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Rearrangements of α-Diazo-β-hydroxyketones for the Synthesis of Bicyclo[*m.n.*1]alkanones

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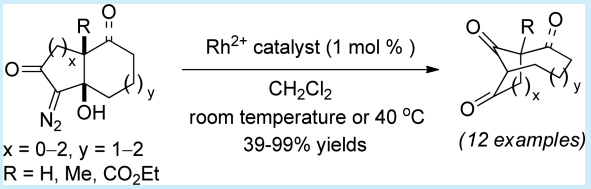
Supporting Information

ABSTRACT: Rhodium-catalyzed decomposition of fused bicyclic α-diazo-β-hydroxyketones results in good yields of bridged bicyclo-[*m.n.*1]ketones via a rearrangement pathway.



Bicyclo[*m.n.*1]alkane frameworks are featured in many architecturally and biologically interesting natural products (Figure 1). The cores of penostatin F and ingenol are [5.3.1] and

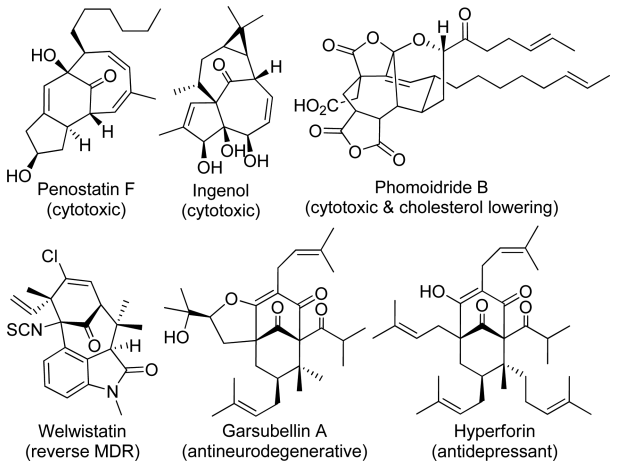


Figure 1. Natural products with bicyclo[*m.n.1*]alkanone core structures.

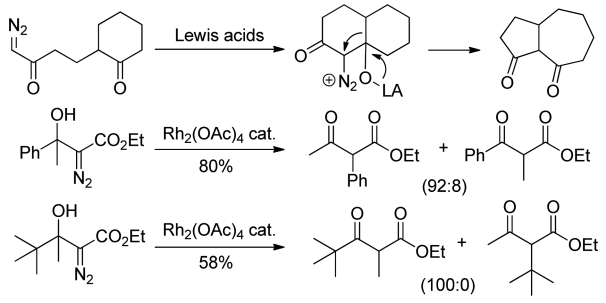
[4.4.1] bicyclic undecane ring systems, respectively.[1,2] Central to phomoidride B,[3] a micromolar inhibitor of farnesyl transferase and squalene synthase, and welwistatin,[4] a compound capable of reversing multidrug resistance in cancer cells, are bicyclo[4.3.1]-decane scaffolds. Garsubellin A[5] and hyperforin[6] possess bicyclo[3.3.1]nonanone skeletons. In addition, the one carbon bridge being a carbonyl group or in an equivalent oxidation state is also a common motif.

The synthesis of these complex natural products must address the construction of the bicyclic frameworks in good yields and selectivities. Depending on the bicyclic ring system, various sequential,[7] domino,[8] and cycloaddition strategies[9] have been used. Some methodologies are applicable only to particular ring systems; some bicyclic frameworks can be synthesized by many strategies,[10] while others are less readily accessible. There are not many examples of a single strategy or reaction type that has been demonstrated to furnish a range of functionalized bicyclo-[*m.n.*1]octane, -nonane, and -decane systems in good yields and selectivities.[11] Herein we describe such a strategy via the synthesis and rearrangements of α-diazo-β-hydroxyalkanones, which not only generates an array of bridged bicyclic compounds but also provides such products endowed with functional groups for further manipulations.

Diazoketones and esters are well-known as nucleophiles for "aldol-type" reactions with aldehydes and ketones.[12] Under acidic conditions, addition generates diazonium intermediates that rearrange by Tiffeneau−Demjanov rearrangements.[13] The Lewis acid catalyzed reaction between diazoesters and cyclic ketones, and their subsequent rearrangement, has been extensively applied as a strategy for ring expansion.[14] The asymmetric version of this reaction has been an area of intense activity in the past few years.[15] There have also been reports on the Lewis acid mediated intramolecular reaction between diazoketones tethered to cyclic ketones, where ring expansion also ensued, and fused bicyclic ketones are produced (Scheme 1).[16]

Under basic conditions, the reactions of diazoketones and diazoesters with aldehydes or ketones generate, respectively,

Scheme 1. 1,2-Migrations of Diazoketones in Literature



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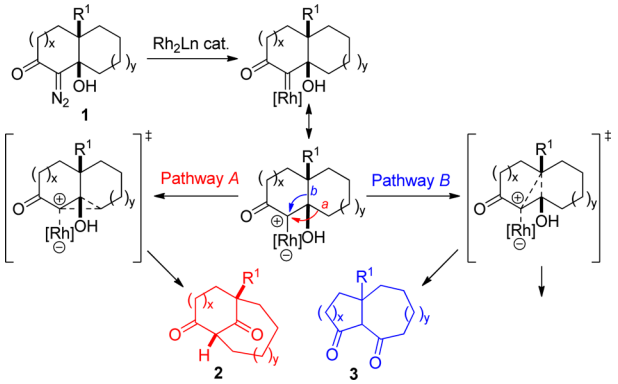
secondary or tertiary alcohol derivatives of α-diazocarbonyl compounds.[17] These functional group-loaded products offering the diazo, hydroxyl, and carbonyl groups in a contiguous arrangement have attracted the attention of researchers.[18] Treatment of α-diazo-β-hydroxycarbonyl compounds with various metals that form carbenes have resulted in 1,2-migrations.[19] Both steric and electronic factors have been implicated to account for the migratory aptitudes of substituents.[20] Generally, 1,2-hydride migration is most commonly observed.[21] α-Diazo-β-hydroxy-carbonyl compounds derived from unsymmetrical ketones undergo rearrangement in the presence of rhodium with a preference for aryl group migration (Scheme 1).[19a,e] Migratory aptitudes between competing alkyl groups are more challenging to predict and vary in selectivity.[19a] Results have been rationalized on the basis of stereoelectronic considerations,[19b] as well as a trend for migrations of the less hindered bonds (Scheme 1).[19a]

However, the analogous metal catalyzed rearrangements of bicyclic α-diazo-β-hydroxyketones such as **1** have not been examined in detail (Scheme 2). This reaction is interesting

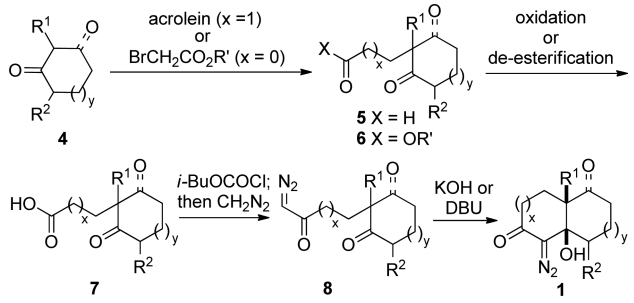
Scheme 2. Possible 1,2-Alkyl Migration Pathways of 1



because the competing 1,2-alkyl migrations in this case can potentially yield different bicyclic diketones, i.e. bicyclo[*m.n.*1]-alkanedione **2** via pathway A, and/or bicyclo[*m.n.*0]alkanedione **3** via pathway B. The rearrangement leading to **2** could be a general method to synthesize a range of bridged bicyclic frameworks for natural product synthesis. However, the most relevant precedents being the Lewis acid mediated reactions reported by Mock,[16a,b] Mander,[16c] Padwa,[16d] Muthusamy,[16f] and recently also by Feng[16g] all showed that rearrangements led to bicyclo[*m.n.*0]alkanediones (Scheme 1), i.e. products analogous to those resulting from rearrangement via pathway B.

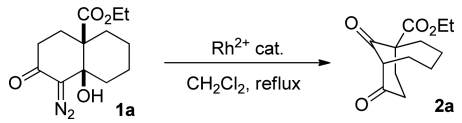
To investigate this reaction, a series of bicyclic α-diazo-β-hydroxyketones **1a**–**n** were synthesized according to the general route shown in Scheme 3. To simplify the assembly of substrates, active methylene compounds **4** were selected as substrates. Alkylation readily generated **5** and **6**, and then each was converted to the corresponding acids **7**. Activation and treatment with diazomethane afforded diazoketones **8**. Intramolecular nucleophilic addition induced in the presence of bases such as KOH[22] or DBU[23] yielded the bicyclic α-diazo-β-hydroxyketones **1** (Scheme 3). Cyclizations afforded uniformly and selectively *cis*-fused **1** as products, except for **7d** which yielded **1d** and *epi*-**1d**. The relative stereochemistries of **1a**–**n** thus obtained were deduced by NOE studies and, in some cases, further confirmed by X-ray crystallographic analyses.

Scheme 3. Synthesis of α-Diazo-β-hydroxyketones 1



We first examined the diazoketone decomposition of **1a** with rhodium catalysts **9a**–**d** of different electronic properties (Table 1). Uniformly, bicyclo[4.3.1]nonanedione **2a** resulting from 1,2-

Table 1. Screening of Catalysts



entry	Rh catalyst		yield (%)
1	$Rh_2(O_2CCF_3)_4$	**9a**	69
2	$Rh_2(OAc)_4$	**9b**	78
3	$Rh_2(O_2CC_7H_{15})_4$	**9c**	58
4	$Rh_2(cap)_4$	**9d**	no reaction

alkyl migration via pathway A was obtained, in up to 78% yield (Scheme 2), except for **9d** (dirhodium tetracaprolactamate), which was unable to promote the diazo decomposition. No product arising from pathway B was observed.

Similarly, bicyclic α-diazo-β-hydroxyketones **1b**–**n** were treated with either catalyst **9a** or **9b**, and the results are summarized in Table 2. The rhodium-catalyzed decomposition of most diazoketones **1** examined proceeded to rearrangement via pathway A leading to bridged bicyclic compounds **2** as the major products. A variety of bicyclo[*m.n.*1]cycloalkanones were obtained, including bicyclo[3.2.1]octanediones **2c**, **2h**; bicyclo-[4.2.1]nonanones **2b**, **2f**, **2j**, **2k**, **2l**, **2n**; bicyclo[3.3.1]nonanone **2i**; and bicyclo[4.3.1]decanones **2a**, **2g**. The structures of all these products were elucidated by NMR spectroscopy and NOE studies. Furthermore, the X-ray crystal structure of **2m** was also obtained to affirm the relative stereochemistries deduced from NOE studies.

The reactions of **1k**–**n** are consistent with the Rh(II)-catalyzed rearrangement being a concerted process, as retention of stereochemistry at the γ-positions of **2k**–**n** is observed. All of these products were obtained in >90% yields except in the reaction of **1m**, in which rearrangement of the rhodium carbene was competitive with a stereoelectronically favorable C–H insertion to the methoxy group, to generate a 60% yield of **10**. This result also provided evidence that the rearrangement occurred via the intermediacy of a rhodium carbene, and not with the metal playing the role of a Lewis acid.[24] In fact, the treatment of **1a** with HCl or with BF_3–Et_2O resulted only in dehydration (see Supporting Information).

Two of the diazoketones (**1b**, **1g**) reacted to generate both rearrangement products, but with a preference for **2**. These results showed that rearrangement via either pathway was stereochemically and conformationally allowed,[25] but pathway A was more favored. Only diazoketones **1d**, *epi*-**1d**, and **1f**

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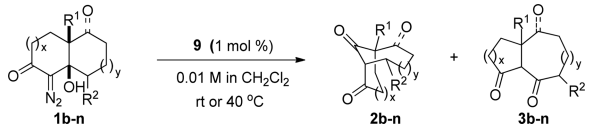
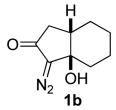
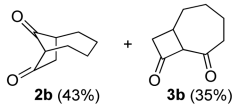
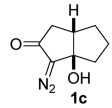
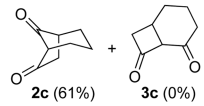
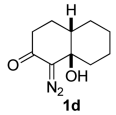
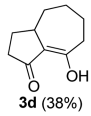
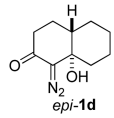
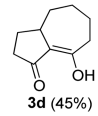
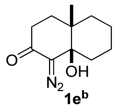
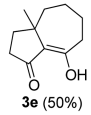
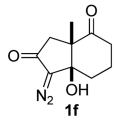
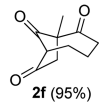
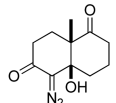
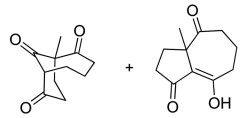
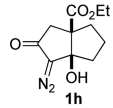
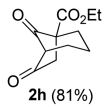
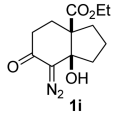
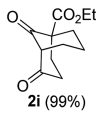
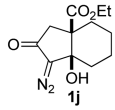
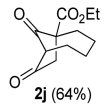
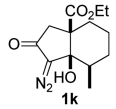
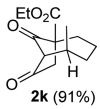
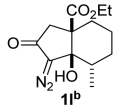
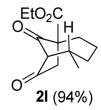
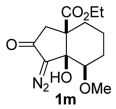
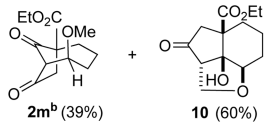
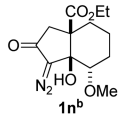
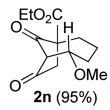
Table 2. Scope of Rhodium-Catalyzed Decomposition of Fused Bicyclic α-Diazo-β-hydroxyketones 1



entry	substrate **1**	catalyst[a]	product (yield)	entry	substrate 1	catalyst[a]	product (yield)
1	 **1b**	**9a**	 **2b** (43%) + **3b** (35%)	2	 **1c**	**9a**	 **2c** (61%) + **3c** (0%)
3	 **1d**	**9b**	 **3d** (38%)	4	 *epi*-**1d**	**9a**	 **3d** (45%)
5	 **1e**[b]	**9a**	 **3e** (50%)	6	 **1f**	**9b**	 **2f** (95%)
7	 **1g**	**9a**	 **2g** (59%) + **3g** (39%)	8	 **1h**	**9a**	 **2h** (81%)
9	 **1i**	**9a**	 **2i** (99%)	10	 **1j**	**9b**	 **2j** (64%)
11	 **1k**	**9a**	 **2k** (91%)	12	 **1l**[b]	**9b**	 **2l** (94%)
13	 **1m**	**9b**	 **2m**[b] (39%) + **10** (60%)	14	 **1n**[b]	**9a**	 **2n** (95%)

[a]The higher of the reaction yields with **9a** or **9b** is shown. [b]X-ray crystal structures obtained.

underwent rearrangement predominantly via pathway B to give **3d** and **3f** as major products. Notably, their isolated yields were relatively low, which could be due to their volatility, as well as their tendency to degradation.[26]

Since the metal carbene is electrophilic, for many substrates in which $R^1 = CO_2Et$ (Scheme 2), pathway A could be rationalized as a migration of the more electron-rich bond *a*, whereas migration of the electron-poor bond *b* would result in intensifying the positive charge developing in the transition state. From comparison of the reaction outcomes of **1a** and **1e**, both being bicyclo[4.4.0]decane derivatives and having similar relative stereochemistry and conformations, whereas the ethoxycarbonyl-substituted bond *b* in **1a** remained inert, it was observed that the comparatively less electron-poor bond *a* migrated to yield **2a**. Similarly, the reaction of **1g** whose bond *b* is electron-poor due to the oxo group in the neighboring ring generated **2g** as the major product.

Ring size is another contributing factor to explain the reaction outcomes, as observed in the reactions of **1b** compared with **1d**. These two compounds have migrating bonds with similar electronic densities, and the reaction of **1b** showed that both migrations are stereoelectronically allowed.[26] However, migration via pathway A predominated for **1b**, probably due to the less favorable transition state for the competitive migration leading to cyclobutanone **3b**. Compounds **1f** and **1j** having electron-withdrawing groups on bond *b* were further disposed to rearrange via pathway A, resulting in **2f** and **2j** as the only products isolated. The rearrangement of **1c** generated only **2c**, probably because the alternative migration would lead to a cyclobutanone, **3c**, that would be even less stable than **3b**.

In summary, our studies on the rhodium-catalyzed decomposition of 15 bicyclic α-diazo-β-hydroxycycloalkanones revealed some key factors that govern the migration of the electrophilic carbene, which can be manipulated to favor bridged bicyclic [*m.n.*1] ketones and to acquire them diastereoselectively, and in moderate to excellent yields. The design and facile synthesis of appropriately substituted, fused bicyclic α-diazo-β-hydroxycycloalkanones, and their rhodium-catalyzed rearrangement under relatively neutral conditions, can furnish a variety of polyfunctionalized bicyclo[*m.n.*1]systems, which could be

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applicable to the synthesis of a number of bioactive natural product scaffolds. The application of this reaction to the synthesis of natural products is being examined, and our results will be reported.[27]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01963.

Experimental procedures, analytical data and ^{1}H, ^{13}C NMR spectra for all new compounds (PDF)
X-ray data (PDF)
Crystallographic data for compound **1e** (CIF)
Crystallographic data for compound **1l** (CIF)
Crystallographic data for compound **1n** (CIF)
Crystallographic data for compound **2n** (CIF)

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Notes

The authors declare no competing financial interest.

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