JOC The Journal of Organic Chemistry

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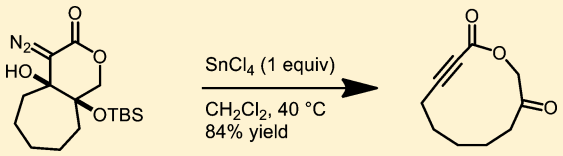
Fragmentation of Bicyclic γ-Silyloxy-β-hydroxy-α-diazolactones as an Approach to Ynolides

Ali Bayir and Matthias Brewer*

Department of Chemistry, The University of Vermont, 82 University Place, Burlington, Vermont 05405, United States

Supporting Information

ABSTRACT: Medium-sized ynolides were prepared by the Lewis acid-mediated fragmentation of bicyclic γ-silyloxy-β-hydroxy-α-diazolactones in which the Cβ−Cγ bond is the ring fusion bond. Although these lactone fragmentation substrates reacted somewhat less efficiently than their carbocyclic counterparts, the fragmentation provided 11-membered ynolides in up to 84% yield. Unlike prior fragmentations of similar substrates, elevated temperatures were required to obtain optimum yields of the ynolide products. The ynolides reported herein have ring sizes of 10 or 11, which are the smallest reported to date.

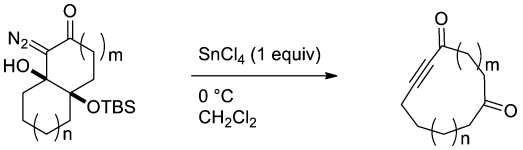


INTRODUCTION

Medium and large rings are common scaffolds in biologically active compounds, and there is growing interest in exploring macrocycles in therapeutic drug discovery programs.[1−4] Thus, the development of methods to prepare these structures is an important and ongoing area of research.[2,3] Large-ring lactones that contain an alkyne within the ring (i.e., ynolides[5,6]) are not common species but have proven to be useful synthetic intermediates in a number of macrolide natural product syntheses. For example, Smith and Malamas[7] subjected an ynolide intermediate to partial reduction as a way to stereoselectively form a *cis*-alkene in their synthesis of *cis*-normethyljatropholactone. Macrolactonization of alkynoates followed by partial reduction has also been used in the syntheses of phorboxazole B[8−10] and laulimalide[11−20] as a way to circumvent isomerization of the requisite *cis*-enoate during the macrolactonization step. In addition, Danishefsky and co-workers took advantage of ynolides as Diels−Alder dienophiles in their approach to resorcinylic fused macrolides.[5,6] These useful synthetic intermediates have been typically prepared through conventional macrocycle formation techniques, namely, macrolactonization and alkene or alkyne ring-closing metathesis.[21] In addition, Ogasawara and co-workers[22] reported a Pd-catalyzed carbomacrolactonization procedure that provides moderate yields of ynolides that are 15-membered or larger. Unfortunately, all of these strategies suffer from the common limitation of macrocyclization strategies, namely, the requirement of high-dilution conditions. To the best of our knowledge, no ynolides having a ring size smaller than 14 have been reported.

We recently disclosed that bicyclic γ-silyloxy-β-hydroxy-α-diazoketones in which the Cβ-Cγ bond is the ring fusion bond fragment in the presence of a Lewis acid to provide 10-, 11-, and 12-membered cyclic 2-alkynones in good to excellent yields (Scheme 1).[23] In view of the fact that γ-silyloxy-β-hydroxy-α-diazoesters fragment as efficiently as their ketone analogues,[24,25] we sought to extend this methodology to the preparation of the corresponding medium- and large-ring ynoates by fragmentation of bicyclic diazo lactones. While ultimately successful in delivering 10- and 11-membered ynolides, the fragmentation of these bicyclic lactones was not as straightforward as the fragmentation of the corresponding ketone species, and we describe our results herein.

Scheme 1. Formation of Medium- and Large-Ring Ynones



1a; n=1, m=1 — **2a**; 80%
1b; n=2, m=1 — **2b**; 99%
1c; n=3, m=1 — **2c**; 93%
1d; n=1, m=0 — **2d**; 3%
1e; n=1, m=2 — **2e**; 67%

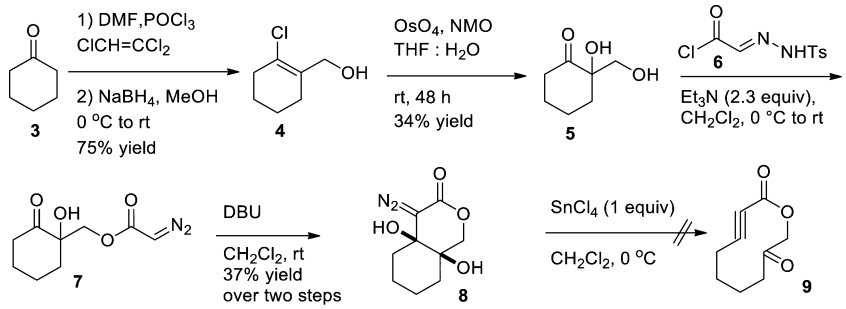
RESULTS AND DISCUSSION

Our initial target for these studies was 10-membered ynolide **9** that we envisioned would come from fragmentation of diazo lactone **8**, which we prepared as shown in Scheme 2. Formylation of cyclohexanone with the Vilsmeier reagent[26] followed by reduction with sodium borohydride[27] gave allylic alcohol **4** in 75% yield over the two steps. Subsequent dihydroxylation with osmium tetroxide provided 1,2-ketodiol **5** in an unoptimized yield of 34%. Reaction of **5** with *p*-toluenesulfonylhydrazone glyoxylic acid chloride (**6**)[28] provided diazoester **7**, which was then treated with DBU to effect an intramolecular aldol addition providing the requisite bicyclic diazo lactone **8** in 37% yield over two steps.[29] Unfortunately, subjecting diazo **8** to the standard fragmentation conditions led only to the formation of an insoluble precipitate; none of the desired fragmentation product was observed. All of the

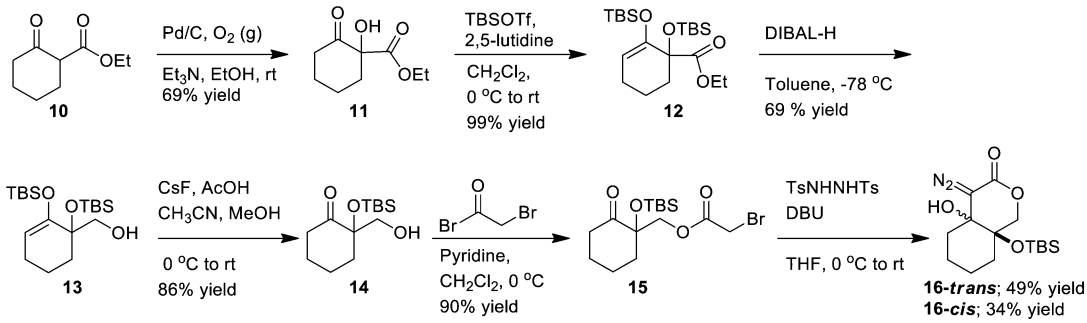
Received: March 18, 2014
Published: June 12, 2014

   dx.doi.org/10.1021/jo500634d | J. Org. Chem. 2014, 79, 6037−6046

Scheme 2. Synthetic Route to Bicyclic β,γ-Dihydroxy-α-diazolactone 8



Scheme 3. Synthesis of Bicyclic Diazo Lactone Fragmentation Precursors 16



fragmentation substrates we previously studied had the γ-oxygen protected as a silyl ether, and with this in mind we attempted to convert diol **5** into the bis(*tert*-butyldimethylsilyl) ether and then selectively deprotect the primary alcohol. Unfortunately, these attempts were not successful.

Ultimately, we prepared γ-silyloxy-β-hydroxy-α-diazolactone **16** by the route shown in Scheme 3. Pd-mediated α-oxygenation[30] of commercially available ethyl 2-oxocyclohexanecarboxylate (**10**) gave α-hydroxy-β-keto ester **11**, which was converted into bis(silyl ether) **12** in which the ketone is conveniently protected as the silyl enol ether. Reduction of the ester with DIBAL-H and subsequent selective cleavage of the silyl enol ether with CsF in acetic acid provided keto alcohol **14**, and acylation of the primary alcohol with bromoacetyl bromide gave bromoacetate **15**. Treatment of **15** with *N,N′*-ditosylhydrazine[31] in the presence of DBU provided the corresponding diazo ester, which spontaneously cyclized to give diazo lactones **16-*trans*** and **16-*cis*** as separable diastereomers.[32]

In view of the high yields we observed for the fragmentation of bicyclic diazo ketones (Scheme 1) and acyclic diazo esters,[25] we were surprised to observe that subjecting diazo lactones **16-*trans*** and **16-*cis*** to the standard fragmentation conditions (i.e., 1 equiv of $SnCl_4$ at 0 °C) provided cyclic ynoate **9** (Figure 1) in only 10% and 12% yield, respectively. We thought that hydrolysis of the strained ynoate might be a facile reaction that would complicate isolation, but carrying out the fragmentation in the presence of molecular sieves did not improve the reaction outcome. We next assessed the ability of other Lewis acids to mediate the fragmentation and found that zinc chloride provided no reaction while indium triflate gave a mixture of epoxide **17** in 5% yield and diene **18** in 31% yield (Figure 1). Treating the fragmentation precursor with $BF_3\cdot OEt_2$ in acetonitrile at 0 °C provided the desired product **9** in only 6% isolated yield. To buffer against any acid that might be formed over the course of the $BF_3\cdot OEt_2$-mediated reaction, we included a proton sponge in the mixture, but this did not provide an increase in the yield. Interestingly, when $BF_3\cdot OEt_2$ was added to a −78 °C solution of the fragmentation precursor in dichloromethane, none of the desired product was formed. Instead, desilylated diene **19**, which had not been observed previously, was formed as the major product. With this in mind, we attempted the fragmentation with $SnCl_4$ at both −78 °C and room temperature. At low temperature the desired product was formed only as a minor component of a complex mixture, but treating the *cis*-fused fragmentation precursor **16-*cis*** with 1 equiv of $SnCl_4$ at room temperature provided the desired lactone product in 21% yield. Ultimately, we discovered that adding **16-*trans*** or **16-*cis*** to a refluxing solution of $SnCl_4$ in dichloromethane provided the desired product in 17% or 33% yield, respectively. Crystallization of **9** from cold methanol provided crystalline material, and the structure of **9** was further confirmed by single-crystal X-ray diffraction, which showed the alkyne to be distorted from linearity by approximately 10°.[33] This distortion is consistent with values computed for cyclodecyne.[34]

In considering why diazo lactone **16-*cis*** fragmented in lower yields than its carbocyclic counterpart **1a** (Scheme 1), we hypothesized that the proximity of the inductively electron-withdrawing ester to the bond that breaks might slow the bond-breaking step and increase the likelihood of competitive side reactions. To evaluate this supposition, we prepared diazoacetate **21** (Scheme 4),[35] which has the ester and the breaking bond in the same relative position as in **16**. Subjecting this

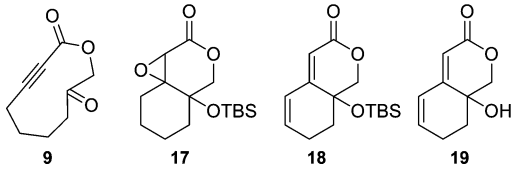


Figure 1. Products observed in various attempts to fragment diazo **16**.

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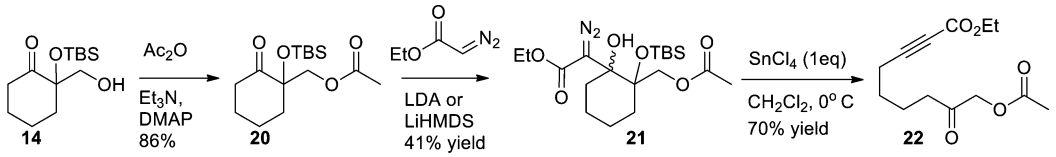
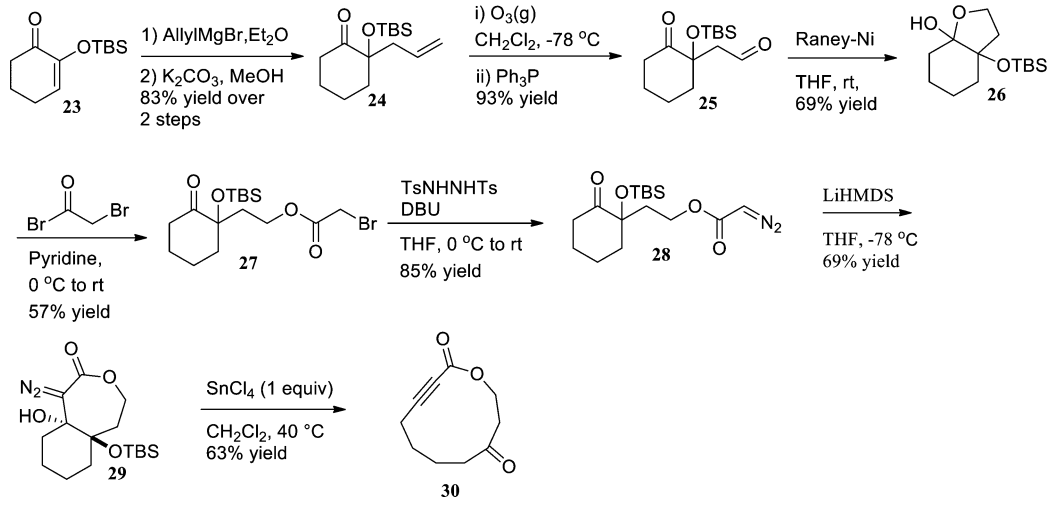
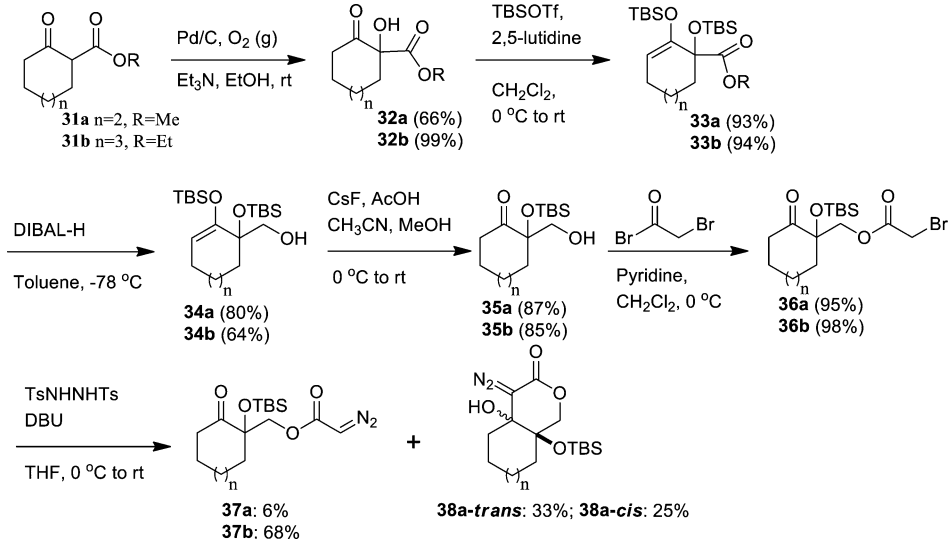
Scheme 4. Preparation of Acetate Diazo Ester 21 and Its Fragmentation



Scheme 5. Preparation and Fragmentation of Diazo Lactone 29



Scheme 6. Preparation of Diazo Lactone 38a and Diazo Ester 37b

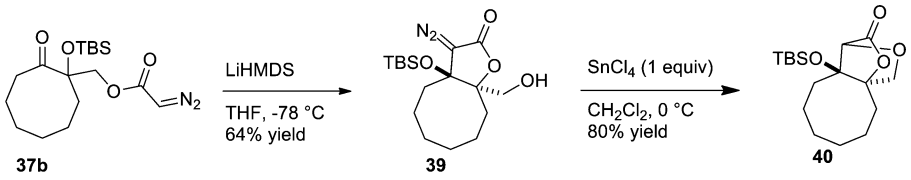


compound to the standard fragmentation conditions resulted in a smooth transformation to give ynoate **22** in 70% isolated yield. This result indicates that the low yields observed in the fragmentation of **16** are most likely not due to the position of the electron-withdrawing ester.

To see whether the ring size affected the outcome of the fragmentation reaction, we envisioned preparing homologues of diazo lactone **16** in which either the carbocyclic ring or the ring containing the diazo ester was enlarged. With this in mind, we prepared diazo lactone **29** (Scheme 5), in which the ring bearing the diazo group has been enlarged by one methylene unit. Addition of allylmagnesium bromide to the known 2-silyloxycyclohex-2-enone **23** provided a tertiary alcohol that was converted into ketone **24** via a base-catalyzed silyl transfer reaction.[36] Ozonolysis of alkene **24** provided aldehyde **25** in high yield, and selective reduction of the aldehyde with Raney nickel[37] provided the primary alcohol as hemiacetal **26**. The hemiacetal was converted into diazo ester **28** by acylation and subsequent diazotization as described for the preparation of **16** (Scheme 3), but in this case cyclization did not spontaneously occur. However, treatment of **28** with LiHMDS under dilute conditions at low temperatures effected the ring closure and gave a single diastereomer (tentatively assigned as *trans*) of the desired bicyclic fragmentation precursor **29** in 69% yield. Upon treatment with 1 equiv of $SnCl_4$ at 0 °C, diazo **29** fragmented to provide the 11-membered cyclic ynoate **30** in 50% yield. The yield of **30** increased to 63% when the reaction was run at reflux temperature. The higher yields obtained for this enlarged ring

dx.doi.org/10.1021/jo500634d | J. Org. Chem. 2014, 79, 6037−6046

Scheme 7. Base-Mediated Formation and Subsequent Reaction of Diazo Ester 39



37b 39 40

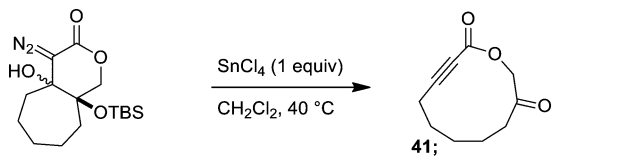
system seem to indicate that ring size does indeed play a role in the fragmentation outcome.

We next focused on preparing homologues of **16** (Scheme 3) in which the carbocyclic ring was expanded by one or two methylene units by routes analogues to that used for the preparation of **16**. While diazotization of **36a** (n = 2; Scheme 6) led directly to the diastereomeric bicyclic fragmentation precursors **38a-*trans*** and **38a-*cis***, diazotization of **36b** (n = 3) provided the linear diazo species **37b**. Interestingly, in our prior work with the carbocyclic derivatives of these diazo compounds[23] we noted a similar difficulty in forming the bicyclo-[4.6.0] ring system (**1c**, Scheme 1) and observed that at equilibrium the system exists predominantly in the ring-opened form. Attempts to convert **37b** to its ring-closed form by treatment with DBU failed to yield any desired product.

In an attempt to drive the ring closure under more strongly basic and nonequilibrating conditions, we treated **37b** with LiHMDS to provide a material we initially assigned as the homologue of **38a-*cis*** in 64% yield. However, attempts to fragment this latter material did not provide any desired ynolide product, which was surprising in view of the fact that the carbocyclic variant **1c** (Scheme 1) had fragmented in 93% yield.[23] Ultimately, full characterization of the cyclization product revealed that it was in fact the spectroscopically similar diazo lactone **39** (Scheme 7). Although the desired ring closure had occurred, the initially formed alkoxide product apparently underwent a subsequent silyl migration and translactonization. We have never encountered silyl migration in any of our prior work with similar substrates, and it is unclear why it occurred in this case. However, considering that the ring-closure step itself is unfavorable, it seems likely that in this case silyl migration is promoted by unfavorable steric interactions in the ring-closed form. This rearrangement is an unanticipated complication that is not possible in the carbocyclic series. Unfortunately, attempts to circumvent this rearrangement have not been fruitful. Subjecting diazo lactone **39** to the standard ring-fragmentation conditions returned cyclic ether **40** in 80% yield.

We were pleased to find that upon treatment with $SnCl_4$ at 0 °C, diazo lactone **38a-*cis*** productively fragmented to give 11-membered cyclic ynoate **41** in 64% yield, while **38a-*trans*** provided the desired product in 57% yield. At 40 °C these yields increased to 84% and 67%, respectively (Scheme 8). These results further support the notion that ring size is an important factor affecting the fragmentation outcome.

Scheme 8. Reactions of Bicyclic Diazo Lactones 38a and 38b



38a-*cis*
38a-*trans*

41;
84% yield from **38a-*cis***
67% yield from **38a-*trans***

CONCLUSIONS

While bicyclo[5.4.0] and -[4.5.0] diazo systems **29** and **38a-*cis*** fragmented to provide the corresponding 11-membered ynolides in 63% and 84% yield respectively, the bicyclo[4.4.0] homologue **16-*cis*** provided the 10-membered ynolide in at best 33% yield; as observed in our prior studies,[23] the corresponding *trans*-fused bicyclic diazo lactones consistently fragmented in slightly lower yields. Attempts to form the bicyclo[4.6.0] diazo lactone system failed because of an unexpected silyl migration and translactonization event. At this point it is clear that the fragmentation of bicyclic diazo lactones to provide ynolide products is not as straightforward or high-yielding as the fragmentation of their carbocyclic counterparts, which gives large-ring ynones (Scheme 1). It is unclear why these systems behave differently, and computational studies to shed light on this interesting reactivity trend are planned. It is noteworthy that the ynolides presented here have the smallest ring size reported to date; all prior examples of this structural motif are 14-membered[2] or larger.

EXPERIMENTAL SECTION[38]

(2-Chlorocyclohex-1-en-1-yl)methanol (4). $POCl_3$ (9.32 mL, 0.1 mmol) was added slowly to a 0 °C solution of DMF (10.84 mL, 0.14 mmol) in trichloroethylene (20 mL) at such a rate as to maintain the reaction temperature below 10 °C. The mixture was allowed to warm to room temperature, and cyclohexanone (11.4 mL, 0.11 mmol) in trichloroethylene (25 mL) was added at such a rate as to maintain the reaction temperature below 60 °C; the reaction mixture was then maintained at 55−60 °C for 3 h. The mixture was cooled in an ice bath, and a solution of NaOAc (40 g) in water (94 mL) was added slowly over 1 h, keeping the reaction temperature below 35 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with brine (2 × 200 mL) and water (200 mL), and dried over anhydrous Na_2SO_4. Anhydrous NaOAc (1 g) was added to the dried organic layer, and the solvent was reduced in vacuo. The residue was dissolved in 50 mL of MeOH, and the pH was adjusted to 8 by addition of a 10% aqueous NaOH solution at ice-bath temperature. $NaBH_4$ powder (3.78 g, 0.1 mmol) was added in small portions, and the mixture was stirred overnight at room temperature. The mixture was treated with 90 mL of water and extracted with EtOAc (3 × 90 mL). The organic layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the crude product was purified via flash silica gel chromatography (hexanes/EtOAc 20:1 to 5:1; R_f = 0.62 in hexanes/EtOAc 2:1) to afford the title compound in 75% yield (10.99 g). The ^1H and ^{13}C NMR data for this material matched previously reported values.[26,27]

2-Hydroxy-2-(hydroxymethyl)cyclohexanone (5). OsO_4 (2.78 g, 0.27 mmol) was added to a room-temperature solution of (2-chlorocyclohex-1-en-1-yl)methanol (**4**) (2 g, 13.67 mmol) and NMO (3.20 g, 27.33 mmol) in a mixture of THF (46 mL) and water (23 mL), and the mixture was stirred for 48 h. Then Na_2SO_3 (10 g) was added, and the mixture was stirred for an additional hour. The mixture was filtered through a pad of silica gel, which was then washed with EtOAc (150 mL). The solvents were removed in vacuo to provide an oily residue that was purified by silica gel flash chromatography (hexanes/EtOAc 2:1; R_f = 0.23 in hexanes/EtOAc 1:1) to afford the known compound 2-hydroxy-2-(hydroxymethyl)cyclohexanone as a

dx.doi.org/10.1021/jo500634d | J. Org. Chem. 2014, 79, 6037−6046

colorless oil (0.66 g, 34%). The ^{1}H and ^{13}C NMR data for this material matched previously reported values.[39,40]

(1-Hydroxy-2-oxocyclohexyl)methyl 2-Diazoacetate (7). 2-Hydroxy-2-(hydroxymethyl)cyclohexanone (**5**) (0.15 g, 1.03 mmol) in CH_2Cl_2 (1 mL) was added to a 0 °C solution of *p*-toluenesulfonylhydrazone glyoxylic acid chloride (**6**)[28,41] (0.29 g, 1.14 mmol) in CH_2Cl_2 (10 mL) to provide a light-yellow solution. Et_3N (0.35 mL, 2.30 mmol) in CH_2Cl_2 (0.7 mL) was added dropwise, causing the color of the reaction mixture to become deep yellow. The reaction mixture was allowed to warm in the ice bath to room temperature over a period of 4 h, at which point the solvent was removed in vacuo. The solid residue was suspended in toluene (10 mL) and mixed with Florisil (1 g), and the solids were removed by filtration and rinsed with toluene (75 mL). The filtrate was concentrated under reduced pressure, and the crude product was used in the next step for the formation of **8** without further purification (R_f = 0.50 in hexanes/EtOAc 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (bs, 1H), 4.72 (d, J = 11.65 Hz, 1H), 4.21 (d, J = 11.72 Hz, 1H), 4.12 (s, 1H), 2.60−2.58 (m, 2H), 2.26−2.22 (m, 1H), 2.16−2.12 (m, 1H), 1.85−1.84 (m, 1H), 1.71−1.65 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 166.6, 78.2, 67.9, 46.5, 38.4, 38.1, 27.7, 22.7; IR (film) 3500 (br), 2940.1, 2866.2, 2111.7, 1692.9, 1453.2, 1389.7, 1337.9, 1246.2, 1175.2, 1128.1, 1050.7, 1008.1, 851.2, 738.6 cm^{-1}.

***rel*-(4a*S*,8a*R*)-4-Diazo-4a,8a-dihydroxyhexahydro-1*H*-isochromen-3(4*H*)-one (8).** DBU (0.15 mL, 0.97 mmol) was added dropwise to a solution of diazoester **7** (0.14 g, 0.65 mmol) in CH_2Cl_2 (13 mL) at room temperature, and the mixture was stirred for 12 h, at which point saturated aqueous NH_4Cl (15 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure to give an orange-red oily residue. Flash column chromatography (hexanes/EtOAc 3:1; R_f = 0.21 in hexanes/EtOAc 1:1) on a Davisil solid support provided the title bicyclic diazo lactone as a yellow solid in 37% yield (0.081 g) over two steps starting from **5**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (d, J = 11.4 Hz, 1H), 4.17 (bs, 1H), 3.90 (d, J = 10.3 Hz, 1H), 3.15 (s, 1H), 1.96 (t, J = 11.6 Hz, 1H), 1.82−165 (m, 5H), 1.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 71.5, 70.9, 68.2, 63.0, 32.6, 30.8, 22.4, 20.5; IR (film) 3371.6, 2935.9, 2106.1, 1659.4, 1392.3, 1298.60 cm^{-1}; MS (ESI) calcd for $[C_9H_{12}N_2O_4H]^+$ 213.08698, found 213.08715.

4-Oxacyclodecyne-3,6-dione (9). *Representative Experimental Procedure 1: Fragmentation Reactions Conducted at 0 °C and at Room Temperature.* A 1 M solution of $SnCl_4$ in CH_2Cl_2 (0.25 mL, 0.25 mmol) was added in a steady stream to a solution of bicyclic diazo lactone ***16-cis*** (0.0826 g, 0.25 mmol) in dry CH_2Cl_2 (6.3 mL) at 0 °C. The yellow solution initially turned colorless and then became deep yellow in color. After 30 min, 5% aqueous $NaHCO_3$ (12 mL) was added, and the mixture was transferred with the aid of CH_2Cl_2 (10 mL) into a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and dried over anhydrous $NaSO_4$. The solvents were removed in vacuo, and the residue was subjected to flash column chromatography on Davisil (hexanes/EtOAc 10:1, 6:1, 1:1; R_f = 0.13 in hexanes/EtOAc 1:1) to afford pure cyclic ynoate **9** in 12% yield (0.005 g). The yield increased to 21% (0.0089 g) when the same procedure was followed at room temperature. According to the same procedure at 0 °C, diazo lactone ***16-trans*** provided the title compound in 10% yield as determined via NMR analysis using mesitylene as an internal standard. Crystallization from cold methanol provided crystals suitable for X-ray crystallography (mp 95 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (s, 2H), 2.53−2.50 (m, 2H), 2.39 (t, J = 6.0 Hz, 2H), 2.04−1.99 (m, 2H), 1.86−1.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 153.5, 99.9, 74.7, 72.2, 41.0, 25.5, 24.6, 19.7; IR (film) 2923.3, 2854.8, 2229.8, 1734.1, 1558.6, 1454.4, 1376.3, 1280.8, 1194.9, 1124.6, 1078.3, 1037.7, 985.7, 922.0, 738.8 cm^{-1}; MS (ESI) calcd for $[C_9H_{10}O_3H]^+$ 167.07027, found 167.07016.

Representative Experimental Procedure 2: Fragmentation Reactions Conducted at 40 °C. A 1 M solution of $SnCl_4$ in CH_2Cl_2 (0.25 mL, 0.25 mmol) was added to refluxing CH_2Cl_2 (4 mL), and bicyclic diazo lactone ***16-cis*** (0.0818 g, 0.25 mmol) in dry CH_2Cl_2 (1 mL) was then added in one portion. The vial containing the bicyclic diazo lactone was rinsed with 1.3 mL of CH_2Cl_2, and this too was added to the refluxing reaction mixture. The mixture was held at reflux for 10 min and then cooled in an ice bath, at which point 5% aqueous $NaHCO_3$ (8 mL) was added and the mixture was transferred with the aid of CH_2Cl_2 (10 mL) into a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. The solvents were removed in vacuo, and the residue was subjected to flash column chromatography on Davisil (hexanes/EtOAc 10:1, 6:1, 1:1; R_f = 0.13 in hexanes/EtOAc 1:1) to afford pure cyclic ynoate **9** in 33% yield (0.0134 g). According to the same procedure, diazo lactone ***16-trans*** provided the title compound in 17% yield as determined by NMR analysis using mesitylene as an internal standard.

Ethyl 1-Hydroxy-2-oxocyclohexanecarboxylate (11). A mixture of commercially available ethyl 2-oxocyclohexanecarboxylate (**10**) (4.69 mL, 29.4 mmol), 10% Pd/carbon (1.5 g), and Et_3N (4.5 mL, 32.3 mmol) in EtOH (150 mL) was attached to a balloon of O_2 via a three-way stopcock. The air in the reaction flask was evacuated via an aspirator and replaced with oxygen three times, and the reaction mixture was stirred under O_2 overnight. The mixture was filtered through Celite, and the solids were rinsed with EtOH (100 mL). The filtrate was concentrated in vacuo, and the oily residue was purified by silica gel flash column chromatography (hexanes/EtOAc 6:1; R_f = 0.35 in hexanes/EtOAc 5:1) to give the α-oxygenated product as a colorless oil in 69% yield (3.77 g). The ^{1}H and ^{13}C NMR spectral data matched previously reported values.[30]

Ethyl 1,2-Bis(*tert*-butyldimethylsilyloxy)cyclohex-2-enecarboxylate (12).[42] 2,5-Lutidine (0.35 g, 3.25 mmol) and TBSOTf (0.86 g, 3.25 mmol) were added sequentially to a 0 °C solution of α-hydroxy-β-ketoester **11** (0.20 g, 1.08 mmol) in CH_2Cl_2 (5 mL). The mixture was allowed to warm to room temperature overnight and was then cooled to 0 °C before the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. Upon removal of the solvent, the filtrate gave an oily residue that was purified by silica gel flash column chromatography (hexanes/Et_2O 40:1; R_f = 0.78 in hexanes/EtOAc 5:1) to give the bis(silyl ether) as a colorless oil in 99% yield (0.44 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (dd, J = 4.9, 3.2 Hz, 1H), 4.19 (qd, J = 10.8, 7.1 Hz, 1H), 4.09 (qd, J = 10.8, 7.2 Hz, 1H), 2.09 (m, 2H), 1.95 (dt, J = 13.2, 3.2 Hz, 1H), 1.85 (dt, J = 13.2, 3.4 Hz, 1H), 1.77−1.68 (m, 1H), 1.62−1.56 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 149.6, 105.9, 78.0, 61.0, 37.0, 26.1, 25.9, 24.1, 18.8, 18.3, 17.8, 14.3, −2.9, −3.0, −4.4, −4.5; MS (ESI) calcd for $[C_{21}H_{42}O_4Si_2Na]^+$ 437.25138, found 437.25164.

(1,2-Bis(*tert*-butyldimethylsilyloxy)cyclohex-2-enyl)methanol (13).[43] DIBAL-H (44.4 mL, 52.97 mmol) was added dropwise to a −78 °C solution of **12** (9.98 g, 24.08 mmol) in toluene (240 mL), and the resulting mixture was stirred for 1 h at −78 °C, transferred to a 0 °C bath, and quenched with 150 mL of saturated potassium sodium tartrate tetrahydrate. The mixture was allowed to warm to room temperature overnight with efficient stirring. The reaction mixture was extracted with EtOAc (3 × 150 mL), and the organic layers were combined, washed with water and brine, and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated in vacuo to give an oily residue that was purified via silica gel flash column chromatography (hexanes/Et_2O 20:1; R_f = 0.68 in hexanes/EtOAc 5:1) to afford the title compound as a colorless oil in 69% yield (6.19 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (t, J = 3.7 Hz, 1H), 3.59 (dd, J = 10.4, 4.5 Hz, 1H), 3.51 (dd, J = 10.5, 8.6 Hz, 1H), 2.10−1.96 (m, 2H), 1.85−1.65 (m, 4H), 1.58−1.51 (m, 1H), 0.94 (s, 9H), 0.87 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 107.5, 75.5, 68.1, 34.6, 26.13, 26.1, 24.5, 18.9, 18.6, 18.4, −2.78, −2.8, −4.2, −4.4; MS (ESI) calcd for $[C_{19}H_{40}O_3Si_2Na]^+$ 395.24082, found 395.24092.

dx.doi.org/10.1021/jo500634d | J. Org. Chem. 2014, 79, 6037−6046

2-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)-cyclohexanone (14).[44] Acetic acid (0.45 g, 0.53 mL, 7.42 mmol) and CsF (0.56 g, 3.7 mmol) were added sequentially to a 0 °C solution of **13** (0.55 g, 1.48 mmol) in a mixture of CH_3CN (21.4 mL) and MeOH (8.6 mL). The mixture was allowed to warm to room temperature overnight and was then recooled to 0 °C and diluted with 20 mL of EtOAc, and saturated $NaHCO_3$ solution was added. The resulting white precipitate was separated via vacuum filtration, and the layers in the filtrate were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL), and the organic layers were combined, washed with saturated $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The solvents were evaporated, and the oily residue was purified by silica gel flash column chromatography (hexanes/EtOAc 8:1; R_f = 0.41 in hexanes/EtOAc 5:1) to give the title compound as an oil in 86% yield (0.33 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (d, J = 7 Hz, 2H), 2.73 (ddd, J = 13.6, 8.8, 5.5 Hz, 1H), 2.36 (t, J = 7.4 Hz, 1H), 2.30 (dt, J = 7.2, 7.0 Hz, 1H), 1.98−1.87 (m, 3H), 1.85−1.73 (m, 2H), 1.66−1.59 (m, 1H), 0.90 (s, 9H), 0.18 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 81.4, 67.4, 39.3, 37.8, 27.7, 26.1, 21.4, 18.7, −2.4, −3.1; MS (ESI) calcd for $[C_{13}H_{26}O_3SiNa]^+$ 281.15434, found 281.15428.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)methyl 2-Bromoacetate (15). Bromoacetyl bromide (0.57 mL, 6.51 mmol) was added dropwise to a 0 °C solution of alcohol **14** (0.56 g, 2.17 mmol) and pyridine (0.44 mL, 5.43 mmol) in dry CH_2Cl_2 (21 mL), and the resulting white suspension was stirred at room temperature for 5 h. The mixture was cooled to 0 °C, and MeOH (0.7 mL) was added, at which point the white suspension became a clear solution. Saturated aqueous NH_4Cl (20 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the organic layers were combined and dried over anhydrous $MgSO_4$. The solvents were removed in vacuo, and the resulting oily residue was purified by flash silica gel column chromatography (hexanes/EtOAc 8:1; R_f = 0.47 in hexanes/EtOAc 5:1) to provide the desired bromoacetate as an oil in 90% yield (0.74 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (d, J = 11.6 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 3.81 (s, 2H), 2.72 (ddd, J = 15.4, 9.9, 5.6 Hz, 1H), 2.32 (td, J = 13.5, 5.6 Hz, 1H), 1.98−1.86 (m, 3H), 1.80−1.74 (m, 2H), 1.68−1.62 (m, 1H), 0.88 (s, 9H), 0.13 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 166.9, 79.5, 68.9, 38.9, 38.1, 27.6, 25.9, 25.6, 21.2, 18.6, −2.4, −3.1; MS (ESI) calcd for $[C_{15}H_{27}BrO_4SiH]^+$ 379.09347, found 379.09340.

8a-(*tert*-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyhexahydro-1*H*-isochromen-3(4*H*)-one (16-*cis* and 16-*trans*).[31] *N*,*N*′-Ditosylhydrazine (3.81 g, 11.19 mmol) was added to a 0 °C solution of bromoacetate **15** (2.12 g, 5.59 mmol) in THF (56 mL), at which point DBU (5.19 mL, 34.6 mmol) was added dropwise. The mixture was stirred at room temperature for 8 h and then cooled to 0 °C, and saturated aqueous $NaHCO_3$ (60 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The organic layers were combined and dried over anhydrous $CaCl_2$, and the solvents were removed by evaporation to give a crude solid product. The crude product was purified via flash column chromatography (hexanes/EtOAc 8:1, 6:1, 4:1, 2:1, 1:1) on a Davisil solid support to provide the bicyclic diazo lactone as two separated diastereomers that had the following spectral data:

*rel-(4aS,8aR)-8a-(tert-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyhexahydro-1H-isochromen-3(4H)-one (**16-cis**).* Yield 0.62 g, 34%; R_f = 0.31 in hexanes/EtOAc 5:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (d, J = 10.2 Hz, 1H), 4.12 (bs, 1H), 2.95 (bs, 1H), 1.98 (bs, 1H), 1.91−1.86 (m, 1H), 1.83−1.73 (m, 2H), 1.71−1.65 (m, 2H), 1.42 (bs, 2H), 0.92 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 72.4, 72.1, 69.7, 63.1, 34.5 (b), 32.0, 25.9, 21.8 (b), 18.4, −2.2, −2.5 (b); IR (film) 2928.1, 2857.7, 2102.5, 1690.7, 1471.7, 1391.7 cm^{-1}; MS (ESI) calcd for $[C_{15}H_{26}N_2O_4SiH]^+$ 327.17346, found 327.17385.

*rel-(4aR,8aR)-8a-(tert-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyhexahydro-1H-isochromen-3(4H)-one (**16-trans**).* Yield 0.90 g, 49%; R_f = 0.45 in hexanes/EtOAc 5:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (d, J = 10.9 Hz, 1H), 3.76 (d, J = 10.9 Hz, 1H), 2.64 (d, J = 1.7 Hz, 1H), 1.94 (dt, J = 14.7, 4.4 Hz, 1H), 1.80−1.67 (m, 5H), 1.61−1.55 (m, 1H), 1.22−1.12 (m, 1H), 0.90 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 75.2, 70.9, 68.4, 61.6, 32.4, 30.0, 25.9, 22.7, 19.5, 18.1, −2.7, −3.2; IR (film) 3538.6, 2952.2, 2859.6, 2103.5, 1699.4, 1465.0, 1388.8, 1302.9 cm^{-1}; MS (ESI) calcd for $[C_{15}H_{26}N_2O_4SiH]^+$ 327.17346, found 327.17401.

Reaction of Diazo Lactone 16-*cis* with Indium Triflate To Provide 17 and 18. A solution of diazo lactone **16-*cis*** (0.100 g, 0.31 mmol) in CH_2Cl_2 (4 mL) was added to a −78 °C suspension of $In(OTf)_3$ (0.173 g, 0.31 mmol, dried in a vacuum oven at 180 °C for 16 h before use) in CH_2Cl_2 (4 mL). The mixture was allowed to warm to room temperature over 2 h, at which point water (8 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated to give an oily residue that was purified by flash column chromatography on Davisil (hexanes/EtOAc 8:1, 5:1, 3:1) to provide epoxide **17** (R_f = 0.46 in hexanes/EtOAc 5:1) in 5% yield (0.005 g) and diene **18** (R_f = 0.21 in hexanes/EtOAc 5:1) in 31% yield (0.027 g) with the following spectral data:

*rel-(11S,5aR,8aR)-5a-(tert-Butyldimethylsilyloxy)-hexahydrooxireno[2,3-d]isochromen-8(8aH)-one (**17**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, J = 12.3 Hz, 1H), 3.93 (d, J = 11.9 Hz, 1H), 3.43 (s, 1H), 2.38 (dt, J = 13.7, 4.2 Hz, 1H), 1.84−1.69 (m, 5H), 1.50−1.43 (m, 2H), 0.90 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 72.6, 71.9, 64.6, 55.9, 32.5, 27.3, 25.9, 23.0, 20.1, 18.5, −2.5, −3.0; IR (film) 2950.3, 2933.9, 2848.9, 1753.4, 1635.7, 1462.1, 1295.3, 1263.4, 1179.5, 1074.4, 957.7, 909.5, 838.1, 778.3, 735.9 cm^{-1}; MS (ESI) calcd for $[C_{15}H_{26}O_4SiH]^+$ 299.16731, found 299.16731.

*8a-(tert-Butyldimethylsilyloxy)-8,8a-dihydro-1H-isochromen-3(7H)-one (**18**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (ddd, J = 9.7, 6.0, 1.9 Hz, 1H), 6.20 (dd, J = 9.9, 2.8 Hz, 1H), 5.69 (s, 1H), 4.31 (d, J = 12.1 Hz, 1H), 4.18 (d, J = 12.1 Hz, 1H), 2.59−2.51 (m, 1H), 2.27 (dt, J = 18.9, 5.4 Hz, 1H), 1.87 (dd, J = 13.2, 4.6 Hz, 1H), 1.47 (ddd, J = 12.9, 11.6, 5.1 Hz, 1H), 0.84 (s, 9H), 0.11 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 151.2, 140.0, 124.6, 113.9, 76.0, 66.4, 32.0, 25.6, 22.2, 18.5, −3.4, −3.9; IR (film) 2956.0, 2929.0, 2856.7, 1725.4, 1631.9, 1472.7, 1462.1, 1290.4, 1250.9, 1250.9, 1222.9, 1201.7, 1161.2, 1114.9, 1060.9, 1028.1, 892.1, 828.5, 777.4 cm^{-1}; MS (ESI) calcd for $[C_{15}H_{24}O_3SiH]^+$ 281.15675, found 281.15654.

8a-Hydroxy-8,8a-dihydro-1*H*-isochromen-3(7*H*)-one (19). $BF_3{\cdot}OEt_2$ (0.045 mL, 0.36 mmol) was added in a steady stream to a solution of bicyclic diazo lactone **16-*trans*** (0.12 g, 0.36 mmol) in dry CH_2Cl_2 (7 mL) at −78 °C. After 1.5 h, distilled water (7 mL) was added at 0 °C, and the mixture was transferred with the aid of CH_2Cl_2 (10 mL) into a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, and the solvents were removed in vacuo. The residue was subjected to flash column chromatography on Davisil (hexanes/EtOAc 2:1, 1:1; R_f = 0.45 in CH_2Cl_2/EtOAc 1:1) to afford **19** in 26% yield (0.0153 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (ddd, J = 11.3, 6.3, 2.2 Hz, 1H), 6.24 (dd, J = 10.3, 2.9 Hz, 1H), 5.71 (s, 1H), 4.34 (d, J = 11.9 Hz, 1H), 4.25 (d, J = 11.8 Hz, 1H), 2.65−2.57 (m, 1H), 2.53 (bs, 1H), 2.33 (dtt, J = 18.8, 5.8, 1.3 Hz, 1H), 1.93 (ddt, J = 13.4, 5.1, 0.8 Hz, 1H), 1.51 (ddd, J = 13.4, 11.6, 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 151.8, 140.7, 124.1, 113.3, 76.3, 64.5, 29.5, 21.9; IR (film) 3394.9 (b), 2920.4, 2854.8, 1720.6, 1694.5, 1681.0, 1624.1, 1455.4, 1288.5, 1248.9, 1229.7, 1101.4, 1057.1, 877.7, 734.9, 710.8 cm^{-1}; MS (ESI) calcd for $[C_9H_{10}O_3H]^+$ 167.07027, found 167.06980.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)methyl Acetate (20).[45] Acetic anhydride (0.43 mL, 4.58 mmol), DMAP (0.0023 g, 0.02 mmol), and Et_3N (0.71 mL, 5.08 mmol) were added sequentially to a 0 °C solution of alcohol **14** (0.26 g, 1 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 2 h at 0 °C, and then water (5 mL) was added. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organics were combined, dried (Na_2SO_4), and concentrated. The product was purified by silica gel flash column chromatography (hexanes/EtOAc

dx.doi.org/10.1021/jo500634d | J. Org. Chem. 2014, 79, 6037−6046

10:1; R_f = 0.42 in hexanes/EtOAc 5:1) to give the keto acetate in 86% yield (0.26 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (d, J = 11.7 Hz, 1H), 4.23 (d, J = 11.7 Hz, 1H), 2.72 (ddd, J = 13.7, 9.5, 5.4 Hz, 1H), 2.33 (ddd, J = 12.7, 6.8, 5.7 Hz, 1H), 2.06 (s, 3H), 1.96−1.85 (m, 3H), 1.82−1.74 (m, 2H), 1.68−1.61 (m, 1H), 0.89 (s, 9H), 0.14 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 170.6, 79.7, 67.4, 38.9, 38.4, 27.6, 25.9, 21.3, 20.9, 18.6, −2.6, −3.2; MS (ESI) calcd for $[C_{15}H_{28}O_4SiH]^+$ 301.18296, found 301.18300.

Ethyl 2-(2-(Acetoxymethyl)-2-(*tert*-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-2-diazoacetate (21). Lithium bis(trimethylsilyl)amide (1 M in THF/ethylbenzene, 0.75 mL, 0.75 mmol) was added dropwise over 1.5 h to a −78 °C solution of ketone **20** (0.20 g, 0.65 mmol) and ethyl diazoacetate (0.08 g, 0.72 mmol) in THF (12 mL). After the mixture was stirred for 30 min at −78 °C, saturated aqueous NH_4Cl (12 mL) was added. The mixture was allowed to warm to room temperature, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL), and the organic layers were combined, washed with brine, and dried over anhydrous $CaCl_2$. The solvents were evaporated, and the crude yellow oily residue was purified via silica gel flash column chromatography (hexanes/Et_2O 7:1, 5:1, 3:1) on a Davisil support to provide the acetate diazoester as two separate diastereomers. Both diastereomers were isolated together with an inseparable unknown impurity. The major diastereomer was obtained in 41% yield (0.14 g) as determined by NMR analysis using mesitylene as an internal standard (R_f = 0.42 in hexanes/EtOAc 5:1), and the minor diastereomer was obtained in 8% yield (0.030 g) as determined by NMR analysis using mesitylene as an internal standard (R_f = 0.26 in hexanes/EtOAc 5:1).

Data for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.46 (d, J = 12.2 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H, overlapped with peaks from the impurity), 3.97 (d, J = 12.2 Hz, 1H), 2.24−2.17 (m, 1H), 2.09 (s, 3H), 1.93−1.89 (m, 2H), 1.71 (apparent tt, J = 13.3, 3.9 Hz, 3H), 1.62 (m, 2H), 1.54−1.51 (m, 1H), 1.26 (t, J = 7.11 Hz, 3H), 0.87 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 166.6, 81.9, 73.3, 66.7, 62.2, 60.7, 32.8, 32.7, 26.2, 22.8, 21.1, 20.3, 18.6, 14.6, 1.9, 2.2; IR (film) 3505.8, 2930.9, 2893.4, 2094.8, 1747.6, 1693.6, 1471.7, 1464.0, 1388.8, 1367.6, 1297.2, 1251.9, 1234.5 cm^{-1}; MS (ESI) calcd for $[C_{19}H_{34}N_2O_6SiNa]^+$ 437.20783, found 437.20797.

Data for the minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (d, J = 11.8 Hz, 1H), 4.21 (q, J = 7.0 Hz, 2H, overlapped with peaks from the impurity), 4.08 (d, J = 11.8 Hz, 1H), 2.09 (s, 3H), 1.94−1.85 (m, 2H), 1.72−1.52 (m, 7H, overlapped with peaks from the impurity), 1.27 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 169.7, 79.1, 75.7, 68.9, 64.1, 61.2, 33.7, 30.4, 26.5, 26.2, 22.7, 21.0, 18.8, 14.6, −1.8, −1.9; IR (film) 3481.7, 2954.1, 2860.6, 2096.7, 1746.6, 1696.5, 1471.7, 1389.8, 1367.6, 1293.3, 1253.8, 1111.1, 1033.9 cm^{-1}; MS (ESI) calcd for $[C_{19}H_{34}N_2O_6SiNa]^+$ 437.20783, found 437.20810.

Ethyl 9-Acetoxy-8-oxonon-2-ynoate (22). According to representative experimental procedure 1 that was used to prepare **9**, the major diastereomer of diazoester **21** (0.060 g, 0.14 mmol) reacted at 0 °C to give tethered ketone ynoate **22** in 70% yield (0.024 g) after purification via flash chromatography on Davisil (hexanes/EtOAc 10:1, 8:1, 6:1, 4:1, 3:1, 2:1, 1:1; R_f = 0.11 in hexanes/EtOAc 5:1); the yield was determined to be 83% via NMR analysis using mesitylene as an internal standard. Under the same experimental conditions, the minor diastereomer of diazoester **21** (0.049 g, 0.12 mmol) provided the title compound in 54% isolated yield (0.012 g); the yield was determined to be 61% via NMR analysis using mesitylene as an internal standard. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 2.45 (t, J = 7.1 Hz, 2H), 2.34 (t, J = 7.1 Hz, 2H), 2.16 (s, 3H), 1.73 (tt, J = 7.9, 7.0 Hz, 2H), 1.60 (tt, J = 7.6, 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 170.4, 153.8, 88.5, 73.7, 68.1, 61.9, 38.1, 26.9, 22.4, 20.6, 18.6, 14.2; IR (film) 2900.1, 2233.7, 1751.4, 1730.2, 1705.2, 1419.7, 1367.6, 1251.9, 1234.5, 1076.3, 1026.2, 910.4, 858.4, 753.2, 735.9 cm^{-1}; MS (ESI) calcd for $[C_{13}H_{18}O_5Na]^+$ 277.10464, found 277.10486.

2-Allyl-2-(*tert*-butyldimethylsilyloxy)cyclohexanone (24). Freshly prepared allylmagnesium bromide (2.40 g, 19.88 mmol) in Et_2O (20 mL) was added dropwise to a 0 °C solution of 2-silyloxycyclohex-2-enone (**23**) (3.0 g, 13.25 mmol) in Et_2O (24 mL). 2-Silyloxycyclohex-2-enone[36] was made according to the literature procedure. During the addition the colorless solution became yellow in color. After 3 h of stirring at 0 °C, the reaction mixture was quenched with 50 mL of aqueous NH_4Cl solution, and the resulting mixture was warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give an oily residue. This residue, which contained the crude tertiary alcohol (2.72 g, 10.13 mmol), was dissolved in 50 mL of dry MeOH and cooled to 0 °C. K_2CO_3 (0.07 g, 0.5 mmol) was added, and the mixture was stirred at room temperature for 1 h. The mixture was concentrated to give an oily residue, which was dissolved in 50 mL of Et_2O and washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated down to an oily residue. Purification via flash silica gel chromatography (hexanes/Et_2O 50:1; R_f = 0.45 in hexanes/EtOAc 40:1) provided the title compound in 83% yield (2.95 g). The ^{1}H and ^{13}C NMR spectral data were identical to the reported values.[46]

2-(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)-acetaldehyde (25).[47] A solution of allyl ketone **24** (1.27 g, 4.73 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C, and ozonized oxygen gas was passed through the solution at a rate of 1 L/min until the solution became blue in color, at which point the solution was purged with nitrogen until the blue color disappeared. Then triphenylphosphine (2.48 g, 9.46 mmol) was added, and after 30 min the mixture was allowed to warm to room temperature over a period of 2 h. The solvent was removed, and the crude product was purified via flash column chromatography on a Davisil support (hexanes/EtOAc 10:1, 2:1; R_f = 0.23 in hexanes/EtOAc 8:1) to afford the title aldehyde in 93% yield (1.19 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (t, J = 2.4 Hz, 1H), 2.76 (dd, J = 15.4, 2.5 Hz, 1H), 2.78−2.73 (m, 1H, overlapped with dd at 2.76), 2.61 (dd, J = 15.4, 2.4 Hz, 1H), 2.36 (ddd, J = 13.6, 6.2, 5.7 Hz, 1H), 2.02−1.87 (m, 4H), 1.82−1.73 (m, 1H), 1.68−1.61 (m, 1H), 0.90 (s, 9H), 0.17 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 200.6, 80.1, 50.5, 41.1, 38.7, 27.5, 25.9, 21.5, 18.6, −2.1, −2.7; MS (ESI) calcd for $[C_{14}H_{26}O_3SiNa]^+$ 293.15434, found 293.15429.

3a-(*tert*-Butyldimethylsilyloxy)octahydrobenzofuran-7a-ol (26).[37] An aqueous suspension of Raney nickel (5.67 g of the suspension) was transferred with THF (20 mL) to a solution of aldehyde **25** (0.87 g, 3.21 mmol) in THF (10 mL). The suspension was stirred at room temperature for 30 min, diluted with Et_2O (50 mL), and filtered through Celite, and the solvent was evaporated to yield an oily residue. The crude product was purified via silica gel flash column chromatography (hexanes/EtOAc 20:1, 10:1; 15:1; 5:1; R_f = 0.40 in hexanes/EtOAc 4:1) to afford the hemiacetal in 69% yield (0.60 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (ddd, J = 8.9, 8.5, 4.6 Hz, 1H), 3.84 (dt, J = 8.4, 6.9 Hz, 1H), 3.29 (s, 1H), 2.14 (ddd, J = 11.2, 10.0, 6.9 Hz, 1H), 1.91 (ddd, J = 12.4, 8.3, 4.1 Hz, 1H), 1.86 (dt, J = 14.3, 4.4 Hz, 1H), 1.79−1.74 (m, 1H), 1.67−1.60 (m, 2H), 1.54−1.47 (m, 2H), 1.44−1.37 (m, 2H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.7, 80.3, 64.3, 36.1, 35.5, 33.6, 25.9, 22.9, 21.7, 18.2, −2.5, −2.6; IR (film) 3438.2 (b), 2933.9, 2857.7, 1471.75, 1360.8, 1295.26, 1252.8 cm^{-1}; MS (ESI) calcd for $[C_{14}H_{28}O_3SiNa]^+$ 295.16999, found 295.17049.

2-(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)ethyl 2-Bromoacetate (27). Pyridine (0.47 mL, 5.81 mmol) and bromoacetyl bromide (0.61 mL, 6.98 mmol) were added sequentially to a 0 °C solution of hemiacetal **26** (0.63 g, 2.33 mmol) in CH_2Cl_2 (23 mL), and the resulting heterogeneous mixture was stirred overnight at room temperature. The mixture was cooled to 0 °C, and then MeOH (0.25 mL) was added, at which point the white suspension became a clear solution. Saturated aqueous NH_4Cl (25 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. The solvents were removed in vacuo, and the resulting oily residue was purified by flash silica gel column chromatography (hexanes/EtOAc 20:1; R_f = 0.48 in hexanes/EtOAc

dx.doi.org/10.1021/jo500634d | J. Org. Chem. 2014, 79, 6037−6046

4:1) to provide the desired bromoacetate as an oil in 57% yield (0.52 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26−4.23 (m, 2H), 3.77 (s, 2H), 2.56−2.45 (m, 2H), 2.30 (dt, J = 21.5, 7.2 Hz, 1H), 1.98−1.93 (m, 3H), 1.86−1.79 (m, 2H), 1.74−1.65 (m, 2H), 0.87 (s, 9H), 0.18 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.9, 167.1, 80.7, 62.3, 42.1, 39.6, 37.1, 27.7, 26.1, 25.8, 22.7, 18.7, −2.4, −2.7; MS (ESI) calcd for $[C_{16}H_{29}BrO_4SiH]^+$ 393.10913, found 393.10952.

2-(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)ethyl 2-Diazoacetate (28). Diazo ester **28** was prepared from bromoacetate **27** by the same procedure used to make ***16-cis***. The product was purified via filtration through a pad of Davisil using an 8:1 hexanes/EtOAc mixture as the eluent to provide the title compound (R_f = 0.28 in hexanes/EtOAc 4:1) in 85% yield (0.51 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (bs, 1H), 4.29−4.19 (m, 2H), 2.53−2.44 (m, 2H), 2.31 (ddd, J = 14.4, 7.3, 7.0 Hz, 1H), 1.99−1.93 (m, 2H), 1.91 (dd, J = 6.1, 5.3 Hz, 1H), 1.87−1.77 (m, 2H), 1.74−1.63 (m, 2H), 0.88 (s, 9H), 0.19 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 166.3 (b), 80.6, 60.6, 45.9 (b), 42.2, 39.4, 37.5, 27.6, 25.9, 22.6, 18.5, −2.6, −2.9; IR (film) 2928.1, 2855.73, 2112.14, 1724.4, 1697.4, 1472.7, 1394.6, 1394.6, 1359.8, 1248.0 cm^{-1}; MS (ESI) calcd for $[C_{16}H_{28}N_2O_4SiNa]^+$ 363.17106, found 363.17147.

***rel*-(5a*R*,9a*S*)-5a-(*tert*-Butyldimethylsilyloxy)-1-diazo-9a-hydroxyoctahydrobenzo[*d*]oxepin-2(1*H*)-one (29).** A solution of diazo ester **28** (0.05 g, 0.15 mmol) in THF (3 mL) was added dropwise over 16 h by a syringe pump to a stirred −78 °C solution of lithium bis(trimethylsilyl)amide (1 M in THF/ethylbenzene, 0.20 mL, 0.18 mmol) in THF (30 mL). After 1 h, saturated aqueous NH_4Cl solution (24 mL) was added to the reaction mixture at −78 °C, and the mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc (3 × 70 mL), and the organic layers were combined, washed with brine, dried over anhydrous $CaCl_2$, filtered, and concentrated to a solid residue. Flash column chromatography of the crude product over Davisil (hexanes/EtOAc 4:1, 2:1, 1:1; R_f = 0.21 in hexanes/EtOAc 3:1) afforded a single diastereomer of the title product in 69% yield (0.035 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (ddd, J = 12.8, 9.8, 1.8 Hz, 1H), 4.26 (ddd, J = 12.8, 6.1, 2.8 Hz, 1H), 2.34 (ddd, J = 15.8, 9.8, 2.8 Hz, 1H), 1.97 (s, 1H), 1.93 (dt, J = 12.6, 4.9 Hz, 1H), 1.80 (dt, J = 13.9, 4.3 Hz, 1H), 1.72−1.55 (m, 6H), 1.52−1.48 (m, 1H), 0.92 (s, 9H), 0.16 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 75.6, 74.0, 67.9, 65.4, 38.6, 35.3, 32.8, 26.1, 20.4, 20.2, 18.8, −1.7, −1.9; IR (film) 3358.2 (b), 2927.1, 2855.7, 2106.4, 1727.3, 1635.7, 1471.7, 1398.5, 1305.9, 1259.6 cm^{-1}; MS (ESI) calcd for $[C_{16}H_{28}N_2O_4SiH]^+$ 341.18911, found 341.18924.

4-Oxacycloundecyne-3,7-dione (30). According to representative experimental procedure 1 or 2 used to prepare **9**, diazo lactone **29** provided 11-membered cyclic ynoate **30** in 50% yield (0.022 g) at 0 °C and 63% yield (0.0063 g) at 40 °C. The title compound was isolated via flash column chromatography on Davisil (hexanes/EtOAc 4:1, 3:1, 2:1, 1:1; R_f = 0.16 in hexanes/EtOAc 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65−4.63 (m, 2H), 2.79−2.77 (m, 2H), 2.76−2.73 (m, 2H), 2.42−2.39 (m, 2H), 1.92 (tt, J = 5.9, 4.0 Hz, 2H), 1.76−1.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 154.4, 97.9, 73.1, 65.5, 44.4, 41.7, 25.0, 20.9, 18.2; IR (film) 2922.3, 2851.9, 2229.8, 1714.8 (b), 1463.1, 1387.8, 1282.7, 1228.7, 1079.2, 740.7 cm^{-1}; MS (ESI) calcd for $[C_{10}H_{12}O_3H]^+$ 181.08592, found 181.08584.

Methyl 1-Hydroxy-2-oxocycloheptanecarboxylate (32a). The title compound was prepared from commercially available methyl 2-oxocycloheptanecarboxylate (**31a**) (2.01 g, 11.8 mmol) by the method described for the preparation of **11**. Purification of the crude product via flash silica gel chromatography (hexanes/EtOAc 8:1; R_f = 0.25 in hexanes/EtOAc 5:1) afforded the title compound in 66% yield (1.44 g). The ^{1}H and ^{13}C NMR spectral data matched previously reported values.[48]

Ethyl 1-Hydroxy-2-oxocyclooctanecarboxylate (32b). The title compound was prepared from commercially available ethyl 2-oxocyclooctanecarboxylate (**31b**) (4.88 g, 24.8 mmol) by the method described for the preparation of **11**. Purification of the crude product via flash silica gel chromatography (hexanes/EtOAc 6:1; R_f = 0.27 in hexanes/EtOAc 5:1) afforded the title compound in 99% yield (5.26 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (d, J = 1.6 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.05 (dd, J = 12.4, 3.9 Hz, 1H), 2.74−2.68 (m, 1H), 2.40−2.36 (m, 1H), 2.15 (dt, J = 15.3, 3.9 Hz, 1H), 1.98−1.93 (m, 1H), 1.82−1.63 (m, 4H), 1.47−1.32 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.90−0.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 170.4, 83.0, 62.0, 36.8, 30.4, 30.1, 25.4, 24.1, 22.2, 13.9. MS (ESI) calcd for $[C_{11}H_{18}O_4Na]^+$ 237.1103, found 237.1105.

Methyl 1,2-Bis(*tert*-butyldimethylsilyloxy)cyclohept-2-enecarboxylate (33a). Compound **33a** was prepared from **32a** (0.15 g, 0.79 mmol) by the method described for the preparation of **12**. Purification by silica gel flash column chromatography (hexanes/Et_2O 50:1; R_f = 0.75 in hexanes/EtOAc 5:1) provided the title compound as a colorless oil in 93% yield (0.30 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (dd, J = 6.9, 5.6 Hz, 1H), 3.68 (s, 3H), 2.14 (ddd, J = 14.5, 11.6, 4.7 Hz, 1H), 2.10−2.02 (m, 2H), 1.94−1.86 (m, 1H), 1.76 (td, J = 14.6, 3.9 Hz, 2H), 1.67−1.52 (m, 2H), 0.91 (s, 9H), 0.89 (s, 9H), 0.16 (s, 6H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 152.9, 110.5, 83.0, 51.9, 35.7, 26.7, 26.3, 26.1, 23.3, 22.4, 19.2, 18.4, −2.7, −2.8, −4.3, −4.6; MS (ESI) calcd for $[C_{21}H_{42}O_4Si_2H]^+$ 415.26944, found 415.26939.

(*E*)-Ethyl 1,2-Bis(*tert*-butyldimethylsilyloxy)cyclooct-2-enecarboxylate (33b). Compound **33b** was prepared from **32b** (0.20 g, 0.91 mmol) by the method described for the preparation of **12**. Purification by silica gel flash column chromatography (hexanes/Et_2O 30:1; R_f = 0.72 in hexanes/EtOAc 5:1) provided the title compound as a colorless oil in 94% yield (0.38 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (dd, J = 9.8, 8.5 Hz, 1H), 4.19 (qd, J = 10.8, 7.2 Hz, 1H), 4.05 (qd, J = 10.8, 7.1 Hz, 1H), 2.42 (tdd, J = 14.2, 9.7, 7.0 Hz, 1H), 2.21 (dt, J = 14.5, 7.3 Hz, 1H), 2.16−2.03 (m, 2H), 1.76−1.64 (m, 3H), 1.58−1.48 (m, 3H), 1.26 (t, J = 7.2 Hz, 3H), 0.89 (two s, 18H), 0.17 (s, 3H), 0.14 (s, 3H), 0.137 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 152.7, 105.6, 82.7, 60.9, 37.0, 27.4, 26.3, 26.1, 23.7, 23.3, 22.6, 19.2, 18.5, 14.2, −2.5, −2.6, −4.3, −4.4; MS (ESI) calcd for $[C_{23}H_{46}O_4Si_2H]^+$ 443.30074, found 443.30074.

(1,2-Bis(*tert*-butyldimethylsilyloxy)cyclohept-2-enyl)-methanol (34a). The title compound was prepared from **33a** (2.84 g, 6.85 mmol) according to the same procedure as used to prepare **13**. Purification by silica gel flash column chromatography (hexanes/Et_2O 40:1; R_f = 0.80 in hexanes/EtOAc 5:1) provided compound **34a** as a colorless oil in 80% yield (2.13 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (dd, J = 7.9, 5.6 Hz, 1H), 3.58 (s, 1H), 3.56 (d, J = 1.6 Hz, 1H), 2.20 (dqd, J = 16.2, 5.3, 2.5 Hz, 1H), 2.00 (dd, J = 7.4, 6.2 Hz, 1H), 1.94 (dq, J = 7.8, 2.3 Hz, 1H), 1.88−1.83 (m, 3H), 1.74−1.68 (m, 1H), 1.65−1.61 (m, 1H), 1.48−1.40 (m, 1H), 0.94 (s, 9H), 0.89 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 111.1, 80.0, 68.8, 34.4, 26.9, 26.2, 26.19, 23.6, 23.1, 18.8, 18.5, −2.6, −2.7, −4.1, −4.4; MS (ESI) calcd for $[C_{20}H_{42}O_3Si_2Na]^+$ 409.25647, found 409.25635.

(*E*)-(1,2-Bis(*tert*-butyldimethylsilyloxy)cyclooct-2-enyl)-methanol (34b). The title compound was prepared from **33b** (0.27 g, 0.61 mmol) according to the same procedure as used to prepare **13**. Purification by silica gel flash column chromatography (hexanes/Et_2O 40:1; R_f = 0.79 in hexanes/EtOAc 5:1) provided compound **34b** as a colorless oil in 64% yield (0.16 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (dd, J = 9.9, 8.6 Hz, 1H), 3.76 (dd, J = 11.0, 3.9 Hz, 1H), 3.47 (dd, J = 10.9, 10.0 Hz, 1H), 2.84 (dddd, J = 14.0, 12.2, 9.9, 5.6 Hz, 1H), 2.18 (dd, J = 9.9, 3.8 Hz, 1H), 1.99−1.88 (m, 2H), 1.80−1.74 (m, 1H), 1.63−1.57 (m, 4H), 1.49−1.37 (m, 2H), 0.94 (s, 9H), 0.89 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 107.5, 80.6, 68.8, 37.0, 28.1, 26.3, 26.1, 24.1, 22.8, 22.4, 18.8, 18.4, −2.6, −3.7, −4.6; MS (ESI) calcd for $[C_{21}H_{44}O_3Si_2H]^+$ 401.29017, found 401.29030.

2-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)-cycloheptanone (35a). Compound **35a** was prepared from **34a** (0.15 g, 0.40 mmol) by the method described for the preparation of **14**. The title compound was obtained in 87% yield (0.09 g) after purification by silica gel flash column chromatography (hexanes/EtOAc 8:1; R_f = 0.36 in hexanes/EtOAc 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (dd, J = 11.4, 7.2 Hz, 1H), 3.60 (dd, J = 11.4, 6.4 Hz, 1H), 2.77−2.72 (m, 1H), 2.44 (ddd, J = 13.7, 12.5, 4.8 Hz, 1H), 2.29 (dd, J = 7.1, 6.5 Hz, 1H), 1.78−1.71 (m, 5H), 1.63−1.56 (m, 2H),

dx.doi.org/10.1021/jo500634d | J. Org. Chem. 2014, 79, 6037−6046

1.47−1.38 (m, 1H), 0.90 (s, 9H), 0.21 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 84.5, 68.5, 40.1, 36.0, 29.3, 26.1, 25.3, 23.9, 18.8, −2.3, −2.8; MS (ESI) calcd for $[C_{14}H_{28}O_3SiNa]^+$ 295.16999, found 295.17004.

2-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)-cyclooctanone (35b). Compound **35b** was prepared from **34b** (0.16 g, 0.39 mmol) by the method described for the preparation of **14**. The title compound was obtained in 85% yield (0.10 g) after purification by silica gel flash column chromatography (hexanes/EtOAc 8:1; R_f = 0.31 in hexanes/EtOAc 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (dd, J = 11.4, 7.2 Hz, 1H), 3.57 (dd, J = 11.4, 6.4 Hz, 1H), 2.69 (ddd, J = 12.1, 7.9, 4.0 Hz, 1H), 2.39 (ddd, J = 12.3, 9.3, 4.2 Hz, 1H), 2.15 (dd, J = 6.5, 7.1 Hz, 1H), 2.04 (dd, J = 14.6, 3.4 Hz, 1H), 1.94−1.80 (m, 3H), 1.74−1.66 (m, 1H), 1.63−1.44 (m, 3H), 1.39−1.34 (m, 2H), 0.91 (s, 9H), 0.21 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.9, 84.4, 68.6, 37.8, 34.1, 28.9, 26.3, 26.2, 25.3, 22.3, 18.9, −2.3, −2.7; MS (ESI) calcd for $[C_{15}H_{30}O_3SiH]^+$ 287.20370, found 287.20376.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocycloheptyl)methyl 2-Bromoacetate (36a). The title compound was prepared from **35a** (1.38 g, 5.08 mmol) according to the same procedure as used to prepare **15**. The crude product was purified via flash silica gel column chromatography (hexanes/EtOAc 10:1; R_f = 0.56 in hexanes/EtOAc 5:1) to provide compound **36a** in 95% yield (1.91 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (d, J = 11.2 Hz, 1H), 4.15 (d, J = 11.3 Hz, 1H), 3.82 (s, 2H), 2.70 (ddd, J = 11.7, 7.1, 4.7 Hz, 1H), 2.52 (ddd, J = 12.8, 10.6, 4.1 Hz, 1H), 1.86−1.75 (m, 4H), 1.68−1.61 (m, 2H), 1.59−1.50 (m, 1H), 1.47−1.38 (m, 1H), 0.88 (s, 9H), 0.19 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 166.8, 82.6, 69.9, 40.3, 35.7, 29.3, 25.9, 25.6, 25.5, 23.6, 18.6, −2.4, −2.9; MS (ESI) calcd for $[C_{16}H_{29}BrO_4SiH]^+$ 393.10913, found 393.10927.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclooctyl)methyl 2-Bromoacetate (36b). The title compound was prepared from **35b** (0.11 g, 0.38 mmol) according to the same procedure as used to prepare **15**. The crude product was purified via flash silica gel column chromatography (hexanes/EtOAc 8:1; R_f = 0.68 in hexanes/EtOAc 5:1) to provide compound **36b** in 98% yield (0.15 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (d, J = 11.6 Hz, 1H), 4.15 (d, J = 11.6 Hz, 1H), 3.80 (s, 2H), 2.63 (ddd, J = 12.3, 7.6, 3.6 Hz, 1H), 2.45 (ddd, J = 12.3, 10.2, 4.0 Hz, 1H), 2.09 (ddd, J = 14.5, 11.2, 3.5 Hz, 1H), 1.95−1.80 (m, 3H), 1.74−1.66 (m, 1H), 1.64−1.57 (m, 1H), 1.52−1.44 (m, 2H), 1.40−1.29 (m, 2H), 0.89 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 166.8, 82.5, 70.2, 37.6, 33.7, 29.1, 26.3, 26.0, 25.4, 24.8, 22.2, 18.8, −2.4, −2.8; MS (ESI) calcd for $[C_{17}H_{31}BrO_4SiNa]^+$ 429.10672, found 429.10707.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclooctyl)methyl 2-Diazoacetate (37b). Diazo ester **37b** was prepared from the corresponding bromo ester **36b** (2.64 g, 6.48 mmol) by the method used to make **16-*cis***. Purification of the crude product by flash chromatography on a Davisil support (hexanes/EtOAc 10:1, 8:1, 6:1, 4:1, 2:1, 1:1; R_f = 0.46 in hexanes/EtOAc 5:1) provided diazoester **37b** in 68% yield (1.57 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (bs, 1H), 4.38 (d, J = 11.5 Hz, 1H), 4.16 (d, J = 11.5 Hz, 1H), 2.57 (ddd, J = 12.3, 6.8, 3.9 Hz, 1H), 2.46 (dt, J = 11.2, 4.3 Hz, 1H), 2.08 (ddd, J = 14.3, 11.6, 3.3 Hz, 1H), 1.92−1.78 (m, 3H), 1.75−1.67 (m, 1H), 1.65−1.58 (m, 1H), 1.51−1.35 (m, 3H), 1.32−1.24 (m, 1H), 0.88 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.0, 166.2 (b), 82.8, 69.1, 46.3 (b), 37.7, 33.6, 29.2, 26.3, 25.9, 24.8, 22.2, 18.8, −2.5, −2.8; IR (film) 3125.8, 2946.4, 2857.7, 2114.1, 1701.3, 1471.8, 1388.8, 1351.2, 1249.9, 1156.4 cm^{-1}; MS (ESI) calcd for $[C_{17}H_{30}N_2O_4SiNa]^+$ 377.18671, found 377.18683.

9a-(*tert*-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyoctahydrocyclohepta[*c*]pyran-3(1*H*)-one (38a-*cis* and 38a-*trans*). Diazo lactones **38a-*cis*** and **38a-*trans*** were prepared from bromoester **36a** (0.16 g, 0.40 mmol) by the same method as used to make **16-*cis***. Purification of the crude product by flash chromatography on a Davisil support (hexanes/EtOAc 12:1, 10:1, 5:1, 3:1) provided the bicyclic diazo lactones as two separated diastereomers with the following spectral data:

38a-*cis*: Yield 0.034 g, 25%; R_f = 0.19 in hexanes/EtOAc 5:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (d, J = 12.3 Hz, 1H), 3.96 (d, J = 12.3 Hz, 1H), 3.60 (d, J = 1.7 Hz, 1H), 2.02−1.90 (m, 3H), 1.87−1.73 (m, 3H), 1.59−1.46 (m, 3H), 1.37−1.28 (m, 1H), 0.92 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 75.5, 75.2, 70.1, 65.9, 35.9, 34.7, 28.9, 25.9, 21.6, 20.2, 18.6, −2.6, −2.9; IR (film) 3503.8, 2929.0, 2857.7, 2102.5, 1693.57, 1464.0, 1392.7, 1287.5, 1128.4 cm^{-1}; MS (ESI) calcd for $[C_{16}H_{28}N_2O_4SiH]^+$ 341.18911, found 341.18928.

38a-*trans*: Yield 0.045 g, 33%; R_f = 0.36 in hexanes/EtOAc 5:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (d, J = 10.8 Hz, 1H), 3.73 (d, J = 10.7 Hz, 1H), 2.99 (d, J = 2.2 Hz, 1H), 2.14−2.04 (m, 2H), 1.84 (tt, J = 13.9, 1.7 Hz, 1H), 1.78−1.69 (m, 3H), 1.68−1.52 (m, 3H), 1.39−1.31 (m, 1H), 0.90 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 79.8, 73.3, 70.8, 62.8, 33.9, 29.9, 25.9, 25.3, 19.9, 18.2, 17.4, −2.6, −3.1; IR (film) 3515.4 (b), 2952.2, 2932.9, 2859.6, 2102.5, 1699.4, 1465.9, 1383, 1302.9, 1264.4 cm^{-1}; MS (ESI) calcd for $[C_{16}H_{28}N_2O_4SiH]^+$ 341.18911, found 341.18915.

***rel*-(3a*S*,9a*R*)-3a-((*tert*-Butyldimethylsilyl)oxy)-3-diazo-9a-(hydroxymethyl)octahydrocycloocta[*b*]furan-2(3*H*)-one (39).** Lithium bis(trimethylsilyl)amide (1 M in THF/ethylbenzene, 1.90 mL, 1.89 mmol) was added to THF (142 mL) at −78 °C. A solution of diazo ester **37b** (0.50 g, 1.42 mmol) in THF (10 mL) was added dropwise via a syringe pump over 24 h while maintaining the temperature at −78 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl (70 mL) and allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 70 mL). The organic layers were combined, washed with brine, dried over anhydrous $CaCl_2$, and concentrated to give a solid residue. Flash column chromatography (hexanes/EtOAc 6:1, 4:1, 2:1, 1:1) afforded 0.32 g (64% yield) of the title compound as an oil (R_f = 0.16 in hexanes/EtOAc 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99−3.94 (m, 1H), 3.88−3.84 (m, 1H), 2.33 (dt, J = 13.3, 2.5 Hz, 1H), 2.04−1.74 (m, 9H), 1.46−1.35 (m, 2H), 1.13−1.05 (m, 1H), 0.98 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 96.4, 81.4, 65.1, 62.6, 33.7, 29.5, 28.6, 28.4, 26.5, 26.3, 25.3, 18.8, −2.9, −3.1; IR (film) 3490.9 (b), 2930.9, 2857.7, 2095.75, 1743.7, 1471.8, 1464.0, 1371.5, 1255.7 cm^{-1}; MS (ESI) calcd for $[C_{17}H_{30}N_2O_4SiH]^+$ 355.20476, found 355.20539.

***rel*-(3a*S*,9a*R*)-3a-((*tert*-Butyldimethylsilyl)oxy)octahydro-2*H*-3,9a-(epoxymethano)cycloocta[*b*]furan-2-one (40).** According to representative experimental procedure 1 that was used to prepare **9**, diazo lactone **39** (0.027 g, 0.075 mmol) reacted at 0 °C to give 0.020 g (80% yield) of ether **40** after purification via flash column chromatography on Davisil (hexanes/EtOAc 10:1; R_f = 0.57 in hexanes/EtOAc 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (d, J = 8.9 Hz, 1H), 3.91 (s, 1H), 3.74 (d, J = 9.0 Hz, 1H), 2.16−2.10 (m, 1H), 2.06−1.93 (m, 5H), 1.86−1.81 (m, 1H), 1.78−1.71 (m, 1H), 1.63−1.55 (m, 1H), 1.31−1.22 (m, 2H), 1.13−1.06 (m, 1H), 0.91 (m, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 95.6, 84.9, 83.4, 70.9, 33.1, 31.1, 29.2, 25.8, 25.7, 23.8, 22.5, 18.4, −2.3, −2.4; IR (film) 2929.0, 2857.7, 1791.9, 1472.7, 1454.4, 1362.8, 1255.7, 1199.8, 1174.7, 1133.2, 1087.9, 1067.7, 1007.9, 907.6, 837.1, 809.2, 778.3, 675.1 cm^{-1}; MS (ESI) calcd for $[C_{17}H_{30}O_4SiH]^+$ 327.19861, found 327.19871.

4-Oxacycloundecyne-3,6-dione (41). According to representative experimental procedure 1 or 2 used to prepare **9**, diazo lactone **38a-*cis*** provided 11-membered cyclic ynoate **39** in 64% yield (0.056 g) at 0 °C and 84% yield (0.089 g) at 40 °C. Diazo lactone **38a-*trans*** provided **39** in 57% yield (0.0093 g) at 0 °C and 67% yield (0.074 g) at 40 °C. The product was purified via flash chromatography on Davisil (hexanes/EtOAc 8:1, 6:1, 4:1, 2:1, and 1:1; R_f = 0.22 in hexanes/EtOAc 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (s, 2H), 2.54−2.51 (m, 2H), 2.45 (t, J = 6.3 Hz, 2H), 1.84 (dtd, J = 12.6, 7.0, 3.5 Hz, 2H), 1.67−1.62 (m, 2H), 1.59 (ddt, J = 19.5, 7.1, 1.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 153.5, 97.2, 72.8, 71.7, 37.7, 24.1, 23.0, 22.9, 18.3; IR (film) 2946.4, 2876.9, 2224.0, 1726.4, 1554.7, 1464.0, 1430.3, 1371.5, 1280.8, 1209.4, 1192.1, 1162.2, 1128.4, 1092.7, 1028.1, 1011.7, 954.8, 738.8 cm^{-1}; MS (ESI) calcd for $[C_{10}H_{12}O_3H]^+$ 181.08592, found 181.08585.

dx.doi.org/10.1021/jo500634d | J. Org. Chem. 2014, 79, 6037−6046

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 992222 contains the supplementary crystallographic data for this paper.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: matthias.brewer@uvm.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Bruce O'Rourke (University of Vermont) for obtaining mass spectral data and Prof. Rory Waterman and Mr. Justin K. Pagano for X-ray data collection. This work was financially supported by Award R01GM092870 from the National Institute of General Medical Sciences (NIGMS), a component of the National Institutes of Health (NIH), and was made possible by the use of a facility supported by the Vermont Genetics Network through Grant P20GM103449 from the INBRE Program of NIH NIGMS. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIGMS or NIH. The National Science Foundation supported this work through instrumentation grants CHE-1039436, CHE-1126265, and CHE-0821501.

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