Communication

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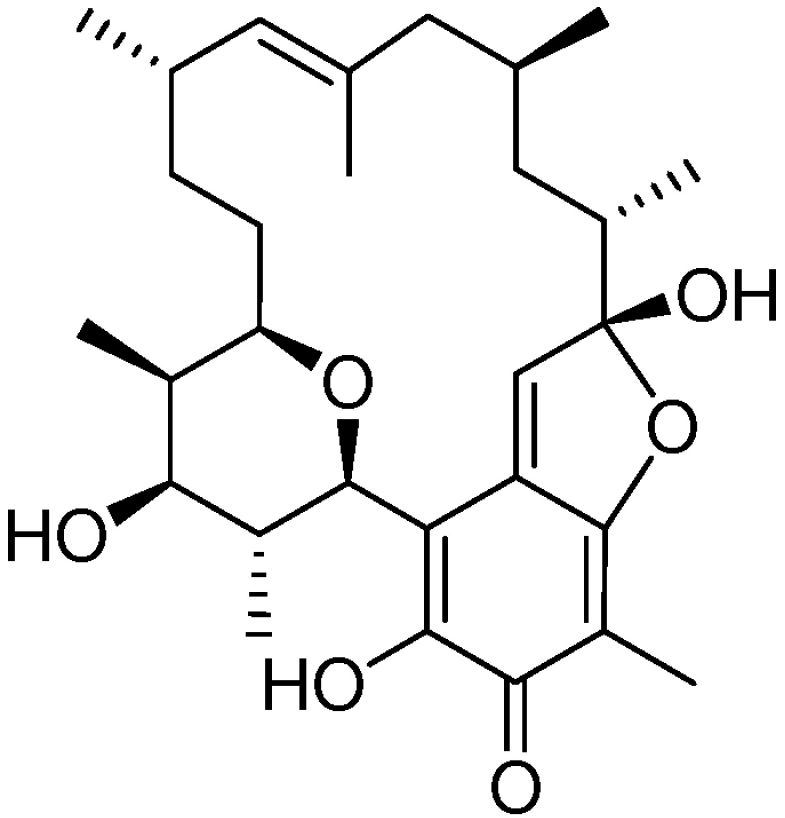


(–)-Kendomycin (**1**)

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

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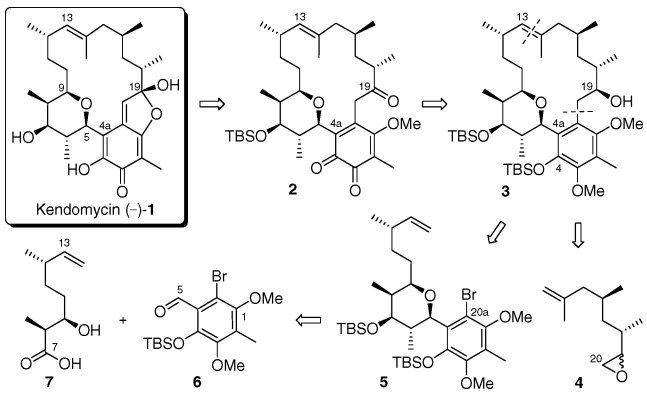
Kendomycin, (−)-**1**, a novel macrocyclic polyketide first isolated in 1996[1] from *Streptomyces violaceoruber*, possesses potent activity as both an endothelin receptor antagonist[1] and an antiosteoporotic agent.[2] Reisolation by the Zeeck group[3] revealed, in addition, significant antibacterial activity against multiresistant bacteria, including vancomycin-resistant strains, and remarkable cytotoxicity against a series of human tumor cell lines ($GI_{50}$ < 0.1 $\mu$M).[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]

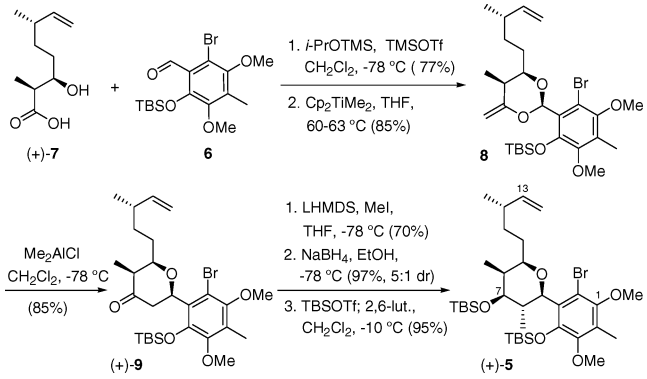
***Scheme 1***




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 $\beta$-hydroxy acid (+)-**7** (3 steps from citronellene), available respectively in 19, 46, and 67% overall yields (see Supporting Information).

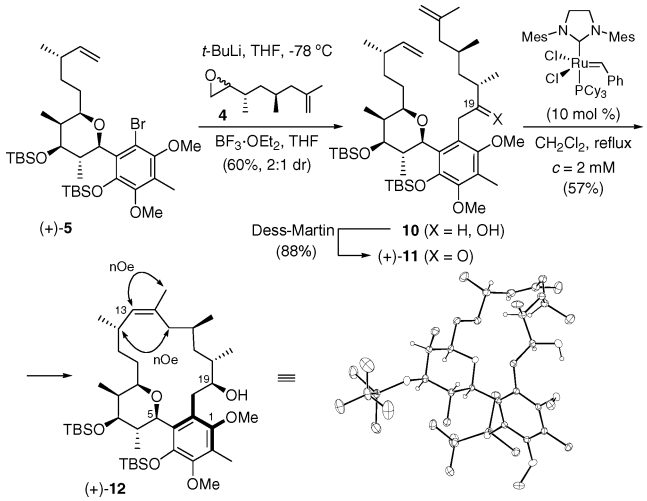
With ample quantities of both **6** and (+)-**7**, execution of the Petasis−Ferrier protocol[8,9] involving union as the dioxanone, Petasis−Tebbe methylenation,[10] and rearrangement of the unstable enol−acetal **8** furnished tetrahydropyran (+)-**9** in 85% yield. Diastereoselective methylation of 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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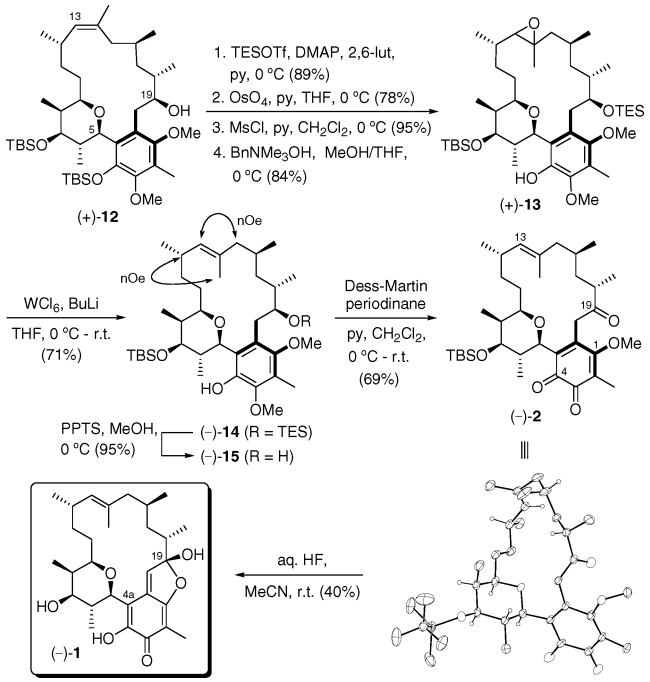
Undaunted, we exposed alcohols **10** to the second generation Grubbs catalyst; pleasingly, macrocycle (+)-**12** was obtained as a single isomer (Scheme 3).[12] Only the major epimer, 19(*S*)-**10**, however, underwent RCM. The configuration of the C(13,14) olefin, assigned initially via NOESY experiments 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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(13) The C(19)−O···O−C(1) distance (2.778 Å) in (+)-**12** in the crystalline state is within the limits of a hydrogen bond (Scheme 3).
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