Rapid synthesis of medium-ring fused polycarbocyclic systems by rearrangement of carbenoid-derived oxonium ylides†

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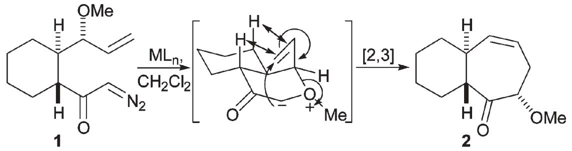
Tandem carbenoid generation, ylide formation and [2,3]-rearrangement is a powerful method for the construction of bicyclic and linearly fused tricyclic systems containing a seven-membered ring.

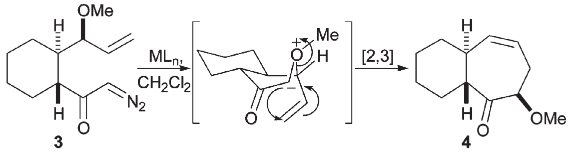
Fused polycarbocyclic natural products containing medium-sized rings embedded in their structural cores present significant synthetic challenges.[1] The well-known difficulties associated with the assembly of seven- and eight-membered rings[2] combined with their common occurrence in natural products makes the development of novel, practical and efficient methods for their construction an important objective. For example, the bioactive diterpenoid natural products guanacastepene A[3] and brevifoliol[4] each contain a seven-membered ring as part of their tricyclic structures and nicely exemplify the synthetic challenges presented by linearly fused polycarbocyclic natural products (Fig. 1).

Many transition metal based reactions have been applied to the construction of fused medium ring systems.[5] Recently, we described a new metal-mediated approach to the preparation of fused carbocyclic systems containing seven- and eight-membered rings. In this approach, [2,3]-sigmatropic rearrangement of a cyclic oxonium ylide,[6–8] generated intramolecularly from a conformationally constrained diazo ketone *via* a carbenoid intermediate, was employed as the key ring-forming reaction.[9,10] In the course of these studies, we found that treatment of each of the diastereomeric diazo ketones **1** and **3** with an appropriate transition metal complex afforded the corresponding metal carbenoids which were immediately trapped by the tethered ether to form a highly reactive oxonium ylide [eqn (1) and (2)].[9] Ylide rearrangement resulted in net ring expansion with repositioning of the ether substituent outside the ring, affording the carbocyclic systems **2** and **4**. The choice of the catalyst and the relative configuration of the stereogenic centres in the substrate were found to be crucial in determining the success of the reaction sequence; reactions of the diazo ketone **3** were found to be much higher yielding than those of the diastereomeric substrate **1**. The low yields obtained from the reactions of the diazo ketone **1** were attributed to unfavourable interactions between axial hydrogens of the cyclohexyl unit and the vinyl substituent in the conformation adopted by the oxonium ylide intermediate during [2,3]-rearrangement.



(1)

Cu(hfacac)$_2$, reflux 51%
Rh$_2$(OAc)$_4$, rt 0%



(2)

Cu(hfacac)$_2$, reflux 84%
Rh$_2$(OAc)$_4$, rt 93%

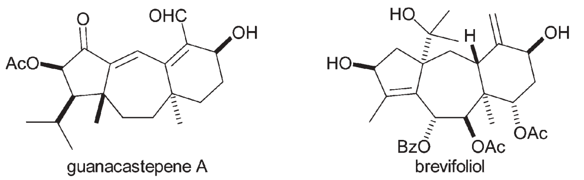


Fig. 1 Examples of linearly fused tricyclic natural products.

In this communication, we present the results of a study in which we explored two aspects of the reaction that would greatly increase its synthetic scope: the use of an ether substituent other than a methyl group to allow subsequent deprotection of the cyclised products, and the use of substrates in which the alkene is embedded in a ring (*i.e.* the union of two single rings with creation of third ring between them).

In the first part of our study we investigated the reactions of substrates in which competing reactions of the carbenoid (*e.g.* cyclopropanation or C–H insertion) or the oxonium ylide (*e.g.* a [1,2]- or a [1,4]-shift) could complicate the reaction. We first examined reactions of the substrates **5** and **10**, in which a *p*-methoxybenzyl protecting group is employed instead of the simple methyl group used in earlier studies, to discover whether it is possible to perform [2,3]-rearrangement when the oxygen is protected with a group that is prone to undergo a [1,2]-shift.

The copper-catalysed reaction of the diazo ketone **5** afforded a mixture of three products: the expected [2,3]-sigmatropic rearrangement product **6**‡ in 33% yield, the [1,4]-migration product **7** in 33% yield and the ketone **8** in 23% yield (2.4 : 1 mixture of diastereoisomers) resulting from a [1,2]-shift of the PMB group [eqn (3)].§ In contrast, the rhodium-catalysed reaction failed to provide any of the [2,3]-rearrangement product **6** but instead produced a small amount of the [1,2]-shift product **8** (8% yield) along with the unexpected cycloheptenone **9** (10% yield), the formal product of carbenoid insertion into an alkenyl C–H bond

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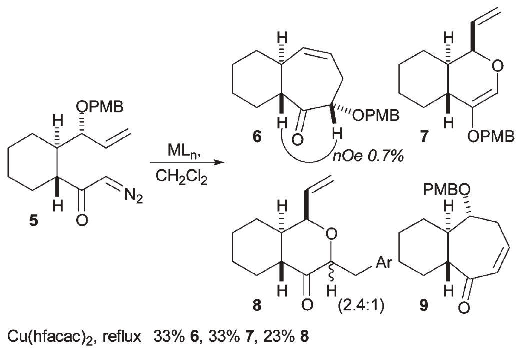
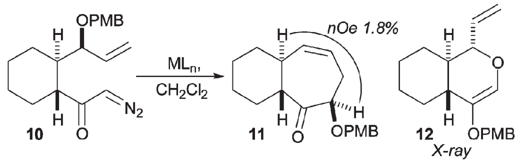
and subsequent conjugation to form the enone. The low yields of the [2,3]-rearrangement product **6** suggest that the configuration at the vinyl-bearing stereogenic centre does not allow the system to adopt a conformation in which there is efficient orbital overlap of the vinyl group and the ylide, leading to a relatively high energy transition state. The results from the cyclisation reactions of the substrate **5** correlate well with previous results [eqn (1), **1** → **2**].[9b]



(3)

Cu(hfacac)$_2$, reflux 33% **6**, 33% **7**, 23% **8**
Rh$_2$(OAc)$_4$, rt 8% **8**, 10% **9**

The main product arising from treatment of the diastereomeric diazo ketone **10** with copper(II) hexafluoroacetylacetonate was the [1,4]-shift product **12**¶ and only a relatively small amount of the [2,3]-rearrangement product **11**‡ was obtained [eqn (4)]. The formation of formal [1,4]-shift products from carbenoid-derived benzyl-substituted oxonium ylides has been reported by West and co-workers, and we have reported the isolation of related products from allylic ether substrates.[7c,11] Karche *et al.* have also demonstrated that formation of a [1,4]-migration product can be the dominant reaction pathway for an oxonium ylide obtained by treatment of an α-diazo β-keto ester with rhodium(II) acetate.[12] In our case, however, treatment of the diazo ketone **10** with rhodium(II) acetate afforded none of the [1,4]-migration product and delivered the required [2,3]-rearrangement product **11** in good yield (79%) instead. Interestingly, products arising from competing C–H insertion or [1,2]-shift were not observed in this case.

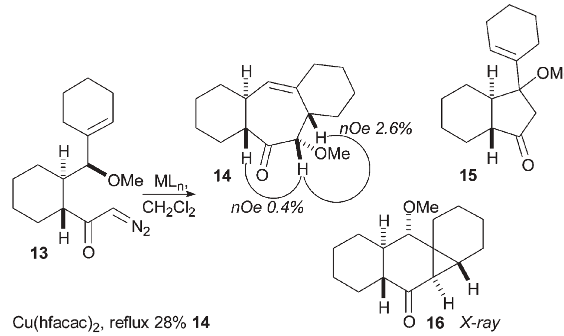


(4)

Cu(hfacac)$_2$, reflux 16% 38%
Rh$_2$(OAc)$_4$, rt *79%*

The successful formation of fused bicyclic carbocycles such as **2**, **4**, **6** and **11** [eqn (1)–(4)] suggested that it might be possible to use the reaction to construct linearly fused tricyclic compounds—formation of such systems using the reaction would require the creation of a third ring between two tethered single rings. To investigate this transformation, the diastereomeric cycloalkenes **13** and **17** were prepared and their reactions explored in order to discover whether substrates bearing a cycloalkene would undergo the required rearrangement reaction to give fused tricyclic systems [eqn (5) and (6)].

Treatment of the diazo ketone **13** with copper(II) hexafluoroacetylacetonate gave the [2,3]-rearrangement product **14**‡ in only 28% yield [eqn (5)]. In contrast, the rhodium(II) acetate catalysed reaction delivered the desired compound **14** in very low yield (3%) and instead afforded the ketone **15**, arising from insertion of the carbenoid into the allylic methine C–H bond, in 36% yield.

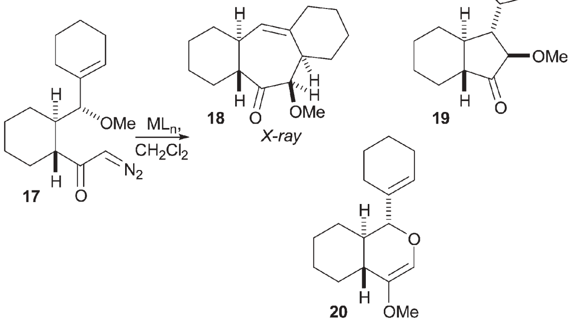


(5)

Cu(hfacac)$_2$, reflux 28% **14**
Rh$_2$(OAc)$_4$, rt 3% **14**, 36% **15**, 27% **16**

Significant amounts of the alkene cyclopropanation product **16**¶ (27% yield) were also obtained. The low yields of the [2,3]-rearrangement product **14** are not surprising given the results obtained in previous studies [eqn (1) and (3)] which had established that [2,3]-rearrangement was unfavourable for systems with this relative configuration.

In the case of the substrate **17** [eqn (6)], the copper-catalysed reaction afforded three ylide-derived products: the [2,3]-rearrangement product **18**¶ in 10% yield, the ring-contracted [1,2]-shift product **19** in 34% yield and the [1,4]-migration product **20** in 28% yield. In contrast, use of rhodium(II) acetate as the catalyst gave the tricyclic [2,3]-rearrangement product **18** in excellent yield. The ketone **18** was a crystalline solid and X-ray crystallography was used to establish the relative configuration.¶ In this case, it appears that the relative configuration of the stereogenic centres in the ylide generated by treatment of the diazo ketone **17** with rhodium(II) acetate facilitated [2,3]-rearrangement *via* a low energy transition state, whereas the copper-mediated reaction provided less of the intermediate ylide and there was significant competitive [1,4]-migration of the methyl group giving the unusual enol ether **20**.



(6)

Cu(hfacac)$_2$, reflux 10% **18**, 34% **19**, 28% **20**
Rh$_2$(OAc)$_4$, rt *90%* **18**

Several important findings emerge from our study. Firstly, we have shown that it is possible to construct fused bicyclic and tricyclic systems (*e.g.* **18**) containing a seven-membered ring *via* carbenoid generation, ylide formation and [2,3]-sigmatropic rearrangement. However, the success of the rearrangement reaction is highly dependent on the relative configuration of the stereocentres in the substrate and the choice of catalyst is crucial if the formation of [1,4]- and [1,2]-shift products is to be avoided. The second significant finding is that *p*-methoxybenzyl ether substrates can be used instead of methyl ethers and under appropriate conditions competing [1,2]-Stevens rearrangement is not a significant problem. Finally, it is significant that in all cases the copper and rhodium mediated reactions lead to widely differing outcomes with regard to ratios of ylide-derived products. These discrepancies are difficult to rationalise if the reactions proceed through a free oxonium ylide intermediate in all cases. *It seems likely that in some or all cases, rearrangement products are being formed directly from metal-bound ylide intermediates.*

The synthetic application of our findings to the construction of polycarbocyclic natural products is ongoing and the results of these studies will be reported in due course.

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Notes and references

‡ Stereochemical assignments for compounds **6**, **11** and **14** were made on the basis of ^{1}H NMR NOE data as shown in eqn (3)–(5).

§ Although NMR and other data are consistent with the ketone **8**, it is conceivable that this minor product could be a seven-membered cyclic ether arising from insertion of the rhodium carbenoid into a benzylic C–H bond. Attempts to distinguish between these possibilities by NMR analysis and chemical modification have not been successful.

¶ The structures and relative stereochemistries of the enol ether **12**, the cyclopropane **16** and the tricyclic ketone **18** were determined by X-ray crystallography. **12**, CCDC 650224; **16**, CCDC 650225; **18**, CCDC 650223. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b709064a

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