LETTER

doi:10.1038/nature10563

Synthesis of macrocyclic natural products by catalyst-controlled stereoselective ring-closing metathesis

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Many natural products contain a C=C double bond through which various other derivatives can be prepared; the stereochemical identity of the alkene can be critical to the biological activities of such molecules. Catalytic ring-closing metathesis (RCM) is a widely used method for the synthesis of large unsaturated rings[1,2]; however, cyclizations often proceed without control of alkene stereochemistry[2]. This shortcoming is particularly costly when the cyclization reaction is performed after a long sequence of other chemical transformations[2]. Here we outline a reliable, practical and general approach for the efficient and highly stereoselective synthesis of macrocyclic alkenes by catalytic RCM; transformations deliver up to 97% of the *Z* isomer owing to control induced by a tungsten-based alkylidene. Utility is demonstrated through the stereoselective preparation of epothilone C (refs 3–5) and nakadomarin A (ref. 6), the previously reported syntheses of which have been marred by late-stage, non-selective RCM[7–12]. The tungsten alkylidene can be manipulated in air, delivering the products in useful yields with high stereoselectivity. As a result of efficient RCM and re-incorporation of side products into the catalytic cycle with minimal alkene isomerization, desired cyclizations proceed in preference to alternative pathways, even under relatively high substrate concentration.

Catalytic RCM of alkenes is indispensable to the preparation of cyclic structures[1]; it is used extensively in the synthesis of biologically active molecules[2]. RCM is broadly used in accessing large rings, despite the lack of a reliably stereoselective variant, the availability of which would substantially enhance the value of this critical class of reactions. The absence of stereochemical control originates from the dependency of the catalytic ring closure on the energetic attributes of the product stereoisomers (rather than being dictated by the catalyst). With small or medium rings, *Z* alkenes are generated exclusively; this is not so with sizeable rings, because, frequently, either the energy difference between the two isomeric alkenes is insufficient for achieving high stereoselectivity by thermodynamic control, or, if one isomer is adequately lower in energy, the catalyst is unable to promote facile equilibration.

The severe shortcoming in the state-of-the-art is illustrated by the two sets of non-selective catalytic RCM, shown in Fig. 1, performed en route to macrocyclic natural products epothilone C[3–5] and nakadomarin A[6]. Efforts from several laboratories have focused on catalytic RCM for synthesis of the macrocyclic moiety of different members of the epothilone family; popular catalysts, like those derived from alkylidene **1** (ref. 13; Fig. 1) and carbenes **2a–d** (refs 14, 15; Fig. 1), deliver little or no stereoselectivity[7,8]. Initiatives regarding nakadomarin A (see **5**→**6**, Fig. 1), consisting of four different routes that incorporate a late-stage catalytic macrocyclic ring closure, have met with equally unsatisfactory outcomes[9–12].

Catalytic stereoselective RCM of dienes **3** and **5** (Fig. 1) constitutes particularly compelling objectives for several reasons. Epothilone C (precursor to epothilone A), as well as nakadomarin A, belong to important classes of natural products that exhibit exceptional biological activity[4–6,16]. Epothilones are potent naturally occurring tubulin polymerization and microtubule stabilizing agents that have been investigated extensively. The geometry of the macrocyclic alkene has been shown to influence their activity[16]; the *Z* macrocyclic alkene of epothilone C is needed for the desired stereochemical outcome in the preparation of epothilone A through epoxidation[7,8]. Nakadomarin A is a potent anti-microbial and anti-cancer agent isolated only in minute quantities[6,12]. An effective method for laboratory synthesis of such important targets could lead to larger quantities of these molecules or their analogues, which might not be easily accessible by fermentation[17]. As synthesis of the large rings in epothilone C or nakadomarin A entails the use of extensively functionalized substrates and occurs late in a multi-step sequence, a non-selective transformation inflicts a costly diminution in efficiency; this difficulty is exacerbated by the fact that the two alkene isomers of epothilone C and nakadomarin A are difficult to separate[12,18]. Moreover, with structurally complicated dienes such as **3** or **5**, the tactic of carrying out preliminary studies involving simpler structural variants to help establish the feasibility of an RCM strategy is unreliable; substituents and their stereochemical identities have a pivotal role in the efficiency and stereoselectivity of catalytic ring closures and their absence often has a major influence on the cyclization process[7]. In a catalyst-controlled RCM, stereoselectivity would become far less dependent on the attributes of the diene starting material and therefore more predictable.

At the time the present investigations were initiated, efforts to address the above complications had centred on the more common but less efficient detour of altering substrate structure (rather than identification of a catalyst that generates the desired alkene stereoselectively). One relatively established two-step approach consists of W- or Mo-catalysed alkyne RCM followed by Pd-catalysed partial hydrogenation[19,20]: the first process affords the ring system and the other adjusts the oxidation state. Syntheses of the methyl-substituted alkyne precursors, required to enhance catalyst longevity and avoid oligomerization[21], necessitate additional manipulations; elevated temperatures (80–140 °C) are required for ring closure, and the presence of Lewis-base alkylamines can lead to a need for high loadings of the metal complex (for example, 50 mol%; ref. 22) or complete catalyst inhibition[23]. More recently, macrocyclic RCM of a limited range of substrates involving reactions between an internal vinylsilane and a terminal alkene, followed by protodesilylation, has been disclosed[24]. Two additional steps are again needed: the requisite vinylsilanes are prepared by Ru-catalysed alkyne hydrosilylation, and the resulting trisubstituted silyl-substituted alkenes are converted to the cyclic *Z* alkene by treatment with a mixture of an ammonium fluoride, a silver fluoride salt and acetic acid. High catalyst loadings (20 mol%) are used in the latter RCM strategy, partly because of the intermediacy of a trisubstituted alkene.

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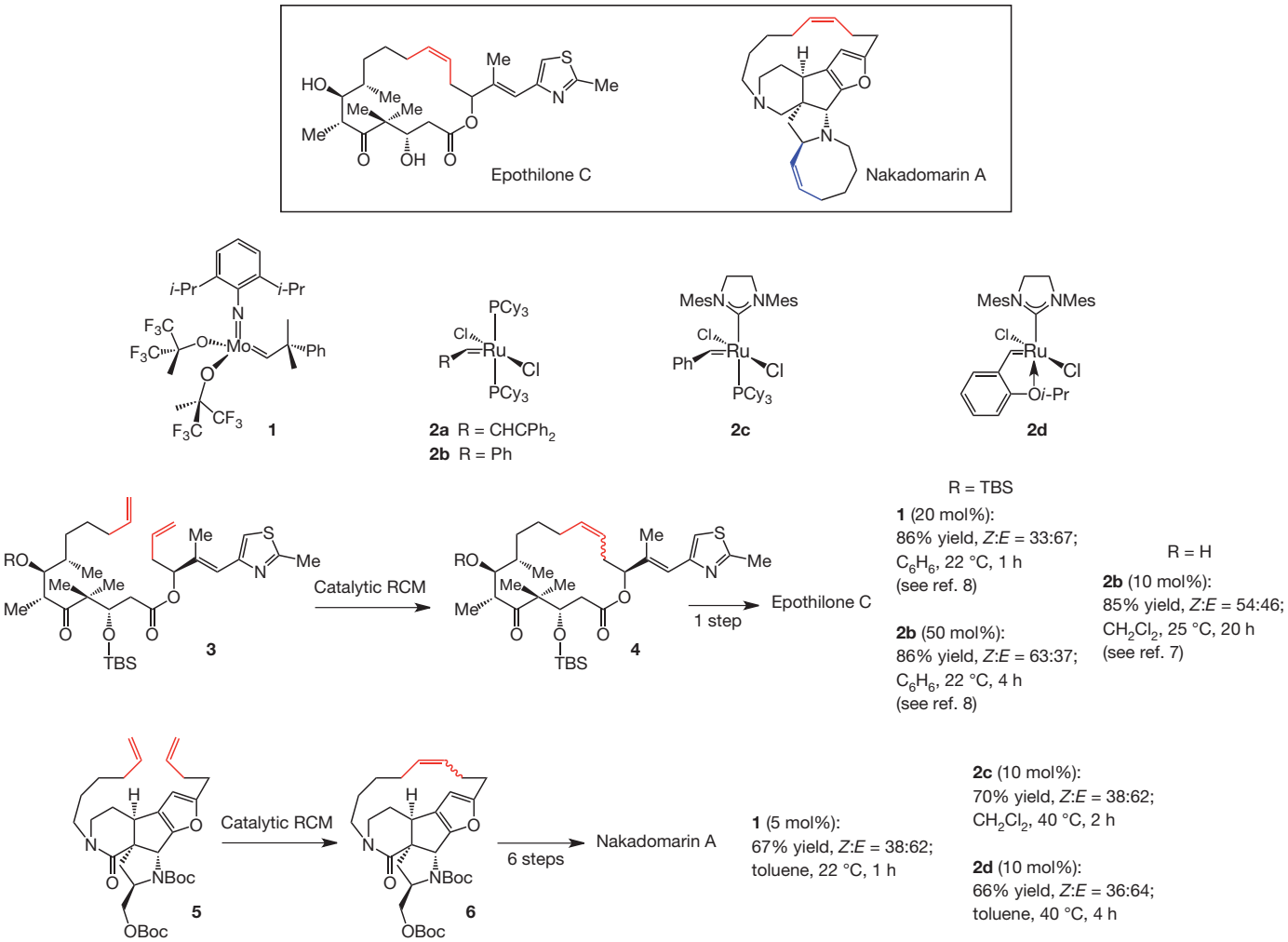
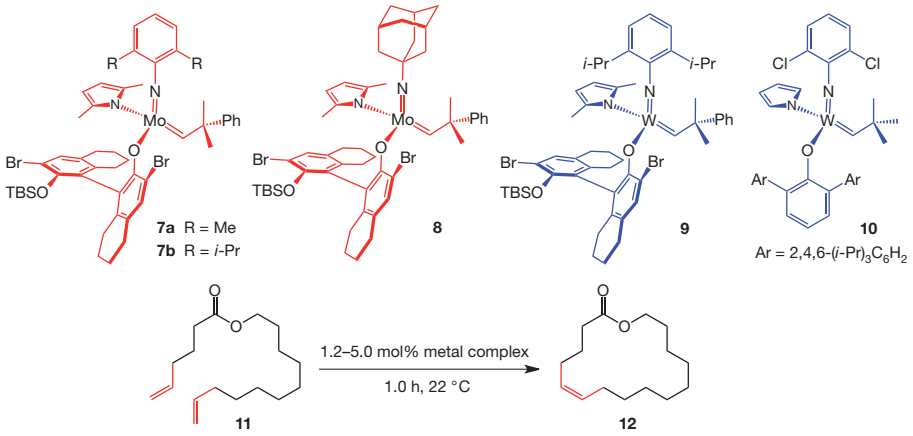


Figure 1 | Two cases in natural product total synthesis where catalytic RCM with commonly used complexes (1, 2b–d) delivers the macrocyclic alkene with minimal stereoselectivity. Top row, target compounds epothilone C and nakadomarin A. Second row, frequently employed complexes **1**, **2b–d**. Third row, catalytic RCM used in synthesis of epothilone C, showing results with different catalysts. Difficulties in stereoselective ring closure are particularly detrimental because the catalytic RCM takes place late in the synthesis route, inflicting substantial loss in efficiency. For example, diene **3**, used in the total synthesis of anti-cancer agent epothilone C, is prepared by a 16-step sequence. Bottom, catalytic RCM used in synthesis of nakadomarin A.TBS, *t*-butyldimethylsilyl; Boc, *t*-butoxycarbonyl; Mes, 2, 4, 6-trimethylphenyl.

We have introduced several types of intermolecular *Z*-selective olefin metathesis reactions promoted by molybdenum and, less commonly, tungsten alkylidenes that bear a pyrrolide and an alkoxide or an aryloxide ligand. Such stereogenic-at-metal[25] catalysts initiate *Z*-selective alkene formation by ring-opening/cross-metathesis[26], homocoupling[27] or the more complicated cross-metathesis[28]. Stereochemical models that provide a mechanistic foundation for high *Z* selectivity have been proposed[28] and are based on the size differential between the large aryloxide and the smaller imido group (metallacyclobutane substituents oriented towards the latter; see Supplementary Information for details). Successful design of stereoselective macrocyclic RCM reactions, however, requires addressing challenges that are distinct from those pertaining to stereoselective cross-metathesis reactions. When RCM or cross-metathesis involves two unhindered alkenes, stereoisomeric purities can be fragile, because the kinetically generated *Z* alkene can more readily undergo isomerization to the *E* isomer[28]. With many cyclizations, such as those in Fig. 1, there is no allylic substituent to discourage association of the macrocyclic *Z* alkene with the catalyst to retard the rate of unwanted equilibration; adventitious ring-opening can pose a serious problem. Achieving high stereoselectivity and yield often calls for a catalyst that delivers the subtle and difficult balance that culminates in an efficient and *Z*- or *E*-selective cyclization with little or no ring-opening/ring-closing that can cause isomerization. Thus, a complicating factor that is critical to RCM but does not apply to cross-metathesis relates to the interplay between ring closure and isomerization by ring-opening. Furthermore, a common strategy in cross-metathesis relates to the use of excess amounts of one cross-partner to favour formation of the desired product (versus homocoupling or isomerization)[28]; in an RCM, on the other hand, the two reacting alkenes can only be present at the same concentration. Whereas the steric and electronic attributes of one alkene may be rendered distinct in cross-metathesis as the means to minimize homocoupling and enhance the yield of the desired product[28], such strategic differentiations are often not possible in RCM (compare Fig. 1). Unlike cross-metathesis, conformational preferences can be critical to the facility of RCM, aiding or resisting the influence of the catalyst. Finally, in cross-metathesis only homocoupling can lead to adventitious substrate consumption, whereas in RCM the same side product continues to deplete the substrate amount through oligomerization.

Examining the ability of different catalysts to promote the RCM of diene **11** to afford the 16-membered-ring lactone *Z*-**12** (Table 1) was first on our agenda. Preliminary density functional theory (DFT) calculations (Supplementary Information) had revealed that the *E* isomer is 1.2 kcal mol^{-1} lower in energy than the *Z* isomer, suggesting that, at equilibrium, there would exist an approximately 12:88 *Z*:*E* mixture. A previously disclosed attempt involving ruthenium carbene **2a** delivered

Table 1 | Initial study of catalytic RCM of diene 11 to generate 12 stereoselectively



Entry no.	Metal complex	Catalyst loading* (mol%)	Pressure	Conv.† (%); yield‡ (%)	*Z*:*E*†
1	**1**	5.0	Ambient	85; 60	22:78
2	**1**	5.0	7.0 torr	96; 58	21:79
3	**2c**	5.0	Ambient	75; 61	21:79
4	**7a**	5.0	Ambient	56; 45	70:30
5	**7a**	5.0	7.0 torr	97; 56	77:23
6	**7b**	5.0	7.0 torr	91; 55	72:28
7	**8**	3.0	7.0 torr	80; 62	85:15
8	**8**	1.2	7.0 torr	75; 56	92:8
9	**9**	5.0	7.0 torr	80; 62	91:9
10	**10**	5.0	7.0 torr	14; 10	95:5

The reactions were carried out in toluene (5.0 mM) at 22 °C for one hour under an atmosphere of nitrogen gas or under vacuum, as noted; reaction in entry 3 performed in CH_2Cl_2 at 40 °C. See Supplementary Information for details.

* Complexes **1**, **2c**, **9**, **10** were prepared before use; alkylidenes **7a**, **b** and **8** were synthesized *in situ* from the bis-pyrrolide and aryl alcohol, which proceeds in >98% yield for **7a**, **b** but in 60% (±5%) yield in the case of **8** (thus, catalyst loading for the latter complex is 3.0 mol%). See Supplementary Information for details.

† Conversion and *Z*:*E* ratios measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures; variance of values is estimated to be <±2%.

‡ Yield of isolated product after purification; variance of values is estimated to be <±5%.

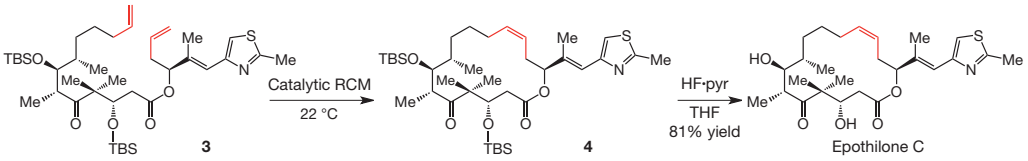
12 with 77% *E* selectivity (that is, 23% *Z*; 4.0 mol%, 22 °C, 30 h)[29]. As demonstrated in entries 1–3 in Table 1, *E*-**12** is formed preferentially with complexes **1** or **2c**; reduced pressure, a strategy used to minimize isomerization[28], does not improve selectivity (compare entries 1 and 2). In contrast, *Z*-**12** is generated with moderate preference when RCM is carried out with monopyrrolides **7a**, **b** (entries 4–6). Adamantylimido **8** furnishes 85% of the *Z* isomer under vacuum (7.0 torr; 62% yield; entry 7); stereoselectivity increases to 92% *Z* with 1.2 mol% catalyst loading (entry 8; versus 3.0 mol% in entry 7) while affording similar efficiency, presumably because isomerization of the cyclic *Z* alkene is reduced when the catalyst is less available. Reaction with tungsten alkylidene **9** leads to equally high yield and stereochemical control (62% and 91% *Z*; entry 9). There is exceptional stereoselectivity with dichloroimido tungsten alkylidene **10** (ref. 27) (95% *Z*; entry 10, Table 1), but the reaction proceeds only to 14% conversion with this less active and sterically more demanding complex; longer reaction times do not result in significantly higher conversion. The preference for generation of the *Z* macrocycle is likely to be due to similar principles that result in stereoselective homocoupling and cross-metathesis reactions (see Supplementary Information for a proposed model).

Next, we turned our attention to the challenge of achieving high *Z* selectivity in RCM reactions that lead to epothilones C and A (compare Fig. 1). We prepared diene **3** along the lines of a formerly devised 16-step sequence[7]. Treatment of **3** with Ru-based **2d** leads to preferential formation of the *E* isomer (66%; entry 1, Table 2). Use of 10 mol% arylimido Mo alkylidene **7a** gives rise to 57% conversion to macrocyclic alkene **4** within three hours, but the *Z* isomer is only generated with 64% selectivity (entry 2). When adamantylimido **8** is used under the same conditions (entry 3), efficiency and stereoselectivity improve (87% conversion in 1.5 h and 85% *Z*), presumably as a result of a more accessible metal centre and larger size differential between the aryloxide and the alkylimido unit (compare the stereochemical model in Supplementary Information). There is only a limited enhancement of conversion and stereoselectivity under reduced pressure (entry 4 versus 3, Table 2). When ring closure is carried out under 1.0 torr of vacuum with tungsten alkylidene **10** (entry 5), which bears a 2,6-dichlorophenylimido and a bulky 2,6-di-[2,4,6-(*i*-Pr)$_3$]-phenoxy ligand (versus aryloxides in **7**–**9**), the reaction proceeds to near completion in the same amount of time (2.5 h, 97% conversion), allowing the desired macrocycle to be isolated in 85% yield (96% *Z*). As the data in entry 6 of Table 2 illustrate, with the reaction mixture 50 times more concentrated (0.05 M), 3.0 mol% of the same alkylidene can be used to synthesize the desired product (**4**) in 63% yield and 97% *Z* selectivity. The wider gap between percentage conversion and yield values (97% and 63%, respectively) is largely the result of adventitious oligomerization, likely to have been facilitated by the increased substrate concentration. Lactone **4** is converted to epothilone C on silyl ether removal (81% yield; Table 2); epoxidation of epothilone C generates epothilone A[7,8].

The higher stereoselectivities furnished by W-based complex **10** are probably because, as stated above, it possesses the desired activity level. The tungsten alkylidene promotes efficient RCM at reasonable catalyst loading without being too active, which would lead it to readily cause *Z*-to-*E* isomerization—even at late stages of the transformation when diene concentration is low. In contrast, the more active Mo-based variants probably initiate a similarly *Z*-selective RCM but also engender subsequent ring-opening/isomerization. It is possibly due to such attenuated reactivity that—contrary to the commonly held perception—tungsten alkylidene **10** proves to be sufficiently stable to be handled in air. An example is shown in entry 7 of Table 2: with 7.5 mol% **10**, weighed in air under up to 80% humidity, and all manipulations performed in a fume hood with standard glassware, macrocyclic alkene **4** is delivered in 82% yield and 94% *Z* selectivity (on the 219 mg scale). It should be mentioned that the faster acting Mo complexes, superior to W-based alkylidenes in effecting intermolecular cross-metathesis reactions[28], are more sensitive to air and moisture.

The above findings broach the question as to whether the low stereoselectivity in the synthesis of the 15-membered ring moiety of nakadomarin A (Fig. 1) can be addressed through the use of monopyrrolide

Table 2 | *Z*-selective catalytic RCM for stereoselective total syntheses of epothilones C and A



Entry no.	Complex; loading (mol%)	Pressure; concentration	Time	Conv.† (%); yield‡ (%)	*Z*:*E*†
1	**2d**; 5	Ambient; 1.0 mM	16 h	96; ND	34:66
2	**7a**; 10	1.0 torr; 1.0 mM	3.0 h	57; ND	64:36
3	**8**; 10	Ambient; 1.0 mM	1.5 h	87; ND	85:15
4	**8**; 10	1.0 torr; 1.0 mM	1.5 h	91; ND	90:10
5	**10**; 10	1.0 torr; 1.0 mM	2.5 h	97; 85	96:4
6	**10**; 3.0	1.0 torr; 0.05 M	3.0 h	97; 63	97:3
7	**10**; 7.5*	0.02 torr; 6.0 mM	4.0 h	96; 82	94:6

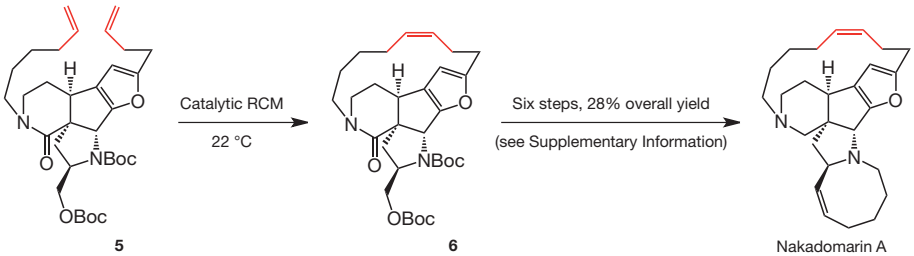
The reactions were carried out at 22 °C in purified benzene (under an atmosphere of nitrogen gas) or toluene (vacuum), except for entry 7 (in mesitylene); see Supplementary Information for details. Note that epoxidation of epothilone C gives epothilone A. THF, tetrahydrofuran; ND, not determined.
* Catalyst was weighed in air and reaction performed in a typical fume hood under argon; see Methods Summary for details.
† Conversion and *Z*:*E* ratios measured by analysis of 500 MHz ^{1}H NMR spectra of unpurified mixtures; variance of values is estimated to be ≤±2%.
‡ Yield of isolated product after purification; variance of values is estimated to be ≤±5%.

complexes. As indicated by the data in entries 1 and 2 of Table 3, arylimido molybdenum alkylidene **7b** affords only 10% conversion to **6**, a precursor to the natural product. In contrast, the sterically more accessible adamantylimido **8** readily converts **5** to pentacycle **6**, but with only 69:31 *Z*:*E* selectivity. Similarly, reaction with tungsten alkylidene **9** is inefficient, probably due to a slow rate of initiation (entry 3, Table 3). The robust tungsten alkylidene **10**, on the other hand, again emerges as the source of a facile and uniquely stereoselective catalyst (entry 4, Table 3): the desired pentacycle **6** is obtained in 90% yield after purification and with 97% *Z* selectivity (performed with 107 mg of **5**).

It is striking that under conditions (0.1 M; entry 6, Table 3) routinely used to perform a typical chemical transformation (versus high dilution typically required for macrocyclic RCM), reaction proceeds to furnish **6** in 52% yield and 94% *Z* selectivity. Equally noteworthy is that when cyclization of **5** is carried out at 0.1 M concentration, reduced pressure is not necessary (that is, ethylene is not removed). Otherwise, **6** is obtained in lower yield and selectivity (39% and 90% *Z* under 7.0 torr, entry 5, Table 3). Since at higher concentration of the diene, homocoupling is rampant, it is likely that the ethylene formed as the by-product raises the availability of the highly reactive methylidene complex[28], which converts the homocoupled product to the monomeric RCM substrate, thus increasing the yield of the desired product. The above scenario, and the fact that *Z* selectivity remains high at 0.1 M concentration (94% *Z*), implies that the tungsten methylidene reacts with the acyclic alkene of the homocoupled triene preferably (rather than with the cyclic alkene **6** to promote isomerization). The somewhat lower stereoselectivity observed under vacuum (90:10 versus 94:6 *Z*:*E*, entries 5 and 6, Table 3) might be because some macrocyclic product is formed through RCM involving the alkylidene derived from the terminal alkene of the homocoupled by-product. The latter pathway to pentacyclic **6** can be less selective than RCM via diene **5**, arising from reaction of two terminal alkenes. It is consequently as a result of several delicate reactivity preferences that the RCM with complex **10** in a 0.1 M solution can be performed efficiently and selectively.

Total synthesis of nakadomarin A might alternatively be accomplished by a late-stage stereoselective RCM (rather than at an earlier point, as in the pathway in Table 3); such a plan, however, can present additional complications and a non-selective RCM translates to loss of a more valuable advanced intermediate. One route proceeds through the especially demanding RCM (compared to **5**→**6**) of azacene-containing **13** (ref. 12; Fig. 2): the higher ring strain within the pentacyclic diene substrate is not only expected to discourage ring closure, it probably lowers the barrier to undesired rupture of the macrocyclic alkene. Accordingly, past attempts at achieving the transformation of **13** to nakadomarin A, as shown in Fig. 2, bottom, have involved the significantly less reactive ruthenium carbene **2b**[14] (compared to **2c**, **d**) in order to minimize post-RCM isomerization of the macrocyclic alkene. Use of such a reluctant catalyst, which must be introduced slowly,

Table 3 | *Z*-selective catalytic RCM for stereoselective synthesis of 6 en route to nakadomarin A



Entry no.	Complex; loading (mol%)	Pressure; concentration	Time	Conv.* (%); yield† (%)	*Z*:*E**
1	**7b**; 5.0	7.0 torr; 5.0 mM	2.0 h	10; ND	ND
2	**8**; 6.0	7.0 torr; 5.0 mM	2.0 h	95; 71	69:31
3	**9**; 5.0	7.0 torr; 5.0 mM	2.0 h	26; ND	ND
4	**10**; 5.0	7.0 torr; 5.0 mM	2.0 h	98; 90	97:3
5	**10**; 5.0	7.0 torr; 0.1 M	0.5 h	>98; 39	90:10
6	**10**; 5.0	Ambient; 0.1 M	2.0 h	95; 52	94:6

The reactions were carried out in purified toluene under an atmosphere of nitrogen gas or under vacuum, as noted. The stereochemical identity of **6** was determined by X-ray crystallography. See Supplementary Information for details. Boc, *t*-butoxycarbonyl.
* Conversion to macrocyclic alkene **6** and *Z*:*E* ratios measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures; variance of values is estimated to be ≤±2%.
† Yield of isolated macrocyclic alkene **6** after purification; variance of values is estimated to be ≤±5%.

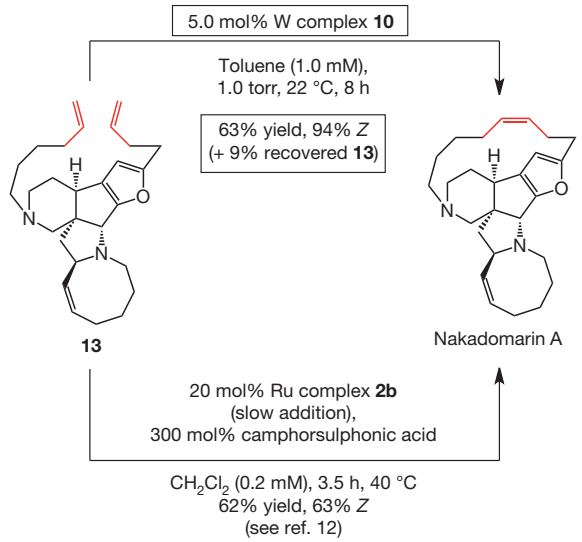


Figure 2 | Total synthesis of nakadomarin A realized through late-stage tungsten-catalysed RCM of pentacyclic 13, and comparison with results delivered by Ru catalysts. RCM of the strained **13** with tungsten complex **10** affords the natural product in 63% yield (69% based on recovered substrate) and 94% *Z*-selectivity (top route in figure). This is in contrast to previous attempts, the best of which involves 20 mol% of a Ru carbene added slowly to a highly dilute solution (0.2 mM) to generate only 63:37 *Z*:*E* mixture (bottom route in figure).

translates to high loadings and elevated temperatures (20 mol%, 40 °C). Extremely dilute conditions (0.2 mM) are also needed, as it is unlikely that under such conditions any homocoupled by-products that would otherwise be formed can be reverted back to the monomeric dienes or converted directly to the desired macrocycle. Additionally, the presence of substantial quantities (300 mol%) of camphorsulphonic acid, a strong Brønsted acid, is required for achieving 63% *Z* selectivity (otherwise, slight excess of the *E* alkene is obtained)[12]. In sharp contrast (Fig. 2, top), treatment of **13** with 5.0 mol% **10** at 22 °C affords nakadomarin A in 94% *Z* selectivity and 63% yield (plus 9% recovered diene). Finally, it should be noted that attempts to effect alkyne RCM of the diyne derivative of **13** (Me-substituted), bearing two Lewis basic tertiary amines, with either Mo- or W-based alkylidynes, leads to <5% conversion even with 30–50 mol% of a metal complex and at 80 °C (up to 24 h); this latter approach must therefore involve the use of the derived bisamide (20–25 mol% catalyst, 80 °C, 16–18 h).

The investigations described above point to stereogenic-at-tungsten alkylidenes as practical and uniquely effective catalysts for *Z*-selective macrocyclic RCM. We demonstrate that, in planning a multi-step pathway for the preparation of a complex molecule, such complexes can be relied on to deliver the desired outcome at the late stages of an extended route. The impact of stereoselective W-catalysed macrocyclizations reaches beyond the target structures probed in this study, as there are numerous other total syntheses[22,30] of biologically active molecules that would similarly benefit from the protocols disclosed here.

METHODS SUMMARY

General procedure for catalytic *Z*-selective macrocyclic RCM. A 250-ml Schlenk flask, fitted with a connecting adaptor attached to an argon-filled manifold, was flame-dried and charged with diene **3** (0.219 g, 0.298 mmol). After azeotropic distillation with dry benzene (three times; freeze-pump), the apparatus was charged with tungsten complex **10** (21.9 mg, 22.4 μmol, weighed in air), evacuated, back-filled with argon and charged with mesitylene (50.0 ml). The mixture was exposed to vacuum (0.02 torr) and allowed to stir for four hours at 22 °C, after which the reaction was quenched by the addition of wet diethyl ether (~1 ml). Purification by silica gel chromatography (hexanes:diethyl ether 20:1) afforded **4** (0.172 g, 0.243 mmol, 82% yield, 94:6 mixture of *Z*:*E* isomers, determined by 500 MHz ^{1}H NMR) as a white foam and 9.3 mg of the recovered starting material (13 μmol, 3.0%).

Received 22 June; accepted 15 September 2011.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Acknowledgements This work was supported by the United States National Institutes of Health, Institute of General Medical Sciences (grant GM-59426 to A.H.H. and R.R.S.). M. Y. is a John LaMattina graduate fellow, A.F.K. the recipient of an EPSRC-GlaxoSmithKline synthesis studentship, and P.J. an EPSRC postdoctoral fellow. D.J.D. is grateful for an EPSRC leadership fellowship. We thank S. J. Meek, S. J. Malcolmson, R. V. O'Brien, T. J. Mann and E. T. Kiesewetter for discussions; A. R. Zhugralin, S. Torker and D. L. Silverio for DFT calculations; K. Wu for experimental

assistance; and Boston College for providing access to computational facilities. The X-ray facilities at Boston College are supported by the United States National Science Foundation (CHE-0923264).

Author Contributions M.Y. and C.W. were involved in the discovery, design and development of the *Z*-selective macrocyclic ring-closing metathesis strategies and applications to the natural product syntheses. A.F.K., P.J. and D.J.D. devised routes for and performed enantioselective syntheses of precursors **5** and **13**. R.R.S. and A.H.H. were involved in the discovery and development of the catalysts used in the study; A.H.H. conceived and directed the investigations and composed the manuscript with revisions provided by M.Y. and C.W.

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