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Studies towards the synthesis of Pentalenene: mechanistic insights on the isomerisation phenomenon during RCM of medium sized rings.

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Introduction

Since their disclosure in the mid-nineties, the first and second generation Grubbs metathesis catalysts have been widely used in numerous area of chemistry such as total synthesis, polymer preparation and material chemistry.^[1-2] The metathesis reaction appeared particularly relevant for the assembly of medium-sized rings, which have always been challenging to construct.^[3] However, double-bond isomerisation in the substrate,^[4] or in the product,^[5-6] has rapidly been reported as a side reaction in this transformation.^[7] Even though advantage can be taken of this process to perform a tandem metathesis/isomerisation procedure,^[8] the isomerisation phenomenon remains an undesirable side reaction which is not yet fully understood.

Several groups have shown that the most plausible mechanism involves a ruthenium hydride species.^[9] The proposed mechanism is presented in **Scheme 1**. The ruthenium hydride complex **B** (which can eventually originate from the metathesis catalyst **A**) coordinates to the terminal olefin **F** to form the π -adduct **C**, which is then converted to **D** by a 1,2-migratory insertion of the olefin in the Ru-H bond. The isomerisation catalyst **B** is recovered after β -elimination of a hydride and decomplexation of the internal olefin **G**.

Scheme 1. Putative isomerisation mechanism.

As suggested by this mechanism, the $[Ru]-H$ species can be generated by decomposition of the active metathesis catalyst **A**, but it can also have a different origin. In fact, two main sources of $[Ru]-H$ can be distinguished: the $[Ru]-H$ is present as an impurity in the initial catalyst or it is formed during the reaction. In the first case, the $[Ru]-H$ is generated during the synthesis of the catalyst, and hence, can be found as traces in the final compound. Indeed, numerous synthesis of the Grubbs catalysts imply a $[Ru]-H$ complex as a reagent or an intermediate ($[RuHCl(H_2)(PR_3)_2]$ or $[RuHCl(PR_3)_2]$).^[10] In fact, Snapper et al. have demonstrated that the purification of commercially available Grubbs 2 catalyst completely suppressed the isomerisation reaction.^[11] Nevertheless, it appears that in most cases, the isomerisation process is due to the degradation of the metathesis catalyst itself. Several groups have tried to isolate the putative $[Ru]-H$ species but it seems that various complexes are involved. For example, **3** and **4** have been isolated from the corresponding Grubbs catalysts (**Scheme 2**).^[12]

Scheme 2. Dinger and Mol mechanism for Grubbs catalysts decomposition.

The amazing binuclear complex **6** has been reported by Grubbs *et al.* This compound is obtained after thermal decomposition of **5** (Scheme 3).^[13] It has to be noted that **3**, **4** and **6** have been shown to be efficient isomerisation catalysts.

Scheme 3. Example of isolated Ruthenium-hydride complex.

To prevent the isomerisation process, it is mandatory to inhibit the formation of the ruthenium hydride species and/or to eliminate the [Ru]-H present in solution. Since the formation of [Ru]-H complexes can follow several pathways, it is easier to quench these undesired catalysts rather than block their formation. To suppress the isomerisation activity, several additives, such as OPCy₃, benzoquinones, phenylphosphoric acids or SnX₂ derivatives have been successfully employed.^[14] It has also been reported that the nature of the solvent can have a significative influence on the metathesis/isomerisation ratio. Indeed, J. Prunet *et al.*, during their studies towards the synthesis of Taxol, have observed that ethereal and aromatic solvents favor isomerisation while the non-polar and non-coordinating dichloroethane can greatly enhance the metathesis/isomerisation ratio.^[14a]

Results and Discussion

We have recently been engaged in the study of a new and efficient approach for the construction of angular triquinane structures, such as Pentalenene (**8**). Our retrosynthetic analysis is depicted in Scheme 4. It involves, as a key step, a transannular cyclisation of **11**, by intramolecular enolate opening of the β-epoxide, leading to the diastereoselective formation of **10**. Subsequent functional group interconversions will then deliver Pentalenene. The key β-epoxide **11** would find its origin in the corresponding alkene **12** which could be accessed by a RCM of the precursor **13**. This ketone can be assembled by the condensation of the silyl enol ether **15** with

the functionalised orthoester **14**, according to a methodology we have already described previously.^[15]

Scheme 4. Retrosynthetic approach to Pentalenene.

To test this approach, the simple model **23** was initially aimed for (Scheme 5). It was anticipated that this bicyclic ketone would be easily obtained, in three steps, from cyclopentenone **18**. Thus, addition of the allyl Grignard reagent **19** on **18**, in the presence of CuBr, generated the silyl enol ether **20** after treatment of the in-situ generated enolate with TMSCl. Adduct **22** was next produced as a single diastereoisomer by the condensation of silyl enol ether **20** with the orthoester **21**, under catalysis by zinc chloride. Finally, treatment of **22** by Grubbs 1 catalyst (10 mol-%) afforded **23** in 70% yield, after 3 days in DCM, at room temperature.

Scheme 5. Synthesis of model compound **23**.

Encouraged by the results obtained in the formation of this 7-membered ring, we decided to study the construction of the bicyclo[3.6.0]undecene system needed for the assembly of the triquinanes. The bis-olefinic precursors, **24** and **26**, were efficiently assembled by our orthoester condensation method. To our delight, bicyclic adduct **25** was obtained in a reasonable yield of 52% by the action of Grubbs 1 catalyst, during 5 days, in DCM, at room temperature. Surprisingly, the corresponding isomer **27** was obtained in only 7% yield when the precursor **26** was submitted to the same conditions. The yield was slightly improved by performing the reaction in refluxing CH₂Cl₂ (Scheme 6).

Scheme 6. RCM of bisolefinic precursors **24** and **26**.

In order to improve the yield and reduce the reaction time, the second generation Grubbs catalyst, which presents an improved

stability and reactivity was employed.^[16] Surprisingly, after 20 hours of reaction in refluxing benzene, a mixture of two compounds was obtained in a 1.1:1 ratio. These proved to be the desired bicycle **27** and the ring-contracted analogue **28** (Scheme 7).

Scheme 7. Grubbs 2 catalysed RCM of **26**.

The structure of adduct **28** suggests that the open precursor **26** undergoes a competitive isomerisation of one of the two alkenes. The position of the alkene in bicycle **28** indicates that the allylic substituent has undergone double-bond migration. This observation can be rationalised by the mechanism proposed in Scheme 8. Starting from **26**, direct RCM generates the desired adduct **27**. However, during this process, a competitive isomerisation of one of the two olefins is also observed. Migration of the allylic double bond, followed by RCM, gives access to compound **28**. Considering that **23** has not been isolated in this transformation, it appears that the isomerisation occurs preferentially at the allylic position. The almost 1:1 ratio of **27** and **28** indicates that the isomerisation and the eight-membered ring closure proceed with similar rates ($k_{\text{met}} \approx k_{\text{iso1}}$). The absence of **23** shows that $k_{\text{iso1}} > k_{\text{iso2}}$ (since k_{met1} should be similar to k_{met2}).

Scheme 8. Possible reaction pathways from adduct **26**.

Based upon literature precedents,^[14] we have tested various conditions to improve the formation of **27**. As shown in Scheme 7, when the reaction was performed in the presence of 10 mol-% of Grubbs 2 catalyst, in refluxing benzene, bicycles **27** and **28** were isolated in a ~1:1 ratio and in 53% yield (Table 1, entry 1). The yield can be slightly improved in the presence of a lower amount of catalyst (entry 2). However, the ratio **27/28** remains unchanged. This observation can be rationalised by considering that metal-carbene dimerisation is a common deactivation pathway for Grubbs catalysts.^[17] Replacement of benzene by 1,2-dichloroethane (DCE) leads to a slight improvement in the **27/28** ratio (entry 3). The concomitant use of Grubbs 2 catalyst and tricyclohexylphosphine oxide (5 mol-%) didn't enhance the **27/28**

ratio but lowered the overall yield (entry 4). In stark contrast, employing 1,4-benzoquinone as a sacrificial quencher for the ruthenium hydride species, led to a remarkable enhancement of the **27/28** ratio and a >20:1 mixture of these two bicycles was obtained in a reasonable yield of 57% (entry 5). Finally, the desired compound **27** can also be produced in a 15:1 ratio when alkene **26** was cyclised by adding Grubbs 1 catalyst portionwise to a solution of the substrate in DCE (entry 6). This result highlights the lower propensity of Grubbs 1 catalyst to generate a [Ru]-H species as compared to its second-generation counterpart.

Entry	Catalyst	Additive	Solvent	Temp.	Time	Yield	27/28
1	Grubbs 2 10 mol-%	-	Benzene	Reflux	20h	53%	1.1:1
2	Grubbs 2 3 mol-%	-	Benzene	Reflux	4h	62%	1:1
3	Grubbs 2 3 mol-%	-	DCE	Reflux	24h	49%	1.4:1
4	Grubbs 2 3 mol-%	O=P(Cy) ₃ 5 mol-%	DCE	Reflux	24h	30%	1.4:1
5	Grubbs 2 3 mol-%	1,4-benzoquinone 5 mol-%	DCE	Reflux	24h	57%	>20:1
6	Grubbs 1 2 x 5 mol-% + 2.5 mol-%	-	DCE	Reflux	72h	51%	15:1

Table 1. Products distribution from the RCM of adduct **26**.

With these results in hand, we next attempted to assemble a useful intermediate for the synthesis of Pentalenene. One of the simplest modifications involved the introduction of one of the four methyl groups present in the natural product. To our surprise, treatment of **30** with Grubbs 2 catalyst in refluxing benzene leads only to the compound **32** in a good yield of 70% (Table 2, entries 1 and 2). This time, the seven membered ring formed during the RCM step results from the isomerisation of the terminal double bond. The use of benzoquinone in DCE improved slightly the ratio, affording a 1:1.25 mixture of the desired product **31** and its ring-contracted counterpart **32** (entry 3). Unfortunately, we were unable to separate them by silica gel chromatography (even impregnated with silver nitrate) or by HPLC.

Entry	Catalyst	Additive	Solvent	Temp.	Time	Yield	Product
1	Grubbs 2 3 mol-% + 1.5 mol-%	-	Benzene	Reflux	20h	67%	32
2	Grubbs 2 3 mol-%	-	Benzene	Reflux	3d	70%	32
3	Grubbs 2 2 x 5 mol-%	1,4-benzoquinone 2 x 10 mol-%	DCE	Reflux	24h	67%	31/32 = 1.25:1

Table 2. Products distribution from the RCM of adduct **30**.

The behaviour of **21** and **30** gives interesting insights on the action of the isomerisation catalyst. Indeed, adding a small methyl substituent is enough to completely inhibit the direct metathesis reaction (Table 2, entries 1 and 2) and to direct the isomerisation on the upper side-chain. These observations indicate that, like the metathesis catalysts, the species responsible for the alkene isomerisation are very sensitive to the steric hindrance around the olefin.

Scheme 9 summarises these transformations. Hence, treatment of **26** (R=H), with Grubbs 2 catalyst, in the absence of benzoquinone, produces a nearly 1:1 mixture of **27/28**, meaning that the rate of metathesis is similar to the rate of isomerisation ($k_{\text{met}} \sim k_{\text{iso1}}$). On the other hand, if R = Me, the eight membered ring closure is dramatically slowed down and competitive isomerisation takes place ($k_{\text{iso2}} > k_{\text{met}}$), leading only to **32**. The exclusive formation of **32**, implies that the double bond migration proceeds exclusively on the upper side-chain to furnish transiently **33**. It is noteworthy that in the case of **26**, no generation of **22** (and hence, **23**) is observed, whilst **30** affords none of the isomerised **34**. Consequently, no **28** is produced. The origin of this selectivity will be discussed latter on.

Scheme 9. Reaction pathways comparison between adduct **26** and **30**.

Knowing that monosubstituted olefins are preferentially isomerised, and since all the ring-contracted products isolated thus far result from the migration of the olefin by one carbon, we envisioned that diene **35** would be the perfect precursor for the assembly of **31**. Indeed, internalisation of the terminal alkene, followed by ring-closing metathesis, should deliver exclusively **31**. Unfortunately, this proved not to be the case and the cyclisation of **35** in the presence of Grubbs 2 catalyst, in refluxing benzene, only afforded the previously isolated bicycle **32** in 65% yield (Scheme 10).

Scheme 10. RCM of the one carbon homologue **35**.

This result implies that the isomerisation catalyst can slide along the alkyl chain of **35**, leading to repeated migration of the C-C double bond. The exclusive generation of **32** indicates that the isomerisation of **35** into **36** and **37** is much faster than the corresponding ring-closure to afford either the nine- or eight-membered ring adducts **38** and **31** respectively (Scheme 11).

Scheme 11. Possible reaction pathways from adduct **35**.

In order to obtain a more precise view on the competition between metathesis and isomerisation, and between the isomerisation of the two side-chains, it was decided to test the substrate **39**, possessing two terminal olefins experiencing a similar steric environment. This means that, at the onset of the reaction, both alkenes are equally prone to be complexed by the catalyst and that the structure of the final product(s) will be dictated by the preference for isomerisation vs metathesis. In the event, treatment of **39** by Grubbs 2 catalyst, in the presence of 10 mol-% of 1,4-benzoquinone in DCE, afforded 27% of bicycle **25** and 2.4% of **28** (Scheme 12).

Scheme 12. Grubbs 2 catalysed RCM of adduct **39**.

A summary of the various processes that can eventually occur during this reaction is presented in Scheme 13. The starting material **39** can follow three different reaction pathways: (1) an RCM leading to the cyclononene derivative **40**, (2) the isomerisation of the upper side-chain affording **24** and (3) alkene migration from the lower side-chain generating **41**. As expected, the formation of the 9-membered ring was not observed. The product distribution clearly indicates that the reaction sequence furnishing **25** from **39**, and transiting through **24**, is far more efficient than the one affording **28** by isomerisation of **39** into **41** and **42**. This seems to indicate a preferential coordination of the catalyst to the upper chain olefin ($k_{\text{iso3}} > k_{\text{iso1}}$). At this stage, the RCM of **24** should be faster than its isomerisation into **43** since compound **23** is not observed ($k_{\text{met3}} > k_{\text{iso4}}$). The absence of **23** is particularly

interesting, considering that it could also be formed by isomerisation/RCM of **41**. These results suggest that the isomerisation catalyst slides along the alkyl chain without dissociating from the substrate, until it meets a sterically hindering obstacle ($k_{\text{iso}2} > k_{\text{iso}5}$), at which stage, complete isomerisation is observed. Hence, **39** should isomerise directly to **42** without formation of free **41**. This hypothesis is strengthened by the fact that **27** and **23** are not observed.

Scheme 13. Possible reaction pathways from adduct **39**.

Formation of the isomerisation catalyst.

All these examples indicate that the product distribution depends upon the relative rate of cyclisation and isomerisation. In fact, the cyclisation rate decreases with increasing ring size and olefin substitution. This phenomenon is strengthened by long reaction times, which favor catalyst decomposition. Unfortunately, the $[\text{Ru}]\text{-H}$ complexes are possible products of this degradation that will increase the isomerisation reaction at the expense of the cyclisation. Indeed, in the formation of **27** and **28** from diene **26**, the ratio **27/28** will be determined by the ratio $V_{\text{met}}/V_{\text{iso}}$ depending itself on the corresponding rate constant of the reaction k_{met} and k_{iso} (Scheme 14). However, these rate constants are apparent constants since they depend upon the catalytic species concentrations (equations (1) and (2)). The product ratio can then be expressed by the equation (3). Consequently, the decomposition of the catalyst will result in a dual effect since the decrease in $[\text{Ru}]=\text{CH}_2$ concentration will not only lower the rate of cyclisation but also increase the amount of $[\text{Ru}]\text{-H}$, culminating in a higher rate of isomerisation.

Scheme 14. Isomerisation/metathesis rate comparison of adduct **26**.

Previous studies on the formation of the catalytic species responsible for the isomerisation have always tackled the problem through the investigation of the decomposition of the metathesis catalyst. However, our substrates react particularly slowly and the isomerisation is extremely important as compared with reactants of similar ring size.^[6] It is therefore plausible that a structural feature of our starting material might also be responsible for this enhanced isomerisation.^[18] We believe that the spatial proximity between the dioxolane and the upper side-chain double bond might be the culprit and that this functional group might be responsible, to a certain extent, for the reaction's sluggishness. Coordination of the ruthenium complex to one of the ketal oxygen lone pairs, could result in catalyst sequestration and/or decomposition.^[19] Indeed, during an attempt to build macrolactones by ring closing metathesis, A. Fürstner *et al.* have observed that the rate of reaction strongly depended upon the distance between the double bond and the ester group. The lowest rates were observed if this distance enabled the formation of a 5- or 6-membered ring bidentate complex.^[19a] The postulated mechanism presented in Scheme 15 takes this observation into account. Thus, intermediate **A**, which could lead to bicycle **26**, could be in equilibrium with the complexed form **B**. The 6-membered ring bidentate coordination should favour form **B** over **A** and act as a sink for the catalyst. Isomerisation will provide **C** which will slowly close to **28**. In addition, it is possible that the complexed form **B** might be an intermediate in the decomposition pathway leading to the ruthenium hydride catalyst. Finally, in the presence of $[\text{Ru}]\text{-H}$, compound **26** could give rise directly to isomerized product **D** (transiting by **41**).

Scheme 15. Possible substrate induced catalyst deactivation mechanism.

Based upon the mechanism proposed by Dinger and Mol,^[12] a plausible mechanism of decomposition, taking into account the particular structure of our substrate, is depicted in **Scheme 16**. The dioxolane present in **A** could be opened to generate the cyclic oxonium cation **B**. This species can be trapped by a chloride ion to afford intermediate **C**. A hydride transfer between the alcohol and the metal-carbene then affords **D**, which could subsequently decompose into complexes **F** and **H** respectively. Finally, the ruthenium hydride derivative **I** can be obtained by loss of CO.

Scheme 16. Proposed mechanism for the decomposition of the catalyst.

It is interesting to note that, once generated, the ruthenium hydride species should attach itself to the ketal oxygens much faster than the RCM catalyst, therefore resulting in rapid isomerisation; steric and chelation control providing the end-point for the alkene migration.

Based upon these observations the functionalised tricyclic core of Pentalenene could be rapidly assembled. Initially, the compound **26** was converted in bicycle **27** by RCM using Grubbs 2 catalyst and 5 mol-% of benzoquinone in refluxing DCE (Scheme 17). Adduct **27** was then treated by mCPBA to furnish the corresponding epoxide as a mixture of the two diastereoisomers **44** and **45**. The almost 1:1 ratio indicated a total lack of facial

selectivity. Since only **45** possess the proper configuration to cyclise, the two diastereoisomers were separated and **45** was reacted with sodium hydride to afford the triquinane **46** in 60% yield. The highly functionalised angular triquinane **28** can thus be obtained in 5 steps from cyclopentenone and in 9% overall yield. This intermediate possesses all the functionalities at the proper positions to build Pentalenene.

Scheme 17. Synthesis of a triquinane structure.

Conclusions

In summary, we have shown that the isomerisation reaction occurs when the metathesis reaction is rather slow. In this case, there is a competition between the two reactions. As Ru hydride species, believed to catalyse the isomerisation reaction, are formed by decomposition of the metathesis catalyst, a prolonged reaction time favors the isomerisation process. The behaviour of the isomerisation catalyst has been investigated. Like its metathesis counterpart, the isomerisation catalyst is sensitive to steric hindrance. Hence, isomerisation will preferentially take place on the less substituted olefin. Moreover, it has been shown that this catalytic species performs the isomerisation by sliding along the carbon chain until a sterically hindered position induces its decomplexation. The efficiency of the isomerisation process, not only depends upon the catalyst employed, but also on the structure of the substrate. In fact, the formation of a favourable complex between the dioxolane moiety and the Ru carbene is thought to act as a sink for the metathesis catalyst and to lead the way to decomposition and Ru-H formation. Finally, we have illustrated the power of this approach by the rapid assembly of an intermediate for the total synthesis of Pentalenene.

Experimental Section

NMR spectra were recorded on BRUKER AC-300 Avance II (¹H: 300 MHz and ¹³C: 75 MHz) or on a BRUKER AM-500 (¹H: 500 MHz and ¹³C: 125 MHz). All spectra were internally referenced to residual *protio* solvent signals. Detailed NMR assignments were done through analysis of 1D (DEPT 135 or DEPTQ) and 2D (COSY, HMQC, HMBC) spectra. Low-resolution mass spectra were recorded using VARIAN MATT-44 and FINNIGAN MAT-TSQ 70 spectrometers with chemical ionisation (CI, 100 eV, ionisation gas: isobutane), atmospheric pressure chemical ionisation (APCI, 100 eV, ionisation gas: isobutane) and electrospray ionisation (ESI).

High resolution mass spectra were performed on THERMO FINNIGAN MAT900XP (CI and EI) and on WATERS LCT Premier XE (ESI). The measured mass was calculated from an average of ten accurate mass calculations. Infrared (IR) spectra were recorded on a SHIMADZU FTIR-8400S spectrometer and are reported in terms of frequency of absorption (cm^{-1}). The samples were analysed as thin films deposited on a ZnSe crystal. Peaks intensities are described as follows: s = strong, m = medium, w = weak, b = broad. Solvents were of technical grade and distilled prior to use. Diethylether and THF were distilled over sodium/benzophenone. Dichloromethane, dichloroethane, toluene, benzene and triethylamine were distilled over CaH_2 . Degassed solvents were prepared on small volume (< 50 mL) by three “freeze/pump/thaw” cycles. On a larger volume, solvents were degassed by bubbling argon for 30 to 60 minutes. All commercially available compounds (Acros, Aldrich, Fluka and Lancaster) were used as received unless otherwise stated. All reactions were carried out under an atmosphere of argon, in flame-dried apparatus and with magnetic stirring. Thin-layer chromatographies (TLC) were performed on TLC aluminium sheets coated with Silica gel 60 F254 (Merck). The plates were visualised using ultra-violet light (256 nm) and developed using KMnO_4 and/or phosphomolybdic acid. Flash chromatographies were performed using Merck Silica Gel 60 (230-400 mesh) under pressure with the stated solvents.

(Z)-3a,5,8,8a-tetrahydro-1H-spiro[azulene-4,2'-[1,3]dioxolan]-3(2H)-one (23): Degassed DCM (25 mL), diene **22** (90 mg, 0.360 mmol, 1 eq.) and Grubbs 1 catalyst (31 mg, 0.038 mmol, 0.105 eq.) are introduced in a three necked flask. The resulting solution is stirred for 3 days at room temperature. After this period, the mixture is concentrated under vacuum and a black residue is recovered. Purification (silica gel column, Hexane/ Et_2O = 6/4, R_f = 0.22) affords 55 mg (0.264 mmol) of a white solid. Yield = 73%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) = 5.77 (dt, $^3J_{\text{cis}}$ = 11.0 Hz, 3J = 5.1 Hz, 1H, $-\text{CO}_2\text{-CH}_2\text{-CH=}$), 5.57-5.51 (m, 1H, $-\text{CH-CH}_2\text{-CH=}$), 4.25-4.21 (m, 1H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 3.96-3.85 (m, 3H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 2.62-2.56 (m, 1H, $-\text{CH-CH}_2\text{-CH=}$), 2.54 (dddd, 2J = 15.2 Hz, 3J = 6.7 Hz, 4J = 2.7 Hz, 4J = 1.4 Hz, 1H, $-\text{CO}_2\text{-CH}_2\text{-CH=}$), 2.47-2.39 (m, 2H, $-\text{CH-CH-}$), 2.33-2.14 (m, 3H, $-\text{CH}_2\text{-CO-CH-CO}_2\text{-CH}_2\text{-CH=}$), 2.13-2.03 (m, 2H, $-\text{CH}_2\text{-CH-CH}_2\text{-CH=}$), 1.37-1.20 (m, 1H, $-\text{CH}_2\text{-CH}_2\text{-CO-}$). ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 215.4 (C=O), 131.1 ($-\text{CO}_2\text{-CH}_2\text{-CH=}$), 124.2 ($-\text{CH-CH}_2\text{-CH=}$), 111.4 ($-\text{CO}_2\text{-}$), 66.0 and 64.8 ($-\text{OCH}_2\text{-CH}_2\text{-O-}$), 62.0 ($-\text{CO-CH-CO}_2\text{-}$), 39.9 ($-\text{CH}_2\text{-CO-}$), 38.3 ($-\text{CO-CH-CH-}$), 37.2 ($-\text{CO}_2\text{-CH}_2\text{-}$), 35.9 ($-\text{CH-CH}_2\text{-CH=}$), 28.7 ($-\text{CH}_2\text{-CH}_2\text{-CO-}$). MS (+APCI): (m/z) = 209 (46, $[\text{MH}]^+$), 179 (100, $[\text{MH-C}_2\text{H}_6]^+$), 165 (14, $[\text{MH-acetaldehyde}]^+$). IR (film, cm^{-1}): ν = 3022 w, 2957 m, 2928 m, 2895 m, 1741 s, 1275 m, 1159 m, 1138 m, 1043 m, 1020 m, 1007 m, 949 m. HRMS (+CI): calcd. for $[\text{MH}]^+$ ($\text{C}_{12}\text{H}_{17}\text{O}_3$): 209.11777, found: 209.11780.

(Z)-3a,5,6,8a-tetrahydro-1H-spiro[azulene-4,2'-[1,3]dioxolan]-3(2H)-one (28): Degassed benzene (50 mL), diene **26** (250 mg, 1.000 mmol, 1 eq.) and Grubbs 2 catalyst (28 mg, 0.033 mmol, 0.033 eq.) are introduced in a three necked flask. The resulting solution is heated to reflux and stirred for 4 hours. After this period, the mixture is concentrated under vacuum and a black residue is recovered (TLC: PE/ Et_2O = 1/1, R_f = 0.26 (**28**), 0.215 (**27**)). Purification (silica gel column, PE/ Et_2O = 7/3) affords 70 mg (0.336 mmol) of **28** and 70 mg (0.315 mmol) of **27** (both as a white solid). Yield = 34%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) = 5.78-5.71 (m, 1H, $-\text{CH}_2\text{-CH=}$), 5.66 (bd, 3J = 10.7 Hz, 1H, $-\text{CH-CH=}$), 4.27-4.18 (m, 1H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 3.94-3.85 (m, 3H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 3.09-2.94 (m, 1H, $-\text{CH-CH=}$), 2.45 (d, 3J = 12.2 Hz, 1H, $-\text{CO-CH-CO}_2\text{-}$), 2.33-2.07 (m, 5H, $-\text{CO-CH}_2\text{-CH}_2\text{-CH=CH-CH}_2\text{-}$), 1.94 (ddd, 2J = 14.0 Hz, 3J = 10.5 Hz, 3J = 2.3 Hz, 1H, $-\text{CO}_2\text{-CH}_2\text{-}$), 1.67 (ddd, 2J = 14.2 Hz, 3J = 7.7 Hz, 3J = 2.1 Hz, 1H, $-\text{CO}_2\text{-CH}_2\text{-}$), 1.54-1.38 (m, 1H, $-\text{CO-CH}_2\text{-CH}_2\text{-}$). ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 215.5 (C=O), 133.2 ($-\text{CH-CH=}$), 131.0 ($-\text{CH}_2\text{-CH=}$), 111.5 ($-\text{CO}_2\text{-}$), 66.0 and 64.8 ($-\text{OCH}_2\text{-CH}_2\text{-O-}$), 59.9 ($-\text{CO-CH-CO}_2\text{-}$), 39.9 ($-\text{CO-CH}_2\text{-}$), 39.1 ($-\text{CH-CH=}$), 36.9 ($-\text{CO}_2\text{-CH}_2\text{-}$), 27.6 ($-\text{CO-CH}_2\text{-CH}_2\text{-}$), 23.9 ($-\text{CH}_2\text{-CH=}$). MS (+ESI): (m/z) = 231 (52, $[\text{M+Na}]^+$), 209 (26, $[\text{MH}]^+$), 165 (26, $[\text{MH-acetaldehyde}]^+$). MS (+APCI): (m/z) = 209 (74, $[\text{MH}]^+$), 179 (100, $[\text{MH-C}_2\text{H}_6]^+$), 191 (34, $[\text{MH-H}_2\text{O}]^+$), 165 (60, $[\text{MH-acetaldehyde}]^+$). IR (film, cm^{-1}): ν = 2924 m, 2852 w, 1745 s, 1458 w, 1437 w, 1317 w, 1277 w, 1261 w, 1217 w, 1196 w, 1151 m, 1089 w, 1036 m, 989 w, 949 w, 914 w, 895 w. HRMS (+EI): calcd. for $[\text{M}]^+$ ($\text{C}_{12}\text{H}_{16}\text{O}_3$): 208.10940, found: 208.10969.

(Z)-7-methyl-3a,5,8,8a-tetrahydro-1H-spiro[azulene-4,2'-[1,3]dioxolan]-3(2H)-one (32): Degassed benzene (170 mL), diene **30** (900 mg, 3.400 mmol, 1 eq.) and Grubbs 2 catalyst (87 mg, 0.102 mmol, 0.03 eq.) are introduced in a three necked flask. The resulting solution is heated to reflux and stirred for 6 hours. Then, a second portion of Grubbs 2 catalyst is added (87 mg, 0.102 mmol, 0.03 eq.). The reaction mixture is stirred 3 days. After this period, the mixture is concentrated under vacuum and a black residue is recovered. Purifications (silica gel column, PE/ Et_2O

= 8/2 then horizontal distillation: 170°C, 1 mbar) affords 564 mg (2.53 mmol) of a colorless liquid. Yield = 75%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) = 5.27 (t, 3J = 6.6 Hz, 1H, $-\text{CH}_2\text{-CH=}$), 4.24 (m, 1H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 3.93-3.81 (m, 3H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 2.53-1.89 (m, 9H), 1.69 (s, 3H, $-\text{CH}_3$), 1.48-1.45 (m, 1H, $-\text{CO-CH}_2\text{-CH}_2\text{-}$). ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 215.4 (C=O), 131.1 ($-\text{CH=}$), 124.2 ($\text{CH}_2\text{-C=}$), 111.4 ($-\text{CO}_2\text{-}$), 66.0 and 64.8 ($-\text{OCH}_2\text{-CH}_2\text{-O-}$), 62.1 ($-\text{CO-CH-CO}_2\text{-}$), 41.1 ($-\text{CO-CH}_2\text{-}$), 39.8 ($-\text{CO}_2\text{-CH}_2\text{-}$), 38.0 ($-\text{CO-CH-CH-}$), 36.8 ($-\text{CH}_2\text{-C-CH}_3$), 28.9 ($-\text{CO-CH}_2\text{-CH}_2\text{-}$), 25.9 ($-\text{CH}_3$). MS (+APCI): (m/z) = 223 (100, $[\text{MH}]^+$), 221 (42, $[\text{MH-H}_2]^+$), 219 (18, $[\text{MH-2H}_2]^+$), 193 (18, $[\text{MH-C}_2\text{H}_6]^+$), 179 (19, $[\text{MH-acetaldehyde}]^+$), 175 (37, $[\text{MH-acetaldehyde-2H}_2]^+$). IR (film, cm^{-1}): ν = 2964 m, 2927 m, 2893 m, 2876 m, 1703 s, 1443 bm, 1275 s, 1142 s, 1130 s, 1040 s, 1016 s, 951 s, 897 m, 854 m, 847 m. HRMS (+CI): calcd. for $[\text{MH}]^+$ ($\text{C}_{13}\text{H}_{19}\text{O}_3$): 223.13342, found: 223.13314. Elemental analysis for $\text{C}_{13}\text{H}_{18}\text{O}_3$ (222.28): calcd. C 70.24, H 8.16; found C 68.04, H 7.94.

(Z)-1,2,5,8,9,9a-hexahydrospiro[cyclopenta[8]annulene-4,2'-[1,3]dioxolan]-3(3aH)-one (25): Degassed DCM (60 mL), diene **24** (300 mg, 1.130 mmol, 1 eq.) and Grubbs 1 catalyst (93 mg, 0.113 mmol, 0.1 eq.) are introduced in a three necked flask. The resulting solution is stirred for 5 days at room temperature. After this period, the mixture is concentrated under vacuum and a black residue is recovered. Purification (silica gel column, PE/ Et_2O = 7/3 then horizontal distillation: 170°C, 1 mbar) affords 130 mg (0.585 mmol) of a white solid. Yield = 52%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) = 5.85 (dt, 3J = 9.8 Hz, 3J = 7.9 Hz, 1H, $-\text{CH}_2\text{-CH}_2\text{-CH=}$), 5.64 (ddd, 3J = 10.3 Hz, 3J = 7.9 Hz, 4J = 1.5 Hz, 1H, $-\text{CO}_2\text{-CH}_2\text{-CH=}$), 4.15-4.07 (m, 1H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 4.00-3.89 (m, 2H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 3.80-3.72 (m, 1H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 2.70 (dd, 2J = 13.1 Hz, $^3J_{\text{trans}}$ = 10.4 Hz, 1H, $-\text{CO}_2\text{-CH}_2\text{-CH=}$), 2.53 (d, 3J = 8.9 Hz, 1H, $-\text{CO-CH-CO}_2\text{-}$), 2.48-2.05 (m, 7H), 1.94 (ddt, 2J = 13.8 Hz, 3J = 5.9 Hz, 3J = 2.3 Hz, 1H, $-\text{CH}_2\text{-CH}_2\text{-CH=}$), 1.35-1.17 (m, 2H, $-\text{CH}_2\text{-CH-CH}_2\text{-CH}_2\text{-CH=}$). ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 217.8 (C=O), 132.7 ($-\text{CH=}$), 127.4 ($-\text{CH=}$), 113.8 ($-\text{CO}_2\text{-}$), 65.4 and 65.0 ($-\text{OCH}_2\text{-CH}_2\text{-O-}$), 57.5 ($-\text{CO-CH-CO}_2\text{-}$), 41.0 ($-\text{CO-CH-CH}_2\text{-}$), 40.3 ($-\text{CO-CH}_2\text{-}$), 36.6 ($-\text{CH}_2\text{-CH}_2\text{-CH=}$), 35.2 ($-\text{CO}_2\text{-CH}_2\text{-CH=}$), 29.1 ($-\text{CO-CH}_2\text{-CH}_2\text{-}$), 26.5 ($-\text{CH}_2\text{-CH}_2\text{-CH=}$). MS (+APCI): (m/z) = 223 (100, $[\text{MH}]^+$), 179 (21, $[\text{MH-acetaldehyde}]^+$). IR (film, cm^{-1}): ν = 3024 w, 2956 m, 2928 m, 2897 m, 2862 m, 1741 s, 1456 w, 1279 m, 1147 s, 1074 m, 1055 s, 966 m, 949 w, 912 m, 744 s. Elemental analysis for $\text{C}_{13}\text{H}_{18}\text{O}_3$ (222.28): calcd. C 70.24, H 8.16; found C 69.83, H 8.13.

(Z)-1,2,5,6,9,9a-hexahydrospiro[cyclopenta[8]annulene-4,2'-[1,3]dioxolan]-3(3aH)-one (27)

Degassed DCE (14 mL), diene **26** (70 mg, 0.280 mmol, 1 eq.), 1,4-benzoquinone (3 mg, 0.028 mmol, 0.1 eq.) and Grubbs 2 catalyst (12 mg, 0.014 mmol, 0.05 eq.) are introduced in a three necked flask. The resulting solution is heated to reflux and stirred for 20 hours. The solution turns to blue. After this period, the mixture is concentrated under vacuum and a black residue is recovered. Purification (silica gel column, PE/ Et_2O = 8/2 then horizontal distillation: 170°C, 1 mbar) affords 35 mg (0.16 mmol) of a white solid. Yield = 57%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) = 5.70-5.63 (m, 1H, $-\text{CH}_2\text{-CH}_2\text{-CH=}$), 5.56-5.47 (m, 1H, $-\text{CH}_2\text{-CH}_2\text{-CH=CH-}$), 4.25-4.15 (m, 1H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 3.99-3.85 (m, 3H, $-\text{OCH}_2\text{-CH}_2\text{-O-}$), 2.85 (dt, 2J = 13.7 Hz, 3J = 6.0 Hz, 1H, $-\text{CH-CH}_2\text{-CH=}$), 2.65-2.51 (m, 2H, $-\text{CO-CH-CH-}$), 2.42-1.91 (m, 7H), 1.88-1.57 (m, 1H, $-\text{CO-CH}_2\text{-CH}_2\text{-}$), 1.48-1.33 (ddd, 2J = 12.1 Hz, 3J = 11.9 Hz, 3J = 8.4 Hz, 1H, $-\text{CO-CH}_2\text{-CH}_2\text{-}$). ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 215.3 (C=O), 132.3 ($-\text{CH=}$), 123.5 ($-\text{CH=}$), 111.3 ($-\text{CO}_2\text{-}$), 65.8 and 64.9 ($-\text{OCH}_2\text{-CH}_2\text{-O-}$), 57.7 ($-\text{CO-CH-CO}_2\text{-}$), 39.44 ($-\text{CO-CH}_2\text{-}$), 39.40 ($-\text{CO-CH-CH-}$), 35.7 ($-\text{CO}_2\text{-CH}_2\text{-}$), 30.1 ($-\text{CH-CH}_2\text{-CH=}$), 27.8 ($-\text{CO-CH}_2\text{-CH}_2\text{-}$), 25.5 ($-\text{CO}_2\text{-CH}_2\text{-CH}_2\text{-}$). MS (+APCI): (m/z) = 223 (100, $[\text{MH}]^+$), 179 (19, $[\text{MH-acetaldehyde}]^+$). IR (film, cm^{-1}): ν = 2955 s, 2926 s, 2897 s, 2874 s, 1743 s, 1473 w, 1458 w, 1338 w, 1277 m, 1201 m, 1151 s, 1061 s, 1038 s, 982 w, 949 m, 908 m. Elemental analysis of $\text{C}_{13}\text{H}_{18}\text{O}_3$ (222.28): calcd. C 70.24, H 8.16; found C 69.61, H 8.09.

(Z)-8-methyl-1,2,5,6,9,9a-hexahydrospiro[cyclopenta[8]annulene-4,2'-[1,3]dioxolan]-3(3aH)-one (31): Degassed DCE (380 mL), diene (2.00 g, 7.560 mmol, 1 eq.), 1,4-benzoquinone (82 mg, 0.756 mmol, 0.1 eq.) and Grubbs 2 catalyst (321 mg, 0.378 mmol, 0.05 eq.) are introduced in a three necked flask. The resulting solution is heated to reflux and stirred for 48 hours. After this period, a second portion of 1,4-benzoquinone (82 mg) and Grubbs 2 (321 mg) is added. The resulting solution is heated to reflux and stirred for additional 48 hours. The mixture is concentrated under vacuum and a black residue is recovered. Purification (silica gel column, PE/ Et_2O = 8/2) affords 1.158 g of an inseparable mixture of **31** and **32** (**32/31** = 1.25:1). **Epoxides (44) and (45):** DCM (4 mL), alkene **27** (57 mg, 0.256 mmol, 1 eq.), NaHCO_3 (43 mg, 0.512 mmol, 2 eq.) and mCPBA (70% purity, 126

mg, 0.512 mmol, 2 eq.) are introduced in a round bottomed flask. The resulting solution is stirred at room temperature for 15 hours. The mixture is washed with NaOH 5% (3 x 15 ml), dried over MgSO₄ and concentrated under vacuum. Purification (silica gel column, Et₂O/PE = 8/2) affords 56 mg (0.235 mmol) of a white solid. Yield = 92%. Two diastereoisomers are isolated in a 1.24/1 ratio ((**44**) = 31 mg, (**45**) = 25 mg). ¹H NMR (300 MHz, CDCl₃): (**44**): δ (ppm) = 4.17-4.11 (m, 1H, -OCH₂-CH₂O-), 4.03-3.99 (m, 2H, -OCH₂-CH₂O-), 3.75 (q, J = 6.8 Hz, 1H, -OCH₂-CH₂O-), 3.09 (ddd, J = 11.2 Hz; J = 4.1 Hz; J = 3.4 Hz, 1H, HC-O-CH), 2.49-2.05 (m, 5H), 1.93 (ddd, J = 12.8 Hz, J = 6.0 Hz, J = 1.7 Hz, 1H, -CH₂-CH-O-), 1.74-1.17 (m, 5H). (**45**): δ (ppm) = 4.10-4.02 (m, 1H, -OCH₂-CH₂O-), 3.99-3.84 (m, 3H, -OCH₂-CH₂O-), 3.10-3.03 (m, 1H, -HC-O-CH-), 2.87-2.76 (m, 1H, -HC-O-CH-), 2.58-2.02 (m, 9H), 1.89 (ddd, J = 14.9 Hz, J = 10.8 Hz, J = 1.9 Hz, 1H, -CH₂-CH-O-), 1.61-1.41 (m, 2H, -CO-CH₂-CH₂-). ¹³C NMR (75 MHz, CDCl₃): (**44**): δ (ppm) = 216.6 (C=O), 111.5 (-CO₂-), 65.4 and 65.1 (-OCH₂-CH₂O-), 59.1 (-CO-CH-CO₂-), 54.4 and 52.6 (-CH-O-CH-), 39.7 (-CO-CH-CH-), 40.3, 35.0, 32.2, 29.1, 28.5. (**45**): δ (ppm) = 214.6 (C=O), 110.7 (-CO₂-), 65.4 and 64.8 (-OCH₂-CH₂O-), 57.2 (-CO-CH-CO₂-), 55.4 and 54.6 (-CH-O-CH-), 39.7 (-CO-CH-CH-), 35.6, 32.4, 30.9, 27.9, 22.5. MS (+ESI): (m/z) = 279 (100, [M+Na+H₂O]⁺), 261 (9, [M+Na]⁺), 239 (7, [MH]⁺). MS (+APCI): (m/z) = 239 (65, [MH]⁺), 221 (32, [MH-H₂O]⁺), 195 (34, [MH-acetaldehyde]⁺), 177 (100, [MH-H₂O-acetaldehyde]⁺). IR (film, cm⁻¹): ν = 2921 s, 2852 s, 1736 s, 1458 m, 1410 w, 1377 w, 1332 w, 1308 w, 1284 w, 1147 s, 1068 s, 1041 s, 949 s, 912 m. HRMS (+CI): calcd. for [MH]⁺ (C₁₃H₁₉O₄): 239.12833, found: 239.12846.

4-hydroxyhexahydro-2H-spiro[cyclopenta[c]pentalene-1,2'-

1,3]dioxolan]-8(3H)-one (46**):** THF (4.5 ml) and epoxide **45** (32 mg, 0.134 mmol, 1 eq.) are introduced in a round-bottomed flask. Then, NaH (60% in paraffin, 11 mg, 0.27 mmol, 2 eq.) is added in one portion. After gas evolution, the reaction mixture is heated to reflux during 3 hours. After cooling, the solution is quenched with NH₄Cl (sat. aq., 3 ml). The aqueous phase is extracted with AcOEt (5 x 3 ml). The combined organic fractions are dried over MgSO₄ and concentrated under reduced pressure. Purification (silica gel column, PE/Et₂O = 1/9) affords 16 mg (0.067 mmol) of colorless oil. Yield = 50%. ¹H NMR (300 MHz, CDCl₃): δ (ppm) = 4.13 (dt, ³J = 9.9 Hz, ³J = 5.1 Hz, 1H, -CH-OH), 3.99-3.95 (m, 2H, -OCH₂-CH₂O-), 3.89-3.85 (m, 2H, -OCH₂-CH₂O-), 2.84 (dq, ³J = 7.4 Hz, ³J = 4.3 Hz, 1H, -CH₂-CH-CH₂-), 2.69 (ddd, ³J = 9.8 Hz, ³J = 6.4 Hz, ³J = 3.6 Hz, 1H, HO-CH-CH-), 2.61 (bd, ³J = 10.6 Hz, 1H, -OH), 2.36-2.29 (m 3H, -CO-CH₂-, -CH₂-CH-OH), 2.04-1.89 (m, 4H), 1.71-1.52 (m, 2H, -CO₂-CH₂-CH₂-), 1.46-1.32 (m, 1H, -CO-CH₂-CH₂-). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 219.4 (C=O), 117.7 (-CO₂-), 71.6 (C_{quat}), 71.2 (-CH-OH), 65.0 and 64.8 (-OCH₂-CH₂O-), 54.9 (HO-CH-CH-), 45.0 (-CH₂-CH-OH), 43.3 (-CH₂-CH-CH₂-), 39.9 (-CO-CH₂-), 34.8 (-CO₂-CH₂-), 24.8 (-CO₂-CH₂-CH₂-), 23.7 (-CO-CH₂-CH₂-). MS (+ESI): (m/z) = 261 (100, [M+Na]⁺), 239 (39, [MH]⁺), 221 (44, [MH-H₂O]⁺), 177 (19, [MH-H₂O-acetaldehyde]⁺). MS (+APCI): (m/z) = 239 (14, [MH]⁺), 221 (100, [MH-H₂O]⁺), 177 (94, [MH-H₂O-acetaldehyde]⁺). IR (film, cm⁻¹): ν = 3430 bm, 2951 m, 2878 m, 1730 s, 1456 w, 1412 w, 1314 m, 1283 m, 1200 m, 1167 m, 1146 m, 1117 m, 1096 m, 1059 m, 1032 m, 951 m. HRMS (+ESI): calcd. for [M+Na]⁺ (C₁₃H₁₈O₄Na): 261.1103, found: 261.1099.

Supporting Information (see footnote on the first page of this article):

Synthetic procedures and characterisation for orthoesters, silylenol ethers and dienes.

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Layout 2:

Ring closing metathesis

The Grubbs 2 catalysed RCM of various bis-olefinic precursors leads to the formation of isomerised products. The isomerisation phenomenon has been studied in a substrate perspective.

Benzoquinone derivatives have been shown to dramatically decrease the isomerisation process. A highly functionalised triquinane intermediate for the synthesis of Pentalenene has been reached.

Guillaume De Bo, István Markó*

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Studies towards the synthesis of Pentalenene: mechanistic insights on the isomerisation phenomenon during RCM of medium sized rings.

Keywords: RCM / Medium sized rings / Isomerisation / Grubbs catalyst / Pentalenene