Synthesis of a C1−C21 Subunit of the Protein Phosphatase Inhibitor Tautomycin: A Formal Total Synthesis

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The synthesis of a C1−C21 subunit of tautomycin is described. The convergent route employs enantioenriched allenylstannane and zinc reagents derived from (*S*)-3-butyn-2-ol methanesulfonate. These reagents react with appropriate aldehyde segments to yield syn and anti adducts with high diastereoselectivity. The derived lithioalkynes are joined stepwise to a CO equivalent, $(MeONMe)_2$-C═O, to afford an intermediate ketone which is converted to the core spiroketal moiety of tautomycin upon acid treatment. Chain elongation by another addition of the aforementioned allenylzinc reagent to a spiroketal aldehyde proceeds with high diastereoselectivity to install the remaining stereocenters. The resulting homopropargylic alcohol adduct is converted to a methyl ketone through intramolecular hydrosilylation of the alkyne and Tamao oxidation of the derived five-membered siloxane. This ketone proved identical to an intermediate employed by Chamberlin in a prior total synthesis of tautomycin.

The antifungal soil metabolite tautomycin has attracted the attention of several groups because of its structural intricacy and novel biological activity relating to its selective inhibition of protein-serine/threonine phosphatase types 1 and 2A.[1] To date four total syntheses have been reported.[1a−d] These and related syntheses of tautomycin subunits have mainly relied upon chiral auxiliary-directed aldol additions and carbohydrate intermediates for introduction of the various stereogenic centers. In recent years we have been developing a complimentary approach to polyketides such as tautomycin in which chiral enantioenriched allenylmetal reagents are added to aldehydes, affording homopropargylic alcohols with contiguous OH- and CH_3-substituted stereocenters characteristic of the propionate segments of these natural products.[2] An appealing feature of this approach is the ability to employ the alkynyl moiety of these adducts to initiate coupling reactions or for introduction of additional functional features of targeted intermediates.[3] The present report details efforts along these lines which have led to a convergent and stereoselective synthesis of the C1−C21 subunit of tautomycin previously prepared by Chamberlin and co-workers in their total synthesis of the natural product.[1a]

Our synthetic plan is summarized in Figure 1. Accordingly allenylmetal reagents derived from (*S*)-3-butyn-2-ol would be used to form C−C bonds at C6/C7 (**D**), C13/C14 (**C**), and C18/C19 (**E**) with the appropriate stereogenicity. The stereocenters at C3 and C15 (**A** and **B**) would originate with commercially available methyl (*R*)- and (*S*)-3-hydroxy-2-methylpropionate.[4] The terminal alkynyl centers at C11 and C9 in the homopropargylic

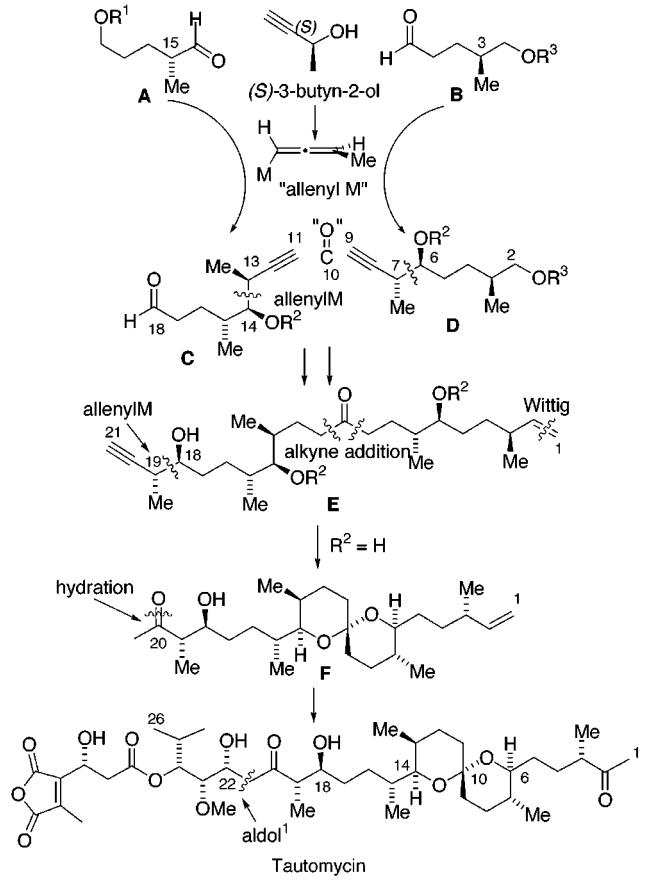

Figure 1. Synthetic plan for the key tautomycin subunit **F**.

(1) (a) Sheppeck, J. E., III; Liu, W.; Chamberlin, A. R. *J. Org. Chem.* **1997**, *62*, 387 and references cited. (b) Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A. *J. Org. Chem.* **1995**, *60*, 5048. (c) Ichikawa, Y.; Tsuboi, K.; Jiang, Y.; Naganawa, A.; Isobe, M. *Tetrahedron* **1997**, *57*, 5123 and references cited. (d) Shimizu, S.; Nakamura, S.; Nakada, M.; Shibasaki, M. *Tetrahedron* **1996**, *52*, 13363. (e) Nagumo, S.; Arai, T.; Akita, H. *Tetrahedron Lett.* **1997**, *38*, 5165.

(2) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

(3) Cf. Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. (b) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501. (c) Marshall, J. A.; Yanik, M. M. *Tetrahedron Lett.* **2000**, *41*, 4717.

(4) Aldrich Chemical Co., Milwaukee, WI.

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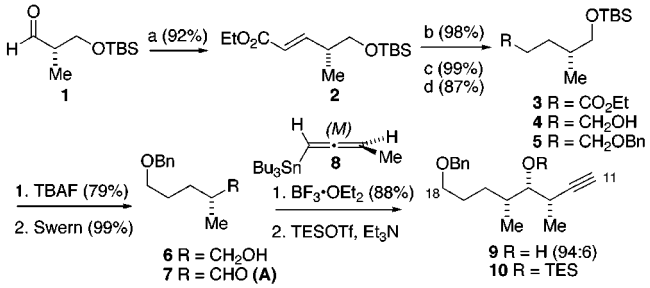
Scheme 1. Synthesis of the C11−C18 Subunit[a]



[a] (a) $(EtO)_2POCH_2CO_2Et$, LiCl, DBU, CH_3CN (92%); (b) H_2/Pd−C, EtOAc (98%); (c) DIBAL-H (99%); (d) $Cl_3CC(=NH)OBn$, TESOTf (1 mol %), CH_2Cl_2 (87%).

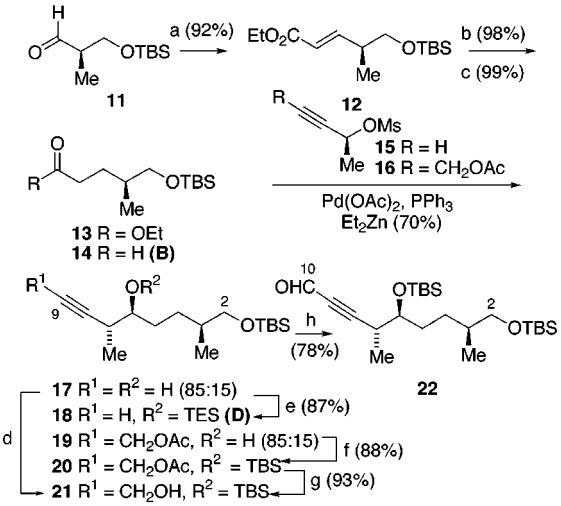
adducts **C** and **D** would be used to effect nucleophilic addition to a C10 carbonyl equivalent producing the C2−C18 chain. Further elaboration of this adduct through Wittig homologation to introduce C1 and a third allenylmetal addition to append C19−C21 would afford intermediate **E** with the correct configuration at all stereocenters. The C20 carbonyl group would be incorporated by directed hydration of the terminal alkyne produced in the allenylmetal addition (**E** → **F**).

Our synthesis of the C11−C18 segment commenced with Horner−Emmons condensation of triethylphosphonoacetate with (*S*)-2-methyl-3-OTBS propanal (**1**), readily obtained from the hydroxy ester precursor upon silyl ether formation and reduction.[5] Use of sodium hydride as base for this condensation resulted in partial epimerization of the aldehyde, whereas the Masamune−Roush protocol employing LiCl and DBU gave product of high ee in excellent yield.[6] The choice of ethyl acetate as solvent for hydrogenation of unsaturated ester **2** over Pd−C was important. In ethanol complete loss of the TBS ether occurred. Reduction of the ester and benzylation of alcohol **4** with benzyl trichloroacetimidate yielded diether **5**.[7] Triflic acid, generated in situ by addition of a small amount of triethylsilyl triflate, proved to be a most convenient method to catalyze the benzylation reaction. The acetimidate methodology solved the problem of 1,5 silyl migration which took place when the benzylation was carried out with NaH and benzyl bromide. Desilylation of the TBS ether **5** with TBAF, followed by Swern oxidation[8] of alcohol **6** afforded aldehyde **7,** corresponding to **A** in our synthetic plan, in near-quantitative yield.[9]

The first of our three allenylmetal additions was conducted on this aldehyde with the (*M*)-allenylstannane **8**, obtained from the mesylate of (*S*)-3-butyn-2-ol by treatment with $Bu_3SnLi{\cdot}CuBr{\cdot}SMe_2$ in THF (Scheme 1). The $BF_3{\cdot}OEt_2$-promoted addition afforded the syn,syn stereotriad **9** as the major diastereomer of a 94:6 mixture.[10] The alcohol was protected as the TES ether **10**.

The preparation of the second major coupling fragment, alkyne **D**, parallels that outlined above for **10**. In this case the (*R*)-enantiomer of 2-methyl-3-OTBS propanal (**11**) was employed in the Horner−Emmons condensation to afford the conjugated ester **12** (Scheme 2). Hydrogenation, as before, afforded ester **13** which was reduced to aldehyde **14**, **B** in our synthetic plan, with DIBAL-H. Addition of the (*M*)-allenylzinc reagent, generated in situ from the mesylate of (*S*)-3-butyn-2-ol (**15**), gave rise to the anti adduct **17** as the major component of an inseparable 85:15 mixture. This result was expected as such additions are most diastereoselective (>90:10) with branched aldehydes.[2] The alcohol adduct **17** and its inseparable diastereomer were converted to the TES ether **18**, corresponding to **D**, also an inseparable mixture.

Scheme 2. Synthesis of the C2−C9/10 Subunit[a]



[a] (a) $(EtO)_2POCH_2CO_2Et$, LiCl, DBU; (b) H_2/Pd−C; (c) DIBAL-H; (d) i. TBSCl, Im; ii. BuLi, CH_2O; (e) Et_3SiCl, (f) TBSCl, Im; (g) K_2CO_3, MeOH; (h) TPAP, NMO.

Several different approaches were examined for coupling of the C2−C9 and C11−C18 alkynyl subunits **10** and **18** to a C10 carbonyl equivalent. Our preliminary experiments were conducted with subunits arrived at by identical routes to those just described with the exception of protecting groups. In the first of these, cleavage of the propargylic acetate **20** (obtained through addition of the allenylzinc reagent, prepared in situ from mesylate **16**, to aldehyde **14** followed by TBS protection of the alcohol adduct **19**), and TPAP oxidation[11] of the resulting alcohol **21**, afforded aldehyde **22** in high overall yield. Alternatively, alcohol **21** could be prepared through protection of alcohol **17** (from **15** plus **14**) as the TBS ether and subsequent addition of the lithioalkyne to formaldehyde.

Addition of the lithium acetylide **23** (prepared along the lines of **10** in Scheme 1) to aldehyde **22** resulted in multiple unidentifiable decomposition products. Others have reported problems associated with acetylide additions to complex aldehydes.[12] We hoped that the use of the saturated aldehyde in the addition reaction might minimize side products and decomposition. Unfortunately, hydrogenation of acetate **20** or alcohol **21** with various Pd or Rh catalysts was accompanied by significant hydrogenolysis of the propargylic moiety.

(5) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556.

(6) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(7) Widmar, U. *Synthesis* **1987**, 568.

(8) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

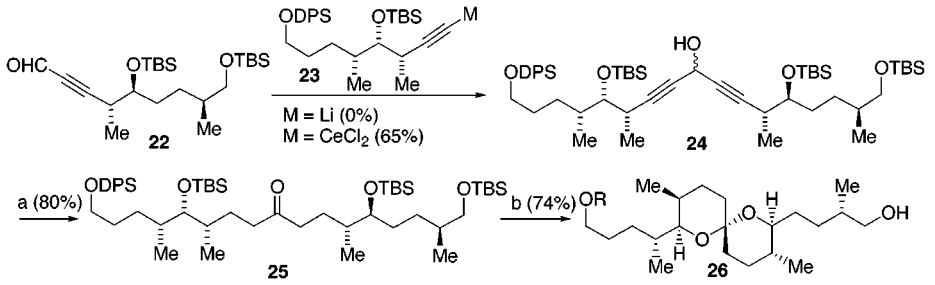
(9) Alcohol **6** could also be prepared in seven steps from 1,5-pentanediol, or in four steps from the known 5-benzyloxypentanoic acid through an Evans oxazolidinone alkylation. See the Supporting Information for details.

(10) Marshall, J. A.; Wang, X-j. *J. Org. Chem.* **1992**, *57*, 1242.

(11) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

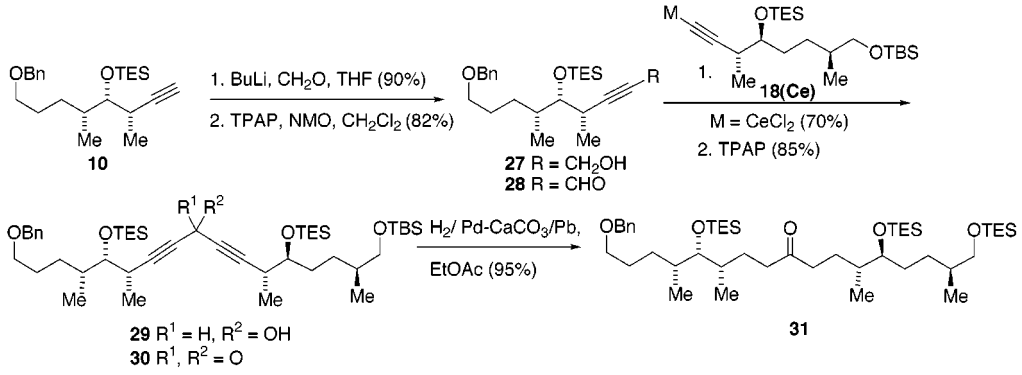
(12) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106 and references cited.

Scheme 3. Initial Route to a Spiroketal Intermediate[a]



[a] (a) i. TPAP, NMO, (85%); ii. H_2/Rh−Al_2O_3, EtOAc (94%); (b) i. PPTs, EtOH; ii. MeOH, HCl (74%).

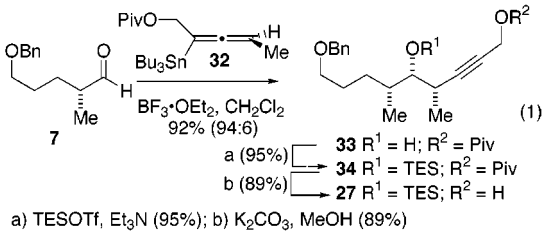
Scheme 4. Synthesis of Ketone 31



Our next option was to attenuate the acetylide reagent through transmetalation of the lithium acetylide **23** with anhydrous $CeCl_3$ forming the less basic and highly nucleophilic cerium acetylide.[13] With this reagent addition to the alkynal **22** proceeded in moderate yield. Ensuing hydrogenation of the dialkynyl carbinol **24** proceeded without hydrogenolysis but led to a 70:30 mixture of the saturated alcohol and ketone **25** (Scheme 3), the latter arising through a presumed alkyne−allene isomerization on the catalyst surface. This complication could be circumvented by switching the order of steps. Thus oxidation of alcohol **24** with TPAP[11] and hydrogenation of the dialkynyl ketone afforded the saturated ketone **25** without incident. Conversion of this ketone to the spiroketal **26** (R = DPS) through selective cleavage of the TBS ethers of ketone **25** could not be achieved. Treatment of **25** with PPTS in ethanol resulted in only partial desilylation of these ethers.[14] The use of TBAF for selective cleavage resulted in multiple partially desilylated products. Finally, with methanolic HCl all silyl ethers were cleaved leading to the spiroketal diol **26** (R = H). This diol contains the spiroketal core of tautomycin, but represents a synthetic dead end for lack of methodology to differentiate the two primary alcohol termini. A similar problematic secondary OTBS deprotection recently noted in a reported synthesis of discodermolide,[3a] was solved by substituting the secondary TBS protecting group to the more labile TES ether.

Accordingly, the foregoing sequence was applied to the TES-protected homopropargylic ether **10** to afford propargylic alcohol **27** which led to ynal **28** (Scheme 4). Addition of the cerium acetylide **18(Ce)**, derived from alkyne **18**, to aldehyde **28** proceeded as expected affording alcohol **29**, which was oxidized with TPAP to ketone **30**. Hydrogenation[15] of this diynone to the saturated ketone **31** on the Lindlar catalyst proceeded smoothly, without concomitant hydrogenolysis of the benzyl group.[16]

Alcohol **27** could be prepared more convergently through addition of the allenic stannane **32** to aldehyde **7** (eq 1). Protection of alcohol **33** as the TES ether **34** and saponification afforded propargylic alcohol **27** in high overall yield.



In the course of these studies we developed an improved and economical route to the propargylic alcohol precursor of stannane **32** based on a procedure for converting aldehydes to acetylenes recently disclosed by a group from DuPont.[17] Accordingly, lithiodichloromethane was prepared in situ and added to the TBS ether **35** of (*S*)-lactic aldehyde affording the dichloro alcohol intermediate which was converted to tosylate **36** without isolation (eq 2). Treatment of this tosylate with 3 equiv of butyllithium and addition of the resulting lithio acetylide to paraformaldehyde afforded the TBS-protect-

(13) (a) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. (b) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (c) Imamoto, T.; Takiyama, N.; Makamura, K.; *Tetrahedron Lett.* **1985**, *26*, 4763.

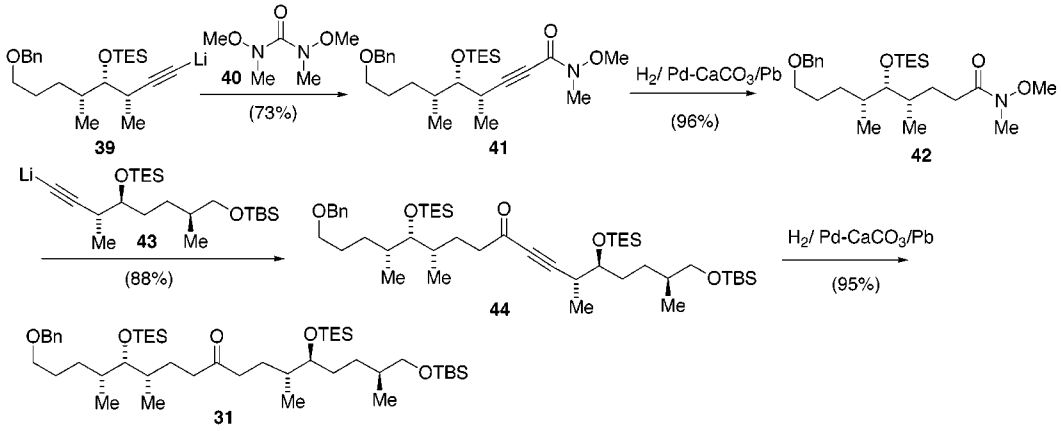
(14) Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19.

(15) Cook, L. R.; Oinuma, H.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 7928.

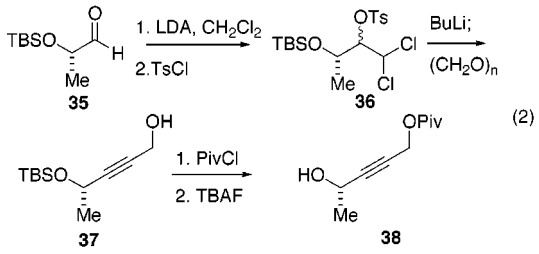
(16) Pd/$CaCO_3$ poisoned with lead was purchased from Aldrich Chemical Co.

(17) Wang, Z.; Yin, J.; Campagna, S.; Pesti, J. A.; Fortunak, J. M. *J. Org. Chem.* **1999**, *64*, 6918.

Scheme 5. Alternative Route to Ketone 31 through Urea Coupling



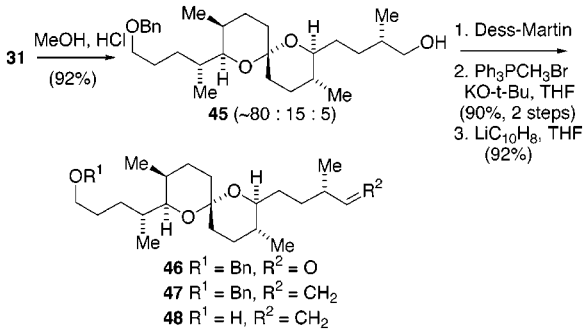
ed (*S*)-pentynediol derivative **37** in 82% yield. Our previous synthesis of this material[18] utilized the Corey–Fuchs[19] reaction, which is difficult to perform on a large scale owing to the significant quantity of triphenylphosphine oxide byproduct. This improved route to alcohol **37**, which is easily amenable to large scale synthesis, should greatly improve accessibility to chiral allenylmetal reagents via propargylic alcohols such as **38**.[10]



A second, slightly more efficient route to ketone **31** was also developed (Scheme 5). This route employs the *N*-methoxy-*N*-methylurea **40** as the C10 carbonyl equivalent.[20] Addition of the lithio acetylide **39** afforded the amide **41**. Hydrogenation over Lindlar's catalyst converted **41** to the saturated amide **42** which yielded ynone **44** upon treatment with the lithio acetylide **43**. Acetylide **43** could also be added to the alkynyl amide **41** to afford the diynone **30**, but this procedure again proved problematic affording multiple decomposition products with a resulting low yield. Hydrogenation of ynone **44** over a poisoned Pd catalyst led to ketone **31** in high yield. A major advantage of this latter route to ketone **31** is the ability to use readily prepared alkynyllithium reagents in the coupling sequence.

Exposure of ketone **31** to methanolic HCl effected cleavage of the silyl ethers with ensuing cyclization to the spiroketal. The spiroketal was obtained in 92% yield as a roughly 80:14:5:1 mixture (based on the ratios of the inseparable diastereomeric adducts, **9** (94:6) and **17** (85:15), obtained in the two allenylmetal additions) of diastereomers favoring **45** (Scheme 6). Through careful chromatography of the mixture, pure spiroketal **45** could be obtained in 50% yield. Dess–Martin periodinane oxidation[21] of alcohol **45** and Wittig methylenation of the derived aldehyde **46** gave the terminal olefin **47**. The

Scheme 6. Spiroketal Formation and Chain Extension



benzyl ether was removed with lithium naphthalenide in THF[22] affording the known alcohol **48**.[1b] Comparison of the ^{1}H NMR spectrum and optical rotation with the reported values confirmed the identity of this material.

Oxidation of alcohol **48** with the Dess–Martin periodinane[21] reagent gave rise to aldehyde **49**, which yielded the anti homopropargylic alcohol adduct **50** as an 86:14 mixture of diastereomers upon treatment with the allenylzinc reagent derived in situ from the mesylate of (*S*)-3-butyn-2-ol (**15**) (Scheme 7). At this point it was necessary to effect hydration of the terminal alkyne. This conversion proved to be one of the more challenging aspects of the synthesis. Direct hydration of the homopropargylic alcohol or ester derivatives with mercury salt catalysis proved ineffective affording mixtures of decomposition products. The next two alternatives, examined in model systems, were selective reduction of the alkyne followed by Wacker oxidation,[23] or Cp_2ZrCl_2-catalyzed carboalumination[24] to be followed by an oxidative cleavage to afford the requisite ketone. Partial hydrogenation of the terminal alkyne proved problematic resulting in rapid overreduction to the alkane. This could be circumvented by hydrozirconation with Cp_2ZrHCl[25] to afford the alkene. Standard and modified conditions for the Wacker oxidation proved to be extremely sluggish; even with stoichiometric quantities of palladium salts

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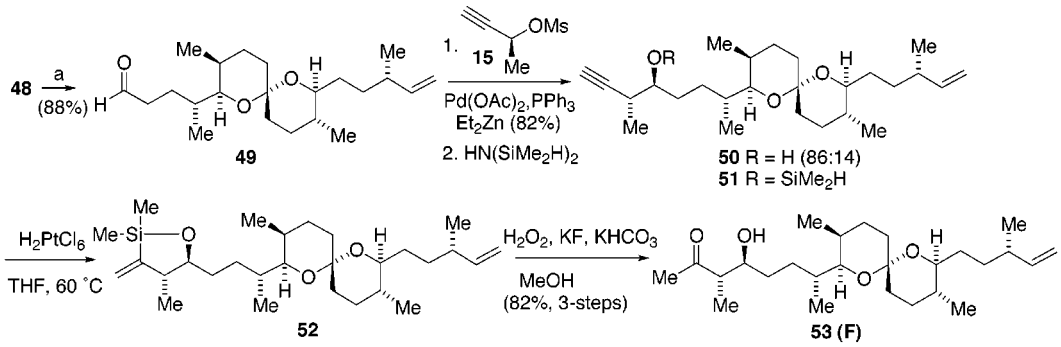
(19) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
(20) Whipple, W. L.; Reich, H. J. *J. Org. Chem.* **1991**, *56*, 2911.
(21) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(22) Liu, H. J.; Yip, J.; Shia, K. S. *Tetrahedron Lett.* **1997**, *38*, 2252.
(23) Smith, A. B., III.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, U.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, 10468 and references cited.
(24) Van Horn, D. E.; Negishi, E.-I. *J. Am. Chem. Soc.* **1978**, *100*, 2252.
(25) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.

Scheme 7. Final Chain Extension and Terminal Alkyne Hydration[a]



[a] Dess−Martin periodane.

extended reaction times (>1 week) were necessary. Attempted carboalumination gave only starting material and, under more forcing conditions, resulted in decompostion products. These problems motivated our search for mild conditions to effect the desired transformation. A solution was eventually developed which employed an intramolecular hydrosilylation−oxidation sequence.[26] Accordingly, the mixture of alcohols **50** was silylated with $(Me_2SiH)_2NH$ and the silyl ether **51** was treated with 0.5 mol % of H_2PtCl_6 in THF affording the cyclic siloxane **52**, a labile intermediate that was best oxidized under Tamao conditions without purification.[27] In this way ketone **53**, corresponding to **F** in our plan, was obtained in 82% yield as a separable 86:14 mixture of diastereomers.

It was found that the silylation/hydrosilylation sequence required complete removal of residual palladium carried over from the allenylzinc addition reaction to prevent exothermic polymer formation. This was achieved efficiently and inexpensively through conversion of alcohol **50** to the acetate, which was then chromatographed and deacetylated with DIBAL-H. This combination of steps, which could be effected in near-quantitative yield, removed all palladium contaminants. Ketone **53** proved identical to an intermediate prepared by Chamberlin in his total synthesis of tautomycin.[1a]

In summary, the allenylmetal approach compares quite favorably with previous routes to the dispiroketal subunit of tautomycin.[1] The present synthesis employs readily available starting materials and takes advantage of allene chirality to control diastereoselection. Moreover it is highly convergent and amenable to the preparation of various analogues and homologues through variations both in the starting materials and the chiral reagents. Also demonstrated was an application of the hydrosilation methodology to form β-hydroxy ketones in a complex substrate. The main drawback to the sequence is the modest diastereoselectivity of allenylzinc additions to unbranched aldehydes. However, it should be noted that the aldol or allylboronate counterparts of the analogous additions used in previous syntheses of tautomycin proceed with only slightly higher diastereoselectivity and comparable or lower yields. [1a,1b]

(26) (a) Marshall, J. A.; Yanik M. M. *J. Org. Chem.* **1999**, *64*, 3798. (b) Marshall, J. A.; Yanik, M. M. *Org. Lett.* **2000**, *2*, 2173.

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Experimental Section

General. Anhydrous THF, diethyl ether, and dichloromethane were purified by pressure filtration through activated alumina. Proton and carbon NMR spectra were acquired in $CDCl_3$ at 300 and 75 MHz, respectively, unless otherwise stated. All aqueous solutions used in the workup procedures were saturated unless otherwise stated. Bulb-to-bulb distillation temperatures refer to the temperature of the bath. Concentration in vacuo refers to high vacuum (0.005−0.1 mmHg). Other "concentrations" were effected on a Rotovap with a water aspirator (ca. 100−20 mmHg). Gas chromatography was conducted on Supelco α or β Dex 120 columns.

(3*S*,4*S*,5*R*)-8-Benzyloxy-3,5-dimethyl-1-octyn-4-ol (9). To solution of aldehyde **7** (3.64 g, 17.7 mmol) and allenyl stannane **8** (7.4 g, 21.4 mmol) in CH_2Cl_2 (80 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (7.6 mL, 60.0 mmol) dropwise over 2 min.[10] After 40 min the reaction was quenched by pouring into a rapidly stirred solution of $NaHCO_3$ and warmed to room temperature. The mixture was extracted twice with ether, dried over $MgSO_4$, and concentrated. Purification by chromatography on silica gel (5% EtOAc/hexanes−20% EtOAc/hexanes) afforded 3.94 g (88%) of acetylene **9** as a 94:6 mixture of inseparable diasteromers. $R_f = 0.50$ (30% EtOAc/hexanes); $[\alpha]_D$ +2.21 (c = 1.9, $CHCl_3$); IR 3458, 3300, 2942, 2855 cm^{-1}; ^{1}H NMR δ 0.91 (d, J = 6.6 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H), 1.15−2.02 (m, 6H), 2.07 (d, J = 2.4 Hz, 1H), 2.57 (m, 1H), 3.41−3.52 (m, 3H), 4.50 (s, 2H), 7.26−7.34 (m, 5H); ^{13}C NMR δ 12.9, 16.8, 27.2, 30.1, 30.4, 35.0, 70.2, 70.5, 72.9, 77.1, 86.4, 127.5, 127.6, 128.3, 138.5; GC β-Dex, 200 °C, 1 °C ramp, 7.95 (6%), 8.28 (94%). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29; Found: C, 78.15; H, 9.52.

(3*R*,4*S*,7*S*)-8-(*tert*-Butyldimethylsilyloxy)-3,7-dimethyl-1-octyn-4-ol (17). To a solution of $Pd(OAc)_2$ (165 mg, 0.74 mmol) in THF (150 mL) at −78 °C was added a solution of PPh_3 (194 mg, 0.74 mmol) in THF (5 mL), followed by mesylate **15** (3.00 g, 20.0 mmol), aldehyde **14** (3.40 g, 14.8 mmol), and diethylzinc (5.42 g, 44.1 mmol). The mixture was warmed to −20 °C for 20 h, quenched with NH_4Cl, extracted with ether, washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Purification by chromatography on silica gel (5% EtOAc/hexanes) afforded 2.95 g (70%) of an orange oil consisting of an inseparable mixture of diastereomeric homopropargylic alcohols **17**. The diastereomeric ratio was determined to be 85:15 by GC analysis. $R_f = 0.33$ (10% EtOAc/hexanes); $[\alpha]_D$ +3.55 (c = 5.6, $CHCl_3$); IR 3431, 3311, 2958, 2854 cm^{-1}; ^{1}H NMR δ 0.04 (s, 6H), 0.87 (s, 2H), 0.88 (s, 10H), 1.22 (d, J = 6.0 Hz, 3H), 1.3−1.7 (m, 5H), 2.11 (d, J = 2.7 Hz, 1H) 2.52 (m, 1H), 3.37−3.51 (m, 3H); ^{13}C NMR δ 85.2, 74.4, 70.8, 8.2, 35.7, 32.8, 32.4, 29.2, 25.9, 18.3, 17.5, 16.7, −5.3.; G. C. β-Dex, 150 °C, 1 °C ramp, 9.16 min (85%), 9.62 min (15%). Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34; Found C, 67.29; H, 11.33.

Tosylate 36. A solution of LDA was generated at 0 °C by dropwise addition of BuLi (2.5 M in hexanes, 16.0 mL, 40.0 mmol) to a solution of diisopropylamine (5.6 mL, 40.0 mmol), in THF (20 mL). The solution of LDA thus formed was added dropwise over 30 min to a solution of aldehyde[18] **35** (5.0 g, 26.6

mmol) and CH_2Cl_2 (5.13 mL, 80.0 mmol) in THF (50 mL) at −78 °C. After 30 min the light yellow solution was warmed to 0 °C for 30 min. The color of the solution changed from yellow to dark brown upon warming. TsCl (5.07 g, 26.6 mmol) was added in one portion, and the mixture was warmed to room temperature. After 1 h, the reaction was quenched with water (3 mL) and stirred for 30 min before dilution with 10% HCl and separation. The aqueous extracts were back extracted with ether. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated affording 10.5 g (92%) of tosylate **36** as a dark brown oil which was used without further purification. The diastereomeric ratio was 45:55 based on ^{1}H NMR analysis. ^{1}H NMR δ 0.08 (s, 6H), 0.09 (s, 6H), 0.88 (s, 18H), 1.24 (d, J = 6.3 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H), 2.44 (s, 6H), 4.04 (dq, J = 6.0, 7.5 Hz, 1H), 4.34 (dq, J = 3.3, 6.3 Hz, 1H), 4.70 (dd, J = 3.3, 6.0 Hz, 1H), 4.74 (dd, J = 2.1, 7.2 Hz, 1H), 5.81 (d, J = 6.3 Hz, 1H), 6.00 (d, J = 2.1 Hz, 1H), 7.31 (d, J = 8.4 Hz, 4H), 7.82 (dd, J = 5.4, 8.4 Hz, 4H).

(*S*) 4-(*tert*-Butyldimethylsilyloxy)-2-pentyn-1-ol (37). To a solution of tosylate **36** (10.5 g, 24.5 mmol) in THF (50 mL) at −78 °C was added BuLi (2.5 M in hexanes, 30.0 mL, 75 mmol) dropwise over 10 min followed by warming to 0 °C for 1 h. The solution was recooled to −78 °C, and paraformaldehyde (1.5 g, 50 mmol) was added in one portion, followed by warming the mixture to room temperature for 3 h. The reaction was quenched by addition of NH_4Cl and brine, extracted with EtOAc, dried over $MgSO_4$, and concentrated. Bulb to bulb distillation (0.05 mmHg, 90 °C) afforded 4.32 g (82%) of alcohol **37** as a colorless oil with spectral characteristics matching those previously reported.[18]

Urea (40) The reported procedure[20] was not easily reproduced; therefore, a modified procedure was developed. To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.0 g, 20 mmol), pyridine (2.37 g, 30 mmol), and CH_2Cl_2 (40 mL) was added carbonyl diimidazole (1.68 g, 10 mmol). The mixture was refluxed for 16 h, quenched with 10% HCl, extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated. Bulb to bulb distillation (0.05 mmHg, 50 °C) afforded 1.10 g (70%) of urea **40** as a colorless oil with spectral characteristics matching those previously reported. IR 2916, 1666 cm^{-1}; ^{1}H NMR δ 3.05 (s, 6H), 3.65 (s, 6H); ^{13}C NMR δ 36.0, 60.5.

(5*R*,6*S*,7*S*)-*N*-Methyl,*N*-methoxy-9-benzyloxy-4,6-dimethyl-5-(triethylsilyl)oxy-2-nonynecarboxamide (41). To a solution of BuLi (2.1 M in hexanes, 5.56 mL, 11.8 mmol) in THF (20 mL) was added a solution of alkyne **10** (4.0 g, 10.8 mmol), in THF (20 mL) at −78 °C. The pale yellow mixture was warmed to 0 °C for 10 min and recooled to −78 °C, and urea **40** (2.0 g, 13.5 mmol) was added. After warming to 0 °C for 1 h, the mixture was quenched with NH_4Cl, extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated. Purification by chromatography on silica gel (10−25% EtOAc/hexanes) afforded 3.60 g (73%) of amide **41** as a light yellow oil. ^{1}H NMR δ 0.58 (q, J = 7.8 Hz, 6H), 0.90 (d, J = 6.9 Hz, 3H), 0.94 (t, J = 7.8 Hz, 9H), 1.24 (d, J = 6.9 Hz, 3H), 1.25−1.94 (m, 5H), 2.73 (dq, J = 6.0, 6.9 Hz, 1H), 3.22 (br, 3H), 3.44 (t, J = 6.6 Hz, 2H), 3.56 (dd, J = 2.7, 8.4 Hz, 1H), 3.73 (s, 3H), 4.50 (s, 2H), 7.26−7.32 (m, 5H).

(4*S*,5*S*,6*R*)-*N*-Methyl,*N*-methoxy-9-benzyloxy-5-(triethylsilyl)oxy-4,6-dimethylnonanecarboxamide (42). To a solution of amide **41** (5.40 g, 11.8 mmol), in EtOAc (120 mL) was added Lindlar's catalyst ($Pd/CaCO_3$/Pb, Aldrich, 5.0 g). A balloon of hydrogen was affixed, and the mixture was vigorously stirred for 22 h and then filtered through Celite-545, washing with additional ether. Concentration afforded 5.30 g (96%) of saturated amide **42** as a clear colorless oil. R_f = 0.22 (25% EtOAc/hexanes); $[\alpha]_D$ −1.11 (c = 2.15, $CHCl_3$); IR 2960, 2872, 1675 cm^{-1}; ^{1}H NMR δ 0.57 (q, J = 8.1 Hz, 6H), 0.85 (dd, J = 6.6, 3.3 Hz, 6H), 0.93 (t, J = 8.1 Hz, 9H), 1.15−1.85 (m, 8H), 2.31 (m, 2H), 3.17 (s, 3H), 3.35 (t, J = 4.5 Hz, 1H), 3.43 (t, J = 6.6 Hz, 2H), 3.67 (s, 3H), 4.50 (s, 2H), 7.25−7.35 (m, 5H); ^{13}C NMR δ 5.5, 7.0, 14.8, 14.9, 27.8, 29.0, 29.8, 30.1, 30.6, 36.4, 61.1, 70.7, 70.9, 72.8, 80.0, 127.3, 127.5, 128.2, 138.6. Anal. Calcd for $C_{26}H_{47}NO_4Si$: C, 67.05; H, 10.17; Found: C, 67.01; H, 10.27.

(2*S*,5*S*,6*R*,12*S*,13*S*,14*R*)-2,6,12,14-Tetramethyl-1-(*tert*-butyldimethylsilyl)oxy-5,13-(triethylsilyl)oxy-17-benzyloxy-7-heptadecyn-9-one (44). A solution of alkyne **18** (2.90 g, 7.00 mmol) in THF (5 mL) was added to a solution of BuLi (2.0 M in hexanes, 3.05 mL, 6.11 mmol) in THF (20 mL) at −78 °C. After 15 min the yellow solution was warmed to 0 °C for 15 min and then recooled to −78 °C. A solution of the amide **42** (2.17 g, 4.70 mmol) in THF (5 mL) was added, and the reaction mixture was warmed to 0 °C for 1 h, quenched with NH_4Cl, extracted with ether, dried over $MgSO_4$, and concentrated. Purification by chromatography on silica gel (2.5% EtOAc/hexanes−10% EtOAc/hexanes) afforded 809 mg (85%) of recovered alkyne and 3.38 g (88%) of ynone **44** as a light yellow oil. R_f = 0.35 (10% EtOAc/hexanes); IR 2951, 2872, 2208, 1675 cm^{-1}; ^{1}H NMR δ 0.03 (s, 6H), 0.56 (q, J = 7.5 Hz, 12 H), 0.83−0.90 (m, 9H), 0.89 (s, 9H), 0.93 (t, J = 8.4 Hz, 18H), 1.19 (d, J = 6.9 Hz, 3H), 1.25−1.85 (m, 13H), 2.48 (m, 2H), 2.71 (dq, J = 7.2, 4.5 Hz, 1H), 3.33−3.51 (m, 5H), 3.67 (m, 1H), 4.50 (s, 2H), 7.25−7.35 (m, 5H); ^{13}C NMR δ −5.4, 5.1, 5.6, 6.9, 7.1, 14.8, 14.9, 15.0, 16.5, 18.3, 25.9, 27.8, 28.5, 29.1, 30.6, 31.1, 35.8, 36.1, 36.5, 43.9, 68.3, 70.7, 72.8, 74.3, 79.8, 95.8, 127.4, 127.5, 128.3, 138.6, 188.2.

(2*S*,5*S*,6*R*,12*S*,13*S*,14*R*)-2,6,12,14-Tetramethyl-1-(*tert*-butyldimethylsilyl)oxy-5,13-(triethylsilyl)oxy-17-benzyloxyheptadecan-9-one (31). A solution of ynone **44** (5.24 g, 6.40 mmol) in EtOAc (250 mL) was purged with argon. To this solution was added Lindlar's catalyst ($Pd/CaCO_3$ poisoned with lead, 8.00 g), and a balloon of hydrogen was affixed. The resulting suspension was vigorously stirred for 26 h. The catalyst was separated by filtration through Celite-545, and the solids were rinsed with ether (250 mL). Concentration afforded 5.13 g (95%) of saturated ketone **31** as a colorless oil which was used in the next step without further purification. An analytical sample was purified by chromatography on silica gel (5% EtOAc/hexanes). R_f = 0.35(10% EtOAc/hexanes); $[\alpha]_D$ +4.16 (c = 0.4, $CHCl_3$); IR 2951, 2872, 1710 cm^{-1}; ^{1}H NMR δ 0.04 (s, 6H), 0.59 (m, 12H), 0.81−0.95 (m, 9H), 0.89 (s, 9H), 0.95 (td, J = 8.1 Hz, 1.8 Hz, 21H), 1.20−1.80 (m, 16H), 2.25−2.55 (m, 4H), 3.25−3.55 (m, 6H), 4.50 (s, 2H), 7.26−7.35 (m, 5H); ^{13}C NMR δ −5.4, 5.2, 5.5, 6.9, 7.1, 14.5, 14.8, 14.9, 16.6, 25.9, 26.5, 27.8, 28.2, 29.2, 29.9, 30.6, 36.0, 36.2, 36.4, 38.2, 40.9, 41.0, 68.2, 68.4, 70.7, 72.8, 76.5, 79.9, 127.4, 127.6, 128.3, 138.6, 211.3. Anal. Calcd for $C_{46}H_{90}O_5Si_3$: C, 68.42; H, 11.23; Found: C, 68.53; H, 11.32.

Spiroketal 45. To a solution of ketone **44** (5.13 g, 6.08 mmol) in MeOH (60 mL) was added aqueous HCl (12 M, 1.4 mL). After 3 h the reaction was judged complete by TLC analysis and quenched by the addition of solid $NaHCO_3$ (ca. 2 g). The mixture was concentrated directly and then partioned between brine and EtOAc, dried over $MgSO_4$, and concentrated. Purification by silica gel chromatography (7.5% EtOAc/hexanes) afforded 1.44 g (50%) of spiroketal **45** as a single diastereomer and another 1.20 g (42%) as a mixture of diasteromers. R_f = 0.44 (25% EtOAc/hexanes); $[\alpha]_D$ −76.8 (c = 0.4, $CHCl_3$); IR 3432, 2925, 2856, 1457 cm^{-1}; ^{1}H NMR δ 0.81 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 1.07−1.84 (m, 19H), 1.99 (m, 1H), 3.17 (td, J = 9.6, 2.4 Hz, 1H), 3.32 (dd, J = 2.4, 10.2 Hz, 1H), 3.40 (m, 2H), 4.50 (s, 2H), 7.32−7.38 (m, 5H); ^{13}C NMR δ 10.9, 16.3, 16.4, 18.0, 25.9, 26.7, 27.4, 27.8, 28.2, 29.1, 29.9, 30.2, 33.9, 34.9, 35.7, 36.0, 68.1, 70.8, 73.0, 74.3, 74.5, 95.7, 127.5, 127.7, 128.3, 138.3. Anal. Calcd for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38. Found: C, 75.09; H, 10.54.

Alcohol 50. To a solution of $Pd(OAc)_2$ (8.0 mg, 0.035 mmol), in THF (15 mL) at −78 °C was added PPh_3 (9.2 mg, 0.035 mmol) in THF (0.35 mL). A solution of mesylate **15** (212 mg, 1.43 mmol) in THF (1 mL) was added followed by aldehyde **49** (250 mg, 0.71 mmol) in THF (1 mL) and finally Et_2Zn (1.0 M in hexanes, 2.10 mL, 2.10 mmol). The mixture was warmed to −20 °C. After 25 h the mixture was quenched with 10% HCl, extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated. Purification by chromatography on silica gel (5% EtOAc/hexanes) afforded 236 mg (82%) of homopropargylic alcohol **50** as a yellow oil. R_f = 0.50 (20% EtOAc/hexanes); $[\alpha]_D$ −36.8 (c = 4.00, $CHCl_3$); IR 3458, 3318,

2951, 2872 cm^{-1}; ^1H NMR δ 0.80 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.99 (m, 6H), 1.24 (d, J = 7.2 Hz, 3H), 1.18−1.75 (m, 18H), 1.85 (m, 1H), 1.95−2.25 (m, 2H), 2.13 (d, J = 2.4 Hz, 1H), 2.54 (ddq, J = 2.4, 4.5, 7.2 Hz, 1H), 3.15 (t, J = 9.3 Hz, 1H), 3.29 (d, J = 9.9 Hz, 1H), 3.36 (m, 1H), 4.89 (dd, J = 1.7, 9.9 Hz, 1H), 4.93 (dd, J = 1.7, 17.4 Hz, 1H), 5.63 (ddd, J = 7.2, 9.9, 17.4 Hz, 1H). Anal. Calcd for $C_{26}H_{44}O_3$: C, 77.18; H, 10.96; Found C, 77.00; H, 11.05.

Dimethylsilyl Ether 51. A 0.5-mL conical vial was charged with alcohol **50** (50 mg, 0.12 mmol), a stirbar, and tetramethyldisilazane (0.200 mL, 1.15 mmol). The mixture was heated to 75 °C for 4 h and then cooled to room temperature. Excess silazane was removed in vacuo at 55 °C overnight to afford silyl ether **51** as a colorless, highly viscous oil, that was used in the next step without further purification. IR 3309, 2968, 2872, 2121 cm^{-1}; ^1H NMR δ 0.22 (s, 6H), 0.80 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 1.00 (m, 6H), 1.17 (d, J = 7.2 Hz, 3H), 1.18−1.90 (m, 18 H), 2.0−2.25 (m, 2H), 2.07 (d, J = 2.7 Hz, 1H), 2.56 (m, 1H), 3.16 (t, J = 9.3 Hz, 1H), 3.28 (d, J = 10.2 Hz, 1H), 3.54 (m, 1H), 4.68 (septet, J = 3.0 Hz, 1H), 4.90 (dd, J = 1.6, 9.6 Hz, 1H), 4.92 (dd, J = 1.6, 17.2 Hz, 1H), 5.65 (ddd, J = 7.2, 9.6, 17.2, Hz, 1H).

Cyclic Siloxane 52. The residue from the previous step was dissolved in THF (0.24 mL) and H_2PtCl_6 (0.057 M in THF, 10 μL, 0.57 μmol) was added. The yellow solution was heated to 60 °C. After 6 h the hydrosilation was judged complete by IR analysis (Si−H, 2121 cm^{-1}). The mixture was diluted with ether (0.25 mL), filtered through Celite-545, washing with additional ether, and concentrated to afford cyclic siloxane **52** as a yellow oil that was used without purification. IR 2942, 2864 cm^{-1}; ^1H NMR δ 0.22 (s, 6H), 0.80 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 6H), 1.04 (d, J = 6.6 Hz, 3H), 1.15−2.40 (m, 21H), 3.18 (t, J = 9.3 Hz, 1H), 3.30 (d, J = 10.2 Hz, 1H), 3.48 (m, 1H), 4.89 (dd J = 1.7, 9.9 Hz, 1H), 4.92 (dd, J = 1.7, 16.2 Hz, 1H), 5.41 (t, J = 2.1 Hz, 1H), 5.62 (t, J = 2.1 Hz, 1H), 5.68 (ddd, J = 7.5, 9.9, 16.2 Hz, 1H).

Ketone 53. To a solution of the cyclic siloxane **52** (ca. 0.12 mmol) in THF (0.50 mL) and MeOH (1.0 mL) were added KF (35 mg, 0.60 mmol), $KHCO_3$ (60 mg, 0.60 mmol), and 30% H_2O_2 (1.0 mL, ca. 8.8 mmol). After 2 h the oxidation was judged complete by TLC analysis, and solid $Na_2S_2O_3$ was added gradually (***Caution: Highly exothermic, induction period***). The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, concentrated, and purified by chromatography on silica gel (15% EtOAc/hexanes) affording 41 mg (82%) of ketone **53** as a colorless oil composed of an 86:14 mixture of diastereomers. Separation was achieved by careful chromatography on silica gel (2.5%-5% EtOAc/hexanes), with the anti diastereomer eluting second, affording 26 mg (52%) of ketone **53** as a 98:2 mixture of diastereomers as judged by ^1H NMR analysis. Spectral charateristics matched those previously reported.[1a] R_f = 0.33 (20% EtOAc/hexanes); $[\alpha]_D$ −63.1 (c = 1.50, $CDCl_3$); IR 3458, 2933, 2872, 1710 cm^{-1}; ^1H NMR δ 0.80 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.6 Hz, 6H), 1.14 (d, J = 7.2 Hz, 3H), 1.20−1.74 (m, 17H), 1.96−2.21 (m, 2H), 2.20 (s, 3H), 2.63 (dq, J = 7.2, 6.9 Hz, 1H), 3.12 (t, J = 7.2 Hz, 1H), 3.27 (d, J = 10.2 Hz, 1H), 3.63 (m, 1H), 4.88 (d, J = 9.9 Hz, 1H), 4.92 (d, J = 17.2 Hz, 1H), 5.65 (ddd, J = 7.5, 9.9, 17.2 Hz, 1H); ^{13}C NMR δ 10.9, 14.1, 16.6, 18.0, 20.1, 26.7, 27.5, 27.6, 28.2, 29.7, 29.9, 30.2, 30.9, 31.3, 32.9, 34.7, 35.1, 36.1, 37.9, 51.8, 74.0, 74.6, 95.6, 112.3, 145.0, 214.1. Anal. Calcd for $C_{26}H_{46}O_4$; C, 73.89; H, 10.97; Found C, 73.73; H, 11.03.

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Supporting Information Available: Characterization data and experimental procedures for **2**−**7**, **10**, **14**, **18**, **20**−**25**, **25a**, **25b**, **26**−**30**, **33**, **46**−**49**, **50-OAc**, alternative synthesis of **6**; ^1H NMR spectra of **5**, **7**, **20**−**25**, **25a**, **25b**, **26**, **28**, **33**, **41**, **48**−**50**, **50-OAc**, **53**, comparison spectra for **48** and **53**, and a ^{13}C spectrum for **53.** This material is available free of charge via the Internet at http://pubs.acs.org.

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