Radical-Mediated Construction of Cyclopentane with Concurrent Formation of a Well-Defined Quaternary Center

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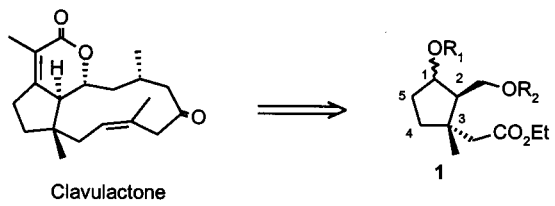
Synthetic efforts toward the total synthesis of clavulactone dealing with enantioselective construction of the cyclopentane moiety are reported. With a novel radical-mediated cyclization as key step, the current approach allows for concurrent enantioselective construction of a quaternary chiral carbon at the cyclization step. The stereochemistries of the newly formed chiral centers are dictated by the configuration of the C-1 (cf. numbering in **1**). The high selectivity observed in this work is ascribed to the conformational advantage of the cyclic acetal, which results in a much better defined transition state than the previously used open-chain counterpart does.

Clavulactone, isolated and structurally elucidated first by us[1] and later by Su[2] et al., is a member of the naturally occurring marine diterpene dolabellane[3] compounds, which are characterized by an unusual *trans*-bicyclo-[9.3.0]tetradecane nucleus. Because of their remarkable bioactivities[4] and unique skeleton, this class of compounds has attracted[5] synthetic organic chemists' interests over the last 5 years. Our initial effort toward the total synthesis of clavulactone was based on the strategy of developing a general method for the construction of the skeleton of this type of compounds. We envisaged that the trisubstituted cyclopentane segment **1** (Scheme 1), with a quaternary center established at an early stage of the synthesis, could be a key intermediate common to many dolabellanes and other naturally occurring compounds containing a similar segment.

In last two decades, organic chemists have witnessed[6] the prosperity of organic free radical chemistry, which is now widely employed in the formation of C−C bonds due to its high chemo-, regeio-, and stereoselectivity and the advantage that the reaction can be carried out under neutral conditions. Its superiority over carbanion or carbocation methodologies is obvious, especially in construction of sterically congested structures such as quaternary and neopentyl centers or the fused rings. Although radical-mediated syntheses[7] of functionalized cyclopentanes using carbohydrates as starting material often appear in the literature, to the best of our knowledge none of them allows for stereoselective construction of a quaternary center in the radical-mediated cyclization leading to cyclopentane framework. In this paper we wish to disclose a chiron approach to multifunctionalized cyclopentanes with stereoselective construction of a quaternary carbon as the key step.

Scheme 1



The synthesis starts from D-glucose (Scheme 2). Ferrier rearrangement[8] gave product **2**, from which after steps of transformations the radical precursor **8** was obtained in moderate to good yields. The radical-mediated cyclization was carried out to afford the diastereomers **9a**, **9b**, and **9c** in a ratio of 24:53:18 in 95% total yield after careful column chromatography on silica gel. Another isomer **9d** was not found in the reaction mixture. Because the absolute configuration of C_1 was retained from natural glucose, the stereochemistries of these diastereomers were established by $^1H-^1H$ COSY and $^1H-^1H$ NOESY spectroscopy.

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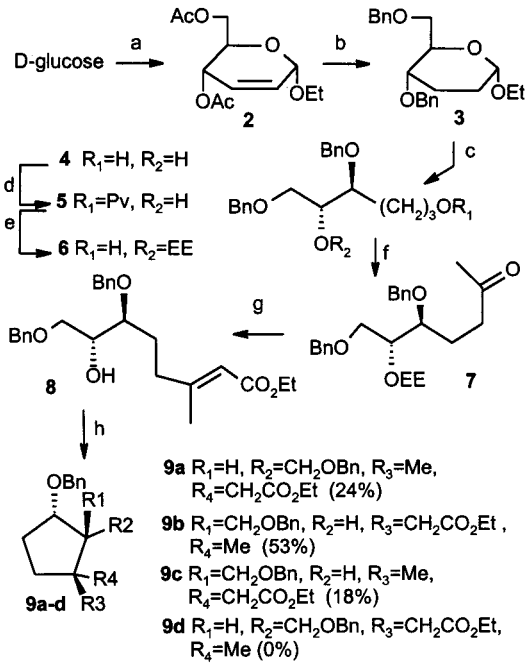
Scheme 2[a]

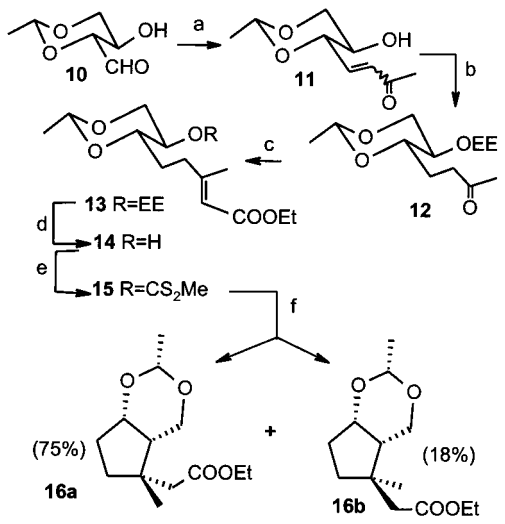


[a] Reaction conditions: (a) MeOH−Et_3N−H_2O; H_2, Pd/C; BnBr, NaH, DMF, 80%; (b) aqueous HCl−HOAc, 95 °C; $NaBH_4$, MeOH, 0 °C, 89%; (c) PvCl, Py, CH_2Cl_2, rt, 24 h, 95%; (d) ethyl vinyl ether, PPTS, CH_2Cl_2; MeLi, ether, rt, 95%; (e) Swern oxidation; MeLi, ether; Swern oxidation, 55%; (f) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, reflux; aqueous HCl−THF, 74%; (g) DBU, CS_2, MeI, DMF, 87%, Bu_3SnH, AIBN, reflux, 94%.

The stereoselectivity is consistent with Beckwith's[9] transition-state model. The two newly formed chiral centers in the major products **9a** and **9b** are in an unwanted cis arrangement, whereas the desired product **9c** is obtained only in 18% yield, presumably due to the flexibility of the chain radical reaction precursor, which allows for several possible approaches for the radical to attack the double bond. Later, we tried to protect the 1,3-dihydroxyl functionality by forming a cyclic acetal with paraldehyde. This was expected to lead to a more rigid (Scheme 3) transition state during the radical cyclization. Thus 2,4-*O*-ethylidene-D-erythrose **10** was prepared according to known[10] methods. Wittig reaction of **10** with triphenylphosphoranylideneacetone provided unsaturated ketone **11**. The radical precursor **15** was prepared in 5 steps using common transformations in good to excellent yields. Two diastereomers **16a** and **16b** were easily isolated by column chromatography on silica gel after radical cyclization in 75% and 18% yields, respectively. The diastereoselectivity was apparently improved. The absolute configuration of the quaternary center in **16a** was also correctly established. However, another newly formed chiral center was of undesired configuration. In fact the two rings are always cis fused, so that the vicinal configuration is only decided by the hydroxyl configuration at C-1.

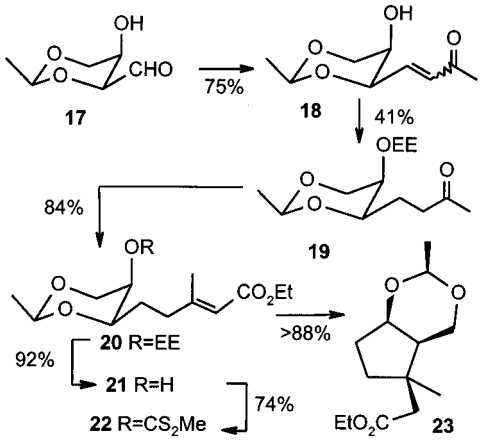
We chose D-galactose as the starting material (Scheme 4); the configuration of the 4-hydroxyl is opposite to that in D-glucose. 2,4-*O*-Ethylidene-D-threose **17** was trans-

Scheme 3[a]



[a] Reaction conditions: (a) $Ph_3P{=}CHCOCH_3$, THF, rt, 45%; (b) H_2/Pd, MeOH; ethyl vinyl ether, PPTS, CH_2Cl_2, 2 steps, 86%; (c) $(C_2H_5O)_2P(O)CH_2CO_2Et$, NaH, THF; (d) 1 N HCl, THF, 2 steps, 77%; (e) CS_2, DBU, MeI, DMF, 93%; (f) Bu_3SnH, AIBN, benzene, reflux, 93%.

Scheme 4



formed according to literature[11] procedures. Except for hydrogenation of **18** and the following hydroxyl protection as the vinyl ethyl ether, moderate to good yields were obtained when similar reaction conditions were applied. The unexpected poor yields were due to incomplete reactions and formation of unidentified byproducts, probably because the hydroxyl group was in the axial position in the chairlike conformation of the 1,3-dioxane. The result of the radical cyclization was very surprising; only one product was isolated and the yield was over 88%! The good selectivity and yield are quite unusual in radical chemistry. Although the two side chains are still cis (instead of trans as we wished) to each other and with the quaternary center of undesired configuration, it should have great potential in asymmetric synthesis of some other target molecules.

On the basis of the results of the two routes, possible transition states were postulated to explain the high stereoselectivity and the difference between them. As we know, the transition state of the radical reaction is early, reactant-like because of the high reactivity of radical. The

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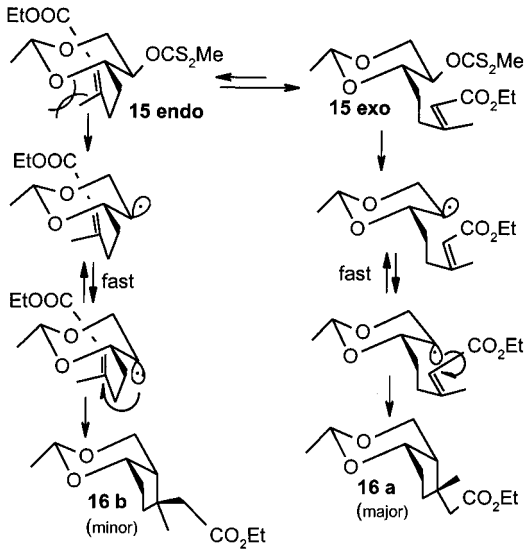
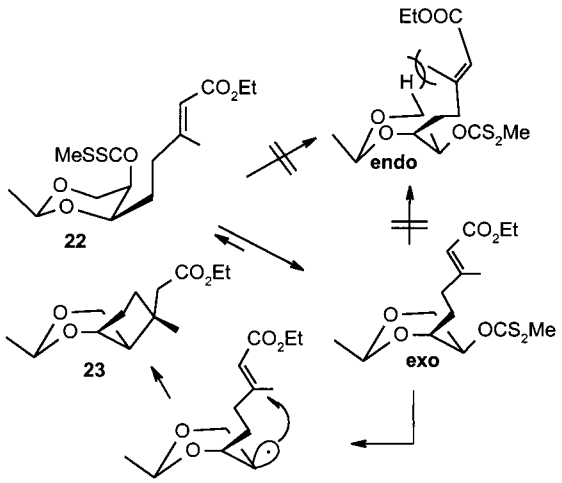
Scheme 5



Scheme 6



α,β-unsaturated ester of **15** has two possible conformations relative to the chairlike 1,3-dioxane, endo and exo. In the endo conformation, the vinyl methyl and the 1,3-dioxygen atoms have spatial repulsion, thereby favoring exo conformation, which results in **16a** as the major product (Scheme 5).

The situation in **22** is quite different. The thioester group is probably too bulky to be in the axial position. It is more likely that the 1,3-dioxane now assumes a boat-like conformation. In this case, the endo conformation is highly disfavored because of the strong steric interaction between the vinyl methyl and the hydrogen atom. Such an interaction can be avoided in the exo conformation, which results in product **23** only (Scheme 6).

It appears that making the chain conformation more rigid by protecting the chain as a cyclic acetal is an effective way to enhance the stereoselectivity at the radical cyclization step. This effect is fully manifested in the D-galactose case, where practically only one isomer is formed. Although the latter two approaches of the three we have examined afforded products with only one of the two newly formed chiral centers in the desired configuration, compound **16a** and its enantiomer **23** can serve as very useful building blocks for other synthetic targets. Based on the knowledge gained from this work, especially the possible transition states, we are able to design better precursors (with two correct chiral centers) to the desired product.

Experimental Section

General. Melting points are uncorrected. Flash column chromatography was performed on silica gel H (10−40 μm) and with a petroleum ethe−ethyl acetate system as eluant. Microanalyses were carried out in the Microanalytical Laboratory at Shanghai Institute of Organic Chemistry.

(2*R*,3*S*,6*S*)-6-Ethoxy-3-phenylmethoxy-2-phenylmethoxymethyltetrahydropyran (3). To a solution of triacetyl glycal (81.6 g 0.30 mol) in benzene (280 mL) were added absolute ethanol (30 mL) and $BF_3{\cdot}Et_2O$ (12.1 mL).[8] The reaction mixture was stirred at 35 °C for 2.5 h. Anhydrous sodium carbonate (27 g) was added, and the stirring was continued for an additional 0.5 h. The reaction mixture was filtered and concentrated under reduced pressure to give **2**. Methanol (650 mL), triethylamine (180 mL), and water (320 mL) were added to the residue, and the mixture was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure with addition of toluene (200 mL × 4). To the solution of the resulting residue in ethyl acetate (500 mL) was added Pd/C (5%, 1.0 g). The mixture was treated with atmospheric hydrogen at room temperature until no more hydrogen was consumed. The catalyst was filtered off, and the solvent was removed under reduced pressure. DMF (200 mL) was added to the residue, followed by a suspension of NaH (80%, 21.6 g) in DMF (300 mL) at 0 °C. When the evolution of hydrogen stopped, a solution of benzyl bromide (85 mL 0.66 mol) in DMF (100 mL) was added dropwise and the mixture was stirred overnight. The reaction mixture was poured into water, extracted with ethyl ether, washed with water and brine, dried (Na_2SO_4), and then concentrated. Triethylamine (100 mL) was added to the residue, and the mixture was heated to reflux for 1 h to destroy excess benzyl bromide. The cooled reaction mixture was diluted with ethyl ether, washed with water and brine, dried (Na_2SO_4), and concentrated to give light yellow liquid **3** (85 g, 80% from triacetyl D-glycal): $[\alpha]^{20}_D$ +101.3 (*c* 0.99, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): 7.21−7.36 (m, 10H), 4.84 (d, 1H, J = 2.9 Hz), 4.40−4.70 (m, 4H), 3.76 (d, 2H, J = 6.0 Hz), 3.69 (q, 2H, J = 7.1 Hz), 3.44−3.49 (m, 2H), 1.80−2.00 (m, 4H), 1.21 (t, 3H, J = 7.1 Hz). IR (film): 2950, 2850, 1455, 1130, 1090, 1060, 1030, 990, 740, 700 cm^{-1}. EIMS: 255 (M − CH_2Ph), 236, 219, 149, 129, 115, 105, 91.

(2*R*,3*S*)-1,3-Diphenylmethoxy-2,6-hexanediol (4). A solution containing **3** (85 g 0.24 mol), acetic acid (800 mL), and 1 N HCl (200 mL) was heated under reflux for 3 h before being cooled, extracted with CH_2Cl_2, washed with water, saturated aqueous $NaHCO_3$ and brine, and dried ($CaCl_2$). Removal of the solvent under reduced pressure and flash chromatography on silica gel gave the product and a small amount of recovered reactant. The above procedure was repeated to give combined product (61.8 g, 79%) after one cycle. To the solution of the above product in methanol (500 mL) was added sodium borohydride (30 g) at 0 °C. Stirring was continued for 2 h before being quenched by adding diluted HCl. The mixture was extracted with CH_2Cl_2 and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (1:1 petroleum ether/EtOAc) gave **4** (55 g, 89%): $[\alpha]^{20}_D$ +9.6 (*c* 0.40, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.27−7.36 (m, 10H), 4.56, 4.55 (s, s; 2H, 2H), 3.91 (m, 1H), 3.67−3.53 (m, 5H), 2.00 (s, 2H), 1.68−1.76 (m, 4H). IR (film): 3400, 1080, 740, 700 cm^{-1}. EIMS: 331 (M + 1), 221, 181, 179, 133, 107, 91, 71.

(2*R*,3*S*)-2-(1-Ethoxyethoxy)-1,3-diphenylmethoxy-6-hexanol (6). To a solution of **4** (55 g, 0.15 mol) in CH_2Cl_2 (200 mL) were added pyridine (18 mL, 0.23 mol) and PvCl (22.7 mL, 0.19 mol). The reaction mixture was stirred for 24 h and then quenched by addition of 1 N HCl (100 mL). The mixture was washed with saturated aqueous $NaHCO_3$ and brine and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was dissovled in CH_2Cl_2 (500 mL). Ethyl vinyl ether (30 mL, 0.31 mol) and PPTS

(200 mg) were added at 0 °C. The solution was warmed to room temperature and stirred for 3 h. The reaction mixture was washed with brine, dried ($MgSO_4$), and then concentrated under reduced pressure. To the solution of the residue in ethyl ether (500 mL) was added dropwise methyllithium (180 mL, 1.68 M, 0.30 mol) at −78 °C with vigorous mechanical stirring. The reaction mixture was stirred at this temperature for 3 h and then allowed to warm to room temperature. The solution was washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (3:1 petroleum ether/EtOAc) gave **6** (51 g, 85% from **4**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27−7.33 (m, 10H), 4.86 (m, 3/8 H), 4.64−4.68 (m, 5/8 H), 4.55 (m, 4H), 3.91 (m, 1H), 3.45−3.73 (m, 7H), 1.62−1.76 (m, 5H), 1.11−1.36 (m, 6H). IR (film, neat): 3400, 1080, 740, 700 cm^{-1}. EIMS: 181, 167, 149), 133, 115, 107, 105, 91. Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.51; H, 8.72.

(5*S*,6*R*)-6-(1-Ethoxyethoxy)-5,7-diphenylmethoxy-2-heptanone (7). A solution of oxalyl chloride (14.5 mL, 0.166 mol) in dry CH_2Cl_2 (100 mL) was cooled to −60 °C before a solution of DMSO (22.5 mL, 0.31 mol) in dry CH_2Cl_2 (60 mL) was introduced slowly. After stirring for 30 min, a solution of **6** in dry CH_2Cl_2 (100 mL) was added dropwise. The mixture was stirred at −60 °C for 2 h. A solution of triethylamine (100 mL) in CH_2Cl_2 (100 mL) was added. The reaction mixture was allowed to warm to room temperature slowly and stirred for an additional 2 h before being poured into water (200 mL), washed with saturated a NH_4Cl solution and brine, dried (Na_2SO_4), and evaporated to give the crude aldehyde. To a solution of the aldehyde in diethyl ether (200 mL) was added methyllithium (110 mL, 1.68 M) at 0 °C with vigorous stirring. The solution was stirred for 2 h and quenched by addition of a saturated NH_4Cl solution (100 mL). The mixture was washed with brine and dried (Na_2SO_4). After removal of the solvent, the residue was subjected to Swern oxidation again as described above. After purification by flash chromatography on silica gel (5:1 petroleum ether/EtOAc), **7** (28.6 g, 55% from **6**) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27−7.33 (m, 10H), 4.87 (m, 1H), 4.41−4.65 (m, 4H), 3.92 (m, 1H), 3.45−3.72 (m, 5H), 2.50 (m, 2H), 2.04 (d, 3H, J = 3.5 Hz), 1.83 (m, 2H), 1.32 (m, 3H), 1.14 (q, 3H, J = 7.0 Hz). IR (film, neat): 1715, 1080, 740, 700 cm^{-1}. EIMS: 325 (M − CH_2Ph), 191, 233, 181, 112, 107, 105, 91. Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.09; H, 8.71. Found: C, 72.40; H, 8.47.

(6*S*,7*R*,*E*)-7-Hydroxy-3-methyl-6,8-diphenylmethoxy-2-octenoic Acid Ethyl Ester (8). To the suspension of NaH (4.2 g, 80%, 0.14mol) in THF (50 mL) was added a solution of triethyl phosphonoacetate (28 mL, 0.14 mol) in THF (50 mL) dropwise at 0 °C. The mixture was stirred until it turned transparent. A solution of **7** (28.3 g) in THF (100 mL) was added, and the stirring was continued for an additional 48 h at room temperature. The reaction mixture was diluted with diethyl ether, washed with water and brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (10:1 petroleum ether/EtOAc) gave a light yellow liquid, which was dissolved in THF (100 mL) and then treated with 1 N HCl (150 mL). The solution was stirred at room temperature for 6 h, before being diluted with diethyl ether. The ether layer was washed with a saturated $NaHCO_3$ solution and brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (5:1 petroleum ether/EtOAc) gave a colorless liquid, 18.4 g (74%): $[\alpha]^{20}_D$ 4.87 (*c* 0.60, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 10H), 5.65 (d, 1H, J = 1.0 Hz), 4.54 (m, 4H), 4.13 (q, 2H, J = 7.1 Hz), 3.89 (m, 1H), 3.61 (m, 2H), 3.50 (m, 1H), 2.28 (m, 2H), 2.16 (bs, 1H), 2.14 (d, 3H, J = 1.0 Hz), 1.78 (m, 2H), 1.29 (t, 3H, J = 7.1 Hz). IR (film, neat): 1710, 1640, 1100, 740, 700 cm^{-1}. EIMS: 413 (M + 1), 367, 275, 215, 181, 169, 125, 91. Anal. Caldcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 73.08; H, 7.83. (Characterization of other minor components in the product mixture was not attempted.)

1-Methyl-3-phenylmethoxy-2-phenylmethoxymethylcyclopentaneacetic Acid Ethyl Ester (9). To a solution of the above alcohol (18.0 g, 43.7 mmol) in DMF (100 mL) were added CS_2 (21 mL) and DBU (14.0 mL, 87.4 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred for 2 h before the addition of MeI (22 mL) at 0 °C. The reaction mixture was stirred at room temperature for an additional hour, followed by addition of 1 N HCl (100 mL), extracted with diethyl ether, washed with water and brine, and then dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (20:1 petroleum ether/EtOAc) gave a light yellow liquid, 19.1 g (87%). To the solution of the thioester (19.1 g) and AIBN (160 mg) in benzene (300 mL) was added dropwise a solution of Bu_3SnH (15.8 mL, 57 mmol) in benzene (50 mL) under reflux. The reaction was cooled after refluxing for 3 h. A saturated KF solution (50 mL) was added, and the mixture was stirred for another 2 h. The reaction mixture was extracted with diethyl ether, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography on silica gel of the residue (40:1 petroleum ether/EtOAc) gave **9a** (3.67 g, 24%), **9b** (7.98 g, 53%), and **9c** (2.75 g, 18%).

(1*S*,2*S*,3*S*)-9 (9a): $[\alpha]^{20}_D$ +32.4 (*c* 0.82, $CHCl_3$). ^{1}H NMR (600 MHz,$CDCl_3$): δ 7.28−7.31 (m, 10H), 4.57, 4,37 (d, d; 1H, 1H; J = 12.1, 12.1 Hz), 4.51 (s, 2H), 4.10 (m, 3H), 3.76 (t, 1H, J = 8.7 Hz), 3.56 (dd, 1H, J = 5.6 Hz, 9.0 Hz, OCH), 2.68, 2.15 (dd, AB system, 2H, J = 14.1 Hz), 2.15 (m, 1H), 1.85−1.91 (m, 3H), 1.42 (m, 1H), 1.24 (t, 3H, J = 7.1 Hz), 1.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 173.0, 139.4, 138.8, 128.4 × 2, 128.3 × 2, 127.6 × 2, 127.5 × 2, 127.3 × 2, 81.4, 73.4, 71.1, 66.9, 59.9, 55.8, 41.8, 40.9, 37.1, 29.9, 27.1, 14.4. IR (film, neat): 2900, 1730, 1100, 1030, 740, 700 cm^{-1}. CIMS: 425 (M^+ + 29), 397 (M^+ + 1), 351, 289, 199, 181, 107, 91. Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13. Found: C, 75.88; H, 8.16.

(1*R*,2*R*,3*S*)-9 (9b): $[\alpha]^{20}_D$ +46.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30−7.33 (m, 10H), 4.43−4.53 (dd, 2H, AB system, J = 11.9 Hz), 4.49−4.45 (dd, 2H of AB system, J = 11.8 Hz), 4.09 (q, 2H, J = 7.1 Hz), 3.89 (m, 1H), 3.55 (d, 2H, J = 6.3 Hz), 2.32−2.23 (dd, 2H of AB system, J = 14.0 Hz), 2.03 (m, 2H), 1.81 (m, 1H), 1.74 (CH), 1.61(m, 1H), 1.25 (m, 6H). IR (film, neat): 2900, 1730, 1100, 1030, 740, 700 cm^{-1}. CIMS: 425 (M + 29, 6.97), 395 (M − 1, 1.25), 351 (3.47), 289 (100, M − OBn), 191(28.9), 107 (110.1), 91 (22.6).

(1*S*,2*R*,3*S*)-9 (9c): $[\alpha]^{20}_D$ +31.0 (*c* 1.61, $CHCl_3$). ^{1}H NMR (600 MHz,$CDCl_3$): δ 7.31−7.34 (m, 10H), 4.53, 4.43 (dd, 2H of AB system, J = 11.9 Hz), 4.51−4.48 (dd, 2H of AB system, J = 12.0 Hz), 4.10 (q, 2H, J = 7.2 Hz), 3.78 (m, 1H), 3.56 (m, 2H), 2.66, 2.37 (dd, 2H of AB system, J = 14.0 Hz), 2.16 (q, 1H, J = 7.0 Hz), 1.59 (m, 2H), 1.74 (m, 1H), 1.58 (m, 1H), 1.25 (t, 3H, J = 7.2 Hz), 0.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.38, 139.09, 138.81, 128.35 × 2, 128.05 × 2, 127.66 × 2, 127.57 × 2, 127.45 × 2, 82.68, 73.19, 71.34, 69.85, 59.91, 54.33, 47.03, 37.60, 29.62, 21.05, 14.38. IR (film, neat): 2900, 1730, 1100, 1030, 740, 700 cm^{-1}. EIMS: 397 (M + 1, 3.61), 307 (2.26), 289 (7.81), 275 (3.70), 261 (5.36), 243 (5.67), 199 (17.91), 181 (34.78), 153 (25.96), 122 (39.65), 105 (95.36), 91(100).

(2*R*,4*S*,5*R*)-4-(3-Butenone-1-yl)-5-hydroxy-2-methyl-1,3-dioxane (11). To the solution of aldehyde **10** (36 g, 0.25 mol) in THF (700 mL) was added triphenylphosphoranylideneacetone (94 g, 0.31 mol). The reaction was stirred for 8 h at room temperature before being refluxed for an additional 5 h. The solvent was removed under reduced pressure. To the residue, water was added with vigorous stirring for 10 min and then filtered. The residue was extracted for another 2 to 3 times. The combined filtrate was evaporated under reduced pressure below 45 °C. The residue was dried under vacuum followed by flash chromatography on silica gel (3:1 petroleum ether/EtOAc) to give **11** (20.7 g, 45%, *E*:*Z* = 2:1).

Z-**11**: $[\alpha]^{17}_D$ + 49.5 (*c* 1.59, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.45 (d, 1H, J = 11.8 Hz), 6.07 (dd, 1H, J = 11.8, 8.0 Hz), 4.65 (q, 1H, J = 5.0 Hz), 4.61 (dd, 1H, J = 8.0, 1.4 Hz), 4.17 (m, 2H), 3.44 (m, 1H), 3.42 (s, 1H), 2.28 (s, 3H), 1.28 (d, 3H, J = 5.0 Hz). IR (KBr): 3480, 1682, 1402, 1193, 1161, 1136 cm^{-1}. EIMS: 187 (M + 1, 6.73), 169 (100.00), 143 (10.31), 125 (53.27), 109 (41.80), 100 (60.82), 87 (63.06).

E-**11**: $[\alpha]^{17}_D$ −80.3 (*c* 1.61, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (dd, 1H, J = 16.0, 4.6 Hz), 6.35 (dd, 1H, J = 16.0, 1.5 Hz), 4.71 (q, 1H, J = 5.0 Hz), 4.11 (m, 1H), 3.99 (m,

1H), 3.45 (m, 3H), 2,25 (s, 3H), 1.32 (d, 3H, J = 5.0 Hz). IR (film, neat): 3440, 1676, 1410, 1161, 1117, 1065 cm^{-1}. EIMS: 186 (M^+, 8.66), 169 (69.08), 141 (16.18), 125 (25.96), 109 (13.47), 97 (55.16), 43 (100.00). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.05; H, 7.78.

(2*R*,4*S*,5*R*)-5-(1-Ethoxyethoxy)-4-(3-butanone-1-yl)-2-methyl-1,3-dioxane (12). Hydrogenation (following the same procedure described for **3**, except in this case methanol was used as a solvent) and EE protection (following the procedure for **6**) of the hydroxyl group of **11** (15.0 g, 81 mmol) gave **12** (18.0 g, 86% from **11**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.66, 4.62 (q, q; 1H; J = 5.2, 5.2 Hz), 4.55 (q, 1H, J = 5.1 Hz), 4.13 (m, 1H), 3.18−3.63 (m, 5H), 2.37−2.66, 1.97−2.17, 1.55−1.69 (m, 4H), 2.08 (s, 3H), 1.22 (d, 6H, J = 5.2 Hz), 1.12, 1.11 (t, t; 3H; J = 7.1, 7.1 Hz). IR (film, neat): 2990, 2956, 2855, 1717, 1412, 1381, 1370, 1151, 1096, 1061 cm^{-1}. EIMS: 207, 141, 125, 77, 73.

(2*R*,4*S*,5*R*,*E*)-5-Hydroxy-4-((3-methyl-2-pentenoic acid ethyl ester)-5-yl)-2-methyl-1,3-dioxane (14). Wittig−Hornner reaction (following the procedure described for **8**) of **12** (15.0 g, 57.7 mmol) followed by removal of EE gave **14**, 11.5 g (77% from **12**): $[\alpha]^{17}_D$ −47.4 (*c* 1.49, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.68 (s, 1H), 4.64 (q, 1H, J = 5.1 Hz), 4.13 (q, 2H, J = 7.1 Hz), 4.08 (m, 1H), 3.49−3.23 (m, 3H), 2.50−2.48, 2.38−1.97, 1.69−1.55 (m, m, m; 1H, 2H, 1H), 2.16 (s, 3H), 1.31 (d, 3H, J = 5.0 Hz), 1.26 (t, 3H, J = 7.1 Hz). IR (KBr): 3516, 2991, 2977, 2941, 2916, 2874, 1701, 1646, 1452, 1415, 1236, 122 cm^{-1}. EIMS: 259 (M + 1, 11.74), 213 (100.00), 197 (8.96), 171 (36.46), 151 (41.59), 125 (47.06). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.18; H, 8.75.

(2*R*,4*S*,5*R*,*E*)-2-Methyl-5-(methylthio)thiocarbonyl-4-((3-methyl-2-pentenoic acid ethyl ester)-5-yl)-1,3-dioxane (15). Treatment of **14** following the procedure for preparing the precursor for **9** gave **15** (93%) as a light yellow syrup: $[\alpha]^{17}_D$ −40.2 (*c* 1.71 EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.67 (s, 1H), 5.48 (m, 1H), 4.70 (q, 1H, J = 5.1 Hz), 4.36 (1H, dd, J = 10.7, 5.3 Hz), 4.14 (q, 2H, J = 7.1 Hz), 3.69 (dt, 1H, J = 9.1, 3.0 Hz), 3.44 (t, 1H, J = 10.3 Hz), 2.56 (s, 3H), 2.36, 2.21, 1.80, 1.68 (m, m, m, m; 1H, 1H, 1H, 1H), 2.15 (d, 3H, J = 1.1 Hz), 1.34 (d, 3H, J = 5.0 Hz), 1.27 (t, 3H, J = 7.1 Hz). IR (film, neat): 2863, 1716, 1650, 1412, 1375, 1212, 1149, 1119, 1068 cm^{-1}. EIMS: 349 (M + 1, 11.82), 305 (24.35), 287 (4.45), 259 (100.00), 241 (10.04), 197 (68.59), 151 (53.67). (Characterization of other minor components in the product mixture was not attempted.)

Radical-Mediated Cyclization of 15 (16a and 16b). Treatment of **15** following the procedure for preparing for **9** gave **16a** (75%) and **16b** (15%).

16a: a colorless oil; $[\alpha]^{27}_D$ +9.3 (*c* 1.25, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (q, 1H, J = 5.1 Hz), 4.22 (dt, 1H, J = 5.3, 1.2 Hz), 4.10 (q, 2H, J = 7.1 Hz), 4.08 (d, 1H, J = 12.1 Hz), 3.95 (dd, 1H, J = 12.6, 4.4 Hz), 2.84, 2.42 (d, d; 1H, 1H; J = 4.8, J = 4.8 Hz), 2.24, 1.96, 1.78, 1.37 (m, m, m, m; 1H, 1H, 1H, 1H), 1.25 (d, 3H, J = 5.4), 1.24 (t, 3H, J = 7.2 Hz), 1.23 (m, 1H), 1.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.29, 21.26, 26.38, 30.56, 37.16, 41.63, 41.88, 48.55, 59.72, 64.21, 79.57, 97.27, 173.04. IR (film, neat): 2956, 2872, 1732, 1454, 1407, 1369, 1325 cm^{-1}. EIMS: 243 (M + 1, 5.84), 213 (6.52), 196 (89.39), 181 (13.68), 171 (49.55), 151 (47.00), 141 (35.03), 95 (100.00). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.35; H, 9.36.

16b: a colorless oil; $[\alpha]^{27}_D$ +12.6 (*c* 1.64, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (q, 1H, J = 5.1 Hz), 4.21 (m, 1H), 4.09 (q, 2H, J = 7.0 Hz), 4.08 (d, 1H, J = 12.9 Hz), 3.96 (dd, 1H, J = 12.5, 4.3 Hz), 2.32, 2.21 (d, d; 1H, 1H; J = 13.8, 13.8 Hz), 1.88−1.68 (m, 4H), 1.54 (t, 1H, J = 4.3 Hz), 1.29 (s, 3H), 1.26 (d, 3H, J = 5.1 Hz), 1.23 (t, 3H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.27, 21.34, 24.61, 30.55, 38.82, 41.49, 44.89, 47.33, 60.08, 64.88, 79.95, 97.21, 172.22. IR (film): 2989, 2939, 2872, 1732, 1649, 1462, 1409 cm^{-1}. EIMS: 241 (M − 1, 6.08), 227 (24.78), 197 (44.28), 181 (96.75), 169 (16.42), 153 (94.97), 107 (100.00).

(2*S*,4*R*,5*R*)-4-(3-Butenone-1-yl)-5-hydroxy-2-methyl-1,3-dioxane (18). Treatment of **17** (following the procedure for preparing for **11**) gave **18** as an *E*,*Z* mixture in 75% total yield. IR (film): 3379, 1678, 1667, 1453, 1411, 1363 cm^{-1}. EIMS: 187 (M^+ + 1, 2.89) 169 (5.12) 143 (8.03) 125 (16.25) 43 (100.00). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.25; H, 7.72.

(2*S*,4*R*,5*R*,*E*)-5-Hydroxy-4-((3-methyl-2-pentenoic acid ethyl ester)-5-yl)-2-methyl-1,3-dioxane (21). Hydrogenation of **18** (2.6 g, 14 mmol) in methylene dichloride (100 mL) was performed in the presence of Pd/C (10%, 300 mg). After removal of Pd/C, concentration of the filtrate, followed by purification on silica gel, gave 1.84 g (70%) of the saturated ketone. Protection of the hydroxy group with vinyl ethyl ether following the procedure for preparing **6** yielded intermediate **19** in only 59% yield after flash chromatography on silica gel. The relatively low yield was due to the incomplete conversion of the starting material and the acetal formation as byproduct. The separated acetal was hydrolyzed with 1 N HCl in THF to give the starting material in a total yield of 40% (together with the unreacted one recovered from the above chromatography). Wittig−Hornner reaction of **19** with triethyl phosphonoacetate followed by deprotection with 1 N HCl in THF gave **21** in 77% yield (following the procedure for preparing **8** and **14**). **21**: $[\alpha]^{25}_D$ −14.0 (*c* 1.77, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.67 (q, 1H, J = 1.1 Hz), 4.71 (q, 1H, J = 5.1 Hz), 4.11 (q, 2H, J = 7.0 Hz), 4.03, 3.82 (d, d; 1H, 1H; J = 11.9, 11.9 Hz), 3.60 (m, 1H), 3.33 (s, 1H), 2.15 (s, 3H), 2.20−2.10, 1.90−1.60 (m, 4H), 1.33 (d, 3H, J = 5.2 Hz), 1.26 (t, 3H, J = 7.2 Hz). IR: 3485, 1714, 1648, 1449 cm^{-1}. EIMS: 259 (M^+ + 1, 100.00) 241 (2.83) 213 (47.21) 197 (12.96). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.71; H, 8.70.

(2*S*,4*R*,5*R*,*E*)-5-(Methylthio)thiocarbonyl-4-((3-methyl-2-penteoic acid ethyl ester)-5-yl)-2-methyl-1,3-dioxane (22). Treatment of **21** following the procedure for preparing the precursor for **9** gave **22** (74%) as a light yellow syrup: $[\alpha]^{23}_D$ −28.2 (*c* 1.58, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.66 (q, 1H, J = 1.2 Hz), 5.50 (t, 1H, J = 1.5 Hz), 4.78 (q, 1H, J = 5.0 Hz), 4.29 (dd, 1H, J = 13.1, 1.5 Hz), 4.14 (q, 2H, J = 7.2 Hz), 3.90 (dd, 1H, J = 13.2, J = 1.6 Hz), 3.82 (dt, 1H, J = 5.2, J = 1.5 Hz), 2.59 (s, 3H), 2.15 (s, 3H), 2.30−2.10, 1.90−1.60 (m, 4H), 1.38 (d, 3H, J = 5.0 Hz), 1.27 (t, 3H, J = 7.1 Hz). IR: 1714, 1650, 1447, 1413 cm^{-1}. EIMS: 349 (M^+ + 1) 348 (M^+), 347 (M^+ − 1) 315, 302. Anal. Calcd for $C_{15}H_{24}O_5S_2$: C, 51.70; H, 6.94. Found: C, 51.76; H, 6.93. (Characterization of other minor components in the product mixture was not attempted.)

Radical-Mediated Cyclization of 22 (23). Treatment of **22** (following the procedure for preparing for **9**) gave **23** as the only product (88% yield obtained after purification twice on silica gel). The ^{1}H NMR and IR spectra were absolutely identical with those of **16a**. **23**: $[\alpha]^{22}_D$ −7.1 (*c* 1.98, EtOH). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.02; H, 8.90.

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Supporting Information Available: ^{1}H NMR spectra of **9a**, **9b**, **9c**, **16a**, **16b**, and **23**. ^{13}C NMR spectra of **9a**, **9c**, **16a**, and **16b**. NOESY and COSY spectra of **9a**, **9b**, and **9c**. NOE difference spectra of **16a** and **16b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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