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## COMMUNICATION

## Selective formation of angular tricyclic compounds by ruthenium-mediated ring-rearrangement metathesis†‡

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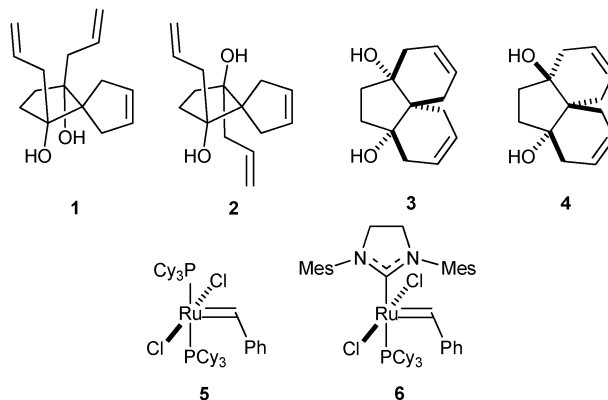
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Unsaturated spirocyclic substrates bearing two alkenyl chains underwent ruthenium-mediated ring-rearrangement metathesis through relaying cyclohexene and cycloheptene moieties to give angularly fused tricyclics. In some instances where two products were expected, high degrees of selectivity were observed. In one instance the structural parameter leading to selectivity was very subtle; in others the transformation favoured the formation of products with a *cis*-fused cyclohexene moiety. An unusual transformation involving ring-opening, double-bond migration, and then ring-closing was observed.

Ruthenium-mediated ring-opening and then ring-closing metathesis (ROM-RCM),<sup>1</sup> or ring-rearrangement metathesis (RRM),<sup>2</sup> is an attractive strategy of consecutive reactions for the skeletal reorganization of a molecule with an unsaturated ring. Consecutive metathesis sequences have usually been designed with cyclopentene or norbornene as the relaying alkene because relief of strain is believed to promote progress toward the formation of products with less strained rings, particularly six-membered rings.<sup>2</sup> The effects of chain length of the acyclic alkenes and relative stereochemistry may also contribute significantly to the efficiency of RRM processes.<sup>2</sup> Therefore, certain combinations of these parameters might guide an RRM process towards a single product, where two products are possible. We sought instances of such selectivity in the formation of angularly fused carbocycles, and the results of our initial explorations are presented here.

Harriety and coworkers<sup>3</sup> converted spirocyclic compounds **1** and **2** into tricyclic [6.5.6] ring-systems **3** and **4** using catalyst **5**. Holtsclaw and Koreeda<sup>4</sup> synthesized angular [6.5.5] and [6.5.6] ring-systems by RRM using catalyst **6** of a norbornene scaffold with two olefinic chains attached at C-7. However, in



both of these studies the substrates were expected, by symmetry or geometry, each to lead to a single product.

The majority of our substrates had a cyclohexene moiety as the relaying alkene, in spite of there being very few instances of the use of cyclohexene in this role.<sup>1,5</sup> All of our substrates were obtained in a straightforward way by reaction of the corresponding diketones<sup>6</sup> with organomagnesium reagents.<sup>7,8</sup>

Our initial substrate was **7** with *cis* allyl groups, from which there could be only one RRM product, but this substrate allowed the conditions to be optimized and the possibility of simple RCM between the allyl groups to be assessed. Substrate **7** was recovered unchanged when **5** was used as the catalyst. In contrast, catalyst **6** smoothly induced RRM with **7**, which led only to **8**, with a [7.5.6] angularly fused ring-system (Scheme 1). Compound **8** was subjected to analysis by X-ray crystallography, but there was an unforeseen complication. The crystal was a 1 : 1 mixture of **8** and **9**, in which a double bond had migrated<sup>10</sup> to an adjacent position. (Compound **9** is more stable than **8** by almost 8 kJ mol<sup>-1</sup>.<sup>11</sup>) Nevertheless, the high yield of **8** demonstrated unequivocally that, although a cyclohexene moiety may be a less willing participant in RRM than cyclopentene, a cyclohexene relay is still effective in RRM. None of the product of direct coupling of the allyl groups was detected.

Substitution of the relaying alkene moiety, as in **10**, stopped the RRM process. Prolonged heating of **10** in the presence of catalyst **6** gave oligomerized material.

The diastereomer of **7** in which the two allyl groups are on the opposite face of the five-membered ring, relative to the unsaturation in the cyclohexene ring, was not assessable by our

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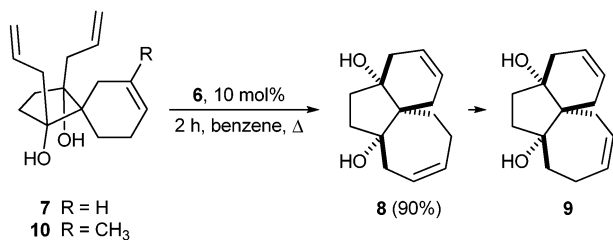
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‡ Electronic supplementary information (ESI) available: Procedures, characterization data for substrates and RRM products, Cartesian coordinates and CIF's for **8** + **9**, **13**, **14**, **22** and **26**. CCDC 841851–841855. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15452d

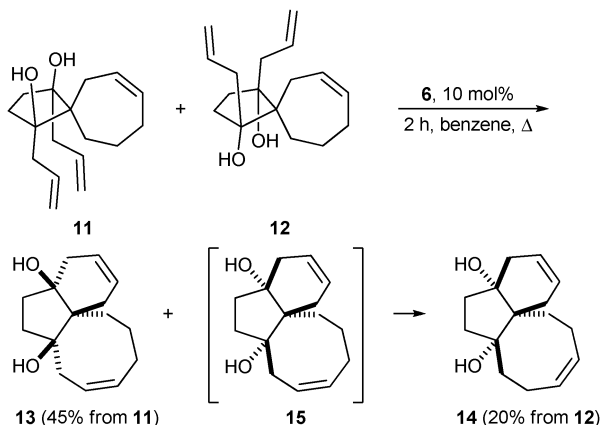
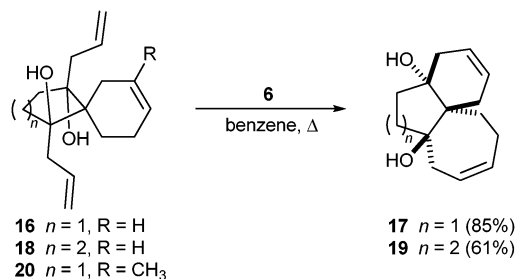


Scheme 1 Ring-rearrangement metathesis (RRM) of 7.

simple process of double addition of allylmagnesium bromide to the spirocyclic diketone.<sup>7</sup> However, both *cis*-isomers **11** and **12** were available, regrettably as an inseparable 1 : 1 mixture, by treatment with excess allylmagnesium bromide of the spirocyclic diketone with a cycloheptene ring. Heating a solution of **11** and **12** in the presence of **6** provided two [8.5.6] tricyclic products **13** and **14** (Scheme 2). The structures of both were determined by X-ray crystallography. It was obvious that **13** was the result of RRM of **11** and **14** was produced by RRM of **12**. However, **15** was the product expected from **12**, and **14** represented, once again, a product of double-bond migration; **14** is more stable than **15** by 3.6 kJ mol<sup>-1</sup>.<sup>11</sup> The reaction of **11** shows that RRM is possible when the initial ring-opening process involves metathesis with an annular alkene on the opposite face of the five-membered ring. Furthermore, cycloheptene can also serve as a relaying alkene in RRM, although lower yields should be expected.

RRM proceeded in high yield with **16**, which has *trans* allyl groups. The [7.5.6] angularly fused product **17** is a diastereomer of **8** (Scheme 3). The initial ROM of **16** could have linked either allyl group to the end of the annular alkene that was closer, and in this way the initial ROM established *cis*-fused rings. Initially linking either allyl group to the more distant end of the annular alkene would have yielded the product with both ring junctions *trans*. In a similar way **18**, with spiro-linked six-membered rings, gave the [7.6.6] angularly fused compound **19**. The methyl-substituted analogue **20** failed to provide any RRM product.

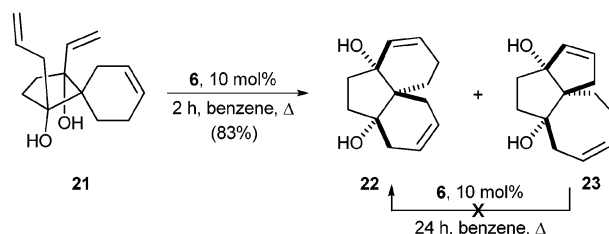
Attention then turned to *cis*-substrates bearing olefinic chains of different lengths for which two products would be possible, depending on whether the initial ROM involved one chain or the other. In the presence of **6** substrate **21**, with allyl and vinyl chains, yielded the [6.5.6] compound **22** and the [7.5.5] compound **23** (Scheme 4). The structure of **22** was

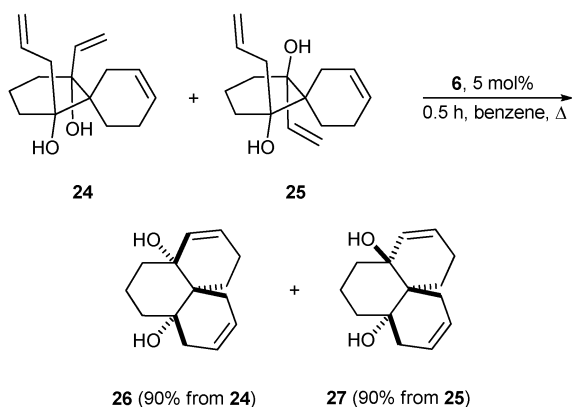
Scheme 2 Ring-rearrangement metathesis (RRM) of **11** and **12**.Scheme 3 Ring-rearrangement metathesis (RRM) of **16** and **18**. For **16**: 10 mol% of **6**, 2 h; and for **18**: 5 mol% of **6**, 1 h.

confirmed by X-ray crystallography. The disappointing 1 : 1 ratio of the products was not a result of equilibration of the products because prolonged heating of a benzene solution of **23** in the presence of **6** returned **23**, only. Calculations<sup>11</sup> indicated that **22** is almost 30 kJ mol<sup>-1</sup> more stable than **23**. Thus, it appeared that if the initial ROM produced *cis*-fused rings, then the initial ROM was equally likely to occur with the allyl or from the vinyl chain.

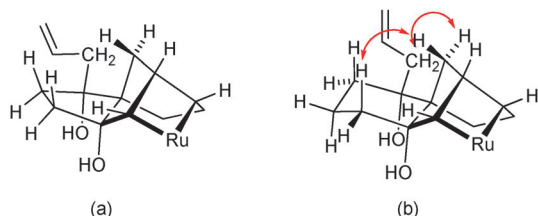
The similar six-membered analogue **24** was readily available only as an inseparable mixture with its *trans* isomer **25**. Given the result of RRM of **21**, the outcome of RRM of **24** was surprising. Heating a solution of the mixture of **24** and **25** in benzene with **6** gave the isomeric, but separable, [6.6.6] tricyclics **26** and **27** in high yield (Scheme 5). Only **26** could have been derived from **24**, and its structure was confirmed by X-ray crystallography. The highly selective formation of **26** was a clear affirmation of the initial hypothesis that selectivity might arise from a substrate that might initially be expected to give two products. With product equilibration being unlikely, it is difficult to identify which step(s) in the multi-step pathway from **24** to a [7.6.5] product would be energetically unfavourable, but the change from five-membered **21** to six-membered **24** would lead to some enhanced through-space interactions in the intermediates towards the [7.6.5] product from the latter, *e.g.* Fig. 1.

Heating **28** in the presence of **6** provided the tricyclic [8.5.6] angularly fused ring-system **14** in 69% yield as the only isolated product<sup>12</sup> (Scheme 6). The formation of no significant amount of a [7.5.7] ring system from **28** indicated that RRM was disfavoured when the initial ROM involved the butenyl group, *i.e.*, the formation of a cycloheptene was not as rapid as the formation of the cyclohexene. This is consistent with dramatic differences having been observed in the ease, or rate, of closure of six-membered *versus* seven-membered rings.<sup>13</sup> There is a second possible explanation regarding the formation of essentially one product from **28**, assuming that the initial association of the ruthenium catalyst was equally facile with either acyclic double bond. When the allyl chain was involved

Scheme 4 Ring-rearrangement metathesis (RRM) of **21**.



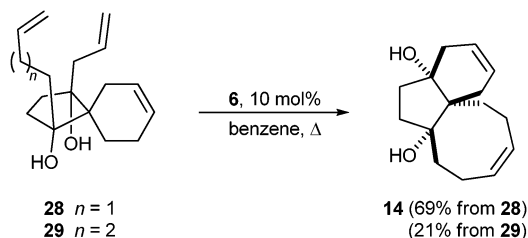
**Scheme 5** Ring-rearrangement metathesis (RRM) of **24** and **25**.



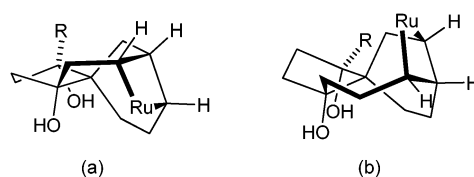
**Fig. 1** Intermediates from initial ROM involving the vinyl groups of (a) **21**, in the pathway to **23**, and (b) **24**, in the pathway to the unobserved [7.6.5] product. Ligands on ruthenium are omitted for clarity. In (b) contacts that are significantly closer in (b) than in (a) are shown.

in the initial ROM, annulation was with the closer carbon of the annular alkene *via* a metalocycle with a geometry represented by Fig. 2(a). However, when the initial ROM involved the butenyl chain, the annulation was with the more distant carbon of the annular alkene. The geometry of the predominant intermediate metalocycle might be represented by Fig. 2(b). The eight-membered ring in this intermediate can attain a boat-chair conformation, which is a conformational minimum for cyclooctane.<sup>14</sup> Both of these ROM reactions would lead to **14**.

The RRM of the *cis*-allyl-pentenyl substrate **29** gave a small amount of **14** as the only RRM product as well as much oligomerized material, but no [9.5.6] tricyclic product was detected. This result indicated that the intramolecular closure of the nine-membered ring was so unfavoured, as an early ROM step or a final RCM step, that the rate of migration of the terminal pentenyl unsaturation became significant, and the final RCM involved a 3-pentenyl chain rather than a 4-pentenyl chain. Some other instances of isomerization-RCM reactions



**Scheme 6** Ring-rearrangement metathesis (RRM) of **28** and **29**.



**Fig. 2** Plausible intermediates in the RRM of **28**. Ligands on ruthenium are omitted for clarity. (a) Intermediate for an initial ROM involving the allyl group ( $R = \text{butenyl}$ ), and (b) intermediate for an initial ROM involving the butenyl group ( $R = \text{allyl}$ ).

have been studied recently,<sup>15</sup> but in those cases seven-membered products were obtained during attempts to secure eight-membered compounds.

In summary, RRM employing a cyclohexene relay is feasible with a second generation ruthenium catalyst, and various geometries in the substrates are amenable to RRM. While the difference in the selectivities in RRM processes involving **21** and **24** are difficult to ascribe to a specific structural feature, although the reason is likely a kinetic one, RRM involving **28** (and **29**) very much favours the product with the six-membered ring *cis*-fused to the adjacent ring.

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