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Triquinanes: A "One-Pot" IMDA-Tandem Metathesis Cascade Strategy: Ring-Closing Metathesis (RCM) Dominates Norbornene ROM!

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ABSTRACT

A general route to linear triquinanes including a formal synthesis of (±)-$\Delta^{9(12)}$-capnellene is described. This cascade strategy combines an intramolecular Diels−Alder reaction tandem metathesis protocol to generate the linear *cis-anti-cis*-tricyclo[6.3.0.0^{2,6}]undecane skeleton directly. Significantly, the ring-closing−ring-opening−cross-metathesis (RCM−ROM−CM) sequence with our norbornene adducts is the only observed mechanism.

The fascinating array of diverse terpenoid structures have captured the imagination of organic chemists beyond their commercial potential. The polyquinanes, like the steroids and triterpenes of an earlier era, provide an impressive arena for the development of synthetic strategies in a facile and efficient manner. The triquinane family contains three dominant structural motifs. Among these variations, the linear *cis-anti-cis*-tricyclo[6.3.0.0^{2,6}]undecane skeleton in the sequiterpene $\Delta^{(9,12)}$-capnellene (Figure 1) has received the most attention as a synthetic target. An impressive number of creative approaches are known.[1]

We anticipated that our "one-pot" linear quinane synthesis would follow an intramolecular Diels−Alder−Ring-Opening Metathesis−Ring-Closing Metathesis (IMDA−ROM−RCM) cascade strategy based on literature precedent and the inherent strain[2] in norbornenes (Scheme 1).[3]

Instead, we have established, contrary to current dogma with most ruthenium catalysts, the alternative cross-metathesis ring-closing−ring-opening (RCM−ROM−CM) pathway dominates. This mechanism may be influenced partly due to the cyclopentane ring attached to the bridgehead, but this is not the only factor, as we have established with metathesis competition and labeling experiments. Consequently, these insights, particularly the behavior of the norbornene, may be more important than our synthesis! A synthetic tradition is that discoveries en route to a molecule reveal unexpected results. Of course, the Woodward−Hoffmann rules are the most famous example.

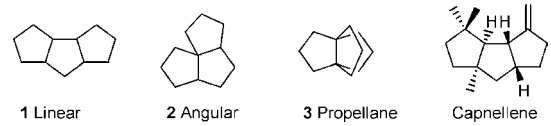

Figure 1. Triquinane structural motifs.

Previously, we have developed controlled intramolecular Diels−Alder reactions of subsutituted cyclopentadienes by tether length restriction to generate the desired product from the 1,5-sigmatropic rearrangement(s). Alternatively, hydrogen migration could be inhibited by a spiro-cyclopropane moiety.[4,5]

Based in part on this experience, we have developed a direct assembly of linear quinanes from the alkylation of the cyclopentadienyl anion with an appropriate tosylate **4** to afford the tricyclic

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(1) Reviews: (a) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647. (b) Mehta, G. A.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671(see the Supporting Informationfor total syntheses of (±)-D9(12)-capnellene). (c) For the most recent synthesis, see: Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993, and references cited therein.

(2) Recent G3 ring strain energy calculations for norbornene (18.8 kcal/mol) norbornadiene (27.6 kcal/mol): Howell, J.; Goddard, J. D.; Tam, W. *Tetrahedron* **2009**, *65*, 4562, and references therein.

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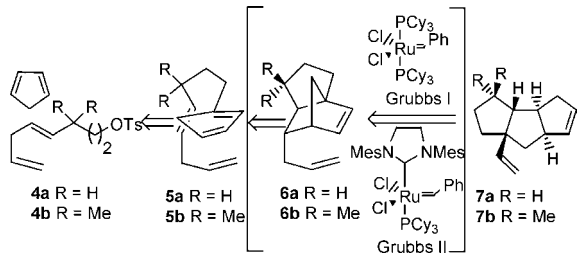
Scheme 1. Retro-Synthetic IMDA Tandem Metathesis to Linear *cis-anti-cis* Triquinanes

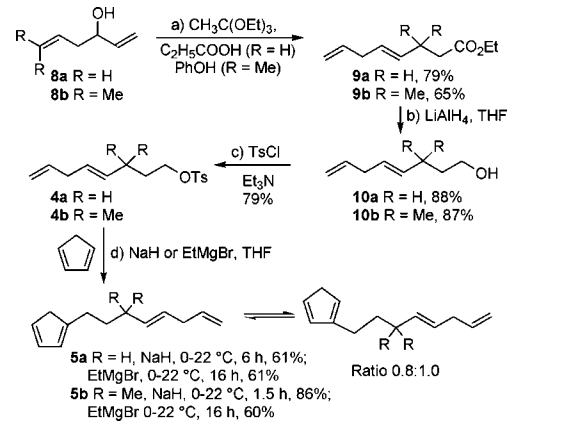


structures **7**. It is preferable to use the isomeric cyclopentadienes **5** (Scheme 2), from the alkylation, directly in the intramolecular cycloaddition to the adducts **6** (microwave). The vessel is opened, and a Grubbs catalyst is added to effect the anticipated tandem ring-opening metathesis of the norbornenes followed by ring-closing metathesis with the allyl substituent to generate the fused tricyclic cyclopentenes **7** (Scheme 1).

We also conducted these reactions stepwise (cycloaddition workup, subsequent tandem metathesis) to establish the best conditions and unravel the metathesis pathways.

The 1,4-diene−ester **9a**[6] was prepared by orthoester Claisen rearrangement of the corresponding 1,5-hexadien-3-ol (**8a**, Aldrich) with catalytic propionic acid or phenol in the case of **8b**[7] to afford **9b**[8] in refluxing triethyl orthoacetate. The esters **9** were reduced individually to the alcohols **10** with $LiAlH_4$, tosylation afforded

Scheme 2. Synthesis of Cyclopentadienes **5a** and **5b**



the desired side chain tosylates **4**, and the cyclopentadienyl anion generated with NaH was exposed to **4a** and **4b** individually to afford **5a**/**5b** (99%). The isomer equilibrium ratio (room temperature, 22 °C) in each series was ~0.8:1.0 (^{1}H NMR). This is irrelevant as the cycloaddition preference is dictated by the tether length. The adduct from the C2 isomer violates Bredt's rule, while an unactived olefin will not react with the C5 isomer. It was not detected by ^{1}H NMR spectroscopy.

We have demonstrated previously the advantage that microwave irradiation is a superior heat source for thermally challenging IMDA reactions.[5,9] Modern microwave instruments have replaced kitchen models.[10,11] Consequently, this is the best method for IMDA reaction of unactivated cyclopentadienes. Exposure of **5a** in chlorobenzene to microwave radiation equipped with a spherical glass-coated Carboflon (for energy transfer)[12] at 210 °C under 310 psi pressure for 1.5 h afforded the desired adduct **6a** in 80% yield (Table 1, entry 1).

Addition of a Grubbs catalyst (22 °C) (entries 4 and 5) under ethylene assisted the ring-opening−ring-closing metathesis conditions to afford triquinanes **7a** and **7b** directly (98−85%). The "one-pot" reactions (entries 7−9) are less efficient, a consequence of the absence of ethylene (entry 3) and trace cycloaddition impurities that reduced the catalytic efficiency. Grubbs I catalysts were more efficient than the second generation. The reduced yield of **6b** (entry 2) reflects the steric interactions induced by geminal methyl groups. COSY, HMQC, and NOESY data for **6** confirmed the regiochemistry and *cis-anti-cis* ring stereochemistry.

The reactions required to convert **7b** to (±)-$\Delta^{9(12)}$-capnellene are established. A parallel allylic oxidation enone reduction method

(3) (a)Tandem norbornene metatheses: (a) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843. (b) Stragies, R.; Blechert, S. *Synlett* **1998**, 169. (c) Wrobleski, A.; Sahasrabudhe, K.; Aubé, J. *J. Am. Chem. Soc.* **2002**, *124*, 9974. (d) Arjona, O.; Csakye, A. G.; Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380. (e) Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357. (f) Hart, A. C.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 1094. (g) Maechling, S.; Norman, S. E.; Mckendrick, J. E.; Basra, S.; Koppner, K.; Blechert, S. *Terahedron. Lett.* **2006**, *47*, 189. (h) Malik, C. K; Ghosh, S. *Org. Lett.* **2007**, *9*, 2537. (i) Maity, S.; Ghosh, S. *Tetrahedron Lett.* **2008**, *49*, 1133. (j) Malik, C. K.; Yadav, R. N.; Drew, M. G. B.; Ghosh, S. *Tetrahedron Lett.* **2009**, *50*, 5277. (k) , C. K.; Hossain, Md. F.; Ghosh, S. *J. Org. Chem.* **2009**, *74*, 1957, and references cited therein. (l) Hetero-norbornenes: Lui, Z.; Rainier, J. D. *Org. Lett.* **2005**, *6*, 131. (m) Lui, Z.; Rainier, J. D. *Org. Lett.* **2006**, *8*, 459. (n) Carreras, J.; Avenoza, A.; Busto, J. H.; Peregrina, J. M. *Org. Lett.* **2007**, *9*, 1235. (o) Calvet, C.; Blanchard, N.; Kouklovsky, C. *Org. Lett.* **2007**, *9*, 1485. (p) Reviews: Arjona, O.; Csaky, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2003**, 611. (q) Astruc, D. *New J. Chem.* **2005**, *29*, 42. (r) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (s) Blechert, S.; Holub, N. *Chem. Asian J.* **2007**, *2*, 1064.

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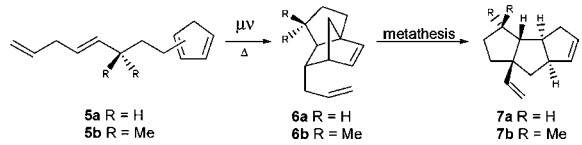
(11) Microwave-assisted organic synthesis: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (b) Loupy, A.; Perreux, L. *Tetrahedron* **2001**, *57*, 9199. (c) Lidström, P.; Tierny, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (d) Loupy, A.; Petit, A.; Hamelin, J; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213. (e) Majetich, G. R.; Hichs, J. *J. Microwave Power* **1995**, *30*, 27.

(12) The glass encased Carboflon absorbs microwave energy, and the temperature and pressure are monitored by a fiber optic probe.

Table 1. Stepwise and "One-Pot" IMDA-Metathesis Tandem Reactions



5a R = H
5b R = Me

6a R = H
6b R = Me

7a R = H
7b R = Me

entry	reactants	solvent	catalyst	temp, °C (psi)	time (h)	yield[a] (%)
1	DA-(**5a**−**6a**)	PhCl		210 (310)	1.5	80
2	DA-(**5b**−**6b**)	PhCl		210 (310)	1.5	54
3	Met-(**6a**−**7a**)	PhH	Grubbs I	22 (atm)	2	85
4	Met-(**6a**−**7a**)	PhH	Grubbs I	22 (atm)	2	98[b]
5	Met-(**6b**−**7b**)	PhH	Grubbs I	22 (atm)	1	98[b]
6	Met-(**6b**−**7b**)	PhH	Grubbs II	22 (atm)	1.5	85[b]
7	DAM(**5a**−**7a**	PhCl	Grubbs I	210 (310)	2 + 2	65
8	DAM(**5a**−**7a**	PhMe	Grubbs II	200 (200)	2 + 1	15
9	DAM(**5b**−**7b**	PhCl	Grubbs I	210 (310)	2 + 2	42

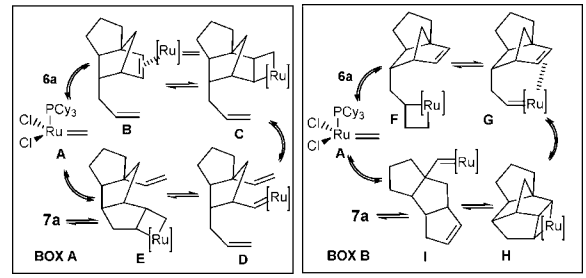
[a] Isolated yield. [b] Reaction run with 1 atm of ethylene.

was used for ceratopicanol.[13] Grubbs and Stille reduced the vinyl group to the methyl substituent in capnellene,[14] and installation of the *exo*-cyclic employed a Wittig reaction[15] or Tebbe reagent[14] to reach the target.

Norbornene Metathesis: A Conundrum Is Resolved. ROM is driven enthalpically by ring strain release while RCM is entropically driven by ethylene production.[16] Alkene substitution decreases the olefin metathesis rate. Thus, initial metathesis occurs preferentially at monosubstituted acyclic alkenes rather than disubstituted, cyclic olefins, depending on ring size and strain. In principle, the metatheses reactions from adducts **6** may follow different mechanistic pathways, whether the Ru-metallo-cyclobutane is generated at the strained, norbornene double bond or the allyl group preferentially. Previous research demonstrated the norbornene ring strain often activates the cyclic double bond in favor of another alkene or allyl group.[16]

Moore and Rule[17] examined the ROMP reactivity of *endo*- and *exo*-dicyclopentadiene and norbornene. The rate constants were $k = 0.019$, 0.37, and 0.43 s^{-1}, respectively, and established the rate retardation of an *endo*-substituent. Hoveyda, Schrock, and coworkers examined 7-*syn*-(1-butenyl)-7-*anti*-(1-oxaallyl)norbornene in competitive metathesis ARCM−AROM transformations.[18a] In all cases, the RCM between the two C7 terminal alkenes dominated except with their unique adamtanylimido Mo complex for which ROM of their norbornene was preferred (4:1). Additional, competitive C7-substituted examples are described in their (+)-africanol synthesis.[18b] Although the catalysts and steric environments differ from the Ru experiments in Table 1, this is consistent with our conclusions below for the *endo*-attachment of the allyl group.

Scheme 3. Box A: Anticipated Steps in ROM−RCM Tandem Pathway. Box B: Key Steps Observed in RCM−ROM−CM Pathway



Koreeda and Holtsclaw[19] observed that *endo*-face attack was absent with 7,7-disubstituted norbornenes (Grubbs I or II catalysts). They confirmed the significant steric interference of the cross ring *endo*-hydrogens. When a Ru-alkylidene species was generated on a C7 *syn*-allyl tether ROM attacked the top face of the norbornene olefin.

Based on these precedents and lack of C7 substitution, we anticipated that the initial ruthenium−alkylidene species **A** initiated the ring-opening cascade from adduct **6a** by preferential association with the norbornene (**B**). Subsequent regioselective, cycloaddition to **C** was influenced by the cyclopentane ring. ROM to **D** and subsequent RCM of the allyl moiety via intermediate **E** should afford **7a** (Scheme 3, box A).

Others have suggested that it is often not obvious with strained cyclic olefins whether ring cleavage always occurs first.[3a,r,q,18b] Consequently, we suspected some of the double-metathesis product might be initiated at the allyl moiety, particularly if this pathway was facilitated by potential *endo*-stabilization in complex **G** from

(13) Baralotto, C.; Chanon, M.; Julliard, M. *J. Org. Chem.* **1996**, *61*, 3576.

(14) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855. This research also utilized the titanocene alkylidene complex to open their norbornene synthon.

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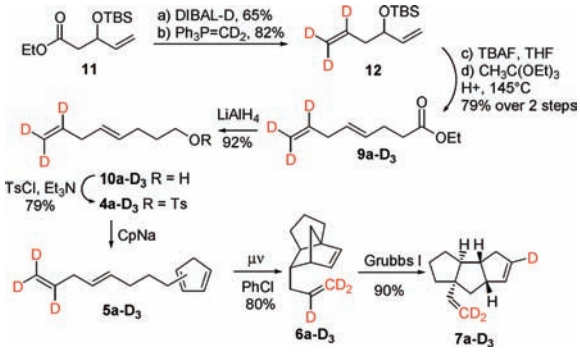
(19) Holtsclaw, J.; Koreeda, M. *Org. Lett.* **2004**, *6*, 3719.

Scheme 4. Truncated Route to Deuterated Compounds



metallocycle **F** (Scheme 3, box B). This mechanism requires either sufficient ethylene or a related alkene source (**7a**?) be available for completion of the final metathesis step to the vinyl product.

These suspicions were confirmed by low-emperature NMR experiments, deuterium-labeling studies (Scheme 4), and competitive metatheses reaction comparisons.

At −78 to −35 °C, the initial metatheses with **6a** were completely suppressed (CD_2Cl_2). The reagents were mixed (NMR tube, −78 °C, no $CH_2{=}CH_2$). The spectra were recorded at −18 °C, the temperature at which the reaction commenced.[20] After 5 min, ^{1}H NMR analysis revealed the presence of the alkylidene ruthenium complex **G** from reaction with the vinyl side chain as a triplet signal at 19.2 ppm (J = 5.0 Hz), in addition to catalyst signal(s). This corresponds to the pattern expected from **G**, not **B** (Figure 2, spectrum a).[21,22]

Competition experiments established a terminal alkene (allyl) was more reactive than norbornadiene at −18 °C. Norbornadiene was selected due to its symmetry and higher strain energy,[2] plus the absence of *endo*-H nonbonded interactions compared to norbornene. Parallel and blank experiments with equimolar norbornadiene and 1-hexene revealed the alkylidene ruthenium complex with the allyl group dominated the norbornadiene ring opening, despite two reactive sites, by a ratio of ∼6:1 (Figure 2, spectrum c).[23] This implies that bicyclo[2.2.1]heptenes react more slowly with a metathesis catalyst than generally assumed. The reactivity effects induced by the steric environment of a double bond are difficult to predict. A competition between 3,3-dimethylbutene and norbornadiene at −18 °C established both were inert. No alkylidene ruthenium complexes were detected by ^{1}H NMR spectroscopy.

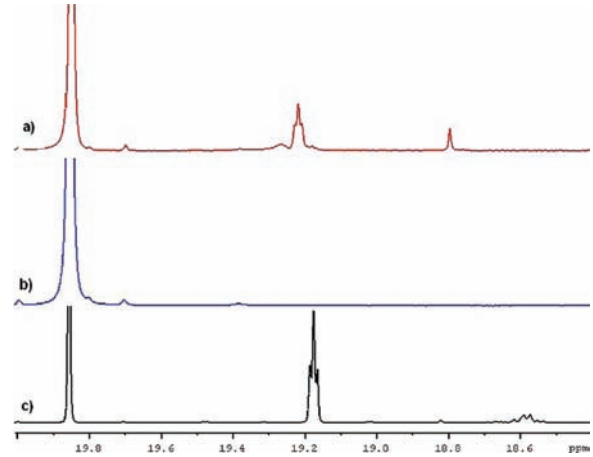


Figure 2. ^{1}H NMR spectra of alkylidene ruthenium complexes using **6a** (a), **6a-D$_3$** (b), or a 1/1 mixture of 1-hexene and norbornadiene (c).

Labeling experiments confirmed the dominance of the initial allyl RCM reaction. Deuterated adduct **6a-D$_3$** and triquinane **7a-D$_3$** were synthesized from **11**,[24] and the −18 °C experiment was repeated. The absence of the ruthenium alkylidene hydrogen signal in the ^{1}H NMR spectrum in Figure 2 (spectrum b) proved the initial ring-metathesis reaction had indeed proceeded via a ring-closing route to **F**, followed by the complexed intermediate **G** to **H** to **I** to quinane **7a-D$_3$**. This proves the mechanism in Scheme 3, box B, is the only one involved in these transformations.

In summary, a cascade intramolecular Diels−Alder−tandem metathesis sequence provided a rapid, stereospecific entry to triquinanes (*cis-anti-cis*-tricyclo[6.3.0.0^{2,6}]undecanes).[25] Our experiments established the ring-closing metathesis−ring-opening metathesis (RCM−ROM) allyl group pathway and excluded the norbornene ROM alternative. Consequently, ring strain[2] in norbornenes may be a less important driving force than previously assumed for metathesis initiation with ruthenium catalysts.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support of this research, S. K. Collins (University of Montreal) for fruitful discussions, and the reviewers for their constructive suggestions.

Supporting Information Available: Experimental details and spectral characterization for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) A solution of **6a** or **6a-D$_3$** (5 mg, 29 μmol) in 0.3 mL of degassed CD_2Cl_2 was cooled to −78 °C. A solution of benzylidenebis(tricyclohexylphosphine)dichlororuthenium (24 mg, 29 μmol) in 0.4 mL of degassed CD_2Cl_2 was slowly added with vigorous stirring. The suspension was then transferred in a NMR tube and quickly introduced to the precooled (−18 °C) NMR probe.

(21) The alkylidene ruthenium complex has been isolated (X-ray) from the reaction of a specially selected tricyclobutene with a full equivalent of catalyst: Tallarico, J. L.; Bonitatebus, P. J., Jr.; M. Snapper, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 5157.

(22) Our result assumes the intermediates in the postulated pathways have sufficient lifetimes to be detected on the NMR time scale, although the back reactions may be fast.

(23) These results indicate the rate of the initial complexation−metallocycloaddition step determines the preferred pathway. This was confirmed by the detection of both competitive species. Consequently, the potential back reactions are not a complication.

(24) Synthesis of **11**: (a) Zibuck, R.; Streiber, J. *Org. Synth.* **1992**, *71*, 236. (b) Sannigrahi, M.; Mayhew, D. L.; Clive, D. J. *J. Org. Chem.* **1999**, *64*, 2776. Deuteride reduction: Kalvim, D. M.; Woodard, R. W. *Tetrahedron Lett.* **1984**, *40*, 3385.

(25) Crinipellins possess a rare angular tetraquinane skeleton for which only one total synthesis of (±)-crinipellin is known: Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11. A second allyl group in the cyclopentadienyl tether should facilitate the extension of our strategy to tetraquinane frameworks.