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Organic Synthesis

Formal Total Synthesis of Kendomycin by Way of Alkyne Metathesis/Gold Catalysis

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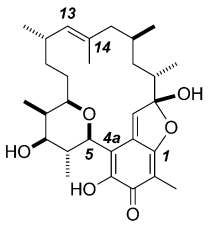
Abstract: In an attempt to study the ability of the latest generation of alkyne metathesis catalysts to process sterically hindered substrates, two different routes to the bacterial metabolite kendomycin (**1**) were explored. Whereas the cyclization of the overcrowded arylalkyne **39** and related substrates turned out to be impractical or even impossible, ring closure of the slightly relaxed diyne **45** was achieved in excellent yield under notably mild conditions with the aid of the molybdenum alkylidyne **2** endowed with triphenylsilanolate ligands. The resulting cycloalkyne **46** was engaged into a gold-catalyzed hydroalkoxylation, which led to benzofuran **47** that had already previously served as a late-stage intermediate en route to **1**.

Introduction

The kendomycin ((−)-TAN 2162) (**1**)[1–3] case nicely illustrates the stimulus that a natural product endowed with pronounced bioactivity and a challenging molecular architecture can provide.[4] No less than six different total or formal total syntheses were disclosed during the last decade in addition to a significant number of model studies.[5–11] Collectively, these efforts reflect the challenges posed by this secondary metabolite isolated from various *Streptomyces* strains, which embodies a rather unique quinone-methide/lactol chromophor within a carbogenic *ansa*-framework. Even the first synthetic forays had already indicated that closure of this macrocyclic scaffold might be difficult because of conformational peculiarities that originate from the restricted rotation about the pseudo-C-glycosidic C4a–C5 bond connecting the densely functionalized pyran and the aromatic sector.[11]



Kendomycin (**1**)

Although this forecast basically proved correct, various creative solutions were found in the following tournament. In the event, kendomycin succumbed to macrocyclizations as distinct as C-glycosidation,[5] Prins reaction,[8] Barbier-type carbonyl addition,[7] lactonization/photo-Fries rearrangement,[9] and Dötz benzannulation,[10] although with largely different efficiency. Furthermore, ring-closing olefin metathesis (RCM) was invoked on several occasions.[6,9,11j] Although this transformation seems to be an obvious choice in view of its outstanding credentials,[12–16] attempted formation of the *ansa*-frame of **1** by RCM was surprisingly difficult or even met with failure; only after careful conformational design of the cyclization precursor and/or probing of various sites of disconnection has olefin metathesis been successfully implemented.[6,9] It is perhaps ironic, however, that the direct formation of the $\Delta^{13,14}$ *E*-alkene was in vain, despite several independent attempts: although it was possible to close the macrocycle by RCM at this site, the undesired *Z*-isomer was invariably and exclusively formed.[6,9,11j] The fact that the subsequent inversion of the double bond geometry required a four-step sequence painfully illustrates that inherently *E*-selective metathesis catalysts are urgently needed but currently unknown.[17]

It is against this backdrop that our approach to kendomycin (**1**) must be seen. Recent progress in catalyst design prompts us to advocate the use of alkyne metathesis in general and ring-closing alkyne metathesis (RCAM) in particular as noteworthy alternatives to the more commonly practiced metathesis of olefins.[18] This methodology is arguably most serviceable when combined with alkyne-specific post-metathetic transformations. Of the many possibilities, it seems particularly lucrative to invoke carbophilic Lewis acid catalysts based on platinum or gold,[19,20] as they allow alkynes to be engaged as privileged substrates into a host of different transformations.

In the present context, we envisaged that a sequence of RCAM[21] followed by noble-metal-catalyzed hydroalkoxylation should open access to the known benzofuran **A**, which has previously served as the penultimate intermediate en route to **1** (Scheme 1).[4] Whereas our experiences with the cyclization of benzofuran rings by addition of a phenolic –OH group onto a lateral alkyne partner made us optimistic for the projected case,[22,23] the formation of the required cycloalkyne precursor definitely needed careful consideration.

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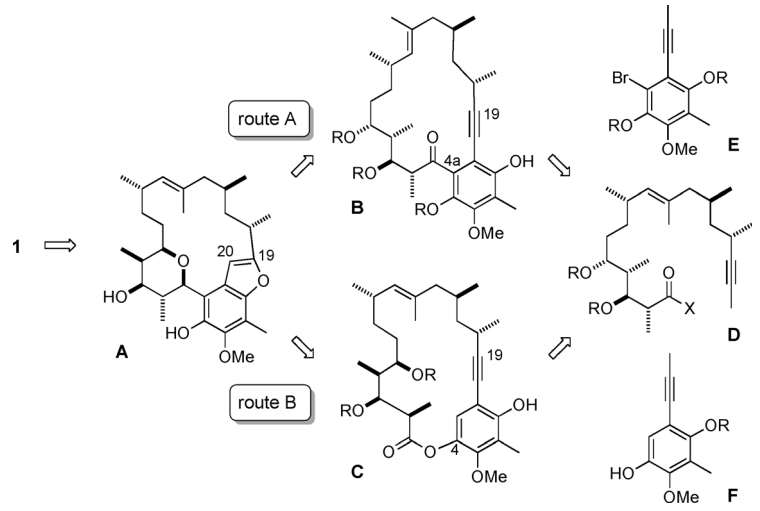


Scheme 1. Retrosynthetic analysis of kendomycin (**1**) based on RCAM followed by benzofuran formation by noble-metal-catalyzed hydroalkoxylation; kendomycin numbering scheme.

RCAM is best performed with the aid of the molybdenum alkylidyne [$(Ph_3SiO)_3Mo{\equiv}CAr$] ($Ar = -C_6H_4OMe$) (**2**) or related complexes recently developed by our group.[24–26] Because these catalysts exhibit an outstanding functional group tolerance and usually operate under mild conditions, they allow rather fragile compounds to be handled.[27,28] Therefore it seemed unlikely that the substitution pattern of kendomycin would pose any problems. Yet, limitations are to be expected for sterically hindered alkynes since the three fairly bulky triphenylsilanolate ligands about the operative alkylidyne in **2** might obstruct efficient substrate binding in such cases.[26,29,30] This issue seemed particularly daunting in the projected formation of cycloalkyne **B**, in which the arylalkyne subunit is *ortho*-disubstituted on the aromatic end and α-branched at the aliphatic side.

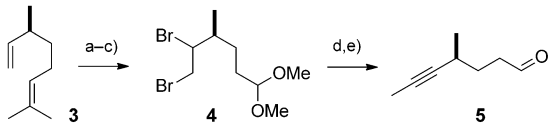
Therefore it appeared prudent to consider an alternative entry that remits some of this steric burden. To this end, we contemplated a tactic based on ring contraction by photo-Fries rearrangement of an ester precursor of type **C**, which follows the beautiful lead previously described by the Mulzer group for a related intermediate.[9] Yet, the topology of the *meta*-bridging *ansa* chain in **C** implies that such a cycloalkyne is strained and hence its formation by RCAM also potentially problematic.

It was these open chemical questions that let us venture into the total synthesis of kendomycin. As the major goal, our study intended to interrogate the new alkyne metathesis catalysts as to the tolerable steric hindrance. To gain the necessary material however, it was planned to take ample advantage of the knowledge gathered in the literature for the preparation of the required building blocks as well as for the envisaged end game.[4–11] Gratifyingly, a single polyketide segment **D** can serve both of the conceived routes to **1**, which reduces the necessary preparative burden. As outlined below, this conceptual frame finally gave rise to a concise approach to this exigent target, while illustrating the power of alkyne metathesis when applied in concert with gold catalysis.

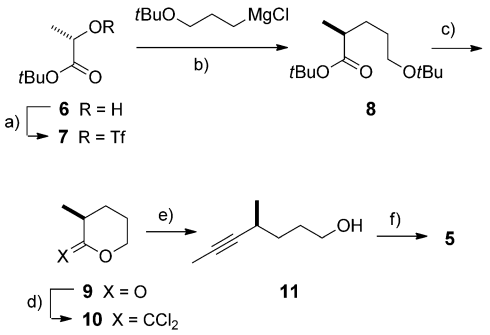
Results and Discussion

Preparation of the polyketide chain

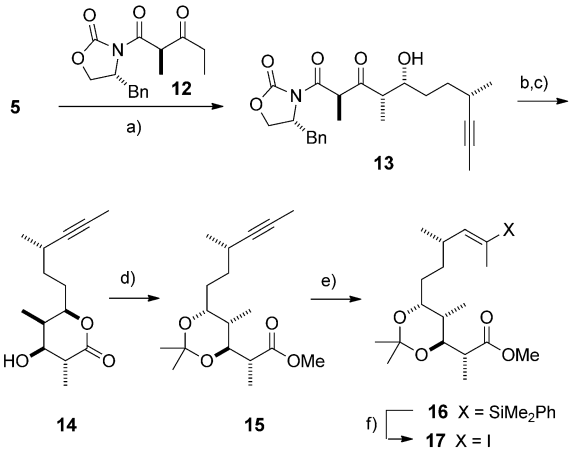
In line with the intentions spelled out above, we pursued a pragmatic route to the aldehyde fragment **5**, which was best prepared on scale in five high yielding operations starting from β-citronellene (Scheme 2).[31] In passing, however, it is noted that **5** has also been made from the lactic acid ester **6** by the elegant zinc-catalyzed triflate alkylation chemistry developed by the Breit group,[32] which furnished the coupling product **8** in respectable yield (Scheme 3). Acid cleavage of the *tert*-butyl ester gave the corresponding lactone **9** that was transformed into the *gem*-dichloroolefin **10** by following a literature procedure.[33] Treatment of this compound with MeLi in the presence of [$Cu(acac)_2$] engendered fragmentation with formation of the nonterminal alkyne **11** without noticeable epimerization of the α-chiral center.[34] A copper- and TEMPO-cocatalyzed air oxidation then gave the targeted aldehyde **5**.[35] Although this route was also satisfactory in terms of yield, it is distinctly longer than the "chiral pool" strategy shown in Scheme 2 and therefore not competitive in this particular case.[36]



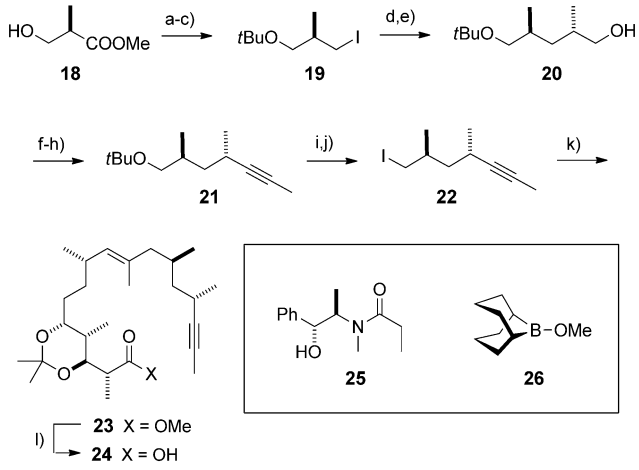
Scheme 2. a) O_3, CH_2Cl_2, −78 °C, then Me_2S; b) $HC(OMe)_3$, K_{10}-montmorilonite, 75% (over both steps); c) 4-dimethylaminopyridinium bromide perbromide, 0 °C→RT, DMAP, CH_2Cl_2, 87%; d) LiHMDS, THF, 50 °C, 90%; e) BuLi, MeI, THF/DMPU, −78 °C→RT, then aq. HCl, 95%; DMAP = 4-dimethylaminopyridine; LiHMDS = lithium hexamethyldisilazide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone.



Scheme 3. a) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 85%; b) $ZnCl_2$ (5 mol%), THF, 0 °C, 66%; c) trifluoroacetic acid, CH_2Cl_2, 66%; d) CCl_4, PPh_3, THF, reflux, 71%; e) MeLi, $Cu(acac)_2$ (10 mol%), Et_2O, 92%; f) TEMPO (5 mol%), bipyridine (5 mol%), $[Cu(MeCN)_4]BF_4$ (5 mol%), *N*-methylimidazole, MeCN, air, 96%; Tf = trifluoromethanesulfonyl; acac = acetylacetonato; TEMPO = 2,2,6,6-tetramethyl-piperidin-1-oxyl, free radical.



Scheme 4. a) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, −78 °C, 57%; b) $Me_4NBH(OAc)_3$, MeCN/HOAc, −50→−10 °C, 80%; c) LiOH, H_2O_2, THF/H_2O, 99%; d) 2,2-dimethoxypropane, camphorsulfonic acid (10 mol%), 90%; e) $PhMe_2SiLi$, CuCN, THF, −78→0 °C, 93%; f) NIS, 2,6-lutidine, hexafluoroisopropanol, 0 °C, 97%; NIS = *N*-iodosuccinimide.

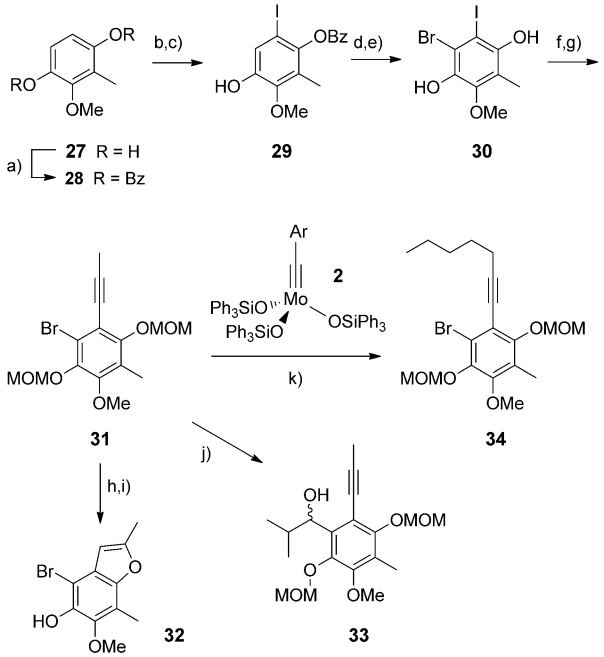


Scheme 5. a) Isobutene, H_2SO_4 cat., CH_2Cl_2, 92%; b) $LiAlH_4$, THF, −78 °C, 80%; c) I_2, PPh_3, imidazole, Et_2O/MeCN, 88%; d) **25**, LDA, LiCl, THF, −78 °C→RT, 96%; e) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C, 96%; f) TPAP cat., NMO, MS 4 Å, CH_2Cl_2, 0 °C→RT, 72%; g) CBr_4, PPh_3, Zn, CH_2Cl_2, 68%; h) BuLi, MeI, THF, −78 °C→RT, 99%; i) i) trifluoroacetic acid, CH_2Cl_2; ii) KOH, MeOH/H_2O, 88%; j) I_2, PPh_3, imidazole, Et_2O/MeCN, 95%; k) i) *t*BuLi, **26**, Et_2O; ii) **17**, K_3PO_4, [$PdCl_2$(dppf)] (10 mol%), DMF/H_2O, quant.; l) LiOH, THF, MeOH, H_2O, 90%; LDA = lithium diisoprpylamide; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine-*N*-oxide; MS = molecular sieves; dppf = 1,1′-bis(diphenylphosphino)ferrocene.

In analogy to a literature precedent,[9] a tin-aldol reaction of **5** with the Evans keto-imide **12** furnished compound **13** in high yield,[37] which was subjected to a 1,3-*anti* reduction with tris(acetoxy)borohydride (Scheme 4).[38] Hydrolytic cleavage of the auxiliary resulted in lactone formation upon work up, which was inconsequential as treatment of **14**[5] with 2,2-dimethoxypropane under acidic condition led to concomitant transesterification and acetal formation. The transformation of **15** thus formed into the alkenyl iodide **17** was best achieved by silylcupration[39,40] followed by iodine-for-silicon exchange.[41] Although this tactic is one step longer than hydrozirconation/iodination, it was found much more reliable and also higher yielding.

The necessary coupling partner **22** derives from Roche ester **18**, which was first converted into iodide **19** by standard means (Scheme 5). A subsequent Myers alkylation followed by reductive cleavage of the auxiliary gave product **20** basically as a single diastereomer,[42] which was readily elaborated into alkyne **21** by oxidation[43] and a subsequent Corey–Fuchs alkyne formation.[44] Acid treatment followed by reaction of the resulting alcohol with PPh_3/I_2 in basic medium furnished the required building block **22** in excellent overall yield. A noteworthy aspect of potentially more general interest is the use of the *tert*-butyl ether moiety, which is a somewhat underrepresented alcohol protecting group even though it is cheap, easy to introduce, robust against many reagents, yet readily cleaved in acidic medium. Anyhow, its use provided a nicely scalable and inexpensive solution for the present case.

Next, fragments **17** and **22** were combined by way of the 9-MeO-9-borabicyclo[3.3.1]nonane (9-MeO-9-BBN) variant of the Suzuki coupling that has already served previous syntheses of kendomycin well.[5,8,10] Parenthetically, we note that this methodology originates from our laboratory[45] and later found extensive use by us and others.[46] As expected, it furnished product **23** in essentially quantitative yield as the last common in-

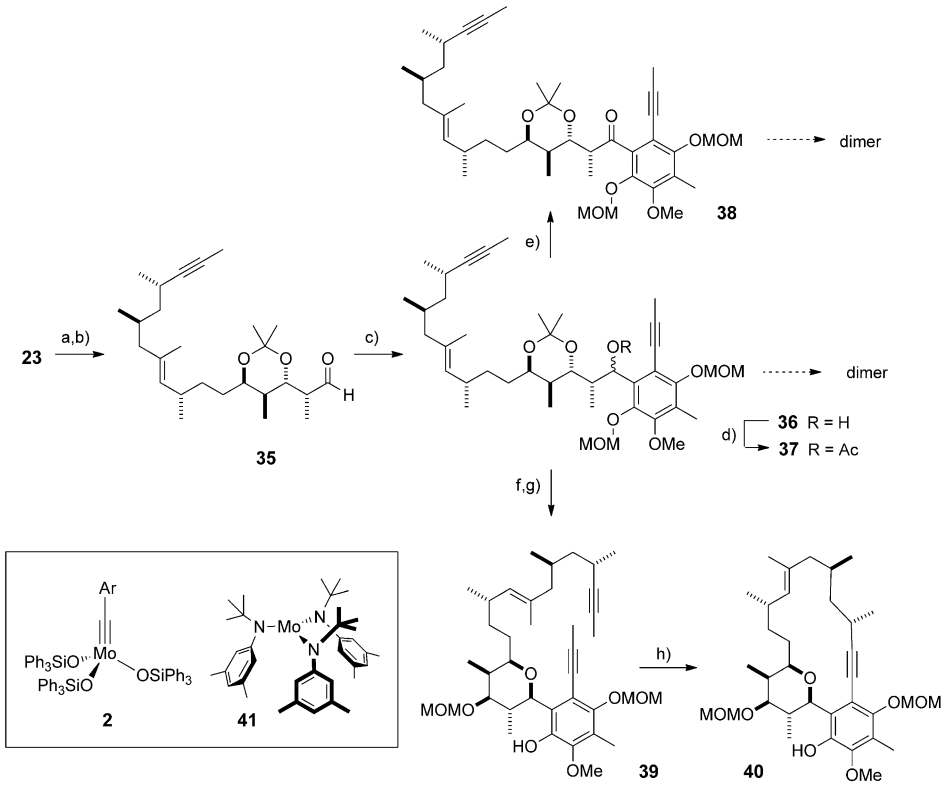


Scheme 6. a) BzCl, Et_3N, THF, 0 °C, 89%; b) NIS, H_2SO_4 cat., HOAc, 94%; c) KOH, MeOH, 80%; d) NBS, MeCN, −10 °C, 49–81%; e) DIBAl-H, CH_2Cl_2; f) MOMCl, DBU, acetone, 61% (over both steps); g) propynylmagnesium bromide, $ZnBr_2$, [$Pd(PPh_3)_4$] (40 mol%), THF, reflux, 82%; h) *p*TsOH cat., MeOH; i) $PtCl_2$ (20 mol%), toluene, 70 °C, 82% (over both steps); j) BuLi, THF, then isobutyraldehyde, 78 °C, 96%; k) **2** (18 mol%), 2-octyne, MS 5 Å, toluene, 100 °C, 54% (91% brsm); NBS = *N*-bromosuccinimide; DIBAl-H = di-isopropylaluminum hydride; MOM = methoxymethyl; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene; Ts = *p*-toluenesulfonyl; brsm = based on recovered starting material.

termediate of the two envisaged RCAM-based routes toward kendomycin (**1**).

Exploration of route A

After considerable experimentation it was found that an adequate hexasubstituted benzene derivative of type **E** can be formed as shown in Scheme 6. Benzoylation of commercial **27** was followed by iodination, which occurred regioselectively *trans* to the methoxy substituent. At this stage, the bulky iodide shields the adjacent ester such that hydrolysis with K_2CO_3 in aqueous MeOH solely unveils one phenol site, which provides the necessary activation for the introduction of a second halide at the remaining open *ortho* position. To this end, **29** was treated with NBS to give product **30** in somewhat variable yield after reductive cleavage of the remaining benzoate. Compound **30** was then MOM-protected prior to a regioselective attachment of the yet missing propynyl moiety by Negishi cross-coupling at the iodide site to give the functional hexasubstituted arene fragment **31**.[47]



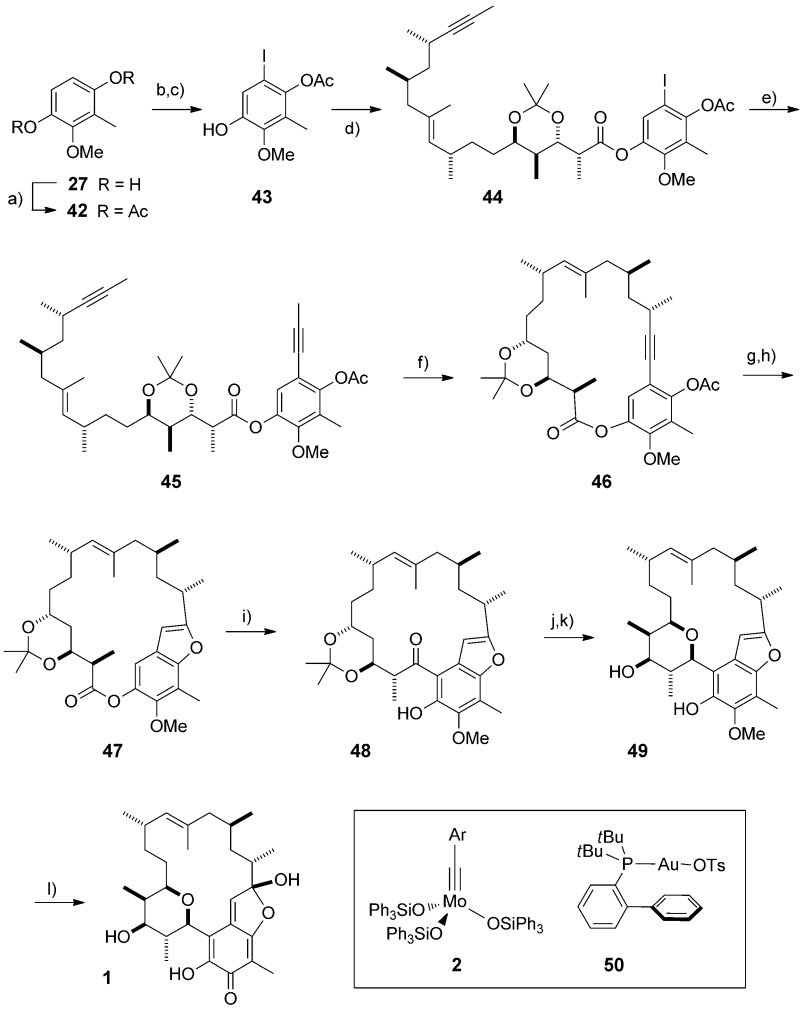
Scheme 7. a) MeNH(OMe)·HCl, *i*PrMgCl, THF, −25 °C→RT, 78%; b) DIBAl-H, THF, −78 °C; c) **31**, *n*BuLi, THF, −78 °C→RT, 70% (over both steps); d) Ac_2O, DMAP, pyridine, 55%; e) Dess–Martin periodinane, CH_2Cl_2, 97%; f) aq. HCl, MeOH, 77%; g) MOMCl, *i*PrNEt$_2$, CH_2Cl_2, 73%; h) **2** (2×30 mol%), toluene, reflux, ≤62%, see text.

A few model reactions were performed at this stage to explore the likelihood of the projected end game. In line with our expectations, MOM-cleavage followed by treatment of the resulting phenol with catalytic amounts of $PtCl_2$ furnished the corresponding benzofuran **32** in good yield.[22] Likewise, lithium-for-halogen exchange and reaction with an α-branched aliphatic aldehyde worked well to give adduct **33**, whereas addition of the organolithium intermediate to an analogous Weinreb amide[48] was low yielding (not shown). Finally, the outcome of an alkyne cross metathesis[49] of the hindered substrate **31** with 2-octyne catalyzed by the molybdenum alkylidyne **2**[25] was encouraging, though certainly not optimal; yet, such a crowded arylalkyne substrate had never been successfully metathesized before. Additional control experiments also augured well for the projected ring closure.[50]

Based on the gathered intelligence, the polyketide sector **23** was first transformed into the corresponding aldehyde **35**, which was then reacted with the lithiated arene segment to give product **36** in good yield. This compound was elaborated into a panel of possible cyclization precursors as shown in Scheme 7. Unfortunately, none of them proved viable, despite considerable experimentation. Suffice it to say that only diyne **39** could be transformed into the desired macrocyclic monomer **40**, even though at an impractically high dilution and for the price of a very high catalyst loading; all other attempts at cyclization of the shown precursors with the help of **2** or other alkyne metathesis catalysts such as **41**[51] resulted in either no reaction, the production of acyclic dimers and/or gradual decomposition.[52] What is more, even the formation of **40** turned out to be fairly erratic, which definitely meant that route A (Scheme 1) does not provide a competitive solution for the kendomycin problem. Hence we conclude that metathesis of aryl alkynes flanked by bulky and/or potentially coordinating substituents at both *ortho*-positions, though not excluded,[50] is currently not yet sufficiently robust.

Metacyclophane/ring-contraction pathway

As a consequence, we increased our efforts to explore the alternative gateway to kendomycin (route B). The preparation of an appropriate phenol derivative basically reiterates the acylation and subsequent iodination chemistry outlined above, in that **27** could be cleanly transformed into compound **43** (Scheme 8). By virtue of steric hindrance, a selective acetate cleavage with K_2CO_3 in aqueous MeOH solely unveiled the proper phenol site for the attachment of the polyketide segment **24** to give ester **44**. Only at this point the missing second alkyne unit was installed by another variant of the Suzuki coupling,[53] which generates an appropriate alkynylboron donor in situ from propynyl sodium and cheap



Scheme 8. a) AcCl, Et_3N, THF, −78→0 °C, 90%; b) NIS, AcOH, H_2SO_4 cat., 99%; c) K_2CO_3, MeOH/H_2O, 97%; d) **24**, EDCI·HCl, DMAP, CH_2Cl_2, 77%; e) propynyl sodium, $B(OMe)_3$, $[PdCl_2(Ph_3P)_2]$ (10 mol%), *t*BuXPhos (20 mol%), THF, reflux, 78%; f) **2** (5 mol%), toluene, MS 5 Å, 95%; g) K_2CO_3, MeOH, 0 °C, 86%; h) **50** (10 mol%), CH_2Cl_2, 79%; i) *hν* (high pressure mercury gas lamp, 125 W), cyclohexane, 85%; j) $NaBH_4$, MeOH; k) aq. HCl, MeOH, 89% (over both steps); l) ref. [9]; EDCI = 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide; *t*BuXPhos = 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl.

$B(OMe)_3$.[46,54] Despite the heavy functionalization, this method worked well and furnished diyne **45** in respectable yield in readiness for macrocyclization by ring-closing alkyne metathesis.

In striking contrast to the difficulties outlined in the previous section, the cyclization of the *meta*-bridged cyclophane derivative **45** proceeded with exceptional ease. Thus, exposure of diyne **45** to complex **2** (5 mol%)[25] furnished the desired product within 1 h at ambient temperature in essentially quantitative and well reproducible yield. The crude material was directly subjected to saponification of the remaining acetate. While treatment of this compound with $PtCl_2$ did not engender cyclization of the benzofuran ring, the use of more electrophilic cationic gold complexes smoothly triggered this second key transformation. Best results were obtained with [Au(JohnPhos)]OTs (**50**) as the catalyst in CH_2Cl_2. Compound **47** intercepts the total synthesis of kendomycin (**1**) published by Mulzer and co-workers.[9] Their subsequent ring contraction by a photo-Fries rearrangement[55] could be nicely reproduced, furnishing ketone **48** in good yield; suffice it to say that the analytical and spectral data of either compound were in excellent agreement with those reported in the literature (see Supporting Information).[9] The remaining steps to the target have also been repeated, even though only in a cursory manner on small scale, as they merely echo established chemistry.[9]

Conclusion

The advent of a new generation of catalysts, as exemplified by the molybdenum alkylidyne **2**,[24–26] entails a significant push for alkyne metathesis in practical and strategic terms.[18] They allow most common functional groups to be handled and hence enable applications to densely functionalized and fairly elaborate compounds, as witnessed by the present case study as well as by a number of earlier examples from this and other laboratories.[27–30,56] Yet, the somewhat crowded ligand sphere in **2**, casted by the triarylsilanolate ligands, suggests that limitations might be encountered with sterically hindered substrates. The two different routes to kendomycin (**1**) and the accompanying model studies described above elaborate on this aspect.

Whereas the intermolecular cross-metathesis of the overcrowded arylalkyne **31** bearing bulky substituents on either side *ortho* to the reacting triple bond could be enforced in a preparatively meaningful yield, the intramolecular versions trying to engage substrates **36**–**39** were either impractical or even impossible. A relatively small relaxation of the steric pressure, however, greatly improved the outcome as evident from the surprisingly smooth cyclization of diyne **45** to the *meta*-bridging and somewhat strained cycloalkyne **46**. This transformation was instrumental for yet another total synthesis of kendomycin, a bacterial metabolite that had already served as a prominent target in the past.[4–11] Although we appreciate that step-counting is not always an unambiguous exercise and certainly not the only relevant index, the present synthesis of **1** is one of the shortest entries into this particular ansamycin

derivative known to date. This fact corroborates the notion that alkyne metathesis, in particular when aligned with noble metal catalysis,[57] opens many opportunities and deserves consideration in other challenging settings in the future.

Experimental Section

All experimental details can be found in the Supporting Information. The material includes compound characterization and copies of spectra of new compounds.

Acknowledgements

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Keywords: alkynes · gold · metathesis · molybdenum · natural products

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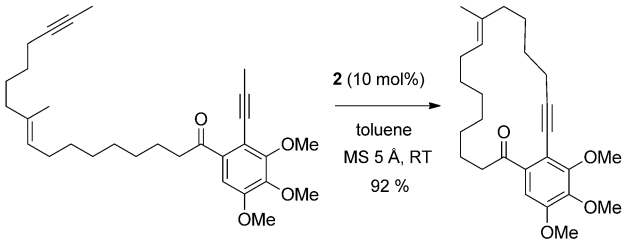

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