

Efforts toward the Total Synthesis of
(–)-Kendomycin

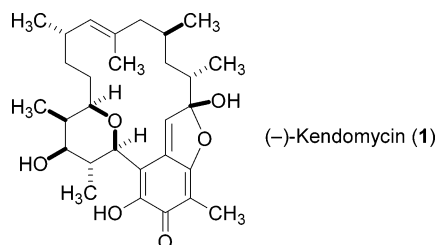
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Received June 28, 2005

ABSTRACT



The synthesis of an advanced component leading to (–)-kendomycin is described. The synthetic scheme features the application of asymmetric conjugate addition methodology for the early generation of the C13–C14 (*E*)-trisubstituted olefin, providing an efficient assembly of the ansa chain. Condensation reactions probe two strategies for attachment of the aromatic system.

Kendomycin (**1**) is a structurally unique polyketide originally isolated from two different *Streptomyces* species and shown to exhibit potent activity as an endothelin antagonist and as an antiosteoporotic agent.¹ In 2000, Zeeck and co-workers reisolated kendomycin from *Streptomyces violaceruber* (strain 3844-33C) and established the structure via X-ray crystallographic analysis.²

(–)-Kendomycin demonstrates notable antibacterial activity against both Gram-positive and Gram-negative bacteria, particularly against multiresistant *Staphylococcus aureus* (MRSA) strains, including vancomycin-resistant *S. aureus* (MU50).^{2a} Cytotoxicity studies of **1** have been investigated with stomach adenocarcinoma (HMO2), hepatocellular carcinoma (HEPG2), and breast adenocarcinoma (MCF7) cell lines. These studies show potency comparable to that of doxorubicin and increased growth inhibition (GI₅₀) compared to that of cisplatin.^{2a}

The structure of kendomycin (**1**) features a novel C-aryl glycoside substructure as conceptualized by the direct linkage of a fully substituted tetrahydropyran and the quinone

methide chromophore. A substituted ansa chain tethers these components in a conformationally restricted macrocyclic system. In 2004, Lee and co-workers³ disclosed the first total synthesis of **1**. However, these challenging structural features have stimulated numerous synthesis studies adopting a ring-closing strategy of olefin metathesis.^{4,5} Although ring-closing metathesis (RCM) has generally proven to be ineffective, Smith and co-workers have recently described conditions for 16-membered macrocyclization by RCM, albeit with formation of the undesired *Z*-olefin.⁶ Subsequently, kendomycin was obtained by epoxidation and inversion of olefin geom-

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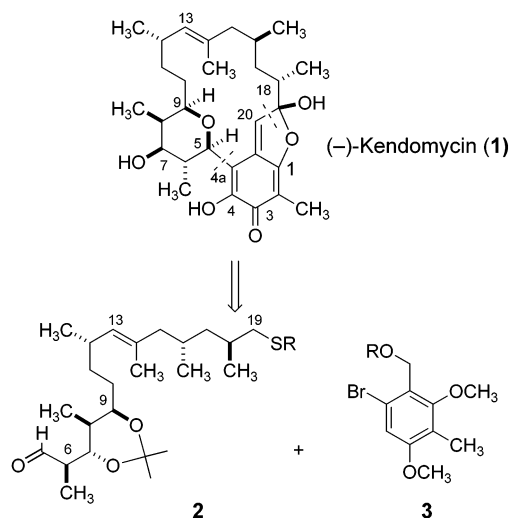
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Scheme 1. Retrosynthetic Analysis of Kendomycin

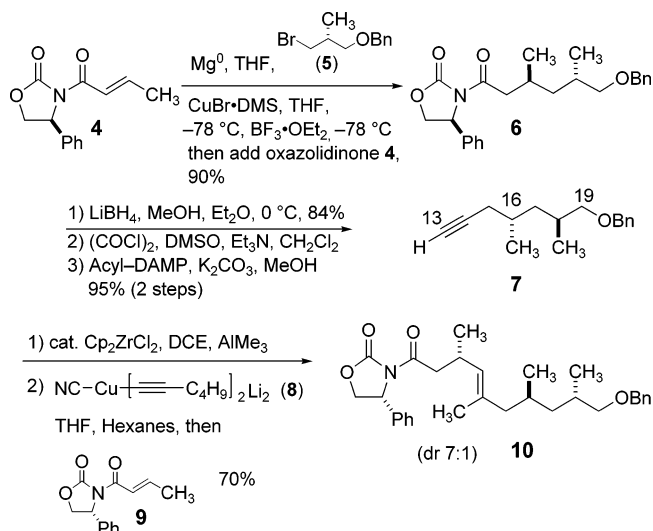


etry. Owing to our interest in atropisomerism of this C-aryl glycoside system, we have chosen to examine a pathway for late-stage introduction of the quinone methide component. Herein, we present a concise and efficient route for the stereocontrolled synthesis of the fully elaborated ansa chain of kendomycin (**1**) as a prelude to ring-closure studies.

The synthesis of the ansa chain began with the construction of the 1,3-*anti* dimethyl substitution in the C14–C19 component (Scheme 2).⁷ *N*-Enoyl oxazolidinone **4**⁸ was treated with the Yamamoto organocopper species derived from the nonracemic bromide **5**,⁹ providing the 1,3-*anti* stereochemistry of **6** with high diastereoselectivity (dr >17:1). Reductive cleavage of the chiral auxiliary of **6** gave a primary alcohol for oxidation under Swern conditions,¹⁰ and high yielding homologation to the terminal alkyne **7** was effected upon subsequent treatment with the Bestmann acyl-DAMP reagent.¹¹

Stereocontrolled formation of the *E*-trisubstituted C13–C14 alkene was undertaken by initial *syn*-carboalumination using Negishi conditions.¹² The intermediate alkenylalane was transformed by the addition of the cyano cuprate **8**,¹³ and in situ formation of a new organometallic reagent facilitated reactivity for conjugate addition. In the event, the introduction of nonracemic oxazolidinone **9** resulted in 70% yield of **10** (dr 7:1) after purification by flash chromatography. Preliminary attempts to use CuCN·LiCl for trans-

Scheme 2. Formation of the (*E*)-Trisubstituted Olefin



metalation of the alkenylalane resulted in significant amounts of product arising from methyl conjugate addition that originated from the trimethylalane.¹⁴ Overall the process leading to **10** was particularly gratifying, since it effected the stereoselective olefin synthesis and stereocontrol at C12 in a single operation.

Removal of the chiral auxiliary of **10** and conversion of the resultant alcohol to aldehyde **11** proceeded in a straightforward fashion (Scheme 3). Asymmetric aldol condensation of **11** with the *Z*(O)-enolate of the ethyl ketone **12** under Paterson conditions using (–)-(Ipc)₂BOTf provided the β-hydroxy ketone adduct **13** in good yield and high diastereoselectivity (dr 9:1).¹⁵ Advantageously, this reagent-controlled process utilizes chirality in the propionate-derived ethyl ketone **12** for diastereofacial discrimination in the aldol transition state, which is fully incorporated in **13**. Internally directed hydride reduction via the Evans protocol¹⁶ gave the expected 1,3-*anti*-diol, which was protected as the corresponding acetone **14**. Hydrogenolysis of the C19-OBn protecting group in the presence of the C5-OPMB ether was readily achieved using W-2 Raney nickel,¹⁷ and the resulting primary alcohol was replaced under Mitsunobu conditions¹⁸ to yield the benzothiazolyl sulfide **15**. Oxidative cleavage of the C5-OPMB ether with buffered DDQ¹⁹ and oxidation

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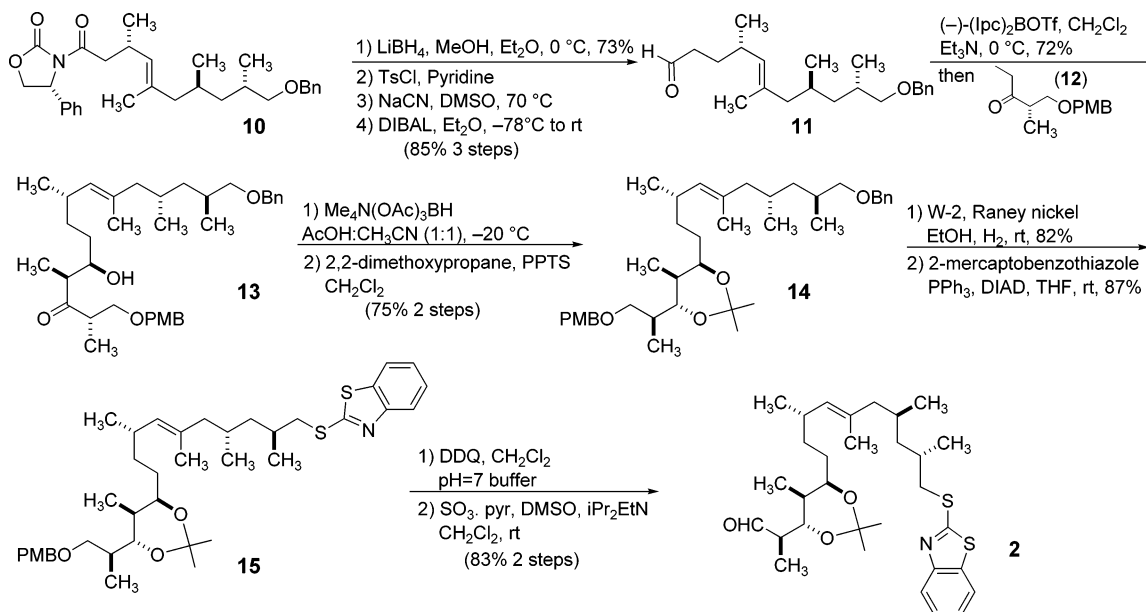
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Scheme 3. Elaboration of **10** to the Advanced Aldehyde **2**



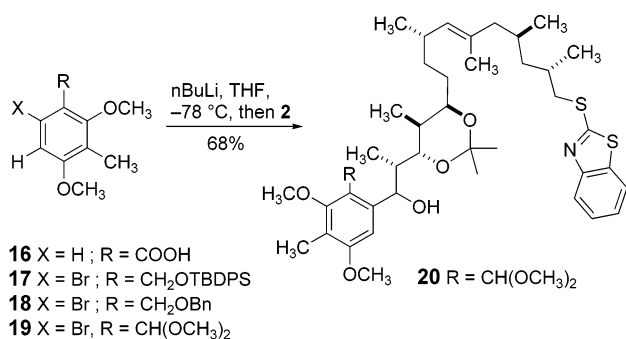
of the resulting alcohol under Parikh–Doering conditions²⁰ provided aldehyde **2** as an advanced component for studies of macrocycle formation. The acyclic aldehyde **2** represents the entire C5–C19 ansa bridge of kendomycin with inclusion of the *E*-trisubstituted alkene and seven additional stereogenic centers.

Preliminary investigations have explored several options for the introduction of the aromatic nucleus. Benzoic acid derivative **16** (Scheme 4) provided for directed deprotonation

able decomposition. Studies of halogen–metal exchange with aryl bromides **17** and **18**, featuring different protecting groups for the benzylic alcohol, gave significant amounts of reduction product resulting from simple protonation.^{22,23} On the other hand, the dimethyl acetal **19** cleanly afforded the advanced intermediate **20** in 68% yield as a mixture of benzylic alcohols (dr 2:1).²⁴ No attempt has been made to secure better stereocontrol in this event since our plan for pyran ring closure supports elimination and subsequent intramolecular capture of a quinone methide intermediate.

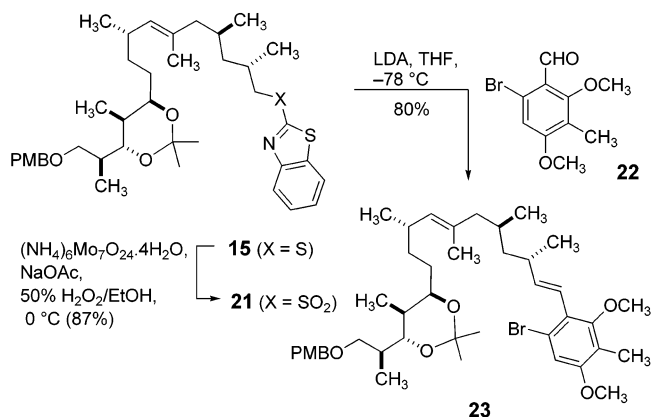
To explore the feasibility of the Julia olefination reaction as a technique for initial attachment of the aromatic system, the benzothiazolyl sulfide **15** (from Scheme 3) was oxidized to the corresponding sulfone **21** using hydrogen peroxide in the presence of ammonium molybdate hydrate (Scheme 5).²⁵ This procedure led to **21** with high yield (87%) while avoiding competing oxidation of the trisubstituted alkene.

Scheme 4



(sBuLi/TMEDA) and moderate yields of condensation products with model aldehydes, which resulted in the expected isolation of five-membered lactones.²¹ However, the corresponding reactions with aldehyde **2** led to consider-

Scheme 5



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Subsequent treatment of **21** with LDA at $-78\text{ }^{\circ}\text{C}$ and the addition of aldehyde **22** exclusively yielded the *E*-olefin **23** upon warming to room temperature (80%).

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In summary, a fully functionalized ansa chain of kendomycin has been prepared with excellent overall stereoselectivity. Two techniques have been examined for successful introduction of the aromatic moiety. Efforts are underway to advance this strategy for synthesis of kendomycin.

Acknowledgment. We acknowledge the National Institutes of Health (GM42897) for their generous support of this work.

Supporting Information Available: Experimental procedures and spectral characterizations for compounds **2**, **7**, **10**, **11**, **13–15**, and **20–23**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL051512R