Studies toward the Total Synthesis of Clavulactone

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Synthetic studies directed toward a total synthesis of clavulactone are reported. In light of the analysis made in our previous work, cyclopentane **4a** (a key intermediate in the present work) was synthesized through a radical-mediated ring closure of a rationally designed substrate **25**. Using HWE reactions, the lower and upper side-chains of **4a** were converted into an allyl chloride and an allyl cyanohydrin, respectively. Subsequent treatment of the allyl chloride/cyanohydrin in a highly diluted THF solution with sodium bis(trimethylsiliyl)amide led to intramolecular alkylation and thus completed a major endeavor in synthesizing the dolabellane framework, construction of the eleven-membered ring. SmI_2-mediated lactonization as a model reaction for the formation of the α,*β*-unsaturated *δ*-lactone segment of clavulactone is also described.

Introduction

Dolabellanes,[1] characterized by the unusual *trans*-bicyclo[9.3.0]tetradecane nucleus, have represented an attractive synthetic target for organic chemists during the past decade.[2] Clavulactone is one of the dolabellanes that was isolated from *Clavularia viridis* collected from the Xisha Islands in the South China Sea and first structurally elucidated by us.[3] Clavulactone is unique due to an additional α,*β*-unsaturated lactone moiety fused onto a commonly encountered dolabellane framework. The extraordinary molecular architecture and remarkable antitumor activity[4] of this unusual compound prompted us to attempt its total synthesis.

Retrosynthetic analysis (depicted in Figure 1) disassembles clavulactone (**1**) into several important building blocks. We envisaged that the α,*β*-unsaturated lactone could be introduced through a Reformatsky-type reaction at a later stage in the synthesis because its precursor is prone to *β*-elimination and reduction. Accordingly, construction of the dolabellane skeleton appeared to be a primary task. Further analysis indicated that diastereoselective establishment of the trisubstituted cyclopentane segment with a well-defined quaternary center would be the key to the success of this synthesis. Previously, we reported a radical-mediated accomplishment of desired cyclopentane **4a** and its diastereoisomer from D-galactose and D-glucose, respectively.[2f,g] Herein, we would like to give a full account of our studies toward the total synthesis of clavulactone and the construction of the dolabellane skeleton from cyclopentane **4a** together with an SmI_2-mediated model lactonization.

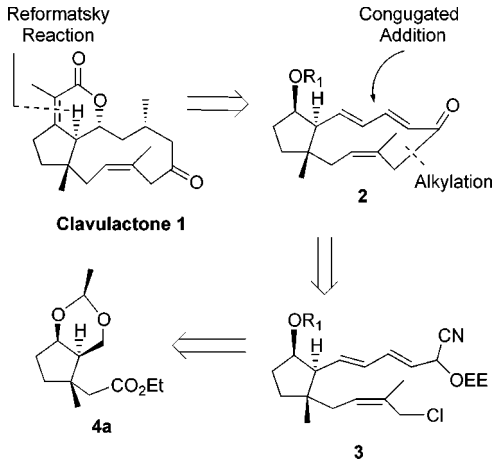

Figure 1. Retrosynthetic analysis of clavulactone.

Result and Discussion

In early 1996, our group succeeded in building the lactone moiety through an improved Reformatsky-type reaction (Scheme 1).[5] By using a conjugate addition of butyl cuprate to 3-methylcyclopent-2-enone (**5**) followed by trapping the enolate with trimethyl chlorosilane we obtained silyl enol ether **6**, which was then transformed into *β*-hydroxyl ketone **7** by an Aldol reaction catalyzed by $TiCl_4$.[6] Compound **7** and its ester **8** are labile to *β*-elimination under either acidic or basic conditions. Traditional Reformatsky reagent (Zn/ZnI_2)[7] failed to drive

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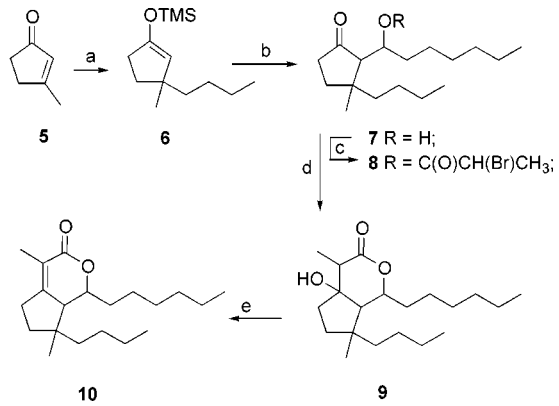
Scheme 1[a]



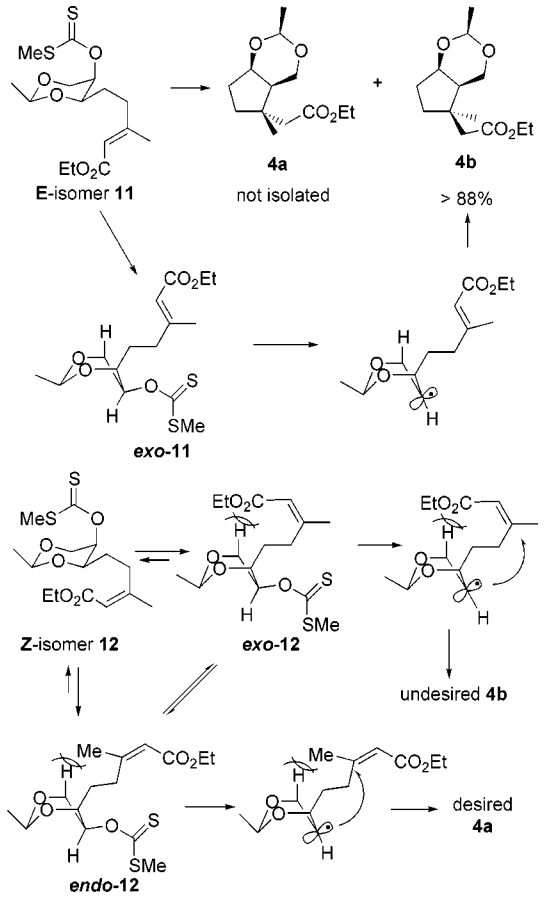
[a] Key: (a) $Bu_2CuMgBr$, THF, 53%; (b) $TiCl_4$, heptyl aldehyde, CH_2Cl_2, −78 °C, 45%; (c) 2- bromopropionyl chloride, Py, DMAP, 77%; (d) SmI_2, THF, −78 °C to room temperature, 42 %; (e) $POCl_3$, Py, 80%.

this reaction to completion. Running the reaction at higher temperatures did not lead to any improvement but resulted in β-eliminated byproduct. Then we noticed that SmI_2 appeared to be a superior[8] reagent for this type of transformations, especially when the substrates were sterically hindered. Subsequent testing of SmI_2 on substrate **8** was indeed gratifying, and lactone **9** finally could be obtained in synthetically useful yields. Further treatment of **9** with $POCl_3$ in pyridine furnished the unsaturated lactone moiety. This methodology has already been employed with an improved yield by another research group in our institute in their preliminary studies on the synthesis of clavulactone.[2h]

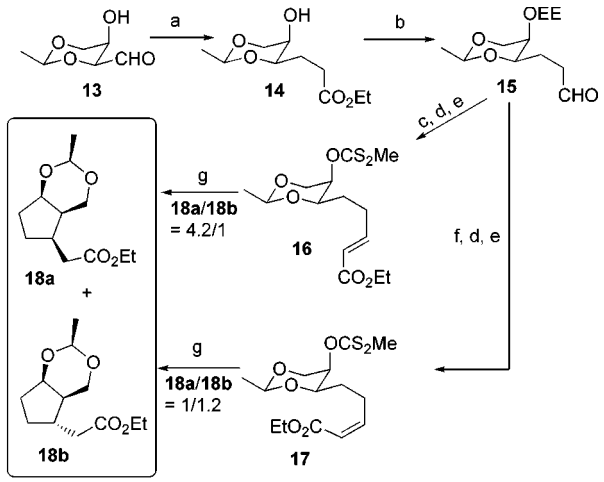
Having discovered an effective route to the α,β-unsaturated lactone, we next turned our attention to establishment of the dolabellane skeleton. Most dolabellane skeletons possess a multifunctional cyclopentane with a quaternary chiral center. Therefore, an optically pure cyclopentane **4** (Figure 1) would be of general utility. Previously, we described a chiron approach to this kind of building block through a radical-medicated ring closure as the key step, although the trans isomer **4a** was not isolated at all.[2f] The unusually high stereoselectivity was attributed to the repulsion between the vinyl methyl group and the 1,3-dioxane in the postulated transition state. The desired stereoselectivity leading to the isomer **4a** was achieved by changing conformation of the double bond in the radical precursor.[2g] A possible mechanism is outlined in Scheme 2.

When the double bond adopts an *E*-configuration as shown in **11**, the exo transition state appears to be predominant, leading to *cis*-cyclopentane **4b** exclusively. The *Z*-isomer **12**, however, may favor the endo disposition to avoid the repulsion between the ethyl ester and the axial hydrogen in the dioxane ring. Therefore, we postulated that the configuration of the double bond might play an important role in the distribution of the endo and

Scheme 2. Possible Mechanism and Transition States for the Radical Reaction



Scheme 3



a. $Ph_3P{=}CHCO_2Et$, THF; H_2/Pd, MeOH rt., 80 %; b. (i) ethyl vinyl ether, PPTS, CH_2Cl_2; (ii) LAH, THF; (iii) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2 79 %; c. $Ph_3P{=}CHCO_2C_2H_5$, THF, reflux; d. 1N HCl, rt.; e. CS_2, DBU, MeI, DMF; f. $(PhO)_2P(O)CH_2CO_2Et$, NaH, THF; *E*:*Z* = 1:11.5; g. Bu_3SnH, AIBN, 91%−98%.

exo forms in the transition states. To confirm this hypothesis, demethyl substrates **16** and **17** were designed and tested. As anticipated, the cis-substituted cyclopentane **18a** was observed as the major product when *E*-**16** was used as substrate. The trans/cis ratio could be markedly improved to 1.2:1 if with *Z*-**17** as substrate (Scheme 3). This value was far from satisfactory. We reasoned that isomerization of the *Z*-olefin into its more

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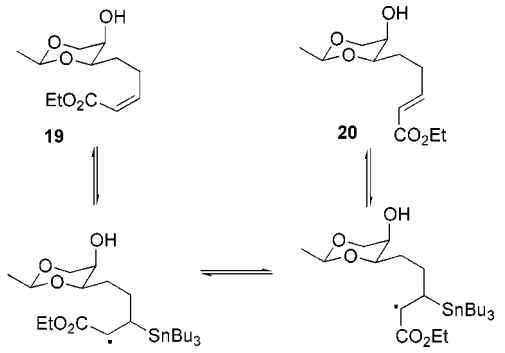
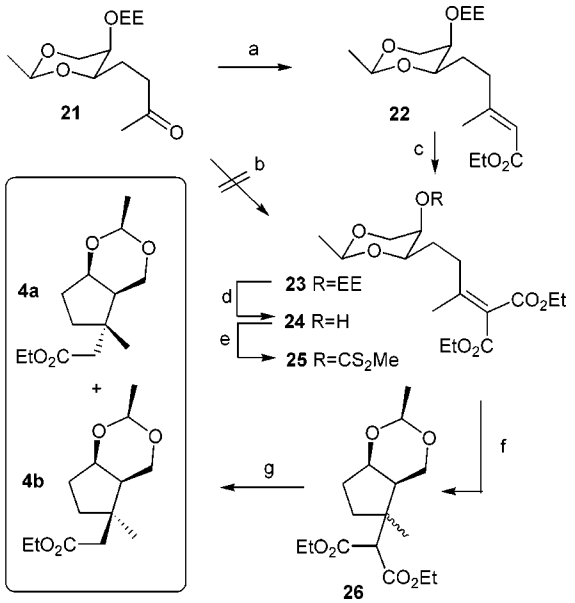
Scheme 4[a]



[a] Reaction conditions: Bu_3SnH (1.5 equiv), AIBN, reflux in benzene, 3 h.

Scheme 5[a]



[a] Key: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 84%; (b) $CH_2(CO_2Et)_2$ or Meldrum's acid; (c) LDA, HMPA, $ClCO_2Et$, −78 °C to room temperature, 20% of starting material recycled; (d) 1 N HCl; (e) CS_2, DBU, MeI, DMF, 45% from **22**; (f) Bu_3SnH, AIBN, benzene, reflux; (g) DMSO, LiCl, H_2O, 190 °C, 52% from 25, **4a**/**4b** = 2.4:1.

stable *E*-counterpart might be the culprit for the poor selectivity. To gain insight into this radical reaction, we then subjected compound **19** to the same reaction conditions (Scheme 4). As expected, almost all of *Z*-**19** was transformed into *E*-**20** by treatment with 1.5 equiv of tributyltin hydride at reflux, revealing the possibility of improving the trans selectivity by tuning the configuration of the olefin.

In an endeavor to maintain a cis double bond in the radical precursor, a tetrasubstituted olefin **24** was designed that was expected to be able to avert the *Z*/*E* isomerization. Initial attempts employing Knoevenagel condensation of methyl ketone **21** with Meldrum's acid or diethyl malonate failed to give any diethyl ester **23** (Scheme 5). However, an alternative route through the deconjugation and α-acylation of α,*β*-unsaturated ester **22**[9] successfully afforded compound **23** in 45% yield.

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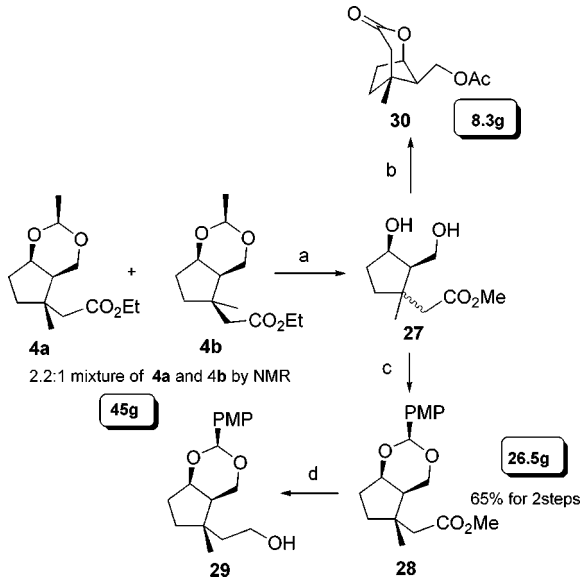
Scheme 6[a]



[a] Key: (a) TsOH, CH_3OH, reflux; (b) Ac_2O, Py; (c) $(EtO)_2CHC_6H_4OCH_3$, DMF; (d) DIBAL, CH_2Cl_2, 83%.

Subsequent radical reaction of xanthate **25** gave rise to a 1.5:1 inseparable mixture as shown by the ^1H NMR spectrum. Thermal decarboxylation[10] delivered the separable **4a** and **4b** (2.4:1) in 52% overall yield from xanthate **25**. By comparison with the authentic enantiomer obtained from our previous study, the structure of **4a** was secured. Thus, the stereochemistry of the cyclopentane could be controlled by the configuration of the carbon−carbon double bond. Since **4a** is readily accessible from inexpensive D-galactose, the present work also provides a general route to enantioselective synthesis of most dolabellanes.

To secure a facile deprotection at a later stage of our synthesis, we attempted to replace the ethylidene acetal with a *p*-methoxybenzylidene group. In the event, we observed an interesting phenomenon: the transacetalization products of **4a** and **4b** showed remarkable difference in solubility in water. Extraction of the reaction mixture with ether provided **28** in the organic layer, whereas the lactones derived from **4b** remained in the aqueous phase unless the aqueous phase was saturated with sodium chloride and using dichloromethane as extracting solvent (Scheme 6). Later in the preparative runs this solubility difference was fully exploited to avoid tedious column chromatographic separation.

Starting from alcohol **29**, extension of the lower side chain was realized by a Swern oxidation followed by an HWE reaction (Scheme 7). Reduction of ester **31** with excess DIBAL in dichloromethane at −20 °C furnished diol **32** in high yield. The less hindered allylic hydroxyl group was then selectively protected as the TBS ether before modification of the upper side chain. The primary alcohol **32** was then oxidized to corresponding aldehyde with Dess−Martin periodane, which proved to be an ideal reagent for this step since it did not cause any *β*-elimination byproduct at all.

Subsequent side-chain extension using strong nucleophiles was frustrating, resulting in PMB-eliminated aldehyde. Fortunately, a modified HWE reaction with

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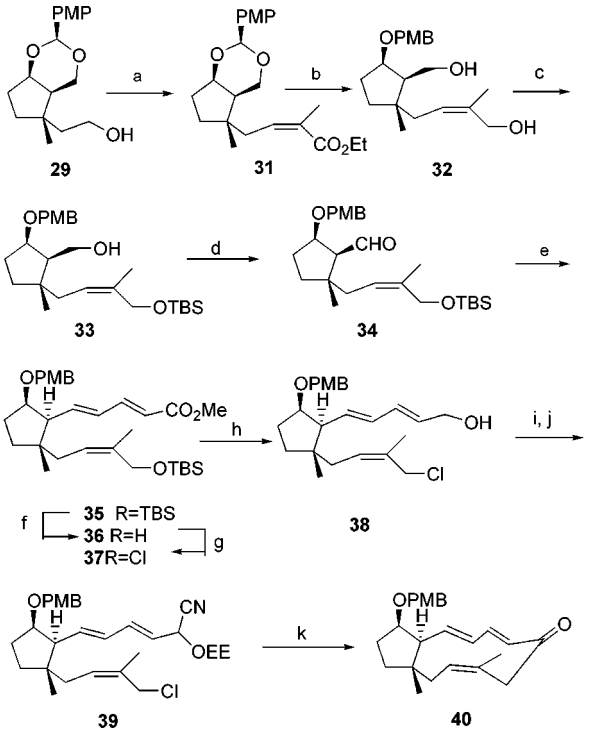
Scheme 7[a]



[a] Key: (a) (I) $(COCl)_2$, DMSO, Et_3N, (II) $(CF_3CH_2O)_2P(O)CHCH_3CO_2Et$, KHMDSA, 18-C-6, THF, 90% overall yield for two steps, Z/E = 26:1; (b) DIBAL-H, CH_2Cl_2, 97%; (c) TBSCl, imidazole, DMF, 73% and 12% of **32** recovered; (d) Dess−Martin, 93%; (e) Methyl diethyl-4-phosphonocrotonate, $LiOH·H_2O$, 4 ≈ MS, THF, reflux, 70%; (f) CSA, MeOH, 95%; (g) CH_3SO_2Cl, Et_3N, LiCl, DMF, 83%; (h) DIBAL-H, CH_2Cl_2, 86% and 13% of **37** recovered; (i) Dess−Martin, CH_2Cl_2, 85%; (j) (I) TMSCN, 18-C-6, KCN, CH_2Cl_2; (II) 1 N HCl, THF, 94%; (III) vinyl ethyl ether, PPTS, CH_2Cl_2, 87%; (k) NaHMDSA, THF; 1 N HCl, 63%.

4-phosphonocrotonate worked out here, affording the conjugated dienyl ester **35** in 70% yield,[11] which on treatment with CAS gave the alcohol **36**. The allylic hydroxyl group in **36** was then transformed into chloride **37** by reaction with MsCl in the presence of LiCl before the ester group was reduced with DIBAL.

Further elaboration[12] of allylic alcohol **38** (Dess−Martin oxidation followed by cyanohydration and replacement of the TMS with the more stable EE group to protect the hydroxyl group) gave the immediate precursor to the 11-numbered ring compound. Finally, the medium-sized ring was successfully closed in highly diluted THF solution using sodium bis(trimethylsiliyl)amide as base. The structure of compound **40** was well supported by IR, ESIMS, and various 1D and 2D NMR data.

In summary, a chiron approach to a versatile building block **4a** starting from D-galactose has been developed. The stereoselectivity was tuned by adjusting the configuration of olefin in the radical precursor. In addition, successful construction of the dolabellane skeleton from **4a** paved the way to its total synthesis. Further efforts to construct the lactone moiety through inter-/intramolecular SmI_2-mediated ring closure are still in progress and will be reported in due course.

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Experimental Section

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

Cyclopentenol, 3-Methyl-3-butyl-1-trimethylsilyl Ether (6). To a solution of butylmagnesium bromide (30 mmol) in THF (80 mL) stirred at −78 °C under nitrogen was added CuBr (260 mg, 1.8 mmol) in Me_2S (6 mL) and HMPA (10 mL, 57 mmol). Stirring was continued at −78 °C for another 30 min before a mixture of 3-methylcyclopentenone (2.0 mL, 20 mmol) and trimethylsilyl chloride (6.3 mL, 48 mmol) in THF (20 mL) was introduced. The reaction was quenched 3 h later by adding a solution of triethylamine (6.6 mL, 52 mmol) in hexane (60 mL). The reaction mixture was allowed to warm to room temperature, filtered through neutral aluminum oxide, and washed with ethyl ether (50 mL × 2). The filtrate was washed with water (50 mL × 2) and brine (50 mL × 2) and dried over Na_2SO_4. After removal of the solvents, the silyl enol ether was distilled under reduced pressure (74−76 °C/2.0 mmHg) to give **6** (2.40 g, 53% yield) as a colorless oil. ^{1}H NMR (CCl_4, 90 MHz): δ 4.20 (s, 1H), 2.43 (m, 1H), 2.05 (m, 3H), 1.20−1.10 (br s, 6H), 0.83 (m, 6H), 0.00 (s, 9H).

Cyclopentanone, 3-Butyl-3-methyl-2-(1-hydroxyheptyl) (7). To a solution of heptanal (1.67 mL, 12 mmol) in dry CH_2Cl_2 (40 mL) stirred at −78 °C under N_2, was added freshly distilled $TiCl_4$ (1.32 mL, 12 mmol). After the mixture was stirred for 30 min, a solution of silyl ether **6** (2.39 g) in CH_2Cl_2 (10 mL) was added. The reaction was maintained at this temperature for another 60 min. The reaction mixture was then poured into a Na_2HPO_4/NaH_2PO_4 buffer (pH = 7.0). The solids were filtered off, and the filter cake was washed with CH_2Cl_2. Three phases were separated. The aqueous layer was further extracted with CH_2Cl_2 (40 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. After concentration, flash chromatography of the residue gave 1.21 g of cyclopentanone **7** as a colorless oil (45%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.90 (m, 1H), 2.20−1.90 (m, 5H), 1.70−1.20 (m, 17H), 1.10 (s, 3H), 0.90−0.80 (m, 6H). IR (film): 3400, 2900, 1725 cm^{-1}. EIMS *m/z*: 269 (M + 1), 251, 233, 193, 183, 52.

Propanoic Acid, 2-Bromo, (1-(2-Butyl-2-methyl-5-oxocyclopentyl)heptyl) Ester (8). To a solution of cyclopentanone **7** (888 mg, 33.1 mmol), DMAP (15 mg), and pyridine (0.40 mL, 50 mmol) in CH_2Cl_2 (15 mL), stirred at −78 °C, was added dropwise a solution of 2-bromopropionyl chloride (0.50 mL, 50 mmol) in CH_2Cl_2 (10 mL). After being stirred at room temperature for 16 h, the reaction was quenched by pouring the reaction mixture into an aqueous buffer (pH = 7). The organic layer was separated, washed with saturated $CuSO_4$ solution, water, and brine, and dried over $MgSO_4$. Concentration and flash chromatography provided 1.03 g of compound **8** as a yellow oil (77%). ^{1}H NMR (CCl_4, 90 MHz): δ 5.25 (m, 1H), 4.32 (q, 1H, J = 7 Hz), 2.33−2.13 (m, 3H), 1.86−1.75 (m, 5H), 1.50−1.16 (m, 16H), 0.92 (m, 9H). IR (film): 2900, 1740 cm^{-1}. EIMS *m/z*: 251 (M − $CH_3CH(Br)COO$), 250, 235, 193, 175, 152, 109.

Bicyclolactone (9). A solution of **8** (212 mg, 0.54 mmol) in THF (10 mL) was added to a solution of SmI_2 (1.28 mmol) in THF (15 mL) stirred at −78 °C under N_2. Stirring was continued at room temperature for another 6 h before the reaction mixture was poured into ice−water (20 mL). The product was then extracted with ether (50 mL), and the organic layer was washed with brine and dried over $MgSO_4$. Concentration and flash chromatography gave 72 mg of desired product as white solid (42%). Mp: 71−73 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.67 (m, 1H), 2.70 (q, 1H, J = 7.6 Hz), 1.95−1.56 (m, 9H), 1.38−1.21 (m, 16H), 1.04 (s, 3H), 0.90 (m, 6H). IR (KBr): 3400, 2950, 1720, 1050, 740 cm^{-1}. EIMS *m/z*: 325 (M + 1), 307, 251, 233, 221, 195, 153. Anal. Calcd for $C_{20}H_{36}O_3$: C, 74.03; H, 11.18. Found: C, 74.16; H, 11.37.

α,β-Unsaturated Lactone (10). To a solution of compound **9** (56 mg) in HMPA (0.5 mL) and pyridine (100 μL) was added

$POCl_3$ (50 μL). The reaction mixture was kept at 50 °C for 1 h and heated to 100 °C for an additional 1 h. After the mixture was cooled, water (5 mL) was added, and the resulting mixture was extracted with ether (10 mL × 3). The combined organic layer was washed with 1 N HCl (5 mL) and brine and dried over Na_2SO_4. After concentration, the residue was purified by column chromatography on silica gel to give 44 mg of desired product **10** (80%) as a semisolid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.62 (m, 1H), 2.94 (br s, 1H), 2.47 (br s, 2H), 1.84 (s, 3H), 1.76 (m, 2H), 1.63−1.27 (m, 16H), 0.96 (s, 3H), 0.95−0.81 (m, 6H). IR (film): 2920, 1715, 1460, 1370, 1100 cm^{-1}. EIMS *m*/*z*: 307 (M + 1), 306, 233, 221, 210, 192, 135. Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.38; H, 11.76.

D-*threo*-Hexose, 2,3-Dideoxy-5-(1-ethoxyethoxy)-4,6-*O*-(1*S*)-ethylidene Ester (14). $Ph_3P{=}CHCO_2Et$ (47.8 g, 144 mmol) was added to a solution of the aldehyde **13** (13.6 g, 92.9 mmol) in THF (250 mL) stirred at 0 °C. The resulting mixture was stirred at room temperature for 11 h before being heated to reflux for another 9 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. Water (50 mL) was added to the residue, and the mixture was stirred vigorously for complete extraction. The solids were filtered off, and the filter cake was extracted with water one more time. The combined aqueous filtrates were extracted with ethyl acetate (100 mL × 2). The organic layer was dried over Na_2SO_4. Concentration and flash chromatography gave 6.43 g of the *E*-isomer unsaturated ester and 9.43 g of the *Z*-isomer in 79% total yield. Data for the *E*-isomer follow. $[\alpha]^{19}_D = +2.1$ (*c* 2.0, EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.87 (dd, 1H, *J* = 15.7, 4.1 Hz), 6.11 (dd, 1H, *J* = 15.8, 1.9 Hz), 4.81 (q, 1H, *J* = 5.1 Hz), 4.40 (m, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), 4.06 (dd, 1H, *J* = 11.9, 1.9 Hz), 3.88 (dd, 1H, *J* = 11.9, 1.3 Hz), 3.56 (m, 1H), 2.39 (br.s, 1H, OH), 1.38 (d, 3H, *J* = 5.0 Hz), 1.28 (t, 3H, *J* = 7.1 Hz). IR (film): 3993, 1706, 1664 cm^{-1}. EIMS *m*/*z*: 217, 199, 181, 173. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.62. H, 7.69. Data for the *Z*-isomer follow. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.28 (dd, 1H, *J* = 11.8, 6.9 Hz), 5.90 (dd, 1H, *J* = 11.7, 1.5 Hz), 5.31 (dt, 1H, *J* = 6.9, 1.4 Hz), 4.83 (q, 1H, *J* = 5.2 Hz), 4.16 (q, 2H, *J* = 7.1 Hz), 3.98 (m, 2H), 3.75 (m, 1H), 2.40 (bs, 1H, OH), 1.36 (d, 3H, *J* = 5.2 Hz), 1.28(t, 3H, *J* = 7.1 Hz).

The *E*- and *Z*-mixed α,β unsaturated ester (14.4 g) in CH_2Cl_2 (300 mL) was hydrogenated (1 atm) over 10% Pd/C (1.48 g). The catalyst was filtered off. The filtrate was concentrated and chromatographed to give 10.8 g of pure **14** (75%). $[\alpha]^{19}_D = +3.3$ (*c* 1.2, EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.67 (q, 1H, *J* = 5.0 Hz), 4.08 (q, 2H, *J* = 7.1 Hz), 3.99 (dd, 1H, *J* = 12.8, 1.9 Hz), 3.78 (dd, 1H, *J* = 11.9, 1.3 Hz), 3.65 (m, 1H), 3.32 (m, 1H), 2.52 (br s, 1H, OH), 2.37 (t, 2H, *J* = 6.9 Hz), 1.95 (m, 1H), 1.80 (m, 1H), 1.28 (d, 3H, *J* = 5.1 Hz), 1.21 (t, 3 H, *J* = 7.1 Hz). IR (film): 3474, 1734 cm^{-1}. EIMS *m*/*z*: 219, 201, 175, 157.

2-Pentenoic Acid, 5-[(2*S*,4*R*,5*R*)-2-Methyl-5-hydroxy-1,3-dioxan-4-yl]-, Ethyl Ester, (2*E*) (19) and (2*Z*) (20). Vinyl ethyl ether (5.6 mL, 58.6 mmol) was added dropwise to a solution of **14** (6.43 g, 29.5 mmol) and PPTS (200 mg) in CH_2Cl_2 (600 mL) and stirred at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred at room temperature overnight before being washed with brine and dried over Na_2SO_4. After removal of the solvent, the crude product was dissolved in dry THF (100 mL) and cooled to 0 °C. LAH (800 mg, 22.8 mmol) was added in several portions. The resulting mixture was stirred at room temperature overnight. Excess hydride was carefully destroyed at 0 °C by dropwise addition of water (5 mL). Ethyl acetate (200 mL) was added with vigorous stirring. The solids were filtered off, and the filter cake was washed twice with ethyl acetate (100 mL × 2). The combined filtrates were washed with brine and dried over Na_2SO_4. After concentration, the residue was purified by column chromatography to give 4.30 of primary alcohol as a colorless oil (83% overall yield for the last two steps).

DMSO (1.84 mL, 25.9 mmol) was carefully added to a solution of oxalyl chloride (1.2 mL, 13.7 mmol) in dry CH_2Cl_2 (10 mL) stirred at −78 °C under argon. After 30 min, a solution of freshly prepared primary alcohol (2.68 g, 10.8 mmol) in CH_2Cl_2 (5 mL) was added dropwise. Stirring was continued for another 2 h at −78 °C before triethylamine (6.67 mL, 47.8 mmol) was introduced. The reaction mixture was allowed to warm slowly to room temperature and diluted with CH_2Cl_2 (100 mL) before being washed with water and brine, dried over Na_2SO_4, and concentrated. Flash chromatography afforded 1.40 g of colorless oil, which was a hemiacetal of the deprotected product as shown by 90 MHz ^{1}H NMR. To a solution of above hemiacetal in THF (100 mL) was added $Ph_3P{=}CHCO_2$-Et (3.36 g, 9.66 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 10 h and then refluxed for an additional 6 h. After removal of the solvent, ethyl ether (200 mL) was added. The precipitates were filtered off. Concentration of the filtrate and flash chromatography of the residue gave 1.66 g of **19** and 88 mg of **20**, respectively (**19**/**20** = 18.9:1; 66% overall yield for the last two steps).

During purification of the Swern oxidation product, addition of 0.5−1% of triethylamine in the eluent could prevent deprotection of the EE group as well as hemiacetal formation. Using a similar procedure, 502 mg of the alcohol was transformed into the corresponding aldehyde **15** (323 mg, 65%). Under nitrogen, to a suspension of sodium hydride (36.7 mg, 75% in mineral oil, 1.146 mmol) in THF (10 mL), was added a solution of $(PhO)_2P(O)CH_2CO_2Et$ (278 mg, 0.87 mmol) in THF (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred until the solution turned transparent. A solution of the aldehyde **15** (235 mg, 0.955 mmol) in THF (10 mL) was added to the above mixture at 0 °C. The reaction mixture was then warmed to room temperature and stirred for another 1.5 h before introducing saturated aqueous NH_4Cl (15 mL) and ethyl acetate. The phases were separated and the organic layer was washed with brine, and dried over Na_2SO_4. After concentration, the residue was passed through a short silica gel column. The filtrate was reconcentrated and dissolved in THF (10 mL). 1 N HCl (5 mL) was added to the solution (to cleave the EE protecting group). The mixture was stirred at room temperature for 1.5 h, and then neutralized with saturated aqueous $NaHCO_3$. The crude product was extracted with ethyl acetate (50 mL), washed with brine, and dried over Na_2SO_4. Concentration and flash chromatography gave **19** (14 mg) and **20** (161 mg) in 83% total yield for two steps (**19**/**20** = 1:11.5). Data for **19** follow. $[\alpha]^{19}_D = -4.7$ (*c* 1.5, EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.95 (dt, 1H, *J* = 15.7, 5.3 Hz), 5.83 (dt, 1H, *J* = 15.7, 1.6), 4.71 (q, 1H, *J* = 5.1 Hz), 4.18 (q, 2H, *J* = 7.1 Hz), 4.03 (dd, 1H, *J* = 11.8, 1.9 Hz), 3.81 (dd, 1H, *J* = 11.8, 1.3 Hz), 3.62 (m, 1H), 3.32 (m, 1H), 2.30 (m, 2H), 1.69 (m, 1H), 1.88 (m, 1H), 1.33 (d, 3H, *J* = 5.1 Hz), 1.28 (t, 3H, *J* = 7.1 Hz). IR (film): 3479, 1718, 1654 cm^{-1}. EIMS *m*/*z*: 245, 199, 157, 111. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.67; H, 8.39. Data for **20** follow. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.23 (dt, 1H, *J* = 11.5, 7.5 Hz), 5.78 (dt, 1H, *J* = 11.4, 1.7 Hz), 4.71 (q, 1H, *J* = 5.1 Hz), 4.15 (q, 2H, *J* = 7.1 Hz), 4.03 (dd, 1H, *J* = 11.8, 1.9 Hz), 3.81 (dd, 1H, *J* = 11.8, 1.3 Hz), 3.64 (t, 1 H, *J* = 7.8 Hz), 3.39 (m, 1H), 2.71 (m, 2H), 2.31 (br s, 1H, OH), 1.75 (m, 2H), 1.31(d, 3H, *J* = 5.1 Hz), 1.27 (t, 3H, *J* = 7.1 Hz). IR (film): 3481, 1718, 1645 cm^{-1}. EIMS *m*/*z*: 245, 199, 157, 111. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.89. H, 8.50.

2-Pentenoic Acid, 5-[(2*S*,4*R*,5*R*)-2-Methyl-5-[(methylthio)thioxomethoxy]-1,3-dioxan-4-yl]-, Ethyl Ester, (2*E*) (16) and (2*Z*) (17). To a solution of **19** (438 mg, 1.80 mmol) in DMF (10 mL) stirred at 0 °C, were added CS_2 (0.87 mL, 14.36 mmol) and DBU (0.53 mL, 3.49 mmol). The solution was warmed to room temperature and stirred for another 1 h before being recooled to 0 °C. MeI (0.89 mL, 14.36 mmol) was introduced. The resulting mixture was stirred for an additional 4 h at room temperature before being poured into 1 N HCl (20 mL). The product was extracted with diethyl ether (100 mL). The organic layer was washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. After concentration, the residue was purified by column chromatography to give xanthate **16** as a pale yellow syrup (506 mg, 83%). Similarly, **20** (392 mg, 1.60 mmol) was transformed into corresponding xanthate **17** (463 mg) in 86% yield. Data for **16** follow. $[\alpha]^{19}_D$

= −31.7 (*c* 1.6, EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.93 (dt, 1H, J = 15.7, 7.0 Hz), 5.84 (dt, 1H, J = 15.6, 1.6 Hz), 5.51 (m, 1H), 4.79 (q, 1H, J = 5.1 Hz), 4.29 (dd, 1H, J = 13.1, 1.5 Hz), 4.19 (q, 2H, J = 7.2 Hz), 3.91 (dd, 1H, J = 13.2, 1.7 Hz), 3.85 (m, 1H), 2.61 (s, 3H), 2.30 (m, 2H), 1.65 (m, 1H), 1.86 (m, 1H), 1.39 (d, 3H, J = 5.1 Hz), 1.29 (t, 3H, J = 7.1 Hz). IR (film): 1717, 1655, 1216, 1071 cm^{-1}. EIMS *m/z*: 335, 301, 245, 183, 137. Anal. Calcd for $C_{14}H_{22}O_5S_2$: C, 50.29; H, 6.64. Found: C, 50.24; H, 6.76. Data for **17** follow. $[\alpha]^{15}_D$ = −20.3 (*c* 1.42, EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.29 (dt, 1H, J = 11.5, 7.6 Hz), 5.77 (dt, 1H, J = 11.5, 1.7 Hz), 5.55 (m, 1H), 4.87 (q, 1H, J = 5.1 Hz), 4.20 (dd, 1H, J = 13.1, 1.5 Hz), 4.12 (q, 2H, J = 7.2 Hz), 4.02 (dd, 1H, J = 13.2, 1.6 Hz), 4.10 (m, 1H), 2.70 (m, 2H), 2.62 (s, 3H), 1.64 (m, 1H), 1.75 (m, 1H), 1.26 (d, 3H, J = 5.1 Hz), 1.26 (t, 3H, J = 7.1 Hz). IR (film): 1718, 1645 cm^{-1}. EIMS *m/z*: 335, 245, 183, 137, 91. Anal. Calcd for $C_{14}H_{22}O_5S_2$: C, 50.29; H, 6.64. Found: C, 50.02; H, 6.75.

Cyclopenta-1,3-dioxin-5-acetic acid, Hexahydro-2-methyl-, Ethyl Ester, (2*S*,4a*R*,5*R*,7a*R*) (18a) and (2*S*,-4a*R*,5*S*,7a*R*) (18b). To a gently refluxing solution of **16** (838 mg, 2.51 mmol) and AIBN (40 mg) in benzene (10 mL) under nitrogen was added dropwise a solution of Bu_3SnH (1.0 mL, 3.77 mmol) in benzene (10 mL) over 30 min. The reaction was refluxed for another 3 h. After the mixture was cooled to room temperature, saturated aqueous NaF solution (20 mL) was introduced. Stirring was continued for an additional 1 h before the reaction mixture was diluted with ether (100 mL), washed with brine, and dried over Na_2SO_4. Column chromatography gave **18a** (420 mg) and **18b** (101 mg) in 73% and 18% yield, respectively. When compound **17** (182 mg, 0.55 mmol) was used as substrate in this reaction, **18a** and **18b** were isolated in 45.5% and 52.7% yield, respectively. Data for **18a** follow. $[\alpha]^{19}_D$ = +23.8 (*c* 1.80, EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.66 (q, 1H, J = 5.1 Hz), 4.16 (q, 2H, J = 7.1 Hz), 4.16 (m, 1H), 4.10 (d, 1H, J = 11.4 Hz), 4.01 (dd, 1H, J = 11.4, 3.8 Hz), 2.60 (m, 2H), 2.75 (m, 1H), 2.05−1.60 (m, 5H), 1.30 (d, 3H, J = 5.1 Hz), 1.28 (t, 3H, J = 7.1 Hz). IR (film): 1733 cm^{-1}. EIMS: 229, 213, 185, 167. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.26; H, 8.92. Data for **18b** follow. $[\alpha]^{19}_D$ = −46.8 (*c* 2.45, EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.62 (q, 1H, J = 5.1 Hz), 4.11 (q, 2H, J = 7.1 Hz), 4.11 (m, 1H), 3.94 (m, 2H), 2.70 (m, 1H), 2.50 (dd, 1H, J = 14.8, 4.9 Hz), 2.21 (m, 1H), 2.20 (m, 1H), 1.90−1.60 (m, 3H), 1.35 (m, 1H), 1.28 (d, 3H, J = 5.1 Hz), 1.24 (t, 3H, J = 7.1 Hz). IR: 1735 cm^{-1}. EIMS *m/z*: 227, 213, 184, 167. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.36; H, 8.94.

Propanedioic Acid, [1-Methyl-3-[(2*S*,4*R*,5*R*)-2-methyl-5-[(methylthio)thioxomethoxy]-1,3-dioxan-4-yl]propylidene]-, Diethyl Ester (25). *n*-BuLi (21 mL, 52.5 mmol) was added to a stirring solution of (*i*-Pr)$_2$NH (6.7 mL, 51.45 mmol) and HMPA (12 mL, 68.6 mmol) in freshly distilled THF (150 mL) stirred at −78 °C under nitrogen. After 15 min, a solution of **22** (11.32 g, 34.3 mmol) in THF (30 mL) was introduced dropwise. The resulting mixture was stirred at −78 °C for 2 h before ethyl chloroformate (4.0 mL, 41.16 mmol) was added. The reaction mixture was warmed to room temperature gradually and stirred for another 45 h. Ether (200 mL) was then added, and the reaction mixture was washed with saturated aqueous NH_4Cl and brine. The organic layer was concentrated, and the residue was taken up into THF (50 mL) with 1 N HCl. When TLC showed that the EE was removed completely, ether (200 mL) was added. The combined organic layer was washed with brine and then dried over Na_2SO_4. After concentration, the residue was carefully column chromatographed to give 1.85 g of the monoester (deprotected product of the unreacted starting material) and 7.34 g of the diester product **24** in 65% yield for two steps.

Using a procedure similar to that for preparing xanthate **16**, compound **25** (11.90 g) was obtained from its precursor **24** (10.5 g, 31.8 mmol) in 89% yield. Data for **25** follow. $[\alpha]^{20}_D$ = +22.0 (*c* 1.40, EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.48 (m, 1H), 4.77 (q, 1H, J = 5.2 Hz), 4.28 (d, 1H, J = 13.2 Hz), 4.21 (q, 4H, J = 7.1 Hz), 3.89 (d, 1H, J = 13.5 Hz), 3.85 (m, 1H), 2.58 (s, 3H), 2.50−2.30 (m, 2 H), 2.04 (s, 3H), 1.84 (m, 1H), 1.70 (m, 1H), 1.35 (d, 3H, J = 5.2 Hz), 1.27 (t, 6H, J = 7.4 Hz). IR (film): 1722, 1637, 1447, 1248, 1216 cm^{-1}. EIMS *m/z*: 421, 376, 358, 330, 223. Anal. Calcd for $C_{18}H_{28}O_7S_2$: C, 51.41; H, 6.71. Found: C, 51.78; H, 6.95.

Cyclopenta-1,3-dioxin-5-acetic Acid, Hexahydro-2,5-dimethyl-, Ethyl Ester, (2*S*,4a*R*,5*S*,7a*R*) (4a) and (2*S*,-4a*R*,5*R*,7a*R*) (4b). A solution of Bu_3SnH (0.54 mL, 2.00 mmol) in benzene (5 mL) was added dropwise to a solution of **25** (560 mg, 1.33 mmol) in benzene (20 mL) containing a catalytic amount of AIBN at reflux under nitrogen. The resulting mixture was refluxed for 10 h before being cooled to room temperature. Aqueous NaF (20 mL) was added. Stirring was continued for a few more hours before the reaction mixture was diluted with ethyl ether (100 mL), washed with brine, and dried over Na_2SO_4. After concentration, the residue was purified by column chromatography to yield 334 mg of the mixture of a pair of inseparable diastereomers of **26** (80%).

A mixture of **25** (4.92 g, 15.67 mmol), LiCl (666 mg, 15.67 mmol), water (564 mg, 31.34 mmol), and DMSO (50 mL) was heated at 190 °C under argon for 5 h. After the mixture was cooled to room temperature, ether (300 mL) was used to extract the product. The organic layer was washed successively with water and brine and dried over Na_2SO_4. Concentration and column chromatography gave **4a** (1.72 g) and **4b** (0.73 g) in 65% yield. Data for **4a** follow. $[\alpha]^{23}_D$ = −20.4 (*c* 1.85, EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): 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), 2.21 (d, 1H, J = 13.8 Hz), 2.32 (d, 1H, J = 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 ($CDCl_3$, 75 MHz): δ 172.23, 97.23, 79.96, 64.89, 60.08, 47.35, 44.90, 41.50, 38.83, 30.56, 24.61, 21.34, 14.28. IR (film): 1733, 1462, 1408, 1370 cm^{-1}. EIMS *m/z*: 243, 227, 199, 181. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.42; H, 9.16. Found: C, 64.14; H, 9.40. Data for **4b**: see ref 2f.

Cyclopenta-1,3-dioxin-5-acetic Acid, Hexahydro-2-(*p*-methoxybenzylidene)-5-methyl, Methyl Ester, (2*S*,4*R*,5*S*,7*R*) (28) and Lactone (30). A mixture of **4a** and **4b** (45.0 g, 2.2:1 by NMR) and *p*-TsOH (70 g) was dissolved in methanol (1 L) and heated to reflux for 13 h. After removal of the solvent, diethoxy *p*-methoxybenzylidene acetal (58.3 g), pyridine (29.8 mL), and DMF (50 mL) were added. The resulting mixture was stirred at 50 °C under reduced pressure (10−15 mmHg) for 3 h. After being cooled to room temperature, the reaction mixture was diluted with ethyl ether (1000 mL), washed in turn with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. After concentration, column chromatography separated unreacted diol **27** from desired PMP-acetal. The aqueous layer was saturated with sodium chloride, and CH_2Cl_2 (500 mL) was used to extract the unreacted diol **27**. Taken together, the recovered **27** was subjected to the same procedure. After two cycles, acetal **28** (26.5 g) was finally obtained in 65% total yield. The extract from the last portion of the aqueous phase was dried (Na_2SO_4) and esterified with acetic anhydride and pyridine system. Normal workup and chromatographic purification gave 8.3 g of the bridged lactone **30** as the sole product. Data for **28** follow. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39 (d, 2H, J = 8.5 Hz), 6.89 (d, 2H, J = 8.5 Hz), 5.40 (s, 1H), 4.44 (m, 1H), 4.22 (m, 2H), 3.81 (s, 3H), 3.67 (s, 3H), 2.42 (d, 1H, J = 14.0 Hz), 2.31 (d, 1H, J = 13.1 Hz), 1.90 (m, 3H), 1.75 (m, 1H), 1.65 (m, 1H), 1.40 (s, 3H). IR (film): 1735, 1673, 1615, 1518 cm^{-1}. EIMS: 321, 320, 319, 289, 241, 227. HRMS: calcd for $C_{18}H_{23}O_5$ 319.1546, found 319.1569. Data for **30** follow. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.30 (m, 1H), 4.23 (d, 2H, J = 6.3 Hz), 2.53 (d, 1H, J = 14.8 Hz), 2.40 (d, 1H, J = 14.8 Hz), 2.26 (m, 1H), 2.07 (s, 3H), 1.98 (m, 1H), 1.80 (m, 2H), 1.59 (m, 1H), 1.18 (s, 3H). IR (film): 1736, 1457, 1435, 1375, 1244 cm^{-1}. EIMS *m/z*: 213, 197, 185, 170, 153, 152. HRMS *m/z*: calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1069.

***Z*-Trisubstituted-α,β-Unsaturated Ester (31).** To a solution of **28** (26.5 g, 82.8 mmol) in CH_2Cl_2 (200 mL) stirred at −78 °C under nitrogen was added DIBAL (182 mL, 1.0 M in cyclohexane). The resulting solution was stirred at −78 °C for another 5 h before the reaction was quenched by slow addition of H_2O (10 mL). The reaction mixture was warmed to room

temperature gradually, and the precipitates were filtered off. The filter cake was washed with ethyl acetate several times. The filtrate was dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography to give 20.1 g of primary alcohol **29** (83%).

Alcohol **29** (1.60 g, 5.48 mmol) was subjected to Swern oxidation using oxalyl chloride (0.72 mL, 8.22 mmol) and DMSO (1.16 mL, 16.44 mmol). The resulting crude aldehyde was used directly without further purification. To a solution of $(CF_3CH_2O)_2P(O)CH_2COOEt$ (2.84 g, 8.22 mmol) and 18-crown-6/acetonitrile complex (6.3 g) in THF (20 mL) stirred at −78 °C under N_2 was added KHMDS (15 mL, 0.55 M in THF, 8.25 mmol). After 30 min, a solution of the aldehyde in THF (15 mL) was added. The reaction mixture was stirred at −78 °C for an additional 1 h before the reaction was quenched with water. Ethyl ether (100 mL) was added, and the phases were separated. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography to give the desired *Z*-**31** (1.788 g) and its *E*-isomer (70 mg) in 90% total yield for two steps (*Z*/*E* = 26:1). Data for *Z*-**31** follow. $[\alpha]^{16}_D = -61.3$ (*c* 2.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (d, 2H, *J* = 8.8 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 5.96 (dt, 1H, *J* = 8.0, 1.2 Hz), 5.37 (s, 1H), 4.42 (m, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), 4.18 (m, 2H), 3.78 (s, 3H), 2.61(dd, 1H), 2.40 (dd, 1H), 1.93 (d, 3H, *J* = 1.4 Hz), 1.84 (m, 3H), 1.64 (m, 1H), 1.42 (m, 1H), 1.31 (s, 3H), 1.30 (t, 3H, *J* = 7.1 Hz). IR (film): 1713, 1645, 1616, 1589 cm^{-1}. EIMS *m*/*z*: 374, 372, 343, 275. HRMS *m*/*z*: calcd for $C_{22}H_{30}O_5$ 374.2093, found 374.2087. Data for *E*-**31** follow. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 6.82 (t, 1H, *J* = 9.1 Hz), 5.38 (s, 1H), 4.43 (m, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), 4.18 (m, 2H), 3.78 (s, 3H), 2.26 (dd, 1H), 2.14 (dd, 1H), 1.84 (m, 3H), 1.83 (d, 3H, *J* = 1.4 Hz), 1.62 (m, 1H), 1.40 (m, 1H), 1.33 (s, 3H), 1.29 (t, 3H, *J* = 7.1 Hz). IR: 1709, 1647, 1616, 1589, 1519, 1248 cm^{-1}.

Primary Alcohol (33). DIBAL (2.9 mL, 1.0 M in hexane) was added to a solution of **31** (144 mg, 0.39 mmol) in CH_2Cl_2 (10 mL) stirred at −78 °C under nitrogen. The reaction mixture was warmed to room temperature and stirred overnight. With cooling (0 °C), CH_3OH (1 mL) was added to the reaction mixture to quench the reaction. The solids were filtered off, and the filter cake was washed with ethyl acetate several times. The filtrate was washed with brine and dried over Na_2SO_4. After concentration, column chromatography provided diol **32** (125 mg, 97%).

To a solution of **32** (102 mg, 0.32 mmol) in DMF (2 mL) were added imidazole (22 mg, 0.32 mmol), DMAP (2 mg), and TBSCl (48 mg, 0.32 mmol) successively. The reaction mixture was stirred at room temperature overnight before the reaction was quenched with water. The reaction mixture was then extracted with ethyl ether. The ethereal layer was dried (Na_2SO_4), concentrated, and chromatographed to afford **33** (100 mg) in 73% yield, together with 12 mg of recovered **32**. $[\alpha]^{22}_D = -64.9$ (*c* 1.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (d, 2H, *J* = 8.6 Hz), 6.89 (d, 2H, *J* = 8.6 Hz), 5.28 (t, 1H, *J* = 7.6 Hz), 4.56 (d, 1H, *J* = 11.5 Hz), 4.29 (d, 1H, *J* = 11.5 Hz), 4.15 (m, 1H), 4.13 (s, 2H), 3.89 (m, 1H), 3.81 (s, 3H), 3.66 (dd, 1H, *J* = 11.2, 4.7 Hz), 2.11(dd, 1H, *J* = 14.1, 8.6 Hz), 1.98 (dd, 1H, *J* = 14.2, 7.7 Hz), 1.85 (m, 3H), 1.77 (s, 3H), 1.55 (m, 2H), 0.95 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H). IR (film): 3446, 1614, 1587, 1515, 1249 cm^{-1}. EIMS *m*/*z*: 212 (M^+ − TBS − PMB), 177, 121. Anal. Calcd for $C_{26}H_{44}O_4Si$: C, 69.60; H, 9.88. Found: C, 69.71; H, 10.07.

Conjugated Diene Ester (35). Dess−Martin periodinane (1.31 g, 3.10 mmol) was added to the solution of **33** (925 mg, 2.06 mmol) in CH_2Cl_2 (30 mL) stirred at room temperature. Stirring was continued for an additional 4 h. The solids were filtered off. The filtrate was concentrated. The residue was chromatographed to afford 857 mg of aldehyde (93%). THF (50 mL) was added to a mixture of the above aldehyde (857 mg, 1.92 mmol), (E)-$(EtO)_2P(O)CH_2CH{=}CHCOOMe$ (544 mg, 2.31 mmol), $LiOH{\cdot}H_2O$ (97 mg, 2.31 mmol), and 4 Å MS (1.0 g). The solution was refluxed for 11 h. After the mixture was cooled to room temperature, the solids were filtered off. The filtrate was diluted with ethyl ether (50 mL). The phases were separated, and the organic layer was washed with water and brine and then dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography to give the unsaturated ester **35** (705 mg, 70%). $[\alpha]^{24}_D = -116.1$ (*c* 1.51, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 (dd, 1H, *J* = 10.9, 15.4 Hz), 7.21 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 6.37 (dd, 1H, *J* = 15.3, 10.0 Hz), 6.17 (dd, 1H, *J* = 15.3, 10.9 Hz), 5.81 (d, 1H, *J* = 15.4 Hz), 5.24 (t, 1H, *J* = 7.2 Hz), 4.43 (d, 1H, *J* = 11.6 Hz), 4.30 (d, 1H, *J* = 11.6 Hz), 4.10 (s, 2H), 3.95 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.31 (dd, 1H, *J* = 10.0, 6.1 Hz), 2.05 (m, 1H), 1.85 (m, 2H), 1.76 (s, 3H), 1.60 (m, 3H), 0.97 (s, 3H), 0.91 (s, 9H), 0.06 (s, 6H). IR (film): 1721, 1641, 1614, 1587, 1250 cm^{-1}. EIMS *m*/*z*: 471, 355, 335, 192, 121. Anal. Calcd for $C_{31}H_{48}O_5Si$: C, 70.41; H, 9.15. Found: C, 70.25; H, 9.35.

Allylic Chloride (37). CSA (35 mg, 0.15 mmol) was added to a solution of **35** (79 mg, 0.15 mmol) in methanol (10 mL) stirred at room temperature. When TLC showed that the TBS group was removed (within 2 h). The reaction mixture was concentrated and chromatographed to afford 59 mg of the allylic alcohol **36** in 95% yield. To a solution of **36** (59 mg, 0.143 mmol) and anhydrous LiCl (30 mg, 0.715 mmol) in anhydrous DMF (8 mL) stirred at 0 °C under nitrogen was added Et_3N (0.10 mL, 0.715 mmol), followed by CH_3SO_2Cl (56 μL, 0.715 mmol). Stirring was continued at room temperature for an additional 10 h. The reaction mixture was diluted with diethyl ether (50 mL), washed with brine, and dried over $MgSO_4$. After concentration, the residue was purified by column chromatography to give allylic chloride **37** (51 mg, 83%). $[\alpha]^{23}_D = -165.6$ (*c* 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34 (dd, 1H, *J* = 10.8, 10.8 Hz), 7.20 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 6.36 (dd, 1H, *J* = 15.3, 9.9 Hz), 6.20 (dd, 1H, *J* = 15.3, 10.8 Hz), 5.83 (d, 1H, *J* = 15.2 Hz), 5.40 (t, 1H, *J* = 7.6 Hz), 4.42 (d, 1H, *J* = 11.6 Hz), 4.30 (d, 1H, *J* = 11.6 Hz), 4.04 (s, 2H), 3.95 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 2.31 (dd, 1H, *J* = 9.9, 6.1 Hz), 2.06 (m, 1H), 1.90 (m, 2H), 1.83 (s, 3H), 1.60 (m, 3H), 1.26 (s, 3H). IR (film): 1719, 1641, 1614, 1587 cm^{-1}. EIMS *m*/*z*: 433 (M^+), 329, 297, 193. Anal. Calcd for $C_{25}H_{33}O_4Cl$: C, 69.35; H, 7.68. Found: C, 69.82; H, 7.92.

Diene, Allylic Alcohol (38). DIBAL (5 mL, 1 M in hexane, 5 mmol) was added to a solution of **37** (425 mg, 0.98 mmol) in CH_2Cl_2 (20 mL) stirred at −78 °C under argon. The reaction mixture was allowed to warm to room temperature and stirred for another 7 h. Methanol was added at low temperature to quench the reaction. The solids were filtered off. The filter cake was washed with diethyl ether several times. The filtrates and washings were combined, washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography to give **38** (341 mg, 86%), together with some unreacted starting material **37** (54 mg, 13%). $[\alpha]^{21}_D = -138.6$ (*c* 0.43, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22 (d, 2H, *J* = 8.2 Hz), 6.86 (d, 2H, *J* = 8.5 Hz), 6.31 (dd, 1H, *J* = 15.2, 10.1 Hz), 6.08 (dd, 1H, *J* = 10.0, 15.3 Hz), 5.92 (dd, 1H, *J* = 15.3, 9.8 Hz), 5.77 (dt, 1H, *J* = 15.1, 6.0 Hz), 5.42 (dt, 1H, *J* = 7.7, 1.3 Hz), 4.41 (d, 1H, *J* = 11.5 Hz), 4.33 (d, 1H, *J* = 11.5 Hz), 4.20 (d, 2H, *J* = 6.0 Hz), 4.05 (d, 2H, *J* = 1.4 Hz), 3.94 (m, 1H), 3.80 (s, 3H), 2.22 (dd, 1H, *J* = 9.8, 6.1 Hz), 2.08 (m, 1H), 1.90 (m, 1H), 1.85 (d, 3H, *J* = 1.1 Hz), 1.60−1.46 (m, 4H), 0.98 (s, 3H). IR (film): 3384, 1658, 1614, 1587, 1514 cm^{-1}. EIMS *m*/*z*: 403, 241, 205. Anal. Calcd for $C_{24}H_{33}O_3Cl$: C, 71.18; H, 8.21. Found: C, 70.57; H, 8.30.

Construction of *trans*-Bicyclo[9.3.0]tetradecane (40). Dess−Martin periodinane (355 mg, 0.84 mmol) was added to a solution of **38** (226 mg, 0.56 mmol) in CH_2Cl_2 (20 mL) stirred at room temperature. After 2 h, the reaction mixture was filtered, and the filter cake was washed with ethyl acetate. Concentration and flash column chromatography of the residue gave 190 mg of aldehyde (85%). To a solution of above aldehyde (190 mg, 0.47 mmol) in CH_2Cl_2 (20 mL) were added a catalytic amount of KCN and 18-crown-6 and TMSCN (0.40 mL, 3.00 mmol). The mixture was stirred at room temperature for an additional 3 h before being washed with brine. The phases were separated. The organic layer was concentrated and diluted with THF (20 mL). HCl (1 N, 5 mL) was added. The resulting solution was stirred for 30 min, diluted with diethyl

ether (50 mL), washed with brine, and dried over Na_2SO_4. Concentration and flash column chromatography gave 190 mg of the corresponding cyanohydrin (94% for two steps). This cyanohydrin was protected as its EE derivative **39** (193 mg, 87%) via an overnight reaction with vinyl ethyl ether (0.40 mL, 4.18 mmol) in CH_2Cl_2 (20 mL) in the presence of PPTS (25 mg).

To a suspension of NaH (155 mg, 75%, 4.84 mmol) in THF (300 mL) was added HMDSA (1.0 mL, 4.80 mmol). The solution became completely transparent after stirring at 30 °C for 1 h. At this temperature, to the resulting NaHMDSA solution was added slowly a solution of the cynaohydrin derivative **39** in THF (100 mL) over 4.5 h. The reaction mixture was heated to 36 °C and stirred for an additional 16 h before being neutralized with 1 N HCl (5 mL). The resulting solution was concentrated to ca. 50 mL. Diethyl ether (100 mL) was added. The phases were separated, and the organic layer was washed successively with water and brine. Without drying, the organic layer was concentrated and redissolved in THF. Another portion of 1 N HCl (5 mL) was added with stirring. Stirring was continued at room temperature for another 2 h, when TLC showed that the EE group had been completely cleaved. The solution was diluted with diethyl ether (100 mL), washed with brine, and dried (Na_2SO_4). Column chromatography gave dolabellane **40** (88 mg, 63% from compound **39**, and 43% total yield for six steps) as a pale yellow syrup. $[\alpha]^{23}_D = -103.0$ (*c* 0.69, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.41 (dd, 1H, J = 15.6, 11.4 Hz), 7.20 (d, 2H, J = 8.4 Hz), 6.86 (d, 2H, J = 8.4 Hz), 6.40 (dd, 1H, J = 15.0, 9.6 Hz), 6.23 (dd, 1H, J = 15.0, 10.8 Hz), 5.82 (d, 1H, J = 15.0 Hz), 5.40 (t, 1H, J = 7.2 Hz), 4.43 (d, 1H, J = 11.4 Hz), 4.30 (d, 1H, J = 12.0 Hz), 4.05 (d, 1H, J = 16.8 Hz), 4.03 (d, 1H, J = 16.8 Hz), 3.98 (m, 1H), 3.80 (s, 3H), 2.33 (dd, 1H, J = 10.2, 6.6 Hz), 2.09 (dd, 1H, J = 14.4, 7.8 Hz), 1.96 (dd, 1H, J = 14.4, 7.8 Hz), 1.89 (m, 2H), 1.84 (s, 3H), 1.65 (m, 1H), 1.54 (m, 1H), 1.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.07, 159.04, 147.31, 144.09, 133.09, 130.93, 130.07, 128.81 × 2, 127.57, 118.56, 113.76 × 2, 83.32, 70.97, 56.71, 55.29, 45.87, 43.61, 40.12, 36.92, 30.71, 23.38, 21.87. IR (film): 1687, 1633, 1614, 1587, 1514, 1249 cm^{-1}. ESIMS *m*/*z*: 413 (M + 2Na).

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Supporting Information Available: ^{1}H NMR spectra of **4a**, **33**, **38**, and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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