Synthesis of platencin core structures via twist-brendane

Faiz Ahmed Khan,*[a] and Basavaraj M. Budanur[b]

[a]*Department of Chemistry, Indian Institute of Technology Hyderabad, Ordnance Factory estate, Yeddumailaram-502205, India*
[b]*Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur-208016, India*
E-mail: faiz@iith.ac.in

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Abstract
The formation of a twist-brendane via intramolecular enolate alkylation is described. Conversion of bicyclo[2.2.1]heptane scaffold present in this twist-brendane through a Grob-type fragmentation to unravel a functionalized bicyclo[2.2.2] system which contains all the necessary carbon atoms of the lipophilic core structure of *nor*-platencin, a platencin analogue is presented. Synthesis of core structure of platencin was also accomplished by extending this strategy to a starting material possessing a surrogate for the exocyclic methylene group.

Keywords: Enones, Grob-type fragmentation, intramolecular enolate alkylation, twist-brendane, platencin

Introduction

Intramolecular enolate alkylation has been a key step for stereoselective construction of cycloalkanes in the total synthesis of natural products of modest complexity,[1-4] and in the synthesis of strain free tricyclononane like twist-brendane.[5-8] The synthesis of natural products involving the Grob fragmentation reaction, a reliable synthetic tool for the cleavage of C–C sigma bond leading to useful building blocks, as a key step has been gaining much attention in recent past due to its high efficiency and stereoselectivity.[9-13]

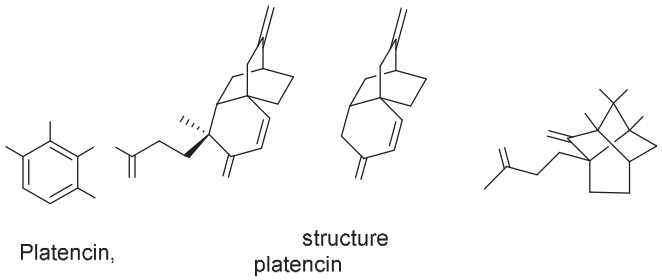


Figure 1. Molecular Structure of Platencin (**1**), Core Structure (**2**) of Platencin. Twist-brendane Derivative (**5**).

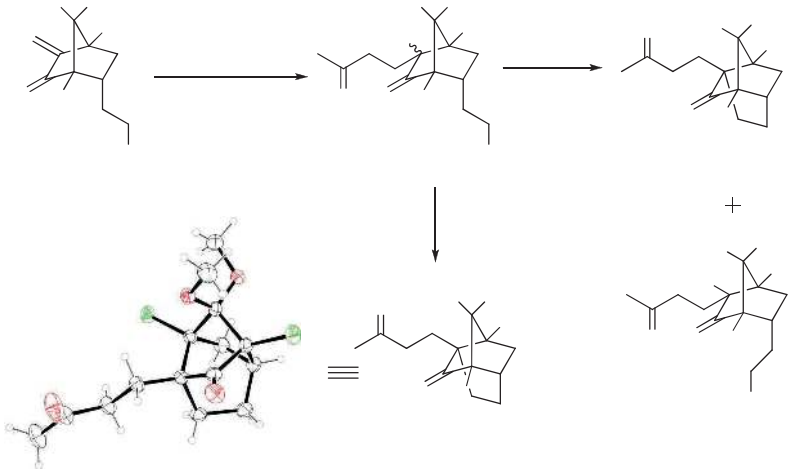
As a novel potent antibiotic, platencin[14,15] inhibits two proteins essential for bacterial fatty acid biosynthesis, β-ketoacyl carrier protein synthase II (FabF) and III (FabH) with similar potency. Owing to their interesting novel chemical scaffold and biological activity as antibacterial agents platencin and its congeners[16] have attracted widespread attention amongst synthetic chemists since their discovery with prospect that these would be used as lead compounds for the development of a valuable class of antibiotics. Although platencin shows the potent antibacterial activity it suffers from the poor *in vivo* efficacy that is attributed to its rapid clearance from tissues.[16,17] So the synthesis of new potent analogues of platencin with improved potency and pharmacokinetic properties suitable for clinical trials is in high demand.[17]

Platencin core structure constitutes tricyclic system with a bicyclic octane ring having *exo*-methylene group, fused with a cyclohexenone ring. Many synthetic strategies have been developed for the construction of platencin core structure involving key steps like homoallyl radical rearrangement of bicyclo[3.2.1]octane to bicyclo[2.2.2]octane,[18-22] intramolecular Diels-Alder reaction,[22-24] intramolecular Michael addition,[25] Michael addition followed by aldol condensation,[26] ring closing metathesis reaction,[27,28] pinacol coupling reaction,[29] radical cyclization reactions[30-33] and intramolecular aldol reaction.[34]

Although *nor*-platencin is less potent than its parent molecule, but serves as a convenient target as it lacks the acid-sensitive *exo*-methylene group present in platencin which is also responsible for the decrease in the metabolic stability of platencin.[35] In this paper we report synthesis of platencin core structures which features the construction of tricyclic core via a twist-brendane derivative, followed by Grob-type fragmentation and Robinson annulation.

Results and Discussion

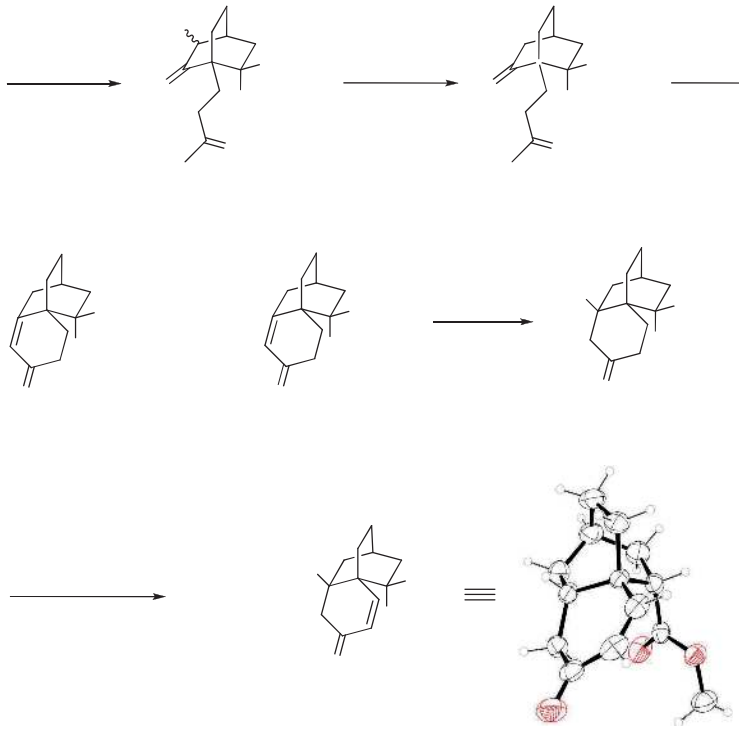
During the course of our studies on base mediated bridgehead elimination and substitution reactions,[36] we observed the formation of a twist-brendane derivative **5** through intramolecular enolate alkylation in 70% yield along with the originally intended product **6** (yield 17%) from **4** (Scheme 1).



Scheme 1. Synthesis of Twist-brendane Derivative **5.**

Synthesis of the parent twist-brendane[5] has been described in the literature by intramolecular enolate alkylation using NaH in DMF at 60 °C followed by deoxygenation. We have also adopted the same protocol, but with slight modification wherein THF was used instead of DMF, to avoid the side product **6** and observed smooth formation of twist-brendane **5** without any side products. The complete sequence involved Michael addition of acetone to the enone **3** to give intermediate **4** which on exposure to NaH in THF at 60 °C provided the twist-brendane **5** in 89% yield (Scheme 1). The structure of twist-brendane was unequivocally proved by single crystal X-ray analysis (Scheme 1). Compared to the parent twist-brendane, compound **5** is equipped with maneuverable functional groups such as a ketal moiety at C-7 and a suitably positioned keto group for the execution of Grob-type fragmentation[12,13] to unravel a useful bicyclo[2.2.2]octane derivative.

As anticipated, the Grob-type fragmentation of **5** with pTSA in toluene afforded a separable mixture of bicyclo[2.2.2]octane derivative **7** (Scheme 2). A closely related compound to **7**, having *exo*-methylene group sans the chloro and ester substitutions has been reported for the synthesis of platencin core.[33] Our attempts to cyclize **7** via Robinson annulation using NaOH/EtOH (or MeOH) even at reflux conditions failed, yielding complex mixtures. The presence of chlorine substituents might be responsible for the observed complications. In this context, we initially carried out the hydrodehalogenation reaction of the mixture **7** using *n*BuSnH/AIBN which yielded a complex mixture. However, treatment of **7** with zinc dust in acetic acid at room temperature furnished the diketone **8** as a single diastereomer (Scheme 2).



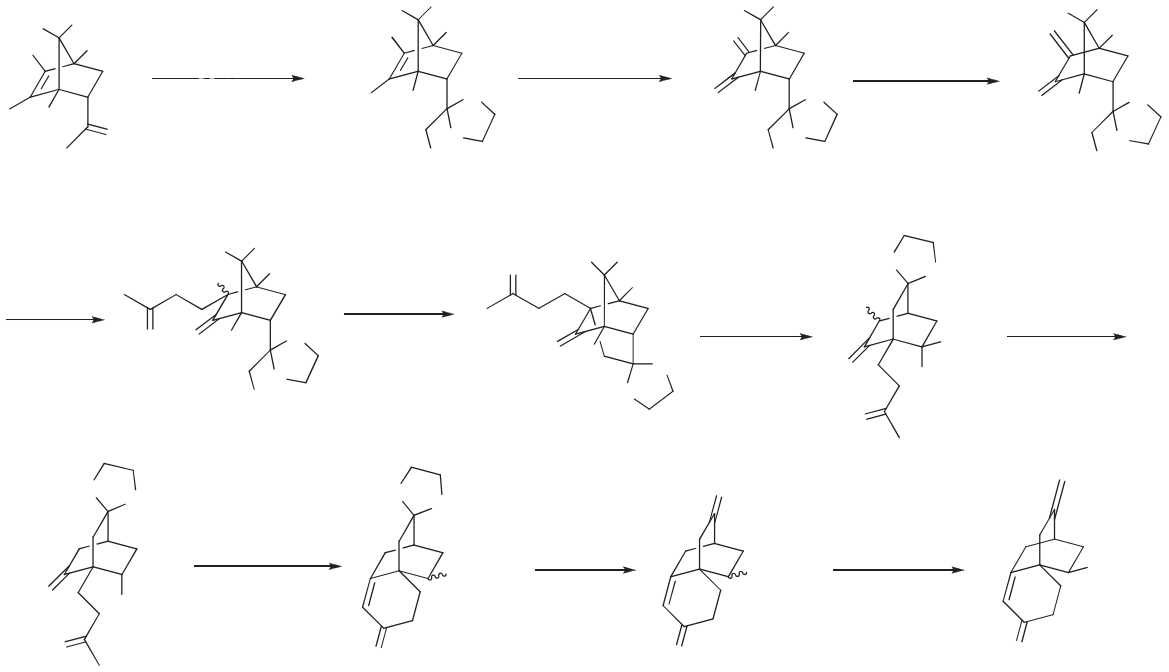
Scheme 2. Synthesis of *nor*-platencin skeleton.

Having the diketo ester **8** in hand, our next task was to convert it to tricyclic enone **9**. This was achieved by refluxing **8** in NaOH/MeOH for 12 h followed by diazomethane workup which provided a separable mixture of diastereomers **9a**/**9b** in 1:1 *exo*/*endo* ratio of methyl ester (Scheme 2). Reduction enone **9a** was carried out using Raney nickel[33,37] in THF to obtain the keto ester **10** as a single diastereomer in 83% yield. Several two-step protocols are available in the literature for the conversion of ketone to enone moiety. Silylation followed by 2-iodoxybenzoic acid (IBX)[38] oxidation is a well practiced method in the synthesis of platencin.[22,23,30] However, in our case Nicolaou's[39] one-step protocol furnished the desired compound **11** when ketoester **10** was treated with IBX in toluene/DMSO at 65 °C along with a minor product **9a** (Scheme 2). Structure of **11** was confirmed by single crystal structure X-ray analysis (Scheme 2).

Next, we planned for the synthesis of the core structure of platencin incorporating a keto functionality and adopted similar reaction sequences of the synthesis of core structure of *nor*-platencin. Synthesis commenced with bromination (Scheme 3). Our initial attempts for bromination at the α-methyl group of ketone **18** with NBS in THF,[40] NBS/TMSOTf in CH_3CN,[41] NBS/DBU in CH_3CN,[42] and NBS/AIBN in CCl_4[43] were sluggish. Nevertheless, conventional brominating agent, Br_2 in MeOH[44] (at 0 °C → rt), provided the bromination product in good yield. Protection of ketone using pTSA in refluxing toluene delivered compound **19** in 79% yield. On exposure to Ru-LDH/$NaIO_4$-$NaHCO_3$[45-47] the intermediate **19** provided diketone **17** in

excellent yield. Subjecting this to Wittig reaction gave enone **16** in 97% yield. Michael addition of enone **16** with acetone using NaOH (aq) gave intermediate **20** in near quantitative yield (Scheme 3). NaH mediated intramolecular enolate alkylation proceeded as expected to provide twist-brendane **15**.

The conversion of twist-brendane to bicyclo[2.2.2]octane **21** was easily achieved through a smooth Grob-type fragmentation by treatment of **15** with pTSA in toluene at 80 °C (Scheme 3). Hydrodechlorination with zinc dust in AcOH gave diketone **14**. Robinson annulation of **14** using NaOH in MeOH at reflux temperature afforded tricyclic enone **22** in 4:1 *exo*/*endo* ratio, as determined from ^{1}H NMR. Deprotection of ketal group with 6N HCl at room temperature gave **13** in good yield. Regioselective Wittig reaction of unconjugated ketone group in **13** to *exo*-methylene proceeded smoothly at -78 °C to give dienone **12** in 72% yield (Scheme 3). As Wittig reaction was carried out under strong basic condition one can expect the abstraction of proton adjacent to the ester group. Once the carbanion is formed the bulky ester group would prefer relatively free room *exo* position and hence the conversion of *endo* isomer to *exo* occurs, which can be accounted for the high diastereoselectivity (*exo:endo* 10:1) in the Wittig reaction.



Scheme 3: Synthesis of platencin core.

The stereochemistry of the major component in **13** was arrived at from 2D NMR data analysis of the mixture. Based on the correlations of proton signals at δ 2.44 (m, 1H) and 2.36 (m, 1H) (CH_2 group adjacent to CO in the bicyclooctane ring) with carbon at δ 210.9 in HMBC,

these were assigned to methylene group attached to ketone. Similarly, methine group attached to methyl ester was deduced by correlation between proton at δ 2.87-2.79 (m, 1H) and carbon at δ 174.3, which also shows correlation with methoxy group at δ 3.72. The absence of correlation between the protons at δ 2.52-2.34 and δ 2.87-2.79 in NOESY confirms that the methine proton is *endo* and the ester group is *exo* in compound **13** and also **12**. As expected, during the strongly basic Witting reaction conditions, further isomerization of **13** resulted in substantial enhancement in *exo/endo* ratio from 4:1 in **13** to 10:1 in **12**.

Conclusions

In conclusion, we have synthesized functionalized twist-brendane derivatives through intramolecular enolate alkylation. We have demonstrated a strategy for the conversion of bicyclo[2.2.1]heptane to bicyclo[2.2.2]octane derivative through the formation twist-brendane followed by Grob-type fragmentation. The fragmented products were carried forward for the synthesis of the core structures of both *nor*-platencin and platencin. Structures and stereochemistry of some of the intermediates were confirmed by single crystal X-ray analysis and 2D NMR analysis.

Experimental Section

General. Unless otherwise specified, all reactions were carried out in oven dried glassware, under argon atmosphere. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. THF was dried by refluxing over sodium metal. Sodium methoxide was prepared from sodium and methanol. Zinc was activated by 10% HCl before use. DMSO was distilled from anhydrous $CaSO_4$/calcium hydride. Potassium *tert*-butoxide was sublimed before use. ^{1}H and proton decoupled ^{13}C NMR spectra were recorded in 400 and 100 MHz, respectively. The NMR samples were prepared by dissolving in $CDCl_3$, chemical shifts (δ ppm) are reported with reference to either internal standard tetramethylsilane, TMS (δ_H= 0.00 ppm) or $CHCl_3$ (δ_H = 7.27 ppm) for ^{1}H NMR and $CHCl_3$ [δ_C=77.00 ppm (central line of the triplet)] chemical shifts (δ ppm) for ^{13}C NMR. The multiplicity are reported as follows s = singlet, d = doublet, dd = double doublet, t = triplet, dt = double triplet, td = triple doublet, q = quartet, br = broad m = multiplet and the coupling constants were in Hz. HRMS was performed using a Q-TOF multimode source.

(1*R,4*R**,6*R**)-6-(2-Bromoethyl)-1,4-dichloro-7,7-dimethoxy-3-(3-oxobutyl)bicyclo[2.2.1] heptan-2-one 4**. To a stirred solution of enone **3**[36] (5 g, 13.96 mmol) in acetone (140 mL) was added aqueous sodium hydroxide solution (8.3 mL, 16.7 mmol, 2M) at 0 ^{o}C for 5 min. After being stirred for 1 h, 5 ml of 10% HCl was added, solvent was evaporated under reduced

pressure and diluted with EtOAc (150 mL), organic phase was separated aqueous phase was extracted with EtOAc (200 ml x 2) combined organic phases were washed with water (200 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude was purified over silica gel column chromatography (eluent: EtOAc-Hexane = 1: 5) to afford Michael product **4** (5.67 g, 98%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.66 (s, 3H, minor isomer), 3.60 (s, 3H), 3.58 (s, 3H, minor isomer), 3.47-3.40 (m, 1H), 3.38-3.30 (m, 1H), 2.99 (ddd, *J* 5.9, 8.8, 18.6 Hz, 1H), 2.86 (ddd, *J* 2.7, 5.0, 7.5 Hz, 1H), 2.79-2.73 (m, 1H), 2.73-2.63 (m, 2H), 2.61-2.52 (m, 1H), 2.19 (s, 3H), 2.17 (s, 3H, minor isomer), 2.08-1.75 (m, 5H), 1.51-1.39 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 202.4, 104.7, 80.4, 69.3, 55.7, 51.8, 51.7, 41.4, 40.4, 36.1, 32.6, 30.4, 30.0, 18.2. HRMS (ESI): *m/z* calcd for $C_{15}H_{25}BrCl_2NO_4$ $[M + NH_4]^+$ 432.0344; found: 432.0298.

Twist-brendane Derivative 5. To a stirred solution of **4** (5 g, 12.01 mmol) in THF (150 mL) was added sodium hydride (625 mg, 15.61 mmol, 60% in mineral oil) in two portions at 0 ^{o}C and allowed to warm to rt and then heated at 60 ^{o}C. After completion of starting material (monitored by tlc) 50 mL of water was added at 0 ^{o}C, solvent was evaporated under reduced pressure diluted with EtOAc (200 ml), organic phase was separated aqueous phase was extracted with EtOAc(150 ml x 2), combined organic phases were washed with water (200 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude was purified over silica gel column chromatography (eluent: EtOAc-Hexane = 1:5) to afford twist-brendane **5** (3.58 g, 89%) as a colorless crystalline solid (solvent: acetonitrile). mp: 142-144 ^{o}C.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.42 (s, 3H), 2.78-2.57 (m, 3H), 2.49 (td, *J* 2.2, 4.4 Hz, 1H), 2.17-2.06 (m, 2H), 2.13 (s, 3H), 2.02-1.91 (m, 1H), 1.85 (d, *J* 11.2 Hz, 1H), 1.73-1.62 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 204.5, 104.5, 78.1, 73.3, 56.6, 51.6, 51.1, 47.9, 39.1, 36.73, 31.2, 29.9, 24.6, 24.3. HRMS (ESI): *m/z* calcd for $C_{15}H_{24}Cl_2NO_4$ $[M + NH_4]^+$352.1082; found: 352.1076.

(1*R*,*3*R,4*R**,6*R**)-6-(2-Bromoethyl)-1-chloro-4,7,7-trimethoxy-3-(3-oxobutyl)bicyclo-[2.2.1]heptan-2-one6.** To a stirred solution of **4** (210 mg, 0.50 mmol) in methanol (2.5 mL) was added sodium methoxide (81 mg, 1.5 mmol) at room temperature and slowly allowed to warm to reflux temperature. After being refluxed for 4 h, reaction mixture cooled to 0 °C, 1 mL of water was added diluted with EtOAc (40 mL), organic phase was separated, aqueous phase was extracted with EtOAc (30 mL x 3) combined organic phases were washed with water (40 mL), brine (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified over silica gel column chromatography (10-20% EtOAc in hexane) to give compounds **5** (117 mg, 70% colorless crystalline solid (needles), crystallized from acetonitrile) and **6** (35 mg, 17%, colorless liquid). Data for compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65-3.59 (m, 1H), 3.62 (s, 3H), 3.59-3.50 (m, 1H), 3.55 (s, 3H), 3.51 (s, 3H), 2.93-2.84 (m, 1H), 2.79-2.64 (m, 3H), 2.64-2.54 (m, 1H), 2.16 (s, 3H), 2.01-1.91 (m, 1H), 1.79 (q, *J* 7.7 Hz, 2H), 1.52 (dd, *J* 3.9, 12.2 Hz, 1H), 1.40-1.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 203.7, 106.1, 83.5, 80.3, 53.4, 52.6, 51.01, 51.00, 42.7, 41.5, 38.1, 32.6, 30.1, 27.6, 18.3. IR (neat)

2927, 1762, 1713, 1451, 1264, 1212, 1164, 1096, 1033, 986 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{25}BrClO_5$ $[M + H]^+$ 411.0574; found: 411.0573.

(1*R,2*R**,4*S**)-Methyl 2,5-dichloro-6-oxo-1-(3-oxobutyl)bicyclo[2.2.2]octane-2-carboxylate 7**: To a stirred solution of **5** (500 mg, 1.49 mmol) in toluene (15 mL) was added pTSA (368 mg, 1.93 mmol) at rt and then slowly heated at 80 ^oC. After being heated for 5 h solvent was evaporated under reduced pressure, the residue was partition between EtOAc (80 mL) and water (25 mL), organic phase was separated aqueous phase was extracted with EtOAc (75 mL x 2) combined organic phases were washed with aq. $NaHCO_3$ solution (30 mL), water (80 mL x 2), brine (40 mL), dried over Na_2SO_4 and evaporated to dryness. The resulting crude was purified over silica gel column chromatography (eluent: EtOAc-Hexane = 1:4) to afford fragmented products **7** (418 mg, 88%) in 1:1 mixture of separable diastereomers as pale yellow solids (needles- crystallized from acetonitrile). Data for less polar compound (**7a**); mp: 76-78 °C (A); R_f = 0.6 (15% EtOAc in hexane). ^1H NMR (400MHz, $CDCl_3$) δ 4.31 (d, *J* 1.5 Hz, 1H), 3.78 (s, 3H), 2.69-2.61 (m, 1H), 2.61-2.50 (m, 2H), 2.45 (d, *J* 2.9 Hz, 1H), 2.39-2.27 (m, 1H), 2.27-2.14 (m, 2H), 2.12 (s, 3H), 1.92-1.78 (m, 2H), 1.77-1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 204.3, 171.5, 72.4, 59.2, 54.0, 53.4, 44.2, 38.1, 34.3, 29.9, 23.3, 23.2, 17.9. HRMS (ESI): *m/z* calcd for $C_{14}H_{22}Cl_2NO_4$ $[M + NH_4]^+$ 338.0926; found: 338.0908. Data for polar compound (**7b**): mp: 80-82 °C; R_f = 0.6 (15% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (t, *J* 2.0 Hz, 1H), 3.81-3.74 (m, 3H), 3.04 (td, *J* 2.1, 15.3 Hz, 1H), 2.56-2.47 (m, 1H), 2.46-2.40 (m, 1H), 2.33 (dd, *J* 2.4, 3.9 Hz, 1H), 2.31-2.27 (m, 1H), 2.20-2.13 (m, 2H), 2.12 (s, 3H), 1.99-1.87 (m, 1H), 1.81 (ddd, *J* 3.7, 6.1, 9.8 Hz, 2H), 1.63-1.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 203.9, 170.2, 74.1, 59.1, 53.7, 52.9, 38.5, 38.0, 35.1, 29.8, 22.8, 22.2, 22.0. HRMS (ESI): *m/z* calcd for $C_{14}H_{19}Cl_2O_4$ $[M + H]^+$ 321.0660; found: 321.0662.

(1*S,2*S**,4*S**)-Methyl 6-oxo-1-(3-oxobutyl)bicyclo[2.2.2]octane-2-carboxylate 8.** To a stirred solution of **7** (290 mg, 0.9 mmol) in AcOH (5 mL) was added zinc dust (236 mg, 3.61 mmol) at room temperature. After being stirred for 6 h (reaction monitored by TLC), reaction mixture was diluted with EtOAc (50 mL) and filtered through cotton washed with EtOAc (80 mL). The filtrate was washed with saturated $NaHCO_3$ solution (25 mL), water (30 mL x 2), brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Silica gel column (eluent:Ethyl acetate- hexane = 1: 3) purification of the resulting crude afforded diketo ester **8** (185 g, 82%) as pale yellow liquid; R_f = 0.5 (30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ3.69-3.59 (m, 3H), 2.81 (dd, *J* 5.4, 11.2 Hz, 1H), 2.58-2.47 (m, 1H), 2.47-2.34 (m, 2H), 2.31 (t, *J* 2.7 Hz, 1H), 2.28-2.19 (m, 1H), 2.14 (s, 3H), 2.07 (tdd, *J* 2.8, 11.1, 13.8 Hz, 1H), 1.88-1.77 (m, 2H), 1.76-1.61 (m, 3H), 1.61-1.49 (m, 2H);). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4, 208.4, 175.1, 52.0, 46.4, 46.3, 44.3, 38.2, 30.2, 29.8, 27.1, 26.8, 25.6, 24.6; IR (neat) 2945, 2873, 1719 (br.), 1440, 1360, 1165, 1094 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{24}NO_4$ $[M + H]^+$ 270.1705; found: 270.1688.

Enone 9. To a stirred solution of **8** (180 mg, 0.71 mmol) in MeOH (32 mL) was added sodium hydroxide (200 mg, 5 mmol) at room temperature and then slowly heated at reflux temperature. After being refluxed for 15 h (monitored by TLC), 3 mL of 10% HCl was added at 0 ^oC, solvent

was evaporated under reduced pressure, the residue was partition between EtOAc (50 mL) and water (10 mL), organic phase was separated and the aqueous phase was extracted with EtOAc (50 mL x 3) combined organic phases were washed with water (30 mL x 2), brine (20 mL), dried over Na_2SO_4 and evaporated dryness. The resulting crude was dissolved in MeOH (3 mL) cooled to 0 ^oC, and then a solution of CH_2N_2 in ether was added until yellow color persist. A pinch AcOH was added to quench excess of diazomethane. Reaction mixture was concentrated under reduced pressure and the resulting crude was purified over silica gel column chromatography (eluent:Ethyl acetate- hexane= 1: 4) to give enone **9** (122 mg, 73%) in 1:1 mixture of separable diastereomers as pale yellow liquids. Data for compound **9a**; R_f = 0.65 (30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (t, *J* 1.7 Hz, 1H), 3.71 (s, 3H), 2.78-2.68 (m, 1H), 2.51-2.44 (m, 2H), 2.45-2.36 (m, 2H), 2.09-1.95 (m, 2H), 1.95-1.89 (m, 1H), 1.89-1.79 (m, 2H), 1.72-1.61 (m, 3H), 1.64-1.54 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 174.6, 169.2, 124.5, 51.7, 43.5, 36.3, 35.6, 33.73, 30.2, 29.6, 25.8, 25.4, 25.2. IR (neat) 2928, 2856, 1723, 1682, 1481, 1392, 1359, 1279, 1194, 1165, 1063 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{19}O_3$ $[M + H]^+$ 235.1334; found: 235.1331. Data for compound **9b**:R_f = 0.6 (30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ5.94 (s, 1H), 3.66 (s, 3H), 2.73 (dd, *J* 2.2, 18.3 Hz, 1H), 2.67 (dd, *J* 4.9, 10.8 Hz, 1H), 2.45 (d, *J* 15.7 Hz, 1H), 2.41-2.34 (m, 1H), 2.26-2.16 (m, 1H), 2.06-1.92 (m, 3H), 1.91-1.81 (m, 2H), 1.74-1.49 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$) δ197.9, 175.4, 168.1, 125.6, 51.8, 47.6, 36.6, 36.0, 33.8, 31.9, 30.4, 30.3, 25.3, 25.2; IR (neat) 2924, 2864, 1729, 1680, 1480, 1392, 1194, 1165, 1063 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{18}O_3Na$ $[M +Na]^+$ 257.1154; found: 257.1151

Keto ester 10. To a stirred solution of **9a** (30 mg, 0.128 mmol) in THF (2 mL) was added Ra-Ni (3 x 0.3 g) three times after every 1 h at room temperature. After being stirred for 10 h, reaction mixture was diluted with EtOAc (20 mL) filtered through silica pad washed with EtOAc (30 mL). The filtrate was concentrated under reduced pressure. The resulting residue was purified over silica gel column chromatography (eluent: Ethyl acetate-hexane = 1:4) afforded keto ester **10** (25 mg, 83%) as a colorless liquid. R_f = 0.5 (15% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ3.70 (s, 3H), 2.77 (t, *J* 14.2 Hz, 1H), 2.57 (dd, *J* 6.6, 10.5 Hz, 1H), 2.29-1.99 (m, 4H), 1.99-1.75 (m, 3H), 1.75-1.62 (m, 2H), 1.61-1.47 (m, 4H), 1.45-1.43 (m, 1H), 1.34-1.27 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 178.2, 52.0, 46.1, 45.4, 38.8, 38.4, 37.9, 35.1, 33.9, 33.6, 31.1, 25.1, 24.3. IR (neat) 2926, 2862, 1725, 1713, 1453, 1434, 1359, 1262, 1193, 1169, 1030, 990 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{14}H_{20}O_3H$ $[M + H]^+$ 237.1491; found: 237.1485.

Enone 11. To a stirred solution of **10** (10 mg, 0.042 mmol) in toluene (0.8 m) and DMSO (0.4 mL) was added IBX (28 mg, 0.096 mmol) at room temperature and slowly heated at 70 °C. After being stirred for 2 days, reaction mixture was diluted with EtOAc (20mL), washed with 5% $NaHCO_3$ aqueous solution, organic phase was separated, aqueous phase was extracted with EtOAc (15 mL x 3) combined organic phase was washed with water (15 mL), brine (10mL) dried over Na_2SO_4 and concentrated in *vacuo*. The resulting crude was purified over silica gel column chromatography (20% EtOAc in hexane) to afford compound **11** (6.4 mg, 70% yield) as colorless solid (crystalline- crystallized from EtOAc: hexane (1:2)), mp: 44-46 °C; R_f = 0.6 (20%

EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, *J* 9.8 Hz, 1H), 5.93 (d, *J* 9.8 Hz, 1H), 3.58 (s, 3H), 2.66 (dd, *J* 3.9, 11.2 Hz, 1H), 2.43-2.13 (m, 4H), 2.01-1.84 (m, 2H), 1.81-1.54 (m, 4H), 1.54-1.40 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 176.0, 155.3, 128.1, 51.6, 45.1, 41.1, 36.7, 35.6, 35.1, 21.4, 28.4, 24.4, 24.1. IR (neat) 2933, 2866, 1727, 1680, 1452, 1435, 1357, 1257, 1200, 1174, 1074, 923 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{14}H_{19}O_3$ $[M + H]^+$ 235.1334; found: 235.1332

2-Bromo-1-((1*S,2*R**,4*S**)-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl)ethanone I.** To a stirred solution of Diels-Alder adduct **17** (5g, 14.97 mmol) in MeOH (20 mL) was added bromine (2.6 g, 16.46 mmol) at 0 ^{o}C and allowed to warm to room temperature. After being stirred for 8 h (monitored by tlc) 15 mL of water was added at 0 °C and stirred for 1 h. The reaction mixture was diluted with EtOAc (150 mL), organic phase was separated, aqueous phase was extracted with EtOAc (100 mL x 3) combined organic phase was washed with 10% Na_2CO_3 solution (30 mL), water (100 mL x 2), brine (60 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified over silica gel column chromatography (3% EtOAc in hexane) to afford intermediate **I** (5.13 g, 83%) as a colorless liquid, R_f = 0.4 (5% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (d, *J* 13.1 Hz, 1H), 4.09 (d, *J* 13.2 Hz, 1H), 3.99 (dd, *J* 5.4, 7.8 Hz, 1H), 3.65 (s, 3H), 3.57 (s, 3H), 2.41-2.37 (m, 2H), 1.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 131.2, 126.4, 112.1, 74.1, 53.9, 52.9, 51.9, 37.8, 35.2. IR (neat): 2986; 2951, 2844, 1728, 1603, 1440, 1390, 1335, 1278, 1252, 1188, 1121, 1096, 985 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{11}H_{15}BrCl_4NO_3$ $[M + NH_4]^+$ 429.8960; found: 429.8934.

2-(Bromomethyl)-2-((1*S,2*R**,4*S**)-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl)-1,3-dioxolane 19.** To a stirred solution of above obtained intermediate **I** (4 g, 9.68 mmol) in toluene (30 mL) were added pTSA (368.4 mg, 1.93 mmol) and ethylene glycol (1.5 g, 24.2 mmol) at room temperature and then refluxed with Dean-Stark apparatus. After being refluxed for 48 h, solvent was evaporated and the residue was partitioned between EtOAc (150 mL) and water (40 mL), organic phase was separated and aqueous phase was extracted with EtOAc (100 mL x 3) combined organic phase was washed with $NaHCO_3$ solution (45 mL), water (150 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified over silica gel column chromatography (5% EtOAc in hexane) to give **19** (3.5 g, 79%) as colorless liquid; R_f = 0.55 (4% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ4.16-4.08 (m, 1H), 4.07-3.97 (m, 3H), 3.60 (s, 3H), 3.54 (s, 3H), 3.50 (d, *J* 11.3 Hz, 1H), 3.44 (dd, *J* 4.9, 9.5 Hz, 1H), 3.42 (d, *J* 11.3 Hz, 1H), 2.47 (dd, *J* 9.8, 11.7 Hz, 1H), 1.80 (dd, *J* 4.9, 11.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.2, 128.1, 112.3, 108.6, 76.3, 73.6, 66.7, 65.1, 52.7, 51.6, 49.2, 38.5, 35.1. IR (neat): 2983; 2951, 2898, 1732, 1605, 1448, 1393, 1335, 1278, 1190, 1119, 1044, 989 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{13}H_{15}BrCl_4O_3Na$ $[M + Na]^+$ 476.8806; found: 476.8805.

(1*R,4*R**,5*R**)-5-(2-(Bromomethyl)-1,3-dioxolan-2-yl)-1,4-dichloro-7,7-dimethoxybicyclo-[2.2.1]heptane-2,3-dione 17.** To a stirred solution of **19** (3 g, 6.56 mmol) in acetonitrile (79 mL) were added sodium periodate (2.3 g, 10.50 mmol), Ru-LDH (262 mg), $NaHCO_3$ (1.65 g, 19.68

mmol) and then water (13.1 mL) at 0 ^{o}C. After being stirred for 4 h, 6 mL of isopropanol was added stirred for another 1 h, then solvent was evaporated the residue was diluted with EtOAc (100 mL), organic phase was separated aqueous phase was extracted with EtOAc (100 mL x 2), combined organic phase was washed with $Na_2S_2O_3$ solution (50 mL x 2), water (100 mL), brine (50 mL) dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified over silica gel column chromatography (15% EtOAc in hexane) to afford **17** (2.52 g, 92%) as yellow colored solid (needles- crystallized from CH_2Cl_2: Hexane (1:5)); mp: 96-98 °C; R_f = 0.5 (15% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ4.11-4.04 (m, 2H), 4.00-3.93 (m, 1H), 3.76-3.69 (m, 1H), 3.73 (s, 3H), 3.60-3.54 (m, 1H), 3.55 (s, 3H), 3.35 (dd, *J* 11.3, 18.5 Hz, 2H), 2.78-2.68 (m, 1 H), 2.11 (dd, *J* 4.4, 12.7 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 186.5, 108.7, 102.4, 77.1, 74.0, 66.4, 65.1, 52.8, 52.3, 48.3, 33.8, 32.9. IR (neat) 2955, 2918, 2850, 1772, 1453, 1330, 1294, 1197, 1119, 1053 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}BrCl_2NO_6$ $[M + NH_4]^+$ 473.9222; found 473.9199.

(1*R,4*R**,6*R**)-6-(2-(Bromomethyl)-1,3-dioxolan-2-yl)-1,4-dichloro-7,7-dimethoxy-3-ethylenebicyclo[2.2.1]heptan-2-one 16.** To a stirred suspension of methyltriphenylphosphonium bromide (3.07 g, 8.61 mmol) in THF (25 mL) was added potassium *tert*-butoxide (900 mg, 8.03 mmol) at 0 °C and then allowed to warm to room temperature and stirred. After being stirred at rt for 2 h the resulting ylied was cooled to -78 °C and a solution of **17** (2.4 g, 5.74 mmol) in THF (8 mL) was added. After being stirred for 30 min (monitored by TLC), 10 mL of water was added slowly drop wise. The reaction mixture was diluted with EtOAc (75 mL), organic phase was separated, aqueous phase was extracted with EtOAc (75 mL x 3) combined organic phase was washed with water (100 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified over silica gel column chromatography (12% EtOAc in hexane) to afford **17** (2.3 g, 97%) as a colorless solid (needles: crystallized from acetonitrile); mp: 80-82 °C; R_f = 0.6 (15% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (s, 1H), 5.67 (s, 1H), 4.15-4.02 (m, 2H), 3.97 (q, *J* 7.3 Hz, 1H), 3.86-3.78 (m, 1H), 3.69 (s, 3H), 3.50 (s, 3H), 3.42-3.31 (m, 3H), 2.74 (t, *J* 12.0 Hz, 1H), 2.01 (dd, *J* 4.9, 11.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 146.1, 116.0, 108.6, 105.1, 78.0, 69.4, 66.5, 65.6, 52.2, 51.8, 46.3, 39.4, 34.8. IR (neat) 2982, 2953, 2904, 2844, 1755, 1660, 1450, 1395, 1295, 1208, 1169, 1112, 1058, 1020 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{21}BrCl_2NO_5$ $[M + NH_4]^+$ 433.9960; found: 433.9951.

(1*R,4*R**,6*R**)-6-(2-(Bromomethyl)-1,3-dioxolan-2-yl)-1,4-dichloro-7,7-dimethoxy-3-(3-oxobutyl)bicyclo[2.2.1]heptan-2-one 20.** To a stirred solution of **16** (2 g, 4.8 mmol) in acetone (30 mL) was added 2N $NaOH_{aq}$ (2.9 mL, 5.8 mmol) at 0 °C. After being stirred for 2 h, 2 mL of 10% HCl was added, diluted with EtOAc (70 mL), organic phase was separated, aqueous phase was extracted with EtOAc (80 mL x 3) combined organic phase was washed with water (100 mL), brine (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The resulting crude was purified over silica gel column chromatography (20% EtOAc in hexane) to give **20** (2.23 g, 98%) as a colorless solid (needles: crystallized from acetonitrile); mp: 70-72 °C; R_f = 0.5 (20% EtOAc in hexane).

NMR data for major isomer.^{1}H NMR (400 MHz, $CDCl_3$) δ4.17-4.09 (m, 1H), 4.08-4.02 (m, 1H), 3.97 (q, *J* 7.3 Hz, 1H), 3.84-3.75 (m, 1H), 3.68 (s, 3H), 3.59 (s, 3H), 3.38 (d, *J* 3.4 Hz, 2H), 3.29 (dd, *J* 5.1, 12.0 Hz, 1H), 2.98-2.84 (m, 1H), 2.84-2.72 (m, 2H), 2.50 (dt, *J* 2.4, 12.5 Hz, 1H), 2.21 (d, *J* 5.4 Hz, 1H), 2.18 (s, 3H), 2.12-1.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 201.4, 108.6, 104.9, 78.4, 68.4, 66.1, 65.4, 55.4, 51.8, 46.4, 41.4, 34.8, 33.4, 30.1, 18.3;
NMR data for minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ4.17-4.09 (m, 1H), 4.08-4.02 (m, 2H), 3.97 (q, *J* 7.3 Hz, 1H), 3.84-3.75 (m, 1H), 3.66 (s, 3H), 3.57 (s, 3H), 3.38 (d, *J* 3.4 Hz, 1H), 3.29 (dd, *J* 5.1, 12.0 Hz, 1H), 2.98-2.84 (m, 1H), 2.84-2.72 (m, 2H), 2.63-2.59 (m, 1H), 2.22-2.18 (m, 1H), 2.17 (s, 3H), 2.12-1.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 201.9, 108.7, 105.3, 77.8, 69.1, 66.3, 65.6, 56.7, 53.7, 51.8, 45.3, 42.4, 41.0, 34.6, 30.0, 23.4. IR (neat) 2953, 2906, 2846, 1765, 1713, 1452, 1364, 1203, 1108, 1049, 979 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{24}BrCl_2O_6$ $[M + H]^+$ 475.0113; found: 475.0088.

Twist-brendane 15. To a stirred solution of **20** (2 g, 4.21 mmol) in THF (42 mL) was added NaH (220 mg, 5.48 mmol, 60% in mineral oil) at 0 °C and slowly allowed to warm to room temperature and then heated at 60 °C. After being heated for 5 h, reaction mixture was cooled to 0 °C and added 10 mL of water drop wise, solvent was evaporated. The resulting residue was diluted with EtOAc (75 mL), organic phase was separated aqueous phase was extracted with EtOAc (80 mL x 3), combined organic phase was washed with water (70 mL), brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified over silica gel column chromatography (25% EtOAc in hexane) to give **15** (1.49 g, 90%) as a colorless solid (needles: crystallized from acetonitrile); mp: 152-154 °C; R_f = 0.5 (25% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02-3.89 (m, 3H), 3.85-3.77 (m, 1H), 3.60 (s, 3H), 3.42 (s, 3H), 2.80-2.69 (m, 2H), 2.66 (dd, *J* 5.1, 11.0 Hz, 1H), 2.53 (d, *J* 7.3 Hz, 1H), 2.49 (d, *J* 14.2 Hz, 1H), 2.17 (d, *J* 11.7 Hz, 1H), 2.14 (s, 3H), 2.08 (dd, *J* 5.1, 10.8 Hz, 1H), 1.96 (dd, *J* 4.9, 10.8 Hz, 1H), 1.81 (dd, *J* 1, 14.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 201.5, 108.1, 104.3, 74.2, 73.3, 65.3, 64.4, 55.0, 54.6, 51.6, 51.2, 42.4, 38.9, 35.6, 29.9, 24.3. IR (neat) 2984, 2950, 2848, 1783, 1713, 1441, 1335, 1192, 1141, 1080 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{23}Cl_2O_6$ $[M+H]^+$ 393.0872; found: 393.0852.

(1*R,4*S**,5*R**)-Methyl 2,5-dichloro-3-oxo-4-(3-oxobutyl)spiro[bicyclo[2.2.2]octane-7,2'-[1,3]dioxolane]-5-carboxylate 21.** To a stirred solution of **15** (500 mg, 1.27 mmol) in toluene (12 mL) was added pTSA (290 mg, 1.52 mmol) at room temperature and then slowly warm to 80 °C. After being stirred for 4.5 h, 2 mL of water was added, diluted with EtOAc (50 mL), organic phase was separated aqueous phase was extracted with EtOAc (50 mL x 3), combined organic phase was washed with $NaHCO_3$ (10 mL), water (50 mL), brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified over silica gel column chromatography (30% EtOAc in hexane) to give **25** (424 mg, 88%) as a colorless liquid in 45:55 (*exo*:*endo*) ratio; R_f = 0.5 (25% EtOAc in hexane). NMR data for *exo* isomer **21b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (d, *J* 3.4 Hz, 1H), 4.12-3.91 (m, 4H), 3.85 (s, 3H), 3.14-3.10 (m, 1H), 3.07 (dd, *J* 2.7, 7.1 Hz, 1H), 2.72-2.45 (m, 3H), 2.45-2.22 (m, 2H), 2.16 (s, 3H), 2.05-1.87 (m, 1H), 1.87-1.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 203.2, 170.8, 106.8, 70.8 (2C), 65.2,

58.1, 54.6, 54.5, 51.2, 39.7, 38.1, 38.0, 30.0, 22.5. NMR data for *endo* isomer **21a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (t, *J* 2.4 Hz, 1H), 4.12-3.90 (m, 4H), 3.78 (s, 3H), 3.14-3.03 (dd, *J* 2.4, 7.3 Hz, 1 H), 2.77-2.62 (m, 3H), 2.61-2.46 (m, 1H), 2.41-2.21 (m, 2H), 2.12 (s, 3H), 2.05-1.87 (m, 1H), 1.86-1.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 203.0, 170.4, 106.8, 72.1 (2C), 64.4, 56.2, 55.3, 53.7, 43.9, 42.3, 38.1, 38.0, 34.8, 29.9, 22.6; IR (neat) 2955, 1745, 1726, 1435, 1355, 1281, 1245, 1164, 1110 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{21}Cl_2O_6$ $[M+H]^+$ 379.0715; found: 379.0695.

(1*S,3*S**,4*R**)-Methyl 5-oxo-4-(3-oxobutyl)spiro[bicyclo[2.2.2]octane-7,2'-[1,3]dioxolane]-3-carboxylate 14.** To a stirred solution of mixture **21** (500 mg, 1.32 mmol) in acetic acid (10 mL) was added zinc dust (517 mg, 7.9 mmol) at room temperature. After being stirred for 6.5 h, reaction mixture was filtered washed with EtOAc (200 mL) filtrate was washed with $NaHCO_3$ (60 mL), organic phase separated, aqueous phase was extracted with EtOAc (100 mL x 2), combined organic phase was washed with water (100 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified over silica gel column chromatography (40% EtOAc in hexane) to give **14** (348 mg, 85%) as a colorless liquid; R_f = 0.4 (45% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98-3.93 (m, 2H), 3.93-3.86 (m, 2H), 3.72 (d, *J* 4.9 Hz, 1H), 3.65 (s, 3H), 2.83 (dd, *J* 5.6, 11.0 Hz, 1H), 2.59-2.54 (m, 1H), 2.54-2.47 (m, 1H), 2.45-2.38 (m, 2H), 2.38-2.34 (m, 1H), 2.21-2.14 (m, 2H), 2.13 (s, 3H), 1.92-1.87 (m, 1H), 1.85-1.74 (m, 1H), 1.54 (ddd, *J* 5.1, 10.3, 14.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 208.0, 174.9, 108.7, 64.6, 64.3, 52.1, 49.2, 45.3, 42.3, 39.8, 38.0, 35.3, 29.8, 26.2, 25.1. IR (neat) 2951, 1728, 1665, 1441, 1362, 1339, 1260, 1196, 1170 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{26}NO_6$ $[M+NH_4]^+$ 328.1760; found: 328.1733

Enone 22. To a stirred solution of **14** (300 mg, 0.967) in MeOH (43 mL) was added NaOH (271 mg, 6.77mmol) and slowly warmed to reflux temperature. After being refluxed for 12 h, solvent was evaporated under reduced pressure, residue was diluted with EtOAc (50 mL), organic phase was separated, aqueous phase was extracted with EtOAc (40 mL x 3) combined organic phase was washed with dil. HCl (20 mL), water (50 mL x 2), brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was dissolved in MeOH (15 mL) cooled to 0 ^{o}C, solution of CH_2N_2 in ether was added till yellow color persist..A pinch AcOH was added to quench excess of diazomethane. Reaction mixture was concentrated under reduced pressure, the resulting residue was purified over silica gel column chromatography (25% EtOAc in hexane) afforded enone **22** (220 mg, 78%, *exo/endo*: 4:1) as a colorless liquid. R_f = 0.5 (50% EtOAc in hexane). NMR data for *exo* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (s, 1H), 3.98-3.94 (m, 2H), 3.92 - 3.86 (m, 2H), 3.66 (s, 3H), 2.73-2.65 (m, 2H), 2.41-2.30 (m, 2H), 2.29-2.22 (m, 1H), 2.21-2.15 (m, 1H), 2.07-1.97 (m, 2H), 1.89-1.79 (m, 2H), 1.74 (ddd, *J* 5.9, 8.1, 13.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 175.1, 164.7, 125.9, 109.4, 64.3 (2C), 52.0, 47.1, 46.4, 39.3, 33.6, 33.5, 31.7, 30.1, 26.3. NMR data for *endo* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 1H), 3.98-3.94 (m, 2H), 3.92 - 3.86 (m, 2H), 3.71 (s, 3H), 2.73-2.65 (m, 2H), 2.41-2.30 (m, 2H), 2.29-2.22 (m, 1H), 2.21-2.15 (m, 1H), 2.07-1.97 (m, 2H), 1.89-1.79 (m, 2H), 1.74 (ddd, *J* 5.9, 8.1, 13.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 173.9, 165.9, 124.4, 109.2, 64.3

(2C), 51.8, 45.3, 42.8, 38.9, 35.3, 34.4, 31.2, 29.5, 26.2. HRMS (ESI): *m/z* calcd for $C_{16}H_{20}O_6Na$ $[M + Na]^+$ 315.1208; found: 315.1210.

Keto ester 13. To a stirred solution of **22** (190 mg, 0.65 mmol) in acetone (2 mL) was added 6N HCl (0.65 mL) at 0 °C and allowed to warm to rt, After being stirred for 2 h (monitored by tlc) reaction mixture was diluted with EtOAc (40 mL), organic phase was separated, aqueous phase was extracted with EtOAc (40 mL x 3) combined organic phase was washed with water (50 mL), brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified over silica gel column chromatography (40% EtOAc in hexane) to afford **13** (134 mg, 83%, *exo:endo*: 4:1) as a colorless solid (needles: crystallized from acetonitrile); mp: 110-112 °C; R_f = 0.4 (50% EtOAc in hexane). NMR data for *exo* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (d, *J* 2.0 Hz, 1H), 3.72 (s, 3H), 3.09-2.98 (m, 1H), 2.87-2.79 (m, 1H), 2.79-2.70 (m, 1H), 2.70-2.60 (m, 1H), 2.52-2.45 (m, 1H), 2.44-2.43 (m, 1H), 2.36-2.34 (m, 1H), 2.33-2.05 (m, 4H), 1.98-1.80 (m, 1H). ^{13}C (100 MHz, $CDCl_3$) δ 210.9, 196.7, 174.3, 161.1, 126.9, 52.4, 48.4, 46.5, 42.3, 40.8, 33.4, 32.4, 29.8, 27.5. NMR data for *endo* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (d, *J* 2.0 Hz, 1H), 3.75 (m, 3H), 3.09-2.98 (m, 1H), 2.87-2.79 (m, 1H), 2.79-2.70 (m, 1H), 2.70-2.60 (m, 1H), 2.52-2.34 (m, 3H), 2.33-2.05 (m, 4H), 1.98-1.80 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 196.7, 174.3, 161.1, 125.7, 50.7, 45.6, 43.7, 42.9, 42.7, 42.4, 40.8, 27.9, 33.3, 29.3, 27.3. IR (neat): 2952, 1725, 1665, 1450, 1434, 1361, 1336, 1258, 1220, 1196, 1167, 1029 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{20}NO_4$ $[M+NH_4]^+$ 266.1392; found: 266.1386.

Enone 12. To a stirred suspension of methyltriphenylphosphonium bromide (237 mg, 0.66 mmol) in THF (3 mL) was added potassium *tert*-butoxide (69 mg, 0.61 mmol) at 0 °C and then allowed to warm to room temperature and stirred for 2 h. A solution of **13** (110 mg, 0.44 mmol) in THF (1.5 mL) was added at -78 °C and after being stirred for 1 h, 1 mL of water was added slowly drop wise. The reaction mixture was diluted with EtOAc (25 mL), organic phase was separated aqueous phase was extracted with EtOAc (25 mL x 3) combined organic phase was washed with water (30 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified over silica gel column chromatography (25% EtOAc in hexane) to afford **12** (78 mg, 72%, *exo/endo:*10:1) as a colorless liquid. R_f = 0.5 (30% EtOAc in hexane).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95-5.91 (m, 1H), 4.97-4.87 (m, 1H), 4.72 (s, 1H), 3.67 (s, 3H), 2.86-2.77 (m, 1H), 2.70 (dd, *J* 5.9, 10.3 Hz, 1H), 2.60-2.52 (m, 3H), 2.42-2.32 (m, 2H), 2.25-2.16 (m, 1H), 2.11-1.92 (m, 3H), 1.78 (ddd, *J* 5.9, 7.6, 13.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 175.1, 166.1, 147.1, 126.0, 107.8, 52.0, 47.4, 40.8, 39.1, 36.2, 35.8, 33.7, 30.9, 30.1. IR (neat): 2924, 2856, 1730, 1668, 1449, 1434, 1354, 1334, 1232, 1194, 1166, 1044 cm^{-1}; IR (neat): 2924, 2856, 1730, 1668, 1449, 1434, 1354, 1334, 1232, 1194, 1166, 1044 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1334; found: 247.1318.

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