Acknowledgment. We thank Professor R. J. Anderson for providing ^1H, ^{13}C, and IR spectra of natural tochuinyl acetate and The Center for Catalytic Science and Technology of the University of Delaware for financial support. We thank Professor Michael P. Doyle for many helpful comments and suggestions.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of **20–22, 25–28, 30,** and **33** (20 pages). Ordering information is given on any current masthead page.

Enantioselective Rh-Mediated Synthesis of (−)-PGE_2 Methyl Ester

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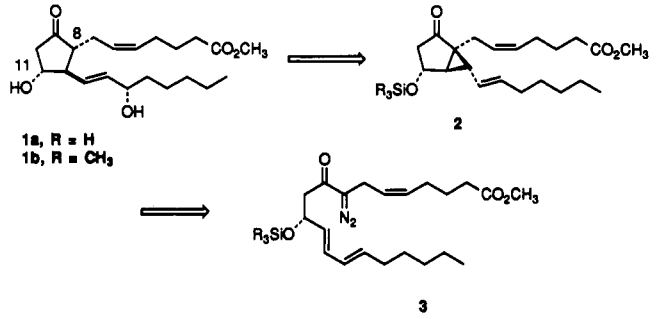
Intramolecular Rh(II) carboxylate catalyzed cyclization of an α-diazo β-methylene ketone to form a fused cyclopropane is shown to compete efficiently with β-hydride elimination, so long as a catalyst derived from an electron-donating carboxylate is used. Cyclization of diazoketone **3** gives **2**, which on opening with thiophenol followed by oxidative rearrangement gives PGE_2 methyl ester **1**. Prostaglandins having the 8-β configuration, recently identified as being physiologically important, can also be prepared using this approach.

Introduction

The prostaglandins are a family of mammalian hormones derived from the essential fatty acids.[1] Prostaglandin E_2 (**1a**), which could be considered the parent of



this series, possesses 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 investigations.[3,4] Most synthetic routes to the prostaglandins depend on addition of the two side chains sequentially to a preformed cyclopentane ring, necessitating a resolution step of some sort or a separation of product diastereomers.

Scheme I. Preparation of Silyloxy Acid 10

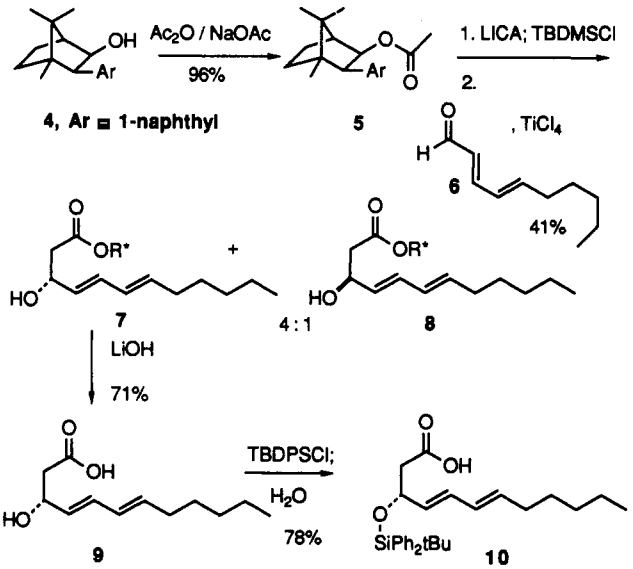
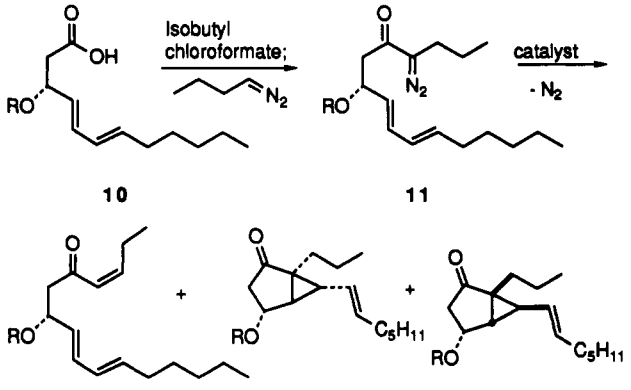


Table I. 1,5-Insertion vs β-Hydride Elimination



catalyst	12	13	14	yield (%)
$Rh_2(CF_3CO_2)_4$	100			90
$Rh_2(C_6H_5CO_2)_4$	14	60	26	84
$Rh_2(CH_3CO_2)_4$		72	28	55
$Cu(TBS)_2$		53	47	78

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Several years ago, we and Kondo[5] independently communicated an alternative strategy, based on cyclization of an α-diazo β-keto ester, that allowed direct control not just of relative configuration around the ring but also of the relative configuration at C-15. We now report the successful completion of the next stage in the evolution of this approach, centering on the preparation and cyclization of the enantiomerically pure diazo ketone **3**. This strategy allows the assembly of (−)-PGE_2 methyl ester (**1b**) in just nine steps from commercially available decadienal (**6**, Scheme I), with control of both relative and absolute configuration. We also report the first direct preparation of (−)-8-*epi*-PGE_2 methyl ester (**31**, Scheme III), the parent of a new family of prostaglandins recently identified as being of physiological importance.[6]

Intramolecular Cyclopropanation vs β-Hydride Elimination. The central uncertainty in the synthesis outlined here was whether (Table I) Rh(II)-catalyzed intramolecular cyclopropanation to form **13** and/or **14** could compete effectively with the expected[7] β-hydride elimination to form **12**. Although diazo insertion chemistry has been widely used in organic synthesis,[8] there has been no report of Rh(II)-mediated intramolecular C–H insertion or cyclopropanation in competition with β-hydride elimination.

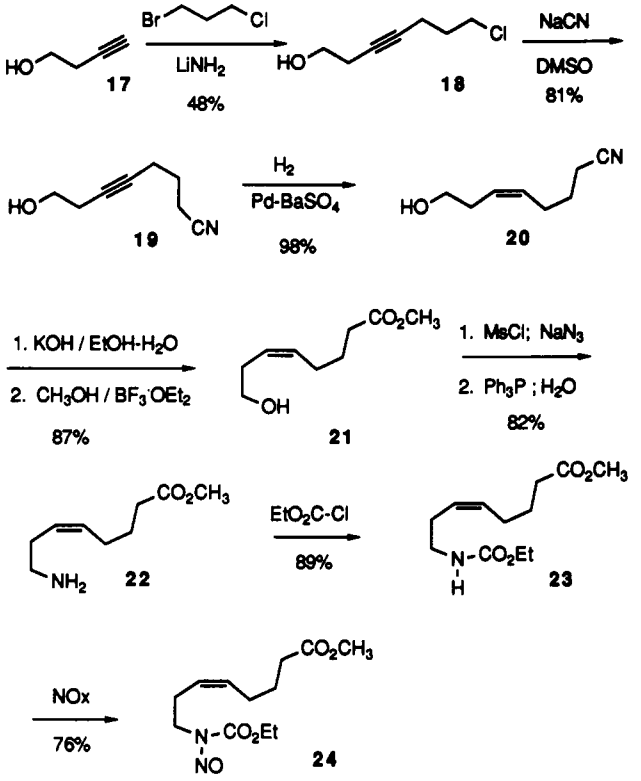
There were reports[9] of efficient intramolecular cyclopropanation of α-diazo ethyl ketones. In other work, we have found that α-diazo ethyl ketones also participate efficiently in Rh(II)-mediated intramolecular C–H insertion to form cyclopentanes.[10] The insertion reaction planned here would be more difficult, however, as β-hydride elimination from a methylene would be expected to be *much* faster than β-hydride elimination from a methyl.[11]

Preparation of β-Silyloxy Acid 10. The requisite enantiomerically pure β-silyloxy acid **10** (Scheme I) was prepared by addition of acetate anion to decadienal (**6**). Aldehyde **6**, from spontaneous air oxidation of vegetable acids, is an unwanted byproduct of commercial margarine production.

For our purposes, enantioselective 1,2-addition was expeditiously accomplished via acetate **5** derived from our previously described[12] naphthylborneol auxiliary **4**. Following the Helmchen modification[13] of the Mukaiyama procedure,[14] $TiCl_4$-mediated addition of the ketene silyl acetal derived from **5** to aldehyde **6** gave alcohols **7** and **8** in a ratio that ranged from 80:20 to 86:14. These were easily separated on a preparative scale by HPLC.

The stereochemical assignment of diastereomers **7** and **8** was based on our previous observations[12] with β-hydroxy esters derived from **5**. In a saturated ester such as these, the methine proton of the *S* diastereomer will appear at 2.81 ppm, whereas the methine proton of the *R* diastereomer will appear at 3.00 ppm. As the methine protons from **7** and **8** appear at 3.32 and 3.64 ppm, respectively, the configurational assignments indicated (Scheme I) were made. The accuracy of these assignments was confirmed by conversion of **7** to (−)-PGE_2 methyl ester.

Scheme II. Preparation of the Upper Side Chain



Silyloxy acid **10** could have been prepared by silylation followed by saponification, but this route led to substantial elimination. As an alternative, **7** was saponified to give (along with recovered **4**) the nicely crystalline **9**. Bis-silylation followed by mild hydrolysis of the unwanted silyl ester than gave the desired acid **10**.[15]

Model Cyclizations: Effect of the Carboxylate Ligand. With β-silyloxy acid **10** in hand, we were in a position to model the cyclization step that, if successful, would be the key to the prostaglandin synthesis. These studies were carried out with α-diazo ketone **11** (Table I), prepared by exposure of the mixed anhydride derived from racemic **10** to an excess of 1-diazobutane.[16]

The results of our first attempt, with rhodium trifluoroacetate (Table I), were not encouraging. The reaction proceeded cleanly, but gave *only* enone **12**, the product from the unwanted β-hydride elimination. Enone **12** was exclusively *Z*, a geometric outcome that had been observed in the past with similar diazo elimination reactions.[7]

The results with rhodium acetate (this abnormally low yield is for a single unoptimized run, on a small scale) were more encouraging. The fused cyclopropane products **13** and **14** were secured, with no trace of enone **12**. Specu-

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(15) This approach easily provided enough material for the studies described here. In more recent work (R. Bhamidipati, U. Delaware) we have developed an expeditious preparation of gram quantities of the nicely crystalline enantiomerically pure acid **9** using the Sharpless kinetic resolution: Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
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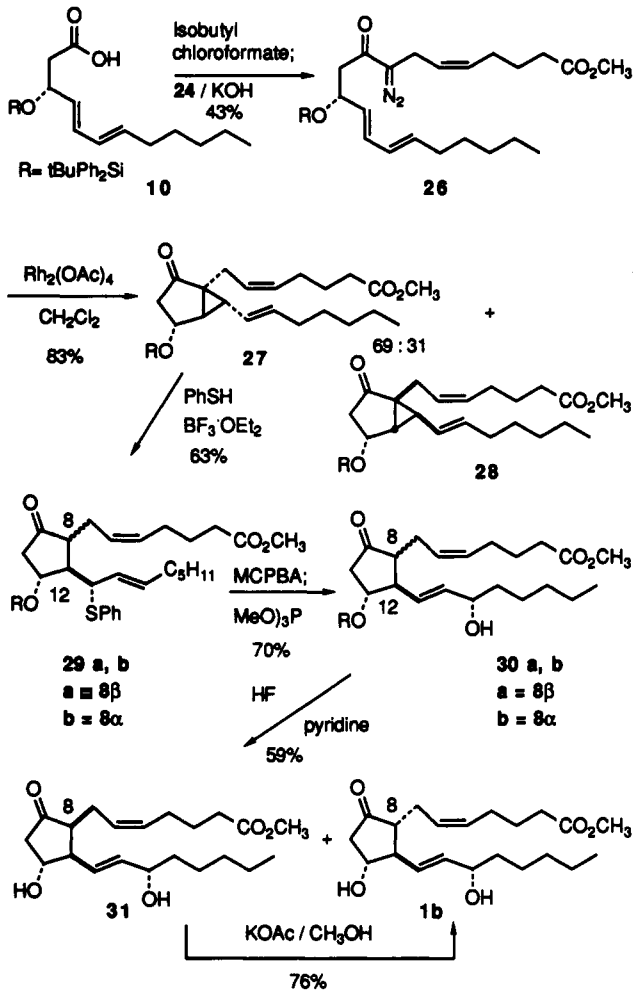
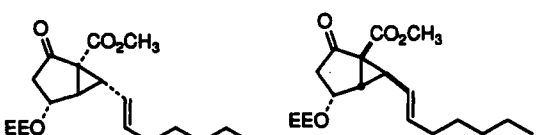
Scheme III. Synthesis of (-)-PGE$_2$ Methyl Ester



lating that the selectivity was a function of the electron-withdrawing ability of the carboxylate ligand, we then tried rhodium benzoate, which should be an intermediate case. Indeed, with rhodium benzoate catalysis all three products were observed.

Diastereoselectivity in the cyclization is also a function of the catalyst used (Table I). The two rhodium catalysts were quite comparable. The bis-salen Cu(I) catalyst,[17] on the other hand, shows very little diastereoselectivity.

We had hoped that the silyloxy group would prefer to be exo in the transition state leading to cyclization. The relative configurations of **13** and **14** (Table I) were tentatively assigned by comparing them (^{1}H NMR) to the known bicyclohexanones **15** and **16**.[5b] The α-alkoxymethine of **15** is reported at 4.31 ppm, while the α-alkoxymethine of **16** is reported at 4.69 ppm. Analogously, the α-alkoxymethine of **13** appears at 4.38 ppm, and the α-alkoxymethine of **14** appears at 4.63 ppm. Thus, it appeared that the major diastereomer had the silyloxy group exo, as had been hoped.



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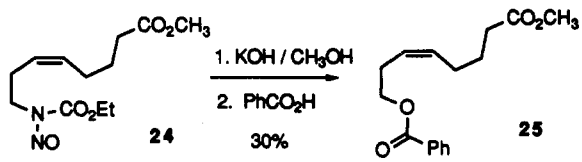
Preparation of the Upper Side Chain. The amino ester **22** (Scheme II) was prepared by a modification of literature methods,[18] by way of the known hydroxy ester **21**. Thus, alkylation of 3-butyn-1-ol with 1,3-bromochloropropane followed by displacement with NaCN and partial hydrogenation gave **20**, which after hydrolysis and esterification provided **21**. Triphenylphosphine-mediated reduction of the derived azide[19] then led to **22**.

A variety of strategies have been developed for generating diazoalkanes. The homoallyic nature of alcohol **21** precluded approaches based on aldehyde hydrazones.[20] The alternative has been base treatment of an *N*-nitrosoamide, -urea, sulfonate, carbonate, or -amine.[21-25] We have tried each of these methods and have found them to be effective for simple diazoalkanes.

Amine **22** offered a particular challenge because of the ease of saponification of the methyl ester.[24] We explored a wide range of experimental conditions, monitoring diazoalkane formation by conversion to benzoate **25**. We eventually found that addition of an ethereal solution of nitrosourethane **24** to a mixture of 50% KOH and ether, precooled to 0 °C, followed by 4 equiv of methanol, reproducibly produced the requisite diazoalkane, as judged by isolation of **25** in about 30% yield.



Synthesis of Prostaglandin E$_2$ Methyl Ester. Exposure of the mixed anhydride from acid **10** (Scheme III) to the crude diazoalkane from *N*-nitrosourethane **24** provided the key diazo ketone **26** in 43% yield, based on recovered **10**. Dropwise addition of a CH_2Cl_2 solution of **26** to a catalytic amount of rhodium acetate in CH_2Cl_2 then led to the expected bicyclic ketones **27** and **28**, which were easily separable chromatographically. The relative configurations of **27** and **28** were assigned by analogy to **13** and **14** (Table I).

Base-catalyzed thiophenoxide opening of the bicyclic system, so effective with doubly activated cyclopropanes,[5] did not proceed with the monoactivated cyclopropane **27**. Fortunately, we were able to develop an alternative procedure based on catalysis with boron trifluoride etherate. The sulfide **29** so produced, though nearly homogeneous by TLC, was clearly (^{1}H, ^{13}C NMR) a 77:23 mixture of diastereomers. We eventually established (see below) that this mixture is epimeric at C-8, with the unexpected *cis*-dialkylcyclopentanone predominating.

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(25) For a detailed comparative study of the several published procedures for generating diazoalkanes from the corresponding amines, see: Hoerrner, R. S., Ph.D. dissertation, University of Delaware, 1989.

As we were unable to separate the sulfide diastereomers, we carried the mixture on through oxidation and Mislow rearrangement.[26] The two C-8 epimers of the C-15 alcohol **30** (still 77:23) were resolvable by TLC. The *minor* epimer was congruent with the 11-silyloxy methyl ester we had prepared from authentic PGE_2.

The mixture of **30a,b** was carried on through desilylation. Again, two diastereomers (77:23), epimeric at C-8, were obtained. The minor epimer was PGE_2 methyl ester (**1b**), by comparison with authentic material. The major diastereomer **31**, while similar (^1H, ^{13}C NMR, TLC) to **1b**, was clearly not the desired material.

Considering the synthetic procedures used to prepare **31**, the only stereogenic center not directly controlled was that at C-8. That **31** was in fact the methyl ester of 8-*epi*-PGE_2 was confirmed by exposure of **31** to potassium acetate in methanol, which gave smooth equilibration to **1b**. It is a tribute to the very neutral conditions of both Mislow rearrangement and desilylation that the configurational integrity of the very unstable 8,12-*cis*-cyclopentanone is preserved through those two steps.

Conclusion

The synthetic approach to PGE_2 methyl ester described here is succinct (10 steps, counting equilibration, from commercially available 2,4-decadienal). It is especially noteworthy that the 8-*epi*-prostaglandins, *uniquely* available by this approach, have recently been shown[6] to be of substantial physiological importance.

Experimental[27] Section

[1*S*-(*exo*,*exo*)]-4,7,7-Trimethyl-3-(1-naphthenyl)bicyclo-[2.2.1]heptan-2-yl Acetate (5). Naphthylborneol **4** (2.0 g, 7.1 mmol), sodium acetate (0.2 g, 2.8 mmol), and acetic anhydride (7.1 mL) were maintained at 60 °C for 18 h. The reaction mixture was partitioned between ethyl acetate and, sequentially, water, 10% aqueous NaOH, and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated to provide **5** as a white solid (2.2 g, 96% yield). An analytical sample was recrystallized from hexane: mp = 86–90 °C; R_f (10% EtOAc/petroleum ether) = 0.59; ^1H NMR δ 7.35–8.10 (m, 7 H), 5.51 (d, 1 H), 4.06 (d, 1 H), 1.38–2.06 (m, 5 H), 1.35 (s, 3 H), 1.28 (s, 3 H), 1.26 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR δ u: 170.1, 135.8, 133.6, 133.4, 49.3, 48.2, 47.2, 24.6, d: 128.9, 127.3, 126.7, 126.0, 125.2, 124.5, 123.8, 80.0, 55.5, 51.2, 24.0, 21.9, 20.8, 15.0; IR 1742, 1600 cm^{-1}; exact mass calcd for $C_{22}H_{26}O_2$ 322.193, found 322.198.

[1*S*-(*exo*,*exo*)]-4,7,7-Trimethyl-3-(1-naphthenyl)bicyclo-[2.2.1]heptan-2-yl 3(*R*)-Hydroxy-(*E*,*E*)-4,6-dodecadienoate (7) and 3(*S*)-hydroxy 8. Following the procedure of Helmchen,[13] *n*-butyllithium (1.4 mL, 3.31 mmol) was added dropwise to isopropylcyclohexylamine (0.54 mL, 3.3 mmol) and THF (4.7 mL) at −78 °C. After 10 min, the mixture was warmed to −20 °C for 20 min, then recooled to −78 °C. The acetate **5** (0.97 g, 3.0 mmol) in THF (1 mL) was added dropwise over 5 min. After 10 min, HMPA (0.52 mL, 3.0 mmol) was added, followed after 3 min by *tert*-butyldimethylsilyl chloride (0.45 g, 3.0 mmol) in a minimum of pentane. After 15 min, the cooling bath was removed, and the mixture was allowed to warm to 0 °C over a period of 30 min. The reaction mixture was partitioned between pentane and water. The combined organic layers were dried (Na_2SO_4) and concentrated (bath below 40 °C). The crude ketene silyl acetal was used without hesitation in the next reaction: ^1H NMR δ 7.30–8.10 (m, 7 H), 4.56 (d, J = 8.9 Hz, 1 H), 4.06 (d, J = 8.8 Hz, 1 H), 3.12 (d, J = 2 Hz, 1 H), 2.99 (d, J = 5, 1 H), 1.50–1.95 (m, 2 H), 1.37 (s, 3 H), 1.20–1.35 (m, 2 H), 1.18 (s, 3 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.97 (s, 3 H), 0.60 (s, 9 H).

Following the outline of Helmchen, $TiCl_4$ (0.52 mL, 4.8 mmol) was added dropwise to freshly distilled *trans,trans*-2,4-decadienal (0.8 mL, 4.5 mmol) and CH_2Cl_2 (4.5 mL) at −78 °C. The ketene silyl acetal prepared above (3.0 mmol) was taken up in CH_2Cl_2 (4.5 mL) and added dropwise over 15 min. After 3 h at −78 °C the reaction mixture was partitioned between ether and, sequentially, saturated aqueous $NaHCO_3$, water, and brine. The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and chromatographed to yield **7** and **8** (582 mg, 41% yield) as a thick oil in an 80:20 ratio. These diastereomers were separated on preparative straight-phase HPLC to yield pure **7**: R_f (20% EtOAc/petroleum ether = 0.44); ^1H NMR δ 7.30–8.10 (m, 7 H), 5.78 (m, 2 H), 5.59 (m, 1 H), 5.51 (d, J = 8.8 Hz, 1 H), 4.98 (m, 1 H), 4.08 (d, J = 8.8, 2 H), 3.32 (bs, 1 H), 1.65–2.14 (m, 7 H), 1.14–1.60 (m, 15 H), 1.00 (s, 3 H), 0.87 (t, J = 6.7, 3 H); ^{13}C NMR δ u: 170.8, 135.7, 133.6, 133.3, 49.6, 48.6, 42.8, 42.2, 32.7, 31.6, 29.0, 24.0, 22.7, d: 136.0, 131.0, 130.7, 129.4, 129.2, 127.4, 127.0, 126.4, 125.6, 124.8, 123.8, 80.3, 68.3, 55.5, 51.3, 24.1, 21.8, 14.9, 14.2; IR 3670–3340, 1738 cm^{-1}.

3(*R*)-Hydroxy-(*E*,*E*)-4,6-dodecadienoic Acid (9). Ester **7** (1.54 g, 3.64 mmol) was dissolved in DME (3.5 mL). Solid LiOH·H_2O (0.92 g, 21.9 mmol) was added, followed by water (3.5 mL). After being heated at 60 °C for 14 h, the reaction mixture was partitioned between ether and 20% aqueous NaOH. The organic layer was dried and concentrated to recover alcohol **4**. The combined aqueous layers were acidified with 10% HCl and partitioned again with ether. The organic extract was dried (Na_2SO_4) and concentrated in vacuo. The crude acid was recrystallized from hexane to give 0.55 g (71% yield) of **9** as a white solid: mp = 58 °C); R_f (20% acetone/CH_2Cl_2) = 0.17; ^1H NMR 6.96 (bs, 2 H), 6.24 (dd, J = 15.32, 10.55 Hz, 1 H), 6.00 (dd, J = 15.0, 10.35 Hz, 1 H), 5.73 (dt, J = 7.0, 7.2 Hz, 1 H), 5.57 (dd, J = 15.1, 6.5 Hz, 1 H), 4.59 (m, J = 6.3 Hz, 1 H), 2.60 (d, J = 5.6 Hz, 2 H), 2.07 (q, J = 6.9 Hz, 2 H), 1.10–1.50 (m, 6 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR δ u: 177.2, 41.5, 32.8, 31.6, 29.0, 22.7, d: 136.9, 130.4, 129.2, 68.9, 14.2; $[\alpha]_D$ = −19.94 (*c* 0.064, EtOH). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.95; H, 9.45.

3(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-(*E*,*E*)-4,6-dodecadienoic Acid (10). Imidazole (0.80 g, 11.80 mmol) and 4-(dimethylamino)pyridine (0.14 g, 1.18 mmol) were added to β-hydroxy acid **9** (0.50 g, 2.36 mmol) in CH_2Cl_2 (3 mL) at 0 °C, followed by *tert*-butyldiphenylsilyl chloride (1.62 g, 5.91 mmol) in CH_2Cl_2 (1 mL). After 3 h, water (1 mL) was added to the cloudy reaction mixture, and stirring was continued for 1 h. The reaction mixture was partitioned between ethyl acetate and, sequentially, water and brine. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed to provide **10** as a viscous oil (0.83 g, 78% yield): R_f (20% EtOAc/petroleum ether) = 0.38; ^1H NMR δ 10.20 (bs, 1 H), 7.20–7.90 (m, 10 H), 5.81 (m, 2 H), 5.51 (m, 2 H), 4.57 (q, J = 6.7 Hz, 1 H), 2.52 (m, J = 7.2 Hz, 2 H), 2.02 (m, 2 H), 1.30 (bs, 6 H), 1.04 (s, 9 H), 0.88 (t, J = 6.2 Hz, 3 H); ^{13}C NMR δ u: 176.4, 133.5, 127.5 (2), 43.1, 32.6, 31.4, 28.8, 22.5, 19.3, d: 136.0 (×2), 131.8, 130.7, 129.7, 129.6, 129.1, 71.1, 26.9 (×3), 14.2; IR 3800–3450, 3075, 3054, 1713 cm^{-1}; MS *m/e* (relative intensity) 451 (M^+ + H, 9), 393 (M^+ + H − C_4H_8, 34), 373 (M^+ + H − C_6H_6, 54), 327 (12), 223 (9), 195 (100); $[\alpha]_D$ = +63.54 (*c* 0.0914, EtOH).

***N*-Nitroso-*N*-(*n*-butyl)urea.** Following the procedure of Arndt,[28] concentrated aqueous HCl (21 mL) was added dropwise to *n*-butylamine (15.0 g, 0.20 mol) in water (40 mL) at 0 °C. After addition of urea (41.0 g, 0.68 mol), the reaction mixture was maintained at 70 °C for 3.5 h and then at 100 °C for an additional 0.5 h. The mixture was cooled to rt, and solid $NaNO_2$ (14.2 g, 0.207 mol) was added. This urea solution was chilled to 0 °C and added dropwise over 30 min to a mixture of H_2SO_4 (13.7 g) and ice/H_2O (82 mL). The product rose to the top of the reaction mixture as a foamy yellow solid which was immediately filtered on a Buchner funnel and washed with water to provide 14.2 g (48% yield) of the *N*-nitrosourea as a light yellow solid (**CAUTION: PRESUMED** HUMAN CARCINOGEN!). This was stored at 0 °C and was used without further purification: ^1H NMR δ 6.85–7.15 (bs, 1 H), 6.24–6.58 (bs, 1 H), 3.83 (t, J = 7.3 Hz, 2 H), 1.18–1.48 (m, J = 7.2 Hz, 4 H), 0.90 (t, J = 7.2 Hz, 3 H); ^{13}C NMR

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(27) For a summary of general experimental procedures, see: Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639.

(28) Arndt, F. *Organic Synthesis*; Wiley: New York, 1943; Collect. Vol. II, p 461.

δ u: 155.0, 39.2, 28.9, 20.1, d: 13.5.

7-[(*tert*-Butyldiphenylsilyl)oxy]-4-diazo-(*E,E*)-8,10-hexadecadien-5-one (11). Isobutyl chloroformate (0.3 mL, 2.3 mmol) was added dropwise to the acid **10** (1.0 g, 2.2 mmol) in THF/ether (1:1, 4.5 mL) at 0 °C. Triethylamine (0.3 mL, 2.4 mmol) was added dropwise, and the reaction mixture was stirred for 30 min. The crude reaction mixture was filtered through glass wool. A solution of diazobutane was generated by adding 2.5 g (17.4 mmol) of *N*-nitroso-*N*-(*n*-butyl)urea to a rapidly stirred mixture of 50% aqueous KOH and ether at 0 °C.[16] The two solutions were combined at 4 °C. After 24 h, the reaction mixture was partitioned between ethyl acetate and, sequentially, saturated aqueous $NaHCO_3$ and brine. The combined organic layers were dried (Na_2SO_4), concentrated, and chromatographed to give siloxy acid **10** (39% yield) followed by diazo ketone **11** (404 mg, 59% yield) as a bright yellow oil: R_f (10% EtOAc/petroleum ether) = 0.42, ^1H NMR δ 7.25–7.76 (m, 10 H), 5.72 (m, J = 14.2 Hz, 2 H), 5.47 (m, 2 H), 4.67 (q, J = 6.4 Hz, 1 H), 2.78 (dd, J = 13.6, 7.3 Hz, 1 H), 2.51 (dd, J = 13.6, 5.8 Hz, 1 H), 2.24 (m, J = 7.8 Hz, 2 H), 1.98 (m, J = 7.1 Hz, 2 H), 1.12–2.75 (m, 8 H), 1.03 (s, 9 H0, 0.88 (m, J = 7.8, 7.2 Hz, 6 H); ^{13}C NMR δ u: 191.4, 134.2, 68.8, 46.5, 32.5, 31.3, 28.8, 24.4, 22.5, 20.3, 19.3, d: 135.9, 135.7, 131.4, 129.6, 129.1, 127.5, 127.4, 72.2, 27.0, 14.0, 13.8; IR 2067, 1636 cm^{-1}.

7-[(*tert*-Butyldiphenylsilyl)oxy]-(*Z,E,E*)-3,8,10-hexadecatrien-5-one (12). Diazo ketone **11** (46 mg, 0.09 mmol) in CH_2Cl_2 (0.9 mL) was added dropwise over 5 min to rhodium trifluoroacetate (<1 mg) in CH_2Cl_2 (0.9 mL) at rt. After 30 min, the reaction mixture was concentrated and chromatographed directly to give enone **12** (39 mg, 90% yield): R_f (10% EtOAc/petroleum ether) = 0.57; ^1H NMR δ 7.20–7.75 (m, 10 H), 5.95 (m, 2 H), 5.80 (m, 2 H), 5.47 (m, J = 6.5 Hz, 2 H), 4.64 (q, J = 6.6 Hz, 1 H), 2.69 (dd, J = 6.2, 14.7 Hz, 1 H), 2.37–2.58 (m, 3 H), 1.98 (q, J = 6.7 Hz, 2 H), 1.10–1.46 (m, 6 H), 1.02 (s, 9 H), 0.97–1.00 (t, J = 7.4 Hz, 3 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR δ u: 199.3, 134.2, 52.9, 32.7, 31.6, 29.0, 26.8, 23.1, 19.5, d: 150.2, 136.2, 135.6, 132.1, 129.8, 129.7, 129.5, 127.7, 127.0, 71.4, 27.2, 14.2, 13.7; IR 1695, 1617 cm^{-1}; MS m/e (relative intensity) 489 (M^+ + H, 17), 431 (M^+ + H − C_4H_8, 34), 411 (M^+ − C_6H_5, 56), 391 (89), 343 (46), 233 (100).

4β-[(*tert*-Butyldiphenylsilyl)oxy]-6β-(1-heptenyl)-1β-propylbicyclo[3.1.0]hexan-2-one (13) and 1α,6α-Diastereomer 14. Diazo ketone **11** (70 mg, 0.135 mmol) in CH_2Cl_2 (1.4 mL) was added dropwise over 10 min to rhodium acetate (<1 mg) in CH_2Cl_2 (1.4 mL) at rt. After 30 min, the reaction mixture was concentrated and chromatographed directly to give the minor diastereomer **14** (10 mg, 15% yield) R_f (10% EtOAc/petroleum ether) = 0.53, followed by the major diastereomer **13** (26 mg, 40% yield): R_f (10% EtOAc/petroleum ether) = 0.46; ^1H NMR δ 7.16–7.60 (m, 10 H), 5.33 (dt, J = 7.2, 15.3 Hz, 1 H), 4.89 (dd, J = 7.8, 15.2 Hz, 1 H), 4.33 (d, J = 4.9 Hz, 1 H), 2.12 (dd, J = 4.9, 18.7 Hz, 1 H), 1.70–2.00 (m, 5 H), 1.10–1.55 (m, 10 H), 0.95 (s, 9 H), 0.86 (t, J = 7.3 Hz, 3 H), 0.78 (t, J = 6.6 Hz, 3 H); ^{13}C NMR δ u: 213.2, 133.8, 44.2, 43.1, 32.7, 31.4, 29.1, 27.0, 25.6, 22.7, 20.9, 19.2, d: 135.9, 134.6, 130.0, 127.9, 124.9, 69.5, 40.3, 31.9, 14.3, 14.2; IR 1728 cm^{-1}; MS (chemical ionization) m/e (relative intensity) 506 (M^+ + NH_4, 100), 489 (M^+ + H, 18), 250 (26), 233 (8), 156 (8).

7-Chloro-3-heptyn-1-ol (18). Following the outline of Perchonock,[18] lithium wire (1.06 g, 23.5 cm, 152.1 mmol) cut into small portions and washed sequentially with hexane, ethanol, and hexane was added to liquid NH_3 (150 mL) containing anhydrous $FeCl_3$ (0.2 g) at −45 °C (bath). After 1 h, 1-butyn-4-ol (5.0 mL, 66.1 mmol) in ether (50 mL) was added over 20 min. After 1 h, 1-bromo-3-chloropropane (7.4 mL, 69.4 mmol) in ether (50 mL) was added dropwise over 30 min. The reaction flask was packed in dry ice, and the mixture was stirred for 12 h, by which time it had reached rt. With cooling in an ice bath, the mixture was acidified to congo red with concentrated aqueous HCl. The mixture was partitioned between ether and, sequentially, aqueous $NaHCO_3$, water, and brine. The organic layers were dried (Na_2SO_4), concentrated and bulk-to-bulb distilled (66–75 °C (bath), 1 mmHg) to give **18** as a clear oil (6.5 g, 48% yield): R_f (30% EtOAc/petroleum ether) = 0.35; ^1H NMR δ 3.67 (m, J = 6.3 Hz, 4 H), 2.40 (m, 4 H), 1.98 (bs, 1 H), 1.94 (m, J = 6.5 Hz, 2 H); ^{13}C NMR δ u: 80.2, 77.7, 62.1, 43.8, 31.5, 23.0, 16.2; IR 3710–3081, 1437 cm^{-1}.

7-Hydroxy-4-heptynenitrile (19). Solid NaCN (1.2 g, 25.1 mmol) and NaI (0.2 g, 1.05 mmol) were added to **18** (3.0 g, 20.9 mmol) in DMF (50 mL). After 3 h at 100 °C the reaction was partitioned between ethyl acetate and, sequentially, water and brine. The organic layer was dried (Na_2SO_4), concentrated, and bulb-to-bulb distilled (bath 90–95 °C, 1 mmHg) to give **19** as a clear oil (2.3 g, 81% yield): R_f (30% EtOAc/petroleum ether) = 0.17; ^1H NMR 3.63 (q, J = 5.8 Hz, 2 H); 2.43 (t, J = 7.1 Hz, 2 H), 2.28–2.38 (m, 4 H), 1.78 (m, J = 6.8 Hz, 3 H); ^{13}C NMR δ u: 119.4, 79.1, 78.9, 61.1, 24.6, 22.9, 17.9, 16.1; IR ($CDCl_3$) 3753–3296, 2643 cm^{-1}.

7-Hydroxy-(*Z*)-4-heptenenitrile (20). A 250-mL hydrogenation flask with a stir bar was charged with 0.5 g of 5% $Pd/BaSO_4$ and 16 mL of ethyl acetate. The catalyst was saturated with H_2, then alkyne **19** (5.0 g, 36.5 mmol) and quinoline (0.2 mL, 1.8 mmol) in EtOAc (20 mL) were added using aspirator suction. The reaction was stirred until 820 mL of H_2 had been taken up. The crude mixture was filtered through Celite to provide 4.97 g (98% yield) of alkene **20**, which was used without further purification: R_f (30% EtOAc/petroleum ether) = 0.21; ^1H NMR δ 5.47 (m, J = 6.6 Hz, 2 H), 3.60 (t, J = 6.7, 2 H), 3.38 (bs, 1 H), 2.10–2.40 (m, J = 7.2, 6 H), 1.72 (m, J = 7.2, 2 H); ^{13}C NMR δ u: 119.8, 62.0, 26.0, 25.2, 16.4, d: 129.6, 128.1; IR ($CDCl_3$) 3622, 3573–3156, 3015 cm^{-1}.

Methyl 8-Hydroxy-(*Z*)-5-octenoate (21). KOH (25.5 g, 454 mmol), nitrile **20** (10.5 g, 75.8 mmol), ethanol (70 mL), and water (70 mL) were combined and heated at 90 °C for 12 h. Brine (50 mL) was added, and the reaction mixture was acidified to congo red with 10% HCl (90 mL). This mixture was extracted with ethyl acetate (7 × 75 mL), each extract being washed once with brine. The organic extracts were dried ($MgSO_4$) and concentrated to give 11.9 g of the acid: R_f (30% EtOAc/petroleum ether) = 0.06; ^1H NMR δ 7.60–7.80 (bs, 1 H), 5.45 (m, J = 6.9 Hz, 2 H), 3.64 (t, J = 6.7 Hz, 2 H), 2.32 (m, 4 H), 2.10 (m, J = 7.1 Hz, 2 H), 1.70 (m, J = 7.2, 2 H); ^{13}C NMR δ u: 178.8, 62.1, 33.4, 30.5, 26.2, 24.6, d: 131.4, 126.6; IR 3753–3218, 3016, 1709 cm^{-1}.

Boron trifluoride etherate (23.3 mL, 189 mmol) was added dropwise to a solution of the crude acid (11.9 g, 75.2 mmol) in MeOH (90 mL). After heating at 60 °C for 5 h, the reaction mixture was partitioned between ethyl acetate and, sequentially, saturated aqueous $NaHCO_3$, water, and brine. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to provide **21** as a clear oil (12.1 g, 87% yield): R_f (30% EtOAc/petroleum ether) = 0.24; ^1H NMR δ 5.45 (m, 2 H), 3.66 (s, 3 H), 3.60 (t, J = 6.8 Hz, 2 H), 2.32 (m, 5 H), 2.10 (m, J = 6.9 Hz, 2 H), 1.69 (m, J = 7.4 Hz, 2 H); ^{13}C NMR δ u: 174.1, 61.9, 33.4, 30.7, 26.3, 24.5, d: 130.9, 126.6, 51.4; IR 3679–3123, 3008, 1738; GC/MS m/e 154 (4), 142 (100), 139 (3), 123 (60), 113 (7), 112 (9) (lit.[29] ^{13}C NMR δ 24.8, 26.7, 30.9, 33.4, 51.6, 62.2, 126.8, 131.5, 174.4).

Methyl 8-Amino-(*Z*)-5-octenoate (22). Triethylamine (10.3 mL, 73.9 mmol) was added dropwise over 5 min to methanesulfonyl chloride (5.5 mL, 70.4 mmol) and **21** (12.1 g, 70.4 mmol) in ether (70 mL) at 0 °C. After 1 h at 0 °C and 2 h at rt, the reaction mixture was partitioned between ether and, sequentially, water and brine. The organic layers were dried (Na_2SO_4) and concentrated to provide 14.2 g of the crude mesylate: R_f (30% EtOAc/petroleum ether) = 0.36; ^1H NMR 5.36–5.60 (m, J = 7.1 Hz, 2 H), 4.21 (t, J = 6.8 Hz, 2 H), 3.67 (s, 3 H), 3.02 (s, 3 H), 2.50 (m, J = 6.8 Hz, 2 H), 2.33 (m, J = 7.3 Hz, 2 H), 2.11 (m, J = 7.2 Hz, 2 H), 1.71 (m, J = 7.3 Hz, 2 H); ^{13}C NMR δ u: 173.9, 69.2, 33.2, 28.3, 26.6, 24.6, d: 133.5, 124.1, 51.2, 37.4; IR 3019, 1738.

Sodium azide (13.7 g, 211 mmol) was added in one portion to a solution of the mesylate (14.2 g) in DMF (70 mL) at rt. After heating at 65 °C for 6 h, the reaction mixture was partitioned between ether and water. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to provide the azide as a colorless oil (12.6 g): R_f (30% EtOAc/petroleum ether) = 0.77; ^1H NMR δ 5.45 (m, J = 6.4 Hz, 2 H), 3.66 (s, 3 H), 3.28 (t, J = 6.8 Hz, 2 H), 1.71 (m, J = 7.2 Hz, 2 H); ^{13}C NMR δ u: 173.7, 50.8, 33.1, 26.9, 26.5, 24.5, d: 131.6, 125.9, 51.3; IR 3013, 2100, 1740 cm^{-1}.

Triphenylphosphine (18.3 g, 70 mmol) was added in one portion to the azide (12.6 g) in ether (70 mL) at 0 °C. After 1 h at 0 °C (gas evolution) and 1 h at rt, water (7 mL) was added. After 14

(29) Pfister, J. R.; Muethy, D. V. K. *J. Med. Chem.* **1983**, *26*, 1099.

h at rt, the reaction mixture was partitioned between ether and, sequentially, water and brine. The combined organic layers were dried (Na_2SO_4), concentrated to 100 mL, and cooled to 0 °C. The solid triphenylphosphine oxide precipitate was filtered off, and the ether solution was again concentrated. The crude product was bulb-to-bulb distilled (bath 70–77 °C, 1 mmHg) to give **22** as a colorless oil (9.8 g, 82% yield from alcohol **21**): R_f (30% EtOAc/pet ether) = 0.07; ^{1}H NMR δ 5.43 (m, J = 7.0 Hz, 2 H), 3.66 (s, 3 H), 2.72 (t, J = 6.8 Hz, 2 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.03–2.22 (m, J = 6.8 Hz, 4 H), 1.69 (m, J = 7.2 Hz, 2 H), 1.25 (s, 2 H); ^{13}C NMR δ 174.0 (u), 130.7 (d), 128.0 (d), 51.5 (d), 42.0 (u), 33.4 (u), 31.6 (u), 26.7 (u), 24.9 (u); IR 3007, 1741; MS m/e (relative intensity) 228 (M^+ + TMS – CH_3, 10), 199 (72), 183 (28), 159 (10), 102 (100); exact mass calcd for $C_9H_{17}NO_2$ + TMS – CH_3 228.142, found 228.141.

Methyl 8-[(Ethoxycarbonyl)amino]-(*Z*)-5-octenoate (23). Under mechanical stirring, ethyl chloroformate (9.3 mL, 97.4 mmol) was added dropwise over 3 min to freshly distilled **22** (15.1 g, 88.5 mmol) in 1:1 THF/ether (175 mL) at 0 °C. Triethylamine (14.8 mL, 106 mmol) was added dropwise over 15 min. The cooling bath was removecd, and vigorous stirring was continued for another 2 h. The reaction mixture was partitioned between ether and, sequentially, water and brine. The organic layers were dried (Na_2SO_4), concentrated, and chromatographed to give **23** as a colorless oil (19.2 g, 89% yield): R_f (20% EtOAc/petroleum ether) = 0.31; ^{1}H NMR δ 5.42 (m, 2 H), 4.09 (q, J = 7.1 Hz, 2 H), 3.66 (s, 3 H), 3.18 (q, J = 6.5 Hz, 2 H), 2.29 (m, 4 H), 2.09 (m, J = 7.1 Hz, 2 H), 1.69 (m, J = 7.3 Hz, 2 H), 1.22 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ u: 173.7, 156.5, 60.2, 40.3, 33.0, 27.6, 26.3, 24.5, d: 130.8, 126.9, 51.1, 14.4; IR: 3463, 3426–3257, 1740, 1728; GC/MS m/e (relative intensity) 228 (M^+, 10), 212 (14), 199 (72), 183 (28), 159 (10), 102 (100). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70. Found: C, 59.18; H, 8.59.

Methyl *N*-Nitroso-8-[(Ethoxycarbonyl)amino]-(*Z*)-5-octenoate (24). N_2, passed over 30 mL of concentrated H_2SO_4 to which solid $NaNO_2$ was added in 1-g portions over 1.5 h, was bubbled through a suspension of urethane **23** (1.80 g, 7.41 mmol) and NaOAc (0.91 g, 11.1 mmol) in CCl_4 (9 mL). The suspension was filtered, concentrated, and chromatographed to provide **24** as a yellow oil (1.44 g, 76% yield from amine **23**) (**CAUTION**: PRESUMED HUMAN CARCINOGEN!): R_f (30% EtOAc/petroleum ether) = 0.65; ^{1}H NMR δ 5.35 (m, 2 H), 4.55 (q, J = 7.1 Hz, 2 H), 3.77 (t, J = 7.4 Hz, 2 H), 3.67 (s, 3 H), 2.30 (t, J = 7.4, 2 H), 2.15 (m, J = 7.3 Hz, 2 H), 2.02 (m, J = 7.3 Hz, 2 H), 1.66 (m, J = 7.3 Hz, 2 H), 1.47 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ u: 173.8, 153.8, 64.3, 40.1, 33.3, 30.1, 24.8, d: 131.9, 125.2, 51.4, 26.3, 14.2.

Methyl 8-(Benzoyloxy)-(*Z*)-5-octenoate (25). Nitrosourethane **24** (544 mg, 2.0 mmol) was added to a rapidly stirred mixture of 50% KOH (1.0 mL) and ether (2 mL) at 0 °C. MeOH (0.33 mL) was added immediately. After 30 min, the layers were separated. Benzoic acid (244 mg, 2.0 mmol) was added to the yellow ether layer, which was then partitioned between ether and saturated aqueous $NaHCO_3$. The organic layers were dried (Na_2SO_4), concentrated, and chromatographed to give benzoate **25** as a colorless oil (166 mg, 30% yield): R_f (20% EtOAc/petroleum ether) = 0.49; ^{1}H NMR δ 7.92–8.10 (m, 2 H), 7.30–7.55 (m, 3 H), 5.43 (m, J = 5.5 Hz, 2 H), 4.25 (t, J = 6.8 Hz, 2 H), 3.59 (s, 3 H), 2.44 (m, J = 5.5 Hz, 2 H), 2.25 (m, J = 7.5 Hz, 2 H), 2.05 (m, J = 6.7 Hz, 2 H), 1.64 (m, J = 7.2 Hz, 2 H); ^{13}C NMR δ u: 174.0, 166.6, 139.5, 64.5, 33.4, 27.0, 26.7, 24.8, d: 132.9, 131.6, 129.6 (2), 128.4 (2), 125.7, 51.5; IR 3015, 1741, 1724 cm^{-1}; GC/MS m/e (relative intensity) 245 (M^+ – OCH_3, 6), 154 (100), 123 (8), 122 (8).

Methyl 11(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-8-diazo-9-oxo-(*Z*,*E*,*E*)-5,12,14-eicosatrienoate (26). Isobutyl chloroformate (0.13 mL, 0.99 mmol) was added to β-siloxy acid **10** (0.42 g, 0.94 mmol) in THF/ether (1:1, 2 mL) at 0 °C. Triethylamine (0.15 mL, 1.2 mmol) was added dropwise over 3 min. After an additional 30 min, the reaction mixture was diluted with ether (5 mL), filtered through glass wool, and concentrated. The residue was redissolved in ether/petroleum ether (4:1, 5 mL) and cooled to 0 °C. The solution was again filtered and concentrated, then added to an ethereal solution of diazoalkane prepared from **24** following 3.3 times the procedure for the preparation of benzoate **25**. The solution was concentrated to 2 mL by a flow of N_2 and stirred at 4 °C for 18 h. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was dried (Na_2SO_4; briefly!), concentrated, and chromatographed to give recovered siloxy acid **10** (218 mg), followed by **26** as a bright yellow oil (129 mg, 43% yield): R_f (15% EtOAc/petroleum ether) = 0.46; ^{1}H NMR δ 7.25–7.90 (m, 10 H), 5.26–5.90 (m, 6 H), 4.67 (q, J = 6.7, 1 H), 3.66 (s, 3 H), 3.00 (d, 2 H), 2.77 (dd, J = 13.8, 7.4 Hz, 1 H), 2.55 (dd, J = 13.5, 5.5 Hz, 1 H), 2.33 (m, 2 H), 2.04 (m, 4 H), 1.68 (m, 2 H), 1.27 (bm, 6 H), 1.03 (s, 9 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR δ u: 191.1, 173.9, 134.1, 133.9, 68.4, 46.7, 33.4, 32.7, 31.5, 29.0, 26.6, 24.8, 22.7, 20.3, 19.4, d: 136.1, 136.0, 135.9, 131.6, 129.8, 129.6, 129.2, 127.6, 127.5, 123.9, 72.4, 51.5, 27.1, 14.2; IR 2068, 1742 cm^{-1}; $[\alpha]_D$ = +73.98 (c 0.0234, $CHCl_3$).

Methyl [(1*R*,4*R*,5*R*,7*R*)-7-[6(*E*)-Heptenyl]-1-oxo-4-[(*tert*-butyldiphenylsilyl)oxy]bicyclo[3.1.0]hexyl]-1(*Z*)-δ-heptenoate (27). Diazo ketone **26** (117 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 10 min to a stirred suspension of rhodium acetate (less than 1 mg) in CH_2Cl_2 (gas evolution; yellow color fades) at rt. After 30 min the mixture was concentrated and directly chromatographed to give the minor diastereomer **28** (29 mg, 26% yield): R_f (ether/hexanes) = 0.49; ^{1}H NMR δ 7.25–7.90 (m, 10 H), 5.61–5.75 (dt, 1 H), 5.13–5.30 (m, 2 H), 4.99–5.12 (dd, 1 H), 4.63 (m, 1 H), 3.62 (s, 3 H), 2.45–2.58 (dd, 1 H), 2.20–2.40 (m, 3 H), 1.82–2.14 (m, 6 H), 1.50–1.82 (m, 6 H), 1.20–1.44 (m, 4 H), 1.10 (s, 9 H), 0.88 (m, 3 H). This was followed by the major diastereomer **27** as a colorless oil (64 mg, 57% yield): R_f (15% Et_2O/petroleum ether) = 0.46; ^{1}H NMR δ 7.20–7.80 (m, 10 H), 5.57–5.91 (m, 1 H), 5.30–5.52 (m, 2 H), 4.89–5.10 (m, 1 H), 4.41 (d, 1 H), 3.65 (s, 3 H), 2.14–2.75 (m, 4 H), 1.85–2.12 (m, 6 H), 1.50–1.85 (m, 6 H), 1.13–1.44 (m, 4 H), 1.08 (s, 9 H), 0.88 (t, 3 H); ^{13}C NMR δ u: 212.3, 174.2, 134.1, 133.8, 46.8, 43.9, 42.9, 33.7, 32.7, 31.5, 29.1, 25.0, 22.6, 21.5, 19.2, d: 136.2, 135.9, 129.8, 129.7, 128.1, 127.9, 127.7, 127.6, 124.7, 69.6, 51.6, 40.1, 31.9, 27.0, 14.2; IR 1741, 1729 cm^{-1}; precise mass calcd for $C_{37}H_{50}SiO_4$ – *tert*-butyl (C_4H_9) 529.277, found 529. 273; $[\alpha]_D$ = +51.72 (c 0.0136, $CHCl_3$).

Methyl (5*Z*,8β,11*R*,12β,13*S*,14*E*)-11-[(*tert*-Butyldiphenylsilyl)oxy]-9-oxo-13-(phenylthio)prosta-5,14-dienoate (29a,b). Boron trifluoride etherate (3.1 mg, 0.22 mmol) was added to thiophenol (5.9 mg, 0.053 mmol) and **27** (26 mg, 0.44 mmol) in CH_2Cl_2 (0.11 mL) at 0 °C. After 1 h, the reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was washed with CH_2Cl_2 (8 × 1 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and chromatographed to give **29** as a colorless oil (19.5 mg, 63% yield). This product was a 77:23 mixture of isomers (**29a** and **29b**) as determined by ^{1}H NMR: R_f (4% CH_3CN/CH_2Cl_2) = 0.62; ^{1}H NMR δ 7.10–7.70 (m, 15 H), 5.29–5.38 (m, 2 H), 4.90–5.23 (m, 2 H), 4.52 (d, J = 5.7 Hz, 0.8 H), 4.25 (m, J = 5.7 Hz, 0.2 H), 3.58 (s, 3 H), 3.53 (dd, J = 5.1, 9.6 Hz, 0.2 H), 3.29 (m, 0.8 H), 2.32–2.88 (m, 2 H), 2.09–2.34 (m, 6 H), 1.52–1.90 (m, 6 H), 1.05–1.30 (m, 6 H), 1.03 (s, 9 H), 0.81 (m, 3 H); IR 1744 cm^{-1}; precise mass calcd for $C_{43}H_{56}SiO_4$ – *tert*-butyl (C_4H_9) 639.2964, found 639.2916.

(5*Z*,8β,11*R*,12β,13*E*,15*S*)-11-[(*tert*-Butyldiphenylsilyl)-oxy]-9-oxoprosta-5,13-dien-1-oic Acid Methyl Ester (30). The mixture of allylic sulfides **29a** and **29b** (20 mg, 0.029 mmol) in CH_2Cl_2 (0.05 mL) was added to 3-chloroperbenzoic acid (5.95 mg, 0.29 mmol) in CH_2Cl_2 (0.12 mL) at –78 °C. The reaction mixture was stirred for 1 h, warming to –60 °C. The progress of the reaction was monitored by TLC. A slow conversion of the starting material to the lower R_f sulfoxide spot was observed. After 1 h an additional 1 mg of 3-chloroperbenzoic acid was added to drive the reaction to completion. Trimethyl phosphite (0.015 mL) and MeOH (0.06 mL) were then added and the reaction mixture was allowed to warm to rt. The resultant mixture was partitioned between CH_2Cl_2 (15 mL) and, sequentially, saturated aqueous $NaHCO_3$, water, and brine. The organic layers were dried (Na_2SO_4), concentrated, and chromatographed to give the allylic alcohol **30b** (2.8 mg, 16% yield) followed by the allylic alcohol **30a** (9.3 mg, 54%). **30b**: R_f (30% EtOAc/petroleum ether) = 0.35; ^{1}H NMR δ 7.30–7.72 (m, 10 H), 5.51–5.60 (dd, J = 6.5, 15.3 Hz, 1 H), 5.28–5.43 (m, 3 H), 4.08 (m, J = 8.1 Hz, 1 H), 3.94 (bs, 1 H), 3.66 (s, 3 H), 2.58 (m, 1 H), 2.12–2.42 (m, 5 H), 1.85–2.10 (m, 4 H), 1.62–1.69 (m, 4 H), 1.14–1.43 (m, 6 H), 1.06 (s, 9 H), 0.88 (t, 3 H); ^{13}C NMR δ 214.9, 174.3, 136.8, 136.1, 133.7, 131.0, 130.6, 130.2, 130.1, 128.0, 127.9, 127.8, 126.9, 73.9, 72.8, 54.0, 53.4, 51.7, 47.6, 37.3, 33.6, 32.0, 27.1, 26.9, 25.5, 25.1, 24.9, 22.8, 19.3, 14.2, identical with material prepared from PGE_2. **30a**: R_f (30%

EtOAc/petroleum ether) = 0.30; ^{1}H NMR δ 7.30–7.70 (m, 10 H), 5.32 (m, J = 7.0 Hz, 2 H), 4.99–5.25 (dd, J = 5.7, 15.1 Hz, 2 H), 4.22 (m, 1 H), 3.90 (m, J = 6.0 Hz, 1 H), 3.65 (s, 3 H), 2.84 (m, J = 9.3 Hz, 1 H), 2.20–2.28 (m, 5 H), 2.00 (m, 3 H), 1.86 (m, 1 H), 1.62 (m, 4 H), 1.13–1.42 (m, 6 H), 1.05 (s, 9 H), 0.87 (t, 3 H); ^{13}C NMR δ 217.8, 174.4, 137.7, 136.8, 136.7, 136.0, 134.0, 133.7, 131.0, 130.7, 130.2, 128.1, 127.9, 126.2, 73.9, 72.3, 51.7, 51.6, 50.6, 45.5, 37.3, 33.6, 31.9, 27.1, 27.0, 25.1, 24.9, 23.2, 22.8, 19.3, 14.2; MS precise mass calcd for $C_{37}H_{52}SiO_5$ (M^+ – *tert*-butyl, C_4H_9) 547.2880, found 547.2921.

(+)-8-*epi*-Prostaglandin E_2 Methyl Ester (31) and (–)-Prostaglandin E_2 Methyl Ester (1b). A 77:23 mixture of allylic alcohols **30a** and **30b** (33 mg, 0.055 mmol) in CH_3CN (0.5 mL) was cooled to 0 °C. Pyridine (.030 mL) was added followed by 52% aqueous HF (0.05 mL). After 2 h, an additional 0.025 mL of HF was added. After an additional 6 h, the reaction mixture was poured into $CHCl_3$ (10 mL) and washed once with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed to give recovered starting **30a** and **30b** (3.4 mg), 8.5 mg (47% yield) of (+)-8-*epi*-PGE_2 methyl ester **31**, and 2.1 mg (12% yield) of (–)-PGE_2 methyl ester **1b**, R_f (4:1 hexane/EtOAc) = 0.14, identical with material prepared from PGE_2. (+)-8-*epi*-PGE_2 methyl ester **31**: R_f (20% acetone/CH_2Cl_2) = 0.22; ^{1}H NMR δ 5.63–5.73 (dd, J = 6.0, 15.3 Hz, 1 H), 5.27–5.41 (m, 3 H), 4.38 (m, 1 H), 4.10 (m, 1 H), 3.67 (s, 3 H), 2.96 (m, 1 H), 2.75 (m, 1 H), 2.51–2.62 (dd, J = 5.9, 19.4 Hz, 1 H), 2.22–2.60 (m, 5 H), 1.82–2.10 (m, 4 H), 1.40–1.75 (m, 4 H), 1.18–1.40 (m, 6 H), 0.88 (t, 3 H); ^{13}C NMR δ 216.2, 174.4, 137.1, 130.3, 127.8, 126.4, 72.5, 72.4, 53.3, 51.6, 50.8, 45.0, 37.5, 33.6, 31.9, 26.9, 25.3, 24.9, 22.8, 19.3, 14.2; $[\alpha]_D$ = +40.95 (c 0.00075, MeOH).

(–)-Prostaglandin E_2 Methyl Ester (1b). The pure C-8 epimer **31** (5 mg, 0.014 mmol) was dissolved in MeOH (0.15 mL) containing potassium acetate (2 mg). The reaction was monitored by TLC. A slow replacement of the upper R_f C-8 epimer **31** by the lower R_f (–)-PGE_2 **1b** was observed. After 8 h, the reaction mixture was diluted with ethyl acetate and washed once with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed to give **1b** (3.8 mg, 76% from **31**): R_f (4:1 hexane/EtOAc) = 0.14; ^{1}H NMR δ 5.57–5.65 (dd, J = 6.4, 12.1 Hz, 2 H), 5.30–5.38 (m, J = 6.0 Hz, 2 H), 4.09 (m, 2 H), 3.66 (s, 3 H), 2.69–2.79 (dd, J = 7.5, 18.0 Hz, 1 H), 2.21–2.45 (m, 6 H), 1.93–2.20 (m, 5 H), 1.45–1.76 (m, 4 H), 1.20–1.42 (m, 6 H), 0.89 (t, 3 H); ^{13}C NMR missing two carbonyls δ 137.4, 131.1, 130.6, 126.7, 72.9, 72.4, 54.7, 53.5, 51.7, 46.4, 37.6, 31.9, 26.8, 25.5, 25.3, 24.9, 22.8, 14.2; $[\alpha]_D$ = –59.87° (c 0.00155, MeOH) (lit. $[\alpha]_D$ –70.4° (c 1.04)).[3b]

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Supplementary Material Available: ^{1}H and ^{13}C spectra for compounds **5**, **7**, **8**, **10–12**, **14**, **22–24**, **26**, **27**, **29**, **30a**, **31**, and **1b** (59 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Chromium–Carbene-Mediated Synthesis of 4-Oxo β-Lactams (Malonimides) and Malonic Acid Derivatives

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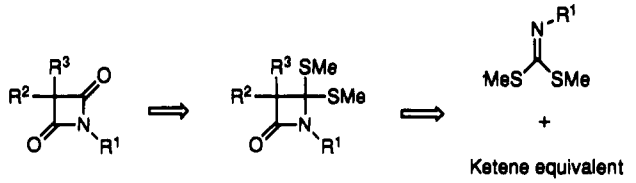
The photochemical reaction of chromium carbene (Fischer) complexes and readily available iminodithiocarbonates forms 4,4-bis(methylthio) β-lactams in good to excellent yields, and upon *N*-bromosuccinimide oxidation, these afford 4-oxo β-lactams (malonimides). Basic hydrolysis of the latter compounds yields malonic acid derivatives that are not otherwise easily accessible.

Recent efforts in β-lactam synthesis are focused not only on preparing novel, more active antibiotic drugs[1] but also on the use of these compounds as intermediates in organic synthesis[2a] (the β-lactam synthon method[2b]). Therefore, functionalized 2-azetidinones that, upon manipulation, would afford either suitable precursors for biologically active drugs or novel, unavailable compounds are always desirable. Among the growing number of monocyclic 2-azetidinones being reported, the synthesis and utility of 4-oxo β-lactams (malonimides) have been scarcely investigated. This is because they can be regarded as imides and not as true β-lactams. Nevertheless, they are very attractive compounds even in the β-lactam field, since the additional oxo group placed at the C-4 of the 2-azetidinone ring is suitable for functionalization either in inter- or intramolecular fashion, leading to interesting compounds. Furthermore, ring opening would lead to functionalized malonic acid derivatives that are potentially interesting compounds. In addition, it has been proven that malonimides are, by themselves, highly active as hypnotic-inducing drugs.[3]

Scheme I



(1) See, for example: (a) Dürckheimer, W.; Blumbach, J.; Latrell, R.; Sheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (b) *Recent Progress In the Chemical Synthesis of Antibiotics*, Lucas, G., Ohno, M., Eds.; Springer-Verlag: Berlin-Heidelberg, 1990. (c) Hungerbühler, E.; Biollaz, M.; Ernest, I.; Kalvoda, J.; Lang, M.; Schneider, P.; Sedelmeier, G. In *New Aspects of Organic Chemistry I*; Yoshida, Z., Shiba, T., Ohshiro, Y., Eds.; VCH: Tokyo, 1989; p 419.

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