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Intramolecular Oxonium Ylide Formation−[2,3] Sigmatropic Rearrangement of Diazocarbonyl-Substituted Cyclic Unsaturated Acetals: A Formal Synthesis of Hyperolactone C

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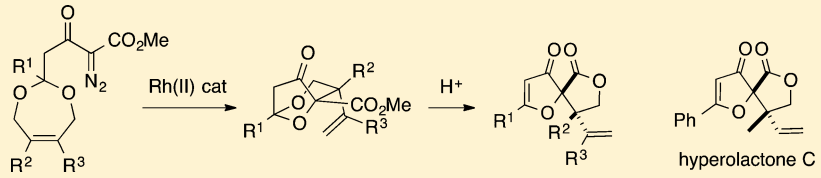
Supporting Information



ABSTRACT: Rh(II)-catalyzed oxonium ylide formation−[2,3] sigmatropic rearrangement of α-diazo-β-ketoesters possessing γ-cyclic unsaturated acetal substitution, followed by acid-catalyzed elimination−lactonization, provides a concise approach to 1,7-dioxaspiro[4.4]non-2-ene-4,6-diones. The process creates adjacent quaternary stereocenters with full control of the relative stereochemistry. An unsymmetrical monomethylated cyclic unsaturated acetal leads to hyperolactone C, where ylide formation−rearrangement proceeds with high selectivity between subtly nonequivalent acetal oxygen atoms.

INTRODUCTION

Hyperolactone C (**4**) forms part of a small family of related lactones, originally isolated from the leaves and stems of *Hypericum chinese* L.[1] It is an attractive target for fundamental and structure−activity relationship synthetic studies, due to a combination of structural complexity and potential as a lead in anti-HIV research.[2,3] We have previously reported approaches to hyperolactone C (**4**) using tandem oxonium ylide formation−[2,3]-sigmatropic rearrangements (**1** → **3**, Scheme 1, R′ = Ph or H, R″ = alkyl).[4−8] However, our earlier studies did not fully control the relative stereochemistry and required post-rearrangement oxidation to introduce the furanone double bond. The present work sought to address both of these latter issues, by constraining the allylic ether as part of a cyclic unsaturated acetal **5** (Scheme 2).

In 1998, Calter and Sugathapala reported a synthesis of bicyclic acetal **7a** (R^1, R^2, and R^3 = H) in 72% yield from the corresponding unsubstituted cyclic acetal **5a**, using cat $Rh_2(OAc)_4$ in benzene at reflux.[9] An initial aim of the current work was, therefore, to establish whether bicyclic acetal **7a** could undergo acid-catalyzed rearrangement with loss of methanol to directly generate the spirofuranone framework **8** of the hyperolactones. In the context of the specific substitution pattern of hyperolactone C (**4**), further challenges identified at the outset that would need to be subsequently addressed were the viability of the sequence from cyclic acetal **5** to spirofuranone **8** with (a) R^1 = Ph (noting that late-stage conjugate addition offers flexibility to introduce this group after rearrangement),[6] and (b) R^2 = Me (to forge the adjacent quaternary stereocenters), and R^3 either = Me (then requiring a late-stage demethylation) or = H (requiring selection between nonequivalent acetal oxygen atoms in the oxonium ylide formation−rearrangement).

RESULTS AND DISCUSSION

Bicyclic acetal **7a** was prepared from methyl α-diazoacetoacetate (**9**)[10] following the acetal exchange approach of Calter and Sugathapala,[9] with some minor variations[11] (Scheme 3). In our hands, use of $Rh_2(tfa)_4$ (tfa = trifluoroacetate) proved significantly more effective than $Rh_2(OAc)_4$ with cyclic acetal **5a** in the oxonium ylide formation−rearrangement. The propensity of bicyclic acetal **7a** to undergo elimination−lactonization was examined using acid catalysts. No reaction was observed with TFA at 70 °C, and aq concd HCl in THF (reflux, 12 h) gave a complicated mixture. However, heating bicyclic acetal **7a** with sulfonic acids (PTSA or CSA) in toluene gave the desired spirofuranone **8a** (structure supported by single-crystal X-ray diffraction studies[12]), albeit in low (<30%) yields; use of diphenyl phosphate [$(PhO)_2PO_2H$] was more promising (45% yield, unoptimized). The dimethylated spirofuranone **8b** could also be accessed through the same sequence (Scheme 3). In the latter case, the bicyclic acetal **7b** was formed with equal efficiency over 1−1.5 h using either $Rh_2(tfa)_4$ or $Rh_2(OAc)_4$, and even the comparatively electron-rich catalyst Rh_2(caprolactamate)$_4$ slowly gave oxonium ylide formation−rearrangement (CH_2Cl_2, 24 h, 60% yield). Elimination−lactonization was achieved in 87% yield from bicyclic acetal **7b**; alternatively, $(PhO)_2PO_2H$ could be added directly to the reaction of cyclic

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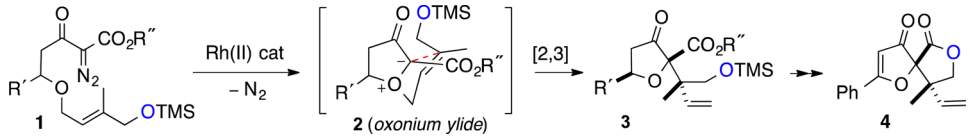
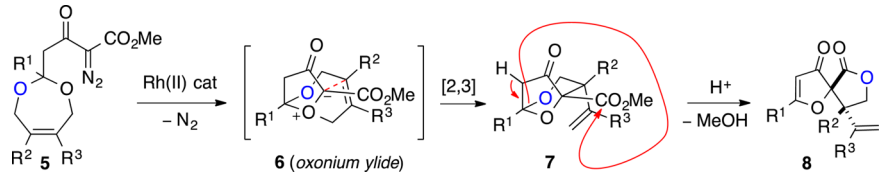
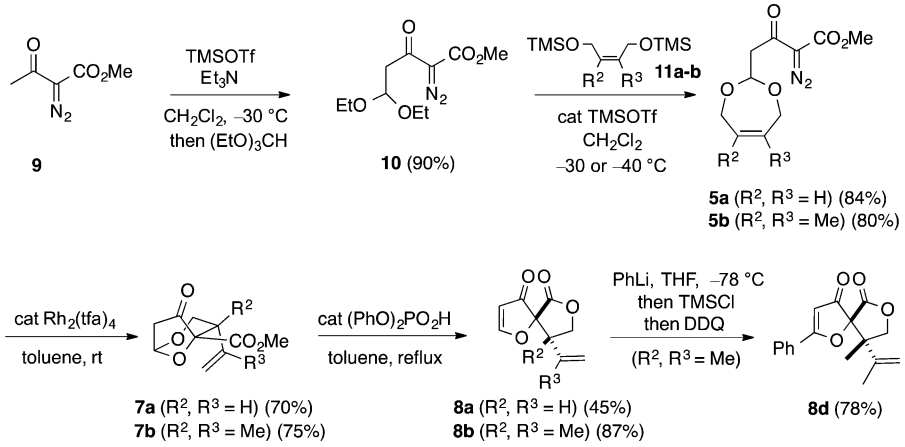
Scheme 1. Previous Oxonium Ylide Formation−Rearrangement Chemistry to Hyperolactone C (4)[4−6]



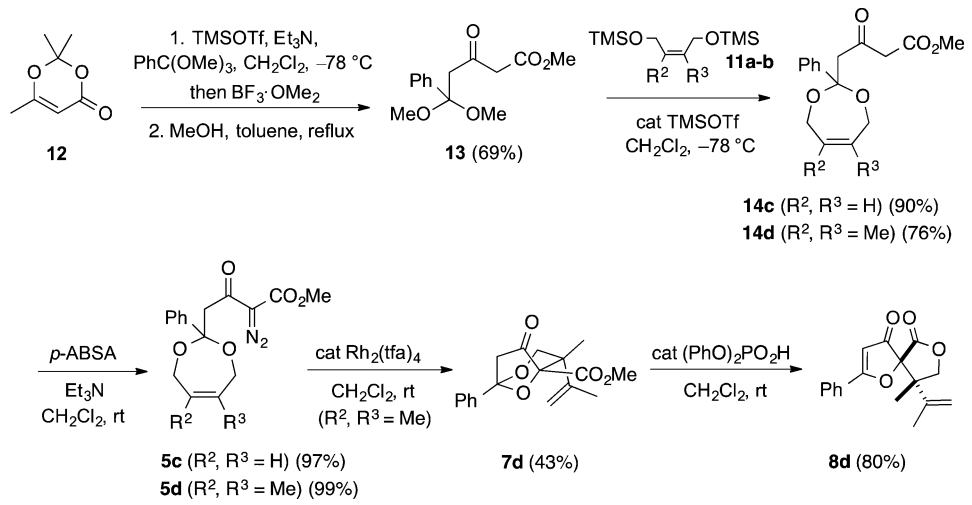
Scheme 2. Proposed Approach to Spirofuranones 8 from Cyclic Unsaturated Acetals 5



Scheme 3. Synthesis of Spirofuranones 8



Scheme 4. Synthesis of Spirofuranone 8d from Phenyl-Substituted Cyclic Acetal 5d



acetal **5b** following sigmatropic rearrangement, to conveniently give dimethylated spirofuranone **8b** (73% from **5b**) after heating.

Following precedent on a closely related system (**8b** with R^3 = H) in our recent synthesis of hyperolactone C (**4**),[6] a phenyl group was introduced into dimethylated spirofuranone **8b** by conjugate addition−oxidation, giving spirofuranone **8d** in 78% yield (Scheme 3). Alternatively, as mentioned in the Introduction, the phenyl group could, in principle, be present prior to the ylide chemistry. Investigation of this strategy required access to cyclic acetals **5c−d**. Although a route similar to that shown in Scheme 3 from α-diazoacetoacetate (**9**) did give acetal **5c**, variable yields for the coupling of the TMS enol ether of **9** with trimethyl orthobenzoate (which required $ZnCl_2$ as Lewis acid)[13] led us to develop a more efficient access, starting from dioxanone **12** (Scheme 4). Diazo transfer using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) was best carried out after acetal exchange, to minimize handling of the more hydrolytically sensitive acyclic acetal functionality. Cyclic acetal **5c** could not be induced to form any of the corresponding bicyclic acetal under Rh(II) catalysis, whereas cyclic acetal **5d** did give bicyclic acetal

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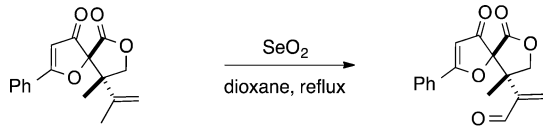
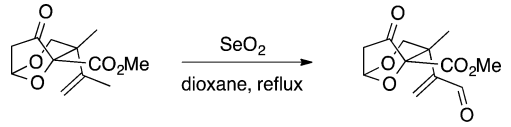
7d, but only in up to 43% yield. While side products were not fully identified, possible competing pathways include intramolecular Buchner reaction,[14] and/or products derived from [1,2] shifts[7] in the intermediate oxonium ylide **6** (R^1 = Ph). Finally, bicyclic acetal **7d** underwent ambient temperature acid-catalyzed elimination (likely phenyl-assisted) and lactonization, to give the same spirofuranone **8d** (80% yield) as prepared earlier (Scheme 3) from dimethylated spirofuranone **8b** by conjugate addition−oxidation.

The lower yielding ylide chemistry in the phenyl-substituted system (**5d** → **7d**, Scheme 4) led us to focus on the conjugate addition−oxidation approach to introduce the phenyl group (Scheme 3). Excision of the methyl group at the terminal alkene of spirofuranones **8b** or **8d** was required to complete a synthesis (formal synthesis in the case of **8b**) of hyperolactone C (**4**). To this end, the first part of an allylic oxidation−deformylation strategy could be achieved using SeO_2 with spirofuranone **8d** (**8b** was a less effective substrate) to give enal **15** (70%, Scheme 5), or from bicyclic acetal **7b** to give enal **16** (67%, Scheme 6). Unfortunately, the enals could not be induced to undergo productive deformylation with Wilkinson's catalyst,[15] or other Rh or Ir catalysts previously used in such transformations.[16,17]

Scheme 5. Synthesis of Enal 15

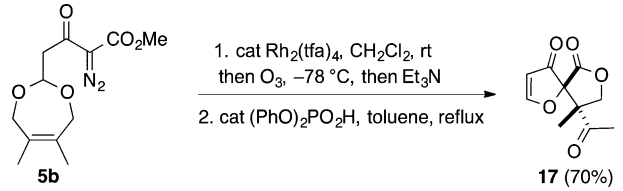


Scheme 6. Synthesis of Enal 16



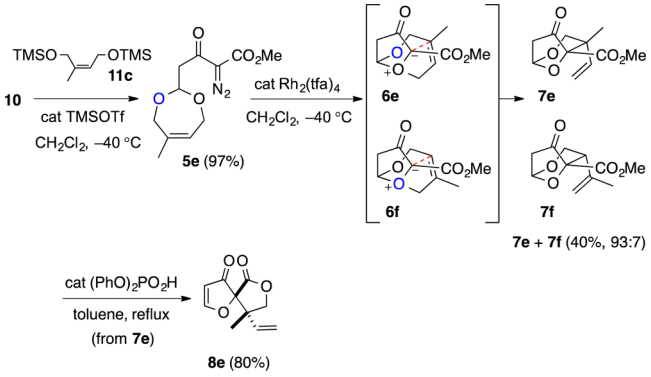
The extraneous carbon could be efficiently removed from cyclic acetal **5b**, through ozonolysis of the intermediate bicyclic acetal **7b**, leading after rearrangement to the corresponding ketone **17** (70% from **5b**, Scheme 7). However, subsequent reductive chemistries to give the alkene (e.g., alcohol formation, followed by dehydration, or via enol derivatives) did not prove viable.

Scheme 7. Synthesis of Ketone 17



Although a synthesis of hyperolactone C (**4**) could not be achieved through demethylation, the greater facility of the oxonium ylide formation−rearrangement chemistry observed using the dimethylated cyclic acetals **5b** and **5d**, compared with the unsubstituted cyclic acetals **5a** and **5c**, led us to consider an examination of the monomethylated system **5e** (Scheme 8). In this unsymmetrical system, it was anticipated that the +I effect

Scheme 8. Synthesis of Spirofuranone 8e from Monomethylated Cyclic Acetal 5e



due to the methyl group would result in formation and rearrangement of oxonium ylide **6e** (Scheme 8) being preferred[18] over ylide formation−rearrangement involving the alternative acetal oxygen (colored blue in Scheme 8, ylide **6f**). In the event, the desired bicyclic acetal **7e** did form preferentially (**7e**:**7f**, 73:27, 43%, CH_2Cl_2 rt, 1 h), and its proportion could be maximized by reducing the reaction temperature (**7e**:**7f**, 93:7, 40%, −40 °C, 72 h). Elimination−lactonization from bicyclic acetal **7e** gave spirofuranone **8e** (80% yield), which we have previously converted into hyperolactone C (**4**) by conjugate addition−oxidation in 86% yield.[6]

With (−)-hyperolactone C (−)-**4**, racemic hyperolactone C (**4**) and a few analogues now available from our previous and current studies, they were tested for their inhibitory activity against HIV-1 replication, using AZT as a control. As expected on the basis of earlier biological evaluations,[2,3] (−)-**4**,[5] **4** and **4** (4-fluorophenyl instead of Ph)[6] showed significant and similar activities in this assay (IC_{50} = 11−15 μM, compared to AZT IC_{50} = 0.063 μM). Reduced potency, although still notable, was observed with analogues possessing an additional vinylic methyl group (**8d**), lacking an aryl substituent (**8e**), **4** (Ph replaced by butyl),[6] and the *E*-styrenyl constitutional isomer of hyperolactone C[6,12] (IC_{50} = 85, 70, 113, and 104 μM, respectively).

■ CONCLUSIONS

The present studies demonstrate a concise approach to the spirolactone motif characteristic of the hyperolactones. This motif is generated by Rh(II)-catalyzed oxonium ylide formation−[2,3] sigmatropic rearrangement of α-diazo-β-ketoesters possessing γ-cyclic unsaturated acetal substitution, followed by acid-catalyzed elimination−lactonization. The process creates adjacent quaternary stereocenters with full control of the relative stereochemistry, and in the desired sense for hyperolactone C (**4**). Use of a chiral rhodium catalyst offers the attractive prospect of additionally controlling the absolute stereochemistry.[6,9,19,20] However, as hyperolactone C (**4**) was shown to be currently accessible through the cyclic acetal strategy only from the unsymmetrical monomethylated system **5e**, which involves an interesting selection between nonequivalent acetal oxygen atoms in the Rh(II)-catalyzed chemistry, then an enantioselective entry to **5e** and related systems based on catalytic asymmetric acetalization[21] also constitutes an area for future investigations.

■ EXPERIMENTAL SECTION[22]

Methyl 2-Diazo-4-(4,7-dihydro-1,3-dioxepin-2-yl)-3-oxobutanoate (5a). TMSOTf (36 μL, 45 mg, 0.2 mmol) was added to a solution of acyclic acetal **10** (977 mg, 4.0 mmol) and (*Z*)-1,4-

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bis(trimethylsilyloxy)but-2-ene (**11a**)[23] (1.12 g, 4.8 mmol) in CH_2Cl_2 (11 mL) at −30 °C. After stirring for 20 h at −30 °C, pyridine (350 μL) was added. The reaction mixture was warmed to rt and concd under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol = 2/8) to give, as a yellow oil, cyclic acetal **5a**[9] (808 mg, 84%). R_f (EtOAc/petrol = 2/8) 0.17; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73−5.65 (m, 2 H; =CH), 5.31 (t, J = 5.8, 1 H; OCHO), 4.41 (dm, J = 14.9, 2 H; OCH_aH_b), 4.19 (d, J = 14.9, 2 H; OCH_aH_b), 3.83 (s, 3 H; OCH_3), 3.29 (d, J = 5.7, 2 H; $CHCH_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 188.5 (C=O), 161.5 (CO_2), 129.4 (=C), 100.6 (OCHO), 65.6 (CH_2C=), 52.2 (OCH_3), 44.1 (O=CCH_2); IR (Diamond ATR): 639 w, 744 m, 1000 m, 1070 s, 1120 s, 1198 m, 1297 m, 1341 m, 1437 w, 1651 m, 1716 s, 2134 m, 2852 w, 2954 w, 3029 w cm^{-1}; HRMS (ESI$^+$): [M + Na^+] 263.0637, $C_{10}H_{12}N_2NaO_5$ requires 263.0638.

Methyl 2-Diazo-4-(5,6-dimethyl-4,7-dihydro-1,3-dioxepin-2-yl)-3-oxobutanoate (5b). TMSOTf (21 μL, 26 mg, 0.116 mmol) was added to a solution of diethyl diazoacetal **10** (568 mg, 2.33 mmol) and disilylated diol (**11b**) (757 mg, 2.91 mmol) in CH_2Cl_2 (24 mL) at −40 °C. After stirring for 24 h at −40 °C, pyridine (0.12 mL) was added. The reaction mixture was warmed to rt and concd under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol = 2/8) to give, as a light yellow solid, cyclic acetal **5b** (499 mg, 80%). R_f (EtOAc/petrol = 2/8) 0.24; mp 79−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.34 (t, J = 5.8, 1 H; O-CH-O), 4.32 (d, J = 14.1, 2 H; OCH_aH_b), 4.04 (d, J = 14.1, 2 H; OCH_aH_b), 3.84 (s, 3 H; OCH_3), 3.27 (d, J = 5.8, 2 H; O=CCH_2), 1.58 (s, 6 H; =CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 188.6 (C=O), 161.5 (CO_2Me), 128.8 (=C), 99.5 (O-C-O), 68.8 (=CCH_2), 52.2 (OCH_3), 43.2 (O=CCH_2), 16.6 (=CCH_3); IR (neat): 745 w, 1018 m, 1072 s, 1125 s, 1198 s, 1299 s, 1343 s, 1387 m, 1438 s, 1659 s, 1723 s, 2136 s, 2859 m, 2928 m cm^{-1}; HRMS (ESI$^+$): [M + Na^+] 291.0949, $C_{12}H_{16}N_2NaO_5$ requires 291.0951.

Methyl 2-Diazo-4-(2-phenyl-4,7-dihydro-1,3-dioxepin-2-yl)-3-oxobutanoate (5c). Et_3N (135 μL, 98 mg, 0.97 mmol) was added to a solution of acetal **14c** (274 mg, 0.944 mmol) and *p*-ABSA (233 mg, 0.97 mmol) in CH_2Cl_2 (10 mL) at rt. After stirring for 14 h, the mixture was concd under reduced pressure and then triturated with Et_2O (4 × 5 mL). The solution was concd under reduced pressure, and the residue was purified by column chromatography (EtOAc/petrol = 1/9) to give, as a yellow oil, cyclic acetal **5c** (290 mg, 97%). R_f (EtOAc/petrol = 1/9) 0.18; R_f (2% Et3N in 4:1 petrol/Et_2O, deactivated silica plate) 0.29; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (dm, J = 6.8, 2 H; Ar), 7.39−7.27 (m, 3 H; Ar), 5.68 (m, 2 H; =CH), 4.44 (dm, J = 15.6, 2 H; OCH_aH_b), 4.19 (dm, J = 15.6, 2 H; OCH_aH_b), 3.66 (s, 3 H; CO_2CH_3), 3.65 (s, 2 H; O=CCH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.5 (C=O), 161.0 (CO_2Me), 140.0 ($Ar_{quat.}$), 129.1 (=CH), 128.0 (Ar), 127.6 (2 × Ar), 126.7 (2 × Ar), 103.7 (O-C-O), 62.4 (OCH_2), 51.9 (CO_2CH_3), 45.8 (O=CCH_2); IR (neat): 1073 s, 1112 s, 1305 m, 1653 m, 1720 s, 2132 s, 2860 w, 2952 w, 3030 w cm^{-1}; HRMS (ESI$^+$): [M + Na^+] 339.0951, $C_{16}H_{16}N_2NaO_5$ requires 339.0951.

Methyl 2-Diazo-4-(5,6-dimethyl-2-phenyl-4,7-dihydro-1,3-dioxepin-2-yl)-3-oxobutanoate (5d). Et_3N (0.35 mL, 0.25 g, 2.5 mmol) was added to a solution of acetal **14d** (664 mg, 2.085 mmol) and *p*-ABSA (0.6 g, 2.5 mmol) in CH_2Cl_2 (22 mL) at rt. After stirring for 20 h, the mixture was concd under reduced pressure and then triturated with Et_2O (4 × 10 mL). The solution was concd under reduced pressure, and the residue was purified by column chromatography (Et_2O; small column) to give, as a yellow oil that later formed light yellow solid, cyclic acetal **5d** (714 mg, 99%). R_f (Et_2O/petrol = 2/8) 0.21; R_f (EtOAc/petrol = 2/8) 0.43; mp 63−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54−7.48 (m, 2 H; Ar), 7.37−7.28 (m, 3 H; Ar), 4.33 (dm, J = 14.6, 2 H; OCH_aH_b), 4.09 (dm, J = 14.6, 2 H; OCH_aH_b), 3.65 (s, 3 H; CO_2CH_3), 3.64 (s, 2 H; O=CCH_2), 1.56 (s, 6 H; =CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.7 (C=O), 161.0 (CO_2Me), 140.2 ($Ar_{quat.}$), 128.0 (Ar.), 127.9 (=CCH_3), 127.6 (2 × Ar), 126.8 (2 × Ar), 103.0 (O-C-O), 66.8 (=CCH_2O), 51.9 (CO_2CH_3), 45.7 (O=CCH_2), 16.3 (=CCH_3); IR (Diamond ATR): 701 s, 1060 m, 1109 s, 1297 m, 1436 w, 1653 w, 1720 m, 2130 m, 2859 w, 2927 w cm^{-1}; HRMS (FI$^+$): 345.1445 [M + H^+], $C_{18}H_{21}N_2O_5$ requires 345.1445.

Methyl 2-Diazo-4-(5-methyl-4,7-dihydro-1,3-dioxepin-2-yl)-3-oxobutanoate (5e). TMSOTf (0.13 mL, 0.16 g, 0.72 mmol) was added dropwise to a solution of diethyl diazoacetal **10** (324 mg, 1.33 mmol) and disilylated diol **11c** (375 mg, 1.52 mmol) in CH_2Cl_2 (14 mL) at −40 °C. After stirring for 4 days, pyridine (0.065 mL, 0.80 mmol) was added, and reaction was warmed to rt and concd under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol = 5% → 10%) to give, as a pale yellow oil, cyclic acetal **5e** (327 mg, 97%). R_f (EtOAc/petrol = 2/8) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43−5.41 (m, 1 H; $CH(O-)_2$), 5.36 (t, J = 5.6 Hz, 1 H; =CH), 4.37−4.27 (m, 2 H; CH_2O), 4.11−4.06 (m, 2 H; CH_2O), 3.84 (s, 3 H; CO_2CH_3), 3.28 (dd, J = 5.6, 1.7, 2 H; C=OCH_2), 1.66 (s, 3 H; =C−CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 188.6 (C=O), 161.5 (CO_2CH_3), 137.7 (=$C(CH_3)$), 123.8 (=CH), 100.5 ($CH(O-)_2$), 69.3 (=$C(CH_3)CH_2$), 64.0 (=$CHCH_2$), 52.2 (CO_2CH_3), 43.7 (C=OCH_2), 20.4 (=C−CH_3); IR (neat): 746 m, 1007 m, 1072 m, 1132 s, 1198 m, 1298 m, 1341 m, 1438 m, 1438 m, 1655 m, 1719 s, 2135 m, 2955 w cm^{-1}; HRMS (ESI$^+$): [M + Na^+] 277.0795, $C_{11}H_{14}N_2NaO_5$ requires 277.0795.

Methyl (1*RS*,4*RS*,5*RS*)-6-Oxo-4-vinyl-2,8-dioxabicyclo[3.2.1]-octane-5-carboxylate (7a). $Rh_2(O_2CCF_3)_4$ (3.3 mg, 0.005 mmol) was added to a solution of cyclic acetal **5a** (120 mg, 0.5 mmol) in toluene (12 mL) at rt. After stirring for 1 h, the mixture was concd under reduced pressure and purified by column chromatography (EtOAc/petrol = 4/6) to give, as a pale yellow oil, bicyclic acetal **7a**[9,19] (74 mg, 70%). R_f (EtOAc/petrol = 4/6) 0.30; mp 45−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.21 (ddd, J = 17.3, 10.3, 8.7, 1 H; =CH), 5.96 (d, J = 5.4, 1 H; O-CH-O), 5.31 (dm, J = 17.3, 1 H; =CH_aH_b), 5.28 (dm, J = 10.3, 1 H; =CH_aH_b), 4.20 (dd, J = 12.6, 3.8, 1 H; OCH_aH_b), 3.87 (d, J = 12.6, 1 H; OCH_aH_b), 3.82 (s, 3 H; OCH_3), 2.92 (dd, J = 18.4, 5.4, 1 H; O=CCH_aH_b), 2.80 (dd, J = 8.7, 3.8, 1 H; =CHCH), 2.71 (d, J = 18.4, 1 H; O=CCH_aH_b); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.3 (C=O), 164.7 (CO_2), 132.8 (CH=CH_2), 119.4 (CH=CH_2), 97.9 (O-C-O), 85.0 (O=$CC_{quat.}$), 63.3 (OCH_2), 52.8 (OCH_3), 44.8 (=CHCH), 40.9 (O=CCH_2); IR (Diamond ATR): 685 m, 849 m, 917 s, 996 s, 1011 s, 1113 s, 1170 m, 1231 m, 1304 m, 1741 s, 1766 m, 2897 w, 2956 w, 2987 w cm^{-1}; HRMS (ESI$^+$): [M^+] 212.0686, $C_{10}H_{12}O_5$ requires 212.0679.

Methyl (1*RS*,4*RS*,5*RS*)-4-Methyl-6-oxo-4-(prop-1-en-2-yl)-2,8-dioxabicyclo[3.2.1]octane-5-carboxylate (7b). $Rh_2(O_2CCF_3)_4$ (1.6 mg, 0.0025 mmol) was added to a solution of cyclic acetal **5b** (67 mg, 0.25 mmol) in toluene (6 mL) at rt. After stirring for 1.5 h, the mixture was concd under reduced pressure and purified by column chromatography (EtOAc/petrol = 2/8) to give, as a colorless solid, bicyclic ester **7b** (45 mg, 75%). R_f (EtOAc/petrol = 2/8) 0.18; mp 122−126 °C (>100 °C sublimated); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.97 (d, J = 5.4, 1 H; O-CH-O), 5.25 (s, 1 H; =CH_aH_b), 5.13 (m, 1 H; =CH_aH_b), 3.94 (d, J = 13.1, 1 H; OCH_aH_b), 3.79 (s, 3 H; OCH_3), 3.63 (d, J = 13.1, 1 H; OCH_aH_b), 2.86 (dd, J = 18.5, 5.4, 1 H; O=CCH_aH_b), 2.66 (d, J = 18.5, 1 H; O=CCH_aH_b), 1.88 (d, J = 0.6, 3 H; =CCH_3), 1.19 (s, 3 H; $C_{quat.}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 204.1 (C=O), 164.9 (CO_2), 144.4 (C=CH_2), 116.2 (=CH_2), 97.6 (O-C-O), 86.7 (O=$CC_{quat.}$), 68.5 (OCH_2), 52.7 (OCH_3), 46.3 ($OCH_2C_{quat.}$), 41.1 (O=CCH_2), 21.8 (=CCH_3), 18.7 ($C_{quat.}CH_3$); IR (Diamond ATR): 624 m, 817 m, 904 s, 917 s, 1007 m, 1099 s, 1187 m, 1285 m, 1737 s, 1756 m, 2933 w, 2985 w cm^{-1}; HRMS (ESI$^+$): [M + Na^+] 263.0890, $C_{12}H_{16}NaO_5$ requires 263.0890.

Methyl (1*RS*,4*SR*,5*SR*)-4-Methyl-6-oxo-1-phenyl-4-(prop-1-en-2-yl)-2,8-dioxabicyclo[3.2.1]octane-5-carboxylate (7d). $Rh_2(O_2CCF_3)_4$ (0.7 mg, 0.001 mmol) was added to a solution of cyclic acetal **5d** (69 mg, 0.2 mmol) in CH_2Cl_2 (60 mL) at rt. After stirring for 20 h, the mixture was concd under reduced pressure and purified by column chromatography (CH_2Cl_2) to give, as a colorless sticky solid, bicyclic acetal **7d** (27 mg, 43%). R_f (CH_2Cl_2) 0.44; mp 55−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67−7.62 (m, 2 H; Ar), 7.46−7.37 (m, 3 H; Ar), 5.30 (s, 1 H; =CH_aH_b), 5.12−5.09 (m, 1 H; =CH_aH_b), 4.15 (d, J = 12.9, 1 H; O-CH_aH_b), 3.81 (s, 3 H; OCH_3), 3.81 (d, J = 12.9, 1 H; O-CH_aH_b), 3.00 (d, J = 18.4, 1 H; O=CH_aH_b), 2.95 (d, J = 18.4, 1 H; O=CH_aH_b), 1.88 (d, J = 1.0, 3 H; =CCH_3), 1.28 (s, 3 H; $C_{quat.}CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.6 (C=O), 165.0 (CO_2), 144.3 (C=CH_2), 138.6 ($Ar_{quat.}$), 129.1 (1 × Ar), 128.4 (2 × Ar), 125.2 (2 × Ar), 116.4 (=CH_2), 104.0 (Ar-C), 89.0 (O=$CC_{quat.}$), 70.4 (OCH_2), 52.7 (OCH_3), 46.4 (O=CCH_2), 45.5 ($OCH_2C_{quat.}$), 21.9 (=CCH_3), 18.6 ($C_{quat.}CH_3$); IR (Diamond ATR): 699 w, 766 w, 1009 w, 1217 m, 1278 w, 1367 m, 1438

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w, 1739 s, 2970 w, 3015 w cm^{-1}; HRMS (ESI^+): $[M + Na^+]$ 339.1204, $C_{18}H_{20}NaO_5$ requires 339.1203.

Methyl (1*RS*,4*RS*,5*RS*)-4-Methyl-6-oxo-4-vinyl-2,8-dioxabicyclo[3.2.1]octane-5-carboxylate (7e). A solution of $Rh_2(O_2CCF_3)_4$ (7 mg, 0.01 mmol) in CH_2Cl_2 (5 mL) was added to a solution of cyclic acetal **5e** (210 mg, 0.83 mmol) in CH_2Cl_2 (20 mL) at −40 °C. After stirring for 70 h, the reaction mixture was warmed to rt and concd under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol = 0% → 15%); first eluted, as a colorless crystalline solid, bicyclic acetal **7e** (61 mg), and second eluted, as a colorless crystalline solid, a mixture bicyclic acetals **7e** and **7f** (12 mg, **7e**:**7f** = 60:40, as determined by ^1H NMR integration: δ = 6.34 (**7e**, 1 H) and 5.13 (**7f**, 1 H)); total bicyclic acetals **7e** + **7f** (73 mg, 40%, **7e**:**7f** = 93:7). R_f (EtOAc/petrol = 2/8) 0.29; mp: 42−46 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.34 (dd, J = 17.7, 10.9, 1 H; −C*H*=CHH′), 5.93 (d, J = 5.3, 1 H; C*H*(O−)$_2$), 5.28 (dd, J = 17.7, 0.8, 1 H; =CH*H*′), 5.27 (dd, J = 10.9, 0.8, 1H; =CH*H*′), 3.75 (s, 3 H; CO_2−CH_3), 3.65 (d, J = 0.8, 2H; O−CH_2), 2.87 (dd, J = 18.6, 5.4, 1 H; O=C−CH*H*′), 2.64 (d, J = 18.6, 1H; O=C−C*H*H′), 1.12 (s, 3 H; C−CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.0 (C=O), 164.2 (CO_2Me), 137.4 (*C*H=CH_2), 116.4 (=CH_2), 97.6 (*C*H(O−)$_2$), 86.5 (*C*−CO_2Me), 68.9 (O−CH_2), 52.6 (CO_2−CH_3), 43.8 (CH_3−*C*−CH=CH_2), 41.1 (O=C−*C*H$_2$), 16.6 (C−CH_3); IR (neat): 628 w, 691 w, 816 m, 838 m, 922 s, 999 s, 1027 m, 1101 s, 1173 m, 1242 m, 1294 m, 1744 s, 1772 s, 2955 br cm^{-1}; HRMS (ESI^+): $[M + H^+]$ 249.0731, $C_{11}H_{14}NaO_5$ requires 249.0733. Discernible data for methyl (1*RS*,4*RS*,5*SR*)-6-oxo-4-(prop-1-en-2-yl)-2,8-dioxabicyclo[3.2.1]octane-5-carboxylate (**7f**): ^1H NMR (400 MHz, $CDCl_3$): δ = 5.69−5.67 (m, 1 H; O−C*H*), 5.13 (t, J = 1.5, 1 H; =CH*H*′), 4.97 (quin, J = 1.5, 1 H; =C*H*H′), 4.22 (d, J = 4.5, 1 H; CH*H*′−O), 4.19 (d, J = 4.5, 1 H; C*H*H′−O), 3.91 (s, 3 H; CO_2CH_3), 1.96-1.93 (m, 1 H; H_2C=CCH_3).

(5*RS*,9*RS*)-9-Vinyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (8a). A solution of bicyclic acetal **7a** (54 mg, 0.26 mmol) and $(PhO)_2PO_2H$ (6 mg, 0.025 mmol) in toluene (1 mL) was heated under reflux for 17 h and then concd under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2) to give, as a colorless solid, spirofuranone **8a** (22 mg, 45%). R_f (CH_2Cl_2) 0.25; mp 56−66 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, J = 2.6, 1 H; O-CH=), 5.78 (ddd, J = 17.1, 10.1, 8.6, 1 H; =CH), 5.67 (d, J = 2.6, 1 H; O=CCH=), 5.35 (dm, J = 17.1, 1 H; =CH_aH_b), 5.29 (d, J = 10.1, 1 H; =CH_aH_b), 4.63 (dd, J = 11.1, 8.8, 1 H; O-CH_aH_b), 4.49 (t, J = 8.8, 1 H; O-CH_aH_b), 3.66 (dt, J = 11.1, 8.6, 1 H; O-CH_2C*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.6 (C=O), 179.8 (O-CH=), 167.3 (CO_2), 128.2 (=CH), 122.8 (=CH_2), 106.8 (O=C*C*H=), 88.6 (O=C$C_{quat.}$-O), 67.9 (OCH_2), 48.3 (*C*HCH=); IR (Diamond ATR) 814 s, 943 m, 1010 m, 1081 m, 1561 s, 1697 s, 1783 m, 2852 w, 2921 w, 3113 w cm^{-1}; HRMS (ESI^+): $[M^+]$ 180.0426, $C_9H_8O_4$ requires 180.0417.

(5*RS*,9*RS*)-9-Methyl-9-(prop-1-en-2-yl)-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (8b). Method A: A solution of bicyclic acetal **7b** (60 mg, 0.25 mmol) and $(PhO)_2PO_2H$ (6 mg, 0.025 mmol) in toluene (1 mL) was heated under reflux for 20 h and then concd under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2) to give, as a colorless solid, spirofuranone **8b** (45 mg, 87%). R_f (CH_2Cl_2) 0.31; mp 91−97 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, J = 2.6, 1 H; O−CH=), 5.73 (d, J = 2.6, 1 H; O=CCH=), 5.06 (d, J = 8.3, 1 H; O-CH_aH_b), 4.90 (q, J = 1.5, 1 H; =CH_aH_b), 4.63 (s, 1 H; =CH_aH_b), 4.16 (d, J = 8.3, 1 H; O-CH_aH_b), 1.63 (s, 3 H; =CCH_3), 1.43 (s, 3 H; $C_{quat.}CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.9 (C=O), 178.3 (O-CH=), 167.3 (CO_2), 142.4 (=*C*CH_3), 113.0 (=CH_2), 107.6 (O=CCH=), 91.6 (O=C$C_{quat.}$-O), 73.6 (OCH_2), 50.8 ($OCH_2C_{quat.}$), 22.0 ($C_{quat.}CH_3$), 19.4 (=CCH_3); IR (Diamond ATR): 811 s, 909 m, 1007 m, 1080 s, 1194 m, 1562 m, 1704 s, 1788 m, 2852 w, 2924 w, 3107 w cm^{-1}; HRMS (FI^+): $[M^+]$ 208.0729, $C_{11}H_{12}O_4$ requires 208.0730. **Method B**: $Rh_2(O_2CCF_3)_4$ (2 mg, 0.003 mmol) was added to a solution of cyclic acetal **5b** (402 mg, 1.5 mmol) in toluene (6 mL) at rt. After stirring for 5 h, $(PhO)_2PO_2H$ (19 mg, 0.075 mmol) was added and the mixture was heated under reflux for 24 h. The mixture was concd under reduced pressure, and the residue was purified by column chromatography (CH_2Cl_2) to give, as a colorless solid, spirofuranone **8b** (227 mg, 73%). Data as Method A above.

(5*RS*,9*RS*)-9-Methyl-2-phenyl-9-(prop-1-en-2-yl)-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (8d). Method A: PhLi (290 μL, 1.9 M in Bu_2O, 0.55 mmol) was added dropwise over 5 min to a solution of spirofuranone **8b** (104 mg, 0.50 mmol) in THF (5 mL) at −78 °C. After stirring for 15 min at −78 °C, TMSCl (70 μL, 60 mg, 0.55 mmol) was added dropwise and the mixture was stirred for 15 min at −78 °C and then for 30 min at rt. DDQ (250 mg, 1.1 mmol) was added, and after stirring for 20 h at rt, the mixture was concd under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL). The solution was washed with aq. $Na_2S_2O_3$·$5H_2O$ (4 × 3 mL, 10%), dried (Na_2SO_4), and concd under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol = 2/8) to give, as a pale yellow solid, spirofuranone **8d** (112 mg, 78%). R_f (EtOAc/petrol = 2/8) 0.31; mp 138−147 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92−7.84 (m, 2 H; Ar), 7.65−7.59 (m, 1 H; Ar), 7.57−7.50 (m, 2 H; Ar), 6.07 (s, 1 H; O=CCH), 5.18 (d, J = 8.3, 1 H; O-CH_aH_b), 4.94 (q, J = 1.5, 1 H; =CH_aH_b), 4.69 (s, 1 H; =CH_aH_b), 4.22 (d, J = 8.3, 1 H; O-CH_aH_b), 1.68 (m, 3 H; =CCH_3), 1.58 (s, 3 H; $C_{quat.}CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.1 (C=O), 186.0 (ArC=), 168.1 (CO_2), 142.7 (=*C*CH_3), 133.5 (1 × Ar), 129.1 (2 × Ar), 127.8 ($Ar_{quat.}$), 127.3 (2 × Ar), 113.0 (=CH_2), 101.0 (O=C*C*=), 93.0 (O=C$C_{quat.}$-O), 73.7 (OCH_2), 51.1 ($OCH_2C_{quat.}$), 22.3 ($C_{quat.}CH_3$), 19.4 (=CCH_3); IR (Diamond ATR): 650 m, 682 s, 774 m, 1092 s, 1349 m, 1567 s, 1687 s, 1786 m, 3088 w cm^{-1}; HRMS (ESI^+): $[M + Na^+]$ 307.0939, $C_{17}H_{16}NaO_4$ requires 307.0941. **Method B**: $(PhO)_2PO_2H$ (2 mL, 0.01 M in CH_2Cl_2) was added to bicyclic acetal **7d** (25 mg, 0.079 mmol) at rt. After stirring for 1 h, Et_3N (10 μL) was added and the reaction mixture was concd under vacuum. The residue was purified by column chromatography (EtOAc/petrol = 2/8) to give, as a colorless solid, spirofuranone **8d** (18 mg, 80%). Data as Method A above.

(5*RS*,9*RS*)-9-Methyl-9-vinyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (8e). $(PhO)_2PO_2H$ (6 mg, 0.02 mmol) was added to a solution of bicyclic acetal **7e** (54 mg, 0.24 mmol) in toluene (1 mL) and heated to reflux. After 24 h, the reaction mixture was concd under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/petrol = 50% → 75%) to give, as a colorless crystalline solid, spirofuranone **8e**[6] (36.9 mg, 80%). R_f (CH_2Cl_2) 0.50; mp: 30−32 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, J = 2.5, 1 H; =C*H*−C−O), 5.90 (dd, J = 17.4, 10.9, 1 H; C*H*=CH_2), 5.67 (d, J = 2.5, 1 H; =C*H*−C=O), 5.30 (d, J = 10.9, 1 H; CH=CH*H*′), 5.26 (d, J = 17.4, 1 H; CH=CH*H*′), 4.91 (dd, J = 8.5, 0.6, 1 H; CH*H*′), 4.08 (d, J = 8.5, 1 H; C*H*H′), 1.42 (s, 3 H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.5 (OC−CH=), 179.5 (O−*C*H=), 167.3 (O=*C*−O), 133.7 (*C*H=CH_2), 119.3 (CH=CH_2), 106.9 (=*C*−CO), 91.7 (O−*C*−CO), 74.0 (CH_2), 48.5 (CH_3), 19.4 (=CH−C−CH_3); IR (neat): 665 w, 691 w, 717 w, 792 m, 814 m, 935 w, 978 m, 1001 s, 1037 m, 1081 s, 1140 m, 1204 s, 1269 w, 1355 w, 1473 w, 1564 s, 1700 s, 1789 s cm^{-1}; HRMS (ESI^+): $[M + Na^+]$ 217.0469, $C_{10}H_{10}NaO_4$ requires 217.0471.

Methyl 2-Diazo-5,5-diethoxy-3-oxopentanoate (10). TMSOTf (5.0 mL, 6.1 g, 27.5 mmol) was added dropwise over 5 min to a solution of methyl β-diazoacetoacetate (**9**)[10] (3.55 g, 25.0 mmol) and Et_3N (3.6 mL, 2.63 g, 26.0 mmol) in CH_2Cl_2 (50 mL) at −30 °C, to give a deep yellow solution. After stirring for 30 min at −30 °C, cooled (−30 °C) triethyl orthoformate (16.6 mL, 14.8 g, 100 mmol) was added in one portion at −30 °C. After stirring for 5 min at −30 °C, pyridine (2.5 mL) was added in one portion. After warming to rt, the mixture was washed with H_2O (4 × 20 mL) and half sat. brine (1 × 20 mL), dried (Na_2SO_4), and concd under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol = 2/8) to give, as a light yellow oil, acyclic acetal **10** (5.49 g, 90%). R_f (EtOAc/petrol = 2/8) 0.19; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.06 (t, J = 5.6, 1 H; C*H*CH_2), 3.85 (s, 3 H; OCH_3), 3.69 (dq, J = 9.4, 7.1, 2 H; C$H_aH_b$$CH_3$), 3.57 (dq, J = 9.4, 7.0, 2 H; C$H_aH_b$$CH_3$), 3.24 (d, J = 5.6, 2 H; CHCH_2), 1.20 (t, J = 7.0, 6 H; CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 188.8 (C=O), 161.5 (CO_2Me), 99.1 (*C*HCH$_2$), 61.8 (CH_2CH_3), 52.2 (OCH_3), 44.5 (CHCH$_2$), 15.2 (CH_2CH_3); IR (neat): 745 m, 1060 s, 1124 s, 1206 s, 1298 s, 1379 s, 1436 s, 1660 s, 1723 s, 2136 s, 2899 m, 2932 m, 2978 s cm^{-1}; HRMS (ESI^+): $[M + Na^+]$ 267.0948 found, $C_{10}H_{16}N_2NaO_5$ requires 267.0951.

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(*Z*)-1,4-Bis(trimethylsilyloxy)-2,3-dimethylbut-2-ene (11b). TMSCl (4.5 mL, 3.83 g, 35.3 mmol) was added dropwise to a solution of (*Z*)-2,3-dimethylbut-2-ene-1,4-diol[24] (1.64 g, 14.1 mmol) and Et_3N (5.9 mL, 4.31 g, 42.3 mmol) in CH_2Cl_2 (80 mL) at 0−5 °C. After stirring for 1.5 h at rt, the reaction mixture was washed with H_2O (4 × 50 mL) and half sat. brine (1 × 50 mL). The solution was dried (Na_2SO_4) and concd under reduced pressure. The residue was purified by column chromatography (Et_2O; small column) to give, as a colorless oil, disilylated diol **11b** (3.51 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (s, 4 H; OCH_2), 1.73 (s, 6 H; =CCH_3), 0.13 (s, 18 H; $SiCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 131.1 (=C), 62.5 (OCH_2), 16.8 (=CCH_3), −0.5 ($SiCH_3$); IR (neat): 840 s, 1060 s, 1251 s, 2957 s cm^{-1}; HRMS (ESI$^+$): [M + Na$^+$] found 283.1519, $C_{12}H_{28}NaO_2Si_2$ requires 283.1520.

(*Z*)-1,4-Bis(trimethylsilyloxy)-2-methylbut-2-ene (11c). TMSCl (1.0 mL, 7.9 mmol) was added dropwise to a solution of (*Z*)-2-methylbut-2-ene-1,4-diol[24] (203 mg, 2.0 mmol) and Et_3N (1.2 mL, 8.6 mmol) in CH_2Cl_2 (19 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then warmed to rt. After 8 h, the reaction mixture was quenched with sat aq $NaHCO_3$ and then washed with H_2O (4 × 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concd under reduced pressure. The residue was purified by column chromatography (Et_2O/petrol: 5% → 10%) to give, as a colorless oil, disilylated diol **11c** (402.5 mg, 82%). R_f (EtOAc/petrol = 1/9) 0.93; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (tq, *J* = 6.6, 1.0, 1 H; =C*H*), 4.19 (dd, *J* = 6.6, 1.0, 2 H; CH_2), 4.12 (s, 2 H; CH_2), 1.77 (d, *J* = 1.0, 3 H; =C−CH_3), 0.13 (s, 18 H; $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.0 (=*C*−CH_3), 126.2 (=*C*H), 61.2 (CH_2OTMS), 58.6 (CH_2OTMS), 21.2 (=C−CH_3), −0.4 ($Si(CH_3)_3$), −0.5 ($Si(CH_3)_3$); IR (neat): 746 m, 835 s, 873.8 m, 1061 m, 1229 m, 1366 w, 1739 s, 2970 w cm^{-1}; MS (ESI$^+$): [M − TMS + Na$^+$] 197.1, $C_8H_{18}NaO_2Si$ requires 197.1; unstable to HRMS analysis.

Methyl 5,5-Dimethoxy-3-oxo-5-phenylpentanoate (13). TMSOTf (2.0 mL, 2.45 g, 11 mmol) was added dropwise over 10 min to a solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**12**) (1.42 g, 10 mmol), $PhC(OMe)_3$ (1.82 g, 10 mmol), and Et_3N (1.55 mL, 1.11 g, 11 mmol) in CH_2Cl_2 (40 mL) at −78 °C. After stirring for 30 min at −78 °C, $BF_3{\cdot}OMe_2$ (0.92 mL, 1.14 g, 10 mmol) was added dropwise over 10 min. After stirring for a further 60 min at −78 °C, the reaction was quenched by addition of aq. sat. $NaHCO_3$ (60 mL) and the mixture was vigorously stirred for 30 min at rt. The organic layer was separated, and the aq layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with half sat. brine (4 × 20 mL), dried (Na_2SO_4), and concd under reduced pressure. MeOH (3.2 mL, 2.56 g, 80 mmol) was added in two portions over 8 h to a solution of the residue in toluene (80 mL) under reflux. The mixture was then concd under reduced pressure and purified by column chromatography (EtOAc/petrol = 1/9) to give, as a yellow viscous oil, acyclic acetal **13** (1.845 g, 69%). R_f (EtOAc/petrol = 1/9) 0.18; R_f (EtOAc/petrol = 2/8) 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): keto tautomer δ = 7.51−7.43 (m, 2 H; Ar), 7.42−7.28 (m, 3 H; Ar), 3.62 (s, 3 H; CO_2CH_3), 3.22 (s, 6 H; $C_{quat.}$-OCH_3), 3.17 (s, 2 H; CH_2), 3.02 (s, 2 H; CH_2); enol tautomer discernible δ = 11.83 (s, 1 H; OH), 4.58 (s, 1 H; =CH), 3.23 (s, 6 H; $C_{quat.}$-OCH_3), 2.84 (s, 2 H; PhCCH_2); ^{13}C NMR (101 MHz, $CDCl_3$): keto tautomer δ = 199.0 (C=O), 167.4 (CO_2Me), 139.5 ($Ar_{quat.}$), 128.43 (Ar), 128.37 (2 × Ar), 126.8 (2 × Ar), 101.0 (O-C-O), 52.1 (CO_2CH_3), 51.1 (CH_2), 49.6 (CH_2), 49.0 ($C_{quat.}$-OCH_3); IR (Diamond ATR): 703 s, 1039 s, 1070 m, 1109 s, 1216 m, 1233 m, 1324 w, 1448 w, 1716 m, 1746 s, 2834 w, 2951 w cm^{-1}; HRMS (ESI$^+$): [M + Na$^+$] 289.1037, $C_{14}H_{18}NaO_5$ requires 289.1046.

Methyl 4-(2-Phenyl-4,7-dihydro-1,3-dioxepin-2-yl)-3-oxobutanoate (14c). TMSOTf (9 μL, 11 mg, 0.05 mmol) was added to a solution of acyclic acetal **13** (146 mg, 0.55 mmol) and (*Z*)-1,4-bis(trimethylsilyloxy)but-2-ene (**11a**)[23] (151 mg, 0.65 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C. After stirring for 24 h at −78 °C, pyridine (50 μL) was added. The reaction mixture was warmed to rt and concd under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol = 2/8) to give, as a pale yellow oil, acetal **14c** (144 mg, 90%). R_f (EtOAc/petrol = 2/8) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$): keto tautomer δ = 7.61−7.46 (m, 2 H; Ar), 7.44−7.30 (m, 3 H; Ar), 5.69 (t, *J* = 1.5, 2 H; =CH), 4.45−4.34 (m, 2 H; =CHCH_aH_b), 4.23−4.14 (m, 2 H; =CHCH_aH_b), 3.66 (s, 3 H; CO_2CH_3), 3.25 (s, 2 H; CH_2), 3.19 (s, 2 H; CH_2); enol tautomer discernible δ = 11.78 (s, 1 H; OH), 4.62 (s, 1 H; =CH), 2.90 (s, 2 H; PhCCH_2); ^{13}C NMR (101 MHz, $CDCl_3$): keto tautomer δ = 198.9 (C=O), 167.5 (CO_2Me), 139.8 ($Ar_{quat.}$), 129.1 (=CH), 128.5 (Ar), 128.3 (2 × Ar), 126.5 (2 × Ar), 103.0 (O-C-O), 62.4 (=CHCH_2O), 52.1 (CO_2CH_3), 51.4 (CH_2), 49.6 (CH_2); IR (Diamond ATR): 635 m, 769 w, 702 s, 1028 m, 1077 s, 1118 m, 1238 m, 1258 m, 1288 m, 1324 w, 1448 w, 1713 m, 1746 m, 2862 w, 2951 w, 3032 w cm^{-1}; HRMS (ESI$^+$): [M + Na$^+$] 313.1037, $C_{16}H_{18}NaO_5$ requires 313.1046.

Methyl 4-(5,6-Dimethyl-2-phenyl-4,7-dihydro-1,3-dioxepin-2-yl)-3-oxobutanoate (14d). TMSOTf (45 μL, 56 mg, 0.25 mmol) was added to a solution of acyclic acetal **13** (732 mg, 2.75 mmol) and disilylated diol (**11b**) (847 mg, 3.25 mmol) in CH_2Cl_2 (7.5 mL) at −78 °C. After stirring for 24 h at −78 °C, pyridine (250 μL) was added. The reaction mixture was warmed to rt and concd under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol = 1/9) to give, as a yellow oil, acetal **14d** (664 mg, 76%). R_f (EtOAc/petrol = 1/9) 0.19; ^{1}H NMR (400 MHz, $CDCl_3$): ketoform δ = 7.55−7.45 (m, 2 H; Ar), 7.42−7.28 (m, 3 H; Ar), 4.27 (dm, *J* = 14.6, 2 H; OCH_aH_b), 4.07 (dm, *J* = 14.6, 2 H; OCH_aH_b), 3.65 (s, 3 H; CO_2CH_3), 3.22 (s, 2 H; CH_2), 3.19 (s, 2 H; CH_2), 1.56 (s, 6 H; =CCH_3); enolform selected δ = 11.78 (s, 1 H; OH), 4.62 (s, 1 H; =CH), 2.87 (s, 2 H; PhCCH_2); ^{13}C NMR (101 MHz, $CDCl_3$): ketoform δ = 198.9 (C=O), 167.5 (CO_2Me), 139.9 ($Ar_{quat.}$), 128.5 (Ar), 128.3 (2 × Ar), 127.9 (=*C*CH_3), 126.4 (2 × Ar), 102.3 (O-C-O), 66.7 (=*C*CH_2O), 52.1 (CO_2CH_3), 51.3 (CH_2), 49.6 (CH_2), 16.3 (=*C*CH_3); IR (Diamond ATR): 701 s, 771 m, 1030 m, 1050 m, 1086 m, 1115 s, 1149 m, 1238 m, 1266 m, 1292 m, 1324 m, 1448 m, 1714 m, 1748 m, 2859 w, 2928 w cm^{-1}; HRMS (ESI$^+$): [M + Na$^+$] 341.1359, $C_{18}H_{22}NaO_5$ requires 341.1359.

2-{(5*RS*,9*RS*)-9-Methyl-4,6-dioxo-2-phenyl-1,7-dioxaspiro[4.4]non-2-en-9-yl}acrylaldehyde (15). A mixture of spirolactone **8d** (57 mg, 0.20 mmol) and SeO_2 (25 mg, 0.23 mmol) in dioxane (2 mL) was heated in a sealed tube at 120 °C for 60 min. After cooling to rt, the reaction mixture was stirred with $NaHCO_3$ (50 mg) and $MgSO_4$ (50 mg) for 1 h. The mixture was filtered through a mixture of Celite/florisil = 1/1 (0.5 g), and the filter cake was rinsed with CH_2Cl_2 (5 mL).[25] The solution was concd under reduced pressure and the residue was purified by column chromatography (EtOAc/petrol = 4/6) to give, as a yellow oil, enal **15** (41 mg, 70%). R_f (EtOAc/petrol = 4/6) 0.27; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40 (s, 1 H; CH=O), 7.93−7.89 (m, 2 H; Ar), 7.69−7.60 (m, 1 H; Ar), 7.59−7.50 (m, 2 H; Ar), 6.17 (s, 1 H; =CH_aH_b), 6.12 (s, 1 H; =CH_aH_b), 6.07 (s, 1 H; ArC=C*H*), 5.03 (d, *J* = 8.8, 1 H; O-CH_aH_b), 4.69 (d, *J* = 8.8, 1 H; O-CH_aH_b), 1.64 (s, 3 H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.0 (C=O), 192.9 (CH=O), 186.9 (ArC=), 167.3 (CO_2), 148.9 (=*C*CH=O), 135.9 (=CH_2), 133.7 (1 × Ar), 129.1 (2 × Ar), 127.7 ($Ar_{quat.}$), 127.5 (2 × Ar), 101.1 (O=C*C*=CAr), 92.7 (O=C$C_{quat.}$-O), 73.6 (OCH_2), 48.3 ($OCH_2C_{quat.}$), 22.6 (CH_3); IR (Diamond ATR): 650 m, 687 s, 734 m, 772 s, 1094 s, 1346 m, 1568 s, 1604 s, 1692 s, 1788 s, 2836 w, 2935 w, 2979 w, 3063 w, 3111 cm^{-1}; HRMS (ESI$^+$): [M + Na$^+$] 321.0735, $C_{17}H_{14}NaO_5$ requires 321.0733.

Methyl (1*RS*,4*RS*,5*RS*)-4-Methyl-6-oxo-4-(3-oxoprop-1-en-2-yl)-2,8-dioxabicyclo[3.2.1]octane-5-carboxylate (16). A mixture of bicyclic acetal **7b** (24 mg, 0.10 mmol) and SeO_2 (14 mg, 0.13 mmol) in dioxane (1 mL) was heated under reflux for 20 min. After cooling to room temperature, the reaction mixture was stirred with $NaHCO_3$ (50 mg) for 1 h and dried $MgSO_4$ (50 mg). The mixture was filtered through a mixture of Celite/florisil = 1/1 (0.5 g), and the filter cake was rinsed with CH_2Cl_2 (5 mL).[25] The solution was concd under reduced pressure and the residue was purified by column chromatography (EtOAc/petrol = 2/8) to give, as a colorless solid, enal **16** (17 mg, 67%). R_f (EtOAc/petrol = 2/8) 0.09; R_f (EtOAc/petrol = 4/6) 0.33; mp 121−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.50 (s, 1 H; HC=O), 6.99 (s, 1 H; =CH_aH_b), 6.38 (s, 1 H; =CH_aH_b), 5.93 (d, *J* = 5.3, 1 H; O-CH-O), 4.12 (d, *J* = 13.1, 1 H; OCH_aH_b), 3.83 (s, 3 H; OCH_3), 3.66 (d, *J* = 13.1, 1 H; OCH_aH_b), 2.88 (dd, *J* = 18.4, 5.3, 1 H; O=CCH_aH_b), 2.67 (d, *J* = 18.4, 1 H; O=CCH_aH_b), 1.35 (s, 3 H; $C_{quat.}CH_3$); ^{13}C NMR (101 MHz,

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$CDCl_3$): δ = 203.3 (C═O), 194.2 (HC═O), 164.3 (CO_2), 148.1 (C═CH_2), 141.4 (═CH_2), 97.7 (O-C-O), 85.2 (O═C$C_{quat.}$C.═O), 68.0 (OCH_2), 52.8 (OCH_3), 44.8 (O-$CH_2C_{quat.}$), 41.4 (O═CCH_2), 16.3 ($C_{quat.}CH_3$). IR (Diamond ATR): 610 s, 919 s, 989 m, 1102 s, 1102 m, 1312 m, 1689 s, 1731 s, 1760 m, 2935 w cm^{-1}; HRMS (ESI^+): [M + Na^+] 277.0679, $C_{12}H_{14}NaO_6$ requires 277.0683.

(5*RS*,9*RS*)-9-Acetyl-9-methyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (17). $Rh_2(O_2CCF_3)_4$ (2 mg, 0.003 mmol) was added to a solution of cyclic acetal **5b** (402 mg, 1.5 mmol) in CH_2Cl_2 (40 mL) at rt. After stirring for 5 h, the mixture was cooled to −78 °C. A stream of ozone was bubbled through a solution of the residue in CH_2Cl_2 (18 mL) at −78 °C. When the mixture turned blue, excess ozone was removed using a stream of oxygen and then a stream of nitrogen. Et_3N (0.42 mL, 3.0 mmol) was added at −78 °C, and the mixture was stirred for 1 h at rt. The solution was washed with H_2O (4 × 10 mL) and half sat. brine (1 × 20 mL), dried (Na_2SO_4), and concd under reduced pressure. The residue and $(PhO)_2PO_2H$ (38 mg) were dissolved in toluene (6 mL). After heating under reflux for 18 h, the mixture was concd under reduced pressure. The residue was purified by column chromatography (Et_2O) to give, as a yellow oil, ketone **17** (220 mg, 70%). R_f (Et_2O) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, J = 2.5, 1 H; O-CH═), 5.79 (d, J = 2.5, 1 H; O═CCH═), 5.02 (d, J = 8.8, 1 H; O-C$H_a$$H_b$), 4.26 (d, J = 8.8, 1 H; O-$CH_a$$H_b$), 2.07 (s, 3 H; O═$CCH_3$), 1.50 (s, 3 H; $C_{quat.}CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.5 (O═CCH_3), 197.7 (O═CC═), 178.7 (O-CH═), 165.9 (CO_2), 107.3 (O═CCH═), 89.0 (O═C$C_{quat.}$-O), 71.4 (OCH_2), 58.7 ($OCH_2C_{quat.}$), 26.0 (O═CCH_3), 18.9 ($C_{quat.}CH_3$); IR (Diamond ATR): 791 m, 814 m, 1018 m, 1079 s, 1181 s, 1356 w, 1564 m, 1700 s, 1790 m, 2922 w, 2981 w, 3087 w, 3119 w, 3156 w cm^{-1}; HRMS (FI^+): [M^+] 210.0525, $C_{10}H_{10}O_5$ requires 210.0528.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds, X-ray diffraction data (CIF) for spirofuranone **8a**, and biological assays data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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