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Total Synthesis and Immunosuppressive Activity of (−)-Pateamine A and Related Compounds: Implementation of a β-Lactam-Based Macrocyclization

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Abstract: The asymmetric synthesis of the potent immunosuppressive agent (−)-pateamine A isolated from the marine sponge *Mycale* sp. is described. A key strategy employed in the synthesis was a β-lactam-based macrocyclization to form the 19-membered dilactone macrolide. The synthesis confirms the relative and absolute stereochemistry as 3*R*,5*S*,10*S*,24*S* and sets the stage for studies into the mechanism of action of pateamine A. Other studies and findings made in the course of the synthesis and described herein include the following: (1) a Stille coupling can be competitive with π-allyl formation, (2) SmI_2 effects a mild N−O cleavage of *N*-benzyloxy-β-lactams, (3) the synthesis of a pateamine A-dexamethasone hybrid molecule for use in a yeast three-hybrid assay was accomplished, and (4) IC_{50} values were determined for synthetic and natural pateamine A and related compounds in the interleukin 2 reporter gene assay.

Introduction

Natural products have proven to be useful probes of various biological processes.[1] In particular, agents that exhibit specific cellular effects have served as powerful biochemical tools for dissecting molecular mechanisms of signal transduction pathways involved in various cellular functions. Immunosuppressive agents are examples of such natural products which have made it possible to discover a number of key signaling molecules involved in the orchestration of the immune response.[2] Prominent among them are FK506, cyclosporin A (CsA), and rapamycin, which have proven extremely useful in shedding new light on intracellular signaling pathways involved in T cell activation (Figure 1).[1,3] These immunosuppressants have an unusual mode of action; their immunosuppressive activities are mediated by immunophilins. CsA binds cyclophilins, while FK506 and rapamycin bind to FKBPs. The cyclophilin−CsA and FKBP−FK506 complexes bind to and inhibit the phosphatase activity of calcineurin, an essential enzyme involved in intracellular signal transduction emanating from the T cell receptor and leading to the production of cytokines including interleukin 2. The FKBP−rapamycin complex inhibits a kinase called FRAP (also known as RAFT) that is involved in interleukin-2 receptor-mediated T cell proliferation with no effect on T cell receptor-mediated signaling.

A novel immunosuppressant which likewise promises to be quite useful as a biochemical probe is the marine natural product pateamine A (**1**, Figure 2).[4] Pateamine A displays potent immunosuppressive properties (MLR (mixed lymphocyte reaction) IC_{50}=2.6 nM) with low cytotoxicity (LCV (lymphocyte viability assay)/MLR ratio >1000).[5] However, which signaling pathway(s) is affected by pateamine A remains unknown. Furthermore, the amount of pateamine A available from the natural source is limited, making it difficult to carry out structural modifications of the compound to prepare biochemical probes. Herein we detail the first total synthesis of (−)-pateamine A that has confirmed its relative and absolute stereochemistry.[6] A streamlined approach which obviates the need for the protecting group exchange required in our original synthesis is also described.[7] We also report that pateamine A specifically inhibits an intracellular step of the T cell receptor signal transduction pathway, leading to IL-2 transcription, making pateamine A an attractive molecular probe to uncover a new signaling molecule(s) in this pathway. As a first step toward identifying the pateamine A target, we have found that the primary C3 amino group in pateamine A can tolerate further chemical modification without significant loss of immunosuppressive activity. In addition, the synthesis of a pateamine A-dexamethasone hybrid to be utilized in the yeast three-hybrid system[8] and other pateamine A-related molecules is also reported.

† Texas A&M University.

‡ Massachusetts Institute of Technology.

(1) (a) Yamamoto, K. R. *Annu. Rev. Genet.* **1985**, *19*, 209−252. (b) Evans, R. M. *Science* **1988**, *240*, 889−895. (c) Schreiber, S. L. *Science* **1991**, *251*, 283−287. (d) Liu, J. *Immunol. Today* **1993**, *14*, 290−295. (e) Hinterding, K.; Alonso-Diaz, D.; Waldmann, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 688−749.

(2) I*mmunosuppressive Drugs: Developments in Anti-rejection Therapy*; Thomson, A. W., Starzl, W. E., Eds.; Edward Arnold: London, 1994.

(3) (a) Schreiber, S. L. *Science* **1991**, *251*, 283−287. (b) Belshaw, P. J.; Meyer, S. D.; Johnson, D. D.; Romo, D.; Ikeda, Y.; Andrus, M.; Alberg, D. G.; Schultz, L. W.; Clardy, J.; Schreiber, S. L. *Synlett* **1994**, 381−392.

(4) Northcote, P. T.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron Lett.* **1991**, *32*, 6411−6414.

(5) Faircloth, G. T., PharmaMar Inc., Cambridge, MA, private communication, 1994.

(6) For other synthetic studies of pateamine A, see: Critcher, D. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 9107−9110.

(7) Our first synthesis has been previously communicated: Rzasa, R. M.; Shea, H. A.; Romo, D. *J. Am. Chem. Soc.* **1998**, *120*, 591−592.

(8) Licitra, E. J.; Liu, J. O. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 12817−12821.

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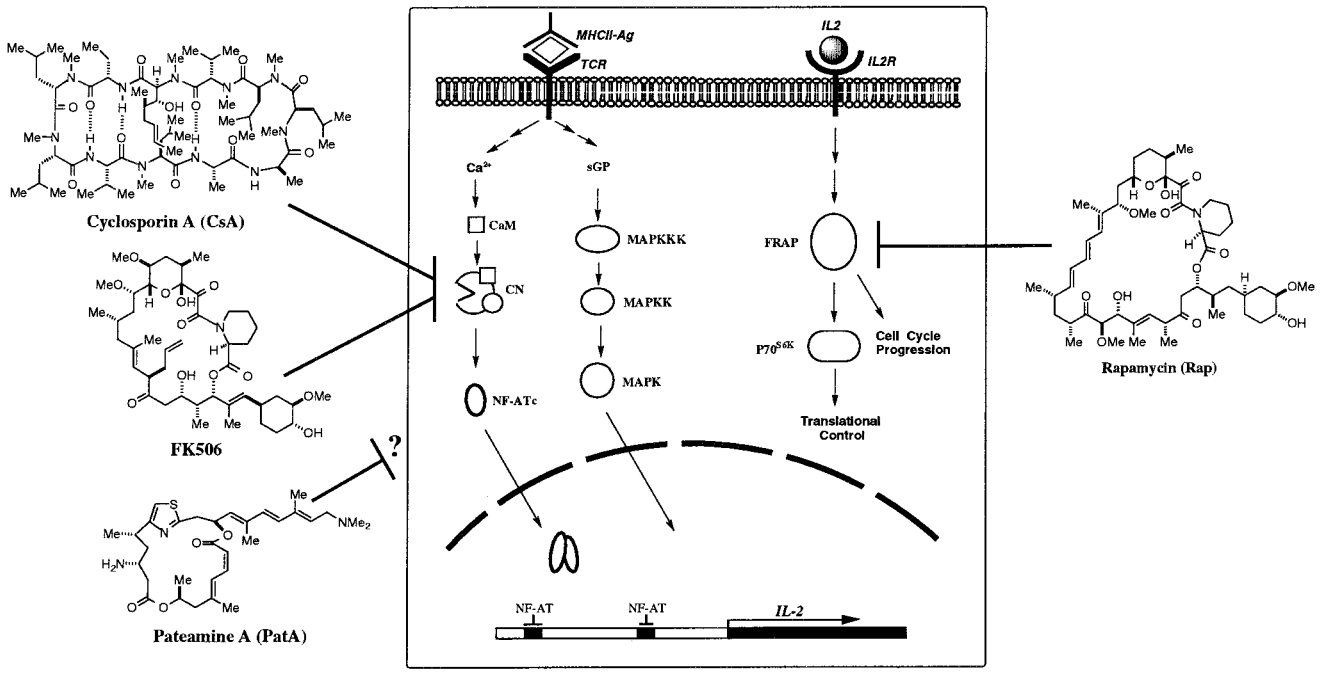
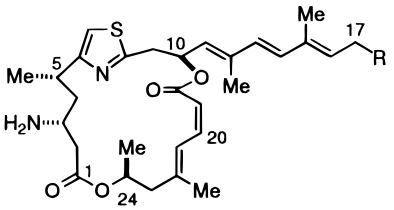


Figure 1. Signal transduction pathways involved in T lymphocyte activation and the site of action of the immunosuppressants cyclosporin A, FK506, rapamycin and pateamine A. Abbreviations: MHCII-Ag, major histocompatibility complex II−antigen complex; TCR, T cell receptor; IL2, interleukin 2; IL2R, the IL2 receptor; CaM, calmodulin; CN, calcineurin; NF-AT, nuclear factor of activated T cells; NF-ATc, the cytoplasmic subunit of NF-AT; FRAP, FKBP−rapamycin-associated protein; sGP, small GTP binding proteins; MAPK, generic MAP kinases; MAPKK, MAPK kinase; MAPKKK, MAPKK kinase.



Pateamine A (1) R = NMe_2
B (2) R = NHMe
C (3) R = $N(O)Me_2$

Figure 2. Structure of pateamines A, B, and C.

Background. Pateamine A was isolated off the shores of New Zealand by Munro and co-workers from the marine sponge *Mycale* sp., and, in the initial report in 1991, only its two-dimensional structure was described. This unique natural product bears a thiazole and an *E*,*Z*-dienoate within a 19-membered macrocycle and a trienylamine side chain. Two minor constituents, pateamines B and C, were also isolated, and their structures differ from pateamine A only in the nature of the terminal group of the trienylamine side chain (Figure 2).[9] Other natural products isolated from this same species of sponge include the mycalamides which are structurally related to the pederins.[10] Pateamine A exhibits antifungal and selective cytotoxic activity;[4] however, our interest in a synthesis of this natural product was sparked by its unique structure, its potent immunosuppressive effects, and, importantly, its low toxicity. On comparison to cyclosporin A in the mouse skin graft rejection assay, pateamine A resulted in a 15-day survival period, whereas cyclosporin A led to only a 10-day survival of skin grafts.[5] For these reasons, we embarked on a total synthesis of this natural product as a means to determine the relative and absolute stereochemistry,[11] to provide further quantities of the natural product, and to provide access to structural derivatives for further biological studies, including isolation of a putative cellular receptor. We also initiated efforts to delineate the site of action of this drug by examining its effect on T cell receptor-mediated IL-2 production and IL-2 receptor-mediated T cell proliferation.

Retrosynthetic Analysis. Several considerations guided our retrosynthetic plan, including the reported lability of the C3 amino group,[4] the potential for isomerization of the *E*,*Z*-dienoate, the desire to introduce and liberate the polar amino groups at a late stage of the synthesis, and the unknown stereochemistry of the natural product. With these considerations in mind, our retrosynthesis called for the synthesis and subsequent union of three principal fragments, namely β-lactam **7**, dienylstannane **4**, and enyne acid **8** (Figure 3). These fragments thus became our initial synthetic targets. An enyne was used to allow a late-stage introduction of the *E*,*Z*-dienoate to minimize the potential for isomerization. A late-stage Stille coupling would append the trienylamine side chain and would allow a variety of side chains to be introduced onto the macrocyclic core structure. A key strategy to be employed to construct the 19-membered dilactone macrolide of pateamine A was a β-lactam-based macrocyclization which was suggested by the pateamine A structure. Thus, a β-lactam would be used to install the C3-amino group and then serve as an activated acyl group for macrocyclization. To address the issue of stereochemical uncertainty, we elected to use reagent-based control to set the four stereogenic centers contained in pateamine A to provide the most stereoflexible approach. In addition, we realized some inherent flexibility was present at C10 based on our synthetic plan since the hydroxyl could be acylated or, alternatively,

(9) Munro, M. H. G.; Northcote, P. T.; Blunt, J. W., University of Canterbury, New Zealand, personal communication, 1993.

(10) For a lead reference, see: Abell, A. D.; Blunt, J. W.; Foulds, G. J.; Munro, M. H. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, *11*, 1647−1654.

(11) For our initial communication on stereochemical determination of the C24 stereocenter of pateamine A in collaboration with the New Zealand group, see: Rzasa, R.; Romo, D.; Stirling, D. J.; Blunt, J. W.; Munro, H. M. G. *Tetrahedron Lett.* **1995**, *36*, 5307−5310.

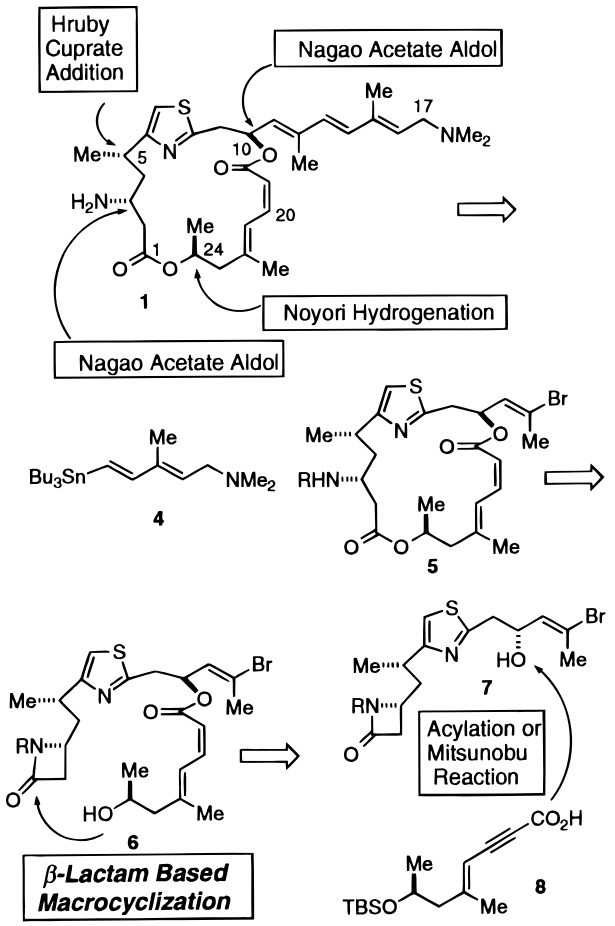
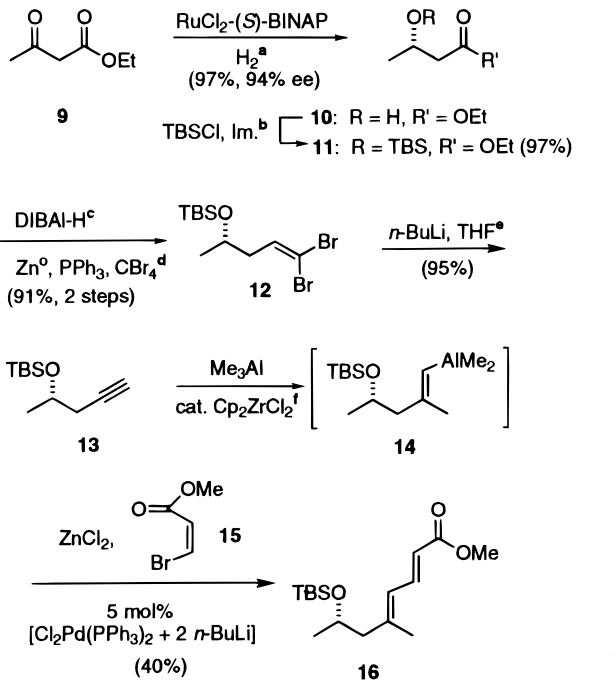


Figure 3. Retrosynthesis of (−)-pateamine A showing key disconnections, including the β-lactam-based macrocyclization strategy and stereoflexible methods for introduction of stereogenic centers. R = Boc (*tert*-butoxycarbonyl) or TCBoc (trichloro-*tert*-butoxycarbonyl).

inverted by a Mitsunobu process to provide both epimers at this position. Two stereogenic centers at C3 and C10 would be introduced using the chiral auxiliary-based acetate aldol methodology of Nagao[12] et al., and the C5 stereocenter would be introduced by an asymmetric conjugate addition by the method of Hruby et al.[13] The C24 stereochemistry would originate from yeast reduction[14] or Noyori asymmetric hydrogenation of ethyl acetoacetate.[15]

As mentioned above, Munro and co-workers described only the two-dimensional structure of pateamine A, and attempts to produce crystalline derivatives were unsuccessful.[4] To embark on a total synthesis of pateamine A, a tenative stereochemical assignment was required to define an initial synthetic target. In collaboration with the New Zealand groups, we set out to determine the absolute stereochemistry at C24. To accomplish this task, we envisioned that a hydroxy dienoate corresponding to the C18−C25 fragment of pateamine A could be secured by

Scheme 1[a]



[a] (a) EtOH, Dowex-50 resin, 200 psi H_2, 130 °C; (b) DMF, 25 °C; (c) CH_2Cl_2, −90 °C; (d) CH_2Cl_2, 25 °C; (e) −78 → 25 °C; (f) CH_2Cl_2, **13** then added to $Pd(PPh_3)_2$, $ZnCl_2$, and **15** in THF, −78 → 25 °C.

methanolysis of pateamine A, and a synthesis of this fragment was devised in order to make a direct comparison of natural and synthetic materials. We were also mindful of the possibility of using the same intermediate for our projected total synthesis and for absolute stereochemical determination at C24.

Results and Discussion

Synthesis of Enyne Acid 8 and Hydroxy Dienoate 20 (C18−C25): Defining a Stereochemical Target. Our first approach to the *E*,*Z*-hydroxy dienoate corresponding to the C18−C25 fragment of pateamine A is outlined in Scheme 1. The known (*S*)-2-hydroxybutyrate **10** was prepared by yeast reduction[12] or by Noyori hydrogenation of ethyl acetoacetate using the modified conditions of Taber et al.[16] The modified Noyori method was readily performed on a large scale, and the enantiomeric purity and product yield were superior to those obtained with the yeast reduction method (94% ee vs 84−90% ee, chiral GC); it was therefore employed for large-scale preparations. After silylation, the known silyloxy ester **11**[17] was reduced to the aldehyde and converted to the acetylene **13** by the Corey−Fuchs procedure.[18] Application of the Negishi protocol,[19] involving carboalumination to give the presumed vinyl alane **14** and direct Pd(0) coupling of the derived vinyl zincate to the *Z*-bromoester **15**,[20] resulted in coupling but also concomitant and complete isomerization of the dienoate to the *E*,*E*-isomer **16**. The origin of this isomerization, which may be reversible Michael addition of PPh_3,[21] was not determined, but a similar isomerization problem has been recently reported.[22]

(12) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391−2393.

(13) (a) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766−770. (b) Li, G.; Patel, D.; Hruby, V. J. *Tetrahedron: Asymmetry* **1993**, *4*, 2315−2318. (c) The X-ray data of imide **37** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(14) Seebach, D.; Sutter, M. A.; Weber, R. H.; Zuger, M. F. *Organic Syntheses*; Wiley: New York, 1990; *Collect. Vol. VII*, pp 215−220.

(15) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858.

(16) (a) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227−4230. (b) Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990−5994.

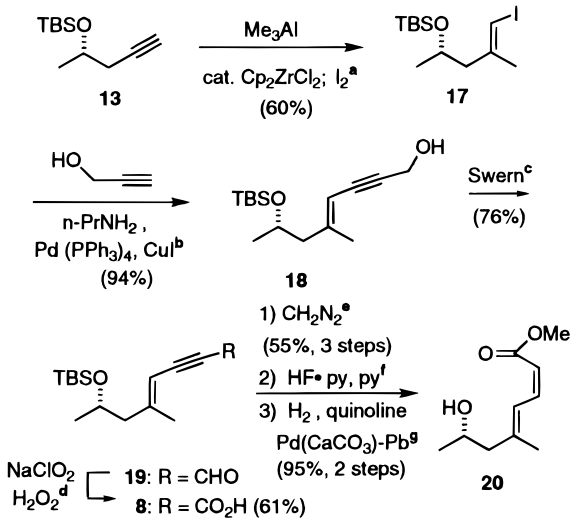
(17) Ireland, R. E.; Wardle, R. B. *J. Org. Chem.* **1987**, *52*, 1780−1789.

(18) Corey, E. J.; Fuchs, P. *Tetrahedron Lett.* **1972**, 3769−3772.

(19) (a) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Speigel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 0. (b) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093−4096.

(20) Ma, S.; Lu, X. *Org. Synth.* **1993**, *72*, 112−115.

Scheme 2[a]



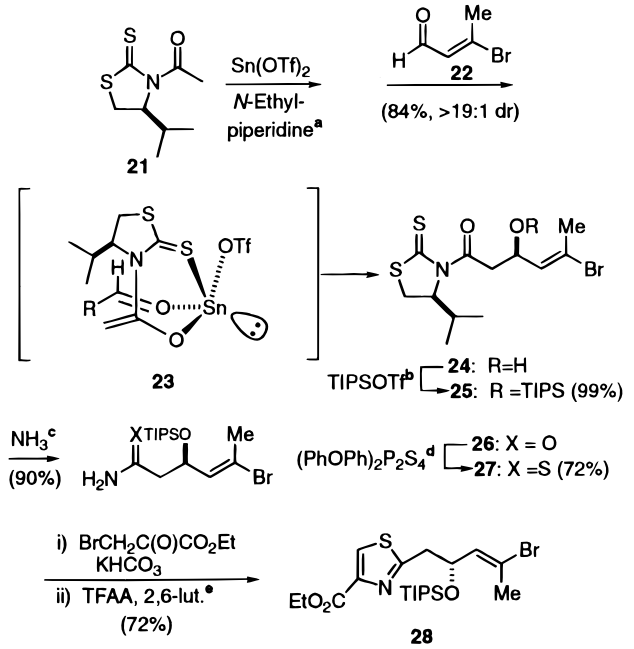
[a] (a) CH_2Cl_2, 0 → 25 °C then I_2, Et_2O, 0 °C; (b) C_6H_6, 0 → 25 °C; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 → 0 °C then Et_3N, −78 °C; (d) CH_3CN, NaH_2PO_4 buffer, *tert*-butyl alcohol, 0 °C; (e) Et_2O, 25 °C (yield includes steps (c) and (d)); (f) THF, 25 °C; (g) MeOH, 1 atm H_2, 25 °C.

Although this isomerization precluded direct comparison to the degradation product of pateamine A, the *E*,*E*-hydroxydienoate **16** did prove useful for comparison to the isomerized product obtained during methanolysis of pateamine A and to the same *E*,*E*-dienoate isolated from the same sponge but in a different location.[9]

The desired *E*,*Z*-dienoate was ultimately obtained by a slightly modified route involving a Lindlar reduction of an enyne (Scheme 2). A carboalumination/iodination sequence[19] delivered the vinyl iodide **17**, which was then subjected to a Sonagshira coupling[23] with propargyl alcohol to provide the enyne alcohol **18**. A two-step oxidation gave the pivotal intermediate, enyne acid **8**. This intermediate proved useful for the total synthesis of pateamine A as well as the synthesis of the *E*,*Z*-hydroxydienoate for stereochemical determination of C24. Toward the latter goal, methylation with diazomethane, deprotection of the silyl group, and Lindlar reduction of enyne acid **8** gave the required *E*,*Z*-dienoate **20** for comparison to the same compound derived from methanolysis of pateamine A. Comparative HPLC analysis on a chiral stationary phase of the derived Mosher esters of both natural and synthetic hydroxydienoate **20** confirmed the (*S*)-configuration at C24.[11] This result, in conjunction with molecular modeling studies and extensive 2-D NMR experiments by the New Zealand group, provided a tentative absolute stereostructure of pateamine A as 3*R*,5*S*,10*R*,24*S*. Thus, this stereoisomer became our initial synthetic target.[24]

Synthesis of the C3−C12 Fragment. The synthesis of the C3−C12 fragment began with a Nagao acetate aldol reaction[12] with known aldehyde **22**[25] and the *N*-acetylthiazolidinethione

Scheme 3[a]



[a] (a) CH_2Cl_2, −40 °C then **22**; (b) CH_2Cl_2, 0 °C; (c) CH_2Cl_2, 0 °C; (d) THF, 25 °C; (e) DME, −20 °C → 0 °C.

21[26] (Scheme 3). This proceeded smoothly to give an 84% yield of the aldol adduct **24** in a highly diastereoselective fashion (>19:1 dr) through the presumed transition-state arrangement **23**. Silylation and transamidation with gaseous ammonia gave amide **26** in high overall yield. Conversion to the thioamide was first attempted with Lawesson's reagent,[27] but this led to exclusive formation of the corresponding volatile nitrile resulting from net dehydration of the starting amide **26**. In contrast, use of the Belleau reagent[28] gave the desired thioamide **27** in 72% yield accompanied by ∼15% of the nitrile. Conversion to the thiazole **28** was effected using the modified Hantzsch conditions reported by Aguilar and Meyers.[29]

After studying several strategies for introduction of the C5 stereocenter, we found that the method of Hruby et al.,[13a] involving an asymmetric conjugate addition to an Evans oxazolidinone-derived enimide, provided an efficient means to introduce this stereogenic center. In the event, half-reduction and Horner−Emmons olefination (*Z*:*E* > 19:1) of thiazole ester **28** simultaneously homologated and introduced the chiral auxiliary required for the asymmetric conjugate addition (Scheme 4).[30] Treatment of enimide **31** with an excess of MeMgBr and an equivalent amount of CuBr·DMS according to the conditions of Hruby et al., led to the methylated product **34** with good diastereoselectivity (6.4:1, dr). The major diastereomer could be isolated in 77% yield. The stereochemical outcome, as evidenced by a subsequent X-ray analysis of a crystalline intermediate (i.e., **37**, vide infra), is consistent with initial

(21) For a lead reference to PPh_3-promoted isomerizations of alkyne esters and enyne esters, see: Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659−2660.

(22) For a discussion of a related isomerization problem observed during a Stille coupling, see: Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1994**, *59*, 5662−5671.

(23) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470.

(24) (a) Blincoe, S. N. M.Sc. Thesis, University of Canterbury, New Zealand, 1994. (b) A full account of this work will be forthcoming: Munro, M. H. G., University of Canterbury, New Zealand, private communication, 1998.

(25) Fischer, H.; Klippe, M.; Lerche, H.; Severin, T.; Wanninger, G. *Chem. Ber.* **1990**, *123*, 399−404.

(26) For a detailed procedure for the synthesis of this auxiliary, see: Calo, V.; Fiandanese, V.; Nacci, A.; Scilimati, A. *Tetrahedron* **1994**, *50*, 7283−7292.

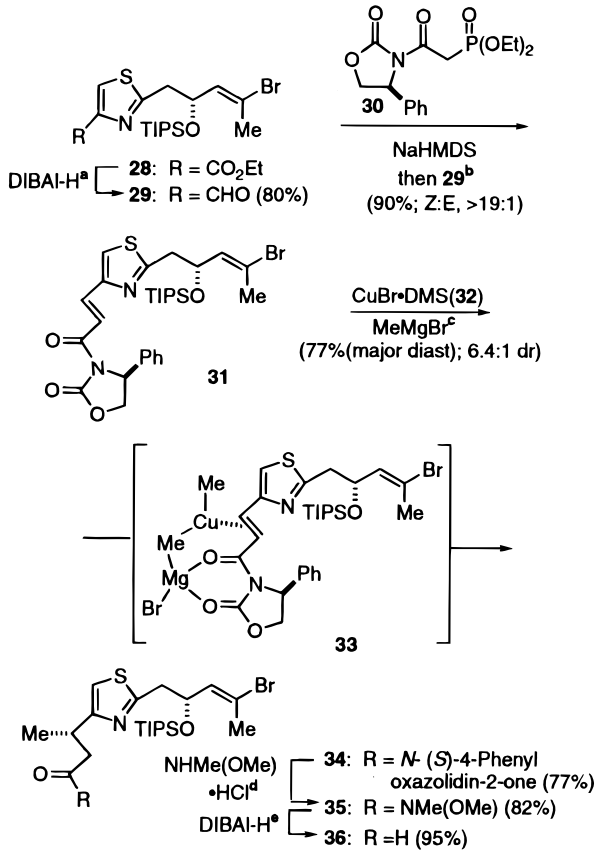
(27) Lawesson, S. O.; Scheibye, S. *Bull. Soc. Chim. Belg.* **1978**, *87*, 227−238.

(28) Lajoie, G.; Lepine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, *24*, 3815−3818.

(29) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473−2476.

(30) For the same homologation strategy applied to the (*S*)-phenylalanine-derived oxazolidinone auxiliary, see: Broka, C. A.; Ehrler, J. *Tetrahedron Lett.* **1991**, *32*, 5907−5910.

Scheme 4[a]



[a] (a) CH_2Cl_2, −90 °C; (b) THF, 25 °C; (c) THF/DMS (3:2), −20 °C; (d) Me_3Al, CH_2Cl_2, 0 °C; (e) CH_2Cl_2, −90 °C.

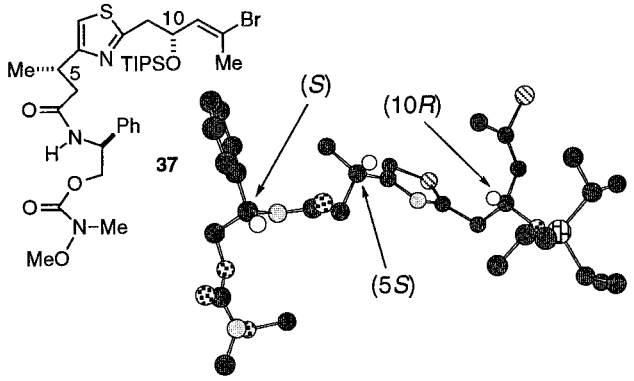


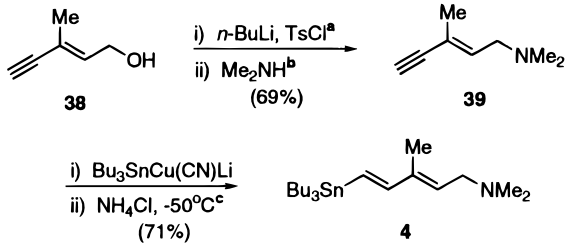
Figure 4. Structure of Weinreb amidation byproduct **37** and its X-ray crystal structure (Chem 3D representation). Hydrogen atoms are omitted, except at stereogenic centers, for clarity.

formation of a Cu(I) π-olefin complex−Mg(II) chelate on the face of the *s-trans* enimide opposite the phenyl group of the auxiliary (cf. **33**), as proposed by Hruby et al. on the basis of NMR studies.[13a] A fortuitous crystalline byproduct, amide **37**, was obtained during transamidation to the Weinreb amide **35**,[31] which results from aluminum amide attack at the endocyclic carbonyl. This allowed verification of the stereochemistry at C5 and C10 (pateamine numbering) as 5*S*,10*R* by X-ray crystallography (Figure 4).[32] Half-reduction of amide **35** to aldehyde **36** provided the substrate required for introduction of the C3 stereocenter.

(31) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171−4174.

(32) The X-ray data of β-lactone **37** have been deposited with the Cambridge Crystallographic Data Centre (see ref 13c).

Scheme 5[a]



[a] (a) THF, −78 °C; (b) THF, −78 → 0 °C; (c) THF, −60 → −40 °C.

Synthesis of the Dienyl Stannane 4 and Model Stille Coupling Reactions. The synthesis of the dienyl amino stannane **4** was accomplished in two steps from the known enyne alcohol **38** (Scheme 5).[33] A one-pot tosylation and displacement with dimethylamine gave the allylic amine **39**. Stannylcupration and quenching at low temperature according to the method of Aksela and Oehlschlager[34] provided the desired dienyl stannane **4** as a mixture of regioisomers (9:1).

One concern with a late-stage Stille coupling was the potential for competing π-allyl formation, since the substrate would be an allylic acetate (cf. **5**) and the product would be a triallylic acetate (cf. pateamine A).[35] To address these concerns, we carried out model studies of the proposed Stille reaction on vinyl bromides **28** and **40** (Scheme 6). Using the conditions of Farina and Krishna,[36] the Stille reaction of vinyl bromide **28** and vinyl stannane **4**, not unexpectedly, gave the desired triene **41** in an unoptimized 46% yield (69% based on recovered starting material). The true test of the feasibility of this transformation was the Stille coupling with allylic acetate **40**. We were pleased to find that Stille coupling proceeded competitively with π-allyl formation under these conditions to provide a 53% yield of triene **42**. With this result in hand, we proceeded with our plan to perform a late-stage Stille reaction to append the trienylamine side chain.

***β*-Lactam-Based Macrocyclization Studies: Intermolecular Model Studies.** β-Lactams have been utilized as acylating agents in both inter- and intramolecular reactions with oxygen,[37] nitrogen,[38] and carbon[39] nucleophiles.[40] Wasserman has described elegant applications of intramolecular transamidation reactions of β-lactams to access a number of alkaloid natural products.[40a] A well-known example of an intermolecular β-lactam-based acylation is the side-chain attachment of baccatin III and derivatives to give taxol or taxotere.[37b] In addition, Kahn

(33) (*E*)-3-Methyl-2-penten-4-yn-1-ol (1-pentol) was generously provided by Drs. E. Gutknecht and P. Weber (F. Hoffman-La Roche Ltd., Basel, Switzerland).

(34) Aksela, R.; Oehlschlager, A. C. *Tetrahedron* **1991**, *47*, 1163−1167.

(35) A very recent report describes Stille reactions in the presence of allylic acetates, see: Nicolaou, K. C.; He, Y.; Roschagar, G.; King, N. P. Vourloumis, D.; Li, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 84−87.

(36) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

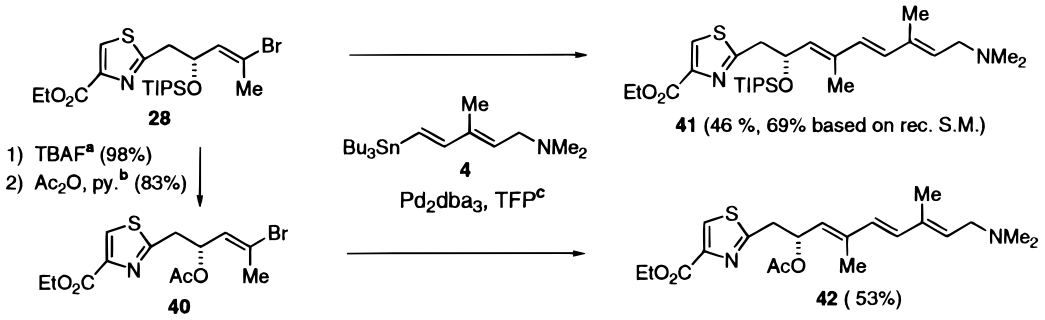
(37) (a) Palomo, C.; Aizpurua, H. M.; Cuevas, C.; Mielgo, A.; Galarza, R. *Tetrahedron Lett.* **1995**, *36*, 9027−9030. (b) Ojima, I.; Sun, C. H.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. *Tetrahedron Lett.* **1993**, *34*, 4149−4152. (c) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985−7012.

(38) (a) Bhupathy, M.; Bergan, J. J.; McNamara, J. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 9445−9448. (b) Ojima, I.; Sun, C. M.; Park, Y. H. *J. Org. Chem.* **1994**, *59*, 1249−1250.

(39) (a) Ojima, I.; Ng, E. W.; Sun, C. M. *Tetrahedron Lett.* **1995**, *36*, 4547−4550. (b) Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Iturburu, M.; Odriozola, J. M. *J. Org. Chem.* **1994**, *59*, 5184−5188.

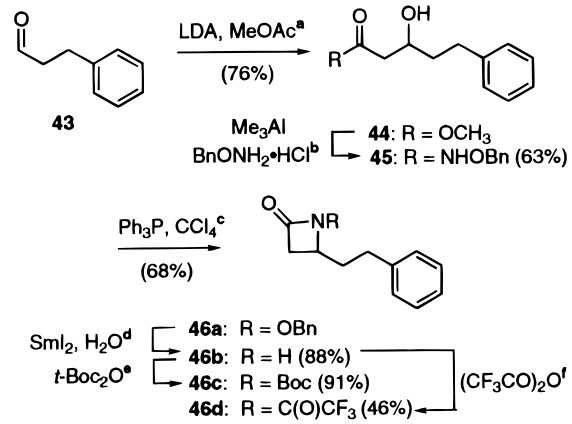
(40) For reviews of the utility of β-lactams as synthetic intermediates, see: (a) Wasserman, H. H. *Aldrichim. Acta* **1987**, *20*, 63−74. (b) Hesse, M. *Ring Enlargements in Organic Chemistry*; VCH Publishers: New York, 1991. (c) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755−1802.

Scheme 6[a]



[a] (a) THF, −20 °C; (b) 25 °C; (c) (1:4 Pd (15 mol %)/ligand), THF or NMP, 25 °C.

Scheme 7[a]

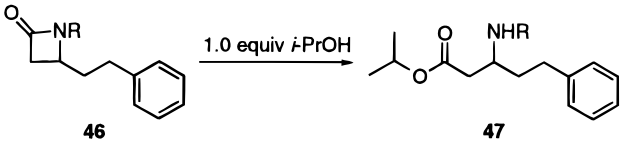


[a] (a) THF, −78 °C; (b) CH_2Cl_2, 0 → 25 °C; (c) CH_3CN, 25 °C; (d) THF, 0 °C; (e) CH_2Cl_2, 25 °C; (f) py, CH_2Cl_2, 0 °C.

et al. reported an intramolecular transamidation approach to 7- and 10-membered β-turn mimetics employing acyl hydrazides as the nucleophilic partner.[42] However, the use of a β-lactam to acylate a secondary alcohol in a macrocyclization strategy has not been reported, to our knowledge. As a means to study the synthesis of α-unsubstituted β-lactams using an aldol−intramolecular Mitsunobu sequence and to explore the proposed β-lactam-based macrocyclization involving a secondary alcohol, we investigated a simple intermolecular version of this transformation. Toward this end, a series of β-lactams **46** were synthesized, beginning with an aldol reaction of hydrocinnamaldehyde with the lithium enolate of methyl acetate (Scheme 7). Conversion of the known aldol adduct **44**[43] to the *N*-benzyloxy amide **45** by the Weinreb procedure followed by intramolecular Mitsunobu reaction using the conditions of Guzzo and Miller[44] delivered the *N*-benzyloxy-β-lactam **46a**. We found that SmI_2 in the presence of H_2O cleanly effects N−O cleavage to give β-lactam **46b** using the conditions reported by Keck et al.[45] and Marco-Contelles et al.[46] for N−O cleavage of *O*-alkyl hydroxylamines to amines. To the best of our knowledge, this is the first application of these conditions to the deprotection of an *N*-benzyloxy-β-lactam.[47]

Our initial studies of the β-lactam-based intermolecular acylation focused on the conditions of Ojima et al. that had been developed for the attachment of the side chain of taxol.[37c] To determine possible nitrogen substituents that would activate the β-lactam toward acylation and serve as a suitable protecting group for late-stage deprotection, we studied several β-lactams **46** as acylating agents.[48] We employed 2-propanol as the nucleophile to mimic the secondary alcohol at C24 (pateamine numbering) that would serve as the nucleophilic partner in the proposed pateamine A macrocycle synthesis (Figure 3). As can be seen in Table 1, both the *N*-benzyloxy and *N*-*t*-Boc-β-lactams, **46a** and **46c**, respectively, provided good yields of the corresponding isopropyl ester **47** using the conditions of Ojima et al.[38b] The *N*-trifluoroacetyl-β-lactam **46d** did not lead to the desired ring opening. The similarities between pK_as for alcohols and amides suggested the possibility of employing the *N*-unprotected-β-lactam **46b**; however, in this case, the starting material was recovered unchanged. We also explored other potential promoters such as 4-pyrrolidinopyridine (4-PPy) to serve as a nucleophilic catalyst and DBU to serve as a mild base with *N*-Boc-β-lactam **46c**, but these gave no reaction. Finally, we explored the conditions of Palomo that were utilized for the intermolecular alcoholysis of β-lactams.[37a] While NaN_3 gave no reaction, even on heating in DMF, KCN in DMF gave

Table 1. Intermolecular Model Studies of the β-Lactam-Based Macrocyclization



entry	R	conditions	time (h)	% yield (**47**)[a]
1	OBn (**46a**)	NaHMDS, THF, −42 °C	1.5	67
2	*t*-Boc (**46c**)	NaHMDS, THF, −42 °C	4	66−80
3	C(O)CF_3 (**46d**)	NaHMDS, THF, −42 °C	4	0
4	H (**46b**)	NaHMDS, THF, −42 °C	4	nr
5	*t*-Boc	4-PPy, $Cl(CH_2)_2Cl$, 80 °C	9	nr
6	*t*-Boc	DBU, $Cl(CH_2)_2Cl$, 25 → 70 °C	5	nr
7	*t*-Boc	NaN_3, DMF, 40 °C	25	nr
8	*t*-Boc	KCN, DMF, 25 °C	1−2	67−84

[a] nr = no reaction. Yields are for the isolated product.

(41) (a) For a lead reference, see: Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383−389. (b) Holton, R. A. Eur. Pat. App. EP 400,971, 1990; *Chem. Abs.* **1990**, *114*, 164568q.

(42) Gardner, B.; Nakanishi, H.; Kahn, M. *Tetrahedron* **1993**, *49*, 3433−3448.

(43) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404−7405.

(44) Guzzo, P. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4862−4867.

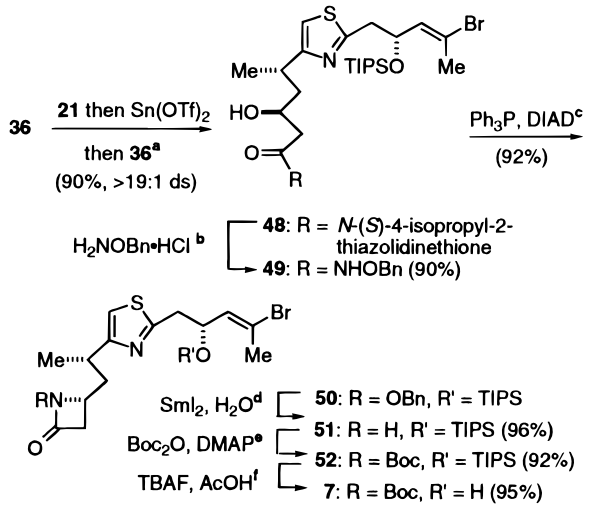
(45) Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *41*, 7419−7422.

(46) Chiara, J. L.; Destabel, C.; Gallego, P.; Marco-Contelles, J. *J. Org. Chem.* **1996**, *61*, 359−360.

(47) Several methods have been described for reductive cleavage of the N−O bond of *N*-benzyloxy-β-lactams, but they are, in general quite harsh. For a lead reference, see: Georg, G. I. *The Organic Chemistry of β-Lactams*; VCH Publishers: New York, 1993.

(48) For related studies of intermolecular acylations with α-substituted-β-lactams, see ref 37.

Scheme 8[a]



[a] (a) *N*-Ethylpiperidine, CH_2Cl_2, −40 °C; (b) Me_3Al, CH_2Cl_2, 0 °C; (c) THF, 25 °C; (d) THF, 0 °C; (e) CH_2Cl_2, 25 °C; (f) THF, 0 °C.

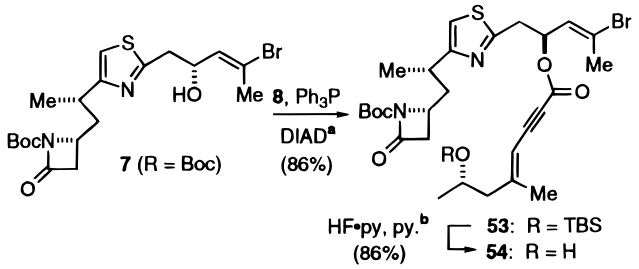
good yields of the isopropyl ester **47** (Table 1, entries 7 and 8, respectively).

Synthesis of the β-Lactam Fragment. What remained to complete the synthesis of the final fragment for pateamine A synthesis was introduction of the C3 stereocenter (pateamine numbering) and construction of the β-lactam ring. Building on our model studies (vide supra), we envisioned the use of a second Nagao acetate aldol to introduce the C3 stereocenter followed by the Miller intramolecular Mitsunobu reaction to construct the β-lactam. Utilizing the same auxiliary previously employed to introduce the C10 stereocenter (i.e., **21**), the Nagao acetate aldol reaction with aldehyde **36** provided a high degree of stereocontrol (>19:1, dr) in excellent yield (Scheme 8). Transamidation of aldol adduct **48** to the *N*-benzyloxy amide **49** followed by an intramolecular Mitsunobu reaction gave the desired *N*-benzyloxy β-lactam in excellent overall yield. We found that diisopropylazodicarboxylate (DIAD) gave superior yields compared to the use of carbon tetrachloride[44] to activate triphenylphoshine in this Mitsunobu reaction. Although our model studies described above had indicated that an *N*-benzyloxy substituent was sufficient for activation of a β-lactam toward intermolecular nucleophilic attack by sodium isopropoxide, we elected to convert this group to a *tert*-butylcarbamate in order to utilize deprotection conditions that were more likely to be compatible with late intermediates. Toward this goal, reductive cleavage of the N−O bond with SmI_2 in the presence of H_2O led smoothly to the unprotected β-lactam **51** in excellent yield, as we had observed in our simple model system. Protection of the β-lactam nitrogen as the *tert*-butylcarbamate (**52**), followed by desilylation of the C10 silyl ether with tetrabutylammonium fluoride (TBAF), provided the final fragment, alcohol **7** (R = Boc), required for the total synthesis of pateamine A.

Coupling of β-Lactam 7 (R = Boc) and Enyne Acid 8 (Acylation vs Mitsunobu Reaction): Revision of the C10 Stereochemistry. Further degradation and derivitization work, including mandelic amide analysis at C3 and Mosher ester analysis at C10 of the product of methanolysis, led to a stereochemical revision at C10.[49] Since a Nagao acetate aldol had introduced the (*R*)-stereochemistry at this center, an inversion was required to obtain the correct stereochemistry.

(49) Munro, M. H. G., University of Canterbury, New Zealand, personal communication, 1996.

Scheme 9[a]



[a] (a) THF, −20 °C; (b) THF, 25 °C.

Table 2. Various Conditions Employed for the β-Lactam-Based Macrocyclization (**54** → **55**)

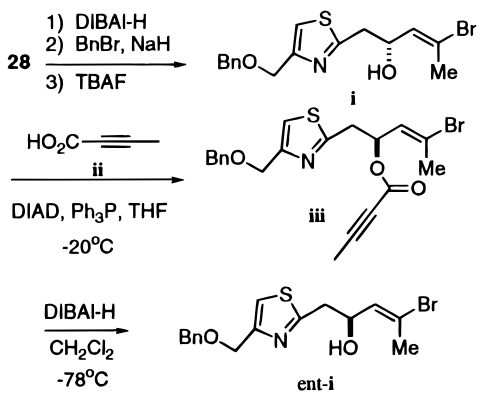
entry	conditions[a]	temp (°C)	% yield (**55**)
1	1.1 equiv of NaHMDS, THF, 45 min	−40	37[b]
2	1.1 equiv of LiHMDS, THF 2.5 h	−40	11[b]
3	1.1 equiv of NaH, THF 1 h	−10	42[b]
4	0.5−0.6 M KCN, DMF, 1−2 h	25	52−72
5	9.0 equiv of Et_4NCN, CH_2Cl_2, 4−9 h	25	59−68

[a] All reactions were run at ∼0.002 M. [b] Varying amounts of an isomeric product were also isolated.

This could be readily accomplished by a Mitsunobu reaction which simultaneously introduced the enyne acid fragment **8** and inverted the C10 stereochemistry to the required (*S*)-configured ester **53** in 93% yield (Scheme 9). A model system verified that the Mitsunobu coupling proceeded with inversion of configuration and minimal loss of stereochemical integrity.[50] A subsequent desilylation of the TIPS ether provided the substrate, alcohol **54**, for the key β-lactam-based macrocyclization.

β-Lactam-Based Macrocyclization Strategy Applied to the Pateamine A Macrocycle. We initially studied the conditions of Ojima et al. that were developed for the intermolecular acylation of a secondary alcohol in baccatin III with a *N*-benzoyl-β-lactam and had proven useful in our model studies (vide supra).[37b] Using the same conditions (Table 2, entry 1) but under high dilution (∼0.002 M), we obtained a 37% yield of the desired macrocycle **55** and 17% of an isomeric macrocycle (not shown), which was not completely characterized but appears to be due to isomerization about the C21−C22 olefinic bond. This may arise from intramolecular deprotonation at the C22 methyl group by the alkoxide formed at C24. In efforts to utilize a less basic alkoxide, LiHMDS was employed, but this led to only 11% yield of the macrocycle **55** and increased quantities of the isomerized product. The use of NaH in THF

(50) The thiazole ester **28** was converted to the alcohol **i** in three steps. Mitsunobu reaction with propynoic acid **ii** gave ester **iii**. Subsequent reduction to the alcohol *ent*-**i** and analysis by chiral HPLC (Chiracel OD.; 10% MeOH, CH_2Cl_2) indicated that the Mitsunobu reaction proceeded with >96% stereochemical fidelity.



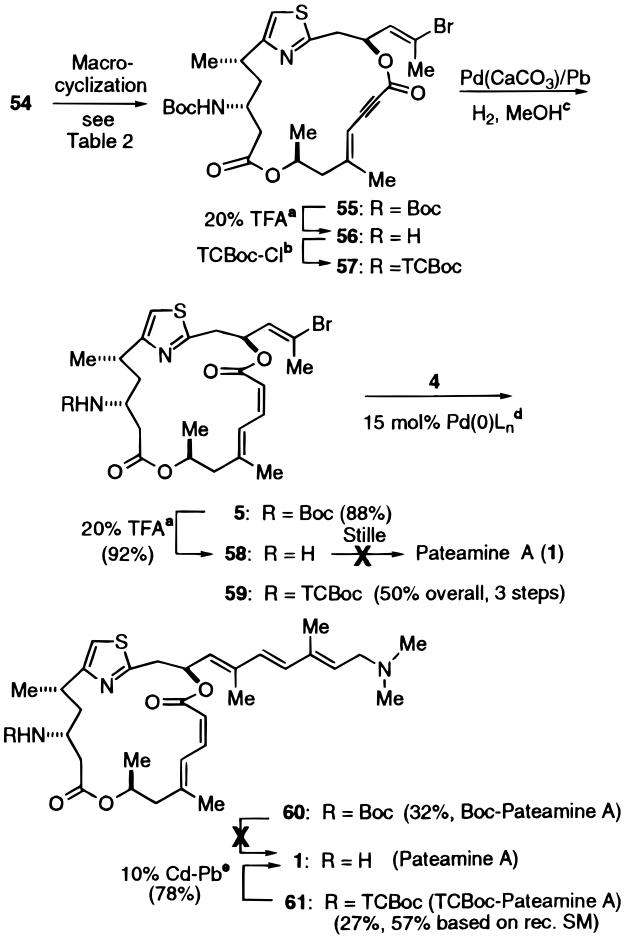
gave yields comparable to those obtained with NaHMDS, and appreciable quantities of the isomeric product were still formed. The yields obtained in these attempts were unsatisfactory to complete the synthesis, so we studied other conditions that were ideally neutral pH. We returned to our model system involving 2-propanol and the *N*-Boc-β-lactam **46c** and employed the conditions[37a] of Palomo for intermolecular alcoholysis of β-lactams (vide supra). When we applied these conditions to alcohol **54**, we were pleased to find that syringe pump addition of alcohol **54** to a 0.5−0.6 M KCN in DMF solution (~0.002 M, final substrate concentration) led cleanly to the desired macrocycle in 52−72% yield (<5 mg scale). An observed polar byproduct in this reaction which was not isolated is presumably the amino acid derived from hydrolysis of the acyl cyanide intermediate.[51] Despite this advance, we were somewhat concerned about product isolation from the large volumes of DMF that would be required as the reaction was performed on larger scale. We therefore explored the use of Et_4NCN, a CH_2Cl_2-soluble source of cyanide ion. To our delight, use of 9.0 equiv of Et_4NCN in CH_2Cl_2 (0.002 M, final substrate concentration) led to practical rates of formation of the desired macrocycle **55** in 4−9 h. Stirring both the alcohol **54** and Et_4NCN in CH_2Cl_2 over freshly activated, powdered molecular sieves prior to reaction to remove traces of H_2O led to slight improvements in yields. The use of CH_2Cl_2 as solvent in this macrocyclization greatly simplified product isolation.

Synthesis of Boc-Pateamine A. With the macrocycle **55** in hand, hydrogenation with Lindlar's catalyst led to slow reduction of the alkyne to the *E*,*Z*-dienoate (Scheme 10). Due to the thiazole present in the substrate, the optimal Lindlar reagent-to-substrate ratio was determined (~600 mg of Lindlar reagent/mmol substrate) for a satisfactory hydrogenation rate. Stille coupling, using methods established previously in the model studies, appended the trienylamine side chain to provide Boc-pateamine A **56** in 32% yield, which correlated well with the same compound derived from the natural product as determined by comparison of 300-MHz ^{1}H NMR.[52] No further characterization data were available for Boc-pateamine A derived from natural material, but this gave us our first indication that we were pursuing the correct stereoisomer. Unfortunately, attempts to deprotect Boc-pateamine A or a simpler model system (e.g., 5 → 100 equiv of TFA, CH_2Cl_2, 0 °C; $MeSO_3H$, CH_2Cl_2, −78 °C; TESOTf, 2,6-lutidine, 0 → 25 °C) only led to decomposition or no reaction. However, Boc-pateamine A led to an interesting insight into the structural requirements for immunosuppressive activity (vide infra) and also led us to explore novel methods for simultaneous deprotection and purification of Boc amines.[53]

An alternative end-game strategy was investigated, involving reversal of the final two steps of the synthesis. In the event, deprotection of the Boc group of macrocycle **5** prior to introduction of the trienylamine side chain (Scheme 10) *led to an excellent yield of the primary amine **58**.* However, application of the Stille conditions previously successful in model studies and also used to access Boc-pateamine A failed to give any detectable pateamine A.

The ability to cleanly deprotect the Boc group prior to introduction of the side chain deserves some comment. This result implies that one plausible decomposition pathway under acidic conditions involves formation of a triallylic cation derived from protonation and loss of the ester group at C10. This could presumably be the first step in an E1 elimination to give a fully conjugated tetraene−thiazole system. Also interesting is that none of the β-elimination previously observed by Munro and co-workers during their derivatization work on pateamine A[4] was observed on deprotection of the Boc macrocycle **5** (R = Boc). The success of this deprotection provided an avenue to perform a protecting group exchange as described below.

Scheme 10[a]



[a] (a) CH_2Cl_2, 0 °C; (b) catalytic DMAP, py, 0 → 25 °C; (c) 1 atm H_2, 25 °C; (d) (1:4 Pd/ligand), TFP or Ph_3As, THF, 25 °C; (e) 1 M NH_4OAc, THF, 25 °C.

Protecting Group Exchange: Completion of the Synthesis of (−)-Pateamine A. Because we were unable to deprotect Boc-pateamine A without decomposition and we had quantities of the Boc macrocycle **55** on hand, we elected to perform a protecting group exchange. We searched for alternative amine protecting groups that could ideally be removed under essentially neutral conditions. In this regard, we were attracted to a recent report by Ciufolini et al. for deprotection of the trichloroethoxy carbamate (TROC) involving the use of Cd−Pb couple and a buffered solvent system of NH_4OAc and THF.[54] In addition, it had been demonstrated that these conditions were tolerated by reducible functionality such as an α-bromoenone, which gave us confidence to apply it to the projected substrate which would contain a triene and a dienoate. We settled on the use of the trichloro-*tert*-butoxy carbamate (TCBoc) rather than the TROC group to ensure a regioselective acylation during the β-lactam-

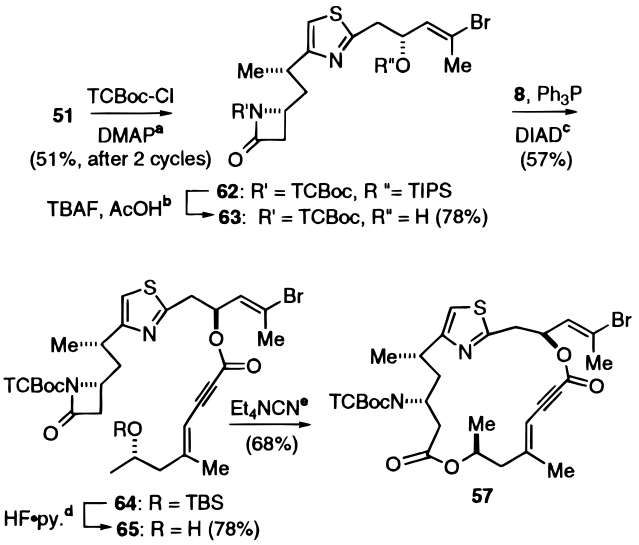
(51) We have recently obtained evidence for an acyl cyanide intermediate in a related model acylation reaction by VT ^{13}C NMR.

(52) We thank Profs. Munro and Blunt for providing a 300-MHz ^{1}H NMR spectrum of Boc-pateamine A derived from natural material.

(53) Liu, Y.-S.; Zhao, C.; Bergbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998**, *63*, 3471−3473.

(54) Dong, Q.; Anderson, C. E.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 5681−5682. We thank Prof. Ciufolini for helpful discussions concerning the suitability of these deprotection conditions for the problem at hand.

Scheme 11[a]



[a] (a) Et_3N, CH_2Cl_2, 25 °C; (b) THF, 0 °C; (c) THF, 25 °C; (d) py, THF, 25 °C; (e) 9.0 equiv of Et_4NCN, CH_2Cl_2 (0.0018 M), 25 °C.

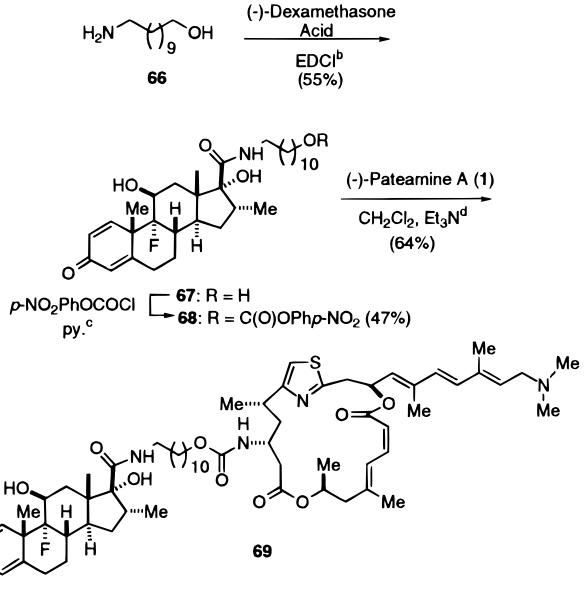
based macrocyclization, since we anticipated an eventual streamlined synthesis wherein the TCBoc group would be introduced at the outset (vide infra).

Deprotection of the Boc macrocycle **55** to the primary amine **56** was cleanly effected with trifluoroacetic acid, and protection with TCBoc-Cl gave the TCBoc macrocycle **57** (Scheme 10). Lindlar reduction proceeded as before to deliver the diene **59** in 50% overall yield for three steps. Stille coupling using conditions established previously delivered TCBoc-pateamine A (**61**) in 27% yield (57% based on recovered bromide **59**). It proved beneficial to stop the Stille reaction prior to completion and recycle recovered bromide **5** (R = TCBoc), since allowing the reaction to proceed to completion gave only 25−32% yields of TCBoc-pateamine A (**61**). This result indicates that π-allyl formation may, indeed, be competitive with the Stille reaction in this system. Final deprotection of TCBoc pateamine A (**61**) by the method of Ciufolini et al. cleanly provided (−)-pateamine A (**1**) after purification by reversed-phase column chromatography and passage through an amino cartridge to free base the final product. Synthetic pateamine A correlated well with the natural product[55] in all respects, including ^1H, ^{13}C NMR, IR, UV, $[\alpha]_D$, CD, HRMS, TLC, and IC_{50} in the IL-2 reporter gene assay (vide infra).

Streamlining the Synthesis. Since our initial report,[7] we have been able to streamline the synthesis of pateamine A by incorporation of the TCBoc group at the outset (Scheme 11). Nitrogen protection of β-lactam **51** with TCBoc-Cl led to incomplete acylation, and this could not be forced to completion by using excess reagents or gentle heating. After one recycle of starting material, we obtained a 51% yield of the *N*-TCBoc-β-lactam **62**. Desilylation followed by Mitsunobu reaction to append the enyne acid **8** and a second desilylation delivered alcohol **65**. Macrocyclization of this alcohol using the previously developed conditions gave the TCBoc macrocycle **57**, which was identical in all respects to the same compound prepared before by the protecting group exchange sequence (Scheme 10).

Synthesis of a Dexamethasone−Pateamine A Hybrid. One approach toward isolation of a putative cellular receptor involves the use of the recently reported yeast three-hybrid assay developed in one of our laboratories.[8] To this end, we developed a synthesis of a pateamine A−dexamethasone hybrid

Scheme 12[a]



[a] (a) 80 °C; (b) HOBT, Et_3N, CH_2Cl_2, 0 °C; (c) CH_2Cl_2, 0 → 25 °C; (d) THF, 25 °C.

69 to be utilized in this assay for either target identification or future studies of the interaction between pateamine A and its target (Scheme 12). Selective coupling of the amino group of 11-hydroxyundecylamine[56] with (−)-dexamethasone acid[57] using standard amide coupling procedures provided the alcohol **67**. In preparation for coupling to pateamine A, the *p*-nitrophenyl carbonate **68** was prepared by treating the alcohol **67** with *p*-nitrophenylchloroformate. Addition of synthetic pateamine A to carbonate **68** in the presence of Et_3N provided the desired dexamethasone−pateamine A hybrid **69** in 64% yield.

Activity in the IL-2 Reporter Gene Assay of (−)-Pateamine A and Related Compounds. Pateamine A has been previously shown to inhibit both murine and human mixed lymphocyte reactions, indicating that it is immunosuppressive.[5] It was not clear, however, which signaling pathway involved in T cell activation is affected by pateamine A. We have found that pateamine A inhibits T cell receptor-mediated IL-2 production but does not appear to affect IL-2 receptor mediated cell proliferation.[58] The TCR signaling pathway can be recapitulated by treatment with the pharmacological agents phorbol myristyl acetate (PMA), which activates protein kinase C, and ionomycin, which allows calcium ion to enter T cells to activate calmodulin and calcineurin. Using a reporter gene (luciferase) under the control of the IL-2 promoter, we found that pateamine A potently blocks PMA/ionomycin-stimulated IL-2 promoter activation.[59] The IC_{50} values for pateamine A were determined to be 0.33 and 0.46 nM for the synthetic and natural pateamine A, respectively (Table 3). These results suggest that pateamine A inhibits an intracellular signaling step in the TCR signaling pathway, leading to IL-2 production. The mode of action of pateamine A is, therefore, similar to those of FK506 and CsA but is distinct from that of rapamycin (Figure 2). The fact that

(55) We thank Prof. Peter Northcote (Victoria University of Wellington, New Zealand), Mr. Lyndon West, and Dr. Chris Battershill (New Zealand National Institute of Water and Atmospheric Research, Ltd.) for kindly providing a sample of natural pateamine A.

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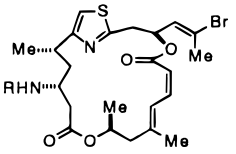
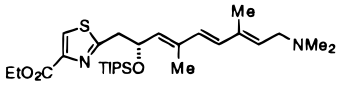
Table 3. IC_{50} Values for Natural and Synthetic (−)-Pateamine A and Related Compounds in the Interleukin-2 Reporter Gene Assay

Compound	IC_{50} (nM)
Natural (-)-Pateamine A (**1**)	0.45 ± 0.04
Synthetic (-)-Pateamine A (**1**)	0.33 ± 0.03
Boc-Pateamine A (**60**)	2.1 ± 0.5
Dexamethasone-Pat. A Hybrid (**69**)	1.0 ± 0.4
 Boc-Macrocycle (**5**, R = Boc)	> 1000
 Triene (**41**)	>1000

synthetic pateamine A and natural pateamine A have similar potency in the inhibition of IL-2 promoter activation provides further (biological) evidence that our synthetic pateamine A is identical to the natural product. Furthermore, the fact that Boc-pateamine A retains a significant amount of immunosuppressive activity suggests a site of attachment for the preparation of biochemical probes for detection and isolation of the molecular target of pateamine A via modification of the amino group in pateamine A. This guided our synthesis of the dexamethasone−pateamine A hybrid **69** described above.[60] The inactivity (>1000 nM) observed for the Boc macrocycle **5** (R = Boc) and the triene **41** suggests that both the macrocycle and the trienylamine side chain are required for a competent immunosuppressive agent.

Conclusion. In conclusion, we have developed a convergent, stereoflexible strategy for the total synthesis of (−)-pateamine A and derivatives which has led to structural verification of this marine sponge isolate as the 3*R*,5*S*,10*S*,24*S* isomer. Other findings made in the course of the synthesis include the use of CH_2Cl_2-soluble Et_4NCN as promoter for the key β-lactam-based macrocyclization, the ability to carry out a Stille coupling in the presence of an allylic and triallylic acetate,[61] and the reductive cleavage of the N−O bond of an *N*-benzyloxy-β-lactam under mild conditions with SmI_2. Our previous synthesis of pateamine A required a protecting group exchange which has now been eliminated by introduction of the TCBoc amine protecting group at the outset. Future synthetic studies will seek to improve the efficiency of the triene synthesis.

We have found that pateamine A inhibits T cell receptor-mediated IL-2 transcription, indicating that its mode of action is similar to those of FK506 and CSA but distinct from that of rapamycin. The fact that Boc-pateamine A retains significant activity suggested a site of attachment (C3 amino group) for hybrid molecules useful for isolation of a putative cellular receptor. One such hybrid molecule, a dexamethasone−pateamine A hybrid to be utilized for either target identification or for further studies of the interaction between pateamine A and its target, was synthesized on the basis of this finding. In addition, preliminary studies of pateamine A derivatives suggest that both the macrocycle and the trienylamine side chain are necessary for a competent immunosuppressive agent. The synthesis of designed derivatives for further understanding of the structural features required for immunosuppressive activity and for isolation of a putative cellular receptor represents our ongoing studies of the pateamines, and the results of these studies will be the subject of future reports.

(60) It should be noted that we have not ruled out the possibility that β-elimination of pateamine A and derivatives, in fact, leads to the same $\Delta^{2,3}$-desamino pateamine A under the conditions of the IL-2 assay, and thus exhibits similar IC_{50} values.

(61) Another report of a Stille reaction with an allylic acetate substrate has recently appeared: Nicolaou, K. C.; He Y.; Roschangar, F.; King, N. P.; Vourloumis; D.; Li, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 84−87.

Experimental Section

General Procedures. All nonaqueous reactions were carried out under a nitrogen atmosphere in oven-dried (120 °C) glassware. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled immediately prior to use from sodium metal/benzophenone ketyl. Methylene chloride (CH_2Cl_2, EM Science) and benzene (EM Science) were distilled from calcium hydride prior to use. 2,6-Lutidine (Acros), *N*-ethylpiperidine (NEP, Acros), triethylamine (Et_3N, EM Science), and pyridine (py, EM Science) were distilled from calcium hydride. Methanol (MeOH, EM Science) was distilled from magnesium methoxide. Dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride and stored over 4-Å molecular sieves. Triethyl phosphite was stirred over sodium metal overnight, decanted, and distilled under reduced pressure. Bromo, acetyl bromide, ethyl bromopyruvate, and dimethyl sulfide were Kugelrohr distilled prior to use. All other commercially obtained reagents were used as received. Rochelle's salt solution refers to 2 M aqueous sodium potassium tartrate. Dexamethasone was purchased from Research Biochemicals (Natick, MA) and converted to dexamethasone acid by the published procedure.[57]

Unless indicated otherwise, deuteriochloroform ($CDCl_3$) served as an internal standard (77.0 ppm) for all ^{13}C spectra. In the case of TCBoc-pateamine A and pateamine A, 0.01% pyridine-d_5 was added to the $CDCl_3$ solvent to buffer any acid present. Combustion analyses were performed by Atlantic Microlabs (Norcross, GA). Flash column chromatography was performed using 60-Å silica gel (Baker, 230−400 mesh) as a stationary phase as described by Still et al.[62] Mass spectra were obtained on a VG analytical 70S high-resolution, double-focusing, sectored (EB) mass spectrometer at the Center for Chemical Characterization and Analysis (Texas A&M).[63] Enantiomeric excess (ee) was determined by GC (Hewlett-Packard 5880A gas chromatograph) analysis using a TBS-β-cyclodextrin column or HPLC (Rainin SD-200 with Dynamax UV−C detector) analysis using a Chiralcel OD column. Thin-layer chromatography (TLC) was performed using glass-backed silica gel $60F_{254}$ (Merck, 250-μm thickness). Amino column chromatography was performed using 200-mg Bakerbond spe* amino (NH_2) disposable extraction columns (40 μm APD, 60 Å).

Ethyl (*S*)-3-Hydroxybutyrate (10). This β-hydroxy ester was prepared according to the modified Noyori procedure.[16] To a dried metal parr reactor were added ethyl acetoacetate (17.2 g, 0.132 mol), absolute ethanol (80 mL), Ru-(*S*)-BINAP catalyst (8 mL; from 80 mg of (*S*)-BINAP) prepared using by the method of Taber et al.,[16] and Dowex-50 resin (1.4 g, washed with water, methanol, diethyl ether, and methanol and then dried). Hydrogenation was carried out at 200 psi H_2 and 130 °C for 10 h. After cooling, the reaction mixture was filtered through Celite and concentrated in vacuo. Flash chromatography eluting with hexanes/EtOAc (4:1) gave 16.4 g (94%) of ethyl (*S*)-3-hydroxybutyrate (**10**) (94.4% ee by chiral GC) as a colorless oil. Spectral data for this compound matched those previously reported.[64]

Ethyl (*S*)-3-(*tert*-Butyldimethylsilyl)oxybutyrate (11). To a solution of β-hydroxy ester **10** (11.0 g, 0.083 mol) in DMF (120 mL) were added imidazole (14.2 g, 0.208 mol) and TBSCl (15.1 g, 0.100 mol) at 25 °C. After being stirred for 12 h at 25 °C, the reaction mixture was quenched with saturated $NaHCO_3$ (100 mL) and extracted with ether

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(3 × 200 mL). The combined extracts were washed with H_2O (5 × 200 mL) and brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography eluting with hexanes/EtOAc (97:3) gave 19.9 g (97%) of silyl ether **11** as a colorless oil. Spectral data for this compound matched those previously reported.[17]

Dibromo Olefin 12. To a cooled (−90 °C) solution of silyl ether **11** (19.2 g, 77.9 mmol) in 300 mL of CH_2Cl_2 was added a solution of DIBAl−H (13.3 g, 93.5 mmol) in 50 mL of CH_2Cl_2 down the inside of the flask over a 1-h period. After 2 h, the reaction was quenched with 20 mL of MeOH and warmed to 25 °C. To the solution was added 150 mL of saturated sodium potassium tartrate solution, and the solution was stirred vigorously for 3 h. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude aldehyde (15.2 g, 96%) was then diluted with 100 mL of CH_2Cl_2. In a separate flask, to a slurry of Zn dust (11.2 g, 0.171 mol) in 600 mL of CH_2Cl_2 were added triphenylphosphine (44.9 g, 0.171 mol) and carbon tetrabromide (56.8 g, 0.171 mol). After 48 h, the solution of aldehyde was added via cannula to the slurry of $Zn^0/Ph_3P/CBr_4$ at 0 °C. After 1 h, the reaction was poured into 1 L of hexanes, resulting in a cloudy brown mixture that was decanted. The residue was dissolved in 500 mL of CH_2Cl_2 and again poured into 1 L of hexanes. This process was repeated four times. The combined hexanes washes were concentrated in vacuo and purified by flash chromatography on SiO_2 eluting with hexanes to give 25.5 g (92%) of dibromo olefin **12**: $R_f = 0.42$ (hexanes); $[\alpha]^{26}_D$ +3.7° (*c* 1.10, $CHCl_3$); IR (thin film) 2936, 1263, 1135 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.46 (t, $J = 7.2$ Hz, 1H), 3.92 (sext, $J = 6.0$ Hz, 1H), 2.23 (dd, $J = 1.8$, 7.2 Hz, 1H), 2.20 (dd, $J = 6.3$, 7.3 Hz, 1H), 1.16 (d, $J = 6.0$ Hz, 3H), 0.89 (s, 9H), 0.061 (s, 3H), 0.059 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.6, 89.7, 66.8, 42.7, 25.8, 23.7, 17.9, −4.6, −4.8; HRMS (EI) calcd for $C_{11}H_{22}{}^{79}Br_2OSi$ [M − C_4H_9] 300.9082, found 300.9086. Anal. Calcd for $C_{11}H_{22}Br_2OSi$: C, 36.89; H, 6.19. Found: C, 36.79; H, 6.15.

Acetylene 13. To a cooled (−78 °C) solution of dibromo olefin **12** (18.5 g, 52 mmol) in 400 mL of THF was added 52 mL of *n*-butyllithium (130 mmol, 2.5 M in hexanes) over a 2-h period. After complete addition, the reaction was allowed to warm to 25 °C. After 10 h, the solution was recooled (−78 °C) and quenched with 200 mL of saturated NH_4Cl solution. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with pentane gave 9.79 g (95%) of the volatile acetylene **13**: TLC $R_f = 0.25$ (hexanes); $[\alpha]^{26}_D$ +2.9° (*c* 0.90, $CHCl_3$); IR (thin film) 2636, 2132 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.92 (d quin, $J = 6.0$, 7.0 Hz, 1H), 2.32 (ddd, $J = 2.7$, 5.6, 16.5 Hz, 1H), 2.18 (ddd, $J = 2.7$, 7.1, 16.5 Hz, 1H), 1.90 (t, $J = 2.7$ Hz, 1H), 1.21 (d, $J = 6.0$ Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.9, 69.7, 67.5, 29.4, 25.8, 23.2, 18.1, −4.7, −4.8; HRMS (EI) calcd for $C_{11}H_{22}OSi$ [M − C_4H_9] 140.0736, found 140.0738. Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.18. Found: C, 66.86; H, 11.24.

***(E,E)*-Dienoate 16.** To a solution of bis(cyclopentadienyl)zirconium dichloride (29 mg, 0.11 mmol) in 1 mL of CH_2Cl_2 was added Me_3Al (0.80 mL, 2.0 M in CH_2Cl_2), and the solution was cooled to 0 °C. A solution of acetylene **13** in 1 mL of CH_2Cl_2 was added, and the reaction was stirred at 25 °C for 10 h. *n*-Butyllithium (0.052 mL, 2.15 M in hexanes) was added to a cooled (−78 °C) solution of $Pd(PPh_3)_2Cl_2$ (17.8 mg, 0.025 mmol) in 1.2 mL of THF, resulting in a bright yellow solution. After 2 h, bromoacrylate **15** (0.071 mL, 0.64 mmol) was added, followed by the alane solution, a solution of $ZnCl_2$ (87.9 mg, 0.67 mmol) in 1 mL of THF was added, and the mixture was warmed to 25 °C. After 21.5 h, the reaction was quenched with 1.6 mL of saturated K_2CO_3 at 0 °C, resulting in gas evolution, and the solution was warmed to 25 °C. The solution was extracted with hexanes (4 × 10 mL) and Et_2O (2 × 10 mL) and the combined organic layers were washed with $NaHCO_3$ (20 mL) and brine (20 mL) and dried over $MgSO_4$. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (100:0 → 93:7) gave 79.6 mg (40%) of enoate **16**: $R_f = 0.27$ (1:9 EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, $J = 11.7$, 15.1 Hz, 1H), 5.97 (d, $J = 11.7$ Hz, 1H), 5.77 (d, $J = 15.1$ Hz, 1H), 3.98 (m, 1H), 2.26 (dd, $J = 7.3$, 13.1 Hz, 1H), 2.15 (dd, $J = 5.1$, 13.1 Hz, 1H), 1.88 (d, $J = 1.2$ Hz, 3H), 1.11 (d, $J = 6.1$ Hz, 3H), 0.84 (s, 9H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.4, 147.0, 140.9, 125.7, 118.7, 67.2, 51.4, 50.5, 25.9, 25.8, 24.0, 18.1, −4.5(2).

Vinyl Iodide 17. To a flask charged with bis(cyclopentadienyl)-zirconium dichloride (292 mg, 8.82 mmol) was added 35.3 mL of trimethylaluminum solution (70.6 mmol, 2.0 M in hexanes), and concomitant evolution of gas was observed. A solution of acetylene **14** (3.5 g, 17.6 mmol) in 60 mL of CH_2Cl_2 was added at 0 °C. After 20 h at 25 °C, the reaction was cooled to 0 °C and quenched with a solution of iodine (6.72 g, 26.4 mmol) in 30 mL of Et_2O. The reaction was poured into 60 mL of saturated K_2CO_3 solution, resulting in a white precipitate. The layers were separated, and the aqueous layer was extracted with hexanes (3 × 100 mL) and Et_2O (3 × 100 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution (200 mL), and brine (200 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes gave 3.59 g (60%) of vinyl iodide **17** as a clear colorless oil: $R_f = 0.35$ (hexanes); $[\alpha]^{26}_D$ +15.6° (*c* 2.16, $CHCl_3$); IR (thin film) 2928, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (q, $J = 1.0$ Hz, 1H), 3.97−3.89 (m, 1H), 2.37 (ddd, $J = 0.8$, 7.3, 13.4 Hz, 1H), 2.26 (ddd, $J = 0.8$, 5.1, 13.4 Hz, 1H), 1.85 (d, $J = 1.1$ Hz, 1H), 1.12 (d, $J = 6.1$ Hz, 1H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.1, 77.2, 66.6, 49.6, 25.8, 24.5, 23.7, 18.0, −4.6, −4.8; HRMS (EI) calcd for $C_{12}H_{25}IOSi$ [M − C_4H_9] 283.0015, found: 283.0007.

Enyne Alcohol 18. To a flask charged with tetrakis(triphenylphosphine)palladium(0) (991.8 mg, 1.1 mmol) was added a solution of vinyl iodide **17** (6.25 g, 18.4 mmol) in 80 mL of benzene, and the mixture was then cooled to 0 °C, resulting in a yellow solution. A solution of propargyl alcohol (1.37 mL, 23.9 mmol) and *n*-propylamine (7.80 mL, 95.7 mmol) in 5 mL of benzene was added via cannula. To this solution was added CuI (698.4 mg, 3.7 mmol) as a solid, and the reaction was warmed to 25 °C. The solution was stirred for 20 h, quenched with 25 mL of saturated NH_4Cl, and extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/Et_2O (20:1 → 3:1) gave 4.64 g (94%) of alcohol **18** as a pale yellow oil: $R_f = 0.26$ (1:4 EtOAc/hexanes); $[\alpha]^{26}_D$ +18.9° (*c* 1.13, $CHCl_3$); IR (thin film) 3600−3100, 2937, 2218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.33−5.29 (m, 1H), 4.42 (dd, $J = 2.0$, 5.9 Hz, 2H), 3.99−3.89 (m, 1H), 2.25 (ddd, $J = 0.9$, 6.6, 13.2 Hz, 1H), 2.13 (ddd, $J = 0.3$, 5.4, 13.2 Hz, 1H), 1.89 (d, $J = 1.5$ Hz, 3H), 1.11 (d, $J = 6.0$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 106.6, 89.8, 83.6, 67.1, 51.7, 48.8, 25.8, 23.6, 20.0, 18.1, −4.6, −4.8; HRMS (FAB) calcd for $C_{15}H_{28}O_2Si$ [M + Na] 291.1756, found 291.1734. Anal. Calcd for $C_{15}H_{28}O_2Si$: C, 67.11; H, 10.51. Found: C, 67.01; H, 10.45.

Enyne Aldehyde 19. To a cooled (−78 °C) solution of oxalyl chloride (1.10 mL, 12.6 mmol) in 30 mL of CH_2Cl_2 was added dimethyl sulfoxide (1.80 mL, 25.4 mmol), with concomitant gas evolution. The resulting solution was stirred at −78 °C for 20 min. A solution of alcohol **18** (1.54 g, 5.8 mmol) in 20 mL of CH_2Cl_2 was added by cannula, resulting in a cloudy solution that was stirred for 20 min at −78 °C. To this solution was added Et_3N (8.00 mL, 57.4 mmol), resulting in gas evolution. After the solution was stirred for 20 min, the reaction was quenched with 15 mL of pH 7 buffer, warmed to 25 °C, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with Et_2O gave 908.4 mg (76%) of aldehyde **19** as a clear yellow oil: $R_f = 0.57$ (1:4 Et_2O/hexanes); IR (thin film) 2926, 2176, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 5.50 (s, 1H), 3.99 (app sext, $J = 6.0$ Hz, 1H), 2.33 (ddd, $J = 0.9$, 7.3, 13.2 Hz, 1H), 2.27 (dd, $J = 5.1$, 13.2 Hz, 1H), 2.03 (d, $J = 0.9$ Hz, 3H), 1.15 (d, $J = 6.3$ Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 160.7, 105.2, 94.3, 92.4, 67.0, 49.4, 25.8, 24.0, 21.1, 18.0, −4.5, −4.9; HRMS (FAB) calcd for $C_{15}H_{26}O_2Si$ [M + H] 265.1624, found: 265.1628.

Enyne Acid 8. To a cooled (0 °C) solution of aldehyde **19** (908.4 mg, 3.4 mmol) in 24 mL of CH_3CN, 24 mL of NaH_2PO_4 buffer (pH

4.26), and 12 mL of *tert*-butyl alcohol was added 7.5 mL of 30% H_2O_2 solution, followed by $NaClO_2$ (6.15 g, 68.0 mmol) as a solid. After 2.5 h, the reaction was diluted with KH_2PO_4 buffer (pH 2.02) until pH 2−3. After extraction with EtOAc, the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc/AcOH (44:5:1 → 63:33:4) gave 585.6 mg (61%) of acid **8** as a yellow oil: $R_f = 0.21$ (1:5:19 AcOH/EtOAc/hexanes); $[\alpha]^{26}_D$ +17.8° (*c* 1.01, $CHCl_3$); IR (thin film) 3500−2500, 2200, 1672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (app d, $J = 1.2$ Hz, 1H), 4.03−3.93 (m, 1H), 2.32 (dd, $J = 7.2$, 13.5 Hz, 1H), 2.22 (dd, $J = 5.1$, 13.5 Hz, 1H), 2.02 (d, $J = 1.2$ Hz, 3H), 1.14 (d, $J = 6.0$ Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 159.1, 105.0, 87.9, 83.5, 67.3, 49.4, 26.0, 24.0, 21.1, 18.2, −4.3, −4.7; HRMS (FAB) calcd for $C_{15}H_{26}O_3Si$ [M + Na]: 305.1549, found 305.1545.

(*S*)-(*E*,*Z*)-Hydroxydienoate 20. To a solution of acid **8** in diethyl ether was added an ethereal solution of diazomethane at 25 °C until no starting material was detected by TLC. To a polypropylene Eppendorf tube charged with the methyl ester (36.5, 0.12 mmol) was added 2 mL of HF·pyr/pyr/THF solution (3.8 g/6 mL/10 mL) at 25 °C. After 9 days, the solution was diluted with EtOAc and poured into 2.5 mL of saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine and dried over Na_2SO_4. Purification in SiO_2 eluting with EtOAc/hexanes (40:60) gave a yellow oil. To a solution of this oil in 1 mL of MeOH was added 10 mg of palladium/$CaCO_3$ poisoned with Pb, followed by 0.030 mL of quinoline. The slurry was evacuated and purged with H_2 four times. After 7.5 h, the reaction was diluted with Et_2O, filtered through Celite, and washed with a saturated $CuSO_4$ solution. Purification on a SiO_2 column eluting with acetone/hexanes (1:9) gave 21.6 mg of dienoate **20** (95% over two steps) as a yellow oil: TLC $R_f = 0.10$ (2:3 EtOAc/hexanes); $[\alpha]^{26}_D$ −13.5° (*c* 1.04, $CHCl_3$); IR (thin film) 3600−3150, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, $J = 1.0$, 11.7 Hz, 1H), 6.89 (t, $J = 11.6$ Hz, 1H), 5.64 (d, $J = 11.5$ Hz, 1H), 4.03 (app sext, $J = 6.3$ Hz, 1H), 3.72 (s, 3H), 2.31 (d, $J = 6.7$ Hz, 2H), 1.90 (d, $J = 1.0$ Hz, 3H), 1.70−1.55 (br s, 1H), 1.23 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 146.3, 139.8, 123.6, 115.5, 65.8, 51.1, 50.2, 23.3, 17.1; HRMS (FAB) calcd for $C_{10}H_{16}O_3$ [M + H] 185.1178, found 185.1167.

Aldehyde 22. To a solution of 3-bromo-2-buten-1-ol[65] (25 g, 166 mmol) in 1.5 L of CH_2Cl_2 was added 122 g of MnO_2. After 24 h, the reaction was filtered through Celite and concentrated in vacuo. The residue was purified by flash chromatography on SiO_2 eluting with pentane/Et_2O (9:1) to give 17.6 g (70%) of aldehyde **22** as a highly volatile, pale yellow liquid. Data not reported previously[25] are provided: $R_f = 0.23$ (1:9 Et_2O/hexanes); IR (thin film) 2857, 1675, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (d, $J = 6.9$ Hz, 1H), 6.45 (app dt, $J = 1.2$, 6.9 Hz, 1H), 2.71 (d, $J = 1.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.1, 149.0, 133.6, 25.3; DCIMS (CH_4) 149. Satisfactory HRMS could not be obtained for this compound.

Aldol Product 24. To a cooled (−50 °C) suspension of stannous triflate[66] (49.3 g, 120 mmol) in 394 mL of CH_2Cl_2 were added *N*-ethylpiperidine (14.5 mL, 120 mmol) and a solution of thiazolidine thione **21** (20 g, 99 mmol) in 20 mL of CH_2Cl_2. The solution was stirred for 4.5 h, then the reaction mixture was cooled to −78 °C, and a CH_2Cl_2 solution of aldehyde **22** (17.6 g, 120 mmol) was added via cannula and stirred for 3 h. The reaction mixture was quenched with pH 7 buffer and warmed to 25 °C. The solids were filtered through Celite, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (3:1 → 1:1) gave 28.94 g (84%) of alcohol **24** as a yellow oil: TLC $R_f = 0.17$ (3:7 EtOAc/hexanes); $[\alpha]^{26}_D$ +304° (*c* 0.83, $CHCl_3$); IR (thin film) 3504 (br), 2968, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (dq, $J =$ 1.4, 8.8 Hz, 1H), 5.14 (dt, $J = 1.1$, 6.3 Hz, 1H), 4.8 (dt, $J = 3.2$, 8.6 Hz, 1H), 3.62 (dd, $J = 3.2$, 17.7 Hz, 1H), 3.52 (dd, $J = 7.9$, 11.5 Hz, 1H), 3.31 (dd, $J = 8.4$, 17.7 Hz, 1H), 3.03 (dd, $J = 1.1$, 11.5 Hz, 1H), 2.40−2.30 (m, 1H), 2.32 (d, $J = 1.3$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.97 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.9, 171.7, 132.4, 124.1, 71.3, 65.6, 44.7, 30.7, 30.6, 24.0, 18.9, 17.6; HRMS (FAB) calcd for $C_{12}H_{18}BrNO_2S_2$ [M + Na] 373.9861, found 373.9866. Anal. Calcd for $C_{12}H_{18}BrNO_2S_2$: C, 40.91; H, 5.15; N, 3.97. Found: C, 40.95; H, 5.07; N, 3.93.

Silylated Aldol Product 25. To a cooled (0 °C) solution of alcohol **24** (24.52 g, 69.7 mmol) in 280 mL of CH_2Cl_2 was added 2,6-lutidine (8.1 mL, 69.4 mmol), followed by triisopropylsilyl triflate (18.7 mL, 69.4 mmol). After warming to ambient temperature for 40 min, the reaction was poured into a brine solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (19:1 → 9:1) gave 35.13 g (99%) of silyl ether **25** as a yellow oil: TLC $R_f = 0.56$ (1:4 EtOAc/hexanes); $[\alpha]^{D}_{26}$ +209.8° (*c* 2.97, $CHCl_3$); IR (thin film) 2962, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (dq, $J = 1.4$, 9.0 Hz, 1H), 5.09 (ddd, $J = 1.2$, 6.6, 7.8 Hz, 1H), 5.04 (ddd, $J = 5.6$, 7.2, 9.2 Hz, 1H), 3.64 (dd, $J = 7.2$, 16.5 Hz, 1H), 3.49 (dd, $J = 7.8$, 11.4 Hz, 1H), 3.39 (dd, $J = 5.7$, 16.5 Hz, 1H), 3.05 (dd, $J = 1.3$, 11.5 Hz, 1H), 2.42−2.30 (m, 1H), 2.32 (d, $J = 1.3$ Hz, 3H), 1.06 (s, 21H), 1.02 (d, $J = 6.5$ Hz, 3H), 0.99 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.7, 170.7, 135.0, 121.5, 71.5, 67.4, 46.1, 30.7, 24.2, 19.0, 17.9, 17.8, 17.7, 12.2. Anal. Calcd for $C_{21}H_{38}BrNO_2S_2Si$: C, 49.59; H, 7.54; N, 2.75. Found: C, 49.59; H, 7.55; N, 2.79.

Amide 26. Gaseous ammonia was bubbled through a cooled (0 °C) solution of silyl ether **25** (35.13 g, 69 mmol) in 3.5 L of CH_2Cl_2 using a Teflon tube until starting material could no longer be detected by TLC analysis. Concentration in vacuo gave a brown oil that was dissolved in hot EtOAc/hexanes. On cooling, the majority of the thiazolidinethione auxiliary could be recovered as a crystalline solid. Concentration of the mother liquor and flash chromatography on SiO_2 eluting with hexanes/EtOAc (3:1 → 3:17) gave 22.55 g (90%) of amide **26** as a white crystalline solid: mp 67.0−68.5 °C (hexanes); $R_f = 0.22$ (3:7 EtOAc/hexanes); $[\alpha]^{26}_D$ +18.4° (*c* 1.03, $CHCl_3$); IR (thin film) 3365−3196, 2959, 1678 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.35−6.18 (br s, 1H), 6.18−6.01 (br s, 1H), 5.96 (dq, $J = 1.2$, 9.0 Hz, 1H), 4.82 (dt, $J = 5.6$, 9.0 Hz, 1H), 2.47 (dd, $J = 5.3$, 14.9 Hz, 1H), 2.42 (dd, $J = 5.9$, 14.9 Hz, 1H), 2.26 (d, $J = 1.2$ Hz, 3H), 1.07 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 134.4, 121.8, 67.8, 44.8, 24.2, 18.1, 18.0, 12.4; HRMS (FAB) calcd for $C_{15}H_{30}{}^{81}BrNO_2Si$ [M + H] 366.1287, found 366.1283. Anal. Calcd for $C_{15}H_{30}BrNO_2SSi$: C, 49.44; H, 8.30; N, 3.84. Found: C, 49.37; H, 8.32; N, 3.89.

Thioamide 27. To a solution of amide **26** (22.55 g, 62 mmol) in 620 mL of THF was added Belleau's reagent (16.0 g, 30 mmol) as a solid at 25 °C. After 30 min, the reaction was diluted with Et_2O and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 3:17) gave 16.96 g (72%) of thioamide **27** as an unstable yellow oil: $R_f = 0.26$ (1:4 EtOAc/hexanes); IR (thin film) 3296, 3182, 2942, 1616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00−7.75 (bs, 1H), 7.90−7.65 (bs, 1H), 5.95 (dq, $J = 1.2$, 8.7, 1H), 4.87 (dt, $J = 5.4$, 9.0, 1H), 2.96 (dd, $J = 6.2$, 14.6, 1H), 2.89 (dd, $J = 5.0$, 14.3, 1H), 2.29 (d, $J = 1.2$, 3H), 1.07 (s, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.7, 133.5, 122.2, 69.8, 53.3, 24.2, 17.9, 12.1; HRMS (FAB) calcd for $C_{15}H_{30}{}^{81}BrNOSSi$ [M + H] 382.1059, found 382.1050.

Thiazole Ester 28. To a cooled (−30 °C) solution of thioamide **27** (17.0 g, 44.7 mmol) in 400 mL of dimethoxyethane was added $KHCO_3$ (22.4 g, 224.0 mmol) as a solid, followed by 16.8 mL of ethyl bromopyruvate (134.0 mmol). The reaction mixture was warmed to 25 °C until TLC analysis indicated the absence of thioamide. The solution was recooled to −30 °C, and 35 mL of 2,6-lutidine (313.0 mmol) and 25 mL of trifluoroacetic anhydride (179.0 mmol) were added sequentially. After 1 h, the solution was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the orange liquid by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 →

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(66) For the preparation of stannous triflate, see: (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757−6761. (b) Batchelor, R. J.; Ruddick, J. N. R.; Sams, J. R.; Aube, F. *Inorg. Chem.* **1977**, *16*, 1414.

6:1) gave 15.3 g (72%) of ester **28** as a yellow oil: R_f = 0.14 (1:9 EtOAc/hexanes); $[\alpha]^{26}_D$ +37.8° (*c* 0.74, $CHCl_3$); IR (thin film) 2939, 2865, 1734, 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 5.87 (dq, *J* = 1.2, 8.9 Hz, 1H), 4.82 (dt, *J* = 5.9, 8.9 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 3.33 (dd, *J* = 6.3, 14.4 Hz, 1H), 3.22 (dd, *J* = 5.4, 14.4 Hz, 1H), 2.17 (d, *J* = 1.2 Hz, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.02 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 161.5, 146.7, 134.5, 128.0, 122.0, 69.6, 61.4, 42.0, 24.2, 18.0, 17.9, 14.5, 12.4; HRMS (FAB) calcd for $C_{20}H_{34}{}^{79}BrNO_3SSi$ [M + H] 476.1290, found 476.1300. Anal. Calcd for $C_{20}H_{34}BrNO_3SSi$: C, 50.41; H, 7.19; N, 2.94. Found: C, 50.33; H, 7.20; N, 2.86.

Thiazole Aldehyde 29. To a cooled (−90 °C) solution of thiazole **28** (5.37 g, 11.29 mmol) in 115 mL of CH_2Cl_2 was added 38 mL of DIBAl-H solution (36.10 mmol, 0.95 M in CH_2Cl_2) down the side of the flask over a 2-h period. After 3 h, the reaction was quenched by *slow and careful addition* of MeOH (4 mL) at −90 °C. The solution was diluted with 100 mL of CH_2Cl_2 and stirred vigorously overnight with 75 mL of Rochelle's salt solution and 75 mL of pH 7 buffer. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 4:1) gave 3.90 g (80%) of aldehyde **29** as a yellow oil: R_f = 0.55 (3:7 EtOAc/hexanes); IR (thin film) 2946, 2867, 1704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.11 (s, 1H), 5.89 (dq, *J* = 1.4, 8.9 Hz, 1H), 4.85 (dt, *J* = 5.9, 8.8 Hz, 1H), 3.32 (dd, *J* = 6.3, 14.4 Hz, 1H), 3.22 (dd, *J* = 5.4, 14.4 Hz, 1H), 2.17 (d, *J* = 1.2 Hz, 3H), 1.02 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 167.3, 154.5, 134.3, 128.5, 121.8, 69.4, 41.8, 23.9, 17.8, 17.7, 12.2; HRMS (FAB) calcd for $C_{18}H_{30}{}^{79}BrNO_2SSi$ [M + Na] 454.0876, found: 454.0836.

Phosphonate 30. To a flask equipped with a reflux condenser and charged with (+)-(*S*)-3-(bromoacetyl)-4-phenyl-2-oxazolidinone[67] (7.13 g, 25.1 mmol) was added freshly distilled triethyl phosphite (13.5 mL, 78.7 mmol), and the mixture was heated to 55−60 °C. After 3 h, the reaction was concentrated by vacuum distillation to remove excess triethyl phosphite. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (1:0 → 1:1) gave 6.52 g (76%) of phosphonate **30** as an orange oil: R_f = 0.14 (1:2 EtOAc/hexanes); $[\alpha]^{26}_D$ +64.6° (*c* 2.43, $CHCl_3$); IR (thin film) 2988, 1782, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 5.47 (dd, *J* = 3.9, 8.7 Hz, 1H), 4.71 (t, *J* = 8.7 Hz, 1H), 4.28 (dd, *J* = 3.9, 9.3 Hz, 1H), 3.79 (app sext, *J* = 13.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4 (J_P = 6.5 Hz), 153.5, 138.4, 129.0, 128.6,126.0, 69.8, 57.8, 34.4 (J_P = 129.7 Hz) 16.2 (J_P = 3.0 Hz); ^{31}P NMR (121 MHz, $CDCl_3$, $H_3PO_{4(ext)}$) δ 19.8; HRMS (FAB) calcd for $C_{15}H_{20}NO_6P$ [M + H] 342.1106, found 342.1118.

Enimide 31. To a solution of phosphonate **30** (8.4 g, 24.6 mmol) in 150 mL of THF was added 9.8 mL of sodium bis(trimethylsilyl)-amide solution (19.7 mmol, 2.0 M in THF) at 25 °C, generating an exotherm. After 15 min, a solution of aldehyde **29** (7.1 g, 16.4 mmol) in 14 mL of THF was added via cannula. After 1.5 h, the reaction was quenched with pH 7 buffer and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 4:1) gave 9.12 g (90%) of imide **31** as a white crystalline solid: mp 123−124.5 °C (hexanes); R_f = 0.26 (3:7 EtOAc/hexanes); $[\alpha]^{26}_D$ −79.2° (*c* 1.30, $CHCl_3$); IR (thin film) 2944, 1780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 15.3, 1H), 7.7 (d, *J* = 15.3, 1H), 7.4 (m, 5H), 5.7 (dd, *J* = 1.5, 9.0, 1H), 5.5 (dd, *J* = 3.9, 8.7, 1H), 4.0 (dt, *J* = 6.3, 8.7, 1H), 4.7 (t, *J* = 8.85, 1H), 4.3 (dd, *J* = 3.9, 8.6, 1H), 3.29 (dd, *J* = 6.3, 14.4, 1H), 2.16 (d, *J* = 1.2 Hz, 3H), 1.03 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 164.9, 153.5, 151.5, 139.2, 138.0, 134.5, 129.0, 128.3, 125.9, 123.2, 121.9, 118.8, 69.9, 69.6, 57.7, 41.9, 24.1, 17.9, 17.8, 12.2; HRMS (FAB) calcd for $C_{29}H_{39}{}^{79}BrN_2O_2SSi$ [M + H] 619.1661, found 619.1671.

Imide 34. To a slurry of copper(I) bromide−dimethyl sulfide complex (15.8 g, 74.3 mmol) in 231 mL of THF was added 90 mL of dimethyl sulfide, and the solution was cooled to −78 °C. Methylmagnesium bromide (30.8 mL, 92.3 mmol, 3.0 M in Et_2O) was added, resulting in a yellow slurry. After being stirred for 15 min, the heterogeneous mixture was warmed to 0 °C for 15 min and then recooled to −78 °C before being transferred, via a 16-gauge cannula, to a cooled (−78 °C) solution of imide **32** in 90 mL of THF and 48 mL of CH_2Cl_2. The reaction was warmed to −30 °C for 3.5 h and quenched *slowly* with pH 7 buffer and saturated NH_4Cl solution. The mixture was extracted with EtOAc, and the combined organic layers were washed several times with a saturated NH_4Cl solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/Et_2O (7:3 → 6:4) gave 7.91 g (77%) of thiazole **34** (major diastereomer) as a clear, colorless oil: $[\alpha]^{26}_D$ +21.5° (*c* 0.93, $CHCl_3$); IR (thin film) 2947, 1785, 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.23 (m, 5H), 5.86 (app dd, *J* = 1.2, 8.7 Hz, 1H), 5.38 (dd, *J* = 3.6, 8.7 Hz, 1H), 4.78 (dt, *J* = 6.3, 8.7 Hz, 1H), 4.64 (t, *J* = 8.7 Hz, 1H), 4.25 (dd, *J* = 3.6, 8.7 Hz, 1H), 3.54−3.40 (m, 2H), 3.21 (dd, *J* = 6.5, 14.3 Hz, 1H), 3.20−3.06 (m, 1H), 3.07 (dd, *J* = 6.5, 14.3 Hz, 1H), 2.07 (d, *J* = 1.2 Hz, 3H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 165.0, 160.1, 153.5, 138.9, 134.8, 129.0, 128.5, 125.8, 121.3, 112.3, 70.1, 69.8, 57.5, 42.0, 41.9, 31.9, 23.9, 20.0, 17.9, 17.8, 12.2; HRMS (FAB) calcd for $C_{30}H_{43}{}^{79}BrN_2O_4SSi$ [M + Na] 635.1974, found: 635.1964. Anal. Calcd for $C_{30}H_{43}BrN_2O_4SSi$: C, 56.67; H, 6.82; N, 4.41. Found C, 56.69; H, 6.79; N, 4.32. Data for minor diastereomer: 1.23 g (12%) as a clear, colorless oil; $[\alpha]^{26}_D$ +24.1° (*c* 1.58, $CHCl_3$); IR (thin film) 2943, 2865, 1781, 1703, 1378, 1196, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.21 (m, 5H), 6.74 (s, 1H), 5.86 (dd, *J* = 1.2, 9.0 Hz, 1H), 5.42 (dd, *J* = 3.8, 9.0 Hz, 1H), 4.78 (dt, *J* = 6.3, 8.7 Hz, 1H), 4.68 (t, *J* = 9.0 Hz, 1H), 4.25 (dd, *J* = 3.8, 9.0 Hz, 1H), 3.56−3.38 (m, 2H), 3.22 (dd, *J* = 6.0, 14.1 Hz, 1H), 3.22−3.07 (m, 1H), 3.05 (dd, *J* = 6.9, 14.1 Hz, 1H), 2.04 (d, *J* = 1.2 Hz, 3H), 1.28 (d, *J* = 6.9 Hz, 1H) 1.02 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 165.0, 160.1, 153.6, 138.9, 134.8, 129.0, 128.6, 125.8, 121.4, 112.3, 70.1, 69.9, 57.5, 42.0, 41.9, 31.9, 23.9, 20.0, 17.9, 17.8, 12.2; HRMS (FAB) calcd for $C_{30}H_{43}{}^{79}BrN_2O_4SSi$ [M + Na] 635.1974, found 635.1970.

Weinreb Amide 35. To a cooled (−10 °C) suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.31 g, 23.8 mmol) in 75 mL of CH_2Cl_2 was added 11.8 mL of trimethylaluminum (23.6 mmol, 2.0 M in toluene) solution, with concomitant evolution of gas. The resultant homogeneous solution was stirred at 25 °C for 30 min. A solution of imide **34** (7.54 g, 11.9 mmol) in 75 mL of CH_2Cl_2 was added at −20 °C. After 3.5 h, a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.15 g, 11.8 mmol) and 5.9 mL of trimethylaluminum (11.8 mmol) in CH_2Cl_2, prepared in a similar fashion as previously described, was added. After 4.5 h, the reaction mixture was quenched *slowly* with 50 mL of 1 M tartaric acid solution, with concomitant evolution of gas. After being stirred vigorously for 10 h, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/EtOAc (3:1 → 1:4) gave 5.22 g (82%) of amide **35** (major product) as a clear, colorless oil: R_f = 0.20 (3:7 EtOAc/hexanes); $[\alpha]^{26}_D$ −12.5° (*c* 0.96, $CHCl_3$); IR (thin film) 2937, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H), 5.88 (dq, *J* = 1.2, 9.0 Hz, 1H), 4.79 (dt, *J* = 6.3, 9.0 Hz, 1H), 3.66 (s, 3H), 3.52 (sext, *J* = 6.6 Hz, 1H), 3.24 (dd, *J* = 5.9, 14.1 Hz, 1H), 3.16 (s, 3H), 3.10 (dd, *J* = 6.6, 14.1 Hz, 1H), 2.96 (dd, *J* = 6.2, 15.9 Hz, 1H), 2.61 (dd, *J* = 8.1, 15.9 Hz, 1H), 2.07 (d, *J* = 1.2 Hz, 3H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 165.1, 160.9, 135.0, 121.3, 112.6, 70.3, 61.3, 42.1, 38.6, 32.4, 24.0, 20.4, 18.0, 17.9, 12.3; HRMS (FAB) calcd for $C_{23}H_{41}{}^{81}BrN_2O_3SSi$ [M + H] 535.1849, found 535.1862. Amide **37** (minor product) was isolated (1.48 g, 18%) as a white crystalline solid: mp 99.5−102 °C (hexanes); R_f = 0.31 (2:3 EtOAc/hexanes); $[\alpha]^{26}_D$ +17.8° (*c* 1.07, $CHCl_3$); IR (thin film) 3500−3100, 2947, 2863, 1715, 1651, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 6.81 (s, 1H), 6.81 (s, 1H), 6.76 (br d, *J* = 7.8 Hz, 1H), 5.86 (app dd, *J* = 1.2, 9.0 Hz, 1H), 5.36−5.22 (m, 1H), 5.04 (dt, *J* = 6.3, 8.7 Hz, 1H), 4.36 (dd, *J* = 7.4, 11.3 Hz, 1H), 4.22 (dd, *J* = 4.8, 11.3 Hz, 1H), 3.56 (s, 3H), 3.41 (sext, *J* = 6.9 Hz, 1H), 3.21 (dd,

(67) Pridgen, L. N.; Abdel-Magid, A. F.; Lantos, I.; Shilcrat, S.; Eggleston, D. R. *J. Org. Chem.* **1993**, *58*, 5107−5117.

J = 6.3, 14.2 Hz, 1H), 3.083 (s, 3H), 3.08 (dd, J = 6.3, 14.1 Hz, 1H), 2.74 (dd, J = 6.6, 14.1 Hz, 1H), 2.44 (dd, J = 7.2, 14.1 Hz, 1H), 2.07 (s, 3H), 1.30 (d, J = 6.9 Hz, 3H), 1.02 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 165.5, 160.2, 156.8, 138.3, 134.7, 128.6, 127.7, 126.6, 121.2, 112.8, 70.1, 67.5, 61.4, 52.6, 43.5, 41.8, 35.4, 33.3, 23.8, 20.0, 17.9, 17.8, 12.2; HRMS (FAB) calcd for $C_{32}H_{50}{}^{79}BrN_3O_5SSi$ [M + H] 696.2501, found 696.2494.

Aldehyde 36. To a cooled (−78 °C) solution of amide **35** (4.20 g, 7.9 mmol) in 6.0 mL of THF was added 17.0 mL (16.2 mmol) of DIBAl-H (0.95 M in CH_2Cl_2), and the resulting solution was stirred for 1.3 h. Excess DIBAl-H was quenched by the addition of 7 mL of acetone, and the solution was transferred via cannula to a vigorously stirred mixture of 30 mL of 1 M aqueous tartaric acid and 90 mL of EtOAc. After 3.5 h, the layers were separated, and the aqueous layer was extracted with three portions of EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 6:1) gave 3.56 g (95%) of aldehyde **36** as a pale yellow oil: R_f = 0.50 (3:7 EtOAc/hexanes); $[\alpha]^{26}_D$ −6.4° (c 1.10, $CHCl_3$); IR (thin film) 2944, 1727 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.81 (s, 1H), 5.87 (app dd, J = 1.2, 9.0 Hz, 1H), 4.78 (dt, J = 6.2, 8.8 Hz, 1H), 3.52 (sextet, J = 6.9 Hz, 1H), 3.23 (dd, J = 6.3, 13.8 Hz, 1H), 3.09 (dd, J = 6.3, 13.8 Hz, 1H), 2.92 (ddd, J = 1.2, 6.6, 16.8 Hz, 1H), 2.61 (ddd, J = 2.1, 7.5, 16.8 Hz, 1H), 2.08 (d, J = 1.2 Hz, 3H), 1.35 (d, J = 7.2 Hz, 3H), 1.02 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 165.5, 159.8, 134.8, 121.2, 112.5, 70.1, 50.1, 41.9, 30.7, 23.8, 20.1, 17.9, 17.8, 12.2; HRMS (FAB) calcd for $C_{21}H_{36}{}^{79}BrNO_2SSi$ [M + Na] 496.1317, found 496.1323.

Enyne Amine 39. To a cooled (−78 °C) solution of alcohol **38** (6.0 g, 63.4 mmol) in 150 mL of THF was added 25.2 mL of *n*-butyllithium (63.0 mmol, 2.5 M in hexanes) via syringe pump over a 1-h period. To the resulting orange solution was added a solution of *p*-toluenesulfonyl chloride (12.0 g, 63.0 mmol) in 60 mL of THF. Dimethylamine was then bubbled through the reaction for 15 min, after which time the reaction was transferred to a sealed tube via cannula and allowed to warm to 25 °C. After 1.5 h, the tube was cooled to −78 °C and opened, and the mixture was concentrated in vacuo to give an orange solid, which was dissolved in distilled water. This solution was acidified with 10% HCl to pH 3 and extracted with Et_2O (4 × 20 mL). The aqueous layer was basified with 20% NaOH and extracted with Et_2O (5 × 20 mL). The latter organic layers were combined and washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give 5.26 g (69%) of amine **39** as a volatile, pale yellow liquid that was of sufficient purity to be employed in the next step without further purification: R_f = 0.41 (5:30:65 Et_3N/acetone/hexanes); IR (thin film) 3297, 2769, 2096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (dtq, J = 0.52, 1.52, 6.96 Hz, 1H), 2.98 (d, J = 6.84 Hz, 2H), 2.81 (s, 1H), 2.23 (s, 6H), 1.83−1.82 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.4, 119.5, 86.4, 74.6, 57.1, 45.5, 17.6; HRMS (EI) calcd for $C_8H_{13}N$ 123.1048, found 123.1048.

Dienyl Stannane 4. To a cooled (−60 °C) suspension of CuCN (656 mg, 7.32 mmol) in 8.6 mL of THF was added 7.1 mL of *n*-butyllithium solution (14.6 mmol, 2.05 M in hexanes) over a 15-min period. The solution was allowed to warm to −40 °C, and 3.93 mL of tri-*n*-butyltin hydride (14.6 mmol) was added, resulting in a deep gold color. After 1 h, a solution of amine **39** (1.0 g, 8.1 mmol) in 14.5 mL of THF was added via cannula. After 1 h, the reaction was quenched with 15 mL of saturated NH_4Cl solution and warmed to 25 °C. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with 20% NH_4OH (15 mL) and brine (15 mL) and then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with Et_3N/acetone/hexanes (1:1:18 → 1:6:13) gave 2.38 g (71%) of stannane **4** as a yellow oil (9:1 ratio of regiosiomers): R_f = 0.39 (1:9 MeOH/Et_2O); IR (thin film) 2954, 2924 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (d, J = 19.2 Hz, 1H), 6.75 (d, J = 19.2 Hz, 1H), 5.54 (t, J = 6.5 Hz, 1H), 3.04 (d, J = 6.9 Hz, 2H), 2.25 (s, 6H), 1.77 (s, 3H), 1.57 (m, 6H), 1.40−1.22 (m, 6H), 0.97−0.80 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 137.5, 129.2, 126.3, 57.3, 45.4, 29.1, 27.3, 13.7, 11.9, 9.4; HRMS (FAB) calcd for $C_{20}H_{41}NSn$ [M + H] 416.2343, found 416.2343.

Aldol Adduct 48. To a cooled (−50 °C) suspension of stannous triflate (6.25 g, 15.0 mmol) in 30 mL of CH_2Cl_2 was added *N*-ethylpiperidine (1.40 mL, 120 mmol) and a solution of thiazolidine thione **21**[26] (3.3 g, 16.3 mmol) in 10 mL of CH_2Cl_2, and the solution was stirred for 4 h. After the reaction mixture was cooled to −78 °C, a solution of aldehyde **36** (3.55 g, 7.5 mmol) was added via cannula, and the mixture was stirred for 1 h. The reaction mixture was quenched with 45 mL of pH 7 buffer and warmed to 25 °C. The solids were filtered through Celite with CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 6:4) gave 4.57 g (90%) of alcohol **48** as a yellow oil: R_f = 0.31 (1:2 EtOAc/hexanes); $[\alpha]^{26}_D$ +151.2° (c 1.29, $CHCl_3$); IR (film) 3018, 1708, 1219 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 5.88 (dd, J = 1.2, 6.0 Hz, 1H), 5.15 (app t, J = 6.6 Hz, 1H), 4.77 (dt, J = 6.3, 8.7 Hz, 1H), 4.38−4.21 (m, 1H), 3.75−3.62 (br s, 1H), 2.56 (dd, J = 2.6, 17.6 Hz, 1H), 3.52 (app dd, J = 8.1, 14.3 Hz, 1H), 3.29−3.12 (m, 2H), 3.10 (dd, J = 6.5, 14.3 Hz, 1H), 3.03 (dd, J = 1.2, 11.6 Hz, 1H), 2.37 (sext, J = 6.9 Hz, 1H), 2.09 (d, J = 1.2 Hz, 3H), 2.00 (ddd, J = 6.6, 9.3, 13.8 Hz, 1H), 1.71 (ddd, J = 3.9, 7.4, 13.8 Hz, 1H), 1.33 (d, J = 6.9 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 1.02 (s, 21H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 172.8, 165.6, 161.3, 134.7, 121.4, 112.1, 71.4, 70.0, 66.5, 46.0, 43.2, 41.7, 32.8, 30.8, 23.9, 20.0, 19.1, 17.9, 17.80, 17.75, 12.2; HRMS (FAB) calcd for $C_{29}H_{49}{}^{81}BrN_2O_3S_3Si$ [M + Na] 701.1736, found 701.1768.

Benzyloxyamide 49. To a cooled (0 °C) suspension of *O*-benzylhydroxylamine hydrochloride (8.4 g, 52.6 mmol) in 60 mL of CH_2Cl_2 was added 9 mL of Et_3N. After warming to 25 °C for 30 min, the solution was recooled (0 °C), and a solution of alcohol **48** in 20 mL of CH_2Cl_2 was added via cannula. The ice bath was removed, and the solution was stirred at ambient temperature for 27 h. The solution was quenched with 20 mL of pH 7 buffer and diluted with 50 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/EtOAc (3:1 → 1:4) gave 2.18 g (90%) of amide **49** as a pale yellow oil: R_f = 0.23 (1:4-acetone/hexanes); $[\alpha]^{26}_D$ +7.1° (c 1.13, $CHCl_3$); IR (thin film) 3100−3600, 2943, 1660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.30 (m, 5H), 6.79 (s, 1H), 5.86 (d, J = 9.0 Hz, 1H), 5.44 (br s, 1H), 4.90 (s, 2H), 4.77−4.68 (m, 1H), 4.15−4.00 (m, 2H), 3.21 (dd, J = 5.9, 14.4 Hz, 1H), 3.15−3.00 (m, 1H), 3.08 (dd, J = 6.3, 14.4 Hz, 1H), 2.40−2.20 (m, 2H), 2.06 (s, 3H), 1.90−1.73 (m, 1H), 1.73−1.55 (m, 1H), 1.31 (d, J = 6.9 Hz, 3H), 1.02 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 165.7, 160.8, 135.4, 134.5, 129.0, 128.4, 128.35, 121.4, 112.4, 78.0, 69.9, 67.4, 43.8, 41.6, 33.6, 23.8, 20.3, 17.9, 17.7, 12.1; HRMS (FAB) calcd for $C_{30}H_{47}{}^{79}BrN_2O_4SSi$ [M + H] 661.2187, found 661.2187.

Benzyloxy-*β*-Lactam 50. To a solution of amide **49** (1.54 g, 2.4 mmol) in 25 mL of THF were added triphenylphosphine (846.4 mg, 3.2 mmol) and 0.65 mL of DIAD (3.3 mmol), sequentially, resulting in a deep red solution. After 2.5 h, 10 mL of pH 7 buffer was added, and the mixture was diluted with 25 mL of EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 3:1) gave 1.37 g (92%) of lactam **50** as a pale yellow oil: R_f = 0.44 (1:2 EtOAc/hexanes); $[\alpha]^{26}_D$ +24.7° (c 1.01, $CHCl_3$); IR (thin film) 2946, 1771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.48 (m, 5H), 6.68 (s, 1H), 5.86 (dq, J = 1.4, 9.0 Hz, 1H), 4.98 (d, J = 10.8 Hz, 1H), 4.93 (d, J = 11.1 Hz, 1H), 4.77 (dt, J = 6.0, 8.7 Hz, 1H), 3.52−3.59 (m, 1H), 3.23 (dd, J = 6.0, 14.1 Hz, 1H), 3.12 (dd, J = 6.2, 14.3 Hz, 1H), 2.97 (sext, J = 7.1 Hz, 1H), 2.56 (dd, J = 5.1, 13.8 Hz, 1H), 2.11 (dd, J = 2.1, 13.8 Hz, 1H), 2.10 (d, J = 1.2 Hz, 3H), 1.22 (d, J = 6.6 Hz, 3H), 1.02 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 164.0, 160.0, 135.2, 134.7, 129.2, 128.9, 128.5, 121.1, 112.8, 78.0, 69.9, 56.6, 42.0, 39.9, 38.2, 33.8, 23.9, 21.0, 17.9, 17.8,

12.2; HRMS (FAB) calcd for $C_{30}H_{45}{}^{79}BrN_2O_3SSi$ [M + Na] 643.2001, found: 643.2022.

Lactam 51. To a solution of β-lactam **50** (1.37 g, 2.20 mmol) in 20 mL of THF and 1.0 mL (25 equiv, 55.5 mmol) of deoxygenated water was added a solution of SmI_2 (~35.0 mL, 10.5 mmol, 0.3 M in THF) at 0 °C until a dark blue color persisted. After 1 h, the solution was partitioned between EtOAc (60 mL) and saturated $NaHCO_3$ (40 mL or enough to dissolve solids). The layers were separated, and the organic layer was washed with saturated $Na_2S_2O_3$ and brine and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on SiO_2 eluting with hexanes/EtOAc (3:1 → 1:1) to give 1.079 g (96%) of the β-lactam **51** as a pale yellow oil: R_f = 0.30 (1:1 EtOAc/hexanes); $[\alpha]^{26}_D$ +30.6° (*c* 0.98, $CHCl_3$); IR (thin film) 3244, 2946, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 5.96 (s, 1H), 5.87 (dq, *J* = 1.4, 8.9 Hz, 1H), 4.76 (dt, *J* = 6.2, 8.9 Hz, 1H), 3.53 (ddt, *J* = 2.7, 5.4, 8.1 Hz, 1H), 3.24 (dd, *J* = 6.0, 14.4 Hz, 1H), 3.12 (dd, *J* = 6.5, 14.4 Hz, 1H), 3.08−2.97 (m, 1H), 2.97 (ddd, *J* = 2.4, 5.1, 14.7 Hz, 1H), 2.48 (ddd, *J* = 0.9, 2.4, 15.0 Hz, 1H), 2.10 (d, *J* = 1.2 Hz, 3H), 2.04 (ddd, *J* = 5.4, 8.7, 14.0 Hz, 1H), 1.88 (ddd, *J* = 5.7, 8.1, 13.8 Hz, 1H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.03 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 165.5, 160.2, 134.8, 121.2, 112.6, 70.0, 46.4, 43.7, 42.7, 42.0, 34.1, 23.9, 20.7, 17.9, 17.8, 12.2; HRMS (FAB) calcd for $C_{23}H_{39}{}^{79}BrN_2O_2SSi$ [M + Na] 537.1582, found: 537.1594.

Boc-Lactam 52. To a solution of β-lactam **51** (1.08 g, 2.09 mmol) in 10 mL of CH_2Cl_2 was added a solution of di-*tert*-butyl dicarbonate (2.73 g, 12.5 mmol) and DMAP (38.2 mg, 0.31 mmol) in 10 mL of CH_2Cl_2 via cannula at ambient temperature. After 5 min, 1.5 mL of Et_3N (10.8 mmol) was added. After 4 h, the reaction was quenched with 20 mL of pH 7 buffer. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 3:1) gave 1.19 g (92%) of β-lactam **52** as a pale yellow oil: R_f = 0.15 (20:80 EtOAc/hexanes); $[\alpha]^{26}_D$ −26.7° (*c* 1.01, $CHCl_3$); IR (thin film) 2943, 2865, 1811, 1722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 1H), 5.88 (dq, *J* = 1.2, 8.9 Hz, 1H), 4.78 (dt, *J* = 6.0, 9.0 Hz, 1H), 3.96 (ddt, *J* = 3.3, 6.2, 9.6 Hz, 1H), 3.22 (dd, *J* = 6.2, 14.3 Hz, 1H), 3.15 (dd, *J* = 6.2, 14.3 Hz, 1H), 3.09−2.98 (m, 1H), 2.85 (dd, *J* = 6.2, 16.1 Hz, 1H), 2.42 (ddd, *J* = 3.6, 7.1, 13.4 Hz, 1H), 2.37 (dd, *J* = 3.5, 16.1 Hz, 1H), 2.12 (d, *J* = 1.5 Hz, 3H), 1.95 (ddd, *J* = 7.5, 9.9, 13.5 Hz, 1H), 1.52 (s, 9H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.02 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 164.5, 160.3, 148.0, 134.8, 112.7, 82.9, 69.9, 50.5, 42.3, 41.9, 39.9, 33.7, 28.0, 23.9, 20.4, 17.9, 17.8, 12.2; HRMS (FAB) calcd for $C_{28}H_{47}{}^{79}BrN_2O_4SSi$ [M + Na] 637.2107, found 637.2101.

Boc-Lactam Alcohol 7 (R = Boc). To a cooled (−20 °C) solution of lactam **52** (650.7 mg, 1.06 mmol) in 10 mL of THF was added 3.0 mL (3 mmol) of 1 M TBAF solution buffered with 20 mol % acetic acid. After 1.5 h, 3 mL of pH 7 buffer was added, and the mixture was warmed to 25 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/EtOAc (3:1 → 1:3) gave 463.3 mg (95%) of alcohol **7** (R = Boc) as a white foam: R_f = 0.18 (1:1 EtOAc/hexanes); $[\alpha]^{26}_D$ −45.5° (*c* 1.01, $CHCl_3$); IR (thin film) 3944, 2975, 1802, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (s, 1H), 5.95 (app dq, *J* = 1.2, 8.7 Hz, 1H), 4.79−4.72 (m, 1H), 3.99−3.92 (m, 1H), 3.20−3.06 (m, 3H), 2.87 (dd, *J* = 5.9, 16.2 Hz, 1H), 2.44 (ddd, *J* = 3.9, 6.3, 13.5 Hz, 1H), 2.38 (dd, *J* = 3.3, 16.2 Hz, 1H), 2.33 (d, *J* = 1.2 Hz, 3H), 1.96 (dt, *J* = 8.7, 13.5 Hz, 1H), 1.52 (s, 9H), 1.35 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 164.4, 160.1, 147.9, 132.9, 124.1, 112.4, 83.2, 68.1, 50.3, 42.2, 39.7, 39.3, 33.4, 28.0, 24.0, 20.5; HRMS (FAB) calcd for $C_{19}H_{27}{}^{81}BrN_2O_4S$ [M + H] 461.0933, found 461.0941.

Ester 53. To a solution of 0.360 mL of DIAD (1.8 mmol) in 9.0 mL of THF was added triphenylphosphine (404.8 mg, 1.5 mmol) as a solid, and the solution was stirred at ambient temperature for 30 min. The resulting orange heterogeneous mixture was cooled (−20 °C), and a solution of acid **8** (310.2 mg, 1.1 mmol) in 6 mL of THF was added. After 5 min, a solution of alcohol **7** (356.2 mg, 0.78 mmol) in 8 mL of THF was added, and stirring was continued for 1 h. The reaction was quenched by addition of 5 mL of pH 7 buffer, followed by warming to 25 °C and diluting with 20 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 4:1) gave 490.3 mg (86%) of ester **53** as a pale yellow oil: R_f = 0.24 (25:75 EtOAc/hexanes); $[\alpha]^{26}_D$ +9.0° (*c* 1.98, $CHCl_3$); IR (thin film) 2923, 2202, 1811, 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 1H), 5.90 (dd, *J* = 1.2, 9.6 Hz, 1H), 5.81 (dt, *J* = 6.6, 9.6 Hz, 1H), 5.40 (s, 1H), 4.04−3.88 (m, 2H), 3.40 (dd, *J* = 6.6, 14.7 Hz, 1H), 3.27 (dd, *J* = 6.6, 14.7 Hz, 1H), 3.07 (sext, *J* = 6.9 Hz, 1H), 2.83 (dd, *J* = 5.9, 16.1 Hz, 1H), 2.41 (ddd, *J* = 3.9, 6.3, 13.5 Hz, 1H), 2.38−2.26 (m, 2H), 2.30 (d, *J* = 1.5 Hz, 3H), 2.21 (dd, *J* = 8.4, 13.1 Hz, 1H), 2.08−1.80 (m, 1H), 2.00 (d, *J* = 1.2 Hz, 3H), 1.52 (s, 9H), 1.42−1.24 (m, 2H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 163.8, 160.5, 159.1, 152.9, 148.0, 128.3, 127.8, 113.1, 104.7, 85.0, 83.1, 82.9, 71.0, 66.8, 50.4, 49.1, 42.3, 39.9, 37.6, 33.8, 28.0, 25.7, 24.3, 23.7, 20.8, 20.5, 17.9, −4.6, −4.9; HRMS (FAB) calcd for $C_{34}H_{53}{}^{81}BrN_2O_6SSi$ [M + Na] 747.2298, found 747.2286.

Alcohol 54. To a cooled (0 °C) solution of silyl ether **53** (481.3 mg, 0.66 mmol) in 7 mL of THF in a polypropylene Eppendorf tube was added 9.0 mL of HF·pyr/pyr/THF solution (3.8 g/6 mL/10 mL), and the solution was then warmed to 25 °C. After 22.5 h, the solution was transferred via cannula to a stirred slurry of 20 g of sea sand in 10 mL of EtOAc. After 1 h, the solvent was reduced with a stream of N_2. Purification of the residue by directly loading on a flash column of SiO_2 and eluting with hexanes/EtOAc (4:1 → 1:1) gave 347.3 mg (86%) of alcohol **54** as a pale yellow oil: R_f = 0.37 (1:1 EtOAc/hexanes); $[\alpha]^{26}_D$ +6.7° (*c* 1.18, $CHCl_3$); IR (thin film) 3017, 2204, 1804, 1707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 5.90 (dd, *J* = 1.2, 9.6 Hz, 1H), 5.86 (ddd, *J* = 5.6, 6.8, 9.6 Hz, 1H), 5.46 (app q, *J* = 1.2 Hz, 1H), 4.01 (sext, *J* = 6.4 Hz, 1H), 3.95−3.89 (m, 1H), 3.39 (dd, *J* = 6.8, 15.0 Hz, 1H), 3.26 (dd, *J* = 5.6, 15.0 Hz, 1H), 3.10−3.01 (m, 1H), 2.81 (dd, *J* = 6.0, 16.0 Hz, 1H), 2.41 (ddd, *J* = 3.8, 6.2, 13.4 Hz, 1H), 2.32 (d, *J* = 1.2 Hz, 3H), 2.34−2.26 (m, 3H), 2.02 (d, *J* = 1.2 Hz, 3H), 1.94 (ddd, *J* = 8.4, 9.6,13.2 Hz, 1H), 1.86 (br s, 1H), 1.52 (s, 9H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 163.7, 160.4, 158.7, 152.8, 147.9, 128.3, 127.7, 113.1, 104.5, 85.7, 83.2, 83.0, 70.9, 65.4, 50.5, 48.6, 42.3, 39.8, 37.5, 33.7, 27.9, 24.2, 23.3, 20.5; HRMS (FAB) calcd for $C_{28}H_{37}{}^{79}BrN_2O_6S$ [M + Na] 631.1453, found 631.1474.

Boc Macrocycle 55. A solution of Et_4NCN (684.7 mg, 4.38 mmol) in 23 mL of CH_2Cl_2 was stirred over freshly activated (flame-dried under high vacuum) powdered 4-Å molecular sieves for 1 h. To this solution was added alcohol **54** (288.9 mg, 0.47 mmol) as a solution at 0 °C, which had been stirred for 1 h over sieves. The solution was stirred for 9.5 h at ambient temperature and then filtered through Celite and concentrated in vacuo. The crude residue was purified by flash chromatography on SiO_2 eluting with hexanes/Et_2O (4:1 → 3:2) and gave 169.5 mg (59%) of Boc macrocycle **55** as a clear, colorless oil (another run beginning with 58.4 mg of alcohol **54** gave 39.9 mg (68%) of Boc macrocycle **55**): R_f = 0.22 (1:3 EtOAc/hexanes); $[\alpha]^{26}_D$ +41.8° (*c* 0.98, $CHCl_3$); IR (thin film) 2981, 2249, 2196, 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.06−5.94 (m, 2H), 5.34 (s, 1H), 5.33−5.22 (m, 1H), 4.66 (br d, *J* = 8.1 Hz, 1H), 3.81−3.62 (m, 1H), 3.32 (d, *J* = 5.7 Hz, 2H), 2.98 (sext, *J* = 6.9 Hz, 1H), 2.67 (dd, *J* = 6.3, 16.5 Hz, 1H), 2.45 (s, 3H), 2.38 (dd, *J* = 5.0, 16.5 Hz, 1H), 2.38−2.17 (m, 2H), 1.96−1.80 (m, 1H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.72−1.63 (m, 1H), 1.46 (s, 9H), 1.29 (app t, *J* = 6.0, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 163.6, 161.0, 157.7, 154.9, 153.1, 128.8, 127.0, 112.7, 105.8, 84.8, 83.9, 79.1, 70.3, 67.2, 46.5, 46.0, 40.8, 39.2, 37.5, 33.6, 28.4, 24.4, 20.7, 19.9, 19.8; HRMS (FAB) calcd for $C_{28}H_{37}{}^{79}BrN_2O_6S$ [M + Na] 631.1453, found 631.1479.

Diene Macrocycle 5. A slurry of macrocycle **55** (10.1 mg, 0.016 mmol) and $Pd/CaCO_3$ poisoned with Pb (10 mg) in 0.5 mL of MeOH was evacuated under water aspirator pressure and purged with H_2. After 14 h, the reaction was filtered through Celite, concentrated in vacuo, and purified by flash chromatography eluting with hexanes/Et_2O (1:1)

to give 10.1 mg (100%) of macrocycle **5** as a clear, colorless oil: R_f = 0.73 (1:1 EtOAc/hexanes); $[\alpha]^{26}_D$ −171.1° (*c* 1.35, $CHCl_3$); IR (thin film) 3440−3366, 2970, 2929, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 11.7 Hz, 1H), 6.80 (s, 1H), 6.75 (app dd, *J* = 11.4, 11.7 Hz, 1H), 5.94−6.05 (m, 2H), 5.47 (d, *J* = 11.4 Hz, 1H), 5.04−5.16 (m, 1H), 4.38−4.65 (br s, 1H), 3.13−3.38 (m, 1H), 3.21 (d, *J* = 4.2 Hz, 2H), 2.92−3.08 (m, 1H), 2.45 (d, *J* = 0.9 Hz, 3H), 2.42−2.47 (m, 1H), 2.34 (dd, *J* = 10.7, 13.5 Hz, 1H), 2.21 (dd, *J* = 3.8, 15.8 Hz, 1H), 1.83 (s, 3H), 1.56−1.91 (m, 2H), 1.42 (s, 9H), 1.244 (d, *J* = 6.9 Hz, 3H), 1.239 (d, *J* = 6.3 Hz, 3H), 1.18−1.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 164.6, 164.4, 161.3, 146.2, 141.1, 129.7, 126.8, 123.8, 114.8, 112.9, 112.3, 79.1, 68.8, 67.5, 47.7, 47.5, 41.3, 39.3, 38.4, 33.7, 29.7, 28.4, 24.6, 24.5, 22.7, 21.0, 16.8; HRMS (FAB) calcd for $C_{28}H_{39}{}^{79}BrN_2O_6S$ [M + Na] 633.1610, found 633.1613.

Boc-Pateamine A (60). A stock solution of 0.04 M Pd(0) catalyst was prepared from 20.7 mg of $Pd_2dba_3{\cdot}CHCl_3$ and 18.4 mg of trifurylphosphine in 1.0 mL of degassed THF. To a solution of bromide **5** (22.3 mg, 0.04 mmol) in 0.2 mL of degassed THF was added 0.09 mL of the Pd(0) catalyst (0.004 mmol, 0.04 M in THF), resulting in a yellow solution. After 15 min, a solution of stannane **4** (20.2 mg, 0.05 mmol) in 0.1 mL of THF was added, and the reaction was monitored by TLC. After 27 h, an additional amount of stannane **4** (10.4 mg, 0.03 mol) and 0.15 mL of Pd(0) catalyst stock solution (0.006 mmol) were transferred to the reaction. After 70 h, the reaction was diluted with Et_2O, filtered through Celite, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with EtOAc/MeOH (1:1 → 1:4) gave 7.6 mg (32%) of Boc-pateamine A (**60**) as a yellow oil: R_f = 0.33 (1:3:46-NH_4OH/MeOH/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 12.0 Hz, 1H), 6.79 (s, 1H), 6.73 (app dd, *J* = 11.2, 12.0 Hz, 1H), 6.37 (d, *J* = 16.0 Hz, 1H), 6.23 (d, *J* = 16.0 Hz, 1H), 6.16−6.29 (m, 1H), 5.64 (t, *J* = 6.4 Hz, 1H), 5.56 (d, *J* = 8.8 Hz, 1H), 5.51 (d, *J* = 11.2 Hz, 1H), 5.07−5.16 (m, 1H), 4.40−4.60 (br s, 1H), 3.26−3.38 (m, 1H), 3.2 (d, *J* = 6.8 Hz, 2H), 3.07 (d, *J* = 6.4 Hz, 2H), 2.97−3.11 (m, 1H), 2.25 (s, 6H), 2.12−2.40 (m, 4H), 1.98 (d, *J* = 0.8 Hz, 3H), 1.81 (d, *J* = 1.2 Hz, 6H), 1.71−1.91 (m, 1H), 1.43 (s, 9H), 1.24 (app d, *J* = 6.8 Hz, 6H), 1.18−1.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 164.6, 140.4, 134.1, 130.6, 128.3, 128.2, 123.9, 115.6, 112.5, 69.2, 67.5, 57.2, 47.7, 45.3, 39.1, 33.6, 30.9, 29.7, 28.4, 20.9, 16.6, 13.4, 12.7; HRMS (FAB) calcd for $C_{36}H_{53}{}^{79}BrN_3O_6S$ [M + H] 656.3733, found 656.3732.

Amino Macrocycle 56. To a flask charged with macrocycle **5** was added a cooled (0 °C) solution of 20% trifluoroacetic acid in CH_2Cl_2. After 3.5 h at this temperature, the reaction was diluted with chloroform and concentrated in vacuo. The residue was dissolved in MeOH and passed through a Bakerbond amino cartridge that was equilibrated with three column lengths of MeOH. Elution with MeOH and concentration in vacuo gave 4.4 mg (92%) of amine **56** as a clear colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 11.7 Hz, 1H), 6.74 (s, 1H), 6.71 (t, *J* = 11.7 Hz, 1H), 6.04 (td, *J* = 4.2, 9.3 Hz, 1H), 5.93 (app dd, *J* = 1.2, 9.3 Hz, 1H), 5.37 (d, *J* = 11.7 Hz, 1H), 5.06−5.19 (m, 1H), 3.21 (d, *J* = 12.0 Hz, 1H), 3.17 (dd, *J* = 4.2, 12.0 Hz, 1H), 2.90−3.12 (m, 1H), 2.49 (d, *J* = 1.2 Hz, 3H), 2.36 (dd, *J* = 2.6, 17.1 Hz, 1H), 2.28−2.56 (m, 2H), 2.09 (dd, *J* = 11.4, 17.1 Hz, 2H), 1.88 (m, 1H), 1.85 (d, *J* = 1.2 Hz, 3H), 1.45−1.65 (br s, 2H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.24−1.35 (m, 1H); HRMS (FAB) calcd for $C_{23}H_{37}{}^{79}BrN_2O_4S$ [M + H] 511.1266, found 511.1256.

TCBoc Diene 59. To a cooled (0 °C) flask charged with Boc macrocycle **55** (92.8 mg, 0.15 mmol) was added 2.5 mL of a precooled solution of 20% trifluoroacetic acid in CH_2Cl_2. After 11 h, the solution was diluted with 20 mL of chloroform and concetrated in vacuo. The crude residue was diluted with a small portion of MeOH and passed through a Bakerbond amino cartridge equilibrated with MeOH to give 72 mg of a clear colorless oil. A solution of crude amine **56** in 1 mL of CH_2Cl_2 was added to a slurry of 1,1-dimethyl-2,2,2-trichloroethyl chloroformate (181 mg, 0.75 mmol) in 1 mL of pyridine at 0 °C. After 4.5 h at 25 °C, the solution was concentrated under reduced pressure, diluted with 10% Et_2O/hexanes, and passed through a short pad of SiO_2 eluting with Et_2O/hexanes (1:9 → 1:0). To a solution of crude TCBoc macrocycle **57** in 2.5 mL of MeOH was added 89.7 mg of Pd/$CaCO_3$ poisoned with Pb. The flask was evacuated with a water aspirator and purged with H_2 four times. After 17 h, the reaction was diluted with EtOAc and filtered through Celite. Purification by SiO_2 eluting with Et_2O/hexanes (1:9 → 1:1), followed by further purification using preparative HPLC (SiO_2, 2-propanol/hexanes, 3:97 → 1:9), gave 54 mg (50% over three steps) of diene **59** as a clear, colorless oil: TLC R_f = 0.23 (1:2 EtOAc/hexanes); $[\alpha]^{26}_D$ −256.6° (*c* 1.09, $CHCl_3$); IR (thin film) 3432, 2973, 1727, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 12.0 Hz, 1H), 6.81 (s, 1H), 6.78 (t, *J* = 11.4 Hz, 1H), 6.04−5.90 (m, 2H), 5.48 (d, *J* = 11.4 Hz, 1H), 5.16−5.05 (m, 1H), 4.83 (d, *J* = 7.2 Hz, 1H), 3.46−3.31 (m, 1H), 3.25−3.14 (m, 2H), 3.07−2.93 (m, 1H), 2.52 (dd, *J* = 11.4, 15.6 Hz, 1H), 2.45 (s, 3H), 2.34 (dd, *J* = 11.1, 13.2 Hz, 1H), 2.23 (dd, *J* = 3.9, 15.3 Hz, 1H), 2.16 (d, *J* = 12.6 Hz, 1H), 1.24 (app d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 164.8, 164.5, 161.1, 153.1, 146.3, 141.1, 129.6, 126.9, 123.9, 114.9, 112.9, 106.7, 87.8, 68.8, 67.6, 48.0, 47.7, 40.8, 39.1, 38.4, 33.7, 24.6, 22.8, 21.7, 21.0, 16.9; HRMS (FAB) calcd for $C_{28}H_{36}{}^{79}BrCl_3N_2O_6S$ [M + Na] 736.0472, found 736.0501.

TCBoc-Pateamine A (61). To a flask charged with $Pd_2(dba)_3{\cdot}CHCl_3$ (17.0 mg, 0.016 mmol) and triphenyl arsine (41.1 mg, 0.13 mmol) was added 1.0 mL of degassed THF (by several freeze/thaw cycles). The final concentration of this palladium catalyst stock solution was ∼0.033 M. To a solution of bromide **59** (25.0 mg, 0.035 mmol) and stannane **4** (25.0 mg, 0.06 mmol) in 1.0 mL of degassed THF was added 0.110 mL of palladium catalyst solution. After 33 h, the reaction was diluted with 5 mL of Et_2O, filtered through Celite and concentrated in vacuo. The residue was purified by C18 reversed-phase chromatography eluting with water/MeOH (1:0 → 1:1 → 0:1) and then MeOH (0.1% TFA)/CH_2Cl_2 (1:0 → 1:1). The pateamine salt was loaded on an amino cartridge preequilibrated with MeOH and eluted with MeOH to give 6.6 mg (27%; 57% based on recovered bromide **59**, 14.1 mg) of TCBoc-pateamine A (**61**) as a pale yellow oil: R_f = 0.13 (1:5:20 Et_3N/acetone/hexanes); $[\alpha]^{26}_D$ −243.5° (*c* 0.46, $CHCl_3$); IR (thin film) 3431, 1733, 1729, 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 11.6 Hz, 1H), 6.80 (s, 1H), 6.77 (t, *J* = 12.0 Hz, 1H), 6.37 (d, *J* = 16.0 Hz, 1H), 6.23 (d, *J* = 16.0 Hz, 1H), 6.26−6.17 (m, 1H), 5.64 (t, *J* = 7.0 Hz, 1H), 5.56 (d, *J* = 9.2 Hz, 1H), 5.52 (d, *J* = 11.6 Hz, 1H), 5.17−5.08 (m, 1H), 4.83 (d, *J* = 6.4 Hz, 1H), 3.46−3.34 (m, 1H), 3.22 (d, *J* = 6.8 Hz, 2H), 3.11−2.98 (m, 1H), 3.07 (d, *J* = 6.8 Hz, 2H), 2.62−2.55 (m, 1H), 2.39−2.07 (m, 4H), 2.25 (s, 6H), 1.97 (s, 3H), 1.95−1.72 (m, 1H), 1.91 (s, 3H), 1.90 (s, 3H), 1.81 (s, 6H), 1.36−1.16 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 165.6, 164.7, 161.0, 153.0, 146.0, 140.5, 138.2, 136.1, 134.1, 130.7, 130.1, 128.6, 124.0, 115.7, 112.5, 106.7, 87.8, 69.1, 67.5, 57.1, 48.1, 47.7, 45.2, 40.3, 39.2, 39.1, 33.6, 23.0, 21.7, 21.0, 16.8, 13.4, 12.7; HRMS (FAB) calcd for $C_{36}H_{50}Cl_3N_3O_6S$ [M + H] 760.2534, found 760.2567.

(−)-Pateamine A (1). To a *vigorously* stirred solution of TCBoc-pateamine A (**61**) (9.9 mg, 0.013 mmol) in 0.30 mL of THF and 0.30 mL of 1 N NH_4OAc was added 38.8 mg of Cd−Pb couple.[52] An additional 9.9 mg of Cd−Pb couple was added after 1 h. After an additional 2.5 h, the mixture was filtered through glass wool, and the solids were washed with deionized water and Et_2O. The solvent was concentrated in vacuo, and the residue was dissolved in MeOH and loaded onto a Varian CBA cartridge (3 cm^3/500 mg) preequilibrated with MeOH. After elution with several column lengths of MeOH, pateamine A was eluted with 1% NH_4OH/MeOH. The pateamine A salt was loaded directly onto an amino cartridge preequilibrated with MeOH and then eluted with MeOH to give 5.6 mg (78%) of (−)-pateamine A **(1)** as a colorless film that correlated well with data for the natural product: R_f = 0.18 (1:3:12 Et_3N/Hexanes/EtOAc); $[\alpha]^{26}_D$ −214.5° (*c* 0.31, MeOH); IR (thin film) 2924, 1737, 1726, 1711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 11.7 Hz, 1H), 6.74 (s, 1H), 6.68 (dd, *J* = 11.4, 11.7 Hz, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.30−6.22 (m, 1H), 6.22 (d, *J* = 15.0 Hz, 1H), 5.64 (t, *J* = 6.9 Hz, 1H), 5.52 (d, *J* = 9.3 Hz, 1H), 5.41 (d, *J* = 11.4 Hz, 1H), 5.20−5.06 (m, 1H), 3.26−3.14 (m, 2H), 3.12−3.00 (m, 3H), 2.61−2.54 (m, 1H), 2.40 (dd, *J* = 2.7, 16.8 Hz, 1H), 2.30 (dd, *J* = 10.8, 12.9 Hz, 1H), 2.24 (s, 6H), 2.18−1.88 (m, 3H), 2.02 (d, *J* = 1.2 Hz, 3H), 1.83 (s, 3H), 1.81 (s, 3H), 1.70−1.50 (br s, 2H), 1.38−1.24 (m, 1H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 165.4, 164.5, 161.2, 145.5, 140.6, 138.1, 133.8, 131.1, 128.7, 128.3, 123.8, 115.1, 112.5, 74.8, 69.2, 67.3, 56.9, 48.2, 45.5, 45.0, 42.8,

38.9, 33.3, 22.8, 21.1, 16.8, 13.4, 12.7; HRMS (FAB) calcd for $C_{31}H_{45}N_3O_4S$ [M + H] 556.3209, found 556.3190.

Natural (−)-Pateamine A (1). Data not previously reported: $[\alpha]^{26}_D$ −253.0° (*c* 0.29, MeOH).

TCBoc-Lactam 62. To a solution of lactam **51** (662.7 mg, 1.28 mmol) in 4.0 mL of CH_2Cl_2 were added 2,2,2-trichloro-1,1-dimethylethyl chloroformate (1.52 g, 6.24 mmol) and DMAP (29.4 mg, 0.24 mmol), followed by Et_3N (2.5 mL, 17.9 mmol) at ambient temperature. After 12 h, the reaction was concentrated and purified by flash chromatography on SiO_2 eluting with hexanes/EtOAc (3:1 → 1:1). Repeating this procedure gave, after two recycles, 465.1 mg (51%) of protected lactam **62** as a pale yellow oil: R_f = 0.46 (1:3 EtOAc/hexanes); $[\alpha]^{26}_D$ −17.9° (*c* 1.45, $CHCl_3$); IR (thin film) 2944, 1817, 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 1H), 5.87 (dq, *J* = 1.2, 8.7 Hz, 1H), 4.77 (dt, *J* = 6.0, 9.0 Hz, 1H), 4.07 (m, 1H), 3.22 (dd, *J* = 6.3, 14.4 Hz, 1H), 3.11 (dd, *J* = 6.3, 14.4 Hz, 1H), 2.99 (sext, *J* = 6.9 Hz, 1H), 2.92 (dd, *J* = 5.9, 16.2 Hz, 1H), 2.57 (ddd, *J* = 3.0, 7.2, 13.5 Hz, 1H), 2.45 (dd, *J* = 3.5, 16.2 Hz, 1H), 2.12 (d, *J* = 1.2 Hz, 3H), 1.97 (s, 6H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 164.8, 160.2, 145.8, 134.8, 121.2, 112.6, 105.5, 90.2, 69.9, 51.7, 43.0, 42.0, 39.8, 33.7, 23.9, 21.4(2), 20.3, 17.9, 17.8, 12.2; HRMS (FAB) calcd for $C_{28}H_{44}{}^{79}BrCl_3N_2O_4SSi$ [M + Na] 741.1072, found 741.1039.

Alcohol 63. To a cooled (−20 °C) solution of lactam **62** (465.1 mg, 0.65 mmol) in 6.5 mL of THF was added 1.6 mL of TBAF solution (1.6 mmol, 1.0 M in THF with 20 mol % AcOH added). After 1 h, the reaction was quenched with 3 mL of pH 7 buffer and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (3:1 → 1:1) gave 283.9 mg (78%) of alcohol **63** as a colorless oil: R_f = 0.18 (1:1 EtOAc/hexanes); $[\alpha]^{26}_D$ −29.2° (*c* 2.06, $CHCl_3$); IR (thin film) 3630−3066, 2962, 1812, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H), 5.95 (dd, *J* = 1.4, 8.7 Hz, 1H), 4.80−4.68 (m, 1H), 4.20−4.05 (m, 1H), 3.18−3.10 (m, 2H), 3.05 (sext, *J* = 6.9 Hz, 1H), 2.93 (dd, *J* = 6.0, 16.2 Hz, 1H), 2.59 (ddd, *J* = 3.0, 6.6, 13.2 Hz, 1H), 2.43 (dd, *J* = 3.3, 16.2 Hz, 1H), 2.33 (d, *J* = 1.2 Hz, 3H), 2.00−1.85 (m, 1H), 1.96 (s, 6H), 1.59 (br s, 1H), 1.34 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 164.7, 160.5, 145.9, 132.8, 124.3, 112.2, 105.5, 90.4, 68.2, 51.6, 42.8, 39.7, 39.4, 33.6, 24.1, 21.4, 20.6; HRMS (FAB) calcd for $C_{19}H_{24}{}^{79}BrCl_3N_2O_4S$ [M + Na] 584.9587, found: 584.9604.

Ester 64. To a stirred solution of DIAD (0.200 mL, 1.0 mmol) in 6 mL of THF was added Ph_3P (215.4 mg, 0.82 mmol) as a solid at 25 °C. After 50 min, a solution of acid **8** (165.5 mg, 0.59 mmol) in 1.0 mL of THF was added at −20 °C, and then a solution of alcohol **63** (232.3 mg, 0.41 mmol) was added after 20 min. The reaction was quenched after stirring for 1.5 h with 3 mL of pH 7 buffer and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (9:1 → 4:1) gave 194.5 mg (57%) of ester **64** as a pale yellow oil: R_f = 0.40 (25:75 EtOAc/hexanes); $[\alpha]^{26}_D$ +9.5° (*c* 1.03, $CHCl_3$); IR (thin film) 2957, 2199, 1817, 1724, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1H), 5.86 (dd, *J* = 1.2, 9.6 Hz, 1H), 5.78 (dt, *J* = 6.6, 9.6 Hz, 1H), 5.37 (s, 1H), 4.06−3.89 (m, 2H), 3.36 (dd, *J* = 6.9, 15.0 Hz, 1H), 3.23 (dd, *J* = 6.9, 15.0 Hz, 1H), 2.98 (sext, *J* = 6.9 Hz, 1H), 2.86 (dd, *J* = 5.9, 16.4 Hz, 1H), 2.54 (ddd, *J* = 2.7, 6.9, 13.2 Hz, 1H), 2.36 (dd, *J* = 3.3, 16.2 Hz, 1H), 2.28 (d, *J* = 1.2 Hz, 3H), 2.17 (dd, *J* = 5.3, 13.2 Hz, 1H), 2.02−1.87 (m, 1H), 1.97 (s, 3H), 1.94 (s, 6H), 1.30 (d, *J* = 7.2 Hz, 3H), 1.30−1.20 (m, 1H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 163.9, 160.5, 159.3, 153.0, 145.9, 128.4, 127.9, 113.0, 105.5, 104.7, 90.2, 86.1, 83.2, 71.0, 66.9, 51.7, 49.2, 43.1, 39.8, 37.7, 33.9, 25.8, 24.5, 23.8, 21.4, 20.9, 20.5, 18.0, −4.5, −4.9; HRMS (FAB) calcd for $C_{34}H_{48}{}^{79}BrCl_3N_2O_6SSi$ [M + Na] 849.1282, found 849.1263.

Alcohol 65. To a cooled (0 °C) solution of silyl ether **64** (194.3 mg, 0.24 mmol) in 3 mL of THF was added 3 mL of HF·pyr/pyr/THF (3.97 g/6.0 mL/10.0 mL) solution, and the mixture was warmed to ambient temperature. After 5 h, the reaction was transferred to a stirred slurry of sea sand (10 g) in 15 mL of THF and stirred for 1 h. The solvent was removed with a stream of N_2, and the residue was loaded directly on a SiO_2 flash column eluting with hexanes/EtOAc (5:1 → 1:3) to give 132.8 mg (78%) of alcohol **65** as a pale yellow oil: R_f = 0.32 (1:1 EtOAc/hexanes); $[\alpha]^{26}_D$ +16.0° (*c* 1.50, $CHCl_3$); IR (thin film) 3655−3164, 2964, 2203, 1814, 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 5.98−5.84 (m, 2H), 4.11−3.99 (m, 2H), 3.42 (dd, *J* = 6.9, 15.0 Hz, 1H), 3.28 (dd, *J* = 5.1, 15.0 Hz, 1H), 3.03 (sext, *J* = 6.9 Hz, 1H), 2.89 (dd, *J* = 6.0, 16.2 Hz, 1H), 2.61 (ddd, *J* = 3.0, 6.6, 13.2 Hz, 1H), 2.40 (dd, *J* = 3.3, 16.2 Hz, 1H), 2.36 (s, 3H), 2.31 (d, *J* = 6.3 Hz, 2H), 2.05 (s, 3H), 2.02−1.93 (m, 1H), 2.00 (s, 6H), 1.62 (br s, 1H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H; ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 163.9, 160.3, 158.7, 152.9, 145.8, 128.4, 127.8, 113.0, 105.5, 104.7, 90.2, 85.7, 83.3, 70.8, 65.5, 51.8, 48.6, 43.0, 39.8, 37.6, 33.9, 24.3, 23.3, 21.3, 20.5, 20.4; HRMS (FAB) calcd for $C_{28}H_{34}{}^{79}BrCl_3N_2O_2SSi$ [M + Na] 735.0422, found 735.0403.

TCBoc Macrocycle 57. To a cooled (0 °C) solution of tetraethylammonium cyanide (53.4 mg, 0.34 mmol) in 20 mL of CH_2Cl_2 was added a solution of alcohol **73** (36.7 mg, 0.05 mmol) in 5 mL of CH_2Cl_2, and then the mixture was warmed to 25 °C. After 6 h, the reaction was quenched with 3 mL of pH 7 buffer, and the layers were separated. The aqueous layer was extrated with Et_2O, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with hexanes/Et_2O (4:1 → 1:3) gave 24.9 mg (68%) of macrocycle **57** as a clear, colorless oil: R_f = 0.72 (1:1 EtOAc/hexanes); $[\alpha]^{26}_D$ +31.8° (*c* 1.52, $CHCl_3$); IR (thin film) 2931, 2182, 1737, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.02 (app s, 2H), 5.43 (s, 1H), 5.24−5.36 (m, 1H), 5.06 (d, *J* = 8.4 Hz, 1H), 3.67−3.84 (m, 1H), 3.38 (d, *J* = 15.9 Hz, 1H), 3.29 (dd, *J* = 8.1, 15.9 Hz, 1H), 2.97 (app q, *J* = 7.2 Hz, 1H), 2.68 (dd, *J* = 6.3, 15.9 Hz, 1H), 2.45 (s, 3H), 2.44−2.53 (m, 1H), 2.30 (d, *J* = 7.5 Hz, 2H), 1.94 (s, 6H), 1.92 (dd, *J* = 4.2, 9.0 Hz, 1H), 1.54−1.72 (m, 3H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.24−1.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 163.8, 160.9, 158.1, 153.2, 153.0, 129.1, 128.8, 127.1, 112.6, 106.2, 87.9, 84.8, 84.2, 70.3, 67.4, 46.5, 40.5, 38.7, 37.4, 33.5, 31.6, 29.7, 24.5, 22.6, 21.73, 21.69, 20.8, 19.7, 19.6, 14.1; HRMS (FAB) calcd for $C_{28}H_{54}{}^{79}BrCl_3N_2O_6S$ [M + H] 735.0421, found 735.0438.

Dexamethasone Alcohol 67. To a slurry of (−)-dexamethasone acid[57] (22 mg, 0.058 mmol), 11-aminoundecan-1-ol[56] (23 mg, 0.125 mmol), and hydroxybenzotriazole (16 mg, 0.12 mmol) in 3 mL of CH_2Cl_2 was added 0.076 mL of Et_3N (0.55 mmol), resulting in a clear solution. This solution was transferred via cannula to a slurry of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (47 mg, 0.24 mmol) in 1 mL of CH_2Cl_2. After 2.5 h, the solution was diluted with 25 mL of EtOAc and washed with 0.1 M HCl (3 × 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ (5 mL) and water (5 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on SiO_2 eluting with EtOAc/Et_2O (0:1 → 1:1) gave 17 mg (55%) of alcohol **67** as a clear, colorless film: $[\alpha]^{26}_D$ +72.8° (*c* 1.73, MeOH); IR (thin film) 3594−3119, 2930, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 10.2 Hz, 1H), 6.59 (app t, *J* = 5.6 Hz, 1H), 6.33 (dd, *J* = 1.8, 10.2 Hz, 1H), 6.11 (s, 1H), 4.34 (br d, *J* = 10.5 Hz, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.35−3.10 (m, 3H), 2.62 (td, *J* = 6.0, 14.0 Hz, 1H), 2.47−2.00 (m, 5H), 1.90−1.44 (m, 7H), 1.55 (s, 3H), 1.44−1.18 (m, 18H), 1.13 (s, 3H), 0.94 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.7, 172.4, 166.4, 152.3, 129.7, 125.0, 101.7, 99.4, 86.8, 72.4, 71.9, 63.0, 48.5, 48.2, 47.9, 43.8, 39.4, 36.5, 35.2, 34.4, 34.2, 32.7, 31.0, 29.7, 29.4, 29.3, 22.2; HRMS (FAB) calcd for $C_{32}H_{50}FNO_5$ [M + Na] 570.3571, found 570.3547.

Dexamethasone Carbonate 68. To a cooled (0 °C) solution of alcohol **67** (17.3 mg, 0.032 mmol) in 1 mL of CH_2Cl_2 was added *p*-nitrophenyl chloroformate (67.3 mg, 0.33 mmol) as a solid. Pyridine (0.035 mL, 34 mg, 0.43 mmol) was added, and the resulting white slurry was warmed to 25 °C. After 1 h, 1 mL of Et_2O was added, and the slurry was directly loaded on a SiO_2 flash column and eluted with CH_2Cl_2/hexanes [(1:4 → 1:1) to EtOAc/hexanes/CH_2Cl_2 (1:9:10 → 1:4:5)] to give 10.7 mg (47%) of carbonate **68** as a clear colorless film: $[\alpha]^{26}_D$ +45.8° (*c* 1.07, $CHCl_3$); IR (thin film) 3575−3200, 2928, 1767, 1658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, *J* = 9.6 Hz, 2H), 7.89 (d, *J* = 9.3 Hz, 2H), 7.22 (d, *J* = 10.2 Hz, 1H), 6.58 (app t, *J* = 5.4 Hz, 1H), 6.33 (dd, *J* = 1.8, 10.2 Hz, 1H), 6.11 (s, 1H), 4.38−4.30

(br d, 1H), 4.29 (t, $J = 6.6$ Hz, 2H), 3.35−3.09 (m, 3H), 2.62 (td, $J = 6.0$, 14.0 Hz, 1H), 2.47−2.07 (m, 5H), 1.64−1.90 (m, 5H), 1.19−1.60 (m, 19H), 1.55 (s, 3H), 1.13 (s, 3H), 0.94 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.6, 172.3, 166.2, 155.5, 152.5, 152.1, 145.3, 129.8, 125.3, 125.1, 121.8, 101.6, 99.3, 86.7, 72.5, 72.0, 69.9, 48.4, 48.1, 47.9, 43.8, 39.4, 36.6, 35.2, 34.4, 34.2, 32.1, 31.0, 29.8, 29.5, 29.42, 29.39, 29.2, 29.1, 28.4, 27.3, 26.9, 25.6, 22.92, 22.85, 17.4, 14.4; HRMS (FAB) calcd for $C_{39}H_{53}FN_2O_9$ [M + Na] 735.3633, found 735.3643.

Dexamethasone−Pateamine A Hybrid 69. To a conical vial charged with synthetic pateamine A **(1)** (2.4 mg, 0.004 mmol) and carbonate **68** (4 mg, 0.006 mmol) in 0.2 mL of THF was added 0.003 mL of Et_3N. After 2 h, an additional 0.003 mL of Et_3N was added. After 16 h, the solvent was reduced with a stream of N_2 and the residue diluted with MeOH. Purification on a C18 reversed-phase silica gel column eluting with MeOH/water (0:1 → 1:0) to 0.5% trifluoroacetic acid/MeOH gave a salt, which was loaded onto a Bakerbond amino cartridge equilibrated with MeOH to give, after elution with MeOH, 3.4 mg (64%) of dexamethasone−pateamine A hybrid **69** as a yellow film: IR (thin film) 3634−3120, 2931, 1732 (br), 1715, 1659 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, $J = 10.5$ Hz, 1H), 7.04, (d, $J = 11.7$ Hz, 1H), 6.80 (s, 1H), 6.73 (t, $J = 11.7$ Hz, 1H), 6.54 (app t, $J = 5.6$ Hz, 1H), 6.37 (d, $J = 15.9$ Hz, 1H), 6.36−6.16 (m, 1H), 6.23 (d, $J = 15.9$ Hz, 1H), 6.12 (s, 1H), 5.64 (t, $J = 6.9$ Hz, 1H), 5.56 (d, $J = 9.3$ Hz, 1H), 5.50 (d, $J = 6.9$ Hz, 1H), 5.19−5.01 (m, 1H), 4.35 (br d, $J = 12.3$ Hz, 1H), 4.08−3.92 (m, 1H), 3.40−3.12 (m, 5H), 3.10−2.98 (m, 1H), 3.06 (d, $J = 7.2$ Hz, 2H), 2.68−2.50 (m, 1H), 2.46−2.08 (m, 6H), 2.42 (s, 6H), 1.99 (s, 3H) 1.92−1.43 (m, 11H), 1.81 (s, 3H), 1.67 (s, 6H), 1.55 (s, 3H), 1.40−1.16 (m, 24H), 1.13 (s, 3H), 0.94 (d, $J = 7.5$ Hz, 3H); HRMS (FAB) calcd for $C_{21}H_{36}{}^{79}BrN_2O_2SSi$ [M + Na] 1151.6490, found 1151.6514.

Interleukin 2 (IL-2) Reporter Gene Assay. The transient transfection was performed using electroporation. Jurkat cells (1 × 107) were harvested, washed once in RPMI medium, resuspended in 300 μL of RPMI, and mixed with 2 μg of IL-2 reporter plasmid. The electroporation was carried out by applying an electric pulse (150 V, 960 μF using the Bio-Rad Gene Pulser II). The cells were allowed to rest for 10 min before they were transferred back to culture medium (RPMI with 10% fetal calf serum and 2 μM glutamine) and incubated at 37 °C for 36 h. Pateamine A and analogues dissolved in DMSO were added to cultured cells and incubated with the cell cultures for 30 min before PMA (final concentration 10 nM) and ionomycin (final concentration 1 μM) were added. After another 12 h of incubation, cells were harvested and prepared for luciferase assay according to manufacturer's instructions (Promega).

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Supporting Information Available: Experimental procedures and characterization data for **40**−**42** and **45**−**47**; ^{1}H NMR spectra for **17**, **19**, **20**, **22**, **27**, **29**−**31**, **34**, **36**, **40**−**42**, **45**, **46a**−**c**, **47a**, **47c**, and **68**−**69** (28 pages, print/PDF). ^{1}H NMR data for several other intermediates, including spectral comparison of natural and synthetic (−)-pateamine A, have previously been reported (see ref 7, Supporting Information). See any current masthead page for ordering information and Web access instructions.

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