Optical Rotation Computation, Total Synthesis, and Stereochemistry Assignment of the Marine Natural Product Pitiamide A

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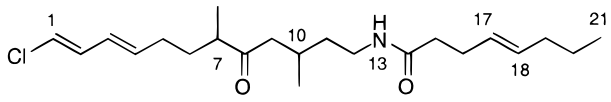
Abstract: We report the joint application of ab initio computations and total synthesis to assign the absolute configuration of a new natural product. The expected specific rotations of the (7*S*,10*R*)- and (7*R*,10*R*)-isomers of pitiamide A in a $CHCl_3$ solvent continuum model were determined as +8 and −39, respectively, by CADPAC calculations of the electric-dipole−magnetic-dipole polarizability tensor. Total syntheses of these two stereoisomers of the marine metabolite were achieved by a convergent strategy that utilized Evans' oxazolidinone alkylation, a novel water-accelerated modification of Negishi's zirconocene-catalyzed asymmetric carbometalation as well as an unusual segment condensation via Mitsunobu alkylation of a nosyl-activated amide. The experimental optical rotation measurements confirmed the results of the computational optical rotation predictions. On the basis of NMR comparisons, the configuration of pitiamide A was assigned as (7*R*,10*R*). These studies highlight the considerable structural significance of $[\alpha]_D$ data, but, because the optical rotation of the natural product was different from either synthetic diastereomer, our work serves also as an illustration of potential problems with obtaining accurate experimental $[\alpha]_D$ data for natural samples.

The chlorinated lipid pitiamide A (**1**) was isolated in 1997 from an extract of a mixed assemblage of *Lyngbya majuscula* and *Microcoleus* sp. growing on intact colonies of the hard coral *Porites cylindrica* on Guam.[1] Pitiamide may act as a feeding deterrent to both vertebrate and invertebrate herbivore species, but the determination of its biological profile has been limited by the lack of availability of sufficient quantities of the natural product.

The structure of this unusual vinyl chloride-containing marine metabolite (Figure 1) was determined by 2D NMR spectral analysis and mass spectroscopy, and its $[\alpha]_D$ was found to be −10.3 (*c* 3.0, $CHCl_3$, 27 °C).[2] The absolute and relative configurations at C(7) and C(10) were not assigned. Pitiamide A is a temperature- and light-sensitive oil, and due to the flexibility of most of its backbone chain, a stereochemical assignment based entirely on NMR spectroscopic methods has not been realized. Elucidation of its relative and absolute stereochemistry by circular dichroism (CD) is also not promising, in particular since the stereocenter at C(10) is not part of a strongly asymmetrically perturbed chromophore absorbing at $\lambda > 180$ nm (vide infra). Accordingly, calculation of the expected molar rotation of pitiamide A diastereomers and enantiomers represents the most attractive solution to this structural problem, but is most challenging due to the unusually high level of flexibility in the lipid backbone.[3]

Recently, we devised a Monte Carlo/ab initio approach to assign the configuration of the complex natural product hennoxazole A from computation of the electric-dipole magnetic-dipole polarizability tensor of suitable fragment molecules.[3] The computed rotations are Boltzmann-weighted averages of values obtained for individual fragments and can be directly compared to experimental specific rotations. Our earlier theoretical analysis of hennoxazole A represented an a posteriori assignment of stereochemistry. We decided to further apply this methodology for the computational prediction of the absolute configuration of a natural product, i.e., an a priori assignment of the relative and absolute stereochemistry of pitiamide A.



Pitiamide A

Figure 1. Structure of pitiamide A as assigned by Paul and coworkers.[1]

Optical Rotation Computations

In accordance with principles developed in our earlier work,[3,4] we dissected pitiamide A into two chiroptically independent fragments **I** and **II** (Figure 2). This structural simplification is necessary because current coupled Hartree−Fock methods are limited to 255 basis functions, a number that correlates at the 6-31G* level approximately with a limit of 14 carbon or heteroatoms in a given molecule. We selected fragments **I** and **II** because they provide increments[5−7] for the contribution of asymmetric carbons C(7) and C(10), respectively, to the molar rotation of pitiamide A. In some cases, an extended π-system can make considerable contributions to the rotation angle,[4]

* To whom correspondence should be addressed.

(1) Nagle, D. G.; Park, P. U.; Paul, V. J. *Tetrahedron Lett.* **1997**, *38*, 6969.

(2) Possibly because of instabilities in the polarimeter, the actual measurements fluctuated from −15.3 to −8.7. Prof. V. Paul, personal communication.

(3) Kondru, R. K.; Wipf, P.; Beratan, D. N. *J. Am. Chem. Soc.* **1998**, *120*, 2204.

(4) Kondru, R. K.; Wipf, P.; Beratan, D. N. *J. Phys. Chem.* **1999**, *103*, 6603.

(5) (a) van't Hoff, J. H. *Arch. Neerl. Sci. Exactes Nat.* **1874**, *9*, 455. (b) van't Hoff, J. H. *Die Lagerung der Atome im Raume*; Vieweg: Braunschweig, Germany, 1894; p 95.

(6) Kondru, R. K.; Lim, S.; Wipf, P.; Beratan, D. N. *Chirality* **1997**, *9*, 469.

(7) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157.

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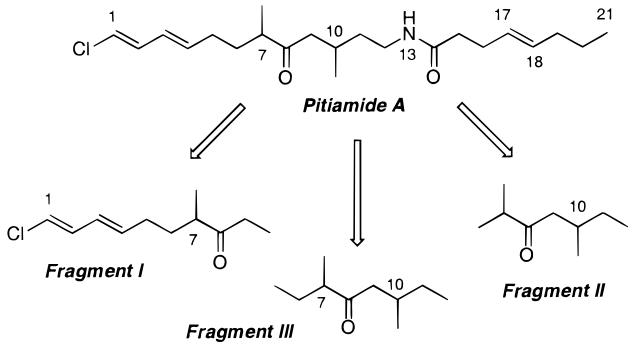


Figure 2. Fragments (**I**−**III**) for pitiamide A molar rotation angle computations.

and therefore we included the diene π-system along with the chlorine atom in fragment **I**. In general, stereocenters more than three atoms removed from each other have negligible mixed-term contributions to the rotation of the plane of polarized light, as long as the rotation of the chain can occur freely.[6] To test this approximation, we selected a fragment **III** that contains both stereocenters at C(7) and C(10).

The selection of amide-containing fragments in our force-field calculations was complicated by the intrinsic trend of the molecular mechanics parametrization to overvalue intramolecular hydrogen-bonded conformations and favor an eight-membered H-bridge between the C(8) carbonyl group and the amide NH. As a molecular dynamics analysis of pitiamide A showed, populated states at room temperature can be significantly different from the minimum energy conformers.[8] Extensive (10 ns) stochastic dynamics analysis[9] of pitiamide A at 300 K using a $CHCl_3$-solvent continuum model[10] indicated that for both diastereomeric configurations, any hydrogen-bonded conformations were unlikely to account for more than 5−10% of the molecular ensemble.[11] Accordingly, our fragmentation strategy was judged to be adequate, and we omitted the C(12)-amide substituent in any subsequent fragment computations. The effect of this structural simplification as well as the omission of the C(17)−C(18) double bond on the optical rotation of pitiamide should be minimal, because both groups are quite remote from the nearest stereocenter at C(10). In fact, subsequent NMR and CD analyses of synthetic derivatives validated this approach (vide infra). Although basing the ab initio calculations on force-field optimized fragment geometries is clearly less than ideal, extensive prior tests have demonstrated the viability of this approach.[3,4,6,12]

For the interpretation of chiroptical data, many empirical,[3−6,13−19] semiempirical,[20−25] classical,[26,27] and quantum mechanical[6,28−35] models have been developed. Direct application of the Rosenfeld equation, the most fundamental quantum mechanical expression for chiroptical effects, is not yet feasible because it includes a sum over all molecular excited states. An alternative approach employed recently with great success for Raman optical activity and vibrational CD is based on ground state linear response calculations.[3,4,37−40] Applications of this theoretical strategy toward quantitatively reliable quantum chemical computations of molar rotation angles are now beginning to have a large impact on the field.[36−40] The expression for the optical rotational angle, ϕ in radians, is[41]

$$\phi = 4\pi N\beta\omega^2(n^2+2)/3c^2 \tag{1}$$

where

$$\beta = -\omega^{-1}(G'_{xx} + G'_{yy} + G'_{zz})/3 \tag{2}$$

and G'_{ii} are the diagonal elements of the electric-dipole−magnetic-dipole polarizability tensor.[37] N is the number of molecules per unit volume, n is the refractive index of the medium, and c is the speed of light. The specific rotation angle (measured at the sodium D-line), in units of deg [dm (g/mL)]$^{-1}$, is

$$[\alpha]_D = 1.343 \times 10^{-4}\, \beta\bar{\nu}^2(n^2+2)/3MW \tag{3}$$

where β is in units of (bohr)^4, MW is the molar mass in g/mole, and $\bar{\nu}$ is the frequency of the sodium D-line in cm^{-1}.[37] From $[\alpha]_D$, the molar rotation is defined as $[M]_D = [\alpha]_D MW/100$. The diagonal elements of the electric-dipole magnetic-dipole polarizability tensor, G'_{ii},[42] are calculated using CADPAC[43] or DALTON.[44] The CADPAC methodology employed here is most reliable far from electronic resonance. Note that the G'_{ii} elements are computed relatively well despite the fact that linear-

(8) See also: McDonald, D. Q.; Still, W. C. *Tetrahedron Lett.* **1992**, *33*, 7747.
(9) Van Gunsteren, W. F.; Berendsen, H. J. C. *Mol. Simul.* **1988**, *1*, 173.
(10) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127.
(11) Calculations of the optical rotation of hydrogen-bonded conformations of C(5)−C(14) segments of pitiamide A provided absolute values that were in the same order of magnitude as open-chain conformations. These control studies addressed the potential pitfall that small percentages of intramolecular hydrogen-bonded conformations could significantly alter the overall optical rotation of pitiamide A and thus introduce a major source of error in our computational strategy.
(12) Kondru, R. K.; Chen, C. H.-T.; Curran, D. P.; Beratan, D. N.; Wipf, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4143.
(13) Walden, P. *Z. Phys. Chem.* **1894**, *15*, 196.
(14) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.
(15) Nakanishi, K.; Berova, N.; Woody, R. W. *Circular Dichroism Principles and Applications*; VCH Publishers Inc.: New York, 1994.
(16) Kauzmann, W.; Eyring, H. *J. Chem. Phys.* **1941**, *9*, 41.
(17) Freudenberg, K.; Todd, J.; Seidler, R. *Ann. Chem.* **1933**, *501*, 199.
(18) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5475.
(19) Brewster, J. H. *Tetrahedron* **1961**, *13*, 106.
(20) Moscowitz, A. *Adv. Chem. Phys.* **1962**, *4*, 67.
(21) Applequist, J. *J. Chem. Phys.* **1973**, *58*, 4251.
(22) Tinoco, I., Jr.; Woody, R. W. *J. Chem. Phys.* **1964**, *40*, 160.
(23) Sathyanarayana, B. K.; Stevens, E. S. *J. Org. Chem.* **1987**, *52*, 3170.
(24) Gould, R. R.; Hoffmann, R. *J. Am. Chem. Soc.* **1970**, *92*, 1813.
(25) Pao, Y. H.; Santry, D. P. *J. Am. Chem. Soc.* **1966**, *88*, 4157.
(26) Kuhn, W. *Stereochemie*; Freudenberg, K., Ed.; Deuticke: Leipzig, **1933**; Chapter 8, p 394.
(27) Born, M. *Proc. R. Soc. London A* **1935**, *150*, 84.
(28) Kirkwood, J. G. *J. Chem. Phys.* **1937**, *5*, 479.
(29) Nolte, H. J.; Buss, V. *Tetrahedron* **1975**, *31*, 719.
(30) Maestro, M.; Moccia, R.; Taddei, G. *Theor. Chim. Acta* **1967**, *8*, 80.
(31) Eyring, H.; Walter, J.; Kimball, G. E. *Quantum Chemistry*; Wiley: New York, 1944.
(32) Rauk, A.; Barriel, J. M. *Chem. Phys.* **1977**, *25*, 409.
(33) Bak, K. L.; Hansen, A. E.; Ruud, K.; Helgaker, T.; Olsen, J.; Jørgensen, P. *Theor. Chim. Acta.* **1995**, *90*, 441.
(34) Hansen, A. E.; Bouman, T. D. *J. Am. Chem. Soc.* **1985**, *107*, 4828.
(35) Snatzke, G. In *Chirality: from Weak Bosons to the Alpha-Helix*; Janoschek, R., Ed.; Springer-Verlag: Berlin, 1991; pp 59−85.
(36) Costante, J.; Hecht, L.; Polavarapu, P. L.; Collet, A.; Barron, L. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 885.
(37) Polavarapu, P. L. *Mol. Phys.* **1997**, *91*, 551.
(38) Kondru, R. K.; Wipf, P.; Beratan, D. N. *Science* **1998**, *282*, 2247.
(39) Polavarapu, P. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3397.
(40) (a) Polavarapu, P. L.; Chakraborty, D. K. *J. Am. Chem. Soc.* **1998**, *120*, 6160. (b) Polavarapu, P. L.; Zhao, C. *J. Am. Chem. Soc.* **1999**, *121*, 246.
(41) Rosenfeld, L. Z. *Physik* **1928**, *52*, 161.
(42) Amos, R. D. *Chem. Phys. Lett.* **1982**, *87*, 23.
(43) Amos, R. D.; Rice, J. E. *The Cambridge Analytic Derivative Package*; issue 6.3, Cambridge, U.K., 1997.

Table 1. Computed Molar Rotation Angles for Fragments **I**−**III**, and Pitiamide A (**1**) Based on Fragment Analysis

	$[M]_D$ (for indicated stereoisomer)	
fragment **I**	+111 (7*S*)	
fragment **II**	+66 (10*S*)	
fragment **III**	+123 (7*S*,10*S*)	+17 (7*S*,10*R*)
pitiamide A	+150 (7*S*,10*S*)	+31 (7*S*,10*R*)

The values shown for fragments **I**−**III** are averages of at least two independent calculations that differ in their results by <10%. The value for pitiamide is the average of fragments (**I** + **II**) and **III**. The configurations of fragments **I**−**III** and pitiamide are indicated next to the computed molar rotation angles.

response methods are not guaranteed to reproduce the molecular electronic absorption spectra.

Conformation has a major influence on specific rotation angles.[3,4,45] Unique low-energy geometries for our fragments were obtained from Monte Carlo conformational searches using the Macromodel[46] program with the MM2* force field. This force field has been found to produce geometries and relative energies of high reliability.[47] After building the required structure of a specified configuration, energy minimization was performed using MM2* with the PRCG algorithm and a $CHCl_3$ continuum solvent model.[46] Low-energy structures were chosen from a Monte Carlo sampling of 5000 conformations (fragments **I** and **II**) or 2000 conformations (fragment **III**); each new conformation was energy minimized using a 3000 step energy minimization iteration method forcing all newly found structures to be fully relaxed, and duplicates were automatically rejected. All conformations generated within ~(2−3) *kT* of the lowest energy structure (those thermally accessible in solution) were used in the optical rotation angle computations.

A total number of 180 conformations of fragments **I**−**III** were subjected to calculations of the molar rotation angles in the static field approximation implemented in CADPAC with a 6-31G* basis set.[48] The results are summarized in Table 1. The composite values for fragments **I** and **II** (a simple additivity of molar rotation angles was assumed based on van't Hoff's principle[5]) were combined with values for fragment **III** and averaged to provide predictions for the molar rotations of pitiamide diastereomers and enantiomers. On the basis of this computational analysis, the syn [(7*S*,10*S*) or (7*R*,10*R*)] and anti [(7*S*,10*R*) or (7*R*,10*S*)] stereoisomers of pitiamide A were assigned molar rotations $[M]_D$ of +150, −150, +31, and −31, respectively. In units of $[\alpha]_D$, (7*S*,10*S*)-, (7*R*,10*R*)-, (7*S*,10*R*)-, and (7*R*,10*S*)-stereoisomers of pitiamide A are thus predicted to have rotations of +39, −39, +8, and −8 deg [dm (g/mL)]$^{-1}$, respectively. Accordingly, the (7*R*,10*S*)-configuration provides the closest agreement in value and sign with the experimental $[\alpha]_D$ of −10.3 reported by Paul et al.[1] It is important to stress that our calculations used a $CHCl_3$ solvation model, and are thus in agreement with the solvent environment used for the specific rotation determination of the natural product.

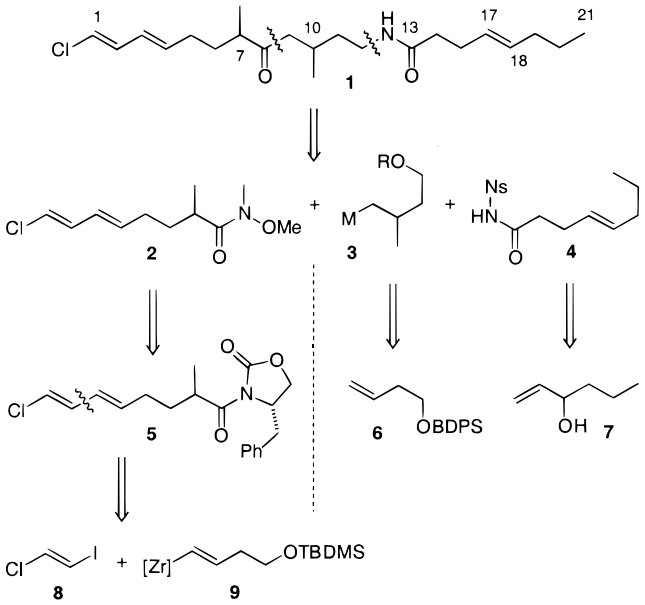


Figure 3. Retrosynthetic analysis of pitiamide A.

Total Syntheses of (7*S*,10*R*)- and (7*R*,10*R*)-Pitiamide A

The 1-chlorodiene moiety of pitiamide A is a highly unusual structural feature among marine natural products,[1,49] and we were interested in devising an efficient synthetic strategy for the preparation of this moiety as well as for the catalytic asymmetric introduction of the β-carbonyl stereocenter at C(10). In addition, total synthesis of pitiamide A stereoisomers offered the opportunity to test the predictive power of our computational methodology for optical rotation calculations. Accordingly, we embarked on a total synthesis of the marine lipid guided by the retrosynthetic analysis shown in Figure 3. Formation of the C(8)−C(9) bond in **1** was envisioned to result from the addition of an organometallic reagent **3** to Weinreb amide **2**. A novel Mitsunobu chain extension[50] with sulfonimide **4** and deprotection of the *o*-nitrophenylsulfonyl group[51] should complete the highly convergent segment assembly.[52] Hydroxamate **2** can be obtained from the Evans-oxazolidinone-derived[53] imide **5**, which also serves to install the α-carbonyl stereocenter at C(7). Inspired by the elegant studies of Negishi and Kondakov,[54] we planned to use an asymmetric zirconocene-catalyzed carbometalation of monosubstituted alkene **6** toward the key organometallic intermediate **3**. The γ,δ-unsaturated carboxylate **4** could be obtained by Johnson ortho ester Claisen rearrangement[55] from allylic alcohol **7**. Finally, a palladium-mediated coupling[56]

(44) Helgaker, T.; Jensen, H. J. A.; Olsen, J.; Ruud, K.; Anderson, A. T.; Bak, K. L.; Bakken, V.; Christiansen, O.; Dahle, P.; Dalskov, E. K.; Enevoldsen, T.; Fernandez, B.; Heiberg, H.; Hettema, H.; Jonsson, D.; Kirpekar, S.; Kobayashi, R.; Koch, H.; Mikkelsen, K. V.; Norman, P.; Packer, P.; Saue, T.; Taylor, P. R.; Vahtras, O.; *DALTON, an electronic structure program*, Release 1.0, 1997.

(45) (a) Kauzmann, W.; Eyring, H. *J. Chem. Phys.* **1941**, *9*, 41. (b) Arndt, E. R.; Stevens, E. S. *Biopolym.* **1994**, *34*, 1527. (c) Arndt, E. R.; Stevens, E. S. *Biopolymers* **1996**, *38*, 567. (d) Johnson, W. C.; Tinoco, I. *J. Am. Chem. Soc*. **1972**, *94*, 4389. (e) Schellman, J. A. *J. Chem. Phys*. **1966**, *44*, 55.

(46) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(47) Pettersson, I.; Liljefors, T. In *Reviews in Conputational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: New York, 1996; Vol. 9, p 167.

(48) Calculations were performed on a 600 MHz dec-alpha workstation and required between 4 and 12 days of CPU time for each fragment.

(49) Mynderse, J. S.; Moore, R. E. *Phytochem.* **1978**, *17*, 1325.

(50) (a) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (c) Mitsunobu, O. *Synthesis* **1981**, 1.

(51) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

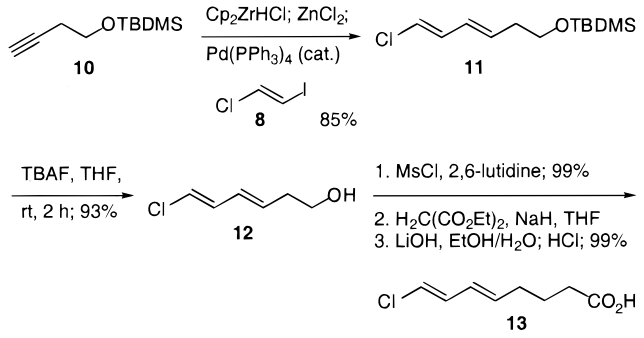
(52) For *N*-methylation of a nosylated amide, see: Katagiri, N.; Takebayashi, M.; Kokufuda, H.; Kaneko, C.; Kanehira, K.; Torihara, M. *J. Org. Chem.* **1997**, *62*, 1580.

(53) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

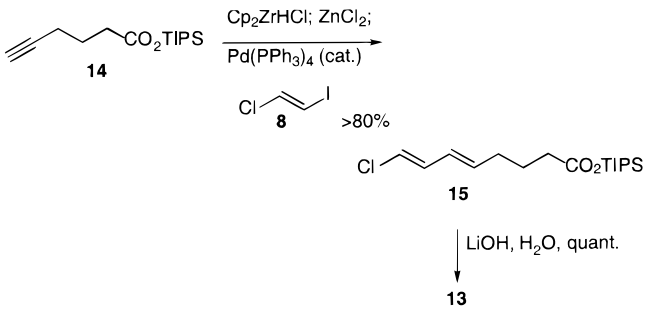
(54) (a) Kondakov, D. Y.; Negishi, E.-I. *J. Am. Chem. Soc.* **1995**, *117*, 10771. (b) Kondakov, D. Y.; Negishi, E.-I. *J. Am. Chem. Soc.* **1996**, *118*, 1577.

(55) (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 827−874. (b) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

Scheme 1



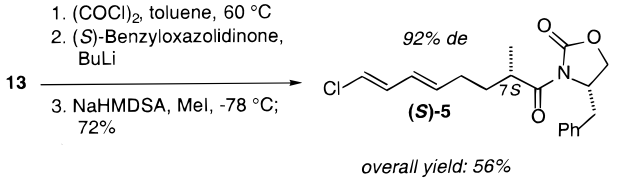
Scheme 2



between alkenyl zirconocene **9**, obtained by hydrozirconation[57] of the corresponding alkyne, and the readily available 1-iodo-2-chloroethene (**8**) should allow access to the chlorodiene moiety. Although some tactical and experimental modifications became necessary, this retrosynthetic plan ultimately proved successful for the preparation of the desired two diastereomers of pitiamide A.

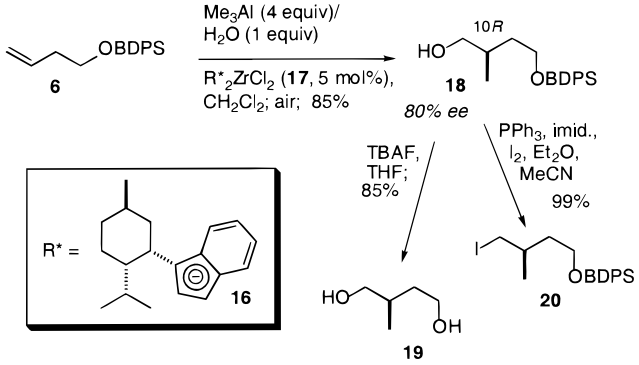
For the synthesis of the C(1)−C(8) segment **5**, *tert*-butyldimethylsilyl-protected butynol **10** was hydrozirconated with Cp_2ZrHCl[57] (Scheme 1). In situ transmetalation to $ZnCl_2$ followed by the addition of vinyl iodide **8** [58] and 5−8 mol % of $Pd(PPh_3)_4$ catalyst[56] cleanly provided the cross coupling product **11** in high yield exclusively in the desired all-(*E*) double bond configuration. The *tert*-butyldimethylsilyl (TBDMS)-ether was cleaved with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) at room temperature to give the somewhat unstable alcohol **12**. Mesylation with methanesulfonyl chloride and 2,6-lutidine followed by nucleophilic displacement with the anion of diethyl malonate provided the diester intermediate which was saponified without further purification. After neutralization with 1 N HCl and bulb to bulb distillation, dienyl acid **13** was isolated in nearly quantitative yield based on alcohol **12**. Although **13** is relatively unstable, it could be obtained in very high purity after only one distillation, and no further purification was necessary. Alternatively, carboxylic acid **13** could also be obtained much more directly by hydrozirconation−cross coupling of alkynoate **14** (Scheme 2) followed by saponification. However, chromatographic separation of the alkene side product derived from **14** and the desired **13** was extremely tedious, especially on large scale, and therefore this route was abandoned in favor of the longer but similarly high yielding sequence shown in Scheme 1.

Scheme 3



overall yield: 56%

Scheme 4



Attachment of the (*S*)- or, alternatively, the (*R*)-benzyloxazolidinone[53] via the acyl chloride followed by deprotonation with sodium hexamethyldisilazane (NaHMDSA) and alkylation at −78 °C with MeI provided **(*S*)-5**[59] in 72% yield over the three-step sequence and in 56% based on **10** (Scheme 3). ^{1}H NMR analysis of the crude reaction mixture revealed a 92% diastereoselectivity for the methylation reaction. It is important to note that the minor diastereomer can readily be removed chromatographically, and essentially stereochemically pure **(*S*)-5** was used for further conversions. The reaction sequence shown in Scheme 3 was repeated with the (*R*)-benzyloxazolidinone substrate, and **(*R*)-5** was obtained in 63% yield and 91% enantiomeric excess (ee) from **13**.

For the preparation of the C(9)−C(12) segment, we initially planned to use an unprotected unsaturated alcohol as a substrate for the zirconocene-catalyzed asymmetric methylalumination, as reported for 5-hexen-1-ol by Negishi and Kondakov.[54] However, we found that 3-buten-1-ol was not a suitable substrate; it remained inert to the reaction conditions. Furthermore, protection of 3-butene-1-ol either as the benzyl ether or as the triisopropylsilyl ether still did not yield any of the desired methylated product, even after the reaction temperature was raised to 40 °C. In earlier work, we were able to demonstrate the use of water as a highly effective additive for the zirconocene dichloride-catalyzed carbometalation of alkynes,[60] and we decided to attempt similarly increasing the reaction rate of the Negishi−Kondakov process by addition of water. Indeed, treatment of a mixture of trimethylaluminum and 5−8 mol % of Erker's chiral catalyst **17**[61] in CH_2Cl_2 with 1 equiv of water led to a vastly more reactive methylating agent (Scheme 4). Methylalumination of alkene **6** proceeded in 12 h at −20 °C and provided, after quenching of the trialkyl alane intermediate with air, the desired (10*R*)-alcohol **18** in 85% yield and 80% ee.[62,63] The absolute configuration of **18** was assigned by

(56) (a) Negishi, E.-I.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254. (b) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912. (c) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4914.

(57) (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (b) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.

(58) Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F.-T. *J. Org. Chem.* **1984**, *49*, 2629.

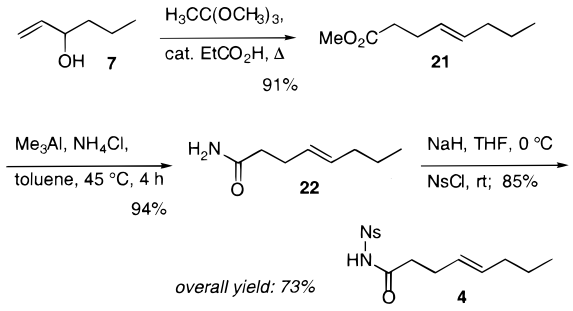
(59) The (*S*)-stereochemistry was assigned based on well-established literature precedence; see ref 53 and Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195. Comparison of the molar rotation angle of **(*S*)-5**, +23.5, to that of the independently assigned structurally closely related compound **11**, +25.9, in the latter paper provides further proof for our assignment of the (*S*)-configuration of the α-methylation product.

(60) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068.

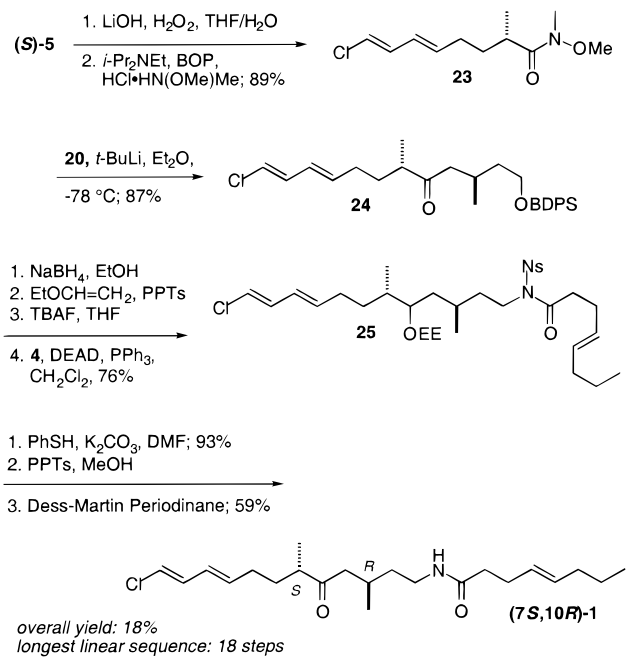
(61) Erker, G.; Aulbach, M.; Knickmeier, M.; Wingbermühle, D.; Krüger, C.; Nolte, M.; Werner, S. *J. Am. Chem. Soc.* **1993**, *1215*, 4590.

(62) The %ee was assigned by chiral HPLC with a Chiracel OD column.

Scheme 5



Scheme 6



desilylation and comparison of the $[\alpha]_D$ of diol **19** to a literature reference.[64] Alcohol **18** was readily converted to iodide **20** with triphenylphosphine and iodine in a mixture of acetonitrile/ether.

The carbon skeleton of the third pitiamide segment, **4**, was constructed in a straightforward manner by Claisen rearrangement of alcohol **7** (Scheme 5).[55] Conversion of the methyl ester into the primary amide **22** with trimethylaluminum and ammonium chloride according to the useful protocol of Weinreb et al.[65] followed by N-nosylation provided imide **4** in 73% overall yield from **7**. The amide nitrogen was activated with the nosyl[51] group to facilitate the planned Mitsunobu displacement.[50,52]

With all three synthetic segments in hand, we proceeded to the segment condensation stage. Conversion of the oxazolidinone **(*S*)-5** to the *N*,*O*-dimethylhydroxamate, followed by addition of the in situ prepared organolithium species derived from **4** provided ketone **24** in good yield (Scheme 6). Unfortunately, silyl ether cleavage of **24** led to an unstable intermediate that could not be alkylated under the standard Mitsunobu conditions with **4**. Neighboring group participation of the ketone functionality in **24** caused significant amounts of pyran side products. Circumventing this problem by a protective group strategy was straightforward but added a few steps to the total synthesis. After reduction of the ketone with $NaBH_4$, the secondary alcohol was protected as the ethoxyethyl ether. Desilylation now proceeded uneventfully, and Mitsunobu displacement of the primary hydroxyl group led to imide **25** in 76% yield from **23**. To the best of our knowledge, this is the first application of a nosyl-protected amide in a segment coupling.[52] The desired (7*S*,10*R*)-diastereomer of pitiamide A was readily obtained after deprotection of the nosyl group with thiophenol and potassium carbonate in dimethylformamide (DMF),[51] removal the ethoxy ethyl ether with pyridinium *p*-toluenesulfonate (PPTs) in MeOH, and oxidation with Dess−Martin periodinane.[66] Calculated for the longest linear sequence of 18 steps originating from **10**, the overall yield in this synthesis is a very satisfactory 18%. Analogous methodology was used for the preparation of the (7*R*,10*R*)-diastereomer of pitiamide A (Scheme 7). Highlights of both synthetic routes are the preparation of the chlorodiene segment by a hydrozirconation−transmetalation sequence and the use of a water-accelerated zirconocene-catalyzed methylalumination for the enantioselective preparation of the linchpin segment **20**.

Scheme 7

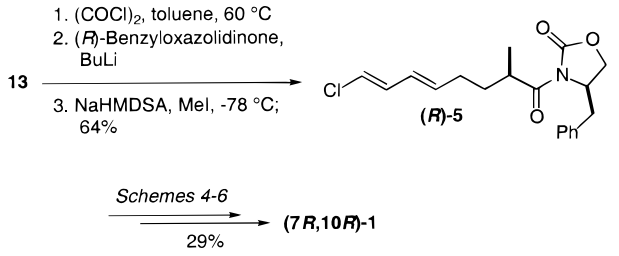


Table 2. Optical Rotation Values for **(7*S*,10*R*)-1** and **(7*R*,10*R*)-1** as a Function of Wavelength, Concentration, Temperature, and Solvent

conditions (nm, *c* [g/100 mL], solvent, *T* [°C])	[α] for **(7*S*,10*R*)-1**	[α] for **(7*R*,10*R*)-1**
589, 0.5−0.7, $CHCl_3$, 22	11.6	−30.3
578, 0.4−0.7, $CHCl_3$, 22	12.1	−31.7
546, 0.4−0.7, $CHCl_3$, 22	13.4	−36.2
436, 0.4−0.7, $CHCl_3$, 22	24.2	−69.3
365, 0.4−0.7, $CHCl_3$, 22	45.8	−131.2
589, 0.05−0.06, $CHCl_3$, 22	12.2	−26.3
589, 0.5, 95% EtOH, 22	13.4	−24.2
589, 0.5, $CHCl_3$, 5	10.2	−37.2

Optical Rotation, CD, IR, and NMR Temperature Shift Coefficient Analysis of (7*S*,10*R*)- and (7*R*,10*R*)-Pitiamide A

With multimilligram quantities of synthetic stereoisomers of pitiamide A in hand, we determined the wavelength-, concentration-, temperature-, and solvent-dependence of the optical rotation for each isomer. The results are summarized in Table 2. It is important to note that a minor amount (ca. 10%) of the (10*S*)-isomer was present as an impurity in either sample, because the enantiomeric excess of the methylalumination reaction was 80%.

As expected, the values of optical rotation measurements for both isomers increase steadily as the probing wavelength is

(63) The water effect in the asymmetric methylalumination of alkenes is a generally useful modification that not only provided considerable rate acceleration but in some cases also increased enantioselectivities: Wipf, P.; Ribe, S. To be submitted for publication.

(64) On the basis of the $[\alpha]_D$ of diol **19**, the %ee of the conversion of **6** to **18** proceeded in 80−82%, in good agreement with the HPLC study. Veith, H. J.; Collas, M.; Zimmer, R. *Liebigs Ann. Org. Bioorg. Chem.* **1997**, 391.

(65) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

(66) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

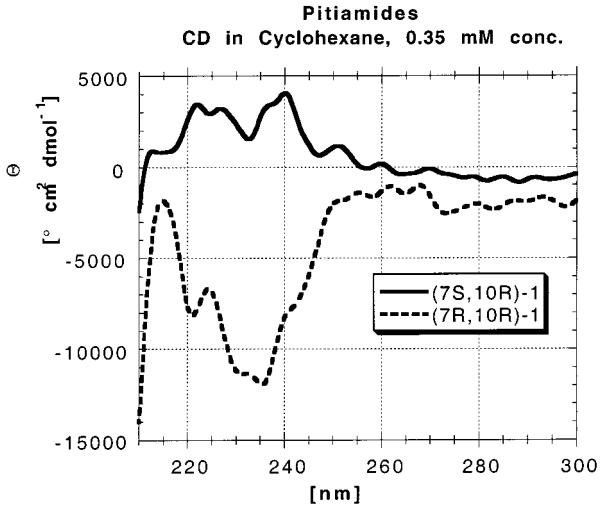


Figure 4. Circular dichroism spectra of pitiamide A isomers obtained from five averaged scans between 210 and 300 nm.

decreased. At 365 nm, **(7*S*,10*R*)-1** exhibits a specific rotation of +45.8, whereas **(7*R*,10*R*)-1** measures −131.2. More importantly, there is no significant concentration dependence of $[\alpha]_D$ for either of the two isomers: Reducing the concentration 10-fold from 0.6 to 0.06 g/100 mL led to a change of $[\alpha]_D$ from +11.6 to +12.2 for **(7*S*,10*R*)-1** and from −30.3 to −26.3 for **(7*R*,10*R*)-1**. Although these fluctuations are close to the experimental error of $[\alpha]_D$ determination, the solvent effect is more noticeable. It is well known that solvent generally alters the magnitude and in rare cases even the sign of optical rotations.[14,67] Switching from $CHCl_3$ to EtOH increased the $[\alpha]_D$ for **(7*S*,10*R*)-1** and **(7*R*,10*R*)-1** to +13.4 and −24.2, respectively.[68] Note that no dramatic changes in sign were observed for either pitiamide A diastereomer. Finally, both compounds demonstrated a moderate temperature sensitivity of the $[\alpha]_D$. Cooling the $CHCl_3$ solutions to 5 °C led to an $[\alpha]_D$ of +10.2 for **(7*S*,10*R*)-1** and −37.2 for **(7*R*,10*R*)-1**. These variations can be explained by changes in conformational equilibria.[69]

In summary, although there were noticeable shifts in specific rotation values as a consequence of solvent and temperature changes, concentration dependence did not appear to be an issue with pitiamide A, and none of the variations were significant enough to cause any concern about the relevance of our theoretical calculations.

In many cases, CD can be used for the assignment of the absolute configuration of organic compounds.[15] In the absence of strong, coupled chromophores or intrinsically chiral chromophores,[70] however, CD spectra tend to be less informative, and in flexible molecules such as pitiamide A a stereochemical assignment based on CD effects would be speculative at best. Nonetheless, we determined the CD spectra for both **(7*S*,10*R*)-1** and **(7*R*,10*R*)-1** in cyclohexane (Figure 4). Although a relative assignment of the configuration of the natural compound by CD might be possible with these two reference spectra in hand, the complexity of the CD bands illustrates the rather problematic nature of any predictive interpretation.[71]

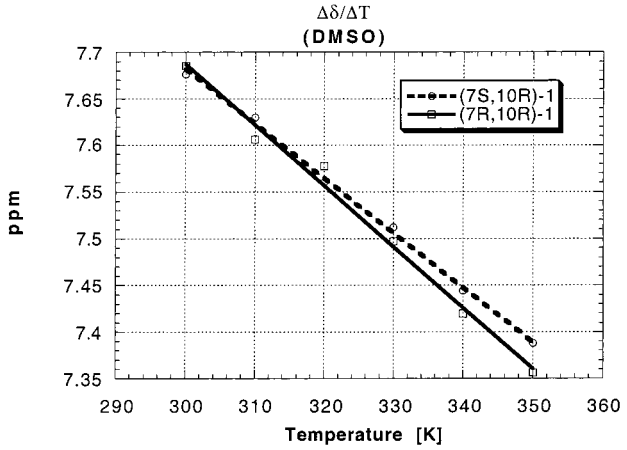


Figure 5. Graphical display of amide proton temperature shifts ($\Delta\delta/\Delta T$) for **(7*S*,10*R*)-1** and **(7*R*,10*R*)-1** in DMSO-d_6. The slope is $\Delta\delta/\Delta T$.

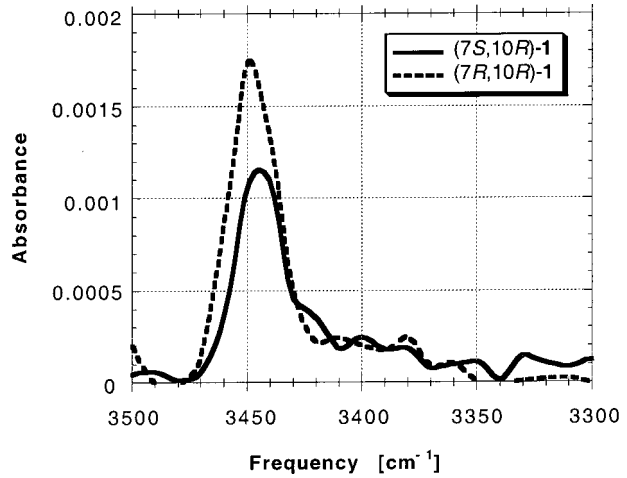


Figure 6. N−H stretch region FT-IR absorptions for **(7*S*,10*R*)-1** and **(7*R*,10*R*)-1** in CH_2Cl_2 at 0.001 M concentration at room temperature, after subtraction of the spectrum of pure CH_2Cl_2.

Because the possibility of intramolecular hydrogen bonding in pitiamide A was an issue that complicated our computational analysis to some degree, we were interested in examining the actual spectroscopic evidence for any intra- or intermolecular association in solution. Amide proton temperature coefficients ($\Delta\delta/\Delta T$) detected by ^{1}H NMR can provide strong evidence for intramolecular hydrogen bonding.[72] However, the large $\Delta\delta/\Delta T$ (−7.4 to −7.5 ppb/K in $CDCl_3$ and −5.8 to −6.5 ppb/K in dimethyl sulfoxide (DMSO)-d_6) measured for both **(7*S*,10*R*)-1** and **(7*R*,10*R*)-1** are in accord with a "random coil" or a relatively flexible backbone structure (Figure 5). This interpretation is also supported by the relatively complex CD spectra of these compounds. Analysis of the IR spectra leads to similar conclusions (Figure 6). In the N−H stretch region, bands at >3435 cm^{-1} are expected to arise exclusively from solvent-exposed amide.[73] As shown in Figure 6, both synthetic pitiamide A stereoisomers show bands at 3445 cm^{-1} in CH_2Cl_2 at 0.001 M

(67) Archelas, A.; Furstoss, R. *J. Org. Chem.* **1999**, *64*, 6112.
(68) However, adding small amounts (5%) of MeOH to the $CHCl_3$ solution did not significantly alter $[\alpha]_D$ values.
(69) Horsman, G.; Emeis, C. A. *Tetrahedron Lett.* **1965**, 3037.
(70) (a) Forster, L. S.; Moscowitz, A.; Berger, J. G.; Mislow, K. *J. Am. Chem. Soc.* **1962**, *84*, 4353. (b) Kirk, D. N. *Tetrahedron* **1986**, *42*, 777. (c) Person, R. V.; Monde, K.; Humpf, H.-U.; Berova, N.; Nakanishi, K. *Chirality* **1995**, *7*, 128. (d) Dong, J.-G.; Guo, J.; Akritopoulou-Zanze, I.; Kawamura, A.; Nakanishi, K.; Berova, N. *Chirality* **1999**, *11*, 707.
(71) Unfortunately, we were unable to record the CD spectrum of a natural sample of pitiamide A. Two samples that were generously provided to us by Professor Paul decomposed during shipment from Guam to Pittsburgh.
(72) Smith, J. A.; Pease, L. G. *CRC Crit. Rev. Biochem.* **1980**, *8*, 315.
(73) (a) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 1806. (b) Boussard, G.; Marraud, M. *Biopolymers* **1979**, *18*, 1297. (c) Maxfield, F. R.; Leach, S. J.; Stimson, E. R.; Powers, S. P.; Scheraga, H. A. *Biopolymers* **1980**, *18*, 2507.

Table 3. Specific Rotation Values for **(7*S*,10*R*)-1** and **(7*R*,10*R*)-1** Based on Ab Initio Computation of the Electric Dipole−Magnetic Dipole Polarizability Tensor and from Measurements of Synthetic Compounds

wavelength [nm]	results of computations [α]		results of total synthesis [α]	
	(7*S*,10*R*)-1	**(7*R*,10*R*)-1**	**(7*S*,10*R*)-1**	**(7*R*,10*R*)-1**
589 ($[\alpha]_D$)	+8	−39	+11.6	−30.3
578	+8	−41	+12.1	−31.7
546	+9	−46	+13.4	−36.2
436	+15	−71	+24.2	−69.3
365	+21	−102	+45.8	−131.2

concentration,[74] and bands at 3320−3410 cm^{-1} that would arise from intramolecular hydrogen bonding are absent.

Comparison of Optical Rotation Data from Computational Analysis to Experimental Values

Total synthesis provided us with (7*S*,10*R*)- and (7*R*,10*R*)-stereoisomers of pitiamide A, and therefore the results of the computational optical rotation analysis could be directly compared to experimental values for both compounds. As Table 3 shows, the calculation provided a priori extremely accurate predictions of optical rotation values. It is important to note that the synthetic material is not 100% diastereomerically pure; minor amounts (<10%) of the (10*S*)-stereoisomer slightly alter the optical rotation in addition to the normal experimental variation.[75] Within the limits of the static-field approximation, the computations provide a quantitatively valid determination of the ORD spectra as close to the UV as 436 nm. This is a consequence of the absence of a strongly absorbing chromophore with maxima >300 nm in compound **1**. It is clear from the results listed in Table 3 that an ab initio computational assignment of the relative and absolute stereochemistry of pitiamide A stereoisomers is not only qualitatively feasible but also quantitatively accurate.

Assignment of the Stereochemistry of Natural Pitiamide A

On the basis of the experimentally reported specific rotation of pitiamide A, $[\alpha]_D$ −10.3 (*c* 3.0, $CHCl_3$),[1] and the chiroptical data obtained both from our computational and synthetic studies, the configuration of the natural product should be assigned as (7*R*,10*S*). However, much to our surprise, a careful comparison of NMR data between the natural and the (7*S*,10*R*)-isomer revealed subtle differences in the ^{1}H NMR shifts that compel a different assignment (Table 4 and Figure 7). Because NMR data are much less susceptible to impurities, comparison of ^{1}H NMR spectra clearly indicates a (7*R**,10*R**) *relative* stereochemistry for the natural product. If one further assumes that the *sign* of the optical rotation of the natural product is correct as measured,[1,2] the absolute configuration of natural pitiamide A is therefore assigned as (7*R*,10*R*). All other physical data, including all ^{13}C NMR resonances, between the two synthetic compounds and the natural product were identical. We can only conclude that (either because of an instrument calibration error or a minor impurity in the natural sample) the specific rotation of the natural product was changed by 20−30 units.[76,77] Another interpretation, albeit speculative at present, is that natural pitiamide A was originally isolated as a mixture of diastereomers or enantiomers. The latter hypothesis is supported by the observation of a set of minor ^{1}H NMR signals between 2.40 and 2.45 and at 2.30 ppm for the natural sample that are characteristic for the (7*S*,10*R*)-isomer. Although relatively rare, natural products have previously been shown to consist of racemic or diastereomeric mixtures.[78]

Conclusions

We used ab initio coupled Hartree−Fock calculations in combination with force-field Monte Carlo conformational analysis and Boltzmann averaging to predict off-resonance optical rotations for all four diastero- and enantiomeric configurations of the marine natural product pitiamide A. On the basis of computations of the electric-dipole−magnetic-dipole polarizability tensor within the CADPAC program and use of the diagonal tensor elements to calculate the optical rotatory parameter β, we predicted specific rotations of approximately +39, −39, +8, and −8 for the (7*S*,10*S*)-, (7*R*,10*R*)-, (7*S*,10*R*)-, and (7*R*,10*S*)-stereoisomers of pitiamide, respectively. This a priori analysis proved to be quantitatively accurate by comparison with experimental values of **(7*S*,10*R*)-1** and **(7*R*,10*R*)-1** subsequently obtained by total synthesis. Highlights of the natural product total syntheses were the preparation of the chlorodiene segment of pitiamide A by a hydrozirconation−transmetalation sequence and the use of a novel water-accelerated zirconocene-catalyzed methylalumination for the enantioselective preparation of the linchpin segment **20** as well as a segment coupling by *N*-alkylation of a nosylated amide.

The dependence of the optical rotation values on solvent, wavelength, temperature, and concentration was extensively explored, and again calculation was found to be an accurate tool for prediction of the ORD spectrum down to relatively short (436 nm) wavelengths. One of the major approximations of the computational work, the neglect of a possible intramolecular hydrogen bonding interaction between the ketone carbonyl and the amide NH in pitiamide A, was validated by solution NMR and IR studies of the synthetic material. The CD curves for **(7*S*,10*R*)-1** and **(7*R*,10*R*)-1** were measured and confirmed that this powerful chiroptical technique is nonetheless unsuitable for a stereochemical assignment of the highly flexible lipid pitiamide A. Finally, ^{1}H NMR studies in combination with the sign of the specific rotation value reported for pitiamide A led to a definitive assignment of the configuration of the natural product as **(7*R*,10*R*)-1**. Our work highlights the considerable structural significance of $[\alpha]_D$ data and the accuracy of current ab initio-based computational chiroptical analysis, but also the potential pitfalls with obtaining meaningful optical activity measurements for natural product isolates.

Experimental Section

(2*R*)-4-(*tert*-Butyl-diphenylsilanyloxy)-2-methyl-butan-1-ol (18). To a solution of 0.314 g (4.36 mmol) of trimethylaluminum in 2 mL of CH_2Cl_2 was added a solution of 0.0368 g (0.0551 mmol) of **17** in 4 mL of CH_2Cl_2. The resulting yellow reaction mixture was chilled to

(74) Variable concentration NMR studies in $CHCl_3$ were used to establish that no intermolecular aggregation occurred at 0.001 M in $CHCl_3$.

(75) Optical rotation values recorded in Table 3 represent the average of three independent measurements. The experimental variations in these three determinations were less than 10% of the average values.

(76) Although the vast majority of total syntheses provides optical rotations in good agreement with data reported for the isolated natural product, it is not uncommon that differences arise. See, for example: (a) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147. (b) Hanessian, S.; Cantin, L.-D.; Andreotti, D. *J. Org. Chem.* **1999**, *64*, 4893. (c) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647. (d) Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556.

(77) The effect of impurities on optical rotation is particularly problematic for small rotation values: Baldwin, J. E.; Hackler, R. E.; Scott, R. M. *Chem. Commun.* **1969**, 1415.

(78) For recent examples, see: (a) Beuerle, T.; Engelhard, S.; Bicchi, C.; Schwab, W. *J. Nat. Prod.* **1999**, *62*, 35. (b) Van Wagoner, R. M.; Jompa, J.; Tahir, A.; Ireland, C. M. *J. Nat. Prod.* **1999**, *62*, 794.

Table 4. ^{1}H NMR Shifts and Assignments for Natural Pitiamide A[1] and Synthetic **(7*R*,10*R*)-1** and **(7*S*,10*R*)-1**

position	natural pitiamide A	**(7*R*,10*R*)-1**	**(7*S*,10*R*)-1**
1	6.10 (d, 13.0 Hz)	6.11 (d, 13.2 Hz)	6.11 (d, 13.2 Hz)
2	6.40 (dd, 13.3, 10.8 Hz)	6.41 (dd, 13.1, 10.9 Hz)	6.41 (dd, 13.1, 10.9 Hz)
3	5.97 (dd, 15.0, 10.5 Hz)	5.98 (dd, 15.1, 10.9 Hz)	5.98 (dd, 15.1, 10.8 Hz)
4	5.64 (dt, 15.0, 7.0)	5.65 (dt, 15.2, 7.0 Hz)	5.65 (dt, 15.2, 7.0 Hz)
5	2.08−2.00 (m)	2.09−2.02 (m)	2.11−2.03 (m)
6a	1.89−1.72 (m)	1.81−1.74 (m)	1.81−1.75 (m)
6b	1.45−1.31 (m)	1.47−1.32 (m)	1.46−1.33 (m)
7	2.50−2.46 (m)	2.52−2.46 (m)	2.52−2.44 (m)
8			
9	2.37 (dd, 6.8, 4.3 Hz)	2.39 (dd, 6.5, 4.3 Hz)	2.52−2.29 (m)
10	2.10−2.00 (m)	2.09−2.02 (m)	2.11−2.03 (m)
11	1.45−1.31 (m)	1.47−1.32 (m)	1.46−1.33 (m)
12a	3.29 (dt, 20.0, 6.5 Hz)	3.30 (dt, 20.1, 6.6 Hz)	3.30 (dt, 20.1, 6.6 Hz)
12b	3.18 (dt, 19.3, 6.5 Hz)	3.20 (dt, 19.3, 6.5 Hz)	3.19 (dt, 19.2, 6.5 Hz)
13	5.72 (bm)	5.73 (bm)	5.72 (bm)
14			
15	2.23 (t, 7.3 Hz)	2.24 (t, 7.2 Hz)	2.24 (t, 7.2 Hz)
16	2.32 (q, 6.5 Hz)	2.33 (q, 6.5 Hz)	2.40−2.29 (m)
17	5.40 (dt, 15.0, 6.3 Hz)	5.41 (dt, 15.3, 6.3 Hz)	5.41 (dt, 15.3, 6.3 Hz)
18	5.48 (dt, 15.5, 6.5 Hz)	5.49 (dt, 15.3, 6.5 Hz)	5.49 (dt, 15.3, 6.4 Hz)
19	1.95 (q, 7.0 Hz)	1.96 (q, 7.0 Hz)	1.96 (q, 6.9 Hz)
20	1.45−1.31 (m)	1.47−1.32 (m)	1.46−1.33 (m)
21	0.87 (t, 7.3 Hz)	0.88 (t, 7.4 Hz)	0.88 (t, 7.4 Hz)
22	0.91 (d, 6.5 Hz)	0.92 (d, 6.7 Hz)	0.93 (d, 6.7 Hz)
23	1.06 (d, 7.0 Hz)	1.07 (d, 7.0 Hz)	1.07 (d, 7.0 Hz)

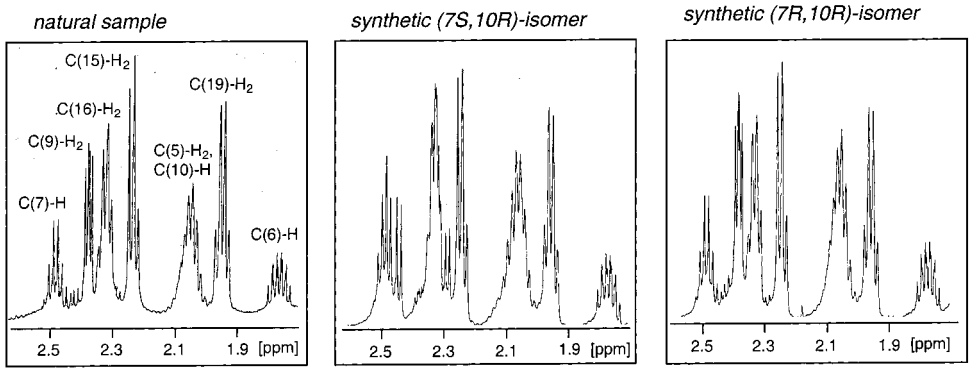


Figure 7. ^{1}H NMR shifts for natural pitiamide A[1] and synthetic **(7*S*,10*R*)-1** and **(7*R*,10*R*)-1**.

−50 °C and then 18 μL (1 mmol) of water was added. The solution was warmed slowly to room temperature to effect complete consumption of water which was accompanied by a color change from a light yellow to a dark orange/red color. *Note*: The addition of H_2O to trimethylaluminum is exothermic and cooling the mixture below −20 °C allows for a controlled reaction. After warming to room temperature, the red/orange solution was cooled to −20 °C and then treated with 0.3350 g (1.081 mmol) of alkene **6**. A change in color back to light yellow was observed upon addition of alkene. The reaction mixture was allowed to stir for 12 h before air was vigorously bubbled through the solution until all volatiles were evaporated. The resulting slurry was washed with 2 N NaOH and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed on SiO_2 (EtOAc/hexane, 1:4) to yield 0.3266 g (0.9550 mmol, 85%) of **(*R*)-18** in 80% ee as a colorless oil. The enantiomeric excess was determined by chiral HPLC on a Chiralcel OD column (1% *i*-PrOH/hexanes): $[\alpha]_D$ +5.6 (*c* 1.0, $CHCl_3$); IR (neat) 3354, 3071, 3050, 2954, 2930, 2858, 1472, 1428, 1390, 1361, 1112, 1041, 997, 823 cm^{-1}; ^{1}H NMR δ 7.71−7.68 (m, 4 H), 7.48−7.38 (m, 6 H), 3.81−3.68 (m, 2 H), 3.57−3.46 (m, 2 H), 2.48 (bs, 1 H), 1.90−1.84 (m, 1 H), 1.68−1.59 (m, 1 H), 1.56−1.47 (m, 1 H), 1.07 (s, 9 H), 0.91 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 135.8, 133.6, 129.9, 127.9, 68.5, 62.7, 37.0, 34.1, 27.0, 19.3, 17.4; MS (EI) *m*/*z* (rel intensity) 285 ([M-*t*-Bu]$^+$, 76), 267 (22), 229 (37), 199 (100), 181 (9), 139 (12), 69 (20); HRMS (EI) Calcd for $C_{17}H_{21}O_2Si$ (M−C_4H_9) 285.1311, found 285.1317.

***N*-Oct-4-enoyl-(2-nitrobenzene)sulfonamide (4).** A suspension of 0.524 g (13.1 mmol) of NaH (60% dispersed in mineral oil) in 30 mL of THF was treated portionwise at 0 °C with 0.731 g (5.18 mmol) of amide **22**. After the evolution of H_2 had subsided, the mixture was warmed to room temperature and then 1.169 g (7.62 mmol) of 2-nitrobenzenesulfonyl chloride was added. The reaction mixture was kept at room temperature overnight before it was carefully quenched first with H_2O and then 1 N HCl. The solution was extracted with EtOAc, and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and chromatographed on SiO_2 (EtOAc/hexanes, 1:3) to afford 1.435 g (4.403 mmol, 85%) of **4** as a light yellow solid: mp 73−75 °C; IR (neat) 3276, 2959, 2928, 2855, 1732, 1699, 1545, 1446, 1362, 1181 cm^{-1}; ^{1}H NMR δ 8.72 (bs, 1 H), 8.45−8.41 (m, 1 H), 7.87−7.78 (m, 3 H), 5.48 (dt, 1 H, J = 15.3, 6.5 Hz), 5.34 (dt, 1 H, J = 15.4, 6.3 Hz), 2.44 (t, 2 H, J = 6.9 Hz), 2.31 (q, 2 H, J = 6.8 Hz), 1.91 (q, 2 H, J = 7.0 Hz), 1.31 (s, 2 H, J = 7.4 Hz), 0.84 (t, 3 H, J = 7.4 Hz); ^{13}C NMR δ 170.7, 148.3, 135.1, 134.1, 133.2, 132.8, 131.9, 127.2, 125.0, 36.7, 34.7, 27.3, 22.6, 13.8; MS (EI) *m*/*z* (rel intensity) 326 (M$^+$, 17), 297 (26), 244 (38), 227 (47), 186 (58), 140 (31), 123 (31), 96 (48), 81 (53), 67 (54), 55 (100); HRMS (EI) Calcd for $C_{14}H_{18}N_2O_5S$ 326.0936, found 326.0922.

(3*R*,6*S*)-1-(*tert*-Butyldiphenylsilanyloxy)-12-chloro-3,6-dimethyldodeca-9,11-dien-5-one (24). To a degassed solution of 0.104 g (0.230 mmol) of alkyl iodide **20** and 3 mL of Et_2O was added 0.35 mL (0.51 mmol) of a 1.45 M solution of *t*-BuLi at −78 °C in hexanes. The reaction mixture was kept at −78 °C for 15 min before warming to room temperature. The solution was then immediately cooled to −78

°C and a solution of 0.0327 g of **23** (0.141 mmol) in 1 mL of Et_2O was added. The reaction mixture was kept at −78 °C for 1 h before quenching by addition of a saturated solution of NH_4Cl. After extraction with Et_2O, the organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed on SiO_2 (EtOAc/hexanes, 1:4) to yield 0.0621 g (0.123 mmol, 87%) of **24** as a colorless oil: $[\alpha]_D$ +13.9 (*c* 1.6, $CHCl_3$); IR (neat) 3070, 2929, 2857, 1711, 1461, 1428, 1362, 1112, 978, 703 cm^{-1}; ^1H NMR δ 7.68−7.66 (m, 4 H), 7.46−7.36 (m, 6 H), 6.40 (dd, 1 H, J = 13.0, 10.8 Hz), 6.08 (d, 1 H, J = 13.2 Hz), 5.96 (dd, 1 H, J = 15.2, 10.7 Hz), 5.64 (dt, 1 H, J = 15.1, 7.0 Hz), 3.69 (t, 2 H, J = 6.6 Hz), 2.49−2.40 (m, 2 H), 2.28−2.19 (m, 2 H), 2.05 (q, 2 H, J = 7.4 Hz), 1.79−1.72 (m, 1 H), 1.59−1.23 (m, 3 H), 1.06−1.04 (m, 12 H), 0.86 (d, 3 H, J = 6.1 Hz); ^{13}C NMR δ 214.0, 135.8, 135.1, 134.2, 133.8, 129.8, 127.9, 127.0, 119.1, 62.2, 49.0, 46.0, 39.6, 32.2, 30.5, 27.1, 26.2, 20.3, 19.4, 16.5; MS (EI) *m*/*z* (rel intensity) 439 ([M-*t*-Bu]$^+$, 46), 219 (6), 199 (100), 169 (12), 139 (14), 126 (17), 113 (18), 101 (20), 79 (29), 57 (35); HRMS (EI) Calcd for $C_{26}H_{32}O_2SiCl$ (M−C_4H_9) 439.1860, found 439.1853.

(3*R*,6*R*)-1-(*tert*-Butyldiphenylsilanyloxy)-12-chloro-3,6-dimethyldodeca-9,11-dien-5-one ((*R*,*R*)-24). Analogous to the preparation of **24**, 0.156 g (0.345 mmol) of alkyl iodide **20**, 0.64 mL (0.77 mmol) of a 1.2 M solution of *t*-BuLi in hexanes, 5 mL of Et_2O, and 0.048 g (0.21 mmol) of **(*R*)-23** afforded 0.083 g (0.17 mmol, 81%) of **(*R*,*R*)-24** as a colorless oil: $[\alpha]_D$ −10.8 (*c* 0.48, $CHCl_3$); IR (neat) 3070, 2930, 2857, 1711, 1472, 1461, 1428, 1377, 1112, 979, 703 cm^{-1}; ^1H NMR δ 7.68−7.66 (m, 4 H), 7.46−7.36 (m, 6 H), 6.40 (dd, 1 H, J = 13.1, 10.7 Hz), 6.08 (d, 1 H, J = 13.2 Hz), 5.96 (dd, 1 H, J = 15.2, 10.7 Hz), 5.64 (dt, 1 H, J = 15.2, 6.9 Hz), 3.69 (t, 2 H, J = 6.6 Hz), 2.51−2.19 (m, 4 H), 2.03 (q, 2 H, J = 7.3 Hz), 1.80−1.72 (m, 1 H), 1.61−1.54 (m, 1 H), 1.49−1.32 (m, 2 H), 1.06−1.04 (m, 12 H), 0.85 (d, 3 H, J = 6.3 Hz); ^{13}C NMR δ 214.0, 135.8, 135.2, 134.1, 133.8, 129.8, 127.9, 126.9, 119.1, 62.2, 49.0, 46.0, 39.6, 32.0, 30.5, 27.1, 26.2, 20.2, 19.4, 16.6; MS (EI) *m*/*z* (rel intensity) 439 ([M-*t*-Bu]$^+$, 68), 355 (6), 263 (21), 247 (6), 225 (12), 199 (100), 181 (16), 135 (15), 101 (17), 79 (21); HRMS (EI) Calcd for $C_{26}H_{32}O_2SiCl$ (M−C_4H_9) 439.1860, found 439.1874.

(3*R*,6*S*)-1-(*tert*-Butyldiphenylsilanyloxy)-12-chloro-3,6-dimethyldodeca-9,11-dien-5-ol ((*R*,*S*)-28). To an ice-cold solution of 0.0645 g (0.129 mmol) of **24** in 1 mL of EtOH was added 0.0162 g (0.428 mmol) of $NaBH_4$. The solution was warmed to room temperature and after 3 h the mixture was carefully quenched by dropwise addition of 1 N HCl. The mixture was extracted with Et_2O, washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on SiO_2 (EtOAc/hexanes, 1:2) to yield 0.055 g (0.11 mmol, 86%) of **(*R*,*S*)-28** as a colorless oil: IR (neat) 3436, 3070, 2930, 1583, 1472, 1462, 1428, 1112, 977, 823, 702 cm^{-1}; ^1H NMR δ 7.69−7.67 (m, 4 H), 7.46−7.34 (m, 6 H), 6.46−6.38 (m, 1 H), 6.08 (d, 1 H, J = 13.2 Hz), 6.03−5.94 (m, 1 H), 5.75−5.64 (m, 1 H), 3.76−3.64 (m, 2 H), 3.60−3.50 (m, 1 H), 2.23−1.96 (m, 2 H), 1.82−1.11 (m, 9 H), 1.06 (s, 9 H), 0.91−0.86 (m, 6 H); ^{13}C NMR δ 136.2, 135.8, 134.2, 134.0, 129.8, 127.8, 126.4, 118.6, 73.7, 72.8, 62.5, 62.2, 41.9, 41.4, 40.5, 38.9, 38.7, 38.6, 32.7, 31.2, 30.6, 27.1, 26.8, 26.7, 21.2, 19.7, 19.4, 15.4, 13.9; MS (EI) *m*/*z* (rel intensity) 498 (M$^+$, 14), 441 (18), 423 (21), 309 (56), 297 (63), 269 (65), 253 (22), 199 (100), 183 (21), 78 (51); HRMS (EI) Calcd for $C_{30}H_{43}O_2SiCl$ 498.2721, found 498.2721.

(3*R*,6*R*)-1-(*tert*-Butyldiphenylsilanyloxy)-12-chloro-3,6-dimethyldodeca-9,11-dien-5-ol ((*R*,*R*)-28). Using an analogous procedure as for the preparation of **(*R*,*S*)-28**, 0.0530 g (0.107 mmol) of **(*R*,*R*)-24** and 0.014 g (0.37 mmol) of $NaBH_4$ in 1 mL of Et_2O afforded 0.0467 g (0.0937 mmol, 88%) of **(*R*,*R*)-28** as a colorless oil: IR (neat) 3433, 3070, 2930, 1583, 1472, 1462, 1428, 1111, 977, 822, 702 cm^{-1}; ^1H NMR δ 7.70−7.67 (m, 4 H), 7.46−7.36 (m, 6 H), 6.42 (dd, 1 H, J = 13.0, 10.8 Hz), 6.09 (d, 1 H, J = 13.1 Hz), 6.00 (dd, 1 H, J = 15.1, 10.8 Hz), 5.71 (dt, 1 H, J = 14.7, 7.3 Hz), 3.79−3.51 (m, 3 H), 2.19−1.16 (m, 11 H), 1.06 (s, 9 H), 0.90−0.85 (m, 6 H); ^{13}C NMR δ 136.2, 135.8, 134.2, 134.0, 129.8, 127.8, 126.4, 118.7, 73.6, 72.7, 62.4, 62.3, 42.2, 41.0, 40.7, 39.3, 39.0, 37.8, 32.8, 31.6, 30.6, 27.1, 26.8, 26.6, 20.9, 19.6, 19.4, 15.3, 13.5; MS (EI) *m*/*z* (rel intensity) 498 (M$^+$, 31), 441 (22), 423 (17), 309 (45), 297 (16), 269 (22), 242 (30), 225 (55), 199 (100), 189 (73), 149 (30), 101 (61); HRMS (EI) Calcd for $C_{30}H_{43}O_2SiCl$ 498.2721, found 498.2728.

(3*R*,6*S*)-*N*-{[12-Chloro-5-(1-ethoxy)-ethoxy]-3,6-dimethyl-dodeca-9,11-dienyl}-2-nitro-(*N*-oct-4-enoyl)benzenesulfonamide ((*R*,*S*)-29). A solution of alcohol **(*R*,*S*)-28** (0.055g, 0.11 mmol) in 2 mL of freshly distilled ethyl vinyl ether was cooled to 0 °C and a few crystals of pyridinium *p*-toluenesulfonate were added. After 1 h, the mixture was diluted with Et_2O and washed with 1 N NaOH. The organic layer was extracted with brine, dried ($MgSO_4$), filtered, and concentrated. A solution of the crude product in 2 mL of THF was treated with 20 μL (0.2 mmol) of a 1 M solution of TBAF in THF. After 4 h the reaction mixture was washed with a saturated NH_4Cl solution and extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. To a solution of the crude alcohol, 0.0358 g (0.136 mmol) of PPh_3, and 0.0557 g (0.171 mmol) of the nosyl-protected amide **4** in 1.5 mL of THF was added 20 μL (0.13 mmol) of diethyl azodicarboxylate at room temperature. After 3 h, the reaction mixture was concentrated under a fast stream of N_2 and chromatographed on SiO_2 (EtOAc/hexanes, 1:4) to yield 0.063 g (0.098 mmol, 89% from **(*R*,*S*)-28** of the nosyl-protected amide **(*R*,*S*)-29** as light yellow oil that was used without further purification.

(3*R*,6*R*)-*N*-{[12-Chloro-5-(1-ethoxy)-ethoxy]-3,6-dimethyl-dodeca-9,11-dienyl}-2-nitro-(*N*-oct-4-enoyl)benzenesulfonamide ((*R*,*R*)-29). Using an analogous procedure as for the preparation of **(*R*,*S*)-29**, 0.0530 g (0.107 mmol) of **(*R*,*R*)-28** in 2 mL of freshly distilled ethyl vinyl ether and a few crystals of pyridinium *p*-toluenesulfonate afforded the ethoxy ethyl ether. The crude product was dissolved in 2 mL of THF and treated with 20 μL (0.20 mmol) of a 1 M solution of TBAF. A solution of the crude desilylated alcohol in 1.5 mL of THF was treated with 0.0363 g (0.138 mmol) of triphenyl phosphine, 0.0543 g (0.166 mmol) of **4**, and 20 μL (0.13 mmol) of diethyl azodicarboxylate to afford after chromatography on SiO_2 (EtOAc/hexanes, 1:4) 0.0534 g (0.0833 mmol, 89%) of **(*R*,*R*)-29** as a light yellow oil.

(7*S*,10*R*)-Pitiamide A ((7*S*,10*R*)-1). To a solution of 0.024 g (0.037 mmol) of **(*S*,*R*)-29** and 0.014 g (0.099 mmol) of K_2CO_3 in 2 mL of DMF was added 12 μL (0.12 mmol) of thiophenol. After 2.5 h, the reaction mixture was diluted with Et_2O and passed through a pad of basic alumina. The filtrate was washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and chromatographed on SiO_2 (EtOAc/hexanes, 1:3) to yield 0.0160 g of the deprotected amide as a colorless oil. This intermediate was immediately dissolved in 1 mL of MeOH and a few crystals of pyridinium *p*-toluenesulfonate were added. After 2 h, the reaction mixture was quenched with a solution of concentrated $NaHCO_3$ and extracted with Et_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated to yield a colorless oil that was dissolved in 2 mL of CH_2Cl_2 and treated with 0.0220 g (0.0512 mmol) of Dess−Martin periodinane. The reaction mixture was stirred for 3 h and then quenched with saturated $NaHCO_3$ solution. The mixture was extracted with Et_2O, dried ($MgSO_4$), and chromatographed on SiO_2 (EtOAc/hexanes, 2:3) to afford 0.0083 g (0.022 mmol, 59%) of **(7*S*,10*R*)-1** as a colorless oil: $[\alpha]_D$ +11.6 (*c* 0.49, $CHCl_3$); IR (neat) 3303, 2959, 2927, 2867, 1708, 1644, 1549, 1457, 1376, 1261, 977, 817 cm^{-1}; ^1H NMR (500 MHz) δ 6.41 (dd, 1 H, J = 13.1, 10.9 Hz), 6.11 (d, 1 H, J = 13.2 Hz), 5.98 (dd, 1 H, J = 15.1, 10.8 Hz), 5.87−5.67 (m, 1 H), 5.65 (dt, 1 H, J = 15.2, 7.0 Hz), 5.49 (dt, 1 H, J = 15.3, 6.4 Hz), 5.41 (dt, 1 H, J = 15.3, 6.3 Hz), 3.30 (dt, 1 H, J = 20.1, 6.6 Hz), 3.19 (dt, 1 H, J = 19.2, 6.5 Hz), 2.52−2.44 (m, 2 H), 2.37−2.29 (m, 3 H), 2.24 (t, 2 H, J = 7.2 Hz), 2.11−2.03 (m, 3 H), 1.96 (q, 2 H, J = 6.9 Hz), 1.81−1.75 (m, 1 H), 1.46−1.33 (m, 5 H), 1.07 (d, 3 H, J = 7.0 Hz), 0.93 (d, 3 H, J = 6.7 Hz), 0.88 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (125 MHz) δ 214.3, 172.7, 134.9, 133.6, 131.7, 128.6, 126.9, 119.1, 48.6, 45.9, 37.3, 36.8, 36.4, 34.7, 32.0, 30.4, 28.7, 25.9, 22.6, 20.2, 16.5, 13.7; MS (EI) *m*/*z* (rel intensity) 381 (M$^+$, 38), 346 (8), 267 (46), 210 (44), 185 (31), 168 (15), 155 (23), 126 (22), 114 (72), 87 (29), 79 (32), 67 (29), 55 (100); HRMS (EI) Calcd for $C_{22}H_{36}NO_2Cl$ 381.2435, found 381.2448.

(7*R*,10*R*)-Pitiamide A ((7*R*,10*R*)-1). Using an analogous sequence as for the preparation of **(7*S*,10*R*)-1**, a solution of 0.0400 g (0.062 mmol) of **(*R*,*R*)-29** in 3 mL of DMF, 0.0180 g (0.130 mmol) of K_2CO_3, and 20 μL (0.2 mmol) of thiophenol afforded 0.0260 g (0.0571 mmol) of the deprotected amide as a colorless oil. To this oil was added 1 mL of MeOH followed by the addition of a few crystals of PPTs to afford the deprotected alcohol as a colorless oil that was dissolved in

2 mL of CH_2Cl_2 and treated with 0.0430 g (0.100 mmol) of Dess−Martin periodinane. Chromatography on SiO_2 (EtOAc/hexanes, 2:3) afforded 0.0150 g (0.039 mmol, 63%) of **(7*R*,10*R*)-1** as a colorless oil: $[\alpha]_D$ −30.3 (*c* 0.71, $CHCl_3$); IR (neat) 3299, 2959, 2928, 2873, 1709, 1644, 1549, 1457, 1376, 1262, 977, 818 cm^{-1}; ^1H NMR (500 MHz) δ 6.41 (dd, 1 H, J = 13.1, 10.9 Hz), 6.11 (d, 1 H, J = 13.2 Hz), 5.98 (dd, 1 H, J = 15.1, 10.9 Hz), 5.75−5.78 (m, 1 H), 5.65 (dt, 1 H, J = 15.2, 7.0 Hz), 5.49 (dt, 1 H, J = 15.3, 6.5 Hz), 5.41 (dt, 1 H, J = 15.3, 6.3 Hz), 3.30 (dt, 1 H, J = 20.1, 6.6 Hz), 3.20 (dt, 1 H, J = 19.3, 6.5 Hz), 2.52−2.46 (m, 1 H), 2.39 (dd, 2 H, J = 6.5, 4.3 Hz), 2.33 (q, 2 H, J = 6.5 Hz), 2.24 (t, 2 H, J = 7.2 Hz), 2.09−2.02 (m, 3 H), 1.96 (q, 2 H, J = 7.0 Hz), 1.81−1.74 (m, 1 H), 1.47−1.32 (m, 5 H), 1.07 (d, 3 H, J = 7.0 Hz), 0.92 (d, 3 H, J = 6.7 Hz), 0.88 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (125 MHz) δ 214.3, 172.8, 135.0, 133.7, 131.9, 128.7, 127.0, 119.2, 48.6, 46.1, 37.5, 37.0, 36.6, 34.8, 32.1, 30.5, 28.9, 26.1, 22.8, 20.3, 16.6, 13.9; MS (EI) *m*/*z* (rel intensity) 381 (M^+, 24), 280 (20), 267 (73), 210 (51), 196 (43), 185 (19), 168 (18), 155 (21), 143 (18), 126 (27), 114 (100), 101 (17), 79 (30), 65 (29); HRMS (EI) Calcd for $C_{22}H_{36}NO_2Cl$ 381.2435, found 381.2439.

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Supporting Information Available: Complete experimental data for **11**, **12**, **13**, **(*S*)-5**, **(*R*)-5**, **19**, **20**, **21**, **22**, and **23**; ^1H and ^{13}C NMR spectra for all synthetic intermediates and pitiamide A stereoisomers. ^1H and ^{13}C NMR spectra for natural pitiamide A (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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