Increasing the Structural Span of Alkyne Metathesis

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Abstract: A new generation of alkyne metathesis catalysts, which are distinguished by high activity and an exquisite functional group tolerance, allows the scope of this transformation to be extended beyond its traditional range. They accept substrates that were previously found problematic or unreactive, such as propargyl alcohol derivatives, electron-deficient and electron-rich acetylenes of various types, and even terminal alkynes. Moreover, post-metathetic transformations other than semi-reduction increase the structural portfolio, as witnessed by the synthesis of a annulated phenol derivative via ring-closing alkyne metathesis (RCAM) followed by a transannular gold-catalyzed Conia-ene reaction. Further examples encompass a post-metathetic transannular ketone–alkyne cyclization with formation of a trisubstituted furan, a ruthenium-catalyzed redox isomerization, and a Meyer–Schuster rearrangement/oxa-Michael cascade. These reaction modes fueled model studies toward salicylate macrolides, furanocembranolides, and the cytotoxic macrolides acutiphycin and enigmazole A; moreover, they served as the key design elements of concise total syntheses of dehydrocurvularin (**27**) and the antibiotic agent A26771B (**36**).

Keywords: alkyne metathesis · gold · molybdenum · natural products · total synthesis · transannular reactions

Introduction

Significant advances in catalyst design has brought new impetus for applications of alkyne metathesis in general and ring-closing alkyne metathesis (RCAM) in particular.[1,2] In this context, complexes **1–3** are particularly noteworthy as they combine excellent reactivity with an outstanding functional group tolerance (Scheme 1).[3] These molybdenum alkylidynes endowed with triarylsilanolate ligands are readily prepared on a multigram scale, turned out to be thermally quite robust, and can be rendered bench-stable upon complexation with phenanthroline. Since the adduct formation is reversible on contact with simple metal salts, the active species can be conveniently released on demand and its exquisite activity profile be harnessed even by a less experienced practitioner.[3] The reactions are best performed in the presence of molecular sieves (MS 5 Å). This additive sequesters the released 2-butyne formed as the generic by-product from methyl capped alkyne substrates; as a consequence, full conversion can often be reached at or even below ambient temperature, which makes the application of static vacuum or other inconvenient reaction set-ups unnecessary.[3]
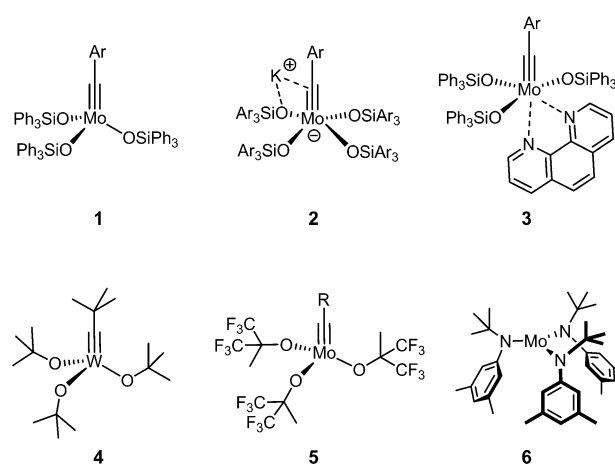
Scheme 1. Assortment of commonly used alkyne metathesis catalysts; for a comprehensive discussion, see ref. [1a]; Ar = Ph, pMeO-C₆H₄-; R = tBu, 2,6-dimethylphenyl.

This progress notwithstanding, most applications of alkyne metathesis known to date merely engaged the (cyclo)alkynes primarily formed into a subsequent semi-reduction.[1] In doing so, rigorous control over the configuration of the newly formed double bond as well as high levels of selectivity in either geometric series are secured, which contemporary olefin metathesis usually cannot guarantee.[4–6] While this approach therefore remains utterly relevant,[7–10] it is also clear that alkyne semi-reduction is by no means the only serviceable post-metathetic transformation. Among the many conceivable options,[11] the use of "alkynophilic"

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Lewis acid catalysts seems particularly lucrative, which allow a host of nucleophiles to be added across a triple bond under notably mild conditions.[12] Although a few recent case studies took advantage of this tactic,[13–16] many possibilities remain yet to be explored. It is the purpose of this article to further increase the span of alkyne metathesis beyond the stereoselective formation of regular olefins. In parallel, we were striving to encompass those types of alkyne substrates that were previously considered problematic or even unreactive; any advance in this regard will expand the portfolio and coverage of alkyne metathesis beyond its customary sphere.

Results and Discussion

Gold-catalyzed transannular functionalization: Several members of the salicylic- and resorcylic acid macrolide family, such as radicicol, zearalenone or lasiodiplodin, have been known for decades (Scheme 2); yet, the interest in these and related polyketide derivatives grew dramatically in the recent past when their pronounced and diverse biological activities were fully recognized.[17] In parallel, new representatives were discovered which became immediate targets for total synthesis. As one might expect, most approaches started with preformed aromatic entities and focused on the formation of the annulated macrocycle. However, a complementary approach to resorcylic acid macrolides pursued by Danishefsky and co-workers showed that the de-novo formation of the arene nucleus may be advantageous in certain cases; specifically, these authors used an intermolecular Diels–Alder strategy to generate the aromatic ring only after the macrocycle had been forged.[18]
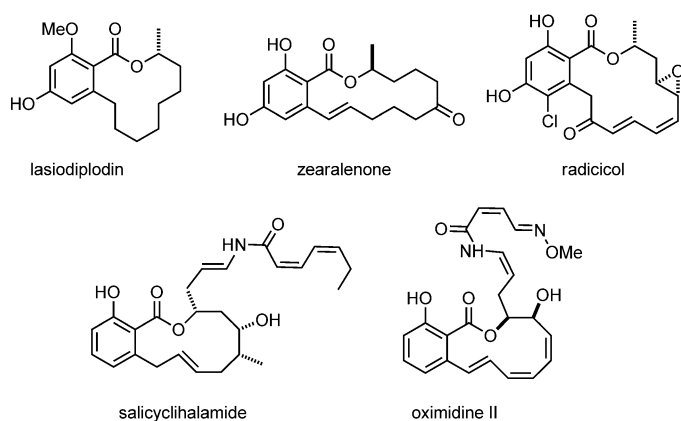
Scheme 2. Representative resorcylate and salicylate macrolides.

Inspired by this precedent and in continuation of our own early investigations in this field,[19,20] we considered that macrocyclization by ring-closing alkyne metathesis (RCAM)[21] followed by a transannular addition of an appropriate soft C-nucleophile across the triple bond might open an entirely different entry. This idea was tested by the

model study summarized in Scheme 3. Starting from β-ketoester **7**,[22] a CsF-catalyzed transesterification[23] with tridec-11-yn-1-ol furnished the envisaged cyclization precursor **8**. According to NMR analysis, this compound is noticeably enolized and was therefore protected in situ on treatment with TMSCl and Et$_3$N; after evaporation of all volatile materials, the resulting crude silyl enol ether was subjected to RCAM with the aid of complex **2a**·Et$_2$O (Ar = Ph). Since the silyl residue was readily cleaved during work up, no extra step was necessary to secure the desired macrocycle **9** in 90% overall yield.
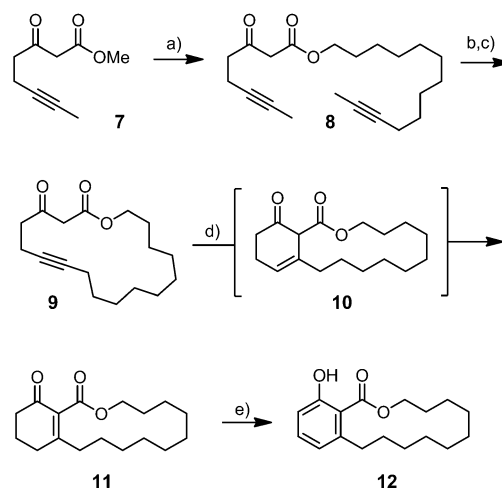

Scheme 3. a) Tridec-11-yn-1-ol, CsF (10 mol%), toluene, reflux, 83%; b) TMSCl, Et$_3$N, CH$_2$Cl$_2$; c) **2a**·Et$_2$O (Ar = Ph, 10 mol%), toluene, MS 5 Å, 80°C, 90%; d) Ph$_3$PAuCl (5 mol%), AgNTf$_2$ (5 mol%), CH$_2$Cl$_2$, 97%; e) DDQ, TMSCl, MeCN, −20 → 90°C (closed vessel), 67%; DDQ = 2,3-dichloro-4,5-dicyano-1,4-benzoquinone; MS = molecular sieves; Tf = trifluoromethanesulfonyl; TMS = trimethylsilyl.

Although 6-*endo* additions of β-ketoesters across internal alkynes are known in the literature, there is ample room for improvement as some of the established procedures are plagued by by-product formation[24] and/or require stoichiometric amounts of a metal promoter.[25] We conjectured that gold catalysis should be particularly well suited to effect this special variant of a Conia-ene type reaction.[26,27] In line with this notion, the transannular cyclization of **9** catalyzed by Ph$_3$PAuNTf$_2$[28] generated in situ proceeded with remarkable ease to furnish enone **11** as the only product in essentially quantitative yield. It is believed that the reaction affords compound **10** as the primary product, which rearranges instantaneously to the much more stable isomer **11** under the influence of the carbophilic catalyst.[29]

The oxidation of **11** to the corresponding phenol **12** turned out to be rather challenging. The elegant aerobic aromatization protocol developed by Stahl and co-workers furnished the desired product, but the yield remained low (32–43%), despite considerable experimentation.[30] Amongst the variety of alternative oxidants, the use of DDQ in MeCN in the presence of TMSCl gave the best results.

Another model study was undertaken to investigate whether transannular reactions of macrocyclic β-ketoesters comprising a triple bond in their framework might ultimately provide access to furanocembranoids (Scheme 4).[31] A sequence of two conventional alkylation reactions converted methyl acetoacetate (**13**) into product **14**, which was transformed into the corresponding silyl enol ether prior to ring-closure; the desired macrocycle **15** was obtained in respectable yield. Exposure of this compound to catalytic AuCl$_3$ in refluxing methanol[32] resulted in clean transannular attack of the enol oxygen atom with formation of the desired furan ring. It is pointed out that product **16** maps onto the framework of pukalide or iopholide and congeners.[31]
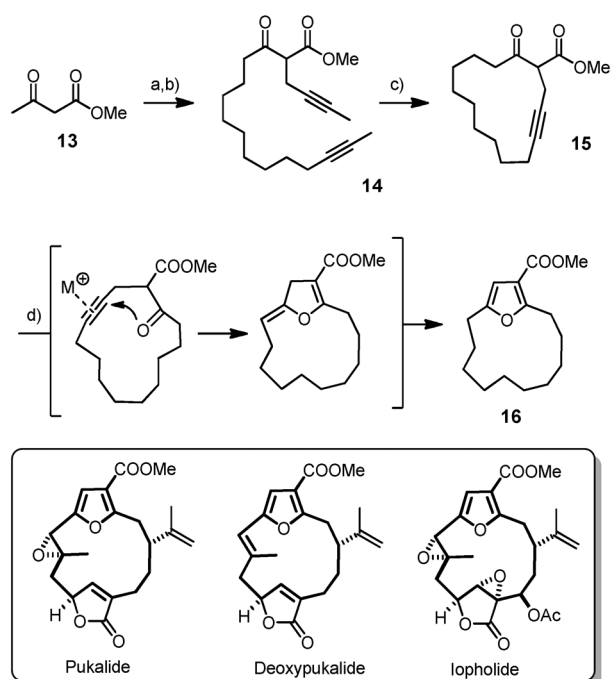

Scheme 4. a) NaH, then BuLi, THF, then 11-bromo-2-undecyne, 0°C → RT, 53%; b) NaH, 1-bromo-2-butyne, THF, 0°C → RT, 64%; c) (i) TMSCl, Et$_3$N, CH$_2$Cl$_2$; (ii) **2**·Et$_2$O (Ar = Ph) (2×5 mol%), toluene, MS 5 Å, 80°C, 66%; d) AuCl$_3$ (7 mol%), MeOH, reflux, 67%.

Propargylic alcohol derivatives: Propargyl alcohols and derivatives thereof are attractive substrates for alkyne metathesis as they provide many opportunities for post-metathetic transformations.[33] A close survey of the literature, however, shows that such compounds have hardly ever been tested; in fact, it is by no means clear that they will qualify since the formation of a metal alkylidyne—which is known to be nucleophilic at carbon[34]—adjacent to a potential leaving group might simply result in the extrusion of the propargylic substituent and, in doing so, destroy the catalyst. Only recently have a few examples of successful alkyne cross-metathesis (ACM) reactions been reported, using the latest generation of molybdenum–alkylidyne complexes endowed with triarylsilanolate ligands.[3] This precedent encouraged us to study whether propargylic alcohol derivatives are ame-

nable to the arguably more challenging RCAM reactions as well.

To this end, the ester derivatives **17** differing in the nature and steric demand of the protecting groups for the propargylic alcohol subunit were reacted with complex **2a**·Et$_2$O (Ar = Ph) as one of the most active and selective alkyne metathesis catalysts known to date (Scheme 5, Table 1).
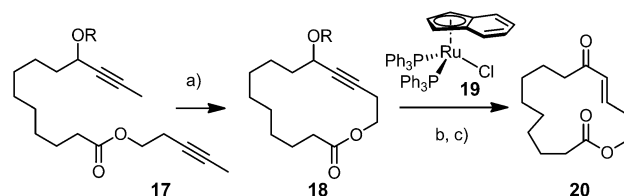
Scheme 5. RCAM of propargyl alcohol derivatives followed by a redox isomerization: a) see Table 1; b) *p*TsOH·H$_2$O, MeOH, 92% (from **18a**, R = TBS); c) **19** (10 mol%), In(OTf)$_3$ (10 mol%), camphorsulfonic acid (17 mol%), THF, reflux, 79%; Ts = *p*-toluenesulfonate (tosyl).

Table 1. RCAM of propargyl alcohol derivatives.[a]

Entry	Substrate	R	c [M]	T [°C]	Yield [%]
1	**17a**	TBS	0.017	RT	69[b]
2	**17a**	TBS	0.002	100	74[b,c]
3	**17b**	Ac	0.017	RT	56
4	**17b**	Ac	0.002	80	86
5	**17c**	MOM	0.002	80	79

[a] Unless stated otherwise, all reactions were performed with 10 mol% of complex **2a**·Et$_2$O (Ar = Ph) in toluene in the presence of MS 5 Å. [b] Ca. 20% of a cyclic dimer was detected. [c] Using 15 mol% of catalyst; Ac = acetyl; MOM = methoxymethyl; TBS = *tert*-butyldimethylsilyl.

Gratifyingly, the cyclization reactions proceeded smoothly, affording the desired macrocycles **18** in respectable yields, although the catalyst loading was not optimized at this stage. Compound **17a** bearing a bulky OTBS group adjacent to one of the alkynes furnished variable amounts of a cyclic dimer in addition to the desired product **18a**. In view of the sterically demanding ancillary ligands on the catalyst, it is hardly surprising that the reaction is responsive to steric hindrance about the triple bonds to be metathesized.[35] Cleavage of the silyl group of **18a** followed by a ruthenium-catalyzed redox isomerization[36] furnished enone **20** in high yield.

Yet another possibility to take advantage of the compatibility of propargylic substrates with RCAM is outlined by the model study directed towards the highly cytotoxic macrolide enigmazole A (Scheme 6).[37] Our approach engaged the readily available diyne **21** (diastereomeric mixture)[38] into ring-closure on treatment with catalytic amounts of complex **1** under high dilution conditions. Oxidative cleavage of the PMB-ether in the resulting product **22** followed by treatment with catalytic [(Ph$_3$P)AuNTf$_2$] gave the tetrahydropyran derivative **24** as a single diastereomer in excellent yield, which can be isolated as such or directly convert-
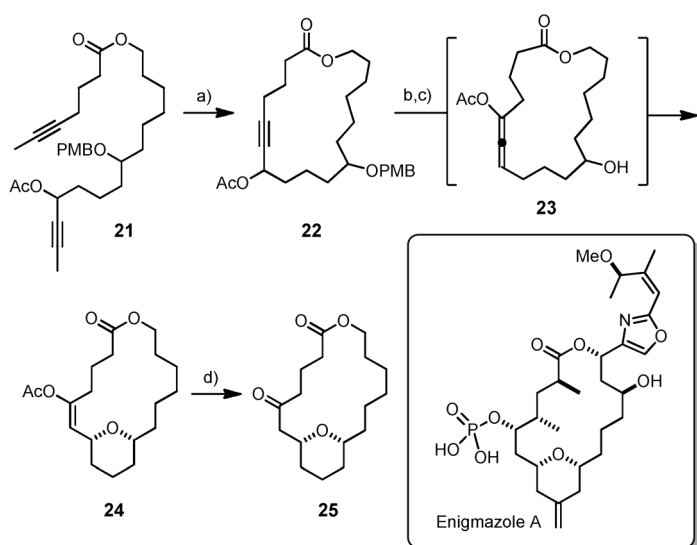
Scheme 6. Model study towards enigmazole A based on a sequence of RCAM followed by a Meyer–Schuster rearrangement/transannular hydroalkoxylation cascade: a) 1 (Ar = pMeOC$_6$H$_4$-, 12 mol%), toluene, MS 5 Å, 80°C, 95%; b) DDQ, CH$_2$Cl$_2$, pH 7 buffer, 97%; c) Ph$_3$PAuNTf$_2$ (5 mol%), CH$_2$Cl$_2$, 95%; d) K$_2$CO$_3$, MeOH, 78% (over two steps).

ed into ketone **25** upon saponification of the crude material. The allenyl acetate **23** primarily formed by the gold-catalyzed Meyer–Schuster rearrangement[39] is subject to a spontaneous transannular hydroalkoxylation mediated by the very same catalyst; the net outcome is synthetically equivalent to enone formation followed by an oxa-Michael addition.[40] The structure of **25** in the solid state confirms the diequatorial substitution of the resulting tetrahydropyran moiety and hence the validity of this model for a projected total synthesis of enigmazole A (Figure 1). Further studies towards this particular target will be reported in due course.
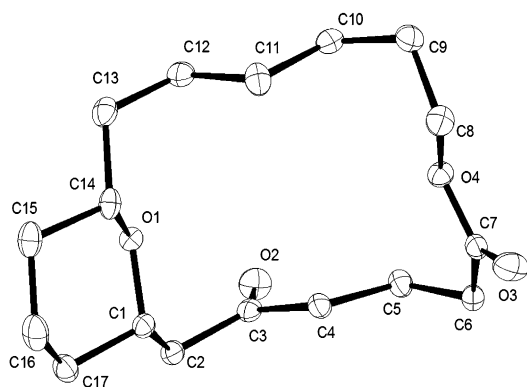

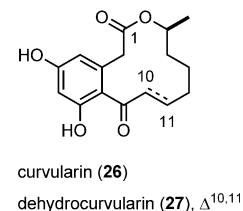Figure 1. Structure of compound **25** in the solid state.[41]

Although only modestly complex in structural terms, these model studies showcase that macrocyclic enones and derivatives thereof are well within reach of RCAM. This new gateway is deemed a valuable addendum to the synthetic repertoire, in particular since successful applications
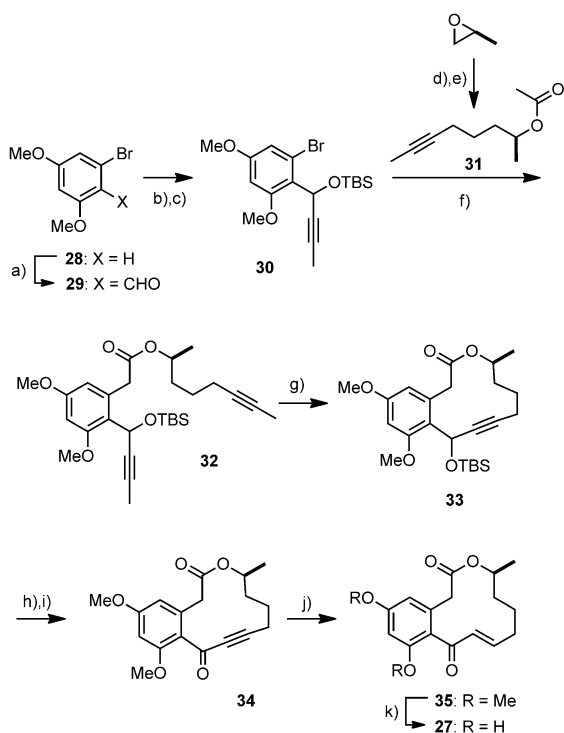
of the popular ring-closing alkene metathesis (RCM) to the formation of macrocyclic enones are surprisingly rare.[42,43]

Total synthesis of dehydrocurvularin: To further scrutinize this notion, we targeted dehydrocurvularin (**27**), a macrolide antibiotic endowed with phytotoxic and nematicidal activity as well as appreciable cytotoxicity.[44] Although this compound is known for decades,[45] no total synthesis has been published,[46,47] even though its saturated sibling curvularin (**26**) had served as a prominent target in the past.[48,49]

Since the enone substructure of **27** is part of a 12-membered ring and hence any cycloalkyne precursor necessarily strained, the macrocyclization by RCAM as well as the rearrangement chemistry are deemed fairly challenging. In fact, additional intelligence had suggested that an approach to dehydrocurvularin via a Meyer–Schuster rearrangement might be stereo-unselective.[50] Therefore we opted for the redox route shown in Scheme 7, which commenced with formylation of the commercial aryl bromide **28** followed by addition of propynylmagnesium bromide and protection of the resulting alcohol with a TBS group. The residual bromide in **30** allowed for the rapid attachment of the entire ester side chain by a palladium-catalyzed enolate arylation reaction. After some experimentation, it was found that this transformation was best achieved by deprotonation of acetate **31** with TMPZnCl·LiCl, followed by palladium-catalyzed cross-coupling of the resulting enolate.[51] Gratifyingly, the resulting diyne derivative **32** could be cyclized in good yield by RCAM, although the somewhat less encumbered complex **6** (Scheme 1), activated in situ on treatment with CH$_2$Cl$_2$ as previously described by our group,[52] had to be used for optimal results.[53] It was necessary to perform the reaction in refluxing toluene; the need for such forcing conditions and a high catalyst loading is ascribed to the very strained and distorted nature of the incipient cycloalkyne **33**.

As evident from the structure in the solid state (Figure 2), the alkyne subunit deviates from linearity; perhaps more consequential is the fact that the bulky −OTBS ether is forced into a pseudo-axial orientation on the macrocyclic frame in order to avoid an even less favorable eclipsing situation with the methoxy group at the α-position of the benzene ring. This particular conformation, which orients the C1−O1 bond almost perpendicularly to the plane of the very electron rich arene, renders the silyl ether an excellent leaving group and lowers the barrier to formation of a highly stabilized carbocation. In any case, attempted deprotection of **33** under standard conditions led to instantaneous decomposition; gratifyingly though, the use of TASF in aqueous DMF allowed the silyl ether to be cleaved in essentially quantitative yield.[54,55] The resulting alcohol is no less sensitive than its silylated precursor, in particular under (Lewis) acidic conditions. As a result, all attempts to engage

Scheme 7. a) DMF, POCl$_3$, 90 °C, then KOH, RT, 91 %; b) propynylmagnesium bromide, THF, 0 °C → RT, 93 %; c) TBSCl, imidazole, DMF, 98 %; d) 3-pentynylmagnesium bromide, CuCN (10 mol %), THF, −78 °C → RT, 97 %; e) Ac$_2$O, Et$_3$N, DMAP (20 mol %), CH$_2$Cl$_2$, 98 %; f) (i) **31**, TMPZnCl·LiCl, THF; (ii) **30**, Pd(OAc)$_2$ (5 mol %), SPhos (10 mol %), THF, 50 °C, 62 %; g) **6** (50 mol %), CH$_2$Cl$_2$, toluene, reflux, 79 %; h) TASF, aq. DMF, 97 %; i) MnO$_2$, CH$_2$Cl$_2$, 77 %; j) CrCl$_2$, THF/H$_2$O (1:1), 71 % (E-**35**, + 7 % of Z-isomer); k) Al, I$_2$, toluene, 90 °C, then **35**, TBAI, toluene, 0 °C, 60 %; DMAP = 4-dimethylaminopyridine; TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate; TBAI = tetra-*n*-butylammonium iodide; TMP = 2,2,6,6-tetramethylpiperidinyl.

this compound into a ruthenium-catalyzed redox isomerization[36] were in vain, despite considerable experimentation. However, the problem could be fixed by an oxidation/reduction sequence,[56] which gave dehydrocurvularin dimethyl ether **35** in good yield and high selectivity (E/Z ≈ 10:1). Cleavage of the methyl groups with AlI$_3$ generated in situ[57] completed the total synthesis of dehydrocurvularin (**27**) in optically pure form (9 steps, longest linear sequence, 13 % overall yield).

Electron deficient enynes—total synthesis of the antibiotic (−)-A26771B: The antibiotic (−)-A26771B, derived from the fungus *Penicillium turbatum*,[58–60] provides an excellent opportunity to explore whether triple bonds conjugated to an electron withdrawing group are amenable to alkyne metathesis. Very little is known about the reactivity of such substrates: whereas two attempted RCAM reactions of alkynoates with the help of the classical Schrock tungsten alkylidyne complex **4** met with failure (see below),[61,62] alkyne cross-metathesis (ACM) reactions of the somewhat less electron-deficient ethyl hex-2-en-4-ynoate with simple alkyne partners proceeded in decent yields when catalyzed by the
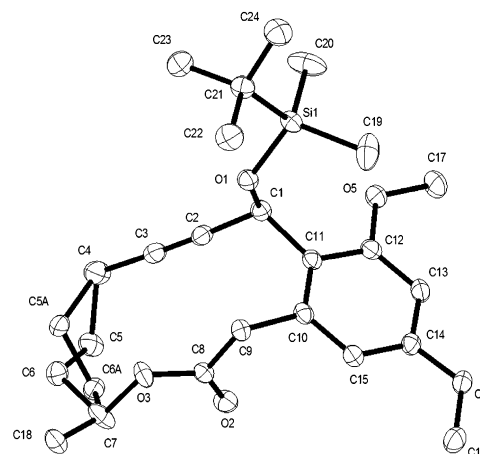

Figure 2. Structure of cycloalkyne **33** in the solid state; the C4–C6 region of the alkyl chain is disordered.[41]

molybdenum–alkylidyne complexes **1–3** endowed with triphenylsilanolate groups.[3] With this precedent in mind, it seemed reasonable to dissect (−)-A26771B at its α-hydroxyketone site, which should be accessible in optically pure form from a precursor with an enyne conjugated to an ester moiety or a surrogate thereof (Scheme 8).
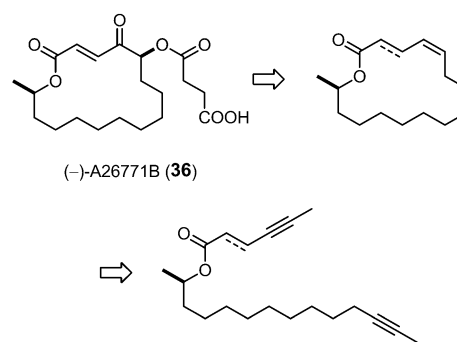
Scheme 8. Retrosynthetic analysis of (−)-A26771B.

The required alcohol component **37** was prepared by a copper-catalyzed ring-opening of optically pure (*R*)-propenoxide with 9-undecynylmagnesium bromide (Scheme 9). Esterificaton with hex-2-en-4-ynoic acid under standard conditions furnished diyne **38**, which reacted without incident on exposure to complex **1** at elevated temperatures. The resulting product, however, was found to be the cyclodimer **39** rather than the desired cyclic monomer. This outcome could not be changed by increasing the dilution; it remained the only detectable product even at 0.0001 M concentration. Compound **39** was formed as a single head-to-tail isomer; this connectivity pattern is evident from the spectral data and was unambiguously confirmed by single crystal X-ray diffraction (Figure 3).

To overcome this pronounced inherent bias, we envisaged the use of an acetylenic aldol motif as surrogate for the enyne moiety (Scheme 10).[63] The appropriate diyne **40**
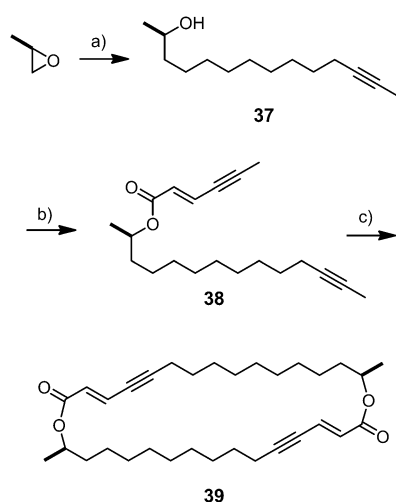
Scheme 9. a) 9-Undecynylmagnesium bromide, CuI (10 mol%), THF, −78°C → RT, 84%; b) hex-2-en-4-ynoic acid, EDCI, DMAP, CH$_2$Cl$_2$, 0°C → RT, 83%; c) **1** (Ar = pMeOC$_6$H$_4$-, 10 mol%), toluene, MS 5 Å, 80°C, 83%; EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

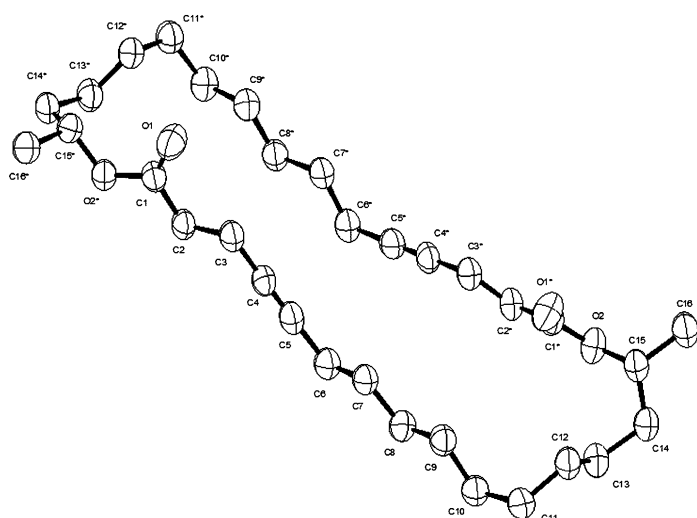Figure 3. Structure of the head-to-tail cyclodimer **39**.[41]

Table 2. Catalyst screening and optimization of the RCAM reaction leading to product **41**.[a]

Entry	Catalyst	T [°C]	t [h]	Conversion [%][c]	41 [%]	Dimer [%][d]
1	**3**[b]	RT	6	93	65	20
2	**3**[b]	80	8	89	78	10
3	**2**	RT	4	>98	72	10
4	**2**	80	3	>98	95	–
5	**1**	RT	1.5	>98	90	6
6	**1**	80	1	>98	92	–

[a] Unless stated otherwise, all reactions were performed with 5 mol% of catalyst in toluene in the presence of MS 5 Å. [b] Using 10 mol% of catalyst which was activated with ZnCl$_2$ (10 mol%) at 80°C for 40 min prior to the addition of the substrate. [c] Determined by ^{1}H NMR of the crude product. [d] According to GC/MS; the exact structure was not determined because the product is a mixture of several diastereomers.
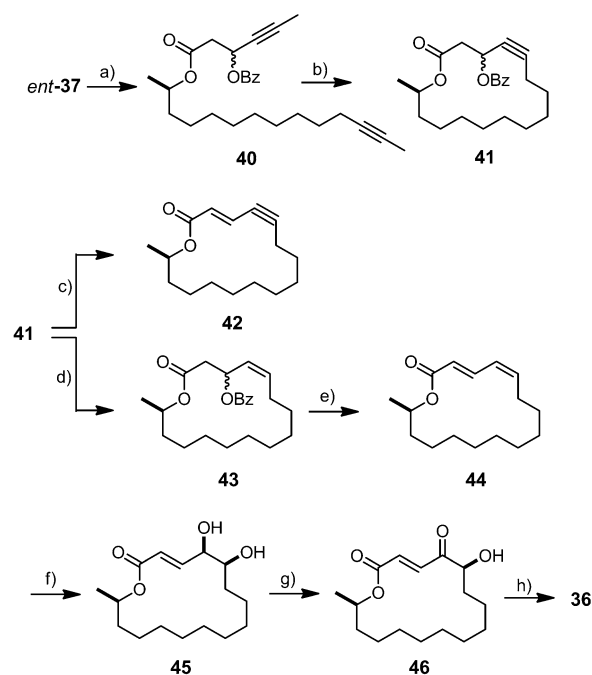

Scheme 10. a) 3-(Benzoyloxy)-hex-4-ynoic acid, DIAD, PPh$_3$, toluene, 98%; b) see Table 2; c) DBU, toluene, 0°C, quant. (E/Z 5:1); d) H$_2$ (1 atm), Lindlar catalyst, quinoline, hexanes, 99%; e) DBU, toluene, RT, 97%; f) AD-mix β, K$_2$OsO$_4$·2 H$_2$O (7 mol%), NaHCO$_3$, methanesulfonamide, tBuOH/H$_2$O (1:1), 0°C, 81% (dr > 95:5); g) TEMPO, pTsOH, CH$_2$Cl$_2$, 62%; h) succinic anhydride, DMAP cat., CH$_2$Cl$_2$, 71%; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DIAD = diisopropyl azodicarboxylate; TEMPO = 2,2,6,6-tetramethylpiperidinyloxyl.

could be cyclized without damaging the labile aldol entity to any noticeable extent. Small amounts of a cyclic dimer were detected in all runs performed at RT, whereas the formation of this by-product could be completely suppressed at higher temperature (Table 2). In line with our expectations, the neutral molybdenum benzylidyne complex **1** bearing three triphenylsilanolate groups was most effective in terms of reaction time and yield.[3] The corresponding ate-complex **2a** (Ar = Ph), which is believed to release the neutral complex **1** in solution,[3] is similarly productive but somewhat slower. The bench-stable adduct **3** (Ar = pMeOC$_6$H$_4$-), after activation with ZnCl$_2$ as an appropriate phenanthroline scavenger,[3] also gave good results, although a higher catalyst loading was necessary.

Elimination of the benzoate group with formation of the corresponding cyclic enyne **42** (E/Z 5:1) proceeded quantitatively on treatment with DBU at 0°C. Although this product potentially opens a route to (−)-A26771B, a more convenient entry was found by subjecting the triple bond to Lindlar reduction[64] prior to benzoate elimination. In this way, diene **44** was secured in isomerically pure form and almost quantitative yield. The subsequent asymmetric dihydroxylation with AD-mix β[65] proceeded with excellent regio- and stereoselectivity; only the less electron-deficient distal olefin

bond got oxidized (d.r. >95:5). The allylic alcohol of **45** could then be selectively converted into the corresponding ketone using TEMPO in acidic medium;[59h] reaction of the remaining hydroxyl group in **46** with succinic anhydride under standard conditions completed this concise and productive total synthesis of (−)-A26771B (**36**) (8 steps from propenoxide, longest linear sequence, 25% overall yield).

Electron deficient alkynes—RCAM of ynoates: To the best of our knowledge, only two attempts were reported at engaging the electron deficient triple bond of an alkynoate into a ring-closing alkyne metathesis reaction. Unfortunately, however, neither the simple diyne **48a** (*n* = 1)[61] nor the much more elaborate substrate **47**[62] could be cyclized on treatment with the classical tungsten alkylidyne complex **4**,[66] which was the benchmark catalyst for many years.

Challenged by this shortfall, we explored whether the new molybdenum alkylidynes endowed with silanolate ligands are more appropriate, since they had proven effective in several challenging cases before.[1,3,7,8,13–16] In fact, treatment of a solution of **48a** (*n* = 1) in toluene at 80°C with **1** (8–10 mol%, unoptimized) furnished the desired product **49a** in respectable 66% yield, together with some head-to-tail cyclodimer,[67] which was easily removed by flash chromatography (Scheme 11). Once again, the product distribution was fairly unresponsive to dilution in the tested concentration range (0.004–0.0005 M). Gratifyingly, the larger homologue **49b** (*n* = 5) was formed under the same conditions as a single compound in excellent yield, with virtually no cyclodimer being detected in the crude mixture. This rewarding outcome may inspire applications to natural product synthesis, as illustrated by the conversion of ynoate *rac*-**50**[38] into cycloalkyne **51** containing an appropriately located silyl ether. After unmasking, the hydroxyl group in **52** is poised for a transannular oxa-Michael addition, which was best effected under the aegis of AuCl₃ in MeOH as an alkynophilic catalyst.[68] Under these conditions, the corresponding ketal **53** is formed in excellent yield
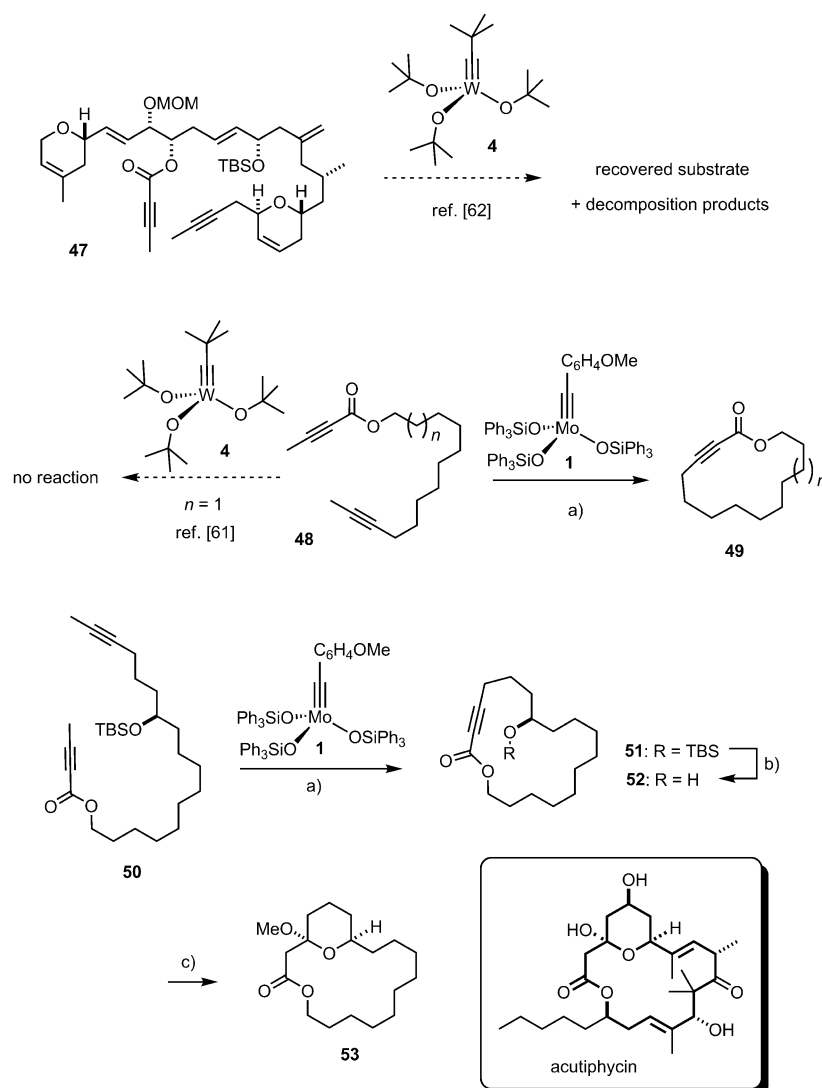
Scheme 11. RCAM reactions of alkynoates: a) **1** (10 mol%), toluene (0.001 M), MS 5 Å, 80°C, 66% (**49a**, *n* = 1, + 23% of cyclic dimer); 92% (**49b**, *n* = 5); 84% (**51**); b) *p*-TsOH (5 mol%), MeOH, 85%; c) AuCl₃ (2 mol%), MeOH, 96%; MOM = methoxymethyl.

as a single diastereomer, which corresponds to the core structure of the potently cytotoxic macrolide acutiphycin.[69]

Electron-rich alkynes and ring-opening/alkyne cross-metathesis: Much like their electron-deficient relatives, electron rich acetylene derivatives have hardly ever been used as substrates for alkyne metathesis.[70] Therefore, a selection of such compounds was prepared and subjected to alkyne cross-metathesis (ACM) reactions in the presence of complex **1** as the arguably most selective catalyst known to date.[3] Although a simple alkynyl ether, -thio ether and sulfur-containing ynamine failed to react under the standard conditions (Figure 4), we were pleased by the good results obtained with a moderately bulky alkynylsilane,[71] -phosphine and -phosphineoxide; even a phosphine-gold complex could be transformed by ACM with 5-decyne without damaging the organometallic entity (Table 3). Furthermore, the
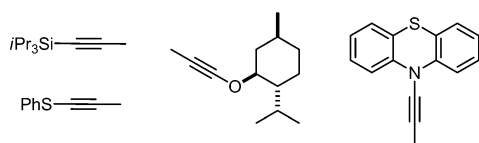
Figure 4. Electron-rich alkynes that were unreactive under the standard conditions.

reactivity of these substrates could be harnessed in an unprecedented mode: whereas ring-closure by RCAM is well established, ring-opening alkyne metathesis has so far been restricted to polymerization reactions.[72] However, entries 3 and 6 illustrate that even a fairly unstrained cycloalkyne undergoes ring-opening/alkyne cross-metathesis when treated with an alkynylsilane or –phosphine in the presence of complex **1**.

Table 3. Alkyne metathesis reactions of electron rich substrates.[a]

Entry	Substrate	Partner	mol%	T [°C]	Product	Yield [%]
1	PhMe₂Si—≡—	PhMe₂Si—≡—	2	RT	PhMe₂Si—≡—SiMe₂Ph	93
2		5-decyne	2	RT	PhMe₂Si—≡—C₄H₉	71
3			10	60		77
4	Ph₂P—≡—	Ph₂P—≡—	2	60	Ph₂P—≡—PPh₂	52
5		5-decyne	2	RT	Ph₂P—≡—C₄H₉	79[b]
6			5	60		36
7		5-decyne	2	RT		67
8		5-decyne	5	RT		92

[a] All reactions were performed with complex **1** (Ar = *p*-MeOC₆H₄-) in toluene in the presence of MS 5 Å. [b] The product contains traces of the corresponding phosphine oxide formed upon air oxidation during work up.

Terminal alkynes: For many years, productive metathesis of terminal acetylene derivatives remained a largely unmet goal because of competing substrate polymerization.[73, 74] Although terminal alkynes react with Schrock alkylidyne complexes by the usual [2+2] cycloaddition mode, the resulting metallacyclobutadienes undergo formal transannular C–H abstraction with formation of a deprotiometallacycle and concomitant loss of one of the ancillary ligands that picks up the released proton.[74, 3b] Recently however, Tamm and co-workers showed that the molybdenum alkylidyne complex **5** (Scheme 1, R = 2,6-dimethylphenyl) endowed with hexafluoro-*tert*-butoxide ligands allows aliphatic terminal al-

kynes to be productively metathesized and competing polymerization to be largely suppressed, provided that even the intermolecular reactions are performed under high dilution.[75, 76]

Although the available dataset is small and further investigations are warranted, one may speculate that the reduced basicity of the fluorinated alkoxide ligands in **5** disfavors the fatal transannular proton abstraction and hence opens a window of opportunity for productive cycloreversion of the metallacyclic intermediate. Under this premise, complex **1** might also qualify as catalyst, since the basicity of silanolates is also significantly lower than that of regular alkoxides.[77] This is in fact the case (Table 4): in line with the results of Tamm et al.,[75] high dilution was necessary to ensure good results even in intermolecular settings; moreover, a rigorously anhydrous reaction medium was mandatory. Therefore all reactions were carried out in the presence of MS 4 Å/5 Å, which are meant to sequester traces of moisture as well as the released acetylene, respectively. Under these conditions, a set of alkyne metathesis reactions of terminal alkyl alkynes were accomplished with appreciable yields that are comparable to the literature results obtained with the fluorinated alkylidyne complex **5**.[75]

Of particular note are the as yet unprecedented cross-metathesis reactions of terminal alkynes with propynyl(trimethyl)silane, which turned out to be particularly productive (entries 6, 7, 12, 15, 16). This transformation represents a new way of introducing a silyl protecting group onto a terminal alkyne, which is compatible with functional groups that might not subsist under conventional silylation conditions.[78]

In contrast, the result for a prototype RCAM reaction was rather disappointing (entry 17), as only a modest yield of the desired macrocycle was secured with **1**, whereas complex **5** was reported to effect this transformation in almost quantitative yield (entry 18).[75] The comparison of entries 17 and 19 is also quite informative, as it shows that the outcome could be significantly improved upon incorporation of a single methyl end-cap.

Overall, these preliminary data are encouraging and further studies to optimize the catalyst design are ongoing. The promising start notwithstanding, the practicality of terminal alkyne metathesis—at the current state of development—does not (yet) rival the robustness of the metathesis of internal alkynes.

Table 4. Metathesis reactions of terminal alkynes.[a]

Entry	Substrate	Partner	Cat.	Product	Yield [%]
1			1		79 (X = H)
2			1		81 (X = OMe)
3			5		92 (X = OMe)[75]
4			1		75 (X = Cl)
5			5		96 (X = Cl)[75]
6		Me₃Si————	1		96 (X = OMe)
7		Me₃Si————	1		94 (X = Cl)
8	RO	RO	1	RO …… OR	74 (R = Bn)
9			1		82 (R = THP)
10			1		67 (R = TBDMS)
11			1		– (R = Ts)[b]
12	THPO	Me₃Si————	1	THPO …… SiMe₃	88
13			1		85 (R = Boc)
14			1		42 (R = Ts)
15		Me₃Si————	1		93 (R = Boc)
16		Me₃Si————	1		91 (R = Ts)
17			1[c]		56
18			5		95[75]
19			1		82

[a] The reactions were performed with 1 mol% of the catalyst in toluene (0.021 M) at ambient temperature in the presence of MS 4 Å and MS 5 Å. [b] Polymerization of the substrate only. [c] With 2 mol% of catalyst; Boc = *tert*-butyloxycarbonyl; Bn = benzyl; TBDMS = *tert*-butyl-dimethylsilyl; THP = tetrahydropyranyl.

Conclusion

The examples presented in this paper illustrate that the structural span of alkyne metathesis in general and ring-closing alkyne metathesis in particular goes far beyond the formation of stereodefined olefins by semi-reduction of the acetylenic products initially formed, which has so far been the most common application.[1,2,79] Specifically, carbophilic catalysts were used to bring a host of important structural motifs into reach, as illustrated by the transannular formation of carbocyclic and heterocyclic aromatic rings, or by the swift access to enones and oxy-Michael adducts thereof. At the same time, the substrate scope has been increased to encompass alkynes that had previously hardly ever been used; this includes secondary propargyl alcohols, alkynoates, enynoates, various types of electron rich triple bonds and even terminal acetylenes. Furthermore, the first examples of ring-opening/alkyne cross-metathesis reactions are disclosed and the use of alkyne cross-metathesis as a novel means of introducing silyl protecting groups to a terminal alkyne substrate is demonstrated. The total synthesis of the antibiotic A26771B and the polyketide dehydrocurvularin, as well as a series of model studies directed toward other bioactive target molecules provide a further glimpse of the preparative potential yet to be harnessed.

Experimental Section

All experimental details can be found in the Supporting Information. The material includes compound characterization, crystallographic abstracts for the X-ray structures of products **25**, **33** and **39**, as well as copies of pertinent NMR spectra.

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R = Me, 89 % (2.45 g scale)
R = Ph, 95 %
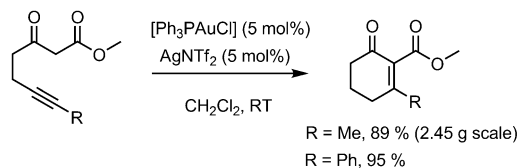
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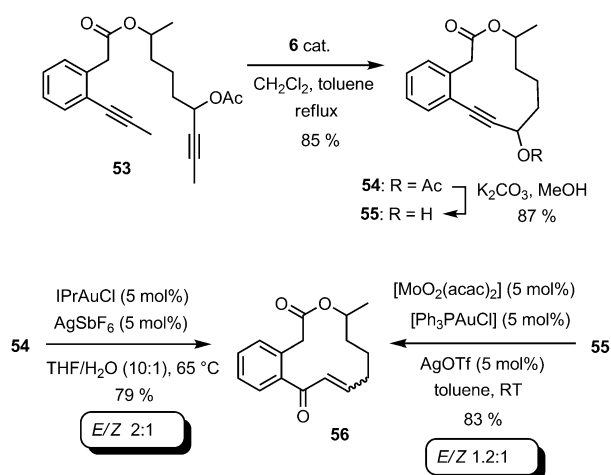
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