

Indenylidene Complexes of Ruthenium: Optimized Synthesis, Structure Elucidation, and Performance as Catalysts for Olefin Metathesis—Application to the Synthesis of the ADE-Ring System of Nakadomarin A

Alois Fürstner,* Oliver Guth, Arno Döffels, Günter Seidel, Monika Liebl, Barbara Gabor, and Richard Mynott^[a]

Abstract: An optimized and large scale adaptable synthesis of the ruthenium phenylindenylidene complex **3** is described which employs commercially available diphenyl propargyl alcohol **5** as a stable and convenient carbene source. Previous ambiguities as to the actual structure of the complex have been ruled out by a full analysis of its NMR spectra. A series of applications to ring closing metathesis (RCM) reactions shows that complex **3** is as good as or

even superior to the classical Grubbs carbene **1** in terms of yield, reaction rate, and tolerance towards polar functional groups. Complex **3** turns out to be the catalyst of choice for the synthesis of the enantiopure core segment **77** of the marine alkaloid nakadomarin A **60** com-

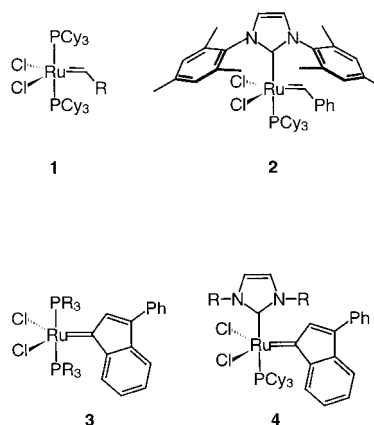
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prising the ADE rings of this target. Together with a series of other examples, this particular application illustrates that catalyst **3** is particularly well suited for the cyclization of medium-sized rings by RCM. Other key steps en route to nakadomarin A are a highly selective intramolecular Michael addition setting the quaternary center at the juncture of the A and D rings and a Takai–Nozaki olefination of aldehyde **73** with CH₂I₂, Ti(OiPr)₄ and activated zinc dust.

Introduction

The advent of well-defined catalysts for alkene metathesis has revolutionized the field within the last few years.^[1] Ruthenium carbene complexes of the general type **1** pioneered by Grubbs are most prominent of these;^[2, 3] they have found widespread applications in organic synthesis and polymer chemistry, because they combine reasonable activity and catalyst durability with an excellent tolerance towards many polar functional groups. As has been outlined recently, replacement of one PCy₃ ligand by an *N*-heterocyclic carbene moiety (e.g. **2**) improves their excellent application profile even further.^[4]

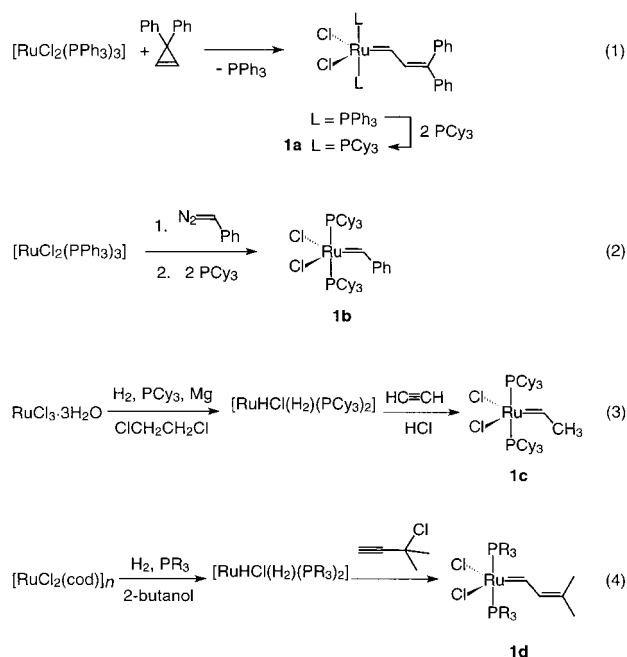
At the beginning of this groundbreaking development, the rather cumbersome preparation of **1a** as the first compound of this series constituted a certain handicap in practical terms [Scheme 1, Eq. (1)].^[2] A much better access to this family of metathesis (pre)catalysts was achieved by using diazoalkanes as carbene sources. Specifically, the phenylcarbene complex **1b** formed by reaction of [RuCl₂(PPh₃)₃] with phenyldiazomethane followed by an exchange of the PPh₃ ligands for PCy₃



[Eq. (2)] became the standard and is now commercially available.^[3] The hazards associated with the use of diazoalkanes on a large scale, however, should not be underestimated. Therefore, alternative routes to Grubbs-type carbenes have been investigated, leading to the large scale adaptable syntheses of **1c**, **d** depicted in Equations (3) and (4), respectively.^[5, 6]

Described below is a full account of our work on a further compound of this series, the indenylidene complex **3**, which is particularly easy to make and exhibits catalytic activity equal

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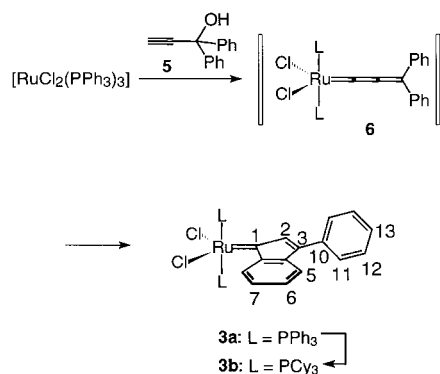


Scheme 1. Established methods for the synthesis of Grubbs-type ruthenium carbene complexes.

to or even better than that of **1**. It can be prepared safely on a large scale using only commercial reagents which are completely stable in the air. An optimized procedure yielding multigram quantities of **3** is presented together with a detailed study of its structure and catalytic performance.

Results and Discussion

Synthesis and structure: Complex **3b** is obtained on treatment of $[\text{RuCl}_2(\text{PPh}_3)_3]$ with propargyl alcohol **5** in refluxing THF, followed by routine exchange of PPh_3 for PCy_3 (Scheme 2).



Scheme 2. Synthesis of the phenylindenylidene complexes **3a,b**.

This reaction was originally performed by Hill et al. and was believed to provide the allenylidene species **6**.^[7] However, shortly after the discovery of the promising catalytic activity of the material thus formed,^[8] our group recognized that the analytical and spectroscopic data of this complex are not in agreement with the proposed structure **6**.^[9] Although a ^{13}C NMR signal was observed at $\delta = 293.9$ (originally ascribed to C_α of the allenylidene unit), the signals for the β - and γ -

carbon atoms which had been reported at $\delta = 210.0$ and 174.1 ,^[7] could not be found irrespective of whether directly observed ^{13}C NMR spectra or HMBC spectra were recorded on a high-field NMR spectrometer (14.1 T, ^1H resonance frequency 600.2 MHz). This holds true for an original sample of the complex kindly provided by Hill as well as for all the samples prepared in our laboratory by the optimized procedure described in the Experimental Section. Furthermore, the aromatic region in the ^1H NMR spectra was found to be far more complicated than that expected for the proposed structure **6**, for which just three signals are to be expected for the two equivalent phenyl groups.

Therefore, two-dimensional NMR techniques were used to determine the connectivities in the organic ligand of the material prepared according to Scheme 2. COSY and C,H -correlated spectra (HSQC and HMBC) showed unambiguously the presence of a *phenylindenylidene* moiety. These conclusions were also supported by NOESY data. The H-2 resonance (arbitrary numbering as shown) is a sharp singlet at $\delta = 7.39$. The signal due to C-2 is observed at $\delta = 139.1$ ($J_{\text{CH}} = 175$ Hz). In the HMBC spectrum, cross peaks are observed between C-3 and H-2, H-5 and H-11. All the chemical shifts and coupling constants (J_{HH} as well as J_{CH}) are consistent with structure **3b** and all signals are accounted for (for the full set of data see the Experimental Section). Since a single resonance is observed for the phosphorous ligands in the ^{31}P NMR spectrum of **3b**, the PCy_3 ligands must be placed symmetrically above and below a plane defined by the organic ligand, the Ru center and the chlorine atoms.

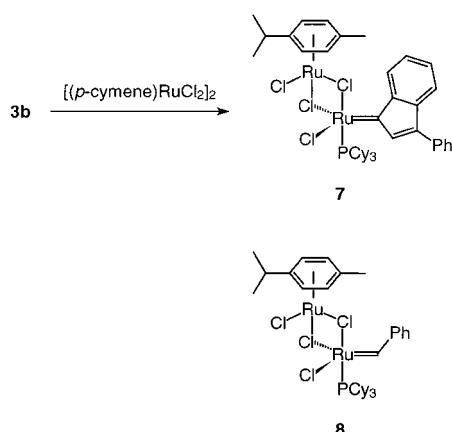
Moreover, our NMR studies confirm that the triphenylphosphine complex **3a** formed as the primary product of the reaction of $[\text{RuCl}_2(\text{PPh}_3)_3]$ with propargyl alcohol **5** also bears a phenylindenylidene substituent. Therefore, it must be concluded that no allenylidene complex is formed as a stable entity at any stage of the synthesis.^[10] We cannot help but ascribe the signals reported at $\delta_{\text{C}} = 210.0$ and 174.1 in support of the allenylidene structure^[7] to have arisen from impurities, artifacts, or accidental noise excursions. Our data, however, leave open as to whether **3** originated from a rearrangement of a *transient* allenylidene **6** or whether it is formed directly.^[11]

After we had communicated our findings on the unexpected constitution of these complexes,^[9] Nolan et al. reported the X-ray structure of complex **4** ($\text{R} = 2,6\text{-di(isopropyl)phenyl}$) derived from **3b** by replacement of one of the PCy_3 ligands by a *N*-heterocyclic carbene.^[12] In this particular compound, the phenylindenylidene moiety occupies the apical site of a distorted square pyramidal complex.

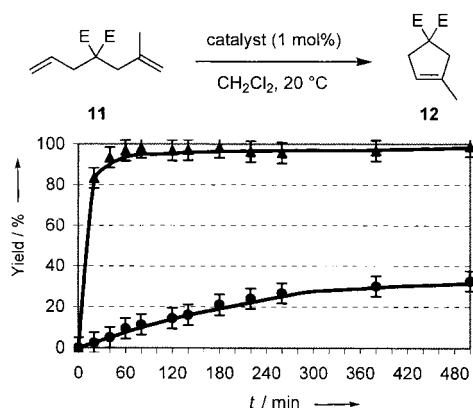
Ring closing metathesis reactions: Irrespective of the actual structure of the complex derived from $[\text{RuCl}_2(\text{PPh}_3)_3]$ and propargyl alcohol **5**, the excellent catalytic activity of this material was very quickly recognized.^[8, 9, 13–17] When applied to bis(allyl)tosylamide **9**, the presence of only 1 mol % of **3b** is sufficient to form the cyclized product **10** in essentially quantitative yield after 2 h reaction time at ambient temperature. The homo-bimetallic complex **7**, prepared from **3b** according to Scheme 3, is similarly effective but requires longer reaction times to reach complete conversion of **9**. In both cases, CH_2Cl_2 turned out to be the solvent of choice.

Table 1. RCM reactions catalyzed by the ruthenium indenylidene complexes **3b** and **7**. Optimization of the reaction conditions.

	Catalyst	Mol %	Solvent	<i>t</i> [h]	<i>T</i> [°C]	Yield [%]
1	3b	10	toluene	1	80	85
2	3b	10	CH ₂ Cl ₂	1	20	93
3	3b	1	CH ₂ Cl ₂	2	20	98
4	7	8	toluene	1	80	90
5	7	1	CH ₂ Cl ₂	17	20	99

Scheme 3. Synthesis of the homobimetallic phenylindenylidene complex **7**.

The cyclization of diene **11** to the trisubstituted cycloalkene **12** was investigated in more detail. This example shows again that the monometallic species **3b** is superior to its bimetallic congener **7**, as evident from the kinetic data shown in Figure 1.

Figure 1. Kinetic of ring closure (GC) of diene **11** to cyclopentene **12** catalyzed by the phenylindenylidene complex **3b** (▲) and the homobimetallic analogue **7** (●); E = COOEt.

While with the former catalyst the cyclization is essentially complete after 1 h at ambient temperature, the latter effects a steady but much slower reaction, reaching only 35% conversion after 6 h. It is noteworthy that this trend is in contrast to a report of Grubbs claiming that the analogous bimetallic complex **8** is more reactive in prototype metathesis reactions than the parent catalyst **1**.^[18]

Complexes **3b** and **7** have been applied to a representative set of RCM reactions in order to study their scope and compatibility with functional groups (Table 2). For comparison, the results obtained with the Grubbs carbene **1** are also included, where available. These data show that **3b** and **1** are roughly equipotent in terms of yield, reaction rate, and tolerance towards an array of polar substituents including ethers, esters, amides, silyl ethers, acetals, ammonium salts, aryl halides, nitro groups, sulfonamides, ketones, urethanes, free hydroxy groups, furan and pyrrole rings. As expected, the phenylindenylidene catalyst **3b** provides access to all ring sizes ≥ 5 , including several medium and macrocyclic derivatives. Particularly noteworthy among them are the high yielding cyclizations of the eight- and nine-membered rings **37**, **39** and **41**, the ten-membered lactones **43**, **45**, and **47**, and the macrocyclic musk **51** which upon hydrogenation converts into exaltolide, a valuable perfume ingredient.^[19] Entries 23–26 depict the high yielding formation of even larger ring sizes.

A few other examples compiled in Table 2 deserve further comment. Thus, cyclization of diene **32** to product **33** constitutes the key step of an unprecedentedly short synthesis of balanol, a potent protein kinase C inhibitor.^[13] In this particular case, the phenylindenylidene complex **3b** gives significantly better results than the standard Grubbs carbene **1b**. The same holds true for the formation of the heterocyclic compound **53**, which on hydrogenation affords the strongly immunosuppressive alkaloid nonylprodigiosin.^[9] Again, the indenylidene complex **3b** is superior to complex **1a** serving as the calibration point. This is ascribed to the somewhat higher stability of **3b** in solution, which is beneficial in RCM reactions requiring longer reaction times. Further noteworthy applications pertain to the synthesis of **49**, which upon N-deprotection converts into the insect repellent azamacrolide epilachnene.^[19b] Similarly efficient is the cyclization of the nonenolide **45**, a precursor to the potent herbicidal agent herbarumin I.^[16] In this case, RCM catalyzed by **3b** delivers only the desired (*E*)-configured product, whereas in all other macrocyclization reactions reported here mixtures of both geometrical isomers are obtained. The stereoselective course of this reaction is probably due to the preexisting ring in vicinity of the olefins which restricts the available conformational space of diene **44** and favorably aligns the reacting sites during the metathetic ring closure.^[20, 21]

Synthesis of the spirotricyclic core of nakadomarin A: The structurally unique alkaloid nakadomarin A **60** which was isolated from *Amphimedon* sp. (SS-264) collected off the Kerama islands, Okinawa, shows promising and diverse physiological activities, including cytotoxicity against L 1210 murine lymphoma cells.^[22] Moreover, nakadomarin A is biogenetically related to the potent antitumor agent manzamine A **61**.^[23]

The intricate hexacyclic skeleton of **60** poses considerable challenges in preparative terms. One of them relates to the stereoselective synthesis of the (*Z*)-configured double bond within the macrocyclic tether; a viable synthetic route to this structural element has recently been found.^[41] Other yet unsolved problems pertain to the enantioselective formation of the quaternary center at the juncture of the ABD rings as

Table 2. RCM reactions catalyzed by the ruthenium indenylidene complexes **3b** and **7** (1–5 mol %) and comparison with the results reported in the literature for complex **1**; E = COOEt.

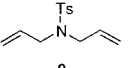
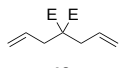
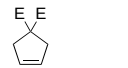
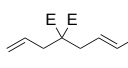
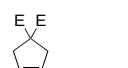
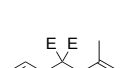
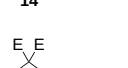
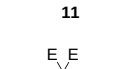
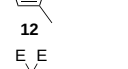
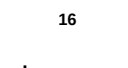
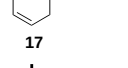
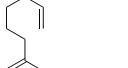
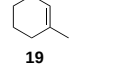
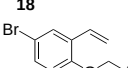
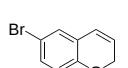
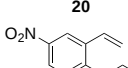
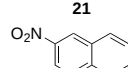
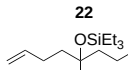
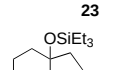
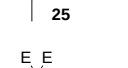
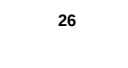
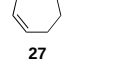
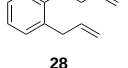
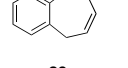
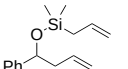
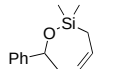
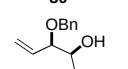
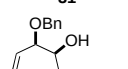
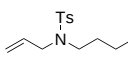
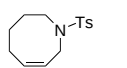
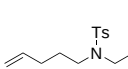
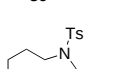
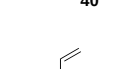
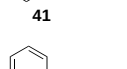
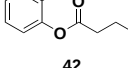
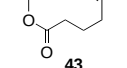
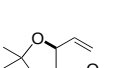
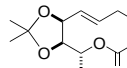
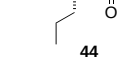
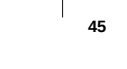
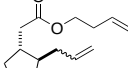
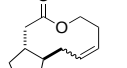
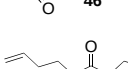
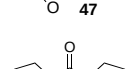
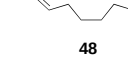
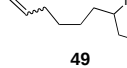
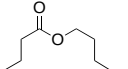
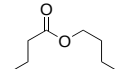
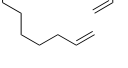
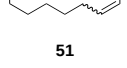
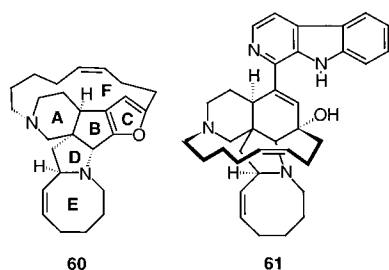
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2 	14 	93	91	
3 	14 	92	89	
4 	12 	83	75	93 ^[37]
5 	17 	92	94	
6 	19 	77		
7 	21 	94	60	99 ^[38]
8 	23 	97	71	97 ^[38]
9 	25 	79	81	95 ^[39]
10 	27 	94	94	
11 	29 	79	81	
12 	31 	97	87	91 ^[40]
13 	33 	87		64 ^[13]
14 	35 	93		97
15 	37 	74	76	74 ^[41]

Table 2 (cont.)

Substrate	Product	Yield [%]		
		3b	7	1
16 	39 	70	72	68 ^[42]
17 	41 	61		
18 	43 	56		
19 	45 	69		
20 	47 	86		88 ^[43]
21 	49 	82	81	89 ^[19b]
22 	51 	89	69	79 ^[19]
23 	53 	65		42 ^[9]
24 	55 	64		
25 	57 	82	85	83 ^[19]
26 	59 	87	83	71 ^[19]

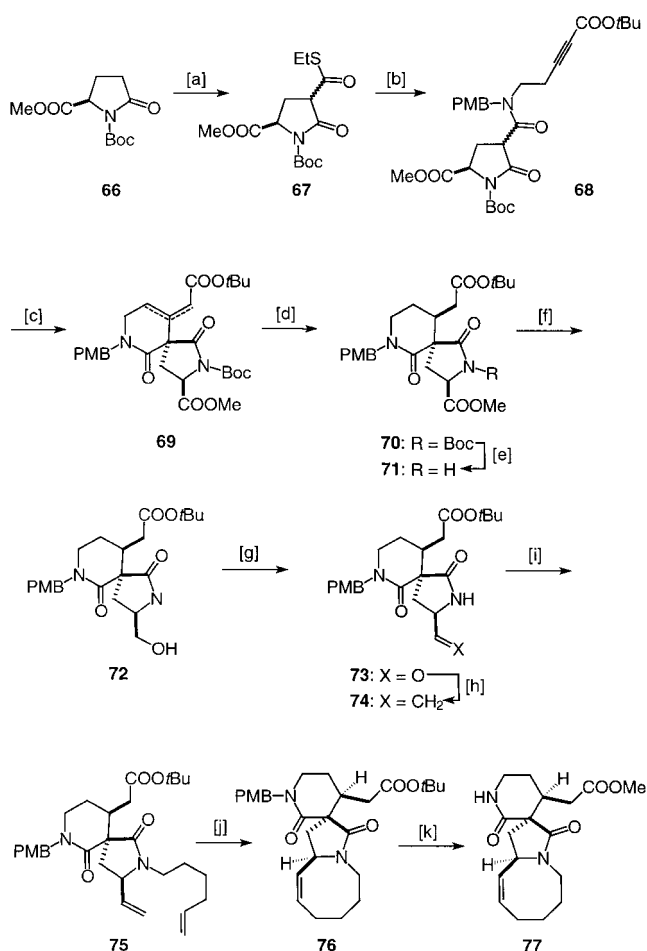


well as to the efficient cyclization of the eight-membered E ring of this target. The latter aspect deserves particular attention as the formation of the analogous ring in manzamine **A** **61** by RCM was very low yielding (26 %) and constituted the major obstacle in a recent total synthesis of this alkaloid.^[24] Therefore we were prompted to explore in detail whether RCM should be employed as a strategic transformation en route to **60** to close the rather strained and congested E ring. Described below is an efficient synthesis of the fully functional ADE-ring system of nakadomarin A in which the quaternary center is set with the correct absolute stereochemistry and the E ring is formed in almost quantitative yield by using the newly developed phenylindenylidene catalyst **3b**; this route can be used to prepare multigram quantities as required for our total synthesis project.



Scheme 4. [a] Mesyl chloride, Et₃N, Et₂O, RT. [b] *p*-Methoxybenzylamine (PMB-NH₂), Et₃N, THF, reflux, 68 % (over two steps). [c] (Boc)₂O, Et₃N, DMAP, CH₂Cl₂, RT, 86 %. [d] i) *n*BuLi, Et₂O, −78 °C; ii) (Boc)₂O, −78 °C → RT, 96 %. [e] i) pTsOH, Et₂O/*t*BuOH 20:1, RT. ii) aq. NaOH (2N), 73 %.

(*R*)-(+)-Pyroglutaminic ester [(*R*)-(+)-**66**] was chosen as a convenient starting material which is converted into thioester **67** by reacting its lithium enolate with ClC(O)SEt (Scheme 5).^[25] Exposure of this product to amine **65** (prepared according to Scheme 4), AgOTf and (*i*Pr)₂NEt in CH₃CN provides β -ketoamide **68** as a mixture of diastereoisomers. Following a recent example reported by Brands et al.,^[26] this compound undergoes an intramolecular Michael addition on treatment with (*i*Pr)₂NEt (2 equiv) in refluxing CH₃CN delivering an inseparable mixture of three isomeric alkenes **69**. Subsequent hydrogenation of this material over palladium on charcoal in MeOH, however, converges this morass of stereoisomers into a single product **70** which is isolated by flash chromatography in 80 % yield on a multigram scale.^[27] Inspection of the recorded NOE effects and comparison with literature data^[26] allow unambiguously to assign the absolute stereochemistry of the newly formed quaternary C atom (cf. Figure 2). Moreover, we have secured the enantiopurity of product **70** thus formed by carrying out the same sequence of reactions starting from (*S*)-(−)-**66** and comparison of both samples by HPLC on a chiral column



Scheme 5. [a] LHMDS, THF, −78 °C, then ClC(O)SEt, −78 °C, 96 %. [b] Amine **65**, AgOTf, (*i*Pr)₂NEt, CH₃CN, RT, 73 %. [c] (*i*Pr)₂NEt, CH₃CN, reflux. [d] H₂ (1 atm), Pd/C, MeOH, 80 % (over two steps). [e] Mg(ClO₄)₂ (25 mol %), CH₃CN, 50 °C, 99 %. [f] LiBH₄, THF, RT, 82 %. [g] Dess–Martin periodinane, H₂O (1 equiv), CH₂Cl₂, RT, 78 %. [h] CH₂I₂, Ti(O*i*Pr)₄, Zn, THF, RT, 84 %. [i] NaH, DMF, 0 °C, then 6-iodo-1-hexene, RT, 88 %. [j] Catalyst **3b** (5 mol %), CH₂Cl₂, reflux, 98 %. [k] i) F₃CCOOH, reflux; ii) Me₃SiCHN₂, toluene/MeOH 3.5:1, 85 %.

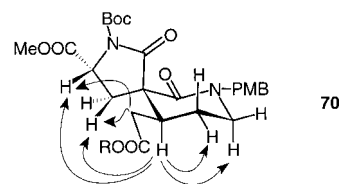


Figure 2. NOE effects recorded in a one-dimensional NOESY experiment relevant for the assignment of the stereochemistry of the quaternary center in compound **70**.

(Shimadzu LC-10A: Chiralpak AD Ø250 × 4.5 mm column, eluent: *n*-heptane/2-propanol 75:25, 0.5 mL min^{−1}).

After deprotection of the *N*-Boc group in **70** by means of Mg(ClO₄)₂,^[28] it was possible to achieve a selective reduction of the methyl ester function in **71** using LiBH₄. Oxidation of the resulting primary alcohol **72** with Dess–Martin periodinane according to the optimized procedure described by Schreiber et al.^[29] proceeded uneventfully, delivering the required aldehyde **73** without any detectable epimerization of the adjacent chiral center. The envisaged methylenation of this material, however, required significant optimization. Best

results were achieved by means of the Takai–Nozaki protocol using CH_2I_2 as the methylene source in combination with $\text{Ti}(\text{OiPr})_4$ and activated zinc dust.^[30] Under these conditions, alkene **74** was obtained in 84 % isolated yield. Subsequent N-alkylation of the sodium salt derived thereof with 6-iodo-1-hexene readily provides diene **75** and sets the stage for the envisaged cyclization of the eight-membered ring by RCM.

We were pleased to see that this key transformation proceeds with essentially quantitative yield (98 %) if a dilute solution of diene **75** (0.002 M) in CH_2Cl_2 is refluxed in the presence of 5 mol % of the phenylindenylidene catalyst **3b** for 18 h. For comparison, the standard Grubbs catalyst **1b** was also tested, delivering only 82 % yield of **76** under otherwise identical conditions; as discussed above, we ascribe the better performance of **3b** to the higher stability of this complex in solution. Even more surprising is the fact that the “second-generation” NHC-carbene complex **2**, which is generally believed to be an even more powerful catalyst than the parent species **1b**, is significantly less efficient in this particular case, affording only 63 % of product **76**. Trace amounts of various by-products are detected by TLC which detract from the yield of the desired hexahydroazocine ring.

Attempted cleavage of the *N*-PMB group in **76** by means of cerium ammonium nitrate led to the rapid destruction of this compound. Fortunately, however, the deprotection is achieved by refluxing product **76** in neat trifluoroacetic acid for 18 h. Since the *tert*-butyl ester is concomitantly cleaved under these vigorous conditions, the crude product was treated with (trimethylsilyl)diazomethane, affording methyl ester **77** in excellent overall yield. Based on this high yielding, large scale adaptable and virtually diastereospecific synthesis of compound **77**, which represents a fully functional synthon for the ADE segment of nakadomarin A **60**, we are presently pursuing the completion of a total synthesis of this challenging target.

Experimental Section

General remarks: The NMR spectra of **3a, b** were measured on a Bruker DMX 600 NMR spectrometer using a 5 mm TXI triple probe with a z -gradient coil. Measurement techniques used include COSY (phase sensitive DQ-filtered), HSQC (optimized for $^1J_{\text{CH}} = 160$ Hz), HMBC (optimized for $^2J_{\text{CH}} = 10$ Hz), NOESY, ^{13}C (cpd-decoupled), and DEPT. The C,H coupling constants were taken from the proton coupled ^{13}C NMR spectrum or a high resolution HSQC spectrum. All reactions were carried out under Ar. 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_2O_{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 of organic compounds 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), HRMS: Finnigan MAT 95, MALDI: Bruker ICR. Melting points: Gallenkamp melting point apparatus (uncorrected). Optical rotation: Perkin Elmer 343 at $\lambda = 589$ nm (Na D-line). Elemental analyses: Kolbe, Mülheim/Ruhr. All commercially available compounds (Lancaster, Aldrich) were used as received.

Optimized synthesis of the phenylindenylidene complexes **3a, b:** A two-necked flask equipped with a reflux condenser, a magnetic stirring bar, and an Ar supply was evacuated, flame dried, and flushed with Ar. The flask

was charged with $[\text{RuCl}_2(\text{PPh}_3)_3]$ (10.37 g, 10.8 mmol). THF (600 mL) and diphenylpropargyl alcohol **5** (3.37 g, 16.2 mmol) were introduced and the resulting mixture was refluxed under Ar for 2.5 h. During this period, the mixture turned dark-red. For work-up, the solvent was evaporated in vacuo (12 mbar), the residue was suspended in hexane (400 mL) and the suspension stirred for about 3 h until the solid was finely ground and had a homogeneous appearance. The powdered solid was filtered off and dried in vacuo, affording complex **3a** in quantitative yield. The NMR data are compiled below.

PCy_3 (9.39 g, 33.5 mmol) was added to a solution of complex **3a** in CH_2Cl_2 (250 mL) and the resulting mixture was stirred for 2 h at ambient temperature under Ar. The solvent was evaporated, the crude product suspended in hexane (400 mL). The suspension was stirred for about 3 h at ambient temperature, the finely powdered complex was filtered off and carefully washed with hexane (100 mL) in several portions. Drying of the product in vacuo afforded complex **3b** as an analytically pure, orange powder (7.90 g, 80 %).

Complex **3b:** ^1H NMR (600.2 MHz, CD_2Cl_2 , 30 °C): $\delta = 8.67$ (dd, $J(\text{H-7, H-8}) = 7.5$ Hz, 1 H, H-8), 7.75 (d, 2 H, H-11), 7.52 (d, 1 H, H-13), 7.40 (dd, 2 H, H-12), 7.39 (s, 1 H, H-2), 7.38 (td, $J(\text{H-5, H-6}) = J(\text{H-6, H-7}) = 7.3$ Hz, 1 H, H-6), 7.29 (td, $J(\text{H-6, H-7}) = J(\text{H-7, H-8}) = 7.5$ Hz, 1 H, H-7), 7.27 (dd, $J(\text{H-5, H-6}) = 7.3$ Hz, 1 H, H-5); cyclohexyl signals: $\delta = 2.60$, 1.77, 1.73, 1.66, 1.65, 1.52, 1.50, 1.47, 1.21, 1.19, 1.18; ^{13}C NMR (150.9 MHz, CD_2Cl_2 , 30 °C): $\delta = 293.9$ (s, $J = 8.1$ Hz (t), $J(\text{P, C})$, C-1), 145.0 (s, C-9), 141.4 (s, C-4), 139.8 (s, C-3), 139.1 (d, $^1J(\text{C, H}) = 175$ Hz, C-2), 136.8 (s, C-10), 129.41 (d, $^1J(\text{C, H}) = 163$ Hz, C-8), 129.40 (2 C, d, C-12), 129.2 (d, C-7), 128.7 (d, C-6), 128.4 (d, C-13), 126.6 (2 C, d, C-11), 117.6 (d, $^1J(\text{C, H}) = 157$ Hz, C-5); cyclohexyl signals: $\delta = 33.1$ (CH), 30.21, 30.16, 28.3, 28.1, 26.9 (all CH_2); ^{31}P NMR (243.0 MHz, CD_2Cl_2 , 30 °C, rel. ext. H_3PO_4): $\delta = 32.6$.

Complex **3a:** ^1H NMR (600.2 MHz, CD_2Cl_2 , 30 °C): $\delta = 7.54$ (d, 1 H, H-13), 7.50 (d, 2 H, H-11), 7.34 (dd, 2 H, H-12), 7.31 (td, $J(\text{H-5, H-6}) = J(\text{H-6, H-7}) = 7.5$ Hz, 1 H, H-6), 7.25 (dd, $J(\text{H-5, H-6}) = 7.5$ Hz, 1 H, H-5), 7.08 (dd, $J(\text{H-7, H-8}) = 7.3$ Hz, 1 H, H-8), 6.67 (td, $J(\text{H-6, H-7}) = J(\text{H-7, H-8}) = 7.4$ Hz, 1 H, H-7), 6.38 (s, 1 H, H-2); phenyl group: $\delta = 7.54$, 7.46 (*para*), 7.33; ^{13}C NMR (150.9 MHz, CD_2Cl_2 , 30 °C): $\delta = 301.0$ (s, $J(\text{P, C}) = 12.9$ Hz (t), C-1), 145.4 (s, C-3), 141.8 (s, $J(\text{P, C}) = 2.7$ Hz (t), C-9), 139.8 (s, C-4), 139.4 (d, $J(\text{P, C}) = 5.2$ Hz (t), $^1J(\text{C, H}) = 175.4$ Hz, C-2), 135.6 (s, C-10), 130.1 (d, C-6), 130.1 (d, C-7), 129.41 (d, 2 C, C-12), 129.36 (d, C-13), 129.33 (d, $^1J(\text{C, H}) = 165$ Hz, C-8), 127.1 (d, 2 C, C-11), 118.6 (d, $^1J(\text{C, H}) = 160$ Hz, C-5); phenyl signals: X part of ABX spin systems (A, B = ^{31}P , X = ^{13}C): $\delta = 135.2$ (d, $[J(\text{P, C}) + J(\text{P', C})] = 11.2$ Hz, *C-ortho*), 131.2 (s, $[J(\text{P, C}) + J(\text{P', C})] = 42.8$ Hz, *C-ipso*) 130.6 (d, *C-para*), 128.4 (d, $[J(\text{P, C}) + J(\text{P', C})] = 9.6$ Hz, *C-meta*); ^{31}P NMR (243.0 MHz, CD_2Cl_2 , 30 °C, rel. ext. H_3PO_4): $\delta = 28.7$.

Representative procedure for RCM catalyzed by complex **3b. Synthesis of 2,5-dihydro-benzo[*b*]oxepine (**29**):** A solution of allyl-(2-allylphenyl)ether (**28**; 167 mg, 0.96 mmol) and complex **3b** (7 mg, 0.01 mmol) in CH_2Cl_2 (50 mL) was stirred at ambient temperature until TLC showed complete conversion of the substrate (ca. 2 h). For work-up, the solvent was evaporated and the residue was purified by flash chromatography affording compound **29** as a colorless syrup. ^1H NMR (300 MHz, CDCl_3): $\delta = 7.19$ –7.01 (m, 5H), 5.86–5.83 (m, 1H), 5.49–5.43 (m, 1H), 4.58 (dt, $J = 2.3$, 5.2 Hz, 2H), 3.50–3.46 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 158.7$, 136.1, 128.8, 127.8, 127.3, 125.7, 124.0, 121.4, 71.2, 31.8; IR (film): $\tilde{\nu} = 2931$, 2882, 1724, 1602, 1583, 1489, 1455, 1230, 1062, 761 cm^{-1} ; MS: m/z (%): 146 (100) [M]⁺, 131 (59), 127 (32), 115 (34), 103 (10), 91 (25), 89 (13), 77 (17), 72 (4), 63 (17), 51 (22), 39 (23), 27 (7). The analytical data were in agreement with those reported in the literature.^[31]

Eleven other compounds displayed in Table 2 have been prepared analogously. Their analytical and spectroscopic data were in agreement with those reported in the literature: **10**,^[32] **12**,^[33] **14**,^[34] **17**,^[35] **21**,^[38] **23**,^[38] **25**,^[39] **31**,^[40] **33**,^[13] **39**,^[42] **45**,^[16] **47**,^[43] **49**,^[19] **51**,^[19] **53**,^[9] **55**,^[15] **57**,^[19] **59**,^[19] The data of new compounds are compiled below.

Cyclohept-4-ene-1,1-diethyldicarboxylate (27**):** ^1H NMR (300 MHz, CDCl_3): $\delta = 5.85$ (dt, $J = 6.1$, 10.6 Hz, 1H), 5.68 (dt, $J = 6.4$, 10.7 Hz, 1H), 4.17 (q, $J = 7.0$ Hz, 4H), 2.67 (d, $J = 6.4$ Hz, 2H), 2.26–2.22 (m, 2H), 2.19–2.13 (m, 2H), 1.68–1.61 (m, 2H), 1.24 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 171.7$, 134.0, 127.1, 61.0, 56.1, 36.6, 32.3, 28.2, 22.7, 14.0; IR (film): $\tilde{\nu} = 3029$, 2981, 2937, 1732, 1656, 1312, 1238, 1213, 1183, 853, 703 cm^{-1} ; MS: m/z (%): 240 (8) [M]⁺, 195 (16), 173 (100), 166 (57), 138 (12), 127 (28), 121 (14), 99 (7), 93 (60), 79 (14), 67 (6), 55 (6), 41 (9), 29 (31);

elemental analysis calcd (%) for $C_{13}H_{20}O_4$: C 64.98, H 8.39; found: C 64.86, H 8.31.

(R)-1,3-Dimethyl-cyclohexene (19): 1H NMR (300 MHz, $CDCl_3$): δ = 5.24 (s, 1H), 2.20–2.05 (m, 1H), 1.90–1.83 (m, 2H), 1.80–1.66 (m, 2H), 1.65–1.62 (m, 3H), 1.58–1.43 (m, 1H), 1.15–1.10 (m, 1H), 0.94 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.3, 127.8, 31.2, 30.3, 30.0, 23.8, 22.0, 21.9; IR (film): $\tilde{\nu}$ = 3038, 2950, 1671, 1454, 1376, 1133, 966, 867, 809 cm^{-1} ; MS (EI): m/z (%): 110 (27) $[M]^+$, 95 (100), 82 (16), 67 (46), 55 (15), 41 (14).

(S)-5-Methyl-1-aza-9-oxa-bicyclo[5.3.0]dec-5-en-10-one (35): 1H NMR (300 MHz, $CDCl_3$): δ = 5.18–5.14 (m, 1H), 4.48–4.41 (m, 1H), 4.36 (t, J = 7.8 Hz, 1H), 3.93 (dd, J = 7.8, 5.6 Hz, 1H), 3.85–3.76 (m, 1H), 3.22–3.15 (m, 1H), 2.23–2.19 (m, 2H), 1.92–1.75 (m, 2H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 141.9, 123.7, 68.8, 54.2, 45.1, 33.2, 26.2, 25.3; MS (EI): m/z (%): 167 (29) $[M]^+$, 152 (100), 108 (20), 94 (12), 81 (26), 80 (11), 79 (11), 67 (13), 53 (10), 41 (20), 39 (16), 27 (11); IR (film): $\tilde{\nu}$ = 3496, 2931, 1745, 1425, 1378, 1315, 1218, 1046, 761 cm^{-1} ; HRMS ($C_9H_{13}NO_2$): calcd 167.09463; found 167.09435.

(S)-1-Aza-10-oxa-bicyclo[6.3.0]undec-6-en-11-one (37): $[\alpha]_D^{20}$ = –84.8° (c = 0.70, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$): δ = 5.91–5.81 (m, 1H), 5.39 (dd, J = 10.9, 5.8 Hz, 1H), 4.47–4.37 (m, 2H), 3.96–3.88 (m, 1H), 3.39–3.30 (m, 2H), 2.39–2.28 (m, 1H), 2.17–2.05 (m, 1H), 1.84–1.73 (m, 1H), 1.67–1.43 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 134.3, 127.0, 68.1, 53.7, 43.1, 27.0, 25.6, 25.4; MS (EI): m/z (%): 167 (70) $[M]^+$, 152 (77), 140 (14), 139 (17), 138 (39), 125 (20), 122 (25), 109 (16), 108 (32), 96 (14), 95 (27), 94 (51), 91 (12), 86 (11), 83 (13), 82 (31), 81 (49), 80 (85), 79 (37), 77 (14), 69 (13), 68 (36), 67 (75), 66 (13), 65 (13), 56 (22), 55 (65), 54 (55), 53 (33), 51 (10), 42 (25), 41 (100), 40 (11), 39 (60), 30 (14), 29 (16), 28 (32), 27 (35); IR (film): $\tilde{\nu}$ = 3017, 2930, 2859, 1747, 1652, 1420, 1247, 1222, 1183, 1053, 1029, 1005, 842, 778, 761, 739, 709, 689 cm^{-1} ; elemental analysis calcd (%) for $C_9H_{13}NO_2$: C 64.65, H 7.84, N 8.38; found: C 64.55, H 7.92, N 8.44.

1-(Toluene-4-sulfonyl)-2,3,4,7,8,9-hexahydro-1H-azonine (41): m.p. 103–104 °C; 1H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 2H), 7.34–7.30 (m, 2H), 5.57–5.46 (m, 2H), 2.97 (t, J = 6.3 Hz, 4H), 2.47–2.41 (m, 4H), 2.43 (s, 3H), 1.90–1.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 134.2, 130.0, 129.4, 127.5, 53.3, 28.2, 22.2, 21.4; IR (KBr): $\tilde{\nu}$ = 3005, 2966, 2922, 2857, 1661, 1595, 1490, 1462, 1330, 1156, 1095, 973, 808, 688, 549 cm^{-1} ; MS: m/z (%): 279 (1) $[M]^+$, 250 (1), 215 (1), 155 (3), 124 (100), 96 (18), 41 (12); elemental analysis calcd (%) for $C_{15}H_{21}NO_2S$: C 64.48, H 7.58; found: C 64.48, H 7.58.

Benzo[2,1-*i*]3,4,5,8-tetrahydrooxecin-2-one (43): Mixture of isomers: $E:Z$ = 1:6.4; 1H NMR (300 MHz, CD_2Cl_2): δ = 7.21–7.05 (m, 2H), 6.93–6.90 (m, 1H), 5.25–5.11 (m, 2H), 2.45–2.21 (m, 4H), 2.05–1.18 (m, 4H); ^{13}C NMR (75 MHz, CD_2Cl_2): E -isomer (resolved signals): δ = 174.1, 149.5, 131.8, 131.5, 131.1, 129.4, 126.9, 125.9, 124.0, 36.2, 34.3, 32.7, 26.6; Z -isomer (resolved signals): δ = 171.7, 149.8, 132.3, 130.2, 130.0, 127.3, 126.9, 126.1, 123.4, 34.7, 30.2, 25.7, 25.1; IR (KBr): $\tilde{\nu}$ = 3062, 3037, 2941, 2923, 1752, 1656, 1491, 1448, 1208, 1171, 1131, 753, 707, 545 cm^{-1} ; MS: m/z (%): 202 (9) $[M]^+$, 173 (19), 145 (11), 131 (11), 118 (47), 107 (11), 91 (10), 84 (100), 55 (23); elemental analysis calcd (%) for $C_{13}H_{14}O_2$: C 77.20, H 6.98; found: C 77.06, H 6.87.

Synthesis of the ADE-Ring Segment of Nakadomarin A

***N*-(4-Methoxybenzyl)-4-amino-1-butyne (63):** Methanesulfonyl chloride (41.6 mL, 0.535 mol) was added at 0 °C to a solution of 3-butyne-1-ol (**62**) (25.0 g, 0.357 mol) in Et_2O (500 mL) followed by dropwise addition of Et_3N (74.6 mL, 0.535 mol) over a period of 60 min. The resulting solution was stirred for 12 h at ambient temperature. The precipitate was then dissolved by addition of water and the aqueous phase was repeatedly extracted with *tert*-butyl methyl ether. The combined organic layers were subsequently washed with sat. aq. NH_4Cl and brine and finally dried over Na_2SO_4 . Evaporation of the solvent afforded a pale yellow syrup which was dissolved in THF (500 mL). Et_3N (101 mL, 0.725 mol) and *p*-methoxybenzylamine (100 mL, 0.759 mmol) were added and the resulting solution was refluxed for 14 h. A standard extractive work-up followed by flash chromatography (silica gel, ethyl acetate) afforded amine **63** (58.3 g, 68%) as a pale yellow oil. 1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 3.76 (s, 2H), 2.80 (t, J = 6.6 Hz, 2H), 2.41 (dt, J = 6.6, 2.6 Hz, 2H), 2.00 (t, J = 2.6 Hz, 1H), 1.68 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 132.2, 129.3 (2C), 113.8 (2C),

82.5, 69.5, 55.2, 52.7, 47.2, 19.5; MS: m/z (%): 189 (6) $[M]^+$, 150 (20), 121 (100); IR (film): $\tilde{\nu}$ = 3291, 3061, 3031, 2952, 2933, 2912, 2835, 2116, 1612, 1585, 1513, 1463, 1301, 1247, 1176, 1109, 1035, 815, 638 cm^{-1} ; HRMS ($C_{12}H_{15}NO$): calcd 189.11536; found 189.11525; elemental analysis calcd (%) for $C_{12}H_{15}NO$: C 76.16, H 7.99, N 7.40; found: C 75.93, H 8.06, N 7.45.

N-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)-5-amino-1-pent-2-ynoic

***tert*-butyl ester (64):** Di-*tert*-butyldicarbonate (55.8 g, 0.256 mol) was slowly added to a solution of amine **63** (44.0 g, 0.233 mmol), DMAP (2.80 g, 23.2 mmol) and Et_3N (35.0 mL, 0.256 mol) in CH_2Cl_2 (500 mL) at 0 °C and the resulting mixture was stirred at ambient temperature for 72 h. Standard extractive work-up followed by flash chromatography (silica gel, hexane/ethyl acetate 15:1) provided *N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxybenzyl)-4-amino-1-butyne (58.1 g, 86%) as a pale yellow syrup. 1H NMR (300 MHz, $CDCl_3$, rotamers): δ = 7.17 (brs, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.32 (brs, 2H), 2.34 (brs, 2H), 1.96 (t, J = 2.7 Hz, 1H), 1.50 (brs, 9H); ^{13}C NMR [75 MHz, $CDCl_3$, (resolved signals of rotamers)]: δ = 158.8, 155.3, 130.2, 129.1 [128.5] (2C), 113.9 (2C), [82.0] 81.8, 79.9, 69.5, 55.2, [50.6] 49.8, 45.2, 28.4 (3C), 18.2 [18.0]; MS (EI): m/z (%): 289 (4) $[M]^+$, 233 (23), 159 (19), 121 (100), 57 (36); IR (film): $\tilde{\nu}$ = 3294, 3064, 3002, 2975, 2933, 2836, 2119, 1692, 1612, 1586, 1513, 1465, 1411, 1366, 1248, 1166, 1121, 1036, 882, 818, 774, 638 cm^{-1} ; HRMS ($C_{17}H_{23}NO_3$): calcd 289.16779; found 289.16786; elemental analysis calcd (%) for $C_{17}H_{23}NO_3$: C 70.56, H 8.01, N 4.84; found: C 70.41, H 8.09, N 4.88.

*n*BuLi (43.6 mL, 69.7 mmol, 1.60 M in hexane) was slowly added at –78 °C to a solution of the compound obtained above (16.8 g, 58.1 mmol) in Et_2O (300 mL). After the mixture had been stirred for 30 min at that temperature, di-*tert*-butyldicarbonate (17.7 g, 81.3 mmol) was introduced, and stirring was continued for another 15 min at –78 °C before the mixture was allowed to reach ambient temperature. After 1 h, the reaction was quenched with sat. aq. NH_4Cl , the aqueous layer was extracted with ethyl acetate, and the combined organic phases were dried over Na_2SO_4 . Evaporation of the solvent followed by flash chromatography of the residue (silica gel, hexane/ethyl acetate 10:1→4:1) afforded the title compound **64** (21.7 g, 96%) as a colorless liquid. 1H NMR (300 MHz, $CDCl_3$, rotamers): δ = 7.17 (brs, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.44 (s, 2H), 3.81 (s, 3H), 3.33 (brs, 2H), 2.46 (brs, 2H), 1.49 (s, 18H); ^{13}C NMR [75 Hz, $CDCl_3$, (resolved signals of rotamers)]: δ = 158.9, 158.8, 152.6, 130.2, 129.2 [128.6] (2C), 113.9 (2C), 84.7, 83.2, 80.2, 75.3, 55.2, [50.8] 49.7, 44.4, 28.4 (3C), 27.9 (3C), 18.5; MS (EI): m/z (%): 389 (< 1) $[M]^+$, 277 (29), 232 (41), 169 (10), 121 (100), 57 (52), 41 (10); IR (film): $\tilde{\nu}$ = 3063, 3002, 2978, 2934, 2837, 2241, 1704, 1612, 1586, 1513, 1468, 1410, 1368, 1282, 1251, 1163, 1121, 1074, 1036, 887, 845, 755 cm^{-1} ; elemental analysis calcd (%) for $C_{22}H_{31}NO_3$: C 67.84, H 8.02, N 3.69; found: C 67.92, H 8.08, N 3.66.

***N*-(4-Methoxybenzyl)-5-amino-1-pent-2-ynoic *tert*-butyl ester (65):** A solution of compound **64** (17.8 g, 45.7 mmol) in Et_2O (100 mL) and *t*BuOH (5 mL) was treated with *p*TsOH· H_2O (17.4 g, 91.4 mmol) and the mixture was vigorously stirred (mechanical stirrer) for 16 h at ambient temperature. The precipitate formed was dissolved by addition of 2 N NaOH (100 mL) and the resulting solution was repeatedly extracted with *tert*-butyl methyl ether. The combined organic layers were dried over Na_2SO_4 , the solvent was evaporated and the residue purified by flash chromatography (silica gel, ethyl acetate) affording product **65** (9.70 g, 73%) as a pale yellow oil. 1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 2H), 2.84 (t, J = 6.7 Hz, 2H), 2.51 (t, J = 6.7 Hz, 2H), 1.60 (brs, 1H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 152.7, 132.0, 129.2 (2C), 113.8 (2C), 84.7, 83.1, 75.4, 55.2, 52.6, 46.4, 28.0 (3C), 19.9; MS (EI): m/z (%): 289 (< 1) $[M]^+$, 232 (20), 150 (17), 122 (11), 121 (100); IR (film): $\tilde{\nu}$ = 2978, 2934, 2835, 2237, 1705, 1612, 1570, 1513, 1461, 1369, 1279, 1249, 1161, 1129, 1074, 1035, 844, 754 cm^{-1} ; elemental analysis calcd (%) for $C_{17}H_{23}NO_3$: C 70.56, H 8.01, N 4.84; found: C 70.50, H 7.93, N 4.76.

(3*rac*, 5*R*)-1-(*tert*-Butoxycarbonyl)-3-(thioethoxycarbonyl)-2-pyrrolidinon-5-carboxylic methyl ester (67): Bis-(trimethylsilyl)-lithiumamide (14.3 g, 85.5 mmol) was slowly added to a solution of (*R*)-**66** (10.4 g, 42.7 mmol) in THF (250 mL) at –78 °C. The resulting yellow solution was stirred for 1 h at that temperature before (chloro)thioformic ethyl ester (6.38 g, 51.2 mmol) was introduced and stirring was continued for another 60 min. The reaction was quenched by adding sat. aq. NH_4Cl at –78 °C. The mixture was extracted with *tert*-butyl methyl ether and water, the combined organic layers were washed with sat. aq. NH_4Cl and brine, dried over Na_2SO_4 , and the solvent was evaporated. Flash chromatography of the

crude product (silica gel, hexane/ethyl acetate 2:1 → 1:1) afforded thioester **67** (13.5 g, 95%) as a colorless solid (mixture of diastereoisomers): m.p. 105–106 °C; $[\alpha]_D^{20} = +4.68^\circ$ ($c = 1.18$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 4.66$ (dd, $J = 9.4$, 3.0 Hz), 4.61 (dd, $J = 9.4$, 4.2 Hz) [1H], 3.78 (s), 3.77 (s) [3H], 2.99–2.70 (m, 3H), 2.62–2.47 (m, 1H), 2.21 (ddd, $J = 9.0$, 3.0 Hz), 2.16 (dd, $J = 9.0$, 3.0 Hz) [1H], 1.48 (s, 9H), 1.30–1.23 (m, 3H); ^{13}C NMR [75 MHz, CDCl_3 , (resolved signals of the diastereoisomer)]: $\delta = 194.2$ [193.1], 171.4 [170.6], 167.5 [167.4], 149.0, 84.3 [84.1], [57.5] 57.0, [56.5] 55.7, [52.7] 52.6, 27.8 (3C), 25.2 [24.4], [24.3] 24.1, [15.5] 14.2; MS: m/z (%): 231 (23), 172 (16), 170 (22), 143 (26), 142 (15), 110 (14), 57 (100), 41 (12); IR (film): $\tilde{\nu} = 3449$, 3343, 2978, 2934, 2877, 1793, 1753, 1724, 1671, 1599, 1455, 1439, 1371, 1314, 1288, 1254, 1212, 1152, 1071, 1017, 975, 844, 774 cm^{-1} ; HRMS ($\text{C}_{14}\text{H}_{21}\text{NO}_6\text{S} + \text{H}$): calcd 332.11678; found 332.11667; elemental analysis calcd (%) for $\text{C}_{14}\text{H}_{21}\text{NO}_6\text{S}$: C 50.74, H 6.30, N 4.23; found: C 50.60, H 6.43, N 4.28.

(3R, 5R)-1-(tert-Butoxycarbonyl)-3-[(N-tert-butoxycarbonyl-N-(4-methoxybenzyl)-but-3-yn-1-yl)-carbamoyl]-2-pyrrolidinone-5-carboxylic methyl ester (68): Silver trifluoromethanesulfonate (6.27 g, 24.4 mmol) was slowly added to a solution of thioester **67** (7.36 g, 22.2 mmol), amine **65** (8.03 g, 27.8 mmol) and (*i*Pr)₂NEt (6.89 g, 53.3 mmol) in CH_3CN (150 mL) and the reaction mixture was stirred for 14 h in the dark. The resulting suspension was filtered through a pad of Celite and the insoluble residues were thoroughly washed with ethyl acetate. Evaporation of the combined filtrates followed by flash chromatography of the residue (silica gel, hexane/ethyl acetate 2:1 → 1:1) afforded **68** as a mixture of diastereoisomers. Pale yellow foam (9.01 g, 73%): m.p. 120–123 °C; $[\alpha]_D^{20} = -10.0^\circ$ ($c = 1.15$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 7.20$ –7.11 (m, 2H), 6.91–6.83 (m, 2H), 5.03–4.54 (m, 2H), 4.48–3.83 (m, 2H), 3.80 (s), 3.789 (s), 3.785 (s), 3.78 (s), 3.75 (s) [6H], 3.41–3.27 (m, 1H), 3.20–2.97 (m, 1H), 2.83–2.37 (m, 2H), 2.30–2.23 (m), 2.07–1.98 (m) [1H], 1.80 (brs, 1H), 1.50 (s), 1.494 (s), 1.487 (s), 1.48 (s), 1.47 (s), 1.46 (s) [18H]; ^{13}C NMR (75 MHz, CDCl_3): $\delta = 171.8$, 170.6, 169.7, 169.5, 169.2, 167.3, 167.2, 166.74, 166.70, 159.3, 159.0, 152.5, 152.0, 148.8, 129.3, 129.0, 128.8, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 114.3, 114.2, 114.1, 84.2, 84.0, 83.52, 83.48, 83.2, 82.5, 76.7, 75.5, 62.0, 57.9, 57.8, 57.5, 57.3, 55.3, 55.2, 52.60, 52.58, 52.53, 52.48, 51.5, 50.5, 48.1, 46.2, 46.0, 45.5, 45.0, 44.9, 44.1, 28.1, 27.91, 27.88, 27.8, 25.2, 25.1, 18.6, 17.4; MS (EI): m/z (%): 558 (<1) [M]⁺, 232 (27), 216 (22), 215 (29), 172 (13), 121 (100), 57 (24), 41 (11); IR (KBr): $\tilde{\nu} = 2980$, 2240, 1790, 1751, 1706, 1651, 1613, 1514, 1457, 1370, 1285, 1252, 1153, 1075, 1033, 845, 755, 641 cm^{-1} ; HRMS ($\text{C}_{29}\text{H}_{38}\text{N}_2\text{O}_9 + \text{H}$): calcd 559.26555; found 559.26617; elemental analysis calcd (%) for $\text{C}_{29}\text{H}_{38}\text{N}_2\text{O}_9$: C 62.35, H 6.86, N 5.01; found: C 62.19, H 6.95, N 4.88.

(3R, 5R, 10R)-10-(tert-Butoxycarbonylmethyl)-7-(4-methoxybenzyl)-1,6-dioxo-2,7-diaza-spiro[4.5]decane-2,3-dicarboxylic 2-tert-butyl ester-3-methyl ester (70): A solution of amide **68** (9.01 g, 16.1 mmol) and (*i*Pr)₂NEt (4.16 g, 32.2 mmol) in CH_3CN (300 mL) was refluxed for 16 h. The reaction mixture was extracted with *tert*-butyl methyl ether and sat. aq. NH_4Cl , and the combined organic layers were dried over Na_2SO_4 . After evaporation of the solvent, the residue was dissolved in MeOH (250 mL), Pd on charcoal was added (4.50 g, 10% Pd) and the resulting mixture was stirred for 16 h under an atmosphere of H_2 (1 atm, introduced after three freeze–thaw cycles). For work-up, the catalyst was filtered off, the insoluble residues were carefully rinsed with ethyl acetate, the combined filtrates were evaporated, and the residue was purified by flash chromatography affording the spirocycle **70** as a colorless foam (7.22 g, 80%): m.p. 132–133 °C; $[\alpha]_D^{20} = +39.1^\circ$ ($c = 1.30$, CHCl_3); ^1H NMR (600 MHz, CDCl_3): $\delta = 7.12$ (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 4.67 (d, $J = 14.2$ Hz, 1H), 4.65 (dd, $J = 10.5$, 3.8 Hz, 1H), 4.32 (d, $J = 14.6$ Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.25–3.14 (m, 2H), 2.87 (dd, $J = 13.8$, 3.8 Hz, 1H), 2.46–2.37 (m, 1H), 2.33–2.21 (m, 4H), 1.72–1.68 (m, 1H), 1.49 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3): $\delta = 171.2$, 171.0, 170.8, 167.8, 159.0, 149.1, 129.2, 128.4 (2C), 114.0 (2C), 83.8, 81.3, 57.2, 55.7, 55.2, 52.6, 50.1, 45.6, 39.0, 36.6, 32.0, 28.0 (3C), 27.8 (3C), 24.1; MS (EI): m/z (%): 560 (<1) [M]⁺, 460 (14), 432 (10), 404 (16), 403 (34), 387 (11), 376 (19), 359 (12), 317 (21), 163 (15), 122 (12), 121 (100), 57 (18), 41 (14); IR (film): $\tilde{\nu} = 2979$, 2934, 2254, 1789, 1727, 1643, 1612, 1513, 1457, 1438, 1393, 1369, 1308, 1248, 1154, 1035, 992, 947, 913, 844, 815, 733, 647 cm^{-1} ; MALDI ($\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_9 + \text{Na}$): calcd 583.2626; found 583.2624; elemental analysis calcd (%) for $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_9$: C 62.13, H 7.19, N 5.08; found: C 62.10, H 7.26, N 4.92.

(3R, 5S, 10R)-10-(tert-Butoxycarbonylmethyl)-7-(4-methoxybenzyl)-1,6-dioxo-2,7-diaza-spiro[4.5]decane-3-carboxylic methyl ester (71): $\text{Mg}(\text{ClO}_4)_2$

(751 mg, 3.37 mmol) was added to a solution of compound **70** (7.55 g, 13.5 mmol) in CH_3CN (100 mL) and the resulting mixture was stirred for 2 h at 50 °C. Standard extractive work-up followed by flash chromatography of the crude product (silica gel, hexane/ethyl acetate, 1:1 → 1:2) afforded title compound **71** (6.15 g, 99%) as a colorless foam: m.p. 66–67 °C; $[\alpha]_D^{20} = +49.6^\circ$ ($c = 1.05$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 7.15$ (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 6.21 (s, 1H), 4.71 (d, $J = 14.6$ Hz, 1H), 4.37 (d, $J = 14.6$ Hz, 1H), 4.18 (dd, $J = 10.0$, 3.3 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.25–3.21 (m, 2H), 3.10 (dd, $J = 13.9$, 3.3 Hz, 1H), 2.50–2.25 (m, 5H), 1.79–1.71 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 175.0$, 171.6, 171.3, 168.9, 158.9, 129.1 (2C), 128.6, 114.0 (2C), 81.1, 55.2, 53.4, 53.3, 52.7, 50.0, 45.8, 38.1, 36.3, 34.9, 28.0 (3C), 24.3; MS (EI): m/z (%): 460 (16) [M]⁺, 432 (13), 404 (24), 403 (48), 387 (18), 376 (25), 317 (38), 163 (26), 162 (17), 136 (10), 122 (14), 121 (100), 57 (12); IR (KBr): $\tilde{\nu} = 3396$, 2975, 2953, 2934, 1712, 1639, 1513, 1439, 1368, 1248, 1153, 1033, 957, 845, 816 cm^{-1} ; HRMS ($\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_7$): calcd 460.22095; found 460.22077; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_7$: C 62.59, H 7.00, N 6.08; found: C 62.65, H 6.88, N 6.03.

(3R, 5S, 10R)-10-(tert-Butoxycarbonylmethyl)-3-(2-hydroxymethyl)-7-(4-methoxybenzyl)-1,6-dioxo-2,7-diaza-spiro[4.5]decane (72): LiBH_4 (48.0 mg, 2.19 mmol) was added to a solution of methyl ester **71** (504 mg, 1.09 mmol) in THF (50 mL) at –20 °C, the cooling bath was removed after 5 min, and the mixture was stirred for 30 min at ambient temperature. The reaction was quenched by addition of aq. sat. NH_4Cl (20 mL), the aqueous phase was repeatedly extracted with ethyl acetate, the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (silica gel, ethyl acetate) affording alcohol **72** as a colorless foam (388 mg, 82%): m.p. 65–68 °C; $[\alpha]_D^{20} = +36.4^\circ$ ($c = 0.470$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 7.18$ (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.68 (s, 1H), 4.72 (s, 1H), 4.63 (d, $J = 14.6$ Hz, 1H), 4.50 (d, $J = 14.6$ Hz, 1H), 3.79 (s, 3H), 3.78–3.76 (m, 2H), 3.32–3.22 (m, 2H), 2.68 (dd, $J = 14.2$, 4.1 Hz, 1H), 2.49–2.12 (m, 5H), 1.77–1.73 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 175.3$, 171.3, 170.9, 159.0, 129.1 (2C), 128.2, 114.1 (2C), 81.1, 65.8, 55.3, 54.4, 53.1, 50.6, 46.3, 39.5, 36.6, 34.6, 28.1 (3C), 24.1; MS (EI): m/z (%): 432 (9) [M]⁺, 404 (11), 376 (17), 375 (34), 359 (17), 348 (21), 289 (29), 163 (25), 162 (13), 136 (10), 122 (13), 121 (100), 57 (11); IR (KBr): $\tilde{\nu} = 3398$, 2974, 2932, 1725, 1698, 1617, 1514, 1456, 1439, 1368, 1248, 1154, 1033, 970, 945, 845, 814, 760 cm^{-1} ; HRMS ($\text{C}_{23}\text{H}_{32}\text{N}_2\text{O}_6$): calcd 432.22604; found 432.22628; elemental analysis calcd (%) for $\text{C}_{23}\text{H}_{32}\text{N}_2\text{O}_6$: C 63.87, H 7.46, N 6.41; found: C 63.94, H 7.45, N 6.48.

(3R, 5S, 10R)-10-(tert-Butoxycarbonylmethyl)-7-(4-methoxybenzyl)-1,6-dioxo-2,7-diaza-spiro[4.5]decane-3-carboxaldehyde (73): Dess–Martin periodinane (868 mg, 2.05 mmol) was added to a solution of alcohol **72** (590 mg, 1.36 mmol) in CH_2Cl_2 (10 mL). A solution of H_2O (28.0 μL , 1.56 mmol) in CH_2Cl_2 (28 mL) was then added dropwise over a period of 30 min during which the mixture became turbid and a colorless precipitate started to form. After stirring for another 30 min at ambient temperature, $\text{Na}_2\text{S}_2\text{O}_5$ (10% in H_2O)/sat. aq. NH_4Cl (30 mL, 1:1) and *tert*-butyl methyl ether (50 mL) were added, the aqueous layer was extracted with ethyl acetate in several portions, the combined organic layers were dried over Na_2SO_4 , the solvent was evaporated, and the residue was rapidly passed through a short column of silica gel using ethyl acetate as the eluent. This afforded aldehyde **73** (459 mg, 78%) as a colorless foam: m.p. 62–64 °C; $[\alpha]_D^{20} = +37.7^\circ$ ($c = 1.60$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 9.73$ (s, 1H), 7.19–7.09 (m, 3H), 6.84 (d, $J = 8.7$ Hz, 2H), 4.62 (d, $J = 14.6$ Hz, 1H), 4.40 (d, $J = 14.6$ Hz, 1H), 3.90 (d, $J = 10.2$ Hz, 1H), 3.78 (s, 3H), 3.25–3.22 (m, 2H), 2.86 (dd, $J = 13.7$, 2.0 Hz, 1H), 2.52–2.18 (m, 5H), 1.79–1.61 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 200.2$, 176.1, 171.3, 169.5, 159.0, 129.1 (2C), 128.3, 114.0 (2C), 81.0, 58.8, 55.2, 52.7, 50.0, 46.0, 37.6, 36.5, 33.8, 28.0 (3C), 24.4; MS (EI): m/z (%): 432 (9) [M]⁺, 404 (11), 376 (17), 375 (34), 359 (17), 348 (21), 289 (29), 163 (25), 162 (13), 136 (10), 122 (13), 121 (100), 57 (11); IR (KBr): $\tilde{\nu} = 3398$, 2974, 2932, 1725, 1698, 1617, 1514, 1456, 1439, 1368, 1248, 1154, 1033, 970, 945, 845, 814, 760 cm^{-1} ; HRMS ($\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_6$): calcd 432.22604; found 432.22628; elemental analysis calcd (%) for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_6$: C 63.87, H 7.46, N 6.41; found: C 63.94, H 7.45, N 6.48.

(3R, 5S, 10R)-10-(tert-Butoxycarbonylmethyl)-7-(4-methoxybenzyl)-3-vinyl-1,6-dioxo-2,7-diaza-spiro[4.5]decane (74): CH_2I_2 (2.20 mL, 27.3 mmol) was added to a suspension of zinc dust (3.20 g, 49.3 mmol; previously activated by washing with 2N HCl and diethyl ether, followed by

drying in high vacuum) in THF (100 mL). After the quite exothermic reaction had ceased after 30 min, $\text{Ti}(\text{O}i\text{Pr})_4$ (16.4 mL, 16.4 mmol, 1.00 M in THF) was introduced and stirring was continued at ambient temperature for another 30 min. Aldehyde **73** (1.18 g, 2.73 mmol) was then added and the mixture was stirred for 14 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL), the aqueous layer was extracted with *tert*-butyl methyl ether and ethyl acetate, the combined organic layers were washed with aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10% w/w) and brine, and were dried over Na_2SO_4 . Evaporation of the solvent followed by flash chromatography of the residue (silica gel, hexane/ethyl acetate 2:1 $\rightarrow$ 1:2) provided **74** (985 mg, 84%) as a colorless foam: m.p. 78–81 °C; $[\alpha]_D^{20} = +42.6^\circ$ ($c = 1.11$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 7.19$ (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.07 (ddd, $J = 18.0, 10.0, 8.2$ Hz, 1H), 5.90 (s, 1H), 5.17–5.12 (m, 2H), 4.71 (d, $J = 14.6$ Hz, 1H), 4.43 (d, $J = 14.6$ Hz, 1H), 4.08 (ddd, $J = 8.4, 8.4, 5.8$ Hz, 1H), 3.79 (s, 3H), 3.29–3.25 (m, 2H), 2.86 (dd, $J = 13.8, 5.8$ Hz, 1H), 2.46–2.21 (m, 5H), 1.80–1.71 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 175.1, 171.3, 169.4, 158.9, 139.5, 129.1$ (2C), 128.7, 116.6, 114.0 (2C), 81.0, 55.22, 55.19, 54.9, 50.4, 46.0, 39.2, 38.9, 36.8, 28.0 (3C), 24.2; MS (EI): m/z (%): 428 (8) $[M]^+$, 400 (13), 372 (13), 371 (48), 355 (21), 344 (30), 285 (39), 163 (28), 162 (13), 136 (11), 122 (13), 121 (100), 57 (12); IR (KBr): $\tilde{\nu} = 3265, 3080, 2978, 2935, 2837, 1727, 1697, 1638, 1513, 1491, 1456, 1434, 1368, 1292, 1248, 1152, 1033, 996, 969, 925, 844, 814, 759, 662, 614, 515\text{ cm}^{-1}$; HRMS ($\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5$): calcd 428.23118; found 428.23093; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5$: C 67.27, H 7.53, N 6.54; found: C 67.34, H 7.51, N 6.44.

(3R, 5S, 10R)-10-(tert-Butoxycarbonylmethyl)-2-(5-hexenyl)-7-(4-methoxy-benzyl)-3-vinyl-1,6-dioxo-2,7-diaza-spiro[4.5]decane (75): NaH (130 mg, 5.42 mmol) was added in portions to a stirred solution of compound **74** (2.11 g, 4.92 mmol) in DMF (150 mL) at 0 °C and the mixture was stirred at ambient temperature for 60 min until the evolution of H_2 had ceased. 6-Iodo-1-hexene (1.55 g, 7.38 mmol) was then introduced at 0 °C and stirring was continued at ambient temperature for another 60 min. For work-up, sat. aq. NH_4Cl (50 mL) and *tert*-butyl methyl ether (200 mL) were added, the aqueous layer was repeatedly extracted with ethyl acetate, the combined organic phases were washed with aq. HCl (1N) and brine, dried over Na_2SO_4 and evaporated. Flash chromatography of the crude product (silica gel, hexane/ethyl acetate 2:1) afforded diene **75** as a colorless foam (2.21 g, 88%): m.p. 84–87 °C; $[\alpha]_D^{20} = +33.2^\circ$ ($c = 1.09$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 7.19$ (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.05 (dt, $J = 17.0, 9.6$ Hz, 1H), 5.86–5.73 (m, 1H), 5.29–5.21 (m, 2H), 5.05–4.93 (m, 2H), 4.74 (d, $J = 14.7$ Hz, 1H), 4.41 (d, $J = 14.7$ Hz, 1H), 4.01 (dt, $J = 9.1, 5.2$ Hz, 1H), 3.79 (s, 3H), 3.56 (ddd, $J = 13.6, 8.7, 6.7$ Hz, 1H), 3.29–3.25 (m, 2H), 2.93 (ddd, $J = 13.6, 8.3, 5.2$ Hz, 1H), 2.70 (dd, $J = 13.9, 5.2$ Hz, 1H), 2.56–2.48 (m, 1H), 2.32–2.04 (m, 6H), 1.73–1.33 (m, 5H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 172.0, 171.4, 169.9, 158.9, 139.2, 138.4, 128.9$ (2C), 128.7, 118.2, 114.7, 114.1 (2C), 81.0, 60.1, 55.2, 55.1, 50.3, 46.2, 40.7, 39.8, 36.8, 36.4, 33.2, 28.0 (3C), 26.3, 26.2, 24.3; MS (EI): m/z (%): 510 (10) $[M]^+$, 482 (16), 454 (22), 453 (43), 426 (32), 367 (36), 163 (31), 162 (15), 122 (11), 121 (100); IR (KBr): $\tilde{\nu} = 3076, 2981, 2926, 1732, 1671, 1635, 1513, 1489, 1426, 1366, 1261, 1251, 1178, 1153, 1101, 1035, 996, 924, 848, 812, 758\text{ cm}^{-1}$; HRMS ($\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_5$): calcd 510.30937; found 510.30975; elemental analysis calcd (%) for $\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_5$: C 70.56, H 8.29, N 5.49; found: C 70.39, H 8.22, N 5.38.

(8'R, 3S, 4R)-1-(4-Methoxybenzyl)-4-(tert-butoxycarbonylmethyl)-spiro[2-piperidone-3,12'-(1'-aza-bicyclo[6.3.0]undec-6'-en-11'-one)] (76): A solution of diene **75** (446 mg, 0.873 mmol) and complex **3b** (40.3 mg, 43.7 μmol) in CH_2Cl_2 (450 mL) was refluxed for 18 h. The reaction mixture was passed through a short pad of silica, the filtrate was evaporated and the crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate 2:1 $\rightarrow$ 1:1) affording compound **76** as a colorless foam (413 mg, 98%): m.p. 84–86 °C; $[\alpha]_D^{20} = +28.9^\circ$ ($c = 0.875$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 7.20$ (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.93 (dt, $J = 10.5, 8.5$ Hz, 1H), 5.59 (dd, $J = 10.6, 7.5$ Hz, 1H), 4.67 (d, $J = 14.6$ Hz, 1H), 4.49 (d, $J = 14.6$ Hz, 1H), 4.34 (q, $J = 7.5$ Hz, 1H), 3.78 (s, 3H), 3.77–3.66 (m, 1H), 3.27–3.12 (m, 2H), 3.14 (dd, $J = 13.8, 6.8$ Hz, 1H), 2.82 (dd, $J = 13.4, 6.8$ Hz, 1H), 2.44–2.00 (m, 8H), 1.73–1.63 (m, 2H), 1.54–1.40 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 171.5, 171.4, 169.9, 158.8, 134.1, 129.8, 129.1$ (2C), 128.8, 114.0 (2C), 80.9, 56.1, 55.2, 53.6, 50.4, 45.3, 41.2, 39.5, 37.4, 36.8, 28.0 (3C), 27.8, 27.0, 26.1, 24.5; MS (EI): m/z (%): 482 (11) $[M]^+$, 454 (13), 426 (25), 425 (35), 409 (18), 398 (25), 339 (35), 163 (29), 162 (13), 122 (11), 121 (100); IR (KBr): $\tilde{\nu} = 3062, 2963,$

2931, 2868, 1727, 1677, 1638, 1513, 1491, 1456, 1438, 1420, 1366, 1354, 1248, 1153, 1109, 1095, 1032, 962, 925, 845, 811, 760, 710, 663, 610, 549 cm^{-1} ; HRMS ($\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_5$): calcd 482.27807; found 482.27816; elemental analysis calcd (%) for $\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_5$: C 69.68, H 7.94, N 5.80; found: C 69.76, H 8.03, N 5.69.

(8'R, 3S, 4R)-4-(Methoxycarbonylmethyl)-spiro[2-piperidone-3,12'-(1'-aza-bicyclo[6.3.0]undec-6'-en-11'-one)] (77): Compound **76** (2.07 g, 4.29 mmol) was dissolved in trifluoroacetic acid (50 mL) and the solution was refluxed for 18 h. The acid was then removed in vacuo and the residue was dried at $<10^{-3}$ Torr. To a solution of the crude product thus formed in toluene/MeOH (3.5:1, 100 mL) was slowly added a solution of (trimethylsilyl)diazomethane (2.00 M in hexane) until a pale yellow color persisted and no further evolution of gas could be detected. Stirring was continued for 30 min before so much HOAc was added dropwise that the yellow color completely disappeared. Evaporation of the solvent followed by purification of the crude product by flash chromatography (silica gel, ethyl acetate/methanol 20:1) delivered title compound **77** as a pale yellow foam (1.17 g, 85%): m.p. 103–106 °C; $[\alpha]_D^{20} = +19.4^\circ$ ($c = 0.825$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 6.68$ (brs, 1H), 5.90 (dt, $J = 10.2, 8.5$ Hz, 1H), 5.49 (dd, $J = 10.2, 7.7$ Hz, 1H), 4.29 (quart, $J = 7.5$ Hz, 1H), 3.70–3.57 (m, 1H), 3.66 (s, 3H), 3.40–3.31 (m, 2H), 3.01 (dd, $J = 13.8, 7.0$ Hz, 1H), 2.70 (dd, $J = 13.4, 7.0$ Hz, 1H), 2.49–2.08 (m, 7H), 2.02–1.93 (m, 1H), 1.76–1.64 (m, 2H), 1.45–1.30 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 172.5, 171.6, 170.9, 134.3, 129.4, 55.5, 53.3, 51.7, 41.0, 40.7, 38.6, 36.8, 35.1, 27.7, 26.9, 26.2, 24.4$; MS (EI): m/z (%): 321 (20), 320 (100) $[M]^+$, 289 (24), 260 (15), 253 (12), 250 (11), 247 (29), 220 (20), 219 (24), 192 (13), 191 (24), 190 (25), 189 (23), 163 (12), 124 (15), 123 (14), 108 (10), 81 (11), 80 (16), 67 (12), 53 (11), 41 (18), 30 (10); IR (KBr): $\tilde{\nu} = 3442, 3090, 3020, 2931, 2867, 1736, 1666, 1491, 1438, 1345, 1285, 1254, 1171, 1086, 999, 948, 922, 862, 841, 783, 668, 570, 539\text{ cm}^{-1}$; HRMS ($\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4$): calcd 320.17361; found 320.17353; elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4$: C 63.73, H 7.55, N 8.74; found: C 63.65, H 7.59, N 8.79.

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- a) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29; b) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; c) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; d) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2144; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2037–2056; e) A. Fürstner, *Top. Catal.* **1997**, *4*, 285–299; f) S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371–388; g) K. J. Ivin, *J. Mol. Catal. A: Chem.* **1998**, *133*, 1–16; h) M. L. Randall, M. L. Snapper, *J. Mol. Catal. A: Chem.* **1998**, *133*, 29–40; i) R. R. Schrock, *Tetrahedron* **1999**, *55*, 8141–8153; j) M. E. Maier, *Angew. Chem.* **2000**, *112*, 2153–2157; *Angew. Chem. Int. Ed.* **2000**, *39*, 2073–2077.
- a) S. T. Nguyen, L. K. Johnson, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975; b) S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859; c) Z. Wu, S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511.
- a) P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem.* **1995**, *107*, 2179–2181; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039–2041; b) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- a) J. Huang, E. D. Stevens, S. P. Nolan, J. L. Petersen, *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678; b) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247–2250; c) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956; d) L. Ackermann, A. Fürstner, T. Weskamp, F. J. Kohl, W. A. Herrmann,

- Tetrahedron Lett.* **1999**, *40*, 4787–4790; e) T. Weskamp, F. J. Kohl, W. Hieringer, D. Gleich, W. A. Herrmann, *Angew. Chem.* **1999**, *111*, 2573–2576; *Angew. Chem. Int. Ed.* **1999**, *38*, 2416–2419; f) A. Fürstner, O. R. Thiel, L. Ackermann, H.-J. Schanz, S. P. Nolan, *J. Org. Chem.* **2000**, *65*, 2204–2207; g) A. Fürstner, L. Ackermann, B. Gabor, R. Goddard, C. W. Lehmann, R. Mynott, F. Stelzer, O. R. Thiel, *Chem. Eur. J.* **2001**, *7*, 3236–3253.
- [5] a) J. Wolf, W. Stüer, C. Grünwald, H. Werner, P. Schwab, M. Schulz, *Angew. Chem.* **1998**, *110*, 1165–1167; *Angew. Chem. Int. Ed.* **1998**, *37*, 1124–1126; b) see also: P. A. van der Schaaf, R. Kolly, A. Hafner, *Chem. Commun.* **2000**, 1045–1046.
- [6] a) T. E. Wilhelm, T. R. Belderrain, S. N. Brown, R. H. Grubbs, *Organometallics* **1997**, *16*, 3867–3869; b) for a very recent development see: M. Gandelman, B. Rybtchinski, N. Ashkenazi, R. M. Gauvin, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 5372–5373.
- [7] K. J. Harlow, A. F. Hill, J. D. E. T. Wilton-Ely, *J. Chem. Soc. Dalton Trans.* **1999**, 285–291.
- [8] A. Fürstner, A. F. Hill, M. Liebl, J. D. E. T. Wilton-Ely, *Chem. Commun.* **1999**, 601–602.
- [9] A. Fürstner, J. Grabowski, C. W. Lehmann, *J. Org. Chem.* **1999**, *64*, 8275–8280.
- [10] For the preparation of true allenylidene species and applications thereof in RCM see: a) A. Fürstner, M. Picquet, C. Bruneau, P. H. Dixneuf, *Chem. Commun.* **1998**, 1315–1316; b) A. Fürstner, M. Liebl, C. W. Lehmann, M. Picquet, R. Kunz, C. Bruneau, D. Touchard, P. H. Dixneuf, *Chem. Eur. J.* **2000**, *6*, 1847–1857; c) see also: H.-J. Schanz, L. Jafarpour, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 5187–5190.
- [11] The generation of indenylidenes from propargyl alcohol derivatives and Ru^{II} species has precedence in the serendipitous formation of an indenylallenylidene complex upon attempted synthesis of metallacumulenes, cf. D. Touchard, N. Pirio, L. Toupet, M. Fettouhi, L. Ouahab, P. H. Dixneuf, *Organometallics* **1995**, *14*, 5263–5272.
- [12] L. Jafarpour, H.-J. Schanz, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 5416–5419.
- [13] A. Fürstner, O. R. Thiel, *J. Org. Chem.* **2000**, *65*, 1738–1742.
- [14] M. T. Reetz, M. H. Becker, M. Liebl, A. Fürstner, *Angew. Chem.* **2000**, *112*, 1294–1298; *Angew. Chem. Int. Ed.* **2000**, *39*, 1236–1239.
- [15] A. Fürstner, J. Grabowski, C. W. Lehmann, T. Kataoka, K. Nagai, *ChemBioChem* **2001**, *2*, 60–68.
- [16] A. Fürstner, K. Radkowski, *Chem. Commun.* **2001**, 671–672.
- [17] B. Schmidt, H. Wildemann, *Perkin 1* **2000**, 2916–2925.
- [18] E. L. Dias, R. H. Grubbs, *Organometallics* **1998**, *17*, 2758–2767.
- [19] a) A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 3942–3943; b) A. Fürstner, K. Langemann, *Synthesis* **1997**, 792–803; c) A. Fürstner, *Top. Organomet. Chem.* **1998**, *1*, 37–72.
- [20] Alternatively, the incipient 10-membered ring itself may enforce the selective formation of the (*E*)-olefin. Assuming the *s-trans* ester functionality in **45** mimics an (*E*)-configured double bond, the product resembles (*E,E*)-1,6-cyclodecadiene with its pronounced conformational preference. This issue will be discussed in more detail in a forthcoming full paper on the synthesis of herbarumin I.
- [21] For the synthesis of 10-membered heterocycles in which RCM is highly stereoselective for either the (*E*)- or the (*Z*)-alkene see: a) B. E. Fink, P. R. Kym, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1998**, *120*, 4334–4344; b) M. Quitschalle, M. Kalesse, *Tetrahedron Lett.* **1999**, *40*, 7765–7768; c) for a review focussing on the synthesis of medium sized rings by RCM see ref. [1j].
- [22] J. Kobayashi, D. Watanabe, N. Kawasaki, M. Tsuda, *J. Org. Chem.* **1997**, *62*, 9236–9239.
- [23] For reviews on mazamine alkaloids see: a) M. Tsuda, J. Kobayashi, *Heterocycles* **1997**, *46*, 765–794; b) E. Magnier, Y. Langlois, *Tetrahedron* **1998**, *54*, 6201–6258; c) N. Matzanke, R. J. Gregg, S. M. Weinreb, *Org. Prep. Proced. Int.* **1998**, *30*, 1–51.
- [24] S. F. Martin, J. M. Humphrey, A. Ali, M. C. Hillier, *J. Am. Chem. Soc.* **1999**, *121*, 866–867.
- [25] S. V. Ley, P. R. Woodward, *Tetrahedron Lett.* **1987**, *28*, 3019–3020.
- [26] K. M. J. Brands, L. M. DiMichele, *Tetrahedron Lett.* **1998**, *39*, 1677–1680.
- [27] Compound **70** is obtained with a *dr* ≥ 20:1 as can be deduced from HPLC runs of the crude product.
- [28] This was the best way to selectively deprotect the *N*-Boc group without affecting the *tert*-butyl ester in compound **70**, cf.: J. A. Stafford, M. F. Brackeen, D. S. Karanewsky, N. L. Valvano, *Tetrahedron Lett.* **1993**, *34*, 7873–7876.
- [29] a) S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549–7552; b) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156.
- [30] T. Okazoe, J. Hibino, K. Takai, H. Nozaki, *Tetrahedron Lett.* **1985**, *26*, 5581–5584.
- [31] T. L. Macdonald, D. E. O'Dell, *J. Org. Chem.* **1981**, *46*, 1501–1503.
- [32] A. Fürstner, L. Ackermann, *Chem. Commun.* **1999**, 95–96.
- [33] E. E. Schweizer, G. J. O'Neill, *J. Org. Chem.* **1965**, *30*, 2082–2083.
- [34] W. A. Nugent, J. Feldman, J. C. Calabrese, *J. Am. Chem. Soc.* **1995**, *117*, 8992–8998.
- [35] M. W. Wright, T. L. Smalley, M. E. Welker, A. L. Rheingold, *J. Am. Chem. Soc.* **1994**, *116*, 6777–6791.
- [36] A. Fürstner, D. Koch, K. Langemann, W. Leitner, C. Six, *Angew. Chem.* **1997**, *109*, 2562–2565; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2466–2469.
- [37] T. A. Kirkland, R. H. Grubbs, *J. Org. Chem.* **1997**, *62*, 7310–7318.
- [38] S. B. Chang, R. H. Grubbs, *J. Org. Chem.* **1998**, *63*, 864–866.
- [39] S.-H. Kim, W. J. Zuercher, N. B. Bowden, R. H. Grubbs, *J. Org. Chem.* **1996**, *61*, 1073–1081.
- [40] J. H. Cassidy, S. P. Marsden, G. Stemp, *Synlett* **1997**, 1411–1413.
- [41] A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, *121*, 11108–11113.
- [42] M. S. Visser, N. M. Heron, M. T. Didiuk, J. F. Sagal, A. H. Hoveyda, *J. Am. Chem. Soc.* **1996**, *118*, 4291–4298.
- [43] A. Fürstner, T. Müller, *Synlett* **1997**, 1010–1012.

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