Natural Product Synthesis

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In Pursuit of a Competitive Target: Total Synthesis of the Antibiotic Kendomycin

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ansa compound · antibiotics · macrocycles · oxidation · total synthesis

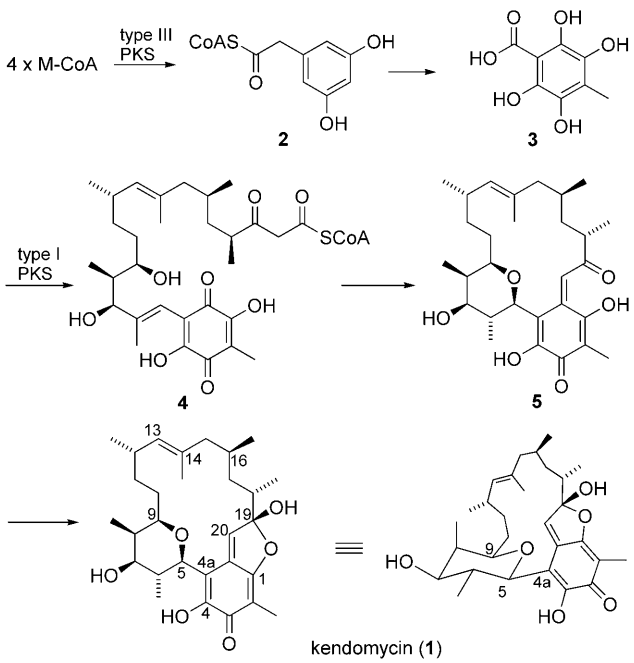
Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday

Kendomycin is a novel polyketide having a unique quinone methide ansa structure and an impressive biological profile. Herein we provide a chronological overview of the synthetic work towards the title compound. Thus far, over a period of about eight years, eight groups worldwide have published on their synthetic efforts resulting in five total syntheses, one formal synthesis, and a number of fragment syntheses. Most approaches roughly mimic the biogenetic pathway, starting with an aromatic polyphenol subunit to which a polyketide chain is attached. Subsequent key steps include macrocyclization and the formation of the densely substituted tetrahydropyran ring, and then a late-stage oxidation and lactol formation.

1. Introduction

Kendomycin (**1**), also known as (−)-TAN 2162, has been isolated from various *Streptomyces* strains and displays an uncommonly diverse bioactivity. The compound was first patented as an endothelin receptor antagonist,[1] and shortly thereafter as an antiosteoporotic drug.[2] During the course of its reisolation from *Streptomyces violaceoruber*[3] it was found that **1** showed strong antibiotic activity against a variety of bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) strains. Additionally, kendomycin exhibits strong cytotoxicity against multiple human tumor cell lines,[3] most likely through proteasome inhibition[4] or Bcl-xl inhibition.[5] Structurally, **1** features an aliphatic ansa chain having a densely substituted tetrahydropyran ring attached to a quinone methide chromophore. The relative and absolute configurations of the nine stereogenic centers were confirmed by both X-ray diffraction and advanced Mosher's ester analyses.[3] The compound has attracted unusual interest both from synthetic and medicinal chemists, as illustrated by approximately 50 entries in CAS Scifinder Scholar. Over a period of eight years, eight groups worldwide have documented synthetic efforts towards **1**, and five total syntheses have been reported so far.[6]

The biosynthesis of kendomycin (Scheme 1) was first explored by Bode and Zeeck,[3,7] and was later elaborated by means of gene expression experiments by Müller and coworkers.[8] It was suggested that initially arene **2** is formed under the mediation of a type III polyketide synthase (PKS). Oxidation, methylation, and a degradation sequence then



Scheme 1. Biosynthesis of kendomycin (**1**). M-CoA = malonyl-coenzyme A.

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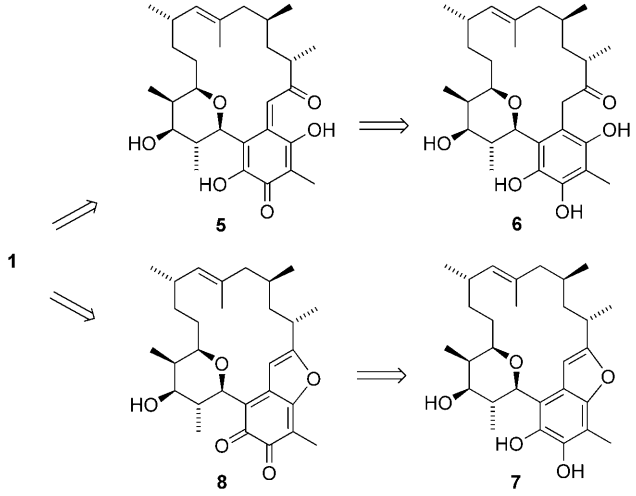
leads to benzoic acid **3** or a quinoid analogue as an unusal starter unit that is loaded onto the type I PKS complex to furnish keto ester **4**. After pyran ring closure a so far unknown termination of the type I PKS furnishes the first macrocycle **5** through decarboxylation and then **1** by hemiketal formation. Remarkably, the syntheses roughly follow the biogenetic sequence of events. This means that they start from an aromatic precursor similar to **3**, to which polyketide ansa fragments are attached. Ring-closure is then achieved somewhere in the ansa chain to form a macrocyclic intermediate that is subsequently converted into the final molecule. Therefore, either the oxidation of polyphenol **6** into *para*-quinone methide **5** and subsequent lactol formation, or the oxidation of benzofuran **7** into *ortho*-benzoquinone **8** and subsequent 1,6-addition of water have been used in the endgame for the synthesis of **1** (Scheme 2).



Scheme 2. Oxidative endgames for the synthesis of **1**.

Harry Martin was a chemical technician before he studied Chemistry in Berlin, Frankfurt, and Vienna. In 1999 he received his PhD from the University of Vienna under the supervision of Johann Mulzer. In 2001, he was a guest scientist at The Scripps Research Institute in La Jolla, California, where he worked with Benjamin List in the field of organocatalysis. Since 2006, he has been an Assistant Professor at the University of Vienna. His research interests include novel stereoselective reactions and their application in total syntheses of natural products.

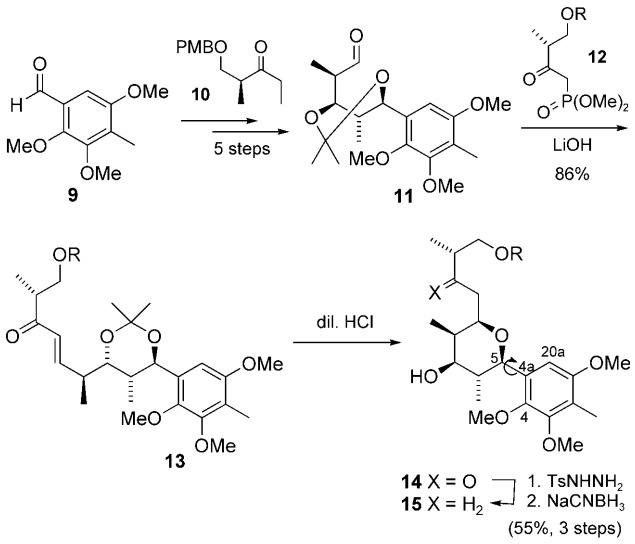
Thomas Magauer was born in 1983 in Linz, Upper Austria. He studied chemistry at the University of Vienna, where he received his masters degree in 2007. In 2009 he completed his PhD under the supervision of Johann Mulzer after working on the total syntheses of kendomycin and echinopine A and B. In 2010 he joined the research group of Andrew Myers at Harvard University as a FWF Erwin–Schrödinger postdoctoral fellow.

Johann Mulzer received his PhD in 1974 at Ludwig Maximilians University in Munich under the supervision of Rolf Huisgen before he joined the group of E. J. Corey at Harvard as a post-doctoral fellow. Between 1982 and 1996 he held professorships at the University of Düsseldorf, Freie Universität Berlin, and Frankfurt University. Currently he holds a position as a full professor of Organic Chemistry at the University of Vienna. His main research interests lie in the field of total synthesis of structurally and physiologically interesting natural products.

2. Early Studies from the Mulzer Group (2001–2004)

The first publication regarding the synthesis of **1** described the attachment of the left-hand ansa chain to the aromatic core and subsequent tetrahydropyran ring formation through intramolecular Michael addition (Scheme 3).[9] The synthesis started with a substrate-controlled aldol reaction of aromatic aldehyde **9** with ketone **10**. Diasteroselective reduction, manipulation of the protecting groups, and subsequent oxidation furnished aldehyde **11**, which gave enone **13** in a Horner–Wadsworth–Emmons (HWE) reaction with keto phosphonate **12**. The removal of the acetonide with aqueous HCl triggered an intramolecular oxa-Michael addition of the free diol to give the tetrahydropyranyl ketone **14**, whose reduction via the tosylhydrazone led to **15**.

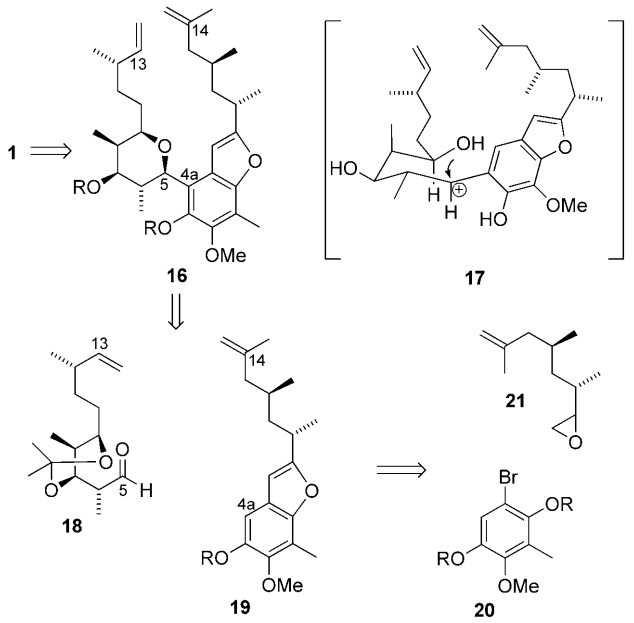
It was not possible at this stage to attach a suitable side chain to C20a, nevertheless the synthesis of **15** and related compounds revealed an important and hitherto unknown feature of this type of C aryl glycoside. All of them show restricted rotation about the $C4a_{(sp^2)}$–$C5_{(sp^3)}$ bond. This observation was important, as it had implications on the



Scheme 3. Tetrahydropyran synthesis by 1,4-addition from the Mulzer group. R = TBDPS; PMB = *p*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, Ts = tolyl-4-sulfonyl.

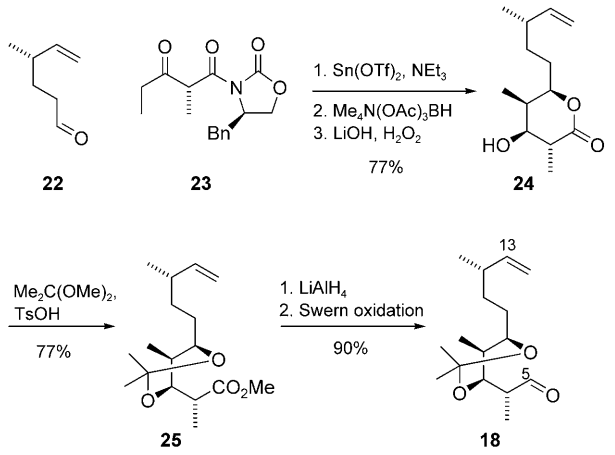
reactivity at C20a and might affect the reactive rotamer conformations in a later macrocyclization. For example, it was shown that a methoxymethyl (MOM) protecting group at the C4–OH could be used to induce the desired antiarrangement relative to the oxygen atom on C5.

The second approach from the Mulzer group[10] (Scheme 4) was centered around a ring-closing metathesis (RCM) of diene **16** for the C13–C14 connection. Tetrahydropyran formation should be achieved by a S_N1 cyclization via carbenium intermediate **17** wherein the aryl group would adopt an equatorial position. Therefore, **16** should be formed from the addition of aldehyde **18** to C4a of benzofuran **19**, which is easily prepared from bromide **20** and epoxide **21**. The synthesis of aldehyde **18** commenced with an aldol addition of the (*S*)-citronellene-derived aldehyde **22**[11] to Evans' keto-imide **23**[12] to give the *syn*-aldol product that was selectively reduced[13] to the corresponding diol (Scheme 5). Removal of the auxiliary gave lactone **24** which was then converted into acetonide-protected methylester **25**. A standard reduction/oxidation sequence furnished aldehyde **18**.

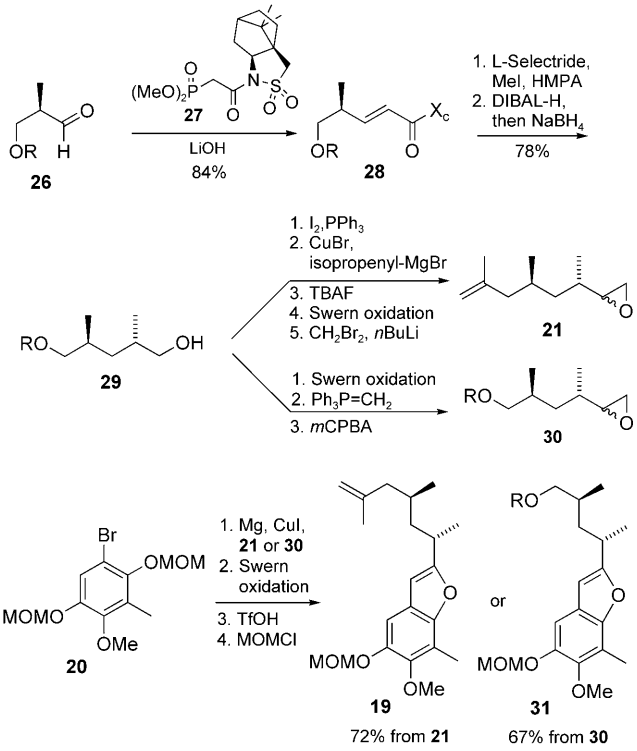


Scheme 4. Second approach from the Mulzer group. R = MOM.

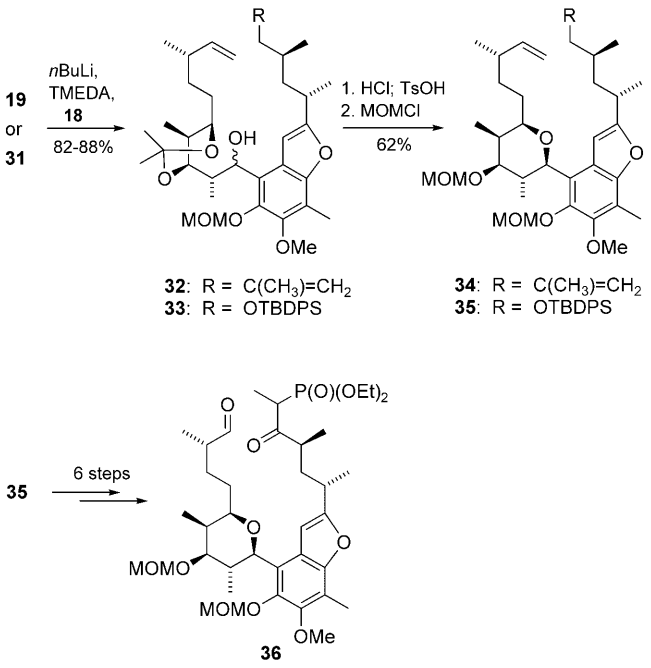
The synthesis of the benzofuran moiety (Scheme 6) started from known aldehyde **26**[14] which was subjected to a HWE reaction with **27** to afford Oppolzer's N-enoyl sultam **28**.[15] Stereocontrolled α methylation[16] and subsequent reductive removal of the auxiliary gave alcohol **29**, which was converted into epoxides **21** and **30**. Epoxide opening of either **21** or **30** with the Grignard compound derived from aryl bromide **20**, and subsequent routine operations furnished benzofurans **19** and **31**, respectively. Directed *ortho* lithiation of benzofurans **19** and **31** and addition of aldehyde **18** gave benzylic alcohols **32** and **33**, respectively, as diastereomeric mixtures (Scheme 7). Removal of the acetal protecting group and S_N1-type cyclization furnished tetrahydropyrans **34** and **35**, respectively, as single stereoisomers with the aryl substituent in an equatorial position. As was soon evident, the RCM of either diene **32** or **34** failed, and a HWE reaction was set up as an alternative ring-closure protocol.[17] To this end, **35** was converted into keto phosphonate **36**, which underwent macrocyclization into **37** upon treatment with LiOH (Scheme 8). Removal of the undesired carbonyl group at C15 proved difficult but was finally achieved by Luche reduction, xanthate formation, and then Barton–McCombie deoxygenation. Although this process involves the formation



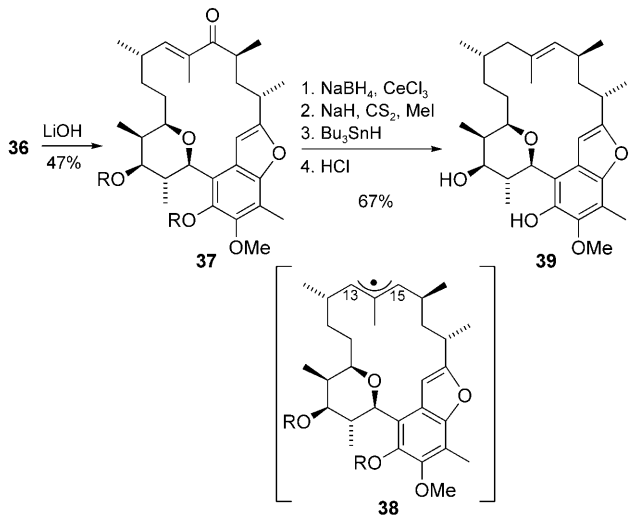
Scheme 5. Synthesis of the aliphatic chain (C5–C13). Bn = benzyl, OTf = trifluormethane sulfonate.



Scheme 6. Benzofuran synthesis. R = TBDPS; X_c = Oppolzer's sultam. DIBAL-H = diisobutylaluminium hydride, HMPA = hexamethylphosphoramide, *m*CPBA = *m*-chloroperbenzoic acid, TBAF = tetra-*n*-butylammonium fluoride.



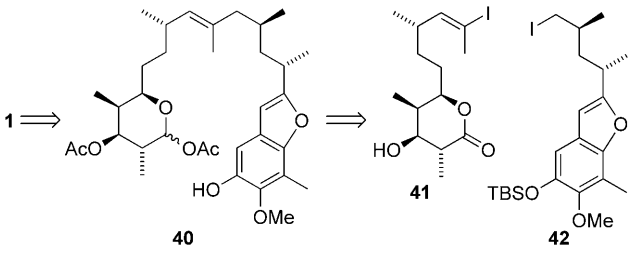
Scheme 7. Synthesis of cyclization precursors **34** and **36**. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylendiamine.



Scheme 8. HWE macrocyclization from the Mulzer group. R = MOM.

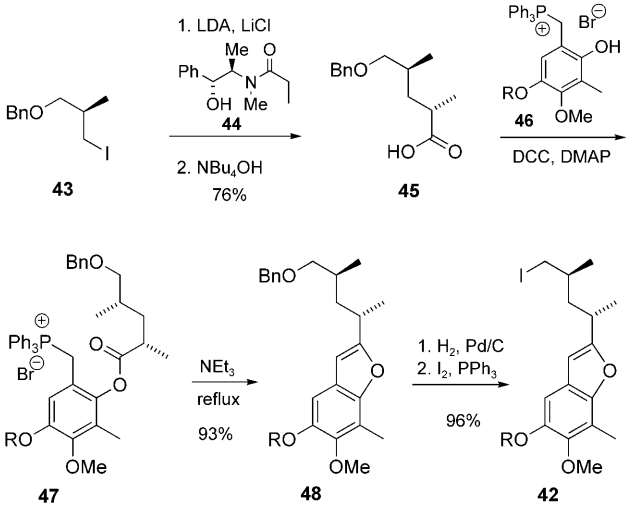
3. The First Total Synthesis by the Lee Group (2004)

A novel and very elegant macrocyclization using C glycosidation as key step was employed by Lee and co-workers in their enantioselective total synthesis of kendomycin.[19] The acyclic intermediate **40** containing the tetrahydropyran and benzofuran moieties was assembled by a *B*-alkyl Suzuki–Miyaura cross-coupling of precursors **41** and **42** (Scheme 9).



Scheme 9. Convergent approach from the Lee group.

The synthesis of the right-hand fragment **42** (Scheme 10) started from known iodide **43**[20] which was converted into carboxylic acid **45** by Myers' alkylation of pseudoephedrine

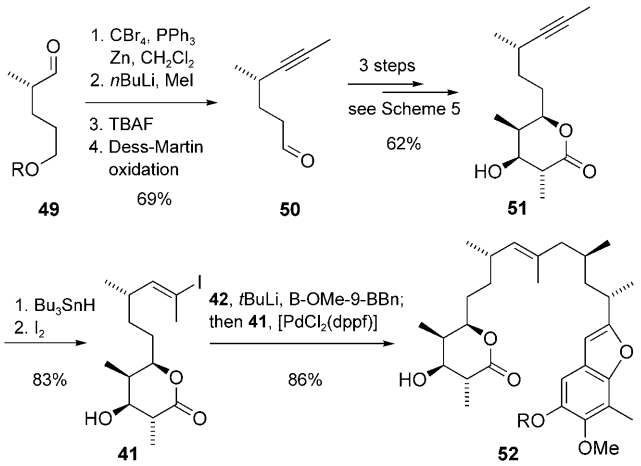


Scheme 10. Synthesis of the benzofuran domain. R = TBS; DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, LDA = lithiumdiisopropylamide, TBS = *tert*-butyldimethylsilyl.

of the pseudosymmetric allyl radical **38**, it was was quenched by the stannane at C13 to exclusively afford the undesired olefin **39**.

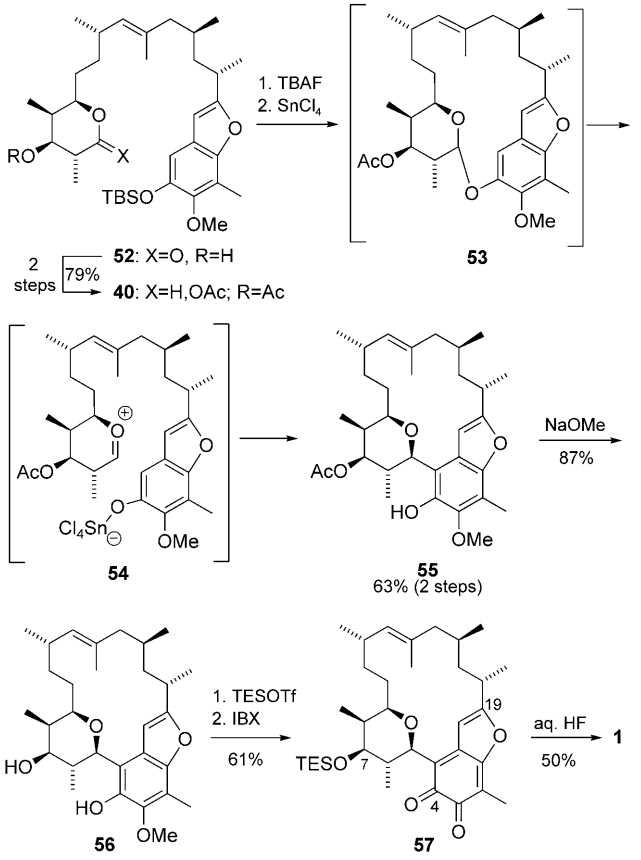
Even though the Mulzer group did not complete the total synthesis at this stage, they provided efficient methods for the synthesis and attachment of the poyketidic side chains as well as a highly stereoselective formation of the tetrahydropyran unit. Additionally, in another model study the envisioned oxidative endgame of benzofuran systems was described.[18] Some of this prior knowledge was utilized by other groups later on.

propionamide **44**[21] and subsequent amide hydrolysis. Esterification of **45** through the phenolic OH of the Wittig salt **46** and subsequent intramolecular Wittig reaction[22] of **47** delivered benzofuran **48**, which was then converted into alkyl iodide **42** in two steps. The construction of the tetrahydropyran domain (Scheme 11) started with a Corey–Fuchs chain elongation of known aldehyde **49**[23] into alkynal **50**. In analogy to Mulzer's approach, lactone **51** was obtained in three additional steps. A hydrostannylation/iodination sequence afforded *E*-vinyl iodide **41** which was cross-coupled with alkyl iodide **42** to provide intermediate **52**.



Scheme 11. Synthesis of acyclic precursor **52** by Suzuki–Miaura coupling. R = TBS; 9-BBN = 9-boranebicyclo[3.3.1]nonane, dppf = 1,1′-bis-(diphenylphosphanyl)ferrocene.

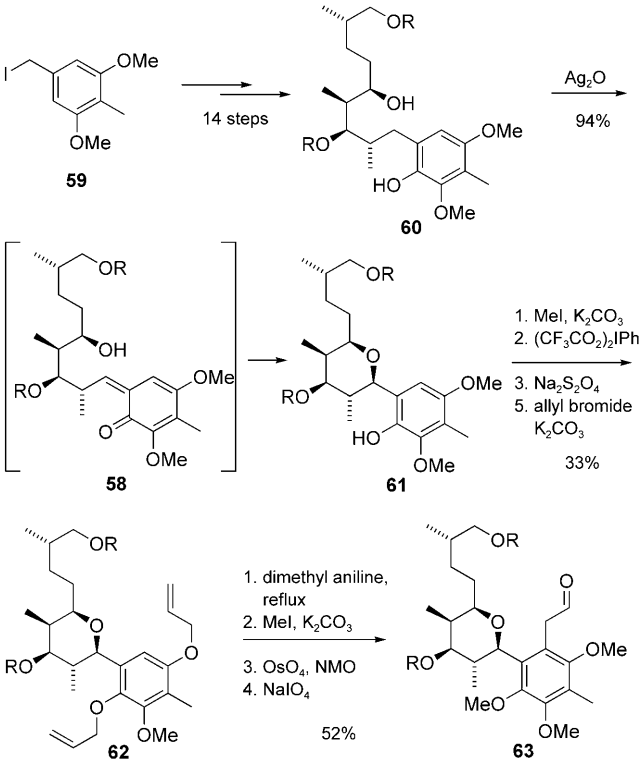
For the macrocyclization through C glycosidation, the lactone was first reduced to lactol acetate **40** which was then cyclized under Friedel–Crafts conditions, using $SnCl_4$ as the Lewis acid (Scheme 12). Apparently, the reaction proceeded via the O-glycosidic intermediate **53**, which, under $SnCl_4$ catalysis was rearranged via zwitterion **54** into the C-glycoside **55**. After deacetylation to **56**, selective silylation of C7–OH and oxidation with IBX furnished *ortho*-quinone **57**. Desilylation with aqueous HF and concomitant 1,6-addition of water furnished kendomycin (**1**).



Scheme 12. Macrocyclization and oxidation to **1**. IBX = *o*-iodoxybenzoic acid, TES = triethylsilyl.

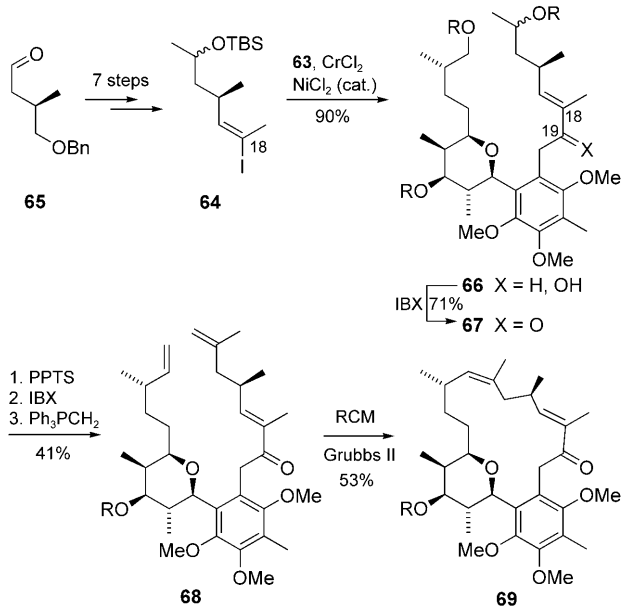
4. Contributions from the Arimoto Group (2004, 2007)

A different approach to the tetrahydropyran core was described by Arimoto and co-workers,[24] who used an intramolecular oxa-Michael 1,4-addition at C5 of *ortho*-quinone methide **58** (Scheme 13). The synthesis started from benzyl iodide **59**, which was converted into **60** in 14 steps including Evans alkylation, Roush crotylation, and a carbonyl addition as key steps. Subsequent oxidation led to the *ortho*-quinone methide **58** that immediately underwent an intramolecular 1,4-additon to generate tetrahydropyran **61**. After conversion into the bisallyloxy derivative **62**, a four-step sequence, including a Claisen rearrangement, gave the fully substituted arene **63**.



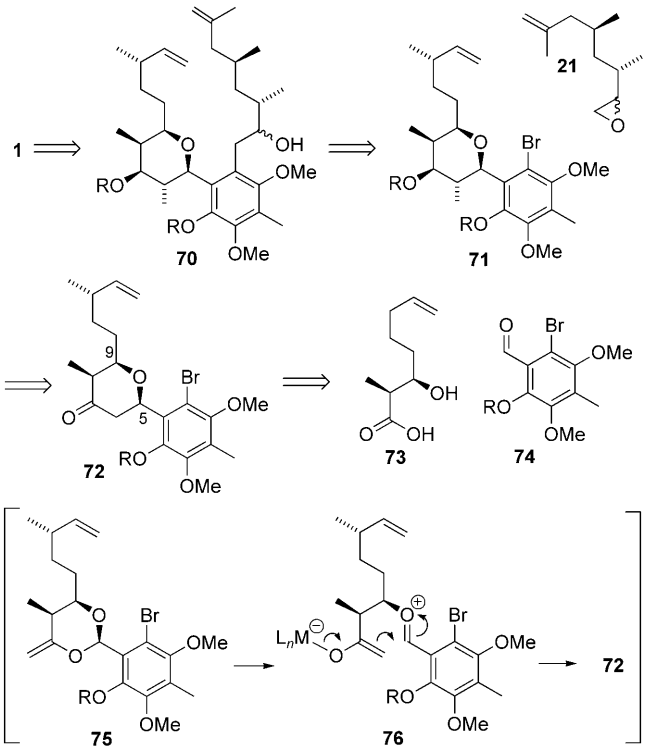
Scheme 13. Tetrahydropyran synthesis by 1,4-addition from the Arimoto group. R = TBS; NMO = 4-methylmorpholin-*N*-oxide.

In a later contribution[25] Arimoto and co-workers reported the attachment of the right-hand appendage at C19. (Scheme 14) In this approach, vinyl iodide **64**, derived from known aldehyde **65**[26] in seven steps, was coupled with aldehyde **63** in a Hiyama–Nozaki–Kishi reaction to furnish alcohol **66** which was then oxidized to ketone **67**. A selective deprotection/oxidation sequence followed by a Wittig methylenation gave the diene **68**. Subsequent RCM reaction



Scheme 14. RCM approach. R = TBS; Grubbs II = Grubbs 2nd generation catalyst, PPTS = pyridinium-*p*-toluenesulfonate.

afforded exclusively the undesired *Z*-olefin **69** (see Smith's synthesis below), however, the synthesis of **1** was not completed.



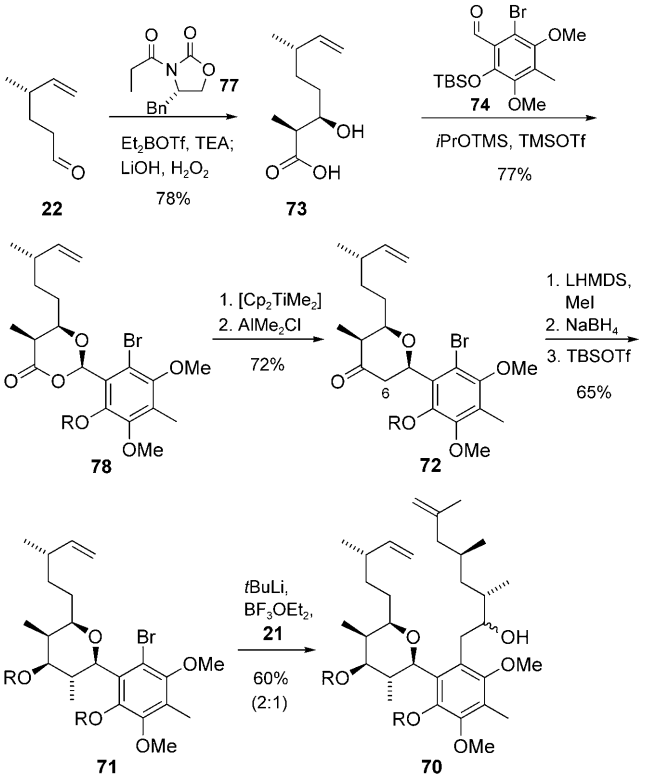
Scheme 15. Retrosynthesis according to the group of Smith III. R = TBS.

5. Total Synthesis by the Group of Smith III (2005)

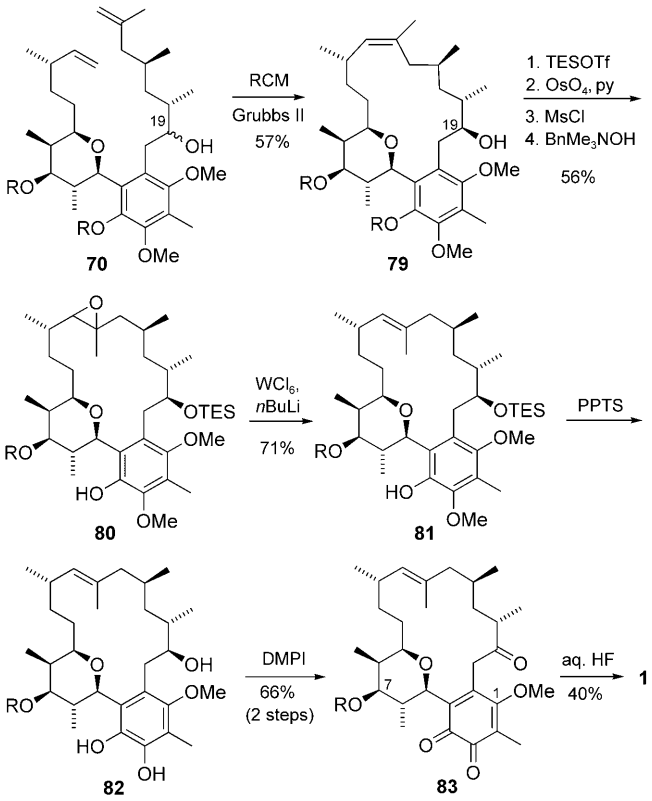
The second total synthesis of **1** was achieved by Smith III and co-workers.[27] They focused on a RCM reaction of diene **70** that was obtained from bromide **71** and epoxide **21**. The tetrahydropyran precursor **72** was assembled by an acetalization of **73** and **74** and subsequent Petasis–Ferrier rearrangement via enolacetal **75** and oxonium intermediate **76** (Scheme 15). The cyclization of **76** proceeds by a S_N1-type reaction and generates a pyran ring having a two equatorial moieties.

The synthesis of the tetrahydropyran domain (Scheme 16) started from known aldehyde **22**, which was converted into acid **73** by a *syn*-selective aldol reaction with **77**[28] and subsequent hydrolysis. By using modified Lewis acid conditions,[29] aldehyde **74** was condensed with β-hydroxy acid **73** to furnish dioxanone **78** as a single diastereomer. A Petasis–Tebbe olefination[30] gave the unstable enol acetal **75**, which underwent a Petasis–Ferrier rearrangement[31] to **72** upon treatment with $AlMe_2Cl$. A highly diastereoselective sequence including C6 methylation, carbonyl reduction, and O silylation afforded the fully substituted tetrahydropyran **71**.

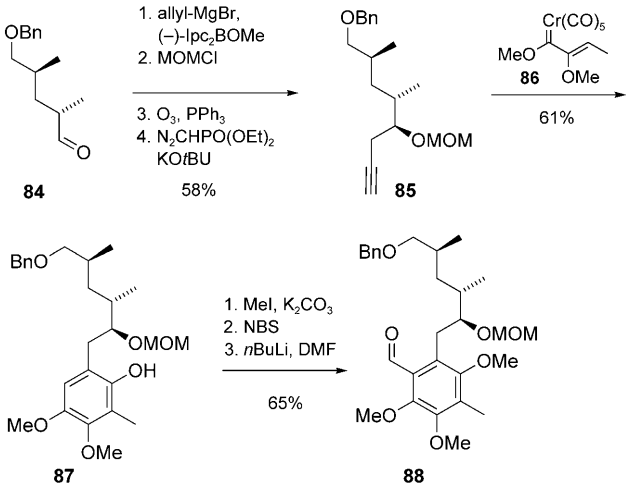
The attachment of the right-hand alkenyl chain was achieved according to Mulzer's epoxide-opening strategy (see Scheme 6). Therefore, conversion of aryl bromide **71** into the corresponding lithium organyl and addition to **21** afforded seco-diene **70** as a 2:1 mixture of C19 epimers. RCM reaction of **70** with the Grubbs II catalyst gave the *Z*-olefin **79** as a single C19-(*S*) epimer, which indicated that only C19-(*S*) **70** had reacted (Scheme 17). The undesired olefin geometry



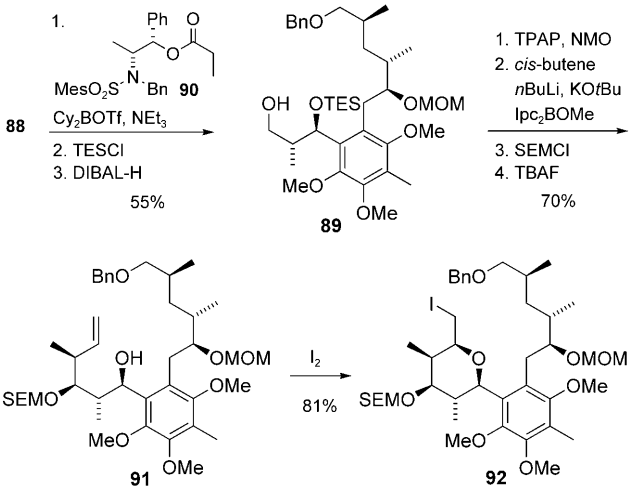
Scheme 16. Synthesis of the RCM precursor by the group of Smith III. R = TBS; Cp = cyclopentadienyl, LHMDS = lithiumhexamethyldisilazide, TEA = triethylamine, TMS = trimethylsilyl.



Scheme 17. Completion of the synthesis. R = TBS; DMPI = Dess—Martin periodinane, Ms = methanesulfonyl, py = pyridine.



Scheme 18. Application of the Dötz reaction by the White group. Ipc = isopinocampheyl, NBS = *N*-bromsuccinimide.



Scheme 19. Tetrahydropyran synthesis. Cy = cyclohexyl, Mes = mesitylene, SEM = trimethylsilylethoxymethyl, TPAP = tetrapropylammonium perruthenate.

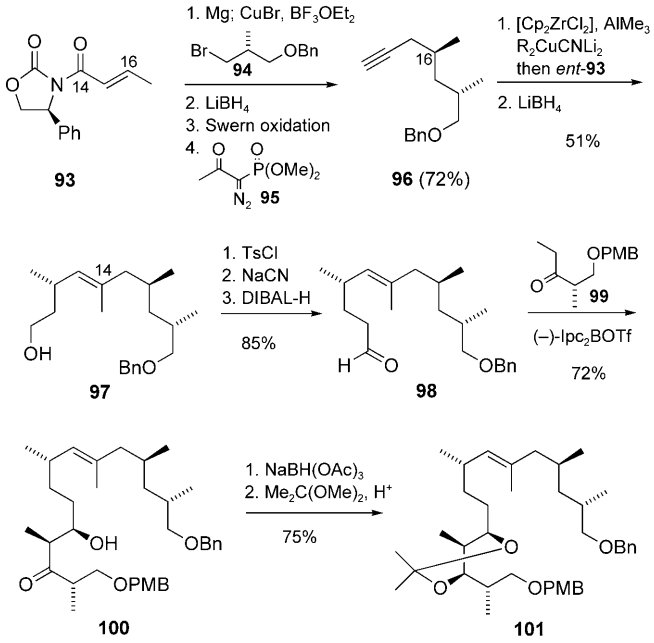
required a contra-thermodynamic isomerization from the *Z* to the *E* isomer. After much experimentation, Smith and coworkers finally developed a four-step sequence starting with the selective formation of a single diol that was mesylated and cyclized into the *trans*-epoxide **80** (absolute configuration was not determined). Deoxygenation with WCl_6/*n*BuLi with retention of configuration led to the *E*-olefin **81**.[32] The oxidative endgame closely followed Zeeck's biosynthetic suggestion. Selective desilylation to **82** and subsequent oxidation gave *ortho*-quinone **83**, which upon treatment with aqueous HF furnished kendomycin (**1**) after 7-O-desilylation, 1-O-demethylation, and lactol formation.

6. Contributions by the White Group (2005)

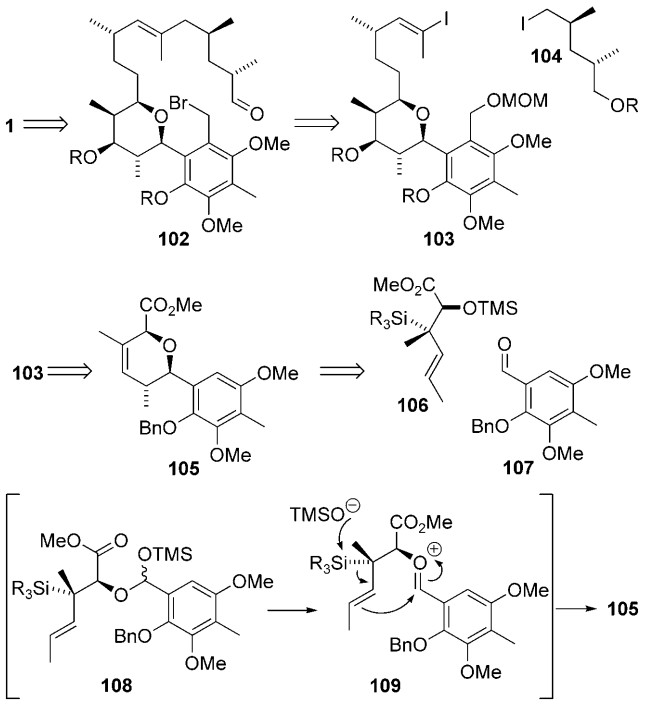
The synthesis from the of an advanced intermediate by the White group employs an iodoetherification for pyran ring formation and a Dötz annulation for the construction of the aromatic domain.[33] The synthesis of the aryl core started from known aldehyde **84**,[34] which was converted into alkyne **85** in four steps including a Brown allylation[35] and a Seyferth–Gilbert homologation[36] as the key steps (Scheme 18). Reaction of **85** with alkenylchromium carbene **86**, available from 1-methoxypropyne in three steps, afforded arene **87**, which was converted into aldehyde **88** in three steps.[37] For the completion of the tetrahydropyran framework (Scheme 19), aldehyde **88** was transformed into alcohol **89** in three steps, including an *anti*-selective aldol reaction with Masamune's propionate **90**[38] as a key step. Oxidation of the primary alcohol into the aldehyde and asymmetric Brown crotylation[39] gave the corresponding alkene, which furnished compound **91** after manipulation of the protecting groups. Ring-closure by iodoetherification was then used to form tetrahydropyran **92**.

7. Contributions by the Williams Group (2005)

The concise synthesis of the ansa chain (C5–C19) by Williams and Shamim involved two auxiliary controlled 1,4-cuprate additions as key steps for the construction of the olefinic domain (Scheme 20).[40] The synthesis started with the formation of the Yamamoto cuprate from known bromide **94**.[41] Conjugate addition to crotylimide **93**, reductive cleav-



Scheme 20. Synthesis of the ansa chain by the Williams group.



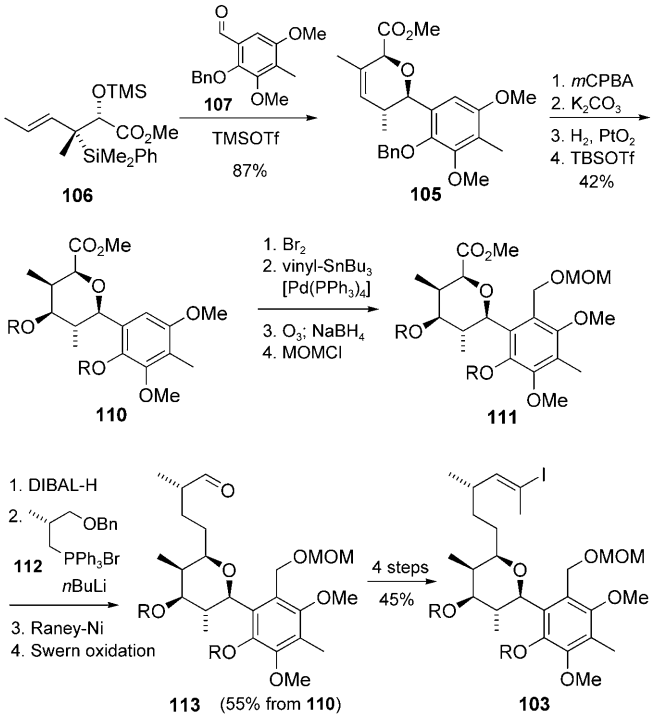
Scheme 21. [4+2]-Annulation approach from the Panek group. R = TBS.

age of the auxiliary, and Swern oxidation gave the corresponding aldehyde which was then converted into alkyne **96** with the Bestmann–Ohira reagent **95**.[42] Carboalumination of **96**, cuprate formation and conjugate addition of the organometallic species to *ent*-**93** and subsequent reductive removal of the auxiliary furnished alcohol **97**. Standard chain elongation gave aldehyde **98** that was subjected to a Paterson aldol reaction with the known ketone **99**[43] to afford **100**. Diastereoselective carbonyl reduction and acetonide protection of the resulting 1,3-diol furnished the fully substituted ansa chain **101**.

8. Total Synthesis by the Panek Group (2005, 2008)

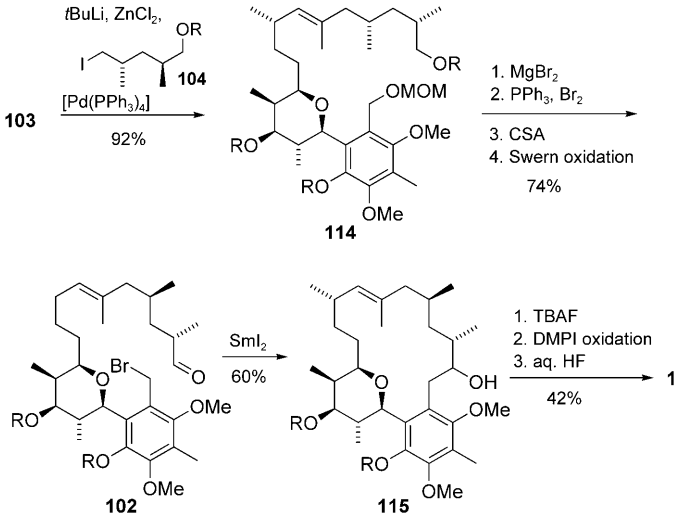
In the synthesis of **1** by Lowe and Panek,[44] the macrocyclization was achieved by an intramolecular SmI_2 Barbier reaction of bromo aldehyde **102**, which had been prepared from a Negishi cross-coupling of vinyl iodide **103** and alkyl iodide **104** (Scheme 21). For the preparation of the tetrahydropyran precursor **105**, Lowe and Panek developed a Lewis acid promoted formal [4+2] cycloaddition of chiral crotylsilane **106**[45] to aldehyde **107**, which presumably proceeds via the acetal **108** and ion pair **109**.

Starting from **105**, a four-step sequence consisting of epoxidation (d.r. = 3:1), epoxide ring-opening, hydrogenation, and silylation gave tetrahydropyran **110** (Scheme 22). Conversion into the fully substituted arene **111** was achieved in four steps including a Stille coupling at C20a. After reduction of the C10 ester into the aldehyde, a Wittig reaction with phosphonium bromide **112**,[46] with subsequent hydrogenation/debenzylation and oxidation gave aldehyde **113**, which was converted into *E*-vinyl iodide **103** in a standard reaction sequence. The preparation of the ansa chain was



Scheme 22. Formation of the tetrahydropyran domain. R = TBS.

completed by a Negishi coupling of iodide **104** with vinyl iodide **103** to give intermediate **114** which was converted into seco-compound **102** in four steps (Scheme 23). The Barbier macrocyclization[47] was performed by exposure of aldehyde **94** to samarium(II)iodide to furnish alcohol **115** (epimeric



Scheme 23. Total synthesis of **1** by Barbier macrocyclization. R = TBS; CSA = (±)-camphorsulfonic acid.

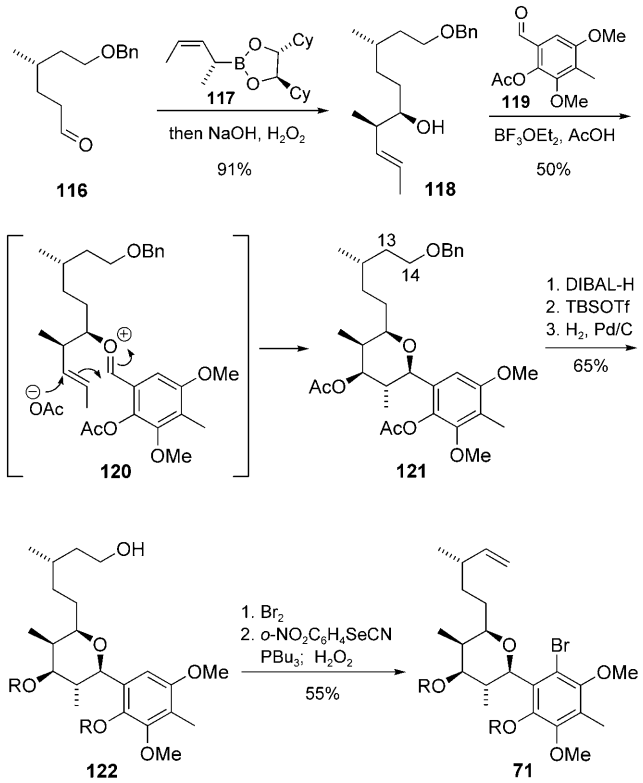
mixture) which was converted into **1** according to Smith's oxidative endgame (see Scheme 17).

9. Two Formal Syntheses by the Rychnovsky Group (2006, 2008)

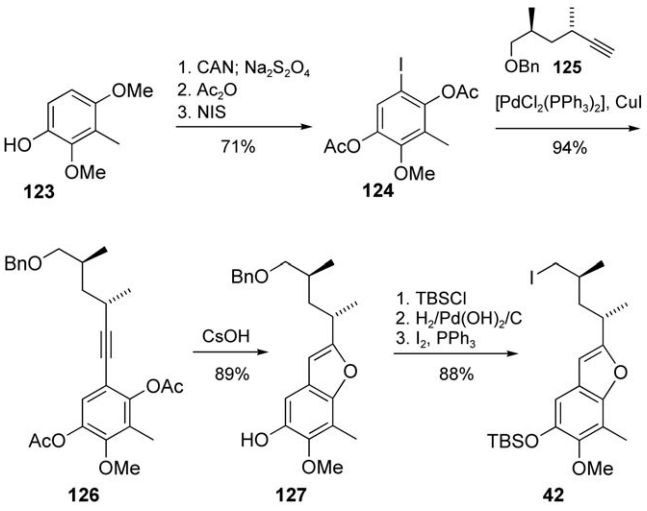
The Rychnovsky group developed two approaches towards kendomycin (**1**). The first one was terminated with the preparation of Smith's advanced intermediate **71**.[48] The second approach led to Lee's macrocyclic benzofuran intermediate **56**.[49] Both routes feature Prins cyclizations to generate the tetrahydropyran core. This reaction was used intermolecularly in the first approach, and as a macrocyclization in the second one.

The synthesis of Smith's fragment **71** started with the known elaboration of (*S*)-citronellol into aldehyde **116**,[50] which was subjected to Hoffmann's chiral crotyl boronate **117**[51] to provide alcohol **118** (Scheme 24). Prins cyclization with aldehyde **119**, presumably via the oxonium intermediate **120**, delivered tetrahydropyran **121**. Manipulation of the protecting groups led to the primary alcohol **122**. Arene bromination and a subsequent Grieco elimination furnished the olefin **71**. Compared to Smith's approach, the pyran ring was formed in one step with all substituents in place. Nevertheless, additional steps were required for the generation of the terminal olefin.

The second synthesis from the Rychnovsky group commenced with the conversion of phenol **123** into aryl iodide **124** in three steps (Scheme 25). Sonogashira coupling with alkyne **125**, available from known aldehyde **84**, furnished the disubstituted alkyne **126**, which gave benzofuran **127** upon treatment with CsOH in a 5-*endo-dig* cyclization. Phenol protection, debenzylation, and iodination finally led to Lee's alkyl iodide **42**. For the synthesis of the left-hand domain (Scheme 26), aldehyde **128**, derived from **50**, was subjected to crotyl boronate **117** to provide vinyl iodide **129**. In analogy to Lee's synthesis, iodide **42** was converted into the 9-BBN

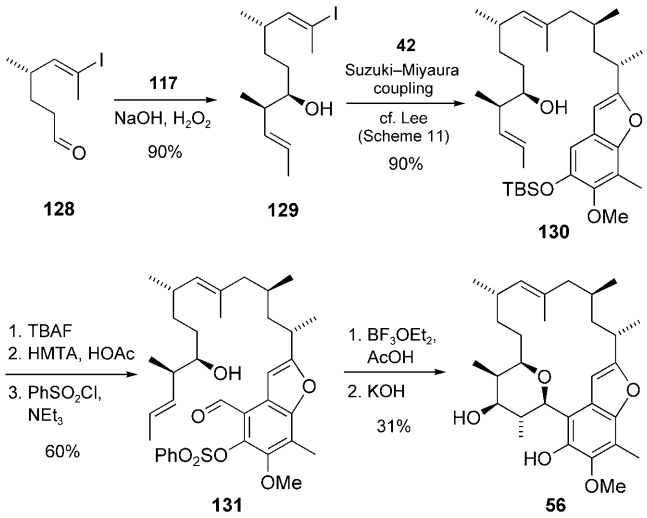


Scheme 24. Synthesis of intermediate **71** by Rychnovsky and Bahnck.

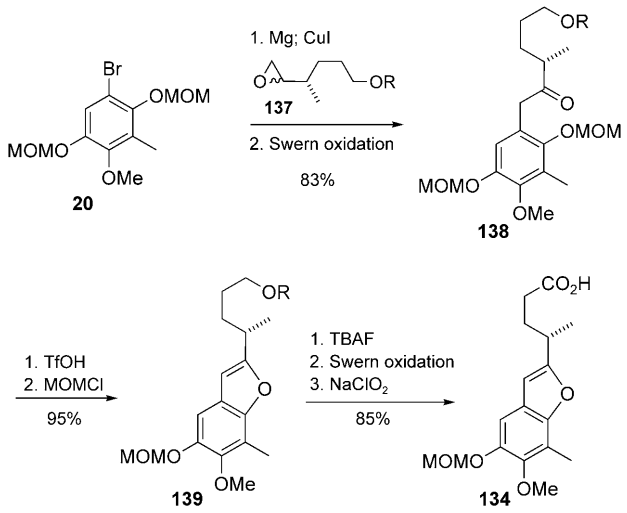


Scheme 25. Synthesis of Lee's intermediate **42**. CAN = ceric ammonium nitrate, NIS = *N*-iodsuccinimide.

derivative and treated with **129** in a Suzuki–Miyaura coupling. The resulting olefin **130** afforded seco-compound **131** after desilylation, *ortho* formylation and O protection through sulfonylation. The Prins reaction was performed with $BF_3{\cdot}OEt_2$ and acetic acid at high dilution to achieve both macrocyclization and pyran ring formation. Finally, desulfonylation afforded Lee's key intermediate **56**. In a footnote, Rychnovsky et al. noted that they were unable to reproduce Lee's conversion of **56** into **1**.



Scheme 26. Formal synthesis of kendomycin. HMTA = hexamethylenetetramine.



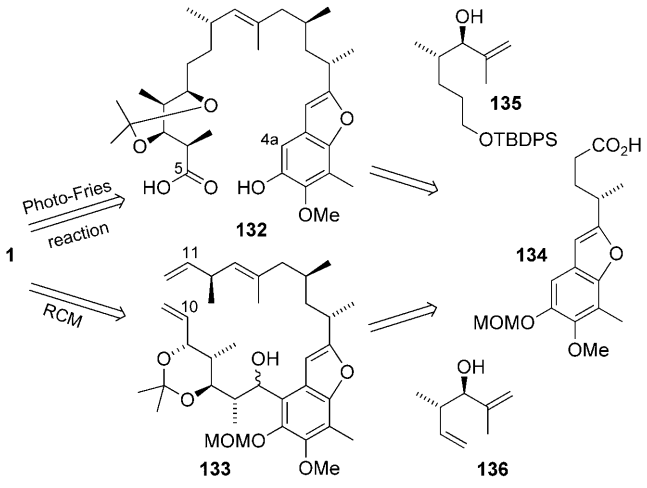
Scheme 28. Benzofuran synthesis. R = TBDPS.

10. Total Syntheses from the Mulzer Group (2009/2010)

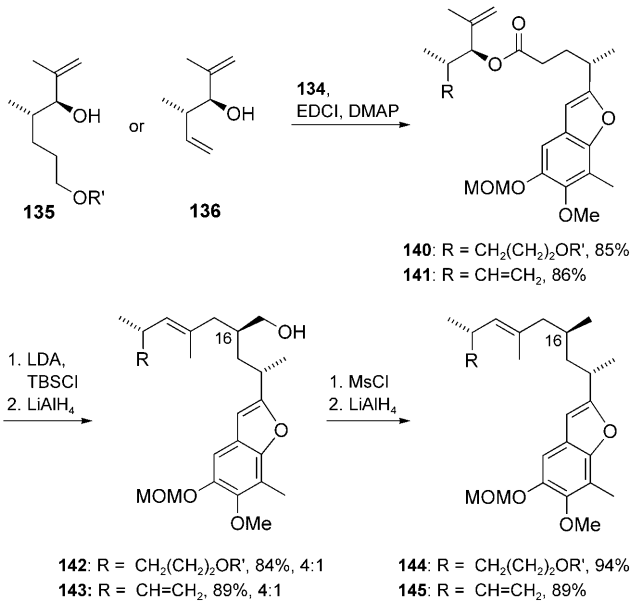
In two recent publications, the Mulzer group described two total syntheses of kendomycin.[52] Both routes (Scheme 27) involve an S_N1-type cyclization reaction for the formation of the tetrahydropyran ring but differ in the macrocyclization, which has been achieved either through a lactonization/photo-Fries sequence (C4a–C5) from **132** or a ring-closing metathesis (C10–C11) of **133**. Additional key steps included Ireland–Claisen rearrangements of the complex carboxylic esters derived from acid **134** and allylic alcohols **135** and **136**, respectively.

The synthesis of the common precursor **134** (Scheme 28) was achieved through the previously established epoxide-opening strategy using aryl bromide **20** and epoxide **137** (derived from (*S*)- citronellene) to afford ketone **138** after oxidation. Acid-promoted condensation and reinstallation of the MOM group furnished benzofuran **139**, which was converted into acid **134** in three steps. For the preparation of the C13/C14 olefinic fragment by Ireland–Claisen rearrangement, acid **134** was esterified with allylic alcohols **135** and **136**. The resulting esters **140** and **141** were converted into the corresponding TBS-protected ketene acetals, which underwent [3,3]-sigmatropic rearrangement upon heating (Scheme 29). After work-up, reduction of the crude acids furnished the primary alcohols **142** and **143**. These alcohols were reduced via the mesylate to provide the C16-methyl derivatives **144** and **145**, respectively, as advanced intermediates.

Mulzer's first approach (photo-Fries) continued with the desilylation and oxidation of **144**. The resulting aldehyde was then elaborated to lactone **146** in three steps using the

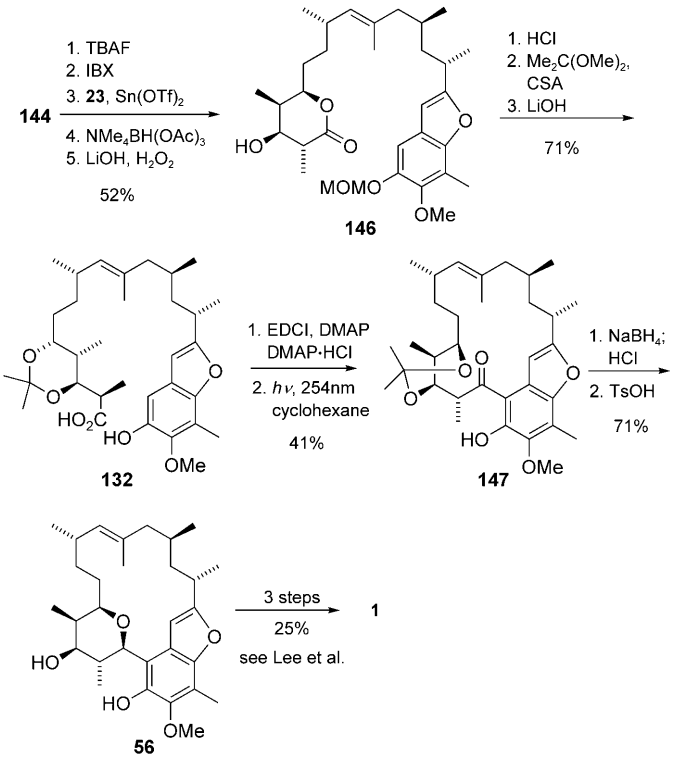


Scheme 27. Macrocyclization approaches from the Mulzer group.

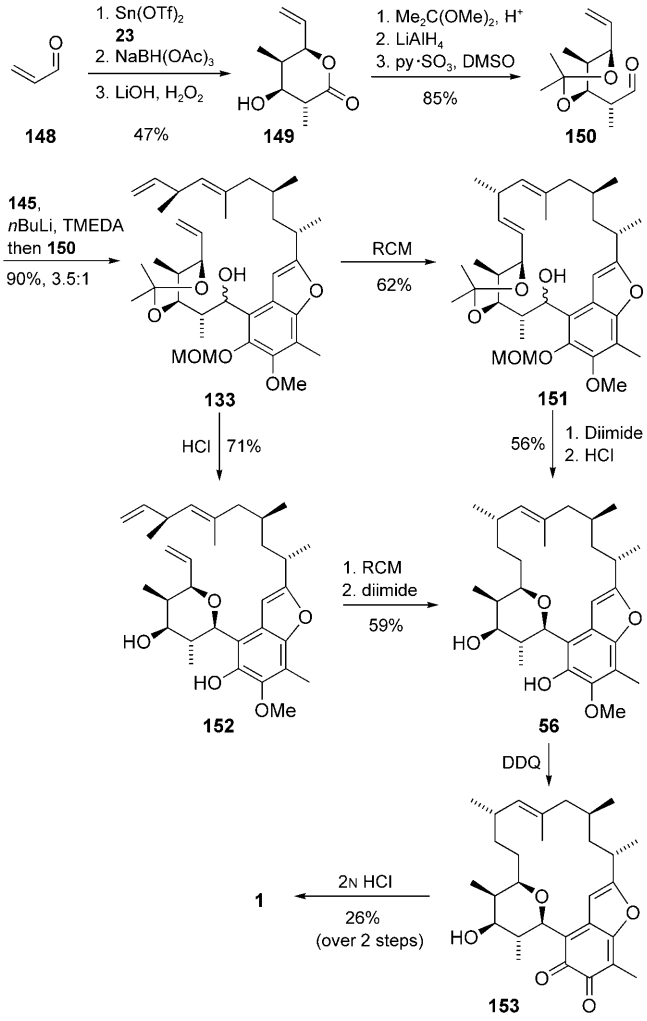


Scheme 29. Application of the Ireland–Claisen rearrangement. R′ = TBDPS; EDCI = 1-ethyl-3-(3-dimethyl-aminopropyl) carbadiimide hydrochloride.

previously established aldol methodology. Subsequent conversion into the 7,9-acetonide-protected seco-acid **132** with subsequent macrolactonization and a photo-Fries rearrangement furnished ketone **147** (Scheme 30). Reduction with $NaBH_4$ and acidic work-up gave the corresponding triol which underwent a S_N1-type cyclization to Lee's intermediate **56** upon waming with *p*TsOH. In keeping with Lee's protocol, **56** was successfully converted into **1**.



Scheme 30. Synthesis of **1** by macrolactonization/photo-Fries rearrangement.



Scheme 31. Synthesis of **1** through RCM/diimide reduction. DDQ = 2,3-dichlor-5,6-dicyano-1,4-benzoquinone.

In Mulzer's second synthesis, the construction of the tetrahydropyranyl moiety started from acrolein (**148**) which was converted into aldehyde **150** by way of lactone **149** in six steps (Scheme 31). *Ortho*-directed lithiation of **145** and addition of aldehyde **150** gave triene **133** as a mixture of diastereomers (3.5:1). The major diasteromer was successfully used in the subsequent RCM reaction to give macrcocyclic diene **151**. Site-selective reduction of the disubstituted olefin with diimide and subsequent S_N1-type cyclization completes the synthesis of precursor **56**. Since the RCM reaction with the minor diastereomer **133** was unsuccessful and therefore led to a loss of material, the order of cyclization reactions was changed. Therefore, the diastereomeric mixture of **133** was first treated with HCl to give tetrahydropyran **152** that exhibited the expected atropisomerism. Although it was expected that restricted rotation should be unfavorable for RCM, it proceeded smoothly and selective diimide reduction of the less substituted double bond again led to kendomycin precursor **56** in even higher yield with improved site selectivity. In this case an alternative endgame devoid of protecting group manipulations was developed. Therefore, treatment of **56** with DDQ directly gave the labile, though isolable *ortho*-quinone **153** which upon treatment with aqueous acid to form **1**.

11. Summary and Outlook

The objective of this review has been to present a chronological overview of the existing approaches to kendomycin (**1**). The salient features in kendomycin synthesis were the construction of the all-carbon ansa chain (Figure 1) along with a densely substituted tetrahydropyran ring. Macrocyclization at C4a/C5 and concomitant tetrahydopyran formation have been achieved by a macrocyclization through C glycosidation (Lee) or an intramolecular Prins reaction (Rychnovsky), whereas Mulzer used a photo-Fries macrolactonization procedure with subsequent reduction and tetrahydropyran formation. Macrocyclization at C19/C20 was successful using a SmI_2 Barbier reaction (Panek). Several attempts have been undertaken to achieve RCM at C13/C14 (Mulzer, Smith III, Arimoto). It was to the credit of the Smith group to realize

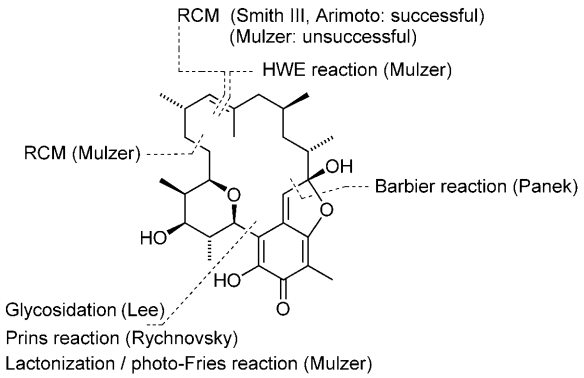


Figure 1. Macrocyclization sites of kendomycin (**1**).

that this required the absence of the rigid benzofuran moiety, although the RCM was still low yielding and furnished the olefin with the incorrect *Z* configuration. The C13/C14 HWE cyclization (Mulzer) was also successful, however the removal of the undesired C15 carbonyl group failed. More effective was the RCM at C10/C11 (Mulzer) which worked in high yield despite the already installed benzofuran and tetrahydropyran moieties.

For the assembly of the macrocylization precursors mainly four simple fragments (Figure 2) have been used, including a polyphenol core, an aldol component (C5–C8), a (*S*)-citronellene-derived fragment (C9–C13), and a dipropionate unit (C15–C19). A broad number of reactions was used for the construction of the tetrahydropyran moiety including oxa-Michael addition, S_N1-cyclization, C glycosidation, Petasis–Ferrier rearrangement, [4+2] annulation, iodoetherification, and a Prins reaction. The oxidative endgame either started from a benzofuran (Lee, Mulzer) or a benzyl ketone precursor (Smith, Panek). With regard to the ansa chain, Williams' approach is the shortest.

In conclusion the kendomycin story provides an illustrative example of how an attractive, novel target was received by the synthetic community. One after another, the various groups have pursued the first total synthesis of **1** and thereafter, the development of alternative routes. Basic elements have rapidly been adapted to the synthetic approaches of the various groups, and led to additional improvements. Typically, in the end there was significant enrichment of synthetic methodology and a variety of reliable routes to access kendomycin. This knowledge should allow detailed structure–activity relationship (SAR) studies, and with regard to the extremely diverse biological properties of **1**, the development of more specific pharmaceutical leads might be possible.

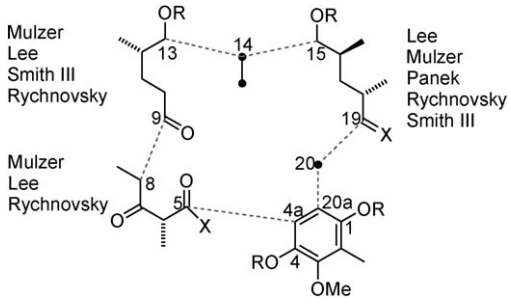


Figure 2. Most commonly used fragments used to assemble **1**.

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