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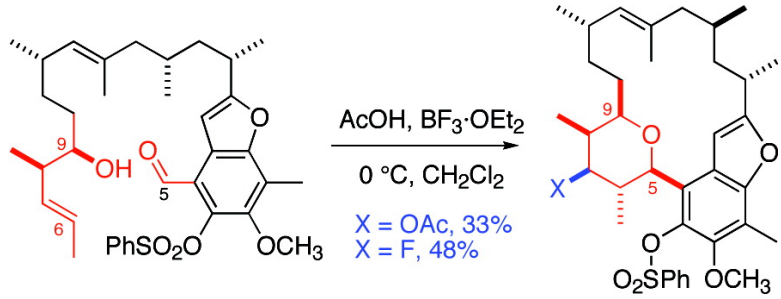

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Formal Synthesis of (−)-Kendomycin Featuring a Prins-Cyclization To Construct the Macrocycle

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Abstract: The kendomycin skeleton was prepared by a highly convergent strategy in which the benzofuran fragment and the acyclic iodide fragment were prepared by standard methods and joined using a Suzuki coupling. The distinctive reaction in our approach was an intramolecular Prins cyclization that assembles the macrocyclic ring in good yield. Modeling studies demonstrate that the acyclic chain is predisposed for macrocycle formation. Ultimately, the product was correlated with one of Lee's advanced intermediates for a formal total synthesis of kendomycin.

Introduction

(−)-Kendomycin (**1**, Figure 1) has a diverse and fascinating pharmacological profile. It was isolated in 1996 from various *Streptomyces* bacteria and exhibits potent antagonism of the endothelin receptor, as well as antiosteoporotic properties from calcitonin receptor agonism.[1] Potent cytotoxicity (GI_{50} < 100 nM) toward carcinoma cell lines has been observed, in addition to broad-spectrum antibacterial activity, even against MRSA and VRSA strains.[1b] A recent report has also described kendomycin's utility in probing the biological processes of the mammalian proteasome *in vitro*.[1c] Along with its fascinating biological profile, kendomycin's distinctive architecture has made it a popular target for synthetic chemists. Both the Lee[2] and Smith[3] groups have reported total syntheses of kendomycin. A number of other groups, including our own,[4] have described the synthesis of complex fragments.[5] The varied approaches to kendomycin arise from the synthetic challenges found in its structure, notably the *p*-quinone methide, the all-carbon macrocyclic polyketide, and the fully substituted tetrahydropyran (THP) ring. Herein we report a formal total synthesis of kendomycin that addresses these structural challenges using a Prins cyclization to assemble the macrocycle.

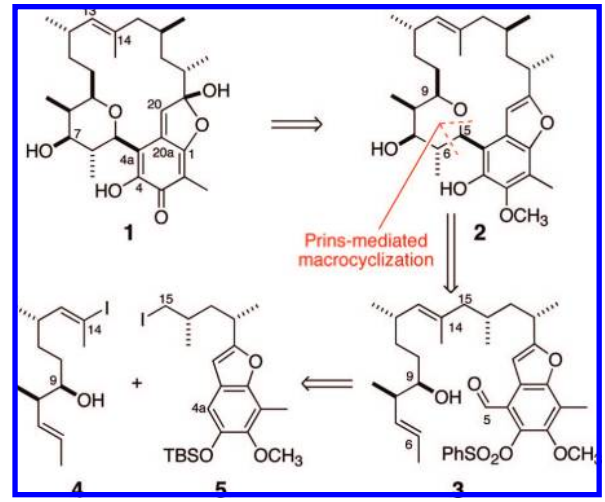

Figure 1. Synthetic analysis of kendomycin (**1**), featuring a Prins-mediated macrocyclization (**3** → **2**) as the key step.

The initial synthetic disconnection that our group and several others applied to kendomycin envisioned a late-stage ring-closing metathesis reaction to assemble the macrocycle at the C13−C14 alkene. Mulzer,[5a] Smith,[3] and Arimoto[5b] clearly demonstrated that disconnection at the trisubstituted alkene was

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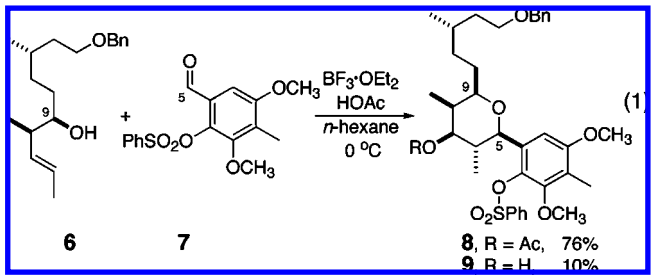
problematic both in generating the macrocycle and in controlling the alkene geometry. The current project began with the supposition that a Prins cyclization[6,7] might facilitate formation of the macrocycle. At the time we began this project, there was little precedent for the formation of macrocycles using a Prins reaction,[8] but in the past six months several very impressive reports have described the successful application of such a strategy. Both Scheidt[9] and Lee[10] used a Prins macrocyclization to prepare neopeltolide, and Wender recently reported a similar strategy in the preparation of a bryostatin analogue.[11] The successful assembly of the kendomycin macrocycle by a ring-closing Prins cyclization is described below.

A retrosynthetic analysis of kendomycin is outlined in Figure 1. Lee demonstrated that the *p*-quinone methide of kendomycin could be prepared by oxidation of hydroxybenzofuran **2**.[2] The key Prins cyclization would generate the THP ring, three new stereogenic centers, and the macrocycle simultaneously from the unsaturated hydroxy aldehyde **3**. Trisubstituted alkene **3** should be available from the two major fragments **4** and **5**, which would be joined using a Suzuki−Miyaura coupling.[12] Syntheses of precursors **4** and **5** have ample precedent from previous synthetic approaches to kendomycin.[2−5] Importantly, this strategy allows for the merger of equally complex fragments with complete stereocontrol of the trisubstituted alkene.

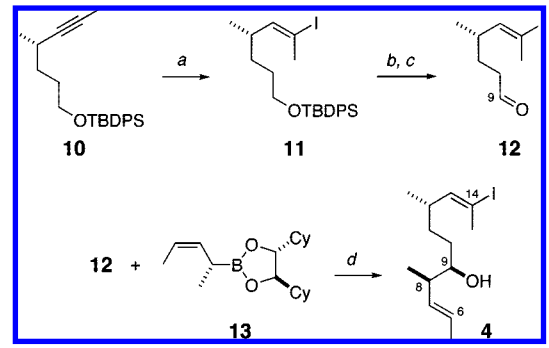
Our enthusiasm for the Prins macrocyclization strategy was derived in part from the previous Prins cyclization approach to kendomycin that we had developed. The Prins reaction between unsaturated alcohol **6** and substituted benzaldehyde **7** efficiently produced tetrahydropyrans **8** and **9** as single diastereomers (eq 1).[4] We reasoned that tethering these components with kendomycin's polyketide chain could harness the power of the Prins reaction in tetrahydropyran construction and provide a driving force for the difficult macrocyclization, while avoiding intermediates prone to C5−C4a atropisomerism.[2,3,5] This strategy had the potential to greatly simplify the construction of kendomycin.



Results and Discussion

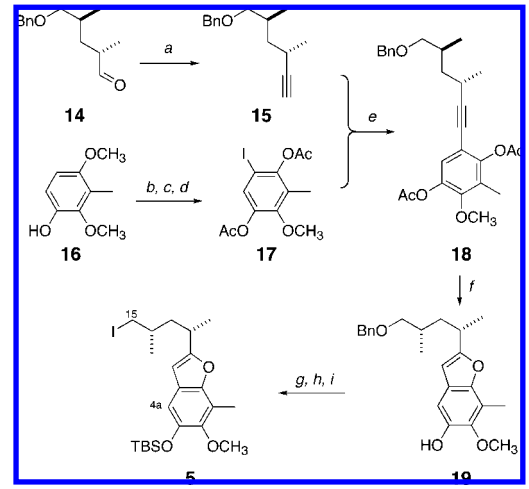
The construction of the cross-coupling partners to assemble Prins-macrocyclization precursor **3** began with the synthesis of vinyl iodide **4** (Scheme 1). Toward this end, the one-pot treatment of Lee's alkyne **10**[2] with freshly prepared Schwartz's reagent,[13] followed by treatment with iodine, afforded *E*-vinyl iodide **11** as a single regioisomer in 89% yield. Deprotection of silyl ether **11** and Parikh−Doering oxidation[14] gave aldehyde **12** which, upon treatment with Hoffmann's dimethallyl borane **13**,[4,15] produced the *E*-homoallylic alcohol **4** as a single diastereomer in excellent yield. The unprotected vinyl iodide **4** was available from alkyne **10** in 63% yield over four steps.

Scheme 1. Synthesis of Homoallylic Alcohol **4**[a]



[a] Reagents and conditions: (a) $Cp_2Zr(H)Cl$, PhH, 50 °C, then I_2, CH_2Cl_2, −30 °C, 89%; (b) TBAF, THF, 93%; (c) pyr·SO_3, DMSO, CH_2Cl_2, 0 °C, 85%; (d) hexane, 0 °C, 90%.

Scheme 2. Synthesis of Benzofuran **5**, Featuring a Sonogashira Coupling and Alkaline 5-*endo*-dig Cyclization[a]



[a] Reagents and conditions: (a) $LiC(N_2)TMS$, Et_2O, −78 °C, 72%; (b) CAN, MeCN−H_2O, then aq. $Na_2S_2O_4$; (c) Ac_2O, pyr., 75% over two steps; (d) NIS, HOAc, cat. H_2SO_4, 95%; (e) $PdCl_2(PPh_3)_2$, CuI, NEt_3, DMF, 94%; (f) aq. CsOH, EtOH, 80 °C, 89%; (g) TBSCl, imidazole, CH_2Cl_2, 94%; (h) $Pd(OH)_2/C$, H_2, THF, 99%; (i) I_2, PPh_3, imid., CH_2Cl_2, 94%.

Lee had used benzofuran iodide **5** in his synthesis of kendomycin.[2] Scheme 2 outlines an improved route to iodide **5** that is based on a Sonogashira coupling[16] and base-induced 5-*endo*-dig cyclization to assemble the benzofuran domain.[17] The addition of aldehyde **14**[5c] to a cold solution of lithium

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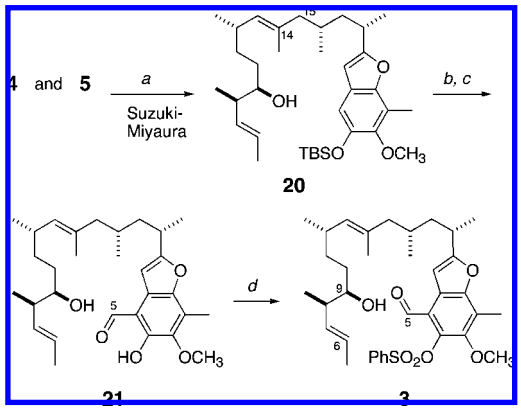
Scheme 3. Suzuki−Miyaura Coupling of Fragments **4** and **5** and Fashioning of the Prins Cyclization Precursor **3**[a]



[a] Reagents and conditions: (a) **5**, *t*-BuLi, Et_2O, 9-(MeO)-BBN, −78°C, then **4**, DMF, aq. K_3PO_4, $PdCl_2$(dppf), rt, 90%; (b) TBAF, THF, 93%; (c) HMTA (5 equiv), H_2O (5 equiv), HOAc, 100 °C, 76%; (d) $PhSO_2Cl$, *i*-$PrNEt_2$, CH_2Cl_2, 0 °C, 85%.

trimethylsilyl diazomethane in Et_2O and subsequent Colvin rearrangement[18] generated terminal alkyne **15** in 72% yield. Its coupling partner, aryl iodide **17**, was available from phenol **16**[4,19] using a three-step sequence, in which oxidation/reduction to form a hydroquinone, bis-acetylation, and H_2SO_4-catalyzed iodination steps were performed without intermediate purifications to afford crystalline iodide **17** in 71% overall yield from phenol **16**. Sonogashira coupling[16,17] of alkyne **15** (1.1 equiv) and aryl iodide **17** using catalytic $PdCl_2(PPh_3)_2$ and CuI in DMF−Et_3N delivered aryl alkyne **18** in 94% yield. Interestingly, the efficiency of this coupling, especially in a gram-scale reaction, strongly depended on the order of addition of reagents. Control experiments showed that adding the amine base last was critical to producing high yields. Treatment of aryl alkyne **18** with aqueous CsOH in EtOH at 80 °C deprotected the phenols and induced a 5-*endo*-dig cyclization onto the alkyne to generate hydroxybenzofuran **19**.[17] Other metal hydroxides (Li, Na, K) and higher-boiling alcohol solvents effected the cyclization; CsOH was preferred because it consistently promoted the highest yields under mild conditions. Finally, silylation of phenol **19**, benzyl deprotection, and iodination afforded the Suzuki−Miyaura coupling precursor **5**[2] in 73% yield over five steps from alkyne **15**.

With convenient access to iodides **4** and **5**, we shifted our attention to the Suzuki−Miyaura coupling[12] of these fragments (Scheme 3). Following the protocols of Lee[2] and Marshall,[12] an alkyllithium boronate complex was prepared from iodide **5** and combined with a premixed solution of aqueous K_3PO_4, vinyl iodide **4**, and $PdCl_2$(dppf) in DMF.[12c] The trisubstituted *E*-alkene **20** was isolated in 90% yield. The final carbon atom to be installed was the C5 aldehyde. Treatment of **20** with TBAF removed the phenol-protecting group, and a modified Duff ortho-formylation introduced the C5 aldehyde. The Duff protocol,[20] which installs C5 at the correct oxidation state for the Prins reaction, employed hexamethylenetetramine (HMTA, 5 equiv) in HOAc at 100 °C, along with H_2O (5 equiv) as a crucial additive, to provide aldehyde **21** as a single regioisomer in 76% yield. The omission of H_2O was detrimental, resulting in variable and lower yields (19−55%). Extensive optimization also showed that reproducibly high yields of **21** strongly depended on reaction times: the formylation required 120−150 min for completion, and longer reaction times led to acylation of the C9 carbinol.[21] Aldehyde **21** contains all 29 carbon atoms of the kendomycin skeleton.

Our previous work with 2-hydroxybenzaldehydes as Prins substrates demonstrated that the use of electron-withdrawing groups on such phenols is essential for efficient Prins cyclizations.[6a,22] Studies with a 2-hydroxybenzaldehyde model system indicated that acetyl, mesyl, benzenesulfonyl, and trifluoromethanesulfonyl groups could fulfill this prerequisite.[21] Only the benzenesulfonyl group, however, could be installed directly into benzofuran **21**. Selective sulfonylation of the phenol with $PhSO_2Cl$ and Hunig's base provided sulfonate **3** in 85% yield. Apparently, steric hindrance around the C9 carbinol and the modest reactivity of the sulfonylation reagent limited deleterious side reactions. All attempts to attach the other electron-withdrawing groups to phenol **21** failed, either returning starting materials or, in the case of triflate, leading to decomposition. The A_{1-3} strain found between the C5 carbonyl moiety and the adjacent protected phenol of compound **3** and its analogues twists the carbonyl group out of the plane, raising the energy and rendering the protecting groups very susceptible to hydrolysis. Hydrolysis would relieve the steric strain, restore full conjugation between the aldehyde and the ring, and restore the stabilizing hydrogen bond found in hydroxybenzofuran **21**. The relatively inert benzenesulfonate increases the kinetic stability of aldehyde **3**, making it a well-suited intermediate for the Prins cyclization.

The key Prins cyclization was investigated using two common acidic conditions for the reaction, TFA and a combination of $BF_3 \cdot OEt_2$ and acetic acid (Scheme 4).[7g,h] Treatment with TFA in CH_2Cl_2 led to decomposition, but treatment of aldehyde **3** with $BF_3 \cdot OEt_2$ and HOAc in CH_2Cl_2 at high dilution (15 mM) generated a mixture of the acetate **22** and fluoride **23** in 33% and 48% yield, respectively. Ethanolysis of macrocycle **22** afforded Lee's kendomycin intermediate **2**.[2] The corresponding fluoride analogue **24** was also available by hydrolysis of cyclization product **23**. Lee demonstrated that a three-step protocol, featuring an IBX oxidation, could be used to convert diol **2** to kendomycin.[2] Thus, synthesis of diol **2** constitutes a formal total synthesis of kendomycin.[23]

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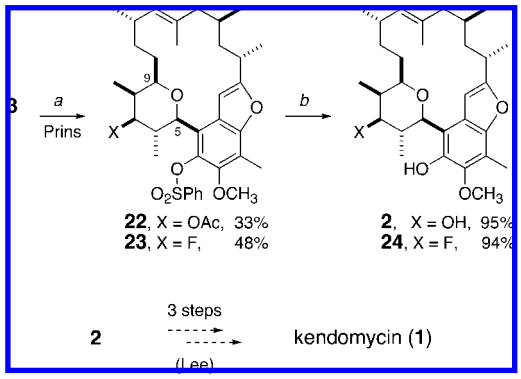
(23) Two attempts to reproduce Lee's oxidation of diol **2** were unsuccessful in our hands. We are convinced that Lee's oxidation, and the similar oxidation reported by Smith, are valid. However, these transformations proceed through reactive *ortho*-quinone intermediates and are difficult to conduct.

Scheme 4. Key Prins-Mediated Macrocyclization in the Preparation of the Kendomycin Skeleton[a]



[a] Reagents and conditions: (a) AcOH, $BF_3 \cdot OEt_2$, CH_2Cl_2; (b) KOH, EtOH, 80 °C.

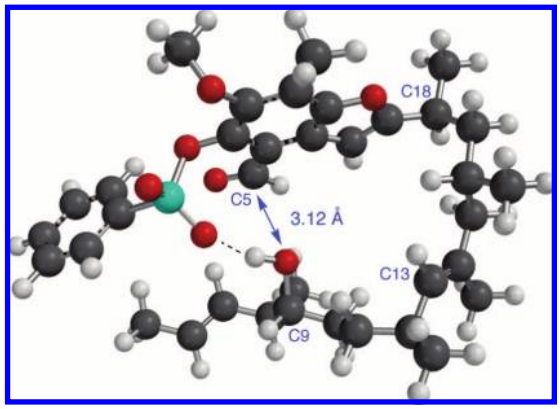


Figure 2. Preferred conformation of unsaturated aldehyde **3**, the Prins macrocyclization precursor, by molecular modeling using the MMFF force field.

The macrocyclization of aldehyde **3** is surprisingly effective. In practice, the yield of cyclized product is split between the fluoride and the acetate, which reduces the synthetic efficiency. Fluoride trapping is occasionally observed in Prins cyclizations, but it usually can be minimized by using alternative acid catalyst systems.[24] In this case, attempted cyclization with TFA or in the presence of TMSOAc was unsuccessful. We will continue to investigate alternative catalyst systems to avoid this problem. The combined yield, however, is a remarkable 81%. To understand why the Prins macrocyclization is so efficient, we investigated the conformation of the hydroxy aldehyde **3**. Compound **3** was modeled using Spartan's conformational search routine and the MMFF force field. The lowest energy conformation is presented in Figure 2. The molecule is well disposed to cyclize, with the aldehyde and alcohol only 3.12 Å apart. The first 12 low-energy conformations all show aldehyde−alcohol bond distances of less than 3.3 Å. In a general sense, this conformational preference is understandable.[25] In order to avoid a *syn*-pentane interaction, C16 and C18 methyl groups force a kink in the chain. The geometry of the trisubstituted alkene introduces a second turn in the chain around the C12−C14 region to avoid unfavorable A_{1-3} interactions. These two features, combined with the preferred extended conformation of the rest of the chain and the rigidity of the benzofuran, reduce the degrees of freedom in hydroxy aldehyde **3**. Molecular modeling identifies a hydrogen bond between the sulfonate and the C9 alcohol that brings the reactive ends of the molecule together and sets up the remarkably efficient macrocyclization event. The kendomycin skeleton is ideally suited to a Prins macrocyclization approach.

Conclusions

The Prins cyclization is an effective method to form the macrocyclic ring in kendomycin. The cyclization precursor was assembled from two fragments of similar complexity using a Suzuki−Miyaura coupling. The final carbon atom was introduced using a Duff ortho-formylation reaction. The Prins macrocycle formation is undoubtedly aided by the conformational preference of the hydroxy aldehyde precursor **3**. The work constitutes a formal total synthesis of kendomycin and demonstrates the potential of the Prins cyclization to form tetrahydropyran-containing macrocyclic rings.

Experimental Section

Alkene 20. Following the Suzuki−Miyaura cross-coupling procedures of Lee,[2] Marshall,[12b] and Novartis chemists,[12c] alkyl iodide **5**[26] (284 mg, 565 μmol, 1.3 equiv) was dissolved in 2 mL of Et_2O and cooled to −78 °C. To this solution was added *t*-BuLi (0.81 mL, 1.40 M in pentane, 2.6 equiv) as a stream. After 3 min of stirring, a solution of 9-BBN (1.30 mL, 1.0 M in hexane, 3.0 equiv) was added, followed by 2 mL of THF. The reaction mixture was held at −78 °C for 30 min and then allowed to warm to room temperature over 2 h. In a separate flask, vinyl iodide **4**[26] (140 mg, 434 μmmol) was dissolved in 2.5 mL of DMF and mixed with 3.0 M aqueous K_3PO_4 (0.72 mL, 5.0 equiv). After a homogeneous mixture was obtained, this vinyl iodide solution was added dropwise to the boronate solution at room temperature. Upon the addition of $PdCl_2(dppf) \cdot CH_2Cl_2$ (18 mg, 5 mol%), the reaction flask was sealed from light with foil and stirred for 15 h. The reaction mixture was partitioned between Et_2O and H_2O. The organic layer was washed with brine and dried over Na_2SO_4. Flash chromatography afforded alkene **20** as a pale oil (223 mg, 90%): $[\alpha]^{24}_D$ +19.6 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.21 (s, 1H), 5.47 (dq, J = 15.2, 6.5, 1H), 5.33 (dd, J = 15.2, 7.5, 1H), 4.87 (d, J = 9.3, 1H), 3.77 (s, 3H), 3.44−3.37 (m, 1H), 2.99 (sext, J = 7.0, 1H), 2.41 (s, 3H), 2.39−2.31 (m, 1H), 2.23−2.15 (m, 1H), 2.08 (dd, J = 12.8, 5.3, 1H), 1.81−1.69 (m, 2H), 1.68−1.64 (m, 1H), 1.65 (d, J = 6.3, 3H), 1.59 (dd, J = 13.9, 6.8, 1H), 1.55 (s, 3H), 1.52−1.45 (m, 1H), 1.44−1.28 (m, 4H), 1.27 (d, J = 6.9, 3H), 1.03 (s, 9H), 0.96 (d, J = 7.0, 3H), 0.94 (d, J = 6.9, 3H), 0.83 (d, J = 6.2, 3H), 0.18 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 148.9, 146.7, 145.2, 133.7, 133.3, 132.6, 126.1, 123.7, 115.1, 108.1, 100.4, 75.2, 60.7, 48.3, 43.3, 42.7, 34.1, 32.5, 31.9, 31.4, 28.4, 26.0, 21.8, 19.6, 19.3, 18.5, 18.3, 16.3, 15.1, 9.4, −4.5; IR (NaCl) 3433(br), 2958, 2929, 2860, 1442, 1352, 1255, 1215, 1119, 1078, 1034, 1005, 893, 835, 783, 735 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{35}H_{58}NaO_4Si$ $(M + Na)^+$ 593.4002, found 593.3998.

Phenol Precursor to Aldehyde 21. To a solution of TBS ether **20** (59 mg, 103 μmol) in 1 mL of THF at −78 °C was added TBAF (113 μL, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for 30 min and then partitioned between Et_2O and aqueous NH_4Cl. The organic layer was washed with brine and dried over Na_2SO_4. Flash chromatography provided the expected phenol (44 mg, 93%) as a pale oil: $[\alpha]^{24}_D$ +23.4 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.23 (s, 1H), 5.57 (s, 1H), 5.51−5.43 (m, 1H), 5.33 (ddd, J = 15.3, 7.6, 1.2, 1H), 4.87 (d, J = 9.3, 1H), 3.82 (s, 3H), 3.43−3.37 (m, 1H), 3.04−2.95 (m, 1H), 2.45 (s, 3H),

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(25) (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124–1134. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054–2070.

(26) See Supporting Information for experimental details.

2.39−2.30 (m, 1H), 2.24−2.16 (m, 1H), 2.08 (dd, J = 12.6, 4.9, 1H), 1.74 (dd, J = 12.6, 8.6, 1H), 1.69−1.64 (m, 1H), 1.65 (d, J = 6.3, 3H), 1.58 (dd, J = 13.8, 6.9, 1H), 1.54 (s, 3H), 1.51−1.45 (m, 1H), 1.44−1.26 (m, 5H), 1.27 (d, J = 7.0, 3H), 0.96 (d, J = 6.9, 3H), 0.93 (d, J = 6.5, 3H), 0.82 (d, J = 6.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 148.0, 145.3, 142.6, 133.7, 133.3, 132.5, 126.1, 124.3, 114.1, 102.2, 100.5, 75.2, 61.6, 48.3, 43.3, 42.7, 34.1, 32.5, 31.9, 31.5, 28.4, 21.7, 19.6, 19.3, 18.3, 16.3, 15.0, 9.6; IR (NaCl) 3413(br), 2960, 2927, 1454, 1419, 1217, 1109, 991, 735 cm^{-1}; HRMS (EI) m/z calcd for $C_{29}H_{44}NaO_4$ $(M + Na)^+$ 479.3137, found 479.3136.

Aldehyde 21. The phenol from the previous step (40 mg, 88 μmol) was dissolved in 1.5 mL of HOAc and heated to 100 °C. A single portion of HMTA (61 mg, 5.0 equiv) was added, followed by the addition of H_2O (8 μL, 5 equiv), and the reaction mixture was stirred for 2.5 h. After cooling to room temperature, the mixture was partitioned between Et_2O and H_2O. The organic layer was washed with aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. Flash chromatography afforded aldehyde **21** (32 mg, 76%): $[\alpha]^{24}_D$ +25.0 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.40 (s, 1H), 10.21 (s, 1H), 6.64 (s, 1H), 5.48 (dq, J = 15.3, 6.3, 1H), 5.34 (dd, J = 15.3, 7.6, 1H), 4.88 (d, J = 9.3, 1H), 3.90 (s, 3H), 3.43−3.37 (m, 1H), 3.07 (sext, J = 7.0, 1H), 2.48 (s, 3H), 2.39−2.31 (m, 1H), 2.23−2.15 (m, 1H), 2.08 (dd, J = 12.9, 5.3, 1H), 1.77 (dd, J = 12.9, 8.5, 1H), 1.71−1.64 (m, 1H), 1.65 (d, J = 6.3, 3H), 1.63−1.59 (m, 3H), 1.57−1.50 (m, 1H), 1.46−1.30 (m, 3H), 1.55 (s, 3H), 1.32 (d, J = 6.9, 3H), 0.96 (d, J = 7.0, 3H), 0.94 (d, J = 6.5, 3H), 0.84 (d, J = 6.4, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 167.7, 153.3, 147.2, 142.7, 133.7, 133.5, 132.3, 126.2, 125.8, 125.2, 110.0, 97.4, 75.2, 61.0, 48.3, 43.2, 42.7, 34.2, 32.6, 31.9, 31.7, 28.4, 21.7, 19.6, 19.2, 18.3, 16.3, 15.0, 10.3; IR (NaCl) 3460(br), 2960, 2927, 1643, 1452, 1294, 1134, 951 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{44}NaO_5$ $(M + Na)^+$ 507.3087, found 507.3086. The corresponding C9 acetate was also produced in up to 18% yield, depending upon reaction times.[21,26]

Sulfonate 3. To a solution of aldehyde **21** (76 mg, 157 μmol) and $PhSO_2Cl$ (24 μL, 1.2 equiv) in 1.5 mL of DCM at 0 °C was added Hunig's base (82 μL, 3.0 equiv). The reaction mixture was allowed to reach room temperature and stirred for 24 h. The mixture was partitioned between Et_2O and H_2O, and the aqueous layer was slowly acidified with 3 N HCl. The organic layer was separated, washed with brine, and dried over Na_2SO_4. Flash chromatography afforded sulfonate **3** as a yellow oil (83 mg, 85%): $[\alpha]^{24}_D$ +21.9 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.97 (d, J = 7.7, 2H), 7.73 (t, J = 7.5, 1H), 7.59 (t, J = 7.7, 2H), 7.14 (s, 1H), 5.48 (dq, J = 15.2, 6.5, 1H), 5.34 (dd, J = 15.2, 7.5, 1H), 4.88 (d, J = 9.3, 1H), 3.64 (s, 3H), 3.43−3.38 (m, 1H), 3.07 (app. sext, J = 7.0, 1H), 2.46 (s, 3H), 2.38−2.30 (m, 1H), 2.23−2.15 (m, 1H), 2.07 (dd, J = 12.8, 5.3, 1H), 1.76 (dd, J = 12.8, 8.6, 1H), 1.72−1.64 (m, 1H), 1.66 (d, J = 6.5, 3H), 1.63−1.48 (m, 3H), 1.55 (d, J = 6.8, 3H), 1.44−1.25 (m, 4H), 1.30 (d, J = 6.9, 3H), 0.96 (d, J = 6.9, 3H), 0.94 (d, J = 6.7, 3H), 0.83 (d, J = 6.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6, 169.4, 152.0, 147.5, 142.5, 135.9, 134.7, 133.7, 133.5, 132.3, 129.5, 128.7, 126.1, 123.8, 123.6, 119.8, 101.9, 75.2, 61.4, 48.3, 43.1, 42.7, 34.1, 32.5, 31.9, 31.7, 28.4, 21.7, 19.6, 19.1, 18.3, 16.3, 15.0, 10.2; IR (NaCl) 3434(br), 2927, 1685, 1581, 1450, 1383, 1190, 1117, 968, 783, 750 cm^{-1}; HRMS (EI) m/z calcd for $C_{36}H_{48}NaO_7S$ $(M + Na)^+$ 647.3018, found 647.3018.

Prins Macrocyclization: Acetate 22 and Fluoride 23. Sulfonate **3** (25 mg, 40 μmol) was dissolved in 3.0 mL of DCM to afford a 0.01 M solution. After the solution was cooled to 0 °C, dry AcOH (34 μL, 15.0 equiv) and freshly distilled $BF_3\cdot OEt_2$ (15 μL, 3.0 equiv) were added. The intensely yellow, homogeneous reaction mixture was stirred at 0 °C for 2 h, prior to the addition of Et_2O and aqueous $NaHCO_3$. The organic layer was washed with brine and dried over Na_2SO_4. Flash chromatography provided macrocycles **22** (9 mg, 33%) and **23** (12 mg, 48%) as pale films.

Data for Acetate 22. $[\alpha]^{24}_D$ +13.1 (c 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 7.7, 2H), 7.74 (app. t, J = 7.5, 1H), 7.65−7.58 (m, 2H), 6.54 (s, 1H), 4.58 (d, J = 9.7, 1H), 4.33 (dd, J = 11.0, 4.7, 1H), 3.80 (d, J = 10.3, 1H), 3.69 (s, 3H), 3.12−3.02 (m, 1H), 2.91 (d, J = 10.8, 1H), 2.45 (s, 3H), 2.42−2.32 (m, 2H), 2.25−2.18 (m, 3H), 2.12−2.01 (m, 1H), 2.03 (s, 3H), 1.95−1.87 (m, 1H), 1.85−1.78 (m, 1H), 1.57 (s, 3H), 1.52−1.39 (m, 4H), 1.38 (d, J = 6.9, 3H), 0.91 (d, J = 7.0, 3H), 0.87 (d, J = 6.7, 3H), 0.80 (d, J = 6.4, 3H), 0.61 (d, J = 6.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 161.0, 152.7, 147.4, 138.6, 136.0, 134.1, 131.9, 129.9, 129.6, 128.2, 125.7, 123.7, 122.3, 115.3, 104.9, 79.1, 78.5, 61.2, 43.8, 42.0, 36.6, 35.9, 34.4, 33.8, 32.7, 31.8, 27.6, 22.1, 21.3, 21.1, 19.8, 18.8, 12.9, 9.6, 7.4; IR (NaCl) 2952, 2927, 1728, 1450, 1381, 1240, 1190, 1099, 754 cm^{-1}; HRMS (EI) m/z calcd for $C_{38}H_{50}NaO_8S$ $(M + Na)^+$ 689.3124, found 689.3130.

Data for Fluoride 23. $[\alpha]^{24}_D$ +16.6 (c 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.8, 2H), 7.71 (app. t, J = 7.4, 1H), 7.59 (app. t, J = 7.8, 2H), 6.53 (s, 1H), 4.58 (d, J = 9.5, 1H), 3.98 (ddd, $J_{F,H}$ = 49.5, $J_{H,H}$ = 10.5, 5.0, 1H), 3.79 (dd, J = 10.1, 1.2, 1H), 3.64 (s, 3H), 3.08 (ddd, J = 11.7, 6.8, 4.2, 1H), 2.89 (d, J = 9.5, 1H), 2.44 (s, 3H), 2.26−2.18 (m, 1H), 2.02−1.93 (m, 1H), 1.92−1.84 (m, 3H), 1.62 (s, 3H), 1.48−1.38 (m, 3H), 1.38 (d, J = 6.8, 3H), 1.35−1.21 (m, 4H), 0.98 (d, J = 6.8, 3H), 0.87 (d, J = 6.6, 3H), 0.80 (d, J = 6.3, 3H), 0.77 (d, J = 6.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 152.7, 147.3, 138.7, 137.3, 133.9, 131.9, 129.5, 128.9, 128.3, 125.7, 122.4, 115.4, 104.9, 97.7 (d, J_{C-F} = 183.7), 77.8 (d, J_{C-F} = 9.2), 76.8 (d, J_{C-F} = 8.8), 61.1, 43.8, 41.9, 38.1 (d, J_{C-F} = 16.2), 37.1 (d, J_{C-F} = 16.6), 33.8, 32.7, 31.7, 30.8, 27.5, 22.1, 21.2, 19.8, 18.7, 12.7, 9.6, 6.9; IR (NaCl) 2925, 2870, 1450, 1383, 1329, 1190, 1099, 999, 968, 924, 754 cm^{-1}; HRMS (EI) m/z calcd for $C_{36}H_{47}FNaO_6S$ $(M + Na)^+$ 649.2975, found 649.2969.

Alcohol 2. [27]To a solution of macrocycle **22** (8.0 mg, 12.0 μmol) in 2 mL of argon-sparged 50% aqueous EtOH was added KOH (10 mg, 15 equiv). The reaction mixture was heated to 78 °C for 4 h. Upon reaching ambient temperature, the reaction was partitioned between Et_2O and H_2O, and the aqueous layer was slowly acidified with 3 N HCl. The organic layer was separated, and the aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. Flash chromatography provided alcohol macrocycle **2** as a film (5.5 mg, 95%): $[\alpha]^{24}_D$ +16.8 (c 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (s, 1H), 5.53 (s, 1H), 4.60 (d, J = 9.4, 1H), 4.54 (d, J = 10.1, 1H), 3.83 (s, 3H), 3.68−3.62 (m, 1H), 3.44 (dd, J = 10.4, 1.2, 1H), 3.12−3.03 (m, 1H), 2.47−2.42 (m, 1H), 2.45 (s, 3H), 2.26−2.18 (m, 1H), 1.93−1.89 (m, 1H), 1.84−1.77 (m, 1H), 1.62 (s, 3H), 1.59−1.50 (m, 2H), 1.47−1.40 (m, 2H), 1.38 (d, J = 6.8, 3H), 1.35−1.25 (m, 5H), 1.04 (d, J = 6.9, 3H), 0.90 (d, J = 6.6, 3H), 0.81 (d, J = 6.6, 3H), 0.76 (d, J = 6.4, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 148.8, 141.9, 141.8, 131.7, 129.2, 122.4, 116.0, 112.7, 105.0, 78.0, 77.6, 77.5, 61.7, 44.0, 42.0, 39.9, 38.9, 33.9, 32.8, 31.7, 31.4, 27.7, 22.0, 21.2, 19.8, 18.9, 13.0, 9.7, 6.8; IR (NaCl) 3533, 2927, 2856, 1456, 1385, 1325, 1215, 1107, 999, 760 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{44}NaO_5$ $(M + Na)^+$ 507.3087, found 507.3086.

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Supporting Information Available: Preparation and characterization of all compounds and complete ref 12c. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) The spectroscopic data for macrocycle **2** matched those reported by Lee and co-workers; the correlation constitutes a formal synthesis of (−)-kendomycin.