2220 (m), 1220 (s) $cm^{-1}$; mass spectrum 159 ($M^+$, 44), 130 (74), 91 (100), 78 (47), 77 (48), 51 (47).

**8b by the Hydrolysis of 11b.** A hydrolysis of **11b**, which was obtained from the reaction of **10** with phenylcarbene, in aqueous methanol as described above for **11a** gave a mixture of cis and trans isomers of **8b** in 49% (based upon **2b**) yield. The cis/trans isomer ratio was 1.68, slightly larger than the ratio 1.55 before hydrolysis.

**2-Methyl-2-phenylcyclopropanone Cyanohydrin (8d).** Acid hydrolysis of **3d** (mixture of isomers, 3.4 mmol) in dioxane (15 mL) with 18% HCl (10 mL) at 80 °C for 1.5 h gave **8d** (88%, isomeric mixture). After repeated chromatography two isomers were separated. *trans*-**8d**: viscous liquid; $^1H$ NMR 1.43 (1 H, d, $J$ = 6.6 Hz), 1.65 (1 H, d, $J$ = 6.6 Hz), 1.59 (3 H, s), 3.24 (1 H, br s), 7.2–7.5 (5 H, m); IR (liquid) 3380 (s), 2240 (m), 1220 (s) $cm^{-1}$. *cis*-**8d**: viscous liquid; $^1H$ NMR 1.25 (1 H, d, $J$ = 6.2 Hz), 1.50 (3 H, s), 1.78 (1 H, d, $J$ = 6.2 Hz), 4.26 (1 H, br s), 7.2–7.6 (5 H, m); IR (liquid) 3380 (s), 2245 (m), 1225 (s) $cm^{-1}$.

**8d by the Hydrolysis of 1-Cyano-2-methyl-2-phenyl-1-((trimethylsilyl)oxy)cyclopropane (11d).** An ethereal solution (20 mL) of **10** (30 mmol) and **2d** (13 mmol) was stirred at an ambient temperature for 15 h (11 mmol of $N_2$ was evolved). The product mixture, without purification, was treated with aqueous 90% methanol and chromatographed to give a mixture of cis and trans **8d** in 24% yield.

**2-(9-Fluorenyl)acetic Acid (9).** Acid hydrolysis of **3c** (2.4 mmol) in dioxane (15 mL) with 18% HCl (12 mL) at 80 °C for 1.5 h gave **9** (99%): mp 131 °C; $^1H$ NMR 2.84 (2 H, d, $J$ = 7.2 Hz), 6.59 (1 H, t, $J$ = 7.2 Hz), 7.2–7.9 (8 H, m), 11.37 (1 H, s); IR (KBr) 3000 (m), 1700 (s), 750 (m) $cm^{-1}$.

**9 from the Reaction of 10 with 2c.** The photolysis of an ethereal mixture of **10** (30 mmol) and **2c** (9.6 mmol) for 10 h evolved $N_2$ gas (8.3 mmol), and the total product mixture was treated with 90% methanol to give **9** (10%) and fluorenone azine (31%). From the 1,3-dipolar addition reaction, **9** was also obtained in 8% yield.

**Cyclopropanone Cyanohydrin (8e).** A solution of **3e** (1.6 mmol) and 35% HCl (0.3 mL) in methanol (4 mL) was warmed under solvent reflux for 0.5 h. After solvent was removed at 25 °C (40 torr), the residue was extracted with 1 mL of ether ten times and dried ($MgSO_4$) for 1 h. The removal of ether yielded the parent cyanohydrin **8e** in 62% yield: $^1H$ NMR 1.23 (s). The hydrolysis product (1 mmol) and acetic anhydride (1 mmol) were mixed in ether (2 mL) to which was added pyridine (3 mg) at 15 °C. After 2 h **8e** disappeared and a bulb-to-bulb distillation yielded **3e** (63%).

**Methanolysis of 3f.** A mixture of **3f** (0.51 mmol), 35% HCl (0.1 mL) and methanol (3 mL) was warmed at 60 °C for 0.75 h. The VPC analysis of the product mixture, using authentic samples, proved that ethyl methyl succinate (65%) and dimethyl succinate (15%) were formed.

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**Registry No.** **1**, 3061-65-2; **2a**, 883-40-9; **2b**, 766-91-6; **2c**, 832-80-4; **2d**, 22293-10-3; **2e**, 334-88-3; **2f**, 623-73-4; **3a**, 87656-16-4; *cis*-**3b**, 87656-17-5; *trans*-**3b**, 87656-18-6; **3c**, 87656-19-7; *cis*-**3d**, 87656-20-0; *trans*-**3d**, 87656-21-1; **3e**, 87656-22-2; *cis*-**3f**, 87681-15-0; *trans*-**3f**, 87681-16-1; **8a**, 87656-23-3; *cis*-**8b**, 87656-24-4; *trans*-**8b**, 87656-25-5; *cis*-**8d**, 87656-26-6; *trans*-**8d**, 87656-27-7; **8e**, 14743-56-7; **9**, 6284-80-6; **10**, 54276-53-8; **11a**, 87656-28-8; *cis*-**11b**, 87656-29-9; *trans*-**11b**, 87656-30-2; $H_3CCOCN$, 631-57-2; $ClSi(CH_3)_3$, 75-77-4; fluorenone azine, 2071-44-5; ethyl methyl succinate, 627-73-6; dimethyl succinate, 106-65-0.

# (4 + 2) Cycloaddition of Ketenes and β-Methoxy α,β-Unsaturated Ketones: 2-Pyranones

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The cycloaddition of diphenyl- and various chloroketenes to β-methoxy α,β-unsaturated ketones afforded (4 + 2) cycloaddition products. The cycloadducts resulting from the choroketenes were converted to 2-pyranones on treatment with zinc in moist acetic acid. The cycloaddition products from chloroketenes and β-(methoxymethylene)-α-tetralone were readily converted to substituted benzocoumarins.

Extensive studies in ketene chemistry indicate the reaction bias of ketenes with 4-π-electron compounds toward (2 + 2) cycloaddition reactions of these heterocumulenes to yield four-membered-ring compounds.[1] While the primary synthetic usefulness of the reactions of ketenes remains the formation of four-membered-ring compounds, there are an increasing number of reports in the literature that deal with the (4 + 2) cycloaddition reactions of ketenes.[2-9] This report decribes an investigation of the reaction of ketenes with β-methoxy α,β-unsaturated ketones to give (4 + 2) cycloaddition products which undergo conversion to 2-pyranones on treatment with zinc in moist acetic acid. We have further described the application of the synthetic methodology described here to the synthesis of 3- and 4-substituted benzocoumarins.

Dichloro- and phenylchloroketenes were generated in situ in the presence of commercially available 4-methoxy-3-buten-2-one (**1a**) by the dehydrochlorination of the corresponding chloro acid chlorides by the use of tri-

(1) (a) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949. (b) Brady, W. T. "The Chemistry of Ketenes, Allenes and Related Compounds"; Patai, S., Ed.; Interscience: New York, 1980; Part I, p 279.
(2) Bargagna, A.; Evangelisti, F.; Schenone, P. *J. Heterocycl. Chem.* **1979**, *16*, 93.
(3) (a) Mosti, L.; Schenone, P.; Menozzi, G. *J. Heterocycl. Chem.* **1978**, *15*, 181. (b) Scarpati, R.; Sica, D.; Santacroce, C. *Tetrahedron* **1964**, *20*, 2735.
(4) Martin, J. C.; Gott, P. G.; Goodlett, V. W.; Hasek, R. H. *J. Org. Chem.* **1965**, *30*, 4175.
(5) Gouesnard, J. P. *Tetrahedron* **1974**, *30*, 3113.
(6) Brady, W. T.; Watts, R. D. *J. Org. Chem.* **1981**, *46*, 4047.
(7) Brady, W. T.; Agho, M. O. *Synthesis* **1982**, 500.
(8) Brady, W. T.; Agho, M. O. *J. Heterocycl. Chem.* **1983**, *20*, 501.
(9) Gompper, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 312.

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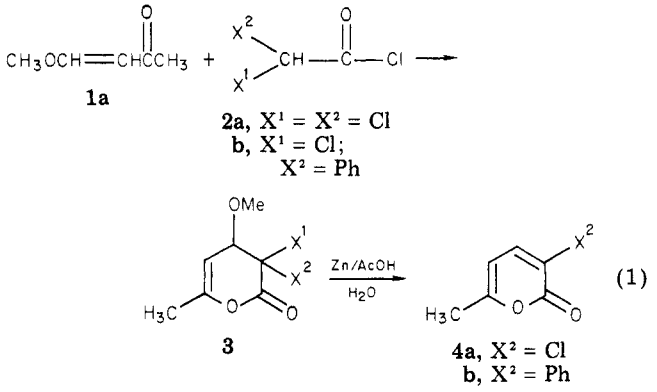
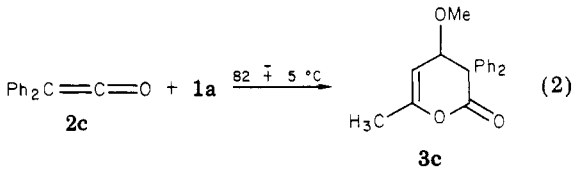
ethylamine in refluxing hexane. The initial cycloadducts, **3**, were not isolated but treated with excess zinc in moist acetic acid to afford the 2-pyranones **4a,b** (eq 1).



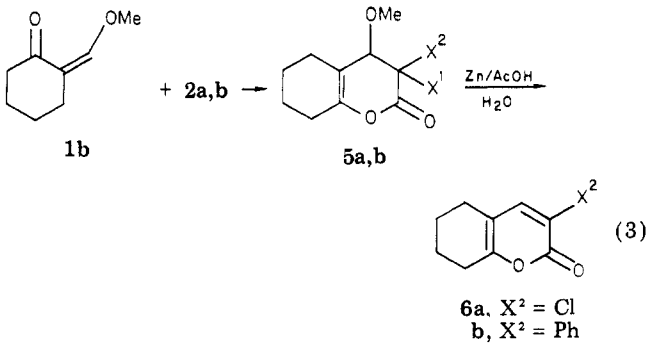

The infrared spectra for compounds **4a,b** revealed absorptions at 1700 and 1620 $cm^{-1}$ for the carbonyl and olefinic bonds; in the NMR, the $CH_3$ proton signals occurred as broad peaks due to slight coupling with the olefinic proton in the 5-position at about 2.20 ppm. The $^{13}C$ spectral data are consistent with the structures assigned.

Diphenylketene (**2c**) reacted with **1a** to give **3c** (eq 2)



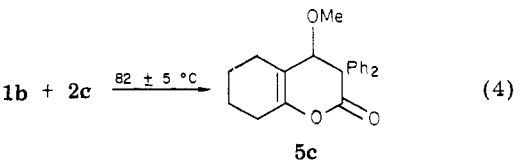

in good yield. The infrared spectrum for **3c** revealed absorptions at 1750 and 1700 $cm^{-1}$, corresponding to the carbonyl and olefinic double bonds. The $^1H$ NMR spectrum of **3c** exhibited fine allylic coupling, with the proton in the 4-position showing up as a doublet (4.36 ppm) and the one in the 5-position as a double doublet (5.43 ppm). The $^{13}C$ NMR data are consistent with **3c**.

(*Z*)-2-(Methoxymethylene)cyclohexanone (**1b**) underwent a similar (4 + 2) cycloaddition reaction with dichloro- and phenylchloroketenes to give **5a,b** which on treatment with zinc in moist acetic acid gave **6a** and **6b** in 56% and 47% yields, respectively (eq 3). Treatment of the con-

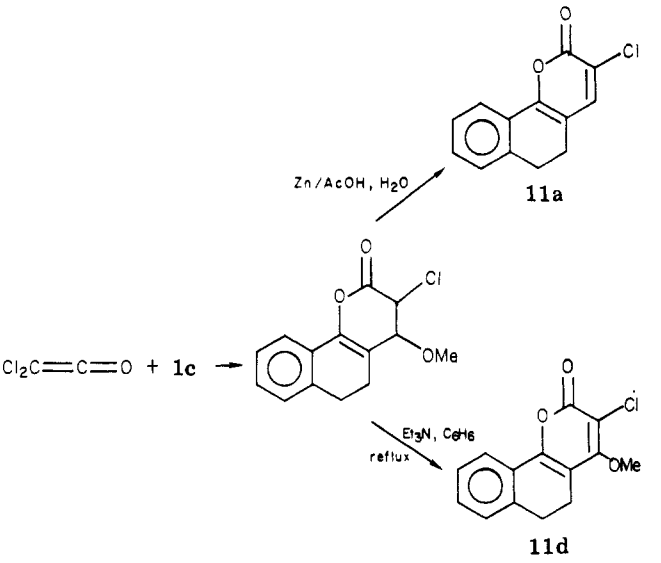



centrated crude reaction mixture with dry ether led to the precipitation and isolation of **5b** in 68% yield.

Diphenylketene reacted with **1b** at 82 ± 5° C to give the 3,4-dihydro-2-pyranone **5c**, in 90% yield[10] (eq 4). The $^{13}C$

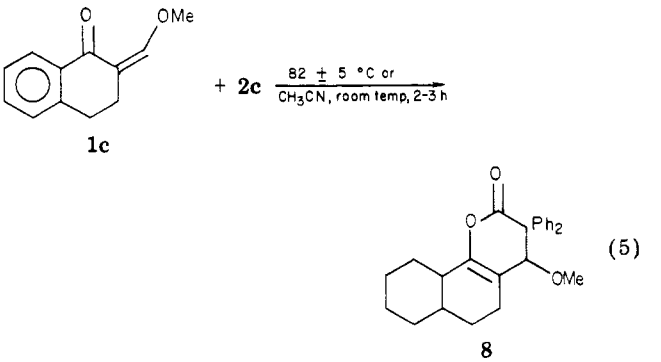



Scheme I

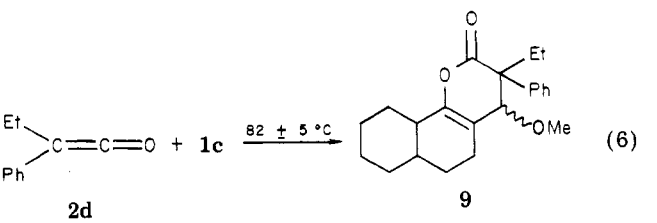



NMR data for compounds **5** and **6** are consistent with structures revealing resonances of pyranone carbonyl in the range of 158–169 ppm.

Diphenylketene reacted with β-(methoxymethylene)-α-tetralone (**1c**) at 82 ± 5 °C to give **8** in good yield (eq 5). The same product was isolated in about the same yield when the reaction was conducted in acetonitrile.



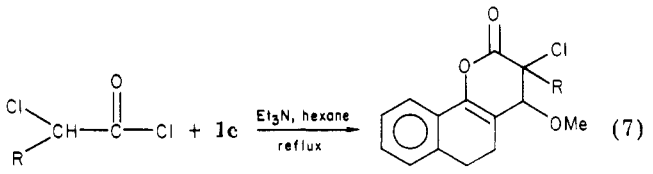

Also, phenylethylketene (**2d**) underwent (4 + 2) cycloaddition with **1c** to give only one isomeric form of **9** (eq 6)




Dichloroketene reacted with **1c** to give a (4 + 2) cycloaddition product which upon treatment with zinc in moist acetic acid or triethylamine in refluxing benzene yielded the substituted 2-pyranone (Scheme I).

The generation of methylchloro- and phenylchloroketenes from the corresponding chlorinated acetyl chlorides by the use of triethylamine in the presence of β-(methoxymethylene)-α-tetralone (**1c**) in refluxing hexane resulted in the 3,4-dihydro-2-pyranones (**10**, eq 7). The dihydropyranones were not isolated but were treated with

(10) A similar reaction was reported for 2-(ethoxymethylene)cyclohexanone[9] but there was no experimental procedure or spectral properties described.

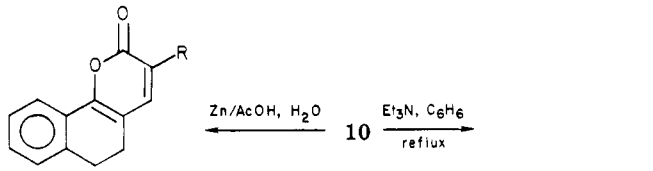



(7)

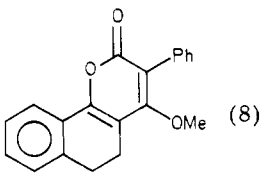
2b, R = Ph
e, R = Me

10

zinc in moist acetic acid or triethylamine in refluxing benzene to give the 5,6-dihydrobenzocoumarins, **11b,c** and **11e**, respectively (eq 8) in respectable yields. However, the




11b, R = Ph
c, R = $CH_3$

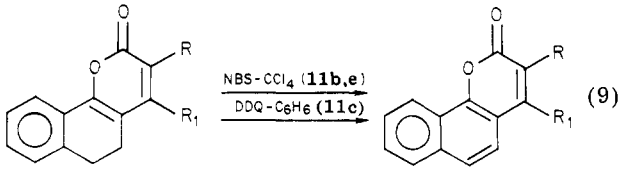



(8)

11e

product from the triethylamine treatment of the initial cycloadduct from the reaction of methylchloroketene with **1c** could not be isolated.

In an effort to demonstrate some utility of the above-described synthetic methods, we converted the dihydrobenzocoumarins **11b,c,e** into the corresponding benzocoumarins by accomplishing the necessary elimination reactions (eq 9). The treatment of compounds **11** with




(9)

11b, R = Ph; $R_1$ = H
c, R = $CH_3$; $R_1$ = H
e, R = Ph; $R_1$ = OMe

12b, R = Ph; $R_1$ = H
e, R = Ph; $R_1$ = OMe

*N*-bromosuccinimide or DDQ for 18 h resulted in good yields of the corresponding substituted 7,8-benzoumarins. The $^1H$ NMR spectra for the benzocoumarins revealed multiplets in the aromatic region, and there was considerable overlapping of the resonances in the aromatic region in the $^{13}C$ NMR spectra.

Clearly a limitation of this method for the synthesis of 3- and 4-substituted benzocoumarins is that a haloketene must be used in the cycloaddition reaction. The halogen substitutent in the 3-position enables an elimination of hydrogen halide or reductive removal of the halogen and then subsequent elimination of methanol. Nevertheless, there are a variety of haloketenes that may be employed, and we have just illustrated examples with dichloro-, methylchloro-, and phenylchoroketenes.

In conclusion, diphenylketene and the studied halogenated ketenes undergo (4 + 2) cycloaddition reactions with β-methoxy α,β-unsaturated ketones to give 3,4-dihydro-2-pyranones which are easily converted to the 2-pyranones. The described (4 + 2) cycloaddition reactions of ketenes represent a new and versatile synthetic route to pyranones. The demonstrated application of (4 + 2) ketene cycloaddition reactions in the convenient and efficient synthesis of 3- and 4-substituted 7,8-benzocoumarins, derivatives of naturally occuring coumarins, underscores the significance of these reactions in potential syntheses.

## Experimental Section

Proton NMR spectra were recorded on a 90-MHz JEOL FX-90Q employing deuteriochloroform as the solvent with tetramethylsilane as the internal standard. $^{13}C$ spectra were determined at 90 MHz in the Fourier mode by using a JEOL FX-90Q spectrometer equipped with a JEC 980B computer. Deuteriochloroform was used as a lock solvent and as the internal standard. The infrared spectra were obtained on a Beckman 1330 spectrophotometer. Flash chromatograpy was performed as described by Still[11] by using J. T. Baker silica gel (product No. 7024-1, ≥25 m). All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were carried out by Midwest Microlab, Ltd., Indianaplis, IN. Hexanes and tetrahydrofuran were dried by refluxing them over and distilling them from sodium–potassium alloy. Triethylamine was distilled from sodium metal, and diethyl ether was refluxed over and distilled from lithium aluminum hydride. Benzene was dried by washing it with sulfuric acid and then distilling it at atmospheric pressure.

**(*Z*)-2-(Methoxymethylene)cyclohexanone (1b).** This enol ether was prepared in a 74% yield from 2-(hydroxymethylene)-cyclohexanone[12] by using the procedure described for the preparation of β-(methoxymethylene)-α-tetralone: bp 84–86 °C (2 mm); IR (neat) 1660, 1610 $cm^{-1}$; NMR δ 1.68 (br, 4 H), 2.23 (br, 4 H), 3.73 (s, 3 H), 6.88 (t, 1 H).

**(*Z*)-β-(Hydroxymethylene)-α-tetralone.** A three-necked, 2-L, oven-dried flask, equipped with a mechanical stirrer, was swept with dry nitrogen. To the flask were added 500 mL of dry ether, 11.5 g (0.50 mol) of sodium metal, 73 g (0.50 mol) of freshly distilled α-tetralone, 55 g (0.75 mol) of ethyl formate, and 5 mL of absolute ethanol. The flask was then placed in an ice bath and stirred vigorously for 6 h. After the mixture was allowed to stand overnight at room temperature, 13 mL of absolute ethanol was added to it, and the mixture was stirred for another 2 h. The mixture was then treated with 100 mL of water, and the organic layer was washed twice with 50 mL of water. The combined aqueous extracts were washed twice with 50 mL of ether and then acidified with 82.5 mL of 6 N hydrochloric acid solution. The acidified aqueous solution was extracted three times with 150 mL of ether. The combined ether extracts were washed with saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. Concentration and fractional distillation of the residue gave 63 g (72%) of the functionalized alcohol: bp 107–114 °C (0.025 mm); IR (neat) 3100–3700 (w, br OH band), 1625, 1600 $cm^{-1}$; NMr δ 2.50 (m, 2 H), 2.85 (m, 2 H), 7.1 (m, 3 H), 7.73 (m, 1 H), 7.91 (s, 1 H), 14.20 (s, 1 H).

**(*Z*)-β-(Methoxymethylene)-α-tetralone (1c).** A three-necked, 500-mL, round-bottomed, oven-dried flask was equipped with a pressure-equalizing dropping funnel, a reflux condenser, a calcium chloride drying tube, and a magnetic stirrer. To the flask were added 300 mL of dry reagent acetone, 24.2 g (0.175 mol) of anhydrous potassium carbonate, and 20.3 g (0.117 mol) of freshly distilled β-(hydroxymethylene)-α-tetralone. The mixture was heated to a gentle reflux with vigorous stirring and 15 g (0.119 mol) of dimethyl sulfate was added over a 20-min period. The reaction mixture was stirred under continued gentle reflux for another 14 h. On cooling, the mixture was filtered, concentrated, and distilled at 125–135 °C (0.025 mm). Recystallization of the solidified distillate from hexanes gave **1c**: 18.7 g (85%); 57.5–59 °C; IR (film) 1675, 1610, 1585 $cm^{-1}$; NMr δ 2.70 (br, 4 H), 3.74 (s, 3 H), 7.15 (m, 4 H), 7.73 (m, 1 H). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.69; H, 6.38. Found: C, 76.34; H, 6.32.

**Typical Procedure for the Cycloaddition Reaction of Diphenylketene with the β-Methoxy α,β-Unsaturated Ketones.** A mixture of freshly distilled diphenylketene (5.67 mmol) and β-methoxy α,β-unsaturated ketone (5.67 mmol) was heated at 82 ± 5 °C. The reaction was monitored by infrared spec-

(11) Still, W. C. *J. Org. Chem.* **1978**, *43*, 2933.
(12) Ainsworth, C. *Org. Synth.* **1959**, *39*, 27.

troscopy, and when the ketene band at 2100 $cm^{-1}$ had disappeared (usually after 2–3 h), the reaction mixture was allowed to cool to about 50 °C. The mixture was treated with about 5–7 mL of petroleum ether and stirred gently. The resulting crystalline product was recrystallized from benzene/hexane.

**3,3-Diphenyl-4-methoxy-6-methyl-3,4-dihydro-2*H*-pyran-2-one (3c).** From 1.1 g (5.67 mmol) of commercially available 4-methoxy-3-buten-2-one (1a) was isolated 1.30 g (78%) of the pyranone: mp 160–161 °C; IR (film) 1750, 1700, 1590 $cm^{-1}$; NMR δ 1.76 (s, 3 H), 3.20 (s, 3 H), 4.40 (d, 1 H), 5.42 (d, 1 H), 7.25 (s, 10 H). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.55; H, 6.12. Found: C, 77.25; H, 6.21.

**3,3-Diphenyl-4-methoxy-5,6-tetramethylene-3,4-dihydro-2*H*-pyran-2-one (5c).** From 1.1 g (5.67 mmol) of diphenylketene and 0.79 g (5.67 mmol) of 2-(methoxymethylene)cyclohexanone was isolated 1.7 g (90%) of the pyranone: mp 135–136 °C; IR (film) 1760, 1700, 1600 $cm^{-1}$; NMR δ 1.10–1.73 (br, 4 H), 3.10 (s, 3 H), 4.20 (s, 1 H), 7.21 (s, 10 H). Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.04; H, 6.59. Found: C, 78.93; H, 6.76.

**3,3-Diphenyl-4-methoxy-3,4,5,6-tetrahydro-2*H*-naphtho[2,1-*e*]pyran-2-one (8).** From 1.1 g (5.67 mmol) of diphenylketene and 1.07 g (5.67 mmol) of β-(methoxymethylene)-α-tetralone was isolated 1.78 g (82%) of the pyranone: mp 161–162 °C; IR (film), 1760, 1760, 1600 $cm^{-1}$; NMR δ 2.30–2.85 (br, 4 H), 3.05 (s, 3 H), 3.05 (s, 3 H), 4.25 (s, 1 H), 6.70–7.30 (aromatic, 14, H). Anal. Calcd for $C_{26}H_{22}O_3$: C, 81.68; H, 5.76. Found: C, 81.50; H, 5.81.

**3-Ethyl-3-phenyl-4-methoxy-3,4,5,6-tetrahydro-2*H*-naphtho[2,1-*e*]pyran-2-one (9).** A mixture of 0.415 g (2.84 mmol) of phenylethylketene and 0.54 g (2.84 mol) of β-(methoxymethylene)-α-tetralone was heated at 82 ± 5 °C. The reaction was monitred by infrared spectroscopy, and when the ketene band at 2100 $cm^{-1}$ had disappeared (usually about 4 h), the reaction mixture was allowed to cool to warm temperature. The 2-pyranone was purified by flash chromatography on silica gel with hexane/ethyl acetate (9:1) as the eluent to afford the product: 0.62 g (65%); mp 122–123 °C; IR (film) 1750, 1660, 1590 $cm^{-1}$; NMR δ 0.72 (t, 3 H), 2.22 (quartet, 2 H), 2.39–2.58 (br, 2 H), 2.58–2.78 (br, 2 H), 3.38 (s, 3 H), 4.25 (s, 1 H), 6.88–7.54 (m, 9 H). Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.04; H, 6.59. Found: C, 79.22; H, 6.57.

**Typical Procedure for the Cycloaddition Reaction of Halogenated Ketenes with β-Methoxy α,β-Unsaturated Ketones.** A solution of 0.0125 mol of the freshly distilled chlorinated acetyl chloride in 50 mL of dry hexane was added over a 2-h period to a stirred, refluxing solution of 0.0125 mol of the β-methoxy α,β-unsaturated ketone and 0.0125 mol of triethylamine in 100 mL of dry hexane under a nitrogen atmosphere. The resulting mixture was stirred for an additional 30-min period. The amine salt was then removed by filtration, and the filtrate was concentrated on a rotatory evaporator. The residue was then subjected to one of the two following treatments.

**Zinc/Acetic Acid Treatment.** To the concentrated residue was added 40 mL of acetic acid and 2 mL of water. The mixture was stirred at room temperature, and 4 g of powdered zinc was added in one portion. The mixture was stirred for 24 h. Excess zinc and the zinc salt were filtered and washed with 40 mL of chloroform. The filtrate was placed in a separatory funnel and washed several times with water until the aqueous layer tested neutral with litmus paper. The chloroform layer was dried over $MgSO_4$ and concentrated to give the substituted 2-pyranones.

**Triethylamine Treatment.** To the concentrated residue was added 40 mL of dry benzene and 6 mL of dry triethylamine. The mixture was stirred, refluxed overnight, cooled, filtered, and then concentrated under vacuum to give compounds **11d,e**.

**3-Chloro-6-methyl-2-pyranone (4a).** From 1.84 g (0.0125 mol) of dichloroacetyl chloride, 1.25 g (0.0125 mol) of 4-methoxy-3-buten-2-one (**1a**), and 1.26 g (0.0125 mol) of triethylamine was isolated, after treatment with zinc, 0.5 g (28%) of the pyranone: mp 83–84 °C; IR (film) 1695, 1625, 1545 $cm^{-1}$ nmr δ 2.29 (br, 3 H), 6.12 (d, 1 H), 7.50 (d, 1 H). Anal. Calcd for $C_6H_5ClO_2$: C, 50.00; H, 3.47. Found: C, 49.88; H, 3.60.

**3-Phenyl-6-methyl-2-pyranone (4b).** From 2.36 g (0.0125 mol) of α-chlorophenylacetyl chloride, 1.25 g (0.0125 mol) of 4-methoxy-3-buten-2-one (**1a**), and 1.26 g (0.0125 mol) of triethylamine was isolated, after the zinc treatment, 0.6 g (26%) of the pyranone: mp 69–70 °C; IR (film) 1700, 1620, 1590, 1555, $cm^{-1}$; NMR δ 2.18 (br, 3 H), 6.01 (d, 1 H), 7.14–7.71 (m, 6 H). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.42; H, 5.38. Found: C, 77.60; H, 5.11.

**3-Chloro-4-methoxy-3-phenyl-5,6-tetramethylene-3,4-dihydro-2*H*-pyran-2-one (5b).** From 2.36 g (0.0125 mol) of α-chlorophenylacetyl chloride, 1.75 g (0.0125 mol) of 2-(methoxymethylene)cyclohexanone (**1b**), and 1.26 g (0.0125 mol) of triethylamine was isolated, after treatment of the cycloaddition residue with ether, 2.5 g (68%) of the dihydro-2-pyranone: mp 111–112 °C; IR (film) 1765, 1685 $cm^{-1}$; NMR δ 1.41–2.20 (m, 4 H), 3.52 (s, 3 H), 4.13 (s, 1 H), 7.35 (s, 5 H). Anal. Calcd for $C_{16}H_{17}ClO_3$: C, 65.75; H, 5.82. Found: C, 65.52; H, 6.04.

**3-Chloro-5,6-tetramethylene-2-pyranone (6a).** From 1.84 g (0.0125 mol) of dichloroacetyl chloride, 1.75 g (0.0125 mol) of 2-(methoxymethylene)cyclohexanone (**1b**), and 1.26 g (0.0125 mol) of triethylamine was isolated, after the zinc treatment, 1.3 g (56%) of the pyranone: mp 124–125 °C; IR (film) 1700, 1625, 1535 $cm^{-1}$; NMR δ 1.61–1.94 (m, 2 H), 2.30–2.69 (br, 2 H), 7.27 (s, 1 H). Anal. Calcd for $C_9H_9ClO_2$: C, 58.70; H, 4.89. Found: C, 59.00; H, 4.86.

**3-Phenyl-5,6-tetramethylene-2-pyranone (6b).** From 2.36 g (0.0125 mol) of α-chlorophenylacetyl chloride, 1.75 g (0.0125 mol) of 2-(methoxymethylene)cyclohexanone (**1b**), and 1.26 g (0.0125 mol) of triethylamine was isolated, after the zinc treatment, 1.3 g (47%) of the pyranone: mp 116–117 °C; IR (film) 1690, 1625, 1550 $cm^{-1}$; NMR δ 1.44–1.72 (m, 2 H), 2.12–2.49 (m, 2 H), 7.03–7.58 (m, 6 H). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.65; H, 6.19. Found: C, 79.40; H, 5.96.

**3-Phenyl-5,6-dihydro-7,8-benzocoumarin (11b).** From 2.36 g (0.0125 mol) of α-chlorophenylacetyl chloride, 2.35 g (0.0125 mol) of β-(methoxymethylene)-α-tetralone (**1c**), and 1.26 g (0.0125 mol) of triethylamine was isolated, after the zinc treatment, 2.0 g (58%) of the substituted dihydrobenzocoumarin: mp 143–144 °C; IR (film) 1690, 1615, 1525 $cm^{-1}$; NMR δ 2.55–2.74 (m, 2 H), 2.82–3.01 (m, 2 H), 7.14–7.85 (m, 10 H). Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.21; H, 5.11. Found: C, 83.04; H, 4.93.

**3-Methyl-5,6-dihydro-7,8-benzocoumarin (11c).** From 1.59 g (0.0125 mol) of α-chloropropionyl chloride, 2.35 g (0.0125 mol) of β-(methoxymethylene)-α-tetralone (**1c**), and 1.26 g (0.0125 mol) of triethylamine was isolated, after the zinc treatment, 1.0 g (38%) of the substituted dihydrobenzocoumarin: mp 133–134 °C; IR (film) 1690, 1625, 1590, 1570, 1540 $cm^{-1}$; NMR δ 2.00 (d, $CH_3$), 2.37–2.64 (m, 2 H), 2.64–2.92 (m, 2 H), 6.92–7.72 (m, 5 H). Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.25; H, 5.66. Found: C, 78.94; H, 5.78.

**3-Phenyl-4-methoxy-5,6-dihydro-7,8-benzocoumarin (11e).** From 2.36 g (0.0125 mol) of α-chlorophenylacetyl chloride, 2.35 g (0.0125 mol) of β-methoxymethylene)-α-tetralone (**1c**), and 1.26 g of triethylamine was isolated, after the triethylamine treatment, 2.2 g (58%) of the substituted dihydrobenzocoumarin: mp 137–138 °C; IR (film) 1680, 1615, 1530 $cm^{-1}$; NMR δ 2.57–2.99 (m, 4 H), 3.38 (s, 3 H), 7.09–7.88 (m, 9 H). Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.95; H, 5.26. Found: C, 79.02; H, 5.42.

**Typical Procedure for the Synthesis of Substituted 7,8-Benzocoumarins via the Use of NBS.** A mixture of 1 g of 5,6-dihydrobenzocoumarin, an equivalent amount of NBS, and 0.1 g of benzoyl peroxide in 50 mL of $CCl_4$ was refluxed for 18 h. The reaction mixture was filtered hot under suction, and the resulting filtrate was concentrated under vacuum to give the crude product. The product was recrystallized from ether or chloroform.

**3-Phenyl-7,8-benzocoumarin (12b).** From 1.0 g (3.65 mmol) of **11b**, 0.65 g (3.65 mmol) of NBS, and 0.1 g of benzoyl peroxide was isolated 0.7 g (71%) of the benzocoumarin: mp 212–213 °C; IR (film) 1690, 1660, (weak), 1625 (weak), 1590 (weak); NMR δ 7.13–7.91 (m, 1 H), 8.41–8.60 (m, 1 H). Anal. Calcd for $C_{19}H_{12}O_2$: C, 83.82; H. 4.41. Found: C, 82.28; H, 4.34.

**3-Phenyl-4-methoxy-7,8-benzocoumarin (12e).** From 1.0 g (3.29 mmol) of **11e**, 0.59 g (3.29 mmol) of NBS, and 0.1 g of benzoyl peroxide was isolated 0.7 g (71%) of the benzocoumarin: mp 152–153 °C; IR (film) 1690, 1620, 1580, 1550 $cm^{-1}$; NMR δ 3.54 (s, 3 H), 7.31–7.90 (m, 5 H), 8.30–8.60 (dd, 1 H). Anal. Calcd for $C_{20}H_{14}O_3$: C, 79.47; H. 4.64. Found: C, 79.53; H, 4.53.

**3-Methyl-7,8-benzocoumarin (12c).** A solution of 0.15 g (0.71 mmol) of **11c** and 0.18 g (0.78 mmol) of DDQ in 30 mL of dry benzene was stirred and refluxed for 18 h. The solution was filtered, and the filtrate was concentrated in vacuo. The resulting black residue was purified by chromatography on a column of acidic alumina upon elution with hexane/ethyl acetate (1:1) to yield 0.10 g (68%) of the benzocoumarin: mp 129–130.5 °C; IR (film) 1690, 1630, 1605 $cm^{-1}$; NMR δ 2.23 (d, 3 H), 7.27–7.92 (m,

6 h), 8.31-8.58 (m, 1 H). Anal. Calcd for $C_{14}H_{10}O_2$: C, 80.00; H, 4.76. Found: C, 78.30; H, 4.91.

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**Registry No.** **1a**, 4652-27-1; **1b**, 87937-54-0; **1c**, 40685-41-4; **2a**, 79-36-7; **2b**, 2912-62-1; **2c**, 525-06-4; **2d**, 20452-67-9; **2e**, 7623-09-8; **3c**, 87937-56-2; **4a**, 61550-09-2; **4b**, 53034-19-8; **5b**, 87937-60-8; **5c**, 87937-57-3; **6a**, 87937-61-9; **6b**, 87937-62-0; **8**, 87937-58-4; **9**, 87937-59-5; **11b**, 87937-63-1; **11c**, 87937-64-2; **11e**, 87937-65-3; **12b**, 50493-12-4; **12c**, 87937-66-4; **12e**, 21315-40-2; 2-(hydroxymethylene)cyclohexanone, 823-45-0; (*Z*)-β-(hydroxymethylene)-α-tetralone, 87937-55-1; α-tetralone, 529-34-0.

**Supplementary Material Available:** $^{13}C$ NMR spectral data for **5b,c**, **6a,b**, and **11a-e** (4 pages). Ordering information is given on any current masthead page.

# Synthesis of 9-Substituted Carbacyclin Analogues

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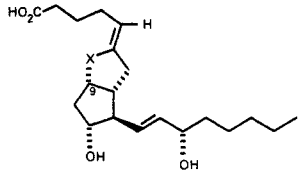
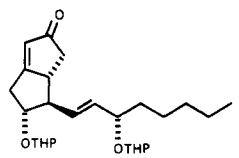
The synthesis of a series of 9-substituted carbacyclin analogues with potent platelet antiaggregatory activity is described. The key step for the formation of 9-acetylene compounds (e.g., **8d**) utilized a modification of the Schwartz procedure involving the nickel-catalyzed conjugate addition of the appropriate alkynyl aluminate to bicyclo[3.3.0]oct-1-en-3-one (**2**). It was found that 9-methylcarbacyclin (**8b**) could be prepared by a similar procedure. In addition, a novel alternative to the Wittig reaction for introducing the carbacyclin upper side chain in base-sensitive substrates was developed which involves the addition of the dianion of 6-((*tert*-butyldimethylsilyl)oxy)hexanoic acid to the appropriate ketone (e.g., **6f** or **2**) followed by decarboxylative dehydration of the resulting β-hydroxy acid.

## Introduction

The potent biological activity of prostacyclin ($PGI_2$, **1a**),[1]




**1a** X = O
**1b** X = $CH_2$




**2**

coupled with its inherent instability ($t_{1/2}$ = 3 min at 37 °C)[2] has sparked an intense search for chemically stable analogues with similar antithrombotic properties.[3] One of the most promising of these prostacyclin mimics is carbacyclin (6a-carbaprostaglandin $I_2$, **1b**)[4,5] which has been shown to have a very similar biological profile to $PGI_2$.[6] As part of a carbacyclin analogue program we had occasion to prepare a number of 9-substituted compounds. Some of the interesting chemical and biological results of this study are described herein. In particular, the conjugate addition of alkynyl groups to a bicyclo[3.3.0]oct-1-en-3-one system was investigated, and a novel method was discovered for introducing the upper side chain.

## Results and Discussion

The starting material for a host of 9-substituted carbacyclin analogues is the optically active bicyclo[3.3.0]-octenone **2**, readily available in three steps (Scheme I) from the well-known lactone **3**.[4] We found that the procedure of Schwartz[7] was an excellent method for introducing the pentynyl side chain. Thus when 1-pentyne was treated with 1 equiv of *n*-butyllithium (to generate 1-lithiopentyne) followed by 1 equiv of diethylaluminum chloride (to form the aluminum complex), then cannulated into a 1:1 mixture of a catalytic amount of nickel 2,4-pentanedionate ($Ni(acac)_2$) and diisobutylaluminum hydride (Dibah), and subsequently treated with bicyclo[3.3.0]octenone **2**, a 64% yield of the desired adduct **6a** (see Scheme II) was obtained. The upper side chain was then introduced in the normal manner.[4] Treatment with 5 equiv of (4-carboxybutyl)triphenylphosphorane in dimethyl sulfoxide ($Me_2SO$) at 40 °C furnished the olefin mixture **7a** in 70% yield. Finally, tetrahydropyranyl ether hydrolysis with 6:3:2 acetic acid–water–tetrahydrofuran at 40 °C for 3 h afforded the desired analogue 9-(1′-pentynyl)carbacyclin (**8a**) (57% yield) along with its corresponding 5*E* isomer **9a** (39% yield).[8]

(1) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* **1976**, *263*, 663. (b) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 915. (c) Vane, J. R.; Bergstrom, S. "Prostacyclin"; Raven Press: New York, 1979.

(2) Moncada, S.; Vane, J. R. *J. Med. Chem.* **1980**, *23*, 591.

(3) Bartmann, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 751 (and references therein).

(4) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954 (and references therein).

(5) 6a-Carba-$PGI_2$ has also been called 9(*O*)-methanoprostacyclin and carboprostacyclin as well as carbacyclin.

(6) (a) Whittle, B. J. R.; Moncada, S.; Whiting, F.; Vane, J. R. *Prostaglandins* **1980**, *19*, 605. (b) Aiken, J. W.; Shebuski, R. J. *Ibid.* **1980**, *19*, 629.

(7) (a) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053. (b) Hansen, R. T.; Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2244.

(8) Initial assignment of stereochemistry at C-5 was based upon analogy with carbacyclin and other carbacyclin analogues wherein the "natural" stereoisomer, i.e., 5*Z* in the 9-substituted series described herein, is the more polar isomer and the "unnatural" (i.e., 5*E* isomer) is the less polar isomer on TLC. The double bond isomers at C-5 can be separated either at the acid bis(THP) ether stage (compound **7**) on acid-washed silica gel or else by HPLC at the acid diol stage (compounds **8** and **9**) using a solvent system containing acetic acid. In each case the initial structural assignments were corroborated by the biological results (see Table I).

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