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Total Synthesis of (−)-Kendomycin Exploiting a Petasis−Ferrier Rearrangement/Ring-Closing Olefin Metathesis Synthetic Strategy

Amos B. Smith, III,* Eugen F. Mesaros, and Emmanuel A. Meyer

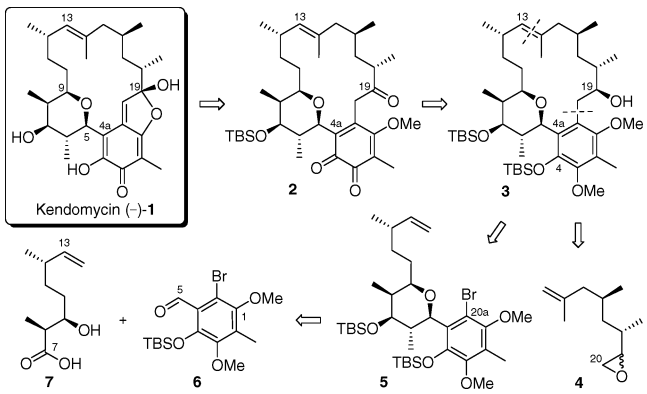
Department of Chemistry, Monell Chemical Senses Center, and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received March 5, 2005; E-mail: smithab@sas.upenn.edu

Kendomycin, (−)-**1**, a novel macrocyclic polyketide first isolated in 1996[1] from *Streptomyces violaceoruber*, possesses potent activity as both an endothelin receptor antagonist[1] and an antiosteoporotic agent.[2] Reisolation by the Zeeck group[3] revealed, in addition, significant antibacterial activity against multiresistant bacteria, including vancomycin-resistant strains, and remarkable cytotoxicity against a series of human tumor cell lines (GI_{50} < 0.1 μM).[3] The impressive biological profile, in conjunction with the challenging architecture, defined by X-ray and Mosher ester analysis,[3] triggered considerable synthetic efforts,[4] culminating in 2004 with the first total synthesis.[5] The structure of kendomycin comprises a unique quinone−methide−lactol chromophore, attached to a densely substituted tetrahydropyran ring, in conjunction with an aliphatic *ansa* ring.

Recently, we launched a synthetic program targeting (−)-kendomycin (**1**). Our end-game was envisioned to rely on the Zeeck biosynthetic hypothesis[3] that the more stable C(19) lactol arises via addition of the C(1) hydroxyl (Scheme 1), available in this case upon hydrolysis of vinylogous methyl ester **2** to the C(19) ketone. In turn, oxidation state adjustment at C(19) and disconnection of the C(13,14) and C(20,20a) bonds in **3** reveals known epoxides **4**[4a] and the tetrahydropyran **5**. In the forward sense, union of **4** and the aryl anion derived from **5** would deliver a prospective ring-closing metathesis substrate. Ring-closing metathesis (RCM) was of course not without considerable risk given the required α-branched, trisubstituted olefin in a 16-membered ring.[6] Notwithstanding this challenge, we reasoned that phenol **3** protected as the TBS ether would maximize the population of the atropisomer required for a productive RCM process (vide infra).[7] Finally, *cis*-5,9-disubstituted tetrahydropyran **5** suggested the powerful Petasis−Ferrier union/rearrangement[8] tactic, developed recently in our laboratory.[9]

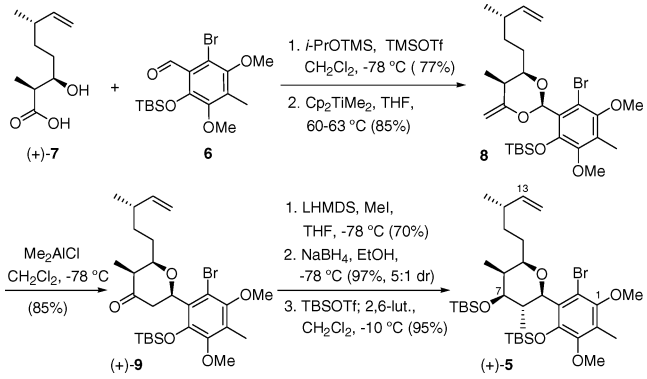
Scheme 1



We began the synthesis of (−)-kendomycin (**1**) with known epoxides **4** (7 steps from methallyl chloride),[4a] aldehyde **6** (5 steps from 2,4-dimethoxy-3-methylbenzaldehyde), and β-hydroxy acid (+)-**7** (3 steps from citronellene), available respectively in 19, 46, and 67% overall yields (see Supporting Information).

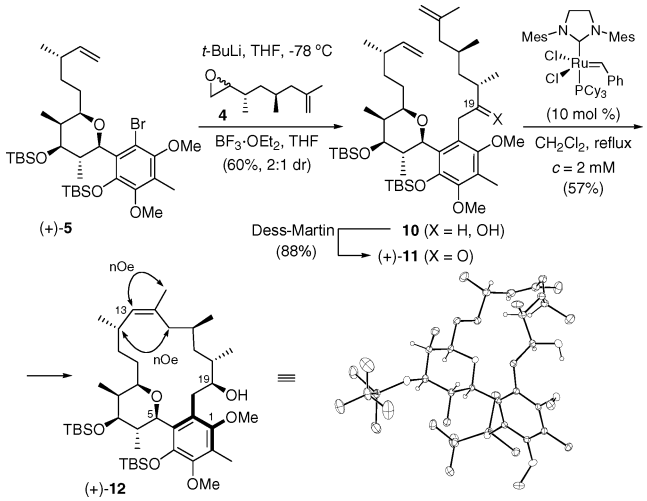
With ample quantities of both **6** and (+)-**7**, execution of the Petasis−Ferrier protocol[8,9] involving union as the dioxanone, Petasis−Tebbe methylenation,[10] and rearrangement of the unstable enol−acetal **8** furnished tetrahydropyran (+)-**9** in 85% yield. Diastereoselective methylation of the kinetic enolate of (+)-**9**, followed by diastereoselective reduction of the C(7) ketone and TBS protection led to (+)-**5** as the major product (Scheme 2); assignment of the relative stereochemistry was secured by vicinal ^{1}H coupling constants.

Scheme 2



Coupling of the anion derived from (+)-**5** with **4** (Scheme 3), promoted by $BF_3{\cdot}OEt_2$ next yielded diene **10**, obtained as a 2:1 mixture of C(19) epimers, which upon oxidation, furnished a single ketone (+)-**11**.[11] Ring-closing metathesis, however, proved ineffective.

Scheme 3



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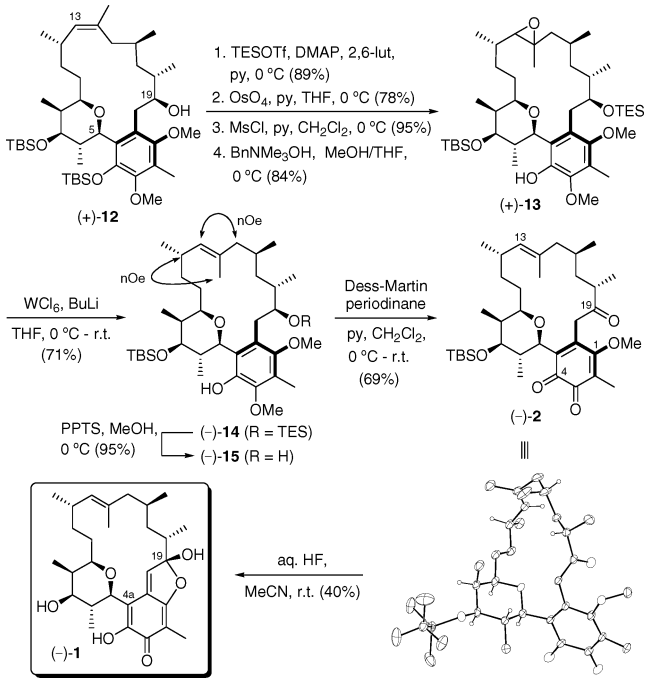
Undaunted, we exposed alcohols **10** to the second generation Grubbs catalyst; pleasingly, macrocycle (+)-**12** was obtained as a single isomer (Scheme 3).[12] Only the major epimer, 19(*S*)-**10**, however, underwent RCM. The configuration of the C(13,14) olefin, assigned initially via NOESY experiments and confirmed by X-ray analysis, proved to be *Z*. Notwithstanding the *Z* configuration, this outcome is noteworthy as the first example of a 16-membered ring formation by RCM, possessing a sterically encumbered olefin.[6]

While the RCM reactivity behavior of 19(*S*)-**10** versus 19(*R*)-**10** and (+)-**11** currently eludes our full understanding, we reason that a hydrogen bond between C(19)−OH and the C(1)−OMe in 19(*S*)-**10** may play a significant role in orienting the side chains.[13] Equally important was selection of the TBS protecting group to ensure the productive C(4a,5) rotamer [i.e., C(4)−OTBS and the C(5)−H are *synclinal*].[7b,4a] Ring-closing metathesis reactions on substrates analogous to **10**, but devoid of bulky protection at C(4), fail.

Isomerization of the *Z* olefin to the desired *E* diastereomer was thus required. Initial attempts involving various free radical processes proved unrewarding; only migration of the olefin to the C(14,15) position was observed.[14] Mulzer and co-workers observed a similar isomerization upon attempted Barton deoxygenation of a related substrate.[4a] Vedejs isomerization[15] also proved ineffective.

We next explored generation of the trans epoxide. Precedent for the conversion of syn vicinal diols to trans epoxides, when set in a relatively rigid 14-membered ring, is available in the work of McMurry;[16] deoxygenation with [W^{4+}] with retention of configuration is also precedented.[17] To this end, protection of the C(19) hydroxyl as the TES ether (Scheme 4), followed by cis dihydroxylation of the C(13,14) olefin, furnished a single diol (^{13}C NMR).

Scheme 4



Selective mesylation of the secondary hydroxyl followed by treatment with TritonB led to trans epoxide (+)-**13** with concomitant removal of the C(4) TBS group (relative stereochemistry not assigned). Sharpless reduction[17] with WCl_6/*n*-BuLi then furnished the *E* olefin (−)-**14**, accompanied by 10−12% of an unidentified isomer. NMR studies (COSY and NOESY) confirmed the olefin configuration. Selective removal of the C(19) TES group in the presence of the C(7) TBS ether, followed by Dess−Martin periodinane oxidation[11] of the resulting C(19) hydroxyl in (−)-**15**, which also led to oxidation of the phenol, furnished a single crystalline *o*-quinone (−)-**2**. X-ray analysis confirmed the structural assignment. Final exposure of (−)-**2** to concentrated aqueous HF led to hydrolysis of both the C(7) TBS ether and C(1) vinylogous methyl ester,[18] followed by addition, as per the biosynthetic hypothesis,[3] of the resultant C(1) hydroxyl to the C(19) carbonyl to complete construction of (−)-kendomycin (**1**). Spectroscopic data (i.e., 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, IR, and HRMS) and chiroptic properties of (−)-**1** were identical to those reported for the natural product.[3,5]

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

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