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# Olefin Metathesis: Remote Substituents Governing the Stereoselectivity of 11-Membered-Ring Formation

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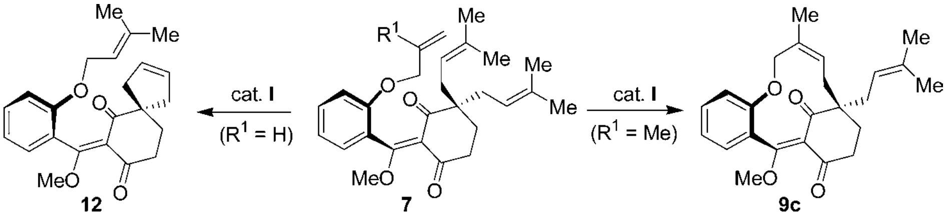
## ABSTRACT



**Stereospecific RCM reaction of 7 ($R^1$ = Me) results in the formation of *(Z)*-11-membered macrocycle 9c. Cascade RCM/ROM/RCM transformation of 7 ($R^1$ = H) affords the thermodynamically more stable spirocycle product 12.**

Recent decades have seen a burgeoning of interest in the olefin metathesis reaction and the intensity of research activity involved has grown exponentially as the power of this reaction became ever more apparent.[1] Much work has focused on unveiling a plethora of olefin metathesis catalysts with improvements in their reactivity profiles, and their sensitivity to air and water, constantly being attained by the judicious tailoring of the ligands employed and by careful selection of an appropriate transition metal to effect the requisite metallocarbene-mediated reactions. Elegant synthetic applications using the knowledge so-garnered have begun to emerge in the literature and such examples are becoming more and more sophisticated as time progresses. The popularity of olefin metathesis as a synthetic tool can disguise the fact that each novel example investigated still has much to teach us about the dynamics of this complex sequence of reactions which eventually leads to the formation of a new olefin upon the union of two precursor olefins. These latter features were never better illustrated than by the recent publication of the first total synthesis of coleophomones B and C.[2]

In this instance two extremely strained and rigid 11-membered rings were formed by employing the second-generation Grubbs' catalyst (**I**)[3] in two independent ring-closing metathesis (RCM) reactions. The surprise elicited by the outcome of this investigation can be said to originate not only from the successful accomplishment of a challenging and relatively unprecedented macrocyclization metathesis employing an isoprenyl coupling partner, but also in the fact that this reaction occurred with complete stereoselectivity. Furthermore, the stereoselectivity observed was reversed in the two substrates examined, in one case the *E* double bond was formed exclusively and in the other the *Z* isomer was the sole product.[2] The proliferation of medium-sized rings among the molecules we seek to synthesize combined with the obvious advantages of RCM as a tool for accomplishing their construction together mean that comprehending the source of this specificity is pivotal for future reference. It is also of broad relevance to ask how general the specificity for formation of a single isomer is when 11-membered rings[4] are targeted, since larger ring sizes are frequently associated with mixed geometries.[5]

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[1] For selected recent reviews in olefin metathesis see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (d) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592.

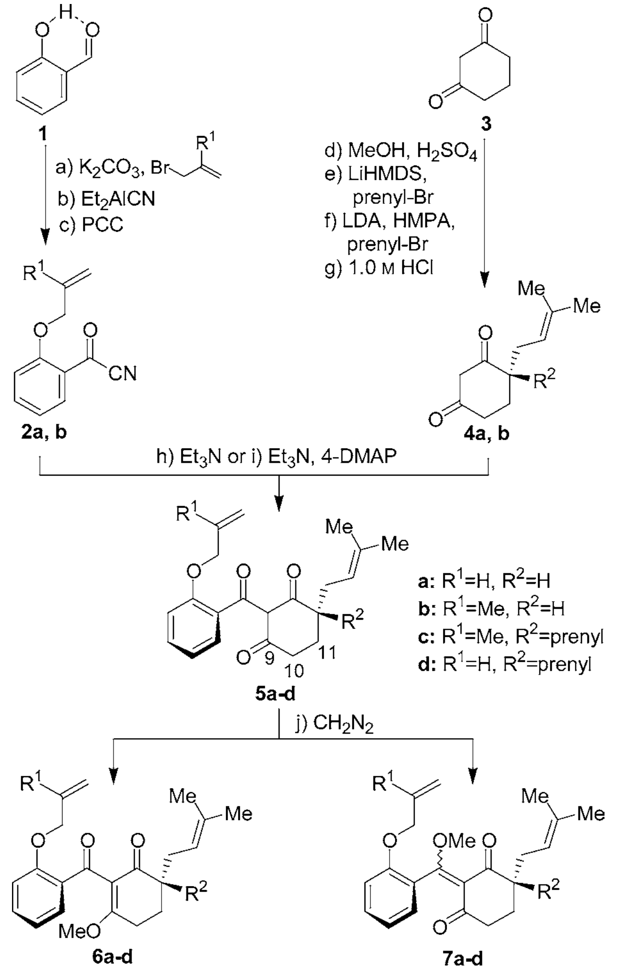
[2] Nicolaou, K. C.; Vassilikogiannakis, G.; Montagnon, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3276.

[3] For the preparation of the catalyst see: Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

10.1021/ol036156w CCC: $27.50

To instigate the probing of such issues, compounds **6a** and **7a** ($R^1 = R^2 = H$) were synthesized by using the methods developed by the Nicolaou group (Scheme 1).[2] Our plan was to validate these compounds as models initially by ensuring they followed the stereochemical precedent.[2] Subsequently, more general explorations would be pursued in search of a set of general rules for selectivity in the formation of 11-membered-ring olefins by metathesis, beginning with substrates where the bridging carbocycle was absent (C9−C11).

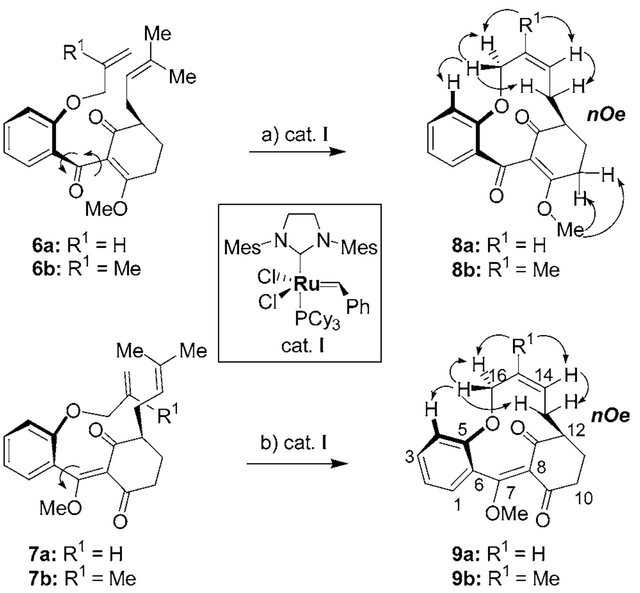
**Scheme 1.** Preparation of the Olefin Metathesis Precursors[a]



[a] Reagents and conditions: (a) $K_2CO_3$ (2.0 equiv), 3-bromo-2-methylpropene or allyl bromide (1.5 equiv), acetone, 56 °C, 2 h, 90−93%; (b) $Et_2AlCN$ (1.2 equiv), toluene, 0 to 25 °C, 1.5 h, 79−85%; (c) PCC (4.0 equiv), $CH_2Cl_2$, 40 °C, 7 h, 64−69%; (d) concentrated $H_2SO_4$ (cat.), MeOH, 65 °C, 12 h, 85%; (e) LiHMDS (1.1 equiv), THF, −78 °C, 1 h, then prenyl-Br (1.2 equiv), −78 to 0 °C, 3 h, 85%; (f) LDA (1.1 equiv), THF, slow addition of a solution of starting material in THF/HMPA (7/1), −78 °C, 1 h; then prenyl-Br (2.0 equiv), −78 to 20 °C, 12 h, 85%; (g) 1.0 M HCl/THF (10/1), 25 °C, 14 h, 95%; (h) $Et_3N$ (2.0 equiv), THF, 25 °C, 12 h, 92−95%; (i) $Et_3N$ (2.0 equiv), 4-DMAP (1.0 equiv), THF, 25 °C, 3 d, 81−85%; (j) excess $CH_2N_2$, $Et_2O$, 0 °C, 1 h, 32−45% of **6a**−**d** plus 30−40% of **7a**−**d**.

When **6a** was treated with Grubbs' catalyst (**I**, 0.1 equiv) in refluxing dichloromethane, macrocycle **8a** was isolated as the sole product in 81% yield (Scheme 2). The newly formed macrocyclic double bond was confirmed as having the predicted *Z*-stereochemical arrangement by extensive nOe studies. Surprisingly, however, when **7a** (*E* configuration at $\Delta^{7,8}$)[6] was likewise treated with catalyst **I** under the same conditions, the *Z*-macrocyclic double bond olefin isomer ($\Delta^{14,15}$) **9a** was once again obtained as the sole product in 83% yield. Since this stereochemical arrangement for $\Delta^{14,15}$ (assigned by nOe studies, Scheme 2) was not as predicted, further support for the geometry of the newly formed macrocyclic double bond of **9a** was desirable. Upon hydrolysis of the vinylogous esters of **8a** and **9a**, facilitated by $K_2CO_3$, tricarbonyl compounds, identical in every respect, were obtained. To explain the discrepancy between this and previously reported results for trisubstituted 11-membered macrocyclic double bond formation,[2] it was first assumed

**Scheme 2.** Stereoselective RCM of Monoprenylated Substrates[a]



[a] Reagents and conditions: (a) cat. **I** (0.1 equiv), $CH_2Cl_2$, 40 °C, 1 h, 81% of **8a**; 14 h, 68% of **8b**; (b) cat. **I** (0.1 equiv), $CH_2Cl_2$, 40 °C, 30 min, 83% of **9a**; 17 h, 71% of **9b**. Mes = mesityl; Cy = cyclohexyl.

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(4) For examples of the synthesis of 11-membered rings by using olefin metathesis see: (a) El Sukkari, H.; Gesson, J. P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043. (b) Winkler, J. D.; Holland, J. M.; Kasparec, J.; Axelsen, P. H. *Tetrahedron* **1999**, *55*, 8199. (c) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429. (d) Arisawa, M.; Kato, C.; Kaneko, H.; Nishida, A.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1873. (e) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061.

(5) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826.

(6) *E*- and *Z*-configured isomers at $\Delta^{7,8}$ of **7a**,**b** were separated by flash column chromatography. *Z* isomers proved inactive to catalyst **I**, which is consistent with previous observation in a similar substrate.[2]

(7) The *Z* geometry of the double bond ($\Delta^{14,15}$) was unambiguously confirmed by extensive nOe studies.

(8) The two geometrical isomers ($\Delta^{7,8}$) of **7d** were independently treated with Grubbs' catalyst after their careful chromatographic separation. The reaction conditions and the yields were similar for both.

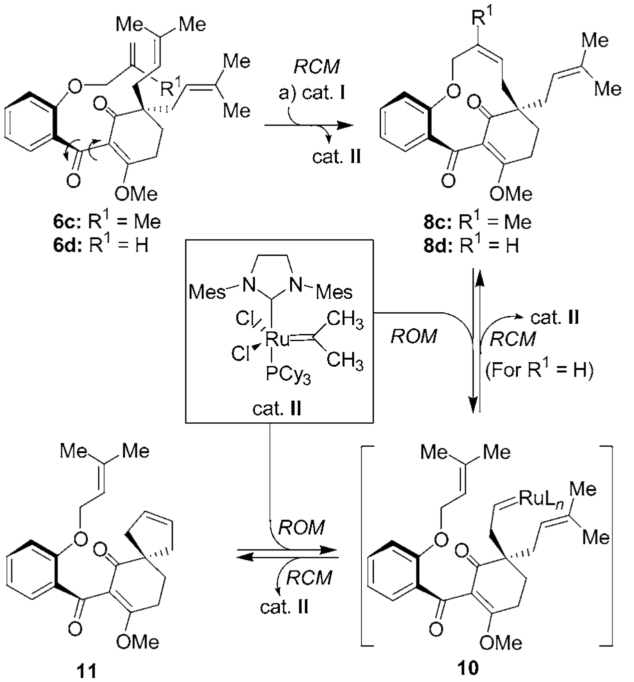
that the *Z*-macrocycle represents the thermodynamic product. Since bisubstituted macrocyclic olefins within strained ring systems are known to readily undergo ring-opening metathesis (ROM) reactions and, thus, can equilibrate to the thermodynamically most stable product, it was also reasonable to assume that **9a** represented just such a thermodynamic product. To confirm this explanation, and despite our initial intention to test general 11-membered macrocycles, we were forced to move closer toward the coleophomone skeleton by adding an extra methyl group ($R^1$ = Me) to the previously examined compounds.

When regioisomers **6b** and **7b**[6] (for their preparation see Scheme 1) were independently treated with Grubbs' catalyst (**I**, 0.1 equiv) in refluxing dichloromethane, **8b** and **9b** were correspondingly formed, as the sole products, and isolated in good yields (68% and 71%, respectively, Scheme 2). The newly formed macrocyclic double bond was, in each case, confirmed[7] as having the *Z*-stereochemical arrangement. Once again and in contrast to the previous report,[2] the regiochemistry of the methyl enol ether used to protect the tricarbonyl moiety was, therefore, not influential in changing the geometry of the macrocyclic double bond in the products obtained from these RCM reactions.

Having examined the stereoselectivity of the RCM reaction of monoprenylated **6a**,**b** and **7a**,**b** we proceeded to examine the bisprenylated congeners **6c** and **6d** in an effort to realize which structural alteration was responsible for the observed discordance. Not surprisingly, treatment of **6c** with catalyst **I** under the established conditions afforded exclusively the *Z*-macrocycle[7] (**8c**, 88%, Scheme 3). On the other hand, application of the same conditions for 15 min to substrate **6d** resulted in the formation of an inseparable mixture of macrocycle **8d** and spirocycle **11** (**8d**:**11** 1:1.1, 95%). Increasing the reaction time further to 3 h led to the complete conversion of **8d** to the more thermodynamically stable product, spirocycle **11** (Scheme 3). These results strongly suggest that trisubstituted macrocyclic bonds of this type (e.g. as in **8c**) are formed in a nonreversible reaction, presumably because the newly formed trisubstituted double bond is too sterically encumbered to easily react further with the large metathesis catalyst, while in the case of a bisubstituted macrocyclic double bond (e.g. **8d**) ring-opening metathesis (ROM) is facile such that the product distribution eventually funnels through to the thermodynamic product, spirocycle **11**. This RCM/ROM/RCM cascade transformation (**6d** → **11**) is illustrated in Scheme 3.

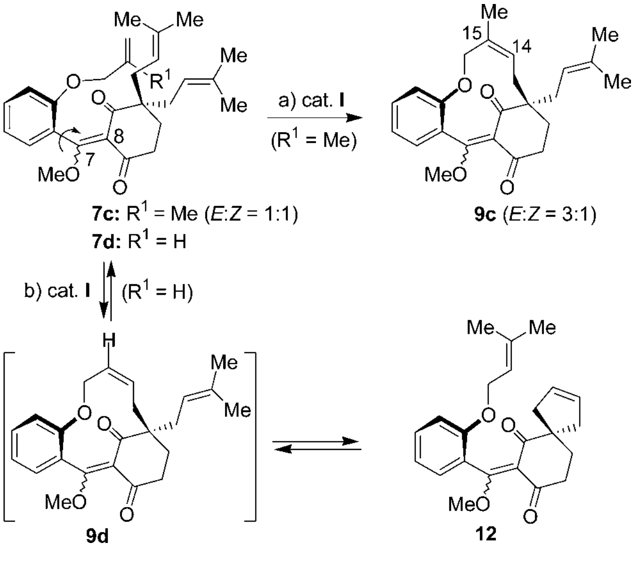
When a 1:1 mixture of geometrical isomers of **7c** was subjected to the action of catalyst **I**, a 3:1 mixture of *E*/*Z* isomers ($\Delta^{7,8}$) of **9c** was isolated (Scheme 4). This transformation increased the ratio of geometrical isomers in favor of the *E* isomer. This observation may be attributed to a closer proximity between the reacting olefins in the *E* substrate and/or to the formation of a more strained macrocycle when starting from the *Z* isomer. The sluggish participation in the RCM reaction and the resultant low yield of macrocycle from the *Z* isomer ($\Delta^{7,8}$) of **7c** is responsible for the moderate overall yield obtained from RCM of the **7c** mixture (63%). The most important feature of this transformation, however, was once again the exclusive formation of the *Z*-macrocyclic double bond in **9c** ($\Delta^{14,15}$).[7]

**Scheme 3.** Olefin Metathesis of Bisprenylated Substrates **6c** and **6d**: Mechanistic Rationale of the Cascade RCM/ROM/RCM Transformation of **6d** into the Spirocycle **11**[a]



[a] Reagents and conditions: for $R^1$ = Me (a) cat. **I** (0.1 equiv), $CH_2Cl_2$, 40 °C, 1.5 h, 88% of **8c**; for $R^1$ = H (a) cat. **I** (0.1 equiv), $CH_2Cl_2$, 40 °C, 45% of **8d** plus 50% of **11** after 15 min; and 87% of spectroscopically pure **11** after 3 h.

**Scheme 4.** Olefin Metathesis of Bisprenylated Substrates **7c** and **7d**[a]

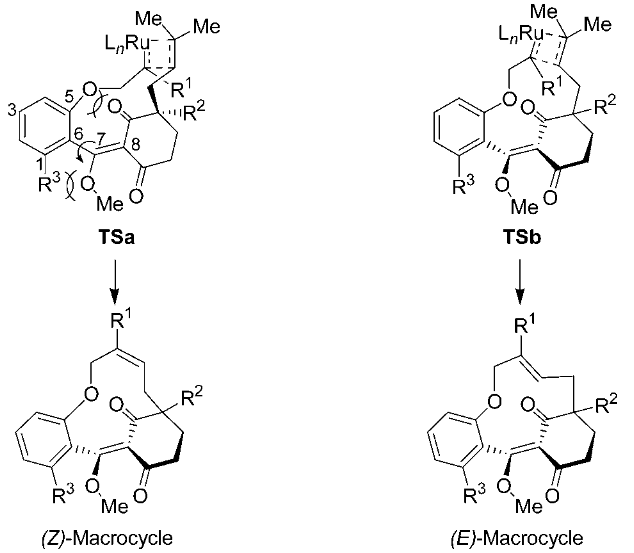


[a] Reagents and conditions: (a) cat. **I** (0.1 equiv), $CH_2Cl_2$, 40 °C, 3 h, 63% of **9c**; (b) cat. **I** (0.1 equiv), $CH_2Cl_2$, 40 °C, 20 min, 81% of **12**.

Reaction of the two geometrical isomers ($\Delta^{7,8}$) of **7d**[8] with catalyst **I** resulted in the rapid formation of spirocycle **12**. Only trace amounts of the more polar macrocycle **9d** were isolated following the application of the reaction conditions (20 min at 40 °C, Scheme 4).

In conclusion, the reaction of substrates **6a**−**c** (where tricarbonyl protection places the methyl enol ether within the pendant six-membered ring) follows the precedent set for RCM reactions of this type by Nicolaou's synthesis of coleophomone C,[2] wherein the more thermodynamically stable *Z*-macrocyclic olefin is formed exclusively. To our surprise, and in stark contrast to the coleophomone B precedent, however, RCM of substrates **7a**−**c** (where tricarbonyl protection situates the methyl enol ether at the benzylic position) also results in the stereospecific formation of the *Z* macrocycle. To explain this anomaly and draw a general conclusion the structural differences between our compounds (**7a**−**d**) and the intermediates used for the construction of coleophomone macrocycles must be considered. The only remaining difference, after the extensive and thorough modifications described above, is the substitution at the aromatic position (C1). When C1 bears a large bulky substituent ($R^3$) rotation around the C6−C7 bond is severely restricted. A large $R^3$ group also, therefore, forces the aromatic ring to stay out of conjugation and perpendicular to the plane of the C7═C8 bond. This arrangement favors (based on molecular model studies) the formation of the trans metalocyclobutane intermediate (see **TSb**, Scheme 5), leading to the (*E*)-macrocycle. On the other hand, rotation around the C6−C7 bond is much easier when C1 is not substituted ($R^3$ = H) as in compounds **7a**−**d**, thus affording the opportunity for this system to adopt a conjugated conformation in which the dihedral angle between the aromatic ring and the C7═C8 double bond is closer to 0. In this instance, the formation of the cis metalocyclobutane between the two coupling partners, far away from the main skeleton of the molecule (see **TSa**, Scheme 5), is favored. On the basis of the previous discussion, the reason for the formation of the *Z* macrocycles from **6a**−**c** now becomes apparent, since rotation around both C6−C7 and C7−C8 bonds is permitted with these examples.

**Scheme 5.** Possible Mechanistic Explanation for the Complete Inversion of the Stereoselectivity of RCM Based on the Substitution at C1



Medium-sized macrocycles (8−13 membered) exhibiting an intrinsic olefin are a common feature in natural products with widespread medicinal, agricultural, and perfumery applications. Despite our initial design endeavoring to seek out rules for the geometrical selectivity of RCM reaction in this type of substrates, the general, and pertinent, conclusion suggested by current work is that the absolute prediction of which of the two possible geometric arrangements for the olefins in these macrocycles is preferred upon RCM is in truth highly dependent on the individual molecular environment. Even a subtle difference in substitution far away from the reaction center is capable of resulting in complete reversion of the configuration at the newly formed double bond. However, once this assessment has been made empirically RCM is a capable and efficient tool for making even highly strained macrocycles stereoselectively. Furthermore, the RCM reaction is not reversible when the olefin formed is trisubstituted, even in very strained macrocycles, but is readily reversible when said olefin is bisubstituted. It would appear that the mystery lies not with the metathesis reaction, which is eminently predictable, but with the conformational character of these substrates and macrocycles individually.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra of the olefin metathesis precursors and products; atropisomerization of macrocycles **8b**, **8c**, **9b**, and **9c** results in a broadening of some $^1$H NMR signals and makes acquiring satisfactory $^{13}$C NMR spectra impossible. This material is available free of charge via the Internet at http://pubs.acs.org.

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