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Total Synthesis of (−)-Kendomycin

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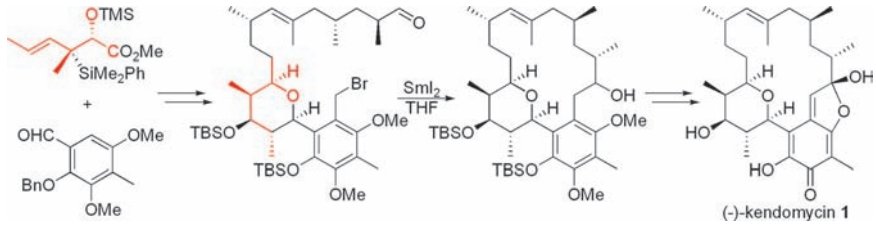
ABSTRACT



An enantioselective synthesis of (−)-kendomycin is described and is based on the application of the organosilane-based [4 + 2]-annulation strategy for the assembly of the C1a−C10 fragment. An underutilized samarium(II) iodide-assisted cyclization (intramolecular Barbier-type reaction) is employed to afford the protected macrocycle.

Kendomycin [(−)-TAN 2162] was originally isolated from *Streptomyces violaceuber* in 1996 by Funahashi and co-workers.[1] Initial screens of the compound revealed potent endothelin receptor antagonist activity[1] as well as its potential as an antiosteoporotic agent.[2] Subsequent reports indicated that kendomycin exhibited effective antibacterial activity against both Gram-positive and Gram-negative strains as well as having enhanced cytotoxic activity toward several human tumor cell lines (average $GI_{50} < 0.10\ \mu M$).[3] Recently, it has been suggested that kendomycin mediates its cytotoxic effects, in part, through proteasome inhibition.[4]

Kendomycin is a 16-membered conformationally restricted macrocycle comprising a densely functionalized pyran ring system and unique quinone methide chromophore through a pseudo *C*-glycosidic bond and further tethered by an aliphatic *ansa* system. The relative and absolute stereochemistry of kendomycin was confirmed by both single crystal X-ray and advanced Mosher's ester analysis.[3]

The biological profile of kendomycin crosses several therapeutic areas, and its unique molecular architecture has led to considerable interest by the synthetic community, which culminated with two total syntheses[5,6] in addition to several fragment syntheses.[7] Herein, we report an enantioselective synthesis of kendomycin.

The synthetic plan for constructing kendomycin intended to utilize an underdeveloped macrocyclization involving an intramolecular Barbier-type reaction of **3**

(1) (a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japan Patent 08231551 [A2960910], 1996; *Chem. Abstr.* **1997**, *126*, 6553. (b) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japan Patent 08231552, 1996; *Chem. Abstr.* **1996**, *125*, 326518.

(2) Su, M. H.; Hosken, M. I.; Hotovec, B. J.; Johnston, T. L. U.S. Patent 5728727 [A 980317], 1998; *Chem. Abstr.* **1998**, *128*, 239489.

(3) (a) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, *n/a*, 323–328. (b) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, *n/a*, 2665–2670.

(4) Elnakady, Y. A.; Rohde, M.; Sasse, F.; Backes, C.; Keller, A.; Lenhof, H. P.; Weissman, K. J.; Mueller, R. *ChemBioChem.* **2007**, *8*, 1261–1272.

(5) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721.

(6) (a) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948–6949. (b) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292–5299.

(7) (a) Sengoku, T.; Uemura, D.; Arimoto, H. *Chem. Lett.* **2007**, *36*, 726–727. (b) Williams, D. R.; Shamim, K. *Org. Lett.* **2005**, *7*, 4161–4164. (c) White, J. D.; Smits, H. *Org. Lett.* **2005**, *7*, 235–238. (d) Mulzer, J.; Pichlmair, S.; Green, M. P.; Marques, M. M. B.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11980–11985. (e) Sengoku, T.; Arimoto, H.; Uemura, D. *Chem. Commun.* **2004**, *n/a*, 1220–1221. (f) Pichlmair, S.; Marques, M. M. B.; Green, M. P.; Martin, H. J.; Mulzer, J. *Org. Lett.* **2003**, *5*, 4657–4659. (g) Marques, M. M. B.; Pichlmair, S.; Martin, H. J.; Mulzer, J. *Synthesis* **2002**, *n/a*, 2766–2770. (h) Martin, H. J.; Drescher, M.; Kählig, H.; Schneider, S.; Mulzer, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3186–3188. (i) Bahnck, K. B.; Rychnovsky, S. D. *Chem. Commun.* **2006**, *n/a*, 2388–2390.

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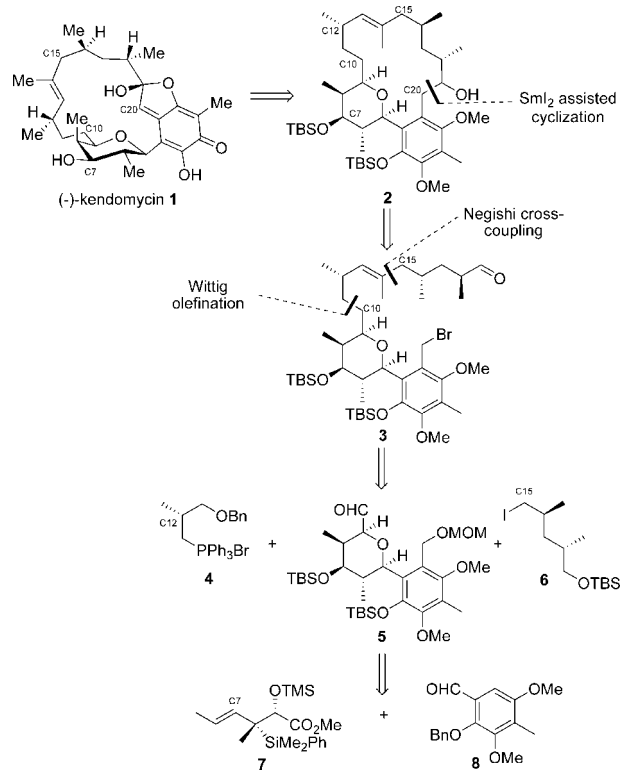
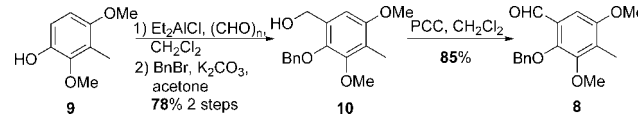
Scheme 1. Retrosynthetic Analysis of Kendomycin **1**



(Scheme 1).[8] In that regard, few examples of samarium(II) iodide-catalyzed macrocyclizations have been described.[9] Disconnection of the C14−C15 trisubstituted olefin of **3** provides an intermediate vinyl iodide and primary alkyl iodide **6**.[10] In the forward sense, this bond construction will be installed through palladium-catalyzed Negishi cross-coupling. The C10−C11 bond was our next disconnection and was accessed via a Wittig olefination using previously described phosphonium salt **4**[11] and fully functionalized tetrahydropyran **5**. Our convergent approach to the pyran portion of kendomycin is highlighted by a stereoselective [4 + 2]-annulation[12] between crotylsilane **7**[13] and aldehyde **8**.

The synthesis of the aromatic fragment **8** (Scheme 2) began with a regioselective hydroxymethylation of known

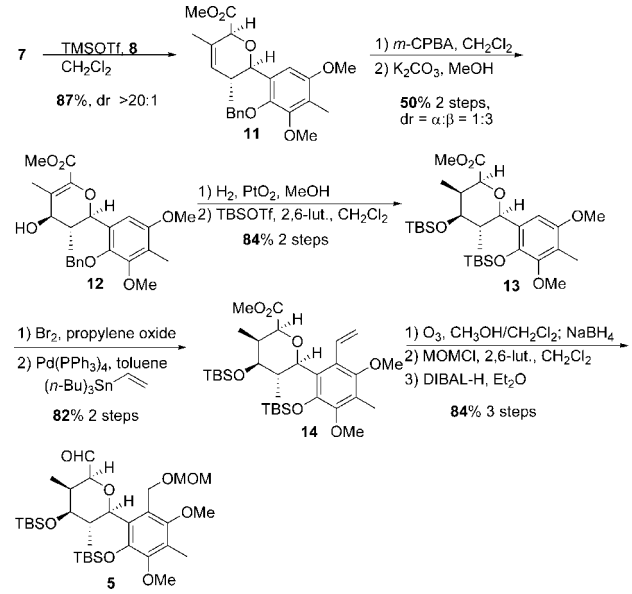
Scheme 2. Synthesis of Aromatic Core **8**



phenol **9**.[14] This material was chemoselectively protected as its benzyl ether furnishing **10**.[15] Oxidation of the remaining benzylic alcohol using pyridinium chlorochromate (PCC) provided aromatic aldehyde **8** in high yield and completed the preparation of the aromatic annulation partner.[16]

Use of crotylsilane **7** in a [4 + 2]-annulation with aldehyde **8** gave the desired 2,5-*syn* dihydropyran **11** in 87% isolated yield (dr > 20:1; Scheme 3). The resulting trisubstituted

Scheme 3. Synthesis of the C1a−C10 Subunit



double bond was treated with *m*-CPBA in methylene chloride at 0 °C to provide the desired β-epoxide as the major isomer (α:β 1:3, 82%). The resulting diastereomers could be separated via column chromatography or taken forward as a mixture of isomers.[17] Epoxide ring opening occurred in the presence of potassium carbonate in methanol to give secondary alcohol **12**. This substrate underwent catalytic hydrogenation in which both the aryl benzyl ether and α,β-unsaturated ester were reduced. Masking the resident hydroxyl

(8) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338.

(9) (a) Nicolaou, K. C.; Rao, P. B.; Hao, J.; Reddy, M. V.; Rassias, G.; Huang, X.; Chen, D. Y.-K.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1753–1758. (b) Nicolaou, K. C.; Huang, X.; Giuseppone, N.; Rao, P. B.; Bella, M.; Reddy, M. V.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4705–4709.

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(11) Gaeta, F. C. A.; Lehman de Gaeta, L. S.; Kogan, T. P.; Or, Y. S.; Foster, C.; Czarniecki, M. *J. Med. Chem.* **1990**, *33*, 964–972.

(12) For recent examples of allyl and crotylsilane reagents utilized in natural product synthesis see: (a) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231–3234. (b) Su, Q.; Panek, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1223–1225. (c) Su, Q; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430. (d) Huang, H.; Panek, J. S. *Org. Lett.* **2003**, *5*, 1991–1993.

(13) (a) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529–1532. (b) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2007**, *9*, 2753–2753.

(14) Obtained in two steps starting from commercial 2,6-dimethoxytoluene: (a) Knolker, H.-J.; Frohner, W.; Reddy, K. R. *Synthesis* **2002**, *4*, 557–564.

(15) Magnus, P.; Matthews, K. S.; Lynch, V. *Org. Lett.* **2003**, *5*, 2181–2184.

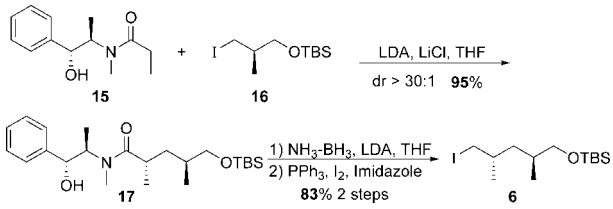
(16) Nakahara, S.; Kubo, A. *Heterocycles* **2003**, *60*, 2717–2725.

(17) The C7 epimer (or isomeric mixture) of **12** could be oxidized under Swern conditions to provide an intermediate ketopyran, which was selectively reduced under Luche conditions (99%, 15:1 β:α) to provide **12** in 50% yield over three steps. See Supporting Information for details.

groups as their TBS ethers furnished **13** in two steps with 84% yield as a single diastereomeric pyran. Bromination of the aromatic ring system followed by a Stille cross-coupling with tri-*n*-butyl(vinyl)stannane provided styrene **14** (two steps, 82%). Oxidative cleavage of the resulting styrene functionality followed by a reductive workup (O_3, $NaBH_4$) gave an intermediate benzyl alcohol that was protected as its MOM ether. Finally, reduction of the methyl ester using DIBAL-H provided aldehyde **5**.

The synthesis of fragment **6** was carried out through the alkylation of Myers' pseudoephedrine-derived auxiliary **15**[18] with primary iodide **16**[19] to provide the desired product **17** containing a 1,3-*anti* relationship between C16 and C18 methyl groups (Scheme 4). Cleavage of the auxiliary was

Scheme 4. Synthesis of the C15−C19 Subunit

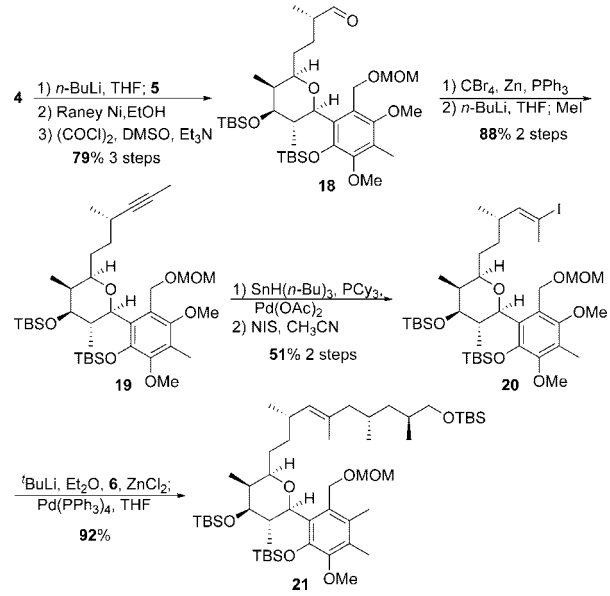


carried out as previously described using a borane−ammonia complex to give a primary alcohol.[20] This material was directly converted to the primary iodide **6** by treatment with I_2/PPh_3 in 83% yield (over two steps).

Generation of the ylide from phosphonium salt **4** by treatment with *n*-butyllithium at 0 °C followed by addition of aldehyde **5** gave a 10:1 (*Z*:*E*) selectivity of the resulting Wittig adduct (Scheme 5). Hydrogenation of the olefin and deprotection of the benzyl ether gave the primary alcohol, which was subsequently oxidized under Swern conditions[21] to give aldehyde **18**. This material was immediately converted to the internal alkyne **19** using conditions developed by Corey and Fuchs (86% over two steps).[22] Formation of vinyl iodide **20** was initially found to be problematic. In that regard, we found that the alkyne undergoes a palladium(0)-mediated hydrostannation with useful levels of regioselectivity (*E*:*Z* 10:1). Conversion of this material to the vinyl iodide (NIS, CH_3CN/CCl_3CN) completed the preparation of the electrophilic cross-coupling partner.[23]

Introduction of the *ansa*-system was brought about through a Negishi cross-coupling[24] with vinyl iodide **20** and alkyl

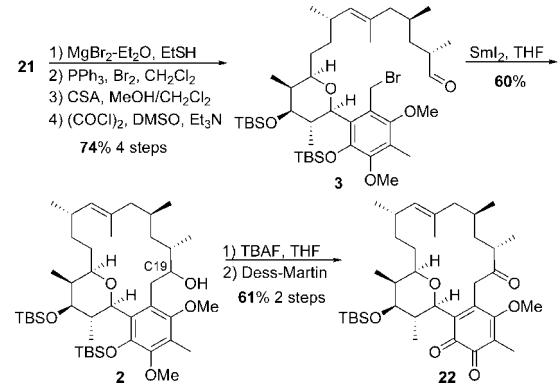
Scheme 5. Installation of the *ansa*-Bridging System



iodide **6**. Treatment of the alkyl iodide with ^{t}BuLi and trapping of the resulting anion with anhydrous $ZnCl_2$ generated an intermediate alkyl zinc species. Coupling of the in situ prepared zinc intermediate with the vinyl iodide **20** in the presence of $Pd(PPh_3)_4$ provided the advanced fragment **21** in 92% yield. This reaction introduced the remaining chiral centers and carbon atoms en route to kendomycin.

The final stages of the synthesis began with the removal of MOM ether of **21** using $MgBr_2$•OEt_2 and ethane thiol initiated (Scheme 6).[25] This transformation was followed by

Scheme 6. Synthesis of the Kendomycin Macrocycle



introduction of a benzylic bromide, which eventually will become the nucleophilic site in the macrocyclization step.[26] Selective removal of the primary TBS ether using CSA in a

(18) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

(19) Friestad, G. K.; Marie, J. C.; Deveau, A. M. *Org. Lett.* **2004**, *6*, 3249–3252. Or Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186–1194.

(20) Myers, A.; Yang, B.; Kopecky, D. *Tetrahedron Lett.* **1996**, *37*, 3623–3626.

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(23) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647–8650.

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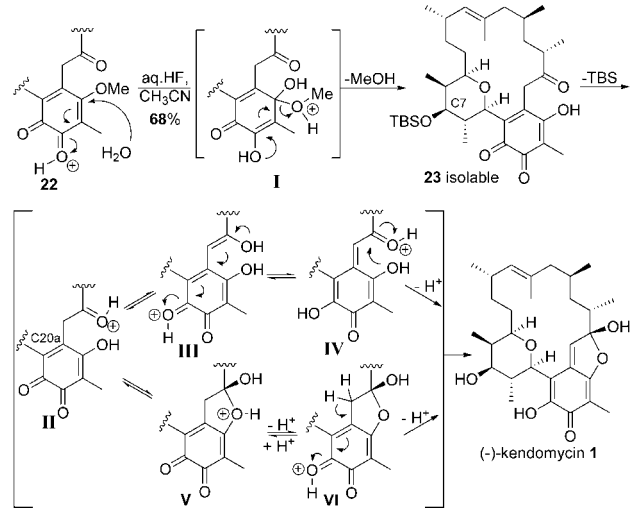
(25) Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett* **1991**, *n/a*, 183–184.

CH_2Cl_2/MeOH mixture followed by oxidation of the alcohol gave **3** in 74% over four steps, which was used without purification. Immediate exposure of the bromide to a dilute solution of freshly prepared samarium(II) iodide[27] in THF resulted in the production of a secondary alcohol **2** in a single stereochemical configuration.[28] Removal of the aromatic silyl ether with TBAF[29] was followed by oxidation of the C19 secondary alcohol, and the aromatic system using hypervalent iodide provided the *ortho*-quinone **22**.[30]

The final deprotection sequence to access kendomycin involved the removal of the secondary silyl ether and formation of the quinone methide portion of the molecule.[6] Interestingly, however, when the reported conditions were applied, only minute amounts of **1** were obtained (<20% isolated yield). The spectroscopic data of the major product isolated was consistent with compound **23**. Resubjecting this material (or **22**) to slightly modified conditions (100 equiv of aq HF, CH_3CN, 2 h, RT) and purification over silica gel provided pure kendomycin as a yellow solid. A plausible mechanistic pathway has been outlined in Scheme 7. Initial Michael-type addition of water to *ortho*-quinone **22** and elimination of methanol (**I**) would provide a reasonable explanation of the formation of structure **23**. The silyl ether eventually lost to arrive at an intermediate product assumed to be **23**-OH (C7). At this point, a number of paths leading to kendomycin may be operative.[31] Initial formation of the enol tautomer (**II** → **III**) could be followed by a reorganization to provide α,β-unsaturated ketone **IV**, which cyclizes to form **1**. Alternatively, hemiketal formation to access **V**, which precedes tautomerization to kendomycin through intermediate **VI**, may also be an operative pathway. Though

Scheme 7. Completion of the Synthesis



the mechanism of a similar system has been proposed,[32] the sequence as applied to kendomycin has only been inferred.[6b]

In summary, the total synthesis of the bacterial metabolite kendomycin has been achieved in 26 steps with a 1.51% overall yield starting from **7**. The approach relied on the application of a silane reagent bearing a fully substituted carbon center to construct the pyran ring. In addition, a SmI_2-promoted macrocyclization strategy was demonstrated to form the macrocycle of the natural product. Future studies to explore the scope and limitation of this strategy are currently underway.

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Supporting Information Available: Experimental details and selected spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801499S

(26) Kim, H. M.; Sendzik, M.; Spencer, J. R.; Zhang, P. PCT Int. Appl. 2005, 117 pp. WO 2005-US18504 20050526.

(27) Freshly prepared in THF from samarium and diiodoethane, see Supporting Information for details.

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(31) A second Michael-type addition of water to C20a carbon of **II** could provide a β-hydroxy alcohol, which upon loss of water and hemiketalization would also provide kendomycin. See reference 3a for details.

(32) Ling, T.; Poupon, E.; Rueden, E. J.; Theodorakis, E. A. *Org. Lett.* **2002**, *4*, 819–822.