Biomimetic Synthesis of the Pentacyclic Nucleus of Ptilomycalin A

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Abstract: The methyl ester of the pentacyclic nucleus of ptilomycalin A (**9**) has been prepared by an efficient, convergent, biogenetic, 14-step route. The key steps involve the conversion of acyclic bis enone **39** to **9** in four steps. Michael addition of *O*-methylisourea to **39** afforded 52% of a mixture of isoureas **40** and **41**, which were both converted to 72% of tricyclic aminals **42** and **43** by ammonolysis. Deprotection of the silyl ethers with HF and cyclization with Et_3N in MeOH afforded **9** (≈34% from **42**) and the diastereomer **45** with an equatorial methyl ester group (≈26% from **42**).

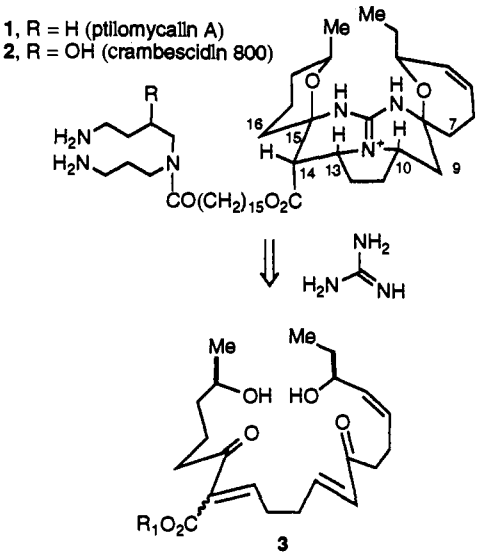
Introduction

The structurally novel, cytotoxic, antifungal, antimicrobial, and antiviral guanidine alkaloid ptilomycalin A (**1**) was isolated from the Caribbean sponge *Ptilocaulis spiculifer* and from a red *Hemimycale spiculifer* of the Red Sea in 1989.[1] The closely related antiviral and cytotoxic crambescidins were isolated from the red, encrusting Mediterranean sponge *Crambe crambe* in 1991.[2] The crambescidins have the same pentacyclic guanidine moiety with an additional hydroxy group on the side chain in crambescidin 800 (**2**) and on both the ring and side chain in other congeners. The relative stereochemistry of the pentacyclic core of **1** and **2** was determined by extensive NMR spectral investigations.[1] The absolute stereochemistry has recently been shown to be that depicted in **1** and **2** by degradation to (*S*)-2-hydroxybutanoic acid.[2b,c]

Ptilomycalin A (**1**) shows cytotoxicity against P388, L1210, and KB cells with IC_{50} = 0.1, 0.4, and 1.3 μg/mL, respectively, and antifungal and antimicrobial activity against *Candida albicans* (MIC = 0.8 μg/mL) as well as antiviral activity (HSV) at 0.2 μg/mL.[1] The crambescidins inhibit HSV-1 completely at 1.25 μg/mL and are 98% effective against L1210 cell growth at 0.1 μg/mL.[2]

We were fascinated by the possibility of an efficient synthetic approach to ptilomycalin A (**1**) based on the addition of guanidine to the double Michael acceptor **3** followed by imine and then aminal formation to give the pentacyclic framework of **1** in a single step. This strategy was especially appealing since it might be related to the biogenesis of ptilomycalin A. The initial justification for this approach came from our synthesis of ptilocaulin, which was also isolated from *Ptilocaulis spiculifer*,[3] by Michael addition of guanidine to an enone followed by intramolecular enamine formation.[4]

Scheme 1



The related bicyclic guanidine alkaloid crambine B (**8**) was also isolated from *Crambe crambe* in 1990.[5] We recently reported a biomimetic synthesis of the methyl ester of the bicyclic moiety of crambine B (**7**) and the alkaloid itself.[6] A major purpose of this synthesis was to develop procedures that could be used for the synthesis of ptilomycalin A (**1**). Addition of guanidine to enone **4** did not give the desired adduct **6a** resulting from Michael addition and enamine formation. Instead, Michael addition was followed by attack of the guanidine on the ester to form a tetrahydropyrimidinone as the only product.[6] Fortunately, a two-step alternative route was successful. Addition of *O*-methylisourea to **4** in DMF for 12 h at 60 °C afforded 79% of the desired dihydropyrimidine **5a**. Hydrolysis of the silyl ether provided **5b**, which reacted with NH_4OAc in MeOH saturated with anhydrous ammonia at 60 °C for 2 d to yield **6b** (61%) and 37% of a 10:6:1 mixture of **7** and two stereoisomers. Heating **6b** with Et_3N in $CHCl_3$ (12 h, 60 °C) gave 94% of a 20:2:1 mixture of **7** and the same two diastereomers.

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(1) (a) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1989**, *111*, 8925. (b) Ohtani, I.; Kusumi, T.; Hakisawa, H. *Tetrahedron Lett.* **1992**, *33*, 2525. (c) Ohtani, I.; Kusumi, T.; Hakisawa, H.; Kashman, Y.; Hirsh, S. *J. Am. Chem. Soc.* **1992**, *114*, 8472.

(2) (a) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712. (b) Jares-Erijman, E. A.; Sakai, R.; Ingrum, A.; Carney, J. R.; Rinehart, K. L. *Abstracts of Papers*, 205th National Meeting of the American Chemical Society, Denver, CO; American Chemical Society: Washington, DC, 1993; ORGN 250. (c) Jares-Erijman, E. A.; Ingrum, A. L.; Carney, J. R.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 4805. (d) Berlinck, R. G. S.; Braekman, J. C.; Dalzoe, D.; Bruno, I.; Riccio, R.; Ferri, S.; Spampinato, S.; Speroni, E. *J. Nat. Prod.* **1993**, *56*, 1007.

(3) Harbour, G. C.; Tymiak, A. A.; Rinehart, K. L., Jr.; Shaw, P. D.; Hughes, R. G., Jr.; Mizsak, S. A.; Coats, J. H.; Zurenko, G. E.; Li, L. H.; Kuentzel, S. L. *J. Am. Chem. Soc.* **1981**, *103*, 5604.

(4) Snider, B. B.; Faith, W. C. *Tetrahedron Lett.* **1983**, *24*, 861; *J. Am. Chem. Soc.* **1984**, *106*, 1443.

(5) (a) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Hallenga, K.; Ottinger, R.; Bruno, I.; Riccio, R. *Tetrahedron Lett.* **1990**, *31*, 6531. (b) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Rogeau, D.; Amade, P. *J. Nat. Prod.* **1992**, *55*, 528.

(6) (a) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1992**, *57*, 2526. (b) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828. Our synthetic work led to a revision of the stereochemistry at the aminal center and the length of the side chain of crambine B.

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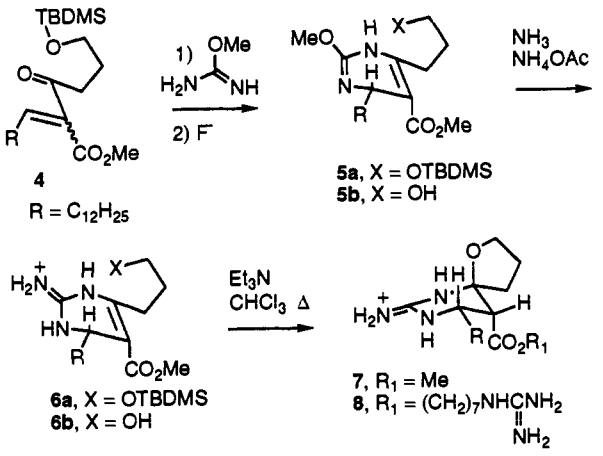
Scheme 2



2D-NMR ROESY experiments on these three stereoisomers established that **7** has the stereochemistry shown.[6] The similarity of the spectra of **7** and crambine B established that crambine B (**8**) has the same stereochemistry as **7**, rather than that of the diastereomer originally reported.[5] The stereochemistry of the three chiral centers in the revised structure of crambine B (**8**) is the same as that of C_{13}, C_{14}, and C_{15} in ptilomycalin A (**1**).

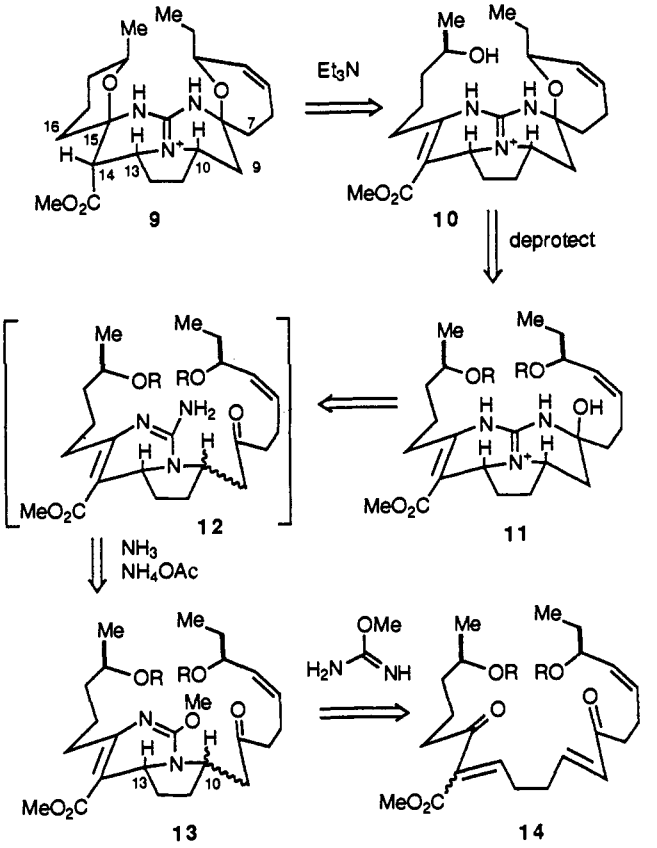
We revised our approach to the pentacyclic portion of ptilomycalin A on the basis of the successful three-step route to the bicyclic guanidine moiety **7** of crambine B (**8**). Reaction of *O*-methylisourea with **14** should result in double Michael addition and condensation with the β-keto ester, as observed in the formation of **5a**, to form dihydropyrimidine **13**. As observed in the formation of **6b**, reaction of **13** with NH_3 and NH_4OAc should convert the isourea to tricyclic guanidine **12**, which will spontaneously form aminal **11**. Finally, deprotection should give tetracyclic intermediate **10**, which should cyclize selectively on treatment with Et_3N in $CHCl_3$ to give **9**, the methyl ester of the pentacyclic nucleus of ptilomycalin A (**1**), in a process that parallels the stereoselective cyclization of **6b** to give **7**, the bicyclic moiety of crambine B (**8**).[6] While our successful synthesis of crambine B provides a firm foundation for this approach to ptilomycalin A, the need to form five rings from **14** while controlling the stereochemistry at five chiral centers makes this a very challenging problem.

Results and Discussion

Synthesis of the Central Tricyclic Moiety of Ptilomycalin A. Our synthesis of crambine B suggested that the desired double Michael addition to **14** could be carried out with *O*-methylisourea and that the cyclization of **10** with Et_3N would introduce the fifth ring with the correct stereochemistry. However, questions remained about the stereochemistry of the double Michael addition reaction to give **13** and the stereochemistry of the aminal center in **10**. We therefore undertook a model study leading to the central tricyclic portion **24** of ptilomycalin A, to demonstrate that the proposed conversion of **14** to **9** is viable.[7,8] We chose to prepare **20**, a simpler analog of **14** with the same carbon skeleton but lacking the cis double bond and the stereochemical and protection problems associated with the two secondary hydroxyl groups of **14**.

Addition of the lithium acetylide prepared from **15**[9] and *n*-butyllithium at −78 °C to octanal afforded 92% of propargyl alcohol **16**. Lithium aluminum hydride (1.3 equiv, THF, 5 h, reflux) reduced the propargyl alcohol and cleaved the silyl ether affording 95% of diol **17**. Swern oxidation of diol **17** provided

Scheme 3



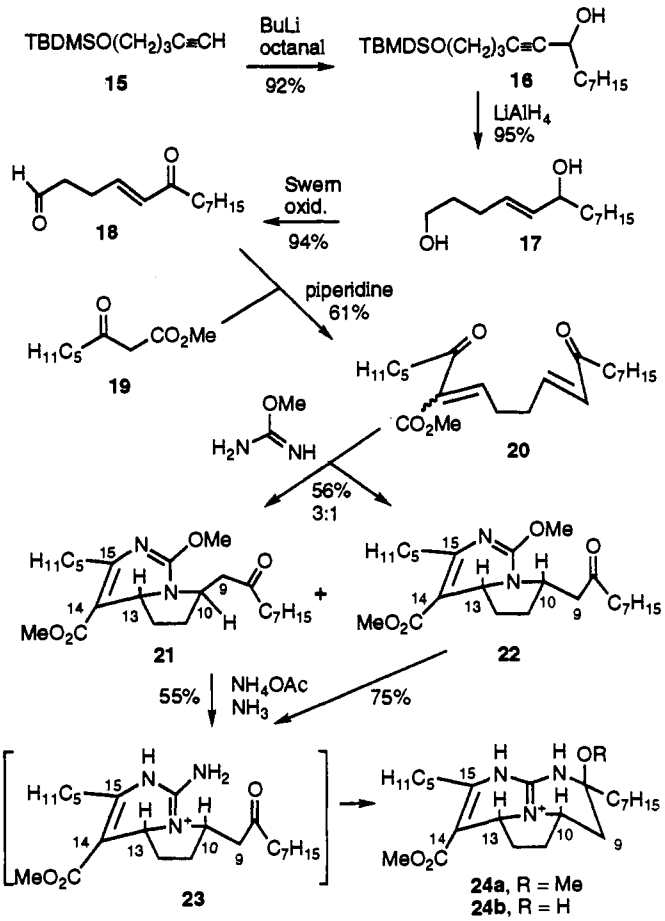
94% of keto aldehyde **18**. Knoevenagel condensation[10] of **18** with **19**[11] (CH_2Cl_2, cat. piperidine, 2 d, −20 °C) gave 61% (89% based on recovered **18**) of bis enone **20** as a 1:1 mixture of *E,E*- and *E,Z*-stereoisomers.[12]

Double Michael addition and enamine formation proceeded as expected. Heating bis enone **20** with *O*-methylisoureido sulfate[13] (2 equiv) and $NaHCO_3$ (4 equiv) in DMF at 50 °C for 2 h afforded 56% of a 3:1 mixture of the *trans*-isomer **21** and the *cis*-isomer **22**. The pure stereoisomers can be obtained by careful flash chromatography. The stereochemistry of these compounds was established by ROESY experiments.[14a] There was a weak cross peak between H_{10} and H_{13} in the *cis*-isomer **22** and a strong cross peak between H_{13} and H_9 in the *trans*-isomer **21**. The formation of *trans*-isomer **21** as the major product is consistent with MM2[14b] calculations that **21** is 2 kcal/mol more stable than *cis*-isomer **22**.

We were delighted to find that both bicyclic stereoisomers **21** and **22** can be converted to the tricyclic target **24** and that the aminal at C_8 forms spontaneously. Heating a solution of the 3:1 mixture of **21** and **22** with excess NH_4OAc in MeOH saturated with anhydrous NH_3 for 4 d at 60 °C in a sealed tube afforded 60% of methyl aminal **24a** as the only isolable product. Both

(7) Snider, B. B.; Shi, Z. *Tetrahedron Lett.* **1993**, *34*, 2099.
(8) For an alternate approach to ptilomycalin A, see: Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1993**, *58*, 3235.
(9) Marshall, J. A.; Deholl, B. S. *J. Org. Chem.* **1986**, *51*, 863.
(10) Jones, G. *Org. React.* **1967**, *15*, 204.
(11) Weiler, L.; Huckin, S. N. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(12) Bogdanov, V. S.; Ugrak, B. I.; Krasnaya, Zh. A.; Stytsenko, T. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 356; *Bull. Acad. Sci. USSR, Chem. Ser.* **1990**, 298.
(13) (a) O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185, 1189. (b) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898.
(14) (a) Bothner-By, A. A.; Stephens, R. L.; Lee, J.-M.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811. Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *63*, 207. Two-dimensional phase-sensitive ROESY spectra were obtained on a 500-MHz Bruker AMX-500 spectrometer. Data workup was performed using D. Hare's FELIX program operating on a Silicon Graphics Iris Workstation. Spin-locking periods of 100 and 200 ms were used with a spin-lock field of 2.5 kHz ($\pi/2 = 100\,\mu s$). (b) Molecular mechanics calculations were carried out using MODEL version KS 2.96 obtained from Prof. Kosta Steliou, University of Montreal.

Scheme 4



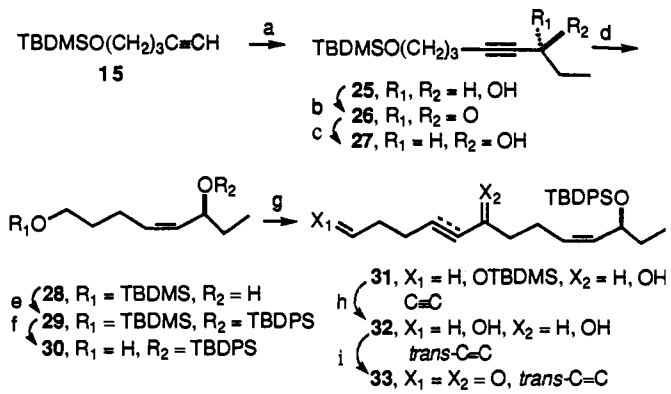
stereoisomers must be converted to **24a** since the starting material contains only 25% of the *cis*-isomer **22**. This was confirmed by carrying out the reaction on the purified stereoisomers. *Cis*-isomer **22** provided 75% of **24a**, while *trans*-isomer **21** afforded 55% of **24a**.

The stereochemistry of **24a** was established by a strong ROESY cross peak between H_{10} and H_{13}. The absence of a ROESY cross peak between H_{10} and H_7 established the stereochemistry at the anomeric center. MM2[14b] calculations indicate that *cis*-isomer **24a** is 3 kcal/mol more stable than the tricyclic *trans*-isomer. This stability order is opposite to that with the bicyclic isoureas in which the *trans*-isomer **21** is calculated to be 2 kcal/mol more stable than the *cis*-isomer **22**. The formation of **24a** from the *trans*-isomer **21** indicates that the stereochemistry at C_{10} can equilibrate, most likely by a retro-Michael reaction to regenerate the enone. Since the *trans*-isomer **21** is more stable, this equilibration is driven by the formation of the more stable *cis*-tricyclic aminal. Therefore this equilibration must be able to occur after formation of the guanidine **23**. Treatment of isourea **21** with Et_3N in MeOH at 60 °C results in some decomposition but provided a 3:1 mixture of **21** and **22**, indicating that equilibration of the isoureas is also possible.

The anomeric substituent also undergoes facile equilibration suggesting that **11** will form tetracyclic intermediate **10** readily. Flash chromatography of **24a** resulted in partial hydrolysis of the aminal, leading to a mixture of **24a** and hemiaminal **24b**. Methyl aminal **24a** was hydrolyzed quantitatively to hemiaminal **24b** in 50% aqueous THF. Hemiaminal **24b** was reconverted quantitatively to aminal **24a** in methanol at room temperature for 4 h.

We briefly examined the reaction of **20** with guanidine and found that **24** was not formed and no methyl ester was present in the crude reaction mixture, probably due to the strong basicity of guanidine. The major product appears to be a tetrahydropyrimidinone analogous to that formed from guanidine and crambine intermediate **4**.[6]

Scheme 5[a]



[a] (a) BuLi, THF/DMPU, −78 °C, CH_3CH_2CHO (94%); (b) Swern ox (91%); (c) 9-BBN, α-pinene, room temperature, 30 h (95%, 93% ee); (d) H_2, Lindlar catalyst, room temperature, 1 h (98%); (e) TBDPSiCl, DMAP, Et_3N, CH_2Cl_2, room temperature, 20 h (93%); (f) PPTS, EtOH, room temperature, 40 h (90%); (g) Swern ox, acetylide prepared from **15**, BuLi, THF/DMPU, −78 °C (92%); (h) LAH, THF, reflux, 4 h (85%); (i) Swern ox (96%).

Synthesis of the Pentacyclic Nucleus of Ptilomycalin A. The successful preparation of the central tricyclic portion **24** of ptilomycalin A from **20** in two steps suggested that the proposed route from **14** to the pentacyclic nucleus of ptilomycalin A **9** was viable. Five new stereocenters will be introduced in the conversion of **14** to **9**, making this a much more difficult problem than the preparation of the tricyclic model **24**, which contains only three chiral centers. From our model studies, we anticipated that **11** would be formed as a 1:1 mixture of diastereomers both with H_{10} and H_{13} *cis*. We did not view this a serious flaw in the synthesis design, since we were confident that steric interactions between the ethyl and methyl substituents would preclude the formation of the pentacyclic bis aminal from the undesired diastereomer, thereby facilitating isomer separation at the end of the synthesis.

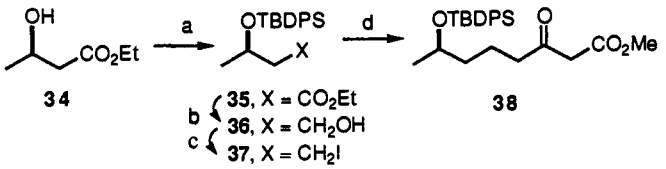
Scalemic keto aldehyde **33** was prepared in nine steps from **15** as shown in Scheme 5. Addition of the lithium acetylide prepared from **15**[9] to propanal afforded racemic propargyl alcohol **25** (94%), which was converted to the *S*-isomer **27** by a two-step sequence. Swern oxidation gave ketone **26**; asymmetric reduction with *B*-3-pinanyl-9-BBN by Midland's procedure afforded (*S*)-propargyl alcohol **27** in 93% ee.[15] The *S*-configuration was assigned on the basis of literature precedent.[15] The ee was determined by preparation of the Mosher ester.[16] Reduction of **27** over Lindlar catalyst (98%), *tert*-butyldiphenylsilylation (93%), and cleavage of the *tert*-butyldimethylsilyl ether (90%) afforded *cis*-allylic silyl ether **30**. Swern oxidation of **30** afforded an aldehyde that was treated with the lithium acetylide prepared from **15**[9] to provide propargyl alcohol **31** (92%). LAH reduced the propargyl alcohol and cleaved the silyl ether affording diol **32** (85%). Swern oxidation provided keto aldehyde **33** (96%).

Scalemic β-keto ester was prepared in five steps as shown in Scheme 6. *R*-alcohol **34** was converted to **37** by *tert*-butyldiphenylsilylation (95%),[17] DIBAL reduction (66%),[18] tosylation, and iodide displacement (91%).[19] Alkylation of the dianion[11] of methyl acetoacetate with **37** afforded 66% of **38**.

Preparation of the key acyclic intermediate **39** by a Knoevenagel condensation[10] was much more challenging than the preparation

(15) (a) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371. (b) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384.
(16) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(17) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(18) Yoon, N. M.; Gyoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443.
(19) (a) Gerlach, H.; Oertle, K.; Thalman, A. *Helv. Chim. Acta* **1976**, *59*, 755. (b) Voss, G.; Gerlach, H. *Helv. Chim. Acta* **1983**, *66*, 2294.

Scheme 6[a]



[a] (a) TBDPSiCl, imidazole, DMF, room temperature, 3 h (95%); (b) DIBAL, hexane, 12 h, −20 °C (66%); (c) TsCl, pyridine, −20 °C, 12 h; NaI, acetone, reflux, 1 h (91%); (d) 2 equiv of LDA then methyl acetoacetate, THF, 0 °C, then **37**, room temperature, 2 h (66%).

of model compound **20**, which lacked the two silyl ether substituents. Attempted piperidine or piperidinium acetate catalyzed condensation of **33** and **38** at 0 °C or higher temperatures in a variety of solvents resulted in the formation of <30% of **39** and destruction of aldehyde **33**. Bis enone ester **39** was finally prepared in 64% yield (1:1 mixture of stereoisomers,[12] 86% based on recovered **33**, 94% based on recovered **38**) by Knoevenagel condensation in CH_2Cl_2 containing a catalytic amount of piperidine (or piperidinium acetate) at low temperature (−78 to −20 °C, 20 h).

The addition of *O*-methylisourea to Michael addition acceptor **39** under the reaction conditions used in the model study for the conversion of **20** to dihydropyrimidines **21** and **22** (*O*-methylisoureido sulfate, $NaHCO_3$, DMF, 50 °C, 2 h) gave <5% of the desired dihydropyrimidines **40** and **41**. The ^1H NMR spectra of the crude reaction mixture indicated the presence of little methyl ester, suggesting that the ester had reacted with the isourea. Similar results were obtained with the analogous *tert*-butyl ester, indicating that use of a more hindered ester does not solve this problem. The double Michael reaction with **39** was also unsuccessful using NaOAc, Et_3N, $NaHCO_3$, or *i*-Pr_2EtN as base in MeOH, EtOH, *t*-BuOH, THF, Me_2CO, PhMe, or DMF. The desired double Michael addition and enamine formation from **39** was finally accomplished in DMSO [*O*-methylisoureido sulfate (5 equiv), *i*-Pr_2EtN (2.5 equiv), DMSO, 80 °C, 1.5 h] to afford 52% of a 4:1 mixture of the two *trans*-diastereomers **40** and the two *cis*-diastereomers **41**. The stereochemistry of **40** and **41** was assigned by the similarity of their ^1H NMR spectra to those of the model compounds **21** and **22**. For instance, H_{10} absorbs at δ 4.3–4.5 in the *cis* fused isomers **21** and **40** and at δ 4.1–4.2 in the *trans* fused isomers **22** and **41**.

Although **40** and **41** can be separated chromatographically, this is not necessary since both are converted to an inseparable 1:1 mixture of **42** and **43** in 72% yield on treatment with excess NH_4OAc in anhydrous *t*-BuOH saturated with anhydrous NH_3 for 40 h at 60 °C in a sealed tube. Once again the stereochemistry was assigned by analogy to the model compound **24**.

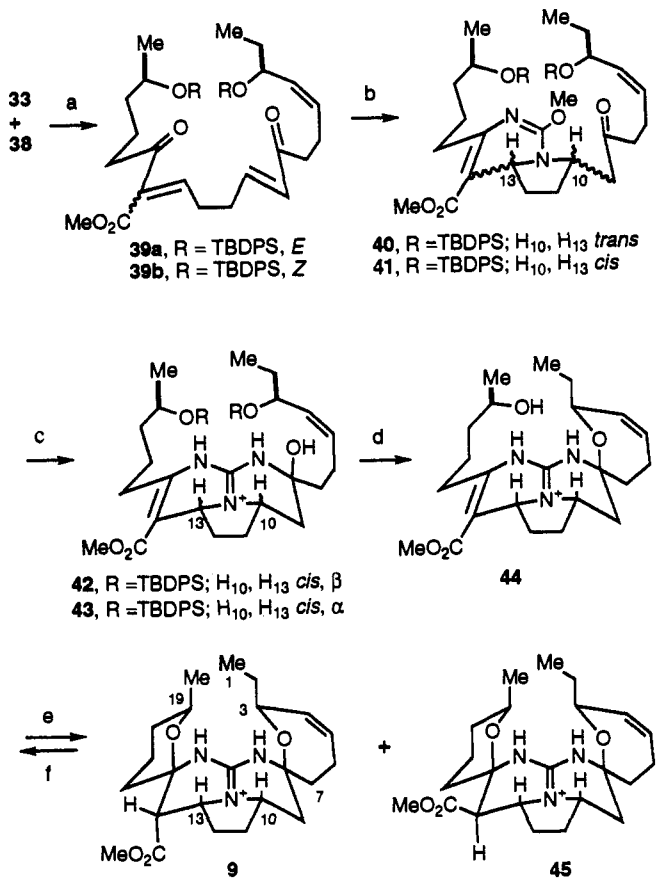
Deprotection of the *tert*-butyldiphenylsilyl ethers without decomposition was eventually accomplished by treatment of **42** and **43** with a 1:2 mixture of 50% aqueous hydrofluoric acid and acetonitrile for 3 d at −30 °C,[20] affording a more polar complex mixture.[21] The protocol used for conversion of **6b** to **7** in the crambine synthesis (Et_3N, $CHCl_3$, reflux, 16 h)[6] converted this polar mixture mainly to **45** and another isomer with a H_{13} and H_{14} *trans* diaxial (δ 2.70, d, 1, J = 11.5, H_{14}) on the six-membered ring.[22] Similar results were obtained in toluene, THF, and 1:1 toluene–MeOH. Treatment of the crude mixture with Et_3N in MeOH at 60 °C for 16 h led to 60% of a ≈65% pure 1.3:1 mixture of the methyl ester of the pentacyclic core of ptilomycalin A (**9**)

(20) Shibasaki, M.; Ogawa, Y.; Nunomoto, M. *J. Org. Chem.* **1986**, *51*, 1625.

(21) Attempted deprotection of **42** and **43** with tetrabutylammonium fluoride in THF at room temperature resulted in ≈50% decomposition with less than 20% deprotection. Attempted deprotection with a 1:19 mixture of 50% aqueous hydrofluoric acid and acetonitrile at room temperature resulted in *cis*/*trans* isomerization of the double bond and decomposition.

(22) We thank Dr. Kenneth L. Rinehart, University of Illinois, for carrying out the bioassays.

Scheme 7[a]



[a] (a) Piperidine, CH_2Cl_2, −78 °C → −20 °C, 20 h (64%, >86% based on recovered **33** and **38**); (b) *O*-methylisourea, *i*-Pr_2EtN, DMSO, 80 °C, 1.5 h (52%, 4:1 **40**:**41**); (c) NH_3, NH_4OAc, *t*-BuOH, 60 °C, 40 h (72%, 1:1 **42**:**43**); (d) 3:7 HF–CH_3CN, −30 °C, 3 d; (e) Et_3N, MeOH, 60 °C, 20 h (≈78% from **42**, 1.3:1 **9**:**45**); (f) Et_3N, 1:1 H_2O–MeOH, 60 °C, 16 h.

and the diastereomer **45** with an equatorial methyl ester. This corresponds to a 78% yield of **9** and **45** from the desired diastereomer **42** in the 1:1 mixture. The remaining, more polar material was presumably tri- and tetracyclic compounds from the undesired diastereomer **43** and some **44**. Careful flash chromatography separated **9** and **45** but gave only 80–85% pure material.

Purification was best accomplished by treating the 1.3:1 mixture of **9** and **45** with Et_3N in 1:1 MeOH–H_2O at 60 °C for 16 h to give tetracyclic alcohol **44**, which was purified by flash chromatography and recyclized with Et_3N in MeOH to give a 1.3:1 mixture of **9** and **45**, which were separated to give pure **9** (≈34% from **42**) and **45** (≈26% from **42**). The ^1H and ^{13}C NMR spectra of **9** are virtually identical to those of the pentacyclic nucleus of ptilomycalin A.[1] The 2D-NMR ROESY spectra[14a] of **9** show intense cross peaks between H_1 and H_{19}, H_3 and H_7-α (δ 2.52), H_1 and H_{13}, and H_{10} and H_{13}, as observed in the ROESY spectra of ptilomycalin A.[1] Pentacyclic methyl esters **9** and **45** are cytotoxic to L1210 murine leukemia cells with IC_{90} values of 2.5 and 1.25 μg/mL and IC_{50} values of 1.25 and 0.5 μg/mL.[22] The comparable values for crambescidin 816,[2a] which has an additional hydroxy group on the ring and a hydroxyspermidine side chain, are 0.18 and 0.09 μg/mL.

In MeOH containing Et_3N, **44** was converted to a 1.3:1 mixture of **9** and **45**, along with a little **44**, which appears to be an equilibrium mixture. Treatment of **45** with Et_3N in MeOH for 1 d afforded a 7:5:8 mixture of **44**, **9**, and **45**, respectively. In 50% aqueous MeOH, the open tautomer **44** was more stable, as we have noted in the crambine series.[6] Heating a mixture of **9**

and **45** with Et_3N in 1:1 MeOH–H_2O at 60 °C for 16 h afforded 50% of **44** and 25% of recovered **9** and **45**.

Conclusion. The methyl ester of the pentacyclic nucleus of ptilomycalin A (**9**) has been prepared by an efficient, convergent, biogenetic, 14-step route. The key steps involve the conversion of acyclic bis enone **39** to **9** in four steps. Michael addition of *O*-methylisourea to **39** afforded 52% of a mixture of isoureas **40** and **41**, which were both converted to 72% of tricyclic aminals **42** and **43** by ammonolysis. Deprotection of the silyl ethers with HF and cyclization with Et_3N in MeOH afforded **9** (≈34% from **42**) and the diastereomer **45** with an equatorial methyl ester group (≈26% from **42**). We are now extending this strategy to the synthesis of ptilomycalin A (**1**) with a complete functionalized ester side chain using procedures developed in our crambine B synthesis.[6b]

Experimental Section

General Procedures. NMR spectra were recorded at 300 MHz in $CDCl_3$ except where otherwise indicated. Chemical shifts are reported in δ and coupling constants in Hertz. IR spectra are recorded in cm^{-1}. Combustion analyses were performed by Baron Consulting Co. and Spang Microanalytical Laboratory. Reactions were run under nitrogen.

5-((*tert*-Butyldimethylsilyl)oxy)-1-pentyne (15). A solution of *tert*-butyldimethylsilyl chloride (3.7 g, 23.5 mmol) in 5 mL of CH_2Cl_2 was added slowly to a solution of 4-pentyn-1-ol (1.68 g, 20 mmol) and Et_3N (3.78 mL, 2.75 g, 27.2 mmol) in 25 mL of CH_2Cl_2 at 0 °C. The mixture was warmed to room temperature, stirred for 4 h, and treated with 30 mL of water. After the organic layer was separated, the aqueous layer was extracted with 1:1 hexane–EtOAc (2 × 30 mL). The combined organic layers were washed with brine (25 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (hexane) gave 3.73 g (94%) of **15** as a colorless oil: ^1H NMR 3.70 (t, 2, J = 6.0), 2.27 (dt, 2, J = 2.6, 7.0), 1.93 (t, 1, J = 2.6), 1.73 (tt, 2, J = 6.0, 7.0), 0.90 (s, 9), 0.06 (s, 6); ^{13}C NMR 84.2, 68.2, 61.4, 31.5, 25.8 (3 C), 18.3, 14.8, –5.4 (2 C); IR (neat) 3320, 2960, 2930, 2860, 1470, 1460, 1390, 1255, 1105, 980, 830, 770. The data are identical to those previously reported.[9]

1-((*tert*-Butyldimethylsilyl)oxy)-4-tridecyn-6-ol (16). *n*-Butyllithium (2.5 M, 5.2 mL, 13 mmol) was added slowly to a solution of **15** (2.44 g, 12.3 mmol) in 35 mL of THF at –78 °C. The mixture was stirred at room temperature for 10 min, and DMPU (2.11 mL) was added to the mixture, which was then cooled to –78 °C. A solution of octanal (1.73 g, 13.5 mmol) in 5 mL of THF was added slowly to the mixture, which was then stirred at room temperature for 12 h. The mixture was treated with saturated NH_4Cl solution (40 mL). The organic layer was separated, and the aqueous layer was extracted with 1:1 hexane–EtOAc (2 × 30 mL). The combined organic layers were washed with brine (25 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 hexane–EtOAc) gave 3.70 g (92%) of **16** as a colorless oil: ^1H NMR 4.34 (tt, 1, J = 2.0, 6.2), 3.69 (t, 2, J = 6.1), 2.29 (dt, 2, J = 2.0, 7.1), 1.80 (br s, 1, OH), 1.67–1.75 (m, 4), 1.43 (m, 2), 1.20–1.37 (m, 8), 0.90 (s, 9), 0.88 (t, 3, J = 6.8), 0.06 (s, 6); ^{13}C NMR 84.9, 81.5, 62.7, 61.6, 38.2, 31.8, 31.7, 29.25, 29.21, 25.9 (3 C), 25.2, 22.6, 18.3, 15.1, 14.1, –5.3 (2 C); IR (neat) 3600–3150, 2960, 2940, 2865, 1475, 1470, 1390, 1260, 1110, 1070, 980, 960, 835, 775. Anal. Calcd for $C_{19}H_{38}O_2Si$: C, 69.87; H, 11.73. Found: C, 69.49; H, 12.10.

(4*E*)-Tridecene-1,6-diol (17). A solution of **16** (1.9 g, 5.82 mmol) in 6 mL of THF was added slowly into a solution of lithium aluminum hydride (1 M, 6.5 mL, 6.5 mmol) in 30 mL of THF. The mixture was heated at reflux for 5 h, cooled to room temperature, and treated with saturated NH_4Cl solution (50 mL). After the organic layer was separated, the aqueous layer was extracted with 1:1 hexane–EtOAc (2 × 40 mL). The combined organic layers were washed with brine (30 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (6:4 hexane–EtOAc) gave 1.25 g (95%) of **17** as a colorless oil: ^1H NMR 5.66 (dt, 1, J = 15.3, 6.7), 5.50 (ddt, 1, J = 15.3, 6.9, 1.2), 4.04 (m, 1), 3.66 (t, 2, J = 6.5), 2.13 (dt, 2, J = 6.7, 7.7), 1.66 (tt, 2, J = 6.5, 7.7), 1.50 (m, 2), 1.20–1.40 (m, 10), 0.88 (t, 3, J = 6.7); ^{13}C NMR 133.6, 130.8, 72.8, 61.8, 37.2, 31.8, 31.7, 29.4, 29.2, 28.4, 25.4, 22.5, 14.0; IR (neat) 3650–3050, 2924, 2855, 1670, 1466, 1378, 1345, 1317, 1134, 1060, 1020, 968, 723. Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23. Found: C, 72.49; H, 12.52.

6-Oxo-(4*E*)-tridecenal (18). Dimethyl sulfoxide (764 mg, 9.8 mmol) was added slowly to a solution of oxalyl chloride (583 mg, 4.6 mmol) in 10 mL of CH_2Cl_2 at –78 °C. After 15 min, a solution of alcohol **17** (380 mg, 1.8 mmol) in 5 mL of CH_2Cl_2 was added slowly to the mixture, which was then stirred at –78 °C for 15 min. Et_3N (2.5 mL, 2.0 g, 20 mmol) was added to the mixture slowly. The mixture was warmed to room temperature, treated with hexane (40 mL), washed with 1 N HCl (15 mL), saturated $NaHCO_3$ solution (15 mL), and water (2 × 15 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (17:3 hexane–EtOAc) gave 354 mg (94%) of **18** as a colorless oil: ^1H NMR 9.81 (t, 1, J = 1.0), 6.81 (dt, 1, J = 16.0, 6.5), 6.12 (dt, 1, J = 16.0, 1.6), 2.67 (m, 2), 2.54 (m, 2), 2.52 (t, 2, J = 7.4), 1.59 (m, 2), 1.20–1.40 (m, 8), 0.88 (t, 3, J = 6.7); ^{13}C NMR 200.29, 200.25, 143.9, 130.9, 41.8, 40.2, 31.5, 29.1, 28.9, 24.5, 24.0, 22.5, 13.9; IR (neat) 2927, 2856, 1726, 1697, 1672, 1631, 1466, 1410, 1376, 1270, 1209, 1190, 1167, 1132, 1072, 979, 916, 724.

Methyl (2*E*,6*E*)- and (2*Z*,6*E*)-2-Hexanoyl-8-oxopentadecadienoate (20a,b). A solution of **18** (186 mg, 0.89 mmol), **19**[11] (200 mg, 1.16 mmol), and piperidine (20 mg) in 10 mL of CH_2Cl_2 was kept at –20 °C for 2 d. The mixture was treated with hexane (25 mL), washed with water (10 mL, containing 2 drops of AcOH) and brine (10 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 hexane–EtOAc) gave 196 mg (61%, 89% based on recovered **18**) of **20a,b** as a 1:1 mixture followed by 60 mg of **18** (17:3 hexane–EtOAc). Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95. Found: C, 72.14; H, 10.24.

Flash chromatography of 50 mg of the mixture of **20a,b** on silica gel (23:2 hexane–EtOAc) gave 16.0 mg of pure **20a**, followed by 23.0 mg of a mixture rich in **20b**, and 10.0 mg of pure **20b**.

Data for the 2*E*,6*E*-isomer (**20a**): ^1H NMR 6.87 (m, 1), 6.77 (m, 1), 6.12 (br d, 1, J = 15.9), 3.79 (s, 3), 2.63 (t, 2, J = 7.4), 2.53(t, 2, J = 7.4), 2.30–2.42 (m, 4), 1.55–1.70 (m, 4), 1.15–1.40 (m, 12), 0.90 (t, 3, J = 6.8), 0.88 (t, 3, J = 6.8); ^{13}C NMR 203.3, 200.4, 164.7, 146.2, 144.0, 136.3, 131.0, 52.1, 43.3, 40.3, 31.6, 31.2, 31.1, 29.2, 29.0, 27.8, 24.1, 23.2, 22.5, 22.3, 14.0, 13.8; IR (neat) 2965, 2940, 2860, 1720, 1680, 1640, 1470, 1440, 1380, 1250, 1050, 975.

Data for the 2*Z*,6*E*-isomer (**20b**): ^1H NMR 6.78 (t, 1, J = 7.8), 6.77 (dt, 1, J = 15.9, 6.6), 6.13 (dt, 1, J = 15.9, 1.4), 3.84 (s, 3), 2.61 (t, 2, J = 7.4), 2.53 (t, 2, J = 7.5), 2.30–2.55 (m, 4), 1.50–1.67 (m, 4), 1.15–1.40 (m, 12), 0.89 (t, 3, J = 6.9), 0.88 (t, 3, J = 6.8); ^{13}C NMR 200.3, 197.5, 166.6, 145.5, 144.0, 137.2, 131.0, 52.1, 40.3, 39.3, 31.6, 31.2, 30.9, 29.2, 29.0, 28.2, 24.1, 23.6, 22.5, 22.3, 14.0, 13.8; IR (neat) 3040, 2970, 2940, 2870, 1740, 1705, 1680, 1640, 1460, 1440, 1380, 1220, 980. The stereochemical assignment was based on the ^{13}C NMR absorptions of the carbonyl carbons.[12]

(4aα,7β)- and (4aα,7α)-1-Methoxy-4a,5,6,7-tetrahydro-3-pentyl-7-(2-oxononyl)pyrrolo[1,2-*c*]pyrimidine-4-carboxylate (21 and 22). A suspension of **20** (200 mg, 0.55 mmol), *O*-methylisoureido sulfate (280 mg, 1.14 mmol), and sodium bicarbonate (180 mg, 2.14 mmol) in 3 mL of DMF was stirred at 50 °C for 2 h. The mixture was treated with water (10 mL) and extracted with 1:1 hexane–EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (17:3 hexane–EtOAc) gave 129.6 mg (56%) of **21** and **22** as a 3:1 mixture of *anti*- and *syn*-isomers. Anal. Calcd for $C_{24}H_{40}N_2O_4$: C, 68.54; H, 9.59. Found: C, 67.62; H, 9.33.

Flash chromatography of 40 mg of the **21** and **22** mixture on silica gel (9:1 hexane–EtOAc) gave 24.0 mg of pure **21**, followed by 8.6 mg of a mixture rich in **21**, and 6.0 mg of pure **22**.

Data for **21**: ^1H NMR 4.52 (dd, 1, J = 10.5, 4.4, H_{13}), 4.39 (ddt, 1, J = 4.5, 8.8, 7.8, H_{10}), 3.80 (s, 3), 3.68 (s, 3), 2.86 (dd, 1, J = 16.6, 4.5, H_9), 2.69 (dt, 1, J = 12.2, 8.0, H_{16}), 2.52 (dd, 1, J = 16.6, 8.8, H_9), 2.40 (t, 2, J = 7.3, H_7), 2.30–2.52 (m, 2, H_{12} and H_{16}), 2.12 (dddd, 1, J = 1.4, 8.2, 9.7, 12.6, H_{11}), 1.45–1.65 (m, 6), 1.20–1.40 (m, 12), 0.89 (t, 3, J = 7.0), 0.88 (t, 3, J = 6.8); ^{13}C NMR 209.2, 167.3, 162.1, 157.0, 101.2, 58.7, 54.7, 54.1, 50.5, 48.0, 43.5, 35.6, 35.5, 31.9, 31.6, 29.1, 29.0, 28.7, 28.1, 23.6, 22.60, 22.56, 14.04, 14.01; IR (neat) 2960, 2940, 2865, 1715, 1685, 1620, 1535, 1485, 1405, 1260, 1240, 1185, 1120, 1070, 1000. The stereochemistry was established by a strong ROESY cross peak between H_{13} and H_9 (δ 2.54) and a weak cross peak between H_{13} and H_9 (δ 2.86). There was no ROESY cross peak between H_{10} and H_{13}.

Data for **22**: ^1H NMR 4.39 (dd, 1, J = 10.3, 4.6, H_{13}), 4.19 (ddd, 1, J = 3.0, 8.0, 9.5, H_{10}), 3.83 (s, 3), 3.68 (s, 3), 2.82 (dd, 1, J = 3.0, 16.8, H_9), 2.68 (m, 1, H_{16}), 2.45 (dd, 1, J = 9.5, 16.8, H_9), 2.36 (dt, 2,

J = 1.6, 7.8, H_7), 2.30–2.55 (m, 2, H_{12} and H_{16}), 2.07 (m, 1, H_{11}), 1.45–1.80 (m, 6), 1.20–1.45 (m, 12), 0.90 (t, 3, J = 6.9), 0.88 (t, 3, J = 6.8); ^{13}C NMR 209.1, 167.1, 163.7, 157.1, 103.2, 59.5, 54.1, 52.5, 50.5, 47.7, 43.5, 35.0, 31.9, 31.6, 30.7, 30.2, 29.1, 29.0, 28.3, 23.7, 22.61, 22.58, 14.1, 14.0; IR (neat) 2970, 2950, 2870, 1720, 1610, 1530, 1490, 1410, 1250, 1125, 1060. There was a weak ROESY cross peak between H_{10} and H_{13}. There was no ROESY cross peak between H_{13} and either H_9.

Methyl 7-Methoxy- and 7-Hydroxy-(2aα,7α,8aα)-7-heptyl-1,2,6,7,8,8a-hexahydro-4-pentyl-2a*H*-5,6,8b-triazaacenaphthylene-3-carboxylate Hydrochloride (24a,b). A solution of the mixture of **21** and **22** (110 mg) and ammonium acetate (80 mg) in 5 mL of methanol was saturated with NH_3 at 10 °C for 5 min, the tube sealed, and the solution warmed to 60 °C for 4 d. After removal of the solvent under reduced pressure, the mixture was treated with brine (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a crude product (125 mg) containing 65% of **24a** (by ^{1}H NMR analysis). Compound **24a** cannot be purified by flash chromatography on silica gel because it decomposes. Flash chromatography of the crude product on silica gel (7:3 to 1:9 CH_2Cl_2–EtOAc) gave 70 mg (60%) of a 1:1 mixture of **24a,b**. Recrystallization (4:1 hexane–EtOAc) of the mixture gave 20 mg of pure **24b**. Compound **24b** in methanol was converted to a 19:1 mixture of **24a,b**.

A solution of pure **21** (20 mg) and ammonium acetate (15 mg) in 8 mL of methanol was saturated with NH_3 at 10 °C for 5 min and heated for 20 h in a sealed tube at 60 °C. Workup as above gave 55% of **24a** (by ^{1}H NMR analysis).

A solution of pure **22** (16 mg) and ammonium acetate (10 mg) in 8 mL of methanol was saturated with NH_3 at 10 °C for 5 min and heated for 20 h in a sealed tube at 60 °C. Workup as above gave 75% of **24a** (by ^{1}H NMR analysis).

Data for **24a**: ^{1}H NMR 10.97 (br s, 1), 10.14 (br s, 1), 4.51 (dd, 1, J = 9.9, 5.8, H_{13}), 3.86 (dddd, 1, J = 12.8, 8.4, 6.5, 5.4, H_{10}), 3.75 (s, 3), 3.26 (s, 3), 2.74 (dd, 2, J = 9.0, 6.9, H_{16}), 2.59 (dddd, 1, J = 12.5, 9.1, 5.8, 3.0, H_{12}), 2.43 (dd, 1, J = 13.4, 5.4, H_9), 2.17 (dddd, 1, J = 12.8, 8.4, 8.4, 8.4, H_{11}), 2.10 (m, 1, H_7), 1.92 (m, 1, H_7), 1.45–1.78 (m, 6), 1.40 (dd, 1, J = 13.4, 12.8, H_9), 1.20–1.45 (m, 12), 0.90 (t, 3, J = 6.8), 0.88 (3, t, J = 6.9); ^{13}C NMR 165.2, 147.8, 145.8, 100.5, 83.4, 57.1, 51.6, 51.4, 49.2, 36.3, 34.5, 33.1, 31.6, 31.5, 31.1, 29.2, 29.0, 27.7, 26.0, 22.9, 22.5, 22.2, 14.0, 13.9; IR (neat) 3220, 3080, 2940, 2865, 1720, 1695, 1590, 1520, 1465, 1440, 1320, 1275, 1190, 1095, 1060. There was a strong ROESY cross peak between H_{10} and H_{13}.

Data for **24b**: mp 120.0–121.0 °C; ^{1}H NMR 10.66 (br s, 1), 9.26 (br s, 1), 4.53 (dd, 1, J = 9.9, 6.0, H_{13}), 4.05 (m, 1, H_{10}), 3.73 (s, 3), 2.78 (ddd, 1, J = 13.0, 9.1, 6.6, H_{16}), 2.52–2.65 (m, 2, H_{12} and H_{16}), 2.38 (dd, 1, J = 13.1, 5.1, H_9), 2.18 (ddt, 1, J = 12.6, 7.8, 8.8, H_{11}), 1.98 (dt, 1, J = 4.4, 12.0, H_7), 1.85 (dt, 1, J = 4.5, 12.0, H_7), 1.45–1.80 (m, 6), 1.44 (dd, 1, J = 13.1, 12.7, H_9), 1.20–1.40 (m, 12), 0.89 (t, 3, J = 6.8), 0.87 (t, 3, J = 6.6); ^{13}C NMR 165.2, 148.0, 145.5, 100.7, 80.1, 56.6, 51.6, 51.3, 40.6, 37.2, 32.9, 31.8, 31.5, 31.0, 29.6, 29.1, 27.9, 26.2, 23.2, 22.6, 22.2, 14.1, 14.0; IR (KBr) 3300, 2965, 2940, 2860, 1720, 1695, 1585, 1515, 1470, 1440, 1265, 1190, 1110, 1090. Anal. Calcd for $C_{23}H_{40}N_3O_3Cl$: C, 62.49; H, 9.12; N, 9.51. Found: C, 62.21; H, 9.06; N, 9.41.

(±)-8-((*tert*-Butyldimethylsilyl)oxy)-4-octyn-3-ol (25). *n*-Butyllithium (2.5 M, 7.0 mL, 17.5 mmol) was added slowly to a solution of **15** (3.0 g, 15.2 mmol) in 35 mL of THF at –78 °C. The mixture was warmed to room temperature for 5 min, and DMPU (3.0 mL) was added to the mixture, which was then cooled to –78 °C. A solution of propionaldehyde (0.96 g, 16.5 mmol) in 8 mL of THF was added slowly to the mixture. After 1 h, the mixture was warmed to room temperature for 2 h and treated with saturated NH_4Cl solution (30 mL) and brine (10 mL). The organic layer was separated, and the aqueous layer was extracted with 1:1 hexane–EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 hexane–EtOAc) gave 3.64 g (94%) of **25** as a colorless oil: ^{1}H NMR 4.30 (tt, 1, J = 2.0, 6.4), 3.69 (t, 2, J = 6.1), 2.30 (dt, 2, J = 2.0, 7.1), 1.81 (br s, 1, OH), 1.71 (tt, 2, J = 6.1, 7.1), 1.69 (m, 2), 1.00 (t, 3, J = 7.4), 0.89 (s, 9), 0.06 (s, 6); ^{13}C NMR 84.9, 81.2, 63.8, 61.5, 31.6, 31.1, 25.9 (3 C), 18.3, 15.0, 9.4, –5.4 (2 C); IR (neat) 3362, 2955, 2930, 2858, 1475, 1464, 1388, 1255, 1106, 1071, 1006, 962, 836, 776. Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.57; H, 11.00.

8-((*tert*-Butyldimethylsilyl)oxy)-4-octyn-3-one (26). Dimethyl sulfoxide (3.20 g, 40 mmol) was added slowly to a solution of oxalyl chloride (2.47 g, 19 mmol) in 60 mL of CH_2Cl_2 at –78 °C. After 15 min, a solution of alcohol **25** (4.4 g, 17.2 mmol) in 10 mL of CH_2Cl_2 was added slowly to the mixture, which was then stirred at –78 °C for 15 min. Et_3N (12.0 mL, 9.6 g, 86 mmol) was added to the mixture slowly. The mixture was warmed to room temperature, treated with hexane (120 mL), washed with 1 N HCl (40 mL), saturated $NaHCO_3$ solution (30 mL), and water (2 × 40 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (19:1 hexane–EtOAc) gave 3.96 g (91%) of **26** as a colorless oil: ^{1}H NMR 3.67 (t, 2, J = 5.9), 2.53 (q, 2, J = 7.4), 2.45 (t, 2, J = 7.1), 1.75 (tt, 2, J = 5.9, 7.1), 1.11 (t, 3, J = 7.4), 0.87 (s, 9), 0.04 (s, 6); ^{13}C NMR 188.6, 93.7, 80.6, 61.1, 38.7, 30.7, 25.8 (3 C), 18.2, 15.3, 8.0, –5.5 (2 C); IR (neat) 2955, 2930, 2857, 2212, 1680, 1472, 1462, 1411, 1388, 1360, 1349, 1256, 1175, 1107, 961, 836, 777. Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 65.70; H, 10.47.

(*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-4-octyn-3-ol (27). A mixture of 9-BBN (2.50 g, 20 mmol) and (*S*)-(–)-α-pinene (3.0 g, 22 mmol) was warmed to 65 °C for 6 h and then cooled to 0 °C.[15] Ketone **26** (3.3 g, 13 mmol) was added to the mixture, which was then stirred at room temperature for 30 h. The mixture was treated with Et_2O (20 mL) and ethanolamine (1.5 mL, 24 mmol) and then cooled to 0 °C. The deposit formed was removed by filtration, and the residue was washed with cold ether (10 mL). The organic layer was washed with brine (2 × 20 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 hexane–EtOAc) gave 3.15 g (95%) of **27** as a colorless oil: $[\alpha]_D$ = –6.0° ($CHCl_3$, 0.45); the ^{1}H and ^{13}C NMR and IR data are identical to those of the racemic compound described above. The major enantiomer was assigned to be the (*S*)-propargylic alcohol on the basis of literature precedent.[15]

The optical purity of **27** was determined by analysis of the ^{1}H NMR spectra of the Mosher's esters of **27** and the racemate **25**, which were prepared in pyridine from the acid chloride formed from (*R*)-(+)-Mosher's acid and oxalyl chloride in ether catalyzed by DMF.[16] The Mosher's ester from **27** contains two diastereomers in a 28:1 ratio, as determined by the integration of the methoxy peaks (δ 3.56, major; δ 3.59, minor).

Data for the major diastereomer of the Mosher's ester from **27**: 7.50–7.57 (m, 2), 7.35–7.42 (m, 3), 5.47 (tt, 1, J = 6.4, 2.0), 3.65 (t, 2, J = 6.1), 3.56 (br s, 3), 2.28 (dt, 2, J = 2.0, 7.1), 1.84 (dq, 2, J = 6.4, 7.4), 1.68 (tt, 2, J = 6.1, 7.1), 1.02 (t, 3, J = 7.4), 0.89 (s, 9), 0.041 (s, 6).

Data for the minor diastereomer of the Mosher's ester from **27**: 7.50–7.60 (m, 2), 7.36–7.43 (m, 3), 5.50 (tt, 1, J = 6.4, 2.0), 3.67 (t, 2, J = 6.1), 3.59 (br s, 3), 2.31 (dt, 2, J = 2.0, 7.1), 1.79 (dq, 2, J = 6.4, 7.4), 1.70 (tt, 2, J = 6.1, 7.1), 0.93 (t, 3, J = 7.4), 0.89 (s, 9), 0.038 (s, 6).

(*Z*)-(*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-4-octen-3-ol (28). A suspension of alcohol **27** (4.10 g, 16.0 mmol), quinoline (0.17 mL), and 5% palladium on calcium carbonate, poisoned with lead (Aldrich 20,573-7, Lindlar catalyst) (340 mg), in 30 mL of hexane was stirred under H_2 (1 atm) at room temperature for 1 h. The solid was removed by filtration, and the residue was washed with hexane (30 mL). Concentration of the filtrate under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 hexane–EtOAc) gave 4.00 g (98%) of **28** as a colorless oil which contained about 1% of the *trans*-isomer: $[\alpha]_D$ = +12.9° ($CHCl_3$, 1.5); ^{1}H NMR 5.37–5.53 (m, 2), 4.35 (dt, 1, J = 7.9, 6.8), 3.63 (t, 2, J = 6.2), 2.28 (m, 1), 2.11 (m, 1), 1.38–1.69 (m, 4), 0.90 (s, 9), 0.89 (t, 3, J = 7.6), 0.06 (s, 6); ^{13}C NMR 133.3, 131.4, 68.6, 62.0, 32.3, 30.1, 25.9 (3 C), 23.8, 18.3, 9.7, –5.3 (2 C); IR (neat) 3350, 3007, 2957, 2930, 2856, 1658, 1471, 1463, 1386, 1255, 1102, 1006, 962, 836, 775. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 64.67; H, 12.09.

(*Z*)-(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-((*tert*-butyldiphenylsilyl)oxy)-4-octene (29). *tert*-Butyldiphenylsilyl chloride (6.3 g, 23.0 mmol) was slowly added to a solution of alcohol **28** (3.8 g, 14.7 mmol), DMAP (180 mg, 1.5 mmol), and triethylamine (3.03 g, 30 mmol) in 50 mL of CH_2Cl_2 at room temperature. After 20 h, the solvent was removed under reduced pressure. The mixture was treated with hexane (60 mL). The solid salt was removed by filtration, and the residue was washed with hexane (30 mL). The organic layer was washed with water (20 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (hexane) gave 6.8 g (93%) of **29** followed by 0.20 g (5%) of recovered alcohol **28**: $[\alpha]_D$ = +18.3° ($CHCl_3$, 0.9); ^{1}H NMR 7.63–7.76 (m, 4), 7.28–7.45 (m, 6), 5.42 (ddt, 1, J = 11.0, 8.8, 1.5), 5.24 (dtd, 1, J = 11.0, 7.2, 0.9), 4.38 (dtd, 1, J = 8.8, 7.2, 0.9), 3.47 (dt, 1, J = 10.0, 6.6), 3.42 (dt, 1, J = 10.0, 6.6), 1.72 (ddtd, 1, J = 14.0, 7.2, 8.0, 1.5), 1.59 (ddtd, 1, J = 14.0, 7.2, 7.5, 1.5), 1.58 (m, 1), 1.48 (m, 1), 1.35 (tt, 2, J = 7.2, 6.6), 1.06 (s, 9), 0.88 (s, 9), 0.80 (t, 3, J = 7.5), 0.02 (s, 6); ^{13}C NMR 135.94 (2 C), 135.85

(2 C), 134.6, 134.5, 133.0, 129.4, 129.3, 129.2, 127.4 (2 C), 127.3 (2 C), 70.7, 62.7, 32.7, 31.2, 27.0 (3 C), 25.9 (3 C), 24.0, 19.3, 18.3, 9.3, -5.3 (2 C); IR (neat) 3071, 3049, 3012, 2957, 2930, 2857, 1472, 1463, 1428, 1389, 1361, 1255, 1106, 836, 701. Anal. Calcd for $C_{30}H_{48}O_2Si_2$: C, 72.52; H, 9.74. Found: C, 72.50; H, 9.60.

(*Z*)-(*S*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4-octen-1-ol (30). A solution of **29** (6.2 g, 12.5 mmol) and PPTS (1.0 g, 4.0 mmol) in 65 mL of EtOH was stirred at room temperature for 40 h. Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel gave 320 mg (5%) of recovered **29** (hexane), followed by 4.3 g (90%) of **30** (19:1 hexane–EtOAc) as a colorless oil: $[\alpha]_D = +19.9°$ ($CHCl_3$, 0.9); ^1H NMR 7.60–7.75 (m, 4), 7.26–7.44 (m, 6), 5.44 (ddt, 1, J = 11.0, 9.0, 1.6), 5.21 (dtd, 1, J = 11.0, 7.3, 0.7), 4.36 (dt, 1, J = 9.0, 6.0), 3.39 (t, 2, J = 6.5), 1.65 (m, 2), 1.58 (m, 1), 1.48 (m, 1), 1.20–1.42 (m, 2), 1.04 (s, 9), 0.79 (t, 3, J = 7.4); ^{13}C NMR 136.0 (2 C), 135.9 (2 C), 134.50, 134.46, 133.4, 129.4, 129.3, 128.8, 127.4 (2 C), 127.2 (2 C), 70.6, 62.3, 32.3, 31.2, 26.9 (3 C), 23.8, 19.3, 9.2; IR (neat) 3330, 3071, 3049, 3012, 2960, 2931, 2857, 1658, 1589, 1472, 1463, 1428, 1390, 1361, 1111, 1080, 1056, 821, 740, 702. Anal. Calcd for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96. Found: C, 75.26; H, 9.29.

(*Z*)-(11*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-11-((*tert*-butyldiphenylsilyl)oxy)-9-tridecen-4-yn-6-ol (31). Dimethyl sulfoxide (2.34 g, 30 mmol) was added slowly to a solution of oxalyl chloride (1.75 g, 13 mmol) in 50 mL of CH_2Cl_2 at -78 °C. After 20 min, a solution of alcohol **30** (4.2 g, 11 mmol) in 6 mL of CH_2Cl_2 was added slowly to the mixture, which was then stirred at -78 °C for 20 min. Et_3N (6.1 g, 60 mmol) was added to the mixture slowly. The mixture was warmed to room temperature, treated with hexane (200 mL), washed with 7% AcOH (90 mL) and brine (2 × 50 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a crude aldehyde (4.3 g) which was used directly for next step.

At -78 °C, a solution of this crude aldehyde in 10 mL of THF was added slowly to a solution of the lithium reagent prepared from **15**[9] (12.5 mmol) in 35 mL of THF, which was prepared from *n*-butyllithium (2.5 M, 5.0 mL, 12.5 mmol) and **15** (2.5 g, 12.5 mmol) as described above. After 1 h, the mixture was warmed to room temperature for 1 h, and treated with hexane (200 mL). The organic layer was washed with saturated NH_4Cl solution (80 mL) and brine (2 × 50 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (19:1 hexane–EtOAc) gave 5.9 g (92%) of **31** as a colorless oil: ^1H NMR 7.62–7.72 (m, 4), 7.29–7.45 (m, 6), 5.38–5.49 (m, 1), 5.20 (dtd, 1 × 0.5, J = 11.5, 7.4, 0.8), 5.19 (dtd, 1 × 0.5, J = 11.4, 7.6, 0.8), 4.39 (dt, 1, J = 8.6, 6.2), 4.09 (m, 1), 3.65 (t, 2 × 0.5, J = 6.1), 3.64 (t, 2 × 0.5, J = 6.1), 2.24 (br t, 2, J = 7.1), 1.74 (m, 2), 1.65 (m, 2), 1.36–1.60 (m, 4), 1.04 (s, 9), 0.892 (s, 9 × 0.5), 0.889 (s, 9 × 0.5), 0.80 (t, 3 × 0.5, J = 7.4), 0.79 (t, 3 × 0.5, J = 7.4), 0.048 (s, 6 × 0.5), 0.043 (s, 6 × 0.5); ^{13}C NMR 136.0 (2 C), 135.9 (2 C), 134.51, 134.48, 133.8 (0.5 C), 133.6 (0.5 C), 129.43 (0.5 C), 129.40 (0.5 C), 129.3, 128.4 (0.5 C), 128.3 (0.5 C), 127.4 (2 C), 127.3 (2 C), 85.0, 81.0, 70.7, 62.1 (0.5 C), 61.9 (0.5 C), 61.5, 37.9 (0.5 C), 37.7 (0.5 C), 31.71 (0.5 C), 31.69 (0.5 C), 31.22 (0.5 C), 31.18 (0.5 C), 27.0 (3 C), 25.9 (3 C), 23.5, 19.3, 18.3, 15.1, 9.2, -5.3 (2 C); IR (neat) 3374, 3071, 3048, 3013, 2957, 2930, 2857, 1658, 1590, 1475, 1463, 1428, 1390, 1361, 1256, 1109, 1007, 836, 702. Anal. Calcd for $C_{35}H_{54}O_3Si_2$: C, 72.61; H, 9.40. Found: C, 72.37; H, 9.09.

(4*E*,9*Z*)-(11*S*)-11-((*tert*-Butyldiphenylsilyl)oxy)-4,9-tridecadiene-1,6-diol (32). A solution of **31** (4.8 g, 8.3 mmol) in 5 mL of THF was added to a solution of lithium aluminum hydride (1 M, 8.3 mL, 8.3 mmol) in 50 mL of THF at room temperature. The solution was heated at reflux for 4 h, cooled to 0 °C, and treated with hexane (200 mL). The organic layer was washed with saturated NH_4Cl solution (50 mL) and brine (2 × 80 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (4:6 hexane–EtOAc) gave 3.3 g (85%) of **32** as a colorless oil: ^1H NMR 7.60–7.73 (m, 4), 7.27–7.44 (m, 6), 5.28–5.60 (m, 3), 5.21 (dtd, 1, J = 11.0, 7.4, 1.0), 4.37 (m, 1), 3.81 (m, 1), 3.61 (t, 2 × 0.5, J = 6.5), 3.60 (t, 2 × 0.5, J = 6.5), 2.07 (dt, 2, J = 7.4, 7.1), 1.51–1.70 (m, 6), 1.47 (m, 1), 1.26 (m, 1), 1.04 (s, 9), 0.78 (t, 3, J = 7.4); ^{13}C NMR 136.0 (2 C), 135.8 (2 C), 134.55 (0.5 C), 134.53 (0.5 C), 134.48 (0.5 C), 134.46 (0.5 C), 133.35 (0.5 C), 133.28 (0.5 C), 133.22 (0.5 C), 133.19 (0.5 C), 131.0 (0.5 C), 130.9 (0.5 C), 129.41 (0.5 C), 129.38 (0.5 C), 129.28, 128.8, 127.4 (2 C), 127.2 (2 C), 72.2 (0.5 C), 72.1 (0.5 C), 70.6, 62.2, 37.0 (0.5 C), 36.8 (0.5 C), 31.98 (0.5 C), 31.95 (0.5 C), 31.19 (0.5 C), 31.14 (0.5 C), 28.4, 26.9 (3 C), 23.7 (0.5 C), 23.6 (0.5 C), 19.2, 9.2; IR (neat) 3340, 3069, 3048, 2959, 2931, 2857, 1472, 1463, 1427, 1111, 1056, 701. Anal. Calcd for $C_{29}H_{42}O_3Si$: C, 74.62; H, 9.07. Found: C, 74.72; H, 9.10.

(*S*)-6-Oxo-11-((*tert*-butyldiphenylsilyl)oxy)-(4*E*,9*Z*)-tridecadienal (33). Dimethyl sulfoxide (1.8 g, 23 mmol) was added slowly to a solution of oxalyl chloride (1.45 g, 11 mmol) in 50 mL of CH_2Cl_2 at -78 °C. After 20 min, a solution of alcohol **32** (1.86 g, 4.0 mmol) in 6 mL of CH_2Cl_2 was added slowly to the mixture, which was then stirred at -78 °C for 20 min. Et_3N (5.05 g, 50 mmol) was added to the mixture slowly. The mixture was warmed to room temperature, treated with hexane (150 mL), washed with 5% AcOH (80 mL) and brine (2 × 50 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (3:1 hexane–EtOAc) gave 1.77 g (96%) of **33** as a colorless oil: $[\alpha]_D = +8.3°$ ($CHCl_3$, 0.8); ^1H NMR 9.79 (t, 1, J = 1.1), 7.56–7.70 (m, 4), 7.28–7.45 (m, 6), 6.66 (dt, 1, J = 16.0, 6.6), 5.99 (dt, 1, J = 16.0, 1.5), 5.43 (ddt, 1, J = 11.0, 9.0, 1.5), 5.16 (dtd, 1, J = 11.0, 7.4, 0.9), 4.36 (m, 1), 2.63 (br t, 2, J = 6.8), 2.51 (br dt, 2, J = 6.6, 6.8), 2.26 (ddd, 1, J = 17.0, 9.0, 6.8), 2.17 (ddd, 1, J = 17.0, 8.4, 6.3), 1.76–2.00 (m, 2), 1.59 (ddq, 1, J = 13.4, 5.6, 7.6), 1.46 (ddq, 1, J = 13.4, 7.1, 7.2), 1.04 (s, 9), 0.79 (t, 3, J = 7.4); ^{13}C NMR 200.2, 199.0, 144.1, 136.0 (2 C), 135.8 (2 C), 134.4, 134.3, 133.7, 130.7, 129.4, 129.3, 127.7, 127.4 (2 C), 127.2 (2 C), 70.5, 41.8, 39.7, 31.1, 26.9 (3 C), 24.5, 21.9, 19.3, 9.2; IR (neat) 3071, 3047, 3013, 2961, 2931, 2857, 1727, 1698, 1674, 1633, 1472, 1463, 1428, 1361, 1110, 703.

Ethyl (*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)butyrate (35). *tert*-Butyldiphenylsilyl chloride (8.1 g, 30.0 mmol) was added to a solution of ethyl *R*-(-)-3-hydroxybutyrate (**34**) (3.0 g, 23.0 mmol) and imidazole (4.0 g, 60 mmol) in 20 mL of DMF at room temperature. After 3 h, the mixture was treated with hexane (80 mL), washed with 2% AcOH (80 mL) and water (3 × 60 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (19:1 hexane–EtOAc) gave 8.1 g (95%) of **35** as a colorless oil: $[\alpha]_D = -6.9°$ ($CHCl_3$, 1.0); ^1H NMR 7.63–7.73 (m, 4), 7.32–7.45 (m, 6), 4.30 (ddq, 1, J = 6.9, 5.9, 6.1), 4.07 (dq, 1, J = 10.9, 7.3), 4.03 (dq, 1, J = 10.9, 7.2), 2.54 (dd, 1, J = 14.6, 6.9), 2.38 (dd, 1, J = 14.6, 5.9), 1.20 (dd, 3, J = 7.2, 7.3), 1.11 (d, 3, J = 6.1), 1.03 (s, 9); ^{13}C NMR 171.4, 135.8 (4 C), 134.3, 133.9, 129.6, 129.5, 127.5 (2 C), 127.4 (2 C), 66.9, 60.2, 44.7, 26.9 (3 C), 23.6, 19.2, 14.1; IR (neat) 3071, 3048, 2965, 2931, 2857, 1737, 1473, 1428, 1377, 1302, 1183, 1112, 1081, 997, 822, 702. Anal. Calcd for $C_{22}H_{30}O_3Si$: C, 71.31; H, 8.16. Found: C, 71.06; H, 7.92.

(*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)butan-1-ol (36). A solution of DIBAL (1 M, 20 mL, 20 mmol) was added slowly to a solution of ester **35** (3.1 g, 8.7 mmol) in 30 mL of hexane at -78 °C. The reaction was stirred at -20 °C for 12 h and then quenched with 1:2 MeOH–benzene (3 mL). The mixture was treated with hexane (50 mL) and saturated NH_4Cl solution (30 mL) at 0 °C. The solid formed was removed by filtration and washed with hexane (30 mL). The organic layer was separated from the aqueous layer, washed with water (2 × 40 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (4:1 hexane–EtOAc) gave 1.8 g (66%) of alcohol **36** as a colorless oil: $[\alpha]_D = -12.4°$ ($CHCl_3$, 2.2); ^1H NMR 7.60–7.75 (m, 4), 7.30–7.48 (m, 6), 4.11 (ddq, 1, J = 4.4, 6.2, 6.2), 3.82 (ddd, 1, J = 4.5, 8.3, 11.0), 3.69 (ddd, 1, J = 5.4, 5.4, 11.0), 2.17 (br s, 1, OH), 1.81 (dddd, 1, J = 4.4, 5.4, 8.3, 14.2), 1.65 (dddd, 1, J = 6.2, 4.5, 5.4, 14.2), 1.08 (d, 3, J = 6.2), 1.06 (s, 9); ^{13}C NMR 135.9 (2 C), 135.8 (2 C), 134.2, 133.7, 129.7, 129.6, 127.7 (2 C), 127.5 (2 C), 68.7, 59.9, 40.7, 27.0 (3 C), 23.0, 19.1; IR (neat) 3353, 3071, 3048, 2963, 2931, 2857, 1472, 1427, 1378, 1111, 1026, 822, 701. Anal. Calcd for $C_{20}H_{28}O_2Si$: C, 73.12; H, 8.59. Found: C, 72.97; H, 8.86.

(*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-1-iodobutane (37). A solution of *p*-toluenesulfonyl chloride (1.0 g, 5.5 mmol) in 5 mL of pyridine was slowly added to a solution of alcohol **36** (1.6 g, 5.0 mmol) in 3 mL of pyridine at -20 °C. After 12 h, the mixture was warmed to room temperature and treated with hexane (50 mL). The organic layer was washed with 2 N H_2SO_4 (15 mL) and water (2 × 20 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave crude tosylate. A suspension of the crude tosylate and NaI (4.0 g, 26.7 mmol) in 50 mL of acetone was heated at reflux for 1 h and then cooled to room temperature. The solvent was removed under reduced pressure, and the mixture was treated with hexane (50 mL). The solid salt was removed by filtration and washed with hexane (20 mL). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (49:1 hexane–EtOAc) gave 1.95 g (91%) of iodide **37** as a colorless oil: $[\alpha]_D = +6.9°$ ($CHCl_3$, 2.5); ^1H NMR 7.63–7.80 (m, 4), 7.32–7.50 (m, 6), 3.91 (ddq, 1, J = 4.6, 6.7, 6.2), 3.20 (t, 2, J = 7.4),

2.05 (ddt, 1, J = 14.1, 6.7, 7.4), 1.92 (ddt, 1, J = 14.1, 4.6, 7.4), 1.05 (s, 9), 1.04 (d, 3, J = 6.2); ^{13}C NMR 135.8 (4 C), 134.4, 133.8, 129.7, 129.5, 127.6 (2 C), 127.4 (2 C), 69.7, 43.5, 27.0 (3 C), 22.9, 19.3, 2.4; IR (neat) 3069, 3048, 2963, 2929, 2856, 1472, 1427, 1377, 1127, 1111, 1058, 822, 740, 701. Anal. Calcd for $C_{20}H_{27}OSi$: C, 54.79; H, 6.21. Found: C, 54.96; H, 6.50.

(*R*)-Methyl 7-((*tert*-Butyldiphenylsilyl)oxy)-3-oxooctanoate (38). A LDA solution (36 mmol) was prepared by adding *n*-butyllithium (2.5 M, 14.4 mL, 36 mmol) to a solution of diisopropylamine (3.6 g, 36 mmol) in 50 mL of THF at 0 °C. Methyl acetoacetate (1.84 g, 16 mmol) was added slowly to the LDA solution at 0 °C. After 1 h, iodide **37** (5.6 g, 12.8 mmol) was added slowly. The mixture was warmed to room temperature for 2 h, treated with hexane (150 mL), washed with saturated NH_4Cl solution (50 mL) and brine (2 × 50 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 hexane–EtOAc) gave 3.6 g (66%) of **38** as a colorless oil: $[\alpha]_D$ = +17.4° ($CHCl_3$, 0.95); ^{1}H NMR 7.55–7.76 (m, 4), 7.25–7.45 (m, 6), 3.83 (m, 1), 3.72 (s, 3), 3.37 (s, 2), 2.39 (t, 2, J = 7.3), 1.59 (m, 2), 1.43 (m, 2), 1.05 (s, 9), 1.06 (d, 3, J = 6.1) (data for the enol isomer: 4.92 (s, 1), 3.84 (m, 1), 2.08 (t, 2, J = 7.3)); ^{13}C NMR 202.5, 167.6, 135.8 (4 C), 134.7, 134.3, 129.5, 129.4, 127.5 (2 C), 127.4 (2 C), 69.0, 52.3, 48.9, 42.9, 38.5, 27.0 (3 C), 23.1, 19.3, 19.1 (data for the enol isomer: 178.8, 173.0, 135.8 (4 C), 134.7, 134.3, 129.5, 129.4, 127.5 (2 C), 127.4 (2 C), 88.7, 69.0, 51.0, 38.5, 34.9, 27.0 (3 C), 21.8, 19.3, 19.2); IR (neat) 3070, 3047, 2955, 2931, 2857, 1750, 1718, 1653, 1472, 1428, 1376, 1318, 1240, 1135, 1111, 1036, 703. Anal. Calcd for $C_{25}H_{34}O_4Si$: C, 70.38; H, 8.03. Found: C, 70.77; H, 8.35.

Methyl (2*E*,6*E*,11*Z*)- and (2*Z*,6*E*,11*Z*)-2-(5-((*tert*-Butyldiphenylsilyl)oxy)hexanoyl)-8-oxopentadecatrienoate (39a,b). A solution of piperidine (25 mg) in 15 mL of CH_2Cl_2 was added slowly to a solution of ester **38** (0.92 g, 2.16 mmol) and aldehyde **33** (0.93 g, 2.01 mmol) in 3 mL of CH_2Cl_2 at −78 °C. The solution was stirred at −20 °C for 20 h, treated with hexane (80 mL), washed with 2% aqueous AcOH (10 mL) and water (2 × 10 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel gave 350 mg (38%) of recovered ester **38** (19:1 hexane–EtOAc) followed by 1.12 g (64%, 96% based on recovered **38** and 86% based on recovered **33**) of **39a,b** (9:1 hexane–EtOAc) as a 1:1 mixture, followed by 242 mg (26%) of recovered **33** (4:1 hexane–EtOAc). Anal. Calcd for $C_{54}H_{70}O_6Si_2$ (mixture of **39a,b**): C, 74.44; H, 8.10. Found: C, 74.26; H, 7.82.

The two isomers **39a,b** can be separated by careful flash chromatography on silica gel (19:1 hexane–EtOAc).

Data for the 2*E*,6*E*,11*Z*-isomer (**39a**): ^{1}H NMR 7.59–7.70 (m, 8), 7.27–7.44 (m, 12), 6.85 (t, 1, J = 7.6), 6.62 (dt, 1, J = 15.9, 6.4), 5.99 (br d, 1, J = 15.9), 5.41 (br dd, 1, J = 10.9, 9.2), 5.16 (br dt, 1, J = 10.9, 7.3), 4.37 (br dt, 1, J = 9.2, 6.2), 3.84 (m, 1), 3.75 (s, 3), 2.53 (t, 2, J = 7.0), 2.10–2.43 (m, 6), 1.88 (m, 2), 1.62 (m, 2), 1.57 (m, 1), 1.45 (m, 2), 1.42 (m, 1), 1.05 (d, 3, J = 6.2), 1.04 (s, 9), 1.03 (s, 9), 0.79 (t, 3, J = 7.4); ^{13}C NMR 203.0, 199.0, 164.7, 146.3, 144.1, 136.0, 135.8 (8 C), 134.7, 134.5, 134.4 (2 C), 133.7, 130.9, 129.45 (2 C), 129.42, 129.3, 127.7, 127.48 (2 C), 127.43 (2 C), 127.39 (2 C), 127.26 (2 C), 70.5, 69.2, 52.2, 43.3, 39.7, 38.7, 31.1 (2 C), 27.8, 27.00 (3 C), 26.95 (3 C), 23.1, 21.9, 19.4, 19.28, 19.24, 9.3; IR (neat) 3070, 3048, 3013, 2998, 2960, 2930, 2857, 1715, 1700, 1678, 1632, 1472, 1462, 1428, 1376, 1362, 1252, 1111, 1079, 1047, 822, 741, 703.

Data for the 2*Z*,6*E*,11*Z*-isomer (**39b**): ^{1}H NMR 7.58–7.68 (m, 8), 7.26–7.44 (m, 12), 6.71 (t, 1, J = 7.4), 6.64 (dt, 1, J = 15.9, 6.4), 6.00 (dt, 1, J = 15.9, 1.5), 5.43 (ddt, 1, J = 10.9, 9.0, 1.5), 5.17 (dtd, 1, J = 10.9, 7.3, 1.0), 4.37 (br dt, 1, J = 9.0, 6.2), 3.85 (m, 1), 3.80 (s, 3), 2.51 (t, 2, J = 7.2), 2.45 (t, 2, J = 7.5), 2.37 (m, 2), 2.22 (m, 2), 1.89 (m, 2), 1.61 (m, 2), 1.59 (m, 1), 1.46 (m, 2), 1.42 (m, 1), 1.06 (d, 3, J = 6.2), 1.05 (s, 9), 1.04 (s, 9), 0.80 (t, 3, J = 7.4); ^{13}C NMR 198.9, 197.1, 166.5, 145.4, 144.1, 135.9, 135.8 (8 C), 134.7, 134.4, 134.3 (2 C), 133.7, 130.8, 129.44 (2 C), 129.38, 129.3, 127.7, 127.46 (2 C), 127.41 (2 C), 127.36 (2 C), 127.23 (2 C), 70.5, 69.1, 52.1, 39.7, 39.3, 38.6, 31.1, 30.9, 28.3, 26.98 (3 C), 26.92 (3 C), 23.0, 21.9, 19.5, 19.25, 19.20, 9.2; IR (neat) 3070, 3048, 3013, 2998, 2960, 2931, 2858, 1732, 1698, 1678, 1632, 1472, 1462, 1428, 1376, 1362, 1214, 1110, 1079, 1045, 822, 741, 703. The stereochemistry was assigned on the basis of the ^{13}C NMR absorptions of the carbonyl carbons.[12]

Methyl (4aα*,7β*)- and (4aα*,7α*)-7-((7*S*)-((*tert*-Butyldiphenylsilyl)oxy)-2-oxo-(5*Z*)-nonenyl)-3-((4*R*)-((*tert*-butyldiphenylsilyl)oxy)-pentyl)-4a,5,6,7-tetrahydro-1-methoxypyrrolo[1,2-*c*]pyrimidine-4-carboxylate (40 and 41). A suspension of **39** (200 mg, 0.23 mmol), *O*-methylisoureido sulfate (300 mg, 1.22 mmol), and diisopropylethylamine (70 mg, 0.54 mmol) in 6 mL of DMSO was stirred at 80 °C for 1.5 h, and then cooled to room temperature. The mixture was treated with 7:3 hexane–EtOAc (10 mL) and 5% $NaHCO_3$ solution (5 mL). After the organic layer was separated, the aqueous layer was extracted with 7:3 hexane–EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 hexane–EtOAc) gave 110 mg (52%) of **40** and **41** as a 4:1 mixture of isomers, which can be separated by careful chromatography on silica gel (15:1 hexane–EtOAc). Anal. Calcd for $C_{56}H_{74}N_2O_6Si_2$: C, 72.53; H, 8.04; N, 3.02. Found: C, 72.59; H, 7.69; N, 2.94.

Data for **40**: ^{1}H NMR 7.56–7.75 (m, 8), 7.28–7.44 (m, 12), 5.432 (br dd, 1 × 0.5, J = 11.0, 9.0), 5.427 (br dd, 1 × 0.5, J = 11.0, 9.0), 5.12 (br dt, 1, J = 11.0, 8.0), 4.49 (dd, 1 × 0.5, J = 10.5, 4.5), 4.47 (dd, 1 × 0.5, J = 10.5, 4.5), 4.25–4.40 (m, 2), 3.88 (m, 1), 3.730 (s, 3 × 0.5), 3.715 (s, 3 × 0.5), 3.648 (s, 3 × 0.5), 3.644 (s, 3 × 0.5), 2.71 (dd, 1, J = 16.5, 4.4), 2.62 (m, 1), 2.35–2.50 (m, 2), 2.36 (dd, 1 × 0.5, J = 16.5, 3.4), 2.34 (dd, 1 × 0.5, J = 16.5, 3.3), 1.95–2.20 (m, 3), 1.70–1.95 (m, 2), 1.34-1.70 (m, 8), 1.05 (d, 3, J = 6.0), 1.04 (s, 9), 1.03 (s, 9), 0.79 (t, 3, J = 7.4); ^{13}C NMR 207.79 (0.5 C), 207.77 (0.5 C), 167.3, 161.62 (0.5 C), 161.60 (0.5 C), 156.9, 136.0 (2 C), 135.8 (6 C), 135.0, 134.7, 134.4, 134.3, 133.9, 129.5, 129.34, 129.31, 129.27, 127.45 (2 C), 127.37 (3 C), 127.30 (2 C), 127.27 (2 C), 101.4, 70.5, 69.71 (0.5 C), 69.65 (0.5 C), 58.7, 54.6, 54.1, 50.5, 48.0, 42.83 (0.5 C), 42.78 (0.5 C), 39.31 (0.5 C), 39.27 (0.5 C), 35.5, 35.3, 31.1, 28.7, 27.0 (3 C), 26.9 (3 C), 24.0 (0.5 C), 23.9 (0.5 C), 23.13 (0.5 C), 23.09 (0.5 C), 21.6, 19.3 (2 C), 9.3; IR (neat) 3070, 3048, 2960, 2931, 2857, 1713, 1682, 1613, 1527, 1473, 1428, 1402, 1258, 1240, 1111, 1026, 1006, 822, 740, 703.

Data for **41**: ^{1}H NMR 7.56–7.73 (m, 8), 7.27–7.45 (m, 12), 5.41 (br dd, 1, J = 11.0, 9.0), 5.10 (br dt, 1, J = 11.0, 7.4), 4.26–4.41 (m, 2), 4.11 (ddd, 1, J = 9.1, 8.0, 3.0), 3.87 (m, 1), 3.77 (s, 3 × 0.5), 3.75 (s, 3 × 0.5), 3.66 (s, 3 × 0.5), 3.64 (s, 3 × 0.5), 2.68 (dd, 1, J = 16.9, 3.0), 2.57 (m, 1), 2.44 (m, 2), 1.36–2.30 (m, 14), 1.05 (d, 3, J = 6.0), 1.04 (s, 9), 1.03 (s, 9), 0.79 (t, 3, J = 7.3); ^{13}C NMR 202.2, 167.0, 163.2, 156.9, 136.0 (2 C), 135.8 (6 C), 134.4, 134.3, 134.0, 133.88, 133.82, 129.5 (2 C), 129.3 (2 C), 127.45 (3 C), 127.39 (2 C), 127.32 (2 C), 127.26 (2 C), 103.3, 70.5, 69.7 (0.5 C), 69.6 (0.5 C), 59.5, 54.1, 52.24 (0.5 C), 52.20 (0.5 C), 50.5, 47.7, 42.6, 39.4 (0.5 C), 39.3 (0.5 C), 34.90 (0.5 C), 34.87 (0.5 C), 31.10, 30.67 (0.5 C), 30.64 (0.5 C), 30.1, 27.0 (3 C), 26.9 (3 C), 24.3 (0.5 C), 24.0 (0.5 C), 23.13 (0.5 C), 23.06 (0.5 C), 21.58 (0.5 C), 21.55 (0.5 C), 19.28, 19.23, 9.25; IR (neat) 3070, 3045, 2958, 2931, 2856, 1715, 1684, 1602, 1522, 1472, 1428, 1400, 1256, 1245, 1111, 1028, 1003, 822, 740, 702.

Methyl [2a*R*-[2aα,7α,8aα]]- and [2a*S*-[2aα,7α,8aα]]-7-((*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-(3*Z*)-heptenyl)-4-((*R*)-4-((*tert*-butyldiphenylsilyl)oxy)pentyl)-1,2,6,7,8,8a-hexahydro-7-hydroxy-2a*H*-5,6,8b-triazaacenaphthylene-3-carboxylate Hydrochloride (42 and 43). A solution of the mixture of **40** and **41** (100 mg) in 5 mL of *tert*-butyl alcohol was dried (Na_2SO_4) and transferred to a resealable tube, and NH_4OAc (50 mg) was added. The solution was saturated with anhydrous NH_3 at 5 °C for 5 min and then was sealed and kept at 60 °C for 40 h. The solution was cooled to room temperature and treated with CH_2Cl_2 (15 mL). The solid salt was removed by filtration and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure, and the residue was taken up in saturated NH_4Cl solution (5 mL) and brine (10 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (2:3 hexane–EtOAc to EtOAc) gave 74 mg (72%) of a 1:1 mixture of **42** and **43** as a colorless oil: ^{1}H NMR 7.56–7.72 (m, 8), 7.24–7.45 (m, 12), 5.43 (br t, 1, J = 9.9), 5.19 (m, 1), 4.44 (dd, 1 × 0.5, J = 9.8, 5.8), 4.43 (dd, 1 × 0.5, J = 9.8, 5.8), 4.33 (m, 1), 3.79–3.93 (m, 2), 3.68 (s, 3 × 0.5), 3.67 (s, 3 × 0.5), 2.40–2.73 (m, 3), 2.13 (m, 1), 2.04 (m, 1), 1.86 (m, 1), 1.35–1.78 (m, 12), 1.03 (d, 3, J = 6.0), 1.02 (s, 18), 0.78 (t, 3, J = 7.3); ^{13}C NMR 165.1, 147.5, 145.39 (0.5 C), 145.31 (0.5 C), 136.0 (2 C), 135.8 (6 C), 134.8, 134.46, 134.34, 133.70, 133.65, 129.4 (2 C), 129.3 (2 C), 127.8, 127.46 (4 C), 127.40 (4 C), 100.83 (0.5 C), 100.80 (0.5 C), 79.66 (0.5 C), 79.62 (0.5 C), 70.6 (0.5 C), 70.5 (0.5 C), 69.2 (0.5 C), 69.1 (0.5 C), 56.7, 51.43, 51.39, 39.9, 38.9 (0.5 C), 38.7 (0.5 C), 36.4 (0.5 C), 36.2 (0.5 C), 32.9, 31.1, 41.0, 27.0 (3 C), 26.9 (3 C), 26.0, 24.0 (0.5 C), 23.8 (0.5 C), 23.0 (0.5 C), 22.9 (0.5 C), 21.70 (0.5 C), 21.57 (0.5 C), 19.26, 19.22, 9.36 (0.5 C), 9.27 (0.5 C); IR (neat) 3233, 3070, 2957, 2931, 2856, 1715, 1682, 1580, 1428, 1266, 1188, 1110,

702. Anal. Calcd for $C_{55}H_{74}N_3O_5ClSi_2$: C, 69.62; H, 7.86; N, 4.43. Found: C, 69.82; H, 7.31; N, 4.47.

Methyl [2*S*,7*S*,2′a*S*,7′*R*,8′*S*,8′a*R*,6″*R*]- and [2*S*,7*S*,2′a*S*,7′*R*,8′*R*,8′a*R*,6″*R*]-7-Ethyl-1′,2′,2′a,3′,3″,4,4″,5″,6″,7,8′,8′a-dodecahydro-6″-methyldispiro[oxepin-2(3*H*),4′-[4*H*-5,6,8b]triazaacenaphthylene-7′(5′*H*),2″-[2*H*]pyran]-8′-carboxylate (9 and 45). A solution of hydrogen fluoride (50%, 1 mL) was added slowly to a stirred solution of **42** and **43** (50 mg) in 2 mL of acetonitrile at −40 °C. The mixture was stirred at −30 °C for 3 d,[20] and a mixture of saturated $NaHCO_3$ solution (5 mL) and saturated NH_4Cl solution (2 mL) was slowly added to the reaction at −30 °C, and water (5 mL) was added at 0 °C. The mixture was extracted with EtOAc (3 × 15 mL) at 0 °C. The combined organic layers were washed with saturated $NaHCO_3$ solution (5 mL) and saturated NH_4Cl solution (5 mL) at 0 °C and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 CH_2Cl_2–MeOH) gave 21.3 mg of a polar mixture, possibly containing tricyclic diols.

A solution of this mixture and Et_3N (20 mg) in 3 mL of MeOH was heated at 60 °C for 20 h. Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel gave 12.3 mg of a mixture rich in **9** and **45** (30:1 to 19:1 CH_2Cl_2–MeOH) followed by 8.6 mg (9:1 CH_2Cl_2–MeOH) of more polar tricyclic and tetracyclic material, which was heated in MeOH containing Et_3N again to give another 2.1 mg of **9** and **45** after chromatography. The combined fractions of **9** and **45** (14.4 mg) contain about 65% (by ^1H NMR) of a 1.3:1 mixture of **9** and **45** (39% yield assuming 65% pure, 78% based on **42**). Flash chromatography of this mixture on silica gel (40:1 EtOAc–MeOH) gave 4.7 mg of 80% pure **9** and 4.0 mg of 85% pure **45**.

Much purer **9** (99%) and **45** (96%) were obtained by heating the mixture of **9** and **45** (12.0 mg) in 4 mL of 1:1 H_2O–MeOH containing Et_3N (15 mg) for 16 h at 60 °C to give, after flash chromatography on silica gel, 3.0 mg of recovered **9** and **45** (97:3 EtOAc–MeOH) followed by 5.8 mg of pure **44** (92:8 EtOAc–MeOH). Recyclization of **44** in 3 mL of MeOH containing Et_3N (15 mg) followed by flash chromatography on silica gel (97:3 EtOAc–MeOH) gave 4.9 mg of a 1.3:1 mixture of **9** and **45**, which were separated by careful flash chromatography on silica gel (39:1 EtOAc–MeOH) to give 2.5 mg of 99% pure **9** followed by 1.2 mg of a mixture of **9** and **45**, and then 1.0 mg of 96% pure **45**.

A solution of 1.0 mg of **45** was heated with Et_3N in MeOH for 20 h. The ^1H NMR spectrum indicated that a 7:5:8 mixture of **44**, **9**, and **45** was formed.

Data for **44**: ^1H NMR 5.69 (ddt, 1, J = 11.0, 7.5, 2.1), 5.48 (dt, 1, J = 11.0, 2.0), 4.53 (dd, 1, J = 10.0, 6.0), 4.47 (m, 1), 4.00 (m, 1), 3.95 (m, 1), 3.76 (s, 3), 2.81 (m, 1), 2.67 (dd, 1, J = 12.9, 5.3), 2.53–2.67 (m, 2), 2.34 (m, 1), 2.10–2.30 (m, 2), 1.96 (br dd, 1, J = 13.9, 5.7), 1.40–1.90 (m, 9), 1.42 (t, 1, J = 14.1), 1.21 (d, 3, J = 6.2), 0.84 (t, 3, J = 7.3); ^{13}C NMR 165.2, 148.1, 146.0, 133.1, 129.9, 100.8, 84.0, 71.3, 56.9, 52.6, 51.6, 37.8, 37.2, 36.8, 33.3, 30.13, 20.09, 29.1, 25.9, 24.2, 23.5, 23.4, 10.1.

Data for **9**: $[\alpha]_D$ = +5.0° ($CHCl_3$, 0.13); ^1H NMR 9.93 (br s, 1, NH), 9.72 (br s, 1, NH), 5.67 (ddt, 1, J = 11.2, 7.8, 2.2), 5.48 (dt, 1, J = 11.2, 2.0), 4.52 (m, 1), 4.29 (dt, 1, J = 9.8, 5.0), 3.98 (m, 2), 3.70 (s, 3), 2.97 (d, 1, J = 5.2), 2.56 (dd, 1, J = 12.3, 6.0), 2.52 (br t, 1, J = 14.1), 2.10–2.42 (m, 6), 1.96 (br dd, 1, J = 14.1, 5.6), 1.40–1.88 (m, 7), 1.42 (t, 1, J = 12.3), 1.20 (m, 1), 1.06 (d, 3, J = 6.1), 0.84 (t, 3, J = 7.2); ^{13}C NMR 168.6, 148.8, 133.7, 129.8, 83.6, 80.7, 71.0, 67.3, 53.9, 52.1, 51.7, 49.7, 37.0 (2 C), 32.0 (2 C), 30.6, 29.1, 26.8, 23.5, 21.4, 18.3, 10.0; IR (neat) 3230, 3106, 2968, 2934, 2872, 1735, 1659, 1614, 1437, 1204, 1165, 1089, 1016, 924, 728.

A 2D-NMR ROESY experiment on **9** showed intense cross peaks between H_1 and H_{19}, H_3 and H_7-α (δ 2.52), H_1 and H_{13}, and H_{10} and H_{13}, which are identical to those observed in the ROESY spectra of ptilomycalin A.[1]

Data for **45**: $[\alpha]_D$ = +23.0° ($CHCl_3$, 0.10); ^1H NMR 10.09 (br s, 1, NH), 9.81 (br s, 1, NH), 5.66 (m, 1), 5.48 (dt, 1, J = 11.0, 1.9), 4.49 (m, 1), 4.33 (dt, 1, J = 11.6, 7.1), 4.09 (m, 1), 3.90 (m, 1), 3.79 (s, 3), 2.57 (dd, 1, J = 12.6, 4.6), 2.51 (br t, 1, J = 14.0), 2.42 (d, 1, J = 11.5), 2.10–2.45 (m, 6), 1.92 (br dd, 1, J = 14.0, 5.1), 1.40–1.85 (m, 7), 1.32 (t, 1, J = 12.6), 1.10 (m, 1), 1.04 (d, 3, J = 6.1), 0.83 (t, 3, J = 7.2); ^{13}C NMR 168.2, 147.9, 133.6, 129.7, 83.4, 81.5, 71.0, 67.8, 53.3, 53.2, 53.0, 52.4, 37.2, 37.0, 32.0, 31.2, 29.8, 29.6, 29.1, 23.5, 21.3, 18.5, 10.2; IR (neat) 3229, 3118, 2967, 2933, 2874, 1737, 1660, 1613, 1438, 1201, 1094, 1018, 727.

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