Table II. Ratios of Undeuterated to Deuterated Ene Adducts for Reaction of 1-Hexenes with Dimethyl Mesoxalate at 130 °C

intermolecular expt		intramolecular expt	
reaction time, h	content of the deuterated ene adduct, %[a]	reaction time, h	content of the deuterated ene adduct, %[a]
5	36.72	6	68.72
8	36.59	7	68.43
10	37.12	9	68.72
12	36.29	16	68.20
	average 36.68		average 68.52

[a] Arithmetical mean from three samples.

Reaction of 1-heptene-3-d_1 (**5**) with 1 was carried out under pseudo-first-order conditions (18 M excess of **5**) at 130 °C as described above. Samples were withdrawn at 1–3-h intervals, quenched by cooling to −20 °C, diluted with benzene, passed through a layer of silica gel, washed with water, dried (anhydrous $MgSO_4$), and evaporated. The deuterium content in the ene adduct was determined with 0.5% accuracy from the relative abundance of M − H_2O ions in its mass spectrum.

The Intermolecular Variant. Reaction of 35 M excess of a mixture (about 1:1) of 1-heptene (**4**) and 1-heptene-3,3-d_2 (**6**) with 1 was followed kinetically, using the experimental procedure and product analysis as in the intramolecular experiment. The results are given in Table II.

Treatment of the Data. The ratios of the undeuterated and deuterated ene adducts of dimethyl mesoxalate with selectively deuterated alkenes **5** and **6** carried out in the intramolecular and intermolecular experiments are related to the primary and secondary isotope effects by eq 1 and 2, respectively, where ([H]/[D])$_{intra}$ = the ratio of undeuterated and deuterated ene adduct in the intramolecular comparison, ([H]/[D])$_{inter}$ = the same ratio for intermolecular comparison, and $k_{H(H)}$, $k_{D(H)}$, $k_{H(D)}$, and $k_{D(D)}$ are rate constants of the respective ene reactions; subscripts denote the atom transferred to the oxygen atom and atom (in parentheses) which remains bonded to the carbon atom.

$$\left(\frac{[H]}{[D]}\right)_{intra} = \frac{k_{D(H)}}{k_{H(D)}} = \frac{k_{H(H)}/k_{H(D)}}{k_{H(H)}/k_{D(H)}} = \frac{k_H''/k_D''}{k_H'/k_D'} \quad (1)$$

$$\left(\frac{[H]}{[D]}\right)_{inter} = \frac{k_{H(H)}}{k_{D(D)}} = \left(\frac{k_{H(D)}}{k_{D(D)}}\right)\left(\frac{k_{H(H)}}{k_{H(D)}}\right) = \left(\frac{k_H'}{k_D'}\right)\left(\frac{k_H''}{k_D''}\right) \quad (2)$$

Since the alkenes **5** and **6** used were not isotopically pure (**5** contained 2.9% **4** and **6** contained 15.4% **5**) the ratios of undeuterated and deuterated ene adducts were related to the primary and secondary isotope effects by appropriately modified eq 3 and 4, where ([H]/[D])^{exp} = the ratios of undeuterated and deuterated

$$\left(\frac{[H]}{[D]}\right)^{exp}_{intra} = \left[1 + \left(\frac{k_H'}{k_D'}\right)\left(\frac{c}{100-c}\right)\right]\left[\left(\frac{k_H''}{k_D''}\right)\Big/\left(\frac{k_H'}{k_D'}\right)\right] \quad (3)$$

$$\left(\frac{[H]}{[D]}\right)^{exp}_{inter} = \frac{1 + \left(\frac{k_D'}{k_H'}\right)\left(\frac{100-(a+b)}{a}\right)}{1 + \left(\frac{k_H'}{k_D'}\right)\left(\frac{100-(a+b)}{b}\right)}\left(\frac{k_H'}{k_D'}\right)\left(\frac{k_H''}{k_D''}\right) \quad (4)$$

adducts (Table II), a = 41.2%, b = 49.7%, 100 − (a + b) = 9.1% − the percentage of 1-heptene (**4**), 1-heptene-3,3-d_2 (**6**), and 1-heptene-3-d_1 (**5**) in the mixture, and c = 2.9% the content of 1-heptene (**4**) in **5**.

Solution of eq 3 and 4 gave kinetic isotope effects values:

$$\frac{k_H'}{k_D'} = 2.16 \pm 0.08$$

$$\frac{k_H''}{k_D''} = 1.05 \pm 0.04$$

Analysis of error from eq 3 and 4, with estimated accuracy of peak measurement in the mass spectra of 0.75%, gave relative error of k_H'/k_D' and k_H''/k_D'' of 3.6%.

Registry No. 1, 3298-40-6; 2, 4038-04-4; 3, 74930-02-2; 4, 592-76-7; 5, 74930-03-3; 6, 10588-82-6; 2-ethylbutanal-2-d_1, 41065-99-0.

A New, Elegant Route to a Key Intermediate for the Synthesis of 9(*O*)-Methanoprostacyclin

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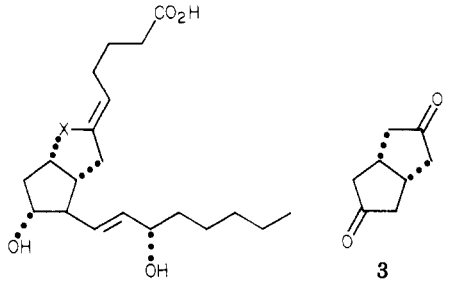
A significant advance in prostaglandin biochemistry has been made with the discovery of PGI_2, **1** (X = O), the most



3

1, X = O
2, X = CH_2

potent of the prostaglandins in inhibiting aggregation of blood platelets.[1] Its very short biological half-life due to hydrolytic lability severely limits its usefulness as potential drug for treatment of thrombosis. In attempts to overcome this problem a sizeable number of papers dealing with the synthesis of stable analogues has already appeared.[2] Interest in the carbocyclic analogue **2** (X = CH_2) has developed rapidly and has generated a good deal of effort on its synthesis, which was first announced by one of us,[3] and later by others,[4,5] starting from *cis*-bicyclo[3.3.0]octa-3,7-dione (**3**) or through different routes.[6-8] Since it became clear that there would be a widespread demand for **2**, we have sought a more straightforward approach, which avoids

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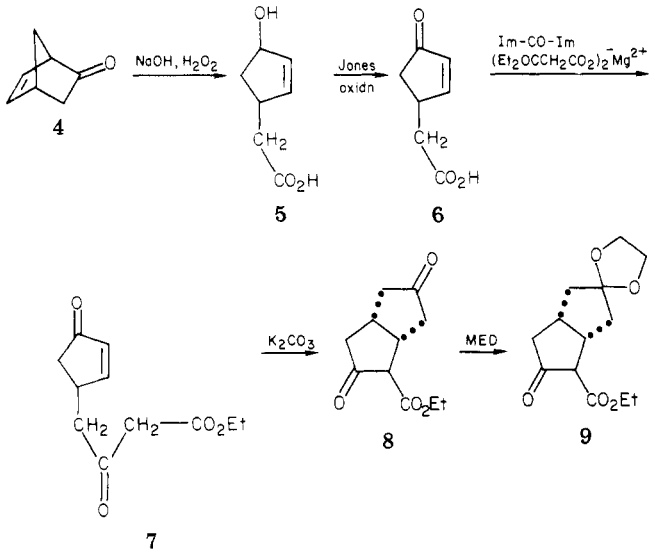
Scheme I



the involvement of the acetalization–selective deacetalization technique, with subsequent loss of overall yield, to differentiate the two carbonyl groups of **3**. We describe here a novel synthesis of the retrosynthetically predictable trifunctionalized bicyclo[3.3.0]octane **9**, an advanced intermediate for the synthesis of 9(*O*)-methanoprostacyclin, as outlined in Scheme I.

Baeyer–Villiger reaction of 5-norbornen-2-one (**4**) with alkaline hydrogen peroxide afforded a high yield of the crystalline hydroxy acid **5**, which was readily transformed into the known[9] keto acid **6** by Jones oxidation. Conversion of **6** with carbonyldiimidazole in THF to its imidazolide was followed by condensation with the magnesium salt of monoethyl malonate under essentially neutral conditions[10] to give a 90% yield of the diketo ester **7**.

Upon exposure of **7** to potassium carbonate in ethanol for 2 h at room temperature, an easy intramolecular Michael addition[11] took place, affording **8** in essentially quantitative yield. Transketalization of **8** with 2-methyl-2-ethyl-1,3-dioxolane[12] at room temperature in the presence of *p*-toluenesulfonic acid proceeded smoothly to produce the desired intermediate **9**, which was transformed to **2** by standard procedures.

A further advantage of this approach is that optical resolution can be carried out at an early stage, thus offering the possibility of obtaining **2** in optically active form.

Experimental Section

Melting and boiling points are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R24A, using Me_4Si as an internal standard; IR spectra were run on a IR Perkin-Elmer Model 257. Anhydrous sodium sulfate was used for all drying operations.

Bicyclo[2.2.1]hept-5-en-2-one (4). 5-Norbornen-2-ol (mixture of endo and exo isomers; 4 g, 36.31 mmol) in CH_2Cl_2 (50 mL) was stirred with PDC[13] (pyridinium dichromate, 15 g) in the presence of pyridinium trifluoroacetate (3 g) at room temperature for 6 h. Ether (150 mL) was added and the mixture was filtered through silica gel (20 g), the filtrate was washed with brine and dried, and solvents were removed with a short Vigreux. The residue was distilled at 25 mmHg to give **4** (3.5 g, 90%), bp 69–70 °C, identical with a sample obtained by Sarrett oxidation.[14]

3-(Carboxymethyl)-5-hydroxycyclopentene (5). A solution of **4** (6.4 g, 58.1 mmol) in ether (25 mL) was mixed with a solution of NaOH (2.84 g, 71.1 mmol) in water (24 mL). The two-phase system was cooled at 0 °C, while 14.6 mL of 30% hydrogen peroxide was added over a period of 40 min, maintaining the internal temperature at 10–25 °C.

The aqueous phase was separated, washed with ether (20 mL), and neutralized (pH 6–7) with concentrated hydrochloric acid. Solid sodium sulfite was added carefully to destroy the excess hydrogen peroxide. Ethyl acetate (20 mL) was added, and the pH was adjusted to 2.8 at 0 °C with concentrated hydrochloric acid. The aqueous phase was separated and extracted with ethyl acetate (4 × 25 mL). The combined extracts were dried and concentrated to yield **5** as a white solid: mp 85 °C (ether); 5.9 g (70%); IR (Nujol) 3400, 1680 cm^{-1}. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.28; H, 6.98.

A sample was esterified with diazomethane to increase the solubility, affording the corresponding ester as an oil: ^{1}H NMR ($CDCl_3$) δ 2.4 (m, 2 H), 3.62 (s, 3 H), 4.13 (s, 1 H, exchangeable with D_2O), 4.73 (m, 1 H), 5.8 (s, 2 H); IR (film) 3350 and 1720 cm^{-1}.

4-(Carboxymethyl)cyclopent-2-en-1-one (6). To a solution of **5** (3 g, 21.1 mmol) in acetone (250 mL) cooled at −30 °C was added Jones reagent dropwise until a reddish color persisted. After excess oxidant was quenched with ethyl alcohol, anhydrous $MgSO_4$ was added and the green mixture filtered through Celite. Removal of the solvents in vacuo gave **6** (2.9 g, 95%) as a white solid: mp 100–101 °C (THF–*n*-hexane, 1:3) (lit.[9] mp 102–103 °C); IR (Nujol) 1700, 1680, 1630, 1585 cm^{-1}. Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 60.18; H, 5.64.

A sample was esterified with diazomethane to increase the solubility, affording the corresponding ester as an oil: ^{1}H NMR ($CDCl_3$) δ 3.7 (s, 3 H), 6.6 (dd, 1 H, J = 6, J = 2 Hz), 7.7 (dd, 1 H, J = 6, J = 2.5 Hz); IR (film) 1730, 1700, 1680, 1585 cm^{-1}.

4-(3-Carbethoxy-2-oxopropyl)cyclopent-2-en-1-one (7). Carbonyldiimidazole (1.8 g, 11 mmol) was added to a solution of the keto acid **6** (1.4 g, 10 mmol) in THF (50 mL). After the mixture was stirred at room temperature for 6 h, the magnesium salt of ethyl malonic acid half-ester [prepared by stirring monoethyl malonate (1.32 g, 10 mmol) and magnesium ethoxide (0.57 g, 5 mmol) in THF (25 mL) for 1 h at room temperature] was added and the mixture was left at 25 °C overnight. The solvent was removed at reduced pressure and the residue was treated with 5% hydrochloric acid (20 mL) and ether (25 mL). The aqueous layer was further extracted with ether (3 × 25 mL), and the combined extracts were washed with aqueous saturated sodium bicarbonate solution and dried. Evaporation of the solvents in vacuo left **7** as an oil (1.4 g, 66.6%), which was used without further purification in the next step. TLC (Et_2O–petroleum ether, 2:1) showed two spots, the faster moving of which revealed the presence of a small amount of cyclized product **8**.

An analytical sample was prepared by column chromatography (silica gel): ^{1}H NMR ($CDCl_3$) δ 1.7 (t, 3 H, J = 7 Hz), 2.81 (m, 2 H), 3.47 (s, 2 H), 3.2–3.6 (m, 2 H), 4.16 (q, 2 H, J = 7 Hz), 6.1 (dd, 1 H, J = 6, J = 2 Hz), 7.6 (dd, 1 H, J = 6, J = 2.5 Hz); IR (film) 1740, 1700, 1650, 1585 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.77; H, 6.69.

Ethyl 3,3a,6,6a-Tetrahydro-2,5-dioxo-1*H*,4*H*-pentalene-4-carboxylate (8). A solution of crude **7** (1.4 g) in ethanol (10 mL) was added to a suspension of potassium carbonate (1.5 g) in ethanol (40 mL) and the mixture stirred at room temperature for 3 h and then filtered. The solvent was removed in vacuo and water (10 mL) and 5% hydrochloric acid (10 mL) were added, followed by extraction with $CHCl_3$ (3 × 30 mL). The dried extracts were concentrated in vacuo to give **8** (1.25 g, 89%) as an oil, homogeneous by TLC: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz), 1.8–3.8 (m, 9 H), 4.3 (q, 2 H, J = 7 Hz); IR (film) 3450, 1725, 1650, 1615 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.98; H, 6.80.

1,2,3,3a,6,6a-Hexahydro-5′-oxo-4′-(carboethoxy)-1,3-dioxolane-2-spiro-2′(1′*H*)-pentalene (9). A mixture of **8** (2.1 g,

(9) This compound can also be obtained by photolysis of α-tropolone methyl ether: Dauben, W. G.; Koch, K.; Smith, S. L.; Chapman, O. L. *J. Am. Chem. Soc.* **1963**, *85*, 2616–2621.

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10 mmol), 2-methyl-2-ethyl-1,3-dioxolane (40 mL), ethylene glycol (1.6 mL), and few crystals of *p*-toluenesulfonic acid was stirred at room temperature for 3 h. Triethylamine (0.15 mL) was added, followed by benzene (20 mL) and water (20 mL). The organic layer was separated, dried, and concentrated to give **9**, as an oil, in a virtually quantitative yield (2.41 g, 95%): ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3 H, J = 7 Hz), 3.9 (s, 4 H), 4.2 (q, 2 H, J = 7 Hz); IR (film) 1725, 1650, 1615 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.22; H, 7.30.

Registry No. 4. 694-98-4; 5, 74877-19-3; 5 methyl ester, 74877-20-6; 6, 74877-21-7; 6 methyl ester, 51388-62-6; 7, 74877-22-8; 8, 74877-23-9; 9, 74923-22-1; *endo*-5-norbornen-2-ol, 694-97-3; *exo*-5-norbornen-2-ol, 2890-98-4; magnesium monoethyl malonate, 37517-78-5.

(5*Z*,8*E*)-3-Heptyl-5-methylpyrrolizidine from a Thief Ant

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Alkyl-substituted piperidines,[1] pyrrolidines,[2] and an indolizidine[3] have been reported as venomous constituents from ant species in the related genera *Monomorium* and *Solenopsis*. In this note, we describe the occurrence, identification, and synthesis of (5*Z*,8*E*)-3-heptyl-5-methylpyrrolizidine (**1**) from the cryptic thief ant *Solenopsis sp.* near *tennesseensis*.[4]

The ants were collected in the Ocala National Forest near Ocala, Florida, and immediately placed in methylene chloride. Analysis of the methylene chloride extracts by GC/MS showed one major component whose mass spectrum showed a molecular ion at m/z 223 and other significant peaks at m/z 208 and 124. These fragments result from the loss of CH_3 and C_7H_{15}, respectively. These losses can occur from carbons adjacent to nitrogen, and, assuming one nitrogen atom, the compound must have two units of unsaturation and a molecular formula of $C_{15}H_{29}N$. Vigorous hydrogenation conditions had no effect on the mass spectrum of the natural product, indicating a bicyclic structure containing seven carbons and one nitrogen. The existence of pyrrolidines in related species[2] suggested that this substance might contain a 3,5-disubstituted pyrrolizidine ring system.

The overall carbon–nitrogen skeleton of 3-heptyl-5-methylpyrrolizidine (**1**) was confirmed by synthesis

Scheme I

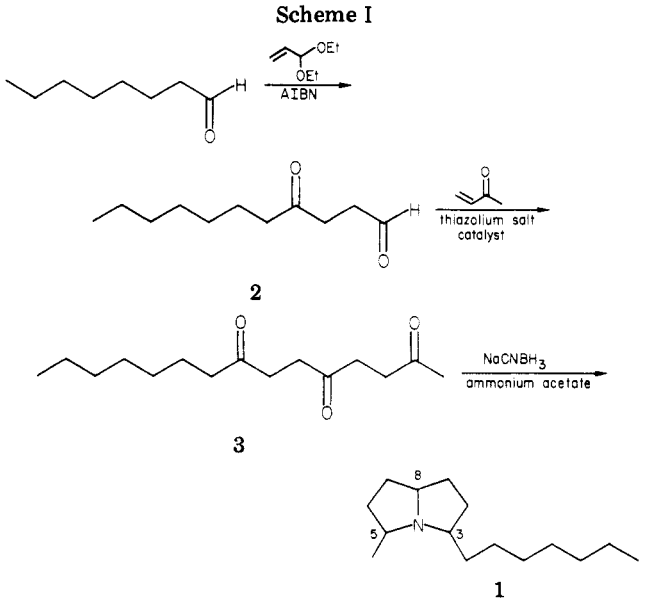
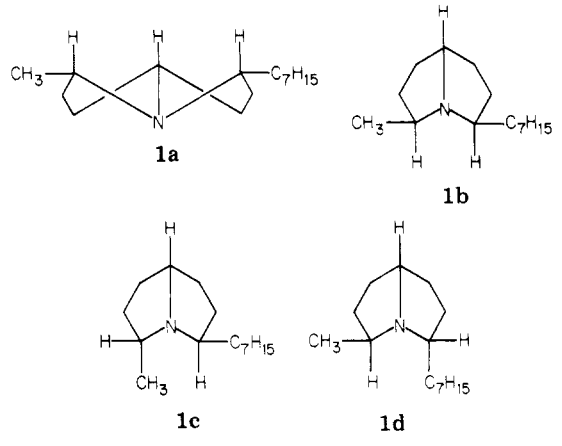


Chart I



(Scheme I). Treatment of a mixture of octanal and acrolein diethyl acetal with azobis(isobutyronitrile) (AIBN) followed by hydrolysis yielded 4–oxoundecanal (**2**), which, when condensed with methyl vinyl ketone in the presence of triethylamine and 5-(2-hydroxyethyl)-4-methyl-3-benzylthiazolium chloride,[5] gave the known 2,5,8-pentadecatrione (**3**).[6] Reductive amination[7] of the triketone **3** with sodium cyanoborohydride and ammonium acetate[2] formed pyrrolizidine **1** in good yield.

Gas chromatographic analysis (SP-1000) of synthetic **1** showed four isomers (**1a–d**) present in a 2:14:2.2:1 ratio. These compounds had essentially identical mass spectra which matched the mass spectrum of the natural material. Pure samples of each isomer were obtained by preparative GLC (SP-1000).

The stereochemistry of the pyrrolizidine ring junction of the isomers of **1** can be determined from their infrared and nuclear magnetic resonance spectra. Only (5*Z*,8*Z*)-3-heptyl-5-methylpyrrolizidine (**1a**)[8] shows strong Bohlmann bands in its infrared spectrum in the region 2600–2800 cm^{-1}, identical with those reported for

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