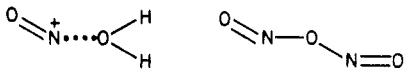
products, two different reaction mechanisms which occur simultaneously are suggested: At high acidity a one electron transfer is predominant (Scheme II, $k_1$), whereas an electrophilic attack of the nitrosyl cation (from dinitrogen oxide, Scheme II, $k_3$) on the sulfur atom and loss of a proton followed by a S- to N-nitroso rearrangement, dominate at low acidity.

The advantage of introducing the two different reaction paths for the nitrosation of thiourea is that it explains the different products formed. To account for the difference in reaction mechanism it might be useful to draw the attention to the nitrosation reagents. At high acidity it is a nitrosyl cation–water complex, **11**, which is the effective nitrosation reagent, whereas at low acidity it is dinitrogen trioxide, **12**.[2] The two nitrosation species, **11** and **12** have different reduction potential, 1.46 V and 0.984 V,[14] respectively (different LUMO energy[5c]), whereas the oxidation peak potential for thiourea remains constant at about 1.5 V in the pH interval 0–7.[15]



**11** **12**

When the nitrosation of thiourea takes place at high acidity the redox potentials indicate that the first step is a one electron transfer from thiourea to the nitrosyl cation ($k_1$) with formation of a thiourea cation radical, **9**, and nitrogen oxide. From **9** there might be two possibilities, dimerization to give the $\alpha,\alpha$-dithiobis(formamidinium) or a reaction between **9** and nitrogen oxide to give **3** ($k_2$).

At low acidity a direct overlap between the HOMO of thiourea and the LUMO of the nitrogen in the nitrosyl group of **12** is necessary for a reaction to take place; the *S*-nitrosothiourea cation, **3**, is then formed.

From **3** there might be two possibilities. A homolytic fission ($k_{-2}$) or loss of a proton to give **10** ($k_4$). At high acidity it might be expected that $k_{-2} > k_4$, whereas at low acidity $k_4 > k_{-2}$.

If a one electron-transfer reaction is occurring at high acidity one should also, according to the Marcus theory,[16] expect to find a very fast reaction compared with the reaction which takes place at low acidity. Stedman et al. have shown that the nitrosation at high acidity occurs much faster than at low acidity,[3c] which supports the mechanism.

Formulation of electrophile attack on a nucleophile as a one electron-transfer mechanism has been suggested by Perrin in 1977.[17] He suggested that the nitronium cation mediated nitration of all aromatic compounds with an oxidation potential lower than that of toluene should follow a one electron-transfer mechanism.[17] Gas-phase ion molecule and $^{15}N$ nuclear polarization nitration studies reveal that an electron-transfer process takes place.[18] A similar result is observed in nitrosation reactions.[18a] For the reaction studied here this idea is supported by the ionization potential of thiourea which is 8.50 eV,[10] whereas it is 8.93 eV for toluene. It should thus be easier to transfer an electron from thiourea compared with toluene to an acceptor.

It is concluded that the difference in reactivity of *S*-methyl-L-cysteine and alanine toward nitrosation can be accounted for by the frontier orbital method. Studies of the total energy functional of the nitrosation of *S*-methyl-L-cysteine followed by the S to N rearrangement of the nitroso group explain and support[1] the experimental results. Similarly the S-nitrosation of thiourea can also be described by the frontier orbital approach, and the difference in products at different acidity can be accounted for by assuming that a one electron-transfer process takes place.

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**Registry No.** 1, 1187-84-4; 2, 56-41-7; 4, 18542-42-2; 5, 75-04-7; thiourea, 62-56-6.

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(15) Lund, H., unpublished observation.
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# A Selective Synthesis of a Mixture of 15-Epimers of (±)-11-Deoxyprostaglandin $E_2$ Methyl Ester[1]

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A highly regio- and stereoselective procedure for allylation of 3-alkenyl-substituted 1-cyclopentenolates involving the use of readily obtainable and thermally stable allylic acetates, $BEt_3$ (2 equiv), and $Pd(PPh_3)_4$ (2 mol %) was applied to the synthesis of a ca. 50:50 diastereomeric mixture of 11-deoxyprostaglandin $E_2$ methyl ester (**1a**) and its 15-epimer (**1b**) as well as [2α(2′*Z*),3β]-2-(6′-methoxycarbonyl-2′-hexenyl)-3-ethenylcyclopentanone (**5**). The isolation yield of the allylated intermediate **8** for **1** was 74%, and that of **5** was 66%. Conversion of **8** into **1** was achieved in 89% yield. Apart from the fact that **8** was a ca. 50:50 diastereomeric mixture, the overall purities of the crude products, i.e., **5** and **8**, were ca. 85–90%. The major byproducts, which presumably were the products of γ-allylation, accounted for 5–10% of the entire products. The regioselectivity with respect to cyclopentenone in each case was estimated to be nearly 100%, and the overall stereoselectivity in each case was estimated to be ca. 95%.

Although conjugate addition to cyclopentenones followed by allylation of the resulting enolates with (*Z*)-allylic electrophiles is a conceptually attractive route to 5-unsaturated prostanoids,[2,3] this approach has been plagued

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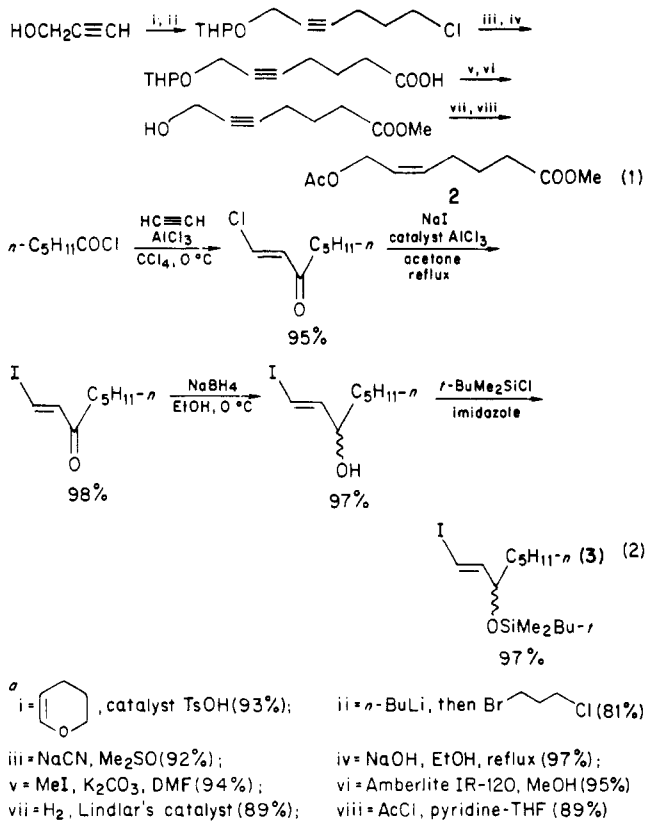
Scheme I[a]

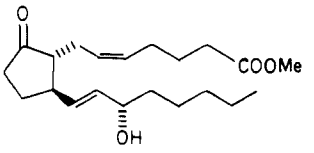



[a] i = , catalyst TsOH (93%); ii = n-BuLi, then Br—Cl (81%); iii = NaCN, $Me_2SO$ (92%); iv = NaOH, EtOH, reflux (97%); v = MeI, $K_2CO_3$, DMF (94%); vi = Amberlite IR-120, MeOH (95%); vii = $H_2$, Lindlar's catalyst (89%); viii = AcCl, pyridine-THF (89%)

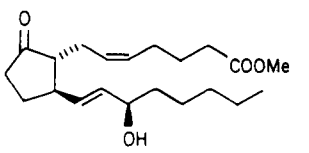
by low product yields in part due to loss of allyl stereochemistry and of ring regiochemistry. The requirement for an excess, typically three- to fivefold excess, of labile (*Z*)-allylic iodides or bromides poses an additional problem.[4]

We have recently developed a highly stereo- and regioselective synthesis of 2-allyl-3-alkenylcyclopentanones via Pd-catalyzed reaction of lithium cyclopentenolates–$BEt_3$ with (*Z*)-allylic acetates,[1,5] which promised to provide a solution to most of the above-mentioned problems. We therefore investigated its applicability to the synthesis of prostanoids.

Herein described is a selective synthesis of 11-deoxyprostaglandin $E_2$ methyl ester (**1a**) and its 15-epimer (**1b**)




**1a**

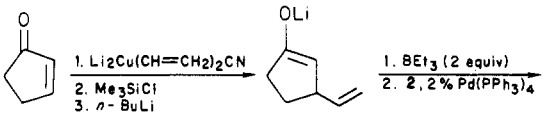



**1b**

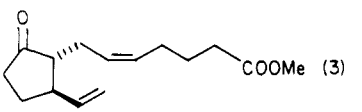
featuring (a) high stereo- and regioselectivities with respect to both the allyl group and the ring moiety, (b) high yield, and (c) the use of relatively stable methyl 7-acetoxy-5-heptenoate (**2**).

The preparation of **2** was achieved by known reactions in 48% yield from propargyl alcohol (eq 1 in Scheme I). A set of minor $^{13}C$ NMR signals (ca. 5%) assignable to the stereoisomer of **2** were discernible. The lower side-chain synthon **3** was also prepared by known reactions in 88% yield in four steps from hexanoyl chloride (eq 2). No signals assignable to the stereoisomer of **3** were detected in the $^{13}C$ NMR spectrum.

To check the feasibility of using **2** in the Pd-catalyzed allylation of enolates we generated lithium 3-vinyl-1-cyclopentenolate (**4**) by the reaction of cyclopentenone with $Li_2Cu(CH{=}CH_2)_2CN$ followed by addition of $Me_3SiCl$, isolation of the silyl enol ether product, and its treatment with *n*-BuLi.[1] Successive addition of 2 equiv of $BEt_3$ (−78 to 0 °C) and a mixture of 1 equiv of **2** and 2 mol % of $Pd(PPh_3)_4$ in THF (0 °C to room temperature) to **4** provided **5**[2b] in 66% yield (74% by GLC) after bulb-to-bulb distillation (eq 3). The IR and $^1H$ NMR spectra of **5** are

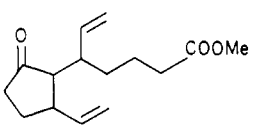



**4**

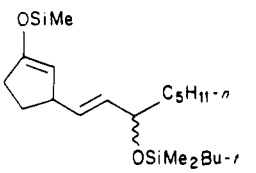



**5** (66%)

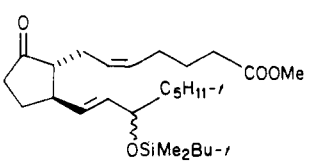
in agreement with those in the literature,[2b] and its $^{13}C$ NMR spectrum shows one set of 8 aliphatic signals, one of which at 24.59 ppm represents 2 carbon atoms and 4 olefinic and 2 carbonyl carbon signals. Additional minor signals, the average intensities of which are <10% of those of **5**, are also present and are tentatively assigned to **6** on




**6**




**7**




**8**

the basis of IR, $^1H$ and $^{13}C$ NMR, and GLC analysis as well as the results of related Pd-catalyzed allylation reactions.[1] The GLC (SE-30) trace of the product region shows just two peaks in a ca. 10:1 ratio. Their relative retention times

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(2) (a) Patterson, J. W., Jr.; Fried, J. H. *J. Org. Chem.* **1974**, *39*, 2506. A 4-fold excess of an allyl bromide was used to convert a lithium-3-alkenyl-1-cyclopentenolate into 11-deoxy $PGE_2$ in 47% yield. However, the regio- and stereoselectivities were not described in detail. (b) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107. (c) Dixon, A. J.; Taylor, R. J. K.; Newton, R. F. *J. Chem. Soc. Perkin Trans. 1* **1981**, 1407. (d) For a successful allylation using vinyl sulfones, see: Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2108.

(3) Trapping enolates with other electrophiles has produced some favorable results. However, it does not permit direct allylation. (a) For trapping with formaldehyde, see: Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260. (b) For other more recent approaches, see: Tanaka, T.; Toru, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 4103 and references therein.

(4) In a recent paper it is reported that trapping of lithium 3-(((α-silylalkoxy)carbonyl)methyl)-1-cyclopentenolates with (*Z*)-2-pentenyl bromide gives the desired allylation products in 56–62% yields [Oppolzer, W.; Guo, M.; Baettig, K. *Helv. Chim. Acta* **1983**, *66*, 2140]. However, no figures for the regio- and stereoselectivities of the reaction with respect to the allyl and ring moieties are presented. We have found that the reaction of lithium 3-vinyl-1-cyclopentenolate with (*Z*)-2-octenyl iodide or bromide in THF is of low regiospecificity with respect to the ring (50–75%).[1] It is conceivable that the presence of an ester functionality leads to a high regiospecificity in Oppolzer's reaction.

(5) See also: (a) Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R. A. *J. Org. Chem.* **1982**, *47*, 3188. (b) Negishi, E.; Luo, F. T.; Pecora, A. J.; Silveira, A., Jr. *J. Org. Chem.* **1983**, *48*, 2427. (c) Negishi, E.; Chatterjee, S. *Tetrahedron Lett.* **1983**, *24*, 1341.

preclude the possibility that the minor peak with a distinctly shorter retention time might be a stereoisomer of **5**. Thus, the overall stereoisomeric purity of **5** without chromatographic separation may be conservatively estimated to be >95%.

The preparation of **1** was achieved in an analogous manner. Treatment of **3** with 2 equiv of *t*-BuLi in ether (−78 °C, 2 h) followed by successive addition of 0.5 equiv of CuI·$PBu_3$ in ether (−78 °C),[6] 1 equiv of cyclopentenone (−78 °C for 30 min and then −20 °C for 1 h), 1.5 equiv of $PBu_3$, and an excess of $Me_3SiCl$ provided **7** in 73% yield based on cyclopentenone. Treatment of **7** with 1.1 equiv of *n*-BuLi followed by successive addition of 2 equiv of $BEt_3$ (−78 to 0 °C, 20 min) and a mixture of 1 equiv of **2** and 2 mol % of $Pd(PPh_3)_4$ in THF (0 °C to room temperature, 2 h) produced, after chromatography (silica gel, 60–200 mesh, *n*-hexane), a 74% isolated yield of **8**. In addition to its IR and $^1H$ NMR spectra consistent with the assigned structure, its $^{13}C$ NMR spectrum strongly indicates that it is essentially free from any contaminants, except that it is a ca. 50:50 diastereomeric mixture of the two 15-C epimers. Conversion of **8** into **1**[7] was achieved by treating **8** with HOAc–$H_2O$–THF[7] (10:3.3:1) at 50 °C for 1.5 h. After extractive workup, evaporation of the volatiles provided a ca. 1:1 mixture of **1a** and **1b** in 89% yield. The overall purity of this material as a distereomeric mixture of **1a** and **1b** is estimated to be >95% by $^{13}C$ NMR analysis.

Application of the above-described procedure to the synthesis of enantiomerically and diastereomerically homogeneous 11-substituted prostanoids is in progress.

## Experimental Section

All organometallic reactions were carried out under an atmosphere of nitrogen. Most of the reagent-grade chemicals purchased from commercial sources were used as received. Tetrahydrofuran (THF) was purified by distillation over Na and benzophenone. Dimethylformamide (DMF) and dimethyl sulfoxide ($Me_2SO$) were dried over BaO and distilled. Acetylene from a cylinder was purified by passing it through water, $H_2SO_4$, KOH pellets, and a trap kept at −78 °C. Lindlar's hydrogenation catalyst,[8] $Pd(PPh_3)_4$,[9] and CuI·$PBu_3$[6] were prepared as reported in the literature.

**6-Chloro-2-hexyn-1-yl 2-Tetrahydropyranyl Ether.** This compound was prepared by the method of Corey and Sachdev[10] from 20.50 g (146 mmol) of propargyl 2-tetrahydropyranyl ether,[11] 76 mL (160 mmol) of 2.1 M *n*-BuLi, and 15.9 mL (25.31 g, 160 mmol) of 1-bromo-3-chloropropane in 81% yield: bp 112–114 °C (0.25 mm); IR (neat) 1115 (s), 1000 (s), 970 (s), 945 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.2–2.2 (m, 8 H), 2.45 (t, $J$ = 7 Hz, 2 H), 3.4–4.1 (m, 4 H), 4.2–4.4 (m, 2 H), 4.7–4.9 (m, 1 H).

**7-(2′-Tetrahydropyranyloxy)-5-heptynoic Acid.** 6-Chloro-2-hexyn-1-yl 2-tetrahydropyranyl ether was converted into 6-cyano-2-hexyn-1-yl 2-tetrahydropyranyl ether by a modification of a literature procedure.[12] The starting compound (19.54 g, 90 mmol) was treated with dry NaCN (4.88 g, 100 mmol) in 150 mL of $Me_2SO$ for 48 h at 40–45 °C and for an additional 3 h at 55 °C. The reaction mixture was poured into water, and the product was extracted with ether (4 × 100 mL). The extract was washed with aqueous NaCl, dried over $MgSO_4$, and concentrated to give 17.15 g (92%) of crude 6-cyano-2-hexyn-1-yl 2-tetrahydropyranyl ether: IR (neat) 2250 (w), 1110 (s), 1010 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.1–2.1 (m, 8 H), 2.2–2.6 (m, 4 H), 3.3–3.9 (m, 2 H), 4.18 (s, 2 H), 4.74 (s, 1 H). Its conversion into the title compound by a modification of a known procedure[13] is as follows. To a solution of 150 mL each of ethanol (190 proof) and 10% aqueous NaOH was added dropwise 5.18 g (25 mmol) of the cyanide prepared above. The reaction mixture was refluxed until evolution of ammonia ceased (ca. 24 h). The mixture was cooled, poured onto 300 mL of ice-cold water, acidified with concentrated HCl, and extracted with ether. The extract was dried over $Na_2SO_4$ and concentrated in vacuo to give 5.48 g (97%) of the title compound: IR (neat) 3500–2500 (br s), 1705 (s), 1200 (s), 1110 (s), 1000 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.3–2.1 (m, 8 H), 2.1–2.6 (m, 4 H), 3.3–4.0 (m, 2 H), 4.2 (br s, 2 H), 4.8 (br s, 1 H), 10.69 (s, 1 H).

**Methyl 7-Hydroxy-5-heptynoate.**[10] According to a literature procedure,[14] a solution of 10.79 g (48 mmol) of crude 7-(2′-tetrahydropyranyloxy)-5-heptynoic acid in 200 mL of DMF was treated with 10 g (72 mmol) of $K_2CO_3$ and 4.5 mL (10.22 g, 72 mmol) of methyl iodide. The mixture was stirred for 8 h at room temperature, poured onto 500 mL of aqueous NaCl, and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 10.83 g (94%) of methyl 7-(2′-tetrahydropyranyloxy)-5-heptynoate: IR (neat) 1730 (s), 1430 (s), 1340 (s), 1320 (s), 1110 (br s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.3–2.1 (m, 8 H), 2.1–2.6 (m, 4 H), 3.3–37 (m, 5 H), 4.24 (br s s, 2 H), 4.80 (br s, 1 H). A solution of 9.72 g (40.5 mmol) of the ester obtained above in 100 mL of methanol was added at room temperature to 1.5 g (5 mequiv) of Amberlite IR-120 (plus), acid form, ion exchange resin. After stirring the mixture for 3 h, the resin was filtered off, and the solvent was removed in vacuo. Distillation provided 6.01 g (95%) of the title compound: bp 92–95 °C (0.55 mm); IR (neat) 3450 (br s), 1720 (s), 1430 (s), 1215 (bs), 1160 (s), 1130 (s), 1000 (br s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.6–2.0 (m, 2 H), 2.2–2.6 (m, 5 H), 3.68 (s, 3 H), 4.2–4.3 (m, 2 H).

**Methyl (*Z*)-7-Hydroxy-5-heptenoate.** A reaction flask of a low-pressure hydrogenation apparatus was charged with 5.95 g (38 mmol) of methyl 7-hydroxy-5-heptynoate, 0.20 g of Lindlar's catalyst,[8] 2 mL (2.19 g, 17 mmol) of quinoline, and 10 mL of hexane. The apparatus was evacuated, and hydrogen was admitted to a pressure slightly above 1 atm. After the mixture had been shaken for 9 h, it was washed with 100 mL of 3 N HCl and extracted with 4 × 75 mL of ether. The combined organic layer was dried over $MgSO_4$, concentrated in vacuo, and distilled to give 5.35 g (89%) of (*Z*)-7-hydroxy-5-heptenoate: bp 90–92 °C (0.5 mm); IR (neat) 3400 (br s), 1730 (s), 1435 (s), 1200 (br s), 1150 (br s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.5–1.9 (m, 2 H), 2.0–2.6 (m, 4 H), 3.15 (s, 1 H), 3.65 (s, 3 H), 4.14 (d, $J$ = 4 Hz, 2 H), 5.3–5.8 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, $Me_4Si$) δ 24.52, 26.39, 32.83, 51.00, 57.37, 129.86, 130.35, 173.79. A set of minor $^{13}C$ NMR signals (ca. 5%) assignable to the stereoisomer were discernible. Its purity by GLC was ca. 96%.

**Methyl (*Z*)-7-Acetoxy-5-heptenoate (2).** A modification of a known procedure[15] was used to prepare the title compound. To a mixture of 4.74 g (30 mmol) of methyl (*Z*)-7-hydroxy-5-heptenoate and 12 mL (150 mmol) of pyridine in 50 mL of THF was added dropwise 3.2 mL (3.53 g, 45 mmol) of acetyl chloride under nitrogen at −78 °C. After the mixture had been stirred for 12 h at room temperature, it was poured onto 300 mL of ice-cold water and extracted with 4 × 50 mL of pentane. The extract was dried over $MgSO_4$, concentrated, and distilled to give 5.34 g (89%) of the title compound: bp 85–87 °C (0.2 mm); IR (neat) 3030 (m), 1725 (s), 1430 (s), 1365 (s), 1240 (br s), 1160 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.6–2.5 (m with one singlet at δ 2.04, 9 H), 3.67 (s, 3 H), 4.64 (d, $J$ = 6 Hz, 2 H), 5.5–5.8 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, $Me_4Si$) δ 19.84, 24.26, 26.39, 32.53, 50.55, 59.41, 124.69, 133.32, 169.51, 172.57. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.07; H, 8.91. A set of minor $^{13}C$ NMR signals (ca. 5%) assignable to the stereoisomer were discernible. Its purity by GLC was ca. 99%.

**(*E*)-1-Chloro-1-octen-3-one.** A modification of a known

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procedure[16] was used to prepare the title compound. To a 2-L flask fitted with a mechanical stirrer and a 250-mL addition funnel were added 0.6 L of $CCl_4$ and 155 g (1.13 mol) of $AlCl_3$ at 0 °C. The system was flushed with acetylene and 123 mL (118 g, 870 mmol) of hexanoyl chloride was added over 1 h. Acetylene was then introduced into the flask, and the rate of absorption was monitored with a mercury bubbler. After 2 h of treatment with a slow acetylene stream, the mixture was poured into a stirred mixture of 700 g of ice and 300 mL of brine. The layers were separated, and the aqueous phase was extracted twice with 200 mL portions of chloroform. The organic fractions were combined, washed with 100 mL of 10% $Na_2CO_3$, dried over $MgSO_4$, and evaporated. The crude product was distilled to give 132 g (95%) of (*E*)-1-chloro-1-octen-3-one which was ≥98% pure by GLC: bp 77–79 °C (0.25 mm); IR (neat) 1680 (s), 1580 (s), $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 0.90 (t, *J* = 7 Hz, 3 H), 1.1–1.9 (m, 6 H), 2.52 (t, *J* = 7 Hz, 2 H), 6.55 (d, *J* = 14 Hz, 1 H), 7.33 (d, *J* = 14 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, $Me_4Si$) δ 13.52, 22.28, 23.19, 31.18, 40.06, 132.48, 135.48, 195.97. No $^{13}C$ NMR signals assignable to the stereoisomer were detected.

**(*E*)-1-Iodo-1-octen-3-one.** The procedure of Kluge, Untch, and Fried[17] was used with minor modifications. To a 2-L flask fitted with a reflux condenser was added 450 mL of acetone and 112 g (746 mmol) of NaI. After NaI had dissolved, (*E*)-1-chloro-1-octen-3-one (64.3 g, 400 mmol) and $AlCl_3$ (0.11 g, 0.91 mmol) were added, and the mixture was heated to reflux for 1 h, cooled, filtered, evaporated (15 mm) to ca. 200 mL, and partitioned between 0.5 L of water and 0.5 L of pentane. The aqueous phase was extracted with 200 mL of pentane. The extract was washed with 100 mL of saturated $Na_2S_2O_3$, dried over $MgSO_4$, decolorized (activated carbon), and evaporated in vacuo. The crude product was recrystallized from 0.5 L of hexane at −20 °C to give 98.8 g (98%) of (*E*)-1-iodo-1-octen-3-one: mp 36–37 °C[18]; IR (neat) 1670 (s), 1560 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 0.89 (t, *J* = 7 Hz, 3 H), 1.1–1.8 (m, 6 H), 2.50 (t, *J* = 15 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, $Me_4Si$) δ 14.09, 22.59, 23.62, 31.50, 40.51, 98.64, 144.82, 197.20. No $^{13}C$ NMR signals assignable to the stereoisomer were detected. Its purity by GLC was ca. 98%.

**(*E*)-1-Iodo-1-octen-3-ol.** This compound was prepared by the method of Corey and Beames.[18] To an ice-cold solution of 4.0 g (106 mmol) of $NaBH_4$ in 500 mL of ethanol (200 proof) in a 2-L flask was added 75.6 g (300 mmol) of (*E*)-1-iodo-1-octen-3-one in 200 mL of ethanol (200 proof) over 4 h. After the reaction mixture had been stirred for 12 h, it was concentrated (15 mm), and the resulting oil was partitioned between 0.5 L of water and 1 L of pentane. The aqueous phase was extracted with 200 mL of pentane. The organic fractions were dried over $MgSO_4$, and evaporated in vacuo to give 73.9 g (97%) of (*E*)-1-iodo-1-octen-3-ol: IR (neat) 3330 (br s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 0.88 (t, *J* = 6 Hz, 3 H), 1.1–1.7 (m, 8 H), 4.00 (br s, 1 H), 4.4–4.6 (m, 1 H), 6.38 (d, *J* = 15 Hz, 1 H), 6.56 (dd, *J* = 5, 15 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, $Me_4Si$) δ 14.54, 22.96, 25.23, 32.08, 36.86, 74.50, 77.48, 148.86. No $^{13}C$ NMR signals assignable to the stereoisomer were detected. Its purity by GLC was ca. 98%.

**(*E*)-3-(*tert*-Butyldimethylsiloxy)-1-iodo-1-octene (3).** This compound was prepared by the method of Corey and Venkateswarlu.[19] To a 0.5-L flask flushed with nitrogen were added 200 mL of DMF and 25.4 g (100 mmol) of (*E*)-1-iodo-1-octen-3-ol. The solution was cooled to 0 °C, and 17.48 (257 mmol) of imidazole and 20 g (130 mmol) of *tert*-butyldimethylchlorosilane were added. The mixture was stirred for 36 h at 25 °C, cooled to 0 °C, and partitioned between 500 mL of hexane and 500 mL of 10% aqueous $NaHCO_3$. The aqueous phase was extracted with 2 × 200 mL of hexane. The extract was dried over $MgSO_4$, evaporated in vacuo, and distilled to give 35.62 g (97%) of (*E*)-3-(*tert*-butyldimethylsiloxy)-1-iodo-1-octene as a colorless oil: bp 95–96 °C (0.09 mm); IR (neat) 1610 (w), 1360 (s), 1250 (s), 1060 (s), 825 (s), 765 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 0.04 (s, 6 H), 0.91 (br s, 12 H), 1.1–1.6 (m, 8 H), 4.0–4.2 (m, 1 H), 6.21 (d, *J* = 15 Hz, 1 H), 6.56 (dd, *J* = 6, 15 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, $Me_4Si$) δ −4.92, −4.49, 13.97, 17.97, 22.51, 24.37, 25.77, 31.72, 37.51, 75.03, 75.26, 148.92. No $^{13}C$ NMR signals assignable to the stereoisomer were detected. Its purity by GLC was ca. 100%.

**3-Ethenyl-1-(trimethylsiloxy)cyclopent-1-ene.** This compound was prepared by the method of Lipshutz, Wilhelm, and Kozlowski[20] using CuCN (2.60 g, 30 mmol), azeotropically dried with 15 mL of toluene at room temperature under vacuum, 25 mL (60 mmol) of 2.4 M vinyllithium, 1.3 mL (1.27 g, 15 mmol) of 2-cyclopentenone, and trimethylsilyl chloride (6.3 mL, 5.43 g, 50 mmol) in 86% yield (2.35 g): bp 33–35 °C (0.15 mm); IR (neat) 1640 (s), 1345 (s), 1265 (s), 1250 (s), 1230 (s), 930 (s), 910 (s), 850 (br s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 0.20 (s, 9 H), 1.2–2.5 (m, 4 H), 3.0–3.4 (m, 1 H), 4.5–5.1 (m, 3 H), 5.5–6.0 (m, 1 H). $^{13}C$ NMR ($CDCl_3$, $Me_4Si$) δ −0.45, 28.46, 32.90, 48.50, 104.33, 111.57, 143.25, 155.48. No $^{13}C$ NMR signals assignable to the stereoisomer were detected. Its purity by GLC was ca. 97%.

**[2α(2*Z*),3β]-2-(6′-Methoxycarbonyl-2-hexenyl)-3-ethenylcyclopentanone (5).**[2b] To a solution of 0.36 g (2 mmol) of 3-ethenyl-1-trimethylsiloxycyclopent-1-ene in 5 mL of THF was added dropwise 1 mL (2.4 mmol) of 2.4 M *n*-BuLi at 0 °C. After 10 min, the mixture was cooled to −78 °C, and 4 mL (4 mmol) of 1 M $BEt_3$ in THF was added. The resultant mixture was warmed to 0 °C over 20 min, and a solution of 0.40 g (2 mmol) of **2** and 0.02 g (0.02 mmol) of $Pd(PPh_3)_4$ in 5 mL of THF was added. After the mixture had been stirred for 2 h at room temperature, it was quenched with 12 mL of 3 N HCl and extracted with 3 × 10 mL of ether. The extract was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, concentrated, and passed through a silica gel column (60–200 mesh, *n*-hexane) to remove Pd compounds, if any. Concentration and distillation gave 0.33 g (66% yield) of the title compound: bp 120–123 °C (0.2 mm); IR (neat) 1730 (unresolved bands, s), 1640 (w), 1430 (m), 1155 (s), 985 (m), 910 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.1–2.8 (m, 14 H), 3.6 (s, 3 H), 4.9–5.5 (m, 4 H), 5.6–6.1 (m, 1 H); $^{13}C$ NMR ($CDCl_3$, $Me_4Si$) δ 24.59, 26.32, 27.31,32.88, 37.09, 45.71, 50.71, 53.92, 114.60, 127.09, 130.05, 140.84, 172.70, 216.34. The purity of **5** by GLC was ca. 90% with one unidentified signal having a shorter retention time (SE-30). In addition to a set of 14 major $^{13}C$ NMR signals, minor signals, the relative intensities of which were <10% of those of **5**, were also present.

**(*E*)-3-[3′-(*tert*-Butyldimethylsiloxy)oct-1-enyl]-1-(trimethylsiloxy)cyclopent-1-ene (7).** Two known procedures[2a,21] for the preparation of the title compound were modified as follows. To a stirred solution of (*E*)-3-(*tert*-butyldimethylsiloxy)-1-iodo-1-octene (2.21 g, 6 mmol) in 20 mL of diethyl ether was added 6 mL (12 mmol) of 2 M *t*-BuLi under nitrogen at −78 °C. After the reaction mixture had been stirred for 2 h at −78 °C, a freshly prepared solution of tri-*n*-butylphosphinecopper(I) iodide complex[6] (1.18 g, 3 mmol) in 10 mL of dry diethyl ether was added. The resultant mixture was stirred for an additional 1 h at −78 °C to ensure complete formation of the cuprate as shown by the negative Gilman test.[22] A solution of 2-cyclopentenone (0.25 g, 3 mmol) in 10 mL of diethyl ether was added over 20 min to the above reaction mixture, and the mixture was stirred for 30 min at −78 °C and then for 1 h at −20 °C. Tri-*n*-butylphosphine (0.91 g, 4.5 mmol) was then added to the mixture,[23] followed by 1.2 mL (1.03 g, 9.5 mmol) of trimethylsilyl chloride. The mixture was allowed to warm to ambient temperature (ca. 1 h), quenched with a solution of 100 mL of water–triethylamine (20:1), and extracted with 4 × 50 mL of hexane. The extract was dried over $MgSO_4$ and evaporated under reduced pressure. Distillation of the residue gave 0.87 g (73%) of crude (*E*)-3-[3′-(*tert*-butyldimethylsiloxy)-oct-1-enyl]-1-(trimethylsiloxy)cyclopent-1-ene: bp 110–120 °C (0.2 mm); IR (neat) 1640 (m), 1250 (s), 1050 (m), 825 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.16 (s, 9 H), 0.7–1.0 (m, 12 H), 1.2–1.7 (m, 10 H), 1.8–2.3 (m, 2 H), 3.0–3.3 (m, 1 H), 3.9–4.1 (m, 1 H), 4.3–4.5 (m, 1 H), 5.2–5.5 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, a

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(23) When the addition of $PBu_3$ was omitted, a significant amount of the corresponding ketone was formed.

diastereostereomeric mixture) δ -5.09, -4.31, -0.42, 13.55, 17.78, 22.42, 24.00, 24.55, 24.72, 25.59, 26.88, 27.63, 28.33, 28.65, 31.64, 32.91, 38.30, 44.23, 73.33, 73.49, 104.44, 104.62, 131.54, 134.94, 155.29. The relative intensities of three pairs of signals at (i) -5.09 and -4.31, (ii) 73.33 and 73.49, and (iii) 104.44 and 104.62 indicate that the material is a ca. 50:50 mixture of two diastereomers.

**Methyl (5*Z*,8α,12β,13*E*)-15-(*tert*-Butyldimethylsiloxy)-9-oxo-5,13-prostadienoate (8).** To a solution of 3-[(*E*)-3'-(*tert*-butyldimethylsiloxy)oct-1-enyl]-1-(trimethylsiloxy)cyclopent-1-ene (1.01 g, 2.54 mmol) in 10 mL of THF was added dropwise 1.2 mL (3 mmol) of 2.5 M *n*-BuLi under nitrogen at 0 °C. After the reaction mixture had been stirred for 10 min at 0 °C, it was cooled to -78 °C, and 0.7 mL (0.49 g, 5 mmol) of neat $BEt_3$ was slowly added to it. The mixture was warmed to 0 °C over 20 min. A solution of methyl (*Z*)-7-acetoxy-5-heptenoate (0.51 g, 2.54 mmol) and $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol) in 5 mL of THF was slowly added to the reaction mixture. The cooling bath was removed, and the mixture was stirred for 2 h at ambient temperature. The reaction mixture was quenched by the addition of 50 mL of water, and the product was extracted with 3 × 50 mL of ether. The organic extract was washed with 50 mL of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, concentrated, and passed through a 10 cm column (silica gel, 60-200 mesh, 5 g, *n*-hexane). Removal of the solvent under reduced pressure afforded 0.87 g (74%) of methyl (5*Z*, 8α, 12β, 13*E*)-15-(*tert*-butyldimethylsiloxy)-9-oxo-5,13-prostadienoate and its 15-epimer, which appeared to be present in approximately equal amounts as judged by the relative intensities of $^{13}C$ NMR signals at δ 126.98 and 127.57 as well as those at δ 131.33 and 131.68. The diastereomeric mixture showed the following $^{13}C$ NMR signals whose relative intensities were ≥10%: δ -5.21, -4.55, 13.65, 17.77, 22.36, 24.56, 25.51, 26.30, 27.62, 31.54, 32.62, 36.97, 38.15, 43.61, 43.96, 50.43, 54.08, 72.83, 126.98, 127.57, 129.86, 131.33, 131.68, 131.77, 134.25, 134.43, 172.14, 215.33. In addition to these signals there were minor (<5%) signals two of which appeared at δ 115.42 and 139.44. The IR and $^1H$ NMR spectral data of the title compound were as follows: IR (neat) 1740 (br, s), 1250 (m), 1150 (m), 1060 (m), 965 (m), 825 (m), 770 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.86 (m, 12 H), 1.0-2.5 (m, 22 H), 3.54 (s, 3 H), 3.9-4.2 (m, 1 H), 5.1-5.6 (m, 4 H).

**Methyl (5*Z*,8α,12β,13*E*)-15-Hydroxy-9-oxo-5,13-prostadienoate (11-Deoxy-PGE$_2$ Methyl Ester and 11-Deoxy-15-epi-PGE$_2$ Methyl Ester) (1).** A modification of a known procedure[7] was used to prepare the title compound. A solution of 0.50 g (1.07 mmol) of methyl (5*Z*,8α,12β,13*E*)-15-(*tert*-butyldimethylsiloxy)-9-oxo-5,13-prostadienoate in 1 mL of THF was added to 10 mL of acetic acid-water-THF (10:3.3:1) at room temperature. The resulting solution was heated to 50 °C for 1.5 h and cooled. The product was extracted with 3 × 50 mL of ether. The combined ether layers were washed with saturated sodium bicarbonate solution and water and then dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded 0.33 g (89%) of 11-deoxy-$PGE_2$ methyl ester and 11-deoxy-15-epi-$PGE_2$ methyl ester. These two compounds appeared to be present in equal amounts as indicated by the $^{13}C$ NMR spectrum. The IR and $^1H$ NMR spectra are indistinguishable from those in the literature,[2a,7] and are as follows: IR (neat) 3500 (s), 1740 (s), 1725 (s), 1150 (bs) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 0.88 (t, *J* = 7 Hz, 3 H), 1.1-2.6 (m, 22 H), 3.00 (br s, 1 H), 3.66 (s, 3 H), 3.9-4.2 (m, 1 H), 5.3-5.5 (m, 2 H), 5.5-5.7 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, $Me_4Si$) δ 14.10, 22.68, 24.69, 24.82, 25.21, 26.69, 27.95, 31.87, 33.31, 37.54, 37.80, 44.14, 44.52, 51.42, 54.72, 72.18, 72.36, 127.14, 127.65, 130.50, 131.96, 132.16, 132.31, 132.48, 134.72, 173.96, 218.88.

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# Total Synthesis of Tetracyclic Triterpenes. 1. The (±)-5-*epi*-Euphane Ring System

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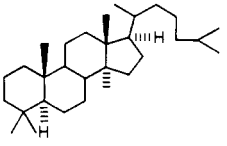
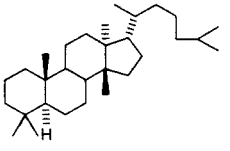
An A + CD Diels-Alder approach to the synthesis of tetracyclic triterpenes generated a lanostane-like configuration of the tetracyclic adduct. An efficient two-step photoepimerization at C-10 provided an equivalent euphane-like intermediate. This intermediate has been converted to the butyrospermol ring system, but unexpectedly, this proved to be a C-5 epimer (AB-cis) of the natural ring system. The configuration of the final product, 13, was established by X-ray diffraction analysis.

Of the tetracyclic triterpenes having a perhydrocyclopentaphenathrene skeleton, the lanostanes, the euphanes, and the cucurbitanes all bear transorientated methyl groups at C-13 and C-14 (CD ring fusion carbons).[1] Although the structures of the lanostane and euphane families have been known since the early 1950s, efforts to effect their total synthesis have been remarkably sparse. A landmark synthesis of lanosterol by Woodward et al. in 1954[2] and van Tamelen's polyene cyclization studies in the early 1970s[3] are the only noteworthy examples of lanostane total synthesis. No equivalent synthesis has yet been reported for any member of the large euphane family.



lanostane skeleton



euphane skeleton

The most challenging aspect of designing and executing a synthesis of these natural products lies in fixing the relative configurations of the angular methyl groups. Furthermore, the tendency of the euphane skeleton to undergo acid-catalyzed rearrangement to the more stable isoeuphane system[1] restricts the tactical options that may

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