Total Synthesis of Roseophilin

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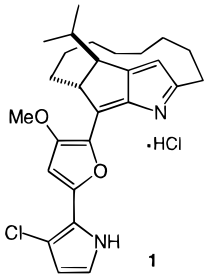
Received November 10, 1997

Abstract: The first total synthesis of the antitumor agent roseophilin **1** is reported. Its intricate macrotricyclic core **2** is obtained by means of a new palladium-catalyzed manifold for the formation of *ansa*-bridged pyrroles which proceeds via vinyl oxirane **8** and allyl lactone **11** as key intermediates. After conversion of the latter into pyrrolophane **14**, a base-induced elimination of the sulfone group followed by the Michael addition of a zincate onto the resulting enone **18** installs the isopropyl substituent in a stereoselective manner. The pyrrolylfuran side chain **3** of roseophilin is prepared from 4-methoxy-2(5H)-furanone (**24**) and methyl 4-chloropyrrole-2-carboxylate (**26**) as the starting materials. The appropriate building blocks **25a** and **28** derived thereof are combined via a sequence comprising a directed metal−halogen exchange reaction, transmetalation of the resulting lithiopyrrole to the corresponding organozinc compound, a palladium-catalyzed cross coupling of the latter, and a subsequent acid-catalyzed closure of the resulting ketone **29** leading to the furan entity of the target. The triisopropylsilyl-protected side chain **3b** is first deprotonated with *n*-BuLi and then transmetalated with $CeCl_3$ to give a highly nucleophilic organocerium reagent, which readily attacks the sterically hindered 2-(trimethylsilyl)ethoxymethyl-protected keto pyrrole **2c**. Deprotection and final dehydration of the tertiary alcohol derivative **30** thus obtained leads to the intact azafulvene chromophore of the natural product and completes our total synthesis of this alkaloid.

Introduction

In 1992, Seto et al. disclosed the structure of roseophilin (**1**), a novel antibiotic isolated from *Streptomyces griseoviridis*.[1] This alkaloid possesses a topologically unique skeleton combining a rather strained macrocyclic entity with an extended heterocyclic chromophore and exhibits very promising cytotoxicity in vitro against K562 human erythroid leukemia and KB human epidermoid carcinoma cell lines in the sub-micromolar range. These properties render roseophilin a new lead structure in the search for anticancer agents and a rewarding target for total synthesis.



1

Although considerable efforts have been directed toward roseophilin,[2,3] no total synthesis of this intriguing alkaloid has yet been achieved. Since it incorporates an azafulvene-type chromophore, **1** may likely be formed by the condensation of a keto pyrrole segment **2** with the appropriately substituted heterocyclic side chain **3** (Scheme 1).

Model reactions corroborate the viability of this approach: acid-catalyzed reactions of **3a** (R^2 = Ts) with simple 2-acylpyrroles lead to the desired chromophore, albeit in rather low yields.[2a] With this background in mind, the development of a concise synthesis of the *ansa*-bridged keto pyrrole core **2** seemed to be the major challenge en route to roseophilin. Two different approaches to this complex macrotricyclic segment have been described so far, both of which are based on efficient transition metal catalyzed C−C-bond formations as the key steps. We have recently outlined a flexible synthesis of **2** relying on a new palladium-catalyzed manifold for the formation of *m*-pyrrolophanes.[3] An alternative route to this intricate target published by Fuchs et al. shortly afterward is based on ring closing olefin metathesis (RCM),[2c] thus providing further evidence for the notion that RCM is likely to evolve into an attractive method for the formation of macrocyclic systems.[4,5]

Described below is the first total synthesis of racemic roseophilin. Specifically, we outline the rationale of our synthetic blueprint, provide full details of our approach to the keto pyrrole entity **2**, disclose a practical route to the heterocyclic side chain **3**, and report a reliable procedure for the condensation

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

(2) (a) Nakatani, S.; Kirihara, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett*. **1995**, *36*, 8461−8464. (b) Kim, S. H.; Fuchs, P. L. *Tetrahedron Lett.* **1996**, *37*, 2545−2548. (c) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett*. **1997**, *38*, 2601−2604.

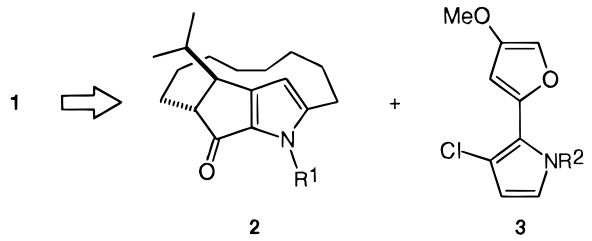
(3) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc*. **1997**, *119*, 2944−2945.

(4) For macrocyclization reactions via RCM from our laboratory, see: (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**, 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.; Koch, D.; Langemann, K.; Leitner, W.; Six, Ch. *Angew. Chem*. **1997**, *109*, 2562−2565. (h) Fürstner, A.; Müller, Th. *J. Org. Chem*. **1998**, *63*, 424−425.

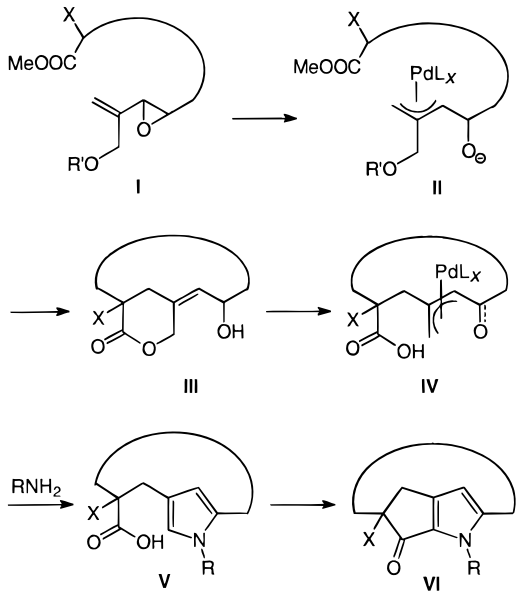
(5) For reviews on RCM, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res*. **1995**, *28*, 446−452. (b) Fürstner, A. *Top. Catal*. **1997**, *4*, 285−299.

S0002-7863(97)03846-8 CCC: $15.00
Published on Web 03/12/1998

Scheme 1



Scheme 2



of these two segments to the intact azafulvene chromophore. This transformation had to be carried out under conditions that are entirely different from those suggested by the model studies in the literature.[2a] Finally, we show that the enantiomers of **1** can be conveniently separated by means of HPLC on a chiral support.

Results and Discussion

Synthesis of the Macrotricyclic Segment. Our plan was to effect the macrocyclization such that it also sets the stage for a convenient construction of the keto pyrrolic entity of the target. On the basis of the subtle differences in reactivity of various allylic precursors in palladium-catalyzed substitution reactions,[6] we perceived a well-orchestrated manifold to achieve this goal (Scheme 2).

Driven by the release of ring strain, the oxidative addition of Pd(0) into a difunctional substrate of the general type **I** should occur in a regioselective manner at the vinyl oxirane site,[7] provided that the allylic OR′ group is properly tuned. The alkoxide **II** thus formed should deprotonate the tethered prenucleophilic malonate entity which will attack the allylpalladium complex and lead to the formation of a macrocyclic ring according to literature precedent.[8] By taking advantage of the juxtaposition of the OR′ group and the incoming ester, a simple lactonization of these entities will activate the remaining allylic position. A second palladium-catalyzed reaction with an amine as the nucleophile will then not only deliver the desired pyrrole ring encoded in the 1,4-dioxygen functionality of the substrate (**III** → **IV** → **V**),[9] but will also liberate the acid for an ensuing intramolecular acylation of the pyrrole C-2 position (**V** → **VI**).

This overall concept allows to forge the macrocyclic entity *before* the strain in the molecule is built-up, which occurs during the kinetically favored formation of the five-membered rings. In contrast, the metathesis approach to **2** reported by Fuchs et al. starts out with a cyclopentene template and forms the fairly rigid *ansa*-chain later on during the synthesis. This strategy succeeded only after the macrocyclization reaction had been conformationally strongly biased in order to override the unfavorable increase in enthalpy during this step.

Our synthetic plan was reduced to practice as shown in Scheme 3. O-Silylation of the known alcohol **4**[10] with tert-butyldimethylsilyl chloride (TBDMSCl), followed by a chloride for iodide exchange and subsequent reaction of the rather unstable allylic iodide with tetrahydrothiophene in the presence of $AgBF_4$ in thoroughly dried acetone afforded the nicely crystalline sulfonium salt **6** in good overall yield.[11] Its deprotonation with *t*-BuLi in THF at −78 °C followed by trapping of the sulfur ylide[12] formed in situ with 9-bromononanal gave the desired vinyl oxirane **7** in 84% isolated yield which was alkylated with methyl (phenylsulfonyl)acetate in DMF under standard conditions at the bromide terminus without affecting the labile functionality at the other end of the chain.[8a] This simple sequence provided gram amounts of compound **8**, which was suitable to test the palladium manifold outlined above.

Gratifyingly, substrate **8** cyclized smoothly to the 13-membered carbocyclic ring **9** in highly reproducible 85% isolated yield when slowly added to a refluxing solution of catalytic amounts of $Pd(PPh_3)_4$ and dppe (dppe = bis(diphenylphosphino)ethane) in THF over a period of 6 h (∼0.0014 M final concentration).[13] The observed, selective activation of the vinyl oxirane group was consistent with our prediction. Some preliminary experiments employing polymer-bound Pd(0) precatalysts previously recommended to facilitate macrocyclization reactions by pseudo-high-dilution[8a,b] led to significantly lower yields. Desilylation of **9** afforded the somewhat strained lactone **10**. The best results in this pivotal step were obtained in a buffered medium with a mixture of TBAF/NH_4F (TBAF = tetrabutylammonium fluoride) as the reagents, whereas TBAF alone led to substantial decomposition of the rather sensitive product. A subsequent oxidation of the OH group with the

(6) For a review, see: Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995.

(7) (a) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc*. **1981**, *103*, 5969−5972. (b) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett*. **1981**, *22*, 2575−2578.

(8) For leading references, see: (a) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc*. **1982**, *104*, 6112−6114. (b) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc*. **1983**, *105*, 5940−5942. (c) Kende, A. S.; Kaldor, I.; Aslanian, R. *J. Am. Chem. Soc*. **1988**, *110*, 6265−6266. (d) Trost, B. M.; Hane, J. T.; Metz, P. *Tetrahedron Lett*. **1986**, *27*, 5695−5698. (e) For a review, see: Trost, B. M. *Angew. Chem*. **1989**, *101*, 1199−1219.

(9) (a) For another palladium-catalyzed pyrrole synthesis, see: Trost, B. M.; Keinan, E. *J. Org. Chem*. **1980**, *45*, 2741−2746. (b) For a timely compilation of pyrrole chemistry, 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.

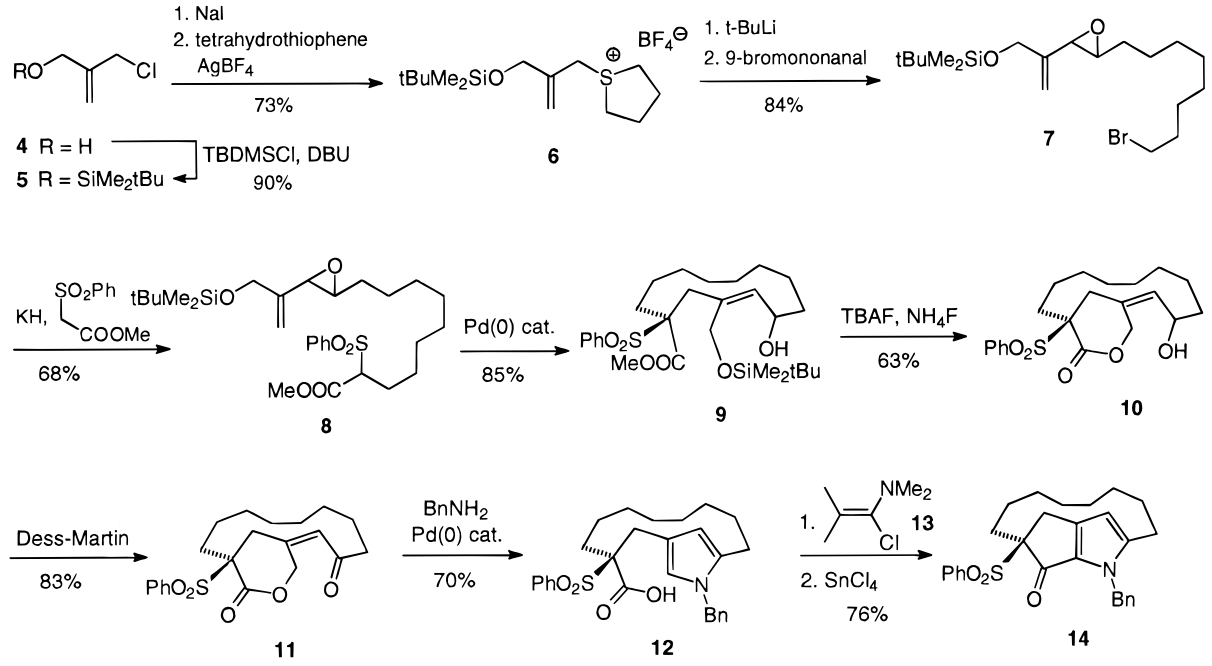
(10) Prepared from 2-(chloromethyl)allyl chloride according to the following: Chalova, O. B.; Christoedova, G. B.; Kiladze, T. K.; Germash, E. V.; Kantor, E. A.; Rakhmankulov, D. L. *Zh. Prikl. Khim*. **1988**, *61*, 934−937; Chem. Abstr. **1989**, *110*, 38603b

(11) Rosenberger, M.; Newkom, C., Aig, E. R. *J. Am. Chem. Soc*. **1983**, *105*, 3656−3661. Since the excess of tetrahydrothiophene can be removed in vacuo, this sulfide is preferred over the nonvolatile PhSPh for practical reasons.

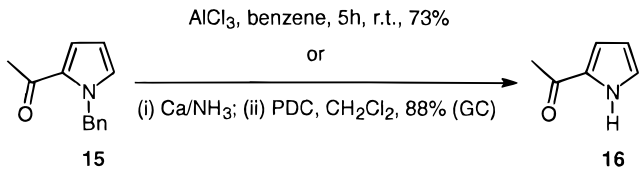
(12) (a) *t*-BuLi was recommended as the deprotonating agent of choice, cf.: LaRochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem*. **1971**, *36*, 1126−1136. (b) For a review, see: Trost, B. M.; Melvin, L. S. *Sulfur Ylides*; Academic Press: New York, 1975; Organic Chemistry Series, Vol. 31.

(13) Products **7**−**11** shown in Scheme 3 were obtained as mixtures of all possible stereoisomers. Since all of them lead to the final product, no attempts were made to separate the individual compounds.

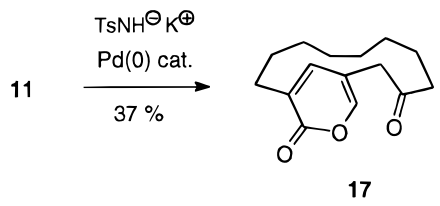
Scheme 3



Scheme 4



Scheme 5



Dess−Martin periodinane[14] provided ketone **11** in 83% yield and set the stage for the envisaged palladium-catalyzed pyrrole formation.

Treatment of **11** with benzylamine in the presence of catalytic amounts of $Pd(PPh_3)_4$ in THF resulted in the clean formation of the desired pyrrole carboxylic acid **12** in 70% yield. The reaction is best carried out at ∼35 °C to avoid problems caused by premature base-induced elimination of the sulfone group and/or concomitant decarboxylation of the acid formed. Benzylamine was selected as the nucleophile because (i) it is known to react readily in palladium catalyzed allylic substitution reactions,[6,9a] (ii) *N*-benzylpyrrole derivatives are stable both under basic and acidic conditions,[9b] (iii) model reactions with 2-acetyl-1-benzylpyrrole (**15**, Scheme 4) have shown that this protecting group can be cleaved either by transalkylation ($AlCl_3$ in benzene)[15] or under reductive conditions (Ca in NH_3).[9,16]

N-Tosylamine and the potassium salt thereof were considered as possible alternatives to benzylamine; however, the former did not participate in the palladium-catalyzed pyrrole formation, while the latter turned out to be too basic and led to the formation of pyrone **17** as the major product via elimination of the sulfone moiety and subsequent rearrangement of the preexisting double bond (Scheme 5).

Compound **12** was then converted into the acid chloride under neutral conditions using the highly convenient α-chloroenamine reagent **13** introduced by Ghosez et al.[17] Subsequent treatment with $SnCl_4$ in refluxing 1,2-dichloroethane cleanly afforded the tricyclic ketone **14** in 76% yield by an intramolecular Friedel−Crafts acylation. This reaction must have occurred regioselectively at C-2 rather than C-4 of the pyrrole ring as can be unambiguously deduced from the observed $^nJ_{C,H}$ correlated NMR spectra of **2a** (vide infra).

We intended to use the sulfone moiety at C-22 (roseophilin numbering) in order to introduce the missing isopropyl substituent at the adjacent position. A base-induced elimination of $PhSO_2H$ followed by a 1,4-addition of an appropriate nucleophile to the resulting enone **18** was expected to effect this transformation. Because the shielding exerted by the fairly rigid *ansa*-chain provides effective facial guidance in the Michael addition step and also forces the protonation of the resulting enolate **19** to occur from the same side, the proper relative configuration of the newly formed chiral centers at C-22 and C-23 is likely to ensue (Scheme 6).

However, our initial attempts along these lines revealed that the tricyclic enone **18** formed upon elimination of the sulfone group with *t*-BuOK in THF at ambient temperature exhibits a peculiar reactivity due to its highly strained character; only a mixture of two dimeric products was formed as suggested by GC/MS analysis of the reaction mixture.[18] We hoped to circumvent this problem by effecting the crucial elimination step

(14) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552.

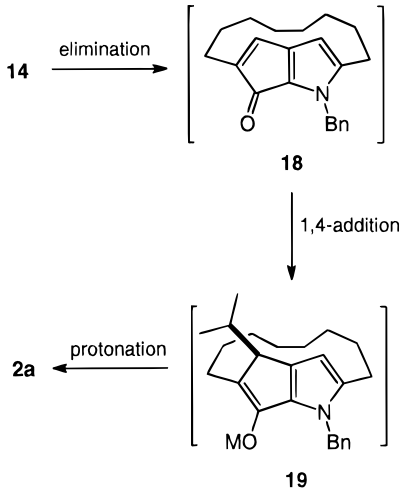
(15) Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. *Synthesis* **1984**, 738−740.

(16) Hwu, J. R.; Chua, V.; Schroeder, J. E.; Barrans, R. E.; Khoudary, K. P.; Wang, N.; Wetzel, J. M. *J. Org. Chem.* **1986**, *51*, 4731−4733.

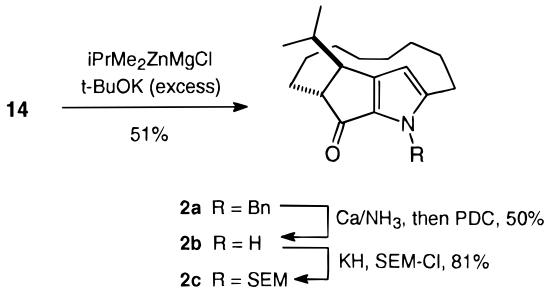
(17) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180−1181.

(18) We did not investigate the structure of these dimers any further. However, there is some precedence in the literature that structurally related heterocyclic ketones are prone to dimerization, cf.: (a) Comer, M. C.; Despinoy, X. L. M.; Gould, R. O.; McNab, H.; Parsons, S. *J. Chem. Soc. Chem. Commun.* **1996**, 1083−1084. (b) Neidlein, R.; Jeromin, G. *Chem. Ber.* **1982**, *115*, 706−713.

Scheme 6



Scheme 7



in the presence of an appropriate nucleophile, thereby intercepting enone **18** directly upon its formation. Cuprates turned out to be unsuitable for this purpose because of their insufficient thermal stability at temperatures where the elimination of the sulfone could be effected.[19] Under these conditions, cuprate decomposition triggers the undesirable reductive cleavage of the sulfone, most likely via single electron-transfer pathways.

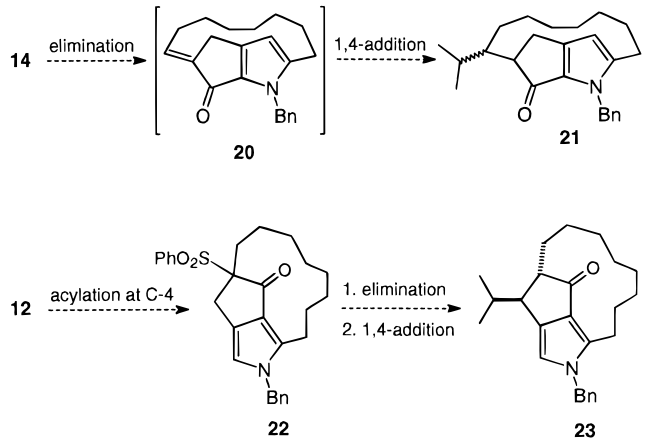
Zincates, which are excellent Michael donors and are known to be thermally more robust, were found to constitute an attractive alternative.[20] Specifically, addition of an excess of *t*-BuOK to a solution of the substrate and *i*-PrMe$_2$ZnMgCl (formed in situ from ZnCl$_2$·TMEDA, 2MeLi, and *i*-PrMgCl) in THF at ambient temperature afforded the desired product **2a** in 51% isolated yield as a single diastereoisomer together with some dimeric byproducts (Scheme 7). The structural integrity of **2a** was unambiguously assigned by extensive 2D NMR investigations (vide infra).

The debenzylation of this compound turned out to be more difficult than anticipated. Since we had verified in model studies that 2-acetyl-1-benzylpyrrole **15** is readily and cleanly deprotected on treatment with AlCl$_3$ in benzene (Scheme 4), it was surprising to find that compound **2a** did not react at all under these conditions. However, the reductive cleavage with Ca in liquid ammonia followed by reoxidation of the adjacent carbonyl group led to the desired macrotricyclic core **2b** of roseophilin.

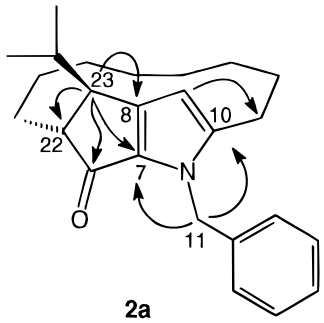
(19) For a comprehensive review on the use of cuprates in 1,4-additions, see: Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631.

(20) (a) Kjonaas, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133−4135. See also: (b) Kjonaas, R. A.; Vawter, E. J. *J. Org. Chem.* **1986**, *51*, 3993−3996. (c) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785−1787. (d) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679−682. (e) Tückwantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581−1593. For a study on the interaction of organozinc reagents with *t*-BuOK, see: (f) Rathke, M. W.; Yu, H. *J. Org. Chem.* **1972**, *37*, 1732−1734.

Scheme 8



Scheme 9



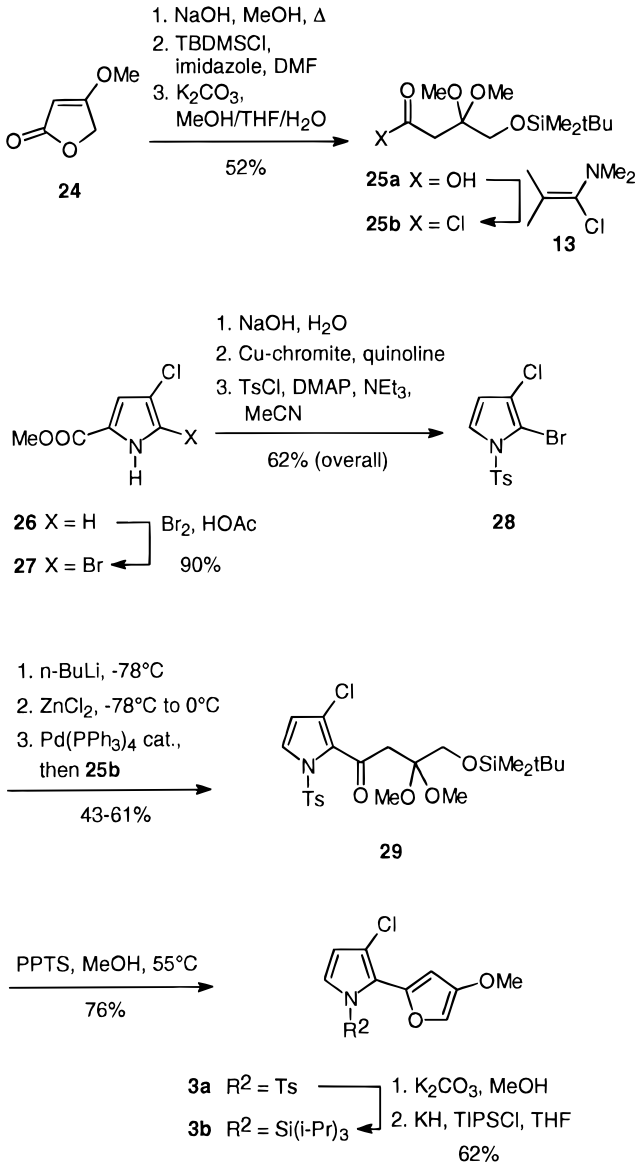
The synthesis of this complex target has thus been achieved in only 11 steps by merging the potential of an established palladium-catalyzed macrocyclization reaction with a conceptually new entry into substituted keto pyrroles. Notably, this strategy is flexible enough to give access to various analogues of **2** as needed for the study of the structure/activity profile of roseophilin.

Structural Investigations. A major concern in this approach to **2** was the regiochemical outcome of the base-induced elimination of the sulfone group (**14** → **18**). One could argue that strain and/or antiaromaticity might prevent the formation of the desired enone **18**, thereby forcing the elimination to occur into the *ansa*-chain. If the resulting product **20** is intercepted by the zincate, this pathway would give rise to a compound of type **21** (Scheme 8).

Yet another question related to the intramolecular Friedel−Crafts acylation: although the C-2 position of an N-benzylated pyrrole ring is generally activated for electrophilic substitution, acylation of C-4 leading to compound **22** and subsequently to **23** could not be ruled out (Scheme 8).

We have addressed these issues by extensive 2D NMR investigations. The results obtained rigorously exclude any undesirable scenario and establish the structural integrity of compound **2a**. A schematic representation of the long-range couplings observed in the $^nJ_{H,C}$ correlated spectra of **2a**, which define the site of acylation of the pyrrole ring and the location of the isopropyl side chain within the cyclopentanone ring, is given in Scheme 9. Specifically, the observed cross-peaks of H-23 with two pyrrolic C-atoms give an unambiguous proof of the site of attachment of the isopropyl group. Moreover, the coupling pattern of H-23 in the ^{1}H NMR spectrum at 600 MHz (d, 2.63 ppm) of $^3J_{H22,H23} \approx 0$ Hz matches that observed in the spectrum of roseophilin itself[1] and confirms the proper relative configuration at these chiral centers.

Scheme 10

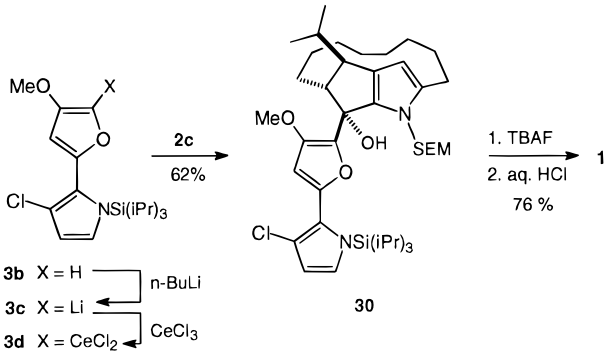


Similar arguments can be advanced to establish the site of acylation of the pyrrole ring. In product **2a**, cross-peaks are observed between the N−C*H*$_2$Ph (H-11) and *two quarternary* α-C-atoms of the trisubstituted pyrrole ring (C-7, C-10), while a cross-peak with the =*C*H atom (C-9) is missing. This excludes the possibility that acylation had occurred at C-4 of the pyrrole and rules out the formation of the isomeric product **23**. Finally, it should be mentioned that the successful completion of this total synthesis and the direct comparison of our synthetic material with an authentic sample of roseophilin confirm the deductions outlined above.

Synthesis of the Heterocyclic Side Chain. Our synthesis of **3** (Scheme 10) started from commercially available 4-methoxy-2(5*H*)-furanone (**24**), which was converted into acid **25a** on a multigram scale by saponification and subsequent adjustment of the silyl protecting groups as shown in Scheme 10. The pyrrole building block was derived from the easily accessible carboxylate **26**[21] which was regioselectively brominated under standard conditions.[22] Saponification of the resulting ester **27** followed by decarboxylation of the crude acid thus

(21) Prepared according to: Bélanger, P. *Tetrahedron Lett.* **1979**, 2505−2508.

Scheme 11



formed afforded a very labile dihalopyrrole which had to be stabilized by tosylation prior to workup. This particular N-substituent also helped to direct the subsequent metal−halogen exchange reaction with *n*-BuLi exclusively to the bromine substituent at the 2-position of the heteroarene **28** without affecting the vicinal chlorine group. The resulting functionalized lithiopyrrole was first transmetalated with $ZnCl_2$ and then cross-coupled in the presence of catalytic amounts of Pd(0)[23] with the crude acid chloride **25b** formed in situ from **25a** on treatment with 1-*N*,*N*-(dimethylamino)-1-chloro-2-methylpropene (**13**).[17] This provided compound **29** in a somewhat variable yield (43−61%), depending on the scale of the reaction. Cleavage of the silyl group on exposure to pyridinium *p*-toluenesulfonate (PPTS) in MeOH[24] led to the cyclization of the side chain with spontaneous aromatization of the newly formed ring to the desired methoxyfuran entity by loss of H_2O and MeOH. This afforded the pyrrolylfuran derivative **3a** on a reasonable scale. This compound had already been employed in previous model studies directed toward roseophilin analogues.[2a]

Completion of the Total Synthesis. It has been reported in the literature that acid-catalyzed condensations of **3a** with simple keto pyrrole derivatives lead to the formation of azafulvene chromophores.[2a] However, our preliminary assays showed that these conditions do not apply to the total synthesis of roseophilin itself since no reaction with the sterically encumbered ketone group of **2** was observed, while the side chain decomposed over prolonged reaction times or under more forcing conditions.

Therefore, we had to develop an alternative method for the end game of our synthesis. We chose an organometallic strategy for the condensation of segments **2** and **3** (Scheme 11), although previous attempts in this direction had been unsuccessful.[25] To secure a regioselective reaction, the *N*-tosyl group in **3a** was replaced by a (*i*-Pr)$_3$Si-substituent (Scheme 10) which should prevent the metalation of the activated 2-position of the pyrrole for steric reasons.[26] Gratifyingly, deprotonation of compound **3b** with *n*-BuLi at low temperature proceeded in fact exclusively on the furan ring. Subsequent transmetalation of the resulting lithium compound **3c** with $CeCl_3$ provided a more highly nucleophilic organocerium species **3d**.[27] Although this reagent added to the potassium salt of 2-acetylpyrrole,[28] no reaction with the potassium salt of **2b** could be achieved. Gratifyingly,

(22) Compare: Hodge, P.; Rickards, R. W. *J. Chem. Soc.* **1965**, 459−470.

(23) (a) Negishi, E.-I.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181−5184. (b) Grey, R. A. *J. Org. Chem.* **1984**, *49*, 2288−2289.

(24) Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19−22.

(25) Terashima et al.[2a] report that they were unable to achieve coupling reactions with model keto pyrroles using lithiated **3a**.

(26) Muchowski, J. M.; Solas, D. R. *Tetrahedron Lett.* **1983**, *24*, 3455−3456.

however, **3d** readily added to the sterically hindered ketone group of the *N*-SEM protected (SEM = 2-(trimethylsilyl)-ethoxymethyl) macrotricyclic ketone **2c**[29] in good yield. Although the resulting tertiary alcohol **30**[30] could be isolated by flash chromatography, it turned out to be rather sensitive and was therefore processed without delay. Thus, exposure of **30** to TBAF in THF at ambient temperature readily cleaved the *N*-Si(*i*-Pr)$_3$ substituent, whereas the SEM group was removed upon warming to ~60 °C. Addition of aqueous HCl then led to the instantaneous appearance of an intense red-orange, fluorescent color which indicated the formation of the protonated azafulvene chromophore of **1** by loss of H_2O. This transformation completed the first total synthesis of the structurally unique target alkaloid. The analytical and spectroscopic data of roseophilin hydrochloride thus obtained match those of an authentic sample in all respects.

Separation of the Enantiomers. The absolute configuration of **1** has not yet been elucidated. However, it is possible to distinguish between the natural and the unnatural enantiomer by HPLC on a Chiraspher column with baseline separation of the antipodes (for details see the Experimental Section and the Supporting Information). This method has also been used on a semipreparative scale to deliver sufficient amounts of (+)-**1** and (−)-**1** for further biological evaluation. Details concerning the physiological activity of unnatural roseophilin as well as of several roseophilin analogues will be reported in due course.

Summary and Outlook

In summary, we have achieved the first total synthesis of the promising antitumor alkaloid roseophilin **1** by a convergent and highly modular approach. The key strategic element for the formation of its macrocyclic entity is a properly balanced palladium manifold leading to the complex pyrrole core. The efficiency and the economy of steps of this sequence are noteworthy. Our synthesis also illustrates that it may require a whole arsenal of organometallic reactions to overcome the problems posed by a seemingly simple heteroaromatic compound such as **3**. Moreover, it should be mentioned that we have been misled by model studies on several occasions during the course of this synthesis, most importantly in the planning of the final steps. This clearly features a still limited capacity to properly assess the extent of homology between recorded and projected cases. Finally, the concept described above may be adapted to afford various analogues of **1** and can also be useful for the synthesis of other natural products containing *m*-pyrrolophane units as found, e.g., in the prodigiosin series.[31] We are presently pursuing some of these possibilities.[32,33]

Experimental Section

General. All reactions were carried out under Ar using Schlenk techniques. All commercially available reagents (Aldrich, Fluka) were used as received. $AgBF_4$ purchased from ACROS gave well-reproducible results in the formation of compound **6**, while samples purchased from other suppliers led to erroneous results. The solvents were dried by distillation over the following drying agents and were transferred under Ar: Et_2O (Mg-anthracene), CH_2Cl_2 (P_4O_{10}), THF (Mg−anthracene), acetonitrile (CaH_2), toluene (Na), DMF (Desmodur/dibutyltin dilaurate), pyridine (KOH), triethylamine (KOH). Flash chromatography was performed with Merck silica gel 60 (230−400 mesh) using hexane/ethyl acetate in various proportions as the eluent. For the instrumentation used, see the Supporting Information.

***tert*-Butyl((2-(chloromethyl)allyl)oxy)dimethylsilane (5).** To a solution of alcohol **4** (4.452 g, 41.8 mmol) in CH_2Cl_2 (80 mL) was added dropwise a solution of TBDMSCl (6.933 g, 46.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 6.88 mL, 46.0 mmol) in CH_2Cl_2 (20 mL) over a period of 1 h at room temperature (rt). After an additional 15 min of stirring, the reaction mixture was poured into $NaHCO_3$ (saturated), the aqueous layer was extracted with CH_2Cl_2, and the organic phases were dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (SiO_2, pentane/ether = 20/1) afforded compound **5** (8.186 g, 90%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.22−5.18 (m, 2H), 4.22 (m, 2H), 4.07 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 114.4, 63.4, 45.0, 25.9, 18.3, −5.4. Anal. Calcd for $C_{10}H_{21}ClOSi$: C, 54.39; H, 9.59. Found: C, 54.55; H, 9.56.

1-[2-(((*tert*-Butyldimethylsilanyl)oxy)methyl)allyl]tetrahydrothiophenium Tetrafluoroborate (6). A solution of allyl chloride **5** (1.369 g, 6.21 mmol) and NaI (0.932 g, 6.21 mmol) in acetone (10 mL) was stirred at 50 °C for 16 h. After the reaction was cooled to rt, the precipitated NaCl was filtered off under argon and washed with acetone (10 mL). Tetrahydrothiophene (1.10 mL, 12.42 mmol) was added to the yellow solution of the allyl iodide, and the flask was wrapped with aluminum foil. After addition of $AgBF_4$ (1.209 g, 6.21 mmol), the resulting suspension was stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), the precipitated AgI was filtered off, and the solvent was evaporated. The crude solid was washed with hexane, the solvent was removed by decantation, and the resulting colorless crystals of the sulfonium salt **6** were dried in vacuo (1.639 g, 73%): mp = 91−92 °C. ^{1}H NMR (200 MHz, THF-d_8): δ 5.55 (d, J = 1.0 Hz, 1H), 5.51 (dd, J = 2.8, 1.5 Hz, 1H), 4.29 (s, 2H), 4.02 (s, 2H), 3.65−3.39 (m, 4H), 2.52−2.22 (m, 4H), 0.95 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (50 MHz, THF-d_8): δ 139.7, 120.8, 65.8, 45.7, 44.2, 29.4, 26.6, 19.3, −5.0. Anal. Calcd for $C_{14}H_{29}BF_4OSSi$. C, 46.67; H, 8.11. Found: C, 46.53; H, 8.06.

{2-[3-(8-Bromooctyl)oxiranyl]allyloxy}-*tert*-butyldimethylsilane (7). To a solution of the sulfonium salt **6** (1.507 g, 4.19 mmol) in THF (50 mL) was added *t*-BuLi (2.79 mL, 4.19 mmol, 1.5 M in hexane) via syringe at −78 °C. After 15 min of stirring at −78 °C, 9-bromononanal (0.842 g, 3.81 mmol) in THF (5 mL) was added, and the mixture was stirred for an additional 15 min at −78 °C and then slowly warmed to rt. The reaction mixture was extracted with H_2O/ethyl acetate, and the organic layer was dried over Na_2SO_4 and evaporated. Purification of the crude product by flash chromatography (SiO_2, hexane/ethyl acetate = 50/1) afforded vinyl oxirane **7** (1.299 g, 84%, mixture of diastereoisomers) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.21−5.15 (m, 1.5H), 4.99 (m, 0.5H), 4.16 (s, 1H), 4.09 (m, 1H), 3.44 (m, 0.5H), 3.38 (t, J = 6.8 Hz, 2H), 3.14 (d, J = 2.1 Hz, 0.5H), 3.03 (m, 0.5H), 2.85 (td, J = 5.3, 2.2 Hz, 0.5H), 1.83 (m, 2H), 1.53−1.18 (m, 12H), 0.90 (s, 4.5H), 0.89 (s, 4.5H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.9, 142.2, 111.9, 111.2, 64.5, 62.7, 60.1, 58.8, 58.4, 56.3, 33.9, 32.8, 32.2, 29.4, 29.3,

(27) For reviews, see: (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. (b) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: New York, 1994.

(28) Fürstner, A.; Weintritt, H. Unpublished results.

(29) The SEM group was chosen because it does not further increase the steric hindrance around the carbonyl group and it can be deprotected simultaneously with the TIPS substituent on the side chain by using fluoride. For a previous application of SEM-protected pyrroles, see: Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723−3729.

(30) The stereochemistry of the newly formed *t*-alcohol has not been rigorously assigned; the configuration shown in Scheme 11 is suggested by the inspection of molecular models.

(31) The prodigiosin tripyrrole pigments are the closest relatives to roseophilin, cf.: (a) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *J. Am. Chem. Soc.* **1969**, *91*, 1264−1265. (b) Laatsch, H.; Kellner, M.; Weyland, H. *J. Antibiot.* **1991**, *44*, 187−191. (c) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *Tetrahedron* **1976**, *32*, 1867−1871. (d) Gerber, N.; N.; McInnes, A. G.; Smith, D. G.; Walter, J. A.; Wright, J. L. C.; Vining, L. C. *Can. J. Chem.* **1978**, *56*, 1155−1163 and literature cited therein.

(32) Fürstner, A.; Krause, H.; Weintritt, H. Unpublished results.

(33) For syntheses of other bioactive natural products from this laboratory see ref 4 and the following: (a) Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637−6641. (b) Fürstner, A.; Ernst, A. *Tetrahedron* **1995**, *51*, 773−786. (c) Fürstner, A.; Ernst, A.; Krause, H.; Ptock, A. *Tetrahedron* **1996**, *52*, 7329−7344. (d) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071−15078. (e) Fürstner, A.; Seidel, G. *J. Org. Chem.* **1997**, *62*, 2332−2336.

28.6, 28.1, 26.6, 26.2, 25.9, 18.4, 18.3, −5.4. Anal. Calcd for $C_{19}H_{37}BrO_2Si$. C, 56.28; H, 9.20. Found: C, 56.32; H, 9.15.

2-(Benzenesulfonyl)-10-{3-[1-(((*tert*-butyldimethylsilanyl)oxy)-methyl)vinyl]oxiranyl}decanoic Acid Methyl Ester (8). Methyl (phenylsulfonyl)acetate (0.656 g, 3.06 mmol) was added to KH (0.123 g, 3.06 mmol) in DMF (15 mL) at rt. After the hydrogen formation had ceased, substrate **7** (1.238 g, 3.06 mmol) in DMF (5 mL) was added and the solution was stirred for 72 h at rt. The mixture was extracted with H_2O/ethyl acetate, and the organic layer was dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (SiO_2, hexane/ethyl acetate = 10/1) afforded compound **8** (1.112 g, 68%, mixture of diastereoisomers) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86−7.82 (m, 2H), 7.68−7.62 (m, 1H), 7.57−7.51 (m, 2H), 5.19−5.13 (m, 1.5H), 4.97 (m, 0.5H), 4.14−4.06 (m, 2H), 3.90 (dd, J = 10.7, 4.3 Hz, 1H), 3.63 (s, 3H), 3.41 (ddd, J = 4.3, 1.2, 0.6 Hz, 0.5H), 3.12 (d, J = 2.1 Hz, 0.5H), 3.02 (m, 0.5H), 2.83 (m, 0.5H), 1.99−1.91 (m, 2H), 1.59−1.48 (m, 1H), 1.37−1.23 (m, 13H), 0.88 (s, 4.5H), 0.87 (s, 4.5H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 144.8, 142.2, 137.1, 134.2, 129.3, 129.0, 111.9, 111.1, 70.9, 64.4, 62.7, 60.0, 58.7, 58.3, 56.2, 52.8, 32.2, 29.3, 29.2, 29.0, 28.9, 26.8, 26.7, 26.6, 26.2, 25.9, 25.8, 18.3, 18.2, −5.39, −5.42. MS: *m*/*z* (rel intensity) 483 (14), 482 (32), 481 (100), 199 (38), 143 (44), 135 (22), 125 (11), 95 (10), 81 (11), 77 (19), 75 (39), 73 (30), 67 (11), 55 (12). IR: 3093, 2952, 2929, 2856, 1745, 1463, 1448, 1327, 1311, 1257, 1150, 1084, 838, 778, 723, 689 cm^{-1}. Anal. Calcd for $C_{28}H_{46}O_6SSi$: C, 62.42; H, 8.61. Found: C, 62.32; H, 8.67.

Macrocycle 9. To a refluxing solution of $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) and dppe (16 mg, 0.04 mmol) in THF (100 mL) was added a solution of substrate **8** (108 mg, 0.20 mmol) in THF (40 mL) dropwise over a period of 6 h. The reaction mixture was refluxed for additional 10 h, cooled to rt, and extracted with H_2O/ethyl acetate, and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 3/1) affording product **7** (92 mg, 85%, mixture of diastereoisomers) as a pale yellow foam. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.83−7.76 (m, 2H), 7.70−7.67 (m, 1H), 7.59−7.54 (m, 2H), 5.89 (d, J = 8.8 Hz), 5.71 (dd, J = 9.6, 1.5 Hz), 5.61 (d, J = 9.0 Hz), 5.25 (d, J = 7.7 Hz) [1H], 4.56−4.07 (m), 4.01 (s), 3.85−3.72 (m) [3H], 3.60 (s), 3.57 (s), 3.56 (s), 3.50 (s) [3H], 3.13−2.78 (m, 2H), 2.20−1.21 (m, 17H), 0.95 (s), 0.92 (s), 0.84 (s), 0.81 (s) [9H], 0.119 (s), 0.117 (s), 0.114 (s), 0.108 (s), 0.014 (s), −0.003 (s), −0.010 (s), −0.015 (s) [6H]. ^{13}C NMR (100 MHz, CD_2Cl_2): δ 169.21, 169.18, 168.92, 168.83, 140.06, 137.45, 137.26, 137.11, 136.73, 136.67, 136.66, 135.94, 135.74, 135.18, 134.45, 134.40, 134.33, 133.96, 132.55, 130.64, 130.57, 130.47, 130.37, 129.21, 129.08, 129.06, 129.01, 77.38, 76.71, 76.47, 76.21, 68.27, 67.94, 67.81, 66.77, 66.34, 66.28, 62.67, 60.52, 38.54, 37.29, 36.85, 36.30, 36.20, 33.95, 31.85, 31.10, 31.07, 30.80, 29.84, 29.30, 29.21, 29.04, 28.63, 27.94, 27.85, 27.43, 27.19, 26.88, 26.72, 26.45, 26.09, 25.99, 25.97, 25.47, 25.14, 24.97, 24.80, 24.67, 24.59, 24.29, 24.13, 24.08, 23.57, 23.41, 21.69, 21.06, 20.57, 18.65, 18.58, 18.44, 18.36, −5.17, −5.19, −5.25, −5.27, −5.30, −5.35, −5.30. MS: *m*/*z* (rel intensity) 481 (17), 431 (16), 339 (28), 322 (11), 321 (42), 307 (16), 265 (30), 233 (29), 200 (15), 199 (100), 187 (18) 135 (30), 91 (11), 81 (11), 79 (11), 75 (49), 73 (39), 67 (12), 55 (12), 41 (10). IR: 3527, 3429, 3065, 2930, 2857, 1736, 1585, 1463, 1447, 1308, 1252, 1144, 1079, 1038, 1005, 838, 778, 721, 691, 610 cm^{-1}. Anal. Calcd for $C_{28}H_{46}O_6SSi$: C, 62.42; H, 8.61. Found: C, 62.36; H, 8.54.

Allyllactone 10. To a solution of silyl ether **9** (736 mg, 1.37 mmol) in THF (125 mL) was successively added NH_4F (253 mg, 6.84 mmol) and TBAF (6.85 mL, 6.85 mmol, 1 M in THF) at rt. After 30 min of stirring, the reaction mixture was extracted with saturated aqueous NaCl/ethyl acetate, and the organic layer was dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (SiO_2, hexane/ethyl acetate = 2/1 → 1/1) afforded lactone **10** (338 mg, 63%, mixture of diastereoisomers) as a colorless foam. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.94−7.84 (m, 2H), 7.73−7.69 (m, 1H), 7.61−7.55 (m, 2H), 5.77−5.69 (m, 1H), 5.08 (dd, J = 13.3, 1.6 Hz), 4.98−4.84 (m), 4.73−4.69 (m), 4.58−4.45 (m), 4.36 (td, J = 9.5, 3.2 Hz) [3H], 3.92 (dd, J = 16.3, 2.6 Hz), 3.75−3.72 (m), 3.53−3.45 (m), 3.42−3.32 (m) 3.02 (dd, J = 16.1, 2.8 Hz), 2.81−2.72 (m) [2H], 2.07−0.89 (m, 17H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 166.60, 166.45, 165.85, 136.28, 135.54, 135.28, 134.63, 134.53, 134.42, 134.35, 134.29, 133.72, 133.37, 133.32, 131.61, 131.45, 131.24, 131.20, 129.50, 129.27, 128.88, 128.76, 128.65, 128.62, 127.92, 127.87, 127.24, 75.73, 74.65, 72.81, 72.76, 72.36, 71.96, 71.88, 70.90, 70.54, 68.52, 67.43, 65.38, 38.32, 37.50, 36.53, 36.23, 35.86, 35.67, 35.38, 34.96, 33.46, 29.82, 29.03, 27.83, 27.76, 27.53, 27.24, 27.02, 26.92, 26.68, 26.03, 25.84, 25.83, 25.36, 25.05, 24.58, 24.39, 24.27, 24.18: 23.63, 23.30, 23.24, 22.71, 22.12. MS: *m*/*z* (rel intensity) 252 (16), 251 (100), 250 (60), 234 (13), 233 (76), 232 (50), 222 (11), 206 (15), 205 (31), 187 (24), 152 (22), 149 (10), 145 (11), 143 (26), 135 (12), 131 (12), 125 (16), 124 (11), 123 (10), 121 (15), 119 (12), 109 (16), 108 (14), 107 (19), 105 (15), 95 (34), 93 (24), 91 (23), 83 (11), 82 (21), 81 (43), 79 (39), 78 (12), 77 (43), 69 (21), 67 (41), 57 (18), 55 (55), 53 (13), 43 (33), 41 (57), 39 (12), 29 (20). IR: 3515, 3066, 2932, 2860, 1730, 1584, 1448, 1307, 1143, 1080, 1000, 722, 689 cm^{-1}. Anal. Calcd for $C_{21}H_{28}O_5S$: C, 64.26; H, 7.19. Found: C, 64.15; H, 7.26.

Ketone 11. Dess−Martin periodinane (825 mg, 1.94 mmol)[14] was added to a solution of alcohol **10** (304 mg, 0.78 mmol) in CH_2Cl_2 (50 mL) at rt. After 3.5 h of stirring, the reaction mixture was filtered through a short pad of silica, the residues were washed with CH_2Cl_2, and the combined organic layers were extracted with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated, and the crude product purified by flash chromatography (SiO_2, hexane/ethyl acetate = 6/1 → 4/1) affording ketone **11** (251 mg, 83%, mixture of diastereoisomers) as a colorless foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97−7.93 (m, 2H), 7.72−7.65 (m, 1H), 7.58−7.55 (m, 1H), 6.55 (m), 6.40 (d, J = 2.7 Hz) [1H], 5.58−5.52 (m), 5.13−5.02 (m), 4.50 (dd, J = 12.2, 2.7 Hz) [2H], 3.70−3.47 (m, 2H), 2.94 (dd, J = 13.0, 1.5 Hz), 2.85 (ddd, J = 16.0, 10.7, 3.1 Hz), 2.70 (m) [2H], 2.35−2.24 (m, 1H), 2.11−1.91 (m, 2H), 1.86−1.66 (m, 1H), 1.62−0.78 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.2, 201.8, 166.2, 165.4, 143.8, 141.3, 134.9, 134.6, 134.5, 133.9, 131.5, 131.2, 129.2, 128.6, 128.5, 127.5, 73.4, 73.1, 70.9, 70.3, 41.8, 40.8, 38.4, 34.6, 34.1, 30.7, 26.4, 26.2, 26.0, 25.8, 25.3, 25.2, 24.8, 23.7, 22.9, 22.4, 22.3, 22.0. MS: *m*/*z* (rel intensity) 250 (16), 249 (100), 248 (92), 221 (16), 220 (11), 151 (14), 150 (15), 142 (11), 137 (21), 136 (11), 124 (21), 123 (18), 122 (11), 119 (10), 107 (11), 105 (13), 95 (14), 94 (14), 93 (15), 91 (22), 81 (18), 79 (28), 78 (18), 77 (54), 69 (11), 67 (30), 66 (12), 65 (16), 55 (42), 53 (13), 51 (17), 43 (25), 41 (51), 39 (19), 29 (16), 27 (12). IR (KBr): 3066, 2941, 2862, 1738, 1688, 1641, 1584, 1447, 1306, 1181, 1142, 1080, 754, 721 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_5S$: C, 64.59; H, 6.71. Found: C, 64.38; H, 6.86.

Pyrrole 12. A solution of $Pd(PPh_3)_4$ (175 mg, 0.15 mmol) and benzylamine (132 μL, 1.21 mmol) in THF (10 mL) was added to a solution of compound **11** (392 mg, 1.01 mmol) in THF (60 mL) at 35 °C. After 1.5 h of stirring, the reaction mixture was extracted with NH_4Cl/ethyl acetate, and the organic layer was dried over Na_2SO_4 and evaporated. After purification of the residue by flash chromatography (SiO_2, hexane/ethyl acetate/acetic acid = 2/1/0 → 2/1/0.1), toluene and then CH_2Cl_2 were successively and repeatedly stripped off in vacuo in order to remove aceotropically any traces of HOAc. The resulting acid **12** was dried in vacuo to yield a yellow solid (340 mg, 70%). ^{1}H NMR (400 MHz, THF-d_8): δ 7.84−7.81 (m, 2H), 7.62−7.57 (m, 1H), 7.51−7.47 (m, 2H), 7.21−7.10 (m, 3H), 6.95−6.93 (m, 2H), 6.46 (d, J = 2.0 Hz, 1H), 5.84 (d, J = 2.0 Hz, 1H), 4.97 (d, AB, J = 16.2 Hz, 1H), 4.91 (d, AB, J = 16.2 Hz, 1H), 3.42 (d, J = 13.8 Hz, 1H), 3.01 (d, J = 13.8 Hz, 1H), 2.52−2.46 (m, 1H), 2.42−2.35 (m, 1H), 2.22−2.14 (m, 1H), 1.65−1.60 (m, 1H), 1.32−0.85 (m, 1H), 0.65−0.62 (m, 1H). ^{13}C NMR (100 MHz, THF-d_8): δ 169.9, 140.5, 138.6, 134.5, 132.4, 131.9, 129.5, 129.4, 128.1, 127.5, 122.3, 117.0, 113.3, 77.8, 51.2, 31.6, 30.3, 28.3, 27.8, 27.7, 27.6, 27.2, 26.7, 23.2. MS: *m*/*z* (rel intensity) 480 (16), 479 ([M$^+$], 47), 339 (19), 338 (78), 337 (24), 91 (100), 44 (11). IR (KBr): 3400−2500, 3065, 2931, 2848, 1701, 1448, 1322, 1307, 1147, 1079, 811, 731, 688 cm^{-1}. HRMS ($C_{28}H_{33}NO_4S$): calcd 479.21303; found 479.21177.

Pyrone 17. A solution of $Pd(PPH_3)_4$ (23 mg, 0.02 mmol) in THF (1 mL) and ketone **11** (50 mg, 0.13 mmol) were successively added to a solution of TsNHK (33 mg, 0.16 mmol) and $TsNH_2$ (2 mg, 0.01 mmol) in THF (9 mL) and DMSO (2 mL). The mixture was stirred at rt for 24 h, the reaction was quenched with aqueous saturated $NaHCO_3$,

the aqueous layer was extracted with ether, the combined organic layers were dried (Na_2SO_4), and evaporated, and the crude product was purified by flash chromatography (hexane/ethyl actetate 4/1) to afford pure **17** as a pale yellow solid (12 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 1H), 6.99 (m, 1H), 3.25 (s, 2H), 2.54−2.48 (m, 4H), 1.69−1.57 (m, 4H), 1.25−1.03 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1, 162.3, 147.3, 139.4, 129.5, 113.1, 43.5, 42.1, 29.1, 26.1, 25.9, 25.7, 24.9, 23.7, 23.2.

Macrotricycle 14. 1-(*N*,*N*-dimethylamino)-1-chloro-2-methylprop-1-ene **(13)** (92 mg, 0.69 mmol) in CH_2Cl_2 (2 mL) was added to a solution of acid **12** (300 mg, 0.63 mmol) in CH_2Cl_2 (35 mL) at rt. After 2 h of stirring, the solvent was removed in vacuo (10^{-2} mbar) at rt, and the resulting oil was dried for 2 h. The acid chloride thus obtained was dissolved in refluxing 1,2-dichloroethane (40 mL) and treated dropwise with $SnCl_4$ (82 μL, 0.7 mmol) via syringe. After 1 h of reaction time, the solution was cooled to rt, extracted with aqueous saturated $NaHCO_3$/CH_2Cl_2, and the organic layer was dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (SiO_2, hexane/ethyl acetate = 6/1) afforded keto pyrrole **14** (222 mg, 76%) as a colorless foam. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.98−7.94 (m, 2H), 7.67−7.61 (m, 1H), 7.55−7.49 (m, 2H), 7.35−7.28 (m, 3H), 7.15−7.12 (m, 2H), 6.03 (s, 1H), 5.59 (d, J = 15.3 Hz, 1H), 4.96 (d, J = 15.3 Hz, 1H), 3.51 (d, J = 16.4 Hz, 1H), 2.90 (d, J = 16.4 Hz, 1H), 2.75−2.55 (m, 2H), 2.23−2.12 (m, 2H), 1.81−1.73 (m, 1H), 1.49−1.44 (m, 1H), 1.28−1.09 (m, 3H), 0.96−0.83 (m, 4H), 0.77−0.68 (m, 2H), 0.44−0.39 (m, 1H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 182.3, 150.3, 149.0, 137.4, 137.1, 133.7, 130.8, 128.8, 128.6, 127.9, 127.1, 108.1, 82.2, 47.9, 31.9, 29.8, 28.0, 27.5, 27.3, 26.4, 25.2, 24.7. MS: *m*/*z* (rel intensity) 461 ([M$^+$], 25), 321 (14), 320 (65), 319 (80), 91 (100). IR (KBr): 2928, 2856, 1680, 1623, 1484, 1457, 1446, 1391, 1301, 1261, 1143, 1084, 720, 689 cm^{-1}. HRMS ($C_{28}H_{31}NO_3S$): calcd 461.20247; found 461.19802.

Macrotricyle 2a. To a solution of $ZnCl_2$·TMEDA (394 mg, 1.56 mmol) in THF (60 mL) was added MeLi (1950 μL, 3.12 mmol, 1.5 M in ether) at 0 °C, and the solution was stirred for 15 min. *i*-PrMgCl (780 μL, 1.56 mmol, 2 M in THF) was then introduced, and the resulting solution was stirred for an additional 5 min prior to the addition of a solution of sulfone **14** (60 mg, 0.13 mmol) in THF (3 mL). After the reaction was warmed to ambient temperature, a solution of *t*-BuOK (875 mg, 8.00 mmol) in THF (10 mL) was added, and the resulting mixture was stirred for 2 h. A standard extractive workup followed by flash chromatography (SiO_2, hexane/ethyl acetate = 20/1) afforded product **2a** (24 mg, 51%) as a colorless oil. ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.32−7.29 (m, 2H), 7.27−7.24 (m, 1H), 7.20−7.18 (m, 2H), 6.00 (s, 1H), 5.67 (d, J = 15.6 Hz, 1H), 4.98 (d, J = 15.6 Hz, 1H), 2.70−2.65 (m, 2H), 2.63 (d, J = 6.6 Hz, 1H), 2.62−2.57 (m, 1H), 1.98−1.93 (m, 1H), 1.81−1.68 (m, 3H), 1.55−1.48 (m, 1H), 1.26−1.21 (m, 1H), 1.11−0.99 (m, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.94−0.89 (m, 3H), 0.88 (d, J = 6.7 Hz, 3H), 0.78−0.69 (m, 2H), 0.61−0.55 (m, 1H). ^{13}C NMR (150 MHz, CD_2Cl_2): δ 193.41 (s), 153.87 (s), 146.72 (s), 138.40 (s), 134.87 (s), 128.74 (d), 127.55 (d), 126.90 (d), 109.13 (d), 59.44 (d), 48.39 (d), 47.67 (t), 33.28 (d), 31.82 (t), 28.17 (t), 27.73 (t), 27.44 (t), 27.18 (t), 25.46 (t), 25.16 (t), 25.06 (t), 21.20 (q), 19.68 (q). MS: *m*/*z* (rel intensity) 364 (29), 363 ([M$^+$], 100), 348 (16), 321 (36), 320 (58), 91 (84). IR (KBr): 3064, 3031, 2929, 2856, 1673, 1496, 1473, 1456, 1391, 1260, 723, 697 cm^{-1}. HRMS ($C_{25}H_{33}NO$): calcd 363.25621; found 363.25401.

Compound 2b. To a solution of calcium (20 mg, 0.5 mmol) in liquid ammonia (5 mL) was added a solution of **2a** (58 mg, 0.16 mmol) in THF (2 mL) at −30 °C. The dry ice/acetone bath was removed, and the resulting mixture was stirred for 2 h in refluxing ammonia using a dry ice condenser. The solution was diluted with THF (5 mL), slowly warmed to rt, carefully hydrolyzed with aqueous saturated NH_4Cl, and extracted with ether. The organic layer was dried over Na_2SO_4, concentrated to a small volume, diluted with CH_2Cl_2 (10 mL), and treated with pyridinium dichromate (PDC, 126 mg, 0.34 mmol). After 1 h of stirring at rt, the reaction mixture was extracted with CH_2Cl_2/H_2O, the organic layer was washed with 10% HCl and aqueous saturated $NaHCO_3$ and evaporated, and the residue purified by flash chromatography (SiO_2, hexane/ethyl acetate = 4/1) affording **2b**[2c] (15 mg, 50% based on 69% conversion) as colorless oil and unreacted substrate **2a** (18 mg). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 10.52 (br s, 1H), 6.00 (d, J = 1.6 Hz, 1H), 2.89−2.83 (m, 1H), 2.72 (vt, J = 4.2 Hz, 1H), 2.63 (d, J = 6.7 Hz, 1H), 2.61−2.55 (m, 1H), 1.89−1.74 (m, 4H), 1.36−1.19 (m, 4H), 1.04−0.81 (m, 5H), 1.01 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.45−0.42 (m, 2H). ^{13}C NMR (100 MHz, THF-d_8): δ 192.7, 154.9, 147.6, 136.1, 107.4, 59.9, 49.4, 34.5, 32.9, 29.53, 29.46, 29.0, 28.8, 28.5, 26.9, 26.3, 22.1, 20.5. MS: *m*/*z* (rel intensity) 274 (22), 273 ([M$^+$], 100), 258 (35), 231 (25), 230 (37), 202 (14).

Macrotricycle 2c. A solution of compound **2b** (11 mg, 0.04 mmol) in DMF (1.5 mL) was added to KH (3.2 mg, 0.08 mmol) at rt. After 5 min of stirring, SEMCl (14 μL, 0.08 mmol) was introduced, and the mixture was stirred for an additional 45 min and extracted with 5% Na_2CO_3/ether. The organic layer was dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 15/1) affording **2c** (13 mg, 81%) as a colorless oil. ^{1}H NMR (200 MHz, CD_2Cl_2): δ 6.01 (s, 1H), 5.63 (d, J = 10.7 Hz, 1H), 5.29 (d, J = 10.7 Hz, 1H), 3.65−3.45 (m, 2H), 2.77−2.60 (m, 4H), 1.85−1.50 (m, 5H), 1.25−0.45 (m, 12H), 0.99 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H), −0.05 (s, 9H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 193.5, 154.2, 147.4, 140.7, 109.7, 72.5, 65.8, 59.4, 48.3, 33.2, 31.8, 28.2, 27.6, 27.5, 27.2, 25.5, 25.1, 25.0, 21.2, 19.5, 17.8, −1.7. MS: *m*/*z* (rel intensity) 302 (10), 288 (23), 287 (100), 259 (15), 244 (20), 73 (41). HRMS ($C_{24}H_{41}NO_2Si$): calcd 403.29066; found 403.29082.

5-Bromo-4-chloro-1-(toluene-4-sulfonyl)-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (27). To a solution of **26** (2.905 g, 18.2 mmol) in acetic acid (60 mL) was added dropwise a solution of bromine (1.03 mL, 20.0 mmol) in acetic acid (20 mL) at rt. The resulting mixture was stirred at 60 °C for 15 min, cooled to rt, poured into water, and extracted with ether. The organic layer was neutralized with aqueous saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated, and the residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 10/1) thus affording **27** (3.911 g, 90%) as colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.89 (br s, 1H), 6.80 (d, J = 3.0 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 122.6, 115.3, 115.0, 104.6, 52.1. Anal. Calcd for $C_6H_5BrClNO_2$: C, 36.22; H, 2.11; N, 5.87. Found: C, 30.28; H, 2.06; N, 5.84.

2-Bromo-3-chloro-1-(toluene-4-sulfonyl)-1*H*-pyrrole (28). Pyrrole **27** (3.170 g, 13.3 mmol) was stirred with a solution of NaOH (4.3 g, 0.11 mol) in water (65 mL) at 70 °C for 3 h. After cooling to rt, the solution was extracted with ether, and the aqueous layer was acidified to pH ≈1 with 10% HCl and extracted with ether. The organic layer was dried over Na_2SO_4, and the solvent evaporated affording the crude acid as pale purple solid (2.764 g, 93%). The crude acid (2.359 g, 10.5 mmol) was heated with copper chromite (329 mg, 1.05 mmol) in quinoline (13 mL) to 180 °C under argon for 30 min, the resulting suspension was cooled to rt, diluted with ether, and filtered through a short pad of silica, and the residues were washed with ether. The combined organic layers were extracted twice with 10% HCl, neutralized with $NaHCO_3$, dried over Na_2SO_4, and concentrated at rt in vacuo to a volume of approximately 15 mL. To the dark brown solution were added acetonitrile (100 mL), Et_3N (3.25 mL, 23.2 mmol), 4-(dimethylamino)pyridine (DMAP) (cat.), and tosyl chloride (2.212 g, 11.6 mmol), and the mixture was stirred at rt for 16 h. After extraction with CH_2Cl_2/10% HCl, the organic layer was stirred with $NaHCO_3$ (sat.) for 45 min, dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (SiO_2, hexane/ethyl acetate = 10/1) furnished **28** (2.347 g, 67%, 62% overall yield) as colorless crystals. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 3.8 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 6.30 (d, J = 3.7 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 146.0, 134.5, 130.0, 128.0, 127.9, 123.2, 112.7, 99.2, 21.7. HRMS ($C_{11}H_9BrClNO_2S$): calcd 332.92260; found 332.92372.

4-((*tert*-Butyldimethylsilyl)oxy)-3,3-dimethoxybutanoic Acid (25a). 4-Methoxyfuran-2(5*H*)-one **24** (4.00 g, 35.1 mmol) was refluxed with a solution of NaOH (1.67 g, 41.8 mmol) in MeOH (40 mL) for 16 h. The solvent was removed at rt in vacuo, the residue was suspended in DMF (120 mL), TBDMSCl (18.4 g, 0.12 mol) and imidazole (16.6 g, 0.24 mol) were added, and the suspension was stirred for 3 d at rt. The mixture was poured into water and extracted with ether, the organic

layer was dried over Na_2SO_4, the solvent was evaporated, and the residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 30/1). The resulting disilylated compound (8.13 g, 20.7 mmol, colorless oil) was dissolved in MeOH/THF/H_2O (3/1/1, 330 mL) and stirred with K_2CO_3 (10.2 g, 73.9 mmol) at rt for 30 min. The mixture was concentrated to about 70 mL and extracted with ether (ca. 30 mL), and the aqueous layer was diluted with brine (200 mL), acidified with 1 M $KHSO_4$ to pH ≈ 4, and extracted with ether. Drying of the organic layer over Na_2SO_4 and evaporation of the solvent afforded pure acid **25a** (5.06 g, 52%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.69 (s, 2H), 3.26 (s, 6H), 2.77 (s, 2H), 0.88 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.0, 100.8, 62.4, 48.5, 38.5, 25.7, 18.2, −5.7. Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 51.77; H, 9.41. Found: C, 51.64; H, 9.36.

Keto Pyrrole 29. To a solution of acid **25a** (147 mg, 0.53 mmol) in CH_2Cl_2 (5 mL) was added a solution of 1-*N*,*N*-(dimethylamino)-1-chloro-2-methyl-1-propene (**13**) (74 mg, 0.55 mmol)[17] in CH_2Cl_2 (1 mL) under argon. The mixture was stirred at rt for 1.5 h, the solvent was removed in vacuo at rt and the resulting crude acid chloride **25b** was dissolved in THF (5 mL).

To a solution of pyrrole **28** (146 mg, 0.44 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M in hexane, 175 μL, 0.44 mmol) via syringe at −78 °C under argon. After 30 min of stirring at this temperature, this solution was added to dry $ZnCl_2$ (60 mg, 0.44 mmol) in THF (5 mL) via cannula at −78 °C, and the resulting mixture was stirred at 0 °C for 1 h. $Pd(PPh_3)_4$ (25 mg, 0.02 mmol) in THF (1 mL) and the solution of the crude **25b** were successively added at rt, and the mixture was stirred for 3 h. After extraction with aqueous saturated NH_4Cl/ether, the organic layer was dried over Na_2SO_4, the solvent was evaporated, and the residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 20/1) affording **29** (138 mg, 61%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 3.5 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 6.23 (d, J = 3.4 Hz, 1H), 3.74 (s, 2H), 3.38 (s, 2H), 3.20 (s, 6H), 2.40 (s, 3H), 0.83 (s, 9H), −0.01 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 187.6, 145.1, 135.8, 130.4, 129.4, 128.4, 126.4, 122.2, 112.7, 101.7, 61.3, 48.2, 42.9, 25.8, 21.7, 18.2, −5.6. Anal. Calcd for $C_{23}H_{34}ClNO_6SSi$: C, 53.52; H, 6.64; N, 2.71. Found: C, 53.42; H, 6.61; N, 2.78.

3-Chloro-2-(4-methoxyfuran-2-yl)-1-tosyl-1*H*-pyrrole (3a).[2a] A solution of compound **29** (527 mg, 1.02 mmol) and pyridinium *p*-toluenesulfonate (109 mg, 0.43 mmol) in MeOH (5 mL) was stirred at 55 °C for 14 h. For workup, the mixture was extracted with H_2O/ether, the organic layer was dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 10/1) affording **3a** (273 mg, 76%) as a yellow oil. ^{1}H NMR (200 MHz, THF-d_8): δ 7.60 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 3.5 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 1.1 Hz, 1H), 6.37 (d, J = 3.6 Hz, 1H), 6.32 (d, J = 1.1 Hz, 1H), 3.72 (s, 3H), 2.39 (s, 3H).

3-Chloro-2-(4-methoxyfuran-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (3b). A solution of **3a** (436 mg, 1.24 mmol) in MeOH (16 mL) was stirred with K_2CO_3 (379 mg, 2.75 mmol) for 24 h. The reaction mixture was extracted with brine/ether, and the organic layer was dried over Na_2SO_4, concentrated to a small volume, and purified by flash chromatography (SiO_2, hexane/ethyl acetate = 6/1), providing the unprotected side chain as colorless solid (195 mg, 0.99 mmol). KH (44 mg, 1.09 mmol) was added to a solution of this fairly labile compound in THF (20 mL) at 0 °C, followed by TIPSCl (233 μL, 1.09 mmol). After 30 min of stirring, the solution was extracted with aqueous saturated NH_4Cl/ether, and the organic layer was extracted with aqueous saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated. Purification of the residue by flash chromatography (SiO_2, hexane/ethyl acetate = 25/1) afforded **3b** (271 mg, 62% overall yield) as a colorless syrup. ^{1}H NMR (200 MHz, THF-d_8): δ 7.27 (d, J = 1.1 Hz, 1H), 6.93 (d, J = 3.1 Hz, 1H), 6.34 (d, J = 1.1 Hz, 1H), 6.26 (d, J = 3.0 Hz, 1H), 3.71 (s, 3H), 1.41−1.23 (m, 3H), 1.09 (d, J = 6.9 Hz, 18H). ^{13}C NMR (50 MHz, THF-d_8): δ 152.7, 145.4, 127.6, 124.7, 123.4, 117.7, 111.9, 106.5, 58.4, 19.0, 13.9. HRMS ($C_{18}H_{28}ClNO_2Si$): calcd 353.15779; found 353.15697.

Roseophilin·HCl (1). To a solution of pyrrolylfuran **3b** (47 mg, 0.133 mmol) in THF (1.5 mL) was added *n*-BuLi (83 μL, 0.133 mmol, 1.6 M in hexane) at −50 °C. After 5 h of stirring at this temperature, this solution was added via cannula to a suspension of dry $CeCl_3$ (33 mg, 0.133 mmol) in THF (1.5 mL) at −78 °C, which had been stirred for 5 h at rt prior to use. After 2 h at −78 °C, a solution of **2c** (13 mg, 0.032 mmol) in THF (3 mL) was introduced, and the suspension was allowed to warm to rt overnight. The mixture was extracted with aqueous saturated NH_4Cl/ether, the organic layer was dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (Al_2O_3 (neutral), hexane/ethyl acetate = 40/1→20/1) affording **30** (15 mg, 62%) as nearly colorless oil which was used without further characterization.

To a solution of **30** (15 mg, 0.02 mmol) in THF (2.5 mL) was added TBAF (0.08 mL, 0.08 mmol, 1 M in THF). After 10 min of stirring, the mixture was heated to 60 °C for additional 45 min, cooled to rt, and extracted with 5% Na_2CO_3/ether. The organic layer was treated with several drops of 10% HCl for 5 min, neutralized with 5% Na_2CO_3, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (Al_2O_3 (neutral), hexane/ethyl acetate = 1.5/1), and the combined fractions were treated with HCl (1.1 M in THF) after concentration to a small volume. Removal of the solvent afforded analytically pure **1** (7.4 mg, 76%) as red salt. Its spectroscopic data are in full agreement with those reported in the literature and with those of an authentic sample. ^{1}H NMR (600 MHz, $CDCl_3$): δ 13.89 (br s, 1H), 13.66 (br s, 1H), 7.26 (vt, J = 3.1 Hz, 1H), 6.93 (s, 1H), 6.29 (vt, J = 2.5 Hz, 1H), 6.19 (s, 1H), 4.14 (s, 3H), 3.83 (dd, J = 4.8, 3.2 Hz, 1H), 3.59 (ddd, J = 13.1, 11.0, 6.2 Hz, 1H), 2.84 (ddd, J = 13.0, 5.6, 3.8 Hz, 1H), 2.71 (d, J = 6.3 Hz, 1H), 2.10 (m, 1H), 2.02 (m, 1H), 1.81 (m, 2H), 1.33 (m, 2H), 1.20 (m, 1H), 1.01 (m, 2H), 1.00 (d, J = 6.7 Hz, 3H), 0.92 (m, 2H), 0.80 (m, 2H), 0.79 (d, J = 6.7 Hz, 3H), 0.41 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.7 (s), 166.0 (s), 160.3 (s), 159.3 (s), 144.7 (s), 135.7 (s), 132.9 (s), 126.8 (d), 119.5 (s), 116.8 (s), 112.1 (d), 110.9 (d), 96.3 (d), 60.0 (q), 55.5 (d), 51.6 (d), 34.1 (t), 33.1 (d), 28.25 (t), 28.2 (t), 27.9 (t), 27.5 (t), 26.9 (t), 24.9 (t), 24.4 (t), 21.4 (q), 19.6 (q). MS (ESI/pos): *m*/*z* (rel intensity) 453.2 ([M + H$^+$], 100).

Separation of Enantiomers of 1. The semipreparative HPLC separation of **1** has been carried out on a Shimadzu LC-10A apparatus using a Chiraspher column (250 mm, i.d. 4.6 mm) with *n*-heptane/2-propanol/triethylamine = 80/20/0.1 as the eluent (flow rate 0.5 mL/min; T = 293 K; pressure = 2.5 Mpa; detection: DAD, 300 nm) affording the enantiomers of **1** as free base each.

Acknowledgment. We thank Prof. H. Seto, University of Tokyo, for kindly providing an authentic sample of roseophilin and Dr. S. Terashima, Sagami Chemical Research Center, for an exchange of information. H.W. is indebted to the Fonds der Chemischen Industrie, Frankfurt, for a stipend. We thank Mr. A. Deege and Ms. H. Hinrichs, Mülheim, for performing the HPLC separation.

Supporting Information Available: Compilation of the MS and IR data of compounds **3b**, **5**−**7**, **17**, **25a**, **27**−**29**; copies of the NMR spectra of the side chain **3b** and of roseophilin **1**; HPLC plot of the separation of the enantiomers of **1** and comparison with the natural product (8 pages). See any current masthead page for ordering information and Web access instructions.

JA973846K