Alkyne Metathesis: Development of a Novel Molybdenum-Based Catalyst System and Its Application to the Total Synthesis of Epothilone A and C

Alois Fürstner,* Christian Mathes, and Christian W. Lehmann[a]

Abstract: Sterically hindered molybdenum(III) amido complexes of the general type [Mo{(*t*Bu)(Ar)N}$_3$] (**1**), upon treatment with CH_2Cl_2 or other halogen donors, have been converted into highly effective catalysts for all kinds of alkyne metathesis reactions. Although the actual nature of the propagating species formed in situ is still elusive, halogen transfer to the Mo center of **1** plays a decisive role in the activation of such precatalysts. It was possible to isolate and characterize by X-ray crystallography some of the resulting molybdenum halide derivatives such as **15**, **16** and **20** which themselves were shown to be catalytically active. Numerous applications illustrate the performance of the catalytic system **1**/CH_2Cl_2 which operates under mild conditions and tolerates an array of polar functional groups. The wide scope allows the method to be implemented into the total synthesis of sensitive and polyfunctional natural products. Most notable among them is a concise entry into the potent anticancer agents epothilone A (**86**) and C (**88**). The macrolide core of these targets is forged by ring closing alkyne metathesis (RCAM) of diyne **113**, followed by Lindlar hydrogenation of cycloalkyne **114** thus formed. Since this strategy opens a stereoselective entry into (*Z*)-alkene **115**, the approach is inherently more efficient than previous syntheses based on conventional RCM.

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

Introduction

The tremendous progress in alkene metathesis arguably constitutes one of the most significant advancements in preparative organic chemistry during the last decade.[1] Novel catalysts combining high activity, good durability and an excellent tolerance towards functional groups have upgraded this transformation into a reliable and remarkably powerful tool.[2–5] Most notable is the success of ring closing alkene metathesis (RCM) which provides access to carbo- and heterocyclic products of all ring sizes ≥ 5 as witnessed by a rapidly growing number of elegant applications.[1] In this context, contributions from our laboratory have focussed on the synthesis of medium- and macrocyclic products and have thereby helped to define the utility of RCM in this particular field.[6] During these studies, however, one significant handicap became obvious on several occasions: While RCM generally allows to form large rings with good to excellent yields, the stereochemistry of the newly formed double bond can hardly be predicted or controlled. In many cases, mixtures of both geometrical isomers are obtained, with the (*E*)-alkene usually dominating. Exceptions to this rule, however, are well documented in the literature and subtle changes in the substrates may have serious implications on the stereochemical outcome.[1] The total synthesis of the strongly cytotoxic marine natural product salicylihalamide described in the accompanying paper in this issue illustrates this aspect.[7]

As compared with the prolific use of alkene metathesis, the closely related metathesis of alkynes is still in its infancy.[1b, 8] This may be surprising since this transformation is known for several decades,[9] it has been thoroughly studied from the mechanistic point of view,[10] and holds the promise to solve some of the selectivity issues hampering conventional RCM. Specifically, ring closing alkyne metathesis (RCAM) followed by a Lindlar reduction of the resulting macrocyclic cycloalkynes constitutes a *stereoselective* route to (*Z*)-alkenes as outlined in a recent contribution from this laboratory (Scheme 1).[11]

Scheme 1. Stereoselective synthesis of (*Z*)-alkenes by ring closing alkyne metathesis (RCAM) followed by Lindlar reduction.

The scope of this strategy, however, is intimately related to the performance of the available alkyne metathesis catalysts. Two different types are known to date. The first one is a structurally unidentified species generated in situ from

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$[Mo(CO)_6]$ or related molybdenum sources and phenol additives.[9, 12] This "instant" method is attractive because all ingredients are cheap, commercially available and easy to handle. Moreover, the solvents do not have to be rigorously dried. Despite considerable optimization,[13] however, this system exerts catalytic activity only at rather elevated temperatures ($\geq 130\,^{\circ}C$), restricting its applicability to robust cases.

Alternatively, well defined metal alkylidyne complexes such as $[(t\mathrm{BuO})_3W{\equiv}CC(Me)_3]$ (**2**) and congeners can be used as alkyne metathesis (pre)catalysts.[14, 15] They are fully operative under rather mild conditions and their behavior is well understood at the molecular level.[10, 14] In fact, complex **2** enabled the first RCAM reactions to be reported[11] and has been successfully employed for natural product syntheses as well.[16–20] Although this catalyst tolerates many functional groups,[21] limits are encountered if thio ethers, amines or crown ether segments are present in the substrates. Such donor sites suppress the catalytic activity of **2**, most likely by coordination onto its high valent tungsten center.

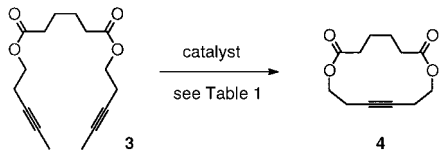
To improve the scope of alkyne metathesis further, we have started a program searching for alternative catalysts. In this context, sterically hindered trisamido molybdenum(III) complexes of the general type $[Mo\{(t\mathrm{Bu})(Ar)N\}_3]$ (**1**) were found to exhibit a truly remarkable application profile. Outlined below is a full account of our work in this field.[22] In addition to a systematic study of this novel catalyst system, its application to the total synthesis of the promising anticancer agents epothilone A and C is reported which illustrates the relevance of this methodology for advanced organic synthesis.[23]

Results and Discussion

Optimized synthesis and activation of $[Mo\{(t\mathrm{Bu})(Ar)N\}_3]$: In a series of spectacular papers, Cummins et al. have reported investigations into monomeric trisamidomolybdenum complexes of the general type $[Mo\{(t\mathrm{Bu})(Ar)N\}_3]$ (**1**) which react with elemental sulfur, selenium, phosphorous, CO, NO, N_2O etc. in a stoichiometric fashion.[24] Most remarkable, however, is their capacity to cleave molecular nitrogen at or below room temperature.[24, 25]

Impressed by these results, we investigated the yet unknown reactivity of such complexes towards organic substrates, hoping that it might be possible to use them in only catalytic amounts. Although **1a** (Ar = 3,5-dimethylphenyl) did not react with alkynes such as **3** in toluene or other hydrocarbon solvents even at elevated temperatures, we were pleased to find that an efficient and rapid alkyne metathesis took place in toluene at 70–80 °C, provided that the catalyst was activated with CH_2Cl_2 or related halogen sources (≥ 5 equiv with respect to Mo, cf. Scheme 2 and Table 1).[22] CH_2Cl_2 can also be used as the solvent; in this case, the conversion was somewhat slower, most likely because of the lower temperature that can be reached in this medium.

These promising results prompted us to investigate this system in more detail. For this purpose an improved synthesis of the required molybdenum complexes **1** was necessary.



Scheme 2. Model reaction for RCAM.

Table 1. Screening of the catalytic performance of complex **1a** (10 mol %) in the presence of various additives for the cyclization of diyne **3** to cycloalkyne **4**.

Entry	Solvent	Additive [equiv]	t [h]	Yield [%]
1	toluene	–	24	–
2	toluene	CH_2Cl_2 (25)	7	81
3	toluene	CH_2Cl_2 (5)	7	80
4	toluene	CH_2Cl_2 (2)	7	–
5	toluene	CH_2Br_2 (25)	7	84
6	toluene	CH_2I_2 (25)	7	84
7	toluene	$C_6H_5CH_2Cl$ (25)	10	81
8	toluene	$C_6H_5CHCl_2$ (25)	10	78
9	toluene	Me_3SiCl	10	75
10	CH_2Cl_2	–	24	80
11	$CHCl_3$	–	24	82
12	CCl_4	–	24	70

These were prepared by reaction of $[MoCl_3(thf)_3]$ with the lithium salt of a suitable secondary amine (tBu)(Ar)NH under carefully controlled reaction conditions.[26, 27] While the access to $[MoCl_3(thf)_3]$ is fairly routine and well described in the literature,[28] a high yielding and flexible entry into the required bulky amines was crucial. The palladium catalyzed amination of aryl halides turned out to be the method of choice.[29, 30] Specifically, *tert*-butyl-3,5-dimethylphenylamine **7a**, required for the preparation of the parent complex **1a**, was obtained in 86 % isolated yield on a multigram scale from **6** and $t\mathrm{BuNH}_2$ if the sterically encumbered phosphine **5** was used as the ligand to palladium.[31, 32] In cases of amines **9a** and **11a**, the use of BINAP as the ligand also gave satisfactory results (Scheme 3).[33]

The amines thus obtained were deprotonated with nBuLi to afford lithium amides **7b**, **9b**, **11b**, and **13b** as colorless solids. Crystals of amide **11b** were suitable for X-ray analysis. Figure 1 shows that this compound is dimeric in the solid state with the aryl- and the *tert*-butyl groups being oriented towards the opposite sides of the plane defined by the Li and N atoms. The coordination sphere of each of the lithium cations is completed by an Et_2O molecule occupying the less crowded aryl side of the Li-N-Li-N plane.

The reaction of these lithium amides with $[MoCl_3(thf)_3]$ was found to be highly dependent on their substitution pattern. While **7b** or **9b** afforded the expected trisamido complexes **1a** and **1b**[65] in high yield,[24] amides **11b** and **13b** deviated from the expected path. The former provides the difluoromolybdenum(v) species **14**, albeit in low yield (ca. 5 %);[34] the latter lead to the Mo^{IV} chloride **15** as the only product that could be isolated from the crude mixture in 30 % yield by fractional crystallization.

The previously unknown paramagnetic complex **15** was unambiguously characterized by X-ray crystallography (Figure 2). The chloride and the three bulky amido ligands form a

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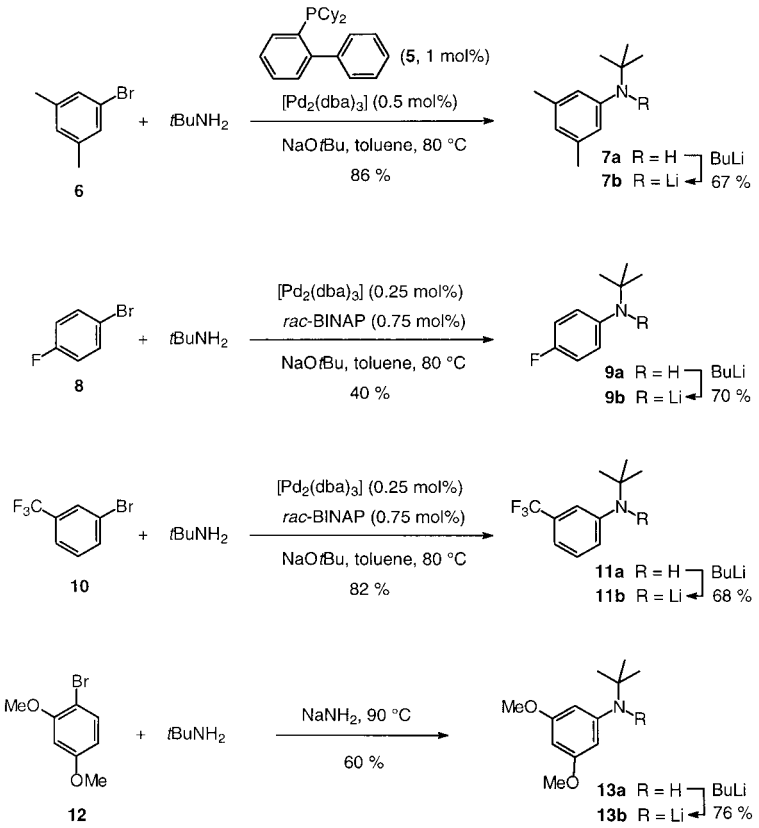
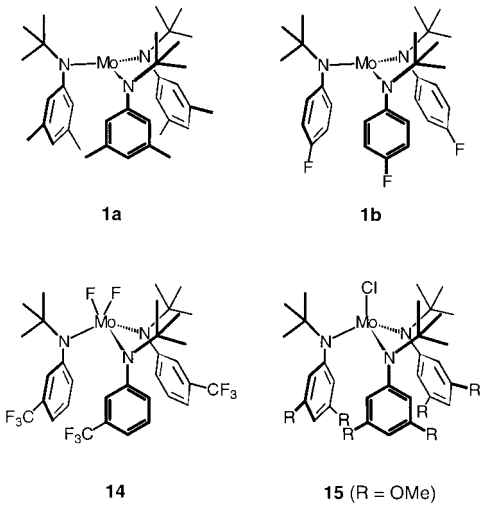


Scheme 3. Preparation of (*t*Bu)(Ar)NH and the lithium salts derived thereof.



MS and NMR spectroscopic investigations of the rather sensitive residue indicated the presence of several molybdenum species; the major ones present in a ratio of about 1:2 were the terminal alkylidyne complex [HC≡Mo{(*t*Bu)(Ar)N}$_3$] (**17**) and paramagnetic [ClMo{(*t*Bu)(Ar)N}$_3$] (**16**), which is analogous to complex **15** described above. Although it is difficult to separate these products by crystallization, both of them were accessible in pure form by independent routes. Thus, methylidyne **17** could be prepared by a sequence previously outlined by Cummins.[35] Complex **16** and its bromo analogue **18**, on the other hand, were available on treatment of a solution of **1a** in ether with Cl_2 or Br_2, respectively.[36] An X-ray analysis of **16** showed the close packing of the amido ligands on one side of this molecule (Figure 3). Unlike **15**, the aryl rings adopts approximately three-fold symmetry in this case. Thereby a pocket is formed around the Mo center which shields the central metal quite efficiently. This congested arrangement may explain some of the favorable chemical properties of this compound (see below).

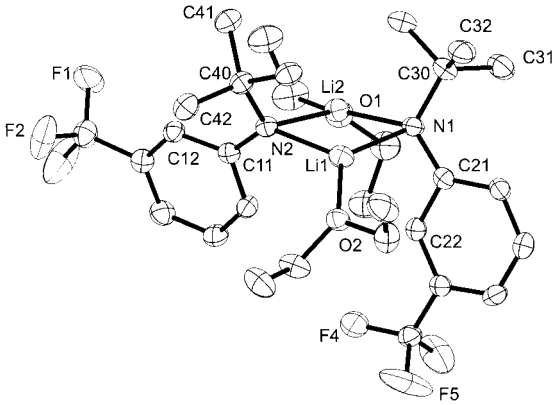


Figure 1. Molecular structure of complex **11b**. Anisotropic displacement parameters are drawn at 50 % probability, hydrogen atoms are omitted for clarity. Selected bond lengths in Å and bond angles in °. Li2–N1 2.036(4), Li1–N2 2.017(4), C21–N1–C30 119.76(16), C11–N2–C40 118.81(16). Mean deviation from plane defined by Li1, Li2, N1, N2 0.089 Å.

distorted tetrahedral arrangement around the strongly shielded metal center. The *tert*-butyl groups are oriented towards the chloride, whereas the three aryl rings block the reverse side of the complex. Two of these aryl rings are parallel to each other within 12° with a $\pi-\pi$ distance of 3.48 Å; the third aryl ring is perpendicular within 0.3°.

Having secured a high yielding access to **1a** as the parent compound of this series (70 % from **7b**), the role of CH_2Cl_2 in the activation of this complex was investigated. For this purpose, a sample of **1a** was dissolved in this solvent and all volatiles were evaporated after the endothermic reaction had ceased (Scheme 4).

If the activation of **1a** by CH_2Cl_2 was carried out in the presence of an alkyne, an even more puzzling redox chemistry ensues. Specifically, reactions of **1a** with 1-methoxy-2-propynylbenzene in toluene/CH_2Cl_2 were allowed to proceed for 5 min at 80 °C and were then abruptly chilled to –20 °C. From

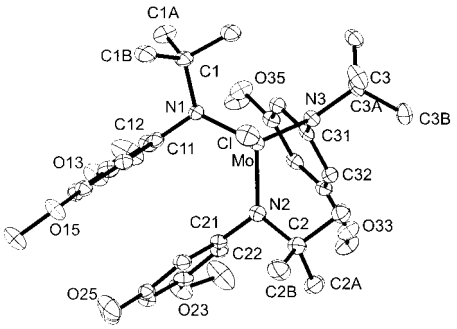
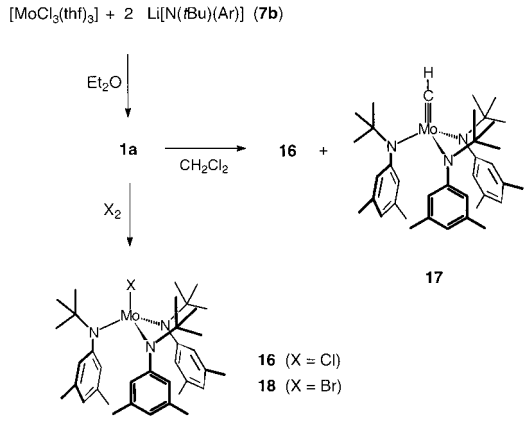


Figure 2. Molecular structure of complex **15**. Anisotropic displacement parameters are drawn at 50% probability, hydrogen atoms are omitted for clarity. Selected bond lengths in Å and bond angles in °. Mo–N 1.959(4), Mo–Cl 2.325(2), Cl–Mo–N1 100.9(1), Cl–Mo–N2 98.23(9), Cl–Mo–N3 126.5(1).



Scheme 4. Preparation of complex **1a** and its reactions with halide donors.

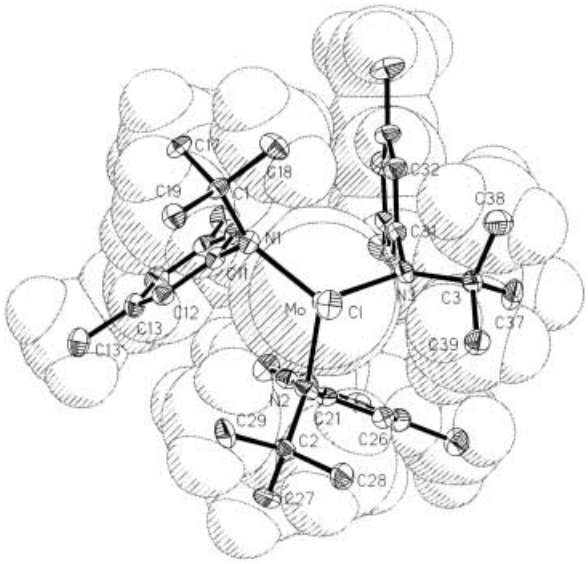
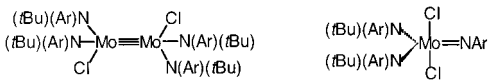


Figure 3. Molecular structure of complex **16**. Anisotropic displacement parameters are drawn at 50% probability, hydrogen atoms are omitted for clarity. A space filling model is superimposed to illustrate the steric shielding of the Mo atom. Selected bond lengths in Å and bond angles in °. Mo–N 1.959(3), Mo–Cl 2.349(1), Cl–Mo–N1 97.36(10), Cl–Mo–N2 102.66(10), Cl–Mo–N3 101.21(10).

various samples prepared in such a way, we were able to obtain crystals of two novel compounds, that is the dimeric complex **19** (Ar = 3,5-dimethylphenyl) and the Mo^{VI}-imido species **20**, both of which were characterized by X-ray crystallography. Unfortunately, however, none of them contains a fragment derived from the alkyne substrate, and the pathway leading to their formation is open for speculation.



As can be seen from Figure 4, the dimeric complex **19** is situated on a crystallographic inversion center. The Mo–Mo bond in **19** can be formally described as a triple bond.[37] The Mo–Mo bond length of 2.272(1) Å is about 0.06 Å longer than the average Mo≡Mo bond extracted from the Crystallographic Structural Database.[38] This bond lengthening can be explained by steric repulsion of the bulky amido substituents, illustrated by the increased *t*Bu–N–Mo angles and N–Mo π bonding. Both N(*t*Bu)(Ar) groups are approximately planar and these planes are parallel within 13.1° (N3) and 23.6° (N1) to the Mo–Mo axis.

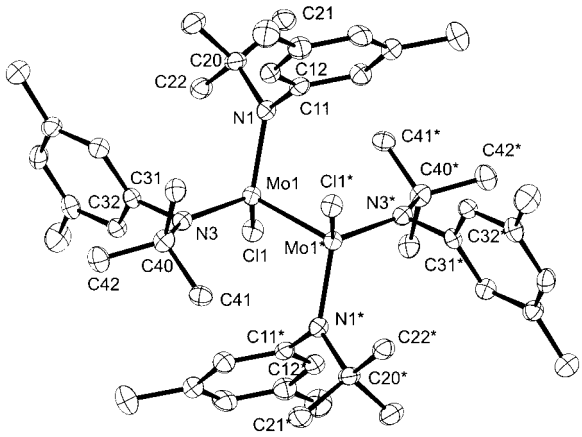


Figure 4. Molecular structure of complex **19**. Anisotropic displacement parameters are drawn at 50% probability, hydrogen atoms are omitted for clarity. Selected bond lengths in Å and bond angles in °. Mo–N1 1.982(11), Mo–Cl 2.353(32), Cl1–Mo1–N1 116.59(11), Cl1–Mo1–N3 114.95(9).

The molybdenum center in **20** (Figure 5) is surrounded by two chlorine and three nitrogen atoms, with the former occupying the axial sites of the trigonal-bipyramidal complex.

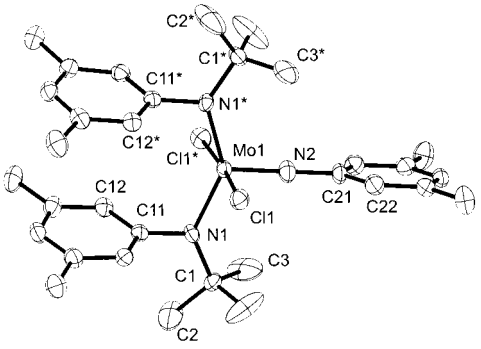


Figure 5. Molecular structure of complex **20**. Anisotropic displacement parameters are drawn at 50% probability, hydrogen atoms are omitted for clarity. Selected bond lengths in Å and bond angles in °. N1–Mo1 1.939(3), N2–Mo1 1.695(4), Mo1–Cl1 2.444(3), N1–Mo1–N2 110.55(8), N1–Mo1–N1* 138.90(12).

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The bond length of 1.69 Å between Mo and N2 is consistent with an imide formed by loss of the *tert*-butyl group which had originally been present at this site. Complex **20** is situated on a crystallographic two-fold axis. Two aryl rings face each other in a parallel fashion (1.6°) with a $\pi-\pi$ interplanar distance of 3.71 Å.

Searching for the active species: The catalytic competence of all novel molybdenum species was studied in the model reaction **3** → **4** (Scheme 2). The results are compiled in Table 2 and deserve some comments.

Table 2. Screening of the catalytic performance of various molybdenum complexes (10 mol% each) for the cyclization of diyne **3** to cycloalkyne **4**. All reactions were carried out in toluene at 80 °C unless stated otherwise; Ar = 3,5-dimethylphenyl.

Entry	Complex	Yield [%]
1	[HC≡Mo{N(Ar)(*t*Bu)}$_3$] (**17**)[a]	38
2	[{(*t*Bu)(Ar)N}$_2$ClMo≡MoCl{N(*t*Bu)(Ar)}$_2$] (**19**)	–
3	[F$_2$–Mo{N(C$_6$H$_4$CF$_3$)(*t*Bu)}$_3$] (**14**)	48
4	[Cl–Mo{N(Ar)(*t*Bu)}$_3$] (**16**)	70
5	[Br–Mo{N(Ar)(*t*Bu)}$_3$] (**18**)	79
6	[Cl–Mo{N(C$_6$H$_3$(OMe)$_2$)(*t*Bu)}$_3$] (**15**)	51
7	[Mo{N(C$_6$H$_4$F)(*t*Bu)}$_3$] (**1b**)[b]	79
8	[{(*t*Bu)(Ar)N}$_2$Cl$_2$Mo=NAr] (**20**)[c]	90

[a] Using 35 mol% of complex **17**. [b] This complex was activated with CH_2Cl_2 (25 equiv). [c] The reaction was performed at ambient temperature using only 5 mol% of complex **20**.

With the established mechanism for alkyne metathesis involving metal carbynes and metallacyclobutadienes in mind,[10] it is rather surprising that the terminal alkylidyne **17** was only poorly effective (entry 1). The yield of **4** was in the same range as the chosen catalyst loading; this indicated that complex **17** was virtually inactive after one turn-over. This result may be explained by the known propensity of terminal alkylidynes to suffer ligand loss along the reaction pathway.[14, 39]

The dimeric molybdenum complex **19** turned out to be totally ineffective (entries 2 and 3), although the Mo≡Mo bond might be considered a suitable site for the initiation of the reaction.[40] This failure is in accordance with the finding that the related complex [(Me$_2$N)$_3$Mo≡Mo(NMe$_2$)$_3$][41] is also unable to effect the alkyne metathesis of substrate **3**.

In striking contrast, however, all molybdenum halide species catalyzed the cyclization of diyne **3** to cycloalkyne **4** (entries 3–7).[42] Complex **16** and its bromo analogue **18** were particularly active, while the analogous complex **15** bearing methoxy substituents on the arene rings as well as the difluoro complex **14** were somewhat less productive. The yields obtained with **16** or **18** were almost as high as that obtained in the experiment carried out with the "in situ" mixture comprising **1a** and CH_2Cl_2 (cf. Table 1, entry 2).

The highest activity of all complexes screened is displayed by the Mo^{VI} species **20** (entry 8). This complex afforded the desired product **4** in 90% isolated yield even if the reaction was performed at *ambient* temperature, whereas all other reactions required heating of the mixture to 70–80 °C.

Although the experiments summarized above do not provide the desired insight into the reaction pathway and the actual nature of the propagating species, they illustrate i) that structurally quite diverse molybdenum halides of different oxidation states are able to trigger a catalytic alkyne metathesis manifold, and ii) that compounds of this type exhibit a rich yet hardly understood redox chemistry and deserve detailed mechanistic studies in the future.

Ring closing alkyne metathesis—Model studies: For the sake of convenience, all preparative investigations have been carried out using complex **1a** as the most readily accessible member of this family, which was activated in situ by means of CH_2Cl_2. A set of representative RCAM reactions is compiled in Table 3, which reveal the truly remarkable scope of this new protocol.

Most importantly, the system **1a**/CH_2Cl_2 was fully operative in the presence of functional groups such as thio ethers, crown ether segments, or amines which completely inactivate the tungsten alkylidyne catalyst [(*t*BuO)$_3$W≡CC(Me)$_3$] (**2**) previously used (cf. entries 3–5). This favorable property is tentatively ascribed to the crowded coordination sphere around the molybdenum center of the (pre)catalyst which likely attenuated its effective Lewis acidity and prevents coordination of potential donor sites to the catalytically active metal template.

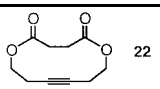
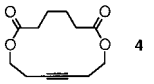
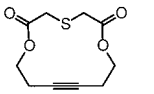
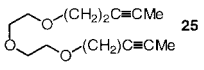
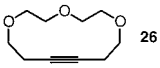
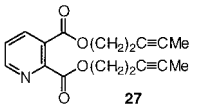
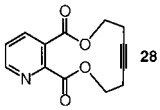
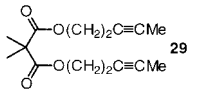
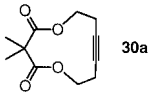
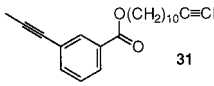
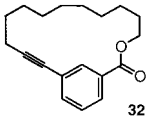
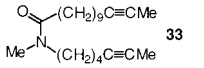
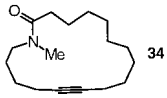
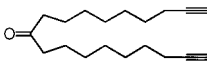
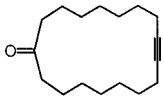
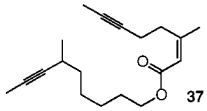
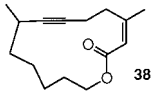
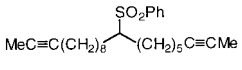
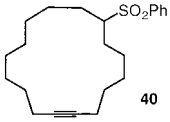
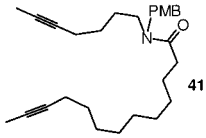
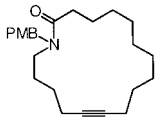
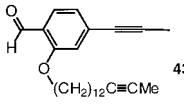
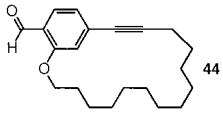
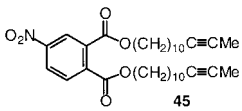
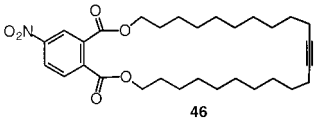
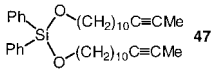
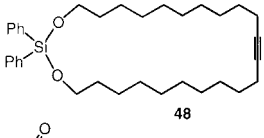
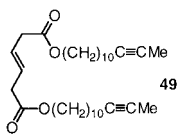
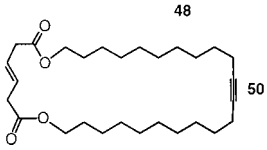
In addition to this remarkable compatibility with soft donors, our studies have revealed that **1a**/CH_2Cl_2 tolerates even unprotected aldehydes, nitro groups, esters, ethers, ketones, sulfones, silyl ethers, acetals, nitriles, sulfonamides, glycosides,[45] alkyl chlorides, and trifluoromethyl groups. Furthermore, entries 10 and 16 illustrate that double bonds remain intact, irrespective of whether they are conjugated or not. Limits, however, were encountered with substrates containing acidic protons (alcohols, acids etc.); even the protons of a secondary amide may suffice to inactivate the catalyst. Tertiary amides, in contrast, posed no problem (entries 8 and 12).

All ring sizes ≥ 12 were formed in good to excellent yields, including very large systems. Cyclization of diyne **29**, however, afforded significant amounts of the cyclodimeric product **30b** in addition to the desired 11-membered monomer **30a** (entry 6). This is ascribed to the high ring strain that has to be built into this particular product. The X-ray structure of compound **32** shows that the alkyne group is strained even if incorporated into a larger ring, as the C3′–C12≡C11–C10 entity in this product clearly deviated from linearity (Figure 6).

Alkyne homodimerization: The broad scope and the excellent compatibility of the new procedure were also evident from the alkyne homodimerization experiments (Scheme 5) summarized in Table 4.[43] Whereas the traditional protocol for alkyne metathesis using [Mo(CO)$_6$] and phenol additives performed rather poorly or even failed completely,[13b,c] complex **1a** activated with CH_2Cl_2 converted propynylated arenes into the desired products in good yields in all but one cases.

Alkyne cross metathesis (ACM): An even larger set of substrates was subjected to alkyne cross metathesis (Table 5),[43] a reaction manifold that had hardly been explored so

Table 3. RCAM reactions catalyzed by complex **1a** activated with CH_2Cl_2. All reactions were carried out in toluene at 80 °C.

Entry	Substrate	Product	Yield [%]
1	$[MeC{\equiv}C(CH_2)_2OOC(CH_2)]_2$ (**21**)	 **22**	91
2	$[MeC{\equiv}C(CH_2)_2OOC(CH_2)_2]_2$ (**3**)	 **4**	81
3	$S[CH_2COO(CH_2)_2C{\equiv}CMe]_2$ (**23**)		84
4	 **25**	 **26**	60
5	 **27**	 **28**	88
6	 **29**	 **30a**	45[a]
7	 **31**	 **32**	83
8	 **33**	 **34**	72
9	 **35**	 **36**	70
10	 **37**	 **38**	63
11	 **39**	 **40**	72
12	 **41**	 **42**	67
13	 **43**	 **44**	75
14	 **45**	 **46**	69
15	 **47**	 **48**	74
16	 **49**	 **50**	82

[a] In addition to the cyclic monomer **30a**, the cyclic dimer **30b** is obtained in 40% yield.

far. All of them afforded the desired products in respectable yields if exposed to a slight excess (1–1.5 equiv) of an aliphatic alkyne as the reaction partner; the latter can be symmetrical (entries 1–12) or unsymmetrical (entry 13). It is particularly noteworthy that even C-silylated alkynes can be employed, although such substrates were beyond the scope of alkyne metathesis so far (entries 10–12).

Applications to natural product synthesis: Despite the fact that some crucial inorganic and organometallic aspects of the present catalyst system for alkyne metathesis remain obscure, the excellent application profile of **1a**/CH_2Cl_2 revealed by the model studies summarized above suggested that applications to more challenging targets are feasible. In fact, several total syntheses of bioactive target molecules have been successfully based upon the favorable properties of **1a**/CH_2Cl_2. The key steps are displayed in Table 6.

This includes a particularly flexible entry into prostaglandins and analogues either by RCAM (entry 2) or ACM (entry 3),[44] as well as the first total synthesis of the complex glycoconjugate sophorolipid lactone **81** (entry 1).[45] In all cases the alkynes originally formed (i.e., **80**, **82**, **84**) were converted into the targeted (*Z*)-alkenes **81**, **83** and **85**, respectively, in a stereoselective fashion by subsequent Lindlar reductions.

Total synthesis of epothilone A and C: This success prompted us to extend our studies even further[23] by targeting members of the epothilone family, 16-membered macrolides isolated from the myxobacterium strain *Sorangium cellulosum 90*.[46] The seminal discovery that these natural products share a common mechanism of action with paclitaxel (Taxol) but exert activity even against various paclitaxel-resistant cell lines has spurred consid-

0947-6539/01/0724-5304 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 24

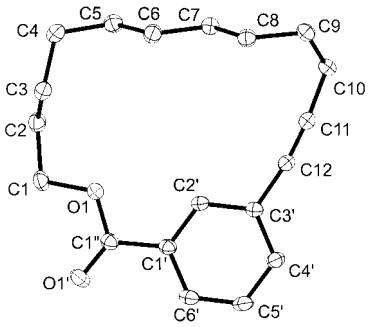
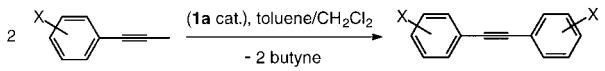
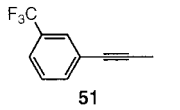
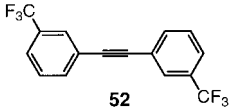
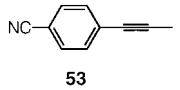
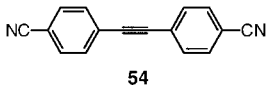
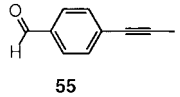
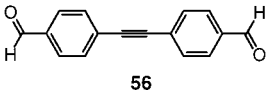
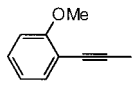
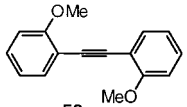
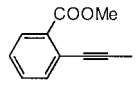
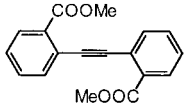
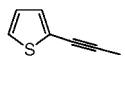
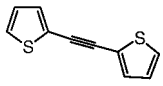


Figure 6. Molecular structure of cycloalkyne **32**. Anisotropic displacement parameters are drawn at 50% probability, hydrogen atoms are omitted for clarity. Selected bond angles in °: C10–C11–C12 173.74(13), C11–C12–C3′ 171.75(13).



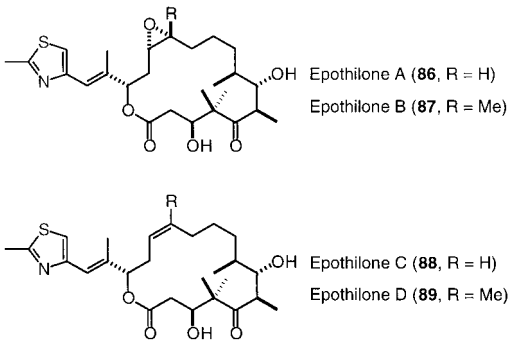
Scheme 5. Alkyne homodimerization.

Table 4. Alkyne homodimerization reactions catalyzed by complex **1a** (10 mol%) activated with CH_2Cl_2. Comparison with the results obtained in a reaction catalyzed by $[Mo(CO)_6]$ activated by *p*-chlorophenol (30 mol%) in 1,2-dichlorobenzene at 140 °C.

Entry	Substrate	Product	Yield [%] $[Mo(CO)_6]$	Yield [%] **1a**
1	 **51**	 **52**	14	59
2	 **53**	 **54**	15	58
3	 **55**	 **56**	0	46
4	 **57**	 **58**	0	68
5	 **59**	 **60**	0	76
6	 **61**	 **62**	0	0

erable drug development programs worldwide.[47] Therefore **86**–**89** and congeners became the focal point of many preparative studies aiming at their total synthesis as well as at a synthesis-driven mapping of the structure/activity profile of these important lead compounds.[48]

In this context it is remarkable that the first three successful entries into these compounds were based on ring closing alkene metathesis (RCM) for the formation of the 16-membered core.[49–51] Product **91** thus formed can be selectively epoxidized at the $\Delta^{12,13}$ bond and hence constitutes an excellent precursor for epothilone A (**86**) (Scheme 6). Although these studies were early highlights showing the enormous potential of RCM for advanced organic synthesis, they *invariably suffered from the fact that there was little—if any—selectivity in favor of the required (Z)-alkene* (*Z*)-**91** (Table 7). As this serious problem arose only towards the very end of rather laborious sequences and since the isomeric alkenes could not be readily separated at this stage, it is hardly surprising that subsequent total syntheses of **86** were largely based on strategies other than RCM that ensure better control over all structural elements of this target.[52, 53]

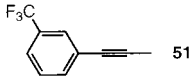
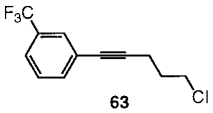
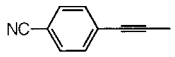
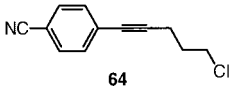
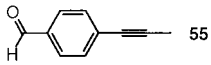
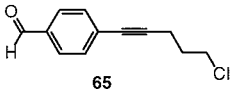
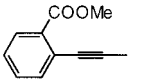
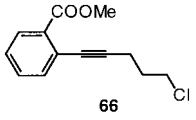
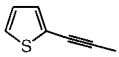
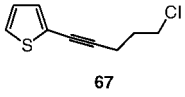
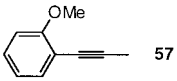
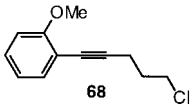
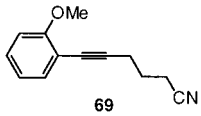
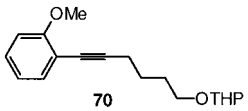
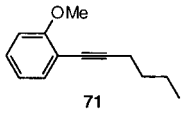
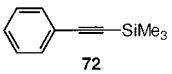
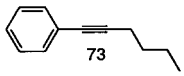
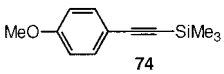
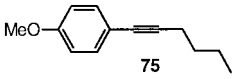
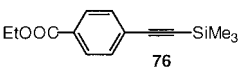
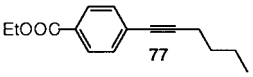
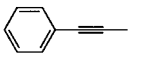
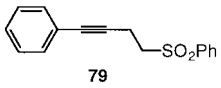


These notions, however, render the epothilones a particularly suitable and relevant testing ground to probe our concept for the stereoselective preparation of (*Z*)-alkenes by RCAM followed by Lindlar reduction. Moreover, the presence of a basic N as well as an S atom in their thiazole ring provides a stringent test for the functional group tolerance of the novel molybdenum-based catalyst.

We envisaged to assemble the targets as shown in Scheme 7. Earlier studies have revealed that the selectivity gained in the formation of the three contiguous stereocenters at C-6, C-7, and C-8 by an aldol reaction strongly depends on the remote functionalization of the enolate partner.[48, 54] The best results were obtained with ethyl ketone **98** bearing a conformationally rigid and chelating 1,3-dioxane unit as control element.[51] Therefore, our first interim goal was to develop an improved and shorter entry into this key building block.

Our synthesis started from commercially available 3-hydroxy-propionitrile **92** which reacted with the zinc enolate derived from bromoester **93** to afford ketoester **94** in 71% yield on a multigram scale (Scheme 8). This Reformatsky-type reaction is best carried out with the assistance of ultrasound.[55] Silylation of **94** with *tert*-butyldiphenylsilyl chloride under standard conditions followed by an asymmetric hydrogenation of **95** catalyzed by $[((S)\text{-BINAP})RuCl_2]\cdot NEt_3$ in the presence of Dowex (H^+ form) to ensure acidic conditions delivered the unprotected diol **96** in high enantiomeric purity (*ee* 94%).[56, 57] The need to perform this reduction under slightly acidic conditions determined the choice of the protecting group for the primary alcohol; the TBDPS group turned out to be optimal, whereas the TBS ether was found to be too unstable. It is also noteworthy that all attempts to perform the reduction directly with the unprotected substrate **94** resulted in rather poor conversion.

Table 5. ACM reactions between propynylated arenes and aliphatic alkynes (1.5 equiv) catalyzed by **1a** (10 mol %). All reactions were carried out in toluene/CH_2Cl_2 at 80 °C.

Entry	Substrates	Product	Yield [%]
1	1,8-dichloro-4-octyne	 **51**	 **63**	70
2		 **53**	 **64**	70
3		 **55**	 **65**	47
4		 **59**	 **66**	62
5		 **61**	 **67**	55
6		 **57**	 **68**	67
7	1,8-dicyano-4-octyne	**57**	 **69**	82
8	1,10-tetrahydropyranyloxy-5-decyne	**57**	 **70**	68
9	5-decyne	**57**	 **71**	72
10		 **72**	 **73**	55
11		 **74**	 **75**	60
12		 **76**	 **77**	65
13	benzosulfonyl-pent-3-yne	 **78**	 **79**	71

Acetalization of **96** followed by reaction of the resulting product **97** with EtMgBr in toluene in the presence of NEt_3 affords compound **98** in excellent overall yield. The presence of the base during the addition of the Grignard reagent to the ester is essential, as it enolizes the ketone primarily formed and thereby avoids the formation of the corresponding tertiary alcohol by addition of a second equivalent of EtMgBr.[58]

Reaction of the lithium enolate derived from **98** with aldehyde **101** afforded aldol **102** in 70% yield with good selectivity (d.r. = 7:1, HPLC) which was easily separated from the minor diastereomer by flash chromatography (Scheme 9). Aldehyde **101** required for this aldol reaction was readily available by exploiting the excellent facial guidance exerted by Oppolzer's bornane sultam in the alkylation of substrate **99** (d.r. = 96:4).[59] Further elaboration of **102** by deprotection of the acetal, per-silylation of the resulting triol **103**, and regioselective cleavage of the primary TBS ether in **104** was performed in analogy to literature routes.[50, 51] Oxidation of the resulting alcohol **105** with PDC in DMF smoothly

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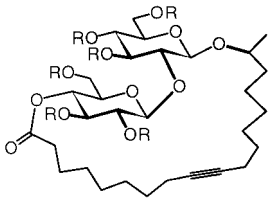
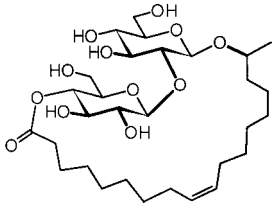
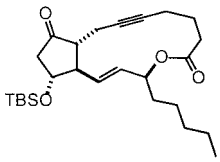
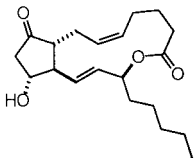
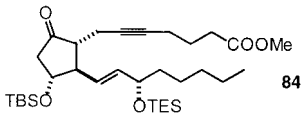
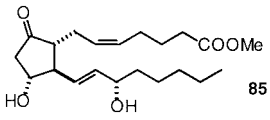
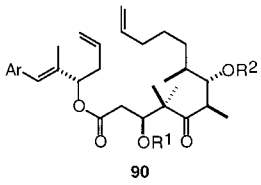
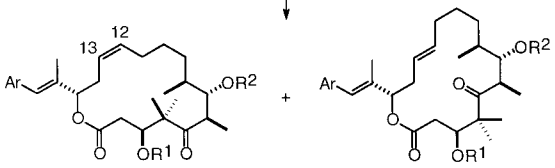
Table 6. Previous applications of RCAM or ACM to the total synthesis of natural products.

Alkyne product	Yield [%]	Target	Ref.
 **80**	78	 **81**	[45]
 **82**	73	 **83**	[44]
 **84**	51	 **85**	[43]



90

RCM



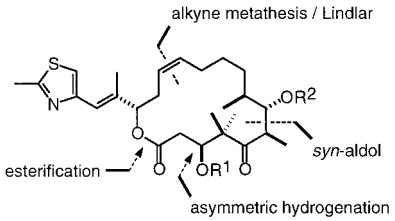
(*Z*)-**91** (*E*)-**91**

Scheme 6. RCM approaches towards epothilone A and C.

Table 7. RCM approaches towards epothilone A and C: Cyclization of dienes **90** invariably leads to the formation of (*E*,*Z*)-mixtures of cycloalkene **91** (Ar = 2-methyl-4-thiazolyl).

Catalyst[a]	R^1	R^2	Yield [%]	*Z*:*E*	Ref.
[Ru][a]	TBS	TBS	86	1.7:1	[49b]
	TBS	TBS	94	1:1	[51a]
	TBS	TBS	81–85	1.5:1	[53]
	TBS	H	85	1.2:1	[50b]
	H	H	65	1:2	[49b]
[Mo][b]	TBS	TBS	86	1:2	[49b]

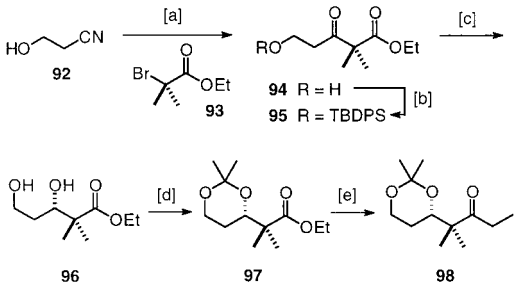
[a] [Ru] = [$(PCy_3)_2(Cl)_2Ru$=CHPh]. [b] [Mo] = [Mo(=NAr)(=$CHCMe_2Ph$)-[$OCMe(CF_3)_2]_2$].



Scheme 7. Retrosynthetic analysis of epothilone C.

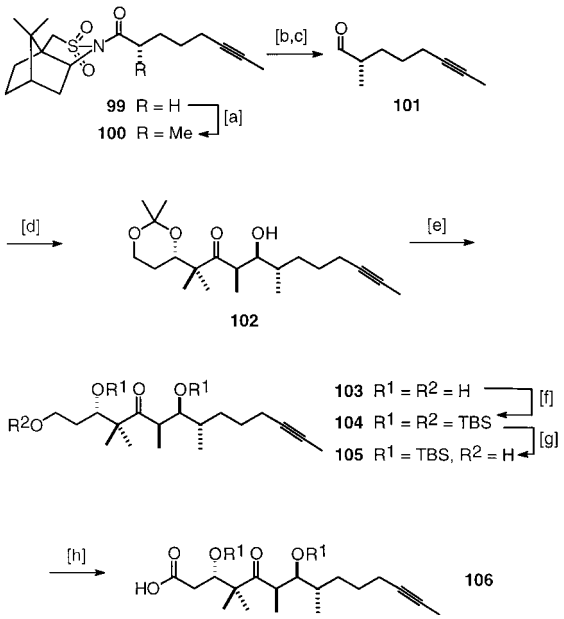
afforded the desired carboxylic acid **106** ready for esterification with a suitable thiazole fragment.

The preparation of the latter involved the allylation of known aldehyde **107** with (+)-Ipc_2B(allyl)[60] followed by silylation of the crude material with TBSCl and imidazole (Scheme 10).[50] These reactions delivered the homoallyl alcohol derivative **108** in 89% yield in excellent enantiomeric excess (*ee* > 97%). Oxidative cleavage of its terminal double bond afforded the somewhat unstable aldehyde **109** which was immediately used for a subsequent Corey–Fuchs reac-



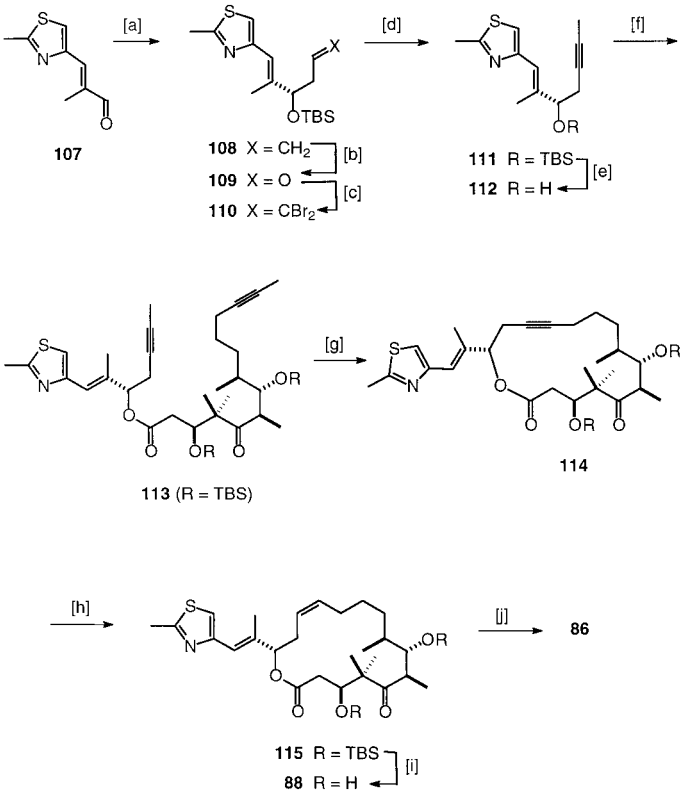
92 **93** **94** R = H **95** R = TBDPS **96** **97** **98**

Scheme 8. a) Zn, ultrasound, THF; then aq. HCl, 71%; b) TBDPSCl, imidazole, DMF, 90%; c) [((*S*)-BINAP)$RuCl_2$](NEt_3) (6 mol%), H_2 (65 bar), Dowex, EtOH, 80 °C, 71%; d) 2,2-dimethoxypropane, acetone, camphorsulfonic acid (cat.), 92%; e) EtMgBr, NEt_3, toluene, 70 °C, 68%.



99 R = H **100** R = Me **101** **102** **103** $R^1 = R^2$ = H **104** $R^1 = R^2$ = TBS **105** R^1 = TBS, R^2 = H **106**

Scheme 9. a) *n*BuLi, THF/HMPA, MeI, −78 °C → −60 °C, 94%; b) $LiAlH_4$, THF, 85%; c) nPr_4NRuO_4 (cat.), NMO, CH_2Cl_2, 4 Å MS, 90%; d) lithium enolate of ketone **98**, THF, −78 °C, 70%; e) PPTS (cat.), MeOH, 85%; f) TBSOTf, 2,6-lutidine, 92%; g) camphorsulfonic acid, CH_2Cl_2/MeOH 1:1, 78%; h) PDC, DMF, 83%.



Scheme 10. a) i) (+)-Ipc$_2$B(allyl); ii) TBSCl, imidazole, DMF, 89% (over both steps); b) i) OsO_4 (cat.), NMO; ii) $Pb(OAc)_4$, 86%; c) CBr_4, PPh_3, CH_2Cl_2, 68%; d) *n*BuLi, then MeI, THF, 65%; e) TBAF·3H$_2$O, THF, 74%; f) acid **106**, DCC, DMAP, CH_2Cl_2, 81%; g) complex **1a** (10 mol%), toluene/CH_2Cl_2, 80 °C, 8 h, 80%; h) Lindlar catalyst, quinoline, H_2 (1 atm), CH_2Cl_2, quant.; i) aq. HF, Et_2O/CH_3CN, 79%; j) dimethyldioxirane, 70% (ref. [49]).

tion.[61] Specifically, treatment of **109** with CBr_4 and PPh_3 gives the expected 1,1-dibromo derivative **110**,[48c] which is converted into alkyne **111** by means of *n*BuLi in THF and trapping of the acetylide anion thus formed with MeI. Desilylation under standard conditions followed by esterification of the resulting alcohol **112** with acid **106** sets the stage for the crucial macrocyclization step. Unfortunately, all attempts to obtain product **112** from aldehyde **107** more directly by asymmetric propargylation using chiral boron or tin reagents for the delivery of the 2-butynyl group were unrewarding in terms of yield and optical purity.[62]

We were pleased to see that diyne **113** cyclized smoothly to the 16-membered cycloalkyne **114** in 80% isolated yield on exposure to catalytic amounts of complex **1a** in toluene/CH_2Cl_2 at 80 °C (Scheme 10). It is noteworthy that this outcome compares well to the best results obtained in the conventional RCM approaches (Table 7) in terms of yield and reaction rate. Furthermore, it confirms the mildness of the method since i) neither the basic N atom nor the sulfur group of the thiazole ring interfere with the catalyst, ii) the labile aldol substructure, the rather electrophilic ketone, as well as the ester- and silyl ether groups are fully preserved, iii) no racemization of the chiral center α to the carbonyl is encountered, and iv) the rigorous chemoselectivity of the catalyst is confirmed, which reacts readily with alkynes but leaves pre-existing alkene moieties unaffected.

Subsequent Lindlar reduction of cycloalkyne **114** followed by cleavage of the silyl ether groups in the resulting (*Z*)-alkene **115** by means of aqueous HF in Et_2O/CH_3CN as the reaction medium delivered epothilone C (**88**) in 79% yield over both steps. Because the selective epoxidation of **115** has already been described by various groups,[48–51] this approach constitutes a formal total synthesis of epothilone A (**86**) as well.

Conclusion

A novel catalyst system for alkyne metathesis has been developed using molybdenum complexes of the type [Mo{(*t*Bu)(Ar)N}$_3$] (**1**) as precatalysts that are activated in situ by CH_2Cl_2. Although the required complexes are rather sensitive to oxygen and moisture, this novel method outperformed exisiting protocols in many respects, independent of whether it was carried out as ring closing alkyne metathesis (RCAM), alkyne homo-dimerization, or in an alkyne cross metathesis (ACM) mode. Particularly noteworthy are the mild conditions which enable applications to labile target molecules and tolerate a host of polar groups. The stereoselective total synthesis of epothilone A and C clearly prove these aspects. From these and related applications,[16–19, 43–45] it must be concluded that alkyne metathesis in general constitutes an attractive tool for advanced organic chemistry which complements conventional alkene metathesis in several respects.[63]

Although the nature of the catalytically active species formed in situ is still elusive, it has been shown that halogen transfer from CH_2Cl_2 to the sterically encumbered molybdenum center in **1** plays an essential role for the activation of the precatalysts. Studies aiming at a better understanding of the organometallic background as well as further applications of this new procedure to target oriented synthesis are actively pursued in this laboratory and will be reported in the near future.

Experimental Section

General: All reactions were carried out under Ar. Note that complexes of the type [Mo{(*t*Bu)(Ar)N}$_3$] (**1**) are able to activate molecular nitrogen at or below room temperature;[24, 25] *therefore N_2 must not be used as a protecting atmosphere for any experiment involving these reagents.*

The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2 (P_4O_{10}), CH_3CN, Et_3N (CaH_2), MeOH (Mg), DMF (Desmodur, dibutyltin dilaurate), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on a DPX 300 or DMX 600 spectrometer (Bruker) in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. IR: Nicolet FT-7199 spectrometer, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), HR-MS: Finnigan MAT 95. Melting points: Büchi Melting Point B-540 (uncorrected). Optical rotation: Perkin Elmer 343 at $\lambda = 589$ nm (Na-D line). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Lancaster, Aldrich) were used as received.

The propynylated arenes used in the homodimerization and ACM experiments were prepared by a modified Suzuki reaction according to a procedure previously described.[64] The methylidyne complex **17** was prepared as described by Cummins.[35]

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Preparation of the ligands and the catalysts

***N*-(3,5-Dimethylphenyl)-*tert*-butylamine (7a)**: tBuNH$_2$ (6.21 g, 85 mmol) and bromide **6** (13.1 g, 71 mmol) were successively added to a mixture of tBuONa (9.54 g, 189 mmol), phosphine **5** (0.25 g, 0.71 mmol) and [Pd$_2$(dba)$_3$] (0.33 g, 0.35 mmol) in toluene (80 mL). The resulting mixture was heated to 80 °C for 8 h. For work-up, the solvent was evaporated, the residue was washed with brine (30 mL), the organic layer was extracted with *tert*-butyl methyl ether (3 × 150 mL), the combined organic layers were dried (Na$_2$SO$_4$) and evaporated, and the crude product was purified by distillation (b.p. 69–70 °C, 10^{-3} bar) affording amine **7a** as a colorless liquid (10.8 g, 86 %). ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 6.50$ (s, 1H), 6.47 (s, 2H), 2.60 (br s, 1H), 2.32 (s, 6H), 1.41 (s, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz): $\delta = 146.9$, 138.4, 120.2, 115.4, 51.3, 30.2, 21.5; MS (EI): m/z (%): 177 (40), 162 (100), 146 (3), 132 (1), 121 (25), 106 (5), 91 (3), 77 (4), 65 (1), 57 (2), 41 (2); IR: $\nu = 3406$, 3022, 2971, 2918, 2869, 1603, 1520, 1475, 1390, 1364, 1341, 1226, 1184, 1031, 822, 694 cm^{-1}. The spectroscopic and analytical data are in agreement with those reported in the literature.[30]

***N*-(4-Fluorophenyl)-*tert*-butylamine (9a)**: Prepared as described above from bromide **8** (10.0 g, 57 mmol), tBuNH$_2$ (5.00 g, 68 mmol), tBuONa (7.67 g, 80 mmol), *rac*-BINAP (0.27 g, 0.43 mmol) and [Pd$_2$(dba)$_3$] (0.13 g, 0.14 mmol) in toluene (114 mL). Flash chromatography of the crude product (EtOAc/hexane 1:10) afforded **9a** as a colorless liquid (3.82 g, 40 %).[65] ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 6.89$ (t, $J = 8.9$ Hz, 2H), 6.80 (d, $J = 4.8$ Hz, 1H), 6.79 (d, $J = 4.8$ Hz, 1H), 3.74 (br s, 1H), 1.27 (s, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz): $\delta = 158.9$, 155.8, 131.1, 131.0, 115.2, 114.9, 52.3, 29.6, 28.7; MS (EI): m/z (%): 167 (40), 152 (94), 136 (3), 111 (100), 95 (6), 83 (6), 76 (3), 57 (13), 41 (8); IR: $\nu = 3418$, 3036, 2974, 2933, 2908, 2871, 1613, 1508, 1460, 1391, 1365, 1318, 1215, 1156, 1103, 822, 780 cm^{-1}.

***N*-(3-Trifluoromethylphenyl)-*tert*-butylamine (11a)**: Prepared as described above from bromide **10** (9.00 g, 40 mmol), tBuNH$_2$ (3.51 g, 48 mmol), tBuONa (5.38 g, 56 mmol), *rac*-BINAP (0.19 g, 0.30 mmol) and [Pd$_2$(dba)$_3$] (0.092 g, 0.10 mmol) in toluene (80 mL). The crude product was purified by distillation (b.p. 62–63 °C, 6×10^{-3} bar) affording amine **11a** as a colorless liquid (7.10 g, 82 %). ^{1}H NMR (CD$_2$Cl$_2$, 300 MHz): $\delta = 7.24$ (t, $J = 4.8$ Hz, 1H), 6.94–6.80 (m, 3H), 3.85 (br s, 1H), 1.37 (s, 9H); ^{13}C NMR (CD$_2$Cl$_2$, 75 MHz): $\delta = 147.9$, 130.9, 129.8, 126.7, 123.1, 119.3, 113.8, 112.3, 51.7, 29.9. The spectroscopic and analytical data are in agreement with those reported in the literature.[66]

***N*-(3,5-Dimethoxyphenyl)-*tert*-butylamine (13a)**: 1-Bromo-2,4-dimethoxybenzene (**12**) (4.50 g, 20.7 mmol) was added to a suspension of NaNH$_2$ (1.62 g, 41.5 mmol) in tBuNH$_2$ (250 mL) and the resulting mixture was heated at 90 °C for 2 h. Methanol (2 mL) was then added, the mixture was diluted with CH$_2$Cl$_2$ (70 mL), filtered through a pad of Celite, and the filtrate was evaporated. Flash chromatography of the residue (EtOAc/hexane 1:10) provided amine **13a** (2.60 g, 60 %) as a colorless solid. ^{1}H NMR (CD$_2$Cl$_2$, 300 MHz): $\delta = 5.90–5.86$ (m, 3H), 3.73 (s, 6H), 1.35 (s, 9H); ^{13}C NMR (CD$_2$Cl$_2$, 75 MHz): $\delta = 161.7$, 149.3, 95.2, 90.1, 55.4, 51.5, 30.1. The spectroscopic and analytical data were in agreement with those reported in the literature.[67]

Lithium *N*-(3,5-dimethylphenyl)-*tert*-butylamide etherate (7b · Et$_2$O): A solution of nBuLi (44.9 mL, 75.1 mmol) was slowly added at −35 °C to a solution of amine **7a** (11.1 g, 62.6 mmol) in hexane (300 mL). After the addition was complete, the reaction mixture was stirred for 12 h during which it was allowed to reach ambient temperature. All volatiles were distilled off and the remaining syrup was triturated with Et$_2$O (28 mL), thereby causing the precipitation of a colorless solid. The crude product was suspended in hexane (50 mL), and the suspension was kept at −20 °C for 8 h. The colorless crystals formed were collected by filtration and were dried in vacuo (10.8 g, 67 %). ^{1}H NMR (C$_6$D$_6$, 300 MHz): $\delta = 6.54$ (s, 2H), 6.13 (s, 1H), 3.17 (q, $J = 7.0$ Hz, 4H), 2.30 (s, 6H), 1.60 (s, 9H), 0.95 (t, $J = 7.0$ Hz, 6H). The analytical data were in agreement with those reported in the literature.[25, 26]

[MoCl$_4$(thf)$_2$]:[28] MoCl$_5$ (6.37 g, 23.3 mmol) was added to acetonitrile (32 mL) and the resulting mixture was stirred for 3 h at ambient temperature. The suspension was filtered, the solid residue was washed with CH$_3$CN (15 mL) and dried in vacuo, affording [MoCl$_4$(CH$_3$CN)$_2$] as a brown powder (5.9 g, 80 %). IR (KBr): $\nu = 3258$, 3223, 2985, 2923, 2315, 2285, 1400, 1355, 1017, 947, 817 cm^{-1}; MS (EI): m/z (%): 238 [M − (2CH$_3$CN)]$^+$ (26), 203 (38), 168 (7), 133(5), 98 (5), 41 (100). A suspension of the [MoCl$_4$(CH$_3$CN)$_2$] (4.39 g, 13.7 mmol) thus obtained in THF (18 mL) was stirred for 2 h at ambient temperature. During this period, the color of the mixture changed from brown to orange. Filtration, washing of the residue with THF (5 mL) and drying in vacuo afforded [MoCl$_4$(thf)$_2$] as an orange powder (3.40 g, 63 %). IR (KBr): $\nu = 2987$, 2951, 1456, 1438, 1342, 1245, 1166, 1042, 990, 920, 809 cm^{-1}.

[MoCl$_3$(thf)$_3$]:[28] Sn shots (7.1 g, 59.8 mmol) were added to a suspension of [MoCl$_4$(thf)$_2$] (3.55 g, 9.3 mmol) in THF (43 mL). While the resulting suspension was vigorously stirred for 30 min, a color change from orange to orange-green was observed. The suspension was then siphoned off such that undissolved tin remained in the flask. Filtration, rinsing of the residue with THF (5 mL) and drying in vacuo afforded [MoCl$_3$(thf)$_3$] (2.5 g, 65 %) as a pale-orange powder. IR (KBr): $\nu = 2980$, 2904, 1487, 1472, 1458, 1449, 1342, 1295, 1244, 1178, 1040, 1012, 928, 852 cm^{-1}.

Tris[*N*-(*tert*-butyl)(3,5-dimethylphenyl)-amido]molybdenum(III) (1a): Anilide **7b** (5.67 g, 22 mmol) was added at −100 °C to a suspension of [MoCl$_3$(thf)$_3$] (4.61 g, 11 mmol) in Et$_2$O (185 mL). The mixture was allowed to reach ambient temperature and was stirred for 2.5 h while turning dark red. The suspension was filtered and the residue was rinsed with Et$_2$O (10 mL). The filtrate was concentrated to ca. ⅕ of its original volume and was then slowly cooled to −60 °C over night, causing the precipitation of dark red crystals. The supernatant liquid was removed through canula and the remaining solid was dried in vacuo for ≈5 min (3.21 g, 70 %). Compound **1a** is paramagnetic: ^{1}H NMR (C$_6$D$_6$, 600 MHz): $\delta = 62.3$ (br s, 27H), −9.5 (s, 18H), −20 (br s, 6H), −50.8 (br s, 3H); MS (EI): m/z (%): 624 (84), 570 (99), 514 (76), 464 (43), 408 (85), 349 (48), 306 (12), 229 (9), 162 (11); IR: $\nu = 3022$, 2963, 2916, 2861, 1600, 1519, 1464, 1381, 1355, 1291, 1183, 1153, 1036, 966, 936, 842, 716, 688 cm^{-1}. The analytical and specroscopic data are in agreement with those reported in the literature.[25, 26]

Monochloro-tris-[(*N*-(*tert*-butyl)(3,5-dimethylphenyl)amido] molybdenum(IV) (16): Complex **1a** (140 mg, 0.22 mmol) was dissolved in Et$_2$O (10 mL) at −78 °C and the flask was evacuated. Chlorine gas (2.73 mL, 0.11 mmol) was introduced through a gas-tight syringe and the reaction mixture was allowed to reach ambient temperature. For work-up, all volatiles were removed in vacuo, the residue was dissolved in Et$_2$O (10 mL), the mixture was filtered through a short pad of Celite, the filtrate was concentrated to ca. ⅓ of the original volume and slowly cooled to −60 °C. The supernatant liquid was removed through canula from the crystals of **16** thus formed (44 mg, 30 %). M.p. 79–80 °C; MS (EI): m/z (%): 661 (< 1), 604 (11), 548 (12), 532 (17), 492 (60), 456 (4), 407 (2), 371 (5), 333 (8), 225 (5), 177 (25), 162 (82); IR: $\nu = 3027$, 3002, 2978, 2917, 1601, 1581, 1457, 1390, 1343, 1223, 1169, 1044, 939, 885, 848, 708, 681, 588, 560 cm^{-1}; elemental analysis calcd (%) for C$_{37}$H$_{57}$MoN$_3$Cl (676.33): C 65.81, H 8.51, N 6.22; found C 65.56, H 8.35, N 6.31.

Monobromo-tris-[(*N*-(*tert*-butyl)(3,5-dimethylphenyl)amido] molybdenum(IV) (18): A solution of Br$_2$ (25.6 mg, 0.16 mmol) in hexane (1 mL) was added at −78 °C to a solution of complex **1a** (200 mg, 0.32 mmol) in Et$_2$O (12 mL) and the resulting mixture was allowed to reach ambient temperature. After stirring for 30 min, all volatiles were removed in vacuo, the residue was dissolved in Et$_2$O (8 mL), the mixture was filtered through a pad of Celite, the filtrate was concentrated to ca. ⅓ of its original volume and was then slowly cooled to −60 °C, causing the precipitation of complex **18** in form of dark-red crystals (65 mg, 29 %). MS (EI): m/z (%): 648 (1), 592 (1), 576 (2), 536 (8), 415 (1), 333 (2), 268 (3), 177 (31), 162 (100); elemental analysis calcd (%) for C$_{37}$H$_{57}$MoN$_3$Br (719.73): C 61.75, H 7.98, N 5.84; found C 61.70, H 7.99, N 5.79.

Dichloro-(3,5-dimethylphenylimido)-bis-[*N*-(*tert*-butyl)(3,5-dimethylphenyl)-amido] molybdenum(VI) (20): 1-Methoxy-2-propynylbenzene (**57**) (106 mg, 0.53 mmol)[64] was added to a solution of complex **1a** (100 mg, 0.16 mmol) in toluene (4 mL) and CH$_2$Cl$_2$ (0.4 mL) and the resulting mixture was heated for 5 min to 80 °C. All volatiles were then removed in vacuo, the residue was dissolved in Et$_2$O (3 mL) and the resulting solution was slowly cooled to −60 °C. One crop of red crystals thus obtained was identified as the title compound **20** by X-ray crystallography, see below (26 mg, 25 %). M.p. 79–80 °C; MS (EI): m/z (%): 639 (< 1), 604 (< 1), 547 (22), 532 (57), 491 (25), 463 (12), 407 (43), 177 (34), 162 (100); elemental analysis calcd (%) for C$_{32}$H$_{45}$MoN$_3$Cl$_2$ (639.20): C 60.19, H 7.10, N 6.58; found C 60.33, H 6.98, N 6.49.

Representative procedure for ring closing alkyne metathesis (RCAM)

Preparation of 7,8,11,12-tetrahydro-6,13-dioxa-1-azabenzocyclododec-9-yne-5,14-dione (28): CH_2Cl_2 (160 μL) and bis(3-pentyn-1-yl) ester **27** (511 mg, 1.70 mmol) were successively added to a stirred solution of complex **1a** (104.4 mg, 0.17 mmol) in toluene (80 mL) and the resulting mixture was stirred at 80 °C for 20 h. For work-up, the solvent was evaporated and the residue was purified by flash chromatography (hexane/EtOAc 4:1), thus affording cycloalkyne **28** as a colorless syrup (369 mg, 88 %). M.p. 96–97 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.76$ (dd, $J = 1.9$, 4.9 Hz, 1H), 8.12 (dd, $J = 1.5$, 7.9 Hz, 4H), 7.52 (dd, $J = 7.8$ Hz, 1H), 4.63 (t, $J = 5.5$ Hz, 2H), 4.42 (t, $J = 5.6$ Hz, 2H), 2.57 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 166.1$, 165.8, 151.1, 151.0, 137.1, 128.7, 125.1, 79.2, 78.8, 63.4, 63.1, 20.0, 19.4; MS (EI): *m/z* (%): 245 (2), 227 (3), 199 (8), 187 (2), 172 (2), 150 (2), 143 (6), 122 (5), 106 (12), 78 (100), 66 (59), 50 (13), 40 (21); IR: $\nu =$ 3057, 2963, 2914, 2835, 1732, 1568, 1436, 1379, 1295, 1152, 1086, 1051, 1006, 755, 645 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{11}NO_4$ (245.07): C 63.67, H 4.52, N 5.71; found C 63.59, H 4.62, N 5.60.

All other cycloalkynes shown in Table 3 were prepared analogously. The analytical data of new compounds are compiled below. For a full set of the analytical and spectroscopic data of product **36** see ref. [19], for those of compounds **4**, **22** and **50** see ref. [16] (Supporting Information).

1,7-Dioxa-4-thiacyclotridec-10-yne-2,6-dione (24): M.p. 75–76 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.28$ (t, $J = 5.4$ Hz, 4H), 3.43 (s, 4H), 2.49 (t, $J =$ 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 169.4$, 78.1, 62.9, 34.6, 19.6; MS (EI): *m/z* (%): 228 (56), 182 (18), 169 (13), 164 (9), 138 (17), 111 (8), 96 (23), 78 (100), 66 (41), 39 (25); IR: $\nu = 2963$, 2924, 2893, 1756, 1738, 1458, 1417, 1286, 1215, 1146, 1018, 857, 711 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{12}O_4S$ (228.05): C 52.62, H 5.30; found C 52.78, H 5.40.

5,8,10-Trioxacyclotridecyne (26): ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 3.68$–3.60 (m, 8H), 3.59–3.53 (m, 4H), 2.36 (t, $J = 5.5$ Hz, 4H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 79.4$, 70.3, 69.9, 69.2, 20.8; MS (EI): *m/z* (%): 184 (<1), 169 (1), 153 (2), 139 (14), 125 (7), 109 (76), 96 (46), 79 (69), 66 (100), 52 (18), 45 (75), 40 (44), 28 (25); elemental analysis calcd (%) for $C_{10}H_{16}O_3$ (184.23): C 65.19, H 8.75; found C 65.13, H 8.67.

3,3-Dimethyl-1,5-dioxacycloundec-8-yne-2,4-dione (30a): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.31$ (t, $J = 5.8$ Hz, 4H), 2.44 (t, $J = 5.9$ Hz, 4H), 1.45 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.0$, 79.8, 61.8, 50.0, 22.1, 19.7; MS (EI): *m/z* (%): 210 (<1), 180 (<1), 152 (2), 137 (2), 111 (4), 87 (4), 78 (100), 70 (45), 65 (17), 51 (3), 41 (13); IR: $\nu = 2982$, 2926, 2850, 1737, 1719, 1464, 1392, 1276, 1171, 1127, 1024, 895, 838 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{14}O_4$ (210.23): C 62.85, H 6.71; found C 63.01, H, 6.67.

3,3,14,14-Tetramethyl-2,4,13,15-tetraoxo-1,5,12,16-tetraoxacyclodocosa-8,19-diyne (30b): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.12$ (t, $J = 6.8$ Hz, 8H), 2.50 (t, $J = 6.9$ Hz, 8H), 1.41 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta =$ 172.2, 63.2, 49.1, 29.4, 22.3, 18.5; MS (EI): *m/z* (%): 420 (5), 342 (1), 306 (1), 219 (1), 174 (8), 156 (51), 141 (14), 115 (6), 96 (8), 78 (100), 69 (30), 41(18); IR: $\nu = 2958$, 2928, 2856, 1732, 1463, 1383, 1282, 1265, 1165, 1131, 1026, 892, 802 cm^{-1}.

3-Oxabicyclo[14.3.1]eicosa-1(19),16(20),17-trien-14-yne-2-one (32): M.p. 95–96 °C; ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 8.17$ (s, 1H), 7.93 (d, $J =$ 7.7 Hz, 1H), 7.51 (d, $J = 7.7$ Hz, 1H), 7.40 (t, $J = 7.8$ Hz, 1H), 4.27 (t, $J =$ 5.3 Hz, 2H), 2.45 (m, 3H), 1.85–1.75 (m, 3H), 1.71–1.31 (m, 12H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 166.0$, 134.7, 134.0, 131.2, 128.9, 128.5, 124.8, 92.9, 81.0, 66.1, 29.8, 29.3, 29.2, 29.1, 29.0, 27.9, 27.7, 26.9, 19.6; MS (EI): *m/z* (%): 284 (100), 214 (8), 200 (12), 186 (29), 170 (20), 155 (28), 142 (47), 129 (58), 115 (42), 91 (14), 81 (53), 67 (46), 55 (54), 41 (44); elemental analysis calcd (%) for $C_{19}H_{24}O_2$ (284.18): C 80.24, H 8.51; found C 79.88, H, 8.46.

1-(*N*-Methyl)-azacycloheptadec-12-yne-2-one (34): ^{1}H NMR (CD_2Cl_2, 300 MHz, rotamers): $\delta = 3.41$ (t, $J = 6.8$ Hz, 1H), 3.28 (t, $J = 7.4$ Hz, 1H), 2.98 (s, 1H), 2.88 (s, 2H), 2.34 (t, $J = 6.9$ Hz, 2H), 2.26–2.13 (m, 4H), 1.80–1.25 (m, 18H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 173.0$, 172.5, 80.9, 80.8, 80.4, 80.0, 50.1, 46.8, 33.3, 31.3, 28.4, 28.3, 28.2, 28.2, 28.1, 28.0, 27.8, 27.5, 27.1, 27.1, 27.0, 25.3, 24.3, 19.1, 18.9, 18.8; MS (EI): *m/z* (%): 263 (30), 248 (25), 234 (6), 220 (11), 206 (6), 192 (5), 180 (10), 166 (11), 152 (13), 138 (6), 124 (21), 111 (30), 93 (13), 79 (24), 70 (82), 55 (29), 44 (100); IR: $\nu = 2926$, 2855, 1647, 1459, 1438, 1401, 1333, 1272, 1170, 1091, 742, 575 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{29}NO$ (263.22): C 77.51, H 11.10, N 5.32; found C 77.38, H 11.18, N 5.19.

(*Z*)-4,9-Dimethyl-2-oxo-1-oxacyclotetradec-3-ene-7-yne (38): ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 5.78$ (s, 1H), 4.55–4.45 (m, 1H), 4.12–4.03 (m, 1H), 3.34–3.22 (m, 1H), 2.60–2.50 (m, 1H), 2.48–2.30 (m, 3H), 1.85 (s, 3H), 1.80–1.20 (m, 8H), 1.09 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 166.9$, 155.9, 119.0, 85.6, 78.7, 62.8, 37.4, 31.0, 28.2, 26.5, 25.9, 23.4, 22.3, 17.3; MS (EI): *m/z* (%): 234 (15), 219 (11), 206 (96), 190 (24), 175 (40), 161 (38), 147 (100), 133 (48), 119 (78), 105 (79), 93 (74), 79 (58), 67 (34), 55 (67), 41 (99); IR: $\nu = 2963$, 2917, 2861, 1719, 1653, 1451, 1385, 1333, 1247, 1164, 1136, 1058, 850, 597 cm^{-1}; HR-MS ($C_{15}H_{22}O_2$): calcd 234.1620, found 234.1616; elemental analysis calcd (%) for $C_{15}H_{22}O_2$ (234.16): C 76.88, H 9.46; found C 76.78, H 9.38.

9-(Phenylsulfonyl)-cyclooctadecyne (40): M.p. 87–88 °C; ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 7.88$ (d, $J = 7.9$ Hz, 2H), 7.74–7.56 (m, 3H), 2.99–2.90 (m, 1H), 2.16 (m, 4H), 1.88–1.60 (m, 4H), 1.59–1.20 (m, 22H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 138.8$, 133.8, 129.5, 129.0, 80.8, 80.7, 64.2, 29.3, 29.1, 29.0, 28.9, 28.7, 28.7, 28.4, 28.0, 27.6, 27.3, 26.4, 26.1, 25.0, 18.9, 18.8; MS (EI): *m/z* (%): 388 (7), 246 (30), 143 (29), 123 (21), 109 (51), 95 (100), 81 (96), 67 (79), 55 (65), 41 (51); IR: $\nu = 2936$, 2854, 1461, 1446, 1305, 1289, 1141, 1084, 735, 692, 583, 549 cm^{-1}; HR-MS ($C_{24}H_{36}O_2S$): calcd 388.2436, found 388.2435.

1-(*N*-4′-Methoxybenzyl)-azacycloheptadec-12-yne-2-one (42): ^{1}H NMR (CD_2Cl_2, 300 MHz, rotamers): $\delta = 7.16$ (d, $J = 12.8$ Hz, 1H), 7.13 (d, $J =$ 12.8 Hz, 1H), 6.89 (d, $J = 13.2$ Hz, 1H), 6.85 (d, $J = 13.2$ Hz, 1H), 4.52 (s, 2H), 3.80 (d, $J = 2.7$ Hz, 3H), 3.36 (t, $J = 7.7$ Hz, 1H), 3.22 (t, $J = 7.7$ Hz, 1H), 2.41 (t, $J = 7.2$ Hz, 1H), 2.38 (m, 1H), 2.20 (m, 4H), 1.80–1.56 (m, 4H), 1.53–1.30 (m, 14H); ^{13}C NMR (CD_2Cl_2, 75 MHz, rotamers): $\delta =$ 173.0, 172.8, 159.3, 157.0, 130.9, 129.5, 128.1, 114.5, 114.2, 81.0, 80.0, 55.6, 50.6, 48.0, 47.3, 31.7, 29.8, 29.1, 28.4, 28.2, 28.0, 27.9, 27.5, 27.1, 27.1, 24.4, 19.2, 18.9, 18.8; MS (EI): *m/z* (%): 369 (23), 248 (11), 199 (1), 162 (2), 136 (12), 134 (2), 121 (100), 91 (3), 77 (4), 55 (5); IR: $\nu = 3072$, 2928, 2856, 1644, 1612, 1512, 1460, 1441, 1417, 1247, 1175, 1035, 817 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{35}NO_2$ (369.27): C 78.00, H 9.55, N 3.79; found C 77.84, H 9.38, N 3.75.

2-Oxabicyclo[15.3.1]heneicosa-1(21),17,19-triene-15-yne-20-carbaldehyde (44): ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 10.41$ (s, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 1.1$ Hz, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 4.27 (t, $J = 7.9$ Hz, 2H), 2.51 (t, $J = 5.7$ Hz, 2H), 1.90–1.80 (m, 2H), 1.78–1.30 (m, 18H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 189.3$, 161.2, 132.0, 128.6, 125.0, 123.4, 116.9, 95.2, 81.3, 68.6, 29.9, 29.6, 28.9, 28.9, 28.6, 28.0, 28.0, 27.5, 27.4, 24.1, 19.7; MS (EI): *m/z* (%): 312 (100), 283 (10), 269 (2), 241 (2), 187 (8), 173 (9), 159 (10), 145 (14), 115 (10), 95 (7), 81 (9), 67 (11), 55 (27), 41 (32); IR: $\nu =$ 3074, 2926, 2854, 2229, 1686, 1600, 1559, 1413, 1264, 1177, 1107, 1025, 855, 824, 631 cm^{-1}; HR-MS ($C_{21}H_{28}O_2$): calcd 312.2089, found 312.2086; elemental analysis calcd (%) for $C_{21}H_{28}O_2$ (312.21): C 80.73, H 9.03; found C 80.62, H 8.91.

2-Nitro-7,8,9,10,11,12,13,14,15,16,19,20,21,22,23,24,25,26,27,28-eicosahydro-6,29-dioxabenzocyclooctacos-17-yne-5,30-dione (46): M.p. 71–72 °C; ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 8.60$ (d, $J = 2.2$ Hz, 1H), 8.40 (dd, $J = 2.3$, 8.4 Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 4.33 (dt, $J = 4.3$, 7.0 Hz, 4H), 2.16 (m, 4H), 1.85–1.65 (m, 4H), 1.54–1.22 (m, 28H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 166.6$, 165.6, 149.2, 138.7, 133.7, 130.5, 126.2, 124.6, 80.8, 67.0, 30.1, 29.9, 29.9, 29.8, 29.5, 29.3, 29.1, 29.0, 28.9, 28.8, 26.2, 26.2, 18.8; MS (EI): *m/z* (%): 513 (3), 496 (9), 371 (2), 319 (4), 194 (33), 178 (25), 135 (14), 121 (20), 107 (19), 95 (43), 81 (62), 67 (71), 55 (100), 41 (72); IR: $\nu = 3109$, 3077, 2920, 2852, 1742, 1724, 1613, 1585, 1534, 1468, 1355, 1304, 1242, 1138, 1062, 963, 934, 835, 734 cm^{-1}; HR-MS ($C_{30}H_{43}NO_6$): calcd 513.3090, found 513.3115; elemental analysis calcd (%) for $C_{30}H_{43}NO_6$ (513.67): C 70.15, H 8.44; found C 69.96, H 8.41.

1,3-Dioxa-2,2-diphenyl-2-silacyclopentacos-14-yne (48): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.64$ (d, $J = 7.7$ Hz, 4H), 7.42–7.26 (m, 6H), 3.75 (t, $J =$ 6.7 Hz, 4H), 2.15 (m, 4H), 1.67–1.18 (m, 32H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 134.9$, 133.2, 130.1, 127.8, 80.6, 63.2, 32.5, 29.7, 29.6, 29.4, 29.2, 28.6, 28.4, 25.6, 18.6; MS (EI): *m/z* (%): 518 (27), 440 (84), 397 (9), 383 (9), 362 (29), 341 (8), 279 (6), 245 (8), 199 (100), 183 (32), 163 (14), 139 (89), 123 (36), 91 (30), 55 (49); elemental analysis calcd (%) for $C_{34}H_{50}O_2Si$ (518.85): C 78.71, H 9.71; found C 78.66, H 9.62.

Representative procedure for alkyne homodimerization reactions and alkyne cross metathesis reactions (ACM)

Preparation of 2-(5-chloro-pent-1-ynyl)-benzoic methyl ester (66): Propynyl ester **59** (160 mg, 0.91 mmol) and 1,8-dichloro-oct-4-yne (247 mg,

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1.38 mmol) were added to a solution of complex **1a** (57 mg, 0.092 mmol) in toluene (10 mL) and CH_2Cl_2 (300 μL) and the resulting solution was stirred at 80 °C for 8 h. After evaporation of the solvent, the residue was purified by chromatography (toluene, then hexanes/EtOAc 15:1) affording product **66** as a colorless oil (135 mg, 62 %). ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 7.89$ (dd, $J = 7.9$, 1.3 Hz, 1H), 7.49 (ddt, $J = 15.2$, 7.8, 1.5 Hz, 2H), 7.37 (dt, $J = 7.5$, 1.6 Hz, 1H), 3.91 (s, 3H), 3.81 (t, $J = 6.4$ Hz, 2H), 2.68 (t, $J = 6.7$ Hz, 2H), 2.09 (q, $J = 6.6$ Hz, 2H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 167.0$, 134.4, 132.6, 131.9, 130.4, 127.8, 124.2, 93.9, 80.3, 52.3, 44.3, 31.8, 17.4; MS (EI): *m*/*z* (%): 236 (1), 201 (6), 187 (2), 174 (100), 159 (16), 143 (8), 131 (7), 115 (12); IR: $\nu = 3068$, 2995, 2951, 2874, 2227, 1730, 1485, 1433, 1294, 1252, 1130, 1085, 758 cm^{-1}; HR-MS ($C_{13}H_{13}O_2Cl + H$): calcd 237.0682; found 237.0681; elemental analysis calcd (%) for $C_{13}H_{13}O_2Cl$ (236.69): C 65.97, H 5.54; found C 65.79, H 5.46.

All other products shown in Tables 4 and 5 were prepared analogously. The full set of their analytical and spectroscopic data is compiled in ref. [43] (Supporting Information).

Total synthesis of epothilone A and C

5-Hydroxy-2,2-dimethyl-3-oxo-pentanoic ethyl ester (94): Bromopropionic ester **93** (34.0 g, 174.3 mmol) was added to a suspension of zinc dust (27.6 g, 422.1 mmol) and 3-hydroxypropionitrile (**92**) (2.0 g, 28.1 mmol) in THF (150 mL) and the suspension was sonicated for 3 h in an ultrasound bath. Excess zinc was allowed to settle, the organic phase was decanted, the zinc was rinsed with THF (15 mL), the combined organic phases were evaporated, the residue was dissoved in EtOAc (40 mL), the organic phase was washed with aq. HCl (2 N, 15 mL), filtered through a pad of Celite and evaporated. Flash chromatography (Et_2O/pentane 1:2) of the crude product afforded compound **94** as a colorless liquid (3.75 g, 71 %). ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 4.17$ (q, $J = 7.1$ Hz, 2H), 3.82 (m, 2H), 2.72 (t, $J = 5.5$ Hz, 2H), 2.41 (br s, 1H), 1.36 (s, 6H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 209.2$, 173.6, 61.8, 58.2, 55.9, 40.7, 21.9, 14.1; MS (EI): *m*/*z* (%): 188 (< 1), 171 (< 1), 143 (14), 116 (100), 88 (75), 73 (83), 70 (26), 55 (13), 43 (27), 29 (22); IR: $\nu = 3519$, 3438, 2984, 2940, 2906, 1712, 1470, 1387, 1269, 1149, 1048, 954, 860, 813, 771 cm^{-1}; HR-MS ($C_9H_{16}O_4 + H$): calcd 189.1127, found 189.1125; elemental analysis calcd (%) for $C_9H_{16}O_4$ (188.10): C 57.43, H 8.57; found C 57.37, H 8.48.

5-(*tert*-Butyldiphenylsilanyloxy)-3-oxo-2,2-dimethyl-pentanoic ethyl ester (95): *tert*-Butyldiphenylsilyl chloride (12.0 g, 43.6 mmol) was added to a solution of compound **94** (6.30 g, 33.5 mmol) and imidazole (4.60 g, 67.0 mmol) in DMF (50 mL) and the resulting mixture was stirred for 14 h at ambient temperature. A standard extractive work-up followed by flash chromatography (EtOAc/hexane 1:30) afforded product **95** as a colorless liquid (12.85 g, 90 %). ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 7.68$ (m, 4H), 7.44 (m, 6H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.93 (t, $J = 6.4$ Hz, 2H), 2.74 (t, $J = 6.4$ Hz, 2H), 1.36 (s, 6H), 1.22 (t, $J = 7.1$ Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 206.4$, 173.7, 135.9, 133.9, 130.0, 128.0, 61.6, 59.7, 56.0, 41.1, 26.9, 21.8, 19.3, 14.2; MS (EI): *m*/*z* (%): 426 $[M]^+$ (< 1), 381 (13), 369 (95), 341 (6), 295 (67), 263 (42), 217 (67), 199 (100), 183 (13), 157 (10), 139 (23), 105 (7), 77 (10), 55 (15); IR: $\nu = 3071$, 3050, 2959, 2933, 2858, 1715, 1589, 1428, 1265, 1148, 1112, 823, 739, 703, 614, 506 cm^{-1}; HR-MS ($C_{25}H_{34}O_4Si + H$): calcd 427.2305, found 427.2302; elemental analysis calcd (%) for $C_{25}H_{34}O_4Si$ (426.22): C 70.38, H 8.03; found C 70.24, H 8.09.

(3*S*)-3,5-Dihydroxy-2,2-dimethylpentanoic ethyl ester (96): Compound **95** (5.88 g, 13.8 mmol) was added to a solution of [((*S*)-BINAP)$RuCl_2$]$_2$(NEt_3) (0.035 mmol)[57] in EtOH (50 mL) and the mixture was stirred at 45 °C for 20 min. This mixture was then transferred into an autoclave (200 mL) charged with Dowex (X4-400, 300 mg). The autoclave was pressurized with H_2 (65 atm) and heated to 80 °C. After 36 h reaction time, the autoclave was vented, the solvent was evaporated and the residue was purified by flash chromatography (EtOAc/hexane 1:1) affording product **96** as a colorless syrup (1.88 g, 71 %). Some starting material **95** was recovered (1.47 g, 25 %). $[\alpha]_D^{20} = -25.5°$ ($c = 0.90$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 4.14$ (q, $J = 7.1$ Hz, 2H), 3.91 (dd, $J = 2.9$, 9.9 Hz, 1H), 3.80 (dt, $J = 2.1$, 4.8 Hz, 2H), 3.19 (br s, 1H), 2.66 (br s, 1H), 1.51 (m, 2H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.18 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 178.3$, 77.1, 62.5, 47.7, 33.9, 22.5, 20.6, 14.7; MS (EI): *m*/*z* (%): 190 (< 1), 175 (< 1), 145 (16), 127 (5), 116 (100), 99 (15), 88 (85), 71 (21), 70 (40), 57 (10); IR: $\nu = 3275$, 2978, 2966, 2937, 2878, 1724, 1464, 1445, 1385, 1320, 1267, 1234, 1133, 1050, 969, 918, 860, 630 cm^{-1}; HR-MS ($C_9H_{18}O_4 + H$): calcd 191.1283, found 191.1284; elemental analysis calcd (%) for $C_9H_{18}O_4$ (190.12): C 56.82, H 9.54; found C 56.91; H 9.66.

2-[(3*S*)-2,2-Dimethyl-1,3-dioxan-4-yl]-2-methylpropionic ethyl ester (97): Camphorsulfonic acid (≈20 mg) was added to a solution of diol **96** (2.0 g, 10.53 mmol) in 2,2-dimethoxypropane (10 mL) and acetone (30 mL). The mixture was stirred for 15 h at ambient temperature, the solvent was removed in vacuo and the residue was purified by flash chromatography (pentane/Et_2O 20:1) affording product **97** as a colorless syrup (2.23 g, 92 %). $[\alpha]_D^{20} = 10.1°$ ($c = 0.98$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 4.17–4.04$ (m, 3H), 3.95 (dt, $J = 2.9$, 11.8 Hz, 1H), 3.82 (ddd, $J = 1.9$, 5.5, 11.6 Hz, 1H), 1.72–1.58 (m, 1H), 1.42 (s, 3H), 1.33 (m, 1H), 1.30 (s, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.15 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 176.5$, 98.7, 73.8, 60.6, 60.3, 46.3, 29.9, 25.7, 20.0, 19.7, 19.3, 14.4; MS (EI): *m*/*z* (%): 230 (< 1), 215 (72), 185 (8), 172 (9), 155 (46), 127 (100), 115 (76), 99 (29), 83 (30), 73 (39), 59 (74), 43 (89), 29 (46); IR: $\nu = 2991$, 2941, 2874, 1735, 1471, 1381, 1371, 1275, 1198, 1142, 1106, 972, 857, 767 cm^{-1}; HR-MS ($C_{12}H_{22}O_4 + H$): calcd 231.1596, found 231.1595; elemental analysis calcd (%) for $C_{12}H_{22}O_4$ (230.15): C 62.58, H 9.63; found C 62.65, H 9.59.

2-[(4*S*)-2,2-Dimethyl-1,3-dioxan-4-yl]-2-methyl-3-pentanon (98): A solution of EtMgBr (14 mL, 3 M in Et_2O) was added to a solution of ester **97** (2.42 g, 10.5 mmol) and NEt_3 (7.44 g, 73.5 mmol) in toluene (20 mL) and the resulting mixture was stirred at 70 °C for 4 h. For work-up, the mixture was cooled to −10 °C, and saturated aq. NH_4Cl (10 mL) and Et_2O (100 mL) were subsequently introduced. Washing of the organic layer with H_2O, repeated extraction of the aqueous layer with Et_2O, drying of the combined organic phases over Na_2SO_4, evaporation of the solvent and flash chromatography (pentane, then Et_2O/pentane 1:10) of the residue afforded ketone **98** as a colorless syrup (1.53 g, 68 %). $[\alpha]_D^{20} = 9.1°$ ($c = 0.98$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 4.06$ (dd, $J = 2.6$, 11.7 Hz, 1H), 3.94 (dt, $J = 2.7$, 11.9 Hz, 1H), 3.84 (m, 1H), 2.51 (q, $J = 7.2$ Hz, 2H), 1.62 (m, 1H), 1.41 (s, 3H), 1.34 (m, 1H), 1.30 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.98 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 215.2$, 98.6, 74.3, 60.2, 50.9, 31.7, 29.9, 25.7, 21.3, 19.1, 19.0, 8.1; MS (EI): *m*/*z* (%): 215 (1), 199 (13), 156 (17), 139 (13), 127 (5), 115 (30), 99 (10), 83 (44), 71 (7), 57 (100), 43 (51), 29 (31), 55 (15); IR: $\nu = 2975$, 2939, 2877, 1706, 1467, 1381, 1372, 1273, 1198, 1105, 971, 855, 764 cm^{-1}; HR-MS ($C_{12}H_{22}O_3$): calcd 215.1647, found 215.1646. The analytical data are in agreement with those previously reported in the literature.[51, 68]

1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-oct-6-yne-1-one (99): A solution of (2*R*)-borane-10,2-sultam (2.140 g, 9.95 mmol)[59] in toluene (10 mL) was added over a period of 30 min to a suspension of NaH (0.239 g, 10.95 mmol) in toluene (20 mL). After the evolution of H_2 had ceased (30 min), a solution of 6-octynoic acid chloride (2.24 g, 12.84 mmol) in toluene (5 mL) was introduced and the resulting mixture was stirred for 12 h at ambient temperature. Quenching of the reaction with aq. sat. NH_4Cl (5 mL) followed by a standard extractive work-up and flash chromatography (*tert*-butyl methyl ether/hexane 1:10) of the crude material afforded product **99** as a colorless syrup (3.10 g, 94 %). ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 3.86$ (dd, $J = 7.3$, 7.4 Hz, 1H), 3.51 (d, $J = 13.9$ Hz, 1H), 3.44 (d, $J = 13.9$ Hz, 1H), 2.69 (dt, $J = 3.3$, 7.3 Hz, 2H), 2.17–2.03 (m, 4H), 2.00–1.84 (m, 2H), 1.80–1.67 (m, 3H), 1.58–1.25 (m, 7H), 1.15 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 171.8$, 78.9, 75.9, 65.5, 53.8, 48.7, 48.0, 45.1, 38.8, 35.3, 33.1, 28.7, 26.7, 24.0, 21.0, 20.0, 18.7, 3.5; MS (EI): *m*/*z* (%): 337 (15), 281 (24), 257 (12), 230 (9), 214 (5), 150 (11), 135 (51), 123 (67), 107 (22), 95 (100), 79 (49), 67 (83), 53 (64), 41 (82); IR: $\nu = 2958$, 2920, 1696, 1456, 1329, 1268, 1236, 1133, 1116, 1055, 988, 773, 537 cm^{-1}; HR-MS ($C_{18}H_{27}NO_3S$): calcd 337.1712, found 337.1713; elemental analysis calcd (%) for $C_{18}H_{27}NO_3S$ (337.17): C 64.06, H 8.06, N 4.15; found C 64.13, H 8.10, N 4.12.

1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-methyl-oct-6-yne-1-one (100): *n*BuLi (5.46 mL, 1.6 M in hexane) was added at −78 °C to a solution of compound **99** (2.95 g, 8.74 mmol) in THF (50 mL) and the resulting mixture was stirred for 1 h. Subsequently, a solution of MeI (6.20 g, 43.7 mmol) in HMPA (4.6 mL) was added and stirring was continued for 6 h at −60 °C. The reaction was quenched at this temperature with aq. sat. NH_4Cl (3 mL), all volatiles were evaporated, the residue was dissolved in *tert*-butyl methyl ether (30 mL), the organic phase was washed with brine, the aqueous layers were extracted with *tert*-butyl methyl ether (3 × 70 mL), the combined organic layers were dried (Na_2SO_4) and evaporated, and the crude product was purified by flash chromatography

(EtOAc/hexane 1:10) delivering compound **100** as colorless crystals (2.88 g, 94%). M.p. 108–112 °C; ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 3.90$ (t, $J =$ 6.3 Hz, 1H), 3.52 (d, $J = 13.9$ Hz, 1H), 3.45 (d, $J = 13.9$ Hz, 1H), 3.04 (m, 1H), 2.16–1.78 (m, 7H), 1.77 (t, $J = 2.5$ Hz, 3H), 1.60–1.29 (m, 6H), 1.19 (d, $J = 6.9$ Hz, 3H), 1.16 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 176.1, 79.1, 75.7, 65.4, 53.8, 48.6, 48.0, 45.1, 40.3, 38.8, 33.1, 32.2, 27.2, 26.7, 21.0, 20.0, 19.2, 19.0, 3.5$; MS (EI): *m*/*z* (%): 351 (7), 336 (1), 309 (5), 295 (58), 271 (15), 244 (6), 214 (6), 154 (16), 137 (66), 109 (88), 93 (32), 81 (41), 67 (100), 55 (54), 43 (52); IR: $\nu = 2984, 2947, 2888, 1681, 1459, 1397, 1334, 1275, 1239, 1133, 1062, 979, 773, 546, 534$ cm^{-1}; HR-MS ($C_{19}H_{29}NO_3S + H$): calcd 352.1946, found 352.1947; elemental analysis calcd (%) for $C_{19}H_{29}NO_3S$ (351.19): C 64.92, H 8.32, N 3.98; found C 64.80, H 8.39, N 3.86.

(*S*)-2-Methyl-oct-6-ynal (101): A solution of compound **100** (2.06 g, 5.86 mmol) in THF (5 mL) was added to a cooled (−78 °C) suspension of $LiAlH_4$ (0.245 g, 6.45 mmol) in THF (50 mL) and the resulting mixture was stirred at that temperature for 2 h. Quenching of the reaction with aq. sat. NH_4Cl (5 mL) followed by a standard extractive work-up and flash chromatography (Et_2O/pentane 1:4) afforded (*S*)-2-methyl-oct-6-yn-1-ol as a colorless syrup (0.70 g, 85%). This compound shows the following analytical and spectroscopic properties: $[\alpha]_D^{20} = -13.9°$ ($c = 0.96$, $CHCl_3$); $[\alpha]_D^{22} = -13.1°$ ($c = 1.03$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 3.48$ (dd, $J = 10.4$ Hz, 1H), 3.40 (dd, $J = 10.4$ Hz, 1H), 2.16–2.05 (m, 2H), 1.77 (t, $J = 2.5$ Hz, 3H), 1.67–1.40 (m, 5H), 1.29–1.12 (m, 1H), 0.92 (d, $J =$ 6.7 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 79.4, 75.7, 68.4, 35.9, 32.8, 27.0, 19.3, 16.7, 3.5$; MS (EI): *m*/*z* (%): 140 (<1), 125 (2), 107 (32), 93 (20), 84 (36), 79 (29), 68 (100), 55 (46), 41 (63); IR: $\nu = 3357, 2936, 2920, 2873, 2737, 2054, 1461, 1380, 1333, 1035, 940, 783$ cm^{-1}; HR-MS ($C_9H_{16}O + H$): calcd 141.1279, found 141.1280; elemental analysis calcd (%) for $C_9H_{16}O$ (140.12): C 77.09, H 11.50; found C 76.89, H 11.62.

To a solution of this alcohol (0.61 g, 4.36 mmol) and *N*-methylmorpholine-*N*-oxide (0.75 g, 6.43 mmol) in CH_2Cl_2 (10 mL) was added powdered 4 Å MS (1.16 g). After stirring the suspension for 10 min, tri-*n*-propylammonium perruthenate (75 mg, 0.21 mmol)[69] was introduced and stirring was continued for 15 min. The mixture was then filtered through a pad of silica, the filtrate was evaporated, and the residue was purified by flash chromatography (Et_2O/pentane 1:5) to afford aldehyde **101** as a colorless syrup. This compound is very sensitive towards oxidation and was therefore immediately used in the next step. Characterisitc data: ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 9.63$ (s, 1H), 2.38–2.30 (m, 1H), 2.19–2.10 (m, 2H), 1.85–1.74 (m, 1H), 1.76 (t, $J = 2.6$ Hz, 3H), 1.57–1.38 (m, 4H), 1.09 (d, $J =$ 6.9 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 205.1, 78.8, 76.1, 46.3, 30.0, 26.8, 19.0, 13.5, 3.5$.

(4*R*,5*S*,6*S*,4′*S*)-2-(2,2-Dimethyl-[1,3]dioxan-4-yl)-5-hydroxy-2,4,6-trimethyl-dodec-10-yne-3-one (102): A solution of ketone **98** (0.650 g, 3.04 mmol) in THF (1 mL) was added at −78 °C to a freshly prepared solution of LDA [from *n*BuLi (1.74 mL, 1.66 M in hexane) and diisopropylamine (0.292 g, 2.88 mmol) in THF (2 mL)]. This mixture was stirred at that temperature for 1.5 h prior to the additon of aldehyde **101** (0.419 g, 3.04 mmol) and stirring was continued for 2 h. The reaction was quenched with sat. aq. NH_4Cl (0.5 mL), the mixture was diluted with Et_2O (150 mL), the organic layer was washed with brine (15 mL), the aqueous layer was extracted with Et_2O, the combined organic phases were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (Et_2O/pentane 1:10) to afford product **102** as a colorless syrup (0.748 g, 70%). $[\alpha]_D^{20} = -22.1°$ ($c = 1.03$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 4.07$ (dd, $J = 2.4$, 11.7 Hz, 1H), 3.96 (dt, $J = 2.8$, 12.3 Hz, 1H), 3.83 (ddd, $J = 1.7$, 5.3, 11.7 Hz, 1H), 3.38–3.25 (m, 3H), 2.18–2.05 (m, 2H), 1.88–1.74 (m, 1H), 1.77 (t, $J = 2.6$ Hz, 3H), 1.70–1.47 (m, 3H), 1.46–1.27 (m, 2H), 1.41 (s, 3H), 1.31 (s, 3H), 1.19 (s, 3H), 1.18–1.10 (m, 1H), 1.10 (s, 3H), 1.00 (d, $J = 5.4$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 222.9, 98.7, 79.6, 75.5, 75.0, 74.7, 60.1, 52.0, 41.5, 35.6, 32.8, 29.9, 26.9, 25.6, 21.8, 19.5, 19.2, 18.5, 15.5, 9.5, 3.5$; MS (EI): *m*/*z* (%): 352 (3), 337 (6), 294 (3), 276 (7), 243 (3), 214 (8), 185 (14), 156 (65), 139 (19), 127 (19), 115 (62), 99 (23), 82 (100), 67 (28), 57 (59), 43 (84); IR: $\nu = 3497, 2990, 2967, 2938, 2874, 1686, 1466, 1381, 1372, 1272, 1197, 1106, 971, 853, 760, 525$ cm^{-1}; HR-MS ($C_{21}H_{36}O_4 +$ H): calcd 353.2692, found 353.2693; elemental analysis calcd (%) for $C_{21}H_{36}O_4$ (352.26): C 71.55, H 10.29; found C 71.44, H 10.35.

(3*S*,6*R*,7*S*,8*S*)-(1,3,7-Trihydroxy-4,4,6,8-tetramethyltetradec-12-yne-5-one (103): A solution of product **102** (0.726 g, 2.07 mmol) and pyridinium-*p*-toluene sulfonate (0.572 g, 2.28 mmol) in MeOH (20 mL) was stirred for 14 h at ambient temperature. Quenching of the reaction with aq. $NaHCO_3$ (10 mL) followed by a standard extractive work-up and flash chromatography (Et_2O/pentane 2:1) afforded triol **103** as a colorless syrup (0.550 g, 85%). $[\alpha]_D^{20} = -42.9°$ ($c = 1.03$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta =$ 4.08–4.00 (m, 1H), 3.94–3.78 (m, 2H), 3.37 (br d, $J = 8.9$ Hz, 1H), 2.18–2.08 (m, 2H), 3.34–3.06 (m, 3H), 2.45–2.35 (m, 1H), 1.87–1.72 (m, 1H), 1.77 (t, $J = 2.6$ Hz, 3H), 1.87–1.72 (m, 1H), 1.70–1.49 (m, 4H), 1.48–1.31 (m, 1H), 1.20 (s, 3H), 1.13 (s, 3H), 1.05 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J =$ 6.7 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 223.7, 79.5, 76.7, 75.5, 75.0, 62.5, 53.0, 41.2, 35.7, 33.0, 32.5, 26.8, 21.6, 21.6, 19.4, 18.5, 15.6, 10.2, 3.5$; MS (ESI): *m*/*z* (%): 312 (<1), 279 (<1), 238 (3), 213 (14), 185 (6), 156 (8), 149 (7), 139 (8), 121 (23), 100 (71), 82 (65), 67 (42), 57 (80), 43 (100), 29 (38); IR: $\nu = 3422, 2969, 2934, 2878, 1686, 1459, 1378, 1332, 1261, 1202, 1097, 995, 975, 852$ cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{32}O_4$ (312.23): C 69.19, H 10.32; found C 69.26, H 10.35.

(3*S*,6*R*,7*S*,8*S*)-1,3,7-Tris-(*tert*-butyldimethylsilanyloxy)-4,4,6,8-tetramethyltetradec-12-yne-5-one (104): TBSOTf (2.06 g, 7.79 mmol) was slowly added at −78 °C to a solution of triol **103** (0.540 g, 1.73 mmol) and 2,6-lutidine (1.390 g, 13.0 mmol) in CH_2Cl_2 (20 mL). The resulting mixture was stirred at that temperature for 45 min and at room temperature for 3 h. Quenching of the reaction with aq. $NaHCO_3$ (10 mL) followed by a standard extractive work-up and flash chromatography (Et_2O/pentane 1:20) afforded product **104** as a colorless syrup (1.035 g, 92%). $[\alpha]_D^{20} = -27.1°$ ($c = 0.96$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 3.93$ (dd, $J =$ 2.8, 7.5 Hz, 1H), 3.79 (dd, $J = 2.1$, 6.9 Hz, 1H), 3.74–3.55 (m, 2H), 3.19 (qui, $J = 6.9$ Hz, 1H), 2.17–2.05 (m, 3H), 1.76 (t, $J = 2.5$ Hz, 3H), 1.57 (s, 3H), 1.64–1.21 (m, 3H), 1.25 (s, 3H), 1.06 (s, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.90 (d, 3H), 0.93 (2s, 18H), 0.90 (s, 9H), 0.13, 0.09, 0.05, 0.05 (4s, 18H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 218.3, 79.4, 78.1, 75.7, 74.3, 61.2, 45.4, 38.8, 38.4, 30.4, 27.6, 26.4, 26.3, 26.1, 25.8, 24.7, 19.5, 19.3, 18.8, 18.6, 18.5, 18.4, 17.8, 15.5, 3.5, −2.8, −3.5, −3.6, −3.6, −3.8, −5.2, −5.2$; MS (EI): *m*/*z* (%): 654 (<1), 545 (1), 465 (1), 373 (5), 303 (100), 253 (87), 171 (7), 145 (21), 121 (42), 89 (53), 73 (70); IR: $\nu = 2956, 2930, 2885, 2857, 1695, 1472, 1387, 11361, 1256, 1104, 986, 836, 775, 671$ cm^{-1}; HR-MS ($C_{36}H_{74}O_4Si_3 + H$): calcd 655.4973, found 655.4975; elemental analysis calcd (%) for $C_{36}H_{74}O_4Si_3$ (654.49): C 65.99, H 11.38; found C 65.83, H 11.44.

(3*S*,6*R*,7*S*,8*S*)-3,7-Bis-(*tert*-butyldimethylsilanyloxy)-1-hydroxy-4,4,6,8-tetramethyltetradec-12-yne-5-one (105): A solution of compound **104** (1.00 g, 1.53 mmol) and camphorsulfonic acid (71 mg, 0.3 mmol) in CH_2Cl_2 (40 mL) and MeOH (40 mL) was stirred at 0 °C for 4 h and was then neutralized with aq. $NaHCO_3$. Standard extractive work-up followed by flash chromatography (Et_2O/pentane 1:4) of the crude product afforded alcohol **105** as a colorless syrup (0.645 g, 78%). $[\alpha]_D^{20} = -22.4°$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 4.07$ (dd, $J = 5.6$ Hz, 1H), 3.82 (dd, $J =$ 1.8, 7.3 Hz, 1H), 3.63 (m, 2H), 3.19 (quin, $J = 7.1$ Hz, 1H), 2.15–2.08 (m, 2H), 1.76 (t, $J = 2.5$ Hz, 3H), 1.80–1.75 (m, 1H), 1.63–1.48 (m, 4H), 1.45–1.20 (m, 3H), 1.25 (s, 3H), 1.10 (s, 3H), 1.08 (d, $J = 7.1$ Hz, 3H), 0.94 (m, 3H), 0.94 (s, 9H), 0.93 (s, 9H), 0.13, 0.10 (2s, 6H), 0.10 (s, 6H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 219.6, 79.4, 78.2, 75.8, 73.5, 60.4, 45.4, 38.7, 38.7, 30.1, 27.6, 26.4, 26.2, 25.1, 19.5, 18.8, 18.5, 17.9, 17.9, 15.9, 3.5, −3.5, −3.6, −3.8, −3.8$; MS (EI): *m*/*z* (%): 540 (<1), 507 (<1), 483 (2), 373 (1), 345 (7), 253 (56), 213 (38), 189 (100), 145 (31), 121 (49), 89 (51), 73 (87), 59 (4), 43 (5); IR: $\nu = 3474, 2954, 2930, 2884, 2857, 1693, 1473, 1386, 1261, 1256, 1103, 987, 837, 775, 673$ cm^{-1}; HR-MS ($C_{30}H_{60}O_4Si_2 + H$): calcd 541.4108, found 541.4107; elemental analysis calcd (%) for $C_{30}H_{60}O_4Si_2$ (540.40): C 66.61, H 11.18; found C 66.49, H 11.24.

(3*S*,6*R*,7*S*,8*S*)-3,7-Bis-(*tert*-butyldimethylsilanyloxy)-4,4,6,8-tetramethyl-5-oxo-tetradec-12-ynoic acid (106): A solution of PDC (4.07 g, 10.8 mmol) in DMF (10 mL) was added to a solution of alcohol **105** (0.650 g, 1.20 mmol) in DMF (10 mL) and the resulting mixture was stirred at ambient temperature for 36 h. The solution was then poored into brine (500 mL), the aqueous phase was repeatedly extracted with *tert*-butyl methyl ether (5 × 70 mL), the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (EtOAc/hexane 1:10 → 1:4), thus affording acid **106** as a colorless syrup (0.550 g, 83%). $[\alpha]_D^{20} = -27.9°$ ($c = 1.06$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 4.40$ (dd, $J = 6.5$ Hz, 1H), 3.81 (dd, $J = 1.7$, 7.4 Hz, 1H), 3.19 (quin, $J = 7.1$ Hz, 1H), 2.50 (dd, $J = 3.3$, 16.4 Hz, 1H), 2.33 (dd, $J = 6.5$, 16.4 Hz, 1H), 2.20–2.05 (m, 3H), 1.76 (t, $J = 2.5$ Hz, 3H), 1.58–1.45 (m, 2H), 1.41–1.21 (m, 3H), 1.27 (s, 3H), 1.13 (s, 3H), 1.07 (d, $J = 6.9$ Hz, 3H), 0.94 (m, 3H), 0.94 (s, 9H), 0.91 (s, 9H), 0.13, 0.10, 0.09, 0.09 (4s, 12H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 218.6, 176.8, 79.4, 78.2, 75.7, 73.8, 53.6,$

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45.5, 40.4, 38.8, 30.2, 27.6, 26.4, 26.1, 24.0, 19.5, 18.9, 18.8, 18.4, 18.0, 16.0, 3.5, −3.5, −3.6, −4.2, −4.6; MS (EI): *m*/*z* (%): 554 (<1), 539 (<1), 497 (6), 445 (3), 387 (1), 359 (10), 295 (10), 253 (26), 229 (3), 203 (100), 185 (10), 143 (10), 115 (58), 73 (87); IR: $\nu = 3430$, 2957, 2930, 2895, 2858, 1713, 1473, 1386, 1361, 1257, 1103, 989, 837, 776, 672 cm^{-1}; elemental analysis calcd (%) for $C_{30}H_{58}O_5Si_2$ (554.38): C 64.93, H 10.53; found C 65.07, H 10.46.

(3*S*,4*E*)-3-(*tert*-Butyldimethylsilanyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)-pent-4-enal (109): A solution of compound **108** (6.63 g, 20.5 mmol),[52b] *N*-methylmorpholine-*N*-oxide (2.97 g, 24.6 mmol) and OsO_4 (52 mg in 5 mL *t*BuOH) in a mixture of THF and *t*BuOH (125 mL each) was stirred for 3 h at 0 °C. Na_2SO_3 (2.5 g) and H_2O (25 mL) were then introduced, the suspension was diluted with Et_2O (500 mL), the organic layer was washed with brine (100 mL), the aqueous phase was extracted with Et_2O (3 × 70 mL), the combined organic phases were dried (Na_2SO_4) and evaporated, and the crude product was purified by flash chromatography (Et_2O, then EtOAc) to afford (4*S*,6*E*)-4-(*tert*-butyldimethylsilanyloxy)-5-methyl-6-(2-methyl-1,3-thiazol-4-yl)-5-hexene-1,2-diol as a colorless syrup which was immediately used in the following step without further characterization.

$Pb(OAc)_4$ (11.13 g, 23.8 mmol) was added in portions at 0 °C to a solution of this diol (7.11 g, 19.9 mmol) in EtOAc (200 mL). After stirring for 2 h, the suspension was filtered through a pad of silica which was carefully rinsed with a mixture of Et_2O/pentane (250 mL each). The combined filtrates were evaporated and the residue was purified by flash chromatography (hexane/Et_2O 2:1) to afford aldehyde **109** as a colorless syrup (5.56 g, 89% over both steps). $[\alpha]_D^{20} = -21.5°$ ($c = 1.16$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 9.78$ (t, $J = 2.7$ Hz, 1H), 6.99 (s, 1H), 6.56 (br s, 1H), 4.74–4.70 (m, 1H), 2.75 (m, 1H), 2.70 (s, 3H), 2.50 (m, 1H), 2.08 (s, 3H), 0.91 (s, 9H), 0.07, 0.02 (2s, 6H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 201.7$, 165.0, 153.2, 140.7, 119.5, 116.4, 74.3, 50.5, 25.8, 19.4, 18.3, 14.3, −4.6, −5.1; MS (EI): *m*/*z* (%): 325 (7), 310 (2), 282 (17), 268 (82), 250 (14), 224 (5), 194 (11), 176 (100), 164 (14), 143 (9), 135 (35), 101 (17), 73 (37), 59 (21), 45 (9); IR: $\nu = 3105$, 2953, 2929, 2855, 2738, 1729, 1504, 1470, 1387, 1255, 1186, 1048, 840, 813, 779 cm^{-1}. The analytical data are in agreement with those reported in the literature.[52b]

(1*E*,3*S*)-4-[6,6-Dibromo-3-(*tert*-butyldimethylsilanyloxy)-2-methyl-hexa-1,5-dienyl]-2-methyl-1,3-thiazole (110): A solution of CBr_4 (0.66 g, 1.98 mmol) in CH_2Cl_2 (5 mL) was added at −60 °C to a solution of aldehyde **109** (0.43 g, 1.32 mmol) and PPh_3 (1.04 g, 3.96 mmol) in CH_2Cl_2 (25 mL). After stirring for 15 min, cold pentane (−60 °C) was introduced, the mixture was concentrated to a total volume of ≈10 mL and filtered through a pad of silica which was carefully rinsed with pentane/Et_2O 5:1. The combined filtrates were evaporated and the crude product was purified by flash chromatography (pentane/Et_2O 20:1) to afford dibromide **110** as a pale yellow syrup (0.43 g, 68%). Since this product is rather unstable, it was immediately used in the next step. Characteristic data: ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 6.99$ (s, 1H), 6.50 (br s, 1H), 6.48 (t, $J = 7.2$ Hz, 1H), 4.27 (t, $J = 6.4$ Hz, 1H), 2.70 (s, 3H), 2.40 (m, 2H), 2.05 (d, $J = 1.2$ Hz, 3H), 0.94 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 164.9$, 153.3, 141.1, 136.2, 119.4, 116.1, 89.8, 76.7, 40.5, 25.9, 19.4, 18.4, 14.3, −4.7, −5.0.

(1*E*,3*S*)-4-[3-(*tert*-Butyldimethylsilanyloxy)-2-methyl-hept-1-ene-5-ynyl]-(2-methyl-1,3-thiazole) (111): *n*BuLi (1 mL, 1.66 M) was slowly added at −78 °C to a solution of dibromide **110** (0.40 g, 0.83 mmol) in THF (10 mL) and the resulting mixture was stirred for 1 h at that temperature. MeI (0.59 g, 4.15 mmol) was then introduced and stirring was continued for another 6 h while the mixture was allowed to reach ambient temperature. For work-up, the mixture was cooled again to −78 °C and aq. sat. NH_4Cl (1 mL) was added. A standard extractive work-up followed by flash chromatography (Et_2O/pentane 1:20) afforded alkyne **111** as a colorless syrup (0.21 g, 65%). $[\alpha]_D^{20} = -24.4°$ ($c = 1.13$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 6.98$ (s, 1H), 6.48 (br s, 1H), 4.27 (t, $J = 6.4$ Hz, 1H), 2.70 (s, 3H), 2.38 (m, 3H), 2.04 (d, $J = 1.3$ Hz, 3H), 1.76 (t, $J = 2.6$ Hz, 3H), 0.93 (s, 9H), 0.10 (d, $J = 18.4$ Hz, 6H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 164.8$, 153.5, 141.4, 119.5, 116.0, 78.2, 77.3, 76.7, 27.8, 25.9, 19.4, 18.5, 13.9, 3.5, −4.7, −4.9. MS (EI): *m*/*z* (%): 335 (<1), 320 (2), 296 (7), 282 (100), 229 (4), 204 (4), 168 (3), 151 (3), 129 (1), 111 (3), 97 (2), 73 (51), 59 (4), 45 (4); IR: $\nu =$ 3105, 2955, 2928, 2856, 1768, 1728, 1506, 1471, 1463, 1388, 1360, 1255, 1183, 1077, 936, 837, 777, 666 cm^{-1}; HR-MS ($C_{18}H_{29}NOSSi + H$): calcd 336.1817, found 336.1816; elemental analysis calcd (%) for $C_{18}H_{29}NOSSi$ (335.17): C 64.42, H 8.71, N 4.17; found C 64.56, H 8.68, N 4.24.

(1*E*,3*S*)-2-Methyl-1-(2-methyl-1,3-thiazol-4-yl)-hept-1-ene-5-yne-3-ol (112): A suspension of 4 Å MS (0.5 g) and TBAF (1.27 g, 4.02 mmol) in THF (16 mL) was stirred for 20 min prior to the addition of product **111** (0.45 g, 1.34 mmol) dissolved in THF (2 mL). Stirring was continued for 3 h prior to quenching the mixture with aq. sat. NH_4Cl (5 mL). A standard extractive work-up followed by flash chromatography (Et_2O/pentane 1:2) provided alcohol **112** as a pale yellow syrup (0.219 g, 74%). $[\alpha]_D^{20} = -2.6°$ ($c = 1.03$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 7.00$ (s, 1H), 6.56 (br s, 1H), 4.26 (m, 1H), 2.70 (s, 3H), 2.60–2.35 (m, 3H), 2.06 (s, 3H), 1.81 (t, $J =$ 2.6 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta = 164.9$, 153.3, 140.6, 119.3, 116.3, 78.6, 75.9, 75.5, 26.9, 19.3, 14.5, 3.6; MS (EI): *m*/*z* (%): 221 (5), 202 (1), 192 (2), 170 (5), 168 (100), 140 (5), 138 (2), 127 (3), 112 (2), 110 (9), 99 (15), 97 (7), 71 (3), 65 (8), 59 (9), 53 (9), 45 (10), 39 (6); IR: $\nu = 3387$, 3126, 2954, 2918, 2855, 1653, 1507, 1437, 1378, 1359, 1270, 1186, 1033, 878, 738 cm^{-1}; HR-MS ($C_{21}H_{15}NOS + H$): calcd 222.0953, found 222.0954; elemental analysis calcd (%) for $C_{12}H_{15}NOS$ (221.09): C 65.12, H 6.83, N 6.33; found C 65.04, H 6.88, N 6.30.

(3*S*,6*R*,7*S*,8*S*)-3,7-Bis-(*tert*-butyldimethylsilanyloxy)-4,4,6,8-tetramethyl-5-oxo-tetradec-12-ynoic 1-[(1*S*,1*E*)-1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-pent-3-ynyl ester (113): A solution of acid **106** (0.550 g, 0.99 mmol), alcohol **112** (0.219 g, 0.99 mmol), DCC (0.266 g, 1.29 mmol) and 4-dimethylaminopyridine (10 mg) in CH_2Cl_2 (14 mL) was stirred for 14 h at ambient temperature. All volatiles were then removed in vacuo and the residue was purified by flash chromatography (pentane/Et_2O 20:1, silica pretreated with NEt_3), providing ester **113** as a colorless syrup (0.604 g, 81%). $[\alpha]_D^{20} = -26.0°$ ($c = 0.96$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 6.95 (s, 1H), 6.52 (br s, 1H), 5.30 (t, $J = 6.7$ Hz, 1H), 4.35 (dd, $J = 6.0$ Hz, 1H), 3.73 (dd, $J = 1.6$, 7.2 Hz, 1H), 3.14 (quin, $J = 7.0$ Hz, 1H), 2.68 (s, 3H), 2.58–2.50 (m, 2H), 2.47 (d, $J = 3.4$ Hz, 1H), 2.31 (dd, $J = 6.1$, 17.0 Hz, 1H), 2.15–2.05 (m, 2H), 2.07 (d, $J = 1.1$ Hz, 3H), 1.73 (dt, $J = 2.4$, 9.1 Hz, 5H), 1.60–1.37 (m, 3H), 1.34–1.11 (m, 2H), 1.22 (s, 3H), 1.04 (s, 3H), 1.02 (d, $J = 6.9$ Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.87 (d, $J = 5.5$ Hz, 3H), 0.09 (s, 3H), 0.05 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 217.8$, 171.0, 164.6, 152.5, 136.4, 121.4, 116.6, 79.2, 77.9, 77.7, 77.4, 77.2, 75.6, 74.3, 73.8, 53.4, 45.3, 40.3, 38.4, 29.9, 27.2, 26.2, 26.0, 23.9, 23.2, 19.9, 19.2, 18.5, 18.2, 17.8, 15.6, 14.6, 3.6, 3.4, −3.6, −3.8, −4.3, −4.8; MS (EI): *m*/*z* (%): 757 (<1), 700 (<1), 497 (2), 406 (2), 301 (2), 272 (2), 253 (7), 204 (100), 185 (4), 151 (6), 73 (18); IR: $\nu = 3105$, 2956, 2930, 2895, 2857, 1740, 1696, 1654, 1506, 1473, 1386, 1362, 1256, 1177, 1089, 989, 837, 776 cm^{-1}; HR-MS ($C_{42}H_{71}NO_5SSi_2 + H$): calcd 758.4670, found 758.4673; elemental analysis calcd (%) for $C_{42}H_{71}NO_5SSi_2$ (757.46): C 66.53, H 9.44, N 1.85; found C 66.67, H 9.36, N 1.81.

(4*S*,7*R*,8*S*,9*S*,16*S*)-4,8-Bis-(*tert*-butyldimethylsilanyloxy)-5,5,7,9-tetramethyl-16-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-vinyl]-1-oxacyclohexadec-13-yne-2,6-dione (114): Diyne **113** (120 mg, 1.58 mmol) was added to a solution of complex **1a** (12 mg, 0.15 mmol) in toluene (10 mL) and CH_2Cl_2 (0.3 mL) and the resulting mixture was stirred at 80 °C for 8 h. All volatiles were then evaporated and the residue was purified by flash chromatography (pentane/Et_2O 20:1) to afford cycloalkyne **114** as a colorless syrup (84 mg, 80%). $[\alpha]_D^{20} = -17.3°$ ($c = 0.75$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.94$ (s, 1H), 6.53 (br s, 1H), 5.30 (m, 1H), 4.68 (dd, $J = 11.3$ Hz, 1H), 3.91 (dd, $J = 1.8$, 6.6 Hz, 1H), 3.22 (quin, $J = 6.9$ Hz, 1H), 2.83–2.70 (m, 1H), 2.69 (s, 3H), 2.69–2.50 (m, 3H), 2.30–2.04 (m, 3H), 2.07 (d, $J = 1.1$ Hz, 3H), 1.80–1.19 (m, 1H), 1.15 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 0.93–0.81(m, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.08 (s, 6H), 0.07 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 216.5$, 170.1, 164.8, 152.4, 136.8, 120.5, 116.8, 82.2, 78.0, 77.4, 76.6, 76.4, 72.6, 54.5, 53.4, 44.4, 41.6, 39.0, 29.7, 26.2, 26.1, 26.0, 24.2, 21.0, 20.5, 19.3, 18.7, 18.5, 18.3, 16.9, 15.0, −3.2, −3.8, −4.0, −4.1; MS (EI): *m*/*z* (%): 703 (6), 688 (4), 646 (100), 604 (7), 444 (78), 402 (17), 344 (9), 288 (8), 272 (6), 270 (20), 204 (21), 185 (11), 151 (17), 101 (13), 73 (47); IR: $\nu = 3105$, 2955, 2929, 2856, 1740, 1702, 1507, 1472, 1385, 1362, 1256, 1100, 837, 775 cm^{-1}; HR-MS ($C_{38}H_{65}NO_4SSi_2 + H$): calcd 704.4200, found 704.4199; elemental analysis calcd (%) for $C_{38}H_{65}NO_4SSi_2$ (703.41): C 56.82, H 9.54; found C 56.91, H 9.66.

(4*S*,7*R*,8*S*,9*S*,16*S*)-4,8-Bis-(*tert*-butyldimethylsilanyloxy)-5,5,7,9-tetramethyl-16-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-vinyl]-(13*Z*)-1-oxacyclohexadec-13-ene-2,6-dione (115): A suspension containing cycloalkyne **114** (25 mg, 0.036 mmol), Lindlar catalyst [30 mg, Pd (5% *w*/*w*) on $CaCO_3$, poisoned with Pb] and quinoline [0.5 mL of a stock solution of quinoline (0.1 mL) in hexane (10 mL)] in CH_2Cl_2 (6 mL) was stirred under

Table 8. Crystal data and structure refinement.

	15	**16**	**19**
empirical formula	$C_{36}H_{54}ClMoN_3O_6$	$C_{36}H_{54}ClMoN_3$	$(C_{24}H_{36}ClMoN_2)_2$
color	red-brown	red	black
formula weight [g mol^{-1}]	756.21	660.21	967.88
crystal system	triclinic	monoclinic	monoclinic
space group	$P\bar{1}$ (no. 2)	$P2_1$ (no. 4)	$P2_1/n$ (no. 14)
a [Å]	10.5705(5)	10.7575(6)	9.3382(19) Å
b [Å]	10.7480(5)	11.1362(6)	19.663(4)
c [Å]	18.4864(8)	14.8699(8)	12.607(3)
α [°]	82.267(2)		
β [°]	85.354(2)	94.480(2)	92.54(3)
γ [°]	63.844(2)		
V [Å^3]	1867.50(15)	1775.94(17)	2312.5(8)
Z	2	2	2
ρ_{calcd}	1.345	1.235	1.390
μ [mm^{-1}]	0.469	0.471	0.695
F(000)	796	700	1012
crystal size [mm]	0.70 × 0.32 × 0.25	0.26 × 0.26 × 0.06	0.63 × 0.17 × 0.09
θ range [°]	2.12 to 25.00	1.90 to 33.15	1.92 to 27.41
reflections collected	14396	19610	12390
independent reflections	6362 [$R_{int} = 0.039$]	10480 [$R_{int} = 0.055$]	4923 [$R_{int} = 0.151$]
reflections with $I > 2\sigma(I)$	5180	7068	3384
completeness to θ [°]/[%]	25.00/96.6	33.15/94.4	27.41/93.5
absorption correction	empirical	empirical	none
max./min. transmission	1.00/0.69	0.97/0.88	–/–
data/restraints/parameters	6362/0/424	10480/1/386	4923/0/264
GoF on F^2	0.94	0.95	0.99
final R indices [$I > 2\sigma(I)$]	$R1 = 0.048$, $wR^2 = 0.124$	$R1 = 0.055$, $wR^2 = 0.090$	$R1 = 0.053$, $wR^2 = 0.123$
R indices (all data)	$R1 = 0.062$, $wR^2 = 0.131$	$R1 = 0.104$, $wR^2 = 0.102$	$R1 = 0.094$, $wR^2 = 0.144$
absolute structure parameter	–	0.48(3)	–
largest diff. peak/hole [e Å^{-3}]	1.6/ − 1.1	0.7/ − 0.6	0.7/ − 2.1
	20	**32**	**11b**
empirical formula	$C_{32}H_{45}Cl_2MoN_3$	$C_{19}H_{24}O_2$	$C_{15}H_{23}F_3LiNO$
color	black	colorless	dark brown
formula weight [g mol^{-1}]	638.55	284.38	297.28
crystal system	monoclinic	triclinic	monoclinic
space group	$C2/c$ (no. 15)	$P\bar{1}$ (no. 2)	$P2_1/c$ (no. 14)
a [Å]	15.0817(7)	8.3672(3)	20.7242(5)
b [Å]	14.8449(5)	9.6694(4)	9.6753(2)
c [Å]	15.3828(7)	10.0958(4)	16.7152(4)
α [°]		94.134(2)	
β [°]	115.232(2)	$\beta = 100.865(2)$	105.3810(10)
γ [°]		99.024(2)	
V [Å^3]	3115.4(2)	787.87(5)	3231.57(13)
Z	4	2	8
ρ_{calcd}	1.361	1.199	1.222
μ [mm^{-1}]	0.618	0.076	0.098
F(000)	1336	308	1264
crystal size [mm]	0.23 × 0.10 × 0.07	0.80 × 0.40 × 0.12	0.46 × 0.22 × 0.04
θ range [°]	2.10 to 31.97	2.14 to 33.12	2.78 to 27.86
reflections collected	16337	7971	54036
independent reflections	5343 [$R_{int} = 0.148$]	4922 [$R_{int} = 0.0216$]	7674 [$R_{int} = 0.1337$]
reflections with $I > 2\sigma(I)$	2869	3277	3861
completeness to θ [°]/[%]	31.97/98.7	33.12/82.2	27.86/99.8
absorption correction	none	empirical	none
max./min. transmission	–/–	0.93/0.58	–/–
data/restraints/parameters	5343/0/180	4922/0/190	7674/0/417
GoF on F^2	0.97	1.05	0.95
final R indices [$I > 2\sigma(I)$]	$R1 = 0.061$, $wR^2 = 0.146$	$R1 = 0.058$, $wR^2 = 0.142$	$R1 = 0.059$, $wR^2 = 0.139$
R indices (all data)	$R1 = 0.141$, $wR^2 = 0.175$	$R1 = 0.092$, $wR^2 = 0.157$	$R1 = 0.144$, $wR^2 = 0.164$
largest diff. peak/hole [e Å^{-3}]	1.1/ − 2.2	0.6/ − 0.3	0.4/ − 0.5

an atmosphere of H_2 (1 atm) for 8 h at ambient temperature. The mixture was then filtered through a pad of Celite, the filtrate was evaporated and the residue was purified by flash chromatography (pentane/Et_2O 20:1) to afford cycloalkene **115** as a colorless syrup (25 mg, 99 %). ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 6.94$ (s, 1H), 6.55 (br s, 1H), 5.51 (dt, $J = 3.5$, 11.1 Hz, 1H), 5.43 – 5.30 (m, 1H), 4.99 (d, $J = 10.0$ Hz, 1H), 4.01 (dd, $J = 1.3$, 10.1 Hz, 1H), 3.88 (d, $J = 8.7$ Hz, 1H), 3.02 – 2.95 (m, 1H), 2.85 – 2.60 (m, 3H), 2.69 (s, 3H), 2.41 – 2.35 (m, 1H), 2.10 (d, $J = 1.1$ Hz, 3H), 2.11 – 2.02 (m, 1H), 1.96 – 1.83 (m, 1H), 1.61 – 1.45 (m, 3H), 1.38 – 1.10 (m, 2H), 1.17 (s, 3H), 1.13 (s, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 0.96 – 0.90 (m, 3H), 0.92,

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0.83 (2s, 18H), 0.10, 0.08, 0.06, −0.11 (4s, 12H); ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 214.9, 171.2, 164.6, 152.5, 138.5, 135.0, 122.9, 119.5, 116.0, 79.5, 79.2, 76.4, 53.4, 47.9, 42.0, 39.0, 38.0, 31.9, 31.4, 29.1, 28.4, 26.4, 26.2, 24.9, 24.2, 19.2, 19.0, 18.7, 18.6, 17.6, 15.2, −3.2, −3.4, −3.7, −5.7. The analytical data are in full agreement with those reported in the literature.[51]

Epothilone C (88): A polyethylene flask was charged with silyl ether **115** (25.0 mg, 0.035 mmol), CH_3CN (1 mL), Et_2O (1 mL), aq. HF (48% *w*/*w*, 1 mL) and glass sand (30 mg) and the suspension was stirred for 8 h at ambient temperature. The reaction was quenched with aq. $NaHCO_3$ (10 mL), the aqueous layer was repeatedly extracted with Et_2O (100 mL in several portions), the combined organic phases were dried (Na_2SO_4) and evaporated, and the crude product was purified by flash chromatography (Et_2O) to afford the title compound **88** as a viscous syrup (13.3 mg, 79%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.02 (s, 1H), 6.72 (br s, 1H), 5.44 (dt, J = 4.7, 10.5 Hz, 1H), 5.35 (dt, J = 4.6, 10.2 Hz, 1H), 5.24 (d, J = 9.2 Hz, 1H), 4.33 (br s, 1H), 3.68 (s, 1H), 3.14 (q, J = 5.3 Hz, 1H), 3.03 (br s, 1H), 2.79 (m, 3H), 2.70–2.63 (m, 1H), 2.48 (dd, J = 14.9 Hz, 1H), 2.27 (d, J = 15.1 Hz, 1H), 2.22–2.15 (m, 2H), 2.07 (d, J = 1.0 Hz, 2H), 2.05–1.96 (m, 1H), 1.77–1.71 (m, 1H), 1.70–1.50 (m, 2H), 1.36 (s, 3H), 1.35–1.13 (m, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.04 (s, 3H), 0.98 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 220.5, 170.4, 165.0, 152.0, 138.6, 133.6, 125.0, 119.5, 115.8, 78.1, 74.2, 72.4, 53.3, 41.8, 39.2, 38.7, 32.4, 31.6, 27.6, 27.4, 26.2, 23.0, 18.6, 17.7, 15.3, 13.4. All analytical data are in full agreement with those reported in the literature.[51]

Crystal structure analysis of compounds 11b, 15, 16, 19, 20, and 32: Suitable single crystals of all compounds were selected, and in case of air or humidity sensitive compounds, protected under inert perfluoro-polyether. Unit cell determinations and data collections were carried out at 100 K using nitrogen gas stream cooling. $Mo_{K\alpha}$ radiation (λ = 0.71073 Å) was used as primary radiation. A Nonius FR591 rotating anode generator in combination with a Nonius KappaCCD system was used for **20**. A sealed tube KappaCCD system was used for **11b** and **19**. All other data collections utilised a Bruker AXS Smart 1k area detector system. Crystal structures were determined using SHELXS-97[70] and full-matrix least-squares refinement based on F^2 was performed using SHELXL-97.[71] Molecular structure diagrams were drawn using the program Diamond.[72] Crystallographic details, individual to each structure are compiled in Table 8. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-165449 for **32**; CCDC-165450 for **19**; CCDC-165451 for **15**; CCDC-165452 for **11b** and CCDC-118587 for **16**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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