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CP-263,114 synthetic studies. Construction of an isotwistane ring system via rhodium carbenoid C–H insertion

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Dedicated to Professor Yoshito Kishi in honor of his receipt of the Tetrahedron Prize and his inspirational contributions to the field of organic chemistry

Abstract—Described is a rhodium carbenoid C–H insertion strategy for the construction of an isotwistane ring system needed for a late-stage fragmentation en route to the total synthesis of CP-263,114.

1. Introduction

Since their isolation in 1995, CP-263,114 (**1**, Phomoidride B, Fig. 1) and CP-225,917 (Phomoidride A) have received enormous attention from the synthetic community.[1] In line with these efforts, our laboratories have been interested in developing methods to construct the carbocyclic core of CP-263,114, and applying these methods to a total synthesis of the natural product. In our approach, we envision the late-stage fragmentation of a heavily functionalized isotwistane skeleton (**2**) to generate the carbocyclic core of the phomoidrides (**2**→**1**). In order to employ this fragmentation strategy, we explored a rhodium carbenoid-mediated C–H insertion reaction to construct the isotwistane skeleton, and a subsequent alkylation to construct the quaternary center found in the natural product (**3**→**2**).

Active research in the area of rhodium carbenoids has illustrated a diverse pattern of reactivity for these species.[2] With regard to the C–H insertion strategy planned for constructing the isotwistane skeleton, the known propensity of rhodium carbenoids to generate 5-membered rings in preference to 4- and 6-membered rings was encouraging and led us to postulate that of the possible products derived from C–H insertion, the desired one would predominate (Fig. 1).[3] Additionally, rhodium carbenoids have been shown to favor insertion into C–H bonds on highly substituted carbon atoms, and are particularly prone to insertion at C–H bonds adjacent to heteroatoms. In a preliminary study, we explored the feasibility of the C–H insertion approach on a model substrate (i.e. **8**, Scheme 1).

2. Results and discussion

As illustrated in Scheme 1, the synthesis commenced with known ketone **4**.[4] Dihydroxylation of **4** with osmium tetroxide resulted in exclusive formation of the desired diol **5**, which was protected as the corresponding acetonide (**6**), and then homologated to its β-ketoester **7**. Treatment of β-ketoester **7** with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) according to the procedure of Davies[5] furnished desired diazo ester **8**. After screening several rhodium catalysts and solvents, it was found that rhodium(II) acetate in methylene chloride at room temperature gave the desired insertion product **9** in excellent yield. Interestingly, only one

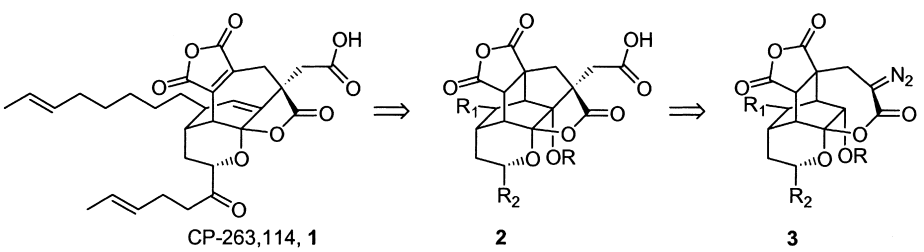

Figure 1. Retrosynthetic analysis.

Keywords: rhodium carbenoid; β-ketoester; isotwistane; CP-263,114; phomoidrides; C–H insertion; diazo.

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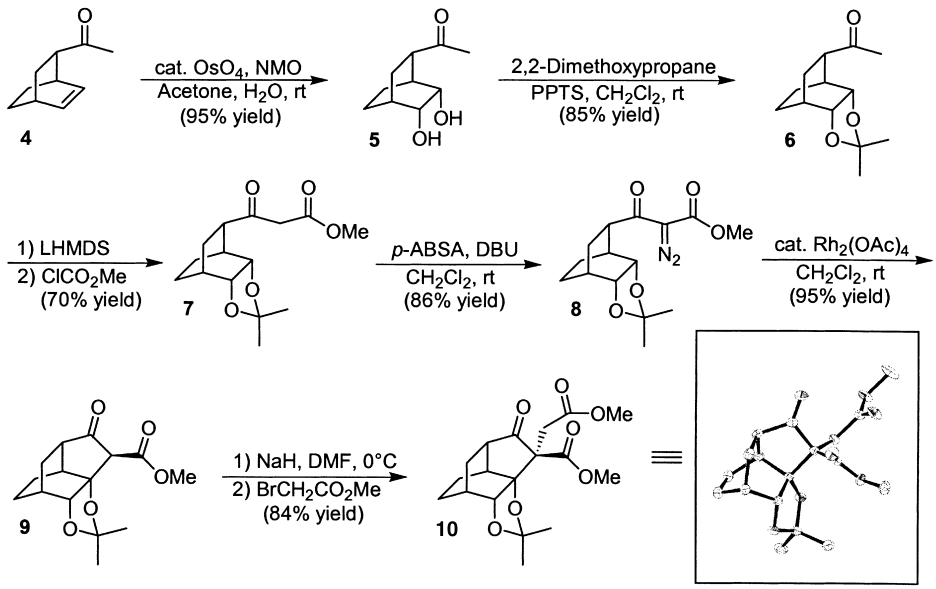
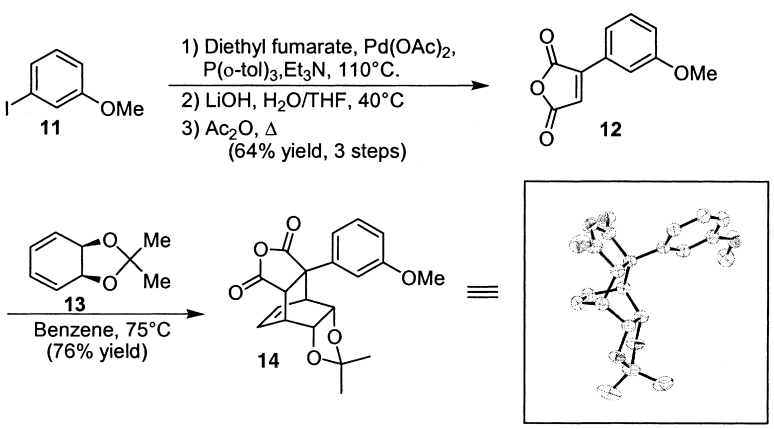


Scheme 1.

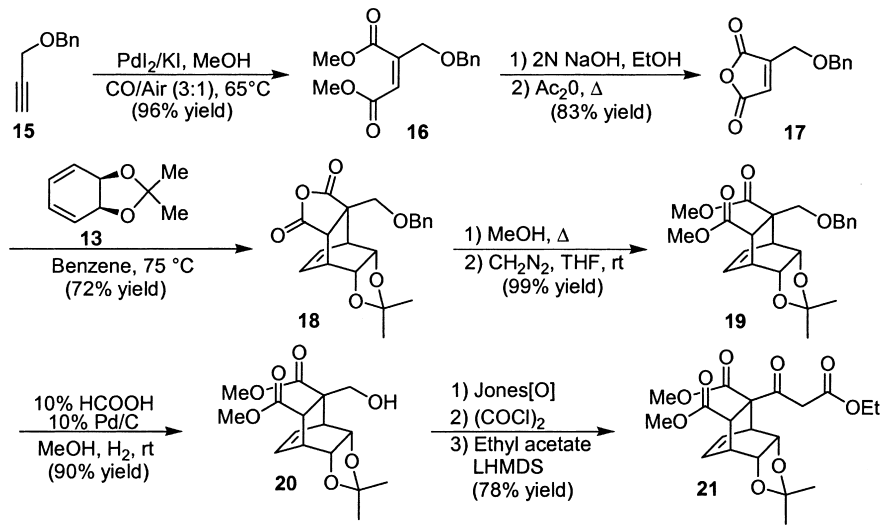
of the two possible diastereomeric products was observed (the structure of **9** was assigned using NOE difference experiments). Following the successful rhodium carbenoid C–H insertion, attention was focused on constructing the quaternary center. Thus, alkylation of β-ketoester **9** with methyl bromoacetate furnished **10** in excellent yield. Single-crystal X-ray analysis confirmed that **10** possessed the stereochemistry required for the natural product. The observed selectivity can be attributed to substrate control, in which the electrophile traps only from the less hindered α-face.

Applying this method to the total synthesis of the phomoidrides required that the C–H insertion chemistry be compatible with the functional groups present in **3**; of particular concern was the neighboring maleic anhydride unit or an appropriate precursor. To investigate the issues of functional group tolerance, a more advanced model system was constructed from acetonide **13**[6] and anhydride **12**[7] (Scheme 2). In the event, the propensity of **13** to undergo dimerization[8] and aromatization made it difficult to effect the desired Diels–Alder cycloaddition. These problems were eventually overcome by the use of high concentrations and moderate reaction temperatures to produce **14** in good yield. As anticipated, the cycloadduct generated was derived from *endo* attack of the dienophile on the side opposite to the acetonide on the sterically more accessible diene face.[9] Structural assignment of the product was secured using X-ray crystallography. Unfortunately, formation of the corresponding β-ketoester via a Birch reduction–ozonolysis sequence on **14** was unsuccessful.

Despite being unable to advance **14**, the Diels–Alder cycloaddition remained an attractive strategy and attention was turned to an alternate route. Propargyl ether **15** was subjected to oxidative dicarbonylation conditions[10] to give maleate **16**, which was then hydrolyzed and dehydrated to produce maleic anhydride **17** (Scheme 3). Subsequent Diels–Alder reaction with acetonide **13** yielded **18** as a single cycloadduct, which was ring-opened to the corresponding diester **19**. Chemoselective removal of the benzyl ether furnished alcohol **20**, which was then converted to **21** in a three-step sequence. Treatment of **21** with *p*-ABSA gave diazo compound **22** (Scheme 4). Unfortunately,



Scheme 2.

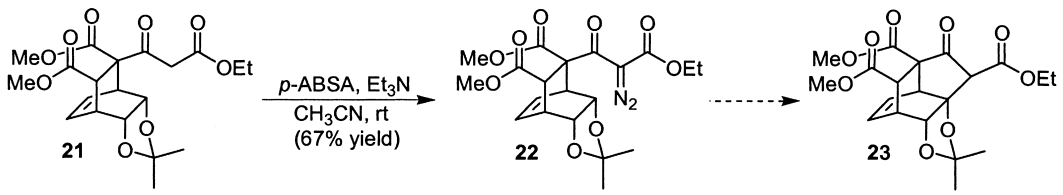


Scheme 3.

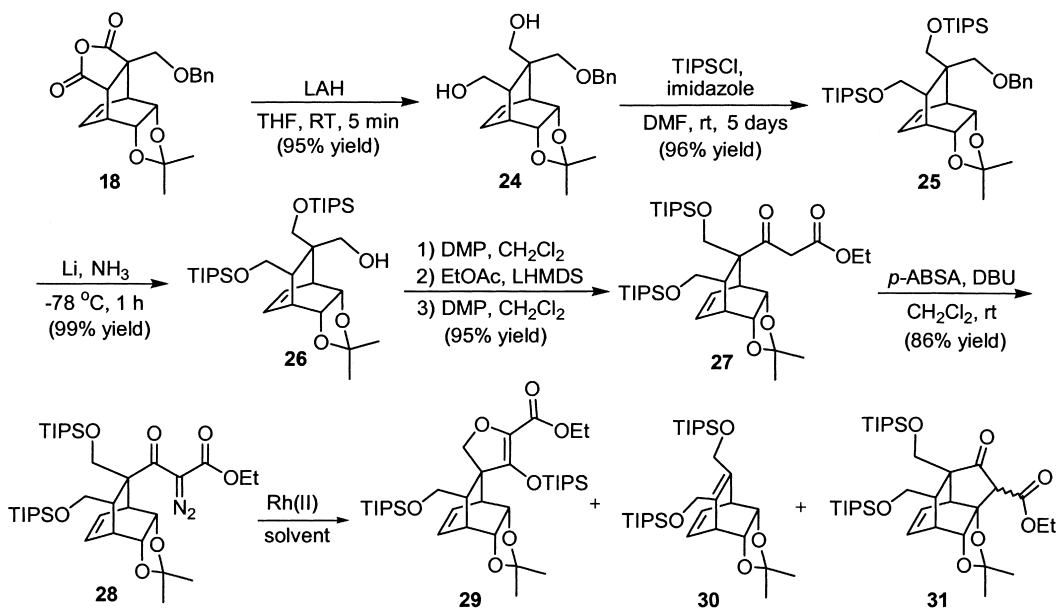
exposure of **22** to a variety of reaction conditions produced none of the desired C–H insertion product **23**. In all cases, intractable mixtures were obtained.

Based on the success of the simpler model system **8**, it is believed that the difficulties with **22** are likely the result of competing carbonyl ylide formation.[11] It was therefore envisioned that removal of the ester groups in **22** might minimize these undesired side reactions. Thus, anhydride **18** was exhaustively reduced to its corresponding diol (**24**) and protected as its bis-triisopropyl silyl (TIPS) ether (**25**, Scheme 5). Reductive removal of the benzyl ether was accomplished in high yield to provide primary alcohol **26**, which, after a three step oxidation–enolate addition–oxidation sequence, was converted to β-ketoester **27**. Finally, smooth diazotization to provide C–H insertion substrate **28** was accomplished using *p*-ABSA and DBU.

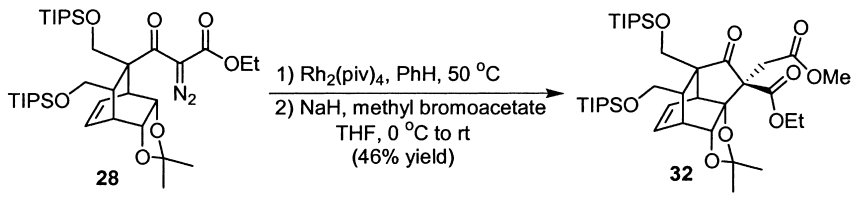
Initial attempts to produce a C–H insertion product by treating **28** with various rhodium(II) catalysts in a variety of



Scheme 4.



Scheme 5.



Scheme 6.

solvents yielded side-products from oxonium ylide formation-[1,4]-silyl migration and oxidative decarbonylation processes, **29** and **30**, respectively (Scheme 5).[12] Early experiments revealed that the electron-poor rhodium(II) trifluoroacetate or rhodium(II) perfluorobutyrate catalysts led almost exclusively to the formation of **30**. The desired compound (**31**)[13] was observed only as a minor product. Additionally, a substantial solvent effect was noted whereby utilization of chlorinated solvents (CH_2Cl_2, 1,2-dichloroethane) clearly favored the formation of compounds **29** and **30** over compound **31**. Formation of these side products was suppressed by employing the rhodium(II) pivalate ($Rh_2(piv)_4$) catalyst system in benzene at 50°C, to yield **32** as a single diastereomer in 46% overall yield after alkylation with methyl bromoacetate (Scheme 6).[14] It is worth noting that in the C–H insertion step, decreasing the reaction temperature from refluxing benzene to 50°C gave rise to a substantial increase in the yield of the desired product. As in earlier systems (see **10**, Scheme 1), subsequent electrophile trapping occurred exclusively on the less hindered α-face of the molecule. Compound **32** contains both the complete isotwistane core and the succinate-derived quaternary center found in the natural product.

3. Experimental

3.1. General

Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride. All other commercially obtained reagents were used as received.

Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Column or flash chromatography was performed with the indicated solvents using silica gel (230–400 mesh) purchased from Bodman. In general, the chromatography guidelines reported by Still et al. were followed.[15] When reactions were adsorbed onto silica gel, the amount of silica gel used was equal to two times the weight of the reagents.

All melting points were obtained on a Gallenkamp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500, Bruker Avance DPX-500 or Bruker Avance DPX-400 spectrometer. Chemical shifts are reported relative to internal chloroform (^1H, δ 7.26 ppm; ^{13}C, δ 77.0 ppm). High-resolution mass spectra were performed at the University of Illinois Mass Spectrometry Center. Single-crystal X-ray analyses were performed by Susan DeGala of Yale University.

3.1.1. 1-(5,6-Dihydroxy-bicyclo[2.2.2]oct-2-yl)-ethanone (5). To a stirred solution of **4** (7.38 g, 49.1 mmol, 1 equiv.) and NMO (12.7 g, 108.1 mmol, 2.2 equiv.) in a mixture of acetone (74 mL) and water (1.5 mL) was added OsO_4 (2.5 wt% solution in 2-methyl-2-propanol: 2.3 mL, 0.2 mmol, 0.004 equiv.). After stirring the reaction mixture at room temperature for 10 h, sodium bisulfite (1 g) was added and stirring continued for an additional 1 h. The resulting slurry was filtered through a Celite cake, thoroughly washed with acetone, and concentrated. The crude mixture was diluted with CH_2Cl_2 (200 mL) and washed with 1N HCl. The aqueous phase was saturated with NaCl and extracted with CH_2Cl_2 (3×30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified using silica gel chromatography, yielding **5** as a clear oil (8.73 g, 95% yield). FTIR (thin film/NaCl) 3389 (s), 2938 (s), 2870 (m), 1704 (s), 1454 (w), 1399 (w), 1355 (m), 1185 (w), 1149 (w), 1065 (m), 1017 (m), 975 (w), 953 (w), 830 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.85–3.83 (m, 1H), 3.73–3.71 (m, 1H), 2.84 (d, J=4.5 Hz, 1H), 2.74–2.70 (m, 1H), 2.68 (d, J=4.0 Hz, 1H), 2.18 (s, 3H), 2.10–2.09 (m, 1H), 2.01–1.96 (m, 1H), 1.93–1.87 (m, 2H), 1.65–1.59 (m, 1H), 1.40–1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 67.8, 65.0, 49.0, 34.2, 31.6, 28.8, 24.4, 18.9, 17.9; HRMS (EI) m/z 184.1103 [calcd for $C_{10}H_{16}O_3$ (M+) 184.1099].

3.1.2. 1-(4,4-Dimethyl-3,5-dioxa-tricyclo[5.2.2.0^{2,6}]undec-8-yl)-ethanone (6). To a stirred solution of **5** (3.31 g, 17.97 mmol, 1 equiv.) in CH_2Cl_2 (100 mL) was added 2,2-dimethoxypropane (6.63 mL, 53.91 mmol, 1 equiv.) and PPTS (100 mg, 0.40 mmol, 0.02 equiv.). The reaction mixture was stirred overnight at room temperature, diluted with CH_2Cl_2 (100 mL), and washed with saturated $NaHCO_3$ (3×50 mL). The organic layer was dried over Na_2SO_4 and purified using silica gel chromatography with 10% EtOAc/hexanes as eluant to furnish **6** as a white crystalline solid (3.43 g, 85% yield). Mp 81–83°C; FTIR (thin film/NaCl) 2986 (m), 2937 (s), 2869 (m), 1708 (s), 1453 (w), 1379 (m), 1262 (m), 1207 (m), 1163 (m), 1145 (w), 1096 (w), 1058 (s), 965 (w), 875 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.05 (ddd, J=7.5, 4.0, 1.0 Hz, 1H), 3.91 (ddd, J=8.0, 4.0, 1.0 Hz, 1H), 2.80–2.76 (m, 1H), 2.25 (t, J=3.0 Hz, 1H), 2.19 (s, 3H), 1.99–1.92 (m, 3H), 1.87–1.80 (m, 1H), 1.61 (ddd, J=13.5, 11.0, 4.0 Hz, 1H), 1.50 (s, 3H), 1.33–1.20 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 107.8, 75.0, 72.4, 48.5, 31.7, 29.0, 28.8, 25.9, 24.3, 23.5, 19.0, 17.9; HRMS (EI) m/z 224.1414 [calcd for $C_{13}H_{20}O_3$ (M+) 224.1412].

3.1.3. 3-(4,4-Dimethyl-3,5-dioxa-tricyclo[5.2.2.0^{2,6}]undec-8-yl)-3-oxo-propionic acid methyl ester (7). To a stirred (−78°C) solution of **6** (5.76 g, 25.68 mmol, 1 equiv.) in THF (25 mL) was added LiHMDS (1.0 M solution in THF: 77.1 mL, 77.1 mmol, 3 equiv.). After stirring the reaction mixture at −78°C for 1.5 h, methyl chloroformate (4 mL, 51.36 mmol, 2 equiv.) was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched by the addition of saturated ammonium chloride (20 mL) solution and extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude oil was subjected to silica gel chromatography (gradient elution, 0–10% EtOAc/hexanes) yielding analytically pure **7** as a crystalline white solid (5.1 g, 70% yield). Mp 61–64°C; FTIR (thin film/NaCl) 2985 (m), 2938 (s), 2870 (m), 1749 (s), 1710 (s), 1453 (w), 1438 (w), 1380 (m), 1316 (m), 1263 (s), 1207 (s), 1163 (s), 1090 (m), 1060 (s), 982 (w), 875 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dd, J=8.0, 4.0 Hz, 1H), 3.96 (app dd, J=8.0, 4.0 Hz, 1H), 3.73 (s, 3H), 3.53 (s, 2H), 2.92 (dq, J=5.5, 2.0 Hz, 1H), 2.23 (app t, J=2.5 Hz, 1H), 2.02–1.82 (m, 3H), 1.67 (ddd, J=11.0, 9.0, 4.0 Hz, 1H), 1.52–1.49 (m, 1H), 1.50 (s, 3H), 1.37–1.23 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 167.8, 107.9, 74.9, 72.2, 52.6, 48.1, 47.7, 31.4, 28.9, 25.9, 242.3, 23.7, 18.9, 17.7; HRMS (EI) m/z 282.1470 [calcd for $C_{15}H_{22}O_5$ (M+) 282.1467].

3.1.4. 2-Diazo-3-(4,4-dimethyl-3,5-dioxa-tricyclo-[5.2.2.0^{2,6}]undec-8-yl)-3-oxo-propionic acid methyl ester (8). To a stirred solution of **7** (1962 mg, 6.95 mmol, 1.0 equiv.) and *p*-ABSA (1838 mg, 7.65 mmol, 1.1 equiv.) in CH_2Cl_2 (35 mL) was added dropwise DBU (1150 μL, 7.65 mmol, 1.1 equiv.). After stirring the reaction mixture for 1 h at room temperature, it was concentrated, poured onto a silica gel column, and chromatographed using 15% EtOAc/hexanes as the eluant to furnish **8** as a yellow oil (1840 mg, 86% yield). FTIR (thin film/NaCl) 2940 (m), 2870 (w), 2138 (s), 1721 (s), 1650 (m), 1437 (m), 1380 (m), 1360 (m), 1306 (s), 1262 (m), 1207 (s), 1164 (m), 1132 (m), 1102 (w), 1060 (m), 973 (m), 876 (m), 812 (w), 763 (w), 739 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (ddd, J=10.1, 5.0, 1.0 Hz, 1H), 4.03 (ddd, J=10.1, 4.5, 2.0 Hz, 1H), 3.82 (s, 3H), 3.74 (ddd, J=12.5, 8.0, 3.0 Hz, 1H), 2.09–1.81 (m, 5H), 1.65 (ddd, J=17.5, 13.0, 6.0 Hz, 1H), 1.49 (s, 3H), 1.44–1.31 (m, 1H), 1.31 (s, 3H), 1.27–1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 161.6, 107.7, 75.1, 72.4, 52.4, 43.7, 32.4, 29.2, 25.9, 24.3, 23.6, 18.7, 17.8; HRMS (CI) m/z 309.1451 [calcd for $C_{15}H_{20}N_2O_5$ (M+H) 309.1451].

3.1.5. Methyl (9*S*)-2,2-dimethyl-8-oxooctahydro-4,7-methanoindeno[3a,4-*d*][1,3]dioxole-9-carboxylate (9). To a stirred solution of **8** (96 mg, 0.31 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) at room temperature was added $Rh_2(OAc)_4$ (2 mg, 0.005 mmol, 0.015 equiv.). This suspension was stirred overnight at room temperature, concentrated, and purified by silica gel chromatography using 10% EtOAc/hexanes as the eluant to give **9** as a white solid (83 mg, 95% yield). Mp 93–95°C (recrystallized from hexanes); FTIR (thin film/NaCl) 2988 (w), 2935 (m), 2887 (w), 1761 (s), 1721 (s), 1455 (w), 1439 (w), 1383 (m), 1373 (w), 1343 (m), 1272 (m), 1252 (w), 1215 (m), 1192 (m), 1134 (s), 1073 (m), 1033 (w), 996 (w), 920 (w), 873 (w), 750 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (d, J=5.0 Hz, 1H), 3.76 (s, 3H), 3.62 (d, J=1.5 Hz, 1H), 2.65–2.62 (m, 1H), 2.16–2.15 (m, 1H), 2.03–1.91 (m, 4H), 1.65–1.58 (m, 2H), 1.54 (s, 3H), 1.26 (s, 3H), 1.21 (ddt, J=14.0, 2.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 168.9, 109.3, 86.0, 75.2, 62.3, 52.4, 47.2, 39.1, 29.0, 27.0, 26.4, 25.8, 18.8, 14.3; HRMS (EI) m/z 280.1312 [calcd for $C_{15}H_{20}O_5$ (M+) 280.1311].

3.1.6. Methyl (9*R*)-9-(2-methoxy-2-oxoethyl)-2,2-dimethyl-8-oxooctahydro-4,7-methanoindeno[3a,4-*d*][1,3]dioxole-9-carboxylate (10). To a stirred suspension of NaH (157 mg, 3.92 mmol, 3 equiv.) in DMF (10 mL) at 0°C was added dropwise **9** (366 mg, 1.31 mmol, 1 equiv.) dissolved in DMF (3 mL). After 1 h, methyl bromoacetate (310 μL, 3.26 mmol, 2.5 mmol) was added and stirring was continued for 12 h at room temperature. The reaction mixture was quenched by the addition of saturated ammonium chloride (20 mL), diluted with benzene (100 mL) and washed sequentially with saturated $CuSO_4$ (3×30 mL) and brine (2×10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified using silica gel chromatography employing 15% EtOAc/hexanes as the eluant to furnish **10** as a white solid (387 mg, 84% yield). Mp 108–111°C (recrystallized from hexanes); FTIR (thin film/NaCl) 2990 (w), 2947 (m), 2871 (w), 1759 (s), 1740 (s), 1434 (w), 1373 (w), 1283 (w), 1254 (w), 1214 (m), 1152 (m), 1117 (m), 1080 (w), 1057 (m), 1036 (m), 1015 (m), 968 (m), 884 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (d, J=5.0 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.33 (d, J=16.0 Hz, 1H), 2.61 (ddd, J=10.0, 4.5, 3.5 Hz, 1H), 2.53 (d, J=16.0 Hz, 1H), 2.16–2.13 (m, 1H), 2.04–1.99 (m, 2H), 1.92–1.75 (m, 2H), 1.64 (ddt, J=15.0, 11.0, 3.5 Hz, 1H), 1.55 (s, 3H), 1.40 (s, 3H), 1.25–1.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 170.9, 170.5, 113.3, 87.7, 78.7, 61.8, 52.5, 52.2, 46.9, 37.0, 36.3, 28.9, 27.6, 27.1, 24.1, 19.2, 14.8; HRMS (EI) m/z 352.1528 [calcd for $C_{18}H_{24}O_7$ (M+) 352.1522].

3.1.7. 3-(3-Methoxy-phenyl)-furan-2,5-dione (12). A mixture of 3-iodoanisole (4 mL, 33.6 mmol, 1 equiv), diethyl fumarate (11 mL, 67.2 mmol, 2 equiv.), $Pd(OAc)_2$ (380 mg, 1.68 mmol, 0.05 equiv.), P(*o*-tol)$_3$ (1020 mg, 3.36 mmol, 0.1 equiv.) and Et_3N (10 mL, 67.2 mmol, 2 equiv.) was heated in a sealed tube at 90°C for 1 h. The crude reaction mixture was cooled to room temperature, concentrated, and purified using silica gel chromatography employing a gradient of 5–25% EtOAc/hexanes as eluant to yield the corresponding aryl diester (6.1 g, 65%). This material was carried on directly to the next step. A solution of the diester (6.1 g, 21.8 mmol, 1 equiv.) and LiOH (9.2 g, 218.3 mmol, 10 equiv.) in a mixture of THF (925 mL) and water (220 mL) was heated to 40°C for 24 h. The crude reaction mixture was cooled, concentrated in vacuo, acidified to pH 4, and extracted with EtOAc (3×100 mL), dried over $MgSO_4$ and evaporated. The resulting crude oil was dissolved acetic anhydride (100 mL) and heated at 60°C for 12 h. The acetic anhydride was evaporated and the resulting solid was recrystallized from EtOAc/hexanes to furnish **12** (2858 mg, 64% yield).

3.1.8. 4a-(3-Methoxyphenyl)-2,2-dimethylhexahydro-4,8-ethenofuro[3,4-*f*][1,3]benzodioxole-5,7-dione (14).

Anhydride **12** (93 mg, 0.46 mmol, 1 equiv.) and acetonide **13** (140 mg, 0.92 mmol, 2 equiv.) were dissolved in benzene (0.5 mL) and heated in a sealed tube at 75°C for 20 h. The crude reaction mixture was cooled to room temperature and purified by silica gel chromatography using 1% HCOOH/15% EtOAc/hexanes as the eluant, yielding **14** as a white solid (125 mg, 76% yield). Mp 183–185°C (recrystallized from hexanes/EtOAc); FTIR (thin film/NaCl) 2978 (w), 2937 (w), 2915 (w), 1853 (w), 1779 (s), 1600 (w), 1583 (w), 1495 (w), 1382 (w), 1293 (w), 1263 (m), 1224 (m), 1208 (m), 1162 (m), 1088 (w), 1066 (m), 989 (m), 961 (w), 937 (w), 912 (w), 874 (w), 764 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, J=8.0 Hz, 1H), 7.12 (t, J=2.5 Hz, 1H), 1.05 (dd, J=8.0, 1.5 Hz, 1H), 6.93 (dd, J=8.0, 2.5 Hz, 1H), 6.38 (t, J=7.0 Hz, 1H), 6.28 (t, J=7.0 Hz, 1H), 4.30 (dd, J=7.0, 3.0 Hz, 1H), 4.10 (dd, J=7.0, 3.0 Hz, 1H), 3.85 (s, 3H), 3.84–3.82 (m, 1H), 3.62–3.60 (m, 1H), 3.48 (d, J=3.0 Hz, 1H), 1.31 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 171.0, 160.7, 135.2, 132.5, 130.7, 130.5, 118.5, 114.0, 113.4, 110.2, 76.9, 74.3, 55.9, 55.6, 46.6, 42.7, 38.6, 25.5, 25.2; HRMS (EI) m/z 356.1254 [calcd for $C_{20}H_{20}O_6$ (M+) 356.1260].

3.1.9. 2-Benzyloxymethyl-but-2-enedioic acid dimethyl ester (16). To a solution of benzyl ether **15** (2924 mg, 20 mmol, 1 equiv.) in MeOH (100 mL) was added potassium iodide (45 mg, 0.2 mmol, 0.01 equiv.) and palladium(II) iodide (10 mg, 0.02 mmol, 0.001 equiv.). This mixture was transferred to a stainless steel autoclave (300 mL). The autoclave was pressurized with CO (400 psi) and air (560 psi). The reaction mixture was stirred and heated at 65°C for 20 h. The autoclave was cooled to room temperature, the mixture diluted with CH_2Cl_2 (150 mL) and filtered first through a Celite cake with a thin charcoal layer on top, and then through a short silica plug to give **16** (5.1 g, 96% yield) as a clear oil. FTIR (thin film/NaCl) 3030 (w), 2952 (m), 2860 (w), 1731 (s), 1658 (m), 1497 (w), 1453 (m), 1436 (s), 1373 (m), 1331 (m), 1270 (s), 1200 (s), 1170 (s), 1132 (m), 1087 (s), 913 (w), 874 (w), 742 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 5H), 6.22 (t, J=2.0 Hz, 1H), 4.57 (s, 2H), 4.25 (d, J=2.0 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 165.6, 145.1, 137.4, 128.6, 128.0, 127.8, 121.3, 72.9, 69.0, 52.5, 52.1; HRMS (CI) m/z 265.1071 [calcd for $C_{14}H_{16}O_5$ (M+H) 265.1076].

3.1.10. 3-Benzyloxymethyl-furan-2,5-dione (17). A solution of maleate **16** (5390 mg, 20.4 mmol, 1 equiv.) in a mixture of EtOH (18 mL) and 2N NaOH (31 mL) was heated to 75°C for 3 h. The reaction mixture was cooled to room temperature and 1N HCl (63 mL) was added. The biphasic mixture was extracted with EtOAc (4×50 mL) and combined organic layers were dried over Na_2SO_4 and evaporated, to yield a crude oil which was dissolved in Ac_2O (100 mL) and heated at 75°C for 1 h. Removal of the excess acetic anhydride on a rotary evaporator, the mixture was purified using column chromatography (10% EtOAc/hexanes) to furnish **17** (3.71 g, 83% yield) as a white solid. FTIR (thin film/NaCl) 3109 (m), 3064 (w), 3030 (w), 2873 (m), 2803 (w), 1860 (w), 1841 (m), 1765 (s), 1655 (m), 1498 (m), 1453 (m), 1369 (m), 1312 (w), 1281 (m), 1229 (m), 1125 (m), 1032 (m), 982 (s), 893 (s), 884 (s), 839 (m), 745 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.34 (m, 5H), 6.88 (t, J=2.0 Hz, 1H), 4.66 (s, 2H), 4.43 (d, J=2.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 163.5, 150.5, 136.7, 129.7, 128.9, 128.6, 128.1, 74.0, 63.5; HRMS (CI) m/z 219.0656 [calcd for $C_{12}H_{10}O_4$ (M+H) 219.0657].

3.1.11. 4a-[(Benzyloxy)methyl]-2,2-dimethylhexahydro-4,8-ethenofuro[3,4-*f*][1,3]benzodioxole-5,7-dione (18). Prepared in the same manner as **14**, yielding **18** as an amorphous white solid (72% yield). FTIR (thin film/NaCl) 2987 (w), 2935 (w), 2871 (w), 1857 (m), 1780 (s), 1455 (w), 1382 (m), 1364 (w), 1266 (m), 1226 (m), 1208 (m), 1164 (m), 1065 (s), 1022 (w), 978 (m), 916 (m), 825 (w), 757 (m), 740 (m), 697 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.30 (m, 3H), 7.24–7.22 (m, 2H), 6.23 (app t, J=7.0 Hz, 1H), 6.16 (app t, J=7.0 Hz, 1H), 4.52 (dd, J=12.0 Hz, 2H), 4.30 (ddd, J=7.5, 3.0, 1.0 Hz, 1H), 4.25 (ddd, J=7.5, 3.0, 1.0 Hz, 1H), 3.81 (d, J=8.5 Hz, 1H), 3.56 (d, J=8.5 Hz, 1H), 3.45–3.43 (m, 1H), 3.25 (ddd, J=6.0, 3.5, 1.5 Hz, 1H), 2.93 (d, J=2.5 Hz, 1H), 1.30 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 171.3, 136.7, 132.1, 130.3, 129.0, 128.8, 128.4, 127.8, 127.7, 110.2, 76.8, 74.7, 74.0, 70.9, 54.4, 45.4, 38.7, 37.8, 25.4, 25.1; HRMS (EI) m/z 370.1418 [calcd for $C_{21}H_{22}O_6$ (M+) 370.1416].

3.1.12. 8-[(Benzyloxy)methyl]-2,2-dimethyl-3a,4,7,7a-tetrahydro-4,7-ethano-1,3-benzodioxole-8,9-dicarboxylate (19). Anhydride **18** (1080 mg, 2.92 mmol, 1 equiv.) was dissolved in MeOH (50 mL) and heated at reflux overnight. The reaction mixture was cooled to room temperature and the MeOH was evaporated. To the crude reaction mixture was added THF (10 mL) and an excess of an etheral solution of diazomethane and stirred for 5 h. The excess diazomethane was quenched by the addition of acetic acid. Evaporation yielded diester **19** (1200 mg, 99% yield) as an amorphous white solid. FTIR (thin film/NaCl) 3064 (w), 2985 (m), 2949 (m), 2872 (w), 1746 (s), 1496 (w), 1454 (m), 1434 (m), 1370 (m), 1283 (m), 1262 (m), 1206 (s), 1165 (m), 1123 (m), 1088 (m), 1065 (m), 1030 (m), 891 (w), 736 (w), 699 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 6.27 (t, J=7.0 Hz, 1H), 6.12 (t, J=7.0 Hz, 1H), 4.58 (d, J=12.5 Hz, 1H), 4.65 (d, J=12.5 Hz, 1H), 4.44 (dd, J=7.0, 3.0 Hz, 1H), 4.10 (dd, J=7.0, 2.5 Hz, 1H), 3.88 (d, J=9.5 Hz, 1H), 3.61 (s, 3H), 3.60 (s, 3H), 3.47–3.45 (m, 2H), 3.07–3.05 (m, 1H), 2.44 (d, J=1.0 Hz, 1H), 1.32 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 172.9, 137.8, 131.8, 128.8, 128.6, 128.0, 127.7, 108.9, 77.9, 74.9, 73.5, 73.4, 55.8, 52.4, 52.1, 46.7, 40.0, 38.4, 25.4, 25.3; HRMS (EI) m/z 416.1831 [calcd for $C_{23}H_{28}O_7$ (M+) 416.1835].

3.1.13. Dimethyl 8-(hydroxymethyl)-2,2-dimethyl-3a,4,7,7a-tetrahydro-4,7-ethano-1,3-benzodioxole-8,9-dicarboxylate (20). To a stirred solution of **19** (94 mg, 0.225 mmol, 1 equiv.) in methanol (5 mL) was added 10% Pd/C (90 mg) and HCOOH (200 μL). The stirred solution was kept under an atmosphere of hydrogen (balloon) for 5 h at room temperature, filtered through Celite washing thoroughly with EtOAc, and concentrated in vacuo to yield **20** (66 mg, 90% yield) as a white crystalline solid. Mp 125–128°C; IR (thin film/NaCl) 3466 (m), 2985 (m), 2951 (m), 1741 (s), 1435 (m), 1373 (m), 1283 (m), 1206 (s), 1165 (s), 1107 (w), 1062 (s), 1027 (m), 888 (w), 832 (w), 723 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.23 (t, J=6.5 Hz,

1H), 6.11 (t, J=6.5 Hz, 1H), 4.46 (ddd, J=6.5, 3.5, 1.0 Hz, 1H), 4.20 (dd, J=7.0, 3.0 Hz, 1H), 4.05 (d, J=11.0 Hz, 1H), 3.82–3.69 (m, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 3.30 (ddd, J=6.0, 3.5, 1.0 Hz, 1H), 3.28–3.26 (m, 1H), 3.13 (d, J=8.0 Hz, 1H), 2.27 (s, 1H), 1.32 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 173.1, 130.5, 130.2, 109.4, 78.0, 74.8, 68.1, 56.4, 52.6, 52.5, 48.5, 40.4, 37.4, 25.4, 25.3; HRMS (EI) m/z 326.1368 [calcd for $C_{16}H_{22}O_7$ (M+) 326.1366].

3.1.14. Dimethyl 8-(3-ethoxy-3-oxopropanoyl)-2,2-dimethyl-3a,4,7,7a-tetrahydro-4,7-ethano-1,3-benzodioxole-8,9-dicarboxylate (21). To a stirred solution of **20** (1380 mg, 4.23 mmol, 1 equiv.) in acetone at 0°C (120 mL) was added Jones' reagent (12.3 mL). The reaction mixture was stirred for 3.5 h at room temperature. At that point, MeOH (20 mL) and water (40 mL) were added and the mixture was concentrated to remove most of the acetone and methanol. The crude reaction mixture was extracted with EtOAc (3×50 mL) and dried over Na_2SO_4 to yield the crude acid (1125 mg, 78% yield). The crude acid was dissolved in CH_2Cl_2 (30 mL) and to this solution was added $(COCl)_2$ (375 μL, 4.30 mmol, 1.3 equiv.) followed by 2 drops of DMF. The reaction mixture was stirred for 12 h and concentrated to yield pure acid chloride that was carried on directly to the next step. In a separate flask, EtOAc (970 μL, 9.9 mmol, 3 equiv.) was dissolved in dry THF (11 mL) and treated with LiHMDS (1.0 M solution in THF: 9.9 mL, 9.9 mmol, 3 equiv.) at −78°C. After 3 h at −78°C, a solution of the acid chloride dissolved in THF (10 mL) was added and stirring was continued for another 1.5 h before quenching with 1N HCl (20 mL) and extracting with EtOAc (3×30 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated to yield a crude oil. This crude oil was purified using silica gel chromatography using 20% EtOAc/hexanes as eluant to give **21** as a pale brown oil (1350 mg, 78% yield over 3 steps). IR (thin film/NaCl) 2984 (m), 2953 (m), 2907 (w), 1745 (s), 1718 (s), 1436 (m), 1326 (m), 1259 (s), 1224 (s), 1206 (s), 1109 (m), 1067 (s), 1048 (m), 1031 (m), 912 (w), 889 (w), 833 (w), 726 (w), 651 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (t, J=6.5 Hz, 1H), 6.12 (t, J=6.5 Hz, 1H), 4.21–4.16 (m, 3H), 4.03 (ddd, J=6.0, 3.0, 1.0 Hz, 1H), 3.74 (d, J=1.5 Hz, 1H), 3.62 (s, 6H), 3.60–3.53 (m, 3H), 3.19–3.17 (m, 1H), 1.29 (s, 3H), 1.27 (t, J=7.0 Hz, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 172.5, 169.4, 166.3, 129.5, 129.4, 109.4, 76.7, 74.2, 67.8, 61.9, 53.0, 52.4, 45.2, 44.3, 40.0, 39.2, 25.3, 25.2, 14.2; HRMS (EI) m/z 410.1577 [calcd for $C_{20}H_{26}O_9$ (M+) 410.1577].

3.1.15. 8-(2-Diazo-2-ethoxycarbonyl-acetyl)-4,4-dimethyl-3,5-dioxa-tricyclo[5.2.2.0^{2,6}]undec-10-ene-8,9-dicarboxylic acid methyl ester (22). Triethylamine (22 μL, 0.15 mmol, 3 equiv.) was added dropwise to a stirred solution of **21** (21 mg, 0.051 mmol, 1.0 equiv.) and p-ABSA (14 mg, 0.056 mmol, 1.1 equiv.) in CH_3CN (1 mL). After stirring for 2 h at room temperature, the reaction mixture was concentrated, poured onto basic alumina column and chromatographed using 25% EtOAc/hexanes as the eluant to furnish **22** as a yellow oil (15 mg, 67% yield). FTIR (thin film/NaCl) 3071 (w), 2986 (m), 2951 (m), 2908 (m), 2148 (s), 1752 (s), 1721 (s), 1638 (m), 1435 (m), 1371 (m), 1316 (s), 1253 (m), 1208 (s), 1165 (m), 1135 (m), 1069 (m), 1021 (m), 917 (m), 881 (m), 833 (w), 736 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (t, J=6.5 Hz, 1H), 6.20 (t, J=6.5 Hz, 1H), 4.30–4.23 (m, 3H), 4.19 (dd, J=7.0, 3.0 Hz, 1H), 3.91 (ddd, J=6.5, 3.5, 1.0 Hz, 1H), 3.88 (ddd, J=6.5, 3.5, 1.0 Hz, 1H), 3.60 (s, 3H), 3.59 (s, 3H), 3.29–3.27 (m, 1H), 1.32 (t, J=6.5 Hz, 3H), 1.31 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 172.0, 169.6, 160.6, 130.0, 128.4, 109.3, 78.8, 76.7, 75.3, 65.3, 62.2, 52.6, 52.4, 45.4, 39.3, 39.0, 25.4, 25.3, 14.4.

3.1.16. (8-Benzyloxymethyl-9-hydroxymethyl-4,4-dimethyl-3,5-dioxa-tricyclo[5.2.2.0^{2,6}]undec-10-en-8-yl)-methanol (24). To a stirred solution of **18** (5.0 g, 13.5 mmol, 1 equiv.) in THF (135 mL) was added LAH (9.7 g, 54 mmol, 4 equiv.). The reaction was allowed to stir for 5 min at room temperature at which time a saturated aqueous solution of Na_2SO_4 (15 mL) was added dropwise over 5 min. This solution was left to stir for another 40 min, at which time it was filtered over a Celite plug. After the filter cake washed thoroughly with EtOAc, the filtrate was concentrated in vacuo to yield analytically pure **24** (4.6 g, 95% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (brs, 1H), 1.21 (s, 3H), 1.33 (s, 3H), 2.67–2.69 (m, 1H), 3.04 (dd, J=2.5, 6.5 Hz, 1H), 3.26 (d, J=9.5 Hz, 1H), 3.44 (dd, J=4, 11.5 Hz, 1H), 3.57–3.71 (m, 4H), 4.15 (dd, J=3, 7 Hz, 1H), 4.33 (dd, J=3, 7 Hz, 1H), 4.53 (d, J=12 Hz, 1H), 4.57 (d, J=12 Hz, 1H), 6.00 (t, J=7 Hz, 1H), 6.08 (t, J=7 Hz, 1H), 7.27–7.39 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 25.4, 25.7, 39.9, 40.0, 45.2, 46.5, 65.0, 65.48, 72.9, 73.6, 75.5, 78.4, 108.6, 128.2, 128.4, 129.0, 129.5, 131.9, 138.2; IR (thin film/NaCl) 885 (m), 967 (w), 1027 (m), 1065 (s), 1165 (m), 1206 (s), 1264 (m), 1314 (w), 1374 (m), 1455 (m), 1496 (w), 1734 (w), 2873 (m), 2926 (s), 3053 (w), 3383 (brs) cm^{-1}; HRMS (FAB) m/z found: 361.2016 [calcd for $C_{21}H_{28}O_5$ (M+H) 361.2015].

3.1.17. 10-Benzyloxymethyl-4,4-dimethyl-10,11-bis-triisopropylsilanyloxymethyl-3,5-dioxa-tricyclo[5.2.2.0^{2,6}]-undec-8-ene (25). To a stirred solution of **24** (2.0 g, 5.6 mmol, 1 equiv.) in DMF (25 mL) was added imidazole (1.9 g, 27.8 mmol, 5 equiv.) and TIPSCl (5.9 mL, 27.8 mmol, 5 equiv.). This solution was allowed to stir at room temperature for 5 days at which time the reaction was diluted with EtOAc (250 mL), and the combined organic phase was washed with water (100 mL) and brine (100 mL). The aqueous phase was then back extracted with EtOAc (2×200 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to yield a crude oil which was chromatographed over a column of silica gel (gradient elution, 0–2.5% EtOAc/hexanes). The early-eluting product-containing fractions were further purified via Kugelrohr distillation (50 Torr, 125°C) of low-boiling impurities to yield pure **25** (3.6 g, 96% yield) as a clear oil. R_f 0.65, 4:1 hexanes/ethyl acetate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00–1.05 (m, 42H), 1.23 (s, 3H), 1.33 (s, 3H), 1.16 (dd, J=4.5, 10 Hz, 1H), 3.09 (dd, J=2.5, 6 Hz, 1H), 3.19–3.20 (m, 1H), 3.26 (t, J=10 Hz, 1H), 3.47 (d, J=9 Hz, 1H), 3.49 (d, J=2 Hz, 2H), 3.68 (d, J=9 Hz, 1H), 3.84 (dd, J=4.5, 9.5 Hz, 1H), 4.18 (dd, J=3, 7 Hz, 1H), 4.41 (dd, J=3, 7 Hz, 1H), 4.45 (d, J=11.5 Hz, 1H), 4.50 (d, J=11.5 Hz, 1H), 6.03 (t, J=7 Hz, 1H), 6.15 (t, J=7 Hz, 1H), 7.24–7.33 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ

11.9, 11.97, 12.3, 17.7, 18.0, 25.0, 25.3, 37.6, 39.5, 44.3, 46.1, 62.4, 63.0, 73.2, 73.8, 75.5, 78.7, 107.7, 127.3, 127.4, 128.1, 129.7, 132.0, 138.5; IR (thin film/NaCl) 809 (m), 884 (m), 918 (w), 996 (w), 1013 (w), 1066 (s), 1087 (s), 1140 (m), 1164 (w), 1206 (m), 1264 (m), 1379 (m), 1463 (m), 1497 (w), 1727 (w), 2866 (s), 2890 (m), 2942 (s), 3055 (w) cm^{-1}; HRMS (FAB) *m/z* found: 673.4684 [calcd for $C_{39}H_{69}O_5$ (M+H) 673.4684].

3.1.18. (4,4-Dimethyl-8,9-bis-triisopropylsilanoxymethyl-3,5-dioxa-tricyclo[5.2.2.0^{2,6}]undec-10-en-8-yl)-methanol (26). A flame-dried 50 mL three-necked round-bottom flask was equipped with a mechanical stirrer and dry ice condenser and cooled to −78°C in a dry ice–acetone bath. The flask was then charged with anhydrous ammonia (20 mL) and freshly cut Li metal (38 mg, 5.5 mmol, 10 equiv.) and allowed to stir for 30 min. At this time, a solution of **25** (374 mg, 0.55 mmol, 1 equiv.) in THF (5 mL) was added dropwise via cannula and stirring was continued for another 30 min at −78°C at which time the reaction was quenched with solid NH_4Cl (1 g). EtOAc (20 mL) was added at this point, and the solution was allowed to warm to room temperature. After stirring at room temperature for 2 h, the reaction mixture was filtered through a Celite plug, which was washed thoroughly with EtOAc, and the filtrate was concentrated in vacuo to yield analytically pure **26** (220 mg, 99% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01–1.09 (m, 42H), 1.27 (s, 3H), 1.33 (s, 3H), 2.70 (m, 1H), 3.36–3.63 (m, 7H), 3.80 (d, *J*=10 Hz, 1H), 4.07 (d, *J*=10 Hz, 1H), 4.26 (dd, *J*=3, 7 Hz, 1H), 4.57 (dd, *J*=3, 7 Hz, 1H), 6.05 (t, *J*=7 Hz, 1H), 6.21 (t, *J*=7 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.7, 11.8, 12.2, 17.6, 18.0, 24.9, 25.3, 37.2, 38.8, 45.1, 45.5, 63.9, 67.5, 70.1, 75.3, 78.6, 108.0, 129.2, 132.3; IR (thin film/NaCl) 997 (m), 1012 (m), 1042 (m), 1063 (m), 1081 (m), 1114 (m), 1163 (m), 1206 (m), 1259 (m), 1379 (m), 1463 (m), 2726 (w), 2867 (s), 2890 (s), 2942 (s), 3054 (w), 3483 (brs) cm^{-1}; HRMS (FAB) *m/z* found: 583.4212 [calcd for $C_{32}H_{63}O_5Si_2$ (M+H) 583.4214].

3.1.19. 3-(4,4-Dimethyl-8,9-bis-triisopropylsilanoxymethyl-3,5-dioxa-tricyclo[5.2.2.0^{2,6}]undec-10-en-8-yl)-3-oxo-propionic acid ethyl ester (27). To a stirred solution of **26** (1.2 g, 2 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) was added Dess–Martin periodinane (3.4 g, 8 mmol, 4 equiv.), and the solution was allowed to stir at room temperature for 2 h. At this time, a saturated aqueous solution of $Na_2S_2O_3$ (15 mL) was added, and the reaction was allowed to stir for another 2 h at which point a saturated aqueous solution of K_2CO_3 was added and the reaction was stirred for another 15 min. This biphasic mixture was transferred to a separatory funnel containing brine (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (50 mL×4). The combined organic layers were dried over Na_2SO_4, and evaporated in vacuo to yield an amorphous yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04–1.08 (m, 42H), 1.23 (s, 3H), 1.36 (s, 3H), 2.33 (t, *J*=7.5 Hz, 1H), 3.07 (m, 1H), 3.41 (dd, *J*=7.5, 10 Hz, 1H), 3.49–3.50 (m, 1H), 3.65 (dd, *J*=7.5, 10 Hz, 1H), 3.83 (d, *J*=10 Hz, 1H), 3.95 (d, *J*=10 Hz, 1H), 4.18 (s, 2H), 6.16 (t, 2H), 9.84 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.8, 11.8, 11.9, 17.6, 17.7, 17.7, 17.7, 17.8, 17.9, 18.0, 18.0, 18.0, 24.9, 25.2, 38.2, 38.2, 39.0, 56.7, 63.0, 63.8, 75.2, 78.1, 108.3, 129.3, 131.5, 204.9; IR (thin film/NaCl) 996 (w), 1014 (w), 1065 (s), 1098 (s), 1142 (w), 1164 (w), 1207 (m), 1262 (m), 1369 (m), 1380 (m), 1463 (m), 1723 (m), 2725 (w), 2866 (s), 2891 (m), 2942 (s) cm^{-1}.

This material was dried azeotropically with benzene, redissolved in THF (8 mL), and added via cannula over 15 min to a −78°C solution of EtOAc (1.1 mL, 11.3 mmol), and LiHMDS (10 mL of 1 M solution in THF) which had been stirring for 0.5 h. The mixture was allowed to stir at −78°C for 1.5 h at which time it was quenched with 1N HCl (10 mL) and warmed to room temperature. This solution was then diluted with EtOAc (200 mL), poured into a separatory funnel, and washed with brine (150 mL). The aqueous layer was back extracted with EtOAc (100 mL×4), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to yield a yellow oil. This residue was dissolved in CH_2Cl_2 (30 mL) and treated with Dess–Martin periodinane (1.5 g, 3.6 mmol) for 11 h. Workup with $Na_2S_2O_3$ and K_2CO_3 (see above), extraction with CH_2Cl_2, drying over Na_2SO_4, and evaporation of organic phases yielded **27** (1.3 g, 95% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86–1.10 (m, 50.4H), 1.23–1.38 (m, 10.8), 2.04 (brs, 0.2H), 3.04–3.04 (brs, 1H), 3.042 (brs, 1.2H), 3.36–3.51 (m, 3.6H), 3.58–3.62 (m, 1.2H), 3.67–3.75 (m, 2.4H), 3.87–3.97 (m, 1.2H), 4.02–4.12 (m, 1.2H), 4.17–4.17 (m, 3.6H), 4.33 (dd, *J*=2.8, 7.2 Hz, 1H), 4.41 (dd, *J*=2.8, 7.2 Hz, 0.2H), 5.32 (s, 0.2H), 6.10–6.19 (m, 2.4H), 12.51 (brs, 0.2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.9, 11.9, 11.9, 11.9, 12.1, 12.4, 17.7, 17.7, 17.7, 17.8, 17.9, 18.0, 18.0, 18.0, 25.0, 25.2, 38.4, 39.7, 40.5, 46.5, 59.3, 61.1, 63.4, 75.3, 78.2, 108.3, 130.2, 130.7, 168.0, 205.0; IR (thin film/NaCl) 1014 (s), 1065 (s), 1096 (s), 1165 (m), 1207 (s), 1224 (m), 1259 (m), 1368 (m), 1380 (m), 1463 (m), 1619 (w), 1709 (m), 1746 (s), 2867 (s), 2892 (m), 2942 (s), 3055 (w) cm^{-1}; HRMS (FAB) *m/z* found: 667.4426 [calcd for $C_{36}H_{67}O_7Si_2$ (M+H) 667.4425].

3.1.20. 2-Diazo-3-(4,4-dimethyl-8,9-bis-triisopropylsilanoxymethyl-3,5-dioxa-tricyclo[5.2.2.0^{2,6}]undec-10-en-8-yl)-3-oxo-propionic acid ethyl ester (28). To a stirred solution of **27** (20 mg, 0.03 mmol, 1.0 equiv.) in CH_2Cl_2 (0.7 mL) was added dropwise DBU (15.5 μL, 0.09 mmol, 3 equiv.) and *p*-ABSA (9 mg, 0.036 mmol, 1.2 equiv.). After stirring the reaction mixture for 1 h at room temperature, it was evaporated onto silica gel, poured onto a column of type III basic alumina and chromatographed (gradient elution, 0–5% EtOAc/hexanes) to yield **28** as a yellow oil (18 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98–1.06 (m, 42H), 1.23 (s, 3H), 1.31–1.34 (m, 6H), 2.85 (dd, *J*=3.6, 10.4 Hz, 1H), 3.27–3.33 (m, 1H), 3.48–3.51 (m, 2H), 3.97 (dd, *J*=3.2, 7.2 Hz, 1H), 4.05 (dd, *J*=3.2, 7.2 Hz, 1H), 4.16–4.30 (m, 4H), 4.53 (d, *J*=11 Hz, 1H), 6.07 (t, *J*=7 Hz, 1H), 6.20 (t, *J*=7 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.9, 12.1, 12.1, 14.3, 17.4, 17.9, 17.9, 18.0, 18.1, 18.1, 25.1, 25.3, 29.7, 37.0, 39.2, 40.6, 60.6, 61.4, 62.6, 64.5, 76.1, 78.1, 108.3, 129.6, 132.4, 160.9, 192.6; IR (thin film/NaCl) 1013 (m), 1065 (s), 1098 (s), 1167 (w), 1196 (m), 1206 (m), 1268 (m), 1288 (m), 1368 (m), 1379 (m), 1463 (m), 1639 (m), 1717 (s), 2139 (m), 2866 (s), 2941 (s) cm^{-1}; HRMS (ESI) *m/z* found: 715.4150 [calcd for $C_{36}H_{64}N_2O_7Si_2$ (M+Na) 715.4150].

3.2. General procedure for catalyst and solvent screening

To a stirred solution of **28** (0.01 M) in the desired solvent was added 10 mol% of rhodium(II) catalyst. This reaction mixture was either stirred with heating or at room temperature until reaction monitoring via TLC or NMR indicated disappearance of starting material. If necessary, additional catalyst was added in 10 mol% increments. The solvent was then evaporated in vacuo, and the products purified using preparative thin-layer chromatography.

3.2.1. Spiro[(2-carboxyethyl-3-silyloxy-4,5-dihydrofuran)-4,10′-(4′,4′-dimethyl-11′-triisopropylsilanyloxymethyl-3′,5′-dioxa-tricyclo[5.2.2.0^{2,6}]undec-8′-ene)] (29). R_f 0.30, 4:1 hexanes/ethyl acetate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97–1.06 (m, 21H), 1.14 (dd, J=7, 11 Hz, 18H), 1.24–1.25 (m, 3H), 1.31–1.34 (m, 6H), 1.39–1.83 (m, 3H), 2.16 (dd, J=6.5, 9 Hz, 1H), 3.12 (dd, J=4, 9 Hz, 1H), 3.26–3.28 (m, 1H), 3.31 (t, J=11.5 Hz, 1H), 3.72 (dd, J=5.5, 11.5 Hz, 1H), 3.80 (d, J=11 Hz, 1H), 3.92 (d, J=11 Hz, 1H), 4.24 (q, J=9 Hz, 2H), 4.33 (dd, J=4, 9 Hz, 1H), 4. 64 (dd, J=3.5, 9 Hz, 1H), 6.18 (t, J=5 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 10.85, 13.58, 16.96, 17.09, 17.13, 24.14, 24.28, 28.68, 36.98, 39.89, 43.75, 52.29, 59.36, 61.82, 72.63, 73.56, 77.47, 107.04, 125.98, 130.07, 131.01, 150.94, 159.35; IR (thin film/NaCl) 967 (m), 995 (m), 1065 (s), 1105 (s), 1151 (m), 1223 (s), 1260 (m), 1379 (m), 1407 (w), 1464 (m), 1620 (m), 1713 (s), 2139 (w), 2866 (s), 2893 (s), 2942 (s), 3054 (w) cm^{-1}; HRMS (FAB) *m/z* found: 665.4261 [calcd for $C_{36}H_{65}O_7Si_2$ (M+H) 665.4269].

3.2.2. 4,4-Dimethyl-8,9-bis-triisopropylsilanyloxymethyl-3,5-dioxa-tricyclo[5.2.2.0^{2,6}]undeca-8,10-diene (30). R_f 0.75, 4:1 hexanes/ethyl acetate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05–1.11 (m, 42H), 1.26 (s, 3H), 1.34 (s, 3H), 4.00 (brs, 2H), 4.20 (dd, J=4, 12.5 Hz, 2H), 4.29 (d, J=2 Hz, 2H), 4.33 (dd, J=4, 12.5 Hz, 2H), 6.33–6.35 (t, J=4 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 12.3, 12.4, 18.1, 18.1, 18.4, 18.4, 25.9, 26.4, 44.4, 60.5, 79.5, 112.5, 132.7, 138.3; IR (thin film/NaCl) 996 (w), 1013 (w), 1043 (m), 1062 (s), 1108 (m), 1160 (m), 1206 (m), 1261 (m), 1369 (m), 1373 (m), 1463 (m), 1666 (w), 1738 (w), 2866 (s), 2893 (m), 2942 (s) cm^{-1}; HRMS (FAB) *m/z* found: 550.3876 [calcd for $C_{31}H_{58}O_4Si_2$ (M+) 550.3874].

3.2.3. Ethyl (9*R*)-9-(2-methoxy-2-oxoethyl)-2,2-dimethyl-8-oxo-7,10-bis{[(triisopropylsilyl)oxy]methyl}-3a,4,6a,7,8,9-hexahydro-4,7-methanoindeno[3a,4-*d*][1,3]dioxole-9-carboxylate (32). To a stirred solution of **28** (70 mg, 0.1 mmol, 1 equiv.) in dry benzene (10 mL) was added $Rh_2(piv)_4$ (12 mg, 0.02 mmol, 0.2 equiv.). The reaction was heated to 50°C and stirred for 20 h at which point the solvent was removed in vacuo to yield a pale green residue. This residue was dried azeotropically with benzene, dissolved in THF (0.5 mL), and added via cannula over 5 min to a 0°C solution of NaH (48 mg, 2 mmol, 20 equiv.) in THF (1.5 mL). After continued stirring at 0°C for 0.5 h, methyl bromoacetate (19 μL, 0.2 mmol, 20 equiv.) was added via syringe, and the solution was allowed gradually to warm to room temperature over 3 h. At this time, the reaction was quenched with saturated NH_4Cl (1 mL), diluted with brine, and extracted with EtOAc (4×20 mL). The organic layer was dried over Na_2SO_4, concentrated in vacuo, and azeotroped with toluene (2 mL) to yield a clear oil. Purification via preparative thin-layer chromatography eluting with 24:1 hexanes/ethyl acetate yielded **32** (34 mg, 46% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93–1.14 (m, 42H), 1.21–1.45 (m, 9H), 2.06–2.09 (m, 1H), 2.68 (d, J=16.5 Hz, 1H), 3.15 (d, J=10 Hz, 1H), 3.28–3.30 (m, 1H), 3.33–3.36 (m, 2H), 3.46–3.49 (m, 3.633H, s, 3H), 4.18–4.25 (m, 2H), 4.30 (d, J=4 Hz, 1H), 4.34–4.37 (m, 1H), 6.21 (t, J=7.0 Hz, 1H), 6.28 (t, J=7.0 Hz, 1H),; ^{13}C NMR (500 MHz, $CDCl_3$) δ 12.2, 12.2, 14.4, 18.3, 18.33 18.4, 27.5, 28.1, 30.1, 36.0, 39.1, 42.2, 52.0, 58.8, 59.3, 61.6, 61.7, 62.0, 81.4, 90.0, 111.8, 127.43, 133.4, 169.9, 170.5, 206.6; IR (thin film/NaCl) 1064 (m), 1098 (s), 1163 (m), 1196 (m), 1217 (m), 1246 (m), 1287 (w), 1369 (m), 1381 (m), 1462 (m), 1738 (s), 1747 (s), 1764 (s), 2866 (s), 2941 (s) cm^{-1}; HRMS (FAB) *m/z* found: 737.4482 [calcd for $C_{39}H_{69}O_9Si_2$ (M+H) 737.4480].

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