Study of the Rearrangements of Oxonium Ylides Generated from Ketals

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Intramolecular exposure of cyclic ketals to metal carbenoids generates a proposed oxonium ylide intermediate that subsequently rearranges to one of three general products. The product resulting from a 1,2-shift to the ketal carbon is favored by larger ketals that lack radical stabilizing groups. A bridged bicyclic structure is formed by competitive 1,2-shift to the exocyclic carbon of the ketal and is favored by smaller ketal ring sizes that possess radical-stabilizing groups. An alternative β-elimination pathway can also operate when neither of the 1,2-shift pathways are favored. The enol ether that is formed in this latter pathway rearranges easily to an isomeric dioxene.

Introduction

While the application of phosphorus and sulfur ylides to organic synthesis is quite common, the use of oxonium ylides for synthetic transformations is encountered less frequently. The reduced synthetic applicability of oxonium ylides has been attributed to the inherent difficulty in forming oxonium ylides via traditional methods such as deprotonation of corresponding onium salts. Although Olah demonstrated that dimethyloxonium methylide could be generated by the deprotonation of the trimethyloxonium salt,[2] the tendency for trivalent oxygen to donate alkyl groups before protons generally excluded the use of strong base for synthetic applications.[3] Gutsche demonstrated in 1954 that generation of oxonium ylides was possible through the decomposition of α-diazo carbonyls (Figure 1, reaction 1),[4] yet this report appeared to stimulate little new chemistry. The recent development of chemoselective rhodium and copper catalysts has renewed interest in oxonium ylides. Subsequent studies have demonstrated that ylides derived from carbonyl and ethereal oxygens can be used as intermediates in a wide variety of subsequent transformations, including dipolar cycloadditions, Steven's 1,2-shifts, 2,3-sigmatropic rearrangements, and simple β-eliminations.[5]

Both the chemistry of carbonyl ylides and the chemistry of oxonium ylides derived from ethers have been studied in some detail; however, ylides derived from ketals have been largely ignored. Nevertheless, evidence

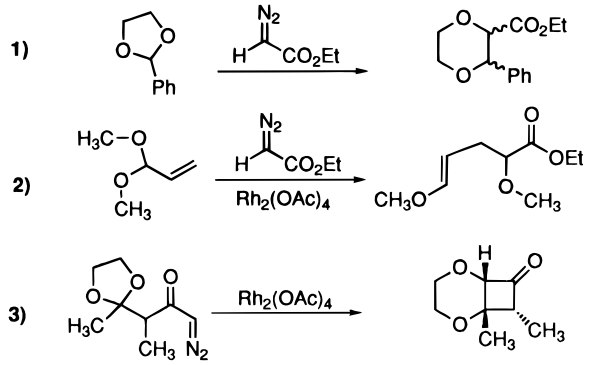

Figure 1.

in the literature suggests that divergent reactivity is possible from ketal-derived ylides. For example, Doyle and co-workers have observed a 2,3-sigmatropic rearrangement of the oxonium ylide generated from the dimethyl acetal of acrolein (Figure 1, reaction 2).[6] This reactivity complements the results of Gutsche and the results of Roskamp and Johnson (Figure 1, reaction 3),[7] who demonstrated that ketal-derived oxonium ylides decompose via 1,2-shift pathways.

We initiated an investigation in order to clarify the factors that influence ylide formation and reactivity through the synthesis and catalytic decomposition of various dioxolane substrates. In short, our initial study addressed the competition between six-membered ring bicyclic ylide formation and C−H insertion, competitive ylide formation between diastereotopic oxygens, the influence of copper(II) and rhodium(II) catalytic systems, and the role substituents on the ketal play in determining the subsequent reactivity of the resultant ylides.[8] We now report the details of our investigation, which suggest that bicyclic ylide rearrangement is dominated by two primary factors: ring-size of the intermediate bicyclic ylide and the nature of substituents on the ketal.

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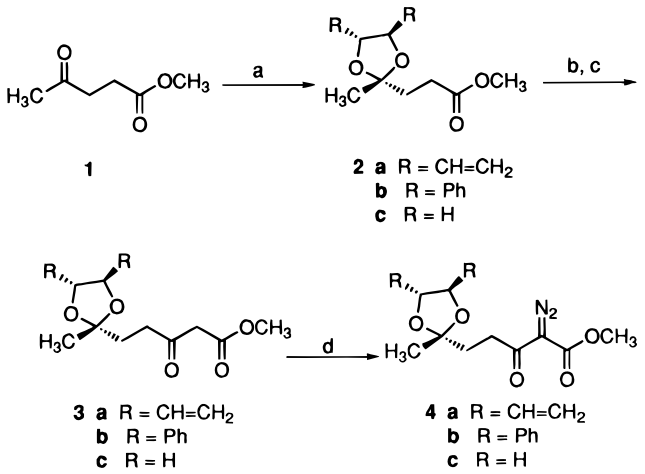
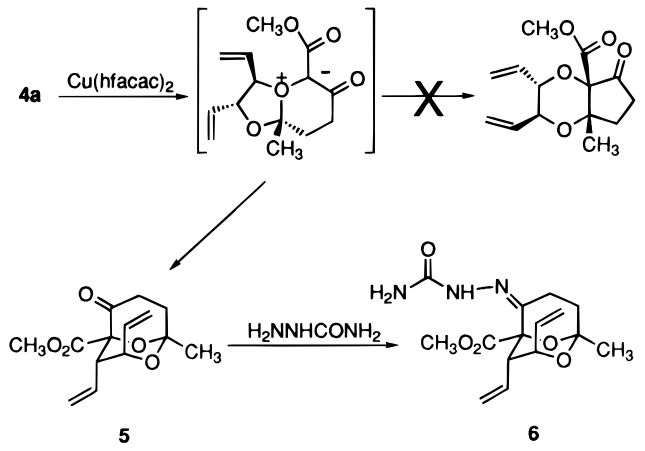
Scheme 1[a]



[a] Key: (a) diol, $(CH_3O)_3CH$, *p*-TsOH; (b) (i) KOH/CH_3OH; (ii) H_3O^+; (c) carbonyldiimidazole; (ii) $Mg^{2+}(CH_3O_2CCH_2CO_2^-)_2$; (d) *p*-carboxybenzenesulfonazide, Et_3N.

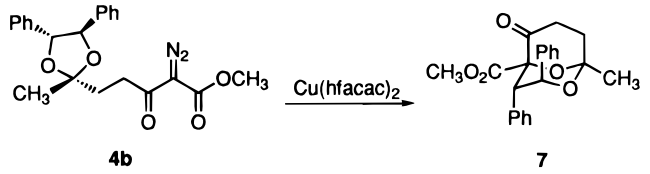
Scheme 2



Results and Discussion

Our initial substrate was chosen for its potential to undergo 1,2- and/or 2,3-shifts from an intermediate oxonium ylide. The preparation of **4a** (Scheme 1) was initiated through the conversion of methyl levulinate (**1**) to a mixture of ketals separable by chromatography. The isomer **2a**, derived from the *d*,*l*-diol, was saponified and converted to the β-keto ester **3a** according to the procedure of Masamune.[9] Diazo transfer was subsequently effected with 4-carboxybenzenesulfonazide and triethylamine.[10] Upon exposure to catalytic $Cu(hfacac)_2$[11] at room temperature, compound **4a** was converted to a single compound **5** in 64% yield (Scheme 2). The compound formed in this reaction was clearly the result of a 1,2-shift, yet connectivity within the ring system and the stereochemical orientation of the vinyl groups could not be determined from the spectroscopic data. Transformation of **5** into its crystalline semicarbazone derivative **6** provided a suitable substrate for X-ray analysis. It was apparent from this X-ray structure that the proposed intermediate ylide was formed through nucleophilic attack of the least sterically hindered oxygen and that 1,2-shift to the exocyclic, allylic carbon occurred with complete retention of configuration. The unusual feature of this rearrangement was that the migration did not involve the ketal carbon as observed in all previous studies. Factors that influence competitive exocyclic and endocyclic 1,2-shifts with cyclic ylides derived from ethers have been reported;[12] however, similar competition has not been explored with ketal substrates. We undertook the preparation and study of additional substrates that would allow the determination of factors that control the competitive rearrangements.

Scheme 3



The generality of the exocyclic 1,2-shifts was confirmed through preparation of the analogous diphenyl-substituted dioxolane **4b** from (±)-1,2-diphenyl-1,2-dihydroxyethane. Exposure of **4b** to $Cu(hfacac)_2$ resulted in its conversion to a single diastereomer in a 65% yield. Analysis of the ^1H and ^{13}C NMR spectra led to the structural assignment of the bridged bicyclic compound **7** (Scheme 3). Since the coupling constant between the two allylic methine protons in **5** (^3J = 8.5 Hz) was consistent with the twist-boat conformation of its crystal structure, the identification of a similar coupling constant between the two benzylic methines in **7** (^3J = 9.1 Hz) was suggestive of structure **7** in a similar twist-boat conformation.

The unsubstituted dioxolane **4c** was prepared through a similar sequence of reactions, and its exposure to $Cu(hfacac)_2$ resulted in the formation of two compounds (Scheme 4). The product **8** resulting from β-elimination was generated in 57% yield, while a ring-fused product **9** was generated in an 18% yield.[13] This latter product, the result of an endocyclic 1,2-shift involving the ketal carbon, is analogous to that observed in the earlier study of Johnson. The appearance of alternative reaction pathways is not unexpected, since major variations in product selectivity have been observed in previous ylide studies.[5k] Although the ring-fused compound that was formed is isomeric with and possesses a proton spin system identical to the analogous bridged bicyclic structure, structural assignment by analysis of the NMR spectra is possible. The difference in ^{13}C chemical shifts of the quaternary carbons (ketal, δ > 100 ppm; ether, $\delta \approx 92$ ppm) and the upfield shift of the methine proton in the bridged bicyclic structure are characteristic of the two ring systems.

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(11) Both Rhodium and Copper catalysts effect this same rearrangement; however, $Cu(hfacac)_2$ has been found to be the most efficient catalyst for the preparation of ylides from ketals (see ref 8). This observation of catalyst efficiency has been made not only in regard to intramolecular ylide formation but also with parallel studies on the formation of ylides through intermolecular reactions. This result is consistent with previous observations. (a) Clark, J. S.; Krowiak, S. K.; Street, J. L. *Tetrahedron Lett.* **1993**, *34*, 4385. (b) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892.

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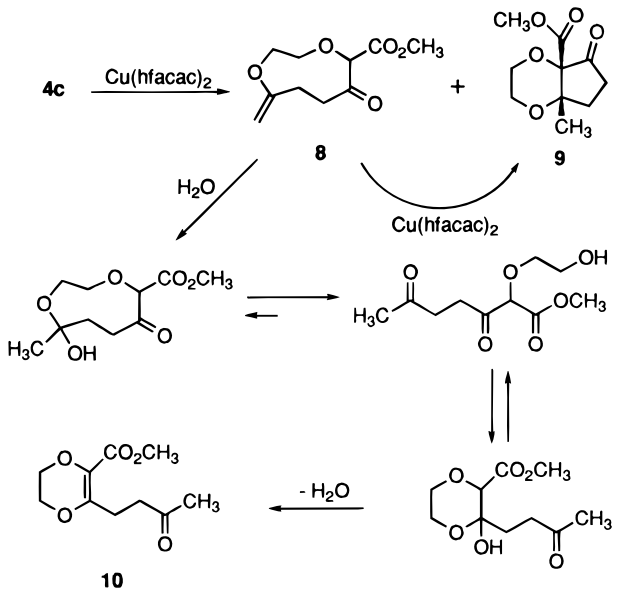
(13) The stereochemical assignment of this ring-fused product is consistent with that observed in two closely related systems. As described later in the text, the assignment of *cis*-stereochemistry in **19** was made by X-ray analysis of a crystalline derivative. Roskamp and Johnson, in their study of oxonium ylide chemistry, reported a *cis*-stereochemical relationship for a ring system that contained one fewer carbon (see ref 7).

Scheme 4



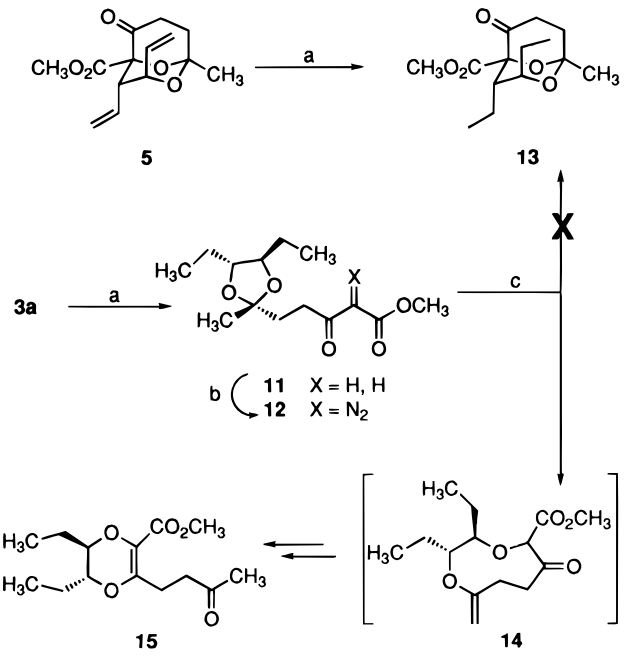
The competitive relationship between the β-elimination product **8** and the ring-fused product **9** merits some discussion. While it has been difficult to completely suppress formation of **8**, the yield of the competitive ring-fused compound **9** was optimized to 51% by dehydration of the catalyst and employment of strictly anhydrous conditions, thereby suggesting that water may act as a base to promote the β-elimination reaction. When the moisture-sensitive enol ether **8** was isolated and re-exposed to catalytic Cu(hfacac)$_2$, significant formation of the ring-fused product **9** was observed. Although the mechanistic details in the formation of **9** from **8** are not known, it is clear that ring-fused products are not necessarily formed through direct 1,2-shifts.

Although it is possible to isolate the β-elimination product **8** by chromatography, the compound is quite sensitive and rapidly isomerizes to dioxene **10** in the presence of H_2O. A reasonable mechanism for this transformation is hydrolysis of the enol ether followed by interconversion of two isomeric hemiacetals. Dehydration of a hemiacetal produces dioxene **10** and regenerates water. This intriguing rearrangement provides a potentially general route to functionalized dioxene derivatives.

In order to determine the influence of alkyl-substituted dioxolanes in this chemistry, substrate **12** was prepared by catalytic reduction of **3a** followed by diazo transfer. An authentic sample of a possible bridged bicyclic structure **13** was prepared by reduction of **5** (Scheme 5). When diazo compound **12** was exposed to Cu(hfacac)$_2$, no evidence of the bridged bicyclic structure **13** was observed. The presence of a β-elimination product **14** was suggested by new olefinic proton resonances in the ^{1}H NMR spectrum. Although this moisture-sensitive compound could not be fully characterized, its subsequent rearrangement to dioxene product **15** provided further confirmation that **14** was the product of β-elimination. It is not at all clear why the ylide derived from the diethyl dioxolane substrate **12** does not participate in a 1,2-shift to provide the ring-fused product as was observed with substrate **4c**; however, the additional steric bulk of the two ethyl groups must be considered as a possible factor.

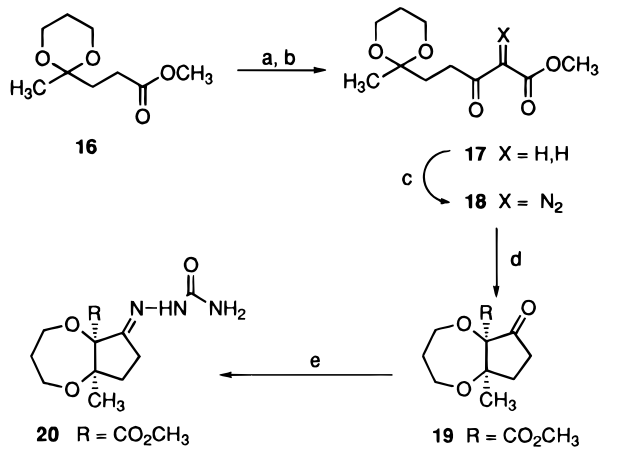
While dioxolane substitution patterns clearly influence the direction and efficiency of the 1,2-shifts, we were

Scheme 5[a]



[a] Key: (a) H_2/Pd/C; (b) *p*-carboxysulfonylazide, Et_3N; (c) cat. Cu(hfacac)$_2$.

Scheme 6[a]

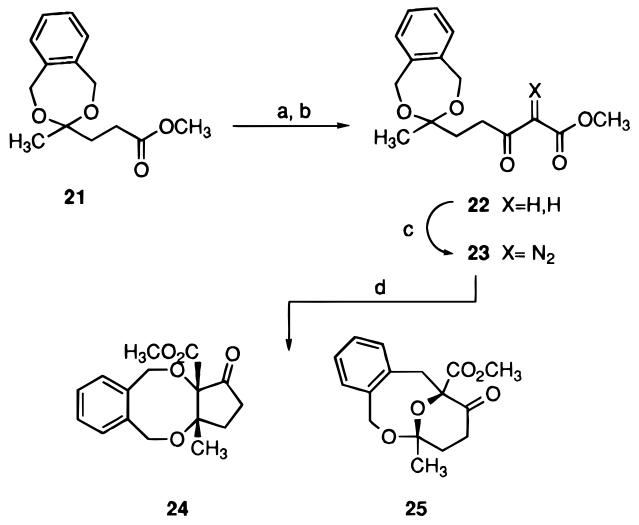


[a] Key: (a) (i) KOH/CH_3OH; (ii) H_3O^+; (b) (i) carbonyldiimidazole, (ii) $Mg^{2+}(O_2CCH_2CO_2CH_3)_2$; (c) *p*-carboxybenzenesulfonazide, Et_3N; (d) cat. Cu(hfacac)$_2$; (e) $H_2NHNCONH_2$.

interested in elucidating the effects of ring size on these rearrangements. Preparation of the dioxane-containing substrate **18** provided a vehicle for studying rearrangements of the homologous bicyclic ylide. In contrast to previous compounds, exposure of compound **18** to catalyst resulted in quantitative conversion to the ring-fused bicyclic structure **19** (Scheme 6). No β-elimination was observed with either rigorously dried or hydrated catalyst. The *cis* ring fusion of **19** was unambiguously determined by X-ray analysis of its semicarbazone derivative **20**.

With a trend emerging whereby larger ketal ring size facilitates endo 1,2-shifts and smaller cyclic ketals that possess radical-stabilizing groups promote exocyclic shifts, the benzodioxepin substrate **23** was prepared. This larger bicyclic ylide should encounter little resistance to transannular ring closure, while, at the same time, the radical-stabilizing benzylic carbons should facilitate exocyclic migration. Exposure of **23** to catalytic Cu(hfacac)$_2$

Scheme 7[a]



[a] Key: (a) (i) KOH/CH_3OH; (ii) H_3O^+; (b) (i) carbonyldiimidazole, (ii) $Mg^{2+}(O_2CCH_2CO_2CH_3)_2$; (c) *p*-carboxybenzenesulfonazide, Et_3N; (d) cat. $Cu(hfacac)_2$.

resulted in the formation of both 1,2-shift products **24** and **25** (Scheme 7). The major product **24**, formed in yields from 57 to 68%, was the result of an endocyclic 1,2-shift to the ketal carbon. The minor component **25**, an unstable bridged bicyclic skeleton resulting from an exocyclic 1,2-shift to the benzylic position, was formed in yields that ranged from trace amounts to 18% yield. The factors that determined the efficiency in which **25** was formed in the reactions are not entirely understood; however, it was abundantly clear that in every reaction the ring-fused bicyclic skeleton **24** was formed with greater efficiency. Therefore, the presence of benzylic stabilization is not the dominant factor in determining the fate of the intermediate oxonium ylide. The intimately related factors of geometry and strain encountered in the 1,2-shift pathways appear to be important factors in determining the fate of these oxonium ylides.

Conclusion

We have demonstrated that intramolecular ylide formation and subsequent rearrangement is a facile process. The efficiency and product selectivity of the rearrangements appear to be influenced by two primary factors. The first factor is the ring size of the bicyclic ylide, while the second is the substitution pattern of the ketal. More flexible bicyclic ylides (larger ring systems) rearrange via 1,2-shifts to the ketal carbon (endocyclic) far easier than their analogues, which possess smaller ring ketals. This could be due to conformational flexibility of the ring system, stereoelectronic factors, or a combination of both. However, it is clear that the presence of radical-stabilizing groups directly attached to the ketal oxygens promote 1,2-shifts to the stabilized exocyclic carbon.

The highly functionalized 2,9-dioxabicyclo[3.3.1]nonane skeleton is rapidly assembled utilizing this methodology. This ring system, represented above in compounds **5** and **7**, constitutes the core of the natural products streptolic acid[14] and tirandamycin.[15] It appears likely that the analogous 2,8-dioxabicyclo[3.2.1]octane core of Zaragozic acid[16] can also be approached in this fashion. Further investigation into the remarkably facile generation of these highly substituted bridged-bicyclic structures is underway. These efforts include the further investigation of substituent effects, stereoelectronic considerations, and the application of this methodology to natural product synthesis.

Experimental Section

General Experimental Methods. Tetrahydrofuran and diethyl ether were distilled from benzophenone ketyl. Benzene and was distilled from calcium hydride. The *p*-carboxybenzenesulfonazide,[10] methyl levulinate,[17] benzenedimethanol,[18] and monomethyl malonate[19] are known compounds. The catalyst, $Cu(hfacac)_2$, was obtained from Aldrich as the dihydrate. The catalyst was dried over H_2SO_4 in a vacuum desiccator (0.1 Torr) for 3 days and transferred in a glovebag under nitrogen atmosphere.[20] All other materials were used as received from commercial suppliers. Column chromatography was performed on Baker 40 νm silica gel. Thin layer chromatography (TLC) was carried out EM Science F254 glass plates and visualized by UV and anisaldehyde stain. All reactions were run in oven-dried glassware under nitrogen atmosphere.

***trans*-4,5-Diethenyl-2-[2-(carboxymethyl)ethyl]-2-methyl-1,3-dioxolane (2a).** A solution of methyl levulinate (**1**) (2.38 g, 18.2 mmol), 1,5-hexadiene-3,4-diol (2.28 g, 20 mmol, ~1:1 mixture of *meso*:*dl*), and trimethyl orthoformate (2.40 mL, 22 mmol) in dry benzene (30 mL) was charged with *p*-TsOH (~20 mg) and stirred for 2 h. The mixture was diluted with Et_2O, washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica (10% EtOAc in hexane, R_f 0.22) to yield a mixture of diastereomers (3.72 g, 90%, ~1:1 mixture of trans: cis (the ratio of the two cis isomers was variable)). Further chromatography on silica (5% EtOAc in hexane, R_f 0.18) provided the desired *trans* isomer **2a** (1.65 g, 40%) as a thick oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.84−5.72 (m, 2H), 5.39−5.22 (m, 4H), 4.13 (m, 1H), 4.02 (m, 1H), 3.7 (s, 3H), 2.48−2.41 (m, 2H), 2.12−2.02 (m, 2H), 1.4 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.9, 134.2, 133.2, 119.02, 118.99, 109.67, 82.9, 82.1, 51.5, 34.8, 28.7, 25.4; IR (film) 3050−2850, 1750, 1450, 1350 cm^{-1}; MS (CI, C_2H_6) 227, 195, 171, 139, 131, 99.

***trans*-4,5-Diethenyl-2-[4-(carboxymethyl)-3-oxobutyl]-2-methyl-1,3-dioxolane (3a).** Ketal **2a** (1.50 g, 6.6 mmol) was treated with methanolic KOH (2 M, 30 mL) for 8 h, acidified to pH 4.0 with saturated aqueous citric acid, and extracted with diethyl ether (5 × 30 mL). The combined organic extracts were carefully dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and dissolved in THF. Carbonyldiimidazole (1.15 g, 7.1 mmol) was added in small portions with stirring, and acylimidazole formation was monitored by TLC. In a separate flask, monomethyl malonate (1.20 g, 10.2 mmol) was dissolved in THF (10 mL), treated with Bu_2Mg (5.1 mL of 1.0 M in heptane, 5.1 mmol) at 0 °C, and warmed to room temperature with stirring. The mixtures were combined and

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stirred for 24 h, diluted with diethyl ether (20 mL), washed with aqueous NH_4Cl and $NaHCO_3$, and concentrated. The residue was chromatographed on silica (20% EtOAc in hexane, R_f 0.20) to yield **3a** (1.1 g, 62%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.83−5.72 (m, 2H), 5.39−5.22 (m, 4H), 4.11 (m, 1H), 4.00 (m, 1H), 3.7 (s, 3H), 3.5 (s, 2H), 2.71−2.65 (m, 2H), 2.10−2.03 (m, 2H), 1.4 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.2, 167.6, 134.2, 133.2, 119.2, 118.9, 109.7, 82.9, 82.2, 52.3, 48.9, 37.7, 33.6, 25.5; IR (film) 3000−2800, 1775, 1725 cm^{-1}; MS (CI, CH_4) 269, 231, 173, 155, 139, 97; HRMS (CI, CH_4) ([M + H]$^+$) calcd for $C_{14}H_{21}O_5$ 269.1389, found 269.1390.

***trans*-4,5-Diethenyl-2-[4-(carboxymethyl)-4-diazo-3-oxobutyl]-2-methyl-1,3-dioxolane (4a).** A solution of **3a** (563 mg, 2.1 mmol) and Et_3N (0.64 mL, 4.95 mmol) in CH_3CN (5 mL) was charged with 4-carboxybenzenesulfonazide (545 mg, 2.4 mmol) at room temperature and stirred for 2.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether washes were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (20% EtOAc in hexane, R_f 0.21) to yield **4a** (598 mg, 97%) as a bright yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.88−5.72 (m, 2H), 5.39.5.21 (m, 4H), 4.12−4.02 (m, 2H), 3.8 (s, 3H), 3.10−2.90 (m, 2H), 2.12−2.02 (m, 2H), 1.5 (s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 192.2, 161.7, 134.3, 133.6, 119.0, 118.8, 110.0, 82.9, 82.2, 75.7, 52.1, 34.9, 34.0, 25.5; IR (film) 3000−2800, 2200 (s), 1750, 1650 cm^{-1}; MS (CI, NH_3) 295, 279, 199, 154, 139, 124, 113, 99, 799, 55; HRMS (MH$^+$) calcd for $C_{14}H_{19}N_2O_5$ 295.1294, found 295.1283.

2-[2-(Carboxymethyl)ethyl]-2-methyl-*trans*-4,5-diphenyl-1,3-dioxolane (2b). A solution of methyl levulinate (**1**) (156 mg, 1.20 mmol), 1,2-diphenyl-1,2-ethane diol (242 mg, 1.13 mmol), and trimethyl orthoformate (0.15 mL, 1.4 mmol) in dry benzene (5 mL) was charged with *p*-TsOH (∼5 mg) and stirred for 6 h. The mixture was diluted with diethyl ether, washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica (5% EtOAc in hexane, R_f 0.22) to yield **2b** as an oil (346 mg, 94%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40−7.21 (m, 10H), 4.83−4.74 (m, 2H), 3.7 (s, 3H), 2.74−2.66 (m, 2H), 2.41−2.34 (m, 2H), 1.7 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.7, 136.8, 136.0, 128.4, 128.3, 128.2,128.1, 126.7, 126.5, 109.7, 85.9, 85.0, 51.5, 35.1, 28.9, 25.4; IR (film) 3200, 3000, 1750 cm^{-1}; MS (CI, C_2H_6) 355, 327, 249, 221, 197, 131, 99.

2-[4-(Carboxymethyl)-3-oxobutyl]-2-methyl-*trans*-4,5-diphenyl-1,3-dioxolane (3b). Ketal **2b** (60 mg, 0.18 mmol) was treated with methanolic KOH (2 M, 3 mL) for 8 h, acidified to pH 4.0 with saturated aqueous citric acid, and extracted with diethyl ether (5 × 30 mL). The combined organic washings were carefully dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and dissolved in tetrahydrofuran. Carbonyldiimidazole (50 mg, 0.31 mmol) was added in small portions. In a separate flask, monomethyl malonate (128 mg, 1.10 mmol) was dissolved in THF (5 mL), treated with Bu_2Mg (1.0 M in heptane, 0.55 mmol) at 0 °C, and warmed to room temperature with stirring. The mixtures were combined and stirred further for 24 h, diluted with diethyl ether (20 mL), washed successively with aqueous NH_4Cl, $NaHCO_3$, and brine, and concentrated *in vacuo*. The residue was chromatographed on silica (5% EtOAc in hexane, R_f 0.21) to yield an oil that was identified as compound **3b** (51 mg, 77%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.47−7.18 (m, 10H), 4.80 (d, J = 14 Hz, 1H), 4.69 (d, J = 14 Hz, 1H), 3.75 (s, 3H), 3.55 (s, 2H), 2.92−2.85 (m, 2H), 2.33−2.26 (m, 2H), 1.7 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.1, 167.6, 136.8, 136.0, 128.6, 128.5, 128.3, 126.8, 126.6, 109.8, 85.9, 85.2, 52.4, 49.0, 38.0, 33.9, 25.5; IR (film) 3200, 1750, 1700 cm^{-1}; MS (CI, NH_3) 369, 344, 330, 214, 190, 173, 156; HRMS (CI, NH_3) ([M + NH_4]) calcd for $C_{22}H_{28}NO_5$ 386.1971, found 386.1971.

2-[4-(Carboxymethyl)-4-diazo-3-oxobutyl]-2-methyl-*trans*-4,5-diphenyl-1,3-dioxolane (4b). A solution of compound **3b** (21 mg, 0.06 mmol) and Et_3N (0.03 mL, 0.36 mmol) in CH_3CN (2 mL) was charged with 4-carboxybenzenesulfonazide (41 mg, 0.18 mmol) at room temperature and stirred for 2.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was flushed through a plug of silica with 5% EtOAc in hexanes and concentrated to yield **4b** (22 mg, 98%) as an oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.37−7.20 (m, 10H), 4.75 (s, 2H), 3.85 (s, 3H), 3.34−3.13 (m, 2H), 2.37−3.32 (m, 2H), 1.7 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 192.2, 161.7, 137.0, 136.2, 128.4, 128.2, 127.0, 126.6, 110.1, 85.9, 85.3, 75.9, 52.2, 35.2, 34.3, 25.6; IR (film) 3000, 2200(s), 1750, 1700, 1500 cm^{-1}; MS (CI, NH_3) 395, 301, 239, 220, 199, 180, 167, 98, 48; HRMS (MH$^+$) calcd for $C_{22}H_{23}N_2O_5$ 395.1607, found 395.1607.

2-[2-(Carboxymethyl)ethyl]-2-methyl-1,3-dioxolane (2c). A solution of methyl levulinate (**1**) (3.48 g, 26.7 mmol), ethylene glycol (1.86 g, 30.0 mmol), and trimethyl orthoformate (3.18 mL, 30.0 mmol) in dry benzene (30 mL) was charged with *p*-TsOH (∼20 mg) and stirred for 2 h. The mixture was diluted with diethyl ether, washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was distilled at reduced pressure to yield **2c** (4.65 g, 69%): bp 60 °C (0.5 mm) (lit.[21] bp (103 °C, 9 mm); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.91−3.82 (m, 4H), 3.62 (s, 3H), 2.38−3.32 (m, 2H), 2.01−1.95 (m, 2H), 1.25 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.9, 109.2, 64.7, 51.5, 33.9, 28.7, 23.9; IR (film) 3000, 2900, 1750, 1700, 1450 cm^{-1}; MS (CI, C_2H_6) (MH$^+$) 175, 159, 143, 119, 99, 73.

2-[4-(Carboxymethyl)-3-oxobutyl]-2-methyl-1,3-dioxolane (3c). Ketal **2c** (1.01 g, 5.9 mmol) was treated with methanolic KOH (2 M, 30 mL) for 8 h, acidified to pH 4.0 with saturated citric acid, and extracted with diethyl ether (5 × 30 mL). The combined organic extracts were carefully dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and dissolved in THF. Carbonyldiimidazole (1.08 g, 6.7 mmol) was added in small portions with stirring. In a separate flask, monomethyl malonate (0.859 g, 7.3 mmol) was dissolved in THF (10 mL), treated with Bu_2Mg (1.0 M in heptane, 3.63 mmol) at 0 °C, and stirred while warming to room temperature. The mixtures were combined and stirred for 24 h, diluted with diethyl ether (20 mL), successively washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, and concentrated *in vacuo*. The residue was chromatographed on silica (25% EtOAc in hexane, R_f 0.18) to yield **3c** (907 mg, 71%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.96−3.87 (m, 4H), 3.72 (s, 3H), 3.48 (s, 2H), 2.62−2.59 (m, 2H), 2.03−1.98 (m, 2H), 1.31 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.2, 167.7, 109.1, 64.8, 52.3, 48.9, 37.6, 32.7, 24.0; IR (film) 3000, 2900, 1750, 1700 cm^{-1}; MS (CI, CH_4) 217, 201, 185, 155, 141, 99; HRMS (CI, CH_4) ([M + H]$^+$) calcd for $C_{10}H_{17}O_5$ 217.1076, found 217.1083.

2-[4-(Carboxymethyl)-4-diazo-3-oxobutyl]-2-methyl-1,3-dioxolane (4c). A solution of **3c** (235 mg, 1.1 mmol) and Et_3N (0.33 mL, 2.4 mmol) in CH_3CN (5 mL) was stirred with 4-carboxybenzenesulfonazide (271 mg, 1.2 mmol) at room temperature for 2.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (25% EtOAc in hexane, R_f 0.21) to yield **4c** (223 mg, 84%) as a bright yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.96 (s, 4H), 3.83 (s, 3H), 3.00−2.94 (m, 2H), 2.09−2.03 (m, 2H), 1.38 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 192.3, 161.8, 109.3, 75.7, 64.8, 52.1, 35.0, 33.0, 24.1; IR (film) 3000, 2900, 2200(s), 1750, 1700, 1500 cm^{-1}; MS (CI, C_2H_6) (MH$^+$) 243, 183, 139, 113, 87.

(±)-(1*S*,3*S*,4*S*,5*S*)-5-(Carboxymethyl)-3,4-diethenyl-1-methyl-6-oxo-2,9-dioxabicyclo[3.3.1]nonane (5). A stirred solution of diazo compound **4a** (94 mg, 0.32 mmol) in dry benzene was charged with Cu(hfacac)$_2$ (∼20 mg) and heated at 80 °C for 4 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether washes were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (20% EtOAc in hexane, R_f 0.19) to yield **5** (55.3 mg, 65%) as a pale yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.77−5.53 (m, 2H), 5.17−5.06 (m, 4H),

(21) Bornowski, H.; Feistkorn, V.; Schwarz, H.; Levsen, K.; Schmitz, P. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1977**, *32B*, 664.

3.89 (m, 1H), 3.64 (s, 3H), 3.40 (m, 1H), 2.63 (m, 1H), 2.49−2.41 (m, 2H), 2.16 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 205.5, 165.3, 134.5, 132.4, 120.5, 116.8, 101.4, 87.1, 73.2, 56.5, 52.8, 37.2, 33.2, 21.3; IR (film) 3000−2800, 1750, 1700 cm^{-1}; MS (EI) 266, 210, 152, 139, 99; HRMS (EI) M$^+$ calcd for $C_{14}H_{18}O_5$ 266.1154, found 266.1159.

Semicarbazone of Compound 5 (6). A solution of semicarbazide·HCl (111 mg, 1.0 mmol) and NaOAc (91 mg, 1.1 mmol) in H_2O (5 mL) was added to compound **5** (223 mg, 8.4 mmol) dissolved in 95% EtOH (3 mL). Additional EtOH was added until the solution became homogeneous, and the mixture was heated on a steam bath for 1 h. Semicarbazone **6** formed as a white precipitate upon cooling (135 mg, 49%), mp > 225 °C dec. Crystals suitable for X-ray analysis[24] were obtained by slow crystallization from CCl_4: ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.0 (s, 1H), 6.0 (br s, 2H), 5.89−5.70 (m, 2H), 5.21−5.11 (m, 4H), 3.97 (m, 1H), 3.70 (s, 3H), 3.30 (m, 1H), 2.87 (m, 1H), 2.29−2.12 (m, 2H), 2.02 (m, 1H), 1.51 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.1, 158.1, 148.5, 135.3, 133.9, 119.4, 116.6, 100.6, 82.6, 73.6, 56.7, 52.7, 34.4, 22.5, 19.0.

(±)-(1*S*,3*S*,4*S*,5*S*)-5-(Carboxymethyl)-1-methyl-6-oxo-3,4-diphenyl-2,9-dioxabicyclo[3.3.1]nonane (7). A stirred solution of diazo compound **4b** (61 mg, 0.15 mmol) in dry benzene was charged with Cu(hfacac)$_2$ (∼5 mg) and heated at 80 °C for 4 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (20% EtOAc in hexane, R_f 0.19) to yield an oil identified as **7** (37 mg, 65%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34−7.07 (m, 10H), 4.82 (d, 1H, J = 9.1 Hz), 4.28 (d, 1H, J = 9.1 Hz), 3.30 (s, 3H), 2.87 (m, 1H), 2.70−2.60 (m, 2H), 2.37 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 206.4, 165.3, 138.6, 137.5, 128.7, 128.5, 128.4, 128.2, 127.6, 127.0, 102.1, 88.9, 77.7, 60.0, 52.5, 37.7, 33.4, 21.6; IR (film) 3000, 1750, 1700, 1500 cm^{-1}; MS (CI, NH_3) 367, 260, 231, 202, 189, 121, 101; HRMS (CI, NH_3) ([M + H]$^+$) calcd for $C_{22}H_{23}O_5$ 367.1545, found 367.1546.

(±)-(1*S*,6*S*)-6-(Carboxymethyl)-1-methyl-7-oxo-2,5-dioxabicyclo[4.3.0]nonane (9) (Optimized).[22] A flame dried round-bottom flask was equipped with a stir bar and cooled in a glovebag under a nitrogen atmosphere. A solution of diazo compound **4c** (129 mg, 0.535 mmol) in dry benzene was added via syringe. The solution was charged with Cu(hfacac)$_2$ (∼10 mg) and heated at 80 °C for 12 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with Et_2O (3 × 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (5% EtOAc in hexane with 1% Et_3N, R_f 0.17) to yield **9** (57.5 mg, 50%) as a pale yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.92 (m, 1H), 3.79 (s, 3H), 3.75−3.61 (m, 2H), 3.48 (m, 1H), 2.59−2.50 (m, 2H), 2.27 (m, 1H), 2.04 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 212.0, 166.5, 87.1, 77.8, 62.4, 59.5, 53.0, 34.2, 32.0, 17.2; IR (film) 3000, 2800, 1800, 1700, 1550 cm^{-1}; MS (EI) 214, 182, 155, 139, 127, 113, 99; HRMS (EI) (M$^+$) calcd for $C_{10}H_{14}O_5$ 214.0841, found 214.0842.

2-(Carboxymethyl)-3-(3-oxobutyl)dioxene (10). A stirred solution of compound **4c** (146 mg, 0.60 mmol) in dry benzene was charged with Cu(hfacac)$_2$ (∼20 mg), heated at 80 °C, and monitored by TLC until the starting material was consumed. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to provide 128 mg of an oil. A portion (77 mg) of this residue was chromatographed on silica (5% EtOAc in hexane with 1% Et_3N, R_f 0.18) to yield **9** (14 mg, 18%) and the acid-sensitive **8** (44 mg, 57%), which isomerized quantitatively in chloroform to generate dioxene **10**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.16−4.12 (m, 2H) 4.09−4.06 (m, 2H), 3.80 (s, 3H), 2.96−2.91 (m, 2H), 2.71−2.67 (m, 2H), 2.17 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.2, 164.0, 150.0, 125.5, 65.2, 63.2, 51.8, 41.1, 30.0, 25.7; IR (film) 3000, 2800, 1700, 1650, 1100 cm^{-1}; MS (EI) 214, 183, 171, 155, 139, 99; HRMS (EI) M$^+$ calcd for $C_{10}H_{14}O_5$ 214.0841, found 214.0839.

***trans*-4,5-Diethyl-2-[4-(carboxymethyl)-3-oxobutyl]-2-methyl-1,3-dioxolane (11).** A solution of **5** (225 mg, 0.86 mmol) in anhydrous methanol (5 mL) was charged with 10% palladium on carbon (10 mg), equipped with a balloon filled with H_2 gas, and stirred for 12 h and monitored periodically by TLC. The reaction mixture was filtered through a plug of silica and concentrated *in vacuo*. The residue was purified by chromatography on silica (20% EtOAc in hexane) to yield **11** (145 mg, 64%) as an oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.53 (m, 1H), 3.41 (s, 2H), 3.38 (m, 1H), 2.69−2.52 (m, 2H), 1.95−1.90 (m, 2H), 1.52−1.41 (m, 4H), 1.28 (s, 3H), 0.95−0.89 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.4, 178.0, 107.2, 81.7, 80.7, 51.3, 47.8, 36.8, 32.8, 25.2, 24.8, 24.4, 9.4, 9.2; IR (film) 3600 (br), 3050−2800, 1750, 1700, 1650 cm^{-1}; MS (CI) 273, 257, 173, 155, 143, 129; HRMS (CI,CH_4) ([M + H]$^+$) calcd for $C_{14}H_{25}O_5$ 273.1702, found 273.1698.

***trans*-4,5-Diethyl-2-[4-(carboxymethyl)-4-diazo-3-oxobutyl]-2-methyl-1,3-dioxolane (12).** A solution of **11** (245 mg, 0.9 mmol) and Et_3N (0.3 mL, 2.4 mmol) in CH_3CN (5 mL) was charged with 4-carboxybenzenesulfonazide (273 mg, 1.2 mmol) at room temperature and stirred for 2.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (20% EtOAc in hexane, R_f 0.21) to yield **12** (229 mg, 85%) as a bright yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.58−3.45 (m, 2H), 3.02−2.81 (m, 2H), 2.02−1.95 (m, 2H), 1.57−1.45 (m, 4H), 1.32 (s, 3H), 0.99−0.91 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 192.4, 161.7, 108.4, 82.5, 81.6, 75.6, 52.1, 35.0, 34.2, 26.1, 25.8, 25.5, 10.3, 10.1; IR (film) 3000−2800, 2200(s), 1750, 1650 cm^{-1}; MS (CI, NH_3) 299, 289, 273, 257, 245,199, 189, 173, 155, 143, 99, 55; HRMS (MH$^+$) calcd for $C_{14}H_{23}N_2O_5$ 299.1607, found 299.1599.

(±)-(1*S*,3*S*,4*S*,5*S*)-5-(Carboxymethyl)-3,4-diethyl-1-methyl-6-oxo-2,9-dioxabicyclo[3.3.1]nonane (13). A solution of **5** (50 mg, 0.19 mmol) in anhydrous methanol (5 mL) was charged with 10% palladium on carbon (∼15 mg), equipped with a balloon filled with H_2 gas, and stirred for 12 h. The reaction mixture was filtered through a plug of silica and concentrated *in vacuo*. The residue was purified by chromatography on silica (20% EtOAc in hexane) to yield compound **13** (26 mg, 50%) as an oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.33 (m, 1H), 2.74 (m, 1H), 2.64 (m, 1H), 2.50−2.42 (m, 2H), 2.16 (m, 1H), 1.61−1.38 (m, 7H), 0.95−0.90 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 206.4, 166.6, 101.1, 87.8, 74.3, 52.9, 51.4, 37.5, 33.1, 28.4, 21.4, 20.8, 11.5, 10.3; IR (film) 3000, 2900, 1750, 1725 cm^{-1}; MS (EI) 270, 215, 194, 185, 172, 141, 99; HRMS (EI) M$^+$ calcd for $C_{14}H_{22}O_5$ 270.1467, found 270.1466.

2-(Carboxymethyl)-*trans*-5,6-diethyl-3-(3-oxobutyl)-dioxene (15). A stirred solution of compound **12** (52 mg, 0.17 mmol) in dry benzene was charged with Cu(hfacac)$_2$ (∼10 mg), heated at 80 °C, and monitored by TLC until the starting material was consumed. The reaction mixture was poured into saturated $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (20% EtOAc in hexane with 1% Et_3N) to yield an acid-sensitive compound (**14**, 17 mg, 36%). This compound isomerized quantitatively to dioxene **15** in $CDCl_3$: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.68 (m, 1H), 3.56 (m, 1H), 3.00−2.93 (m, 2H), 2.71−2.64 (m, 2H), 2.19 (s, 3H), 1.72−1.53 (m, 4H), 1.10−0.98 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.2, 164.3, 148.5, 123.8, 78.3, 75.7, 51.5, 41.2, 29.7, 25.6, 23.9, 23.4, 9.4, 9.1; IR (film) 3000, 2900, 1750, 1700 cm^{-1}; MS (EI) 270, 239, 227, 195, 169, 145; HRMS (EI) M$^+$ calcd for $C_{14}H_{22}O_5$ 270.1467, found 270.1474.

2-[2-(Carboxymethyl)ethyl]-2-methyl-1,3-dioxane (16). A solution of methyl levulinate (**1**) (3.13 g, 24.0 mmol), 1,3-propanediol (2.28 g, 30.0 mmol), and trimethyl orthoformate (3.25 mL, 30.0 mmol) in dry benzene (50 mL) was charged with *p*-TsOH (∼20 mg) and stirred for 12 h. The mixture was diluted with diethyl ether, washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The

(22) The catalyst that was used had been rigorously dried.

residue was distilled at reduced pressure to yield **16** (1.9 g, 42%) as an oil: bp 75 °C, 0.5 mm; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.85−3.79 (m, 4H), 3.64 (m, 3H), 2.45−2.40 (m, 2H), 2.03−1.98 (m, 2H), 1.75 (m, 1H), 1.52 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.8, 98.5, 60.1, 51.9, 34.0, 28.7, 25.7, 21.0; IR (film) 3000, 2800, 1750 (br), 1450 cm^{-1}; MS (CI, C_2H_6) ([M + H]$^+$) 189, 171, 145, 119, 99, 87, 83.

2-[4-(Carboxymethyl)-3-oxobutyl]-2-methyl-1,3-dioxane (17). Ketal **16** (1.60 g, 8.5 mmol) was treated with methanolic KOH (2 M, 50 mL) for 8 h, acidified to pH 4.0 with saturated aqueous citric acid, and extracted with diethyl ether (5 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and dissolved in tetrahydrofuran. Carbonyldiimidazole (1.76 g, 11 mmol) was added in small portions while the solution was stirred. In a separate flask, monomethyl malonate (1.12 g, 9.5 mmol) was stirred in THF (10 mL), treated with Bu_2Mg (1.0 M heptane, 4.75 mmol) at 0 °C, and allowed to warm to room temperature. The mixtures were combined and stirred for 24 h, diluted with diethyl ether (20 mL), successively washed with aqueous NH_4Cl, aqueous $NaHCO_3$, and brine, and finally concentrated *in vacuo*. The residue was chromatographed on silica (20% EtOAc in hexane; R_f 0.19) to yield **17** (1.2 g, 61%): ^{1}H NMR (360 MHz, acetone-d_6) δ 3.94−3.86 (m, 2H), 3.79−3.74 (m, 2H), 3.65 (m, 3H), 3.52 (s, 2H), 2.67−2.63 (m, 2H), 1.92−1.87 (m, 2H), 1.72 (m, 1H), 1.58 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (90 MHz, acetone-d_6) δ 207.6, 172.9, 103.2, 64.5, 56.4, 53.8, 41.9, 38.2, 30.6, 24.9; IR (film) 3000, 2800, 1800, 1750 cm^{-1}; MS (CI, NH_3) 231, 215, 199, 189, 173, 155, 101; HRMS (CI, NH_3) ([M + H]$^+$) calcd for $C_{11}H_{19}O_5$ 231.1231, found 231.1232.

2-[4-(Carboxymethyl)-4-diazo-3-oxobutyl]-2-methyl-1,3-dioxane (18). A solution of **17** (740 mg, 3.2 mmol) and Et_3N (1.0 mL, 7.2 mmol) in CH_3CN (10 mL) was charged with 4-carboxybenzenesulfonazide (953 mg, 4.2 mmol) at room temperature and stirred for 2.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (20% EtOAc in hexane, R_f 0.21) to yield **18** (714 mg, 87%) as a bright yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.81−3.69 (m, 7H), 2.86−2.81 (m, 2H), 1.93−1.88 (m, 2H), 1.62 (m, 1H), 1.43 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 192.1, 161.3, 98.0, 75.2, 59.3, 51.8, 34.1, 32.1, 25.0, 20.6; IR (film) 3000, 2900, 2200(s), 1750, 1650, 1450 cm^{-1}; MS (CI, NH_3) 257, 229, 216, 199, 117, 101, 94, 83, 64; HRMS (MH^+) calcd for $C_{11}H_{19}N_2O_5$ 257.1137, found 257.1135.

(±)-(1*S*,7*S*)-7-(Carboxymethyl)-1-methyl-8-oxo-2,6-dioxabicyclo[5.3.0]decane (19). A stirred solution of compound **18** (252 mg, 0.98 mmol) in dry benzene was charged with Cu(hfacac)$_2$ (∼20 mg) and heated at 80 °C for 4 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether washes were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (20% EtOAc in hexane, R_f 0.19) to yield **19** (217 mg, 97%) as a pale yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.05 (m, 1H), 3.95−3.82 (m, 2H), 3.76 (s, 3H), 3.75 (m, 1H), 2.62−2.45 (m, 2H), 2.25−1.96 (m, 4H), 1.45 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 212.1, 168.2, 91.9, 85.8, 64.7, 61.3, 52.8, 34.6, 34.0, 32.6, 19.2; IR (film) 3050, 2900, 1800, 1775, 1750 cm^{-1}; MS (EI) 228, 196, 169, 152, 140, 127, 119, 99; HRMS (EI) M^+ calcd for $C_{11}H_{16}O_5$ 228.0998, found 228.1007.

Semicarbazone of 19 (20). To a solution of semicarbazide·HCl and NaOAc in H_2O (5 mL) was added compound **19** dissolved in 95% EtOH (3 mL). Additional EtOH was added until the solution became homogeneous, and the mixture was heated on a steam bath for 0.5 h. Semicarbazone **20** was formed as a white precipitate upon cooling. Crystals suitable for X-ray analysis[24] were obtained by slow crystallization from CCl_4: mp > 225 °C dec; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.50 (s, 1H), 6.0 (br s, 1H), 5.2 (br s, 1H), 3.92−3.80 (m, 3H), 3.70−3.61 (m, 4H), 2.58−2.40 (m, 2H), 2.10−1.89 (m, 4H), 1.30 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.7, 157.6, 91.6, 86.4, 63.1, 60.6, 52.7, 35.9, 32.1, 25.4, 18.4.

3-[2-(Carboxymethyl)ethyl]-3-methyl-1,5-dihydro-3*H*-2,4-benzodioxepin (21). A stirred solution of benzenedimethanol (1.13 g, 8.2 mmol), trimethyl orthoformate (1.3 mL, 12 mmol), and *p*-TsOH (30 mg) in benzene (250 mL) was distilled until the volume was reduced to 50 mL, at which time methyl levulinate (**1**) (1.02 g, 7.80 mmol) was added. The reaction was stirred at room temperature for 12 h and poured into saturated $NaHCO_3$. The solution was extracted with ether (3 × 30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica (10% EtOAc in hexane; R_f 0.18) to yield ketal **21** (995 mg, 51%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.22−7.02 (m, 4H), 4.85 (s, 4H), 3.71 (s, 3H), 2.51−2.43 (m, 2H), 2.20−2.15 (m, 2H), 1.45 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.7, 138.0, 126.7, 126.1, 103.1, 64.8, 51.7, 31.3, 29.6, 20.8; IR (film) 3200, 3000, 1750, 1725, 1450 cm^{-1}; MS (CI, C_2H_6) 251, 219, 149, 131, 99.

3-[4-(Carboxymethyl)-3-oxobutyl]-3-methyl-1,5-dihydro-3*H*-2,4-benzodioxepin (22). Ketal **21** (635 mg, 2.7 mmol) was treated with methanolic KOH (2 M, 30 mL) for 8 h, acidified to pH 4.0 with saturated aqueous citric acid, and extracted with diethyl ether (5 × 30 mL). The combined organic extracts were carefully dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and dissolved in tetrahydrofuran. Carbonyldiimidazole (438 mg, 2.7 mmol) was added in small portions. In a separate flask, monomethyl malonate (515 mg, 4.4 mmol) was stirred in THF (10 mL), treated with Bu_2Mg (1.0 M in heptane, 2.2 mmol) at 0 °C, and allowed to warm to room temperature. The two solutions were combined and stirred for an additional 24 h, diluted with diethyl ether (20 mL), successively washed with aqueous NH_4Cl, aqueous $NaHCO_3$, and brine, and finally concentrated *in vacuo*. The residue was chromatographed on silica (20% EtOAc in hexane; R_f 0.21) to yield **22** (543 mg, 69%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.20−7.14 (m, 4H), 4.82 (s, 4H), 3.75 (s, 3H), 3.50 (s, 2H), 2.73−2.67 (m, 2H), 2.19−2.12 (m, 2H), 1.45 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.9, 167.6, 137.9, 126.7, 126.1, 103.1, 64.7, 52.2, 49.1, 38.2, 29.9, 21.0; IR (film) 3200, 2950, 1800, 1750, 1250 cm^{-1}; MS (CI, NH_3) 293, 283, 275, 261, 243, 196, 173; HRMS (CI, NH_3) ([M + H]$^+$) calcd for $C_{16}H_{21}O_5$ 293.1389, found 293.1380.

3-[4-(Carboxymethyl)-4-diazo-3-oxobutyl]-3-methyl-1,5-dihydro-3*H*-2,4-benzodioxepin (23). A room-temperature solution of **22** (499 mg, 1.7 mmol) and Et_3N (0.67 mL, 5.0 mmol) in CH_3CN (10 mL) was charged with 4-carboxybenzenesulfonyl azide (467 mg, 2.0 mmol) and stirred for 2.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether washes were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (20% EtOAc in hexane, R_f 0.22) to yield **23** (492 mg, 91%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.20−7.00 (m, 4H), 4.92−4.86 (m, 4H), 3.85 (s, 3H), 3.06−2.99 (m, 2H), 2.22−2.18 (m, 2H), 1.49 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 192.0, 161.6, 138.0, 126.6, 126.0, 103.3, 75.8, 64.8, 52.1, 35.5, 30.5, 21.0; IR (film) 3000, 2900, 2200(s), 1750, 1650 cm^{-1}; MS (CI, NH_3) 319, 273, 241, 219, 259, 199, 163, 119, 99; HRMS (MH^+) calcd for $C_{16}H_{19}N_2O_5$ 319.1294, found 319.1296.

Tricyclic Ring-Fused Compound 24. A stirred solution of diazo compound **23** (72 mg, 0.24 mmol) in dry benzene was charged with Cu(hfacac)$_2$ (∼10 mg) and heated at 80 °C for 4 h. The cooled reaction mixture was charged with *p*-TsOH (20 mg) and H_2O (1 mL) and heated for 4 h.[23] The reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica (10% EtOAc in hexane, R_f 0.22) to yield **24** (39 mg, 56%) and **25** (13 mg, 19%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.22−

(23) The bicyclic structure of **25** was easily destroyed by acidic hydrolysis. Small amounts of **25** could be isolated by a nonacidic workup followed by careful chromatography on silica.

(24) The author has deposited atomic coordinates for **6** and **20** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

7.02 (m, 4H), 5.39 (d, 1H, J = 13.9 Hz), 5.05 (d, 1H, J = 13.5 Hz), 4.88 (d, 1H, J = 13.5 Hz), 4.70 (d, 1H, J = 13.9 Hz), 3.78 (s, 3H), 2.64−2.50 (m, 2H), 2.26−2.20 (m, 2H), 1.55 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 212.0, 169.0, 136.8, 135.8, 128.5, 127.9, 127.5, 127.1, 90.3, 83.2, 71.3, 68.0, 52.7, 36.4, 34.8, 20.8; IR (film) 3000, 2800, 1800, 1700 cm^{-1}; MS (CI, NH_3) 291, 273, 119, 104, 78; HRMS (CI, NH_3) ([M + H]$^+$) calcd for $C_{16}H_{19}O_5$ 291.1232, found 291.1236.

Bridged tricyclic compound 25: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25−7.03 (m, 4H), 5.35 (d, 1H, J = 15 Hz), 4.6 (d, 1H, J = 15 Hz), 4.1 (d, 1H, J = 16.8 Hz), 3.2 (d, 1H, J = 16.8 Hz), 3.85 (s, 3H), 3.2 (d, 1H, J = 16.8 Hz), 2.1−2.2 (m, 2H), 1.8−1.9 (m, 2H), 1.75 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.3, 137.7, 133.9, 130.7, 127.1, 126.8, 126.2, 109.8, 89.7, 66.9, 52.9, 36.8, 35.5, 32.1, 18.4; MS (EI) 290, 220, 203, 143, 128, 73, 43.

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Supporting Information Available: ^{1}H spectra of **2a**−**c**, **3a**−**c**, **4a**−**c**, and **5**−**24** and ^{13}C NMR spectra of **2a**−**c**, **3a**−**c**, **4a**−**c**, **5**−**13**, and **15**−**24** (57 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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