Total Synthesis of the Serine/Threonine-Specific Protein Phosphatase Inhibitor Tautomycin[1]

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A convergent, asymmetric synthesis of the protein phosphatase inhibitor, tautomycin, is described. The natural product was constructed by joining two major fragments of comparable complexity at the C21−C22 bond. Absolute stereochemistry of the C1−C21 ketone originates from (*S*)-citronellene and (2*R*,3*S*)-geraniol epoxide. The anti stereochemical relationships at C6−C7 and C18−C19 were introduced with Duthaler's chiral titanium propionic enolate. Syn stereochemical relationships at C13−C14 and C23−C24 were established using an Evan's oxazolidinone chiral auxiliary. The spiroketal was efficiently constructed via a one-pot double-alkylation−spirocyclization sequence with acetone *N*,*N*-dimethylhydrazone serving as the central linchpin. Final coupling of the two halves using a chelation-controlled Mukaiyama aldol addition followed by deprotection yielded synthetic tautomycin that is identical to the natural product.

Introduction

One of the most pervasive controllers of signal transduction in eukaryotic cells is the reversible phosphorylation of serine-, threonine-, and tyrosine-containing proteins by protein phosphatases (PPs) and protein kinases (PKs). This molecular "on-off switch" is responsible for regulating such diverse and important processes as memory, cell growth, neurotransmission, glycogen metabolism, muscle contraction, and many others.[2] Much of the current knowledge of the serine/threonine-specific protein phosphatases has disseminated from studies of their inhibition by a strikingly diverse collection of natural products known as the okadaic acid class of inhibitor,[3] which is comprised of three structural types: (1) cyclic peptides such as the microcystins[4] and nodularins;[5] (2) terpenoids including cantharidin[6] and thyrsiferyl 23-acetate;[7] and (3) polyketides such as the calyculins,[8] tautomycin (TM),[9] okadaic acid (OA), and the okadaic acid congeners acanthafolicin and the dinophysistoxins.[10] Many of these structurally dissimilar inhibitors have been exploited as small molecule probes in molecular biology[11] because they all selectively inhibit two of the four major types of serine/threonine PPs (PP1 and PP2A over PP2B (calcineurin) and PP2C). Cantharidin, OA, and thyrsiferyl 23-acetate further exhibit varying selectivity for PP2A over PP1, whereas the other inhibitors are essentially equipotent for both phosphatases. The specific inhibition of particular PPs is physiologically important since four endogenous proteins, DARPP-32,[2] inhibitor-1, inhibitor-2, and NIPP-1,[12] act to stringently regulate PP1, and abnormally low levels of PP activity have been implicated in human cancer[13] and Alzheimer's disease.[14]

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(1) Dedicated to our brilliant colleague and friend, Jim D. Bain, who died March 2, 1995, of leukemia.

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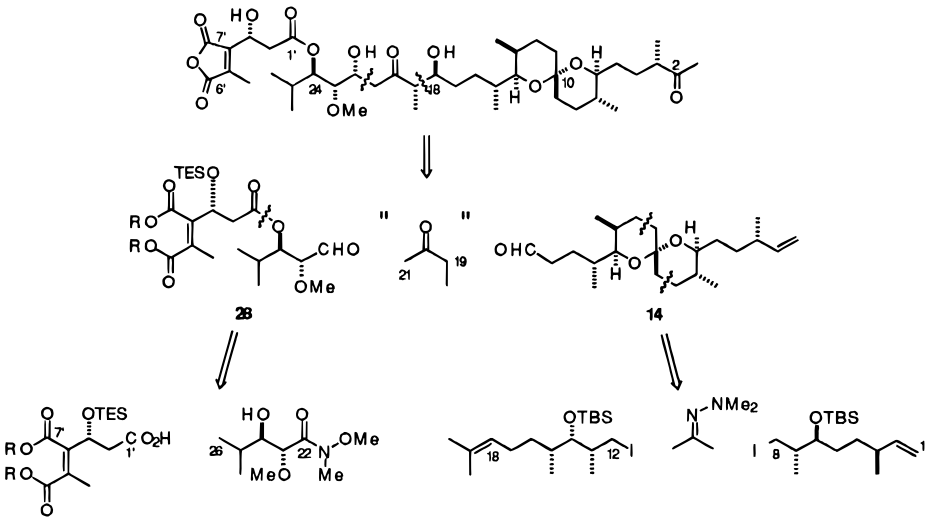
Scheme 1



Our interest in the serine/threonine-specific protein phosphatases stems from their central role in cellular regulation. The discovery of new selective PP inhibitors would be of great value in elucidating the physiological roles of the PPs, and an important component of that process is an effort to establish the relationship between structure and inhibition potency/selectivity among these molecules. We believe that all of these natural products, whether in part or in whole, are acting as sophisticated peptidemimetics of phosphorylated DARPP-32[15] and that a combination of molecular design and synthesis promises to lead to important new selective inhibitors. Among other targets, we chose tautomycin because it is the only small molecule that is selective for PP1 over PP2A (albeit only slightly: IC_{50} = 22 and 32 nM, respectively). TM was discovered in 1987, and its structure was elucidated in 1993.[9a,16] Two groups have reported total syntheses of TM, and others have published synthetic progress toward the molecule.[17] We have independently developed a convergent and efficient synthetic route that will allow us to pursue the goal of discovering PP1-selective inhibitors.

Synthetic Strategy

We envisioned a highly convergent synthesis that would rely upon efficient coupling reactions of readily prepared subunits. Since the stereochemistry of TM resides in clusters separated by unfunctionalized hydrocarbon regions, asymmetric centers were to be introduced using more reagent control than substrate-directed reactions. Our antithetic analysis begins with the retroaldolization of the C21−C22 and C18−C19 bonds to give aldehydes **28** and **14** and a central C19−C21 linchpin that is a formal 2-butanone equivalent (Scheme 1). Saponification of **28** yields the C1′−C7′ anhydride subunit and the C22−C26 Weinreb amide. This strategy is akin to that also used by Oikawa's group for the C18−C26 segment[18] but is markedly different in the construction of each subunit and the spiroketal. The aldehyde **14** was disconnected to take advantage of a spiroketal synthesis via sequential alkylations of acetone *N*,*N*-dimethylhydrazones to give the C1−C8 and C12−C18 iodide subunits. Disconnection at C8−C9 also conveniently allows for the introduction of the C6−C7 and C18−C19 stereogenic centers using the same chiral auxiliary, since both stereochemical features bear the same absolute and relative stereochemistry.

We planned silyl protection of all potentially labile functionality throughout the synthesis, anticipating that a single deprotection step at the end of the synthesis would directly yield TM. The C1−C2 methyl ketone was to be carried through as the corresponding alkene, which would require a selective oxidative cleavage of the C18 alkene in the presence of the C1 alkene after spirocyclization. The final coupling of the C1−C21 subunit and the aldehyde **28** was envisioned as a chelation-controlled Mukaiyama aldol reaction that should give the requisite stereochemistry at C22.[18]

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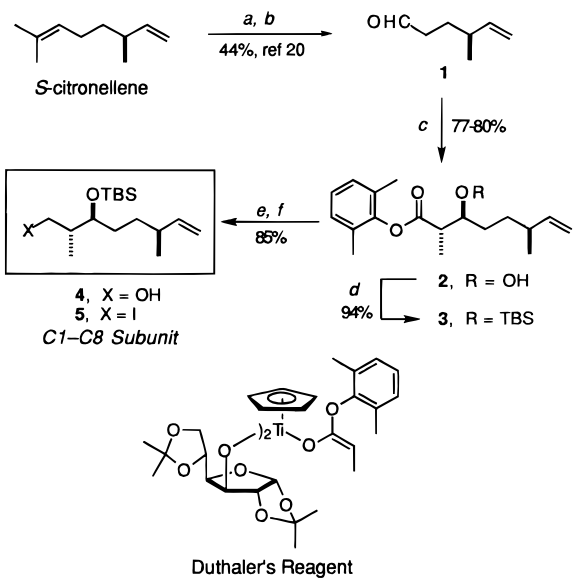
Scheme 2[a]



[a] Key: (a) *m*-CPBA, CH_2Cl_2, 0 °C; (b) H_5IO_6, Et_2O, 0 °C; (c) Duthaler's reagent, Et_2O, −78 to −20 °C; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt; (e) DIBAL, hexanes, −78 °C; (f) Ph_3PI_2, imidazole, CH_3CN/Et_2O, 0 °C to rt.

Results and Discussion

Synthesis of the C1−C8 Subunit. The synthesis of the C1−C8 primary iodide (Scheme 2) begins with the selective oxidative cleavage of *S*-citronellene[19] via a two-step procedure published by Ireland.[20] After attempting several types of enantioselective anti aldol additions to this aldehyde, we settled on the Duthaler reagent[21] for several reasons. This chiral titanium enolate reagent exhibits excellent enantioselectivity (albeit modest diastereoselectivity) and is also conveniently scaled up. Addition to the aldehyde **1** consistently gave the desired anti aldol product, **2**, in good yield with 94−96% ee and approximately 8:1 diastereoselectivity.[22] Silylation of the newly formed hydroxyl substituent, reduction of the aryl ester with DIBAL, and conversion of the resultant primary alcohol into an iodide leaving group[23] completed the C1−C8 subunit **5**.

Synthesis of the C12−C18 Subunit. Our plans for the synthesis of the C12−C18 subunit required a syn aldol addition to a chiral α-methyl aldehyde fragment that contained a second latent aldehyde at C18, and geraniol epoxide was chosen for this purpose. While this compound is readily obtained, as described below, the regioselective reductive opening of the epoxide to give a 1,2-diol initially was problematic. $LiAlH_4$ and DIBAL give statistical mixtures of the desired 1,2-diol and the undesired 1,3-diol (from reduction of the epoxide at the 3 and 2 positions of geraniol epoxide, respectively), although Dai had reported a 7:1 preference for the desired 1,2-diol isomer using a mixture of $Ti(OiPr)_4$ and excess $LiBH_4$ in benzene.[24] However, we experienced solubility problems with $LiBH_4$ in benzene while trying to scale up this reaction, so we sought another reagent that might also be more selective. After screening a variety of conditions, we found that 2−3 equiv of $NaBH_3CN$ in THF with 2−3 equiv of glacial acetic acid smoothly reduces chiral geraniol epoxide (90−93% ee from Sharpless epoxidation)[25] at room temperature with >20:1 regioselectivity to form the 1,2-diol **6** in good to excellent yield.[26] Smaller scale reactions (1−2 mmol) consistently proceed in over 90% isolated yield, whereas larger scale reactions (50−100 mmol) requires more reagent and longer reaction times due to competitive destruction of $NaBH_3CN$ by HOAc. This reduction proceeds stereospecifically with inversion (chiral GC) and gives no reaction without added HOAc. We were surprised to find that such mild conditions reductively opened the epoxide and suspect that the reduction may take place with neighboring-group participation by the primary hydroxyl substituent. The observation that the TBS ether of geraniol epoxide is inert under the reaction conditions supports this contention.

Next, the diol **6** was cleaved with $NaIO_4$ to give the corresponding aldehyde, which reacted with the boron enolate of Evan's norephedrine-derived chiral auxiliary in a "matched," double diastereoselective aldol reaction.[27] Oxazolidinone **7** was the major component of two separable diastereomeric products, the other one arising from mismatched aldol addition to the 3−5% of the minor enantiomeric aldehyde (from geraniol epoxide). Analogous to the C1−C8 subunit, **7** was protected as a TBS ether and then reduced with $LiBH_4$ with 1 equiv of MeOH or H_2O, but these conditions[28] gave unacceptable amounts of competitive reduction of the carbamate carbonyl. This problem was circumvented using the standard lithium benzyloxide transesterification method[29] followed by DIBAL reduction to give primary alcohol **10**, which was

(19) Although (*S*)-citronellene is commercially available from Fluka, we prepared it from (*S*)-citronellol using the Chugaev method of Kocienski and Cernigliaro (*J. Org. Chem.* **1977**, *42*, 3622−3624) on a 200 g scale (50% yield). We wish to thank Takasago Ltd. for the generous gift of (*S*)-citronellol.

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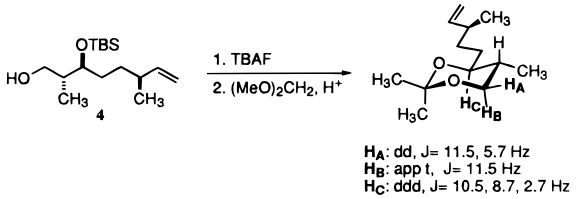
(22) The enantiomeric excess was judged by 500 MHz ^1H NMR analysis of the Mosher ester using a racemic control. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. The relative and absolute stereochemistry was predicted using the Duthaler precedent but unambiguously determined using the following reaction sequence:



Absolute stereochemistry was determined later in the synthesis by spectroscopic identity of a derivative of **14** with an authentic tautomycin intermediate degraded from the natural product (see ref 9a,b).

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(26) During the course of our synthetic investigations, a paper appeared describing the reduction of geraniol epoxide with $NaCNBH_3$ and BF_3OEt_2: Taber, D. F.; Hoaze, J. B. *J. Org. Chem.* **1994**, *59*, 4004−4006.

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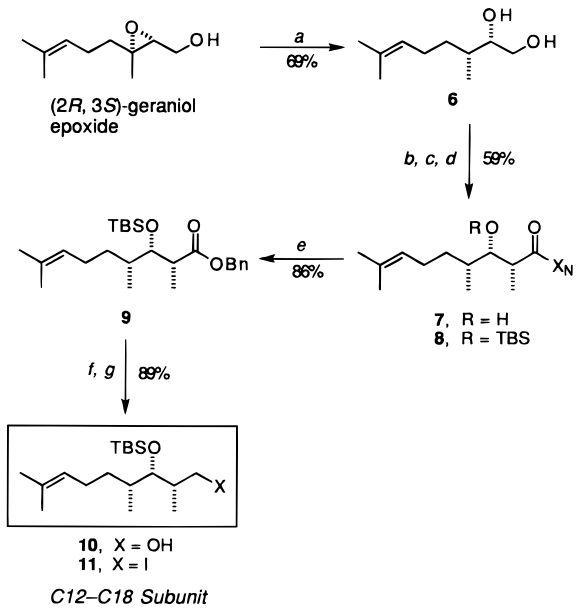
Scheme 3[a]



[a] Key: (a) $NaBH_3CN$, HOAc, THF, rt; (b) $NaIO_4$, Et_2O, rt; (c) (4*R*,5*R*)-4-methyl-5-phenyl-*N*-propionyl-2-oxazolidinone, Bu_2BOTf, TEA, THF, −20 °C; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2; (e) LiOBn, THF; 0 °C to rt; (f) DIBAL, CH_2Cl_2, −78 to 0 °C; (g) Ph_3PI_2, imidazole, CH_3CN/Et_2O, 0 °C to rt.

transformed into the C12−C18 iodide **11**, as before (Scheme 3).

Construction of the C1−C18 Subunit via *in Situ* Double Alkylation. The concise assembly of the spiroketal-containing subunit was conveniently achieved using α,α′ sequential alkylations of acetone *N*,*N*-dimethylhydrazone with the previously prepared iodide subunits.[30] Treatment of lithiated acetone *N*,*N*-dimethylhydrazone with the iodide **5**, followed by a second lithiation (*n*-BuLi) and subsequent treatment with an equimolar amount of the iodide **11**, cleanly afforded the bis(silyloxy)hydrazone. Aqueous workup and treatment of the crude reaction product with HF in a mixture of CH_3CN and *i*-PrOH removed both TBS groups and induced spiroketalization to give **12** as a single isomer in 77% overall yield (based on **5**) (Scheme 4). The completion of the synthesis of **14** required selective oxidative cleavage of the trisubstituted olefin of **12** (a transformation that is nearly identical to that of citronellene in Scheme 2), which was achieved by reapplying the Ireland conditions at lower temperature to give a 98% yield of the desired monoepoxide **13**. Oxidative cleavage of this product gave a disappointingly low yield (53%) of the aldehyde **14** on a large scale, but the abundant quantity of **14** that was readily available discouraged further optimization of this reaction.

Synthesis of the ketone **17** required installation of the C18−C19 anti stereochemistry and further manipulation to a methyl ketone. Using the same Duthaler reagent as before (Scheme 2), but with the aldehyde **14** as the electrophile, gave two inseparable diastereomers (7:1 anti/syn ratio) in 76% combined yield. Attempts to convert the ester mixture directly into the Weinreb amides using the standard $Me_2AlN(Me)OMe$ conditions[31] failed, perhaps due to the extreme steric bulk of the ortho-substituted aryl ester. Instead, **15** was first saponified using the original conditions of Heathcock and Pirrung[32] and then coupled to the Weinreb amine using DCC and HOAt.[33] No epimerization of the α-methyl substituent was observed, and the syn and anti diastereomers were chromatographically separated at this point. Finally, treatment of the anti isomer with MeLi (3.3 equiv) afforded the β-hydroxy ketone **17** in good overall yield without the need for hydroxyl protection.[34]

Synthesis of the C22−C26 Subunit. This simple subunit was constructed from the methoxyacetyl-substituted oxazolidinone **18**. Following Evan's precedent,[35] the tin enolate of **18** was allowed to react with isobutyraldehyde in the presence of TMEDA to give all four possible diastereomers (79% yield total) in a ratio of 73:14:9:4 favoring the desired stereoisomer **19**.[36] Oxazolidinone **19** was easily separated and then transaminated in standard fashion[31] to give quantitative conversion to **20** (Scheme 5).

Synthesis of the C1′−C7′ Anhydride Subunit: Coupling to 20. Surprisingly, the greatest challenge in this synthesis of tautomycin proved to be in the construction of the simple-looking diester subunit **26**. Controlling both the geometry of the alkene and the allylic hydroxyl stereochemistry with high fidelity prompted us to explore a number of synthetic avenues. The most direct strategy that we investigated was the double carbonylation of a propargylic β-keto or β-hydroxy ester (and protected variants) using Hoberg's $Ni(CO)_2$bipy reagent.[37] Although this reagent reportedly reacts with internal alkynes to form a dioxonickelacyclopentane intermediate that directly gives disubstituted maleic anhydrides when oxidized with O_2, only addition to excess 2-butyne and diphenylacetylene had been described. We were disappointed to find that under a variety of conditions no detectable nickelacyclopentane adduct was formed with our electron-deficient substrates. After unsuccessfully testing a number of other strategies, we finally settled on the addition of a mixed methyl cuprate to a symmetrical acetylenedicarboxylic ester, followed by trapping of the intermediate with an electrophile (Scheme 6).[38] Not surprisingly, the use of malonic acid chlorides as the electrophile quenched the intermediate vinyl cuprate by depronation of the highly acidic α-proton. Attempts to

(29) (a) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23−32. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.

(30) (a) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3, 11. (b) Jung, M. E.; Shaw, T. J. *Tetrahedron Lett.* **1979**, 4149. (c) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1079**, *101*, 6789−6791. (d) Enders, D.; Dahmen, W.; Dederichs, E.; Weuster, P. *Synth. Commun.* **1985**, *13*, 1235−1242. (e) Yamashita, M.; Matsumiya, K.; Tanabe, M.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 407−408. (f) Reddy, G. B.; Mitra, R. B. *Synth. Commun.* **1986**, *16*, 1723−1729. (g) Enders, D.; Dahmen, W.; Dederichs, E.; Gatzweiler, W.; Weuster, P. *Synthesis* **1990**, 1013−1019. (h) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260−6268.

(31) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993.

(32) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087−4095.

(33) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.

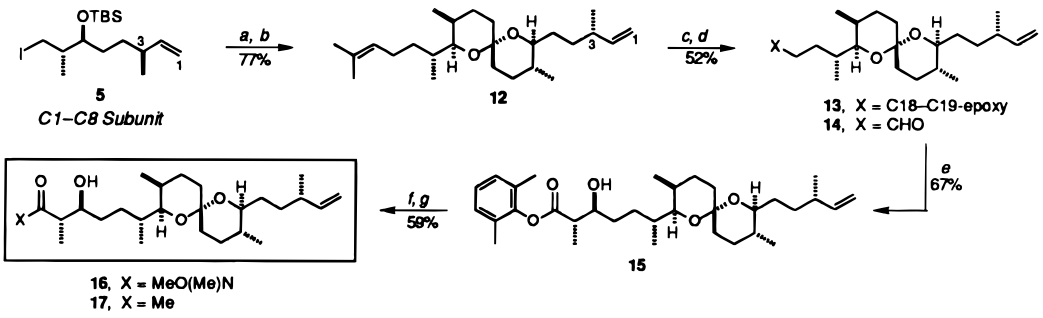
(34) We observed small (3−5%) amounts of retroaldolization upon quenching this reaction into a 0 °C solution of 1 N HCl.

(35) (a) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961−1963. For use of a methoxyacetyl-substituted oxazolidinone in a syn aldol reaction, see: (b) Ku, T. W.; Kondrad, K. H.; Gleason, J. G. *J. Org. Chem.* **1989**, *54*, 3487−3491. (c) Andrus, M. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10420−10421.

(36) Unambiguous stereochemical assignment of **19** was determined by X-ray crystallographic analysis of the TBS ether and confirms the Evan's precedent.

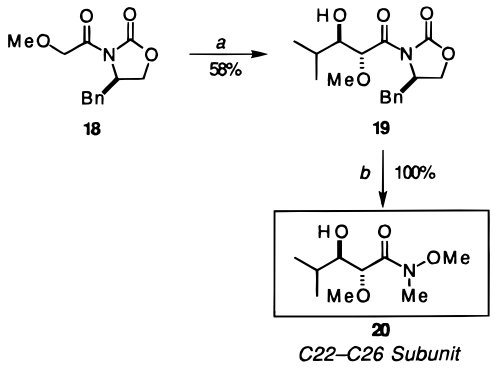
(37) (a) Herrera, A.; Hoberg, H. *Synthesis* **1981**, 831−833. (b) Herrera, A.; Hoberg, H.; Mynott, R. *J. Organomet. Chem.* **1981**, *222*, 331−336.

Scheme 4[a]



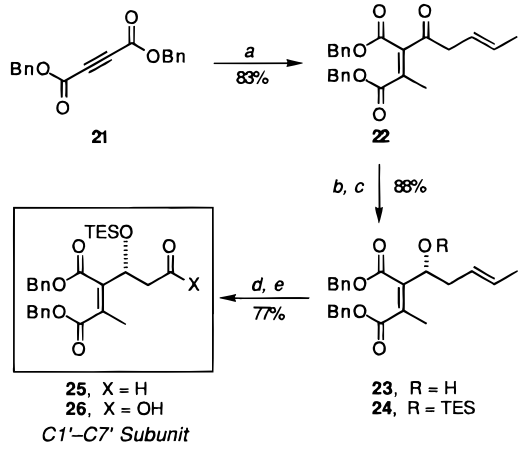
[a] Key: (a) lithioacetone *N*,*N*-dimethylhydrazone, THF, −78 °C to rt; then *n*-BuLi (2.41 M) −78 to 0 °C, then **11**, −78 °C to rt; (b) HF (concd 47%), 6:1 CH_3CN/*i*-PrOH; (c) *m*-CPBA, CH_2Cl_2, −20 °C; (d) H_5IO_6, Et_2O, 0 °C; (e) Duthaler's reagent, Et_2O, −78 to −20 °C; (f) KOH, 1:2 MeOH/H_2O; DCC, HOAt, *i*-Pr_2NEt, DMF, 0 °C to rt; (g) MeLi, THF, −78 to −20 °C.

Scheme 5[a]



[a] Key: (a) $Sn(OTf)_2$, TEA, CH_2Cl_2, −78 °C, TMEDA, then *i*-PrCHO; (b) $Me_2AlN(Me)OMe$, CH_2Cl_2, −10 °C, then **19**.

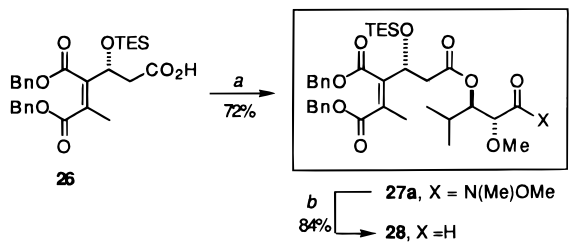
Scheme 6[a]



[a] Key: (a) MeCuLiCN, Et_2O, −78 °C, then 3-pentenoyl chloride, −78 to 0 °C; (b) (+)-DIP-Chloride, THF, −20 °C, 3 days, 0 °C, 4 h; (c) TESCl, TEA, CH_2Cl_2, 0 °C to rt; (d) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C to rt; (e) $NaClO_2$, 2-methyl-2-butene, *t*-BuOH/H_2O, 0 °C.

prepare the analogous ketenes resulted in polymeric precipitates, and trapping with malonic anhydride[39] also proved unsuccessful. However, use of the malonic acid equivalent 3-pentenoyl chloride[40] ultimately worked well, giving the unstable enone **22** as a >20:1 mixture of geometrical isomers in 83% yield. This synthetic sequence was originally carried out using a bis(2-(trimethylsilyl)ethyl ester) protecting group, but we were forced to change to a bis-benzyl ester for reasons described below.

Scheme 7[a]



[a] Key: (a) Ph_2POCl, DMAP, TEA, toluene, **20**; (b) DIBAL (4.0 equiv), THF, −78 °C.

At this point, we thought that the requisite 3′(*R*) stereogenic center might be introduced via a kinetic resolution of the racemic acid **26** (derived from (±)-**23**) using the easily-obtained subunit **20** as a "chiral resolving agent" in the ester-coupling reaction. The racemic acid (±)-**26** was synthesized by reducing enone **22** with $NaBH_4$ to give the alcohol (±)-**23** in 82% yield. Protection of the hydroxyl substituent as a TES ether, ozonolytic cleavage of the disubstituted alkene, and subsequent oxidation of the aldehyde to a carboxylic acid gave (±)-**26** in 77% overall yield. With both **20** and (±)-**26** in hand, the kinetic resolution was attempted using a mixed phosphonic anhydride esterification method (Scheme 7).[41] The reaction proceeded rapidly to give one diastereomer at 50% conversion and could be forced to produce the second diastereomer only at higher temperature, clearly suggesting that a kinetic resolution might be possible. Unfortunately, the rapidly formed diastereomer proved to have the incorrect 3′-stereochemistry, thwarting our plans. The two diastereomers were easily separated, however, and both **27a** and its $C_{3'}$ epimer **27b**[42] were independently reduced by DIBAL with high chemoselectivity (in preference to the three esters) to give aldehydes **28** and 3′-*epi*-**28**, respectively, that ultimately provided access to both TM itself and 3′-*epi*-TM.

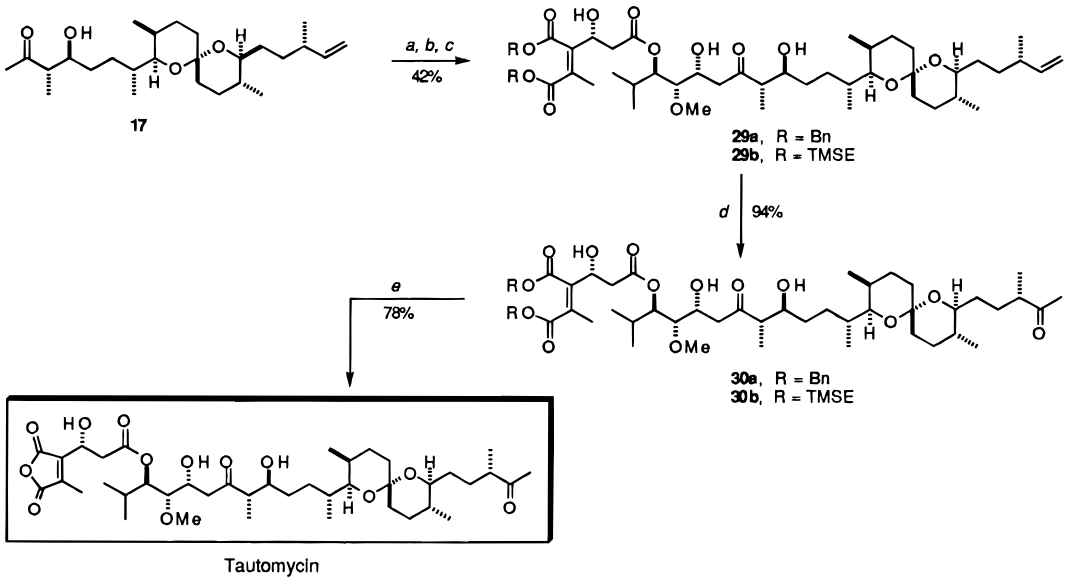
(38) (a) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696−3702. (b) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1983**, *48*, 4621−4628. (c) Yamamoto, Y.; Yatagai, H.; Kazuhiro, M. *J. Org. Chem.* **1979**, *44*, 1744−1746. (d) Nishyama, H.; Sasaki, M.; Itoh, K. **1981**.

(39) Perrin, C. L.; Arrhenius, T. *J. Am. Chem. Soc.* **1978**, *100*, 5249−5251.

(40) 3-Pentenoyl chloride was synthesized according to the procedure of Martin and Sanders (Martin, M. M.; Sanders, E. B. *J. Am. Chem. Soc.* **1967**, 3777−3782) from the commercially available acid (Fluka).

(41) Jackson, A. G.; Kenner, G. W.; Moore, G. A.; Ramage, R.; Thorpe, W. D. *Tetrahedron Lett.* **1976**, *40*, 3627−3630.

Scheme 8[a]



[a] Key: (a) TMSOTf, TEA, CH_2Cl_2, 0 °C; (b) **28**, $TiCl_4$, CH_2Cl_2, −78 to −20 °C; (c) HF (5%), CH_3CN/H_2O, rt; (d) $PdCl_2$, CuCl, O_2, DMF, rt; (e) 5% Pd/C, H_2, 9:1 THF/H_2O.

An improvement upon the resolution above was later realized by reduction of ketone **22** with a chiral reducing agent. With this substrate, stoichiometric amounts of Corey's (+)-oxazaborolidine reagent[43] gave 25% ee of the alcohol favoring the (*S*) enantiomer, the opposite product predicted by the Corey paradigm (assuming the maleate is the "large" group). However, reduction of the same substrate with (+)-DIP-Chloride[44] gave 80% ee (Mosher ester analysis) of the desired (*R*) enantiomer in 88% yield, which was taken through the synthetic sequence in Scheme 6, as before, to give **26**. Esterification with **20**, as described above, again gave **27a** and its 3′-diastereomer, but now in a 9:1 ratio favoring the former.

Coupling of Subunits 28 and 17: Completion of the Synthesis. The coupling of **28** and **17** was originally planned as the obvious chelation-controlled (anti-Felkin) Mukaiyama aldol reaction.[18] As depicted in Scheme 8, treatment of **17** with TMSOTf and TEA concommitantly protected the hydroxyl substituent and formed the silyl enol ether, which was used without purification. Reaction with **28** occurred cleanly, and the mixture of silyl ethers was directly subjected to deprotection conditions (HF, CH_3CN/H_2O) to afford a single detectable diastereomer, **29**, in 42% overall yield for three steps (based on **17**). Wacker oxidation of the terminal alkene group in **29** gave the methyl ketone **30** without detectable epimerization, which was now poised for the final deprotection.

Our original synthetic design employed silyl protection throughout the synthesis, anticipating that a single desilylation step would unmask all of the functionality in the molecule and leave only the final alkene oxidation. Unfortunately, complete desilylation of the bis-silyl ester **29b** (from bis(2-(trimethylsilyl)ethyl)acetylenedicarboxylate)[45] under many reaction conditions proved unmanagable due to the robust 2-(trimethylsilyl)ethyl esters. The commonly used reagent TBAF could remove these protecting groups, but the basicity associated with "dry" sources of fluoride-induced acyl migration followed by β-elimination at C22—a known degradative process of tautomycin.[9b,46] Faced with no obvious alternatives, we were forced to retrace our steps with the bis-benzyl ester in place of the bis-TMSE ester (Schemes 6 and 7).[45] With this change, we were gratified to find that the bis-benzyl ester **30a** smoothly deprotected under hydrogenolytic conditions to give a 78% yield of tautomycin (quantitative based on recovered starting material). Synthetic tautomycin was spectroscopically and chromatographically indistinguishable from an authentic sample of TM (^1H, ^{13}C, IR, HRMS, HPLC coinjection).

Conclusions

A highly efficient, modular synthesis of tautomycin has been completed. Use of the readily available chiral terpenes citronellene and geraniol epoxide allowed for the concise assembly of both halves of the spiroketal, which were coupled in a one-pot double alkylation−spirocyclization sequence. Judicious use of Duthaler's and Evan's chiral auxiliaries enabled us to install all of the remaining stereochemistry of the molecule and prepare reasonable quantities of late synthetic intermediates. The overall yield of TM is 1.5%, and the longest linear sequence is 19 steps starting from geraniol epoxide. Use of this synthetic route for structure−activity studies of tautomycin and the mechanistic elucidation of serine/threonine-specific protein phosphatase inhibition is underway.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were obtained on 300 and 500 MHz spectrometers. ^1H NMR and

(42) We predicted that the lower R_f diastereomer, **27a**, possessed the desired stereochemistry at C3′ because it correlated much better with the ^1H NMR spectrum of authentic tautomycin. This prediction proved to be correct because we have taken the high R_f diastereomer (**27b**) through the synthetic sequence to make 3′-epitautomycin that is spectroscopically distinct from tautomycin itself (^1H NMR).

(43) Corey's oxazaborolidine reagent is reviewed in: Deloux, L.; Srenbik, M. *Chem. Rev.* **1993**, *93*, 763−784.

(44) Brown's DIP-Chloride reagent is reviewed in: Dhar, R. K. *Aldrichim. Acta* **1994**, *27*, 43−51.

(45) Dibenzylacetylene dicarboxylate was prepared from ADA using the procedure of Radell J.; Brodman, B. W.; Hirshfeld, A.; Bergman, E. D. *J. Phys. Chem.* **1965**, *69*, 928−932. Bis[2-(trimethylsilyl)ethyl]-acetylene dicarboxylate was prepared using the method of Charlton, J. L.; Chee, G.; McColeman, H. *Can. J. Chem.* **1995**, *73*, 1454−1462.

(46) Sugiyama, Y.; Ohtani, I. I.; Isobe, M.; Takai, A.; Ubukata, M.; Isono, K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3−8.

^{13}C NMR data are reported in ppm from internal tetramethylsilane. MS was done in house. Thin-layer chromatography (TLC) was performed on 0.25 mm precoated silica gel plates (60 F-254), and silica gel chromatography was performed using 200−400 mesh silica gel. Medium-pressure liquid chromatography (MPLC) was conducted on an SiO_2 column (3.7 × 44 cm). Normal-phase preparative HPLC was conducted with a 25 × 100 mm silica cartridge, and reversed-phase preparative HPLC was conducted with a 25 × 100 mm cartridge. Reversed-phase analytical HPLC was conducted with a 4.6 × 250 mm column.

2′,6′-Dimethylphenyl (2*S*,3*S*,6*S*)-2,6-Dimethyl-3-hydroxy-7-octenoate (2). To LDA (86.3 mmol) generated in 380 mL of Et_2O in the standard fashion and cooled to −78 °C was added a −78 °C-cooled solution of 2′,6′-dimethylphenyl propionate (12.8 g, 72.0 mmol) in Et_2O (130 mL) via cannula over 30 min. After 3 h, a solution of chloro(cyclopentadienyl)bis-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl)titanium (1.08 L, 90.0 mmol, 83.3 mM in Et_2O) was cooled to −78 °C and transferred to the enolate solution via cannula over 25 min, keeping the internal temperature below −70 °C. The heterogeneous, deep reddish-brown solution was stirred at −78 °C for 20 h, allowed to warm to −30 °C, and then was kept between −25 and −30 °C for 5 h before being cooled back to −78 °C. The transmetalated solution was then treated with neat (*S*)-4-methyl-5-hexenal (9.29 g, 82.2 mmol) over 15 min and stirred for 12 h at −78 °C. The rapidly stirred, bright yellow, heterogeneous solution was quenched with a 1:1 mixture of THF and 8.1 M NH_4Cl (120 mL) all at once and then allowed to warm to rt for 3 h. The pale yellow suspension was filtered through Celite with Et_2O (200 mL), and the organic phase was sequentially washed with 1 N HCl (320 mL), saturated $NaHCO_3$ (125 mL), and brine (100 mL). The aqueous extracts were combined and back-extracted with EtOAc (2 × 300 mL), consolidated with the ethereal extracts, dried with $MgSO_4$, and then filtered and concentrated *in vacuo*. Purification by SiO_2 chromatography (11 × 17 cm, 70:25:5 EtOAc/CH_2Cl_2/hexanes → 80:20 EtOAc/hexanes) gave 16.00 g (77%) of a 6.1:1 mixture of the anti and syn diastereomers. Purification of the anti isomer was effected by flash chromatography on a LOBAR SiO_2 column using 3−5 g loadings (E. Merck, 3.7 × 44 cm, 10:90 EtOAc/hexanes, flow rate 20 mL/min). Diastereoselectivity was determined using ^1H NMR analysis (500 MHz, $CDCl_3$) of a crude reaction aliquot by integration of the C3 methines at 3.75 and 4.01 ppm for the threo and erythro diastereomers, respectively. Proof of relative stereochemistry for the presumed (2*S*,3*S*,6*S*) diastereomer was unambiguously determined from coupling constants of the acetonide in ref 23. Enantioselectivity for the (2*S*,3*S*,6*S*) diastereomer was determined by Mosher ester analysis using commercially available (Fluka) (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride under standard conditions. ^1H NMR analysis (500 MHz, C_6D_6) gives cleanly resolved methoxy singlets at 3.47 and 3.44 ppm for the (2*S*,3*S*) and (2*R*,3*R*) diastereomers, respectively. **(2*S*,3*S*,6*S*) Diastereomer 2a:** R_f 0.42 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (m, 3H), 5.69 (ddd, 1H, J = 17.5, 10.5, 7.5 Hz), 4.98 (d, 1H, J = 16 Hz), 4.93 (d, 1H, J = 10.5 Hz), 3.75 (m, 1H), 2.83 (dq, 1H, J = 14.5, 7.5 Hz), 2.67 (br d, 1H, J = 7.0 Hz), 2.15 (s, 6H), 2.14 (m, superimposed, 1H), 1.70−1.35 (m, 4H), 1.41 (d, 3H, J = 7.5 Hz), 1.02 (d, 3H, J = 7.0 Hz); ^{13}C NMR (125.1 MHz, $CDCl_3$) δ 174.0, 147.9, 144.4, 130.0, 128.6 (3), 125.9, 112.9, 73.6, 45.5, 37.9, 32.50, 32.47, 20.2, 16.5, 14.8; IR (thin film) 3521 (br), 1740, 1639 cm^{-1}; CI HRMS calcd for $C_{18}H_{27}O_3$ $(M + H)^+$ m/z 291.1961, found 291.1949. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.12; H, 9.07.

(2*R*,3*S*,6*S*) Diastereomer (2b): R_f 0.32 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (m, 3H), 5.68 (m, 1H), 4.97 (dd, 1H, J = 18.5, 1.5 Hz), 4.93 (dd, 1H, J = 10.5, 1.0 Hz), 4.01, (ddd, 1H, J = 11.5, 8.0, 4.0 Hz), 2.81 (dq, 1H, J = 7.5, 4.0 Hz), 2.67 (br d, 1H, J = 4.0 Hz), 2.13 (s, 6H), 2.10 (m, superimposed, 1H) 1.6−1.5 (m, 3H), 1.37 (d, 3H, J = 7.0 Hz), 1.30 (m, 1H), 1.02 (d, 3H, J = 6.5 Hz).

2′,6′-Dimethylphenyl (2*S*,3*S*,6*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-7-octenoate (3). To a 0 °C solution of 2,6-lutidine (9.45 mL, 81.1 mmol) in 250 mL of CH_2Cl_2 was added *tert*-butyldimethylsilyl triflate (11.2 mL, 48.7 mmol). A solution of **2a** (11.58 g, 39.89 mmol) in CH_2Cl_2 (20 mL) was added via cannula using an additional 30 mL to assist the transfer, and then the reaction was allowed to warm to room temperature for 12 h. The mixture was quenched into 5% $NaHCO_3$ (200 mL) and separated and the aqueous layer extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by SiO_2 chromatography (11 cm × 16 cm, 5:95 Et_2O/hexanes) to give 15.20 g (94%) of a pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (m, 3H), 5.66 (ddd, 1H, J = 18, 10, 7.5 Hz), 4.95 (br d, 1H, J = 18 Hz), 4.90 (dd, 1H, J = 10.5, 2 Hz), 4.14 (dt, 1H, J = 8, 4 Hz), 2.95 (ddd, 1H, J = 12, 7.5, 5 Hz), 2.13 (s, 6H), 2.10 (m, 1H), 1.60−1.32 (m, 4H), 1.29 (d, 3H, J = 7.5 Hz), 1.00 (d, 3H, J = 6.5 Hz), 0.91 (s, 9H), 0.10 (s, 3H), 0.098 (s, 3H); ^{13}C NMR (125.1 MHz, $CDCl_3$) δ 171.8, 148.2, 144.4, 130.1, 128.5 (3), 125.7, 112.8, 73.3, 45.4, 37.9, 32.7, 30.9, 25.9 (3), 20.2, 18.1, 16.6 (2), 11.3, −4.48, −4.55; IR (thin film) 1757, 1640 cm^{-1}; CI HRMS calcd for $C_{24}H_{41}O_3Si$ $(M + H)^+$ m/z 405.2825, found 405.2841. Anal. Calcd for $C_{24}H_{40}O_3Si$: C, 71.29; H, 9.96. Found: C, 71.2; H, 9.99.

(2*R*,3*S*,6*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-7-octenol (4). To a −78 °C solution of **3** (13.30 g, 32.87 mmol) in hexanes (300 mL) was added neat diisobutylaluminum hydride (11.70 mL, 65.74 mmol) dropwise over 45 min (precipitation occurred toward the end of the addition). After the mixture was stirred for 2.5 h, MeOH (2 mL) was carefully added and the mixture was allowed to warm to ambient temperature. Sodium potassium tartrate (132 mL, 0.5 M) was added, followed by Et_2O (70 mL), and the biphasic mixture was rapidly stirred for 10 h. The crude mixture was extracted with Et_2O (3 × 300 mL), dried with $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed in two portions by MPLC (3.7 × 44 cm, 50:50 CH_2Cl_2/petroleum ether → 50:50 Et_2O/hexanes, flow rate 20 mL/min) to give 8.61 g (91%) of a colorless oil and 100 mg of unreacted starting material: ^1H NMR (500 MHz, $CDCl_3$) δ 5.67 (ddd, 1H, J = 17.5, 10.5, 7.5 Hz), 4.96 (br d, 1H, J = 17.5 Hz), 4.93 (br d, 1H, J = 10.5 Hz), 3.78 (dd, 1H, J = 11, 3.5 Hz), 3.68 (dt, 1H, J = 6.5, 4.5 Hz), 3.52 (br dd, 1H, J = 11, 4.5 Hz), 2.78 (br s, 1H), 2.07 (m, 1H), 1.76 (m, 1H), 1.58 (m, 1H), 1.53 (m, 1H), 1.29 (dd, 1H, J = 16, 7.5 Hz), 1.25 (app s, 1H), 0.99 (d, 6H, J = 7 Hz), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125.1 MHz, $CDCl_3$) δ 144.4, 112.9, 77.5, 65.4, 37.9, 37.6, 32.4, 31.6, 25.9 (3), 20.3, 18.0, 14.7, −4.2, −4.8; IR (thin film) 3357 (br), 1640 cm^{-1}; CI HRMS calcd for $C_{16}H_{35}O_2Si$ $(M + H)^+$ m/z 287.2407, found 287.2405. Anal. Calcd for $C_{16}H_{34}O_2Si$: C, 67.07; H, 11.96. Found: C, 67.20; H, 12.02.

(2*R*,3*S*,6*S*)-1-Iodo-3-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-7-octene (5). Imidazole (2.25 g, 33.1 mmol) and Ph_3P (8.67 g, 33.1 mmol) were dissolved into a solution of **4** (8.61 g, 30.0 mmol) in 60 mL of 3:1 Et_2O/CH_3CN. The mixture was cooled to 0 °C and treated portionwise with I_2 (7.63 g, 30.0 mmol) over 30 min and then allowed to warm to ambient temperature. This reaction is self-titrating, and 50 mg portions of I_2 (150 mg, 0.59 mmol total) were added to the colorless solution until a faint yellow color persisted indicating completion (note: the color takes ca. 5 min to fade). The heterogeneous solution was concentrated to ca. 15 mL volume *in vacuo*, diluted with pentane (20 mL), and filtered through a plug of freshly prepared activity IV Al_2O_3 with 10:90 Et_2O/pentane (400 mL) and then 50:50 Et_2O/pentane (300 mL) until TLC (anisaldehyde stain) showed no residual product eluting. Concentration *in vacuo* precipitated residual Ph_3PO that was largely removed by decanting, and the diluted product was filtered through a plug of SiO_2 with 10% Et_2O/pentane (50 mL) and concentrated to give 11.11 g of a colorless oil (93%) contaminated with 538 mg of Ph_3PO that did not interfere with subsequent reactions. An analytical sample was prepared by SiO_2 chromatography (5:95 Et_2O/pentane), but the remaining material was used without further purification: ^1H NMR (500 MHz, $CDCl_3$) δ 5.67 (ddd, 1H, J = 18, 10.5, 7.5 Hz), 4.95 (br d, 1H, J = 18.5 Hz), 4.92 (dd, 1H, J = 13, 1.5 Hz), 3.58 (q, 1H, J = 5 Hz), 3.28 (dd, 1H, J = 9.5, 4.5 Hz), 3.15 (dd, 1H, J = 9.5, 7 Hz), 2.06 (m, 1H), 1.67 (m, 1H), 1.41 (m, 2H), 1.33 (m, 2H), 0.99 (d, 3H, J = 6.5 Hz), 0.96 (d, 3H, J = 6.5 Hz), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125.1 MHz, $CDCl_3$) δ 144.5, 112.7, 74.8, 39.8, 38.0, 31.1, 30.5, 25.9 (3), 20.1, 18.1, 16.9, 14.0,

−4.2, −4.4; CI HRMS calcd for $C_{16}H_{34}IOSi$ $(M + H)^+$ m/z 397.1425, found 397.1446.

(2*S*,3*R*)-3,7-Dimethyl-6-octene-1,2-diol (6). To (2*R*,3*S*)-geraniol epoxide (2.01 g, 11.8 mmol, 91% ee) in THF (25 mL) at rt was dissolved $NaBH_3CN$ (1.84 g, 29.6 mmol), and then the mixture was treated with glacial acetic acid (3.55 g, 59.2 mmol). After 12 h, another 744 mg of $NaBH_3CN$ (11.4 mmol) and 3.55 g acetic acid (59.2 mmol) were added with vigorous stirring. After an additional 8 h, the completed reaction was concentrated *in vacuo*, diluted with Et_2O (40 mL), cooled to 0 °C, and carefully treated with 15% aqueous NaOH (40 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 80 mL). The organic layers were combined, washed with brine (20 mL), and dried over $MgSO_4$ (the aqueous layer was very slowly treated with dilute HCl in the back of the hood—CAUTION: exotherm and HCN evolution!). Filtration of the ethereal extracts, concentration *in vacuo*, and SiO_2 chromatography (radial, 4 mm plate, 25:75 CH_3CN/CH_2Cl_2) gave 1.37 g (67%) of a colorless oil. Chiral GLC analysis of the unpurified material established the 1,2-diol/1,3-diol ratio as 50:1 and the ee as 91%—identical to that of the starting geraniol epoxide: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (t, 1H, 3.63 (dd, 1H, J = 10.4, 2.1 Hz), 3.55 (m, 1H), 3.52 (t, 1H), 3.36 (s, 2H), 2.02 (m, 1H), 1.96 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.55 (m, 1H), 1.45 (m, 1H), 1.17 (m, 1H), 0.91 (d, 3H, J = 6.8 Hz); ^{13}C (125.1 MHz, $CDCl_3$) δ (TMS) 131.5, 124.3, 75.7, 65.1, 35.3, 33.1, 25.6, 25.5, 17.6, 14.4; IR (thin film) 3364 (br), 822, 830; CI HRMS calcd for $C_{10}H_{21}O_2$ $(M + H)^+$ m/z 173.1542, found 173.1538; GLC analysis (Cyclodex B 0.25 mm × 30 m), t_R (2*S*,3*R*) = 19.99 min, t_R (2*R*,3*S*) = 20.35 min, t_R (1,3*R*)-diol = 22.88 min, t_R (1,3*S*)-diol = 23.29 min; 150 °C isothermal, 15 psi head pressure, H_2 22.7 mL/min, He 20.7 mL/min, air 402 mL/min.

[3(2*R*,3*S*,4*R*),4*R*,5*R*]-3-(3-Hydroxy-1-oxo-2,4,8-trimethyl-7-nonenyl)-4-methyl-5-phenyl-2-oxazolidinone (7). To diol **6** (16.3 g, 95 mmol) in 600 mL of CH_2Cl_2 and 600 mL of pH 7 phosphate buffer was added 65 g of $NaIO_4$ at room temperature. The reaction mixture was sealed and vigorously stirred for 8 h. The aqueous layer was extracted with Et_2O (2 × 600 mL), and the combined organic extracts were washed with 300 mL of saturated NaCl, dried over anhydrous Na_2SO_4, and filtered. The solvent was carefully evaporated on a rotary evaporator, but not all of it was removed due to the volatility of the aldehyde. The fragrant oil was used immediately in the following step without further purification. In a separate reaction vessel, freshly prepared di-*n*-butylboryl triflate (30.0 mL, 118.8 mmol) was added over a 5 min period to a −78 °C solution of (4*R*,5*R*)-4-methyl-5-phenyl-*N*-propionyl-2-oxazolidinone (25.4 g, 109.3 mmol) in freshly distilled CH_2Cl_2 (150 mL). The solution became heterogeneous, and after 10 min, triethylamine (18.5 mL, 133 mmol) was added dropwise over a 15 min period. After 30 min at −78 °C, the dry ice bath was removed and the mixture was allowed to warm to 0 °C slowly. The heterogeneous mixture was stirred at this temperature for 1 h and then recooled to −78 °C. The aldehyde prepared above was then added in one portion. After 45 min, the reaction was allowed to warm to 0 °C and stirred at this temperature for 7 h. The reaction was quenched with pH 7 phosphate buffer (160 mL buffer in 320 mL MeOH) and then treated with 160 mL of H_2O_2 (30%) in 530 mL of MeOH and stirred at 0 °C for 1 h. The organic solvent was removed *in vacuo*, 530 mL of 10% aqueous $NaHCO_3$ was added, and the resultant solution was extracted with CH_2Cl_2 (3 × 600 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to a light yellow oil that was analyzed by ^{1}H NMR (C_6D_6) and indicated 100:1 diastereoselectivity. The crude mixture was first purified by SiO_2 flash chromatography (7:1 hexane/EtOAc), followed by MPLC (3.7 × 44 cm, 7:1 hexanes/EtOAc, flow rate 20 mL/min) to give 22.8 g of the desired product as a colorless oil (64% yield for two steps). **(2*R*)-2,6-Dimethylheptenal:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (d, 1H, J = 2.0 Hz), 5.06 (m, 1H), 2.27 (m, 1H), 1.74 (m, 1H), 1.67 (s, 3H), 1.07 (d, 3H, J = 7.1 Hz); ^{13}C NMR δ 205.1, 132.6, 123.3, 54.7, 30.6, 25.6, 25.2, 17.6, 13.2; IR ($CHCl_3$) 1726 cm^{-1}.

7: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.28 (m, 5H), 5.69 (d, 1H, J = 7.4 Hz), 5.10 (m, 1H), 4.79 (m, 1H), 3.94 (m, 1H), 3.70 (m, 1H), 2.69 (d, 1H, J = 3.9 Hz), 2.05 (m, 1H), 1.97 (m, 1H), 1.68 (s, 3H), 1.62 (s, 3H), 1.59 (m, 1H), 1.45 (m, 1H), 1.24 (d, 3H, J = 7.1 Hz), 1.16 (m, 1H), 1.01 (d, 3H, J = 6.5 Hz), 0.94 (d, 3H, J = 6.4 Hz), 0.94 (d, 3H, J = 6.44 Hz); ^{13}C NMR (125, MHz, $CDCl_3$) δ 177.4, 152.4, 133.2, 131.6, 128.8, 128.7, 125.6, 124.3, 78.8, 75.3, 54.8, 39.9, 35.3, 32.9, 25.7, 25.2, 17.6, 15.0, 14.3, 10.9; IR (thin film) 3498 (br), 1691 cm^{-1}; CI HRMS calcd for $C_{22}H_{32}NO_4$ $(M + H)^+$ m/z 374.5046, found 374.2326.

[3-(2*R*,3*S*,4*R*),4*R*,5*R*]-3-[[(3-*tert*-Butyldimethylsilyl)oxy]-2,4,8-trimethyl-3-hydroxy-1-oxo-7-nonenyl]-4-methyl-5-phenyl-2-oxazolidinone (8). To a solution of alcohol **7** (22.4 g, 60 mmol) in 600 mL of CH_2Cl_2 at 0 °C were added 2,6-lutidine (9.08 mL, 78 mmol) and, 10 min later, *tert*-butyldimethylsilyl trifluoromethanesulfonate (16.5 mL, 72 mmol). After 3 h, the solution was quenched by the addition of 240 mL of saturated aqueous $NaHCO_3$. The aqueous layer was reextracted with CH_2Cl_2 (2 × 600 mL), and the combined organic extracts were washed with 300 mL of $NaHSO_4$ (0.5 M). The aqueous layer was back-extracted with CH_2Cl_2 (2 × 600 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resultant light yellow oil was purified by SiO_2 flash chromatography (10:1 hexane/EtOAc) to give a colorless oil, 26.8 g, in 92% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.29 (m, 5H), 5.63 (d, 1H, J = 7.1 Hz), 5.08 (m, 1H), 4.72 (m, 1H), 3.96 (m, 2H), 2.01 (m, 1H), 1.93 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.55 (m, 2H), 1.19 (d, 3H, J = 6.4 Hz), 1.18 (m, 1H), 0.90 (s, 9H), 0.87 (2 d, overlapping, 6H, J = 7.9, 12.0 Hz), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 152.5, 133.2, 131.2, 128.7, 125.5, 124.6, 78.7, 77.3, 55.1, 41.5, 38.3, 33.4, 26.1, 25.7, 18.4, 17.7, 14.7, 14.6, 14.1, −3.8, −4.1; IR (thin film) 2958, 2928, 1784, 1698 cm^{-1}; CI HRMS calcd for $C_{28}H_{46}NO_4Si$ $(M + H)^+$ m/z 488.7686, found 488.3196.

Phenylmethyl (2*R*,3*S*,4*R*)-(3[(*tert*-Butyldimethylsilyl)-oxy]-2,4,8-trimethyl-7-nonenoate (9). To a 0 °C solution of benzyl alcohol (11.95 mL, 115.5 mmol) in 55 mL of THF was added *n*-BuLi (57.7 mL, 92.4 mmol, 1.6 M in hexane). The reaction mixture was maintained at 0 °C for 15 min and then cannulated into a cooled (0 °C) solution of **8** in 55 mL of THF. The reaction mixture was kept at 0 °C for 3.5 h and then was quenched by adding 460 mL of H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 × 460 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to obtain a crude colorless oil. The product was purified by SiO_2 flash chromatography (10:1 hexane/EtOAc) to give 19.49 g of colorless oil in 86% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 5.11 (s, 3H), 5.07 (m, 1H), 3.87 (dd, 1H, J = 6.6, 6.4 Hz), 2.67 (m, 1H), 1.99 (m, 1H), 1.89 (m, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.46 (m, 1H), 1.19 (d, 3H, J = 7.1 Hz), 0.92 (s, 9H), 0.87 (d, 3H, J = 6.8 Hz), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 135.0, 131.3, 128.5, 128.13, 128.10, 124.5, 66.1, 43.5, 38.0, 33.4, 26.0, 25.9, 25.7, 18.3, 17.6, 14.5, 13.7, −4.0, −4.1; IR (thin film) 1735 cm^{-1}; CI HRMS calcd for $C_{25}H_{43}O_3Si$ $(M + H)^+$ m/z 419.7052, found 419.2981.

(2*R*,3*S*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2,4,8-trimethyl-7-nonenol (10). To a cooled (−78 °C) stirred solution of benzyl ester **9** in 180 mL of CH_2Cl_2 was added neat DIBAL (18.0 mL, 101.6 mmol) dropwise over 15 min. The reaction temperature was held at −78 °C for 30 min and then allowed to warm to 0 °C and maintained at this temperature for an additional 30 min. Excess DIBAL was quenched with 2.5 mL of MeOH, and the reaction mixture was diluted in 160 mL of CH_2Cl_2. A solution of 200 mL of K-Na tartrate (0.5 M) was added at 0 °C, and the viscous solution was stirred vigorously for 18 h, whereafter two clear layers had formed. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 120 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solution was filtered and concentrated *in vacuo*. SiO_2 flash chromatography (5:1 hexanes/EtOAc) afforded a colorless oil, 14.01 g, 96% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (m, 1H), 3.61 (m, 2H), 3.45 (m, 1H), 2.20 (br, 1H), 1.92 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.60 (m, 1H), 1.45 (m, 1H), 1.15 (m, 1H), 0.91 (d, 3H, J = 6.8 Hz), 0.84 (d, 3H, J = 6.8 Hz), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 131.3, 124.6, 76.7, 66.4, 39.3, 35.9, 34.5, 26.1, 26.0, 25.7, 18.2, 17.6, 15.7, 12.5, −4.1, −4.3: IR (thin film) 3345 (br) cm^{-1}; CI HRMS calcd for $C_{18}H_{39}O_2Si$ $(M + H)^+$ m/z 315.5958, found 315.2728.

(2*R*,3*S*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-iodo-2,4,8-trimethyl-7-nonene (11). A 0 °C solution of alcohol **10** (14 g, 44 mmol), PPh_3 (12.87 g, 49.06 mmol), and imidazole (3.34 g, 49.06 mmol) in 84 mL of Et_2O/CH_3CN (3:1) was treated with iodine (11.32 g, 44 mmol) portionwise. The solution was then allowed to warm to rt and after 45 min was concentrated *in vacuo*. The oil was filtered through basic alumina (activity IV, hexane/Et_2O 9:1), concentrated *in vacuo*, and then flushed through a SiO_2 plug using 9:1 hexane/Et_2O. The solvent was removed on a rotary evaporator to give 16.75 g of the desired iodide (93% yield) that was used without further purification: ^1H NMR (500 MHz, $CDCl_3$) δ 5.08 (m, 1H), 3.55 (t, 1H, J = 4.0 Hz), 3.27 (dd, 1H, J = 9.53, 6.0 Hz), 3.08 (dd, 1 H, J = 9.53, 7.0 Hz), 2.01 (m, 1H), 1.95−1.85 (m, 2H), 1.68 (s, 3H), 1.58 (s, 3H), 1.58 (m, overlapping, 1H), 1.45 (m, 1H), 1.0 (d, 3H, J = 6.8 Hz), 0.90 (s, 9H), 0.88 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.3, 124.6, 77.8, 39.9, 36.6, 33.8, 26.2, 26.1, 26.0, 25.8, 18.4, 17.7, 16.2, 15.5, 14.6, −3.8; IR (thin film) 2928, 2856 cm^{-1}.

Spirocyclic Diene 12. To a −78 °C solution of acetone *N*,*N*-dimethylhydrazone (2.590 g, 25.91 mmol) in 68 mL of THF was added BuLi (10.8 mL, 2.41 M in hexanes) over 5 min, and the reaction was warmed in a 0 °C bath for 2 h. The reaction mixture was cooled back to −78 °C and treated with neat **5** (10.06 g, 25.40 mmol) via cannula using 4 mL of additional THF to assist the transfer. The heterogeneous solution was allowed to warm to rt and became a bright yellow homogeneous solution after 15 min. TLC after 1 h showed no remaining **5**, so the reaction was cooled to −78 °C, treated with BuLi (10.8 mL, 2.41 M in hexanes), warmed in a 0 °C bath for 2 h, cooled back to −78 °C, and treated with neat **11** (11.00 g, 25.91 mmol), and the heterogeneous orange mixture was allowed to warm to rt. After 5 h, the reaction was quenched into pH 7.2 phosphate buffer (200 mL, 1.0 M), extracted with Et_2O (4 × 200 mL), dried with $MgSO_4$, filtered, concentrated *in vacuo*, and transferred to a 200 mL polyethylene bottle using 60 mL of CH_3CN and 10 mL of *i*-PrOH. To the unpurified material was added concentrated aqueous HF (47%, 1 mL every 8 h for 3 d), and the reaction vessel was capped and stirred vigorously. After a total of 72 h, the reaction contents were cautiously quenched into a stirring mixture of Et_2O (200 mL) and saturated aqueous Na_2CO_3 (600 mL) and separated, and the aqueous layer was extracted with Et_2O (4 × 300 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by MPLC (LOBAR, 3.7 × 44 cm, 5:95 Et_2O/hexanes, flow rate 20 mL/min) to give 7.36 g of **11** (77% total yield based on **5** equivalence): ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddd, 1H, J = 18, 10.5, 7.5 Hz), 5.10 (br t, 1 H, J = 7 Hz), 4.96 (br d, 1H, J = 18 Hz), 4.91 (br d, 1H, J = 11 Hz), 3.29 (dd, 1H, J = 10, 2 Hz), 3.17 (dt, 1H, J = 7.5, 2 Hz), 2.13 (m, 1H), 2.04 (m, 2H), 1.95 (m, 1H), 1.85 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.73−1.35 (m, 12 H), 1.3−1.2 (m, 3H), 1.01 (d, 3H, J = 6.5 Hz), 0.99 (d, 3H, J = 6.5 Hz), 0.88 (d, 3H, J = 7 Hz), 0.82, (d, 3H, J = 6.5 Hz); ^{13}C NMR (125.1 MHz, $CDCl_3$) δ 145.0, 131.4, 124.7, 112.4, 95.6, 74.8, 74.6, 37.9, 36.1, 35.1, 34.1, 32.9, 31.8, 30.9, 30.3, 28.3, 27.5, 26.7, 25.7, 24.6, 20.1, 18.1, 17.7, 16.4, 10.8; IR (thin film) 1640 cm^{-1}; $[\alpha]^{21}_D$ −62.5 (c = 0.665, $CHCl_3$); CI HRMS calcd for $C_{25}H_{45}O_2$ $(M + H)^+$ m/z 377.3419, found 377.3420. Anal. Calcd for $C_{25}H_{44}O_2$: C, 79.73; H, 11.78. Found: C, 80.02; H, 11.82.

Epoxide 13. To a −20 °C solution of **12** (6.62 g, 17.11 mmol) in 200 mL of CH_2Cl_2 was added *m*-CPBA (3.55 g, 83.2% by iodometric titration, actual = 2.95 g, 17.09 mmol) via a solid addition funnel over 30 min. After 5.5 h, the cold solution was filtered through a Buchner funnel, the cake was washed with 0 °C 10:90 Et_2O/pentane (150 mL), and the solution was shaken sequentially with 10% aqueous Na_2SO_3 (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and chromatographed on SiO_2 (10:90 Et_2O/hexanes → 25:75 Et_2O/hexanes) to give 6.56 g of **13** and 321 mg of unreacted starting material (98% yield, 100% based on recovered **12**): ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (m, 1H), 4.96 (br d, 1H, J = 17 Hz), 4.92 (br d, 1H, J = 10.5 Hz), 3.30 (m, 1H), 3.16 (m, 1H), 2.71 (t, 1H, J = 6 Hz), 2.11 (m, 1H), 2.04 (m, 1H), 1.85 (m, 1H), 1.70−1.20 (m, 17H), 1.31 (s, 3H), 1.27 (2 s, 3H), 1.00 (app t, 6H), 0.90 (d, 3H, J = 7 Hz), 0.81 (d, 3H, J = 6.5 Hz); CI HRMS calcd for $C_{25}H_{45}O_3$ $(M + H)^+$ m/z 393.3368, found 393.3358.

Aldehyde 14. To a 0 °C solution of **13** in 200 mL of Et_2O was added H_5IO_6 (4.15 g, 18.2 mmol) portionwise over 20 min, and then the resulting mixture was allowed to warm to rt. After 3 h, the reaction mixture was filtered through a SiO_2 plug with Et_2O, concentrated *in vacuo*, and chromatographed on SiO_2 using 5:95 EtOAc/hexanes to give 3.09 (53%) of a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 5.72 (ddd, 1H, J = 17.5, 10.5, 7.5 Hz), 4.96 (br d, 1H, J = 17.5 Hz), 4.92 (br d, 1H, J = 10.5 Hz), 3.29 (dd, 1H, J = 10.5 Hz), 3.14 (br t, 1H, J = 9.5 Hz), 2.47 (m, 2H), 2.13 (m, 1H), 2.05 (m, 1H), 1.85 (m, 1H), 1.80 (m, 1H), 1.70−1.20 (m, 14H), 1.00 (d, 3H, J = 6.5 Hz), 0.99 (d, 3H, J = 8 Hz), 0.91 (d, 3H, J = 7 Hz), 0.81 (d, 3H, J = 6.5 Hz); ^{13}C NMR (125.1 MHz, $CDCl_3$) δ 202.5, 144.9, 112.4, 95.7, 74.7, 74.5, 41.0, 37.9, 36.0, 35.0, 34.0, 32.9, 30.9, 30.2, 28.2, 27.5, 26.6, 23.9, 20.1, 18.1, 16.3, 10.8; IR (thin film) 1639 cm^{-1}; $[\alpha]^{22}_D$ −57.9 (c = 1.835, $CHCl_3$); CI HRMS calcd for $C_{22}H_{39}O_3$ $(M + H)^+$ m/z 351.2900, found 351.2908.

***β*-Hydroxy Ketone 15.** To LDA (10.08 mmol) generated in 43 mL of Et_2O in the standard fashion and cooled to −78 °C was added a −78 °C-cooled solution of 2′,6′-dimethylphenylpropionate (1.44 g, 8.08 mmol) in Et_2O (15 mL) via cannula over 15 min, keeping the internal temperature under −70 °C. After 3 h, a −78 °C solution of chloro(cyclopentadienyl)bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl)titanium (120 mL, 10.0 mmol, 83.3 mM was transferred to the enolate solution via cannula, keeping the internal temperature below −70 °C. The reaction was stirred at −78 °C for 24 h, allowed to warm to −30 °C, and then was kept between −20 and −25 °C for 5.5 h before being cooled back to −78 °C. The reagent was treated with a solution of **14** (2.80 g, 8.00 mmol) in Et_2O (8 mL + 4 mL to assist transfer) and stirred for 12 h at −78 °C after which the reaction was quenched with a 1:1 mixture of THF and saturated aqueous NH_4Cl (32 mL) all at once and then stirred vigorously for 3 h at 0 °C. The solution was filtered through a plug of Celite with EtOAc (50 mL), and the organic phase was sequentially washed with 0.5 N HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (50 mL). The aqueous extracts were combined and back-extracted with EtOAc (1 × 200 mL), and the organic extracts were combined, dried with $MgSO_4$, and then filtered and concentrated *in vacuo*. Purification by SiO_2 chromatography (8:92 EtOAc/hexanes → 25:75 EtOAc/hexanes) gave 3.23 g of a 7.4:1 anti/syn aldol product mixture and 590 mg of recovered **14** (76% yield, or 97% based on recovered starting material). An analytical sample was purified by HPLC (8:92 EtOAc/hexanes, t_R 24 min, 5 mL/min), but the two diastereomers were not separated at this point since they are easier to purify after convertion into **16**: R_f 0.31 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (br s, 3H), 5.72 (ddd, 1H, J = 17.5, 10.5, 7.5 Hz), 4.96 (br d, 1H, J = 17.5 Hz), 4.91 (br d, 1H, J = 10.5 Hz), 3.76 (dt, 1H, J = 7, 3 Hz), 3.31 (dd, 1H, J = 10, 1.5 Hz), 3.16 (br dt, 1H, J = 9, 1.5 Hz), 2.87 (dq, 1H, J = 14, 7 Hz), 2.16 (s, 6H), 2.17−2.00 (m, 2H), 1.88 (m, 1H), 1.8−1.2 (m, 18H), 1.45 (d, 3H, J = 7.5 Hz), 1.03 (d, 3H, J = 6.5 Hz), 1.00 (d, 3H, J = 6.5 Hz), 0.91 (d, 3H, J = 7 Hz), 0.82, (d, 3H, J = 6.5 Hz); ^{13}C NMR (125.1 MHz, $CDCl_3$) δ 174.0, 147.8, 144.9, 130.0, 128.7 (3), 126.0, 112.4, 95.6, 74.7, 73.9, 45.2, 37.9, 36.1, 65.1, 34.8, 32.9, 31.6, 30.9, 30.2, 28.2, 27.7, 27.6 (2), 26.7, 20.1, 18.1, 16.7, 16.5 (2), 14.9, 10.9; IR (thin film) 3492 (br), 3070, 1738, 1639 cm^{-1}; CI HRMS calcd for $C_{33}H_{52}O_5$ $(M)^+$ m/z 528.3815, found 528.3827.

Weinreb Amide 16. Following the procedure of Heathcock *et al.*,[32] a 7.4:1 mixture of **15a** and **15b** (2.49 g, 4.33 mmol) was dissolved in MeOH (26 mL) and treated with a solution of KOH (2.43 g, 43.3 mmol) in 1:2 MeOH/H_2O (17 mL). After 2 h, the reaction was diluted with Et_2O, cooled with dry ice, and quenched with 1 N HCl (100 mL). The ethereal phase was separated, and the aqueous phase was extracted with additional Et_2O (4 × 150 mL), dried with $MgSO_4$, filtered,

concentrated to a bright yellow oil *in vacuo*, and chromatographed on a short SiO_2 column (3.5 × 6 cm, 20:80 EtOAc/hexanes until the 2,6-dimethylphenol eluted, and then 100% EtOAc). The bright yellow oil was dissolved in DMF (8 mL) and 1-hydroxy-7-azabenzotriazole (589 mg, 4.33 mmol), *N*,*N*-diisopropylethylamine (1.46 mL, 8.66 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride were added sequentially, and the mixture was stirred until it became homogeneous (5 min). The reaction was cooled to 0 °C and treated with solid dicyclohexylcarbodiimide (3.13 g, 15.16 mmol) portionwise over 10 min, and the reaction mixture was allowed to warm to rt after it became homogeneous. After 8.5 h, the heterogeneous solution was quenched into 400 mL of a 1:1 mixture of Et_2O and saturated aqueous $NaHCO_3$ and separated, and the ethereal phase was washed with 1 N HCl, filtered through a glass frit, and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo*, and crude ^{1}H NMR indicated no detectable epimerization at the 2 position (i.e., the anti/syn ratio is still exactly 7.4:1). The oil was purified by radial SiO_2 chromatography (2 mm plate, 25:75 EtOAc/petroleum ether → 60:40 EtOAc/petroleum ether) to give 1.59 g of **16a** and 215 mg of **16b** (89% for two steps): **(2*R*,3*S*) Diastereomer 16a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddd, 1H, J = 17.5, 10.5, 7.5 Hz), 4.96 (br d, 1H, J = 17.5 Hz), 4.91 (br d, 1H, J = 10.5 Hz), 3.72 (s, 3H), 3.58 (dt, 1H, J = 9, 4.5 Hz), 3.28 (dd, 1H, J = 10.5, 2 Hz), 3.21 (br s, 3H), 3.16 (dt, 1H, J = 9, 1.5 Hz), 2.97 (br m, 1H), 2.12 (m, 1H), 2.03 (m, 1H), 1.86 (m, 1H), 1.72−1.12 (m, 18H), 1.24 (d, 3H, J = 7.5 Hz), 1.23 (m, 3H, superimposed), 1.00 (d, 3H, J = 6 Hz), 0.89 (d, 3H, J = 7 Hz), 0.81, (d, 3H, J = 6.5 Hz); ^{13}C NMR (125.1 MHz, $CDCl_3$) δ 177.4, 144.9, 112.3, 95.5, 74.6, 74.5, 61.5, 39.7, 37.8, 36.0, 34.7, 34.6, 32.8, 32.2, 31.7, 30.8, 30.2, 28.2, 28.0, 27.4, 26.7, 26.6, 20.0, 18.0, 11.7, 15.1, 10.9; IR (thin film) 3451 (br), 3075, 1640 cm^{-1}; CI HRMS calcd for $C_{27}H_{50}NO_5$ (M + H)$^+$ m/z 468.3688, found 468.3692.

(2*S*,3*S*) Diasteromer 16b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddd, 1H, J = 17.5, 10.5, 7.5 Hz), 4.96 (br d, 1H, J = 17.5 Hz), 4.91 (br d, 1H, J = 10.5 Hz), 3.84 (m, 1H), 3.71 (s, 3H), 3.29 (dd, 1H, J = 9.5, 2 Hz), 3.20 (br s, 3H), 3.16 (dt, 1H, J = 7.5, 1.5 Hz), 2.89 (br d, 1H), 2.13 (m, 1H), 2.03 (m, 1H), 1.85 (m, 1H), 1.70−1.20 (m, 18H), 1.18 (d, 3H, J = 7 Hz), 1.00 (app t, 6H, J = 7 Hz), 0.90 (d, 3H, J = 7 Hz), 0.82, (d, 3H, J = 6.5 Hz).

***β*-Hydroxy Ketone 17.** To a −78 °C solution of **16a** (1.115 g, 2.384 mmol) in THF (20 mL) was added MeLi (5.70 mL, 7.98 mmol, 1.40 M in Et_2O) dropwise over 15 min, and the reaction mixture was warmed in a −20 °C bath. After 3 h, the reaction was quenched into a rapidly stirring, 0 °C mixture of 1:1 Et_2O and 1 N HCl (100 mL) via cannula, the ether layer was separated, and the aqueous layer was extracted with more Et_2O (3 × 120 mL). The organic phases were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed on SiO_2 (10:90 → 50:50 EtOAc/hexanes gradient) to give 669 mg of product and 258 mg of unreacted starting material (66%, 86% based on recovered **16a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddd, 1H, J = 17.5, 10, 7.5 Hz), 4.96 (br d, 1H, J = 17.5 Hz), 4.91 (br d, 1H, J = 10.5 Hz), 3.64 (br d, 1H, J = 5.5 Hz), 3.29 (dd, 1H, J = 10, 2 Hz), 3.15 (dt, 1H, J = 9.5, 1.5 Hz), 2.68 (d, 1H, J = 6.5 Hz), 2.64 (m, 1H), 2.20 (s, 3H), 2.13 (m, 1H), 2.03 (m, 1H), 1.85 (br m, 1H), 1.7−1.2 (m, 17H), 1.15 (d, 3H, J = 7 Hz), 1.00 (d, 6H, J = 7 Hz), 0.89 (d, 3H, J = 7 Hz), 0.81, (d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 144.9, 112.3, 95.5, 74.6, 74.0, 51.8, 37.9, 36.0, 35.0, 34.7, 32.9, 31.2, 30.9, 30.2, 29.9, 28.2, 27.6, 27.5, 26.7, 20.1, 18.0, 16.6, 14.0, 10.9; IR (thin film) 3458 (br), 3076, 1711 cm^{-1}; CI HRMS calcd for $C_{26}H_{47}O_4$ (M + H)$^+$ m/z 423.3474, found 423.3499.

[3(2*R*,3*R*),4*R*]-3-(3-Hydroxy-2-methoxy-4-methyl-1-oxopentyl)-4-(phenylmethyl)-2-oxazolidinone (19). Following the method of Evans *et al.*,[35] a rapidly stirring suspension of $Sn(OTf)_2$ (13.1 g, 31.43 mmol) in 101 mL of CH_2Cl_2 was added triethylamine (4.38 mL, 31.43 mmol) at rt, and after 2 min, the yellow-brown suspension was cooled to −78 °C. After 15 min, a solution of (*R*)-(methoxyacetyl)oxazolidinone **18** in 34 mL of CH_2Cl_2 was added dropwise over 40 min and the resulting mixture then stirred at −78 °C for 2 h. The reaction mixture was treated with TMEDA (3.11 mL, 31.43 mmol) dropwise and, after 15 min, with freshly distilled, neat isobutyraldehyde (2.00 mL, 22.0 mmol). The reaction was stirred for 5 h at −78 °C and then poured into a rapidly stirring mixture of 400 mL of 1 M $NaHSO_4$ (aq) and 300 mL of CH_2Cl_2. The organic phase was separated, the aqueous phase was extracted with EtOAc (2 × 300 mL), and the organic phases were consolidated and washed with saturated aqueous $NaHCO_3$. The resulting solution was filtered through a Buchner filter, washed with brine, and dried over Na_2SO_4. The desiccant was filtered off, and the solution was concentrated *in vacuo* to give 6.10 g of crude material that was analyzed by ^{1}H NMR to determine the diastereomeric ratio. Integration of the methoxy singlets gives a ratio of 73.4 (2*R*,3*R*):14.1 (unassigned):9.0 (2*R*,3*S*):3.5 (unassigned). The chemical shifts (500 MHz, $CDCl_3$) are as follows: starting oxazolidinone, 3.521 ppm; (2*R*,3*R*)-isomer, 3.415 ppm; (2*R*,3*S*)-isomer, 3.372 ppm; other two isomers, 3.476 ppm, 3.449 ppm. SiO_2 chromatography on a LOBAR column (E. Merck, 3.7 × 44 cm, 5:95 acetone/CH_2Cl_2, flow rate 20 mL/min) gave 3.92 g of (2*R*,3*R*), 1.41 g of the other diastereomers, and 764 mg of unreacted starting material (93% conversion). The product solified upon standing and was recrystallized from a mixture of hot Et_2O/hexanes (2:5). Four crops gave a total of 3.89 g of product (58%, 68% based on recovered oxazolidinone): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5H), 5.15 (d, 1H, J = 8.5 Hz), 4.78 (m, 1H), 4.25 (dd, 1 H, J = 17, 9 Hz), 4.21 (dd, 1H, 9, 3 Hz), 3.62 (dt, 1H, J = 9, 3 Hz), 3.42 (s, 3H), 3.38 (dd, 1H, J = 13.5, 3.5 Hz), 2.83 (dd, 1H, J = 13.5, 9.5 Hz), 2.07 (m, 1H), 1.95 (br d, 1H, J = 9 Hz), 1.00 (d, 3H, J = 7 Hz), 0.95 (d, 3H, J = 7 Hz); ^{13}C NMR (125.1 MHz, $CDCl_3$) δ 173.1, 154.3, 135.0, 129.3(2), 128.9(2), 127.4, 79.5, 77.09, 66.8, 58.1, 55.5, 38.1, 29.7, 19.4, 14.9; IR (KBr) 3493 (br), 3078, 3022, 1775, 1698 cm^{-1}; mp 94−95 °C; $[\alpha]^{22}_D$ −102.3 (c = 2.00, MeOH); CI HRMS calcd for $C_{17}H_{24}NO_5$ (M + H)$^+$ m/z 322.1655, found 322.1655. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.77; H, 7.34; N, 4.33.

(2*R*,3*R*)-2,*N*-Dimethoxy-3-hydroxy-4,*N*-dimethylpentanamide (20). To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.06 g, 21.08 mmol) in 54 mL of CH_2Cl_2 cooled to −20 °C was added Me_3Al (10.5 mL, 21.08 mmol, 2.0 M) dropwise over 5 min. After another 5 min, the reaction mixture was allowed to warm to rt for 1 h (it became homogeneous) and was then cooled back to −20 °C. A solution of **19** (2.26 g, 7.03 mmol) in 54 mL of CH_2Cl_2 was added via addition funnel over 30 min to the above solution and then stirred between −10 to −15 °C for 4 h and finally at rt for 1 h. The completed reaction was quenched with 1 N tartaric acid (54 mL) over 10 min and stirred rapidly for 1 h at rt, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and chromatographed on SiO_2 (10:90 acetone/CH_2Cl_2 → 20:80 acetone/CH_2Cl_2, then EtOAc) to give 1.44 g (100%) of **19**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (br d, 1H, J = 5.5 Hz), 3.77 (s, 3H), 3.73 (br s, 1H), 3.38 (s, 3H), 3.26 (br s, 3H), 2.45 (br s, 1H), 1.92 (m, 1H), 0.99 (d, 3H, J = 7 Hz), 0.95 (d, 3H, J = 6.5 Hz); ^{13}C (125.1 MHz, $CDCl_3$) δ 172.4, 77.8, 75.6, 61.4, 57.5, 32.1, 29.7, 19.6, 15.8; IR (KBr) 3440 (br), 1647; mp 44−46 °C; CI HRMS calcd for $C_9H_{20}NO_4$ (M + H)$^+$ m/z 206.1396, found 206.1384. Anal. Calcd for $C_9H_{19}NO_4$: C, 52.67; H, 9.33; N, 6.82. Found: C, 52.63; H, 9.36; N, 6.80.

2′-(Phenylmethoxy)-(2*Z*,6*E*)-4-oxo-2-methyl-3-[2″-[(phenylmethoxy)carbonyl]]octadienoate (22). To a suspension of CuCN (898 mg, 10 mmol) in 40 mL of THF at −40 °C was added MeLi (7.14 mL, 10 mmol, 1.40 M in Et_2O), and after 20 min, the mixture was cooled to −78 °C for 1 h. To this cuprate solution was added neat **21** (2.94 g, 10 mmol) over 5 min using 2 mL of THF to assist the transfer to immediately produce a deep orange-red color. After 2 h, *t*-3-pentenoyl chloride[41] (1.3 g, 11 mmol) was added all at once, and the mixture was stirred for 2 h at −78 °C and then allowed to warm to 0 °C for 15 min. The greenish, heterogeneous solution was quenched with 5.6 mL of water and filtered through a Celite pad with Et_2O, and the filtrate was washed with 150 mL of brine and separated. The brine was extracted with 300 mL of Et_2O, and

the combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed on SiO_2 (10:90 EtOAc/hexanes) to give 3.25 g (83% yield) of a pale yellow oil as a single detectable geometrical isomer. This material is semistable and should be reduced the day it is prepared: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 10H), 5.46 (m, 2H), 5.01 (s, 4H), 3.26 (m, 2H), 2.03 (s, 3H), 1.65 (d, 2H, J = 3.5 Hz); IR (thin film) 3033, 1731, 1704, 1643 cm^{-1}; CI HRMS calcd for $C_{24}H_{25}O_5$ $(M + H)^+$ m/z 393.1702, found 393.1694.

1′-(Phenylmethyl)-(2*Z*,4*R*,6*E*)-4-hydroxy-2-methyl-3-[1″-(phenylmethoxy)carbonyl]octadienoate (23). To a −20 °C solution of **22** (1.6 g, 4 mmol) in 8 mL of THF was added a solution of (+)-DIP-Chloride (1.92 g, 6 mmol, Aldrich). The reaction was stirred for 3 days at −18 °C and then allowed to warm to 0 °C for 4 h. The reaction mixture was poured into a 0 °C mixture of H_2O_2 (0.5 mL, 30%) and MeOH (10 mL). After the mixture was stirred for 2 h, the solvents were removed *in vacuo*, the aqueous layer was extracted with ether (3 × 30 mL), and the combined ethereal extracts were washed with brine (20 mL) and then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by radial SiO_2 chromatography (2 mm plate, 12:88 → 25:75 EtOAc/hexanes) to give 1.4 g of a colorless oil (88% yield). The enantioselectivity of the reduction was determined to be 80% ee using standard Mosher ester analysis[22] with a racemic control: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 10H), 5.55 (m, 1H), 5.42 (m, 1H), 5.03 (s, 4H), 4.57 (dt, 1H, J = 8.5, 6.0 Hz), 2.50 (d, 1H, J = 6.5), 2.46 (overlapping, 1H), 2.33 (ddd, 1H, J = 10.5, 6.0, 5.0 Hz), 1.96 (s, 3H), 1.66 (dd, 3H, J = 6.5, 0.5 Hz); ^{13}C NMR (125.1 MHz, $CDCl_3$) δ 167.46, 167.37, 141.4, 135.3, 131.1, 129.7 (2), 128.5 (4), 128.3, 125.8 (2), 69.7, 67.1 (2), 39.2, 18.0, 15.0; IR (thin film) 3499 (br), 3032, 1714, 1643 cm^{-1}; CI HRMS calcd for $C_{24}H_{27}O_5$ $(M + H)^+$ m/z 395.1858, found 395.1866.

1′-(Phenylmethyl)-(2*E*,4*R*,6*E*)-4[(triethylsilyl)oxy]-2-methyl-3-[1″-(phenylmethoxy)carbonyl]octadienoate (24). To a 0 °C solution of **23** (1.283 g, 3.22 mmol) in 15 mL of CH_2Cl_2 was added triethylamine (0.90 mL, 6.44 mmol), 20 mg of DMAP, and then chlorotriethylsilane (3.44 mL, 15.2 mL). After 2 h, the reaction was quenched into saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude, purple oil was purified by flash SiO_2 chromatography (10:90 EtOAc/hexanes) to give 1.62 g (99% yield) of a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 10H), 5.47 (ddd, 1H, J = 15.3, 12.3, 6.3 Hz), 5.41 (m, 1H), 5.09 (d, 1H, J = 12.6 Hz), 5.03 (d, 1H, J = 12.3 Hz), 5.00 (d, 1H, J = 12.3 Hz), 4.92 (d, 1H, J = 12.6 Hz), 4.57 (dd, 1H, J = 7.8, 6.0 Hz), 2.50 (m, 1H), 2.36 (m, 1H), 1.94 (s, 3H), 1.62 (dd, 3H, J = 5.8, 0.8 Hz), 0.89 (t, 9H, J = 7.8 Hz), 0.52 (q, 6H, J = 7.8 Hz); ^{13}C NMR (125.1 MHz, $CDCl_3$3) δ 167.4 (2), 144.8, 135.7, 135.5, 128.4 (3), 128.3 (3), 128.2 (3), 127.9 (2), 126.8 (2), 71.4, 67.0, 66.6, 40.2, 17.9, 14.8, 6.6 (3), 4.6 (3); IR (thin film) 3032, 1641 cm^{-1}; CI HRMS calcd for $C_{30}H_{41}O_5Si$ $(M + H)^+$ m/z 509.2723, found 509.2716.

1′-(Phenylmethyl) (2*Z*,4*R*)-4-[(Triethylsilyl)oxy]-2-methyl-6-oxo-3-[(phenylmethyl)oxy]carbonyl]hexenoate (25). To a rapidly stirring, −78 °C solution of **23** (1.09 g, 2.15 mmol) in 20 mL of CH_2Cl_2 was bubbled O_3 portionwise, and the reaction was followed by TLC for the disappearance of starting material. The reaction was purged with N_2 for 10 min and then treated with Ph_3P (562 mg, 2.15 mmol) in 5 mL of CH_2Cl_2 and allowed to warm to rt. After 1 h, the reaction mixture was concentrated on a rotary evaporator and loaded directly on a SiO_2 column (9 × 11 cm, 15:85 EtOAc/hexanes → 25:75 EtOAc/hexanes) to give 855 mg (80%) of a colorless oil (lachrymatory!): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.32 (m, 10H), 5.21 (dd, 1H, J = 8.0, 4.0 Hz), 5.07 (d, 1H, J = 12.5 Hz), 5.03 (d, 1H, J = 12.5 Hz), 5.01 (d, 1H, J = 12.5 Hz), 4.97 (d, 1H, J = 12.5 Hz), 3.12 (2 dd, 1H, J = 17.0, 8.0 Hz), 2.73 (dd, 1H, J = 17.0, 4.0 Hz), 2.01 (s, 3H), 0.87 (t, 9H, J = 8.0 Hz), 0.55 (q, 6H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 167.2, 166.9, 142.7, 135.3, 135.2, 129.5, 128.5 (3), 128.3 (6), 128.1, 67.2, 66.9, 65.6, 50.3, 14.7, 6.6 (3), 4.4 (3); IR (thin film) 3034, 1728, 1644 cm^{-1}; CI HRMS calcd for $C_{28}H_{35}O_6Si$ $(M - H)^+$ m/z 495.2159, found 495.2162.

(2*Z*,4*R*)-4-[(Triethylsilyl)oxy]-2-methyl-3-[1″-(phenylmethoxy)carbonyl]hexenedioic Acid, 1′-Phenylmethyl Ester (26). To a rt solution of **25** (782 mg, 1.56 mmol) and 2-methyl-2-butene (709 μL, 6.69 mmol) in 3:1 *t*-BuOH/H_2O (17 mL) were added $NaHPO_4 \cdot H_2O$ (228 mg, 1.65 mmol) and then $NaClO_2$ (427 g, 4.72 mmol) all at once to give a yellow solution that faded to colorless after 10 min. After 0.5 h, the reaction was diluted with brine (100 mL) and extracted with EtOAc (3 × 150 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was chromatographed on SiO_2 (50:50 EtOAc/hexanes → 100% EtOAc) to give 778 mg (96%) of a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 10H), 5.14 (dd, 1H, J = 9.0, 4.0 Hz), 5.08 (d, 1H, J = 12.0 Hz), 5.02 (d, 1H, J = 12.0 Hz), 5.01 (d, 1H, J = 12.0 Hz), 4.95 (d, 1H, J = 12.0 Hz), 2.99 (dd, 1H, J = 16.0, 9.0 Hz), 2.67 (dd, 1H, J = 16.0, 4.0 Hz), 2.02 (s, 3H), 0.87 (t, 9H, J = 8.0 Hz), 0.55 (q, 6H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 167.3, 166.9, 142.5, 135.4, 135.2, 129.9, 128.5 (2), 128.4 (3), 128.3 (3), 128.1 (2), 67.3, 67.2, 66.9, 41.8, 14.8, 6.6 (3), 4.4 (3); IR (thin film) 3500−2600 br, 3034, 1714, 1644 cm^{-1}; CI HRMS calcd for $C_{28}H_{37}O_7Si$ $(M + H)^+$ m/z 513.2308, found 513.2321.

(2*R*,3*R*,3′*R*)-Triester 27a. To **26** (550 mg, 1.07 mmol) in 4 mL of toluene was added 450 μL of triethylamine (3.2 mmol) and then diphenylphosphoryl chloride (230 μL, 1.18 mmol) over 10 min at rt. The bright yellow, heterogeneous solution was stirred at rt for 2 h, and then a mixture of **20** (242 mg, 1.18 mmol) and DMAP (20 mg, 0.16 mmol) in 1 mL of toluene was transferred with a cannula over 1 min (1 mL used to assist the transfer). The yellow mixture was stirred at rt for 13 h. The reaction was quenched into saturated aqueous $NaHCO_3$ and Et_2O and separated, and the aqueous layer was extracted with additional Et_2O (3 × 80 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed on SiO_2 (40:60 EtOAc/hexanes → 50:50 EtOAc/hexanes) to give 540 mg (72%) of a pale yellow oil comprising an exactly 1:1 ratio of diastereomers. The two diastereomers were easily purified by HPLC (35:65 EtOAc/hexanes, 5 mL/min, t_R **27a**: 13.5 min, t_R **27b**: 18.2 min). The low R_f diastereomer was established as having the desired (*R*) absolute stereochemistry at the 3′ position.[41] **3′(*R*) Diastereomer 27a:** R_f 0.49 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.17 (dd, 1H, J = 8.5, 3.5 Hz), 5.12 (br m, 1H), 5.08 (d, 1H, J = 12.5 Hz), 5.06 (d, 1H, J = 12.5 Hz), 5.01 (d, 1H, J = 12.5 Hz), 4.95 (d, 1H, J = 12.5 Hz), 4.26 (br d, 1H, J = 4.5 Hz), 3.65 (s, 3H), 3.33 (s, 3H), 3.11 (br s, 3H), 2.92 (dd, 1H, J = 17.0, 8.5 Hz), 2.60 (dd, 1H, J = 17.0, 3.5 Hz), 2.15 (m, 1H), 2.01 (s, 3H), 0.94 (t, 6H, J = 7.5 Hz), 0.86 (t, 9H, J = 8.0 Hz), 0.53 (q, 6H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 169.6, 167.4, 167.0, 143.0, 135.4, 135.2, 129.4, 128.5 (3), 128.3 (5), 128.0 (2), 77.2, 76.4, 67.1, 66.9, 66.8, 61.3, 57.8, 41.5, 32.4, 28.6, 19.3, 16.4, 14.8, 6.6 (3), 4.4 (3); IR (thin film) 3034, 1738, 1732, 1674 cm^{-1}; FAB HRMS calcd for $C_{37}H_{54}NO_{10}Si$ $(M + H)^+$ m/z 700.3517, found 700.3521.

3′(*S*) Diastereomer 27b: R_f 0.55 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.16 (t, 1H, J = 6.6 Hz), 5.09 (overlapping, 1H), 5.06 (d, 1H, J = 12.5 Hz), 4.99 (d, 1H, J = 12.5 Hz), 4.96 (d, 1H, J = 12.5 Hz), 4.95 (d, 1H, J = 12.5 Hz), 4.30 (br dd, 1H, J = 3.5, 1.5 Hz), 3.69 (s, 3H), 3.34 (s, 3H), 3.18 (br s, 3H), 2.87 (dd, 1H, J = 16.5, 6.0 Hz), 2.83 (dd, 1H, J = 16.5, 6.6 Hz), 2.11 (m, 1H), 2.02 (s, 3H), 0.88 (t, 9H, J = 8.0 Hz), 0.85 (overlapping, 6H), 0.57 (q, 6H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 169.4, 167.5, 167.0, 142.3, 135.5, 135.3, 130.2, 128.5 (3), 128.32 (5), 128.26 (2), 77.7, 76.5, 67.0, 66.8 (2), 61.4, 58.0, 41.7, 32.4, 28.7, 19.3, 16.5, 15.1, 6.7 (3), 4.4 (3); IR (thin film) 3034, 1732, 1679 cm^{-1}; FAB HRMS calcd for $C_{37}H_{54}NO_{10}Si$ $(M + H)^+$ m/z 700.3517, found 700.3522.

Aldehyde 28. To a −78 °C solution of **27a** (160 mg, 0.230 mmol) in 8 mL of THF was added DIBAL (610 μL, 0.91 mmol, 1.5 M in toluene) dropwise over 5 min. After 4 h, the reaction was quenched with 400 μL of acetone and then AcOH (2 equiv, 0.36 mmol). The reaction was warmed to 0 °C and transferred using a cannula into a rapidly stirring mixture of 1:1 Et_2O/0.5 N tartaric acid. After 20 min, the crude mixture was extracted with Et_2O (3 × 80 mL), and the combined organics

phases were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and chromatographed on SiO_2 (1.5 × 13 cm, 25:75 EtOAc/hexanes → 50:50) to give 124 mg of **28** and 35 mg of recovered **27a** (84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (d, 1H, J = 2.0 Hz), 7.30 (m, 10H), 5.16 (dd, 1H, J = 8.5, 4.0 Hz), 5.08 (d, 1H, J = 12.0 Hz), 5.04 (d, 1H, J = 12.5 Hz), 5.00 (d, 1H, J = 12.0 Hz), 5.00 (overlapping, 1H), 4.93 (d, 1H, J = 12.5 Hz), 3.58 (dd, 1H, J = 4.0, 2.0 Hz), 3.39 (s, 3H), 2.96 (dd, 1H, J = 16.2, 8.5 Hz), 2.68 (dd, 1H, J = 16.2, 4.0 Hz), 2.03 (m, overlapping, 1H), 2.02 (s, 3H), 0.91 (t, 6H, J = 6.0 Hz), 0.87 (t, 9H, J = 8.0 Hz), 0.54 (q, 6H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 170.3, 167.4, 166.9, 142.6, 135.5, 135.3, 129.8, 128.4 (3), 128.3 (5), 128.0 (2), 85.2, 77.2, 67.0, 66.9, 67.2, 58.7, 41.7, 28.2, 19.1, 17.8, 14.9, 6.7 (3), 4.5 (3); IR (thin film) 3034, 1737, 1644 cm^{-1}; FAB HRMS calcd for $C_{35}H_{49}O_9Si$ $(M + Na)^+$ m/z 663.2964, found 663.2964.

Dibenzylalkene 29. Analogous to Oikawa's procedure,[17c] to a solution of **17** (41 mg, 97 μmol) in 2 mL of CH_2Cl_2 at 0 °C was added trimethylsilyl triflate (90 μL, 0.47 mmol) over 5 min. The reaction mixture was stirred for 4 h and then transferred into a 1:4 mixture of saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Crude NMR indicated clean formation of both the silyl enol ether and the C18-(trimethylsilyl)oxy ether, and this material was used without further purification. In another reaction vessel, a solution of **28** (52 mg, 81 μM) in 2 mL of CH_2Cl_2 was cooled to −78 °C and treated with a −78 °C solution of $TiCl_4$ (122 μL, 0.12 mmol, 1.0 M in toluene). After 3 min, a dry solution of the crude silyl enol ether in 1 mL of CH_2Cl_2 was transferred via cannula to the reaction. After 30 min at −78 °C, the reaction was warmed in a −20 °C bath for 3 h and then transferred by cannula into a mixture of CH_2Cl_2 and pH 7.0 phosphate buffer. The layers were separated, and the aqueous phase was extracted three times with CH_2Cl_2 and twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed on a SiO_2 column (13 cm × 12 mm, 25:75 EtOAc/hexanes → 50:50 EtOAc/hexanes) to give 25 mg of the low R_f product. The higher eluting compounds were all combined, concentrated, diluted with 1.5 mL of CH_3CN, and treated with 200 μL of dilute HF (9:1 H_2O/47% HF). After 5 h at rt, the reaction was worked up by extraction from brine with Et_2O. Purification as before yielded another 8.7 mg of product for a total of 33.7 mg of **29** and 14.1 mg of **17** (44% yield, 56% based on recovered starting material). C18-TMS **17** silyl enol ether: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddd, 1H, J = 17.5, 10.5, 7.0 Hz), 5.65 (br d, 1H, J = 17.5 Hz), 4.92 (br d, 1H, J = 10 Hz), 4.07 (s, 1H), 4.04 (s, 3H), 3.74 (dt, 1H, J = 8.0, 1.5 Hz), 3.28 (dd, 1H, J = 10, 1.5 Hz), 3.16 (dt, 1H, J = 8, 1.5 Hz), 2.24 (qn, 1H, J = 7 Hz), 2.12 (m, 1H), 2.04 (m, 1H), 1.83 (m, 1H), 1.70−1.10 (m, 18H), 0.98 (d, 3H), 0.96 (d, 3H), 0.88 (d, 3H), 0.81 (d, 3H), 0.21 (s, 9H), 0.12 (s, 9H).

29: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.72 (ddd, 1H, J = 17.5, 10.5, 7.5 Hz), 5.14 (dd, 1H, J = 7.0, 4.0 Hz), 5.08−5.01 (m, 4H), 4.96 (d, 1H, J = 17.5 Hz), 4.91 (d, 1H, J = 10.5 Hz), 4.28 (br d, 1H, J = 2.0 Hz), 3.73 (d, 1H, J = 4.5 Hz), 3.69 (br s, 1H), 3.44 (s, 3H), 3.29 (dd, 1H, J = 10.5, 2.0 Hz), 3.25 (dd, 1H, J = 6.5, 2.0 Hz), 3.15 (br t, 1H, J = 10.0 Hz), 3.04 (br t, 1H, J = 2.0 Hz), 2.98 (m, 2H), 2.62 (m, 4H), 2.15−2.00 (m, 4H), 2.00 (s, 3H), 1.84 (m, 1H), 1.70−1.20 (m, 17H), 1.10 (d, 3H, J = 7.5 Hz), 0.99 (d, 6H, J = 7.0 Hz), 0.95 (d, 6H, J = 6.5 Hz), 0.88 (d, 3H, J = 7.0 Hz), 0.81 (d, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 170.5, 167.2, 167.0, 145.0, 140.0, 135.2, 131.5, 128.5 (2), 128.46 (4), 128.36 (3), 128.30 (2), 112.4, 95.6, 80.7, 76.5, 76.3, 74.6, 74.0, 67.2, 66.4, 66.2, 59.3, 52.6, 45.5, 40.7, 37.9, 36.0, 35.0, 34.7, 32.9, 31.2, 30.9, 30.2, 28.5 (2), 28.2, 27.5, 27.3, 26.7, 20.1, 19.6, 18.1, 17.4, 16.7, 15.0, 13.7, 11.0; IR (thin film) 3451, 3033, 1728, 1713, 1641 cm^{-1}; FAB HRMS calcd for $C_{55}H_{81}O_{13}$ $(M + H)^+$ m/z 949.5677, found 949.5698.

Tautomycin, Bis(benzyl ester) 30. To a solution of **29** (17.7 mg, 19 μmol) in a mixture of 1 mL of THF and 1 mL of DMF (10% water) were added $PdCl_2$ (6.6 mg, 37 μmol) and CuCl (20 mg, 0.21 mmol) at rt. The reaction was put under a balloon of O_2 for 22 h, after which it was filtered through Celite with EtOAc, diluted with Et_2O, and washed with brine. The aqueous layer was back-extracted twice with Et_2O, and the combined organic extracts were dried over $MgSO_4$. After being filtered and concentrated *in vacuo*, the crude oil was purified by SiO_2 chromatography (1.2 × 15 cm, 40:60 EtOAc/hexanes) to give 17.2 mg (96% yield) of a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.15 (ddd, 1H, J = 7.5, 4.5, 3.0 Hz), 5.07 (d, 1H, J = 12.0 Hz), 5.04 (d, 1H, J = 12.0 Hz), 5.03 (d, 1H, J = 12.0 Hz), 4.99 (d, 1H, J = 12.0 Hz), 4.29 (br m, 1H), 3.72 (d, 1H, J = 5.0 Hz), 3.69 (dt, 1H, J = 8.0, 5.0 Hz), 3.44 (s, 3H), 3.26 (m, 2H), 3.16 (dt, 1H, J = 10.0, 1.5 Hz), 3.05−2.95 (m, 2H), 2.70−2.50 (m, 6H), 2.15 (s, 3H), 2.11 (m, 1H), 2.01 (s, 3H), 2.00 (m, overlapping, 1H), 1.85 (br m, 1H), 1.70−1.20 (m, 18 H), 1.09 (t, 6H, J = 6.5 Hz), 1.00 (d, 3H, J = 6.5 Hz), 0.95 (d, 3H, J = 6.5 Hz), 0.94 (d, 3H, J = 6.5 Hz), 0.88 (d, 3H, J = 7.0 Hz), 0.80 (d, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 213.0, 170.5, 167.2, 135.2, 131.5, 128.4 (7), 128.33 (3), 128.26 (2), 95.6, 80.8, 76.3, 74.8, 74.2, 74.1, 67.2, 66.4, 66.2, 59.3, 52.5, 47.3, 45.5 (2), 40.7, 36.0, 34.8 (2), 31.4, 30.6, 30.2, 29.0, 28.5, 28.2, 28.1, 27.6, 27.4, 26.7, 19.6, 18.0, 17.5 (2), 16.7, 16.2, 15.0, 13.7, 11.0; IR (thin film) 3454, 1728, 1714, 1644 cm^{-1}; FAB HRMS calcd for $C_{55}H_{81}O_{14}$ $(M + H)^+$ m/z 965.5626, found 965.5622.

Tautomycin. To a solution of **30** (10.7 mg, 11 μmol) in 2 mL of THF and 200 μL of H_2O was added 3 mg of Pd (5% on C). H_2 was added to the solution via a balloon through a 20 gauge needle for a total of 5 min while intermittently monitoring the reaction by TLC. After this time, the reaction contents were passed through a plug of Celite with Et_2O, concentrated, and purified by reversed-phase HPLC (C18 column, 5 mL/min of 70:30 CH_3CN/10 mM AcOH, t_R = 19.6, 20.3 min) to give 7.0 mg of tautomycin and 1.9 mg of unreacted starting material after lyophilization (82% yield, 100% based on recovered **30**). Chemical correlation of authentic TM (CalBiochem) and synthetic TM was performed by analytical HPLC (C18 column, 1 mL/min of 70:30 CH_3CN/10 mM AcOH, t_R = 16.2 min for each sample and t_R = 16.1 min for a coinjection of the mixed sample): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (br d, 1H, J = 9.5 Hz), 5.10 (t, 1H, J = 6.0 Hz), 4.57 (br m, 1H), 4.36 (br m, 1H), 3.71 (m, 1H), 3.45 (s, 3H), 3.27 (dt, 2H, J = 8.0, 2.0 Hz), 3.16 (dt, 2H, J = 9.5, 2.0 Hz), 2.99 (dd, 1H, J = 17.5, 8.5 Hz), 2.93 (dd, 1H, J = 16.0, 3.0 Hz), 2.77 (dd, 1H, J = 16.5, 10.0 Hz), 2.68 (dd, 1H, J = 13.0, 5.0 Hz), 2.67 (dd, overlapping, 1H, J = 7.0, 1.5 Hz), 2.53 (m, 1H), 2.45 (m, 1H), 2.28 (s, 3H), 2.15 (s, 3H), 2.12 (m, 1H), 2.01 (tt, 1H, J = 13.5, 4.5 Hz), 1.84 (m, 1H), 1.70−1.20 (m, 20 H), 1.12 (app t, 6H, J = 7.5 Hz), 1.00 (d, 3H, J = 7.0 Hz), 0.98 (d, 3H, J = 6.5 Hz), 0.97 (d, 3H, J = 7.5 Hz), 0.89 (d, 3H, J = 7.0 Hz), 0.80 (d, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 213.2, 169.5, 165.8, 164.9, 143.0, 142.1, 95.7, 80.6, 76.4, 74.8, 74.31, 74.28, 66.4, 63.9, 59.1, 52.3, 47.3, 45.8, 41.0, 36.0, 34.9, 34.8, 31.4, 30.7, 30.2, 29.1, 28.7, 28.2, 28.1, 27.6, 27.4, 26.8, 19.4, 18.0, 16.7, 16.3, 13.8, 11.0, 10.2; IR (thin film) 3439, 2924, 2851, 1832, 1767, 1739, 1711 cm^{-1}; FAB HRMS calcd for $C_{55}H_{81}O_{14}$ $(M + H)^+$ m/z 965.5626, found 965.5622. Synthetic tautomycin was spectroscopically indistinguishable from authentic TM spectra kindly provided to us by Dr. Ubukata.

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Supporting Information Available: ^{1}H NMR spectra of **2b**, **5**−**15**, **16a,b**, **17**, **22**−**26**, **27a,b**, and **28**−**30** and a comparison of authentic and synthetic tautomycin (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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