Ring Closing Alkyne Metathesis. Comparative Investigation of Two Different Catalyst Systems and Application to the Stereoselective Synthesis of Olfactory Lactones, Azamacrolides, and the Macrocyclic Perimeter of the Marine Alkaloid Nakadomarin A

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Abstract: Previously unknown ring closing metathesis reactions of diynes are described which open an efficient and stereoselective entry into macrocyclic (*Z*)-alkenes if the resulting cycloalkyne products are subjected to Lindlar reduction. This new two-step strategy offers significant advantages in stereochemical terms over conventional RCM of dienes which usually leads to (*E*,*Z*)-mixtures when applied to the formation of large rings. The tungsten alkylidyne complex $(tBuO)_3W{\equiv}CCMe_3$ (**1a**) and analogues thereof as well as a structurally unknown species formed in situ from $Mo(CO)_6$ and *p*-chlorophenol effect the crucial alkyne metathesis reactions in a highly efficient manner, with the former catalyst being more tolerant toward structural variations of the substrates and polar functional groups. Applications to the stereoselective synthesis of the olfactory compounds ambrettolide **23** and yuzu lactone **24**, the insect repellent azamacrolides epilachnene **31** and homoepilachnene **33**, as well as to the fully functional building block **64** required for a total synthesis of the cytotoxic alkaloid nakadomarin A **51** highlight the relevance of this new concept for natural product chemistry. In the latter case, the diyne substrate **62** necessary for ring closing alkyne metathesis was obtained via a novel furan synthesis relying on a palladium-catalyzed opening of a vinyl epoxide followed by an oxidative cyclization of the heterocyclic ring.

Introduction

The advent of well-defined catalysts for *alkene* metathesis combining high activity, durability, and functional group tolerance has revolutionized the field.[1,2] The past decade has seen the rapid embrace of these reagents as tools for advanced organic chemistry and the success of this development is witnessed by a plethora of elegant applications to the synthesis of natural and non-natural products.[3] Ring closing metathesis of dienes (RCM) deserves particular mentioning because it provides ready access to carbo- and heterocycles of almost any size including medium and macrocyclic rings.[4,5] In the latter series, however, the cycloalkenes formed are usually obtained as mixtures of the (*E*)- and (*Z*)-isomers, the ratio of which can, at present, be neither controlled nor properly predicted. This constitutes a significant drawback which is exemplified, e.g., by several approaches to epothilone A: although different research teams succeeded in forming the 16-membered ring of this promising chemotherapeutic agent by RCM,[6] separation of the resulting (*E*,*Z*)-mixtures was inevitable because only the (*Z*)-alkene can be converted into the target. The fact that the required (*Z*)-isomer was formed as the minor product in many cases attests to the relevance of this stereochemical issue.

On the long term, this fundamental problem calls for the development of stereoselective RCM catalysts. One may, however, contemplate that ring closing *alkyne* metathesis

(1) For leading references see: (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc*. **1993**, *115*, 9858. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (c) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc*. **1990**, *112*, 3875.

(2) For recent innovations see: (a) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (b) Huang, J.; Stevens, E. D.; Nolan, S. P.; Pedersen, J. L. *J. Am. Chem. Soc*. **1999**, *121*, 2674. (c) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett*. **1999**, *40*, 4787. (d) Hansen, S. M.; Rominger, F.; Metz, M.; Hofmann, P. *Chem. Eur. J*. **1999**, *5*, 557. (e) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1999**, *121*, 791. (f) Fürstner, A.; Hill, A. F.; Liebl, M.; Winton-Ely, J. D. E. T. *Chem. Commun*. **1999**, 601. (g) Demonceau, A.; Stumpf, A. W.; Saive, E.; Noels, A. F. *Macromolecules* **1997**, *30*, 3127. (h) Hafner, A.; Mühlebach, A.; van der Schaaf, P. A. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2121. (i) Fürstner, A.; Ackermann, L. *Chem. Commun*. **1999**, 95. (j) Fürstner, A.; Picquet, M.; Bruneau C.; Dixneuf, P. H. *Chem. Commun*. **1998**, 1315.

(3) For recent reviews on RCM see the following for leading references: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Top. Catal*. **1997**, *4*, 285. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2036. (d) Fürstner, A. *Top. Organomet. Chem*. **1998**, *1*, 37. (e) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Methathesis Polymerization*, 2nd ed.; Academic Press: New York, 1997.

(4) For recent reviews on macrocycle syntheses via RCM see: (a) Nicolaou, K. C.; King, N. P.; He, Y. *Top. Organomet. Chem*. **1998**, *1*, 73. (b) Hoveyda, A. H. *Top. Organomet. Chem*. **1998**, *1*, 105 and literature cited therein.

(5) For RCM-based macrocycle syntheses from our laboratory see: (a) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 3942. (b) Fürstner, A.; Müller, T. *J. Am. Chem. Soc*. **1999**, *121*, 7814. (c) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc*. **1997**, *119*, 9130. (d) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005. (e) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 8746. (f) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010. (g) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem*. **1999**, *64*, 2361. (h) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215.

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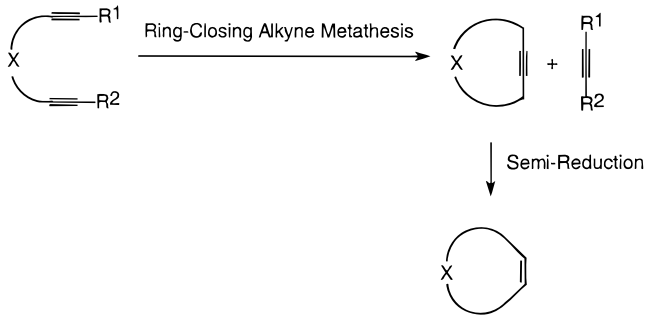
Scheme 1



followed by semireduction of the resulting cycloalkyne also provides a viable solution (Scheme 1). Despite the close mechanistic ties of alkyne metathesis with RCM,[7] this transformation has received comparatively little attention so far although different pre-catalysts have been reported in the literature.[8] Among them, Schrock alkylidyne complexes of various transition metals are particularly attractive and well behaved reagents which have been thoroughly studied from the mechanistic point of view.[9−11] Moreover, some multicomponent initiator systems for alkyne metathesis have been described in which a structurally unknown catalyst is formed in situ, e.g., by heating $Mo(CO)_6$ in the presence of phenol additives.[12] So far, however, applications of these reagents are essentially confined to the preparation of speciality polymers [13] and to the dimerization or cross-metathesis of rather simple acetylene derivatives.[14]

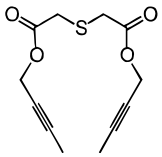
We now describe the first efficient synthesis of functionalized macrocycles by ring closing metathesis of diyne substrates using well-defined alkylidyne complexes as well as catalysts formed "in situ".[15] Subsequent partial reduction of the resulting cycloalkynes by Lindlar hydrogenation opens an efficient and stereoselective route to (*Z*)-configurated cycloalkenes. Several applications to the synthesis of macrocyclic musks, azamacrolides, as well as to the macrocyclic perimeter of the marine alkaloid nakadomarin A illustrate the versatility and scope of this new strategy.

Results and Discussion

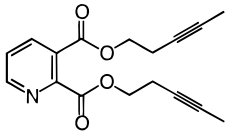
Model Studies. Initially, we tested the tungsten alkylidyne complex $(tBuO)_3W{\equiv}CCMe_3$ (**1a**)[10] developed by Schrock et al. as a pre-catalyst for ring closing alkyne metathesis. This reagent is readily prepared on a large scale by cleavage of the metal−metal triple bond of $[(tBuO)_3W{\equiv}W(OtBu)_3]$ (**2**)[16] with neoheptyne according to a literature procedure.

Gratifyingly, complex **1a** turned out to catalyze the cyclization of *nonterminal* diynes [17] to cycloalkynes very efficiently as illustrated by the examples compiled in Table 1. Different functional groups such as ethers, esters, enoates, amides, silyl ethers, sulfonamides, carbamates, and sulfones were found to be compatible with the reaction conditions. Moreover, **1a** rigorously distinguishes between alkyne and alkene groups, the latter remaining untouched. This favorable profile allows the formation of different cycloalkynes of ring sizes ≥12 (including even very large rings) in good to excellent yields provided that the reactions are carried out under reasonably high dilution (≤0.02 M). Chlorobenzene was found to be slightly superior to toluene or THF as the reaction medium (Table 2). With 1,2,4-trichlorobenzene as the solvent (bp 214 °C) it is possible to remove the alkyne byproduct $R_1{-}C{\equiv}C{-}R^2$ (usually 2-butyne) from the mixture by running the reactions under reduced pressure (ca. 20 mbar); this seems to have a positive effect on the conversion.[18]

Another noteworthy feature is the high activity of **1a** combined with the surprisingly strong bias for cyclization. In contrast to conventional RCM that often requires prolonged reaction times when applied to the macrocyclic series,[4,5] cyclizations effected by **1a** are usually complete within 30−60 min. Traces of cyclodimeric products are detected in a few cases; however, we have never observed any cycloallene byproducts which frequently interfere with the preparation of cycloalkynes by more conventional methods.[19]



20



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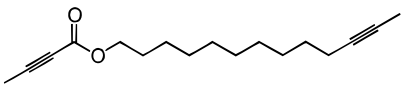


22

Limitations for ring closing alkyne metathesis reactions catalyzed by **1a** were encountered with functional groups showing high affinity to the Lewis acidic tungsten center of

(7) A mechanism for alkyne metathesis via alkylidyne- and metallacyclobutadiene complexes has been proposed early on by Katz et al., cf.: Katz, T. J.; McGinnis, J. *J. Am. Chem. Soc*. **1975**, *97*, 1592. This hypothesis has been verified by the first alkyne metathesis reactions involving defined metal alkylidyne catalysts and by the isolation of metallacyclobutadiene intermediates, cf. ref 9.

(8) For a short review see: Bunz, U. H. F.; Kloppenburg, L. *Angew. Chem*. **1999**, *111*, 503; *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 478.

(9) For the first alkyne metathesis reaction using a defined metal alkylidyne catalyst see: Wengrovius, J. H.; Sancho, J.; Schrock, R. R. *J. Am. Chem. Soc*. **1981**, *103*, 3932.

(10) Preparation and applications of tungsten alkylidyne complexes: (a) Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645. (b) Freudenberger, J. H.; Schrock, R. R.; Churchill, M. R.; Rheingold, A. L.; Ziller, J. W. *Organometallics* **1984**, *3*, 1563. (c) Listemann, M. L.; Schrock, R. R. *Organometallics* **1985**, *4*, 74. (d) Schrock, R. R. *Polyhedron* **1995**, *14*, 3177.

(11) For the use of Schrock-type alkylidyne complexes of transition metals other than tungsten in alkyne metathesis see the following for leading references: (a) McCullough, L. G.; Schrock, R. R.; Dewan, J. C.; Murdzek, J. C. *J. Am. Chem. Soc*. **1985**, *107*, 5987. (b) Weinstock, I. A.; Schrock, R. R.; Davis, W. M. *J. Am. Chem. Soc*. **1991**, *113*, 135.

(12) (a) Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun*. **1974**, 786. (b) Mortreux, A.; Dy, N.; Blanchard, M. *J. Mol. Catal*. **1975**, *1*, 101. (c) Du Plessis, J. A. K.; Vosloo, H. C. M. *J. Mol. Catal*. **1991**, *65*, 51. (d) Vosloo, H. C. M.; du Plessis, J. A. K. *J. Mol. Catal. A* **1998**, *133*, 205. (e) For related initiator systems see also: Bencheick, A.; Petit, M.; Mortreux, A.; Petit, F. *J. Mol. Catal*. **1982**, *15*, 93.

(13) (a) Weiss, K.; Michel, A.; Auth, E.-M.; Bunz, U. H. F.; Mangel, T.; Müllen K. *Angew. Chem*. **1997**, *109*, 522; *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 506. (b) Kloppenburg, L.; Song, D.; Bunz, U. H. F. *J. Am. Chem. Soc*. **1998**, *120*, 7973. (c) Zhang, X.-P.; Bazan, G. C. *Macromolecules* **1994**, *27*, 4627. (d) Krouse, S. A.; Schrock, R. R. *Macromolecules* **1989**, *22*, 2569.

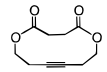
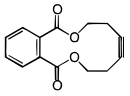
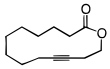
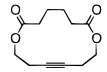
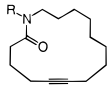
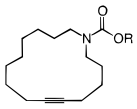
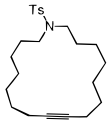
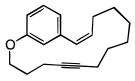
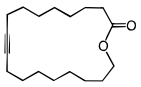
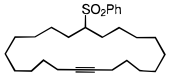
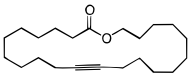
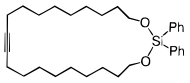
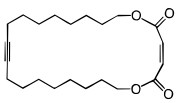
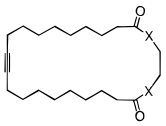
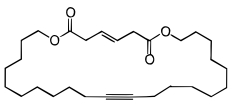
(14) (a) Villemin, D.; Cadiot, P. *Tetrahedron Lett*. **1982**, *23*, 5139. (b) Pschirer, N. G.; Bunz, U. H. F. *Tetrahedron Lett*. **1999**, *40*, 2481. (c) Kaneta, N.; Hirai, T.; Mori, M. *Chem. Lett*. **1995**, 627. (d) Kaneta, N.; Hikichi, K.; Asaka, S.-I.; Uemura, M.; Mori, M. *Chem. Lett*. **1995**, 1055.

(15) (a) For a preliminary communication see: Fürstner, A.; Seidel, G. *Angew. Chem*. **1998**, *110*, 1758; *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1734. (b) See also: Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc*. **1999**, *121*, 9453.

(16) For a convenient preparation of **2** see: Akiyama, M.; Chisholm, M. H.; Cotton, F. A.; Extine, M. W.; Haitko, D. A.; Little, D.; Fanwick, P. E. *Inorg. Chem*. **1979**, *18*, 2266.

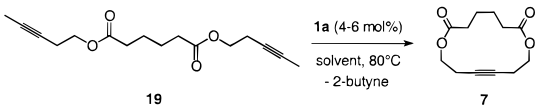
(17) Terminal alkynes are mainly polymerized in the presence of **1a** and related catalysts, cf.: Bray, A.; Mortreux, A.; Petit, F.; Petit, M.; Szymanska-Buzar, T. *J. Chem. Soc., Chem. Commun*. **1993**, 197.

Table 1. Ring Closing Alkyne Metathesis Catalyzed by the Tungsten Alkylidyne Complex **1a** or by a [Mo]-Catalyst Formed in Situ from $Mo(CO)_6$ and *p*-Chlorophenol

Entry	Product		1a[a]	[Mo][b]
1		**3**	73[c]	64
2		**4**	68	0
3		**5**	62	0
4		**6**	52	
5		**7**	79	
6		**8a**	62 (R = H)	0 (R = H)
7		**8b**	72 (R = Me)	64 (R = Me)
8	 R = 9-fluorenylmethyl	**9**	62	68
9		**10**	66[e]	
10		**11**	79[e]	
11		**12**	69[d]	71
12		**13**	75[d,e]	
13		**14**	64	72
14		**15**	55	decomp.
15		**16**	62	58
16		**17a**	97 (X = O)	
17		**17b**	90 (X = NH)	
18		**18**	53	70

[a] Using **1a** (5 mol %) in chlorobenzene at 80 °C unless stated otherwise. [b] Using $Mo(CO)_6$ (5 mol %) and *p*-chlorophenol (1 equiv) in chlorobenzene at 140 °C. [c] Ca. 10% of starting material recovered. [d] Ca. 5% of cyclic dimer formed. [e] The reaction was carried out in toluene at 80 °C.

Table 2. Solvent Dependence of the Ring Closing Alkyne Metathesis Catalyzed by the Tungsten Alkylidyne Complex **1a**



19 **7**

entry	solvent	yield (%)
1	THF	64
2	toluene	69
3	chlorobenzene	73[a]
4	1,2,4-trichlorobenzene	79[b]

[a] 10% of the substrate were recovered unchanged. [b] The reaction was carried out under reduced pressure (ca. 20 mbar).

Table 3. Screening of the Catalytic Activity of Different Tungsten Alkylidyne Complexes in the Cyclization of Diyne **19** to Cycloalkyne **7**[a]

entry	pre-catalyst		yield (%)
1	$(tBuO)_3W{\equiv}CCMe_3$	**1a**	69
2	$(tBuO)_3W{\equiv}CPh$	**1b**	70
3	$[(F_3C)_2CHO]_3W{\equiv}CCMe_3{\cdot}dme$	**1c**	61
4	$Cl_3W{\equiv}CCMe_3{\cdot}dme$	**1d**	0[b]

[a] All reactions are carried out in toluene at 80 °C using 4−6 mol % of the respective pre-catalyst. [b] Substrate recovered unchanged.

this complex. This holds true for substrates **20** and **21** containing thioether or basic nitrogen groups, respectively, which were recovered unchanged. Likewise, treatment of the 2-butynoate **22** with catalytic amounts of **1a** failed to afford the desired cycloalkyne product.

Evaluation of Related Tungsten Alkylidyne Pre-Catalysts. Inspired by publications of Schrock et al.[10] we compared the reactivity pattern of different tungsten alkylidyne complexes to that of compound **1a** serving as the calibration point for this investigation.

As can be seen from the data compiled in Table 3, however, no major improvement in terms of yield or reaction rate has been noticed by choosing either a different alkylidyne substituent (cf. entries 1/2) or by replacing the *tert*-butoxy ligands of **1a** by more electron withdrawing hexafluoro-2-propoxy groups (cf. entries 1/3). In line with literature reports, the trichlorotungsten alkylidyne complex **1d**[20] was found to be catalytically inert. Therefore we have routinely used the easily accessible complex **1a** in all further applications.

$Mo(CO)_6$/*p*-Chlorophenol as an "Instant" Catalyst System for Ring Closing Alkyne Metathesis. The first homogeneous catalyst for alkyne metathesis was reported by Mortreux et al. and consisted of $Mo(CO)_6$ activated in situ by phenolic additives.[12] Although it was assumed that a molybdenum alkylidyne complex is formed in situ from these ingredients, the precise nature of the active species is still unknown. The ease of application of this "instant procedure", however, is

(18) In some cases, reactions performed in chorobenzene or toluene stop at ca. 90% conversion of the diyne substrate (cf. Table 1) and complete conversion can be reached neither by increasing the catalyst loading nor by prolonged reaction times.

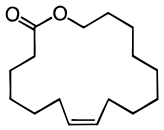
(19) For literature methods allowing the preparation of cycloalkynes (and/or cycloallenes) see the following for leading references: (a) Review: Meier, H. *Synthesis* **1972**, 235. (b) Boivin, J.; Huppé, S.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 5737. (c) Schreiber, J.; Felix, D.; Eschenmoser, A.; Winter, M.; Gautschi, F.; Schulte-Elte, K. H.; Sundt, E.; Ohloff, G.; Kalvoda, J.; Kaufmann, H.; Wieland, P.; Anner, G. *Helv. Chim. Acta* **1967**, *50*, 2101. (d) Mandeville, W. H.; Whitesides, G. M. *J. Org. Chem.* **1986**, *51*, 3257. (e) Brummond, K. M.; Gesenberg, K. D.; Kent, J. L.; Kerekes, A. D. *Tetrahedron Lett.* **1998**, *39*, 8613.

(20) Stevenson, M. A.; Hopkins, M. D. *Organometallics* **1997**, *16*, 3572.

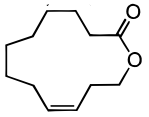
appealing because it employs only off-the-shelf reagents and does not require any particular precautions with regard to drying and handling of the solvents.

Recent investigations have shown that dimerizations and polymerizations of propynylated arene derivatives are best carried out with $Mo(CO)_6$ (5−10 mol %) in combination with *p*-chlorophenol or 4-trifluoromethylphenol (50−150 mol %) in chlorobenzene or 1,2-dichlorobenzene at 140−150 °C.[14] The results summarized in Table 1 show that these conditions also apply to the formation of cycloalkynes. A more detailed assessment of the data, however, reveals a somewhat limited scope of this particular initiator system with regard to structure (cf. entries 2 and 3) and functional group tolerance. Specifically, a secondary amide turned out to be incompatible, although this group poses no problem for Schrock's pre-catalyst **1a** (entry 6). Similarly, a silyl ether group was found to be unstable in the presence of the phenol additives (entry 14). The rather high temperature (140−150 °C) can also be problematic with elaborate and polyfunctional substrates. Therefore we conclude that the "instant procedure" is useful in certain cases and deserves attention for its user-friendly setup, although more advanced compounds will almost certainly require well-defined pre-catalysts such as **1** which effect ring closure under less forcing conditions.

Stereoselective Synthesis of Olfactory Macrolides: Ambrettolide and Yuzu Lactone. The results compiled in Table 1 show that lactones of various ring sizes are readily accessible by ring closing alkyne metathesis using either **1a** or $Mo(CO)_6$ plus phenol as initiators. An obvious application relates to the synthesis of the musk-odored macrolide ambrettolide **23**[21] and the camphor-like and minty-odored yuzu lactone **24**[22] which are biodegradable ingredients for the perfume industry. Since both of them contain (*Z*)-configurated double bonds, a stereoselective formation via RCM of the appropriate diene precursors cannot be expected. Therefore these simple targets provide a first test for our alkyne metathesis/Lindlar reduction strategy.



23



24

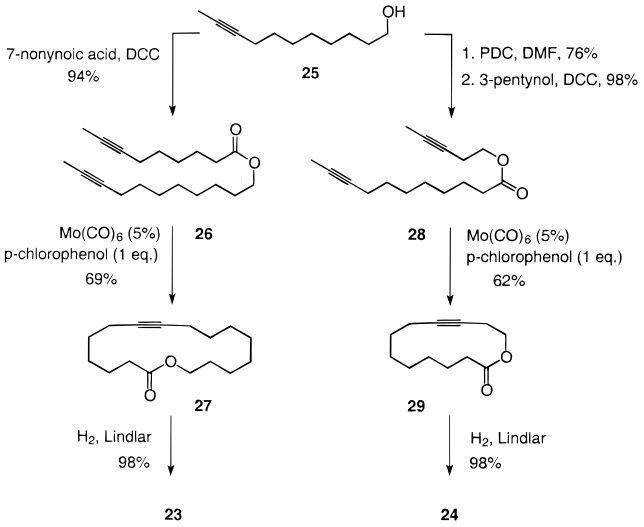
Both targets can be prepared from 9-undecynol **25** as the common starting material as shown in Scheme 2. Specifically, treatment of diynes **26** and **28** derived thereof with $Mo(CO)_6$ (5 mol %) and *p*-chlorophenol (1 equiv) in chlorobenzene at 140 °C led to the clean formation of the desired cycloalkynes **27** and **29**, respectively. Subsequent Lindlar reduction proceeds smoothly in both cases and delivers the olfactory products with excellent overall yields in a stereoselective manner.

Epilachnene and Homoepilachnene. A series of homologous azamacrolides **30**−**33** discovered in 1993 in the defense secretions of the pupae of the Mexican beetle *Epilachnar varivestis* constitute a rather unique family of alkaloids which has attracted considerable attention over the last years.[23−25] They are the first examples of naturally occurring macrolactones containing a basic nitrogen atom in the tether that do not ring-contract to the corresponding amides. Moreover, these compounds prove for the first time that insects in the pupal state can defend themselves by chemical means.

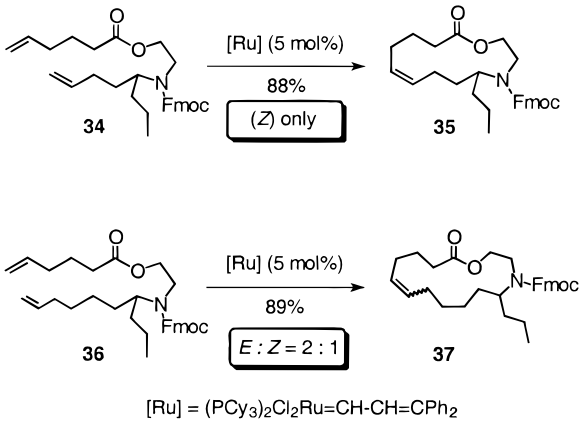
(21) (a) Ohloff, G. *Riechstoffe und Geruchssinn*; Springer: Berlin, 1990. (b) Lehmann, J.; Tochtermann, W. *Tetrahedron* **1999**, *55*, 2639.

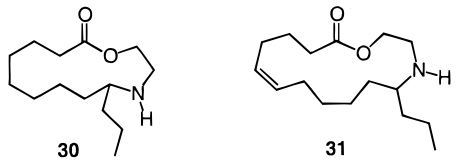
(22) (a) Doss, R. P.; Gould, S. J.; Johnson, K. J. R.; Flath, R. A.; Kohnert, R. L. *Phytochemistry* **1989**, *28*, 3311. (b) Rodefeld, L.; Tochtermann, W. *Tetrahedron* **1998**, *54*, 5893.

Scheme 2



Scheme 3





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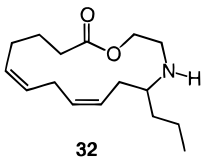
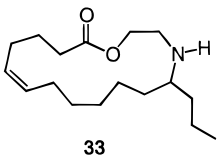


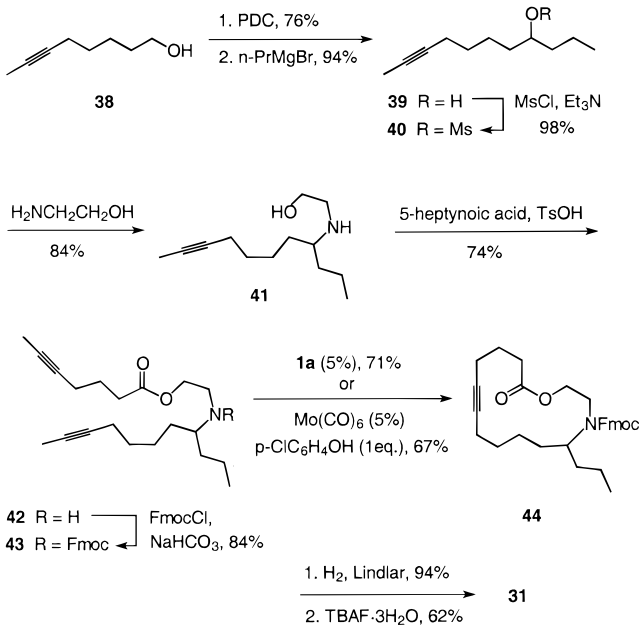
32



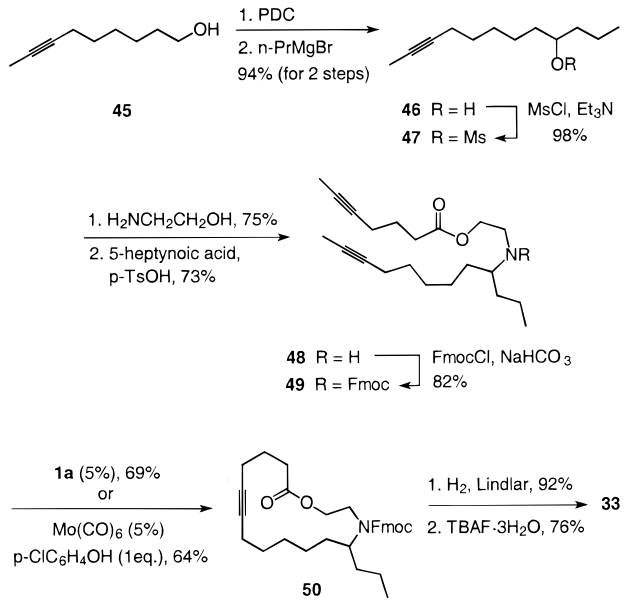
33

Our previous approach to these bioactive targets was based on conventional RCM and has clearly revealed the problems in predicting and controlling the stereochemical outcome of this reaction (Scheme 3).[25] While cyclization of diene **34** catalyzed by the Grubbs carbene $(PCy_3)_2Cl_2Ru{=}CHCH{=}CPh_2$ surprisingly led to the exclusive formation of (*Z*)-**35** (which was subsequently hydrogenated to afford the natural product **30**), the homologous substrate **36** afforded N-protected epilachnene (*Z*)-**37** together with its (*E*)-analogue in a 1:2 ratio. The fact that the separation of the desired (*Z*)-**37** from the predominating (*E*)-isomer could only be achieved by HPLC detracts from the

Scheme 4



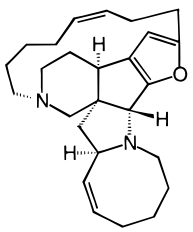
Scheme 5



appeal of this approach and underscores the basic dilemma of RCM in applications to stereochemically defined target molecules.

Ring closing alkyne metathesis followed by Lindlar reduction provides once again a convenient, high yielding, and stereoselective solution to this problem (Scheme 4). Specifically, oxidation of 6-octyn-1-ol **38** with PDC in CH_2Cl_2 and treatment of the resulting aldehyde with *n*-propylmagnesium bromide affords alcohol **39**. Conversion into the corresponding mesylate **40**, substitution of the latter with ethanolamine, esterification of the resulting alcohol **41** with 5-heptynoic acid, followed by protection of the secondary amine by an Fmoc group delivers diyne **43** required for the envisaged ring closing diyne metathesis reaction. This transformation proceeds readily on exposure of **43** to either catalytic amounts of **1a** (71% isolated yield of **44**) or by means of the "instant procedure" using $Mo(CO)_6$ and *p*-chlorophenol (67% isolated yield of **44**). Lindlar reduction of the resulting cycloalkyne **44** followed by deprotection of the N-Fmoc group with TBAF·$3H_2O$ affords epilachnene **31** in excellent overall yield. Its higher homologue homoepilachnene **33** was obtained by following a similar route as depicted in Scheme 5.

Concise Appraoch to the Macrocyclic Perimeter of the Marine Alkaloid Nakadomarin A. During the search for bioactive natural products of marine origin, Kobayashi et al. isolated in 1997 the novel hexacyclic alkaloid nakadomarin A (**51**) from the sponge *Amphimedon* sp. (SS-264) collected off



51

the coast of Okinawa.[26] Although this compound is biosynthetically related to the manzamine alkaloids,[27] the impressively complex array of carbo- and heterocyclic rings of its backbone has no precedent in the literature. This unique molecular topology, the poor accessibility of **51** from the natural source, and its pronounced cytotoxicity as well as inhibitory activity against cyclin dependent kinase 4 render nakadomarin A a challenging target for total synthesis.

Our approach to **51** is guided by the idea to elaborate its most demanding structural features early on, as potential lack of control in a later stage of the synthesis may imperil the entire project. These strategic structural elements comprise (i) the 15-membered ring containing a (*Z*)-configurated double bond, (ii) the rather strained hexahydroazocine moiety, and (iii) the potentially labile furan unit. The envisaged key building blocks **52** and **53** which embody these motifs may then be assembled by taking advantage of the ancillary group X in **52** (X = SO_2-Ph etc.) and the pronounced bias of the furan moiety for regioselective metalations and/or electrophilic substitution reactions (Scheme 6).

We felt that the 15-membered ring of the nakadomarin A skeleton constitutes a challenging testing ground for the validity of the alkyne metathesis /semireduction concept. Our approach (Scheme 7) starts with sulfonium salt **54** which is available on a multigram scale from commercial 3-chloro-2-chloromethyl-1-propene as previously described.[28] Deprotonation of **54** with tBuLi followed by trapping of the resulting sulfur ylide with 4-hexynal **55** delivers vinylepoxide **56** in 71% yield which

(23) Isolation: Attygalle, A. B.; McCormick, K. D.; Blankespoor, C. L.; Eisner, T.; Meinwald, J. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 5204.

(24) Previous syntheses: (a) Farmer, J. J.; Attygalle, A. B.; Smedley, S. R.; Eisner, T.; Meinwald, J. *Tetrahedron Lett*. **1997**, *38*, 2787. (b) Rao, B. V.; Kumar, V. S.; Nagarajan, M.; Sitaramaiah, D.; Rama Rao, A. V. *Tetrahedron Lett*. **1996**, *37*, 8613. (c) Gribble, G. W.; Silva, R. A. *Tetrahedron Lett*. **1996**, *37*, 2145. (d) King, A. G.; Meinwald, J.; Eisner, T.; Blankespoor, C. L. *Tetrahedron Lett*. **1996**, *37*, 2141. (e) Rama Rao, A. V.; Rao, B. V.; Bhanu, M. N.; Kumar, V. S. *Tetrahedron Lett*. **1994**, *35*, 3201.

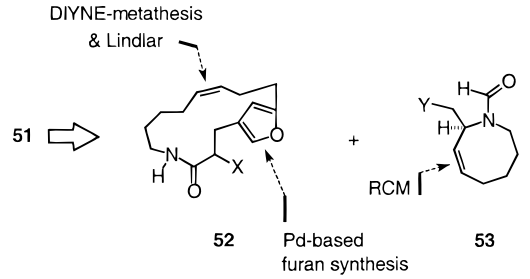
(25) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792.

(26) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236.

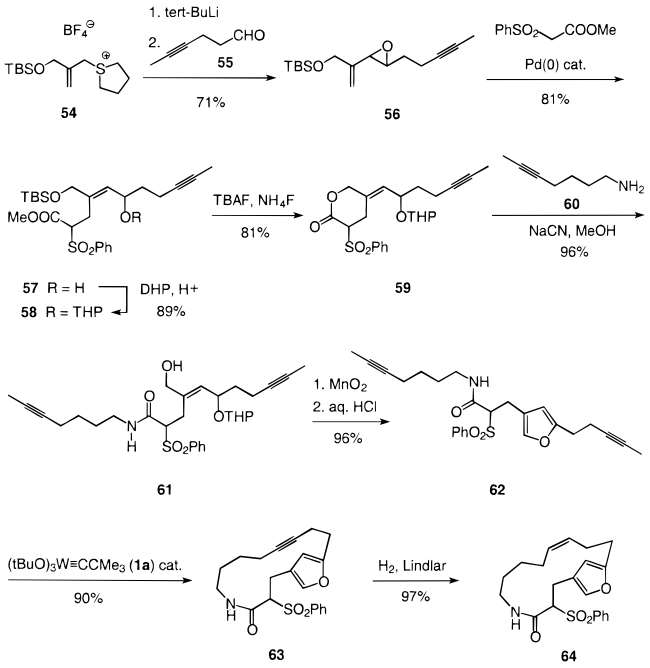
(27) For reviews on manzamines and related alkaloids see: (a) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201. (b) Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *Org. Prep. Proc. Int*. **1998**, *30*, 1. (c) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765. For recent total syntheses of manzamine A see: (d) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc*. **1999**, *121*, 866. (e) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc*. **1998**, *120*, 6425.

(28) (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc*. **1998**, *120*, 2817. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc*. **1997**, *119*, 2944.

Scheme 6

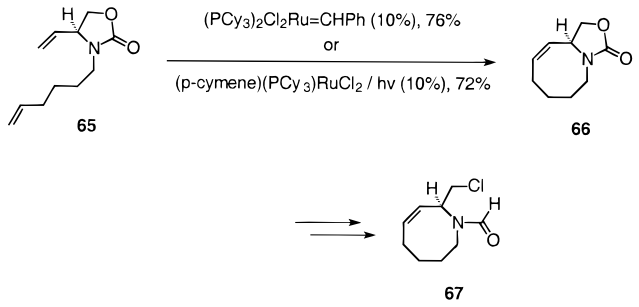


Scheme 7



readily reacts with methyl (phenylsulfonyl)acetate in the presence of catalytic amounts of $Pd(PPh_3)_4$ via the corresponding π-allylpalladium intermediate.[29,30] Protection of the secondary alcohol in **57** as a THP acetal followed by cleavage of the terminal OTBS group by means of TBAF in buffered medium affords compound **59** in excellent yield. Exposure of this lactone to 1-amino-5-heptyne **60** in the presence of NaCN as a promotor leads to the clean formation of amide **61**[31] which encodes the furan ring of the target in its 1,4-dihydroxy segment. Thus, oxidation of the primary alcohol by means of MnO_2 followed by acid-catalyzed cleavage of the OTHP function results in an almost quantitative formation of the 2,4-disubstituted furan **62**[32] and sets the stage for the crucial diyne metathesis reaction. Gratifyingly, this key step performs exceptionally well: treatment of diyne **62** with catalytic amounts of the Schrock-alkylidyne complex **1a**[10] in chlorobenzene at 80 °C results in the rapid formation of the desired cycloalkyne **63** that is isolated in 90% yield on a gram scale. This example is the most elaborate application of a ring closing alkyne metathesis reaction so far; it illustrates once again the great potental of this transformation and highlights the excellent application profile of pre-catalyst **1a**, which tolerates even the rather labile furan moiety of the substrate in addition to the amide and the sulfone group. Subsequent Lindlar reduction of **63** provides (*Z*)-alkene **64** in 97% yield which constitutes a fully functional building block for the envisaged total synthesis of nakadomarin A.

Scheme 8



The other required key segment, i.e., a suitably functionalized hexahydroazocine segment **53**, can be prepared on a multigram scale in analogy to a literature procedure[33] via conventional RCM of diene **65** using different ruthenium-based catalysts (Scheme 8). The bicyclo[6.3.0]undecene **66** thus formed is readily converted into chloride **67** by standard transformations.[34]

On the basis of these straightforward and productive routes to both macrocyclic perimeters of nakadomarin A, our current efforts are focused on the end game of the envisaged total synthesis of this challenging alkaloid, which will be reported in due course.

Acknowledgment. Generous financial support by the Max-Planck-Gesellschaft, the Deutsche Forschungsgemeinschaft (Leibniz program), the Fonds der Chemischen Industrie, and the European Union (Marie Curie grant to A.R.) is acknowledged with gratitude.

Supporting Information Available: Full Experimental Section and NMR spectra of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992074K

(29) Products **56**−**61** shown in Scheme 7 were obtained as mixtures of different stereoisomers. Since all of them converge into the final product, no attempts were made to separate the individual compounds.

(30) Reviews: (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173.

(31) Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033. These authors describe the catalytic effect of NaCN in the transformation of esters to amides; in our case, however, the addition of ≥1 equiv of this promotor was necessary to achieve quantitative conversion.

(32) The excellent yield shows that both the (*Z*)- and the (*E*)-isomer of **61** cyclize to furan **62** under the acidic reaction conditions. For another application of this new approach to furans see: Fürstner, A.; Gastner, T.; Rust, J. *Synlett* **1999**, 29.

(33) Compound **66** was analogously prepared in a model study toward manzamin A, cf.: Winkler, J. D.; Stelmach, J. E.; Axten, J. *Tetrahedron Lett.* **1996**, *37*, 4317.

(34) Details will be reported in a separate publication.