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Cyclic oxonium ylides: building blocks for iterative synthesis of polycyclic ethers

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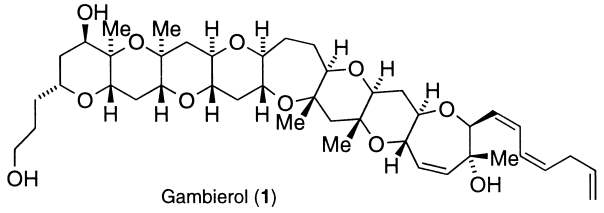
Abstract—A series of diazoketones bearing remote benzyl or allyl ethers was subjected to a variety of conditions for catalytic diazodecomposition and cyclic oxonium ylide formation as a possible method for polycyclic ether synthesis. Allyl ethers **19**, **25** and **29** underwent efficient conversion to the corresponding bis(pyran) and tris(pyran) products in the presence of $Cu(tfacac)_2$, while benzyl ether **15** was converted to bicyclic products **16** and **34** with $Rh_2(tpa)_4$. Treatment of homologous substrate **32** with $Rh_2(tpa)_4$ provided novel medium-ring cyclopropanation products **35** in good yield.

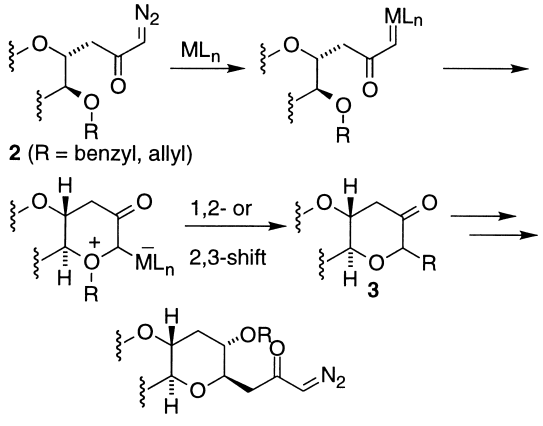
1. Introduction

Marine ladder toxins, exemplified by gambierol (**1**),[1] have attracted considerable attention in recent years. These compounds are produced by dinoflagellate organisms associated with 'red tide' events and cases of food poisoning.[2] Their apparent mechanism of action, binding to voltage-gated sodium ion channels,[3] has provoked interest in the biomedical community regarding the possible development of antagonists,[4] and some have displayed promising antifungal activity.[5] However, most of these toxins are quite scarce, suggesting that de novo synthesis may be the best approach for probing structure-activity effects.



Gambierol (**1**)

The ladder toxins contain a unique *trans*-fused polycyclic ether skeleton made up repeating of 6-, 7-, 8- and 9-membered ether rings. This regular motif suggests that iterative installation of successive ether rings may be an especially suitable method of construction. Indeed, several highly effective iterative strategies for polyether synthesis have been described in recent years.[6] We recently disclosed preliminary results of our efforts to apply metallocarbene/oxonium ylide chemistry in an iterative approach to polypyran domains such as those found in **1**.[7] Our general strategy relied on the conversion of a 5-alkoxy-1-diazo-2-pentanone such as **2** to a 2-substituted tetrahydropyran-3-one such as **3** via catalytic decomposition of the diazoketone, cyclization of the resulting carbenoid onto the pendant ether oxygen, and migration of the exocyclic group on the intermediate cyclic oxonium ylide to furnish **3** (Scheme 1). The migration was envisioned to occur by either [1,2]-shift of a benzyl group or [2,3]-shift of an allyl group. A particularly attractive feature of this approach is the convenient placement of oxygenation and a carbon side-chain at the appropriate points to permit their elaboration to new ether and diazoketone groups for a subsequent iteration. Here we detail the full scope of this study, including some fascinating and unexpected catalyst effects.



Scheme 1.

Keywords: polycyclic ethers; oxonium ylides; sigmatropic rearrangement.

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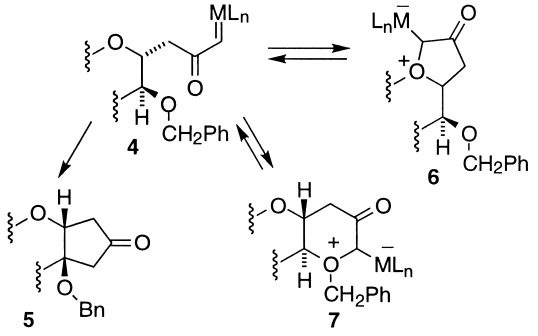
2. Results and discussion

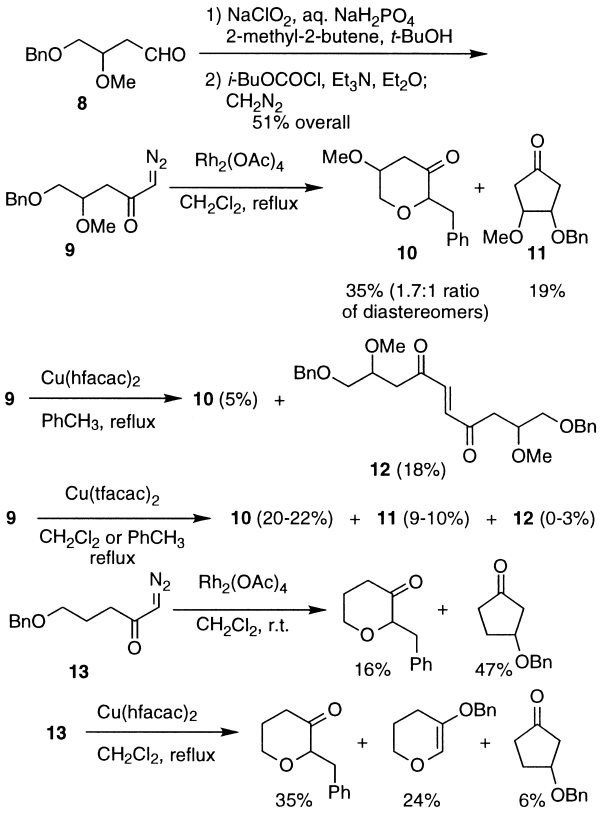
2.1. An acyclic model system for [1,2]-shifts

Given our earlier studies with [1,2]-benzyl shifts,[8] we initially focused our attention on this approach, with the expectation that the 2-benzyl substituent could be oxidatively degraded to a two-carbon carboxylic acid side-chain with RuO_4.[9] Competing carbenoid pathways were a major concern with this approach: formation of cyclopentanone **5** via C–H insertion into the benzyl ether methine could be facile, and formation of the alternative oxonium ylide **6** derived from addition to the neighboring pyran oxygen was also possible (Scheme 2). Adams had previously shown that C–H bonds next to ether oxygens are particularly activated for insertion by rhodium carbenoids.[10] Generation of ylide **6** might be tolerated, since it would have no low-energy rearrangement pathways available. Several studies have provided indirect evidence for interconversion between metallocarbenes and oxonium ylides;[11] if such an equilibrium were possible, ylide **6** might be expected to revert to carbenoid **4** and eventually provide the desired ylide **7** and/or C–H insertion product **5**. However, this argument also raised the possibility that slow rearrangement of **7** could lead to reversion to **4** and greater amounts of **5**.



Scheme 2.

Given these uncertainties, we chose to initially examine the simple, acyclic model compound **9** (Scheme 3). Substrate **9** was prepared from known aldehyde **8**[12] via Pinnick oxidation followed by carboxyl activation and diazomethane addition via the mixed anhydride. Treatment of **9** with $Rh_2(OAc)_4$ gave both diastereomers of the desired [1,2]-shift product **10** along with C–H insertion product **11**. Given the questionable synthetic utility of this result, we then examined other catalysts for diazodecomposition. Prior studies by Clark[13] and by us[8a,b] had shown that use of soluble copper(II) catalysts led to much more favorable ratios of ylide-derived products to C–H insertion products, as exemplified in the case of benzyl ether **13**. Accordingly, we next turned to copper(II) hexafluoroacetoacetonate in refluxing CH_2Cl_2, conditions which had worked well with **13**. None of the insertion product **11** was isolated, but to our surprise, only traces of **10** were obtained. Instead, the major product in a largely intractable and complex mixture was the dimeric alkene **12**. A somewhat more favorable **10/11/12** ratio could be obtained by using the optimal conditions employed for [2,3]-shifts ($Cu(tfacac)_2/CH_2Cl_2$/reflux; see Section 2.3), but the overall yields were unacceptably low. Minor dimerization pathways have been observed in other carbenoid chemistry,[14] and can predominate in certain intramolecular cases.[15] However, we had not previously observed this type of reactivity in systems in which viable ylide rearrangement pathways were available. The close structural similarity of **9** and **13** is especially striking, suggesting that the methoxy group may play a significant role in the surprising reactivity differences observed for these substrates.

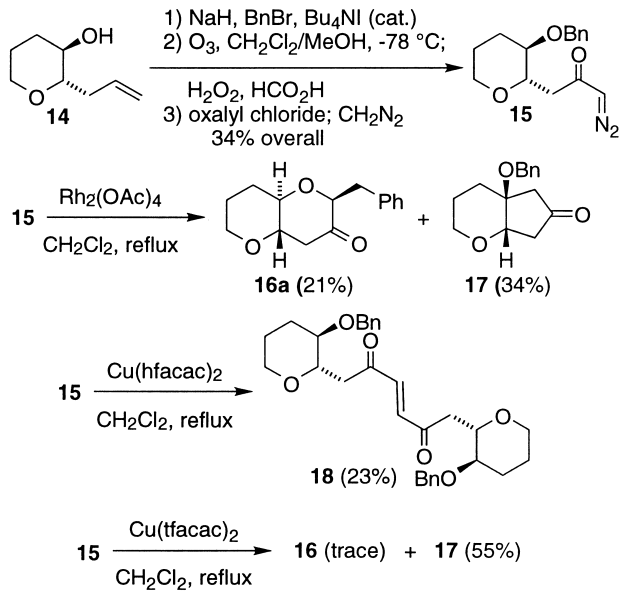


Scheme 3.

2.2. [1,2]-Shift of a cyclic substrate

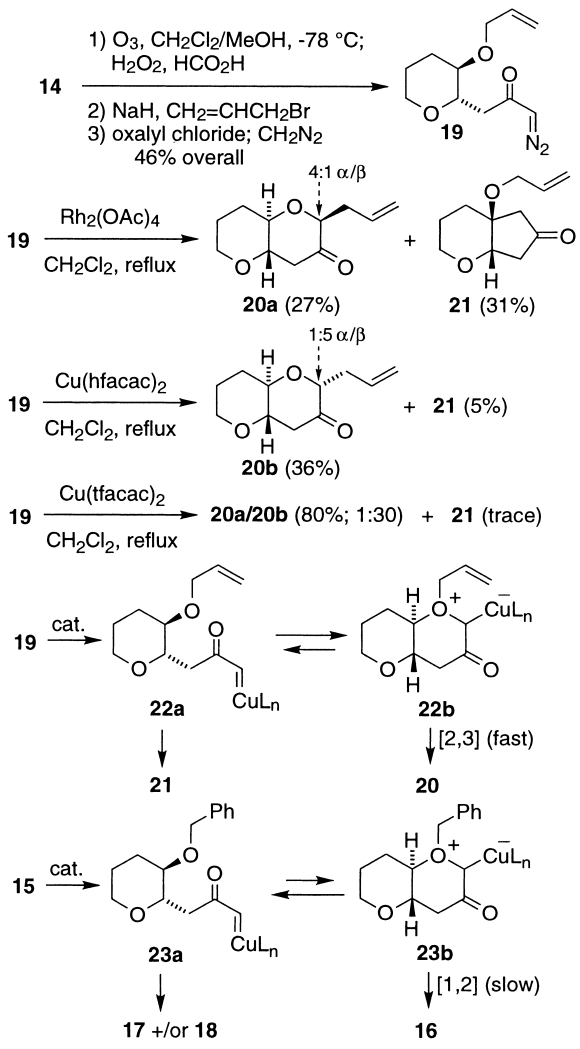
The unexpected results with **9** prompted us to prepare a more elaborate substrate, **15**, whose greater rigidity could favor the desired ylide pathway (Scheme 4). The known *trans*-2-allyl-3-hydroxytetrahydropyran **14**[16] could be converted to **15** via a 3-step sequence of O-benzylation, ozonolysis with oxidative work-up and carboxyl activation/diazomethane acylation. Treatment of **15** with $Rh_2(OAc)_4$ gave a combined 55% yield of oxonium ylide [1,2]-shift products **16** and C–H insertion product **17** in a 2:3 ratio. Although the [1,2]-shift product was formed exclusively as the desired epimer (**16a**), the yield was unacceptably low. As with acyclic model **9**, use of $Cu(hfacac)_2$ furnished mainly the dimeric product (**18**). To our surprise, the optimal conditions for [2,3]-shifts ($Cu(tfacac)_2/CH_2Cl_2$/reflux; see Section 2.3) gave C–H insertion product **17** in good yield, with only a trace of the [1,2]-shift product.

Our prior experience with carbenoid-based methods of ylide generation suggested that the conditions employed should



Scheme 4.

permit efficient formation of the desired oxonium ylides. Why then were products of alternative carbenoid pathways (C–H insertion and dimerization) predominating in these systems? We wondered if the activation barrier for [1,2]-shift, which is believed to occur via a 2-step homolysis/recombination mechanism,[8c,17] might be sufficiently high to permit competing reversion of the ylide to metallocarbene, with eventual drain-off via the undesired pathways. If this were the case, we reasoned that rearrangement of *O*-allyl oxonium ylides might have a greater likelihood for success, as the concerted [2,3]-shifts would be expected to experience lower activation barriers.[8d]

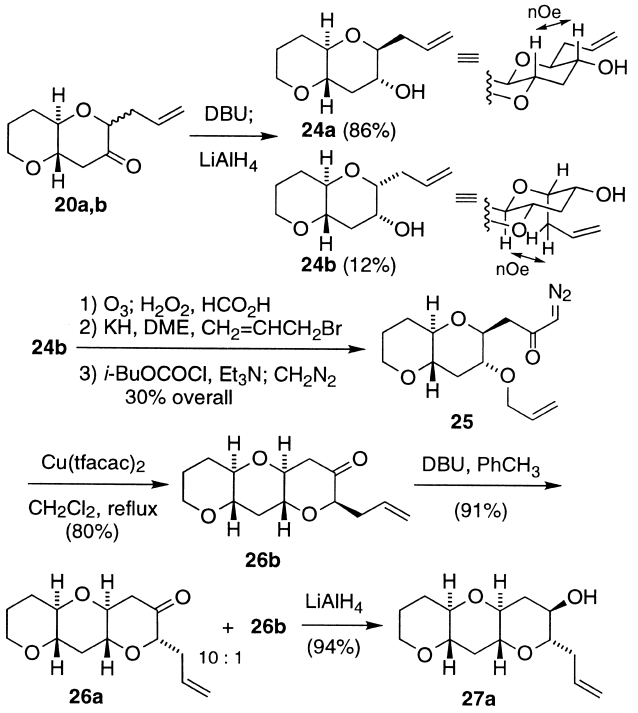


Scheme 5.

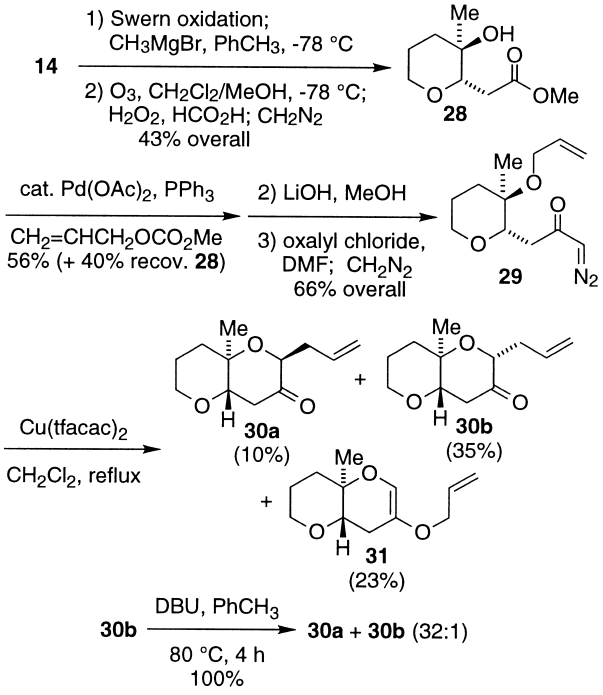
2.3. [2,3]-Shift with iteration

The necessary substrate **19** to examine an approach based on oxonium ylide [2,3]-shifts could be prepared from **14** via a route analogous to that used in the synthesis of **15** (Scheme 5). Treatment with $Rh_2(OAc)_4$ furnished roughly equal amounts of ylide rearrangement products **20** (4:1 ratio of inseparable epimers) and C–H insertion product **21** in a combined 59% yield. $Cu(hfacac)_2$ provided diminished quantities of **21** and slightly greater amounts of **20**. Notably, the ratio of diastereomers in this case now favored axial allyl isomer **20b** (5:1 β/α). Further efforts to optimize for the ylide pathway revealed that copper(II) trifluoroacetoacetonate in refluxing CH_2Cl_2 gave high yields of **20b**, along with traces of **20a** and **21**. Dropwise addition via cannula over a 5 min period was found to be superior to slow addition by syringe pump, likely due to slow thermal diazoketone degradation. It is notable that no carbenoid dimers were observed under any of the conditions surveyed. The striking contrast in reactivity between **19** and the closely related **15** is consistent with different rates of rearrangement by their respective ylides. Ylide **22b**, derived from **19**, undergoes efficient [2,3]-shift to give mainly **20**, with only small amounts of **21** formed via C–H insertion by open carbenoid **22a**. Ylide **23b**, derived from **15** is slow to rearrange, allowing a greater degree of reversion to carbenoid **23a**, which leads to insertion product **17** and dimer **18**. Similar arguments apply in the case of **9**.

The high-yield conversion of **19** to **20b** now raised the possibility of a successful iterative strategy for polypyran construction. However, this would require an adjustment of the configuration at the allyl-substituted carbon, selective reduction of the adjacent ketone, and establishment of the relative stereochemistry of the rearrangement products with greater confidence. To this end, the inseparable mixture was reduced to give separable alcohols **24a** and **24b** (Scheme 6). Prior treatment with base effected the epimerization of **20b** to the more stable equatorial isomer **20a** needed for eventual iteration, and reduction of the resulting mixture could be carried out in situ. As expected, hydride delivery occurred exclusively via axial attack for both **20a** and **20b**. Following reduction, the relative stereochemistry of **24a** and **24b** was determined by 2D NOESY experiments, which revealed cross peaks between the 1,3-diaxial protons of **24a** and between one of the bridgehead axial protons and the methylene protons of the axial allyl group of **24b**. While this procedure afforded synthetically useful quantities of **24a**, additional material could be obtained by recycling the undesired **24b** to **20b** by TPAP oxidation, followed by



Scheme 6.



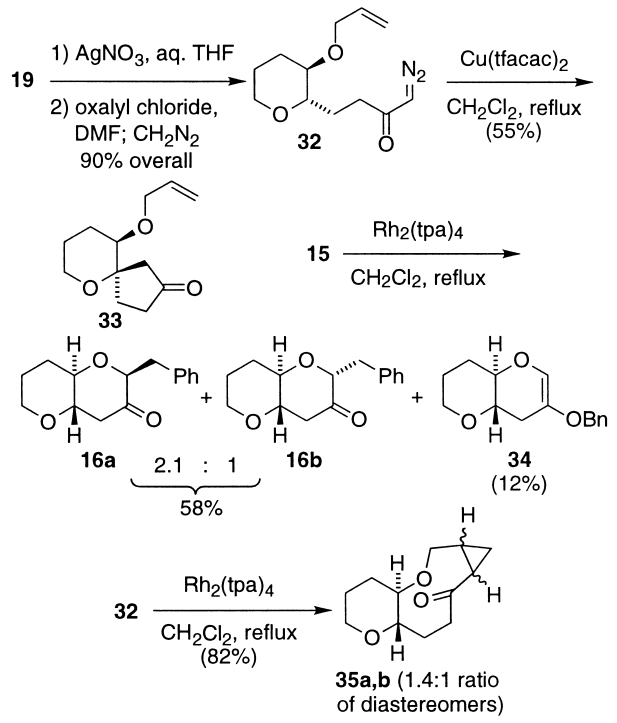
Scheme 7.

another epimerization/reduction sequence. With **24a** in hand an additional iteration was investigated. The same sequence of: (1) ozonolysis with oxidative work-up, (2) allyl ether formation and (3) carboxyl activation/diazomethane acylation generated diazoketone **25**. Application of the optimum conditions from Scheme 5 effected the conversion of **25** to **26b**, isolated as the only detectable isomer in 80% yield. Tris(tetrahydropyran) **26b** was then subjected to the epimerization conditions, providing a 10:1 mixture of **26a** and **b**. A series of 2D NOESY experiments analogous to those used with **24a**, **b** once again established the relative stereochemistry to be as shown. This mixture could be reduced as before to give **27a** and a trace of an isomer.

2.4. Other cases and catalyst effects

Given the frequent occurrence of angular methyl groups in ladder toxin polypyran arrays, we sought to examine whether the successful approach described earlier (Section 2.3) could be carried out using a tertiary allylic ether such as **29** (Scheme 7). This substrate could be prepared from **14** via a sequence involving oxidation,[18] addition of methylmagnesium bromide, ozonolysis with oxidative work-up and protection as the methyl ester to give hydroxyester **28**. The tertiary alcohol was resistant to allylation under standard conditions, but the palladium-catalyzed procedure of Stoner cleanly provided a mixture of **28** and its allyl ether.[19] Saponification and diazoketone acylation then provided **29**. When **29** was subjected to $Cu(tfacac)_2$ in refluxing dichloromethane, the expected [2,3]-shift products **30a** and **30b** were isolated, but in a disappointing 45% combined yield, and with somewhat lower diastereoselectivity (1:3.5). Since the desired *trans* isomer was readily available via base-catalyzed epimerization, the latter issue was of little concern, but the low chemical yield was troubling. An additional major product was isolated from this reaction, whose structure proved to be enol ether **31**. This compound presumably also arises from the intermediate oxonium ylide via a [1,4]-shift of the allyl group. Thus, a total of 68% of the material was formed via the oxonium ylide. [1,4]-Shift products from oxonium ylides have been observed previously, though typically during attempted [1,2]-shift of benzyl or simple alkyl substituents.[8b,20] To our knowledge, this is the first example of a [1,4]-shift by an oxonium ylide occurring in competition with a [2,3]-shift.[21]

To examine the applicability of this strategy to oxepane construction, we also prepared diazoketone stubstrate **32** by Arndt–Eistert homologation of **19** (Scheme 8). Clearly, efficient reaction via the ylide pathway would be difficult when C–H insertion via 5- and 6-membered transition states was possible. In fact, the $Cu(tfacac)_2$ conditions successfully applied to **19** converted **32** exclusively to 5-membered spirocyclic C–H insertion product **33**. This result was somewhat reminiscent of the unexpected conversion of **15** to **17** (Scheme 4). Earlier observations by Clark[13a] and by us[8a,b] had led to the generalization that the C–H insertion pathway was not favored with copper catalysts when viable ylide rearrangements were available, but these results clearly indicated that the situation was somewhat more complicated. At this point, we chose to examine the behavior of **15** and **32** with the bulky rhodium complex $Rh_2(tpa)_4$ (tpa=triphenylacetate), as carbenoids derived from this catalyst are reported to be quite sensitive to steric demand,[22] which we thought might disfavor C–H insertion involving the angular methine relative to the ylide pathway. In the event, addition of **15** to $Rh_2(tpa)_4$ (3 mol% in refluxing CH_2Cl_2; 5 min addition via cannula) gave the desired [1,2]-shift products **16a** and **16b** in a combined 58% yield (2.1:1 ratio of epimers), along with another 12% of the



Scheme 8.

[1,4]-shift product **34**. Given the isolation of a combined 70% of oxonium ylide-derived products from a case (**15**) that had previously given mainly C–H insertion or dimerization products, we revisited substrate **32** with considerable optimism. However, exposure of **32** to the same conditions unexpectedly furnished a mixture of cyclopropanes **35a** and **35b** in 82% yield as the only isolated products. The connectivity of the novel 2,11-dioxatricyclo[8.4.0.0^{4,6}]tridecan-7-ones was verified through a combination of 2D COSY, HMQC and HMBC NMR experiments, although the relative configuration of the two new cyclopropane stereocenters could not be established. Cyclopropanation to close a new nine-membered ring in preference to C–H insertion (5- and 6-membered ring-closure available) or ylide formation (via a 7-membered ring) is quite surprising. The applicability of this process to medium-ring formation merits further study.[23]

3. Conclusions

5-Benzyloxydiazoketones **9** and **15** undergo primarily C–H insertion or carbenoid dimerization processes under the standard oxonium ylide [1,2]-shift conditions that have been successfully applied to simpler substrates. However, the bulky catalyst $Rh_2(tpa)_4$ provided a combined 70% yield of ylide-derived [1,2]- and [1,4]-shift products from **15**. The related allyloxydiazoketones **19**, **25** and **29** all underwent efficient conversion to bi- or tricyclic oxonium ylides, with diastereoselective [2,3]-shift to the corresponding 2-allyltetrahydropyran-3-ones. These examples demonstrate the suitability of the oxonium ylide approach for the iterative construction of polypyran arrays such as those found in many marine ladder toxins. Finally, homologous substrate **32** reacted exclusively through a C–H insertion spirocyclization pathway with $Cu(tfacac)_2$ and cyclopropanation to form a nine-membered ring with $Rh_2(tpa)_4$. Further studies are underway to explore the generality of the last process.

4. Experimental

4.1. General

Reactions were carried out in flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannula. Solvents were distilled before use: methylene chloride from calcium hydride, tetrahydrofuran and diethyl ether from sodium/benzophenone ketyl, toluene from sodium metal. Ethereal diazomethane was prepared from Diazald according to literature procedures.[24] Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F_{254} (Merck). Flash chromatography columns were packed with 230–400 mesh silica gel (Merck). Radial chromatography was carried out on a Chromatotron model 7924T (Harrison Research) with plates prepared using silica gel 60 F_{254} with gypsum binder (EM) on glass rotors. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 or 500 MHz and coupling constants (J) are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 75 or 125 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-*d* (77.23 ppm). Yields reported in this section are for specific runs; yields given in Section 2 are average values taken from two or more runs.

4.1.1. 5-Benzyloxy-1-diazo-4-methoxypentan-2-one 9. To a solution of aldehyde **8** (0.675 g, 3.24 mmol) in ^{t}BuOH (36 mL) and 2-methyl-2-butene (16 mL) at rt was added a solution of $NaClO_2$ (0.879 g, 9.72 mmol), NaH_2PO_4 (1.52 g, 9.72 mmol), and H_2O (36 mL) in three portions over a 15 min period. The resulting mixture becomes increasingly yellow before returning to clear. The solution was mixed at rt for a further 4 h before being poured into sat. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (4×50 mL). The organics were dried (Na_2SO_4), filtered, and concentrated. The crude acid was carried on without further purification: IR (neat); 3440, 2934, 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (br s, 1H), 7.38–7.25 (m, 5H), 4.57 (d, J_{AB}=12.1 Hz, 1H), 4.56 (d, J_{AB}=12.1 Hz, 1H), 3.88–3.80 (m, 1H), 3.60–3.51 (m, 2H), 3.44 (s, 3H), 2.71–2.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 138.0, 128.6, 128.0, 128.0, 76.6, 73.6, 70.8, 58.1, 37.2.

To a solution of the acid (0.702 g, 3.13 mmol) in ether (13 mL) at rt was added Et_3N (0.50 mL, 4.07 mmol) followed by isobutylchloroformate (0.53 mL, 4.07 mmol). A white salt formed immediately and the solution became very thick. Mixing was continued for 3 h at rt at which time the salt was carefully filtered off and the filtrate concentrated. The crude mixed anhydride was then dissolved in dry ether (10 mL) and added to an ethereal solution of diazomethane at −10°C dropwise via cannula. The resulting mixture was allowed to warm to rt over night. Concentration and silica gel chromatography (3×8.5 cm column eluting

with 15% EtOAc/hexanes) provided the desired diazoketone **9** (0.407 g, 51% from aldehyde) as a yellow oil: IR (neat); 3087, 3031, 2863, 2103, 1635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 5.29 (br s, 1H), 4.57 (d, J_{AB}=12.1 Hz, 1H), 4.53 (d, J_{AB}=12.1 Hz, 1H), 3.89–3.85 (m, 1H), 3.58–3.49 (m, 2H), 3.41 (s, 3H), 2.61–2.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 138.2, 128.6, 127.9, 127.9, 77.0, 73.6, 70.9, 58.0, 55.6, 43.4.

4.1.2. Decomposition of diazoketone 9 with $Rh_2(OAc)_4$. A solution of **9** (0.158 g, 0.637 mmol) in CH_2Cl_2 (5 mL)) was added via cannula to a refluxing solution of Rh_2OAc_4 (0.008 g, 0.03 equiv.) in CH_2Cl_2 (42 mL). The resulting mixture was stirred for a further 5 min before being cooled to rt, then washed with sat. $NaHCO_3$ (10 mL). The aqueous phase was further washed with EtOAc (3×10 mL) and the combined organics were dried ($MgSO_4$) and concentrated to leave a yellow oil. The oil was eluted through a short silica gel plug (pipette) using EtOAc and the eluant was concentrated. The resulting oil was purified using radial chromatography on a 4 mm plate eluting with 50 mL each of 5, 10, 20, 40 and 60% EtOAc/hexanes to yield two main fractions consisting of an inseparable mixture of C–H insertion product **11** (0.026 g, 19%)+the minor diastereomer of 1,2-shift product **11** (0.0182 g, 13%) and the major diastereomer of **11** (0.0316 g, 22%)+an uncharacterized product, all as clear, colorless oils.

4.1.3. 2-Benzyl-5-methoxytetrahydropyran-3-one 10. Major diastereomer: R_f 0.40 (50% EtOAc/hexanes); IR (neat); 3458, 2931, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.18 (m, 5H), 4.13 (ddd, J=12.7, 2.1, 2.1 Hz, 1H), 4.01 (dd, J=9.1, 3.5 Hz, 1H), 3.86–3.81 (m, 1H), 3.71 (dd, J=12.7, 2.5 Hz, 1H), 3.36 (s, 3H), 3.22 (dd, J=14.7, 3.5 Hz, 1H), 2.89 (dd, J=14.7, 9.0 Hz, 1H), 2.74 (ddd, J=15.6, 4.1, 2.0 Hz, 1H), 2.68 (ddd, J=15.6, 4.9, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 138.2, 129.6, 128.5, 126.7, 84.5, 68.0, 56.5, 43.2, 35.8; Anal. calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; Found: C 71.35; H, 7.40. Minor diastereomer: R_f 0.50 (50% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.20 (m, 5H), 4.21 (ddd, J=12.0, 5.6, 0.8 Hz, 1H), 3.99 (dd, J=8.7, 3.6 Hz, 1H), 3.85 (dddd, J=10.3, 5.8, 5.8, 4.5 Hz, 1H), 3.54 (dd, J=12.0, 5.8 Hz, 1H), 3.32 (s, 3H), 3.21 (dd, J=14.6, 3.4 Hz, 1H), 2.81 (dd, J=14.7, 8.8 Hz, 1H), 2.80–2.76 (m, 1H), 2.60 (ddd, J=18.4, 5.9, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 137.9, 128.7, 128.1, 126.6, 83.1, 75.4, 69.3, 56.6, 42.5, 36.2.

4.1.4. 3-Benzyloxy-4-methoxycyclopentanone 11. R_f 0.50 (50% EtOAc/hexanes); IR (neat); 3462, 2931, 1746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.21 (m, 5H), 4.59 (d, J_{AB}=12.0 Hz, 1H), 4.58 (d, J_{AB}=12.0 Hz, 1H), 4.23–4.17 (m, 1H), 4.05–4.02 (m, 1H), 3.36 (s, 3H), 2.63–2.52 (m, 2H), 2.36–2.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 137.9, 129.6, 128.4, 127.8, 81.4, 79.0, 71.5, 57.1, 42.6, 42.2.

4.1.5. Decomposition of diazoketone 9 with $Cu(hfacac)_2$. A solution of diazoketone **9** (0.048 g, 0.19 mmol) in freshly distilled toluene (5 mL) was added dropwise via cannula to a refluxing solution of $Cu(hfacac)_2$ (0.010 g, 0.02 mmol) in toluene (13 mL). The resulting mixture was stirred a further 5 min before being cooled to rt. The reaction mixture was washed with a 30% aqueous solution of NH_4OH in sat. NH_4Cl (10 mL), the aqueous phase was washed with EtOAc (3×10 mL) and the combined organics were dried with $MgSO_4$ and concentrated to leave a yellow oil. The oil was eluted through a pipette with silica gel using EtOAc and the eluent concentrated. The resulting oil was purified using radial chromatography on a 1 mm plate eluting with 50 mL each of 40% and 60% EtOAc/hexanes to yield 0.004 g (5%) of 1,2-shift product **10** and 0.016 g (18%) of dimer **12** as colorless oils.

4.1.6. Carbene dimer 12. (3.2:1 mixture of *E*/*Z* isomers as measured by alkene singlets in ^1H NMR). Major isomer: R_f 0.11 (50 % EtOAc/hexanes); IR (neat); 3475, 2923, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.25 (m, 10H), 6.85 (s, 2H), 4.60–4.49 (m, 4H), 3.95–3.82 (m, 2H), 3.57–3.49 (m, 4H), 3.38 (s, 6H), 2.97–2.77 (m, 2H), 2.76–2.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 138.1, 137.1, 128.6, 128.0, 127.9, 76.3, 73.6, 70.7, 58.1, 43.8. Minor isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (s, 2H).

4.1.7. Decomposition of diazoketone 9 with $Cu(tfacac)_2$. A solution of diazoketone **9** (0.028 g, 0.11 mmol) in freshly distilled CH_2Cl_2 (2 mL) was added via syringe pump over a period of 1 h to a refluxing solution of $Cu(tfacac)_2$ (0.004 g, 0.01 mmol) in CH_2Cl_2 (12 mL). The resulting mixture was stirred a further 5 min before being cooled to rt. The reaction mixture was washed with a sat. $NaHCO_3$ (10 mL) solution. The aqueous phase was washed with CH_2Cl_2 (3×10 mL) and the combined organics were dried with $MgSO_4$ and concentrated to leave a yellow oil. The oil was eluted through a pipette with silica gel using EtOAc and the eluent was concentrated. The resulting oil was purified using radial chromatography on a 1 mm plate eluting with 50 mL each of 5, 10, 20, 40 and 60% EtOAc/hexanes to yield 0.002 g (9%) of C–H insertion product **11**, 0.005 g (22%) of 1,2-shift **10** product and 0.001 g (3%) of dimer **12** as oils.

4.1.8. *trans*-(2*R,3*S**)-2-Allyl-3-hydroxytetrahydropyran 14.** *t*-Butyllithium (100 mL, 170 mmol, 1.1 equiv.) was added via cannula to a vigorously stirring solution of dihydropyran (14.0 mL, 154 mmol) in THF (28.3 mL) at −78°C. The mixture was then carefully allowed to warm to −30°C. When all of the yellow–orange precipitate had dissolved the solution was allowed to warm to 0°C and stirred for 1 h. The solution was then cooled to −78°C, added via cannula to CuI (14.9 g, 78.5 mmol, 0.51 equiv.) in THF (60 mL), in a three neck flask equipped with an addition funnel charged with allyl bromide (5.07 mL, 58.5 mmol, 0.38 equiv.) in THF (39 mL), at −78°C. The mixture was stirred for 1 h and the allyl bromide solution was then added drop-wise over 15 min. After the addition was complete, the solution was stirred at −78°C for 1 h and then allowed to warm to room temperature and stirred for an additional 3 h. The reaction was diluted with Et_2O (100 mL) and quenched with a 30% NH_4OH saturated with NH_4Cl solution (100 mL). The resulting slurry was allowed to stir for 1 h and then sit undisturbed until two layers formed. The aqueous phase was extracted with Et_2O (200 mL) and the combined organic phase was washed with a 30% NH_4OH saturated with NH_4Cl solution (300 mL), dried with

anhydrous $MgSO_4$, concentrated to a small volume (~20 mL) and immediately dissolved in MeOH (146 mL) and cooled to 0°C. After slow, careful addition of mCPBA (18.8 g, 76.1 mmol) the reaction was stirred until completion as determined by TLC (1 h) and then diluted with Et_2O (130 mL). The reaction was then carefully quenched with sat. $NaHCO_3$/ice mixture (200 mL). The aqueous phase was extracted with Et_2O (2×100 mL). The combined organic phase was washed with equal volumes of sat. $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography to yield 7.87 g of 2-methoxy-2-allyl-3-hydroxytetrahydropyran as a mixture of diastereomers (78% over two steps). R_f 0.22, 0.28 (30% EtOAc/hexanes) Major diastereomer: R_f 0.22, (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94–5.08 (m, 1H), 5.19–5.09 (m, 2H), 3.58–3.44 (m, 3H), 3.28 (s, 3H), 2.57–2.46 (m, 2H), 1.85–1.78 (m, 2H), 1.73–1.57 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 118.3, 99.8, 69.9, 60.8, 47.8, 38.1, 28.3, 25.4.

To a solution of Et_3SiH (36.5 mL, 228 mmol, 5 equiv.) and 2-methoxy-2-allyl-3-hydroxytetrahydropyran (7.86 g, 45.7 mmol) in CH_2Cl_2 (152 mL) and CH_3CN (152 mL) at 0°C was added $BF_3{\cdot}OEt_2$ (11.6 mL, 91.5 mmol, 2 equiv.). The reaction was stirred for 3 h and poured into a sat $NaHCO_3$/ice mixture (200 mL). The aqueous phase was then extracted with CH_2Cl_2 (2×100 mL) and the combined organic phase was washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography to yield 5.16 g (80%) of **14** as a colorless oil: R_f 0.14 (30% EtOAc/hexanes); IR (neat) 3405, 2936, 2852, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (dddd, J=17.1, 10.1, 7.1, 7.1 Hz, 1H), 5.15–5.06 (m, 2H), 3.93–3.86 (m, 1H), 3.41–3.28 (m, 2H), 3.1 (ddd, J=8.8, 7.5, 3.9 Hz, 1H), 2.63–2.53 (m, 1H), 2.33–2.23 (m, 1H), 2.13–2.05 (m, 1H), 1.72–1.71 (m, 3H), 1.46–1.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 117.1, 81.9, 70.5, 67.9, 37.2, 33.0, 25.8.

4.1.9. 1-Diazo-3-((2*R,3*S**)-3-benzyloxytetrahydropyran-2-yl)propan-2-one 15.** *trans*-2-Allyl-3-benzyloxytetrahydropyran: to a solution of NaH (193 mg, 4.84 mmol, 1.1 equiv.) in THF (8.8 mL, 0.5 M) at 0°C was added 2-allyl-3-hydroxytetrahydropyran (**14**) (625 mg, 4.40 mmol) in THF (1.0 mL) via cannula. The reaction was stirred for 10 min and benzyl bromide (0.56 mL, 4.62 mmol, 1.05 equiv.) was added via syringe follwed by tetrabutyl ammonium iodide (87 mg, 0.44 mmol, 10 mol%). The reaction was allowed to warm to rt and stirred overnight. The mixture was diluted with Et_2O (40 mL) and was then quenched by the addition of water (40 mL). The aqueous phase was then extracted with Et_2O (2×40 mL) and the combined organic phase was washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography to yield 791 mg (77%) of *trans*-2-allyl-3-benzyloxytetrahydropyran as a colorless oil. R_f 0.61 (50% Et_2O/hexanes); IR (neat) 3072, 3010, 2939, 2849, 1453, 1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5H), 5.93–5.85 (m, 1H), 5.13–5.05 (m, 2H), 4.63 (d, J_{AB}=11.4 Hz, 1H), 4.46 (d, J_{AB}=11.4 Hz, 1H), 3.93–3.89 (m, 1H), 3.34 (ddd, J=11.5, 11.5, 2.9 Hz, 1H), 3.26 (ddd, J=8.9, 7.9, 3.1 Hz, 1H), 3.16 (ddd, J=10.6, 9.0, 4.2 Hz, 1H), 2.70–2.64 (m, 1H), 2.31–2.22 (m, 2H), 1.71–1.59 (m, 2H), 1.41 (dddd, J=12.6, 10.6, 10.6, 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 135.6, 128.6, 128.1, 127.9, 116.9, 80.7, 77.0, 70.9, 68.1, 36.9, 29.5, 25.6. Anal. calcd for $C_{15}H_{20}O_2$: C, 77.55, H, 8.68. Found, C, 77.37, H, 8.78.

4.1.10. General procedure for ozonolysis: *trans*-3-benzyloxytetrahydropyran-2-yl)acetic acid. Ozone was bubbled into a solution of 2-allyl-3-benzyloxytetrahydropyran (228 mg, 0.98 mmol) in CH_2Cl_2 (6.9 mL) and MeOH (1.3 mL) at −78°C until the solution turned a persistent blue color. The solution was then allowed to stir for 30 min. Argon was bubbled into the solution until it was colorless, after which the cooling bath was removed and argon was bubbled until the reaction mixture reached rt. The reaction mixture was then concentrated and the residue was dissolved in 88% formic acid (0.73 mL) and 30% H_2O_2 (0.36 mL) and heated to 60°C for 6 h. The reaction mixture was then concentrated and the residue was dissolved in Et_2O (50 mL) and extracted with 1 M KOH (3×10 mL). The combined basic aqueous phase was washed with Et_2O (30 mL). The aqueous phase was then acidified with 3N HCl until pH~1–2, saturated with NaCl, then extracted with EtOAc (4×50 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated and placed under high vacuum overnight to afford 191 mg (78%) of *trans*-3-benzyloxytetrahydropyran-2-yl)acetic acid as a thick oil. IR (neat) 3035, 2949, 2868, 1706, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H), 4.64 (d, J_{AB}=11.5 Hz, 1H), 4.45 (d, J_{AB}=11.5 Hz, 1H), 3.95–3.92 (m, 1H), 3.64 (ddd, J=12.7, 8.8, 3.7 Hz, 1H), 3.42 (ddd, J=11.7, 11.7, 2.8 Hz, 1H), 3.19 (ddd, J=10.7, 9.0, 4.1 Hz, 1H), 2.94 (dd, J=15.5, 3.5 Hz, 1H), 2.48 (dd, J=15.5, 8.4 Hz, 1H), 2.33–2.30 (m, 1H), 1.74–1.65 (m, 2H), 1.48–1.41, (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 133.9, 128.7, 128.1, 128.0, 77.7, 76.7, 70.8, 68.2, 38.1, 29.1, 25.3. HRMS (FAB, M+1) for $C_{14}H_{19}O_4$ calcd 251.1285, found: *m*/*z* 251.1287.

4.1.11. General procedure for diazoketone formation: 1-diazo-3-((2*R,3*S**)-3-benzyloxytetrahydropyran-2-yl)-propan-2-one (15).** Freshly distilled oxalyl chloride (0.22 mL, 2.45 mmol, 1.2 equiv.) was added to a solution of acid *trans*-3-benzyloxytetrahydropyran-2-yl)acetic acid (996 mg, 3.97 mmol) in CH_2Cl_2 (15.9 mL, 0.25 M). One drop of DMF was added (gas evolution) and the reaction was stirred at rt for 4 h. The solvent was then evaporated with a stream of nitrogen, and the residue was placed under high vacuum for 30 min. The residue was then dissolved in Et_2O (15 mL) and added via cannula to a freshly prepared solution of CH_2N_2 (~16 mmol) in Et_2O (45 mL) at −45°C. After stirring at −45°C for 60 min, the bath was removed and the reaction stirred for an additional 60 min. A stream of nitrogen was introduced, after the solvent was evaporated, the yellow residue was dissolved in Et_2O (12 mL) and the solvent was again evaporated with a stream of nitrogen. The crude reaction mixture was purified by radial chromatography (4 mm plate, 200 mL of 25% followed by 200 mL of 35% EtOAc/hexanes) to yield 628 mg (57%) of **15** as a yellow oil: R_f 0.31 (50% EtOAc/hexanes); IR (neat) 3127, 2960, 2944, 2863, 2104, 1620, 1335, 1066 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 5.31 (br s, 1H), 4.64 (d, J_{AB}=11.5 Hz, 1H), 4.43 (d, J_{AB}=11.5 Hz, 1H),

3.89–3.86 (m, 1H), 3.62 (ddd, J=8.7, 8.7, 3.0 Hz, 1H), 3.36 (ddd, J=11.8, 11.8, 2.7 Hz, 1H), 3.16 (ddd, J=10.6, 9.1, 4.4 Hz, 1H), 2.86 (dd, J=14.7, 2.5 Hz, 1H), 2.42–2.38 (m, 1H), 2.31–2.28 (m, 1H), 1.72–1.58 (m, 2H), 1.42 (dddd, J=12.7, 12.7, 10.6, 4.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 138.5, 128.6, 128.0, 127.9, 78.3, 76.9, 70.7, 68.1, 55.5, 44.3, 29.3, 25.5; Anal. calcd for $C_{15}H_{18}N_2O_3$: C, 65.68, H, 6.61, N, 10.21. Found, C, 65.88, H, 6.58, N, 9.68.

4.1.12. General procedure for decomposition of diazoketones using rhodium catalysts: decomposition of diazoketone 15 with $Rh_2(OAc)_4$. To a solution of $Rh_2(OAc)_4$ (6 mg, 0.014 mmol, 3 mol%) in CH_2Cl_2 (32 mL, 0.015 M) and heated to reflux was added via syringe pump (addition time 1 h) a solution of diazoketone **15** (133 mg, 0.48 mmol) in CH_2Cl_2 (5.0 mL). When the addition was complete the reaction mixture was concentrated. Radial chromatography (2 mm plate, 200 mL 25% EtOAc/hexanes followed by 200 mL 30% EtOAc/hexanes) yielded 25 mg (21%) of **16a** and 41 mg (34%) of **17**.

4.1.13. (1S^*,3R^*,6R^*)-3-Benzyl-2,7-dioxabicyclo[4.4.0]-decan-4-one (16a). R_f 0.52 (50% EtOAc/hexanes); IR (neat) 3029, 2944, 2849, 1723, 1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.19 (m, 5H), 3.99 (dd, J=8.1, 3.5 Hz, 1H), 3.93–3.89 (m, 1H), 3.42–3.35 (m, 1H), 3.32–3.24 (m, 3H), 2.89–2.85 (m, 1H), 2.80 (dd, J=14.7, 8.1 Hz, 1H), 2.47–2.40 (m, 1H), 2.16–2.13 (m, 1H), 1.76–1.68 (m, 2H), 1.55–1.47 (m, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 205.4, 138.4, 129.9, 128.4, 126.5, 84.4, 77.4, 77.1, 67.8, 45.7, 35.7, 29.4, 25.3; HRMS (EI) for $C_{15}H_{18}O_3$ calcd 246.1256, found: m/z 246.1260.

4.1.14. (1S^*,6R^*)-6-Benzyloxy-2-oxabicyclo[4.3.0]nonan-8-one (17). R_f 0.44 (50% EtOAc/hexanes); IR (neat) 3032, 2935, 2860, 1745, 1454, 1097 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H), 4.49 (d, J_{AB}=11.2 Hz, 1H), 4.41 (d, J_{AB}=11.2 Hz, 1H), 3.96–3.90 (m, 2H), 3.50–3.40 (m, 1H), 2.76 (ddd, J=18.4, 5.1, 1.1 Hz, 1H), 2.64 (dd, J=18.2, 1.2 Hz, 1H), 2.42 (d, J_{AB}=18.1 Hz, 1H), 2.33–2.29 (m, 1H), 2.22 (d, J_{AB}=18.2 Hz, 1H), 1.93–1.70 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.1, 138.4, 128.7, 127.8, 127.5, 80.1, 79.9, 67.1, 64.0, 44.8, 41.8, 28.9, 23.5; HRMS (EI) for $C_{15}H_{18}O_3$ calcd 246.1256, found: m/z 246.1258.

4.1.15. General procedure for decomposition of diazoketones using copper catalysts: decomposition of diazoketone 15 with Cu(hfacac)$_2$. To a solution of Cu(hfacac)$_2$ (14 mg, 0.028 mmol, 10 mol%) in CH_2Cl_2 (30 mL, 0.01 M) heated to reflux was added via syringe pump (addition time 1 h) a solution of diazoketone **15** (76 mg, 0.28 mmol) in CH_2Cl_2 (3.0 mL). When the addition was complete the reaction mixture was cooled to rt and a solution of 30% NH_4OH saturated with NH_4Cl (60 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (2×50 mL), the combined organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated. Purification by radial chromatography (2 mm plate, solvent ramp: 100 mL each of 20, 30, 50, 60% Et_2O/hexanes) yielded 28 mg (20%) of **18** as a yellowish crystalline solid.

4.1.16. Carbene dimer 18. R_f 0.33 (50% EtOAc/hexanes); IR (neat) 2936, 2873, 1680, 1098, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 6.81 (d, J=1.8 Hz, 1H), 4.63 (d, J_{AB}=11.5 Hz, 1H), 4.39 (d, J_{AB}=11.5 Hz, 1H), 3.86–3.81 (m, 1H), 3.70 (ddd, J=8.8, 8.8, 3.7 Hz, 1H), 3.35 (ddd, J=11.3, 11.3, 2.9 Hz, 1H), 3.15 (ddd, J=10.4, 9.8, 4.5 Hz, 1H), 3.04 (ddd, J=15.4, 3.6, 2.1 Hz, 1H), 2.68 (dd, J=15.9, 8.6 Hz, 1H), 2.33–2.28 (m, 1H), 1.72–1.54 (m, 2H), 1.48–1.34 (m, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 199.1, 138.3, 136.9, 128.6, 128.0, 127.9, 77.5, 77.0, 70.6, 68.0, 45.0, 29.2, 25.4; HRMS (EI) for $C_{30}H_{36}O_6$ calcd 492.2511, found: m/z 492.2506.

4.1.17. Decomposition of diazoketone 15 with Cu-(tfacac)$_2$. Compound **15** (141 mg, 0.57 mmol) was treated to the general procedure (Cu(tfacac)$_2$ (21 mg, 0.056 mmol, 10 mol%), CH_2Cl_2 (57 mL, 0.01 M)) and purification by flash chromatography (silica gel, 2 cm×18 cm column, solvent ramp: 100 mL each of 20, 30, 50, 60% Et_2O/hexanes) yielded 77 mg (55%) of **17** as a colorless oil.

4.1.18. 1-Diazo-3-((2R^*,3S^*)-3-allyloxytetrahydropyran-2-yl)propan-2-one (19). Compound **14** (2.037 g, 14.35 mmol) was treated to the general ozonolysis procedure (CH_2Cl_2 (100 mL), MeOH (18 mL), 88% formic acid (10.8 mL) 30% H_2O_2 (5.6 mL)) to afford 1.95 g (85%) of *trans*-3-hydroxytetrahydropyran-2-yl)acetic acid as a thick brown oil. R_f 0.22 (5% MeOH/CH_2Cl_2/2 drops HOAc in 10 mL); IR (neat) 3224, 2501, 1686 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.9 (br s, 1H), 3.96–3.89 (m, 1H), 3.49 (ddd, J=9.0, 7.8, 3.9 Hz, 1H), 3.43–3.34 (m, 2H), 2.92 (dd, J=15.4, 3.9 Hz, 1H), 2.54 (dd, J=15.4, 7.8 Hz, 1H), 2.18–2.08 (m, 2H), 1.76–1.67 (m, 2H), 1.51–1.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 79.2, 70.4, 68.1, 38.2, 33.2, 25.7.

The acid (2.28 g, 14.3 mmol) was dissolved in THF (20 mL) and then added via cannula to a vigorously stirring mixture of NaH (1.03 g, 42.8 mmol, 3 equiv.) in THF (5 mL) at 0°C. After 10 min, allyl bromide was added via syringe (1.24 mL, 14.3 mmol, 1 equiv.) and the mixture was heated to reflux. After 10 h, the reaction was cooled to rt, diluted with Et_2O (15 mL), quenched with water (10 mL) and the aqueous phase was then washed with Et_2O (30 mL), acidified with 3N HCl until the pH~1–2, and then extracted with Et_2O (8×50 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 2.67 g (95%) of *trans*-3-allyloxytetrahydropyran-2-yl)acetic acid as a thick yellow oil. R_f 0.53 (5% MeOH/CH_2Cl_2/2 drops HOAc in 10 mL); IR (neat) 3224, 2544, 1686 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (br s, 1H), 5.88 (dddd, J=17.1, 10.6, 5.8, 5.8 Hz, 1H), 5.25 (ddd, J=17.1, 3.3, 1.6 Hz, 1H), 5.18–5.15 (m, 1H), 4.13–4.09 (m, 1H), 3.94–3.89 (m, 2H), 3.59 (ddd, J=9.0, 3.8, 3.8 Hz, 1H), 3.40 (ddd, J=11.7, 11.7, 2.8 Hz, 1H), 3.10 (ddd, J=10.6, 9.2, 4.4 Hz, 1H), 2.91 (dd, J=15.5, 3.8 Hz, 1H), 2.49 (dd, J=15.5, 8.3 Hz, 1H), 2.26–2.23 (m, 1H), 1.71–1.64 (m, 2H), 1.42–1.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 134.9, 117.4, 77.7, 76.8, 69.9, 68.2, 38.2, 29.3, 25.4. HRMS (FAB, M−1) for $C_{10}H_{15}O_4$ calcd 199.0970, found: m/z 199.0974.

3-Allyloxytetrahydropyran-2-yl)acetic acid (409 mg,

2.05 mmol) was subjected to the general procedure for diazoketone formation (oxalyl chloride (0.22 mL, 2.45 mmol, 1.2 equiv.), CH_2Cl_2 (14 mL), one drop of DMF at rt, CH_2N_2 (~8 mmol), Et_2O (30 mL) at −10°C for 60 min then rt for 60 min) and purified by radial chromatography (4 mm plate, solvent ramp: 100 mL each of 20, 30, 40, 50, 60% Et_2O/hexanes) to yield 307 mg (67%) of **19** as a yellow oil. R_f 0.15 (50% Et_2O/hexanes); IR (neat) 3082, 2939, 2856, 2102, 1736, 1640, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (dddd, J=17.2, 10.4, 5.6, 5.5 Hz, 1H), 5.35 (br s, 1H), 5.25 (dddd, J=17.1, 1.7, 1.7, 1.7 Hz, 1H), 5.16 (dddd, J=10.4, 1.2, 1.2, 1.2 Hz, 1H), 4.10 (dddd, J=12.6, 5.4, 1.4, 1.4 Hz, 1H), 3.9 (dddd, J=12.6, 5.7, 1.3, 1.3 Hz, 1H), 3.87–3.82 (m, 1H), 3.57 (ddd, J=9.1, 9.0, 3.1 Hz, 1H), 3.35 (ddd, J=11.6, 8.8, 2.9 Hz, 1H), 3.07 (ddd, J=10.7, 9.1, 4.5 Hz, 1H), 2.85 (dd, J=14.5, 2.9 Hz, 1H), 2.41 (app br s, 1H), 2.27–2.17 (m, 1H), 1.71–1.59 (m, 2H), 1.36 (dddd, J=12.7, 12.7, 10.7, 4.9 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 193.5, 135.7, 116.8, 78.5, 77.2, 69.9, 68.2, 55.3, 44.7, 29.7, 25.8; Anal. calcd for $C_{11}H_{16}N_2O_3$: C, 58.91, H, 7.19. Found, C, 59.28, H, 7.20.

4.1.19. Decomposition of diazoketone 19 with $Rh_2(OAc)_4$. Compound **19** (50 mg, 0.22 mmol) was treated according to the general procedure (CH_2Cl_2 (15 mL, 0.015 M), $Rh_2(OAc)_4$ (3 mg, 0.007 mmol, 3 mol%), addition time 3 h via syringe pump) and flash chromatography yielded 12 mg (25%) of ketone **21** and 14 mg (32%) of an inseparable mixture of **20a/20b** (**5a/5b**, 4:1 determined by GC).

4.1.20. (1*S,3*R**,6*R**)-3-Allyl-2,7-dioxabicyclo[4.4.0]decan-4-one (20a).** R_f 0.38 (30% EtOAc/hexanes); IR (neat) 2945, 2854, 1724, 1641, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.85 (dddd, J=17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.16–5.15 (m, 1H), 5.12–5.11 (m, 1H), 3.96–3.92 (m, 1H), 3.85 (dd, J=7.6, 4.3 Hz, 1H), 3.45–3.39 (m, 1H), 3.37–3.30 (m, 2H), 2.89 (dd, J=15.8, 5.0 Hz, 1H), 2.64 (app br s, 1H), 2.50–2.41 (m, 1H), 2.39–2.32 (m, 1H), 2.22–2.05 (m, 1H), 1.80–1.75 (m, 2H), 1.57–1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 134.2, 117.6, 83.1, 77.5, 77.1, 67.7, 45.6, 33.8, 29.3, 25.3.

4.1.21. (1*S,3*S**,6*R**)-3-Allyl-2,7-dioxabicyclo[4.4.0]decan-4-one (20b).** R_f 0.38 (30% EtOAc/hexanes); IR (neat) 3077, 2944, 2855, 1722, 1641, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (dddd, J=14.2, 9.6, 9.6, 7.1 Hz, 1H), 5.16–5.15 (m, 1H), 5.13–5.12 (m, 1H), 4.09 (dd, J=9.8, 5.4 Hz, 1H), 3.95–3.94 (m, 1H), 3.50 (ddd, J=10.7, 9.2, 4.5 Hz, 1H), 3.44–3.38 (m, 1H), 3.34 (ddd, J=11.7, 9.3, 5.5 Hz, 1H), 2.85 (ddd, J=16.4, 5.5, 1.1 Hz, 1H), 2.61 (ddddd, J=14.4, 9.6, 7.1, 1.2, 1.2 Hz, 1H), 2.45 (dd, J=16.4, 11.7 Hz, 1H), 2.39 (ddddd, J=14.5, 6.7, 5.3, 1.2, 1.2 Hz, 1H), 2.13–2.08 (m, 1H), 1.81–1.76 (m, 2H), 1.53–1.45 (m 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 132.9, 118.6, 81.8, 76.8, 70.1, 67.8, 43.7, 34.5, 29.4, 25.5.

4.1.22. (1*S,6*R**)-6-Allyloxy-2-oxabicyclo[4.3.0]nonan-8-one (21).** R_f 0.34 (30% EtOAc/hexanes); IR (neat) 2934, 2860, 1750, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (dddd, J=17.2, 10.4, 5.6, 5.6 Hz, 1H), 5.22 (dddd, J=17.2, 1.7, 1.7, 1.7 Hz, 1H), 5.13 (dddd, J=10.4, 1.5, 1.5, 1.5 Hz, 1H), 3.99–3.83 (m, 4H), 3.46–3.38 (m, 1H), 2.73 (ddd, J=18.5, 4.9, 1.3 Hz, 1H), 2.56 (dd, J=18.3, 1.3 Hz, 1H), 2.30 (dd, J=17.9, 1.1 Hz, 1H), 2.20–2.17 (m, 1H), 2.19 (d, J=17.8 Hz, 1H), 1.83–1.69 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 135.0, 116.6, 80.0, 77.5, 67.1, 62.9, 44.8, 41.8, 28.8, 23.5.

4.1.23. Decomposition of diazoketone 19 with Cu(tfacac)$_2$. Compound **19** (230 mg, 1.02 mmol) was treated to the general procedure (CH_2Cl_2 (102 mL, 0.01 M), $Cu(tfacac)_2$ (19 mg, 0.05 mmol, 5 mol%), 5 min addition via cannula) and purification by flash chromatography (silica gel, 3 cm×18 cm column, solvent ramp: 200 mL each of 20, 30, 50, 60% Et_2O/hexanes) yielded 10 mg (5%) of **21** and 162 mg (80%) of an inseparable mixture of **20a/20b** (**20a/20b**, 1:30 determined by GC).

4.1.24. Epimerization and reduction of 20a/20b (one-pot procedure). Catalytic DBU (1 drop) was added to mixture of **20a/20b** (142 mg, 0.72 mmol, **20a/20b**, 1:30) in THF (3.6 mL). The reaction was monitored by GC and stirred until no further change in epimer ratio was observed (16 h). The reaction was cooled to 0°C and $LiAlH_4$ was added (14 mg, 0.36 mmol), and the reaction was stirred until complete consumption of the ketone was evident by TLC. The reaction was quenched with 1:1 $Na_2SO_4{\cdot}10H_2O$/Celite and the resulting slurry was stirred for 30 min. Anhydrous $MgSO_4$ was added and the slurry stirred for and additional 30 min. The slurry was then filtered, concentrated and the products separated by flash chromatography to afford **24a** (95 mg, 67%) and **24b** (14 mg, 10%).

Two pot procedure: catalytic DBU (1 drop) was added to a mixture of **20a/20b** (307 mg, 1.57 mmol, **20a/20b**, 1:30) in toluene (15 mL, 0.1 M). The reaction was heated to reflux and monitored by GC until no further no further change in epimer ratio was observed (5 h). The mixture was then condensed and passed through a short pad of silica gel (3 cm in a disposable pipette) eluting with 50% Et_2O/hexanes. The solution was then concentrated to yield 301 mg (98%) of a mixture of **20a/20b** enriched in **20a**. The mixture was dissolved in THF, cooled to 0°C and $LiAlH_4$ (30 mg, 0.8 mmol) was added, the reaction was then allowed to stir until complete consumption of the ketone was evident by TLC. The reaction was quenched with 1:1 $Na_2SO_4{\cdot}10H_2O$/Celite and the resulting slurry was stirred for 30 min. Anhydrous $MgSO_4$ was added and the slurry stirred for and additional 30 min. The slurry was then filtered, concentrated and the products separated by flash chromatography (silica gel, 2 cm×28 cm column, solvent ramp: 100 mL each of 40, 50, 60, 70% Et_2O/hexanes) to afford 261 mg, (86%) of **24a** (84% from **20a/20b**) and 37 mg (12%) of **24b**.

4.1.25. (1*S,3*R**,4*S**,6*R**)-3-Allyl-2,7-dioxabicyclo[4.4.0]-decan-4-ol (24a).** R_f 0.12 (30% EtOAc/hexanes); IR (neat) 3435, 3075, 2943, 2868, 1103, 1066 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.94 (dddd, J=17.1, 10.1, 6.9, 6.9 Hz, 1H), 5.15 (dddd, J=17.2, 1.5, 1.5, 1.5 Hz, 1H), 5.09–5.07 (m, 1H), 3.92–3.88 (m, 1H), 3.50 (ddd, J=10.7, 9.4, 4.5 Hz, 1H), 3.44–3.38 (m, 1H), 3.34 (ddd, J=11.7, 9.3, 5.5 Hz, 1H), 3.02–2.95 (m, 2H), 2.58–2.53 (m, 1H), 2.36–2.03 (m, 2H), 2.07– 2.03 (m, 1H), 1.76–1.68 (m, 2H), 1.63 (br s, 1H), 1.51–1.37 (m 2H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 135.7, 117.7, 82.1, 78.4, 77.5, 70.5, 68.5, 39.6, 37.4, 29.9, 26.2; Anal. calcd for $C_{11}H_{18}O_3$: C, 66.64, H, 9.15. Found, C, 66.37, H, 9.19.

4.1.26. (1*S,3*S**,4*S**,6*R**)-3-Allyl-2,7-dioxabicyclo[4.4.0]-decan-4-ol (24b).** R_f 0.08 (30% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (dddd, J=17.2, 10.1, 7.1, 7.1 Hz, 1H), 5.17–5.08 (m, 2H), 4.08 (ddd, J=11.0, 5.5, 5.5 Hz, 1H), 3.99 (ddd, J=15.7, 5.4, 5,4 Hz, 1H), 3.93–3.89 (m, 1H), 3.59–3.50 (m, 1H), 3.17 (ddd, J=10.9, 9.2, 4.3 Hz, 1H), 2.98 (ddd, J=11.6, 9.3, 4.4 Hz, 1H), 2.59–2.53 (m, 1H), 2.43–2.38 (m, 1H), 2.14 (ddd, J=11.5, 4.5, 4.5 Hz, 1H), 1.95–1.92 (m, 1H), 1.75–1.61 (m, 4H), 1.40–1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 117.2, 77.6, 76.2, 69.1, 68.2, 68.1, 34.4, 29.5, 28.8, 25.9.

Oxidation of **24b**: TPAP (30 mg, 0.086 mmol, 6 mol%) was added to a mixture of NMO (388 mg, 3.31 mmol), **24b** (285 mg, 1.44 mmol), crushed and oven dried 4 Å molecular sieves, and CH_2Cl_2 (9.56 mL, 0.15 M). After 10 min the reaction was complete as ascertained by TLC, the mixture was filtered and condensed. The resulting oil was passed through a short pad of silica gel (2 cm in a disposable pipette) eluting with 50% Et_2O/hexanes and condensed to yield 248 mg (88%) of pure **20b**.

4.1.27. 1-Diazo-3-((1*S,3*R**,4*S**,6*R**)-4-allyloxy-2,7-dioxabicyclo[4.4.0]decan-3-yl)propan-2-one (25).** Compound **24a** (489 mg, 2.47 mmol) was treated to the general ozonolysis procedure (CH_2Cl_2 (17.3 mL), MeOH (3.3 mL), 88% formic acid (1.85 mL), 30% H_2O_2 (0.96 mL)) to afford 453 mg (85%) of 2-((1*S**,3*R**,4*S**,6*R**)-4-hydroxy-2,7-dioxabicyclo[4.4.0]decan-3-yl)acetic acid as a white solid. Alternatively, the crude reaction mixture can be purified directly after the oxidation by concentration followed by flash chromatography (silica gel, solvent ramp: 100 mL each of 2.5, 5, 7.5, 10% MeOH/CH_2Cl_2/20 drops glacial HOAc). R_f 0.25 (5% MeOH/CH_2Cl_2/2 drops glacial HOAc in 10 mL); mp 149–153°C; IR (KBr) 3433, 2960, 1724, 2858, 1690 cm^{-1}; ^1H NMR (500 MHz, d_6-acetone) δ 10.6 (br s, 1H), 3.98–3.88 (br s, 1H), 3.81–3.78 (m, 1H), 3.55 (ddd, J=9.1, 9.1, 2.7 Hz, 1H), 3.37 (ddd, J=10.8, 9.4, 4.5 Hz, 1H), 3.33–3.28 (m, 1H), 2.96–2.88 (m, 2H), 2.87 (dd, J=15.7, 2.8 Hz, 1H), 2.26 (dd, J=15.7, 9.3 Hz, 1H), 2.55–2.22 (m, 1H), 1.94–1.91 (m, 1H), 1.66, 1.59 (m, 2H), 1.44 (ddd, J=11.2, 11.2, 11.2 Hz, 1H), 1.38–1.30 (m, 1H); ^{13}C NMR (125 MHz, d_6-acetone) δ 173.5, 80.7, 79.1, 78.2, 70.1, 68.5, 40.5, 38.5, 30.5, 26.7; HRMS (FAB, M−1) for $C_{10}H_{15}O_5$ calcd 215.0920, found: m/z 215.0912.

The acid (25 mg, 0.12 mmol) was dissolved in DME (0.3 mL) and then added via cannula to a mixture of KH (40 mg of 35% dispersion in mineral oil, 0.35 mmol, 3 equiv., washed with hexanes prior to addition[25]) in DME (0.3 mL) at 0°C. After 10 min, allyl bromide was added (11 μL, 0.13 mmol, 1.1 equiv.). The reaction was carefully quenched after 4 h with water (0.3 mL). The organic phase was extracted with 1N KOH (0.3 mL) and the combined aqueous phase was then washed with Et_2O (2 mL), acidified with 3N HCl until the pH~1–2, and then extracted with Et_2O (8×2 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 24 mg (80%) of 2-((1*S**,3*R**,4*S**,6*R**)-4-allyloxy-2,7-dioxabicyclo[4.4.0]decan-3-yl)acetic acid as a golden oil. If a small amount of the bicyclic hydroxy-acid remained, the two acids could be separated by flash chromatography (silica gel, solvent ramp: 100 mL each of 2.5, 5, 7.5, 10% MeOH/CH_2Cl_2/20 drops glacial HOAc). R_f 0.55 (5% MeOH/CH_2Cl_2/2 drops glacial HOAc in 10 mL); IR (neat) 3100, 2944, 2871, 1712, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.6 (br s, 1H) 5.87 (dddd, J=16.3, 10.3, 5.9, 5.9 Hz, 1H), 5.26 (dddd, J=17.3, 1.6, 1.6, 1.6 Hz, 1H), 5.18 (dddd, J=10.3, 1.2, 1.2, 1.2 Hz, 1H), 4.12 (dddd, J=12.5, 5.4, 1.2, 1.2 Hz, 1H), 3.94–3.89 (m, 2H), 3.69 (ddd, J=8.9, 8.9, 3.8 Hz, 1H), 3.39–3.34 (m, 1H), 3.22 (ddd, J=10.9, 9.3, 4.5 Hz, 1H), 3.08 (ddd, J=11.1, 8.9, 4.5 Hz, 1H), 2.95 (ddd, J=11.5, 8.9, 4.2 Hz, 1H), 2.88 (dd, J=15.6, 3.8 Hz, 1H), 2.50 (dd, J=15.7, 8.2 Hz, 1H), 2.48–2.45 (m, 1H), 2.07–2.04 (m, 1H), 1.72–1.68 (m, 2H) 1.47–1.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 134.6, 117.7, 77.9, 77.2, 76.7, 76.0, 69.9, 68.0, 37.9, 35.4, 29.3, 25.4; HRMS (FAB, M−1) for $C_{13}H_{19}O_5$ calcd 255.1233, found: m/z 255.1234.

Isobutyl chloroformate (70 μL, 0.53 mmol, 1.0 equiv.) was added to a mixture of triethylamine (74 μL, 0.53 mmol, 1.0 equiv.) and the allyl ether prepared above (137 mg, 0.53 mmol) in Et_2O (2.12 mL). The reaction was heated to reflux for 2.5 h then filtered and added via cannula to a solution of CH_2N_2 (~4 mmol) in Et_2O (~12 mL) at 0°C. The reaction was allowed to stand for 12 h and then diluted with Et_2O (12 mL) and carefully quenched with 0.1 M HOAc (10 mL) until gas evolution ceased. The organic phase was then washed with sat. $NaHCO_3$ (20 mL). The aqueous phase was extracted with Et_2O (10 mL) and the combined organic phase was washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography (silica gel, 2 cm×12 cm column, 30% EtOAc/hexanes) to yield 58 mg (44%) of **25** as a yellow solid. R_f 0.13 (30% EtOAc/hexanes); IR (KBr) 3124, 2954, 2852, 2104, 1635, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, J=16.3, 10.4, 5.0, 5.0 Hz, 1H), 5.34 (br s, 1H), 5.34–5.22 (m, 1H), 5.17–5.15 (m, 1H), 4.12–4.08 (m, 1H), 3.92–3.87 (m, 2H), 3.65 (ddd, J=8.9, 8.9, 2.8 Hz, 1H), 3.37–3.32 (m, 1H), 3.19 (ddd, J=10.6, 9.3, 4.4 Hz, 1H), 3.03 (ddd, J=11.1, 8.9, 4.4 Hz, 1H), 2.92 (ddd, J=11.6, 8.9, 4.3 Hz, 1H), 2.81 (app br d, J=14.8 Hz, 1H), 2.45 (ddd, J=11.6, 4.4, 4.4 Hz, 1H), 2.47–2.36 (s, br 1H), 2.04–2.01 (m, 1H) 1.72–1.66 (m, 2H), 1.44–1.32 (m, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2, −25°C) δ 193.2, 134.9, 117.1, 77.8, 77.4, 76.5, 75.8, 69.8, 67.9, 55.5, 43.8, 35.4, 29.3, 25.5; HRMS (FAB, M+1) for $C_{14}H_{21}N_2O_4$ calcd 281.1501, found: m/z 281.1501.

4.1.28. Tris(pyran) 26b (α-isomer). Compound **25** (35 mg, 0.13 mmol) was treated under the general procedure (CH_2Cl_2 (12.5 mL, 0.01 M), $Cu(tfacac)_2$ (2 mg, 5 mol%)) and purified by flash chromatography (silica gel, 2 cm×12 cm column, solvent ramp: 100 mL each of 10, 20, 30, 40% Et_2O/hexanes) to afford 25 mg (80%) of **26b** as a white solid. R_f 0.30 (50% Et_2O/hexanes); mp 84–85°C; IR (KBr) 2955, 2874, 1722, 1107, 1021 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 5.78 (dddd, J=17.0, 10.2, 6.9, 6.9 Hz, 1H), 5.16–5.10 (m, 2H), 4.04 (ddd, J=9.8, 5.5, 0.6 Hz, 1H), 3.91–3.86 (m, 1H), 3.56 (ddd, J=11.1, 9.3,

4.5 Hz, 1H), 3.43 (ddd, J=11.7, 9.4, 5.6 Hz, 1H), 3.39–3.34 (m, 1H), 3.10–3.05 (m, 2H), 2.82 (ddd, J=16.3, 5.5, 1.1 Hz, 1H), 2.60 (ddddd, J=14.5, 9.7, 7.2, 1.2, 1.2 Hz, 1H), 2.45 (ddd, J=16.4, 11.7, 0.6 Hz, 1H), 2.36 (ddddd, J=14.9, 6.9, 5.5, 1.4, 1.4 Hz, 1H), 2.28 (ddd, J=11.4, 3.9, 3.9 Hz, 1H), 2.06–2.00 (m, 1H) 1.77–1.67 (m, 2H) 1.55–1.38 (m, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 207.4, 133.6, 118.4, 81.7, 78.5, 77.6, 76.7, 69.6, 68.5, 43.9, 36.1, 34.8, 29.8, 26.1; HRMS (EI) for $C_{14}H_{20}O_4$ calcd 252.1362, found; m/z 252.1369.

4.1.29. Tris(pyran) 26a (β-isomer). Catalytic DBU (1 drop) was added to **26b** (22 mg, 0.087 mmol) in toluene (0.9 mL, 0.1 M). The reaction was heated to reflux and monitored by GC until no further change in epimer ratio was observed (6 h). The mixture was then cooled to rt, condensed and passed through a short pad of silica gel (2 cm in a disposable pipette) eluting with 50% Et_2O/hexanes. The solution was then concentrated to yield 20 mg (91%) of a mixture of **26a/26b** enriched in **26a** as a white solid (**26a/26b**, 10:1 determined by GC). R_f 0.36 (30% EtOAc/hexanes); mp 88–94°C; IR (KBr) 2955, 2861, 1723, 1098, 1023 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dddd, J=17.0, 10.2, 6.7, 6.7 Hz, 1H), 5.13 (dddd, J=17.6, 2.4, 2.4, 2.4 Hz, 1H) 5.08–5.05 (m, 1H), 3.96–3.92 (m, 1H), 3.83 (dd, J=7.4, 4.3 Hz, 1H), 3.46–3.37 (m, 3H), 3.13–3.06 (m, 2H), 2.92 (dd, J=15.5, 4.9 Hz, 1H), 2.68–2.61 (m, 1H), 2.49–2.32 (m, 3H), 2.09–2.04 (m, 1H), 1.78–1.72 (m, 2H), 1.63–1.56 (m, 1H), 1.49–1.40 (m, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 205.2, 134.8, 117.5, 83.1, 78.4, 77.5, 77.2, 76.4, 68.4, 45.6, 36.0, 34.2, 29.7, 26.1.

4.1.30. Tris(pyran) 27a. $LiAlH_4$ (2 mg, 0.04 mmol) was added to a solution of **26a/26b** (19 mg, 0.075 mmol) in THF (0.75 mL, 0.1 M) cooled to 0°C. The reaction was then allowed to stir until complete consumption of the starting material was evident by TLC. The reaction was quenched with 1:1 $Na_2SO_4{\cdot}10H_2O$/Celite and the resulting slurry was stirred for 30 min. Anhydrous $MgSO_4$ was added and the slurry stirred for and additional 30 min. The slurry was then filtered, concentrated and the products separated by flash chromatography (silica gel, 2 cm×10 cm column, solvent ramp: 100 mL each of 50, 60, 70, 80, 90% Et_2O/hexanes) to afford 18 mg (94%) of **27a** as a white solid and 1 mg (5%) of an isomer. R_f 0.32 (100% Et_2O); IR (KBr) 3391, 2939, 2852, 1113, 1088 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (dddd, J=17.2, 10.1, 6.9, 6.9 Hz, 1H), 5.17–5.13 (m, 1H), 5.10–5.08 (m, 1H), 3.93–3.90 (m, 1H), 3.54–3.48 (m, 1H), 3.38 (ddd, J=11.4, 11.4, 4.0 Hz, 1H), 3.18 (ddd, J=9.2, 6.9, 4.2 Hz, 1H), 3.12–2.99 (m, 4H), 2.58–2.53 (m, 1H), 2.40–2.28 (m, 3H), 2.08–2.05 (m, 1H), 1.76–1.69 (m, 2H), 1.61 (app br d, 1H), 1.54–1.39 (m, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 135.7, 117.1, 82.0, 78.7, 77.8, 77.2, 77.0, 69.9, 68.4, 39.2, 36.9, 36.1, 29.8, 26.1; HRMS (EI) for $C_{14}H_{22}O_4$ calcd 254.1518, found; m/z 254.1508.

4.1.31. 2-((2R^*,3S^*)-3-Hydroxy-3-methyltetrahydropyran-2-yl)aceticacidmethyl ester (28). To a solution of oxalyl chloride (1.26 mL, 14.4 mmol, 1.1 equiv.) in CH_2Cl_2 (20 mL) cooled to −78°C was added DMSO (2.0 mL, 28.8 mmol, 2.2 equiv.) dropwise. The solution was stirred for 2 min after which **14** (1.857 g, 13.1 mmol) in CH_2Cl_2 (13 mL) was added via cannula. After 15 min triethylamine (9.12 mL, 65.4 mmol, 5 equiv.) was added via syringe. The solution was stirred for 5 min after which the cooling bath was removed and the solution warmed to rt. The reaction was quenched by the addition of water (30 mL), the aqueous phase was back extracted with CH_2Cl_2 (30 mL) and the combined organic phase wash washed with 2% HCl, sat. $NaHCO_3$, and brine (50 mL each), dried with anhydrous $MgSO_4$, filtered and carefully concentrated. The crude yellow oil was dissolved in toluene (120 mL) and cooled to −78°C and MeMgBr (4.0 mL, 12.0 mmol) was added via syringe. The reaction was stirred until the starting material was consumed as ascertained by TLC plus an additional 30 min. The reaction was quenched by the addition of sat. NH_4Cl solution (100 mL) and the aqueous phase was back-extracted with Et_2O (100 mL). The combined organic phase was dried with anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography (silica gel, 5 cm×13 cm column, 50% Et_2O/hexanes) to yield 1.581 g (77%) of (2R^*,3S^*)-2-allyl-3-methyl-3-hydroxytetrahydropyran as a faintly yellow oil (5:1 inseparable mixture of diastereomers). R_f 0.23 (50% Et_2O/hexanes); IR (neat) 3466, 3073, 2939, 2852, 1636, 1098 cm^{-1}; ^{1}H NMR, major diastereomer, (500 MHz, $CDCl_3$) δ 5.94–5.85 (m, 1H), 5.15–5.04 (m, 2H), 4.02–3.98 (m, 1H), 3.41–3.35 (m, 1H), 3.18 (dd, J=9.5, 3.3 Hz, 1H), 2.39–2.33 (m, 1H), 2.30–2.25 (m, 1H), 1.93–1.82 (m, 1H), 1.77–1.67 (m, 1H), 1.64–1.46 (m, 3H), 1.13 (s, 3H); ^{13}C NMR, mixture of diastereomers, (125 MHz, $CDCl_3$) δ 136.5, 136.3, 116.6, 116.5, 84.3, 84.1, 70.2, 69.1, 68.9, 68.0, 39.6, 37.6, 33.9, 33.7, 24.9, 22.6, 20.8 (one overlapping signal); HRMS (EI) for $C_9H_{16}O_2$ calcd 156.1151, found: m/z 156.1152.

The tertiary alcohol prepared above (256 mg, 1.64 mmol) was treated to the standard ozonolysis procedure (CH_2Cl_2 (11.5 mL), MeOH (2.2 mL), 88% formic acid (1.2 mL), 30% H_2O_2 (0.65 mL)). Directly following the oxidation, the reaction mixture was concentrated and the residue was placed under high vacuum for 6 h. The residue was then dissolved in Et_2O (10 mL) and cooled to 0°C. Freshly prepared diazomethane was then added by pouring through a glass funnel (behind a blast shield, in a fume hood) and the reaction was complete after 10 min as ascertained by TLC. The solvent was evaporated with a stream of nitrogen (in a fume hood) and the yellow residue was purified by flash chromatography (silica gel, 2 cm×3 cm column, 50% EtOAc/hexanes) to yield 147 mg (48%) of **28** as a white solid. R_f 0.25 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (dddd, J=11.4, 4.8, 1.7, 1.7 Hz, 1H), 3.70 (s, 3H), 3.61 (dd, J=9.5, 3.5 Hz, 1H), 3.41 (ddd, J=11.6, 11.6, 2.8 Hz, 1H), 2.72 (dd, J=15.3, 3.4 Hz, 1H), 2.38 (dd, J=15.4, 9.5 Hz, 1H), 1.90–1.86 (m, 1H), 1.78–1.68 (m, 1H), 1.63–1.53 (m, 3H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 81.5, 69.7, 68.4, 52.1, 40.2, 35.3, 25.1, 20.2; Anal. calcd for $C_9H_{16}O_4$: C, 57.43, H, 8.56. Found, C, 57.58, H, 8.75.

4.1.32. 1-Diazo-3-((2R^*,3S^*)-3-allyloxy-3-methyltetrahydropyran-2-yl)propane-2-one 29. To a degassed solution of **28** (50 mg, 0.27 mmol) and allylmethylcarbonate (124 μL, 1.08 mmol, 4 equiv.) in THF (2.65 mL, 0.1 M) was added $Pd(OAc)_2$ (1.2 mg, 0.0054 mmol,

2 mol%). The solution was degassed again and triphenylphosphine was added (5.6 mg, 0.022 mmol, 0.08 equiv.) and the solution was heated to reflux for 20 h. The reaction was then allowed to cool to rt, then condensed and passed through a short pad of silica gel (3 cm in a disposable pipette) eluting with 50% EtOAc/hexanes. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography to obtain 33 mg (55%) of 2-((2*R**,3*S**)-3-allyloxy-3-methyltetrahydropyran-2-yl)aceticacid methyl ester and 20 mg (40% recovery) of the starting material. R_f 0.54 (50% EtOAc/hexanes); IR (neat) 2950, 2863, 1744, 1125 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.90–5.82 (m, 1H), 5.25–5.20 (m, 1H), 5.11–5.07 (m, 1H), 3.97–3.90 (m, 3H), 3.75–3.72 (m, 1H), 3.68–3.67 (app br t, 3H), 3.44–3.39 (m, 1H), 2.74 (ddd, *J*=15.3, 2.8, 1.1 Hz, 1H), 2.30 (ddd, *J*=15.3, 10.0, 1.2 Hz, 1H), 2.02–1.99 (m, 1H), 1.70–1.58 (m, 3H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 136.0, 115.7, 80.1, 73.6, 68.7, 62.1, 51.9, 35.3, 35.2, 24.6, 16.9; HRMS (CI, M+1) for $C_{12}H_{21}O_4$ calcd 229.1440, found: *m/z* 229.1445.

To a solution of the allylated product from above (151 mg, 0.66 mmol) in MeOH (1.32 mL, 0.5 M) was added 2N LiOH (0.66 mL). The reaction was stirred until completion as ascertained by TLC (12 h). The solution was transferred to a separatory funnel and diluted with 2 M NaOH (1 mL) and water (5 mL) and washed with Et_2O (2x10 mL). The aqueous phase was acidified with 3N HCl until the pH~1–2 and extracted with EtOAc (5×10 mL). The combined organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated to afford 138 mg (98%) of 2-((2*R**,3*S**)-3-allyloxy-3-methyltetrahydropyran-2-yl)acetic acid as a brownish oil. IR (neat) 3048, 2944, 2863, 1722, 1136 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.93 (br s, 1H), 5.86 (dddd, *J*=17.1, 10.5, 5.3, 5.3 Hz, 1H), 5.25–5.22 (m, 1H), 5.11–5.09 (m, 1H), 3.97–3.91 (m, 3H), 3.71 (dd, *J*=10.0, 2.7 Hz, 1H), 3.46–3.41 (m, 1H), 2.81 (dd, *J*=15.6, 2.8, Hz, 1H), 2.35 (ddd, *J*=15.6, 10.1, 1.7 Hz, 1H), 2.09–2.02 (m, 1H), 1.72–1.58 (m, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 135.8, 115.9, 79.8, 73.6, 68.8, 62.2, 35.2, 35.1, 24.5, 16.9; HRMS (FAB, M+1) for $C_{11}H_{19}O_4$ calcd 215.1283, found: *m/z* 215.1289.

The acid prepared above (63 mg, 0.29 mmol) was treated according to the general procedure for diazoketone formation (oxalyl chloride (31 μL, 0.35 mmol, 1.2 equiv.), CH_2Cl_2 (2 mL), one drop of DMF, CH_2N_2 (~4 mmol), Et_2O (12 mL)) and purified by radial chromatography (2 mm plate, 100 mL of 20% followed by 100 mL of 35% EtOAc/hexanes) to yield 46 mg (67%) of **29** as a yellow solid. R_f 0.36 (50% EtOAc/hexanes); IR (neat) 3084, 2943, 2860, 2102, 1636, 1352, 1130 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J*=17.2, 10.4, 5.1, 5.1 Hz, 1H), 5.33 (br s, 1H), 5.23 (dddd, *J*=17.2, 1.8, 1.8, 1.8 Hz, 1H), 5.09 (dddd, *J*=10.4, 1.4, 1.4, 1.4 Hz, 1H), 3.97–3.89 (m, 3H), 3.70 (dd, *J*=10.1, 2.1 Hz, 1H), 3.42–3.37 (m, 1H), 2.72 (dd, *J*=14.9, 1.8 Hz, 1H), 2.28 (app br t, 1H), 2.01–1.97 (m, 1H), 1.73–1.58 (m, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 136.0, 115.7, 80.1, 73.6, 68.7, 62.1, 55.3, 41.5, 35.2, 24.6, 17.1; HRMS (CI, M+1) for $C_{12}H_{19}N_2O_4$ calcd 239.1396, found: *m/z* 239.1403.

4.1.33. Decomposition of diazoketone 29 with Cu(tfacac)$_2$. The compound **29** (21 mg, 0.082 mmol) was treated according to the general procedure ($Cu(tfacac)_2$ (3.3 mg, 0.009 mmol, 10 mol%), CH_2Cl_2 (8.8 mL, 0.01 M)) and purification by radial chromatography (2 mm plate, solvent ramp: 100 mL each of 10, 15, 20% EtOAc/hexanes) yielded 4 mg (23%) of **31**, 2 mg (10%) of **30a** and 6 mg (35%) of **30b**.

4.1.34. (1*S,3*R**,6*R**)-1-Methyl-3-allyl-2,7-dioxabicyclo[4.4.0]decan-4-one (30a).** R_f 0.60 (50% EtOAc/hexanes); IR (neat) 3078, 2946, 2856, 1721, 1134, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (dddd, *J*=17.1, 10.1, 6.9, 6.9 Hz 1H), 5.11 (ddd, *J*=17.2, 3.4, 1.5 Hz, 1H), 5.07–5.05 (m, 1H), 4.10–4.08 (m, 1H), 4.00–3.96 (m, 1H), 3.47 (ddd, *J*=12.6, 11.6, 2.8 Hz, 1H), 3.40 (dd, *J*=12.6, 5.9 Hz, 1H), 2.73–2.68 (m, 1H), 2.60–2.54 (m, 1H), 2.45–2.39 (m, 2H), 1.95–1.84 (m, 2H), 1.70–1.59 (m, 2H), 1.31 (d, *J*=0.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 134.1, 117.8, 77.9, 77.8, 72.1, 68.7, 41.8, 37.1, 35.4, 24.3, 14.2; HRMS (CI) for $C_{12}H_{18}O_3$ calcd 210.1256, found: *m/z* 210.1237.

4.1.35. (1*S,3*S**,6*R**)-1-Methyl-3-allyl-2,7-dioxabicyclo[4.4.0]decan-4-one (30b).** R_f 0.55 (50% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J*=17.2, 10.3, 7.1, 7.1 Hz, 1H), 5.15–5.08 (m, 2H), 4.15 (dd, *J*=8.4, 4.4 Hz, 1H), 3.99–3.96 (m, 1H), 3.66 (dd, *J*=11.7, 6.7 Hz, 1H), 3.49–3.44 (m, 1H), 2.80 (dd, *J*=18.8, 6.7 Hz, 1H), 2.66–2.60 (m, 1H), 2.41 (ddd, *J*=18.8, 11.7, 0.6 Hz, 1H), 2.38–2.31 (m, 1H), 1.96–1.93 (m, 1H), 1.87–1.77 (m, 1H), 1.67–1.61 (m, 2H), 1.19 (d, *J*=0.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 134.5, 117.8, 79.8, 76.5, 72.3, 68.6, 40.5, 38.3, 37.6, 24.3, 18.0.

4.1.36. (1*S,6*R**)-1-Methyl-4-allyloxy-2,7-dioxabicyclo[4.4.0]dec-3-ene (31).** R_f 0.69 (50% EtOAc/hexanes); IR (neat) 2942, 2852, 1157, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.01 (dd, *J*=2.2, 0.7 Hz, 1H), 5.95 (dddd, *J*=17.2, 10.4, 5.6, 5.6 Hz, 1H), 5.32 (dddd, *J*=17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.24–5.21 (m, 1H), 4.15 (dddd, *J*=12.2, 5.5, 1.5, 1.5 Hz, 1H), 4.11 (dddd, *J*=12.3, 5.7, 1.5, 1.5 Hz, 1H), 3.97 (dddd, *J*=11.4, 5.0, 1.3, 1.3 Hz, 1H), 3.44 (ddd, *J*=12.6, 11.5, 2.4 Hz, 1H), 3.35 (dd, *J*=10.6, 6.1 Hz, 1H), 2.35 (dd, *J*=15.8, 6.3 Hz, 1H), 2.14 (ddd, *J*=15.8, 10.7, 2.2 Hz, 1H), 1.94–1.78 (m, 2H), 1.65–1.55 (m, 2H), 1.18 (d, *J*=0.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 133.9, 124.0, 117.8, 76.3, 73.2, 69.5, 68.7, 36.7, 28.4, 24.6, 15.2; HRMS (CI) for $C_{12}H_{18}O_3$ calcd 210.1256, found: *m/z* 210.1253.

4.1.37. Epimerization of 30a/30b. Catalytic DBU (1 drop) was added to mixture of **30a/30b** (7 mg, 0.03 mmol, **30a/30b**, 1:5 as determined by GC) in toluene (0.33 mL). The reaction was heated to 80°C and monitored by TLC and stirred until only **30a** was observed (4 h). The reaction was cooled to rt and loaded onto a short pad of silica (1 cm in a disposable pipette) eluting with 10% EtOAc/hexanes (10 mL). The solvent was evaporated under reduced pressure to afford 6 mg of **30a** (86%, **30a/30b**, 32:1 as determined by GC).

4.1.38. 1-Diazo-4-((2*R,3*S**)-3-allyloxytetrahydropyran-2-yl)butane-2-one 32.** To a solution of diazoketone **19**

(108 mg, 0.48 mmol) in THF (20 mL) and water (10 mL) was added silver nitrate (86 mg, 0.51 mmol, 1.05 equiv.). The reaction was stirred for 16 h and then diluted with water (30 mL) and extracted with CH_2Cl_2 (5×30 mL). The combined organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated to yield 100 mg (98%) of 3-((2*R**,3*S**)-3-allyloxytetrahydropyran-2-yl)propanoic acid as a yellow oil. IR (neat) 3080, 2940, 2860, 1710, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (br s, 1H), 5.89 (dddd, *J*=17.1, 10.3, 6.0, 6.0 Hz, 1H), 5.25 (ddd, *J*=17.2, 1.6, 1.6 Hz, 1H), 5.16 (ddd, *J*=10.3, 1.2, 1.2 Hz, 1H), 4.10 (dddd, *J*=12.6, 5.6, 1.5, 1.5 Hz, 1H), 3.95–3.85 (m, 2H), 3.35–3.26 (m, 1H), 3.12 (ddd, *J*=8.8, 8.8, 2.8 Hz, 1H), 3.02 (ddd, *J*=10.3, 8.9, 4.2 Hz, 1H), 2.60–2.38 (m, 2H), 2.29–2.19 (m, 2H), 1.76–1.55 (m, 3H), 1.40–1.24 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 135.1, 117.3, 80.3, 77.3, 70.0, 67.9, 30.7, 29.4, 27.5, 25.5. HRMS (FAB, M+1) for $C_{11}H_{19}O_4$ calcd 215.1283, found: *m/z* 215.1283.

The acid prepared above (128 mg, 0.59 mmol) was treated according to the general procedure for diazoketone formation (oxalyl chloride (63 μL, 0.72 mmol, 1.2 equiv.), CH_2Cl_2 (4 mL), one drop of DMF) and purified by radial chromatography (2 mm plate, 200 mL of 50% EtOAc/hexanes) to yield 129 mg (91%) of **32** as a yellow oil. R_f 0.33 (50% EtOAc/hexanes); IR (neat) 3089, 2933, 2853, 2099, 1642, 1372, 1345, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (dddd, *J*=17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.26 (dddd, *J*=17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.25 (br s, 1H), 5.16 (dddd, *J*=10.3, 1.3, 1.3, 1.3 Hz, 1H), 4.10 (dddd, *J*=12.5, 5.6, 1.3, 1.3 Hz, 1H), 3.92 (dddd, *J*=12.5, 5.8, 1.4, 1.4 Hz, 1H), 3.89–3.83 (m, 1H), 3.3 (ddd, *J*=11.3, 11.3, 3.0 Hz, 1H), 3.11–2.96 (m, 2H), 2.54–2.39 (m, 2H), 2.30–2.17 (m, 2H), 1.73–1.54 (m, 3H), 1.39–1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 135.2, 117.2, 80.3, 77.0, 70.1, 67.9, 54.4, 37.3, 29.5, 27.9, 25.6; Anal. calcd for $C_{12}H_{18}N_2O_3$: C, 60.49, H, 7.61. Found, C, 60.62, H, 7.58.

4.1.39. Decomposition of diazoketone 32 with Cu(tfacac)$_2$. The compound **32** (40 mg, 0.17 mmol) was treated according to the general procedure ($Cu(tfacac)_2$ (6 mg, 0.017 mmol, 10 mol%), CH_2Cl_2 (17 mL, 0.01 M)) and purification by flash chromatography (silica gel, 2 cm×15 cm, 100 mL 20% EtOAc/hexanes, 200 mL 25% EtOAc/hexanes, 100 mL 35% EtOAc/hexanes) yielded 19 mg (55%) of ketone **33** as a colorless oil. R_f 0.37 (50% Et_2O/hexanes); IR (neat) 3080, 2941, 2863, 1743, 1091, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.94–5.81 (m, 1H), 5.23 (dddd, *J*=17.2, 1.5, 1.5, 1.5 Hz, 1H), 5.15 (dddd, *J*=10.3, 1.4, 1.4, 1.4 Hz, 1H), 4.14 (dddd, *J*=12.8, 2.8, 1.5, 1.5 Hz, 1H), 3.92 (dddd, *J*=12.7, 5.8, 1.4, 1.4 Hz, 1H), 3.71–3.65 (m, 1H), 3.42 (ddd, *J*=11.4, 11.4, 3.2 Hz, 1H), 3.28 (dd, *J*=10.5, 4.2 Hz, 1H), 2.51 (d, J_{AB}=18.0 Hz, 1H), 2.47 (d, J_{AB}=18.0 Hz, 1H), 2.45–2.22 (m, 2H), 2.08–1.94 (m, 2H), 1.74–1.59 (m, 3H), 1.42–1.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.7, 135.0, 117.1, 83.1, 78.2, 70.1, 62.4, 42.1, 36.6, 33.2, 25.9, 24.8; HRMS (EI) for $C_{12}H_{18}O_3$ calcd 210.1256, found: *m/z* 210.1241.

4.1.40. Decomposition of diazoketone 15 with Rh$_2$(tpa)$_4$. Compound **15** (60 mg, 0.22 mmol) was treated according to the general procedure ($Rh_2(tpa)_4$ (10 mg, 0.007 mmol, 3 mol%), CH_2Cl_2 (24 mL, 0.01 M)) and purification by radial chromatography (2 mm plate, 200 mL 25% EtOAc/hexanes followed by 200 mL 30% EtOAc/hexanes) yielded 22 mg (41%) of **16a**, 9 mg (17%) of **16b**, and 6 mg (12%) of **34**.

4.1.41. (1*S,3*S**,6*R**)-3-Benzyl-2,7-dioxabicyclo[4.4.0]-decan-4-one (16b).** R_f 0.48 (50% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.19 (m, 5H), 4.28–4.25 (m, 1H), 3.96–3.91 (m, 1H), 3.55 (ddd, *J*=10.6, 9.4, 4.5 Hz, 1H), 3.43–3.34 (m, 2H), 3.16 (dd, *J*=14.2, 9.9 Hz, 1H), 2.93–2.86 (m, 2H), 2.50 (dd, *J*=16.5, 11.5 Hz, 1H), 2.09–2.06 (m, 1H), 1.81–1.76 (m, 2H), 1.52–1.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 137.0, 129.5, 128.8, 127.1, 83.3, 76.6, 70.4, 67.8, 44.1, 36.2, 29.3, 25.5.

4.1.42. (1*S,6*R**)-4-Benzyloxy-2,7-dioxabicyclo[4.4.0]-dec-3-ene (34).** R_f 0.60 (50% EtOAc/hexanes); IR (neat) 3031, 2033, 2849, 1145, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.17 (m, 5H), 6.16–6.15 (m, 1H), 4.59 (d, J_{AB}=11.4 Hz, 1H), 4.53 (d, J_{AB}=11.4 Hz, 1H), 3.87–3.83 (m, 1H), 3.36–3.27 (m, 2H), 3.18 (ddd, *J*=10.9, 9.4, 4.5 Hz, 1H), 2.42 (dd, *J*=15.9, 6.5 Hz, 1H), 2.24 (ddd, *J*=15.9, 9.6, 2.2 Hz, 1H), 2.08–2.05 (m, 1H), 1.72–1.62 (m, 2H), 1.45–1.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 137.4, 128.7, 128.2, 127.9, 126.3, 74.6, 74.5, 70.6, 67.9, 31.5, 29.1, 25.5; HRMS (EI) for $C_{15}H_{18}O_3$ calcd 246.1256, found: *m/z* 246.1262.

4.1.43. Decomposition of diazoketone 25 with Rh$_2$(tpa)$_4$. The compound **32** (44 mg, 0.18 mmol) was treated according to the general procedure ($Rh_2(tpa)_4$ (7 mg, 0.005 mmol, 3 mol%), CH_2Cl_2 (17 mL, 0.01 M)) and purification by flash chromatography (silica gel, 2 cm×15 cm, 100 mL 20% EtOAc/hexanes, 200 mL 25% EtOAc/hexanes, 100 mL 35% EtOAc/hexanes) yielded 16 mg (42%) of **35a** and 13 mg (35%) of **35b**.

4.1.44. Cyclopropane diastereomer 35a. R_f 0.39 (50% EtOAc/hexanes); IR (neat) 3005, 2931, 2849, 1695, 1378, 1209, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.26 (dd, *J*=11.7, 5.1 Hz, 1H), 3.84–3.81 (m, 1H), 3.28–3.23 (m, 1H), 3.09 (ddd, *J*=9.5, 6.7, 3.5 Hz, 1H), 2.79 (dd, *J*=14.6, 10.1 Hz, 1H), 2.72 (ddd, *J*=10.6, 9.4, 4.9 Hz, 1H), 2.58 (dd, *J*=11.0, 11.0 Hz, 1H), 2.54 (dd, *J*=14.9, 10.5 Hz, 1H), 2.37–2.32 (m, 1H), 2.20–2.13 (m, 2H), 2.02–1.96 (m, 1H), 1.79–1.71 (m, 1H), 1.58–1.40 (m, 3H), 1.28–1.20 (m, 1H), 0.88 (ddd, *J*=8.2, 6.8, 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 80.7, 79.7, 71.0, 67.8, 39.6, 31.6, 28.8, 26.2, 25.6, 24.4, 9.9; HRMS (CI, M+1) for $C_{12}H_{19}O_3$ calcd 211.1334, found: *m/z* 211.1327.

4.1.45. Cyclopropane diastereomer 35b. R_f 0.24 (50% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$, 45°C) δ 3.87–3.84 (m, 1H), 3.73 (dd, *J*=11.8, 4.8 Hz, 1H), 3.34 (dd, *J*=11.1, 6.8 Hz, 1H), 3.29 (ddd, *J*=11.5, 11.5, 3.2 Hz, 1H), 3.20 (ddd, *J*=10.0, 10.0, 4.9 Hz, 1H), 2.98 (ddd, *J*=9.9, 9.9, 2.9 Hz, 1H), 2.68 (ddd, *J*=15.9, 13.1, 1.6 Hz, 1H), 2.47 (dd, *J*=15.9, 7.9 Hz, 1H), 2.31 (dddd, *J*=14.4, 12.4, 10.1, 1.8 Hz, 1H), 2.10–1.98 (m, 3H), 1.84–1.77 (m, 1H), 1.66–1.54 (m, 3H), 1.28 (dddd, *J*=12.6, 12.6, 11.0, 5.3 Hz, 1H), 0.93 (ddd, *J*=7.9, 7.9, 4.9 Hz, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$, 45°C) δ 207.7, 80.3, 77.1, 67.8, 65.3, 40.8, 31.5, 29.4, 25.4, 24.3, 22.5, 11.7.

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