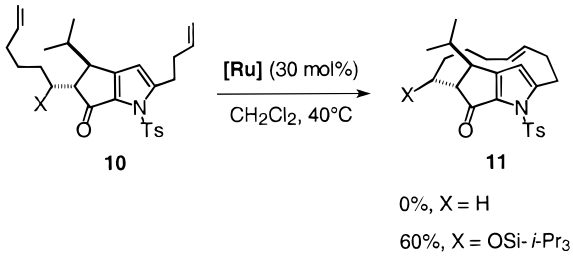
(10) (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974−3975. (c) See also: Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem.* **1995**, *107*, 2179−2181.

(11) In preparative runs, the cyclization can been carried out with a mixture of different isomers of substrate **8** since all isomers of product **9** formed converge into the desired target **2**. For analytical purposes, however, small scale experiments using individual isomers have been performed which are described in the Experimental Section. During these reactions it was noticed that the rate of cyclization of (*Z*)-**8** is significantly higher than that of (*E*)-**8**, although both runs lead essentially to the same yields of the corresponding macrocycles. NOE data have been used to assign the configuration of the trisubstituted double bond of (*E*)-**8**. We thank Mrs. B. Gabor for the NOE measurements.



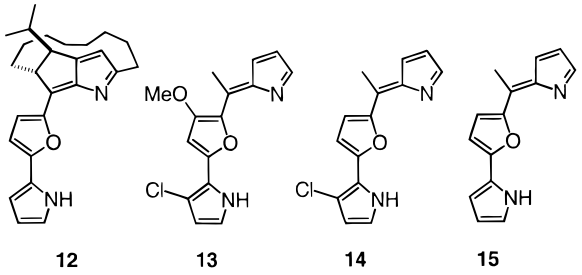
(*E*)-**8**

Scheme 5



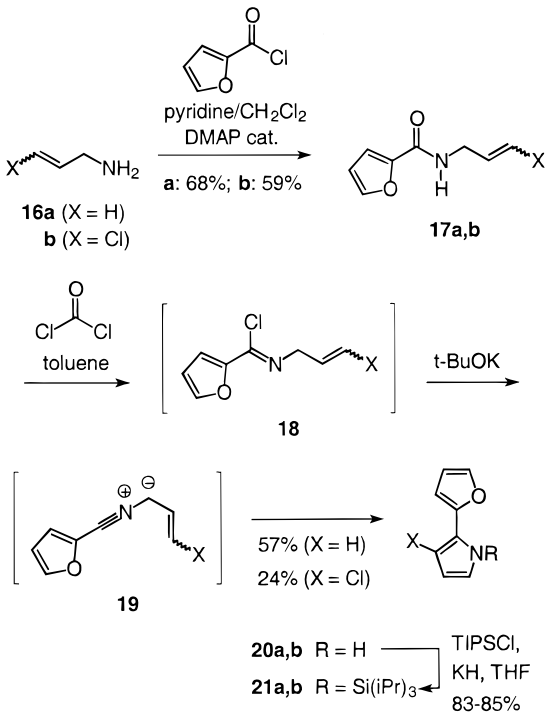
reaction. Finally, a comparison of this route with another RCM-based approach to **2** (Scheme 5)[3d] sheds light on a more general notion concerning the use of metathesis in synthetic maneuvers: We avoid difficulties caused by the inherent strain in **2** by deliberately forging the macrocycle in an early stage of the synthesis, prior to the formation of the five-membered rings. As reported by Fuchs et al., the inverse order of events, i.e. cyclization of the five-membered rings preceding the construction of the *ansa* chain is significantly more delicate: thus, cyclization of diene **10** required substantial amounts of catalyst and succeeded only after it was strongly biased by the introduction of a conformational control element X which helps to bring the unsaturated chains close together and thereby lowers the enthalpic barrier during ring formation.[3d]

Roseophilin Chromophore Analogues. As experienced during our total synthesis of roseophilin,[2a] the unusual substitution pattern of the heterocyclic segment **3** and the inherent lability of this compound and some of its precursors pose considerable problems. Therefore the development of improved entries into pyrrolylfuran derivatives in general and the biological evaluation of truncated roseophilin analogues mimicing its intricate chromophore entity constitute prime goals for further studies in this field. In this context we now report the synthesis of deschloro-desmethoxyroseophilin **12** as a rather elaborate derivative of **1** as well as the preparation of the simplified targets **13**−**15**.[12]



For this purpose, unsubstituted pyrrolylfuran **20a** (X = H) was prepared according to a procedure of Steglich et al. (Scheme 6).[13] Thus, acylation of allylamine **16a** with furan-2-carboxylic acid chloride under standard conditions delivers amide **17a**. Reaction of this compound with a solution of phosgene in toluene affords iminoyl chloride **18** which is exposed to *tert*-BuOK without further purification. The resulting nitrile ylide **19** cycloaromatizes spontaneously to the desired product **20a**. We were pleased to find that this method also applies to the preparation of the chloro-substituted analogue **20b** (X = Cl) albeit in lower yield. Unfortunately, however, the incorporation of a methoxy substituent at the 4-position of the furan ring leads to intractable mixtures. That is why the fully substituted side chain **3** was prepared according to the route previously described.[2a]

Scheme 6



After protection of the pyrrolic N−H function with a TIPS (= triisopropylsilyl) group,[14] derivatives **3** and **21**, respectively, can be selectively metalated with *n*-BuLi in THF at the 2-position of their furan ring. Transmetalation with $CeCl_3$ and addition of the resulting organocerium reagents **22**[15] to the potassium salt of 2-acetylpyrrole delivers the corresponding tertiary alcohols **23** which spontaneously lose water on addition of aqueous HCl. Fluoride-induced desilylation affords the labile azafulvene derivatives **13**−**15** which are protonated for convenience of workup. This sequence of reactions provides the desired truncated chromophore analogues of roseophilin in 23−32% overall yield.

A better result is obtained if N-SEM protected 2-acetylpyrrole **24** is used as substrate for the condensation reaction instead of the potassium salt (Scheme 8). This particular protecting group has been chosen i.a. because it is concomitantly cleaved with the TIPS group on the side chain and therefore does not prolongate the sequence by an additional deprotection step.[16] This method furnishes pigment **15** in 55% overall yield.

(12) Terashima et al. have described an alternative synthesis of compound **13** and related products by acid-catalyzed condensation reactions, cf. ref 3a.

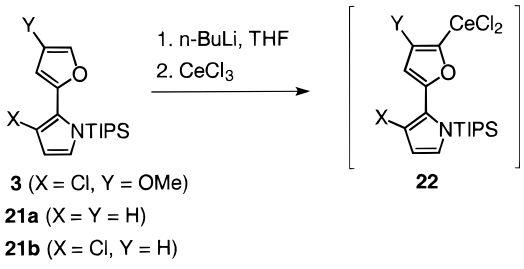
(13) Engel, N.; Steglich, W. *Angew. Chem.* **1978**, *90*, 719−720.

(14) TIPS was chosen since it prevents metalation of the pyrrole by mere steric bulk, cf.: (a) Muchowski, J. M.; Solas, D. R. *Tetrahedron Lett.* **1983**, *24*, 3455−3456. (b) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317−6328.

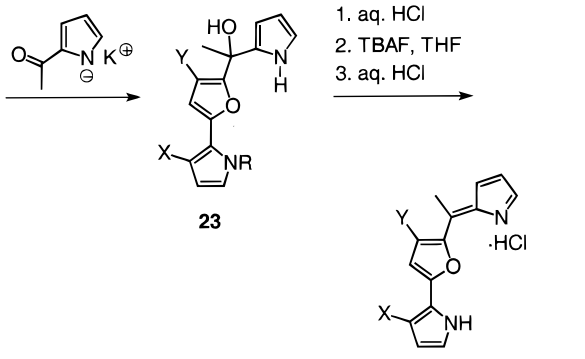
(15) For reviews on organocerium compounds, see: (a) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: New York, 1994. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. (c) See also: Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904−3912.

(16) The SEM protecting group was essential in our previous total synthesis of roseophilin, cf. ref 2a. For another application of N-SEM protected pyrrole derivatives see: Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723−3729.

Scheme 7

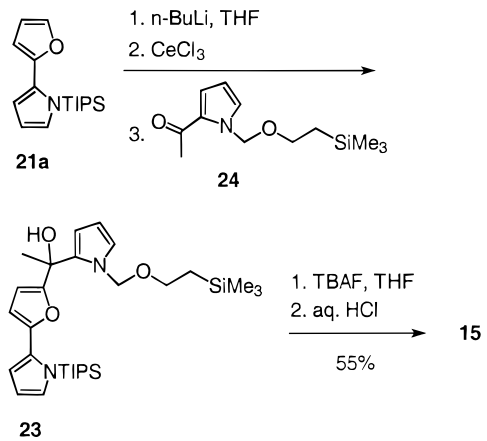


3 (X = Cl, Y = OMe)
21a (X = Y = H)
21b (X = Cl, Y = H)

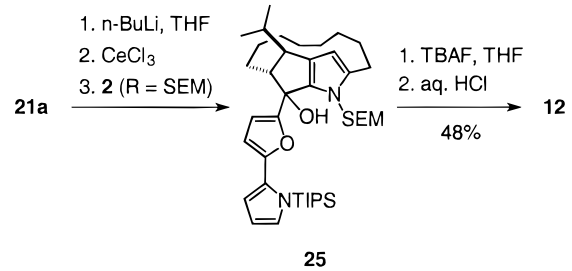


32% **13** (X = Cl, Y = OMe)
23% **14** (X = Cl, Y = H)
25% **15** (X = Y = H)

Scheme 8



Scheme 9



Having good access to the macrotricyclic core **2** (vide supra) as well as to the side chain analogue **21a**, we were able to prepare deschloro-desmethoxyroseophilin **12** by closely following the above-mentioned protocol. As shown in Scheme 9, this product was obtained without incident and constitutes the most elaborate derivative of roseophilin reported so far. Together with the less complex models **13**−**15** it will help to assess the structure/activity profile of this promising cytotoxic agent in more detail. Work along these lines as well as complementary synthetic endeavors directed to bioactive pyrrole alkaloids are underway and will be reported in due course.[17]

Finally, a noteworthy physicochemical property of these compounds is briefly mentioned. Whereas roseophilin **1** and its truncated analogue **13** are intensively red-colored pigments, all derivatives lacking the methoxy substituent on the furan ring, i.e. **12**, **14**, and **15**, are ink blue compounds.

Experimental Section

General. All reactions were carried out under Ar in flame-dried glassware using Schlenk techniques. The solvents were dried by distillation over the drying agents indicated and were stored and transferred under Ar: CH_2Cl_2 (P_4O_{10}), toluene (Na/K), THF (magnesium/anthracene), pyridine (KOH), DMF (dibutyltin laurate and Desmodur-15, Bayer AG), EtOH (Mg). Flash chromatography: Merck silica gel (230−400 mesh) or alumina (Macherey-Nagel, Darmstadt, activity 1, neutral) using hexane/ethyl acetate in various proportions as eluent. For the instrumentation used and the spectra formats see Supporting Information. Elemental analyses: Dornis & Kolbe, Mülheim. CAUTION: Pure KH, free of mineral oil, is highly pyrophoric! It is obtained by repeatedly washing the commercially available suspension of KH in mineral oil with pentane on a sinter funnel under Ar and subsequent drying of the powder in vacuo. Anhydrous $CeCl_3$ was obtained by flame-drying commercially available $CeCl_3 \cdot 7H_2O$ (Aldrich, 99.9%) in vacuo; the material was then rapidly pulverized in a mortar and redried for 24 h at 150 °C at ca. 10^{-2} Torr. Other commercially available reagents (Aldrich, Fluka) were used as received.

Methyl 2-(Phenylsulfonyl)-6-heptenoate (7). Methyl (phenylsulfonyl)acetate (1.596 g, 7.45 mmol) is added in portions to a suspension of KH (298 mg, 7.45 mmol) in DMF (10 mL) at ambient temperature, and stirring is continued until the evolution of gas has ceased. 5-Bromo-1-pentene (0.8 mL, 6.77 mmol) is added, and the resulting mixture is stirred overnight at room temperature. A standard extractive workup followed by flash chromatography on silica with hexane/ethyl acetate (10/1) affords product **7** as a colorless syrup (1.378 g, 72%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53−7.96 (m, 5H), 7.21 (ddt, J = 16.9, 10.3, 6.6, 1H), 4.93−5.04 (m, 2H), 3.95 (dd, J = 10.2, 4.9, 1H), 3.67 (s, 3H), 1.86−2.14 (m, 4H), 1.40 (quint, J = 7.5, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.0, 136.8, 136.7, 133.9, 128.9, 128.7, 115.2, 70.4, 52.6, 32.6, 25.8, 25.7.

{2-[3-(4-Penten-1-yl)oxiranyl]allyloxy}-*tert*-butyldimethylsilane (6). *tert*-BuLi (787 μL, 1.26 mmol, 1.6 M in hexane) is added via syringe to a solution of sulfonium salt **5** (450 mg, 1.25 mmol)[2] in THF (25 mL) at −78 °C. After 15 min at that temperature, 5-hexenal (123 mg, 1.25 mmol) is introduced, and the mixture is stirred for an additional 15 min at −78 °C and then slowly warmed to room temperature. The reaction is extracted with H_2O/ethyl acetate, and the organic layer is dried over Na_2SO_4 and evaporated. Purification of the crude product by flash chromatography (SiO_2, hexane/ethyl acetate = 50/1) furnishes compound **6** as a pale yellow oil (283 mg, 80%, mixture of isomers): ^{1}H NMR (200 MHz, $CDCl_3$): δ

(17) For syntheses of other bioactive pyrrole and indole derivatives from this laboratory, see: (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305−8314. (b) Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637−6641. (c) Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*. 5215−5229. (d) Fürstner, A.; Ernst, A.; Krause, H.; Ptock, A. *Tetrahedron* **1996**, *52*, 7329−7344. (e) Fürstner, A.; Ernst, A. *Tetrahedron* **1995**, *51*, 773−786. (f) Fürstner, A.; Ptock, A.; Weintritt, H.; Goddard, R.; Krüger, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 678−681. (g) Fürstner, A.; Jumbam, D. N.; Seidel, G. *Chem. Ber.* **1994**, *127*, 1125−1130. (h) Fürstner, A.; Jumbam, D. N. *J. Chem. Soc., Chem. Commun.* **1993**, 211−212. (i) Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442−2469.

5.76 (m, 1H), 5.22−5.12 (m, 1.6H) 5.06−4.88 (m, 2.4H), 4.17−4.13 (m, 1.2H), 4.08 (m, 0.8H), 3.43 (m, 0.6H), 3.14 (d, J = 2.2 Hz, 0.4H), 3.04 (m, 0.6H), 2.86 (m, 0.4H), 2.18−1.98 (m, 2H), 1.67−1.33 (m, 4H), 0.89 (s, 5.4H), 0.88 (s, 3.6H), 0.05 (s, 3.6H), 0.04 (s, 2.4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.8, 142.2, 138.3, 138.2, 114.9, 114.7, 112.0, 111.3, 64.5, 62.7, 59.9, 58.6, 58.4, 56.3, 33.5, 33.4, 31.7, 26.1, 25.9, 25.5, 25.1, 18.4, 18.3, −5.4. Anal. Calcd for $C_{16}H_{30}O_2Si$: C 68.03, H 10.70. Found C 68.15, H 10.65.

Triene 8. Epoxide **6** (170 mg, 0.6 mmol) is added to a solution of $Pd(PPh_3)_4$ (75 mg, 0.06 mmol) and sulfone **7** (165 mg, 0.58 mmol) in THF (20 mL), and the resulting yellow mixture is stirred at room temperature for 24 h. An extractive work up with H_2O/ethyl acetate, drying of the organic layer over Na_2SO_4, evaporation of the solvent, and flash chromatography (SiO_2, hexane/ethyl acetate = 10/1) afford (*E*)-**8** (118 mg, 36%) and (*Z*)-**8** (160 mg, 49%) as colorless syrup each. Data of (*E*)-**8:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83−7.78 (m, 2H), 7.64 (m, 1H), 7.58−7.48 (m, 2H), 5.86−5.67 (m, 2H), 5.59 (d, J = 9.3 Hz, 1H), 5.04−4.89 (m, 4H), 4.48 (dt, J = 9.2, 6.0 Hz, 1H), 3.96 (dd, J = 13.7, 1.1 Hz, 1H), 3.84 (dd, J = 13.7, 1.0 Hz, 1H), 3.61 (s, 3H), 3.17 (d, J = 14.3 Hz, 1H), 2.64 (d, J = 14.3 Hz, 1H), 2.18−1.20 (m, 13H), 0.80 (s, 9H), −0.03 (s, 3H), −0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 138.5, 138.0, 136.8, 134.1, 134.0, 133.8, 130.5, 128.5, 115.2, 114.6, 76.3, 67.5, 66.4, 52.7, 36.6, 34.2, 33.6, 31.4, 30.0, 25.8, 24.5, 23.5, 18.2, −5.3, −5.4. HRMS ($C_{30}H_{48}O_6SSi$ + Na): calcd 587.28386; found 587.28182. Anal. Calcd for $C_{30}H_{48}O_6SSi$: C 63.79, H, 8.56. Found C 63.81, H, 8.66.

Data of (*Z*)-**8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94−7.76 (m, 2H), 7.63 (m, 1H), 7.58−7.47 (m, 2H), 5.84−5.65 (m, 2H), 5.60 (d, J = 9.5 Hz, 0.75H), 5.29 (d, J = 8.3 Hz, 0.25H), 5.04−4.88 (m, 4H), 4.33 (m, 0.25H), 4.20 (m, 0.75H), 4.09 (m, 0.5H), 3.93−3.86 (m, 1.5H), 3.67 (s, 2.25H), 3.61 (s, 0.75H), 2.88 (d, J = 13.7 Hz, 0.75H), 2.78 (d, J = 13.7 Hz, 0.75H), 2.77 (m, 0.5H), 2.19−1.26 (m, 13H), 0.82 (s, 6.75H), 0.80 (s, 2.25H), −0.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.84, 168.48, 138.50, 138.36, 137.89, 137.65, 137.08, 137.02, 136.41, 135.00, 134.60, 134.00, 133.90, 133.19, 130.89, 130.57, 128.48, 115.20, 115.09, 114.69, 114.59, 76.48, 76.31, 67.36, 66.99., 66.07, 61.19, 52.65, 52.49, 37.45, 36.55, 36.36, 34.26, 34.19, 33.58, 32.74, 31.98, 30.61, 25.79, 25.74, 24.62, 24.56, 23.69, 23.45, 18.23, 18.05, −5.33, −5.38, −5.48. HRMS ($C_{30}H_{48}O_6SSi$ + Na): calcd 587.28386; found 587.28327.

Macrocycle 9. Solutions of (*E*)-**8** (52 mg, 0.09 mg) and of the ruthenium carbene $Cl_2(PCy_3)_2Ru{=}CHCH{=}CPh_2$ (8 mg, 0.009 mmol)[10] in CH_2Cl_2 (30 mL each) are simultaneously added via two dropping funnels to refluxing CH_2Cl_2 (30 mL) over a period of ≈10 h. Stirring is continued at that temperature until TLC shows complete conversion of the substrate (≈120 h). For workup the solvent is evaporated and the crude product purified by flash chromatography (SiO_2, hexane/ethyl acetate = 10/1 → 4/1) affording compound **9** (40 mg, 81%, mixture of isomers) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93−7.78 (m, 2H), 7.69−7.46 (m, 3H), 5.86 (d, J = 9.0 Hz, 0.3H), 5.62 (d, J = 8.7 Hz, 0.7H), 5.53−5.22 (m, 2H), 4.49 (m, 1H), 4.39 (d, J = 15.2 Hz, 0.3H), 4.13 (d, J = 15.2 Hz, 0.3H), 3.84 (s, 1.4H), 3.61 (s, 0.9H), 3.60 (s, 2.1H), 3.17 (m, 0.6H), 3.01 (d, J = 15.0 Hz, 0.7H), 2.59 (d, J = 15.0 Hz, 0.7H), 2.33−1.15 (m, 13H), 0.90 (s, 2.7H), 0.86 (s, 6.3H) 0.07 (s, 1.8H), 0.00 (s, 2.1H), −0.01 (s, 2.1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.44, 169.22, 137.60, 135.08, 134.32, 133.94, 131.87, 131.78, 131.54, 130.76, 130.72, 130.08, 128.63, 128.52, 68.01, 66.52, 66.36, 66.12, 52.81, 52.57, 36.47, 34.14, 33.94, 32.54, 31.77, 30.99, 30.44, 30.33, 27.29, 26.96, 25.96, 25.89, 25.81, 25.31, 24.68, 23.54, 23.12, 22.02, 18.29, −5.27, −5.32. Anal. Calcd for $C_{28}H_{44}O_6SSi$: C 62.65, H, 8.26. Found C 62.67; H, 8.28.

The cyclization of (*Z*)-**8** (87 mg, 0.15 mmol) proceeds analogously and is worked up after a reaction time of 72 h affording **9** (67 mg, 81%) as a mixture of isomers. A cyclization carried out with a (*E,Z*)-mixture of **8** afforded product **9** in 85% yield.

Macrocycle 4. A solution of compound **9** (60 mg, 0.112 mmol) and $RhCl(PPh_3)_3$ (26 mg, 0.028 mmol) in EtOH (20 mL) is stirred under H_2 (1 atm) for 16 h at ambient temperature. For workup the solvent is evaporated, and the crude product is purified by flash chromatography (SiO_2, hexane/ethyl acetate = 10/1 → 4/1) affording compound **4** (54 mg, 90%) as a colorless oil. Its analytical and spectroscopic data are identical in all respects to those previously reported.[2a]

***N*-Allylfuran-2-carboxylic Acid Amide (17a).** A solution of furan-2-carboxylic acid chloride (2.0 mL, 20.3 mmol) in CH_2Cl_2 is slowly added to a stirred solution of allylamine (1.27 mL, 16.9 mmol) and catalytic amounts of DMAP in CH_2Cl_2 (30 mL) and pyridine (3 mL). After stirring for 2 h, the reaction is quenched with sat. aqueous $NaHCO_3$. Standard extractive work up followed by flash chromatography (SiO_2, hexane/ethyl acetate 4/1 → 2/1) provides compound **17a** as a colorless syrup (1.73 g, 68%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39 (dd, J = 1.8, 0.9, 1H), 7.08 (dd, J = 3.5, 0.8, 1H), 6.50 (br s, 1H), 6.45 (dd, J = 3.5, 1.7, 1H), 5.97−5.78 (m, 1H), 5.27−5.10 (m, 2H), 4.01 (tt, J = 5.8, 1.5, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.2, 147.9, 143.8, 133.9, 116.6, 114.2, 112.1, 41.4. Anal. Calcd for $C_8H_9NO_2$: C 63.57, H 6.00, N 9.27. Found: C 63.62, H 5.98, N 9.21.

***N*-(3-Chloro-2-propenyl)furan-2-carboxylic Acid Amide (17b).** Obtained as described above starting from (*E,Z*)-3-amino-1-chloro-1-propene (1.01 g, 11.0 mmol) and furan-2-carboxylic acid chloride (1.36 mL, 13.8 mmol) as a pale yellow oil (1.167 g, 59%). Mixture of stereoisomers, characteristic data: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39 (dd, J = 1.8, 0.8, 1H), 7.09−7.07 (m, 1H), 6.60 (br s, 1H), 6.46 (dd, J = 3.4, 2.0, 1H), 6.24−6.13 (m, 1H), 6.03−5.85 (m, 1H), 4.19 (dt, J = 6.2, 1.5, 1H), 4.00 (dt, J = 6.2, 1.3, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.3, 158.1, 147.6, 147.5, 144.0, 143.9, 129.2, 127.7, 121.3, 120.9, 114.5, 114.3, 112.1, 112.0, 38.9, 35.8. Anal. Calcd for $C_8H_8ClNO_2$: C 51.77, H 4.34, N 7.55. Found: C 51.85, H 4.30, N 7.48.

2-(Furan-2-yl)-1*H*-pyrrole (20a). Amide **17a** (1.69 g, 11.2 mmol) is added to a solution of phosgene in toluene (20% w/w, 25 mL) containing a catalytic amount of DMF. The resulting mixture is stirred for 16 h at ambient temperature. The volatiles are removed in vacuo (1 mbar) at 40−50 °C, the residue is dissolved in THF (15 mL), and the resulting solution is added dropwise to a solution of *tert*-BuOK (3.76 g, 33.6 mmol) in DMF (15 mL) at 5−10 °C. After stirring for 10 min at that temperature, the mixture is poured into chilled water, the aqueous phase is extracted with ether, the organic layer is dried (Na_2SO_4), and the solvent is evaporated. Flash chromatography of the residue (SiO_2, hexane/ethyl acetate 10/1) affords the compound **20a** as a pale yellow solid (0.847 g, 57%).[13] ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.51 (br s, 1H), 7.34 (dd, J = 1.8, 0.7, 1H), 6.81−6.77 (m, 1H), 6.44−6.41 (m, 2H), 6.35−6.33 (m, 1H), 6.28−6.25 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.3, 140.3, 118.1, 111.4, 109.7, 105.3, 102.2.

3-Chloro-2-(furan-2-yl)-1*H*-pyrrole (20b). Prepared as described above starting from amide **17b** (1.167 g, 6.29 mmol). This product is a rather unstable syrup (255 mg, 24%) and is immediately N-silylated for characterization.

2-(Furan-2-yl)-1-triisopropylsilyl-1*H*-pyrrole (21a). A solution of compound **20a** (400 mg, 3.01 mmol) in THF (5 mL) is added to a suspension of KH (132 mg, 3.31 mmol) in THF (20 mL). After the evolution of H_2 has ceased, TIPSCl (0.71 mL, 3.31 mmol) is added, and the resulting mixture is stirred for 15 min. Standard extractive workup followed by flash chromatography (SiO_2, hexane/ethyl acetate 20/1) delivers compound **21a** as a pale yellow syrup (739 mg, 85%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39 (dd, J = 1.8, 0.9, 1H), 6.94 (dd, J = 2.8, 1.5, 1H), 6.44−6.39 (m, 2H), 6.34−6.27 (m, 2H), 1.38−1.19 (m, 3H), 1.06 (d, J = 6.8, 18H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.1, 140.9, 127.6, 115.1, 111.1, 109.8, 18.3, 12.9. HRMS ($C_{17}H_{27}NOSi$) calcd 289.18619; found 289.18653.

3-Chloro-2-(furan-2-yl)-1-triisopropylsilyl-1*H*-pyrrole (21b). Prepared as described above from substrate **20b** (210 mg, 1.25 mmol), KH (55 mg, 1.38 mmol), and TIPSCl (0.30 mL, 13.8 mmol). Colorless syrup (336 mg, 83%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44 (dd, J = 1.8, 0.8, 1H), 6.82 (d, J = 3, 1H), 6.51−6.45 (m, 2H), 6.28 (d, J = 3, 1H), 1.29−1.12 (m, 3H), 1.05 (d, J = 6.4, 18H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.1,

141.7, 126.3, 116.8, 112.0, 111.2, 110.6, 18.2, 12.6. HRMS ($C_{17}H_{26}ClNOSi$): calcd 323.14722; found 323.14594.

Prototype Condensation Procedure: 2-{5-[1-(2*H*-Pyrrol-2-ylidene)ethyl]-2-furanyl}-1*H*-pyrrole Hydrochloride (15·HCl). n-BuLi (1.6 M in hexane, 275 μL, 0.44 mmol) is added to a solution of compound **21a** (128 mg, 0.44 mmol) in THF (5 mL) at −78 °C. After stirring for 6 h at that temperature, the resulting solution is transferred via cannula to a cooled (−78 °C) suspension of $CeCl_3$ (108 mg, 0.44 mmol) in THF (5 mL), which has been stirred for 4 h at room temperature prior to use. After another 2 h, a solution of the potassium salt of 2-acetylpyrrole [prepared upon treatment of 2-acetylpyrrole (34 mg, 0.31 mmol) with KH (12 mg, 0.31 mmol) in THF (3 mL)] is added at −78 °C, and the resulting mixture is allowed to reach ambient temperature overnight. The reaction mixture is extracted with aq NH_4Cl and ether, and the organic layer is treated with aq HCl (10% w/w, ca. 0.5 mL) for 5 min, neutralized (Na_2CO_3), and dried (Na_2SO_4). The resulting, labile product is rapidly passed through a plug of alumina (neutral) using hexane/ethyl acetate (10/1) as the eluent. The product-containing fractions are concentrated to a total volume of ca. 3 mL, diluted with THF (5 mL), and then treated with TBAF (1 M in THF, ca. 0.2 mL) for 5 min. Extraction of the resulting labile product **15** with ether, drying of the organic layer, rapid flash chromatography over alumina (neutral; hexane/ethyl acetate, 2/1), treatment of the combined, product-containing fractions with a saturated solution of HCl in THF, and subsequent evaporation of the solvents provides the desired condensation product **15**·HCl as a dark blue solid (20 mg, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.36 (br s, 1H), 12.83 (br s, 1H), 8.17 (virt quint, J = 1.8, 1H), 7.80 (d, J = 4.7, 1H), 7.49 (m, 1H), 7.23 (m, 1H), 7.05 (m, 1H), 6.86 (d, J = 4.7, 1H), 6.50 (m, 1H), 6.39 (virt quint, J = 2.0, 1H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 150.3, 142.7, 137.4, 133.8, 132.4, 130.4, 128.6, 121.6, 120.6, 115.9, 114.2, 114.0, 17.7. MS (ESI pos): m/z (rel intensity) 225 (100, $[(M + H)^+]$.

3-Chloro-2-{5-[1-(2*H*-pyrrol-2-ylidene)ethyl]-2-furanyl}-1*H*-pyrrole Hydrochloride (14·HCl). Prepared as described above employing substrate **21b** (145 mg, 0.45 mmol), n-BuLi (281 μL, 0.45 mmol), $CeCl_3$ (111 mg, 0.45 mmol), and the potassium salt of 2-acetylpyrrole [prepared from 2-acetylpyrrole (35 mg, 0.32 mmol) and KH (13 mg, 0.32 mmol)]. The product is obtained as a dark blue solid (22 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.34 (br s, 1H), 13.13 (br s, 1H), 8.34 (m, 1H), 7.86 (d, J = 4.6, 1H), 7.43 (d, J = 4.6, 1H), 7.39 (m, 2H), 6.61 (m, 1H), 6.38 (virt. t, J = 2.3, 1H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 149.8, 145.5, 137.1, 135.5, 131.2, 130.5, 129.6, 123.4, 117.3, 116.9, 114.2, 113.7, 18.1. MS (ESI pos): m/z (rel intensity) 259 (100, $[(M + H)^+]$.

3-Chloro-2-{4-methoxy-5-[1-(2*H*-pyrrol-2-ylidene)ethyl]-2-furanyl}-1*H*-pyrrole Hydrochloride (13·HCl). Prepared as described above employing substrate **3** (R = Si(^{i}Pr)$_3$, 39 mg, 0.11 mmol), n-BuLi (69 μL, 0.11 mmol), $CeCl_3$ (27 mg, 0.11 mmol), and the potassium salt of 2-acetylpyrrole [prepared from 2-acetylpyrrole (6 mg, 0.06 mmol) and KH (3.2 mg, 0.08 mmol)]. The product is obtained as a dark red solid (5.7 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.50 (br s, 1H), 12.50 (br s, 1H), 8.10 (m, 1H), 7.44 (m, 1H), 7.24 (m, 1H), 7.08 (br s, 1H), 6.50 (virt. quint. J = 2.1, 1H), 6.40 (t, J = 2.3, 1H), 4.21 (s, 3H), 2.67 (s, 3H). All other spectroscopic data are identical to those reported in the literature.[3a]

2-Acetyl-1-(trimethylsilylethoxymethyl)-1*H*-pyrrole (24). To a suspension of KH (48 mg, 1.20 mmol) in DMF (5 mL) is added 2-acetylpyrrole (87 mg, 0.80 mmol). After stirring for 5 min at room temperature, SEMCl (0.29 mL, 1.6 mmol) is added via syringe, and the resulting mixture is stirred for 1 h to reach complete conversion. A standard extractive workup followed by flash chromatography of the crude product (SiO_2, hexane/ethyl acetate 10/1) affords compound **24** as a colorless syrup (157 mg, 82%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.04 (dd, J = 2.6, 1.7, 1H), 6.96 (dd, J = 4.0, 1.7, 1H), 6.17 (dd, J = 4.0, 2.6, 1H), 5.70 (s, 2H), 3.41 (m, 2H), 2.35 (s, 3H), 0.86 (m, 2H), −0.06 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 188.5, 130.6, 129.7, 120.9, 109.2, 77.3, 66.0, 27.3, 17.8, −1.5. Anal. Calcd for $C_{12}H_{21}NO_2Si$: C 60.21, H 8.84, N 5.85. Found: C 60.05, H 8.88, N 5.83.

Alternative Condensation Procedure: 2-{5-[1-(2*H*-Pyrrol-2-ylidene)ethyl]-2-furanyl}-1*H*-pyrrole Hydrochloride (15·HCl). A solution of compound **21a** (200 mg, 0.69 mmol) in THF (5 mL) is treated with n-BuLi (1.6 M in hexane, 430 μL, 0.69 mmol) at −50 °C for 4 h. The resulting mixture is transferred via cannula to a cooled (−78 °C) suspension of $CeCl_3$ (170 mg, 0.69 mmol) in THF (5 mL), which has been stirred for 4 h at room temperature prior to use. After stirring for 1.5 h at that temperature, a solution of compound **24** (100 mg, 0.42 mmol) in THF (5 mL) is introduced and the temperature gradually raised to room temperature overnight. Extraction with aq NH_4Cl and ether, drying of the organic phase (Na_2SO_4), evaporation of the solvent, and passing of the crude product through a plug of alumina (neutral, hexane/ethyl acetate 10/1) affords alcohol **23** (180 mg, 81%) as a rather unstable oil which is deprotected without delay. For this purpose, a mixture of **23** (90 mg, 0.17 mmol) and TBAF (1 M in THF, 0.7 mL, 0.7 mmol) in THF (5 mL) is stirred for 3 h at 60 °C. Et_2O and aqueous $NaHCO_3$ (sat.) are added, and the resulting organic layer is acidified with HCl (10% w/w) and stirred for 5 min at room temperature to effect the elimination of the OH group. Neutralization with aqueous Na_2CO_3 (5% w/w), drying of the organic phase (Na_2SO_4), rapid elution of the crude material through a plug of alumina (hexane/ethyl acetate, 2/1), and treatment of the concentrated, product-containing fractions with a saturated solution of HCl in THF, followed by evaporation of the solvent in vacuo, affords product **15**·HCl as a dark blue solid. The analytical and spectroscopic data are identical to those compiled above.

Deschloro-desmethoxyroseophilin Hydrochloride (12·HCl). Prepared as described above starting from substrates **21a** (37 mg, 0.128 mmol) and **2** (R = Si(^{i}Pr)$_3$, 11 mg, 0.027 mmol). The product is obtained as a dark blue solid (5.5 mg, 48%) which exhibits the following spectroscopic properties: ^{1}H NMR (600 MHz, $CDCl_3$): δ 14.27 (br s, 1H), 13.61 (br s, 1H), 7.47 (d, J = 4.3, 1H), 7.33 (m, 1H), 6.90 (m, 1H), 6.80 (d, J = 4.3, 1H), 6.32 (m, 1H), 6.26 (s, 1H), 3.69−3.64 (m, 1H), 3.60 (m, 1H), 2.90 (ddd, J = 13, 5.6, 3.8, 1H), 2.77 (d, J = 6.3, 1H), 2.20−2.16 (m, 2H), 1.88−1.78 (m, 2H), 1.41−1.34 (m, 2H), 1.20−1.17 (m, 2H), 1.09−1.01 (m, 1H). 1.02 (d, J = 6.7, 3H), 0.96−0.92 (m, 2H), 0.83−0.76 (m, 2H), 0.81 (d, J = 6.7, 3H), 0.43−0.34 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.6 (s), 162.9 (s), 161.5 (s), 145.6 (s), 144.4 (s), 137.4 (s), 131.4 (d), 127.9 (d), 121.0 (s), 115.8 (d), 112.2 (d), 111.8 (d), 110.3 (d), 56.5 (d), 51.9 (d), 35.8 (t), 33.1 (d), 28.7 (t), 28.2 (t), 27.9 (t), 27.2 (t), 26.8 (t), 24.7 (t), 24.5 (t), 21.4 (q), 19.6 (q). ^{15}N NMR (60 MHz, $CDCl_3$): δ −211, −218. MS (ESI pos): m/z (rel intensity) 389 (100, $[(M + H)^+]$.

Acknowledgment. H.W. is indebted to the Fonds der Chemischen Industrie, Frankfurt, for a stipend.

Supporting Information Available: Compilation of the instrumentation used, list of IR and MS (EI) data, and copies of NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO982088T