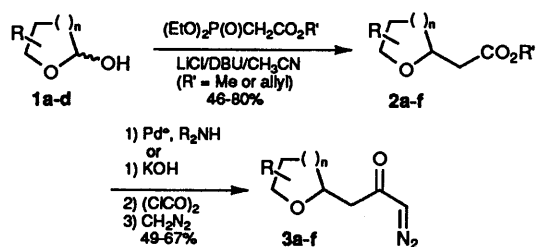# O-Bridged Medium Sized Rings *via* Bicyclic Oxonium Ylides[1]

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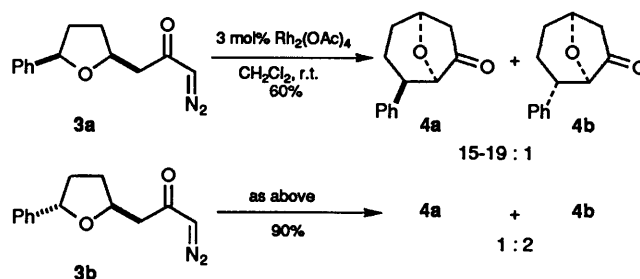
Fused bicyclic oxonium ylides, generated with catalytic Rh₂(OAc)₄ from cyclic ethers bearing pendant diazo ketones, undergo a [1,2]- or [2,3]-shift to give O-bridged seven- or eight-membered carbocycles, in several cases with a high degree of stereoselectivity.

Seven- and eight-membered rings are found in the structures of many important natural products. The well known energetic penalties incurred in direct closure of medium rings[2] have prompted the development of approaches to their formation by routes not involving ring closure of acyclic precursors.[3] In the course of our studies on the synthetic utility of the Stevens [1,2]-shift,[4] we have investigated the use of fused bicyclic oxonium ylides as precursors to oxygen-bridged medium rings. We report here our initial results, which entail a concise, stereoselective route to medium rings bearing oxygen functionality suitable for elaboration to natural product targets. We have demonstrated that [1,2]-shifts of oxonium ylides are efficient given the appropriate migrating group, leading to substituted tetrahydrofuranones in two steps from 3-alkoxypropionic acids. If the migrating carbon were part of a fused bicyclic skeleton, a [1,2]-shift would entail formation of an ether-bridged medium ring from a simple heterocyclic precursor.

Our approach required the formation and rearrangement of transient cyclic oxonium ylides, high energy species which had been previously generated *via* the addition of rhodium carbenoids to ether oxygens.[4-6] Preparation of the necessary cyclic ethers bearing pendant diazo ketones was straightforward from the lactols 1.† Olefination[7] followed by *in situ* Michael addition of alkoxide yielded the cyclic ethers 2. The diastereoisomeric precursors to 3a, b and 3c, d underwent epimerization *via* reversible β-elimination/Michael addition during saponification. The use of allyl esters in these cases permitted deprotection under conditions mild enough to avoid equilibration.[8] Formation of the acid chlorides and condensation with diazomethane[9] efficiently yielded the requisite diazoketones 3a–f, in 23–54% overall yield from the lactols.
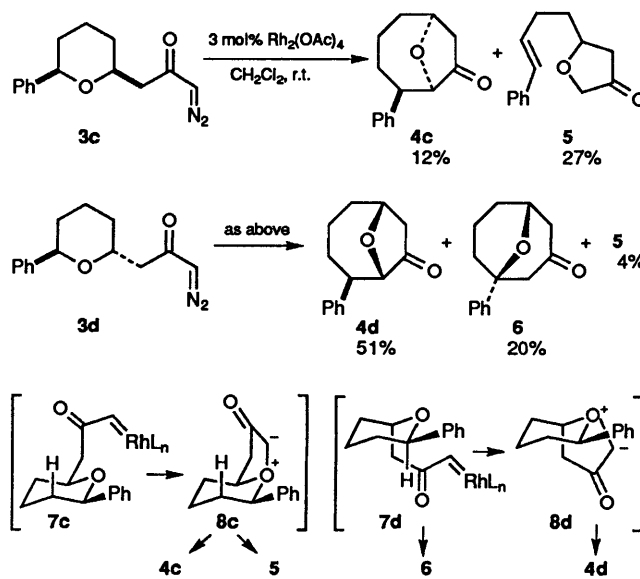

Scheme 1

efficient [1,2]-shift to give the diastereoisomeric cycloheptanones **4a, b** (Scheme 1). The extent of the stereoselectivity deserves comment. In each case, the major diastereoisomer arose from migration with retention of configuration by the presumed ylide intermediates, but the *cis* substrate **3a** showed a much higher degree of retention. Assuming migration *via* homolysis to give a biradical intermediate,[4,10] it appears that the biradical derived from **3b** suffers more randomization prior to recombination than does that derived from **3a**. Stereochemistry was rigorously determined *via* single crystal X-ray diffraction analysis of **4b**.[11]

The *cis*-tetrahydropyran **3c** gave disappointingly low yields of the cyclooctanone **4c** as a single diastereoisomer, and formed numerous side-products among which the tetrahydrofuranone **5** was the major component (Scheme 2). The *trans* isomer **3d** underwent a [1,2]-shift to give the cyclooctanone **4d** in good yield and again with complete retention of configuration. The

Addition of **3a–f** to catalytic Rh₂(OAc)₄ led to the desired carbocycles in 0–90% yield. In all cases complete group selectivity was seen in the [1,2]-shift, consistent with the notion that the carbon bearing the best radical stabilizing substituent should preferentially migrate.[4,10] Both **3a** and **3b** underwent an

† The lactol precursors of **3a–e** were obtained by standard half reduction of the corresponding lactones, while the precursors of **3f–g** were prepared in three straightforward steps from 3,4-dihydro-2-methoxypyran.

Scheme 2

structures of **4c, d** were assigned by their close spectral analogy (^{1}H NMR) to **4a, b**.* The isomeric O-bridged cyclooctanone **6**, the product of carbenoid insertion into the axial C–H bond adjacent to the ether oxygen,[12] was also formed, along with traces of **5**. This disparate chemoselectivity may arise from the different options available to the diastereoisomeric carbenoids **7c, d** and the ylides **8c, d**. The C–H insertion route is accessible only to the *trans* carbenoid **7d**. Assuming formation of *cis*-fused bicyclic ylides and preferred equatorial disposition of the phenyl group, **8c** and **8d** should exist in the conformations shown. While **8d** can only undergo the [1,2]-shift pathway, **8c** has an available α',β-fragmentation alternative *via* the axial hydrogen 1,3-disposed to the basic ylide carbon.[13] The small amounts of **5** formed from **3d** may arise from a different conformer of **8d**.

The isolation of only C–H insertion products **9** and **10** in the case of the benzodihydropyran **3e** is notable (Scheme 3). The ether oxygen should possess normal reactivity toward electrophilic attack by carbenoid, and insertion into one of the benzylic methylene C–H bonds is unlikely to be unusually favourable.[14] This result might be explained by reversible ylide formation. If equilibrium between carbenoid and ylide were possible, an ylide without an available low energy [1,2]-shift pathway might revert to carbenoid and follow alternative paths.[15] For the ylide **8e**, homolytic cleavage of the benzylic C–O bond should be slow, since the emerging radical would be constrained from receiving significant overlap stabilization in the transition state.[16] Unproductive ylide decomposition pathways may account for the remaining mass in this reaction.

Finally, clean conversion of **3f** into the methylenecyclooctanone **4f** demonstrates the applicability of this approach to more synthetically versatile migrating groups. The transformation could, in theory, occur by a [2,3]-sigmatropic rearrangement of the ylide **8f** rather than a [1,2]-shift. In order to
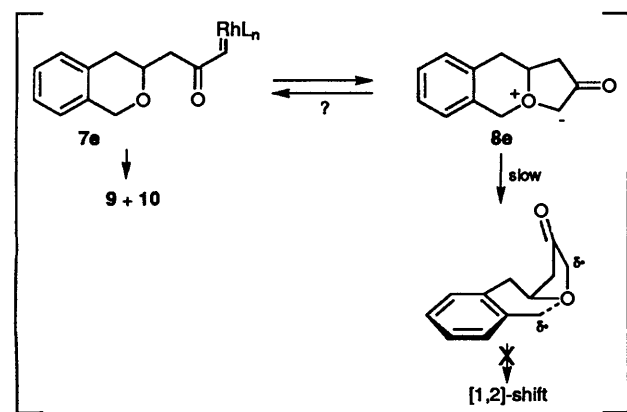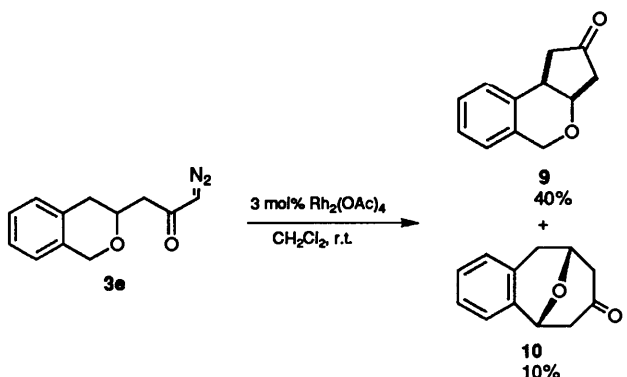
distinguish between these two mechanisms, we prepared the substituted analogue **3g** as a *ca.* 5:3 mixture of alkene isomers. Upon treatment with catalyst, this substrate yielded exclusively the diastereoisomeric cyclooctanones **4g** in good yield. This suggests that exocyclic allylic substituents migrate preferentially through the concerted [2,3]-shift pathway, although homolysis followed by regioselective recombination at the more substituted allylic terminus cannot be ruled out.

3f R = H
3g R = Me

3 mol% Rh$_2$(OAc)$_4$ | CH$_2$Cl$_2$, r.t.

8f

4f 65%
4g 54%
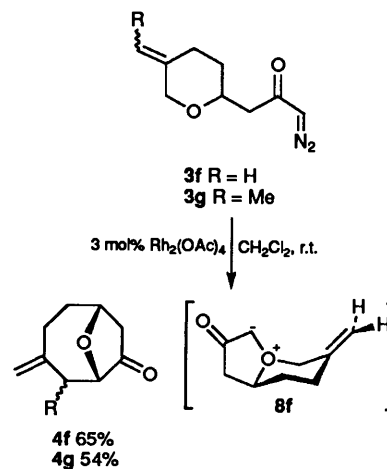
In summary, we have reported a novel and concise route to functionalized medium-sized carbocyclic rings *via* transient fused bicyclic oxonium ylides. The necessary precursors could be readily assembled from simple lactols. For one pair of diastereoisomers, an interesting divergence in ylide reactivity was seen, and a high degree of stereoselectivity was observed in three of four cases. Carbenoid addition to the ether oxygen may be reversible when the ylide does not have a low energy rearrangement pathway available. Reversible ylide formation, if it is occurring, may suggest the intermediacy of a metal-associated ylide. Studies are underway in our laboratories to further probe this issue. The application of this methodology to the synthesis of natural products containing oxygenated medium sized carbocycles will be reported elsewhere.

Experimental

Represenative Procedure: Preparation of **4a, b** *from* **3b**.—*trans*-1-Diazo-3-(5-phenyltetrahydrofuran-2-yl)propan-2-one **3b** (112 mg, 0.487 mmol) in CH$_2$Cl$_2$ (36 cm^3) was added (0.5 mmol h^{-1}) to a stirred suspension of Rh$_2$(OAc)$_4$ (6.5 mg, 0.0146 mmol) in CH$_2$Cl$_2$ (12 cm^3). Once addition was complete the mixture was stirred (15 min) to allow for complete consumption of starting material, concentrated and filtered through a short plug of silica gel (EtOAc) and then purified *via* radial chromatography (silica gel, 1 mm plate; 20:80, EtOAc–hexanes) to give a 1:2 mixture of **4a** and **4b** as a colourless oil (89 mg, 90%). Analytically pure samples were obtained by careful iterative radial chromatography (silica gel, 1 mm plate; 20:80, EtOAc–hexanes): **4a** (colourless oil): R_f 0.19 (20:80, EtOAc–hexanes); v_{max}(neat)/cm^{-1} 1757; δ_H(300 MHz, CDCl$_3$) 7.37–7.21 (m, 5 H), 4.83–4.80 (m, 1 H), 4.08 (d, *J* 3.4, 1 H), 3.29–3.22 (m, 1 H), 2.72 (dd, *J* 18.0, 7.9, 1 H), 2.33–2.21 (m, 2 H), 2.10–1.97 (m, 2 H) and 1.82–1.74 (m, 1 H); δ_C(75 MHz, CDCl$_3$) 213.4, 139.0, 128.3, 127.3, 126.9, 80.3, 73.7, 45.5, 41.7, 29.5 and 22.7 (Found: C, 77.35; H, 7.0. Calc. for C$_{13}$H$_{14}$O$_2$: C, 77.20; H, 6.98%). **4b** (colourless solid): m.p. 32–33 °C; R_f 0.28 (20:80, EtOAc–hexanes); v_{max}(neat)/cm^{-1} 1751; δ_H(300 MHz, CDCl$_3$) 7.51–7.21 (m, 5 H), 4.88 (dd, *J* 7.8, 3.2, 1 H), 4.22 (s, 1 H), 3.01 (d, *J* 6.6, 1 H), 2.80 (dd, *J* 17.9, 8.0, 1 H), 2.43–2.31 (m, 2 H), 2.24–2.10 (m, 1 H), 1.94 (dd, *J* 15.1, 5.2, 1 H) and 1.51 (dd, *J* 13.7, 5.6, 1 H); δ_C(75 MHz,

3e

3 mol% Rh$_2$(OAc)$_4$
CH$_2$Cl$_2$, r.t.

9 40%

+

10 10%

7e

8e

9 + 10

slow

[1,2]-shift

Scheme 3

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* Key methine protons: **4c**, 4.93–4.87 (m, 1H), 4.24 (d, *J* 5.7, 1 H) and 3.43–3.37 (m, 1 H); **4d**, 4.94 (dd, *J* 8.6, 4.2, 1 H), 4.21 (d, *J* 1.0, 1 H) and 3.17 (dd, *J* 11.5, 6.4, 1 H).

CDCl$_3$) 215.8, 142.2, 128.3, 127.8, 126.3, 80.7, 74.1, 41.1, 40.2, 26.2 and 21.8 (Found: C, 77.3; H, 7.0. Calc. for C$_{13}$H$_{14}$O$_2$: C, 77.20; H, 6.98%).

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