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SYMMETRY IN RETROSYNTHETIC ANALYSIS: (±)-PENTALENOLACTONE E METHYL ESTER[1]

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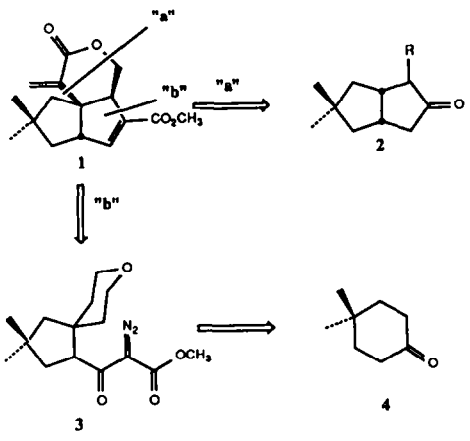
Abstract--A simple route to the sesquiterpene antibiotic pentalenolactone 3 has been established. Thus, spiroannulation of 4,4-dimethyl cyclohexanone with bis-(2-iodoethyl)ether, followed by diazo transfer and Wolff rearrangement, gives acid 6. Homologation to the corresponding β-ketoester, followed by diazo transfer and Rh-mediated intramolecular C-H insertion, then gives ester 8. Reduction of 8 followed by dehydration leads to the α,β unsaturated ester, which on exposure to CrO_3 in acetic acid is oxidized preferentially at the less hindered methylene. α-Methylenation then completes the synthesis of 1.

Scheme I

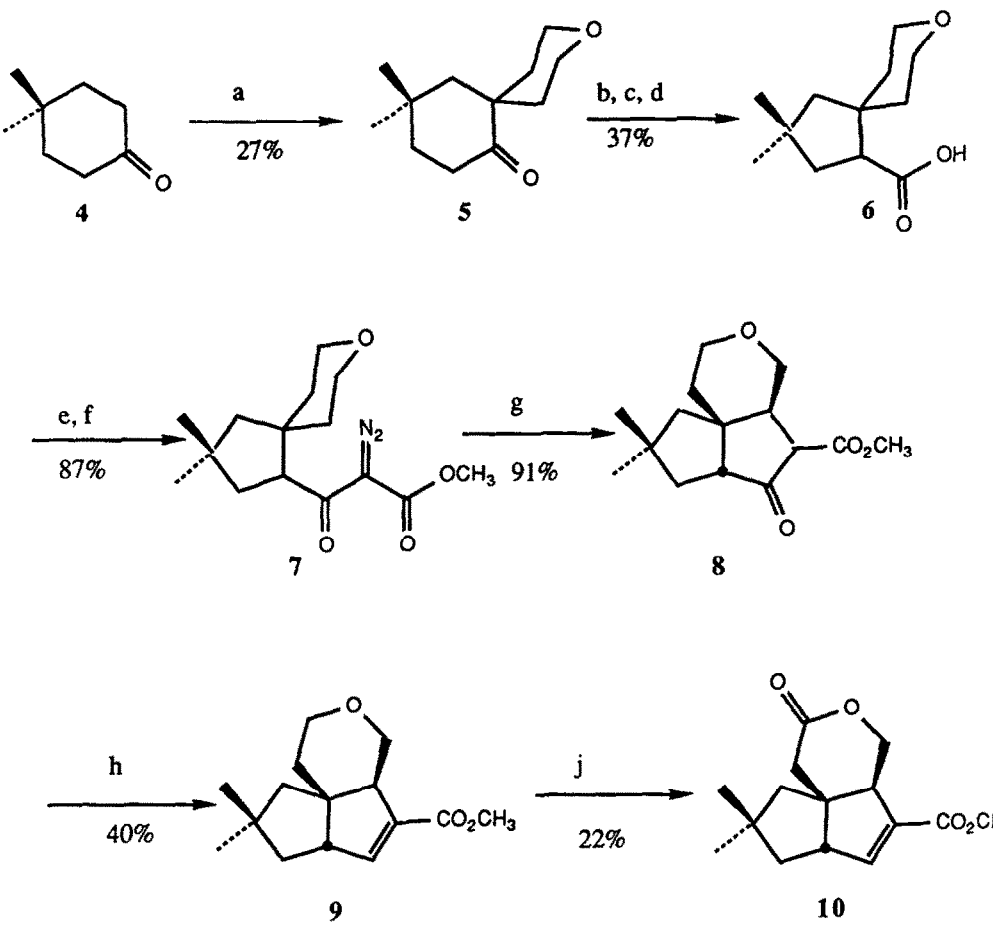


The discernment of masked symmetry can significantly simplify retrosynthetic planning. This principle is nicely illustrated by a synthetic route to the Streptomyces antibiotic pentalenolactone E 1[3] (Scheme I) recently developed[1] in our laboratory. Previous routes[4a,b] to 1 had been based on a retrosynthetic dissection at "a" (Scheme I) leading to a substituted bicyclo[3.3.0]octan-3-one such as 2. After a single carbon-carbon bond cleavage, following this analysis, the hypothetical precursor 2 retains three stereogenic centers, and is still a reasonably complex synthetic target. In the approach described herein, the discernment of masked symmetry in the course of an alternative retrosynthetic dissection allowed a more straightforward preparation of 1.

The first assistance from such hidden symmetry came on hypothetical scission at "b" (Scheme I). Using this approach, it was observed that after a single carbon-carbon bond cleavage, the putative (and actual, Scheme II) spiro precursor 3 would have only a single stereogenic center. Already, it was apparent that it might be easier to assemble 3 than 2.

On considering methods for retrosynthetic disassembly of 3, hidden symmetry again appeared. While 3 might have been prepared by direct homologation of the corresponding cyclopentanone, recognition that carbomethoxy-cyclopentanes can also be derived from the corresponding

Scheme II



4 5 6 7 8 9 10

(a) $(ICH_2CH_2)_2O$, NaH, THF, Δ; (b) trisyl azide, KOH, $PhCH_3$, PTC; (c) MeOH, hv; (d) LiOH, DME, Δ; (e) oxalyl chloride, $LiCH_2COOMe$; (f) TsN_3, Et_3N; (g) $Rh_2(OAc)_4$, CH_2Cl_2, room temperature; (h) $NaBH_4$, MeOH, 0° C, dicyclohexylcarbodiimide, Cu_2Cl_2, THF, Δ; (i) CrO_3, HOAc, CH_2Cl_2, room temperature.

cyclohexanone by carbonyl extrusion suggested a more pleasing precursor, the symmetrical 4,4-dimethyl cyclohexanone 4.

The requsite starting ketone is readily available by acid-catalyzed Robinson annulation of isobutyraldehyde,[5] to give 4,4-dimethyl cyclohexenone, followed by catalytic hydrogenation[6]. As spiroannulation of 4 involves the coupling of two symmetrical precursors, 4, and bis-(2-iodoethyl)ether[7],only one 1:1 product, 5, can be formed, and it still retains a plane of symmetry.

Operationally, ether 5 was separated from residual 4 and some bis-spiroannulated material by distillation. Carbonyl extrusion was then effected by diazo transfer,[8] followed by photolysis in methanol. Saponification[9] of the resultant ester gave a nicely crystalline acid, 6. Using this approach, multi-gram quantities of 6 could easily be prepared.

A variety of procedures for two-carbon homologation of an acid to the corresponding β-ketoester have been developed. In our hands, the method

of Rathke,[10] exposure of the acid chloride to an excess of lithio-methyl acetate, has proven the most efficient. Diazo transfer[11] then set the stage for intramolecular C-H insertion.

We had demonstrated[12] that Rh_2OAc_4-mediated intramolecular C-H insertion proceeded smoothly in acyclic cases, to give exclusively cyclopentane formation. The transition state for the cyclization of **7**, however, appeared significantly more strained. We were therefore gratified to find that on exposure to a catalytic amount of Rh_2OAc_4 in CH_2Cl_2, **7** indeed cyclized smoothly to **8**.

Reduction of **8**, followed by dehydration,[13] gave the α,β-unsaturated ester **9**. The seemingly trivial oxidation of the cyclic ether to the lactone then proved to be the most difficult step in the synthesis. The best reagent found was chromium trioxide in acetic acid,[14] which gave ether-to-lactone conversion in 30% yield,[14b] with a 3:1 preference for oxidation at the desired less hindered methylene. Lactone **10** so prepared was identical (TLC, ^1H NMR, IR) with authentic material.[4b] Methylenation to **1** had previously been demonstrated.[4]

It is apparent that discernment of masked symmetry can significantly simplify retrosynthetic analysis. The utility of the key reaction that made this analysis possible, Rh-mediated intramolecular C-H insertion, should also be apparent. Unlike most methods for ring construction, in which two functionalized carbon atoms are joined, intramolecular C-H insertion allows bond formation to an unfunctionalized carbon atom, generating a striking increase in molecular complexity[15] in a single step. Further investigations of the scope and limitations of this reaction are under way.

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EXPERIMENTAL

General Information: Melting points were obtained with a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Unicam SP 1100 spectrometer as solutions in CCl_4 with reference to the polystyrene absorption at 1601.4 cm^{-1}. ^1H NMR spectra were determined on a Bruker AM-250 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in parts per million downfield from the internal reference tetramethylsilane. Couplings (J) are in hertz. ^{13}C NMR spectra were obtained on a Bruker Spectrospin Model WM-250 at 62.9 MHz in $CDCl_3$ solution with shifts reported in parts per million downfield from Me_4Si. ^{13}C NMR multiplicities were assigned by an INEPT pulse sequence. These abbreviations are used for NMR multiplicities: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (dd) doublet of doublets, (dt) doublet of triplets. Mass

spectra (MS) and precise mass (by peak matching) were determined with a Du Pont 21-492-B spectrometer at 100 eV. Organic chemicals were purchased from Aldrich Chemical Co; n-butyllithium was purchased from Alfa Inorganics and titrated prior to use. Tetrahydrofuran (THF) was used immediately following distillation from sodium-benzophenone ketyl. Diisopropylamine and pyridine were dried by distillation from and storage over KOH pellets. Dry methylene chloride was filtered from anhydrous K_2CO_3. Other solvents--dimethoxyethane, acetonitrile, dimethylformamide--were stored over 4-Å molecular sieves. Solvent mixtures used for chromatography are volume/volume mixtures. The R_f values refer to thin-layer chromatography on Analtech 2.5 x 10 cm, 250-μm analytical plates coated with silica gel GF. Column chromatography on TLC-mesh silica gel (EM 7747) has been previously described.[16] Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Preparation of bis-(2-iodoethyl) ether: A modification of the literature method[7] was employed. Sodium iodide (225 g, 1.50 mol) and reagent-grade acetone (220 mL) were mechanically stirred under nitrogen in a three-necked flask equipped with a condenser. Bis-2-chloroethyl ether (71.5 g. 0.50 mol, 59 mL) was cautiously added, and the heterogeneous mixture was refluxed overnight (18 h). After cooling, the solution was filtered through Celite (10 g) and rinsed through with petroleum ether (200 mL). The filtrate was diluted with water (100 mL) and the layers were separated. The aqueous phase was extracted with petroleum ether (3 x 100 mL), and the combined organic layers were washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was vacuum distilled through a Vigreux column from copper bronze powder to obtain clear, colorless bis-(2-iodoethyl) ether (114 g, 70%) which was stored in the refrigerator over copper wire. Boiling range: 110-120° C (0.5 mm); literature[7]: 123-124° C (10 mm). 60 MHz ^1H NMR ($CDCl_3$) δ 3.60 (t, J = 6, 4H), 3.80 (t, J = 6, 4H).

Spiroannulation of 4: Sodium hydride (14.4 g of 50% suspension in mineral oil, 0.30 mol, 2.5 eq) was added to a flame-dried three-necked flask equipped with mechanical stirrer, condenser, addition funnel, and nitrogen inlet. Pentane (4 x 50 mL) followed by dry THF (50 mL) was used to rinse out the mineral oil. A fresh 50-mL portion of dry THF was added. 4,4-Dimethylcyclohexanone[5,6] (15 g, 0.12 mol) in dry THF (25 mL) was added in rapid drops over 5 min at 25° C. Bis-2-iodoethyl ether (43 g, 0.13 mol, 1.1 eq) was quickly added, and the mixture was slowly heated to 65° C. An exothermic reaction occurred, and external heating was discontinued. After 1-2 h of stirring at room temperature, the mixture was heated briefly (15 min) to reflux. TLC (silica gel; 8:2 hexane/ethyl acetate) indicated little remaining 4,4-dimethylcyclohexanone. The mixture was poured slowly into ice-water and extracted with petroleum ether (3 x 80 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), and concentrated in vacuo. Short-path fractional distillation gave 9.4 g of ~80% pure spiroketone 5 (boiling range 80-130° C at 1 mm) that was used without further purification.

A pure sample of 5 was obtained from an analogous experiment with 0.40 g of 4,4-dimethylcyclohexanone. After workup, the crude material was purified by TLC-mesh column

chromatography on silica gel (10 g) using 91:9 petroleum ether/ethyl acetate eluent. Spiroketone 5 (R_f 0.27 on silica gel; 8:2 hexane/ethyl acetate) was isolated as a colorless oil. Yield: 188 mg (30%). IR (CCl_4) 1710, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 6H), 1.50 (m, 2H), 1.65 (s, 2H), 1.75 (t, J = 7, 2H), 2.00 (dt, J = 14, 3.5, 2H), 2.45 (t, J = 7, 2H), 3.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 30.2 (q) (2), 30.9 (s), 35.5 (t), 35.6 (t) (2), 39.3 (t), 45.5 (s), 52.7 (t), 64.3 (t) (2), 216.4 (s); MS, m/e (relative intensity) 196 (M^+) (6), 195 (18), 153 (34), 139 (24), 109 (35), 97 (45), 96 (46), 83 (48), 69 (76), 55 (88), 43 (100); precise mass m/e 196.146 (calcd for $C_{12}H_{20}O_2$ m/e 196.146).

Preparation of 6: Spiroketone 5 (14 g of ~80% pure material, ~45 mmol) in toluene (50 mL) was added to a three-necked flask equipped with a wire propeller mechanical stirrer and nitrogen inlet. Following the procedure of Mander,[8] trisyl azide (10 g, 32 mmol), tetrabutylammonium bromide (3.5 g, 11 mmol), and 18-Crown-6 (0.40 g, 0.20 mmol) were added, followed by 66% aqueous KOH (150 mL). The two-phase mixture was stirred vigorously for 4 h at 40° C. Two additional 8.5-g portions of trisyl azide were added at 4-h intervals; virtually all of the spiroketone 5 reacted (TLC) within 12-16 h. The solution was cooled and the layers were separated. The aqueous phase was extracted with ether (3 x 75 mL). The combined organic layers were washed with water (40 mL), brine (40 mL), and dried ($MgSO_4$). Ether and toluene were removed in vacuo; toluene was stripped at low pressure (40° C, 1 mm). The crude α-diazoketone was used without further purification. TLC R_f 0.15 on silica gel; 8:2 hexane/ethyl acetate. Partial ^1H NMR ($CDCl_3$) δ 1.1 (s, 6H), 1.7 (s, 2H), 2.5 (s, 2H).

The crude α-diazoketone (~35 g of material) was dissolved in methanol (150 mL) and photolyzed[17] in a Pyrex Erlenmeyer flask at 300 nm for 48 h in a photochemical reaction chanber. TLC was used to follow the progress of the reaction, which was usually complete within 2-3 days. Methanol was removed in vacuo, and the crude methyl ester was used without purification.

An analytical sample of the methyl ester was obtained as follows. A sample of photolysis product (0.5 g) was purified using TLC-mesh column chromatography on silica gel (10 g) with 96.5:3.5 petroleum ether/ethyl acetate. The desired methyl ester (50 mg) was obtained as a colorless oil that was further purified by bulb-to-bulb distillation (Bp: 110-130° C, 1 mm). TLC R_f 0.35 on silica gel; 8:2 hexane/ethyl acetate; IR (CCl_4) 1740, 1170, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (s, 3H), 1.1 (s, 3H), 1.1-1.7 (m, 6H), 1.95 (t, J = 13, 1H), 2.15 (dt, J = 5, 13, 1H), 2.7 (dd, J = 6, 1H), 3.45 (m, 2H), 3.7 (s, 3H), 3.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.5 (q), 31.3 (q), 34.9 (t), 37.2 (s), 39.1 (t), 42.1 (t), 43.9 (s), 50.4 (t), 51.4 (d), 54.9 (q), 64.6 (t), 65.9 (t), 174.0 (s); MS, m/e (relative intensity) 226 (M^+) (52), 167 (93), 166 (71), 151 (100), 149 (71), 123 (82), 121 (78), 107 (80), 83 (80), 55 (75), 41 (79); precise mass m/e 226.156 (calcd for $C_{13}H_{22}O_3$ m/e 226.157).

The crude methyl ester (~35 g) was heated to reflux with 3.5 M lithium hydroxide (50 mL, 0.17 mol) in dimethoxyethane (70 mL) for 48 h. TLC indicated that complete conversion of methyl ester occurred. The layers were separated. The aqueous layer was extracted with ether (2 x 30 mL) to remove neutral impurities, then acidified with 6 N HCl (20 mL). Upon cooling to 0° C, carboxylic acid 6 crystallized from the aqueous layer. Yield: 3.4 g (10%

from 4,4-dimethylcyclohexanone). Recrystallization from 1:1 methanol/water (40 mL) gave fine white crystals (mp: 151-152° C). TLC R_f 0.30 on silica gel; 75:25 hexane/acetone IR (CCl_4) 3500-2700, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (s, 3H), 1.1 (s, 3H), 1.35 (t, J = 14, 2H), 1.5-1.7 (m, 2H), 1.7 (t, J = 13, 2H), 1.9 (t, J = 13, 1H), 2.2 (dt, J = 7, 14, 1H), 2.7 (dd, J = 7, 1H), 3.4 (q, J = 11, 2H), 3.8 (m, 2H); ^{13}C NMR ($CDCl_3$ δ 30.7 (q), 31.4 (q), 34.4 (t), 37.1 (s), 38.8 (t), 41.8 (t), 43.9 (s), 50.3 (t), 54.7 (d), 64.5 (t), 65.9 (t), 178.3 (s); MS, m/e (relative intensity) 212 (M^+) (60), 194 (72), 166 (91), 153 (78), 151 (93), 123 (76), 107 (85), 95 (74), 93 (70), 83 (100), 81 (79), 79 (68), 69 (76), 55 (94), 41 (96); precise mass m/e 212.142 (calcd for $C_{12}H_{20}O_3$ m/e 212.1412). Anal. calcd for $C_{12}H_{20}O_3$: C 67.89 H 9.50. Found C 67.69 H 9.44.

Preparation of α-diazo-β-ketoester 7: Carboxylic acid 6 (1.0 g, 4.7 mmol) was dissolved in dry methylene chloride (20 mL) and dimethylformamide (~7 drops). Oxalyl chloride (1.27 g, 10 mmol, 0.87 mL) was added to the magnetically stirred solution under nitrogen dropwise at 0° C. The mixture was allowed to stir at room temperature for 1 h while acetate anion was prepared.[9] Lithium diisopropylamide (LDA) was prepared by dropwise addition of n-butyllithium (13 mL of 2.35 M solution in hexane, 30.6 mmol) to diisopropylamine (3.03 g, 30 mmol, 4.2 mL) in dry THF (5 mL) at -10° C over 5 min. Methyl acetate (1.11 g, 15 mmol, 1.2 mL) in dry THF (2 mL) was added dropwise to the stirred LDA solution at -60° C. Methylene chloride and oxalyl chloride (excess) were removed in vacuo (1 mm) from the acid chloride. The solid residue was dissolved in dry THF (10 mL) and added immediately to the acetate anion solution over 3 min, at -60° C. TLC showed that conversion to a single UV-active product occurred almost instantly (R_f 0.25 on silica gel; 8:2 hexane/ethyl acetate). Ice (~5 g) and 6 N HCl (15 mL) were added to give two clear layers which were separated and concentrated using a rotary evaporator. The layers were recombined and extracted with ether (3 x 50 mL). The combined ether layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), and dried ($MgSO_4$). Removal of solvent gave 1.0 g of the β-ketoester which was used without further purification. Partial ^1H NMR ($CDCl_3$) 1.0 (s, 3H), 1.1 (s, 3H), 3.5 (s, 2H), 3.75 (2 singlets, 3H).

The crude β-ketoester (1.0 g 4.4 mmol) was dissolved in dry acetonitrile (20 mL). Tosyl azide[11] (1.0 g, 5.1 mmol) and triethylamine (0.95 g, 9.4 mmol) were added, and the solution was magnetically stirred under nitrogen at 25° C for 18 h. The reaction mixture was diluted with ether (50 mL) and washed with 10% aqueous NaOH (20 mL), brine (20 mL), and dried ($MgSO_4$). Solvents were removed in vacuo. TLC-mesh column chromatography on silica gel (40 g) with 9:1 petroleum ether/ethyl acetate eluent was used to separate unreacted tosyl azide from the desired α-diazoester 7, a white crystalline solid. Yield: 1.20 g (87% from acid 6). mp: 90-92° C (d). TLC R_f 0.25 on silica gel; 8:2 hexane/ethyl acetate. IR (CCl_4) 2140, 1725, 1650 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.05 (s, 3H), 1.10 (s, 3H), 1.40 (m, 2H), 1.55 (d, J = 5.5, 1H), 1.62 (s, 2H), 1.72 (d, J = 13, 2H), 1.8 (dt, J = 5.5, 13, 1H), 2.05 (t, J = 13, 1H), 3.42 (m, 2H), 3.75 (m, 1H), 3.8 (s, 3H), 4.15 (q, J = 6, 1H), ^{13}C NMR ($CDCl_3$) δ 30.9 (q), 31.3 (q), 35.2 (t), 37.2 (s), 39.6 (t), 42.6 (t), 45.9 (s), 50.7 (t), 52.1 (d), 55.3 (q), 64.9 (t), 65.8 (t), 77.4 (s), 162.0 (s), 193.3 (s); MS, m/e (relative intensity) 266 (M^+-N_2) (5), 238 (18), 165 (32), 151 (26), 137 (100), 135 (63), 123 (32), 121 (28), 109 (33), 105 (45), 81 (99), 55

(86); MS (chemical ionization using 1% NH_3/CH_4 and direct insertion probe at 170° C) 312 (21) ($M^+ + NH_4$), 296 (32), 295 (100), 267 (38), 249 (13), 235 (14), 212 (15), 195 (26), 179 (15), 165 (12), 151 (11); precise mass m/e 294.158 (calcd for $C_{15}H_{22}N_2O_4$ m/e 294.158).

Cyclization of α-diazoester 7 with rhodium acetate: Rhodium acetate (30 mg, 0.068 mmol) was added to a magnetically stirred solution of α-diazoester 7 (1.20 g, 4.12 mmol) in dry methylene chloride (25 mL) under nitrogen at 25° C. After 3 h, TLC showed complete conversion to a single, more polar, UV-active product. Methylene chloride was removed in vacuo. TLC-mesh column chromatography on silica gel (35 g) with 85:15 petroleum ether/ethyl acetate yielded the tricyclic β-ketoester 8 as a colorless oil. Yield: 993 mg (91%). TLC R_f 0.21 on silica gel; 8:2 hexane/ethyl acetate. IR (CCl_4) 1760, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.10 (s, 3H), 1.4-1.8 (m, 6H), 2.30 (d, J = 13, 1H), 2.65 (dd, J = 11, 12, 1H), 3.27 (dt, J = 2.4, 12, 1H), 3.65-3.9 (m, 4H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 29.3 (q), 30.1 (q), 35.3 (t), 41.9 (t), 42.9 (s), 45.0 (d), 46.5 (s), 52.4 (t), 52.5 (d), 57.5 (d), 61.6 (q), 64.8 (t), 65.7 (t), 169.3 (s), 211.3 (s); MS, m/e (relative intensity) 266 (M^+) (20), 235 (29), 234 (39), 221 (19), 206 (24), 165 (21), 150 (31), 137 (100), 135 (53), 81 (95), 79 (56), 55 (65); precise mass m/e 266.153 (calcd for $C_{15}H_{22}O_4$ m/e 266.1518).

Preparation of α,β-unsaturated ester 9: Sodium borohydride (75 mg. 2.0 mmol) was added in portions to a magnetically stirred solution of tricyclic β-ketoester 8 (150 mg, 0.56 mmol) in methanol (4 mL) at -15° C (dry ice/brine bath). TLC indicated complete conversion to two UV-inactive products (TLC R_f 0.25 and 0.16 on silica gel; 7:3 hexane/ethyl acetate) within 10 min. Water (1 mL) and 6 N HCl (4 mL) were added, and the solution was extracted with methylene chloride (4 x 5 mL). The combined CH_2Cl_2 layers were dried (K_2CO_3) and evaporated to give 145 mg of the crude diastereomeric β-hydroxyesters, IR (CCl_4) 3510, 1745, 1735 cm^{-1}.

The crude β-hydroxyester mixture (145 mg, ~0.55 mmol) was combined with dicyclohexylcarbodiimide[13] (250 mg, 1.2 mmol, 2 eq) and cuprous chloride (5 mg, 0.03 mmol) in dry THF (5 mL) and refluxed for 18 h. TLC showed disappearance of both hydroxyesters in favor of a single UV-active product (TLC R_f 0.50 on silica gel; 7:3 hexane/ethyl acetate). Water was added, and undissolved solids were removed by suction filtration. The residue was washed with ether (3 x 10 mL). The aqueous phase was extracted with ether (3 x 5 mL), and the combined organic portions were dried ($MgSO_4$) and concentrated in vacuo. TLC-mesh column chromatography on silica gel (5 g) with 9:1 petroleum ether/ethyl acetate eluent gave α,β-unsaturated ester 9. Yield: 56 mg (40% from 10). IR (CCl_4) 1725, 1630 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.1 (s, 3H), 1.2-1.9 (m, 6H), 2.8 (m, 1H), 3.05 (m, 1H), 3.5 (m, 2H), 3.75 (s, 3H), 3.75 (m, 1H), 4.0 (q, J = 6, 1H), 6.8 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.1 (q), 31.4 (q), 34.7 (t), 39.7 (s), 44.5 (t), 50.8 (d), 51.3 (d), 51.7 (s), 54.7 (q), 55.5 (t), 64.7 (t), 67.8 (t), 135.4 (s), 149.1 (d), 165.4 (s); MS, m/e (relative intensity) 250 (M^+) (4), 219 (30), 218 (100), 192 (23), 150 (24), 145 (27), 136 (56), 133 (30), 105 (81), 91 (51, 77 (36); precise mass m/e 250.157 (calcd for $C_{15}H_{22}O_3$ m/e 250.157).

Oxidation of cyclic ether 9 to lactone 10: Chromium trioxide[14] (200 mg, 2.0 mmol) was added

in portions to a magnetically stirred solution of cyclic ether 9 (75 mg, 0.30 mmol) in glacial acetic acid (0.30 mL) and methylene chloride (2 mL) at room temperature. TLC showed that no starting material remained after 1 h. Ice-water (3 mL) and CH_2Cl_2 (5 mL) were added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic portions were washed with 10% $NaHCO_3$ (10 mL) and dried ($MgSO_4$). Methylene chloride was removed in vacuo. TLC-mesh column chromatography on silica gel (2 g) with 9:1 petroleum ether/acetone yielded 17 mg (22%) of the desired lactone 10 (R_f 0.26 on silica gel; 7:3 hexane/ethyl acetate). Lactone 10 gave IR and ^1H NMR data identical to that previously reported by Cane.[5] ^{13}C NMR ($CDCl_3$) δ 29.1 (q), 29.5 (q), 40.7 (s), 42.1 (t), 45.9 (t), 51.7 (d), 51.8 (s), 53.5 (d), 56.4 (t), 58.2 (q), 67.8 (t), 131.6 (s), 150.3 (d), 164.6 (s), 172.6 (s); MS, m/e (relative intensity 264 (M^+) (17), 233 (22), 232 (32), 205 (46), 192 (100), 177 (31), 136 (82), 133 (32), 105 (51), 91 (40), 77 (29), 55 (34); precise mass m/e 264.136 (calcd for $C_{15}H_{20}O_4$ m/e 264.136).

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