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# An efficient ring-closing metathesis reaction of geminally disubstituted olefins using first generation Grubbs' catalyst: enantiospecific synthesis of pacifigorgianes

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**Abstract**—An efficient ring closing metathesis reaction with first generation Grubbs' catalyst [$PhCH{=}RuCl_2(PCy_3)_2$] involving geminally disubstituted olefins has been discovered. It has been extended to the enantiospecific synthesis of pacifigorgiane sesquiterpenes.

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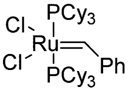
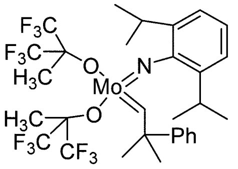
The last decade has witnessed an exponential growth in the application of the olefin metathesis reaction in organic synthesis.[1] The catalytic nature of the reaction in combination with its operational simplicity, the remarkable tolerance of the catalyst **1** to various functional groups and its stability to various conditions are key factors responsible for the increased use of this reaction, particularly the intramolecular version, i.e. the ring-closing metathesis (RCM) reaction. Of the three commonly employed catalysts **1**–**3**, developed by Schrock and Grubbs, the first generation Grubbs' catalyst **1** is more selective, less reactive, generally provides a cleaner reaction and is less expensive. In general, the catalyst **1** is found to be highly selective towards terminal monosubstituted olefins to form disubstituted cyclic olefins, and is reluctant to react with sterically demanding geminally disubstituted olefins to yield trisubstituted olefins. It is well documented that a more reactive catalyst, such as the highly sensitive Schrock molybdenum catalyst **2** or the Grubbs' second generation ruthenium catalyst **3**, is required for generating tri- and tetrasubstituted cyclic olefins by RCM reactions of dienes.[2,3] Now we have discovered a highly efficient RCM reaction using the Grubbs' first generation catalyst **1** and involving a geminally disubstituted olefin. Herein, we report our finding, and its extension to the enantiospecific synthesis of the pacifigorgiane sesquiterpenes.



**1**



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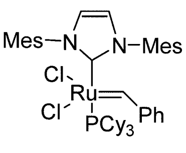

**3**

We realised that C-6 allylation of (*R*)-carvone **4** followed by an RCM reaction would be a convenient method for the enantiospecific generation of hydrindanes, and that it would be possible to generate both *cis*- and *trans*-hydrindanes by controlling the stereochemistry at C-6. In order to generate the hydrindanes containing a bridgehead methyl group (as in the CD rings of steroids), (*R*)-carvone **4** would have to be converted into both epimers of 6-allyl-6-methylcarvone. Kinetic alkylation of **4** using LDA and allyl bromide generated a 6:1 epimeric mixture of 6-allylcarvones **5**, which on a second alkylation with LDA and methyl iodide generated, exclusively, the *cis*-6-allyl-6-methylcarvone **6**.[4] Reversing the sequence of alkylations transformed **4** into the *trans*-6-allyl-6-methylcarvone **7** (Scheme 1).

As expected, the RCM reactions of the compounds **6** and **7** with Grubbs' catalyst **1** under a variety of conditions were found to be inefficient. For example, refluxing a 0.005 M methylene chloride solution of the compounds **6** or **7** with 20 mol% of the catalyst **1** for 12 h generated the hydrindanones **8** or **9** in only 10–15% yields (Scheme 2). In contrast, the RCM reaction of the

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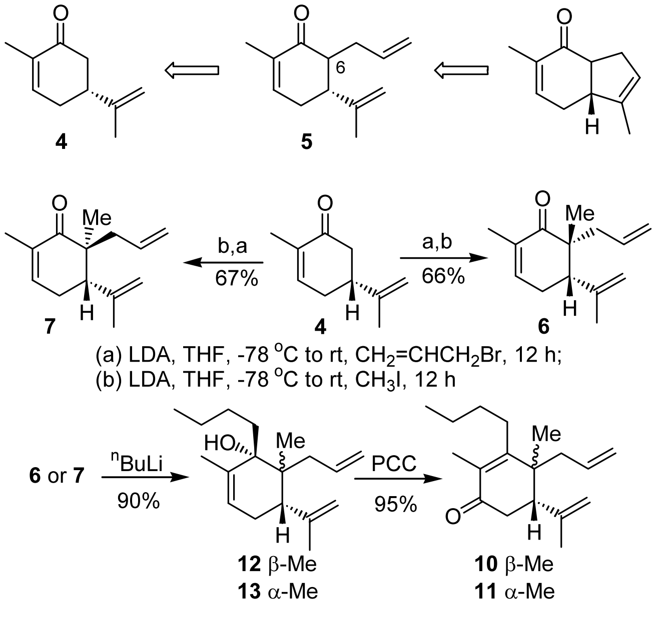
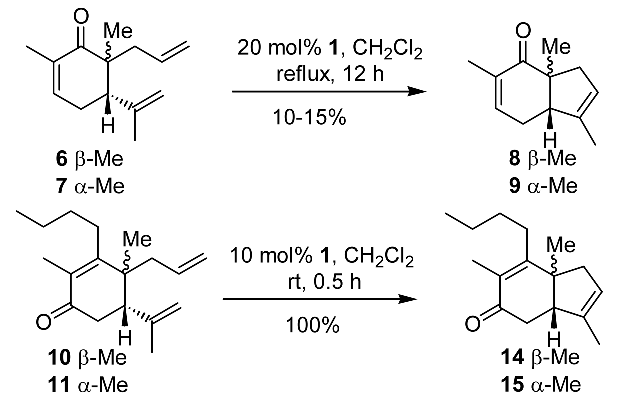


**Scheme 1.**

compounds **10** and **11**, which were prepared from **6** and **7** by a 1,3-alkylative enone transposition strategy via the alcohols **12** and **13**, were found to be extremely easy even under mild conditions. Treatment of the *cis*-isomer **10** with 10 mol% of the catalyst **1** in methylene chloride at room temperature for 30 min furnished the hydrindanone **14**, $[\alpha]_D^{23} = -99$ (*c* 0.9, $CHCl_3$), in quantitative yield. In a similar manner, RCM of the *trans*-isomer **11** under the same conditions furnished the hydrindanone **15**, $[\alpha]_D^{23} = +69$ (*c* 2.7, $CHCl_3$), again in quantitative yield.[†]



**Scheme 2.**

One possible reason for the dramatic acceleration of the RCM reaction of the compounds **10** and **11** under mild conditions in comparison with that of **6** and **7** could be the entropy effect.[5] As shown in Fig. 1, in the intermediate ruthenium carbenoid, population of the reactive rotamer **B** dominates because of the steric repulsion between ruthenium carbenoid and butyl group on the next carbon atom in the rotamer **A**, thus accelerating the reaction. This was further substantiated by carrying out the RCM reactions of the alcohols **12** and **13**. Treatment of the alcohol **13**, containing the allyl and butyl side chains *cis* to each other, with 10 mol% of the catalyst **1** in refluxing methylene chloride for 4 h furnished the RCM product **16**, $[\alpha]_D^{22} = -122$ (*c* 2.4, $CHCl_3$), in near quantitative yield (Scheme 3). In contrast, reaction of the alcohol **12**, containing the allyl and butyl groups in *trans*-pseudo diaxial orientation, was found to be inefficient and produced only 10% of the RCM product **17**, $[\alpha]_D^{22} = -114$ (*c* 0.35, $CHCl_3$), after 8 h reflux with 10 mol% of the catalyst **1**.

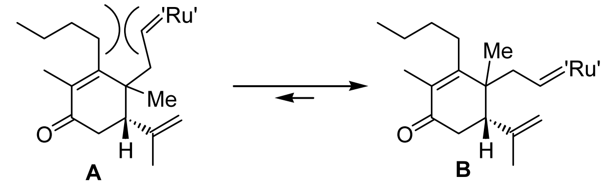
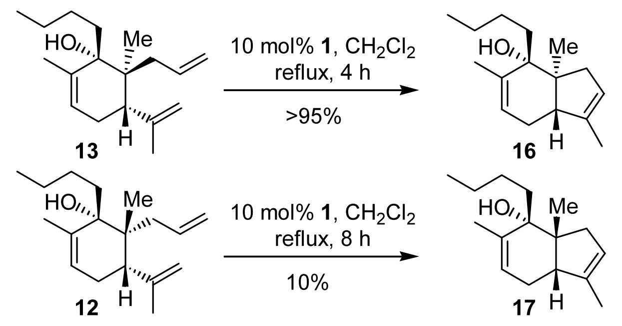
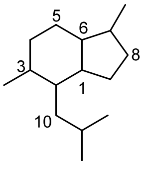


**Figure 1.**

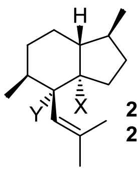


**Scheme 3.**

After the discovery of an efficient RCM reaction for the enantiospecific generation of hydrindanes **14**–**16**, it has been extended to the enantiospecific synthesis of the pacifigorgiane sesquiterpenes. In 2001, Konig and coworkers reported[6] the isolation of five pacifigorgiadienes **18**–**22** from the liverwort *Frullania fragilifolia*, belonging to a small group of hydrindane based sesquiterpenes pacifigorgianes, found to be present in both marine and terrestrial sources. The first member of this group, ichthyotoxic pacifigorgiol **23** was isolated[7] from the Pacific gorgonian coral *Pacifigorgia* cf. *adamsii* and also from the essential oil of *Valeriana officinalis*, and the second member tamariscol **24** was isolated[8] from the liverwort *Frullania tamarisci*.



pacifigorgianes
**18** Δ-1(9),10-diene
**19** Δ-1,10-diene
**20** Δ-1(6),10-diene
**21** Δ-2(10),11-diene
**22** Δ-2,10-diene



**23** X=OH; Y=H
**24** X=H; Y=OH

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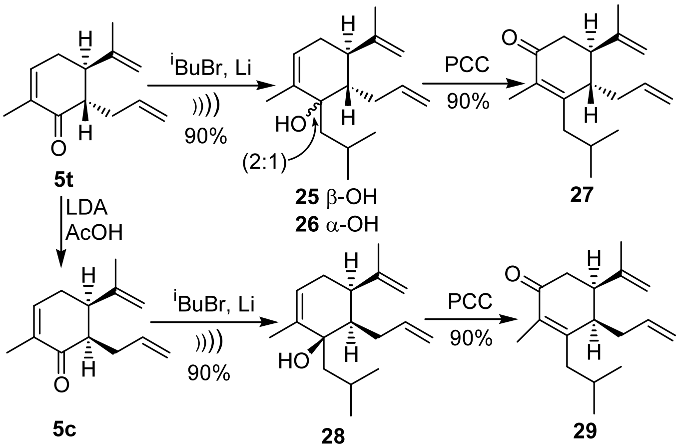
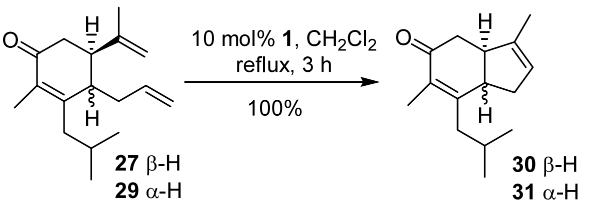
[†] Yields refer to isolated and chromatographically pure products. All the compounds reported here exhibited spectral data (IR, $^1H$ and $^{13}C$ NMR and mass spectra) consistent with their structures.

It was readily identified that addition of the isobutyl group followed by a RCM reaction transforms 6-allylcarvones **5** into pacifigorgianes.[9] Thus, careful column chromatography of the epimeric mixture of allylcarvone **5** on silica gel furnished the *trans*-isomer **5t**. Generation of the kinetic enolate of **5t** with LDA at −70°C followed by quenching with acetic acid generated the *cis*-isomer **5c** (Scheme 4). Sonochemically accelerated Barbier reaction of **5t** with lithium and isobutyl bromide furnished the allyl alcohols **25** and **26** in a 2:1 ratio. Oxidation of the alcohols **25** and **26** with PCC and silica gel in methylene chloride furnished the enone **27**, $[\alpha]_D^{24}=+77$ (*c* 2.8, $CHCl_3$). Similarly, Barbier reaction of **5c** gave the alcohol **28**, which on oxidation furnished the enone **29**, $[\alpha]_D^{25}=+214$ (*c* 1.7, $CHCl_3$).

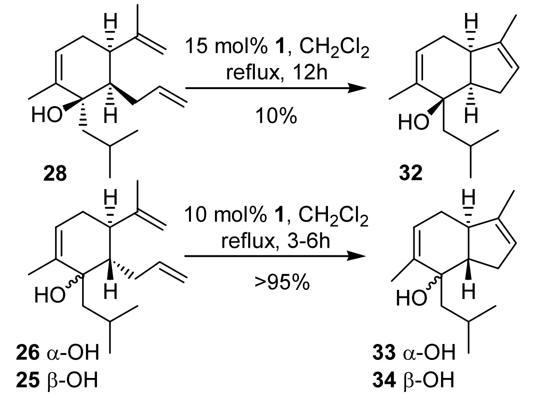


**Scheme 4.**

In line with the earlier observations, reaction of the enones **27** and **29** with 10 mol% of the catalyst **1** in refluxing methylene chloride for 3 h furnished pacifigorgia-2,7-dien-4-ones **30**, $[\alpha]_D^{24}=+20$ (*c* 3.5, $CHCl_3$), and **31**, $[\alpha]_D^{22}=-137$ (*c* 1.1, $CHCl_3$), in quantitative yield (Scheme 5). The RCM reaction of the alcohol **28**, containing the isobutyl and allyl groups *trans*-diaxial to each other, was found to be inefficient, like that of **12**, and produced the RCM product **32**, $[\alpha]_D^{22}=-202$ (*c* 0.4, $CHCl_3$), in less than 10% yield after refluxing in methylene chloride with 15 mol% of the catalyst **1** for 12 h (Scheme 6). Whereas the alcohol **26** containing the isobutyl and allyl groups in a *trans*-pseudo diequatorial orientation furnished a 1:1 mixture of the pacifigorgia-3,7-dien-2-ol **33**, $[\alpha]_D^{24}=-94$ (*c* 1.2, $CHCl_3$), and starting material in quantitative yield under the same conditions. In contrast, treatment of the alcohol **25** with 10 mol% of the catalyst **1** in refluxing methylene chloride for 3 h furnished the pacifigorgia-3,7-dien-2-ol **34**, $[\alpha]_D^{24}=-103$ (*c* 2, $CHCl_3$), in quantitative yield.

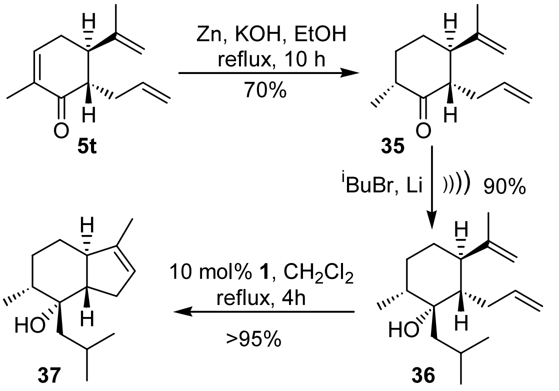


**Scheme 5.**



**Scheme 6.**

In order to find the effect of the ring olefin on the RCM, the reaction was carried out on the saturated compound. Thus, reaction of 6-allylcarvone **5** with zinc and potassium hydroxide in refluxing ethanol furnished the dihydro compound **35** (Scheme 7). Barbier reaction of the compound **35** with isobutyl bromide and lithium furnished the *tert*-alcohol **36**, $[\alpha]_D^{22}=-11.3$ (*c* 7, $CHCl_3$). RCM of **36**, containing the isobutyl and allyl side chains in a *trans*-diequatorial orientation, with 10 mol% of the catalyst **1** in refluxing methylene chloride for 4 h was also found to be efficient, like that of **26**, and furnished the pacifigorgia-7-en-2-ol **37**, $[\alpha]_D^{23}=+29$ (*c* 0.7, $CHCl_3$), in near quantitative yield.



**Scheme 7.**

In conclusion, we have discovered an efficient RCM reaction with first generation Grubbs' catalyst **1** involving geminally disubstituted olefins. The presence of an alkyl group on the carbon next to the allyl bearing carbon, either in a *cis* orientation or in a *trans*-diequatorial orientation or on an $sp^2$ carbon was found to accelerate the RCM reaction of the allyl group with the isopropenyl group. It has been further extended to the enantiospecific synthesis of a number of pacifigorgianes.

## Acknowledgements

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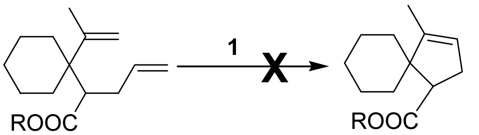

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