Diastereoselective Synthesis of Protected Syn 1,3-Diols by Base-Catalyzed Intramolecular Conjugate Addition of Hemiacetal-Derived Alkoxide Nucleophiles

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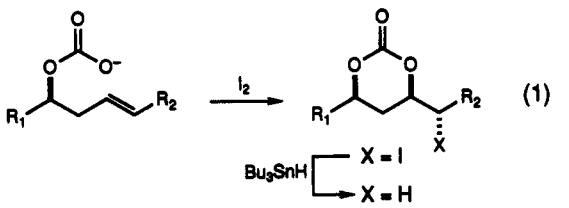
Reaction of the illustrated unsaturated hydroxy esters (X = OMe, R_2 = H, Me) and amides (X = N(Me)OMe, R_2 = H, Me) with benzaldehyde and potassium alkoxide or amide bases is reported. The resulting benzylidene acetals are obtained in good yields (71–84%) and with high selectivity (>90:10). In addition to an exploration of the scope of the reaction, a mechanistic study, involving the use of deuterated benzaldehyde to ascertain the rate-determining step of the process, is described.

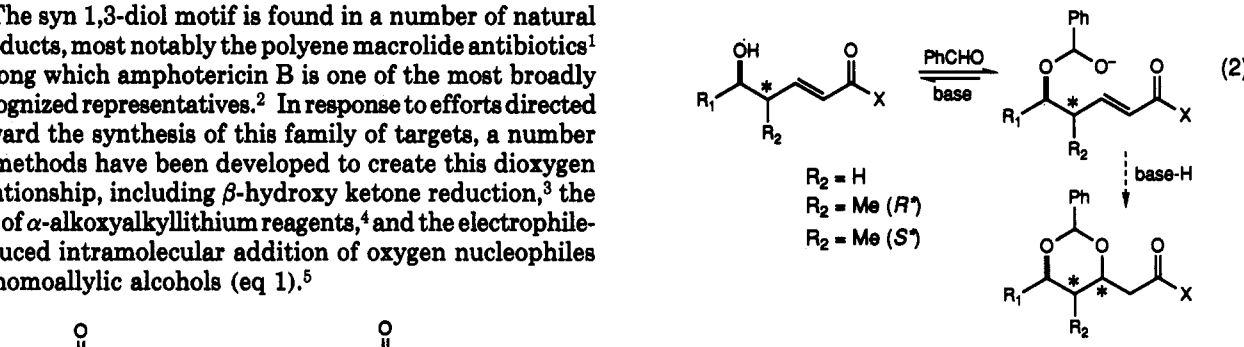
The syn 1,3-diol motif is found in a number of natural products, most notably the polyene macrolide antibiotics[1] among which amphotericin B is one of the most broadly recognized representatives.[2] In response to efforts directed toward the synthesis of this family of targets, a number of methods have been developed to create this dioxygen relationship, including β-hydroxy ketone reduction,[3] the use of α-alkoxyalkyllithium reagents,[4] and the electrophile-induced intramolecular addition of oxygen nucleophiles to homoallylic alcohols (eq 1).[5]



(1)

For projected studies in the area of polyene macrolide synthesis we have had the occasion to evaluate the transformation outlined below (eq 2). As illustrated, the intention was to attempt to stereoselectively direct the conjugate addition of a reversibly formed hemiacetal alkoxide from a resident homoallylic alcohol function. The substrates chosen for study were unsaturated esters and amides (X = OMe, N(Me)OMe) bearing either no substituent (R_2 = H) or a methyl group in either configuration in the allylic position. The objectives were to evaluate the scope and mechanism of the transformation.

Preparation of Starting Materials. Homoallylic alcohols **1a–c** were readily prepared by the allylsilane-based γ-alkylation methodology of Katzenellenbogen.[6] Addition of methyl 2-[(dimethylphenyl)silyl]-3-butenoate[7] to the illustrated aldehydes under the influence of titanium tetrachloride catalysis (eq 3) afforded the (*E*) homoallylic alcohols in the unoptimized yields of 65–70%.



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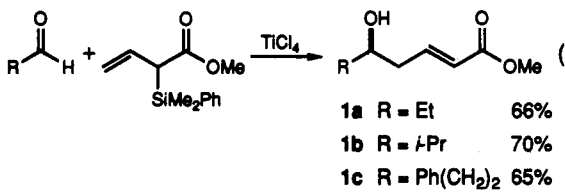
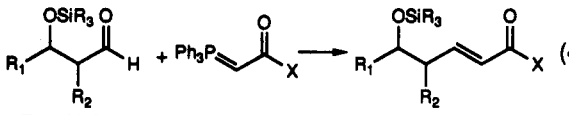


(3)

1a R = Et 66%
1b R = *i*-Pr 70%
1c R = $Ph(CH_2)_2$ 65%

The other substrates employed in the study were prepared through homologation of the requisite silyl-protected aldehydes with the indicated phosphoranes (eq 4). The illustrated *N*-methoxy-*N*-methylamides were also employed as precursors for the derived ketones using the Weinreb methodology.[8]



(4)

R_2 = H, Me X = OMe, N(Me)OMe

Results and Discussion

Reaction of alcohols **1a–c** with benzaldehyde in the presence of potassium *tert*-butoxide (*t*-BuOK) at 0 °C in

(1) Omura, S. *Macrolide Antibiotics, Chemistry, Biology and Practice*; Academic Press: New York, 1984.

(2) For the synthesis of amphotericin B see: Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4672–4685. Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *Ibid.* 4685–4696. Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *Ibid.* 4696–4705.

(3) (a) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190–5192. (b) Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 6467–6470. (c) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923–1926. (d) Bonadies, F.; DiFabio, R.; Gubioti, A.; Mecozzi, S.; Bonini, C. *Tetrahedron Lett.* **1987**, *28*, 703–706. (e) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009–3112. (f) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803–805. (g) Narasaka, K.; Pai, F.-C. *Tetrahedron Lett.* **1984**, *40*, 2233–2238. (h) Narasaka, K.; Pai, F.-C. *Chem. Lett.* **1980**, 1415–1418.

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(5) (a) Cardillo, G.; Oreno, M.; Porzi, G.; Sanzi, S. *J. Chem. Soc., Chem. Commun.* **1981**, 465–466. (b) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1149–1151.

(6) Albaugh-Robertson, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288–5302.

(7) Naruta, Y.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, 609–612.

(8) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174. (b) Levin, J. L.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993. (c) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.

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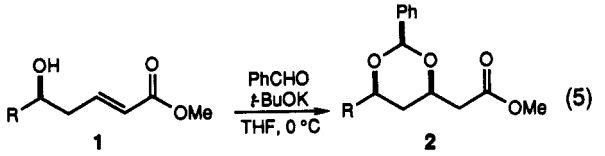
Table I. Base-Catalyzed Acetalization of Esters 1 (eq 5)

	R	yield[a] (%)	selectivity
2a	Et	79	>95:5[b]
2b	*i*-Pr	71	>95:5[b]
2c	$PhCH_2CH_2$	73	96:4[c]

[a] Isolated yields of purified 2. [b] Ratios of unpurified products determined by 400-MHz NMR. [c] Ratios of unpurified products determined by GLC.

THF furnished benzylidene acetals **2a–c** in 71–79% yield (eq 5, Table I). In optimizing this transformation we found



1 2 (5)

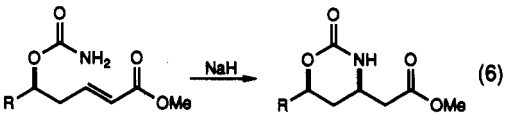
it necessary to add 1.1 equiv of benzaldehyde and 0.1 equiv of *t*-BuOK three times at 15-min intervals to effect complete conversion of starting materials to the product benzylidene acetals. Presumably, competing Cannizzaro aldehyde disproportionation is the origin of the nonproductive consumption of this reaction constituent.

In all instances, the reaction diastereoselectivity was greater than 95% favoring the more stable syn diastereomer with all substituents being equatorial on the dioxane ring. The use of other bases such as potassium hexamethyldisilazide (KHMDS) afforded similar yields and selectivities, and this base has been used interchangeably with *t*-BuOK throughout the study. In some instances minor differences in yields have been noted between the two bases; however, this could be due to the fact that the KHMDS experiments were routinely carried out at −20 °C rather than 0 °C due the greater reactivity of the base. The stereochemistry of each product was determined by NOE difference experiments which indicated that the three ring protons α to each oxygen are axial.

Other aromatic aldehydes were also investigated. When *p*-anisaldehyde was substituted for benzaldehyde, the reaction was sluggish, suggesting that formation of the hemiacetal alkoxide intermediate might be rate determining for this case. With *p*-nitrobenzaldehyde, the reaction proceeded rapidly but was accompanied by the formation of several side products, an observation which was not unexpected due to the problems associated with electron transfer with nitroaromatics. When aliphatic aldehydes such as isobutyraldehyde or acetaldehyde were employed in the reaction, acetals possessing the syn and the anti 1,3-dioxygen relationship were formed in a 1:1 ratio. One possible explanation for the lack of selectivity in this instance could be associated with the irreversibility of the conjugate addition step; in these cases, the hemiacetal-based alkoxide might be somewhat less stabilized thus retarding equilibration which is apparently responsible for the stereoselectivity (vide infra).

The syn stereochemical outcome of these reactions was anticipated based on the premise that thermodynamic control would be expressed. It is noteworthy that the same stereochemical outcome is observed in the related base-catalyzed intramolecular conjugate addition of carbamates derived from δ-hydroxy unsaturated esters (eq 6);[9] however, the origin of the observed stereoselectivity was not addressed.

(9) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797–1798.



(6)

Mechanism. To ascertain whether the reaction with benzaldehyde is thermodynamically or kinetically controlled, the diastereomeric anti acetals **5a** and **5b** were prepared (Scheme I), and their fate under the reaction conditions was evaluated. It was anticipated that diastereomer **5a**, possessing the more stable configuration at the acetal center, retained the option of undergoing C_3 isomerization under base-catalysis to the syn benzylidene acetal **2c** without direct dissociation of the intervening hemiacetal alkoxide; however, anti acetal **5b**, being diastereomeric at both the acetal and C_3 stereocenters, would be required to fully dissociate into alkoxide and aldehyde fragments during the isomerization to acetal **2c**.

Accordingly, β-hydroxy ketone **3** was selectively reduced with $Me_4NBH(OAc)_3$[10] to afford a 15:1 mixture of diols from which the crystalline anti diastereomer **4** was isolated in 68% yield (Scheme I). Anti diol **4** was then transformed into a 2.4:1 mixture of benzylidene acetals **5a** and **5b** which were separated by preparative HPLC. The stereochemistry of each diastereomer was unequivocally determined by ^1H NMR NOE difference experiments. For **11a**, an enhancement of 11% was observed between the acetal proton and the C_5 proton, and none was observed between the acetal proton and the C_3 proton or between the C_5 proton and the C_3 proton. For **11b**, an enhancement of 10% was observed between the acetal proton and the C_3 proton but not between the acetal proton and the C_5 proton or between the C_3 proton and the C_5 proton.

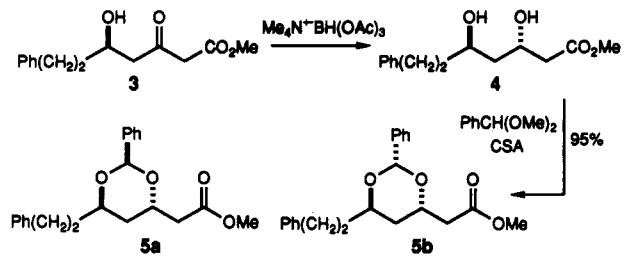
When anti acetal **5a** was subjected to the reaction conditions (1.1 equiv of PhCHO, 0.1 equiv of *t*-BuOK, 15 min, 0 °C), the isomeric syn diastereomer **2c** was obtained as the exclusive product (Scheme II). As illustrated, it is reasonable that the first step of the equilibration process is a base-catalyzed elimination to give intermediate **6** which may then recyclize or dissociate. In order to evaluate the partitioning of hemiacetal alkoxide **6** between recyclization and loss of benzaldehyde, **5a** was treated with *t*-BuOK (0 °C) and deuteriobenzaldehyde PhCDO. In this case, the product **2c** incorporated 50% deuterium at the acetal center at 0 °C.[11] The equilibration of **5a** → **2c** at 0 °C thus proceeds at least in part via **7** at 0 °C. However, if the same experiment was carried out at −40 °C, equilibration of **5a** occurs without deuterium incorporation, demonstrating that direct equilibration via the hemiacetal alkoxide **6** is the preferred path at lower temperatures.

In contrast, acetal **5b**, only after five addition cycles of base and benzaldehyde (75 min), afforded a 10:1 mixture of **2c** along with recovered **5b**. This diastereomer was also subjected to base-catalyzed equilibration in the presence of PhCDO to afford product **2c** with 80% deuterium incorporation along with undeuterated starting acetal. This experiment indicates that the conjugate addition step is also reversible and that the anti acetal **5b** can equilibrate to the more stable syn diastereomer isomer **2c** through full dissociation to **7** and aldehyde. The slow rate of

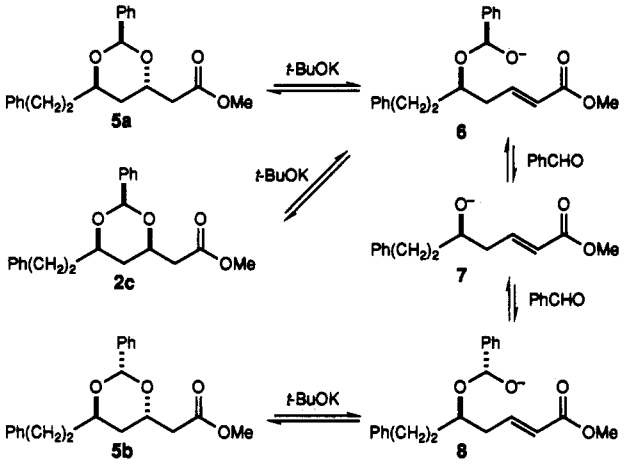
(10) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

(11) As shown by integration of the acetal proton in the 400-MHz ^1H NMR spectrum and by mass spectroscopy. In each case, the amount of deuterium incorporation corresponds to the amount of PhCDO added.

Scheme I



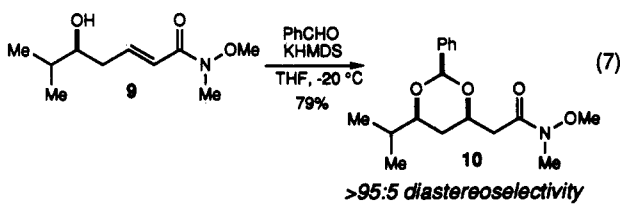
Scheme II



isomerization of **5b** was unexpected in comparison to the behavior of the diastereomeric acetal **5a**. Unfortunately, the present experiments do not distinguish between a slow elimination step (**5b** → 8) and a slow dissociation process (8 → 7 + PHCHO).[12]

These experiments allow us to conclude that the diastereoselection associated with the C_3 benzylidene acetal center is governed by thermodynamic considerations. On the other hand, the origin of the diastereoselectivity at the C_1 acetal center is less clear but is probably also thermodynamically controlled.

Scope. The reaction is not restricted to the use of α,β-unsaturated esters. For example, the analogous reaction of unsaturated *N*-methoxy-*N*-methylamide **9** with benzaldehyde and KHMDS[13] at −20 °C (eq 7) produced the

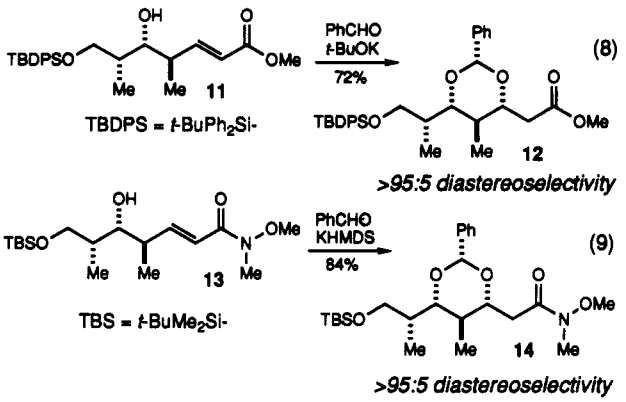


(7)

>95:5 diastereoselectivity

syn-benzylidene acetal **10** in good yield (79%) and high selectivity (>95:5). These hydroxamic acid derivatives are particularly versatile since they are excellent precursors to the derived ketones through organometallic addition.[8]

Substrates with intervening γ-methyl substituents are also good substrates for this reaction. Under standard conditions, ester **11** provided the *syn*-benzylidene acetal **12** in 72% yield as a single diastereomer as determined by 400-MHz ^{1}H NMR spectroscopic analysis of the unpurified product (eq 8).[14] Similarly, treatment of amide **13** with



(8)

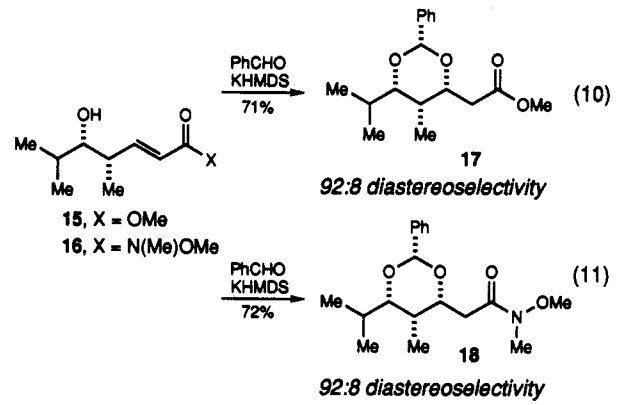
>95:5 diastereoselectivity

(9)

>95:5 diastereoselectivity

benzaldehyde and KHMDS furnished **14** in 84% yield with >95:5 selectivity (400-MHz ^{1}H NMR).[14]

The analogous reactions with unsaturated ester and amide **15** and **16** (eqs 10 and 11) are somewhat less stereoselective than the preceding cases. For the reaction



(10)

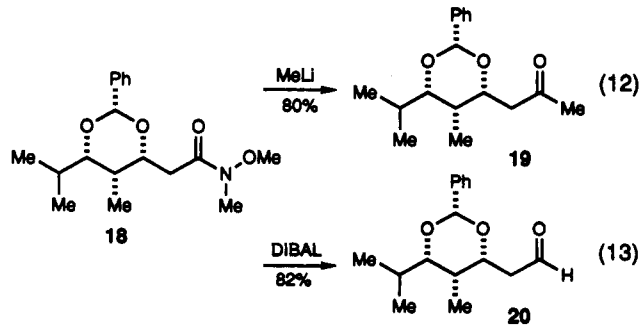
92:8 diastereoselectivity

(11)

92:8 diastereoselectivity

of ester **15** wherein the hydroxyl and intervening methyl groups are in a syn relationship, the selectivity drops to 92:8. Similarly, amide **16** affords acetal **18** in 72% yield with identical selectivity. This drop in diastereoselectivity was anticipated since the major product diastereomer in each of these cases possesses a destabilizing axial ring methyl group which lowers the energy difference between the syn and anti diastereomer product manifolds.

Aldehyde and ketone derivatives are available from *N*-methoxy-*N*-methylamides.[8] For example, addition of methyllithium to amide **18** afforded the corresponding methyl ketone **19** (80%) while the corresponding reduction with DIBAL furnished aldehyde **20** in 82% yield (eqs 12 and 13).



(12)

(13)

(12) The yield of these reactions has not been determined. The ^{1}H NMR spectra of the unpurified products did not show any decomposition of the acetals, except for the equilibration of **5b** where traces of the corresponding unsaturated ester could be detected. Cannizaro byproducts were also observed.

(13) With *t*-BuOK, **10** is obtained in 77% yield with a >95:5 diastereoselectivity.

(14) These experiments were performed by Dr. P. K. Somers in the laboratory of S. L. Schreiber.

In principle, ketone derivatives such as **19** might also be accessible from their unsaturated hydroxy ketone precursors through the application of these acetal-based conjugate addition reactions; however, attempts to develop these cases were unsuccessful.

Conclusions

A previous study from this laboratory has exploited the directed reduction of β-hydroxy ketones through an intramolecular samarium-catalyzed Tishchenko reaction,[15] a process which relies on the transient formation of hemiacetal-derived metal alkoxides which serve as an internal hydride source. The preceding discussion provides complementary precedent for the utilization of the similarly formed acetal alkoxides as tethered oxygen nucleophiles which have been shown to undergo diastereoselective intramolecular conjugate addition to internal electrophilic olefins. Both reactions provide expanded capabilities in the area of acyclic stereocontrol.

Experimental Section

General Methods. All nonaqueous reactions were performed under an oxygen-free atmosphere of nitrogen with rigid exclusion of moisture from reagents and glassware. Liquid chromatography was performed using a forced flow (flash chromatography)[16] of the indicated solvent system on EM Reagents silica gel 60 (230–400 mesh). Data are reported as follows: eluant composition and column diameter (cm) × column length (cm). ^{1}H NMR spectra were recorded in $CDCl_3$, and chemical shifts are reported in ppm on the δ scale from an internal standard of residual chloroform (7.26 ppm) or added tetramethylsilane (0.00 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, oct = octet, m = multiplet), integration, coupling constants in Hz, and assignment. ^{13}C NMR spectra were recorded in deuteriochloroform on a Bruker AM-300, AM-400, or AM-500 spectrometer. Chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.0 ppm) on the δ scale. Optical rotations were determined with a JASCO DIP-181 digital polarimeter at 546 nm using a Hg lamp. Data are reported as follows: $[\alpha]_{546}$ (concentration g/100 mL, solvent). When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl. Dichloromethane and triethylamine were distilled from calcium hydride.

Methyl (*E*)-5-Hydroxy-2-heptenoate (1a).[17] To a solution of 690 μL (6.3 mmol, 3.0 equiv) of $TiCl_4$ in 10 mL of CH_2Cl_2 at −23 °C was added 228 μL (2.10 mmol, 1.50 equiv) of propionaldehyde, followed by a solution of 493 mg (2.10 mmol) of methyl 2-[(dimethylphenyl)silyl]-3-butenoate[7] in 6 mL of CH_2Cl_2 (rinse 3 × 2 mL). The resulting orange mixture was stirred at −23 °C for 2 h and quenched with 50 mL of pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted with 3 × 50 mL of ether. The combined organic layers were washed twice with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (7:3 hexane/ethyl acetate, 3 × 23 cm) afforded 221 mg (66%) of **1a** as a colorless oil: R_f 0.22 (7:3 hexane/ethyl acetate); IR (thin film) 3450, 2970, 2940, 1720, 1660, 1440, 1325, 1275, 1215, 1170, 1115, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dt, 1 H, J = 15.6, 7.5 Hz, C*H*CHCOOCH$_3$), 5.88 (dt, J = 15.6, 1.2 Hz, C*H*COOCH$_3$), 3.70 (s, 3 H, OC*H*$_3$), 3.66 (m, 1 H, C*H*OH), 2.37 (m, 1 H, C*H*CHOH), 2.31 (m, 1 H, C*H*CHOH), 2.02 (s, 1 H, O*H*), 1.50 (m, 2 H, CH$_3$C*H*$_2$), 0.93 (t, 3 H, J = 7.4 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 145.7, 123.2, 71.7, 51.4, 39.6, 29.8, 9.8. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.93; H, 8.85.

Methyl (*E*)-5-Hydroxy-6-methyl-2-heptenoate (1b). The indicated compound was prepared and purified according to the procedure described for compound **1a** to afford **1b** as a colorless oil: R_f 0.37 (7:3 hexane/ethyl acetate); IR (thin film) 3440, 2960, 2880, 1720, 1660, 1440, 1325, 1275, 1215, 1170, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (dt, 1 H, J = 15.6, 7.0 Hz, C*H*CHCOOCH$_3$), 5.92 (dt, J = 15.6, 1.5 Hz, C*H*COOCH$_3$), 3.73 (s, 3 H, OCH$_3$), 3.52 (m, 1 H, C*H*OH), 2.41 (m, 1 H, C*H*CHOH), 2.31 (m, 1 H, C*H*CHOH), 1.69 (m, 1 H, (CH$_3$)$_2$C*H*), 1.64 (s, 1 H, O*H*), 0.93 (d, 3 H, J = 6.8 Hz, C*H*$_3$), 0.93 (d, 3 H, J = 6.8 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 146.4, 123.0, 75.2, 51.4, 37.1, 33.3, 18.6, 17.2. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.84; H, 9.40.

Methyl (*E*)-5-Hydroxy-7-phenyl-2-heptenoate (1c). The indicated compound was prepared and purified according to the procedure described for compound **1a** to afford **1c** as a colorless oil: R_f 0.30 (7:3 hexane/ethyl acetate); IR (thin film) 3450, 3040, 2950, 1730, 1660, 1605, 1500, 1455, 1440, 1320, 1280, 1220, 1175, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2 H, Ar*H*), 7.21 (m, 3 H, Ar*H*), 6.98 (dt, 1 H, J = 15.5, 7.6 Hz, C*H*CHCOOCH$_3$), 5.91 (dt, 1 H, J = 15.5, 1.4 Hz, C*H*COOCH$_3$), 3.78 (m, 1 H, C*H*OH), 3.73 (s, 3 H, OC*H*$_3$), 2.81 (dt, 1 H, J = 13.8, 7.9 Hz, PhC*H*), 2.69 (dt, 1 H, J = 13.8, 8.2 Hz, PhC*H*), 2.46–2.32 (m, 2 H, C*H*$_2$-CHCHCOOCH$_3$), 1.81 (m, 2 H, PhCH$_2$C*H*$_2$), 1.76–1.71 (m, 1 H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 145.2, 141.5, 128.4, 128.4, 126.0, 123.6, 69.8, 51.5, 40.3, 38.6, 31.9. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.72; H, 7.59.

(2*R,4*R**,6*R**)-4-(Carbomethoxymethyl)-6-ethyl-2-phenyl-1,3-dioxane (2a).** To a solution of 54.6 mg (0.350 mmol) of ester **1a** in 3.5 mL of THF at 0 °C was added 39 μL (0.38 mmol, 1.1 equiv) of freshly distilled benzaldehyde, followed by 3.9 mg (0.035 mmol, 0.10 equiv) of *t*-BuOK, and the resulting yellow solution was stirred for 15 min at 0 °C. This sequence (addition/stirring) was repeated twice, and the reaction mixture was quenched with 10 mL of pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted with 3 × 10 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica get (9:1 hexane/ethyl acetate, 1 × 16 cm) afforded 71.6 mg (79%) of **2a** as a colorless oil: R_f 0.71 (7:3 hexane/ethyl acetate); IR (thin film) 2960, 2880, 1745, 1455, 1440, 1350, 1305, 1250, 1220, 1170, 1140, 1100, 1065, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 2 H, Ar*H*), 7.35 (m, 3 H, Ar*H*), 5.56 (s, 1 H, C*H*Ph), 4.31 (m, 1 H, CH$_3$-OOCCH$_2$C*H*O), 3.76 (m, 1 H, CH$_3$CH$_2$C*H*O), 3.71 (s, 3 H, OC*H*$_3$), 2.75 (dd, 1 H, J = 15.7, 7.0 Hz, C*H*COOCH$_3$), 2.53 (dd, 1 H, J = 15.7, 6.2 Hz, C*H*COOCH$_3$), 1.74 (dt, 1 H, J = 13.0, 2.4 Hz, OCHC*H*CHO), 1.74–1.52 (m, 2 H, CH$_3$C*H*$_2$), 1.42 (dt, 1 H, J = 13.0, 11.2 Hz, OCHC*H*CHO), 1.00 (t, 3 H, J = 7.5 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 138.6, 128.6, 128.1, 126.0, 100.6, 77.9, 73.2, 51.7, 40.8, 36.1, 28.8, 9.5. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.07; H, 7.73.

(2*S,4*R**,6*S**)-4-(Carbomethoxymethyl)-6-(1-methylethyl)-2-phenyl-1,3-dioxane (2b).** The indicated compound was prepared according to the procedure described for compound **2a**. Purification by chromatography on silica gel (9:1 hexane/ethyl acetate, 3 × 20 cm) afforded 602 mg (71%) of **2b** as a colorless oil: R_f 0.69 (7:3 hexane/ethyl acetate); IR (thin film) 2960, 2880, 1745, 1455, 1440, 1405, 1385, 1350, 1220, 1170, 1145, 1105, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 2 H, Ar*H*), 7.33 (m, 3 H, Ar*H*), 5.55 (s, 1 H, C*H*Ph), 4.30 (m, 1 H, CH$_3$OOCCH$_2$C*H*O), 3.71 (s, 3 H, OC*H*$_3$), 3.54 (ddd, 1 H, J = 11.2, 6.7, 2.4 Hz, (CH$_3$)$_2$-CHC*H*O), 2.75 (dd, 1 H, J = 15.7, 7.0 Hz, C*H*COOCH$_3$), 2.53 (dd, 1 H, J = 15.7, 6.2 Hz, C*H*COOCH$_3$), 1.81 (oct, 1 H, J = 6.8 Hz, (CH$_3$)$_2$C*H*), 1.72 (dt, 1 H, J = 12.8, 2.4 Hz, OCHC*H*CHO), 1.44 (dt, 1 H, J = 12.8, 11.2 Hz, OCHC*H*CHO), 1.02 (d, 3 H, J = 6.8 Hz, C*H*$_3$), 0.95 (d, 3 H, J = 6.8 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 138.7, 128.5, 128.1, 126.0, 100.4, 81.6, 73.3, 51.7, 40.9, 33.5, 32.9, 18.4, 17.9. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.04; H, 7.89.

(2*R,4*R**,6*R**)-4-(Carbomethoxymethyl)-2-phenyl-6-(2-phenylethyl)-1,3-dioxane (2c).** The indicated compound was prepared according to the procedure described for compound **2a**. Purification by chromatography on silica gel (85:15 hexane/

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(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(17) Prepared according to the procedure outlined in ref 6.

ethyl acetate, 1 × 17 cm) afforded 55.4 mg (73%) of **2c** as a colorless oil that solidified slowly on standing: mp 65–66 °C; R_f 0.65 (7:3 hexane/ethyl acetate); IR (thin film) 3030, 2950, 2920, 2860, 1745, 1495, 1455, 1440, 1405, 1350, 12125, 1200, 1160, 1135, 1120, 1090, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2 H, Ar*H*), 7.41–7.29 (m, 5 H, Ar*H*), 7.23 (m, 3 H, Ar*H*), 5.57 (s, 1 H, OC*H*O), 4.30 (m, 1 H, OC*H*CH_2COOCH_3), 3.85 (m, 1 H, PhCH_2CH_2C*H*O), 3.72 (s, 3 H, OCH_3), 2.85 (m, 1 H, PhC*H*), 2.77 (m, 1 H, PhC*H*), 2.77 (dd, 1 H, J = 15.7, 7.0, C*H*COOCH_3), 2.53 (dd, 1 H, J = 15.7, 6.2, C*H*COOCH_3), 2.02 (m, 1 H, PhCH_2C*H*), 1.83 (m, 1 H, PhCH_2C*H*), 1.72 (dt, 1 H, J = 12.9, 2.4 Hz, OCHCH_2-CHO), 1.50 (dt, 1 H, J = 12.9, 11.2 Hz, OCHCH_2CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 141.7, 138.5, 128.6, 128.5, 128.4, 128.1, 126.0, 125.8, 100.5, 75.4, 73.1, 51.7, 40.7, 37.3, 36.5, 31.1. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.90; H, 7.12.

Methyl 5-Hydroxy-3-oxo-7-phenylheptanoate (3). To a solution of 7.40 mL (52.5 mmol, 2.63 equiv) of diisopropylamine in 50 mL of THF at −78 °C was added 19.4 mL (2.56 mmol, 2.56 equiv) of 2.64 M butyllithium in hexanes. The resulting solution was stirred at −78 °C for 15 min and treated with 2.70 mL (25.0 mmol, 1.25 equiv) of methyl acetoacetate. The yellow solution was stirred at −12 °C for 30 min, cooled to −78 °C, and treated with a solution of 2.68 g (20.0 mmol) of hydrocinnamaldehyde in 10 mL of THF (rinse 3 × 5 mL). The reaction mixture was stirred at −78 °C for 30 min and quenched with 3 mL of acetic acid. The resulting mixture was warmed to 20 °C and poured into 100 mL of saturated aqueous ammonium chloride, and the aqueous layer was extracted with 3 × 150 mL of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (7:3 hexane/ethyl acetate/6 × 28 cm) afforded 3.54 g (71%) of **3** as a colorless oil: R_f 0.15 (7:3 hexane/ethyl acetate); IR (thin film) 3500, 3130, 2950, 2860, 1750, 1715, 1650, 1605, 1500, 1455, 1440, 1410, 1325, 1265, 1155, 1100, 1055, 1030, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2 H, Ar*H*), 7.19 (m, 3 H, Ar*H*), 4.09 (oct, 1 H, J = 4.1 Hz, C*H*OH) 3.74 (s, 3 H, OCH_3), 3.48 (s, 2 H, OCCH_2COOCH_3), 2.84 (d, 1 H, O*H*), 2.85–2.65 (m, 4 H, CHOHCH_2CO and ArCH_2), 1.84 (m, 1 H, ArCH_2CH_2), 1.71 (m, 1 H, ArCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 167.2, 141.6, 128.4, 125.9, 66.7, 52.4, 49.6, 49.6, 37.9, 31.7. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.34; H, 7.33.

(3*S,5*R**)-Methyl 3,5-Dihydroxy-7-phenylheptanoate (4).** A solution of 14.5 g (55.0 mmol, 4.20 equiv) of trimethylammonium triacetoxyborohydride[10] in 50 mL of acetonitrile and 50 mL of acetic acid was stirred at 20 °C for 30 min, cooled to −40 °C, and treated with a solution of 3.25 g (13.0 mmol) of the keto ester in 10 mL of acetonitrile (rinse 2 × 10 mL). The reaction mixture was stirred at −40 °C for 24 h and at 0 °C for 1 h. The reaction was cooled to −40 °C and quenched with 50 mL of acetone and 50 mL of 1 M aqueous sodium–potassium tartrate. The acetone was removed in vacuo and the residue poured slowly into 300 mL of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with 4 × 150 mL of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Recrystallization from ether afforded 2.235 g (68%) of **4** as a white crystalline solid: mp 78 °C; R_f 0.25 (1:1 hexane/ethyl acetate); IR (thin film) 3600, 3500, 3030, 2950, 1730, 1605, 1495, 1455, 1440, 1200, 1175, 1075 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2 H, Ar*H*), 7.18 (m, 3 H, Ar*H*), 4.37 (m, 1 H, C*H*OHCH_2COOCH_3), 3.94 (m, 1 H, ArCH_2CH_2C*H*OH), 3.72 (s, 3 H, OCH_3), 3.40 (m, 1 H, O*H*), 2.81 (ddd, 1 H, J = 13.8, 9.9, 5.6 Hz, ArC*H*), 2.68 (ddd, 1 H, J = 13.8, 9.7, 6.6 Hz, ArC*H*), 2.51 (m, 2 H, CH_2COOCH_3), 1.87 (m, 1 H, ArCH_2C*H*), 1.77 (m, 1 H, ArCH_2C*H*), 1.73 (m, 2 H, CHOHCH_2-CHOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 141.9, 128.4, 128.4, 125.8, 68.3, 65.6, 51.8, 42.0, 41.0, 39.1, 32.1. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.80; H, 7.88.

A small portion of the unpurified diol was converted to the corresponding dibenzoate (PhCOCl, Et_3N, DMAP, CH_2Cl_2, 20 °C, 18 h). Integration of the ^{1}H NMR signals at 3.65 (anti) and 3.62 (syn) ppm indicated a 15:1 ratio of diastereomers.

(2*R,4*S**,6*R**)-4-(Carbomethoxymethyl)-6-(2-phenylethyl)-2-phenyl-1,3-dioxanes (5a and 5b).** To a solution of 1.02 g (4.00 mmol) of diol **4** in 40 mL of CH_2Cl_2 at 20 °C were added 1.8 mL (12 mmol, 3.0 equiv) of benzaldehyde, a catalytic amount of camphosulfonic acid, and 50 mg of 4-Å sieves. The resulting mixture was stirred at 20 °C for 4 h. The reaction was quenched with 0.5 mL of triethylamine, and the solvents were evaporated in vacuo. Purification by chromatography on silica gel (9:1 hexane/ethyl acetate, 4 × 23 cm) afforded 1.31 g (95%) of a colorless oil (2.4:1 ratio of diastereomers by ^{1}H NMR). These compounds were separated by HPLC.

Major isomer **5a**: R_f 0.78 (1:1 hexane/ethyl acetate); IR (thin film) 3030, 2960, 2860, 1740, 1500, 1455, 1440, 1405, 1370, 1315, 1195, 1175, 1120, 1050, 1030, 1000 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2 H, Ar*H*), 7.38–7.29 (m, 5 H, Ar*H*), 7.21 (m, 3 H), Ar*H*), 5.78 (s, 1 H, OC*H*O), 4.72 (m, 1 H, C*H*CH_2COOCH_3), 3.96 (m, 1 H, ArCH_2CH_2C*H*), 3.71 (s, 3 H, OCH_3), 3.06 (dd, 1 H, J = 14.6, 8.5 Hz, C*H*COOCH_3), 2.85 (ddd, 1 H, J = 14.0, 9.2, 5.5 Hz, ArC*H*), 2.75 (ddd, 1 H, J = 14.0, 8.9, 7.3 Hz, ArC*H*), 2.70 (dd, 1 H, J = 14.6, 7.0 Hz, C*H*COOCH_3), 2.08 (ddd, 1 H, J = 13.6, 11.8, 6.2 Hz, CHOCH_2CHO), 2.00 (m, 1 H, ArCH_2C*H*), 1.80 (m, 1 H, ArCH_2C*H*), 1.52 (ddd, 1 H, J = 13.6, 2.2, 1.0 Hz, CHOCH_2CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 141.7, 138.7, 128.7, 128.5, 128.4, 128.2, 126.0, 125.9, 94.6, 71.2, 69.4, 51.8, 37.6, 36.5, 33.4, 31.1. Anal. Calcd for $C_{21}H_{14}O_4$: C, 74.09; H, 7.11. Found: C, 74.04; H, 7.14.

Minor isomer **5b**: R_f 0.78 (1:1 hexane/ethyl acetate); IR (thin film) 3040, 2950, 1740, 1500, 1455, 1440, 1370, 1195, 1175, 1015, 1060, 1030, 1000 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2 H, Ar*H*), 7.38–7.18 (m, 8 H, Ar*H*), 5.86 (s, 1 H, OC*H*O), 4.52 (m, 1 H, C*H*CH_2COOCH_3), 4.26 (m, 1 H, ArCH_2CH_2C*H*), 3.70 (s, 3 H, OCH_3), 2.83 (ddd, 1 H, J = 13.8, 9.6, 5.4 Hz, ArC*H*), 2.73 (ddd, 1 H, J = 13.8, 9.3, 7.0 Hz, ArC*H*), 2.71 (dd, 1 H, J = 15.7, 7.3 Hz, C*H*COOCH_3), 2.55 (m, 1 H, ArCH_2C*H*), 2.48 (dd, J = 15.7, 5.8, C*H*COOCH_3), 2.03 (ddd, J = 13.3, 12.0, 6.2 Hz, OCHCH_2CHO), 1.87 (m, 1 H, ArCH_2C*H*), 1.57 (ddd, 1 H, J = 13.3, 2.4, 1.0 Hz, OCHCH_2CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 141.5, 138.7, 128.7, 128.5, 128.2, 126.0, 126.0, 94.6, 71.7, 69.1, 51.7, 41.0, 33.6, 32.2, 32.0. Anal. Calcd for $C_{21}H_{14}O_4$: C, 74.09; H, 7.11. Found: C, 74.37; H, 7.20.

Equilibration of Acetal 5a. To a solution of 29.6 mg (0.087 mmol) of **5a** in 1 mL of THF at 0 °C was added 10 μL (96 μmol, 1.1 equiv) of freshly distilled benzaldehyde, followed by 1.0 mg (8.7 μmol, 0.10 equiv) of *t*-BuOK, and the resulting yellow solution was stirred for 15 min at 0 °C. This sequence (addition/stirring) was repeated twice, and the reaction mixture was quenched with 10 mL of pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted with 3 × 10 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR analysis of the unpurified product revealed the presence of **2c** only.

Equilibration of Acetal 5a with PHCDO. To a solution of 29.4 mg (0.087 mmol) of **5a** in 1 mL of THF at 0 °C was added 10 μL (96 μmol, 1.1 equiv) of freshly distilled deuteriobenzaldehyde, followed by 1.0 mg (8.7 μmol, 0.10 equiv) of *t*-BuOK, and the resulting yellow solution was stirred for 15 min at 0 °C. The reaction mixture was quenched with 10 mL of pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted with 3 × 10 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Integration of the acetal peak in the ^{1}H NMR spectrum of the unpurified product revealed a 1.11:1 ratio of deurated **2c**/**2c**. Mass spectroscopy analysis (chemical ionization) indicated a ratio of 1.07:1. When performed at −40 °C, the equilibration afforded a 2:1 ratio of **2c**/**5a**, with no detectable incorporation of deuterium by ^{1}H NMR spectroscopy.

Equilibration of Acetal 5b. To a solution of 14.4 mg (0.042 mmol) of **5b** in 0.5 mL of THF at 0 °C was added 5.0 μL (4.7 μmol, 1.1 equiv) of freshly distilled benzaldehyde, followed by 0.5 mg (4.7 μmol, 0.10 equiv) of *t*-BuOK, and the resulting yellow solution was stirred for 15 min at 0 °C. This sequence (addition/stirring) was repeated four times, and the reaction mixture was quenched with 10 mL of pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted with 3 × 10 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR analysis of the unpurified product revealed a 10:1 ratio of **2c**/**5b**.

Equilibration of Acetal 5b with PHCDO. To a solution of 24.5 mg (0.072 mmol) of **5b** in 1 mL of THF at 0 °C was added

8.0 μL (79 μmol, 1.1 equiv) of freshly distilled deuteriobenzaldehyde, followed by 0.8 mg (7.9 μmol, 0.10 equiv) of *t*-BuOK, and the resulting yellow solution was stirred for 15 min at 0 °C. This sequence (addition/stirring) was repeated three times, and the reaction mixture was quenched with 10 mL of pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted with 3 × 10 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Integration of the acetal peak in the ^1H NMR spectrum of the unpurified product revealed a 4.10:1 ratio of deurated **2c**/**2c**. Mass spectroscopy analysis (chemical ionization) gave 2.67:1 for this same ratio.

Equilibration of Acetal 2c with PHCDO. To a solution of 9.8 mg (29 μmol) of **2c** in 0.5 mL of THF at 0 °C was added 3.0 μL (32 μmol, 1.1 equiv) of freshly distilled deuteriobenzaldehyde, followed by 0.3 mg (3 μmol, 0.1 equiv) of *t*-BuOK, and the resulting yellow solution was stirred for 15 min at 0 °C. The reaction mixture was quenched with 10 mL of pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted with 3 × 10 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Integration of the acetal peak in the ^1H NMR spectrum of the unpurified product revealed a 0.48:1 ratio of deurated **2c**/**2c**. Mass spectroscopy analysis (chemical ionization) gave 0.31:1 for this same ratio.

(*E*)-*N*-Methoxy-*N*-methyl-5-hydroxy-6-methyl-2-heptenamide (9). Step 1: 4-Hydroxy-5-methyl-1-hexene. To a solution of 33 mL (33 mmol, 1.1 equiv) of 1.0 M allyl magnesium bromide in ether in 40 mL of ether at −78 °C was added a solution of 2.72 mL (30.0 mmol) of isobutyraldehyde in 50 mL of ether (rinse 3 × 10 mL). The resulting solution was stirred at −78 °C for 30 min, quenched with 100 mL of saturated aqueous NH_4Cl, and allowed to warm to 20 °C. The aqueous phase was extracted with 3 × 100 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by distillation (52 °C/20 mmHg) afforded 2.25 g (66%) of a colorless oil: R_f 0.46 (4:1 hexane/ethyl acetate); IR (thin film) 3400, 2960, 2940, 2900, 2880, 1645, 1470, 1435, 1385, 1370, 1050, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (m, 1 H, C*H*CH_2), 5.18–5.10 (m, 2 H, CHCH_2), 3.39 (m, 1 H, C*H*OH), 2.32 (m, 1 H, CH_2CHOH), 2.11 (m, 1 H, CH_2-CHOH), 1.69 (m, 1 H, C*H*$(CH_3)_2$), 1.57 (d, 3 H, J = 3.6 Hz, CH_3), 1.56 (d, 3 H, J = 3.1 Hz, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 117.9, 75.3, 38.8, 33.1, 18.7, 17.5. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.70; H, 12.33.

Step 2: 4-Methyl-3-(triethylsiloxy)pentanal. To a solution of 2.24 g (19.6 mmol) of the allylic alcohol in 200 mL of CH_2Cl_2 at −78 °C was added 4.57 mL (39.2 mmol, 2.00 equiv) of 2,6-lutidine, followed by 5.32 mL (23.5 mmol, 1.20 equiv) of triethylsilyl trifluoromethanesulfonate. The resulting solution was stirred at −78 °C for 30 min and quenched with 100 mL of 0.25 M aqueous KH_2PO_4. The layers were separated, and the aqueous phase was extracted with 3 × 100 mL of ether. The combined organic layers were washed with 1 M aqueous $NaHSO_4$ and saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered through a short plug of silica gel, and concentrated in vacuo to give a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1 H, C*H*CH_2), 5.07–5.00 (m, 2 H, CHCH_2), 3.49 (m, 1 H, C*H*O), 2.19 (m, 2 H, CH_2CHOH), 1.69 (m, 1 H, C*H*$(CH_3)_2$), 0.96 (t, 9 H, J = 8.0 Hz, Si$(CH_2CH_3)_3$), 0.87 (d, 3 H, J = 6.8 Hz, CH$(CH_3)_2$), 0.86 (d, 3 H, J = 6.8 Hz, CH$(CH_3)_2$), 0.59 (q, 6 H, J = 8.0 Hz, Si$(CH_2CH_3)_3$). The product was carried onto the next step without further purification.

A solution of the olefin in 200 mL of CH_2Cl_2 at −78 °C was treated with a dilute stream of ozone in oxygen until the solution turned blue. Oxygen was then bubbled through the solution until the blue color disappeared, and the resulting solution was treated with 5.40 g (20.6 mmol, 1.05 equiv) of triphenylphosphine. The reaction mixture was stirred at 20 °C for 3 h, and the solvent was evaporated in vacuo. Purification of the residue by chromatography on silica gel (95:5 hexane/ethyl acetate, 6 × 25 cm and 95:5 hexane/ether, 5 × 21 cm) afforded 3.52 g (78% for the two steps) of a colorless oil: R_f 0.43 (9:1 hexane/ethyl acetate); IR (thin film) 2970, 2920, 2885, 1735, 1465, 1415, 1390, 1370, 1240, 1090, 1060, 1010 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (dd, 1 H, J = 2.9, 2.0 Hz, C*H*O), 4.04 (ddd, 1 H, J = 9.0, 7.4, 4.4 Hz, C*H*OSi), 2.51 (ddd, 1 H, J = 15.8, 7.4, 2.9 Hz, C*H*CHO), 2.40 (ddd, 1 H, J = 15.8, 4.4, 2.0 Hz, C*H*CHO), 1.76 (dsept, 1 H, J = 9.0, 6.8 Hz, C*H*$(CH_3)_2$), 0.94 (t, 9 H, J = 8.0 Hz, Si$(CH_2CH_3)_3$), 0.88 (d, 3 H, J = 6.8 Hz, CH_3), 0.87 (d, 3 H, J = 6.8 Hz, CH_3), 0.59 (q, 6 H, J = 8.0 Hz, Si$(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 72.4, 47.3, 34.2, 18.1, 17.2, 6.8, 5.0.

Step 3: (*E*)-*N*-Methoxy-*N*-methyl-5-(triethylsiloxy)-6-methyl-2-heptenamide. To a solution of 464 mg (2.01 mmol) of 4-methyl-3-(triethylsiloxy)pentanal in 20 mL of CH_2Cl_2 at 20 °C was added 878 mg (2.42 mmol, 1.20 equiv) of (*N*-methoxy-*N*-methylcarboxamido)methylenetriphenylphosphorane.[18] The resulting yellow solution was stirred at 20 °C for 24 h, and the solvent was evaporated in vacuo. Purification of the residue by chromatography on silica gel (85:15 hexane/ethyl acetate, 3 × 24 cm) afforded 458 mg (72%) of a colorless oil: R_f 0.29 (4:1 hexane/ethyl acetate); IR (thin film) 2970, 2920, 2880, 1670, 1645, 1465, 1415, 1385, 1240, 1180, 1060, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (dt, 1 H, J = 15.4, 7.7 Hz, C*H*CHCON), 6.42 (d, 1 H, J = 15.4 Hz, C*H*CON), 3.69 (s, 3 H, OCH_3), 3.59 (m, 1 H, C*H*OSi), 3.23 (s, 3 H, NCH_3), 2.36 (m, 2 H, CH_2CHOSi), 1.69 (m, 1 H, $(CH_3)_2$C*H*), 0.95 (t, 9 H, J = 7.8 Hz, Si$(CH_2CH_3)_3$), 0.88 (d, 3 H, J = 5.2 Hz, CH_3), 0.86 (d, 3 H, J = 5.2 Hz, CH_3), 0.58 (q, 6 H, J = 7.8 Hz, Si$(CH_2CH_3)_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 144.9, 120.3, 76.03, 61.6, 37.4, 33.2, 32.3, 18.3, 17.4, 7.0, 5.1. Anal. Calcd for $C_{16}H_{33}NO_3Si$: C, 60.90; H, 10.54. Found: C, 60.90; H, 10.44.

Step 4: (*E*)-*N*-Methoxy-*N*-methyl-5-hydroxy-6-methyl-2-heptenamide (9). To a solution of 495 mg (1.57 mmol) of the silyl ether in 8 mL of THF at 20 °C was added 8 mL of 0.4 M pyridinium fluoride (with excess pyridine) in THF. The resulting solution was stirred at 20 °C for 3 h and partitioned between 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of ethyl acetate. The layers were separated, and the aqueous layer was extracted with 3 × 50 mL of ethyl acetate. The combined organic layers were washed with 1 M aqueous $NaHSO_4$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (3:7 hexane/ethyl acetate, 3 × 20 cm) afforded 310 mg (98%) of **9** as a colorless oil: R_f 0.13 (1:1 hexane/ethyl acetate); IR (thin film) 3440, 2960, 1665, 1620, 1465, 1420, 1385, 1180, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (dt, 1 H, J = 15.4, 7.9 Hz, C*H*CHCON), 6.47 (d, 1 H, J = 15.4 Hz, C*H*CON), 3.68 (s, 3 H, OCH_3), 3.49 (m, 1 H, C*H*OH), 3.21 (s, 3 H, NCH_3), 2.42 (m, 1 H, CHC*H*CHOH), 2.32 (m, 1 H, CHC*H*CHOH), 2.24 (br d, 1 H, J = 4.0 Hz, O*H*), 1.68 (m, 1 H, C*H*$(CH_3)_2$), 0.92 (d, 3 H, J = 6.8 Hz, CH_3), 0.92 (d, 3 H, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 144.6, 121.0, 75.2, 61.7, 37.5, 33.3, 32.3, 18.7, 17.3. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52. Found: C, 59.51; H, 9.53.

(2*S,4*R**,6*S**)-4-[(*N*-Methoxy-*N*-methylcarboxamido)-methyl]-6-(1-methylethyl)-2-phenyl-1,3-dioxane (10).** To a solution of 62.9 mg (0.310 mmol) of amide **9** in 3 mL of THF at −20 °C was added 35 μL (0.34 mmol, 1.1 equiv) of freshly distilled benzaldehyde, followed by 32 μL (0.031 mmol, 0.10 equiv) of 0.96 M KHMDS in THF, and the resulting yellow solution was stirred for 15 min at −20 °C. This sequence (addition/stirring) was repeated twice, and the reaction mixture was quenched with 10 mL of pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted with 3 × 10 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (3:1 hexane/ethyl acetate, 1 × 20 cm) afforded 76 mg (79%) of **10** as a colorless oil: R_f 0.51 (1:1 hexane/ethyl acetate); IR (thin film) 2970, 2880, 1665, 1455, 1425, 1385, 1345, 1175, 1110, 1025, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H, Ar*H*), 7.33 (m, 3 H, Ar*H*), 5.56 (s, 1 H, C*H*Ph), 4.37 (m, 1 H, NCOCH_2C*H*O), 3.67 (s, 3 H, OCH_3), 3.56 (m, 1 H, $(CH_3)_2$CHC*H*O), 3.20 (s, 3 H, NCH_3), 3.05–2.94 (m, 1 H, NCOC*H*), 2.56 (dd, 1 H, J = 15.6, 6.3 Hz, NCOC*H*), 1.84–1.66 (m, 2 H, $(CH_3)_2$C*H*, OCHC*H*CHO), 1.43 (dt, 1 H, J = 12.8, 11.2 Hz, OCHC*H*CHO), 1.02 (d, 3 H, J = 6.7 Hz, CH_3), 0.95 (d, 3 H, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 138.9, 128.4, 128.0, 126.0, 100.4, 81.6, 73.5, 61.3, 38.3, 33.8, 32.9, 31.9,

(18) Kaldor, S. W. Ph.D. Dissertation, Harvard University, Cambridge, MA, 1989.

18.3, 17.9. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20. Found: C, 66.60; H, 8.11.

(2*R*,4*R*,5*R*,6*S*)-4-(Carbomethoxymethyl)-6-[(1*R*)-2-(*tert*-butyldiphenylsiloxy)-1-methylethyl]-5-methyl-2-phenyl-1,3-dioxane (12). To a solution of 101 mg (0.236 mmol) of ester **11** in 2.4 mL of THF at 0 °C was added 26 μL (0.26 mmol, 1.1 equiv) of freshly distilled benzaldehyde, followed by 2.6 mg (0.024 mmol, 0.10 equiv) of *t*-BuOK, and the resulting yellow solution was stirred for 15 min at 0 °C. This sequence (addition/stirring) was repeated twice, and the reaction mixture was quenched with 10 mL of pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted with 3 × 10 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (85:15 hexane/ethyl acetate, 1 × 17 cm) afforded 92.7 mg (72%) of **12** as a colorless oil: R_f 0.60 (4:1 hexane/ethyl acetate); $[\alpha]_D$ −5.6° (*c* 0.3, $CHCl_3$); IR (thin film) 2920, 2850, 1725, 1650, 1450, 1420, 1120, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.61 (m, 4 H, Ar*H*), 7.43–7.33 (m, 8 H, Ar*H*), 7.32–7.20 (m, 3 H, Ar*H*), 5.56 (s, 1 H, C*H*Ph), 4.03 (ddd, 1 H, *J* = 9.2, 9.0, 3.3 Hz, OC*H*CH_2COOCH_3), 3.90 (d, 1 H, *J* = 10.1 Hz, OC*H*CH(CH_3)CH_2OTBDPS), 3.79 (dd, 1 H, *J* = 9.7, 9.6 Hz, C*H*OTBDPS), 3.72 (s, 3 H, OCH_3), 3.55 (dd, 1 H, *J* = 9.7, 5.7 Hz, C*H*OTBDPS), 2.75 (dd, 1 H, *J* = 15.5, 3.1 Hz, C*H*COOCH_3), 2.58 (dd, 1 H, *J* = 15.5, 9.0 Hz, C*H*COOCH_3), 2.09 (m, 1 H, C*H*CH_2OTBDPS), 1.73 (m, 1 H, C*H*CH(O)CH_2COOCH_3), 1.07 (d, 3 H, *J* = 6.6 Hz, OCHCH(CH_3)CHO), 1.05 (s, 9 H, SiC(CH_3)$_3$), 0.85 (d, 3 H, *J* = 6.7 Hz, CH(CH_3)CH_2OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$), δ 171.9, 138.7, 135.6, 135.5, 133.7, 129.5, 128.4, 127.9, 127.6, 127.5, 126.0, 99.9, 80.0, 79.1, 65.3, 51.7, 38.8, 36.4, 35.0, 26.9, 26.5, 19.3, 11.7, 9.5; exact mass calcd for $C_{33}H_{42}O_5SiNa$ 569.269, found 569.270.

(2*R*,4*R*,5*R*,6*S*)-6-[(1*R*)-2-(*tert*-Butyldimethylsiloxy)-1-methylethyl]-4-[(*N*-methoxy-*N*-methylcarboxamido)methyl]-5-methyl-2-phenyl-1,3-dioxane (14). The indicated compound was prepared according to the procedure described for compound **10** on a 6.1 mmol scale. Purification by chromatography on silica gel (9:1 hexane/ethyl acetate, 3 × 20 cm) afforded 2.3 g (84%) of **14** as a colorless oil: R_f 0.25 (9:1 hexane/ethyl acetate); $[\alpha]_D$ −28.7° (*c* 1.67, $CHCl_3$); IR (thin film) 2945, 2910, 1830, 1610, 1470, 1445, 1395, 1370, 1230, 1135, 1050, 1010 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (m, 2 H, Ar*H*), 7.33–7.28 (m, 3 H, Ar*H*), 5.56 (s, 1 H, C*H*Ph), 4.11 (ddd, 1 H, *J* = 9.7, 9.7, 3.0 Hz, OC*H*CH_2CON), 3.74 (dd, 1 H, *J* = 10.1, 1.7 Hz, OC*H*CH(CH_3)CH_2OTBS), 3.68 (dd, 1 H, *J* = 9.6, 9.4 Hz, C*H*OTBS), 3.65 (s, 3 H, OCH_3), 3.50 (dd, 1 H, *J* = 9.6, 5.8 Hz, C*H*OTBS), 3.20 (s, 3 H, NCH_3), 2.98–2.88 (m, 1 H, C*H*CON), 2.63 (dd, 1 H, *J* = 15.3, 3.0 Hz, C*H*CON), 2.01 (m, 1 H, C*H*CH_2OTBS), 1.77 (m, 1 H, C*H*CH(O)CH_2CON), 0.90 (d, 3 H, *J* = 6.6 Hz, OCHCH(CH_3)CHO), 0.89 (s, 9 H, SiC(CH_3)$_3$), 0.84 (d, 3 H, *J* = 6.6 Hz, CH(CH_3)CH_2OTBS), 0.03 (s, 6 H, Si(CH_3)$_2$) ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 139.1, 128.3, 127.8, 126.0, 99.9, 80.3, 64.9, 36.6, 35.3, 25.9, 18.3, 11.8, 9.6; exact mass calcd for $C_{24}H_{41}O_5SiNa$ 474.263, found 474.264.

(*E*)-(4*S*,5*S*)-Methyl 4,6-dimethyl-5-hydroxy-2-heptenoate (15). To a solution of 255 mg (1.04 mmol) of 2,4-dimethyl-3-[(*tert*-butyldimethylsilyl)oxy]pentanal in 10 mL of CH_2Cl_2 at 20 °C was added 419 mg (1.25 mmol, 1.2 equiv) of carbomethoxymethylenetriphenylphosphorane. The resulting clear solution was stirred at reflux for 24 h. The reaction failed to go to completion, and then 627 mg (1.87 mmol, 1.80 equiv) of the phosphorane was added and the reaction mixture was stirred at reflux for 24 h. The solvent was then evaporated in vacuo. Purification of the residue by chromatography on silica gel (2:1 hexane/CH_2Cl_2, 3 × 22 cm) afforded 291 mg (93%) of the TBS-protected ester **15** as a colorless oil: R_f 0.67 (CH_2Cl_2); $[\alpha]_{546}$ −39.9° (*c* 0.9, CH_2Cl_2); IR (thin film) 2970, 2945, 2870, 1735, 1665, 1480, 1470, 1440, 1390, 1340, 1260, 1180, 1060 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (dd, 1 H, *J* = 15.8, 7.8 Hz, C*H*CHCOOCH_3), 5.78 (dd, 1 H, *J* = 15.8, 1.2 Hz, C*H*COOCH_3), 3.73 (s, 3 H, OCH_3), 3.37 (m, 1 H, C*H*OSi), 2.51 (m, 1 H, C*H*CH_3), 1.72 (m, 1 H, (CH_3)$_2$C*H*), 1.04 (d, 3 H, *J* = 6.7 Hz, CHCH_3), 0.91 (s, 9 H, (CH_3)$_3$Si), 0.89 (d, 3 H, *J* = 6.8 Hz, (CH_3)$_2$CH), 0.84 (d, 3 H, *J* = 6.7 Hz, (CH_3)$_2$CH), 0.04 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 153.3, 119.7, 80.1, 51.4, 41.0, 32.0, 26.1, 20.3, 18.4, 17.5, 15.1, −3.7, −3.8. Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 64.18; H, 10.85.

Deprotection. To a solution of 187 mg (0.620 mmol) of the silyl ether in 3 mL of acetonitrile at 20 °C was added 1 mL of 48% aqueous HF. The resulting cloudy mixture was stirred at 20 °C for 1.5 h and quenched with 25 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 3 × 25 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (9:1 hexane/ethyl acetate, 1 × 17 cm) afforded 119 mg (96%) of **15** as a colorless oil: R_f 0.45 (7:3 hexane/ethyl acetate); $[\alpha]_{546}$ −34.5° (*c* 0.405, CH_2Cl_2); IR (thin film) 3500, 2970, 2880, 1730, 1710, 1660, 1465, 1440, 1380, 1340, 1275, 1195, 1180, 1155, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (dd, 1 H, *J* = 15.8, 8.1 Hz, C*H*CHCOOCH_3), 5.86 (dd, 1 H, *J* = 15.8, 1.2 Hz, C*H*COOCH_3), 3.73 (s, 3 H, OCH_3), 3.26 (m, 1 H, C*H*OH), 2.50 (m, 1 H, C*H*CH_3), 1.71 (m, 1 H, (CH_3)$_2$C*H*), 1.43 (d, 1 H, *J* = 5.4 Hz, O*H*), 1.09 (d, 3 H, *J* = 6.7 Hz, CHCH_3), 0.93 (d, 3 H, *J* = 6.8 Hz, (CH_3)$_2$CH), 0.91 (d, 3 H, *J* = 6.7 Hz, (CH_3)$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 152.0, 120.7, 79.2, 51.5, 40.0, 31.0, 19.7, 16.5, 14.0. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.41; H, 9.84.

(2*S,4*R**,5*S**,6*S**)-4-(Carbomethoxymethyl)-5-methyl-6-(1-methylethyl)-2-phenyl-1,3-dioxane (17).** The indicated compound was prepared according to the procedure described for compound **10** on a 0.560 mmol scale. Purification by chromatography on silica gel (95:5 hexane/ethyl acetate, 1 × 22 cm) afforded 116 mg (71%) of **17** as a colorless oil: R_f 0.57 (4:1 hexane/ethyl acetate); $[\alpha]_{546}$ +4.3° (*c* 0.44, CH_2Cl_2); IR (thin film) 2960, 2880, 1745, 1455, 1440, 1410, 1390, 1370, 1350, 1335, 1315, 1280, 1265, 1195, 1175, 1150, 1105, 1055, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 2 H, Ar*H*), 7.35 (m, 3 H, Ar*H*), 5.55 (s, 1 H, C*H*Ph), 4.37 (ddd, 1 H, *J* = 8.1, 5.5, 2.3 Hz, CH_3OOCCH_2C*H*O), 3.71 (s, 3 H, OCH_3), 3.37 (dd, 1 H, *J* = 9.9, 2.1 Hz, (CH_3)$_2$CHC*H*O), 2.74 (dd, 1 H, *J* = 15.7, 8.1 Hz, C*H*COOCH_3), 2.50 (dd, 1 H, *J* = 15.7, 5.5 Hz, C*H*COOCH_3), 1.85 (m, 1 H, (CH_3)$_2$C*H*), 1.72 (qt, 1 H, *J* = 6.9, 2.3 Hz, C*H*CH_3), 1.05 (d, 3 H, *J* = 6.4 Hz, CH(CH_3)$_2$), 0.97 (d, 3 H, *J* = 6.9 Hz, CHCH_3), 0.86 (d, 3 H, *J* = 6.8 Hz, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 138.7, 128.5, 128.1, 126.0, 101.4, 86.8, 77.3, 51.7, 37.9, 32.5, 29.2, 19.8, 17.3, 5.8. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.75; H, 8.31.

(*E*)-*N*-Methoxy-*N*-methyl-4,6-dimethyl-5-hydroxy-2-heptenamide (16). To a solution of 975 mg (2.01 mmol) of 2,4-dimethyl-3-[(*tert*-butyldimethylsilyl)oxy]pentanal in 40 mL of CH_2Cl_2 at 20 °C was added 1.48 g (4.07 mmol, 1.02 equiv) of (*N*-methoxy-*N*-methylcarboxamido)methylenetriphenylphosphorane.[17] The resulting yellow solution was heated at reflux for 24 h, and the solvent was evaporated in vacuo. Purification of the residue by chromatography on silica gel (4:1 hexane/ethyl acetate, 4 × 23 cm) afforded 263 mg (27%) of starting aldehyde and 718 mg (55%) of TBS-protected **16** as a colorless oil: R_f 0.28 (4:1 hexane/ethyl acetate); $[\alpha]_{546}$ −41.1° (*c* 1.065, CH_2Cl_2); IR (thin film) 2960, 2940, 2860, 1670, 1640, 1470, 1410, 1385, 1255, 1180, 1150, 1115, 1055, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, 1 H, *J* = 15.5, 8.2 Hz, C*H*CHCON), 6.36 (d, 1 H, *J* = 15.5 Hz, C*H*CON), 3.69 (s, 3 H, OCH_3), 3.38 (dd, 1 H, *J* = 5.5, 4.2 Hz, C*H*OSi), 3.24 (s, 3 H, NCH_3), 2.53 (m, 1 H, C*H*CH_3), 1.73 (m, 1 H, C*H*(CH_3)$_2$), 1.06 (d, 3 H, *J* = 6.8 Hz, CHCH_3), 0.91 (s, 9 H, SiC(CH_3)$_3$), 0.89 (d, 3 H, *J* = 7.0 Hz, CH(CH_3)$_2$), 0.84 (d, 3 H, *J* = 6.8 Hz, CH(CH_3)$_2$), 0.04 (s, 3 H, SiCH_3), 0.04 (s, 3 H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 151.4, 117.4, 80.2, 61.6, 41.3, 32.3, 32.0, 26.1, 20.4, 18.4, 17.3, 15.8, −3.7, −3.8. Anal. Calcd for $C_{17}H_{35}NO_3Si$: C, 61.95; H, 10.71. Found: C, 62.05; H, 10.75.

Deprotection. To a solution of 526 mg (1.59 mmol) of the silyl ether in 16 mL of acetonitrile at 20 °C was added 1 mL of 48% aqueous HF. The resulting cloudy mixture was stirred at 20 °C for 3 h and quenched with 50 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 3 × 50 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (2:3 hexane/ethyl acetate, 2 × 20 cm) afforded 332 mg (97%) of **16** as a colorless oil: R_f 0.20 (1:1 hexane/ethyl acetate); $[\alpha]_{546}$ −42.7° (*c* 0.59, CH_2Cl_2); IR (thin film) 3450, 2970, 1940, 2880, 1665, 1625, 1460, 1420, 1385, 1180, 1150, 1105, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)

δ 6.91 (dd, 1 H, J = 15.5, 8.2 Hz, C*H*CHCON), 6.43 (d, 1 H, J = 15.5 Hz, C*H*CON), 3.70 (s, 3 H, OCH_3), 3.28 (m, 1 H, C*H*OH), 3.24 (s, 3 H, NCH_3), 2.54 (m, 1 H, C*H*CH$_3$), 1.74 (m, 1 H, C*H*(CH$_3$)$_2$), 1.53 (m, 1 H, O*H*), 1.11 (d, 3 H, J = 6.7 Hz, CHCH_3), 0.93 (d, 3 H, J = 6.8 Hz, CH(CH_3)$_2$), 0.91 (d, 3 H, J = 6.6 Hz, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 150.1, 118.5, 79.2, 61.7, 40.3, 32.4, 30.8, 19.8, 16.3, 14.5. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83. Found: C, 61.32; H, 9.89.

(2*R*,4*R*,5*S*,6*S*)-4-[(*N*-Methoxy-*N*-methylcarboxamido)-methyl]-5-methyl-6-(1-methylethyl)-2-phenyl-1,3-dioxane (18). The indicated compound was prepared according procedure described for compound **10** on a 0.470 mmol scale. Purification by chromatography on silica gel (85:15 hexane/ethyl acetate, 1 × 18 cm) afforded 111 mg (72%) of **18** as a colorless oil: R_f 0.56 (1:1 hexane/ethyl acetate); $[\alpha]_{546}$ −16.4° (c 0.405, CH_2Cl_2); IR (thin film) 2970, 2880, 1665, 1455, 1425, 1390, 1350, 1315, 1290, 1180, 1165, 1150, 1115, 1055, 1030, 1000 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 2 H, Ar*H*), 7.33 (m, 3 H, Ar*H*), 5.56 (s, 1 H, OC*H*O), 4.44 (m, 1 H, OC*H*CH$_2$CON), 3.68 (s, 3 H, OCH_3), 3.39 (dd, 1 H, J = 9.9, 1.9 Hz, (CH$_3$)$_2$CHC*H*O), 3.20 (s, 3 H, NCH_3), 2.97 (dd, 1 H, J = 15.7, 7.3 Hz, C*H*CON), 2.52 (dd, 1 H, J = 15.7, 5.3 Hz, C*H*CON), 1.87–1.77 (m, 2 H, C*H*(CH$_3$)$_2$ and C*H*CH$_3$), 1.04, 0.99 and 0.86 (3 d, 3 × 3 H, CH(CH_3)$_2$ and CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 139.0, 128.4, 128.1, 126.0, 101.5, 86.9, 77.6, 61.4, 35.0, 32.6, 32.0, 29.3, 19.8, 17.3, 6.0. Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47. Found: C, 67.37; H, 8.56.

(2*R*,4*R*,5*S*,6*S*)-4-(2-Oxopropyl)-5-methyl-6-(1-methylethyl)-2-phenyl-1,3-dioxane (19). To a solution of 65.3 mg (0.200 mmol) of amide **18** in 2 mL of THF at −78 °C was added 960 μL (1.32 mmol, 6.60 equiv) of 1.4 M MeLi in ether. The resulting solution was stirred at −78 °C for 30 min, quenched with 25 mL of saturated aqueous NH_4Cl, and diluted with 25 mL of ether. The layers were separated, and the aqueous phase was extracted with 3 × 25 mL of ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by preparative thin-layer chromatography on silica gel (4:1 hexane/ethyl acetate, 0.25 mm plate) afforded 44.9 mg (80%) of **20** as a colorless oil: R_f 0.40 (4:1 hexane/ethyl acetate); $[\alpha]_{546}$ +11.3° (c 0.515, CH_2Cl_2); IR (thin film) 2970, 2920, 1870, 1725, 1455, 1410, 1385, 1350, 1150, 1105, 1055, 1030, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 2 H, Ar*H*), 7.34 (m, 3 H, Ar*H*), 5.54 (s, 1 H, OC*H*O), 4.37 (ddd, 1 H, J = 8.2, 4.6, 2.2 Hz, OC*H*CH$_2$COCH$_3$), 3.37 (dd, 1 H, J = 9.9, 2.2 Hz, (CH$_3$)$_2$CHC*H*O), 2.90 (dd, 1 H, J = 16.3, 8.2 Hz, C*H*COCH$_3$), 2.47 (dd, 1 H, J = 16.3, 4.6 Hz, C*H*COCH$_3$), 2.22 (s, 3 H, COCH_3), 1.84 (m, 1 H, (CH$_3$)$_2$C*H*), 1.69 (qt, 1 H, J = 6.9, 2.2 Hz, CH$_3$C*H*), 1.05 (d, 1 H, J = 6.4 Hz, (CH_3)$_2$CH), 0.95 (d, 1 H, J = 6.9 Hz, CH_3CH), 0.85 (d, 1 H, J = 6.8 Hz, (CH_3)$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 138.8, 128.5, 128.1, 126.0, 101.3, 86.9, 77.1, 46.6, 32.7, 31.2, 29.3, 19.8, 17.3, 6.1. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.95; H, 8.62.

(2*R*,4*R*,5*S*,6*S*)-4-(Formylmethyl)-5-methyl-6-(1-methylethyl)-2-phenyl-1,3-dioxane (20). To a solution of 40.6 mg (0.130 mmol) of amide **18** in 1.3 mL of THF at −78 °C was added 170 μL (0.25 mmol, 2.0 equiv) of 1.5 M DIBAL in toluene. The resulting solution was stirred at −78 °C for 30 min and quenched with 1 mL of methanol and 1 mL of water. The mixture was partitioned between 10 mL of water and 10 mL of ether, and enough 1 N HCl was added so that the two layers were clear. The layers were separated, and the aqueous phase was extracted with 3 × 10 mL of ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by preparative thin-layer chromatography on silica gel (4:1 hexane/ethyl acetate, 0.25 mm plate) afforded 27.3 mg (82%) of **19** as a colorless oil: R_f 0.37 (4:1 hexane/ethyl acetate); $[\alpha]_{546}$ +9.8° (c 0.25, CH_2Cl_2); IR (thin film) 2970, 2920, 2880, 1730, 1455, 1385, 1350, 1215, 1165, 1150, 1115, 1060, 1035, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (t, 1 H, J = 1.9 Hz, C*H*O), 7.48 (m, 2 H, Ar*H*), 7.36 (m, 3 H, Ar*H*), 5.58 (s, 1 H, OC*H*O), 4.45 (ddd, 1 H, J = 8.9, 4.3, 2.3 Hz, OC*H*CH$_2$CHO), 3.40 (dd, 1 H, J = 9.9, 2.1 Hz, (CH$_3$)$_2$CHC*H*O), 2.87 (ddd, 1 H, J = 16.9, 8.9, 1.9 Hz, C*H*CHO), 2.49 (ddd, 1 H, J = 16.9, 4.3, 1.9 Hz, C*H*CHO), 1.86 (m, 1 H, (CH$_3$)$_2$C*H*), 1.70 (m, 1 H, CH$_3$C*H*), 1.06 (d, 3 H, J = 6.4 Hz, (CH_3)$_2$CH), 0.98 (d, 1 H, J = 6.9 Hz, CH_3CH), 0.87 (d, 3 H, J = 6.8 Hz, (CH_3)$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 138.5, 128.6, 128.1, 126.0, 101.4, 86.9, 75.8, 46.7, 32.7, 29.2, 19.8, 17.30, 6.0.