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A ONE-FLASK MULTICOMPONENT ANNULATION REACTION AS THE KEY STEP IN A TOTAL SYNTHESIS OF SPIROBICYCLIC (±)-β-VETIVONE†

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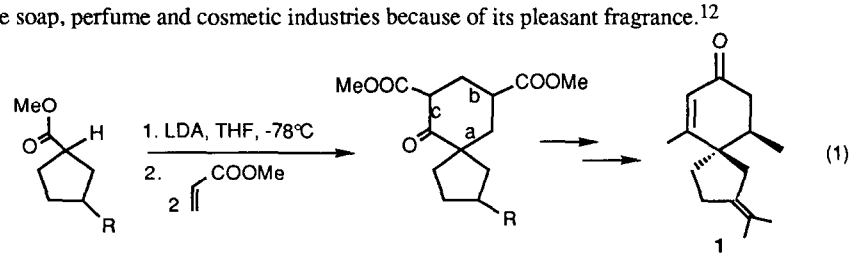
Abstract – One-flask, 3-component Michael-Michael-Dieckmann cyclizations are applied to 2+2+2 construction of spirobicyclic cyclohexanone β-keto esters **7** and **11** as pivotal intermediates for synthesis of naturally-occurring spiro[4.5]decane β-vetivone (**1**). Some unexpected difficulties were encountered and are discussed. A novel BF_3-promoted unidirectional dehydration of tertiary alcohol silyl ether **15** exclusively into isopropylidene cyclopentane **16** is reported.

Our interests generally in developing efficient new synthetic methods and specifically in multicomponent annulations forming several new bonds in one reaction flask[1] have led us to develop five different protocols including: (1) sequential Michael–Michael–Aldol additions for 2+2+2 construction of polyfunctionalized cyclohexanols [2a] including application to total synthesis of juncunol, an unusual vinyldihydrophenanthrene;[2b] (2) sequential *Mi*chael–*Mi*chael–*Ri*ng *C*losure (MIMIRC) reactions for 3–different component 2+2+2 construction of acylcyclohexenes;[3] (3) sequential *Mi*chael–*Mi*chael–*Mi*chael–*Ri*ng *C*losure (MIMI–MIRC) reactions for 4–component coupling;[4] (4) sequential 4–different–component annulations for conversion of n–sized cycloalkenones into n+4–alkenolides and subsequently into aromatic and heteroaromatic compounds;[5] and (5) sequential Michael–Michael–Dieckmann cyclization reactions for 2+2+2 construction of regiospecifically substituted cyclohexanones.[6] This fifth protocol has allowed rapid and easy synthetic access to various spirobicyclic cyclohexanones, a structural unit common to several classes of natural products[7] including the spiro[4.5]decane vetivones. The spiro- [4.5]decane structural unit has been important in syntheses of quadrone,[8] perhydrohistrionicotoxin,[9] and propellanes.[10] Several synthetic approaches to the spiro[4.5]decane ring system have been developed.[7,11] To showcase our methodology in the context of a natural product synthesis, we report here use of the Michael–Michael–Dieckmann cyclization protocol as the key step forming three new carbon–carbon bonds a, b, and c in one flask in a total synthesis of spiro[4.5]decane (±)–β–vetivone (**1**, eq. 1).[12] This sesquiterpene, which can be isolated from the vetiver plant found in many tropical and subtropical areas, is valuable to the soap, perfume and cosmetic industries because of its pleasant fragrance.[12]



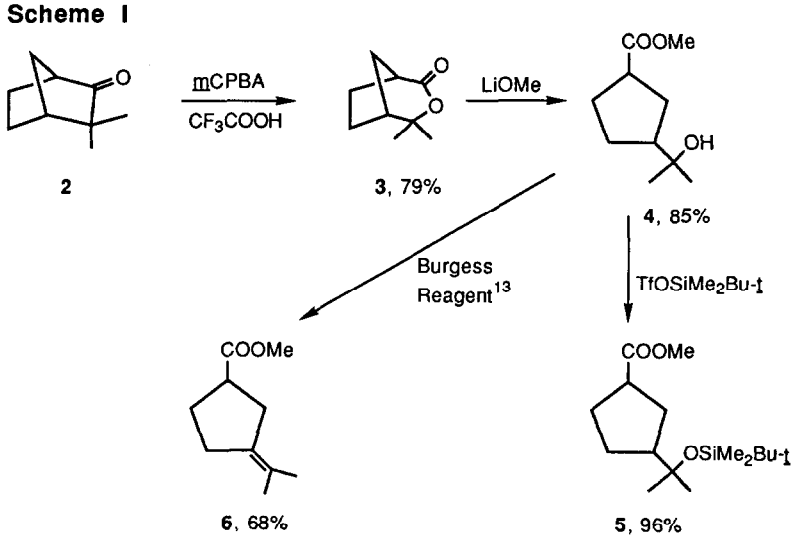
(1)

†Dedicated to Professor Gabor Fodor on the occasion of his 75th birthday.

Results and Discussion

Design of our synthetic strategy started with choosing an appropriate cyclopentyl R–substituent in eq. 1; an obvious candidate was R = isopropylidene because the target molecule bears this substituent and because any saturated bond to substituent R would introduce an additional stereogenic center on the 5–membered ring and would therefore probably complicate purification of intermediates. Methyl 3–isopropylidenecyclopentanecarboxylate (**6**) was prepared according to Scheme I terminating in a Burgess dehydration[13] and was subjected to the Michael–Michael–Dieckmann cyclization protocol[6] to afford spirobicycle **7** in 40% yield or in 61% yield after one recycling reaction as described in the experimental section (Scheme II).

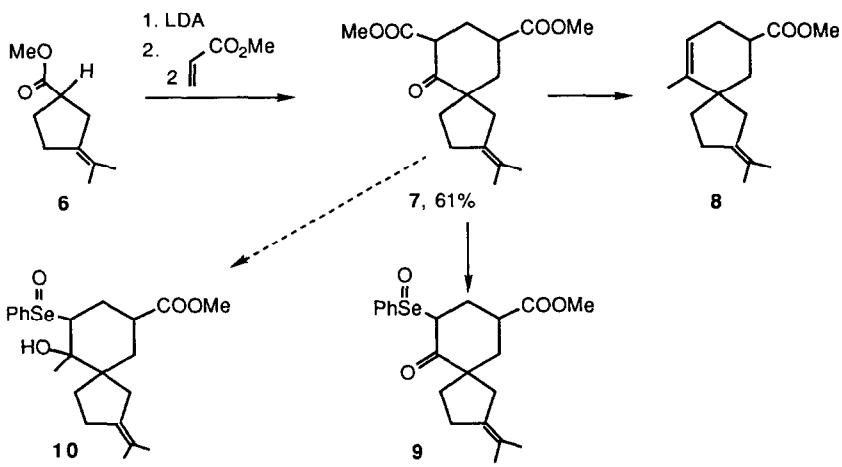
Scheme I



Several different sequences were envisioned for conversion of isopropylidene spirobicycle **7** into *β*–vetivone **1**. Unfortunately and unexpectedly, each sequence ran into trouble. For example, decarboxylation[14] of β–keto ester **7** followed by chemospecific addition of methylmagnesium bromide to the ketone carbonyl group and then thionyl chloride/4-dimethylaminopyridine promoted dehydration produced diene **8** in 50% overall yield from β–keto ester **7**. All attempts including chromium trioxide/3,5–dimethylpyrazole[15] to carry out allylic oxidation regiospecifically in the 6–membered ring, however, gave inseparable mixtures of 6– *and* 5–membered cyclic ketones despite good literature precedent for allylic methylene group oxidation of cyclohexenes selectively over acyclic alkenes and of cyclohexenes selectively over alkylidene cycloalkanes.[15] For another example, decarboxylation[14] of β–keto ester **7** and then α–phenylselenylation of the resultant ketone followed by selenide → selenoxide oxidation using hydrogen peroxide produced β–keto selenoxide **9**.[16] All thermal reactions involving β–elimination of benzeneselenenic acid, in the absence as well as in the presence of base (e.g. calcium carbonate[17]), produced mixtures of double bond positional isomers with the desired conjugated enone predominating; attempts to isolate this enone by column chromatography or by preparative tlc even using preparative silica gel tlc plates pre-eluted with triethylamine to diminish acidity as well as alumina tlc plates caused decomposition of the desired enone into many unidentified products. Yet another example involved selenoxide **10** that was designed to undergo thermal β–elimination to form an allylic tertiary alcohol capable

of chromium(III) oxidation with allylic rearrangement. Formation of selenoxide **10** from its precursor selenide using two equivalents of hydrogen peroxide[16b] or *m*–chloroperbenzoic and then room temperaure thermolysis did indeed introduce unsaturation into the 6–membered ring but also, even in the presence of base,[16b] caused epoxidation of the isopropylidene double bond as evidenced in the 400 MHz NMR spectrum of the major product (yield 30–40%) having a new *gem*–dimethyl signal appearing as a singlet at 1.29 δ compared to the isopropylidene *gem*–dimethyl signal in the reactant at 1.59 δ; mass spectrometry supported the assignment of this epoxide. Problems have been noted before in some selenoxide *syn*–eliminations,[16] including *in situ* reaction of excess hydrogen peroxide with benzeneselenenic acid to form benzeneperoxyselenenic acid capable of epoxidizing isolated alkene units.[16,18] It was surprising, however, that we produced an epoxide even when only two equivalents of hydrogen peroxide were used as recommended by Grieco[18b] and also when *m*–chloroperbenzoic acid in methylene chloride with base was used as recommended by Reich.[16b]

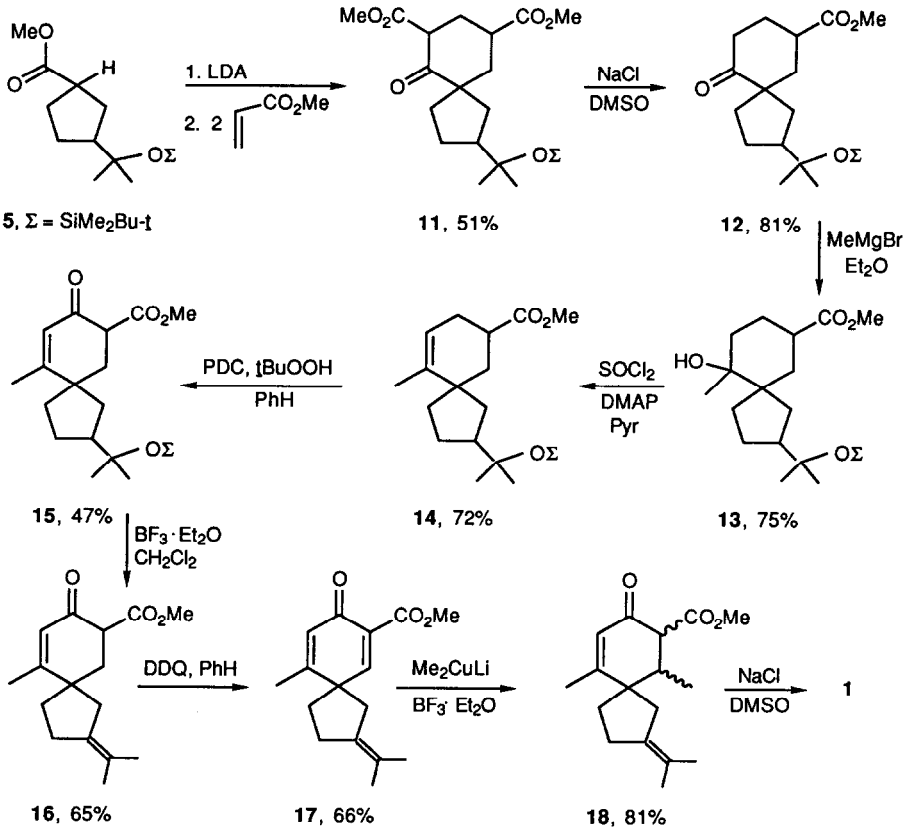
Scheme II



Because of these difficulties, caused in large part by the isopropylidene group, we designed a different and somewhat less direct synthetic plan starting with tertiary silyl ether–protected cyclopentanecarboxylate **5** (Scheme I). Submitting cyclopentanecarboxylate ester **5** to the Michael–Michael–Dieckmann cyclization conditions gave spirobicycle **11** in good yield as a mixture of two major diastereomers (stereochemistry unassigned). These β–keto esters were then decarboxylated[14] to form cyclohexanones **12** (Scheme III). Highly chemoselective addition to the ketone carbonyl group of keto ester **12** was achieved using 1.6 equivalents of methylmagnesium bromide in diethyl ether at 0°C to produce ester tertiary alcohols **13**. Dehydration to form endocyclic olefin **14** was achieved best using thionyl chloride with one equivalent of 4–dimethylaminopyridine in pyridine solvent at reflux during two hours; under these conditions the ratio of endocyclic cyclohexene **14** to its exocyclic methylenecyclohexane double bond positional isomer was greater than 10:1, and as expected under these basic conditions no undesired product of 5-membered ring expansion was formed. Allylic–oxidation to give enone **15** was optimal using 20 equivalents of *t*–butyl hydroperoxide and pyridinium dichromate[19] at room temperature. Removal of the silyl ether protecting group and dehydration *both*

proceeded smoothly at room temperature in one flask using BF_3–etherate[20] to form dienone **16** importantly with no detectable amount of the corresponding isopropenyl double bond isomer; other initial results confirm that BF_3-etherate promoted β-elimination of tertiary alcohol silyl ethers has excellent potential as an overall dehydration procedure characterized by unusually high control of new double bond regiochemistry, and a full report on this process will appear in due course. Further oxidation of enone **16** into cross–conjugated cyclohexadienone **17** was achieved most conveniently and in one step by dehydrogenation using dichlorodicyanobenzoquinone (DDQ)[21] refluxing in benzene. Thus, the sequence of dehydration to dienone **16** and then dehydrogenation allowed effective formation of racemic trienone **17** having only one stereogenic center at the spiro carbon atom.

Scheme III



Conjugate methylation of trienone ester **17** was explored with various nucleophilic methylmetallic reagents. Following closely a literature procedure for conjugate methylation of an almost identical trienone *aldehyde* using amido(methyl)cuprates[22,23] unhappily gave a mixture of several products including one formed apparently by 1,2-addition to the ketone carbonyl group of trienone ester **17**. A similar result was obtained using methylmagnesium bromide and a catalytic amount of cuprous iodide.[24] Virtually no reaction occurred using methylcopper-dimethylsulfide-lithium bromide from -78°C to room temperature.[25] Best results (~80% yield) were obtained using

dimethylcopperlithium or dimethylcopperlithium-boron trifluoride;[26] in the second case, there was a 1.7:1 stereochemical preference for β-methylation *vs.* α-methylation (see structure **1** for indication of methyl group β-stereochemistry) of trienone ester **17** in contrast to the 5:1 β:α-methylation stereoselectivity reported for the corresponding trienone aldehyde.[22] This difficulty of conjugate methylation at the neopentylic disubstituted carbon atom adjacent to the spiro ring junction in trienone **17** was underscored by the failure of trimethylzinclithium[27] and of methyltitanium triisopropoxide[12,28] to achieve conjugate methylation. Finally, decarboxylation[14] of β-keto esters **18** and chromatographic separation gave (±)-β-vetivone (**1**) identical spectroscopically to an authentic sample prepared previously.[12]

Conclusion

The surprises encountered because of the lability of the isopropylidene group in spirobicycles **6–8** toward several different reagents underscore (1) the importance of testing reagents on polyfunctional molecules and (2) the importance of total synthesis not only to achieve preparation of the target molecule but also as a testing ground to reveal limitations of new as well as of established reagents and procedures. Also, the final successful conjugate methylation emphasizes the usefulness of stoichiometric cuprate reagents over other organocopper reagents and over other transition metal organometallics especially for conjugate additions to sterically hindered systems such as trienone **17**. The 9–step total synthesis of racemic β–vetivone shown in Schemes I and III highlights use of a one–flask 3–component spiroannulation reaction as the key step for assembling the carbon skeleton of this deceptively simple natural product and also suggests application of this Michael-Michael-Dieckmann methodology to rapid synthesis of other spiro-fused, physiologically active, sesquiterpene natural products.[29]

Acknowledgment

We thank the Petroleum Research Fund, administered by the American Chemical Society, for financial support, Mr. Todd Nelson for suggesting Scheme I, Ms. Tizah Anjeh for help in preparing isopropylidenecyclopentanecarboxylate **6** and Takashi Kishimoto for his help at the beginning stages of this project.

Experimental Section

All solvents were distilled before use. ^{1}H NMR spectra were recorded at 400 MHz. The purity of all title compounds was judged to be >95% by ^{1}H NMR spectroscopy. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. All reagents were purchased from Aldrich unless otherwise noted and were used as received.

3,3-Dimethylnorcamphor (2). LDA (25.0 mmol) was generated in 20 mL of THF at -78°C for 1 h. Norcamphor (2.5 g, 22.7 mmol) in THF (12 mL) was added dropwise and the reaction mixture stirred for 45 min. Iodomethane (7.07 mL, 114 mmol, 5 eq passed through a 2 in column of neutral alumina) was added dropwise neat. The reaction was warmed to room temperature and stirred for 1.5 h. After quenching with saturated aqueous NH_4Cl (2 mL), the excess MeI was removed under reduced pressure. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with ether (3 x 25 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford 2.88 g of crude monomethylated product. This crude material in THF (10 mL) was added dropwise to a solution of LDA (30 mmol) in THF (18 mL) at -78°C. The reaction mixture was stirred for 45 min. Then, iodomethane (7.23 mL, 116 mmol, 5 eq, purified as before) was added dropwise neat. The ice bath was removed and the reaction was stirred for 1.5 h. After a quenching and workup as before, the crude product was purified by column chromatography (5% ether/hexane) yielding the desired product as a pale yellow oil (2.52 g, 80.4%): IR ($CHCl_3$, cm^{-1}) 3018, 2970, 2878, 2736, 1463, 1384, 1233, 1058. ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 3H), 1.05 (s, 3H), 1.47 (dt, J=11.2, 1.2 Hz, 2H), 1.60 (m, 1H), 1.81 (m, 2H), 1.97 (dt, J=10.6, 2.0 Hz, 1H), 2.23 (d, J=2.0 Hz, 1H), 2.56 (dd, J=5.2, 1.2 Hz, 1H).

4,4-Dimethyl-3-oxobicyclo[3.2.1]octan-2-one (3). 3,3-Dimethylnorcamphor, (2.52 g, 0.018 mol) was dissolved in 50 mL of CH_2Cl_2 and cooled to 0°C. m-Chloroper-benzoic acid (as a solid) (2.36 g, 50-60%, 0.027 mol) was added at one time to the 0°C solution. Trifluoroacetic acid[30] (1.39 mL, 0.018 mol) was added dropwise and the reaction mixture was stirred at room temperature for four days. The reaction mixture was then poured into ether (50 mL) and washed with 10% aqueous sodium sulfite (1 x 100 mL), saturated aqueous $NaHCO_3$ (2 x 100 mL), and saturated aqueous K_2CO_3 (1 x 100 mL). The organic portion was dried over magnesium sulfate, filtered and concentrated, yielding a white solid. Recrystallization from hexanes afforded the desired lactone (2.50 g, 90.2%): mp 95-97°C (lit.[31] 94-96°C), ^1H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.41 (s, 3H), 1.59 (dt, J=12.2, 4.5 Hz, 1H), 1.69 (m, 1H), 1.81 (m, 1H), 1.93 (m, 1H), 2.05 (m, 1H), 2.16 (t, J=5.5 Hz, 1H), 2.21 (d, J=12.2 Hz, 1H), 2.85 (dd, J=7.0, 4.0 Hz, 1H).

Methyl 3-(1-Hydroxy-1-methylethyl)cyclopentanecarboxylate (4). Methanol (10 mL) was added to benzene (25 mL) and cooled to 0°C. n-BuLi (11.5 mL, 1.55 M in hexanes, 0.018 mmol) was added dropwise and the reaction mixture was stirred for 5 min after the evolution of butane had ceased. 4,4-Dimethyl-3-oxobicyclo[3.2.1]octan-2-one (2.52 g, 0.02 mol) in 6 mL of benzene was added dropwise. The reaction was warmed to room temperature and then heated at 75°C for 3 h. The reaction mixture was then cooled to room temperature and water was added. The layers were separated and the aqueous layer was washed with ether (2 x 40 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (50% ether/hexanes) yielding the desired hydroxy ester as a yellow oil (2.59 g, 85.2%): IR ($CHCl_3$, cm^{-1}) 3610, 3490, 3010, 2970, 2876, 1725, 1438, 1371. ^1H NMR ($CDCl_3$) δ 1.20 (s, 3H), 1.21 (s, 3H), 1.50-2.15 (m, 7H), 2.79 (m, 1H), 3.67 (s, 3H).

Methyl 3-(1-t-Butyldimethylsiloxy-1-methylethyl)cyclopentanecarboxylate (5). Alcohol 4 (2.59 g, 0.01 mol) was dissolved in 45 mL of methylene chloride. 2,6-Lutidine (324 mL, 0.03 mol, 2 eq) was added dropwise followed by t- butyldimethylsilyl trifluoromethanesulfonate (6.40 mL, 0.03 mol, 2 eq).[32] The reaction mixture was stirred for 20 min. at room temperature. Half of the solvent was removed under reduced pressure and 20 mL of ether was added. The mixture was then filtered through silica gel (3 cm). The solution was concentrated to afford a crude reaction mixture which was purified by column chromatography (3% ether/hexanes) yielding the desired product as a colorless oil (4.01 g, 96.2%): IR ($CHCl_3$, cm^{-1}) 3004, 2950, 2872, 1725, 1450, 1360. ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.86 (s, 9H) [other diastereomer 0.85 (s, 9H)], 1.18 (s, 3H), 1.19 (s, 3H), 1.62-2.02 (m, 7H), 2.72 (m, 1H), 3.65 (s, 3H) [other diastereomer 3.66 (s, 3H)].

Methyl 3-Isopropylidenecyclopentanecarboxylate (6). Methyl 3-(1-hydroxy-1-methylethyl)cyclopentanecarboxylate (2.59 g, 0.01 mol) in 15 mL of benzene was added dropwise to freshly prepared Burgess reagent (8.06 g, 0.03 mol) in 45 mL of benzene under N_2 at room temperature. The reaction mixture was then heated at 50°C for 1 h. It was cooled to room temperature and water (50 mL) was added. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (1% ether/hexanes) yielding the desired product as an oil (1.54 g, 67.7%): IR ($CHCl_3$, cm^{-1}) 3023, 2954, 1728, 1438, 1364, 1202, 1174. ^1H NMR ($CDCl_3$) δ 1.62 (s, 6H), 1.84 (m, 1H), 2.01 (m, 1H), 2.19 (m, 1H), 2.40 (m, 2H), 2.56 (m, 1H), 2.79 (m, 1H), 3.68 (s, 3H).

Dimethyl 3-Isopropylidene-6-oxospiro[4.5]decane-7,9-dicarboxylate (7). LDA (6.55 mmol) was generated in 12 mL of THF at -78°C for 1 h. Methyl 3-isopropylidenecyclopentanecarboxylate (1030 mg, 6.14 mmol) in 12 mL of THF was added dropwise and the solution turned yellow after a few minutes. The reaction mixture was stirred for 30 min. After dilution with 7 mL of -78°C THF, methyl acrylate (1.30 mL, 13.5 mmol) in 5 mL of THF was added dropwise. The reaction was allowed to stir at -78°C for exactly 2 h and 5 min. The reaction was then quenched with saturated aqueous ammonium chloride and the aqueous portion was extracted with ether (3 x 60 mL). The combined organic portions were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (5% ether/hexanes) yielding the desired product as an oil (803 mg, 39.8%): IR ($CHCl_3$, cm^{-1}) 2960, 2929, 2856, 1726, 1646, 1609, 1378, 1261, 1224, 1032. ^1H NMR ($CDCl_3$) δ 1.45-1.72 (m, 3H), 1.60 (s, 3H), 1.62 (s, 3H), 1.93-2.10 (m, 2H), 2.20-2.60 (m, 5H), 2.68 (m, 1H), 2.87 (m, 1H), 3.70 (s, 3H), 3.76 (s, 3H). HRMS calculated for $C_{17}H_{24}O_5$ 308.1624 found 308.1628. The reaction also yielded the monoadduct (a compound formed from the diadduct via a reverse Dieckmann reaction[33]). (597 mg, 35.9%): IR ($CHCl_3$, cm^{-1}) 2959, 2927, 2855, 1721, 1447, 1376, 1193, 1023. ^1H NMR ($CDCl_3$) δ 1.59 (s, 3H), 1.61 (s, 3H), 1.94 (m, 2H), 2.17 (m, 3H), 2.28 (m, 4H), 2.72 (m, 1H), 3.66 (s, 3H), 3.67 (s, 3H). LDA (2.59 mmol) was generated in 5 mL of THF at -78°C for 1 h. The monoadduct (597 mg, 2.41 mmol) in 3 mL of THF was added dropwise and the reaction stirred for 30 min. After dilution with 3 mL of THF, methyl acrylate (0.466 mL, 5.17 mmol) in 1 mL of THF was added dropwise. The reaction was allowed to stir at -78°C for exactly 2 h and 5

min and was quenched with saturated aqueous ammonium chloride. The aqueous portion was extracted with ether (3 x 40 mL) and the combined organic portions were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (5% ether/hexanes) yielding the desired product as an oil (155.7 mg, 21.5% overall - combined yield for the reaction 61.3%).

Methyl 3-Isopropylidene-6-methylspiro[4.5]dec-6-ene-9-carboxylate (8). Cyclohexanone **7** (1000 mg, 4.00 mmol) was combined with sodium chloride (200 mg, 3.51 mmol) and water (0.18 mL, 10.1 mmol) in 2 mL of DMSO along with a magnetic stir bar in a flask fitted with a reflux condensor. The reaction mixture was then heated at 150°C for 4.5 h. The reaction mixture was poured into 50 mL of water and 10 mL of ether was added. The aqueous and organic layers were separated. The aqueous portion was extracted with ether (3x20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (10% ether/hexanes) yielding the desired product as an oil as a mixture of two diastereomers (977 mg, 91.8%): IR ($CHCl_3$, cm^{-1}) 3029, 2954, 2930, 1732, 1706, 1461, 1437, 1375; ^1H NMR ($CDCl_3$) δ 1.59 (s, 3H), 1.60 (s, 3H) [other diastereomer δ 1.58 (s, 3H), 1.61 (s, 3H)], 1.82 (m, 6H), 2.09 (tt, J=13.6, 3.4 Hz, 1H), 2.33 (m, 4H), 2.5 (td, J=14.2, 6.0 Hz, 1H), 2.85 (tt, J=12.0, 3.8 Hz 1H), 3.70 (s, 3H) [other diastereomer δ 3.69 (s, 3H)].

Methyl magnesium bromide (1.34 mL, 4.00 mmol, 3.0*M* in ether) was added dropwise to the 4-carboxycyclohexanone (630 mg, 2.50 mmol) in 50 mL of dry ether at 0°C under nitrogen. The reaction mixture was immediately warmed to room temperature and stirred for 1 h. The reaction was then quenched with saturated aqueous ammonium chloride. The layers were separated and the organic layer was washed with ether (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (20% ether/hexanes) yielding the desired product as an equal mixture of two stereoisomers as a colorless oil (600 mg, 89.7%): IR ($CHCl_3$, cm^{-1}) 3610, 2951, 1728, 1460, 1437, 1380; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H) [other diastereomer δ 1.26 (s, 3H)], 1.60 (s, 3H), 1.61 (s, 3H) [other diastereomer δ 1.57 (s, 3H), 1.61 (s, 3H)], 1.75-1.95 (m, 8H), 2.13-2.60 (m, 5H), 3.66 (s, 3H) (other diastereomer 3.65 (s, 3H)].

Thionyl chloride (0.41 mL, 5.63 mmol, 2.5 eq) was added dropwise to the alcohol (600 mg, 2.26 mmol) in 8 mL of pyridine at 0°C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was then diluted with 60 mL of ether and poured into 60 mL of 5% HCl. The two phases were stirred vigorously for 10 min., then separated. The organic layer was washed with water, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (1% ether/hexanes) yielding the desired product as an oil (338 mg, 60.4%, 50% overall from cyclohexanone **7**): IR ($CHCl_3$, cm^{-1}) 3020, 2929, 2854, 1731, 1649, 1519, 1475, 1423; ^1H NMR ($CDCl_3$) δ 1.55 (s, 3H), 1.61 (s, 3H), 1.66 (s, 3H), 1.87-2.38 (m, 9H), 2.55 (m, 2H), 3.67 (s, 3H) [other diastereomer δ 3.68 (s, 3H)], 5,42 (s, 1H).

Dimethyl 3-(1-t-Butyldimethylsiloxy-1-methylethyl)-6-oxospiro[4.5]decane-7,9-dicarboxylate (11). LDA (6.55 mmol) was generated in 20 mL of THF at -78°C for 1 h. Methyl 3-(1-t-butyldimethylsiloxy-1-methylethyl)cyclopentanecarboxylate (1500 mg, 5.00 mmol) in 10 mL of THF was added dropwise and the solution turned yellow after a few minutes. The reaction mixture was stirred for 30 min. After dilution with 15 mL of -78°C THF, methyl acrylate (0.96 mL, 11.0 mmol) in 5 mL of THF was added dropwise. The reaction was allowed to stir at -78°C for exactly 5 h and 5 min. The reaction was then quenched with saturated aqueous ammonium chloride and the aqueous portion was extracted with ether (3 x 60 mL). The combined organic portions were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (2% ether/hexanes) yielding the desired product as an oil as a mixture of two diastereomers (895 mg, 40.7%): IR ($CHCl_3$, cm^{-1}) 2955, 2931, 2857, 1732, 1651, 1608, 1441, 1363, 1038; ^1H NMR($CDCl_3$) δ 0.07 (s, 6H) [other diastereomer 0.06 (s, 6H)], 0.86 (s, 9H) [other diastereomer 0.87 (s, 9H)], 1.20 (s, 6H) [other diastereomer 1.18 (s, 6H)], 1.28-2.68 (m, 12H), 3.70 (s, 3H) [other diastereomer 3.69 (s, 3H)], 3.75 (s, 3H) [other diastereomer 3.75 (s, 3H)]; HRMS calculated for $C_{22}H_{37}O_6Si$ (M-CH_3) 425.2359, found 425.2355 and the monoadduct (367 mg, 19.0%): IR ($CHCl_3$, cm^{-1}) 2955, 2930, 1726, 1437, 1364, 1254; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H) [other diastereomer 0.06 (s, 6H)], 0.85 (s, 9H) [other diastereomer 0.84 (s, 9H)], 1.15 (s, 3H), 1.16 (s, 3H) [other disastereomer 1.16 (s, 3H), 1.17 (s, 3H)], 1.37-2.30 (m, 11H), 3.64 (s, 3H), 3.65 (s, 3H) [other diastereomer 3.66 (s, 3H), 3.67 (s, 3H)]. LDA (1.04 mmol) was generated in 5 mL of THF at -78°C for 1 h. The monoadduct (367 mg, 0.95 mmol) in 2 mL of THF was added dropwise and the reaction stirred for 30 min. After dilution with 2 mL of THF, methyl acrylate (0.19 mL, 2.09 mmol) in 1 mL of THF was added dropwise. The reaction was allowed to stir at -78°C for exactly 5 h and 5 min and was quenched with saturated aqueous ammonium chloride. The aqueous portion was extracted with ether (3 x 20 mL) and the combined organic portions were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (2%

ether/hexanes) yielding the desired product as an oil (221 mg, 10.1% overall - combined yield for the reaction 50.8%).

Methyl 3-(1-t-Butyldimethylsiloxy-1-methylethyl)-6-oxospiro[4.5]decane-7-carboxylate (12). Cyclohexanone **11** (1116 mg, 2.54 mmol) was combined with sodium chloride (160 mg, 2.74 mmol) and water (0.14 mL, 7.86 mmol) in 2 mL of DMSO along with a magnetic stir bar in a flask fitted with a reflux condensor. The reaction mixture was then heated at 150°C for 4.5h. The solution was poured into 50 mL of water and 10 mL of ether was added. The aqueous and organic layers were separated. The aqueous portion was extracted with ether (3x20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (7% ether/hexanes) yielding the desired product as an oil as a mixture of two diastereomers (785 mg, 81.1%): IR ($CHCl_3$, cm^{-1}) 2955, 2857, 1731, 1706, 1437, 1381, 1038; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H) [other diastereomer 0.05 (s, 6H)], 0.81 (s, 9H) [other diastereomer 0.86 (s, 9H)], 1.16 (s, 6H), 1.44-1.98 (m, 8H), 2.09 (dt, J=13.6, 3.4Hz, 1H), 2.32-2.64 (m, 4H), 2.84 (tt, J = 12.4, 3.4Hz, 1H), 3.70, (s, 3H) [other diastereomer 3.69 (s, 3H)]; HRMS calculated for $C_{20}H_{35}O_4Si$ (M-CH_3) 367.2305, found 367.2309. Anal. calculated for $C_{21}H_{38}O_4Si$: C, 65.97; H, 9.95. Found C, 65.94; H, 9.97.

Methyl 3-(1-t-Butyldimethylsiloxy-1-methylethyl)-6-hydroxy-6-methylspiro [4.5]decane-9-carboxylate (13). Methyl magnesium bromide 1.10 mL, 3.29 mmol, 3.0M in ether, 1.6 eq) was added dropwise to 4-carboxycyclo-hexanone **12** (785 mg, 2.05 mmol) in 60 mL of dry ether at 0°C under nitrogen. The reaction mixture was immediately warmed to room temperature and stirred for 1 h. The reaction was then quenched with water. The layers were separated and the aqueous layer was washed with ether (3 x 60 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (20% ether/hexanes) yielding the desired product as a mixture of two stereoisomers as a colorless oil (615 mg, 75.2%): IR ($CHCl_3$, cm^{-1}) 3910, 2955, 2929, 2857, 1728, 1463, 1380, 1254, 1035; ^1H NMR ($CDCl_3$) δ 0.07 (s, 3H) [other diastereomers 0.07 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H)], 0.86 (s, 9H), 1.19 (s, 6H) [other diastereomers 1.20 (s, 6H), 1.18 (s, 6H)], 1.27 (s, 3H) [other diastereomers 1.25 (s, 3H), 1.22 (s, 3H), 1.23 (s, 3H)], 1.10-1.95 (m, 13H), 2.51 (m, 1H), 3.64 (s, 3H) [other diastereomers 3.65 (s, 3H), 3.66 (s, 3H), 3.67 (s, 3H); HRMS calculated for $C_{21}H_{39}O_4Si$ (M-CH_3) 383.2618, found 383.2621. Anal. calculated for $C_{22}H_{42}O_4Si$: C, 66.33; H, 10.63. Found C, 66.35; H, 10.57.

Methyl 3-(1-t-Butyldimethylsiloxy-1-methylethyl)-6-methylspiro[4.5]dec-6-ene-9-carboxylate (14). Thionyl chloride (0.28 mL, 3.86 mmol, 2.5 eq) was added dropwise to alcohol **13** (615 mg, 1.54 mmol) and 4-dimethylaminopyridine (189 mg, 1.54 mmol) in 21 mL of pyridine at 0°C under nitrogen. The reaction mixture was stirred at 0°C and then allowed to warm to room temperature over 30 min. The reaction mixture was then refluxed for 2 h. After cooling to room temperature, the mixture was diluted with 40 mL of ether and poured into 40 mL of 5% HCl. The two phases were stirred vigorously for 15 min, then separated. The aqueous layer was extracted with ether (2 x 40 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (1% ether/hexanes) yielding the desired product as a yellow oil (423 mg, 72.1%): IR ($CHCl_3$, cm^{-1}) 2955, 2856, 1728, 1462, 1437, 1381, 1364, 1254, 1169, 1036; ^1H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H) [other diastereomer 0.87 (s, 9H)], 1.17 (s, 6H) [other diastereomer 1.18 (s, 6H)], 1.20-2.22 (m, 11H), 1.66 (s, 3H), 2.55 (m, 1H), 3.67 (s, 3H) [other diastereomers 3.66 (s, 3H), 3.68 (s, 3H)], 5.29 (broad s, 1H) [other diastereomers 5.33 (broad s, 1H), 5.38 (broad s, 1H); HRMS calculated for $C_{21}H_{37}O_3Si$ (M-CH_3) 365.2512, found 365.2509. Anal. calculated for $C_{22}H_{40}O_3Si$: C, 69.47; H, 10.53. Found C, 69.06; H, 10.48.

Methyl 3-(1-Hydroxy-1-methylethyl)-6-methylspiro[4.5]dec-6-en-4-one-9-carboxylate (15). Alkene **14** (423 mg, 1.11 mmol) was combined with celite (1350 mg) and 29 mL of benzene. At 5°C, pyridinium dichromate (8.38 g, 22.3 mmol, 20 eq) was added (as a solid) slowly and was immediately followed by the dropwise addition of t-butyl hydroperoxide (3.05 mL, 22.3 mmol, 20 eq, 70% in water). The reaction mixture was warmed to room temperature and stirred overnight. Following dilution with 30 mL of ether and an additional stirring period of 15 min, the reaction mixture was filtered through a 3 in column of celite. The solution was concentrated and then purified by column chromatography (10% ether/hexanes) yielding the starting material (94.8 mg, 22.4%) and the desired product as a pale yellow oil (207 mg, 47.2%): IR ($CHCl_3$, cm^{-1}) 2956, 2930, 2856, 1734, 1668, 1614, 1462, 1438, 1381, 1364, 1256, 1150, 1037; ^1H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.08 (s, 3H) [other diastereomers 0.08 (s, 3H), 0.09 (s, 3H)], 0.86 (s, 9H) [other diastereomer 0.85 (s, 9H)], 1.22 (s, 6H) [other diastereomer 1.20 (s, 6H)], 1.96 (d, J = 1.2Hz, 3H) [other diastereomer 1.94 (d, J = 1.2Hz, 3H)], 1.10-2.55 (m, 9H), 3.48 (m, 1H), 3.76 (s, 3H) [other diastereomer 3.75 (s, 3H)], 5.78 (d, J = 1.2Hz, 1H) [other diastereomers 5.80 (d, J = 1.2Hz, 1H), 5.68 (d, J = 1.2Hz, 1H)]; HRMS calculated for $C_{22}H_{38}O_4Si$ (M-CH_3) 394.2539, found 394.2544. Anal. calculated for $C_{23}H_{41}O_4Si$: C, 67,00; H, 9.64. Found C, 66.83; H, 9.72.

Methyl 3-Isopropylidene-1-methylethyl)-6-methylspiro[4.5]dec-6-en-4-one-9-carboxylate (16). Cyclohexenone **15** (105 mg, 0.27 mmol) was dissolved in 4 mL of CH_2Cl_2. Freshly distilled boron trifluoride etherate (0.49 mL, 4.00 mmol, 15 eq) was added dropwise with fuming. The reaction mixture was subsequently stirred for 3 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ and 5 mL of ether was added. The layers were separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (8% ether/hexanes) affording the desired product as a yellow oil (45.2 mg, 64.8%): IR ($CHCl_3$, cm^{-1}) 2958, 1737, 1668, 1615, 1438, 1262; ^1H NMR ($CDCl_3$) δ 1.57 (s, 3H), 1.60 (s, 3H) [other diastereomer 1.59 (s, 3H), 1.63 (s, 3H)], 1.94 (d, J = 1.2 Hz, 3H) [other diastereomer 1.95 (d, J = 1.2 Hz, 3H)], 1.61-2.68 (m, 8H), 3.48 (m, 1H), 3.76 (s, 3H) [other diastereomer 3.75 (s, 3H)], 5.88 (d, J = 1.21 Hz, 1H); HRMS calculated for $C_{16}H_{22}O_3$ 262.1569, found 262.1571.

Methyl 3-Isopropylidene-6-methylspiro[4.5]dec-6,9-dien-8-one-9-carboxylate (17). Enone **16** (45.2 mg, 0.17 mmol) was combined with 2,3-dichloro-2,3-dicyanobenzo-quinone (58.7 mg, 0.26 mmol, 1.5 eq) and 1.5 mL of benzene in a flask fitted with a reflux condensor. The orange mixture was refluxed for 5 h. After the reaction mixture was cooled to room temperature, 5 mL of ether was added. The solution was washed with 5% HCl (1 x 5 mL). The layers were separated and the aqueous layer was extracted with ether (2 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chroma-tography (35% ether/hexanes) affording the desired product as a pale yellow oil (29.7 mg, 66.2%): IR ($CHCl_3$, cm^{-1}) 2927, 2856, 1737, 1716, 1664, 1632, 1438, 1281; ^1H NMR ($CDCl_3$) δ 1.64 (s, 3H), 1.69 (s, 3H), 2.01 (d, J = 1.2 Hz, 3H), 1.71-2.68 (m, 6H), 3.85 (s, 3H), 6.21 (d, J = 1.2 Hz, 1H), 7.58 (s, 1H); HRMS calculated for $C_{16}H_{20}O_3$ 260.1412, found 260.1414. Anal. calculated for $C_{16}H_{20}O_3$: C, 73.85; H, 7.69. Found C, 73.49; H, 7.63.

Methyl 3-Isopropylidene-6,10-dimethylspiro[4.5]dec-6-en-8-one-9-carboxy-late (18). Dimethylcopperlithium (0.09 mmol, 3 eq) was generated by the addition of methyllithium (0.14 mL, 0.19 mmol, 1.4 M in ether) to copper iodide (18.0 mg, 0.09 mmol) in 1 mL of ether at 0°C. The colorless solution was cooled to -78°C and boron trifluoride etherate (0.01 mL, 0.09 mmol) was added dropwise. The reaction was then stirred for 15 min. Trienone **17** (8.2 mg, 0.03 mmol) in 0.5 mL of ether was subsequently added dropwise and the yellow solution was stirred at -78°C for 1.5 h. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous portion was extracted with ether (3 x 3 mL). The combined organic portions were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (20% ether/hexanes) yielding the desired product as a mixture of two diastereomers (1.7:1) as an oil: (7.1 mg, 81.4%): IR ($CHCl_3$, cm^{-1}) 2927, 2855, 1739, 1650, 1620, 1597, 1441, 1358, 1274; ^1H NMR ($CDCl_3$) δ 0.89 (d, J = 6.8 Hz, 3H) [other diastereomer (0.90 (d, J = 6.8 Hz, 3H)], 1.57 (s, 3H), 1.62 (s, 3H) [other diastereomer 1.63 (s, 3H), 1.67 (s, 3H)], 1.84 (s, 3H), 1.50-2.65 (m, 7H), 3.21 (dd, J = 13.6, 2.4 Hz, 1H), 3.76 (s, 3H), 5.72 (s, 1H); HRMS calculated for $C_{17}H_{24}O_3$ 276.1725, found 276.1728.

(±)-β-Vetivone (1). β-Keto ester **18** (7.1 mg, 0.02 mmol) was combined with sodium chloride (1.6 mg, 0.03 mmol) and water (0.001 mL, 0.08 mmol) in 0.03 mL of DMSO together with a magnetic stir bar in an ampule which was then evacuated and flame-sealed (by heating the neck of the ampule while applying a vacuum). It was then heated at 150°C for 4.5 h. The contents of the ampule was poured into 4 mL of water and 2 mL of ether was added. The aqueous and organic layers were separated. The aqueous portion was extracted with ether (3 x 2 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by column chroma-tography (15% ether/hexanes) affording β-vetivone and epi-β-vetivone (1.7:1) (4.3 mg, 77.1%): β-vetivone: IR ($CHCl_3$, cm^{-1}) 2980, 2756, 1660, 1615, 1435, 1378. ^1H NMR ($CDCl_3$) δ 0.97 (d, J=6.8 Hz, 3H), 1.63 (s, 3H), 1.67 (s, 3H), 1.89 (d, J=1.2 Hz, 3H) 1.90-2.70 (m, 9H), 5.79 (m, 1H); HRMS calculated for $C_{12}H_{22}O$ 218.1671, found 218.1667. And epi-β-vetivone: IR ($CHCl_3$, cm^{-1}) 2980, 2820, 1660, 1615, 1432, 1380. ^1H NMR ($CDCl_3$) δ 0.98 (d, J=6.8 Hz, 3H), 0.98 (s, 3H), 1.63 (s, 6H), 1.90 (d, J=1.2 Hz, 3H), 1.82-2.65 (m, 9H), 5.80 (m, 1H); HRMS calculated for $C_{12}H_{22}O$ 218.1671, found 218.1665.

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