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

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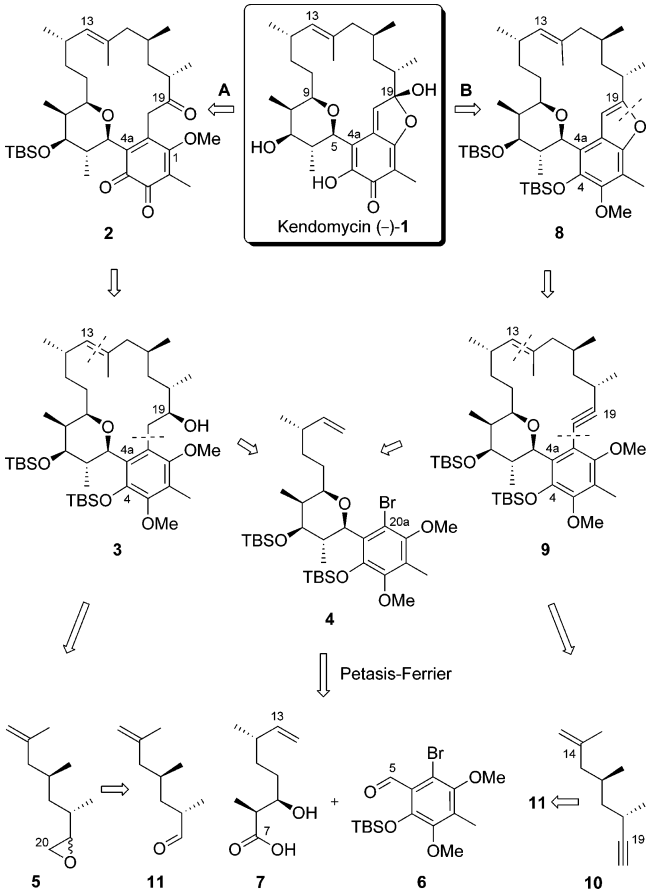
Abstract: A convergent stereocontrolled total synthesis of (−)-kendomycin (**1**) has been achieved. The synthesis proceeds with a longest linear sequence of 21 steps, beginning with commercially available 2,4-dimethoxy-3-methylbenzaldehyde (**12**). Highlights of the synthesis include an effective Petasis−Ferrier union/rearrangement tactic to construct the sterically encumbered tetrahydropyran ring, a ring-closing metathesis to generate the C(4a−13−20a) macrocycle, an effective epoxidation/deoxygenation sequence to isomerize the C(13,14) olefin, and a biomimetic quinone−methide−lactol assembly to complete the synthesis.

In 1996, Funahashi and co-workers disclosed the isolation of kendomycin (−)-**1** (Scheme 1), an architecturally novel polyketide macrocycle derived from *Streptomyces violaceoruber*, possessing activity as an endothelin receptor antagonist.[1] Two years later, the same macrocycle was reported to have antiosteoporotic properties.[2] However, it was not until 2000 and the re-isolation of kendomycin (−)-**1** by the Zeeck group from various strains of *Actinomycetes* that the full three-dimensional structure, including absolute stereochemistry, was established via single-crystal X-ray analysis in conjunction with the modified Mosher ester protocol.[3] Additional in vitro cell assays revealed kendomycin (−)-**1** to possess significant activity as an anti-bacterial, against multi-resistant strains of *Staphylococcus aureus*, as well as remarkable cytotoxicity, having potency similar to that of the clinically important drugs doxorubicin and cisplatin, against a series of human tumor cell lines (HMO2, HEP G2, MCF7, $GI_{50} < 0.1\ \mu M$).[3a]

From the synthetic perspective, kendomycin (−)-**1** comprises a significant challenge, given the densely substituted C(5−9) tetrahydropyran ring directly linked to the distinctive C(4a-19) quinone−methide−lactol chromophore, in conjunction with the C(10−18) aliphatic *ansa* chain, possessing an *E*-13,14-trisubstituted olefin, which completes the all-carbon macrocyclic ring (Scheme 1). Recognition of the intricate architecture, as well as the extraordinary panel of biological properties, rapidly promoted kendomycin (−)-**1** to center stage in a number of synthetic laboratories,[4] with the first total synthesis reported by Lee and co-workers in 2004.[5] Given our longstanding interest

Scheme 1



in the synthesis of architecturally complex natural products possessing significant bio-regulatory properties, we recently disclosed our endeavors also culminating in the total synthesis

(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, Terra 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**, 323−328. (b) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2665−2670.

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of (−)-kendomycin (**1**).[6] Herein we present a full account of that work.

From the outset, we envisioned two possible scenarios for the construction of (−)-kendomycin (**1**) (Scheme 1, routes **A** and **B**). The cornerstone of both strategies would comprise ring-closing metathesis (RCM) to construct the macrocyclic system. To the best of our knowledge, however, RCM construction of α-branched, trisubstituted olefins embedded in 16-membered macrocycles had not been reported. Further raising the level of risk of the RCM tactic was the disclosure by the Mulzer group that attempts to construct (−)-kendomycin (**1**) employing a RCM tactic had proven unsuccessful.[4a] Nonetheless, we envisioned that, by careful design of the RCM substrate, this problem might be overcome and thereby permit use of this powerful transformation (vide infra).

With this scenario in mind, two distinct end games were envisioned to introduce the potentially labile C(4a−19) quinone−methide−lactol (Scheme 1). The first, End Game **A**, was inspired by the biosynthetic postulate, introduced by Zeeck et al.,[3a] that the C(19) lactol in kendomycin (−)-**1** derives from an open-chain C(19) ketone tautomer. We reasoned that hydrolysis of the C(1) methyl enol ether in *o*-quinone **2** (or a *p*-quinone congener) would occur with simultaneous cyclization of the intermediate C(1) alcohol onto the C(19) carbonyl to generate the thermodynamically more stable C(19) lactol. Quinone **2**, in turn, would derive from homobenzylic alcohol **3** via oxidation of both the C(19) hydroxyl and the electron-rich aromatic ring. Continuing with route **A**, disconnection of the C(13,14) olefin and the C(20,20a) σ-bond in **3** reveals tetrahydropyran **4** and known epoxides **5**.[4a] Importantly, tetrahydropyran **4** comprises a common intermediate for both the **A** and **B** synthetic strategies (vide infra). In the synthetic sense, an aryl anion equivalent obtained from aromatic bromide **4** via lithium−halogen exchange would effect epoxide ring-opening of **5** to deliver the substrate for ring-closing metathesis.

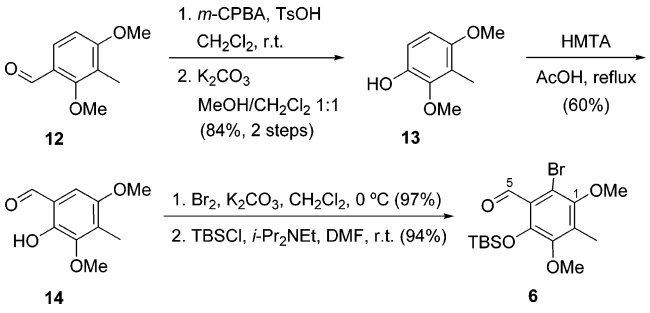
To facilitate the RCM process, we envisioned a substrate wherein the C(4)-phenol would be protected with a bulky *tert*-butyldimethylsilyl (TBS) group (Scheme 1) to induce hindered rotation about the C(4a,5) bond (i.e., sp^2-sp^3 atropisomerism).[7] The potential advantage of the bulky C(4) substituent would be to increase the population of the C(4)−OTBS−C(5)−H *synclinal* rotamer of the RCM substrate (vide infra), thereby bringing the terminal olefins into close proximity, as required for productive ring-closure.

Continuing with this analysis, recognition of the *cis*-5,9-disubstituted tetrahydropyran in (−)-kendomycin (**1**) suggested the Petasis−Ferrier union/rearrangement tactic recently developed in our laboratory to construct similarly substituted *cis*-2,6-disubstituted tetrahydropyrans.[8,9] Required here would be the sterically congested aromatic aldehyde **6** and β-hydroxy acid **7**.

For End Game **B**, the advanced C(4a−19) chromophore of (−)-kendomycin (**1**) was envisioned to emerge from benzofuran **8** via oxidation/hydration. After initiation of our synthetic program, the viability of such an approach was demonstrated independently, both by the Mulzer group in model studies[4c] and by Lee and co-workers in their total synthesis of (−)-kendomycin (**1**).[5] From our perspective, disconnection of the C(19)−O bond in **8** reveals alkyne **9** as the intermediate of choice. In the forward sense, benzofuran **8** would arise from acetylene **9** via a [Hg^{2+}]-mediated 5-*endo*-*dig* cyclization.[10] Application of the C(13,14) RCM retron and the C(20,20a) Sonogashira union to **9** then leads to alkyne **10** and tetrahydropyran **4**, the common intermediate proposed in route **A**. Epoxide **5** (required for route **A**) and alkyne **10** (required for route **B**) would each be available in one step also from a common intermediate, aldehyde **11**. Should either the high-risk RCM or the biomimetic tactics in route **A** meet with difficulties, route **B** would provide access both to a different RCM substrate and to an alternate tactic to construct the quinone−methide−lactol core. Importantly, the two strategies are unified via the proposed Petasis−Ferrier union/rearrangement to construct tetrahydropyran **4**.

Early Intermediates 5−7 and 10. We initiated the synthesis of kendomycin (−)-**1** with construction of the C(1−5) aldehyde **6** (Scheme 2). Commercially available, albeit expensive, aldehyde **12** was readily prepared on multigram scale from inexpensive 2,6-dimethoxytoluene via formylation with dichloromethyl methyl ether in the presence of $TiCl_4$ (93% yield).[11] Aldehyde **12** was then converted to known phenol **13** via Baeyer−Villiger oxidation, followed by hydrolysis of the intermediate formate.[12] Duff *ortho*-formylation[13] next provided

Scheme 2



(4) Synthetic studies: (a) 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 and references cited therein. (b) Martin, H. J.; Drescher, M.; Kahlig, H.; Schneider, S.; Mulzer, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3186−3188. (c) Green, M. P.; Pichlmair, S.; Marques, M. M. B.; Martin, H. J.; Diwald, O.; Berger, T.; Mulzer, J. *Org. Lett.* **2004**, *6*, 3131−3134. (d) Sengoku, T.; Arimoto, H.; Uemura, D. *Chem. Commun.* **2004**, 1220−1221. (e) White, J. D.; Smits, H. *Org. Lett.* **2005**, *7*, 235−238. (f) Williams, D. R.; Shamim, K. *Org. Lett.* **2005**, *7*, 4161−4164. (g) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529−1532.

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

(6) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948−6949.

(7) Even though documented, this type of atropisomerism is little explored relative to sp^2-sp^2 atropisomerism: (a) Reference 4b. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 1150. (c) Oki, M. *Top. Stereochem.* **1983**, *14*, 1−81.

(8) (a) Petasis, N. A.; Lu, S. P. *Tetrahedron Lett.* **1996**, *37*, 141−144. (b) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779−2831. (c) For an extension of this methodology to the conversion of cyclopropyl diols to oxepanes, see: O'Neil, K. E.; Kingree, S. V.; Minbiole, K. P. C. *Org. Lett.* **2005**, *7*, 515−517. (d) For a mechanistically related Prins cyclization entry to tetrahydropyrans, see: Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216−12217.

(9) (a) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909−912. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913−916. (c) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834−4836. (d) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942−10953. (e) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426−12427. (f) Smith, A. B., III; Safonov, I. G. *Org. Lett.* **2002**, *4*, 635−637. (g) Smith, A. B., III; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *6*, 3637−3640. (h) Smith, A. B., III; Fox, R. J.; Vanecko, J. A. *Org. Lett.* **2005**, *7*, 3099−3102. (i) Smith, A. B., III; Razler, T. M.; Pettit, G. R.; Chapuis, J.-C. *Org. Lett.* **2005**, *7*, 4403−4406. (j) Smith, A. B., III; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T. *Org. Lett.* **2005**, *7*, 4399−4402.

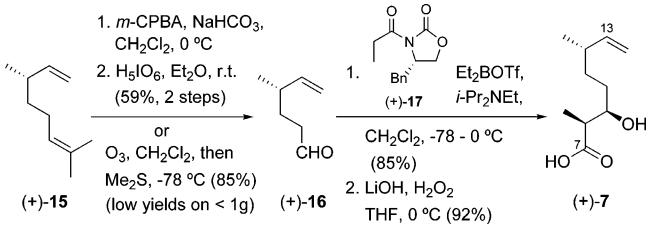
(10) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218−4227.

(11) Shawe, T. T.; Liebeskind, L. S. *Tetrahedron* **1991**, *47*, 5643−5666.

known aldehyde **14**,[12] which upon bromination and protection of the C(4) phenol as the TBS ether furnished aldehyde **6** in 46% overall yield from **12**.

Construction of C(7−13) β-hydroxy acid **7** began with commercially available β-citronellene (+)-**15**, which via the literature-reported ozonolysis furnished known aldehyde (+)-**16**[14] (Scheme 3). In our hands, a two-step procedure comprising epoxidation/

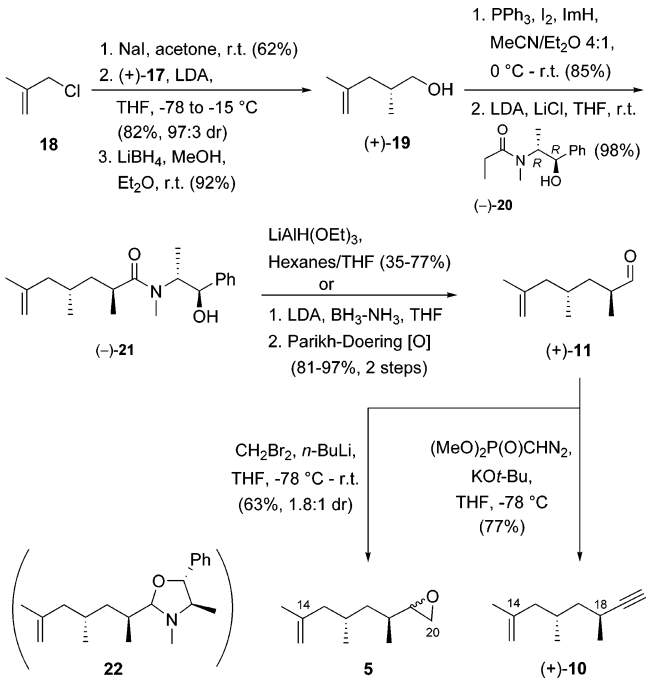
Scheme 3



olefin cleavage (*m*-CPBA/H_5IO_6)[14a] was found to be superior when working on a relatively small scale (ca. 1 g). Diastereoselective Evans aldol condensation[15] with known oxazolidinone (+)-**17**, followed by removal of the chiral auxiliary, then led to the requisite β-hydroxy acid (+)-**7** in 66% yield from citronellene.

Construction of epoxide **5**, the coupling partner required to elaborate tetrahydropyran **4** (Scheme 1, route **A**), began via Finkelstein conversion of commercial methallyl chloride (**18**) to the more reactive iodide, followed in turn by a highly diastereoselective Evans alkylation[16] with oxazolidinone (+)-**17** and reduction of the resulting adduct to furnish alcohol (+)-**19** (Scheme 4).[17] Introduction of the second chiral center, after

Scheme 4



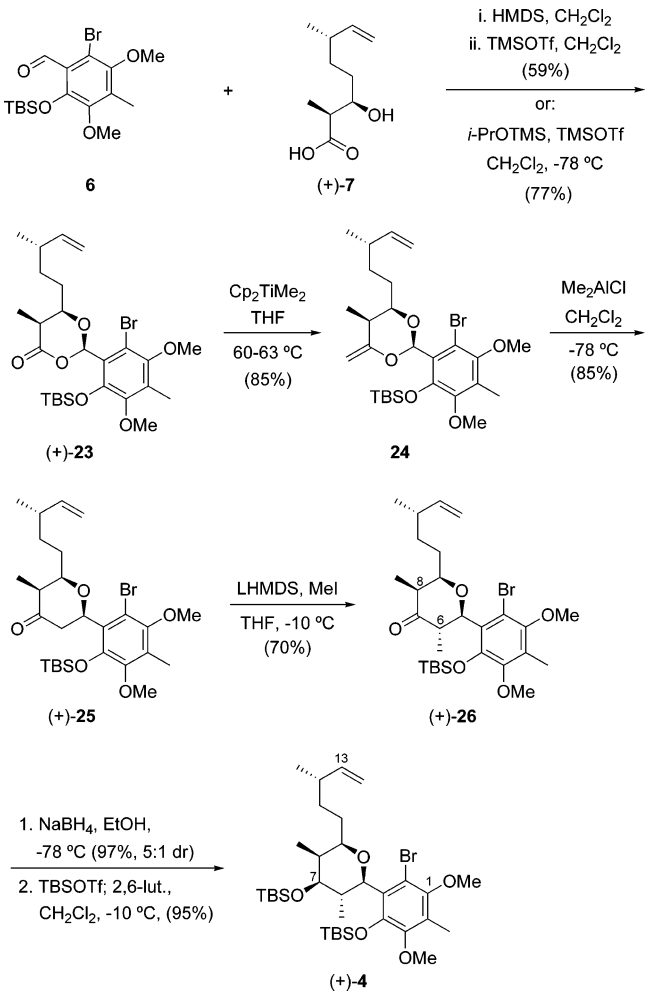
conversion of (+)-**19** to the corresponding iodide, was achieved via a Myers alkylation with pseudoephedrine propionate **20**[18] to provide adduct (−)-**21** in both excellent yield and diastereoselectivity (98:2). Removal of the auxiliary from (−)-**21** was next achieved in one step by partial reduction to provide aldehyde (+)-**11**.[18] This transformation was not without considerable variability in the yield, due primarily to formation of the cyclic aminal byproduct **22**, the latter tentatively assigned by ^{1}H NMR. We therefore turned to a two-step sequence involving reduction of (−)-**21** to the corresponding alcohol with in situ-generated lithium amidotrihydroborate,[18] followed by Parikh−Doering oxidation to provide aldehyde (+)-**11** (Scheme 4).[19] Matteson methylenation[20] with CH_2Br_2/*n*-BuLi then secured the requisite C(14−20) epoxide (**5**)[4a,21] in gram quantities as a difficult-to-separate mixture of C(19) epimers (ca. 1.8:1); the overall yield from methallyl chloride (**18**) was 20%. The low diastereoselectivity at this stage in the synthesis was viewed as inconsequential, given that C(19) becomes a carbonyl group in route **A** (vide infra).

To access the C(14−20) alkyne (**10**) for route **B** (Scheme 1), aldehyde (+)-**11** was treated with dimethyl(1-diazo-2-oxopropyl)phosphonate (Bestmann's reagent);[22] unfortunately, racemization at the C(18) α-center occurred (Scheme 4). This difficulty could be completely overcome with the Seyferth−Gilbert reagent (dimethyl-diazomethylphosphonate);[23] under these conditions, alkyne (+)-**10** was obtained in 77% yield without noticeable epimerization.

The Petasis−Ferrier Union/Rearrangement: Construction of Tetrahydropyran 4. Having secured gram quantities of both aldehyde **6** and β-hydroxy acid (+)-**7**, we embarked on the construction of tetrahydropyran **4** via the Petasis−Ferrier union/rearrangement tactic.[8,9] Condensation of **6** with (+)-**7** was performed by initial conversion of the hydroxy acid to the corresponding bis-TMS derivative, followed by treatment with aldehyde **6** in the presence of TMSOTf to furnish (+)-**23** (Scheme 5).[9] The yield of dioxanone (+)-**23** was at best modest (ca. 59%), presumably due to the steric hindrance of the bis-ortho-substituted carbonyl in aldehyde **6**. Better results were obtained by exploiting the recently introduced Kurihara condensation protocol[24] involving *i*-PrOTMS and TMSOTf to effect in situ bis-silylation. In this fashion, the dioxanone was consistently generated in 77% yield as a single stereoisomer (by NMR). Needless to say, we were quite pleased with the enhanced efficiency of this union tactic. Continuing with the Petasis−Ferrier union/rearrangement, initial attempts to execute a Takai *ethylidenation*[25] of the carbonyl in dioxanone (+)-**23** [e.g., CH_3CHBr_2; Zn/$TiCl_4$/$PbCl_2$(cat.)], which upon Ferrier

(12) Kitahara, Y.; Nakahara, S.; Numata, R.; Kubo, A. *Chem. Pharm. Bull.* **1985**, *33*, 2122−2128.
(13) Duff, J. C.; Bills, E. J. *J. Chem. Soc.* **1934**, 1305−1308.
(14) (a) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988−2006. (b) Barrett, A. G. M.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840−4856.
(15) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.
(16) (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77−82. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.
(17) Organ, M. G.; Bilokin, Y. V.; Bratovanov, S. *J. Org. Chem.* **2002**, *67*, 5176−5183.
(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) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.
(20) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631−632.
(21) Even though epoxides **5** were previously reported (ref 4a), to the best of our knowledge this is the first account where spectroscopic analysis for these species is provided (see Supporting Information).
(22) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522.
(23) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379−1386. (b) Okada, N.; Nishimura, S. *J. Biol. Chem.* **1979**, *254*, 3061−3066. (c) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837−1845. (d) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564.
(24) Kurihara, M.; Hakamata, W. *J. Org. Chem.* **2003**, *68*, 3413−3415.

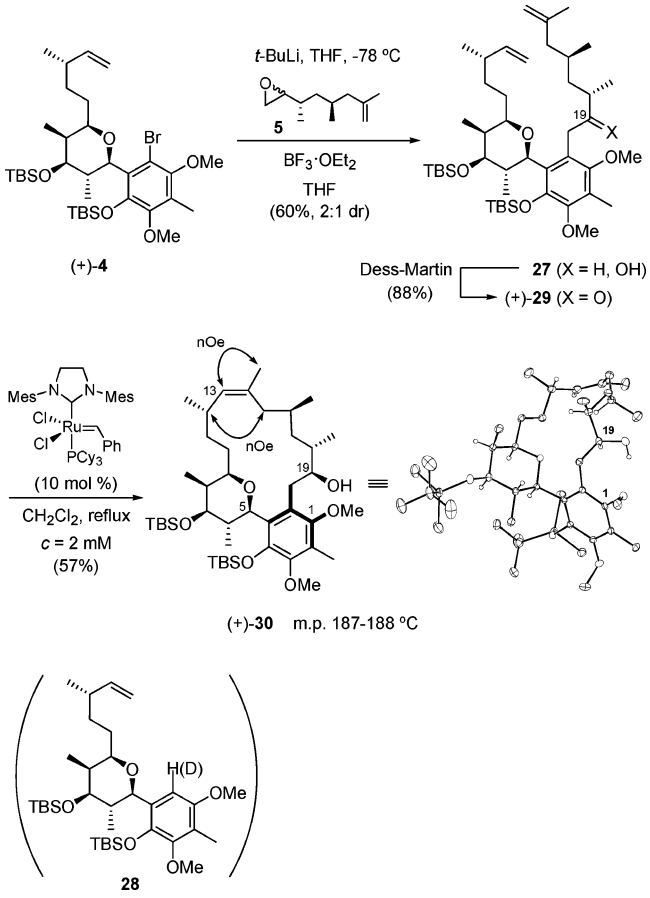
Scheme 5



rearrangement would directly install the required C(6) methyl group, failed.[9d] This result was not totally unexpected, given that neighboring olefins are known to reduce significantly the yield of such olefinations, due to the metathesis activity of the Ti^{2+} species.[25] It also appeared that proto-debromination of (+)-**23** had occurred (LRMS), presumably by Zn insertion in the C−Br bond.[26] Undaunted, we turned to a Petasis−Tebbe *methylidenation*[27] of (+)-**23**. Success with this tactic would require installation of the requisite C(6) methyl group after the Ferrier rearrangement. Pleasingly, the Petasis−Tebbe reaction led to a somewhat unstable enol-acetal, **24**, in good yield, which was immediately subjected to the Petasis−Ferrier rearrangement (Me_2AlCl) to furnish tetrahydropyran (+)-**25** in 85% yield (Scheme 5).[9] Diastereoselective methylation then led to the equatorial methyl ketone (+)-**26** in 70% yield after careful chromatographic removal of minor amounts of the axial isomer and bis-alkylation products.[9j] Although axial alkylation of simple cyclohexanones via a chair-like transition state is the anticipated process, exceptions have been documented.[28] For ketone (+)-**25**, axial attack of the kinetically derived enolate via a skewed-boat-like transition state presumably takes place to introduce the C(6) methyl group in (+)-**26** in the equatorial position. This stereochemical outcome can be understood in terms of severe 1,3-diaxial steric repulsion between the C(8) methyl group and the incoming methyl electrophile, thereby disfavoring a chair-like transition state.

Tetrahydropyran (+)-**4** was next generated via two straightforward steps: diastereoselective reduction of the carbonyl with $NaBH_4$ and protection of the C(7) hydroxyl of the derived major epimer as the TBS ether (Scheme 5). The relative stereochemistry of (+)-**4**, assigned initially via analysis of vicinal coupling constants, was later confirmed by X-ray analysis of macrocycle (+)-**30** (Scheme 6).

Scheme 6



Construction of Macrocycle 3: Route A. With both tetrahydropyran (+)-**4** and epoxides **5** in hand, we advanced toward construction of macrocycle **3** (Scheme 1). The first issue was union of bromide (+)-**4** with epoxides **5**. Despite earlier reports on uncatalyzed nucleophilic additions of aryl-lithiums possessing bis-ortho substitutents to simple epoxides,[29] a similar process in our hands failed to deliver coupled product **27** (Scheme 6). Addition of catalytic amounts of CuI to the reaction did not change the outcome. Quenching the reaction with CD_3OD did, however, lead to both good mass recovery (95−99%) and high levels of deuterium incorporation (85−89% by NMR) in the debromination product **28** (Scheme 6), suggesting that the

(25) (a) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410−4412. (b) Takai, K.; Kataoka, Y.; Miyai, J.; Okazoe, T.; Oshima, K.; Utimoto, K. *Org. Synth.* **1996**, *73*, 73−84.
(26) For a mechanistic study of the Zn insertion in the C−Br bond, see: Guijarro, A.; Rosenberg, D. M.; Rieke, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 4155−4167.
(27) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−6394.
(28) (a) Valls, J.; Toromanoff, E. *Bull. Soc. Chim. Fr.* **1961**, 758−764. (b) Toromanoff, E. *Bull. Soc. Chim. Fr.* **1962**, 1190−1192.
(29) (a) Wilson, R. M.; Wunderly, S. W.; Walsh, T. F.; Musser, A. K.; Outcalt, R.; Geiser, F.; Gee, S. K.; Brabender, W.; Yerino, L., Jr.; Conrad, T. T.; Tharp, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 4429−4446. (b) Ramacciotti, A.; Fiaschi, R.; Napolitano, E. *J. Org. Chem.* **1996**, *61*, 5371−5374.

aryl anion derived from (+)-**4** does not undergo adventitious protonation during reaction. Taken together, these results support our suspicion that the C(18) α-branched epoxide **5** is simply not sufficiently reactive. Eventually, the successful union of the lithium anion derived from (+)-**4** was achieved by activating epoxide **5** with $BF_3{\cdot}OEt_2$ at low temperature (Scheme 6). Under these conditions, diene **27** was obtained as a 2:1 mixture of C(19) epimers in 60% yield, accompanied by variable amounts of **28**; Dess−Martin oxidation then led to (+)-**29** as a single ketone.[30] Unfortunately, albeit not surprising in view of the Mulzer precedent,[4a] all attempts to effect ring-closing metathesis of (+)-**29** to the corresponding 16-membered macrocycle proved fruitless. Aware that subtle structural changes in RCM substrates, even at positions remote from the reacting olefins, can significantly influence the outcome of RCM reactions, we subjected alcohols **27** to the second-generation Grubbs catalyst in dichloromethane at reflux. Pleasingly, ring-closure proceeded in 57% yield (based on the mixture of epimers **27**) to furnish a *single* macrocycle.[31] Eventually, we determined that only the major diastereomer, 19(*S*)-**27**, reacted.[32] The stereogenicity of C(19), assigned first via the modified Mosher esters procedure, was later confirmed by X-ray analysis of macrocycle (+)-**30** (vide infra).[33] To our dismay, however, the geometry of the C(13,14) olefin was exclusively *Z*, as assigned via NOESY NMR experiments [cf. (+)-**30** in Scheme 6]. Single-crystal X-ray analysis later confirmed the *Z* configuration (Scheme 6). Despite the incorrect *Z* geometry in (+)-**30**, this result is notable as the first example of ring-closing metathesis leading to the construction of an α-branched trisubstituted olefin in a 16-membered macrocyclic ring.[4a,34]

Although currently we do not have a complete understanding of the RCM reactivity difference between alcohol 19(*S*)-**27** and congeners 19(*R*)-**27** and (+)-**29**, we suggest that a hydrogen bond between C(19)−OH and the C(1)−OMe in 19(*S*)-**27** may play a significant role in positioning the C(14−19) side chain in close proximity to C(10−13) RCM counterpart. The distance derived from the X-ray crystal structure of (+)-**30** between the C(19)−OH and C(1)−OMe groups [i.e., C(19)−O···O−C(1) = 2.778 Å] and the corresponding O···H···O angle (159.6°) both suggest a strong hydrogen bond between these groups, albeit in the RCM product.

We also reasoned that the C(4) TBS ether holds considerable importance for the success of this reaction, by ensuring a preponderance of the productive C(4a,5) rotamer [i.e., wherein the *large* C(4)−OTBS group and the *small* C(5)−H are *synclinal*; see *syn*-19(*S*)-**27** in Figure 1], thereby placing the terminal olefins in close proximity to each other.[7b] This conformational bias becomes relevant only when the rotational barrier is sufficiently high as to render rotation about the C(4a,5)

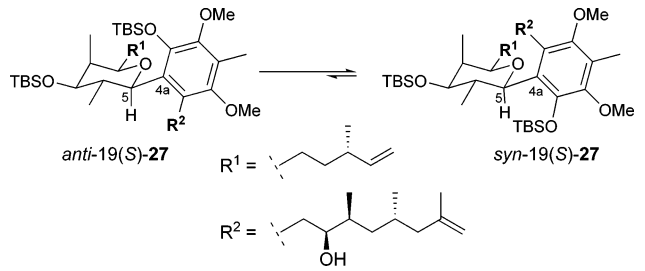
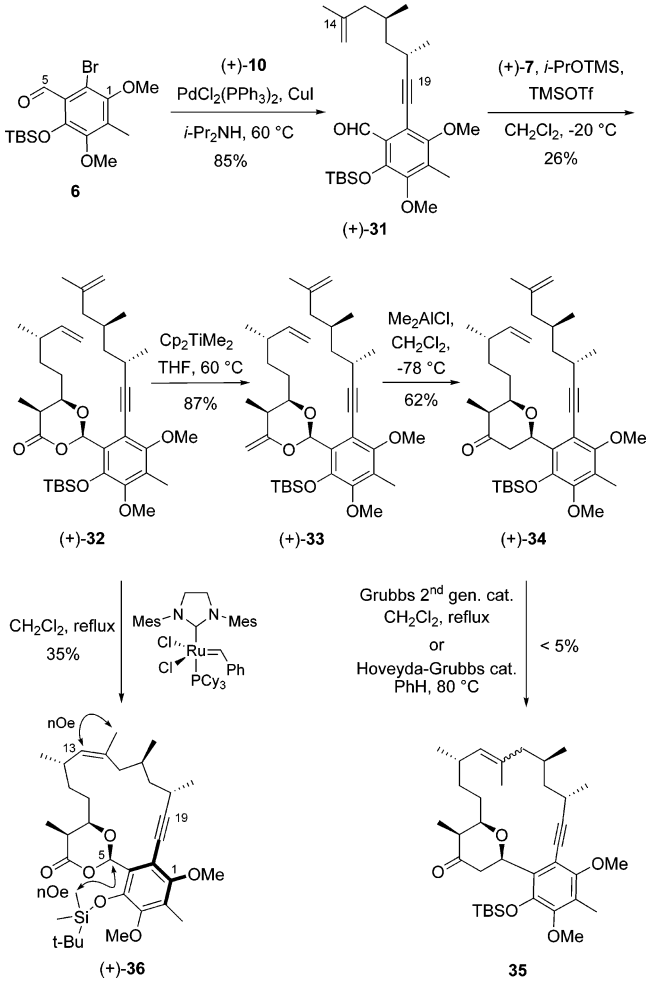


Figure 1. Rotational equilibrium associated with the C(4a,5) bond in 19(*S*)-**27**. The syn rotamer has the reacting side-chain olefins R^1 and R^2 in a favorable cisoid orientation.

bond restrictive (i.e., atropisomerism) at the reaction temperature (Curtin−Hammett principle),[35] as previously implied by Mulzer et al. to be the case for their systems[4a,b] and observed when the RCM process failed with *un*protected C(4)-hydroxyl substrates analogous to **27**.

Construction of Macrocycle 9: Route B. Having obtained solely the *cis*-olefin [(+)-**30**] in the RCM of 19(*S*)-**27** instead of the desired *trans*-olefin, we directed our attention toward a different RCM substrate (route **B**, Scheme 1). Despite extensive efforts, we could not couple the advanced bromide (+)-**4** with alkyne (+)-**10** via Sonogashira reaction (see Scheme 1). Success was, however, achieved upon Sonogashira union of alkyne (+)-**10** with bromo-aldehyde **6** rather than with bromide (+)-**4** (Scheme 7);[36] degassing of the reaction mixture to avoid facile

Scheme 7



(30) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(31) (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. **(b)** Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155−7158.
(32) We revisited the synthesis of epoxides **5** at this point with the purpose to obtain epimeric mixtures enriched in the major isomer, that in turn would maximize the yield of 19(*S*)-**27** and thus the yield of macrocycle (+)-**30**. However, treatment of aldehyde (+)-**11** with (*R*)-(dimethylamino)methylphenyloxosulfoxonium fluoroborate generated **5** as a diastereomeric mixture (3.7:1) in favor of the desired epimer, which we considered only a modest improvement relative to Matteson methylenation. See: (a) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594−6598. (b) Johnson, C. R.; Schroek, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418−7423.
(33) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (b) Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2939−2942.

dimerization of the alkyne was a significant prerequisite. Adduct (+)-**31** was then coupled with acid (+)-**7**, again employing the protocol of Kurihara (*i*-PrOTMS/TMSOTf) to generate dioxanone (+)-**32**; the yield in this case was modest.[24] Varying the concentration of TMSOTf and decreasing the temperature from −20 to −78 °C did not improve the outcome.

Carrying forward, Petasis−Tebbe methylenation provided enol ether (+)-**33** in good yield,[27] which in turn was subjected to the Me_2AlCl-promoted Petasis−Ferrier rearrangement to furnish pyranone (+)-**34**, the substrate for the RCM in route **B**.[8,9] Unfortunately, neither the Grubbs second-generation catalyst nor the Hoveyda−Grubbs second-generation catalyst proved effective for ring-closure.[37] Only trace amounts of **35** were generated (ca. <5% by ^{1}H NMR); assignment of the olefin geometry, given the small amount of material available, was not possible.[38]

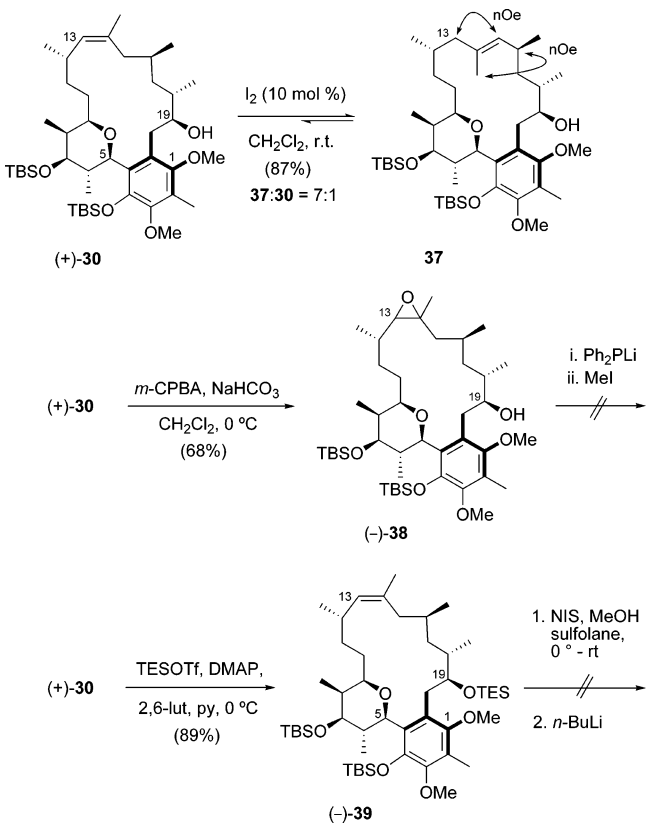
Dioxanone (+)-**32**, on the other hand, proved to be a viable RCM substrate with the Grubbs second-generation catalyst when the reaction was carried out in dichloromethane at reflux. However, again the C(13,14) olefin possessed the Z configuration, as assigned via careful NOESY and COSY NMR experiments; the unoptimized yield was 35% (Scheme 7).[39]

In retrospect, the alkyne moiety in (+)-**34** presumably rigidifies the C(18−20a) segment when combined with the *locked* chair conformation of the C(5−9) tetrahydropyran, to reduce the rotational degrees of freedom within the C(14−20a) segment, thereby placing the requisite olefins too far apart for productive RCM. On the other hand, NOESY experiments suggest that dioxanone (+)-**32** adopts a boat or skewed-boat conformation, thus orienting the C(14−20a) fragment closer to the olefin in the C(10−13) side chain.

Having achieved access to two RCM macrocycles, albeit both possessing a *cis*-olefin, we turned to the possibility of olefin isomerization. We selected macrocycle (+)-**30** to explore first, given the potential for additional complications with (+)-**36**, possessing both a labile dioxanone ring and an alkyne within the macrocyclic structure.

Isomerization of the C(13,14) Olefin: Route A Revisited. Initially, we attempted to effect isomerization of the C(13,14) *Z*-olefin in (+)-**30** by exploiting equilibrating conditions, specifically treatment of (+)-**30** with a catalytic amount (10 mol %) of iodine to achieve free radical isomerization. This tactic led primarily to migration of the olefin to the C(14,15) position, to furnish a mixture (7:1) of the *E*- and *Z*-olefins **37** and **30** (Scheme 8).[40] Again, this result was not totally unexpected, given that Mulzer[4a] had observed olefin migration

Scheme 8



in the context of an attempted Barton free radical deoxygenation protocol employing a similar substrate. Taken together, these results directed us to kinetically controlled conditions to achieve and maintain the required isomerization.

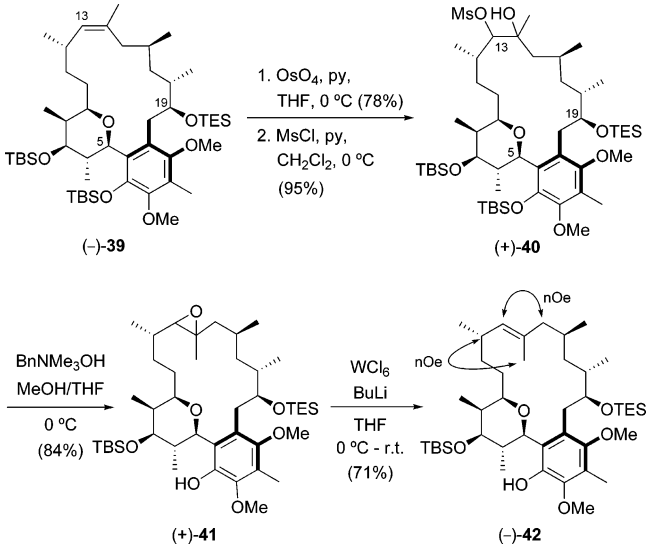
We first explored a Vedejs isomerization[41] exploiting the *cis*-C(13,14) epoxide derived from olefin (+)-**30** via *m*-CPBA oxidation. Although a single epoxide was obtained in 68% yield, the relative stereochemistry was not established. Unfortunately, we were unable to open the epoxide with Ph_2PLi. Only recovered starting material was found; under more forcing conditions, complete decomposition occurred (Scheme 8). We turned next to the Oshima isomerization protocol, which calls for anti methoxyiodination of the olefin, followed by syn elimination (Scheme 8).[42] Again, under the described conditions,[42] methoxyiodination of macrocycle (−)-**39**, the latter derived from (+)-**30** by protection of the C(19) hydroxyl as a TES ether, could not be achieved. We reasoned, based on analysis of the ORTEP diagram of (+)-**30** (Scheme 6) and the assumption that the solid-state conformation also pertains in solution, that epoxide opening in (−)-**38** and methoxyiodination of (−)-**39** fail because attack of the corresponding nucleophiles (i.e., Ph_2P^- and MeOH, respectively) must occur from the internal face of the macrocycle, syn to the C(12) Me group. Clearly, there is a significant barrier. We were thus led to the idea of an *intramolecular* nucleophilic inversion.

Our earlier observation of a single epoxide [(−)-**38**] upon *m*-CPBA oxidation of (+)-**30** suggested that *cis*-dihydroxylation

(34) Macrocyclization to access a variety of small and medium rings via RCM that generate olefins with a dense substitution pattern have been documented but were unprecedented in 16-membered or larger rings. For a recent review on RCM, see: Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.
(35) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.
(36) Sonogashira, K.; Tohda, Y.; Hagihara, N. A. *Tetrahedron Lett.* **1975**, *50*, 4467−4470.
(37) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (b) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799.
(38) The ^{1}H NMR of the reaction mixture revealed a doublet of low intensity at 5.05 ppm (J = 10.1 Hz), characteristic of the vinyl proton expected in **35**; correct mass for the RCM product was observed by LRMS.
(39) A NOESY cross-peak was also observed between the methyl of the 4-OTBS group and the C(5)−H benzylic proton in (+)-**36**, supporting a C(4)−OTBS−C(5)−H *synclinal* orientation.
(40) COSY and NOESY NMR experiments were employed to assign the regio- and stereochemistry of the C(14,15) *E*-olefin **37**.
(41) (a) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822−825. (b) Vedejs, E.; Snoble, K. A. J.; Fuchs, P. L. *J. Org. Chem.* **1973**, *38*, 1178−1183.
(42) Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1996**, *61*, 6770−6771.

would also afford a similar single diol, from which we might be able to generate the corresponding *trans*-epoxide via a stereospecific intramolecular ring-closure. Precedent for this tactic in a 14-membered macrocycle, in a system more rigid compared to (−)-**39**, can be found in the elegant total synthesis of (±)-crassin by McMurry and co-workers.[43] Subsequent stereospecific deoxygenation of the epoxide, exploiting the kinetic Sharpless WCl_6/*n*-BuLi conditions, would then afford the desired *trans*-olefin (Scheme 9).[44]

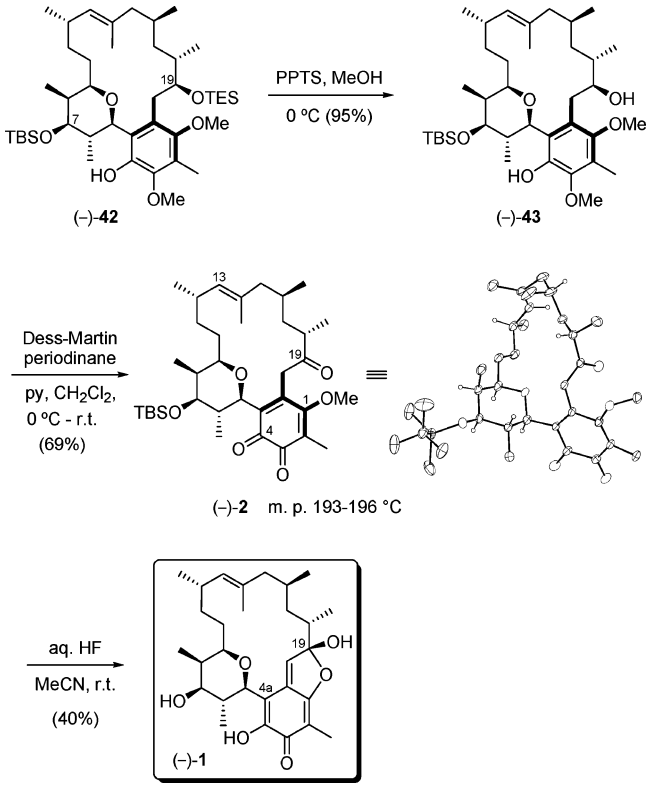
Scheme 9



With this scenario in mind, dihydroxylation of the C(13,14) olefin in TES ether (−)-**39** led, as expected, to a single *cis*-diol (^{1}H and ^{13}C NMR); the relative stereochemistry vis-à-vis the macrocyclic ring was not defined. Selective mesylation of the C(13) secondary hydroxyl over the tertiary C(14) alcohol furnished monomesylate (+)-**40**, which was exposed to benzyltrimethylammonium hydroxide. Pleasingly, the C(13,14) *trans*-epoxide was obtained, albeit with simultaneous removal of the C(4) TBS group to yield (+)-**41** as a single isomer (Scheme 9). Although the relative stereochemistry of the epoxide was not assigned rigorously, we suggest an anti disposition with respect to the C(12) Me group based on earlier arguments involving hydroxylation of the double bond from the periphery of the macrocycle (cf. the ORTEP diagram of (+)-**30** in Scheme 6). Pleasingly, Sharpless deoxygenation[44a] of epoxide (+)-**41** led to olefin (−)-**42**, accompanied by 10−12% of an unidentified isomer. The *E*-olefin configuration at C(13,14), secured initially via a series of COSY and NOESY NMR experiments, was subsequently confirmed by single-crystal X-ray analysis of (−)-**2** (vide infra).[45]

Application of the Zeeck Biosynthetic Postulate: Total Synthesis of Kendomycin (−)-1. With the *E*-olefin (−)-**42** in hand, we focused on the proposed biomimetic end game strategy. Treatment of (−)-**42** with pyridinium *p*-toluenesulfonate in methanol selectively removed the C(19) TES protecting group in the presence of the C(7) TBS ether (Scheme 10).[46] Dess−

Scheme 10



Martin oxidation of the resulting alcohol (−)-**43**,[30] conditions known to effect oxidation of an aromatic ring to the corresponding *o*-quinone, furnished (−)-**2** as a highly crystalline solid. Single-crystal X-ray analysis unequivocally confirmed not only the overall connectivity but in particular both the correct position and *E* geometry of the C(13,14) olefin, as assigned initially by NMR.

Final conversion of (−)-**2** to (−)-kendomycin (**1**) entailed exposure to concentrated aqueous HF, which cleanly resulted in concomitant cleavage of the C(7) TBS ether[46] and hydrolysis of the C(1) vinylogous methyl ester,[47] which in turn underwent 1,2-addition to the C(19) carbonyl to construct the C(4a−C19) quinone−methide−lactol, as inspired by the biosynthetic pathway proposed by Zeeck.[3a] The spectroscopic data of synthetic kendomycin (−)-**1** (i.e., 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, IR, HRMS, and chiroptic properties) were identical in all respects to those reported for the natural[3] and synthetic kendomycin (−)-**1**.[5]

Summary. We have achieved a stereocontrolled total synthesis of kendomycin (−)-**1**. The synthesis proceeded with a longest linear sequence of 21 steps, beginning with commercially available 2,4-dimethoxy-3-methylbenzaldehyde (**12**), with an

(43) (a) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8928−8929. (b) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942−6949.

(44) (a) Sharpless, K. B.; Umbreit, M. A.; Nieh, M. T.; Flood, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 6538−6540. (b) For a computational study, see: Bäckvall, J. E.; Bökman, F.; Blomberg, M. R. A. *J. Am. Chem. Soc.* **1992**, *114*, 534−538. (c) For a recent application in the synthesis of epothilone analogues, see: Borzilleri, R. M.; Zheng, X.; Schmidt, R. J.; Johnson, J. A.; Kim, S.-H.; DiMarco, J. D.; Fairchild, C. R.; Gougoutas, J. Z.; Lee, F. Y. F.; Long, B. H.; Vite, G. D. *J. Am. Chem. Soc.* **2000**, *122*, 8890−8897.

(45) Prior to 2D NMR and crystallographic analyses, our first hint that (−)-**42** might indeed have the desired *trans*-olefin came from the following chemical correlation: the C(4) phenol derived directly from *cis*-olefin (−)-**39** by removal of the TBS ether with $BnNMe_3OH$ revealed ^{1}H NMR signals distinct from those of (−)-**42**, indicating that the two samples were isomers.

(46) For a review, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031−1069.

(47) For a related example of acid-catalyzed hydrolysis of a vinylogous methyl ester in a *p*-quinone system, see: Ling, T.; Poupon, E.; Rueden, E. J.; Theodorakis, E. A. *Org. Lett.* **2002**, *4*, 819−902.

overall yield of 0.49% (i.e., an average yield of 78% per step). Highlights of the synthesis include an effective Petasis−Ferrier union/rearrangement to construct the sterically encumbered tetrahydropyran ring, a ring-closing metathesis to generate the C(4a−13−20a) macrocycle, an effective epoxidation/deoxygenation sequence to isomerize the C(13,14) olefin, and a biomimetic quinone−methide−lactol assembly to complete the total synthesis of kendomycin (−)-**1**.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for the new compounds (PDF), and X-ray crystallographic data for compounds (+)-**30** and (−)-**2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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