Total Synthesis of the Ethyl Ester of the Major Urinary Metabolite of Prostaglandin E_2

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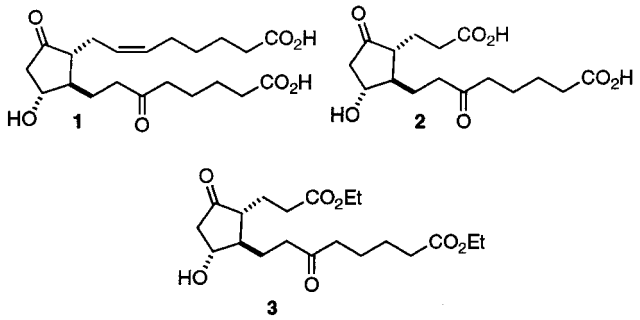
The preparation of the ethyl ester of the major urinary metabolite of prostaglandin E_2 **3** is described. The key step is the kinetic opening of the TBS-protected bicyclic ketone **7** with thiophenol.

Introduction

The prostaglandins are a family of mammalian hormones derived from the essential fatty acids.[1] Prostaglandin E_2 **1**, which could be considered the parent of this series, displays a wide array of biological activity, including blood platelet aggregation, relaxation of smooth muscle, and inflammatory action.[2] The intense interest in the biological activity of the prostaglandins has led to extensive synthetic investigation.[3] The best way to measure whole body production of the locally acting hormone prostaglandin E_2 is to assess the accumulation of the major urinary metabolite, PGE_2U_m **2**.[4] The material originally used in these assays was produced by Upjohn,[5] but this supply has been depleted. We therefore undertook the preparation of the ethyl ester **3** of PGE_2U_m.[6]

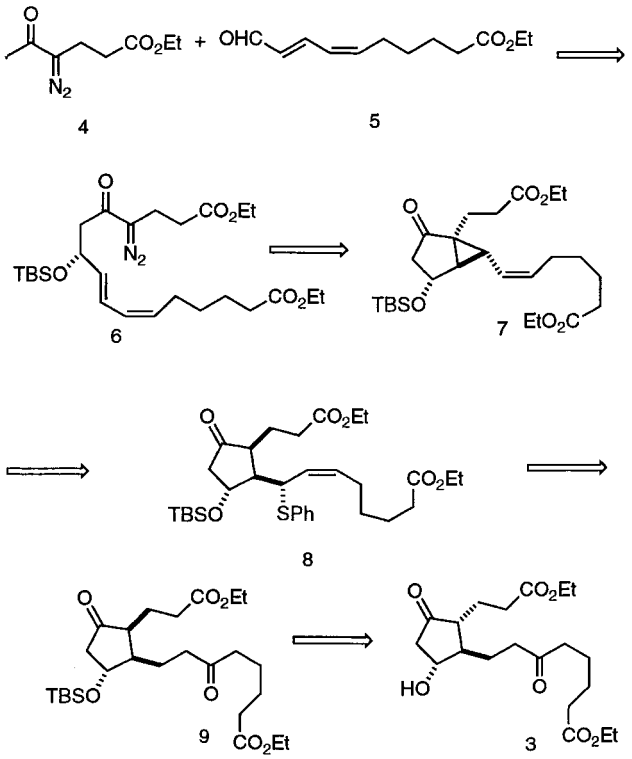


Result and Discussion

We proposed (Scheme 1) to prepare the ethyl ester **3** of PGE_2U_m by aldol condensation of the diazoketone **4** with the dienal **5**. Cyclization of the silyloxy ketone **6**, kinetic opening of the cyclopropane ring of the bicyclic ketone **7**, and oxidation and Mislow rearrangement of the thioether **8** would then lead to **3**.

Although we had effected analogous transformations in our previous approaches to prostaglandin derivatives,[3d,i,n] we had used in each of those syntheses the *tert*-butyl*diphenyl*silyl protecting group. We were concerned about the ability to remove this group from **9** to make **3**.[3n] The *tert*-butyldimethylsilyl group is more easily removed. The key question was whether this more labile protecting group would survive the $BF_3{\cdot}OEt_2$-mediated opening of the cyclopropyl ketone **7** with thiophenol.

Scheme 1



The diazoketone **4** was prepared by Michael addition of benzoylacetone to ethyl acrylate, to give diketone **10** (Scheme 2). The diketone **10** was smoothly converted to the diazoketone **4** on exposure to *p*-nitrobenzenesulfonyl azide (p-NBSA) and DBU.[7]

The requisite dienal **5** was prepared by ozonolysis[8] of cyclohexene to give ethyl 6-oxohexanoate **11** (Scheme 2). Wittig reaction of the phosphonium salt with 1 mol equiv of KHMDS proceeded smoothly to give *Z*,*E*-dienol **12**.[9] The geometry of the conjugated diene was assigned by comparison of the ^{13}C NMR of the C-5 and C-10 methylenes with similar compounds that we had previously prepared.[9] By comparing the C-5 and C-10 ^{13}C chemical shifts of the dienol **12** (δ 63.7, 27.5) with the analogous *Z*,*E* (δ 63.0, 26.8), *E*,*E* (δ 61.9, 31.8), *Z*,*Z* (δ 51.3, 26.5), and *E*,*Z* (δ 58.4, 31.9) dienols from the synthesis of 5-F_{2t}-isoprostane,[9c] we confirmed that the C-5 methylene is

(1) von Euler, U. S.; Eliasson, R. *Prostaglandins*; Academic Press: New York, 1967.

(2) Pace-Asciak, C.; Granstrom, E. *Prostaglandins and Related Substances*; Elsevier: Amsterdam, 1983.

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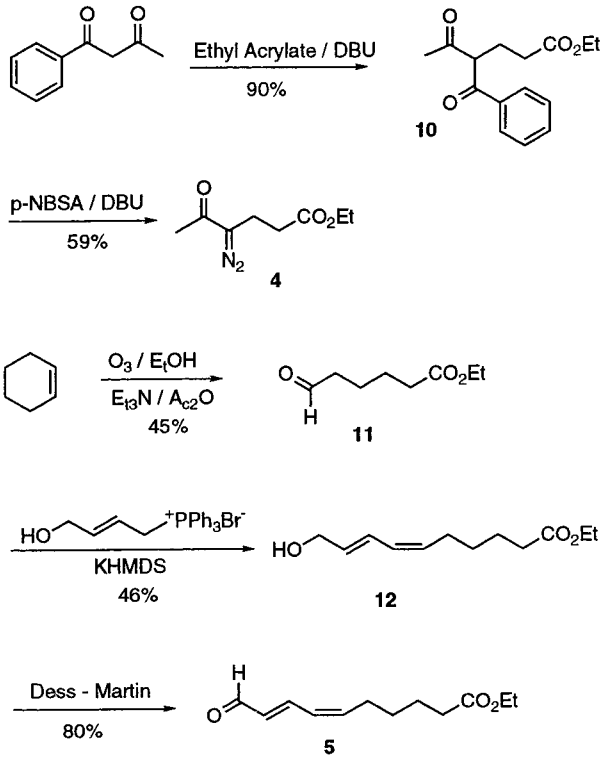
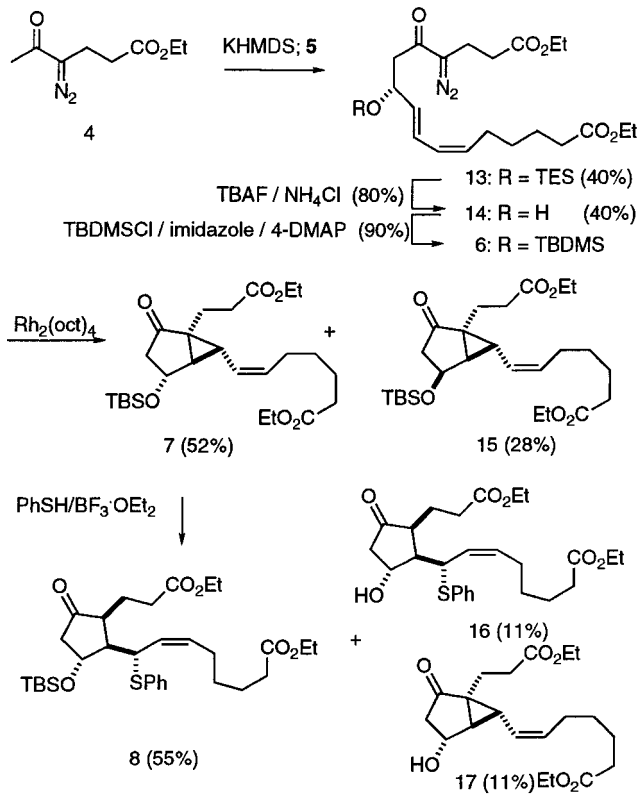
Scheme 2



next to a *Z*-double bond and the C-10 methylene is next to a *E*-double bond. Oxidation of **12** with the Dess−Martin periodinane[10] furnished the dienal **5**.

Scheme 3



With the two components **4** and **5** in hand, we embarked on the preparation of the aldol product **6** (Scheme 3). Condensation of the potassium enolate of the diazoketone **4** with the dienal **5** in the presence of triethylchlorosilane (TESCl) in toluene gave the TES-protected aldol **13** together with the free aldol **14**.[9] The TES-group of **13** does not survive under the conditions for cyclopropane ring opening with thiophenol and BF_3·OEt_2, so it was necessary to change the protecting group from TES to *tert*-butyldimethylsilyl (TBDMS).[9]

The diazoketone **6** was cyclized with rhodium octanoate catalyst in CH_2Cl_2 to provide the bicyclic ketones **7** and **15** in a ratio of 65:35. The chemical shifts of the oxygenated methine of **7** (^{1}H δ 4.43, d, J = 4.9 Hz and ^{13}C δ 68.3) are quite different from those of **15** (^{1}H δ 4. 63, dt, J = 5.1 and 8.0 Hz and ^{13}C δ 67.3). We were not able to separate the diastereomers **7** and **15**, so the yields cited are based on the ratio of the two, as determined by ^{1}H NMR. We did find that the alcohols **21** and **22** (Scheme 4), each a pair of diastereomers, could be separated from each other by chromatography. Reduction of the mixture of **7** and **15** with sodium borohydride in EtOH, separation, and oxidation of the alcohol **21** with Dess−Martin periodinane[10] gave the desired bicyclic ketone **7**.

We were then ready to address the opening of the cyclopropyl ketone **7** in the presence of the fragile *tert*-butyldimethylsilyl group. We eventually found that treatment of **7** with 3 equiv of thiophenol and 4 equiv of

(3) For reviews of synthetic approaches to the prostaglandins, see: (a) Mitra, A. *The Synthesis of Prostaglandins*; John Wiley & Sons: New York, 1977. (b) Bindra, R. *Prostaglandin Synthesis*; Academic Press: New York, 1977. (c) Newton, R. F.; Roberts, S. M. *Prostaglandins and Thromboxanes*; Butterworth: London, 1982. For leading references to more recent work, see (d) Taber, D. F.; Hoerrner, R. S. *J. Org. Chem.* **1992**, *57*, 441. (e) Noyori, R.; Suzuki, M. *Science (Washington, D.C)* **1993**, *259*, 44. (f) Yoshida, Y.; Ono, N.; Sato, F. *J. Org. Chem.* **1994**, *59*, 6153. (g) Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Peersen, J. *J. Org. Chem.* **1998**, *63*, 5971. (h) Mikolajczyk, M.; Zurawinski, R. *J. Org. Chem.* **1998**, *63*, 8894. (i) Taber, D. F.; Kanai, K. *Tetrahedron* **1998**, *54*, 11767. (j) Sannigrahi, M.; Mayhew, D. L.; Clive, D. L. J.; *J. Org. Chem.* **1999**, *64*, 2776. (k) Rodrigues, A.; Nomen, M.; Spur, B. W.; Godfroid, J.-J. *Eur. J. Org. Chem.* **1999**, *2655*, 5. (l) Dragoli, D. R.; Thompson, L. A.; O'Brien, J.; Ellman, J. A. *J. Comb. Chem.* **1999**, *1*, 534. (m) Fürstner, A.; Grela, K.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **2000**, *122*, 11799. (n) Taber, D. F.; Jiang, Q. *Tetrahedron* **2000**, *56*, 5991. (o) Manzotti, R.; Tang, S.-Y.; Janda, K. D. *Tetrahedron* **2000**, *56*, 7885. (p) Shimazaki, Y.; Kameo, K.; Tanami, T.; Tanaka, H.; Ono, N.; Kiuchi, Y.; Okamoto, S.; Sato, F.; Ichikawa, A. *Biorg. Med. Chem.* **2000**, *8*, 353. (q) Arnold, L. A.; Baasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841. (r) Kobayashi, Y.; Murugesh, M. G.; Nakano, M. *Tetrahedron Lett.* **2001**, *42*, 1703.

(4) Green, K.; Hamberg, M.; Samuelsson, B.; Smigel, M.; Frolich, J. C. *Advances in Prostaglandin and Thromboxane Research*; Raven Press: New York, 1978; Vol. 5, Chapt. 2.

(5) For previous syntheses of the major urinary metabolite of PGE_2, see (a) Boot, J. R.; Foulis, M. J.; Gutteridge, N. J. A.; Smith, C. W. *Prostaglandins* **1974**, *8*, 439. (b) Taub, D.; Zelawski, Z. S.; Wendler, N. L. *Tetrahedron Lett.* **1975**, 3667. (c) Lin, C. H. *J. Org. Chem.* **1976**, *41*, 4045. (d) For a synthetic route to the closely related major urinary metabolite of 15-F_{2t} isoprostane, see Durand, T.; Henry, O.; Vidal, J.-P.; Rossi, J.-C. *Tetrahedron Lett.* **2001**, *42*, 4333.

(6) The GC-MS standard for the assay is prepared by methoximation of **3**, followed by saponification.

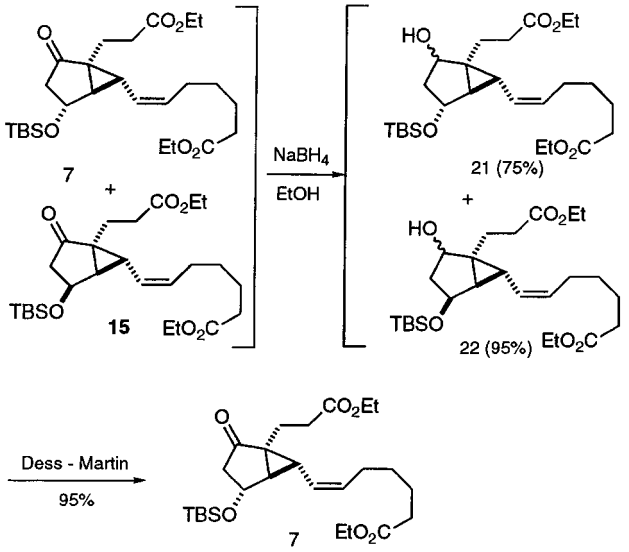
(7) (a) Taber, D. F.; Gleave, D. M.; Herr, R. J.; Moody, K.; Hennessy, M. J. *J. Org. Chem.* **1995**, *60*, 2283. (b) For an earlier preparation of diazoketone **4** using this approach, see Wood, J. L.; Moniz, G. A. *Org. Lett.* **1999**, *1*, 371.

(8) For the unsymmetrical ozonolysis of alkenes, see (a) Schreiber, S. L.; Claus, R. E.; Reagen, J. *Tetrahedron Lett.* **1982**, *23*, 3867. (b) Claus, R. E.; Schreiber, S. L. *Organic Synthesis, Coll. Vol. VIII*, p 168; Wiley: New York, 1990. (c) Taber, D. F.; Nakajima, K.; *J. Org. Chem.* **2001**, *66*, 3426 and references therein. (c) For an earlier preparation of **11**, see Chou, T. S.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 479.

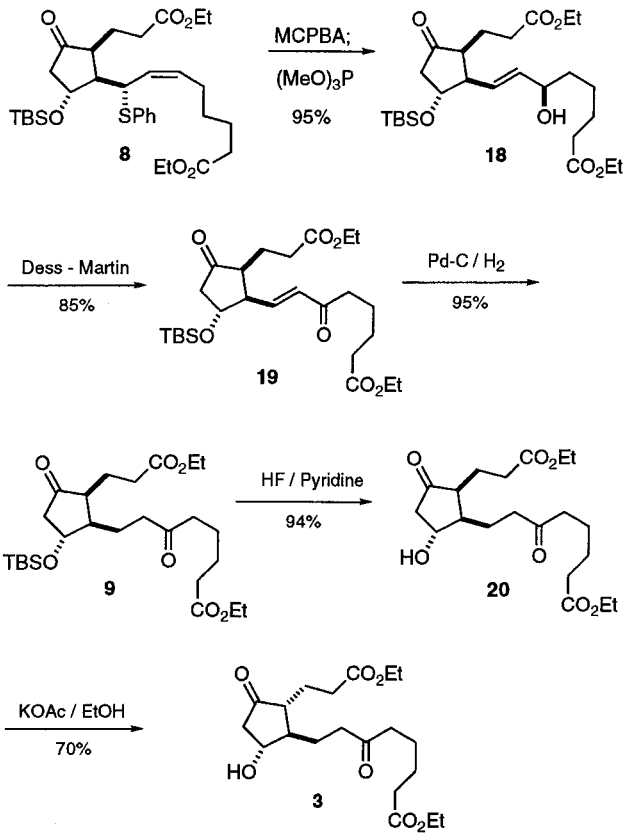
(9) For a detailed discussion of the ^{13}C NMR chemical shifts of allylic methylenes, see (a) Taber D. F.; You, K. *J. Org. Chem.* **1995**, *60*, 139. (b) Taber, D. F.; Kanai, K. *J. Org. Chem.* **1998**, *63*, 6607. (c) Taber D. F.; Kanai, K.; Pina R. *J. Am. Chem. Soc.* **1999**, *121*, 7773 and references therein.

(10) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

Scheme 4



Scheme 5



$BF_3{\cdot}OEt_2$ in CH_2Cl_2 (0.2 M in **7**) at −45 °C for 8 h gave the desired thioether **8** in 55% yield, together with 11% of the free thioether **16** and 11% of the free bicyclic ketone **17**.

Oxidation (Scheme 5) and Mislow rearrangement[11] of the sulfide **8** gave the allylic alcohol **18**. The side chains of the allylic alcohol **18** were established to be cis on the cyclopentane ring by comparing the ^{13}C NMR with those for the analogous ketones that are intermediates in the synthesis of the 5-F_{2t}-isoprostanes.[9b] The ^{13}C chemical shifts of the ring methines of **18** (δ 52.3, 48.9) are closer to the cis diastereomer in that series (δ 51.6, 50.6) than to the trans diastereomer (δ 54.0, 53.4).

Oxidation of the allylic alcohol with Dess−Martin periodinane[10] gave the enone **19**, which on exposure to hydrogen gas and palladium on charcoal gave the diketone **9**. The diketone **9** was then desilylated with HF in acetonitrile−pyridine to give the *cis* diastereomer **20**. Epimerization[12] with KOAc in ethanol gave the desired *trans* product **3**.

We have found three pairs of signals that are particularly useful for distinguishing **3** and **20**. The chemical shifts of the oxygenated methine of **3** (^{13}C δ 72.8, ^1H NMR δ 3.96, q, J = 7.5 Hz) are different from those of **20** (^{13}C δ 70.8, ^1H NMR δ 4.24, quint, J = 3.1 Hz). The ^{13}C chemical shifts of the ketone carbonyls of **3** (δ 215.7, 211.5) are also different from **20** (δ 216.9, 210.0), and the ^{13}C chemical shifts of ring methines C-4 and C-8 of **3** (^{13}C δ 53.1, 49.0) are different from **20** (δ 49.5, 47.2).

Conclusion

We have developed a practical synthesis (13 steps, 3.1% overall yield from the aldehyde ester **11**) of the ethyl ester of the major urinary metabolite of prostaglandin E_2. This synthesis has made PGU_mE_2 available in sufficient quantity to allow continuation of the ongoing physiological studies. We have also demonstrated that the *tert*-butyldimethylsilyl group is compatible with the thiophenol opening of the cyclopropyl ketone.

Experimental Section

Each reaction with air- and moisture-sensitive components was performed under a nitrogen atmosphere in a flame-dried reaction flask. Tetrahydrofuran was distilled from sodium/benzophenone, and dichloromethane was distilled from calcium hydride. ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, as solution in deuteriochloroform. Chemical shifts are reported in ppm downfield from TMS. ^{13}C NMR H substitution was determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine as "down", from methylene and quaternary carbons as "up". IR spectra were determined as neat oils. Mass spectra were obtained at an ionizing potential of 100 eV. R_f values indicated refer to thin-layer chromatography (TLC) on 2.5 × 10 cm, 250 μm analytical plates coated with silica gel GF. Solvents for TLC are reported as volume/volume mixtures. MTBE is methyl *tert*-butyl ether.

Diketone 10. To a stirred solution of 1-benzoylacetone (20.0 g, 123 mmol) in CH_2Cl_2 (500 mL) at 0 °C was added DBU (3.76 g, 24. 6 mmol). After 10 min, a solution of ethyl acrylate (24.7 g, 247 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 15 min. After an additional 5 min, the reaction mixture was warmed to room temperature. After an additional 20 h, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, saturated aqueous $NaHCO_3$, water, and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the diketone **10** (29.5 g, 90% yield from 1-benzoylacetone) as a pale yellow oil; TLC R_f (MTBE/petroleum ether = 3/7) = 0.39. ^1H NMR δ 8.04 (m, 2H), 7.61 (m, 1H), 7.54 (m, 2H), 4.67 (t, 1H, J = 6.8 Hz), 4.12 (q, 2H, J = 7.2 Hz), 2.39 (m, 2H), 2.29 (m, 2H), 2.17 (s, 3H), 1.22 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ up: 203.6, 196.3, 172.8, 136.1, 60.6, 31.5, 23.7; down: 133.9, 129.0 (×2), 128.8 (×2), 61.2, 28.6, 14.2; IR (film) 2982, 1729, 1676,

(11) (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (b) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100.

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1596, 1580, 1448, 1182, 695 cm^{-1}; EI MS (*m*/*z*) 285 (M^+ + Na, 100), 263 (15), 216 (6); HRMS calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1202.

Ethyl 4-Diazo-5-oxohexanoate 4. To a stirred solution of the diketone **10** (9.84 g, 37.6 mmol) in CH_2Cl_2 (110 mL) at 0 °C was added DBU (8.56 g, 56.3 mmol). After 20 min, a solution of *p*-nitrobenzenesulfonyl azide (15.4 g, 56.3 mmol) in CH_2Cl_2 (80 mL) was added dropwise over 15 min. After an additional 8 h, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, saturated aqueous $NaHCO_3$, water, and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the diazoketone **4** (3.82 g, 59% yield from **10**) as a pale yellow oil; TLC R_f (MTBE/petroleum ether = 3/7) = 0.23. ^{1}H NMR δ 4.15 (q, 2H, J = 7.1 Hz), 2.59 (dt, 4H, J = 5.3 and 18.5 Hz), 2.23 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ up: 191.1, 172.7, 67.0, 60.8, 31.9, 19.1; down: 25.3, 14.2; IR (film) 2983, 2935, 2079, 1734, 1638, 1420, 1374, 1326, 1252, 1196, 1095, 1018, 977, 920, 847 cm^{-1}; EI MS (*m*/*z*) 185 (M^+ + H, 10), 157 (65), 139 (10), 128 (100), 111 (80), 99 (55); HRMS calcd for $C_8H_{12}O_3N_2$ 184.0849, found 184.0852.

Ethyl 6-Oxohexanoate 11. To a stirred solution of cyclohexene (33.2 g, 400 mmol), $NaHCO_3$ (18.4 g, 220 mmol), and ethanol (50 mL) in CH_2Cl_2 (150 mL) at −78 °C was introduced O_3 gas. After 7 h, the reaction mixture became slightly blue. The solution was purged with N_2 for 20 min, and then the reaction mixture was filtered and concentrated. The residue was dissolved in CH_2Cl_2 (150 mL) and Ac_2O (80 mL, 0.85 mol). To this stirred solution at 0 °C was added triethylamine (139 mL, 0.93 mol) dropwise over 30 min. After an additional 30 min, ethanol (50 mL) was added. After an additional 15 min, the reaction mixture was concentrated. The residue was partitioned between MTBE and, sequentially, 3 M aqueous HCl and saturated aqueous K_2CO_3. The combined organic extract was dried ($MgSO_4$) and concentrated. Bulb to bulb distillation (pot = 55−90 °C, 0.02 mmHg) afforded ethyl 6-oxohexanoate **11** (28.10 g, 45% yield from cyclohexene) as a colorless oil; TLC R_f (ethyl acetate/petroleum ether = 3/7) = 0.15. ^{1}H NMR δ 9.71 (s, 1H), 4.06 (m, 2H), 2.41 (s, 2H), 2.26 (s, 2H), 1.60 (s, 4H), 1.19 (m, 3H); ^{13}C NMR δ up: 173.1, 60.4, 43.5, 34.0, 24.4, 21.5; down; 202.2, 14.3; IR (film) 2981, 2941, 2874, 1732, 1713, 1374, 1184 cm^{-1}; EI MS (*m*/*z*) 159 (M^+ + H, 100), 130 (26), 113 (100), 101 (45); HRMS calcd for $C_8H_{14}O_3$ 158.0943, found 158.0949.

Dienol 12. To a solution of phosphonium salt **23** (1.01 g, 2.46 mmol) in THF (20 mL) at −78 °C was added a 0.5 M toluene solution of KHMDS (4.7 mL, 2.35 mmol) dropwise over 10 min. After an additional 1 h, a solution of ethyl 6-oxohexanoate **11** (0.30 g, 2.24 mmol) in THF (4 mL) was added. After an additional 5 min, the reaction mixture was warmed to 0 °C. After an additional 6 h, the reaction mixture was partitioned between ethyl acetate and, sequentially, saturated aqueous NH_4Cl and brine. The residue was chromatographed to afford the alcohol **12** (186 mg, 46% yield from **11**) as a colorless oil. TLC R_f (ethyl acetate/petroleum ether = 3/7) = 0.25. ^{1}H NMR δ 6.53 (m, 1H), 6.02 (t, 1H, J = 11.0 Hz), 5.82 (dt, 1H, J = 5.8 and 15.1 Hz), 5.44 (dd, 1H, J = 7.6 and 18.3 Hz), 4.21 (t, 2H, J = 5.8 Hz), 4.12 (q, 2H, J = 7.2 Hz), 2.31 (t, 2H, J = 7.6 Hz), 2.21 (q, 2H, J = 7.6 Hz), 1.65 (quint, 2H, J = 7.6 Hz), 1.55 (s, 1H), 1.43 (quint, 2H, J = 7.6 Hz), 1.26 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ up: 173.9, 63.7, 60.5, 34.4, 29.2, 27.5, 24.7; down: 132.4, 132.2, 128.3, 126.8, 14.4; IR (film) 2981, 2940, 1732, 1373, 1183, 1157, 1096, 1032 cm^{-1}; EI MS (*m*/*z*) 194 (M^+-H_2O, 36), 149 (41), 131 (8), 121 (26), 106 (100), 91 (37); HRMS calcd for $C_{12}H_{20}O_3$ 212.1413, found 212.1417.

Dienal 5. To a stirred solution of the alcohol **12** (2.16 g, 10.1 mmol) in CH_2Cl_2 (60 mL) at room temperature was added Dess−Martin periodinane (6.48 g, 15.3 mmol). After an additional 2 h, the reaction mixture was cooled in an ice bath. The resulting precipitate was filtered and washed with Et_2O. Evaporation of the filtrate gave a residue that was chromatographed to afford the dienal **5** (1.86 g, 81% yield from **12**) as a pale yellow oil. TLC R_f (ethyl acetate/petroleum ether = 3/7) = 0.58. ^{1}H NMR δ 9.59 (d, 1H, J = 8.1 Hz), 7.42 (dd, 1H, J = 11.5 and 15.2 Hz), 6.26 (m, 1H), 6.12 (dd, 1H, J = 7.9 and 15.2 Hz), 5.97 (dt, 1H, J = 7.9 and 10.6 Hz), 4.13 (q, 2H, J = 7.1 Hz), 2.36 (m, 4H), 1.68 (m, 2H), 1.52 (m, 2H), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ up: 173.6, 60.5, 34.1, 28.8, 28.2, 24.6; down: 194.1, 146.8, 143.2 132.1, 127.2, 14.4; IR (film) 2937, 1734, 1679, 1631, 1374, 1161, 1030, 856 cm^{-1}; EI MS (*m*/*z*) 211 (M^+ + H, 25), 193 (37), 165 (100), 147 (57), 136 (55), 119 (65), 104 (51), 93 (41); HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1265.

TES-Ether 13 and Free Aldol 14. To a stirred solution of the diazoketone **4** (328 mg, 1.78 mmol) in toluene (28 mL) at −78 °C was added dropwise a 0.5 M toluene solution of KHMDS (3.8 mL, 1.90 mmol) over 15 min. After an additional 10 min, a solution of the dienal **5** (380 mg, 1.70 mmol) and TESCl (300 mg, 2.04 mmol) in toluene (5 mL) was added. After an additional 3 h, the reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to gave the recovered dienal **5** (144 mg, 38% recovered) followed by the TES-protected aldol **13** (207 mg, 40% yield from **5**) as a pale yellow oil; TLC R_f (ethyl acetate/petroleum ether = 3/7) = 0.59. ^{1}H NMR δ 6.48 (dd, 1H, J = 11.2 and 15.0 Hz), 5.95 (t, 1H, J = 10.9 Hz), 5.64 (dd, 1H, J = 6.5 and 15.0 Hz), 5.43 (dt, 1H, J = 7.6 and 10.7 Hz), 4.67 (q, 1H, J = 5.7 Hz), 4.13 (quint, 4H, J = 7.0 Hz), 2.73 (dd, 1H, J = 8.5 and 13.7 Hz), 2.61 (m, 4H), 2.45 (dd, 1H, J = 4.3 and 13.7 Hz), 2.30 (t, 2H, J = 7.6 Hz), 2.19 (q, 2H, J = 7.3 Hz), 1.65 (m, 2H), 1.42 (quint, 2H, J = 7.3 Hz), 1.26 (t, 6H, J = 7.3 Hz), 0.92 (t, 9H, J = 8.0 Hz), 0.57 (q, 6H, J = 8.0 Hz); ^{13}C NMR δ up: 191.7, 173.8, 172.8, 68.5, 60.9, 60.4, 46.8, 34.4, 32.1, 29.3, 27.6, 24.7, 19.4, 4.9 (×3); down: 135.3, 132.4, 128.1, 125.3, 71.2, 14.4, 14.3, 6.9 (×3); IR (film): 2955, 2876, 2079, 1735, 1630, 1374, 1188, 1066, 743 cm^{-1}; EI MS (*m*/*z*): 531 (M^+ + Na, 100); HRMS: calcd for $C_{26}H_{44}O_6N_2Si$ 508.2971 found 508.2961. Further elution gave the free aldol **14** (172 mg, 40% yield from **5**) as a pale yellow oil; TLC R_f (ethyl acetate/petroleum ether = 3/7) = 0.20. ^{1}H NMR δ 6.56 (dd, 1H, J = 11.1 and 15.1 Hz), 5.98 (t, 1H, J = 11.1 Hz), 5.67 (dd, 1H, J = 6.1 and 15.1 Hz), 5.45 (dt, 1H, J = 7.7 and 10.7 Hz), 4.69 (d, 1H, J = 5.7 Hz), 4.14 (m, 4H), 3.43 (bs, 1H), 2.62 (m, 6H), 2.30 (t, 2H, J = 7.6 Hz), 2.21 (q, 2H, J = 7.6 Hz), 1.65 (m, 2H), 1.42 (m, 2H), 1.26 (m, 6H); ^{13}C NMR δ up: 193.2, 173.9, 172.8, 68.2, 61.0, 60.4, 44.2, 34.4, 32.0, 29.2, 27.6, 24, 7, 19.2; down: 133.5, 132.9, 128.0, 126.2, 69.2, 14.4 (×2); IR (film) 2935, 2084, 1732, 1621, 1733, 1301, 1186, 1031 cm^{-1}; EI MS (*m*/*z*) 417 (M^+ + Na, 65), 389 (100), 361 (10), 329 (46), 261 (12), 216 (6), 186 (10); HRMS calcd for $C_{20}H_{30}O_6N_2$ 394.2105 found 394.2106.

Diazoketone 6 from TES-Ether 13. To a solution of the TES-ether **13** (1.16 g, 2.28 mmol) in THF (35 mL) at 0 °C was added solid NH_4Cl (0.61 g, 11.4 mmol) followed by a 1 M THF solution of n-Bu_4NF (3.5 mL, 3.5 mmol). After an additional 1 h, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. This residue was dissolved in CH_2Cl_2 (30 mL). To this solution at room temperature were added imidazole (0.352 g, 5.18 mmol), 4-DMAP (10.0 mg, cat), and *tert*-butylchlorodimethylsilane (0.52 g, 3.45 mmol). After an additional 18 h, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the *tert*-butylchlorodimethylsilyl ether **6** (745 mg, 81% yield from **13**) as a pale yellow oil; TLC R_f (ethyl acetate/petroleum ether) = 3/7) = 0.59.^{1}H NMR δ 6.46 (dd, 1H, J = 11.2 and 15.1 Hz), 5.93 (t, 1H, J = 11.2 Hz), 5.61 (dd, 1H, J = 6.2 and 15.1 Hz), 5.40 (dt, 1H, J = 7.7 and 10.7 Hz), 4.64 (m, 1H), 4.11 (quint, 4H, J = 7.1 Hz), 2.69 (dd, 1H, J = 8.8 and 13.6 Hz), 2.48 (m, 4H), 2.39 (dd, 1H, J = 4.0 and 9.6 Hz), 2.27 (t, 2H, J = 7.6 Hz), 2.16 (q, 2H, J = 7.4 Hz), 1.62 (m, 2H), 1.39 (m, 2H), 1.26 (dt, 6H, J = 7.1 Hz), 0.85 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR δ up: 191.9, 173.7, 172.7, 68.6, 60.9, 60.3, 46.5, 34.3, 32.1, 29.2, 27.5, 24.7, 19.4, 18.2; down: 135.3, 132.3, 128.1, 125.2, 71.2, 25.9 (×3), 14.4, 14.3, −4.3, −4.9; IR (film) 2931, 2857, 2082, 1735, 1629, 1374, 1254, 1186, 1160, 838, 779 cm^{-1}; EI MS (*m*/*z*), 509

($M^+ + H$, 100), 377(65); HRMS Calcd $C_{26}H_{44}O_6N_2Si$, 508.2970, found 508.2966.

Diazoketone 6 from the Free Aldol 14. To a stirred solution of the free aldol **14** (100 mg, 0.254 mmol) in CH_2Cl_2 (4 mL) were added imidazole (51.8 mg, 0.761 mmol), 4-DMAP (2 mg, cat.), and *tert*-butylchlorodimethylsilane (76.5 mg, 0.508 mmol). After an additional 18 h, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the *tert*-butyldimethylsilyl ether **6** (116 mg, 90% yield from **14**) as a pale yellow oil.

Bicyclic Ketones 7 and 15. To a stirred solution of $Rh_2(oct)_4$ (56 mg, 0.072 mmol) in CH_2Cl_2 (dried by filtration through anhydrous K_2CO_3, 30 mL) at room temperature was added dropwise over 15 min a solution of the diazoketone **6** (730 mg, 1.44 mmol) in CH_2Cl_2 (20 mL). After an additional 8 h, the reaction mixture was concentrated. The residue was chromatographed to afford the mixture of bicyclic ketone **7** (358 mg, 52% yield from **6**) and **15** (193 mg, 28% yield from **6**) as a colorless oil, TLC R_f (MTBE/petroleum ether = 16/84) = 0.47. To the mixture of bicyclic ketones **7** and **15** (215 mg, 0.447 mmol) in EtOH (10 mL) at 0 °C was added $NaBH_4$ (50.7 mg, 1.34 mmol). After 40 min, 5 mL of pH = 7 aqueous buffer was added. After an additional 1 min, the reaction mixture was partitioned between EtOAc and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the alcohol **21** (104 mg, 75% yield from **7**), followed by **22**.

To the solution ofalcohol **21** in CH_2Cl_2 (3.5 mL) was added Dess−Martin periodinane (126 mg, 0.260 mmol) at room temperature. After an additional 1 h, the reaction mixture was cooled in an ice bath. The resulting precipitate was filtered and washed with Et_2O. Evaporation of the filtrate gave a residue that was chromatographed to afford the bicyclic ketone **7** (98 mg, 95% yield from **21**). ^{1}H NMR δ 5.57 (dt, 1H, J = 7.4 and 10.3 Hz), 5.05 (dd, 1H, J = 9.1 and 10.3 Hz), 4.43 (d, 1H, J = 4.9 Hz), 4.11 (m, 4H), 2.43 (m, 2H), 2.30 (t, 2H, J = 7.4 Hz), 2.18 (m, 1H), 2.14 (m, 2H), 1.99 (m, 2H), 1.84 (m, 1H), 1.76 (m, 2H), 1.65 (m, 2H), 1.41 (quint, 2H, J = 7.6 Hz), 1.25 (dt, 6H, J = 7.2 and 5.8 Hz), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ up 212.8, 173.8, 173.6, 60.5 (×2), 44.1, 42.1, 34.3, 31.9, 29.0, 27.6, 24.7, 19.6, 18.1; down: 133.8, 124.9, 68.3, 42.3, 27.8, 25.9 (×3), 14.4 (×2), −4.5, −4.6; IR (film): 2931, 2857, 1732, 1254, 1178, 1085, 1058, 836, 777 cm^{-1}; EI MS (*m*/*z*) 503 (M^+ + Na, 100), 481 (20), 349 (20), 303 (48), 257 (27); HRMS: calcd $C_{26}H_{44}O_6Si$ 480.2908 found 480.2916.

Thioether 8. To a stirred solution of the bicyclic ketone **7** (474 mg, 0.988 mmol) and thiophenol (326 mg, 2.96 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C was added BF_3·OEt_2 (561 mg, 3.95 mmol). After 20 min, the mixture was warmed to −45 °C. After an additional 8 h, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, saturated aqueous $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the thioether **8** (318 mg, 55% yield from **7**) as a colorless oil; TLC R_f (MTBE/benzene = 2/98) = 0.42. ^{1}H NMR δ 7.38 (m, 2H), 7.26 (m, 3H), 5.53 (t, 1H, J = 10.6 Hz), 5.32 (m, 1H), 4.66 (d, 1H, J = 6.1 Hz), 4.11 (m, 4H), 3.84 (dd, 1H, J = 5.3 and 10.6 Hz), 2.72 (m, 2H), 2.59 (m, 2H), 2.46 (m, 1H), 2.26 (m, 2H), 2.14 (m, 2H), 1.9 (m, 1H), 1.7 (m, 1H), 1.4 (M, 3H), 1.25 (t, 6H, J = 7.1 Hz), 1.05 (M, 1H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR δ up: 217.2, 173.6, 173.3, 133.9, 60.5, 60.4, 47.0, 34.2, 33.1, 28.8, 27.0, 24.7, 20.6, 18.1; down: 134.5, 131.1 (×2), 129.5 (×2), 129.1, 129.0, 69.5, 53.1, 49.6, 47.0, 25.9 (×3), 14.4 (×2), −4.5 (×2); IR (film): 2930, 2856, 1736, 1583, 1472, 1462, 1438, 1372, 1253, 1180 cm^{-1}; EI MS (*m*/*z*): 613 (M^+ + Na, 100), 503 (6), 417 (10); HRMS calcd $C_{32}H_{50}O_6SiS$ 590.3099, found 590.3107; Further elution gave the free thioether **16** (50.4 mg, 11% yield from **7**) as a colorless oil, TLC R_f (MTBE/petroleum ether = 3/2) = 0.33; ^{1}H NMR δ 7.46 (m, 2H), 7.29 (m, 3H), 5.42 (m, 2H), 4.35 (m, 1H), 4.22 (dd, 1H, J = 5.0 and 10.0 Hz), 4.11 (m, 4H), 3.10 (d, 1H, J = 3.7 Hz), 2.72 (dd, 1H, J = 7.1 and 18.4 Hz), 2.52 (m, 1H), 2.35 (m, 2H), 2.26 (m, 2H), 2.20 (m, 2H), 1.84 (m, 2H), 1.64 (m, 2H), 1.47 (quint, 2H, J = 7.5 Hz), 1.25 (t, 6H, J = 7.2 Hz), 1.11 (m, 2H); ^{13}C NMR δ up: 216.0, 174.1, 173.4, 133.8, 60.6 (×2), 47.1, 34.1, 31.4, 28.8, 27.1, 25.3, 24.6; down: 134.1, 132.9 (×2), 129.0, 128.1 (×2), 127.4, 71.0, 53.0, 50.5, 48.7, 14.4 (×2); IR (film) 3448, 2933, 1728, 1374, 1183, 1079, 1028 cm^{-1}; EI MS (*m*/*z*) 499 (M^+ + Na, 100); HRMS calcd for $C_{26}H_{36}O_6S$ 476.2234, found 476.2213. Further elution gave the free bicyclic ketone **17** (37.5 mg, 11% yield from **7**) as a colorless oil, TLC R_f (MTBE/petroleum ether = 3/2) = 0.20; ^{1}H NMR δ 5.60 (dt, 1H, J = 7.3 and 10.3 Hz), 4.98 (dd, 1H, J = 9.0 and 10.3 Hz), 4.43 (dd, 1H, J = 7.3 and 5.8 Hz), 4.12 (quint, 4H, J = 7.2 Hz), 3.48 (d, 1H, J = 7.3 Hz), 2.55 (m, 2H), 2.30 (m, 4H), 2.10 (m, 4H), 1.86 (m, 1H), 1.61 (m, 2H), 1.41 (m, 2H), 1.26 (dt, 6H, J = 7.1 and 8.7 Hz); ^{13}C NMR δ up: 212.3, 174.6, 173.8, 61.1, 60.5, 44.1, 41.5, 34.3, 32.0, 28.9, 27.6, 24.6, 19.6; down: 134.4, 124.4, 67.9, 41.5, 28.2, 14.4, 14.3; IR (film) 3478, 2934, 1738, 1714, 1583, 1440, 1374, 1182, 1026, 748, 693 cm^{-1} ; EI MS (*m*/*z*): 389 (M^+ + Na, 100); HRMS calcd for $C_{20}H_{30}O_6$ 366.2043, found 366.2049.

Allylic Alcohol 18. To a stirred solution of the thioether **8** (268 mg, 0.455 mmol) in CH_2Cl_2 (18 mL) at −78 °C was added a solution of 3-chloroperoxybenzoic acid (157 mg, 0.910 mmol) in CH_2Cl_2 (2.0 mL). The mixture was stirred for 1 h, after which a solution of trimethyl phosphite (564 mg, 4.55 mmol) in EtOH (7 mL) was added. The mixture was stirred at −78 °C for 10 min and then warmed to room temperature. After an additional 2 h, the reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the allylic alcohol **18** (230 mg, 95% yield from **8**) as a colorless oil; TLC R_f (MTBE/petroleum ether = 3/7) = 0.16. ^{1}H NMR δ 5.68 (dd, 1H, J = 6.5 and 15.1 Hz), 5.26 (dd, 1H, J = 10.4 and 15.1 Hz), 4.21 (d, 1H, J = 5.4 Hz), 4.12 (m, 5H), 2.92 (t, 1H, J = 9.0 Hz), 2.67 (q, 1H, J = 7.4 Hz), 2.2−2.5 (m, 6H), 1.3−1.9 (m, 9H), 1.25 (M, 6H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ up: 217.7, 173.9, 173.6, 60.7, 60.5, 45.8, 36.9, 34.4, 32.2, 25.1, 24.9, 21.1, 18.2; down: 137.6, 126.8, 72.9, 72.2, 52.3, 48.9, 25.9 (×3), 14.4 (×2), −4.6, −4.7; IR (film): 3458, 2930, 2857, 1738, 1254, 1179, 1033, 837, 778 cm^{-1}; EI MS (*m*/*z*): 521 (M^+ + Na, 100), 503 (6), 481 (5), 349 (4), 303 (5); HRMS: calcd.$C_{26}H_{46}O_7Si$ 498.3014 found 498.3030.

Enone 19. To a stirred solution of the allylic alcohol **18** (212 mg, 0.426 mmol) in CH_2Cl_2 (12 mL) at room temperature was added Dess−Martin periodinane (247 mg, 0.511 mmol). After an additional 1 h, the reaction mixture was cooled in an ice bath. The resulting precipitate was filtered and washed with Et_2O. Evaporation of the filtrate gave a residue that was chromatographed to afford the enone **19** (169 mg, 80% yield from **18**), TLC R_f (MTBE/petroleum ether = 3/7) = 0.37. ^{1}H NMR δ 6.41 (dd, 1H, J = 10.3 and 15.6 Hz), 6.26 (d, 1H, J = 15.6 Hz), 4.27 (m, 1H), 4.11 (m, 4H), 3.06 (dd, 1H, J = 8.0 and 9.9 Hz), 2.77 (dd, 1H, J = 7.5 and 15.6 Hz), 2.54 (m, 3H), 2.40 (m, 2H), 2.31 (m, 2H), 1.98 (m, 1H), 1.65 (m, 5H), 1.51 (m, 1H), 1.25 (m), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ up: 216.4, 199.1, 173.6, 173.0, 60.7, 60.5, 45.9, 40.6, 34.2, 32.2, 24.6, 23.4, 21.2, 18.1; down: 141.7, 132.9, 72.1, 52.7, 49.3, 25.9 (×3), 14.4 (×2), −4.6 (×2); IR (film): 2931, 2587, 1739, 1676, 1629, 1464, 1255, 1181, 837, 778 cm^{-1}; EI MS (*m*/*z*): 519 (M^+ + Na, 100) HRMS calcd $C_{26}H_{44}O_7Si$, 496.2857 found 496.2881.

Diketone 9. To a solution of the enone **19** (18. 7 mg, 0.038 mmol) in ethanol (1.2 mL) at room temperature was added Pd/C (1.0 mg, cat.), and then a hydrogen gas balloon was attached. After 2 h, the reaction mixture was filtered and concentrated. The residue was chromatographed to afford the diketone **9** (18.6 mg, 99% yield from **19**) as a colorless oil,TLC R_f (MTBE/petroleum ether = 3/7) = 0.29. ^{1}H NMR δ 4.20 (quint, 1H, J = 2.9 Hz), 4.13 (q, 4H, J = 7.1 Hz), 2.62 (q, 1H, J = 7.2 Hz), 2.49 (m, 6H), 2.32 (m, 2H), 2.21 (m, 2H), 1.88 (m, 1H), 1.66 (m, 8H), 1.27 (t, 6H, J = 7.1 Hz), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ up: 217.5, 209.6, 173.6, 173.4, 60.6, 60.5, 45.6, 42.6, 40.7, 34.2, 32.3, 24.6, 23.3, 20.9, 19.9, 18.1; down: 71.1, 49.4, 47.8, 25.9 (×3), 14.4 (×2), −4.5, −4.6; IR (film): 2930, 2857, 1736, 1253, 1178, 836, 777 cm^{-1}; EI MS

(*m*/*z*): 521 (M^+ + Na, 100); HRMS calcd for $C_{26}H_{46}O_7Si$ 498.3014 found 498.2996.

Cis-Diastereomer of Ethyl Ester of PGE_2U_m 20. To a stirred solution of the silyl ether **19** (72.6 mg, 0.145 mmol) in CH_3CN (2 mL) at 0 °C was added pyridine (0.1 mL) followed by 52% aqueous HF solution (0.2 mL). After 6 h, an additional 0.1 mL of HF was added. After an additional 20 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and then extracted with $CHCl_3$. The organic extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed to afford the cis-diastereomer **20** of the ethyl ester of PGE_2U_m (52.5 mg, 94% yield from **19**) as a colorless oil, TLC R_f (ethyl acetate/petroleum ether = 1/1) = 0.20. ^{1}H NMR δ 4.24 (quint, 1H, J = 3.1 Hz), 4.05 (q, 4H, J = 7.2 Hz), 2.59 (m, 1H), 2.50 (m, 2H), 2.41 (m, 4H), 2.19 (m, 4H), 1.81 (m, 1H), 1.66 (m, 2H), 1.56 (m, 6H), 1.18 (t, 6H, J = 7.2 Hz); ^{13}C NMR δ up: 216.9, 210.0, 173.9, 173.4, 60.7 (×2), 45.0, 42.6, 40.4, 34.1, 32.1, 24.4, 23.5, 20.7, 20.1; down: 70.8, 49.5, 47.2, 14.4 (×2); IR (film): 3462, 2936, 2732, 1376, 1182, 1028, 860 cm^{-1}; EI MS (*m*/*z*): 407 (M^+ + Na, 100); HRMS calcd for $C_{20}H_{32}O_7$ 384.2149, found 384.2140.

Ethyl Ester of PGE_2U_m 3. To a solution of the cis diastereomer **20** (6.2 mg, 0.016 mmol) in ethanol (0.6 mL) at room temperature was added anhydrous KOAc (7.9 mg, 0.08 mmol). After 12 h, the reaction mixture was partitioned between $CHCl_3$ and saturated NH_4Cl. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the ethyl ester of PGE_2U_m **3** (4.3 mg, 70% yield from **20**), TLC R_f (ethyl acetate/petroleum ether = 1/1) = 0.22.l ^{1}H NMR δ 4.05 (m, 4H, J = 7.2 Hz), 3.96 (q, 1H, J = 7.5 Hz), 2.61 (m, 3H), 2.41 (m, 4H), 2.25 (m, 2H), 2.15 (dd, 1H, J = 8.3 and 18.5 Hz), 1.86 (m, 4H), 1.69 (m, 2H), 1.56 (s, 4H), 1.19 (t, 6H, J = 7.2 Hz); ^{13}C NMR δ up: 215.7, 211.5, 173.8, 173.5, 60.7, 60.6, 49.0, 42.7, 39.9, 34.2, 31.6, 25.0, 24.5, 23.7, 23.4; down: 72.8, 53.1, 49.0, 14.4 (×2); IR (film): 3500, 2931, 1736, 1448, 1376, 1181, 1098, 1030, 838, 778 cm^{-1}; EI MS (*m*/*z*): 407 (M^+ + Na, 100); HRMS calcd for $C_{20}H_{32}O_7$ 384.2149 found 384.2140.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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