A Ring Fragmentation Approach to Medium-Sized Cyclic 2-Alkynones
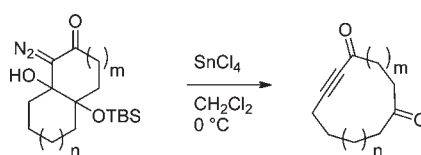
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ABSTRACT

Bicyclic *γ*-silyloxy-*β*-hydroxy-α-diazoketones, in which the C_β–C_γ bond is the ring fusion bond, productively fragment when treated with tin(IV) chloride to provide medium-sized cyclic 2-alkynones. This method provides good to excellent yields of 10-, 11-, and 12-membered alkynone products.

In view of the synthetic utility of ynones, and the fact that medium-sized rings are an underexplored[1] but important[2] structural motif in biologically active compounds, medium-sized cyclic 2-alkynones should be decidedly useful synthetic intermediates. However, these types of compounds have rarely been used in synthetic sequences;[3–7] a fact that can undoubtedly be attributed to a lack of available methods to prepare this structural motif. While functional group manipulations on medium-sized cycloalkynes[8–12] or medium sized cycloalkenes[13] have on occasion been used to prepare cyclic 2-alkynones, methods to directly prepare these compounds from precursors that do not contain a medium-sized ring are limited to the aluminum trichloride promoted intramolecular cyclization of silylalkynes and acid chlorides developed by Utimoto and co-workers.[14] Unfortunately, this strategy suffers from the common limitation of macrocyclization strategies, namely the requirement of high dilution conditions. With this in mind, we became interested in determining whether the Lewis acid promoted fragmentation of cyclic *γ*-silyloxy-*β*-hydroxy-α-diazocarbonyls (e.g., **1** to **2**, Figure 1) we recently discovered[15,16] could be applied to the direct formation of medium-sized cyclic 2-alkynones.
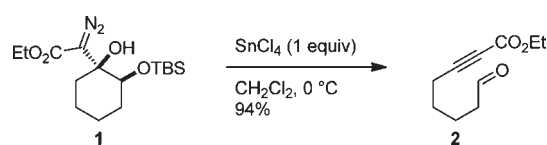

Figure 1. Fragmentation of cyclic *γ*-silyloxy-*β*-hydroxy-α-diazoesters yields aldehyde tethered ynoates.

In this letter we wish to report that bicyclic *γ*-silyloxy-*β*-hydroxy-α-diazoketones, in which the C_β–C_γ bond is the ring fusion bond, productively fragment to provide medium-sized cyclic 2-alkynones in good to excellent yields.[17]

To test our hypothesis that bicyclic diazoketones could be precursors to medium-sized cyclic 2-alkynones we

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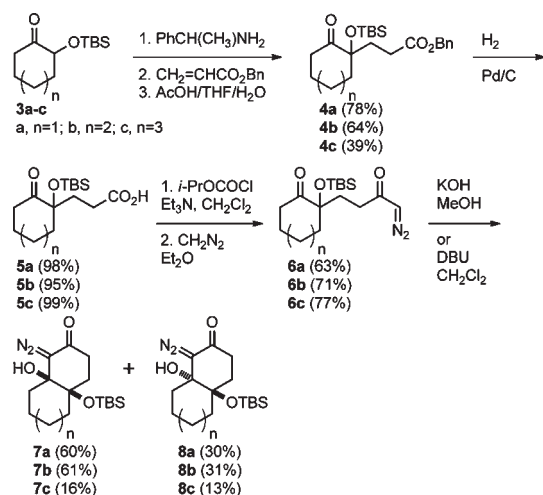
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Scheme 1. Preparation of Bicyclic Fragmentation Substrates

Table 1. Fragmentation of Fused Bicyclic Substrates

substrate	product	yield
7a	9	80%
8a	9	71%
7b	10	99%
8b	10	93%
7c	11	93%
8c	11	80%

prepared the diastereomeric bicyclo[4.4.0]decane diazo compounds **7a** and **8a** by the route shown in Scheme 1. d'Angelo-type[18] conjugate addition provided ester **4a** in 78% yield, and subsequent hydrogenolysis provided the free acid **5a** in 98% yield. The requisite diazo carbonyl **6a** was then formed in 63% yield over two steps from acid **5a** via the corresponding mixed anhydride. It was interesting to note the facility by which the pendant diazo ketone (**6a**) underwent intramolecular aldol-type addition to provide bicycles **7a** and **8a**; this intramolecular reaction was achieved with the mild base DBU over the course of 12 h. Intermolecular aldol-type additions of diazo carbonyl compounds to ketones require the generation of a lithiated diazo species, which is most often formed by deprotonation of the corresponding diazo carbonyl with either *n*-butyl lithium or LDA.[19,20] Due to their greater electrophilicity, aldehydes do react with diazo carbonyl compounds in the presence of DBU,[21] and in our case the proximity of the reacting partners likely makes the aldol-type addition more favorable. Potassium hydroxide in methanol induced the ring closure[22] more efficiently and

provided bicycles **7a** and **8a** as a separable mixture of diastereomers in 60% and 30% yield respectively after only 15 min.[23]

With the requisite fragmentation precursors in hand, we turned our attention to the fragmentation reaction. Treating the cis-fused bicyclo[4.4.0]decane diazo **7a** with 1 mol equiv of SnCl$_4$ at 0 °C resulted in observable gas evolution and provided essentially pure cyclodec-5-yne-1,4-dione (**9**, Table 1) in near-quantitative yield as determined by ^{1}H and

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(23) The relative stereochemistry of diastereomer **7a** and **8a** were easily distinguishable by NMR. The conformational flexibility of cis-fused bicyclic **7a** led to broad signals in the ^{1}H and ^{13}C NMR spectra, which sharpened upon warming. Trans-fused diastereomer **8a**, on the other hand, had sharp signals in the ^{1}H and ^{13}C NMR spectra at room temperature. The structures of the other diastereomers were assigned by analogy based on the following consistent observations: (a) the hydroxyl proton appeared further downfield in each bicyclic structure assigned as cis-fused, presumably due to intramolecular hydrogen bonding with the adjacent silyl ether; (b) the methyl groups of the silyl ether showed a greater difference in chemical shift for the bicycles assigned as trans-fused compared to the cis-fused diastereomers.

^{13}C NMR analysis. Purification resulted in some compound loss, and isolation by chromatography returned cyclic ynone **9** in 80% yield. The trans-fused diastereomer **8a** also productively fragmented to give alkyne **9** in 71% yield.

Applying the same sequence of reactions shown in Scheme 1 to the corresponding 2-silyloxycycloheptanone (**3b**) and 2-silyloxycyclooctanone (**3c**) provided the diazo bicyclo[5.4.0]undecane and bicyclo[6.4.0]dodecane systems (**7b**, **8b** and **7c**, **8c**; Table 1) respectively. While the intramolecular cyclization of diazo compound **6b** occurred in high yield (92%) to give the expected diastereomeric aldol-products **7b** and **8b**, the cyclization of diazo compound **6c** did not go to completion. Under the reaction conditions this latter system existed as an equilibrium mixture of the starting material **6c** and the two diastereomeric products (**7c** and **8c**) in a 4.6 to 1.2 to 1 ratio. Separating these compounds was trivial, and the isolated bicyclic products were stable once removed from the basic reaction conditions. However, resubjecting bicycle **7c** to the cyclization reaction conditions provided the same equilibrium mixture of starting material and diastereomeric products, which highlights the reversibility of this aldol-type addition reaction. Attempts to shift the equilibrium toward the ring closed products by changing the solvent or base, or by trapping the bicyclic products as the silyl protected tertiary alcohols, failed. It seems likely that transannular interactions in the bicyclo[6.4.0]dodecane system make the ring closed form less favorable at equilibrium.

Scheme 2. Preparation of Bicyclo[4.3.0]nonane Fragmentation Precursor
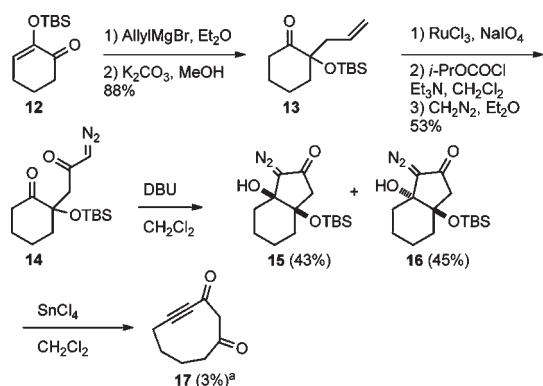

^{a} Compound **17** appears to decompose during purification. Based on NMR analysis of crude reaction mixture, the initial yield was estimated at 40%.

Both the cis (**7b**) and trans (**8b**) diastereomers of the bicyclo[5.4.0]undecane system productively fragmented to provide cycloundec-5-yne-1,4-dione (**10**) in 99% and 93% yield respectively after purification. The larger bicyclo[6.4.0]dodecane systems (**7c** and **8c**) were also competent fragmentation substrates and provided cyclododec-5-yne-1,4-dione (**11**) in 93% and 80% yield respectively after purification.

In order to extend the utility of this transformation we examined the possibility of varying the size of the diazo containing ring, which would allow a variety of different

medium-sized rings to be formed from a common 5- or 6-membered ring precursor. Our synthetic routes to the bicyclo[4.3.0]nonane systems **15** and **16** and bicyclo[5.4.0]undecane systems **20a** and **21a**, in which the diazo functional group resides on a 5- and 7-membered ring respectively, are shown in Schemes 2 and 3. The known[24] 2-silyloxycyclohex-2-enone (**12**) was converted in two steps to α-silyloxy ketone **13** by Grignard addition followed by base catalyzed silyl migration.[25] The olefin was oxidatively cleaved to the carboxylic acid, which was subsequently converted to diazo ketone **14** under standard conditions. Diazo compound **14** smoothly cyclized to diastereomeric bicycles **15** and **16** in 43 and 45% yield respectively. Fragmentation of **15** and **16** provided complex mixtures which appeared to contain ynone **17** in up to 40% yield, but the desired product was isolated in at most 3% yield. Ynone **17** proved to be unstable and upon standing decomposed to an intractable mixture of products. It is not clear at this point if the low yield obtained of ynone **17** is due to an unproductive fragmentation or the inherent instability of **17**.

Scheme 3. Preparation and Fragmentation of Bicyclo-[5.4.0]undecane Ring System
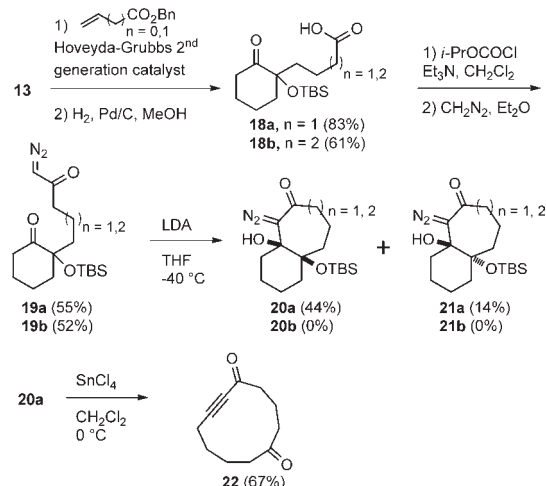
Diazo compounds **20a** and **21a** were prepared from ketone **13** by cross metathesis[26,27] to incorporate the requisite side chain functionality and subsequent simultaneous reduction of the alkene and hydrogenolysis of the benzyl ester to provide acid **18a**. Incorporation of the diazo functionality under standard conditions proceeded as expected to provide diazo ketone **19a**. Subsequent intramolecular aldol-type cyclization to form the 7-membered ring failed in the presence of DBU and KOH in methanol, but diazo compound **19a** did provide the expected cis- and trans-fused bicycles **20a** and **21a** in 44% and 14% yield

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respectively upon treatment with LDA. Fragmentation of bicycle **20a** with $SnCl_4$ returned cycloundec-6-yne-1,5-dione (**22**) in 67% yield. Ynone **22** differs from ynone **10** by the relative positions of the carbonyls. Attempts to apply this same sequence to the preparation of the bicyclo-[6.4.0]dodecane system (**20b** and **21b**), in which the diazo resides on an 8-member ring, were also made. Although the linear diazo precursor **19b** was formed without incident, all attempts to induce cyclization failed to yield any of the desired bicyclic products. We suspect that in this case the unfavorable equilibrium noted above for the closure of diazo compound **6c** is compounded by the fact that 8-member rings are inherently more difficult to form,[28] which prevents a productive cyclization from occurring.

The preliminary results presented here demonstrate that bicyclic γ-silyloxy-β-hydroxy-α-diazoketones are competent fragmentation substrates that can provide access to 10-, 11-, and 12-membered cyclo 2-alkynone products in good to excellent yields. It is not clear if the low yield obtained for the 9-membered cyclo 2-alkynone (**17**) is an inherent limitation of this method to form 9-membered ynones, or if this low yield is due to the instability of **17** under the reaction conditions. Further studies of this medium-sized ring forming reaction and applications of this method toward the synthesis of medium-ring containing natural products are underway and will be disclosed in future publications.

Supporting Information Available. Experimental details and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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