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Construction of Fused Medium-Ring Carbocycles by Catalytic Generation and Rearrangement of Oxonium Ylides

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Fused carbocyclic systems containing seven- and eight-membered rings can be constructed from allylic ethers in a stereoselective manner by tandem carbenoid generation, ylide formation and [2,3] rearrangement. Exceptionally high yields are obtained in cases where the substrate possesses favourable relative stereochemistry. The dienes resulting from [2,3] rearrangement of *gem*-divinyl ylides undergo Diels–Alder cycloaddition with reactive dienophiles at room temperature. Ylide formation, rearrangement and cycloaddition can be performed in a one-pot process to generate complex tetracyclic systems in a highly stereoselective manner.

Fused polycyclic compounds possessing seven- and eight-membered carbocycles are ubiquitous in nature. Structurally complex natural products of this type (e.g. phorbol and taxol, Figure 1) frequently possess potent and selective biological activities, and as a consequence they have been very popular targets for total synthesis.[1,2] In spite of recent advances with regard to medium-ring construction and the total synthesis of several highly complex natural product targets containing embedded medium-sized carbocycles, the discovery of new reactions and novel strategies for the rapid construction of these systems continues to be an important endeavour.

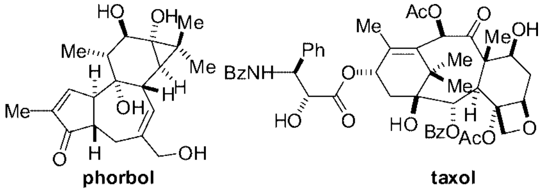

Figure 1. Examples of bioactive polycyclic compounds containing embedded medium-ring carbocycles.

Several research groups, including our own, have shown that functionalised cyclic ethers can be prepared by a [1,2] or [2,3] rearrangement of cyclic oxonium ylides formed upon intramolecular reaction of catalytically generated carbenoids, and that in some cases high levels of diastereocontrol can be obtained.[3–12] Recently, we described a novel method for the preparation of medium-ring cycloalkenones in which tandem intramolecular generation and [2,3] rearrangement of an oxonium ylide was used to construct a carbocycle (Scheme 1).[13] Treatment of each of the diazo ketones **1a**–**c** with rhodium(II) acetate resulted in the formation of a rhodium carbenoid species which was immediately trapped by the tethered allylic ether to generate a highly reactive ylide. Subsequent ylide rearrangement, with repositioning of the oxygen substituent outside the ring, delivered the cyclic ketones **3** and **4**; the major reaction pathway was ring-expanding [2,3] rearrangement of the intermediate ylide to give the medium-ring ketone **3**, and the cyclic ketone **4** was formed as a minor product by a ring-contracting [1,2] rearrangement. These results contrasted with the only previously reported example of the reaction in which treatment of 1-diazo-4-methoxyhex-5-en-2-one with rhodium(II) acetate delivered mainly the [1,2] shift product 2-methoxy-3-vinylcyclobutanone in modest yield.[6] Although the yield of the cycloheptenone **3b** obtained from the reaction of the substrate **1b** was reasonable, the product yields obtained from the reaction of monovinyl or longer chain substrates (e.g. diazo ketones **1a** and **1c**, Scheme 1) were low.

The results obtained from the metal-mediated reactions of the acyclic diazo ketones **1** (Scheme 1) prompted us to explore the synthesis of fused polycyclic systems by using the method to construct a ring onto a pre-existing cyclic structure (Scheme 2). For example, the metal-mediated reaction of the substrate **i**, in which both the α-diazo ketone and the side-chain allylic ether are attached to a ring, would

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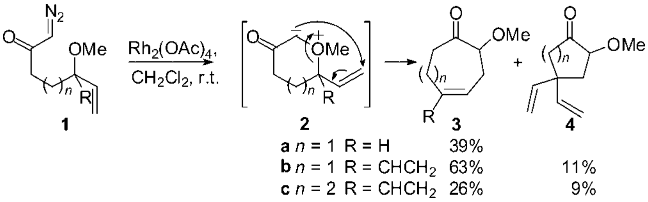
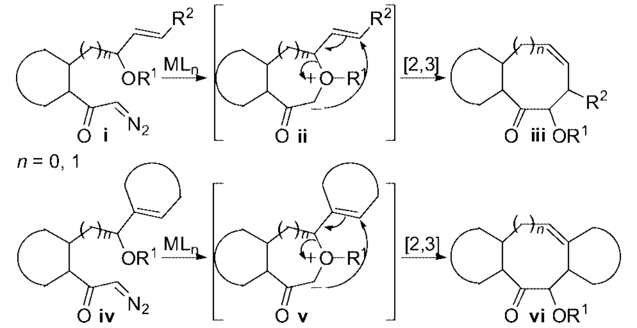


Scheme 1. Synthesis of simple medium-ring ketones from acyclic precursors by [2,3] rearrangement of catalytically generated oxonium ylides.[13]

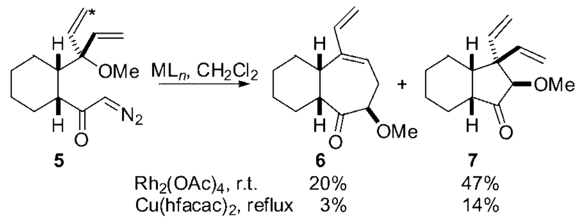
generate the cyclic oxonium ylide **ii** and [2,3] rearrangement would result in ring expansion of the ylide to give the stable carbocyclic system **iii** with the creation of two stereogenic centres. In principle, the reaction could be used as a powerful method to bring two tethered single rings together with the creation of a third ring to produce a linearly fused tricyclic system. This transformation would simply require the alkene to be contained in a ring as in the diazo ketone **iv**; the derived ylide intermediate **v** would then undergo [2,3] rearrangement to give the fused tricyclic system **vi**.



Scheme 2. Synthesis of fused medium-sized carbocycles by catalytic carbenoid generation, oxonium ylide formation and [2,3] rearrangement.

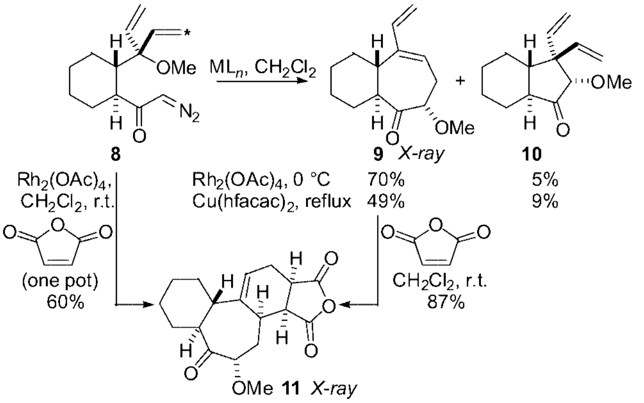
For the purposes of the present study, diazo ketones containing a cyclohexane unit as the conformational constraint were chosen as test substrates because the conformational behaviour of a substituted six-membered ring is arguably better understood than that of any other ring system. Initially, systems possessing *geminal* divinyl substitution were used in order to avoid having an additional stereogenic centre at the methoxy-bearing carbon atom and because one of the vinyl groups should be disposed to participate in the ring-expanding [2,3] rearrangement process irrespective of the conformation of the intermediate ylide. Divinyl substrates had also been used in our previously published preliminary work and had given the highest yields of [2,3] rearrangement products.

Reactions of the diazo ketone **5**, containing a *cis*-substituted cyclohexane, were explored first [Equation (1)]. Reaction of the substrate **5** with rhodium(II) acetate (2 mol-%) afforded a reasonable yield of ylide-derived products (67% combined yield), but the fused cyclopentanone **7** arising from [1,2] rearrangement of the intermediate oxonium ylide was the major product and the required [2,3] rearrangement product **6** was obtained in only 20% yield. When copper(II) hexafluoroacetylacetonate (2 mol-%) was employed as the catalyst, the yield of ylide-derived products dropped to 17% with the [1,2] shift product **7** predominating. The relative configuration of the ketone **6** indicates that the vinyl* group [Equation (1)] participates in the [2,3] rearrangement process.[14]



(1)

In spite of the modest yields of the [2,3] rearrangement product obtained from the metal-mediated reactions of the substrate **5**, cyclisation of the diastereoisomeric *trans*-substituted cyclohexyl diazo ketone **8** was investigated (Scheme 3). In contrast to the reaction of the substrate **5**, the rhodium(II) acetate catalysed reaction of the diazo ketone **8** afforded the required ylide [2,3] rearrangement product **9** in 70% yield along with a small amount of the ring-contracted [1,2] shift product **10**.[14] The reaction catalysed by copper(II) hexafluoroacetylacetonate also delivered viable amounts (58% combined yield) of ylide-derived products with the [2,3] ylide rearrangement product **9** predominating (Scheme 3).



Scheme 3. Catalytic carbenoid generation, ylide formation and rearrangement using the diazo ketone **8**, and subsequent Diels–Alder reaction of maleic anhydride with the diene product **9**.

The [2,3] rearrangement product **9** was a crystalline solid and X-ray crystallography was used to establish the relative configuration as $(4\mathrm{a}S^*,6S^*,9\mathrm{a}S^*)$, indicating that the vinyl* group (Scheme 3) had participated in the rearrangement reaction.[16] The relative stereochemistry in the [1,2] shift product **10** was assigned by NMR analysis.[14]

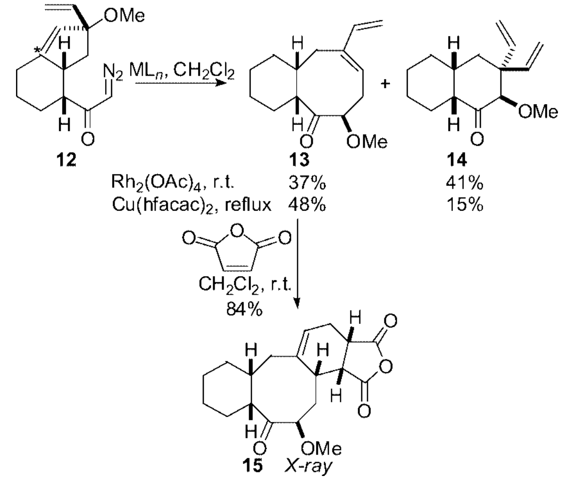
The diene **9** produced by [2,3] rearrangement of the ylide was an excellent substrate for subsequent Diels–Alder cycloaddition and reacted with maleic anhydride at room temperature in the absence of a catalyst to give the tetracyclic product **11** as single isomer in high yield (Scheme 3). The solid Diels–Alder product **11** was crystalline and the relative stereochemical relationship of the newly created stereogenic centres was established unambiguously by X-ray crystallography,[16] revealing that the cycloaddition had proceeded via the expected *endo* transition state.

The sequence of carbenoid formation, ylide generation, ylide rearrangement and Diels–Alder cycloaddition could also be performed in a one-pot fashion (Scheme 3). In this case, the tetracyclic compound **11** was prepared directly from two monocyclic starting materials (diazo ketone **8** and maleic anhydride) in 60% yield with the creation of two rings and four stereogenic centres in a single operation. This result demonstrates the potential of the reaction for the rapid assembly of complex polycyclic systems containing medium rings.

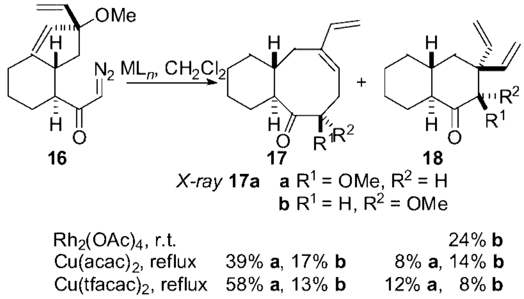
The successful formation of the fused seven-membered carbocycle from the diazo ketone **8** suggested that it might be possible to construct cyclooctenone-containing fused systems using the reaction. In preliminary work using the conformationally non-constrained diazo ketone precursor **1b** (Scheme 1), very poor yields of ylide-derived products had been obtained, so it was important to discover whether the introduction of a conformational constraint would lead to a higher yield of the [2,3] rearrangement product.

Metal-catalysed reactions of the diazo ketone **12**, possessing a *cis*-substituted cyclohexane, were explored first. Gratifyingly, both rhodium- and copper-catalysed reactions delivered good yields of ylide-derived products (Scheme 4); in the case of the reaction catalysed by rhodium(II) acetate roughly equal amounts of [2,3] and [1,2] rearrangement products **13** and **14** with a combined yield of 78%.[15] The reaction catalysed by copper(II) hexafluoroacetylacetonate delivered a lower combined yield of ylide-derived products but more of the [2,3] product was obtained relative to the [1,2] rearrangement product (48% **13**, 15% **14**). The relative stereochemistry of the [2,3] rearrangement product implies that the vinyl* group participated in [2,3] rearrangement reaction as in the case of diazo ketone **5** [Equation (1)]. The stereochemistry of the [2,3] rearrangement product **13** was confirmed after subjecting the diene **13** to a Diels–Alder reaction with maleic anhydride. The resulting crystalline tetracyclic compound **15** was obtained as a single isomer and analysis by X-ray crystallography permitted the stereochemical outcome of both the [2,3] rearrangement reaction and the cycloaddition reaction to be determined unambiguously.[16]

The cyclisation reactions of the diazo ketone **16**, possessing a *trans*-substituted cyclohexane, gave fascinating results [Equation (2)]. High yields of ylide-derived products were obtained from the copper-catalysed reactions, but in these cases isomeric mixtures of both [2,3] rearrangement product **17** (**a** and **b**) and the ring-contracted [1,2] Stevens rearrangement product **18** (**a** and **b**) were obtained.[14] In contrast, the yield from the rhodium(II) acetate mediated reaction was poor and only the [1,2] rearrangement product **18b** was isolated (24% yield) along with the perhydroindanone (47% yield) arising from intramolecular C–H insertion of the initially formed rhodium carbenoid species. The yields of ylide-derived products obtained from the copper-catalysed reactions ranged from 78–91%; in the case of the reaction mediated by copper(II) trifluoroacetylacetonate, the combined yield of the isomeric [2,3] rearrangement products **17a** and **17b** was 71% with a further 20% combined yield of the [1,2] rearrangement products **18a** and **18b**. The relative configuration of the crystalline diene **17a** was determined unambiguously by X-ray crystallography.[16]



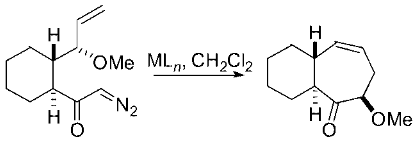
Scheme 4. Catalytic carbenoid generation, ylide formation and rearrangement using the diazo ketone **12**, and subsequent Diels–Alder reaction of maleic anhydride with the diene product **13**.



(2)

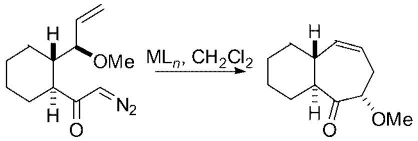
In all of the reactions described above, products arising from [1,2] rearrangement of the putative oxonium ylide intermediate were obtained. Although it was usually a minor issue, competitive [1,2] ylide rearrangement was the dominant pathway in some cases. The *geminal* divinyl group had been incorporated into the substrates because it was expected that it would increase the likelihood of a vinyl group being suitably orientated for rearrangement in a low-energy conformation of the intermediate cyclic ylide. However, the propensity for the ylides derived from these substrates to undergo competitive [1,2] rearrangement suggested that the *geminal* divinyl group might be stabilizing the putative diradical intermediate in this reaction.

In order to test the hypothesis and discover whether substrates bearing a single vinyl group would undergo the required rearrangement reaction, the diastereoisomeric diazo ketones **19** and **21** were prepared [Equations (3) and (4)]. The *trans*-substituted cyclohexyl systems **19** and **21** differ only in the relative configuration at the vinyl-bearing stereogenic centre, but substrates of this type are potentially problematic because the stereochemistry of the additional stereogenic centre in the substrate must be defined and may have an unfavourable conformational influence i.e. in order for the vinyl group to be correctly aligned to permit ylide rearrangement, the substrate might have to adopt a high energy conformation.



19 $Rh_2(OAc)_4$, r.t. 0% **20**
$Cu(hfacac)_2$, reflux 51%

(3)



21 $Rh_2(OAc)_4$, r.t. 93% **22**
$Cu(hfacac)_2$, reflux 84%

(4)

The diazo ketone **19** underwent ylide formation and rearrangement when treated with copper(II) hexafluoroacetylacetonate to give the [2,3] rearrangement product **20** in modest yield [Equation (3)].[14] However, the reaction catalysed by rhodium(II) acetate failed to deliver any of the [2,3] rearrangement product and instead delivered a diastereomeric mixture of [1,2] shift products (42% yield) along with a small amount (8% yield) of the product arising by C–H insertion of the intermediate rhodium carbenoid into the ether methine.

In contrast, the rhodium- and copper-catalysed reactions of the substrate **21** afforded the [2,3] rearrangement product **22** in excellent yield, with the reaction catalysed by rhodium(II) acetate giving an exceptionally high yield (93%) [Equation (4)].[14] It should be noted that the yield of the product **22** is the highest that we have observed for any oxonium ylide [2,3] rearrangement reaction.[4]

In the case of the ylide generated from the substrate **21** [Equation (4)], the relative configurations of the stereogenic centres apparently deliver a favourable low energy conformation facilitating [2,3] rearrangement, whereas in the case of the ylide generated from the substrate **19** [Equation (4)] they do not. It is interesting to note that the diastereotopic vinyl group that participates in the [2,3] rearrangement reaction of the ylide derived from in the divinyl substrate **8** correlates with that in the monovinyl substrate **21**. It is also noteworthy that the copper-catalysed reaction of the diazo ketone **19** [Equation (3)] delivered a reasonable yield of the required [2,3] rearrangement product **20** whereas the rhodium-mediated reaction produced none of this compound.

In summary, we have demonstrated that carbenoid generation, ylide formation and [2,3] rearrangement can be used to construct fused carbocyclic systems containing seven- and eight-membered rings. In most cases, the only isolable products from these reactions are those arising from [2,3] and [1,2] ylide rearrangement, and competitive cyclopropanation of the vinyl group is not observed. The relative configurations of the stereogenic centres in the substrate have an important influence on the course of the rearrangement reaction and dictate the relative amounts of [2,3] and [1,2] rearrangement products obtained, and catalyst choice is also highly substrate-dependent. Reactions of substrates possessing favourable relative stereochemistries deliver exceptionally high yields of the required [2,3] rearrangement products. In case of *geminal* divinyl systems, the dienes resulting from [2,3] rearrangement are very good Diels–Alder substrates and undergo cycloaddition with reactive dienophiles at room temperature. Ylide formation, rearrangement and Diels–Alder cycloaddition can be performed in a one-pot process to generate complex tetracyclic systems from monocyclic precursors in a highly stereoselective manner.

Supporting Information (see footnote on the first page of this article): Spectroscopic and other data for compounds **5**–**16**, **17a**, **17b**, **18a**, **18b**, **19**–**22**.

Acknowledgments

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[14] The relative configurations of the stereogenic centres in ylide rearrangement products **6**, **7**, **10**, **18a**, **18b**, **20** and **22** were deduced from ^{1}H NOE or *HH* NOESY experiments.

[15] The relative configuration at the methoxy-bearing stereogenic centre of the decalin **14** was not established conclusively, but it is likely to be that shown by analogy with the other [1,2] shift products.

[16] Crystal structure data for the diene **9**: $C_{14}H_{20}O_2$, M_r = 220.30, colourless tablet, crystal dimensions $0.56 \times 0.43 \times 0.20$ mm, monoclinic, space group $P2_1/n$, a = 8.6579(6), b = 10.4824(7), c = 13.3815(8) Å, β = 91.956(1)°, V = 1213.74(14) Å^3, Z = 4, $\rho_{calcd.}$ = 1.206 Mg/m^3, μ(Mo-K_α) = 0.079 mm^{-1}, T = 150(2) K; 8434 reflections collected of which 2754 independent, $2\theta_{max}$ = 55°. Structure solved by direct methods (SHELXS-97) and refined using full-matrix least squares against F^2 (SHELXTL), R_1 = 0.0378, wR_2 = 0.1084, 145 parameters. All hydrogen atoms were placed in geometrically calculated positions and refined as part of a riding model. Maximum and minimum residual electron density 0.32 and –0.19 e·Å^{-3}. Crystal structure data for the tetracyclic anhydride **11**: $C_{18}H_{22}O_5$, M_r = 318.36, colourless needle, crystal dimensions $0.70 \times 0.08 \times 0.08$ mm, monoclinic, space group $P2_1$, a = 8.166(2), b = 8.567(3), c = 11.293(3) Å, β = 99.430(2)°, V = 779.4(4) Å^3, Z = 2, $\rho_{calcd.}$ = 1.357 Mg/m^3, μ(Mo-K_α) = 0.098 mm^{-1}, T = 150(2) K; 6810 reflections collected of which 1886 independent, $2\theta_{max}$ = 55°. Structure solved by direct methods (SHELXS-97) and refined using full-matrix least squares against F^2 (SHELXTL), R_1 = 0.069, wR_2 = 0.209, 209 parameters. All hydrogen atoms were placed in geometrically calculated positions and refined as part of a riding model. Maximum and minimum residual electron density 0.53 and –0.29 e·Å^{-3}. Crystal structure data for the tetracyclic anhydride **15**: $C_{19}H_{24}O_5$, M_r = 332.38, colourless tablet, crystal dimensions $0.68 \times 0.41 \times 0.08$ mm, monoclinic, space group $P2_1/n$, a = 8.1190(8), b = 30.031(3), c = 14.1578(13) Å, β = 103.348(2)°, V = 3358.7(6) Å^3, Z = 8, $\rho_{calcd.}$ = 1.315 Mg/m^3, μ(Mo-K_α) = 0.094 mm^{-1}, T = 150(2) K; 13991 reflections collected of which 5544 independent, $2\theta_{max}$ = 50°. Structure solved by direct methods (SHELXS-97) and refined using full-matrix least squares against F^2 (SHELXTL), R_1 = 0.057, wR_2 = 0.140, 433 parameters. All hydrogen atoms were placed in geometrically calculated positions and refined as part of a riding model. Maximum and minimum residual electron density 0.30 and –0.22 e·Å^{-3}. Crystal structure data for the diene **17a**: $C_{15}H_{22}O_2$, M_r = 234.33, colourless column, crystal dimensions $0.43 \times 0.12 \times 0.12$ mm, orthorhombic, space group $Pca2_1$, a = 16.098(2), b = 5.4001(5), c = 31.372(3) Å, V = 2727.2(5) Å^3, Z = 8, $\rho_{calcd.}$ = 1.141 Mg/m^3, μ(Mo-K_α) = 0.074 mm^{-1}, T = 150(2) K; 14978 reflections collected of which 3163 independent, $2\theta_{max}$ = 55°. Structure solved by direct methods (SHELXS-97) and refined using full-matrix least squares against F^2 (SHELXTL), R_1 = 0.034, wR_2 = 0.098, 309 parameters. All hydrogen atoms were placed in geometrically calculated positions and refined as part of a riding model, except the methyl hydrogen atoms which were located from difference Fourier syntheses and refined as a rigid rotating group. Maximum and minimum residual electron density 0.20 and –0.18 eÅ^{-3}. CCDC-280588 (**9**), -280589 (**11**), -280591 (**15**), and -280590 (**17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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