# Intramolecular C–H Insertion by an Alkylidene Carbene: Diastereoselective Synthesis of a Taxol A Ring Synthon

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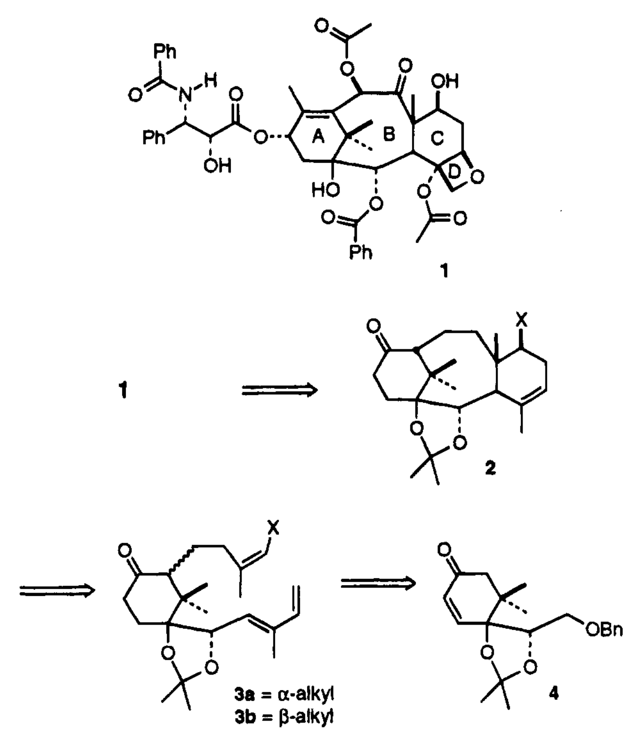
The first stage in a proposed total synthesis of the clinically effective anticancer agent taxol **1** is reported. A key step in this synthesis is the development of a new procedure for the generation and cyclization of the alkylidene carbene derived from ketone **9**, to give cyclopentene **10** (formation of three new carbon–carbon bonds) in 72% yield. Ozonolysis of **10** followed by aldol condensation furnished the crystalline cyclohexenone **4**.

Taxol (**1**), isolated[1] originally from the bark of the Pacific yew *Taxus brevifolia*, has demonstrated substantial clinical activity.[2] We are currently engaged in a total synthesis of **1**,[3,4] focusing on the possibility of an internal Diels–Alder cycloaddition (**3a** → **2**) to construct the tricyclic carbon skeleton. We report a diastereoselective synthesis of **4**, a sufficient A-ring synthon[5] for the preparation of **3**. The key step in the synthesis of **4** is construction of the quaternary stereogenic center by intramolecular C–H insertion of an intermediate alkylidene carbene.




**Background.** Pioneering studies of the Diels–Alder-based A → ABC assembly of the taxane skeleton have appeared.[4a,l] In both cases, a strategem had to be adopted to ameliorate the rapid increase in nonbonding interactions across the forming eight-membered ring, that otherwise would obviate cycloaddition. Desiring a minimally-substituted synthetic intermediate, we have pursued detailed conformational analysis of a series of substituted trienes. This led us to the discovery that the lowest energy conformation of acetonide **3a** is well-aligned for cycloaddition.

Although **3b** is in fact more stable than **3a**, the calculated[6] energy difference between **3a** and **3b** is only 1.8 kcal/mol. Under equilibrating conditions at 200 °C (the usual temperature for such unactivated cycloadditions), there should be a sufficient steady state concentration of **3a** for the cyclization to proceed. The cyclization itself is calculated[7] to be exothermic by about 18 kcal/mol.

Enone **4** appeared to be a suitable precursor for the preparation of **3**. We report here a diastereoselective

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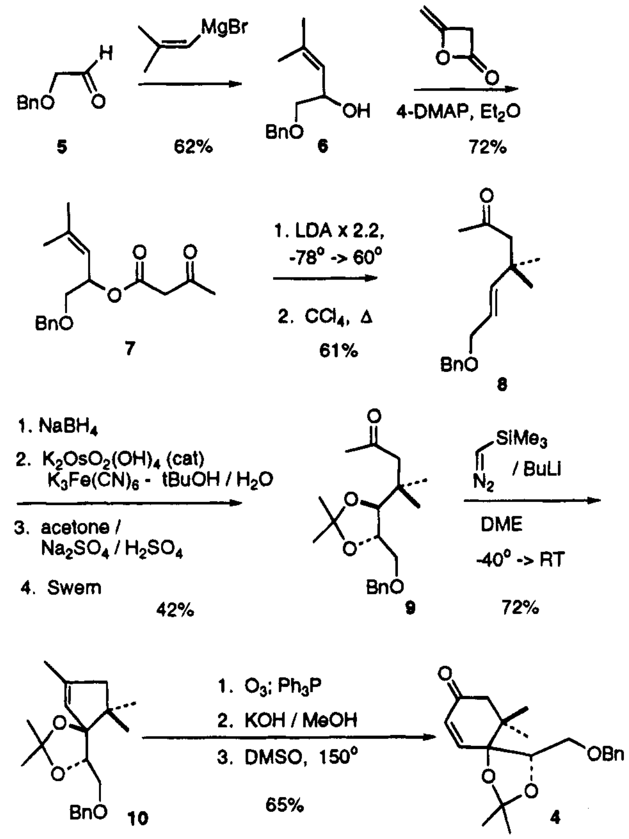
0022-3263/94/1959-6014$04.50/0 

**Scheme 1**

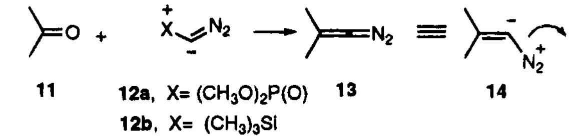


synthesis that is straightforward enough to allow the preparation of gram quantities of the crystalline enone **4**.

**Preparation of Alkene 8.** The key intermediate for the synthesis of **4** was the alkene **8** (Scheme 1). Aldehyde **5**[9] was readily prepared on a substantial scale using the $P_2O_5$/DMSO oxidation procedure that we have reported.[10] Grignard addition led to the unstable alcohol **6**.[11] We carried **6** on to **8** using the Wilson[12] modification of the Carroll rearrangement.

**Intramolecular C—H Insertion by an Alkylidene Carbene.** To set the stage for intramolecular C—H insertion (**Scheme 1**), we first effected catalytic osmylation[13] of the alkene **8**. We found that it was important to first reduce the ketone, since the osmylation proceeded more efficently on the secondary alcohol. In practice, it was most expedient to carry out the four steps (reduction, dihydroxylation, protection, and oxidation) without purificaton of the intermediates.

With ketone **9** in hand, we were prepared to investigate procedures for the generation of the alkylidene carbene. Intramolecular C—H insertion into a methine by an intermediate alkylidene carbene was first demonstrated by Gilbert,[14a] using dialkyl diazomethyl phosphonate anion **12a**. It is assumed that condensation of **12** with a ketone proceeds through **13**, which then thermally (but well below ambient temperature) α-eliminates, via **14**. A limitation to this method for the generation of alkylidene carbenes from ketones is the multistep synthesis of **12a**.



A variation on this approach was recently reported by Ohira,[15] using the anion of (trimethylsilyl)diazomethane. An obvious advantage is that the TMS diazomethane is commercially available.[16] Our early investigations using the Ohira protocol, in THF, were not successful. We were gratified, however, to find that the use of dimethoxyethane as solvent was much more rewarding. Exposure of ketone **9** to the anion of TMS diazomethane in DME/hexane led to cyclopentene **10** in 72% yield.

It should be noted that alternative cyclopentenes could have been formed in the cyclization, by insertion into a C—H bond of one of the methyl groups. As has been observed before,[14a] a methine is much more reactive than a methyl group. In this particular case, the methine is further activated by α-oxygen substitution.[17]

Ozonolysis of **10** followed by aldol condensation provided a small quantity of enone **4** and a much larger proportion of a more polar substance that was deduced to be the β-hydroxy ketone. Brief warming of the crude aldol reaction mixture in DMSO gave the nicely crystalline enone **4** in 65% yield from **10**.

**Conclusion.** A particular appealing aspect of the taxol A ring preparation reported here is that application of asymmetric dihydroxylation[19] to **8** should lead to symchiral[20] **4**. The DME modification of the Gilbert–Ohira cyclization reported here should make intramolecular C—H insertion by an alkylidene carbene a generally useful procedure in organic synthesis.

## Experimental Section[21]

**4-Methyl-1-(phenylmethoxy)-3-penten-2-ol (6).** $CH_2Cl_2$ (500 mL), $P_2O_5$ (51.0 g, 360 mmol), and DMSO (31.2 g, 400 mmol)[9] were combined sequentially with mechanical stirring at rt. The mixture was cooled in an ice—water bath, and then

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(16) (Trimethylsilyl)diazomethane, purchased from Aldrich, was contaminated with a 29% impurity, $^1$H NMR (δ) = 2.63. We separated the (trimethylsilyl)diazomethane from solvent hexane by spinning band distillation. This did not, however, remove the impurity.

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(20) For the use of "symchiral" to mean "having high enantiomeric purity", see: (a) Taber, D. F. *Chem. Eng. News* **1991**, August 19, 5. (b) Magar, S. S.; Fuchs, P. L. *Tetrahedron Lett.* **1992**, *33*, 745. (c) Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990.

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2-(phenylmethoxy)ethanol[22] (32.0 g, 210 mmol) in $CH_2Cl_2$ (25 mL) was added dropwise over 10 min. The ice bath was removed, and stirring was continued for 3 h. The mixture was cooled in an ice−water bath, and then $Et_3N$ (101.2 g, 1.0 mol) was added dropwise over 30 min. After stirring for an additional 2 h, 10% aqueous HCl (150 mL) was added dropwise over 30 min. After stirring for an additional 2 h, the layers were separated, and the organic layer was washed with water (3 × 200 mL) to remove excess DMSO. The organic layer was dried ($Na_2SO_4$), concentrated, and distilled bulb-to-bulb ($bp_{0.5}$ (bath) = 80−95 °C) to yield 22.9 g (74% yield) of aldehyde **5** as a colorless oil.

The Grignard reagent prepared from 1-bromo-2-methyl-1-propene (25.7 g, 190 mmol) and Mg (4.6 g, 190 mmol) in THF (50 mL) was stirred vigorously and chilled in an ice−water bath. Aldehyde **5** (25.7 g, 170 mmol) in THF (80 mL) was added dropwise over 30 min. Saturated aqueous $NH_4Cl$ (100 mL) was added, followed by sufficient water to dissolve the solids. The mixture was extracted with EtOAc (2 × 100 mL). The organic extract was washed with saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. The residue was chromatographed to yield 21.7 g (105 mmol, 62%) of alcohol **6** as a colorless oil, TLC $R_f$ (20% EtOAc/petroleum ether) = 0.35. Spectroscopic data were congruent with those reported.[10]

**4-Methyl-1-(phenylmethoxy)-3-penten-2-yl 3-Oxobutanoate (7).** Alcohol **6** (17.6 g, 85.3 mmol) in ether (170 mL) was chilled in an ice−water−salt bath to an internal temperature of −12 °C. Diketene (Aldrich; 50% in acetone, 17 mL, 102 mmol) was added with stirring, followed by 4-(dimethylamino)pyridine (104 mg, 0.85 mmol). The mixture was stirred and allowed to come to rt over 18 h. Aqueous NaOH (0.1%, 50 mL) was added, and then the pH of the solution was adjusted to 8 with 1% aqueous NaOH. The layers were separated, and then the organic layer was washed sequentially with 0.1% aqueous NaOH (50 mL) and saturated aqueous NaCl (50 mL), dried ($Na_2SO_4$), concentrated, and chromatographed to give ester **7** (19.0 g, 65.4 mmol, 77% yield): TLC $R_f$ (20% EtOAc/petroleum ether) = 0.48, as a colorless oil; $^1$H NMR ($\delta$) 1.12−1.93 (m, 6 H), 2.21 (s, 3 H), 3.41 (s, 2 H), 3.48 (dd, $J$ = 10.8 Hz, $J$ = 3.9 Hz, 1 H), 3.57 (dd, $J$ = 10.8 Hz, $J$ = 7.3 Hz, 1 H), 4.51 (d, $J$ = 12.0 Hz, 1 H), 4.55 (d, $J$ = 12.0 Hz, 1H), 5.13 (m, 1 H), 5.7 (m, 1 H), 7.3 (m, 5 H); Enol (ca. 18%) (partial) 1.93 (s, 3 H), 5.00 (s, 1 H), 12.12 (s, 1 H); $^{13}$C NMR ($\delta$) down 18.4, 25.6, 29.7, 71.1, 120.0, 127.4, 128.2; up 50.2, 71.3, 72.9, 137.8, 139.5, 166.3, 200.3; IR (cm$^{-1}$) 2931, 2860, 1740, 1717, 1645; MS ($m/z$, %) 260 (0.5), 188 (5), 169 (12), 91 (100); HRMS calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1520.

**(*E*)-4,4-Dimethyl-7-(phenylmethoxy)-5-hepten-2-one (8).** n-BuLi (58 mL of 2.3 M in hexane, 133 mmol) was added dropwise over 15 min, with stirring and cooling in an ice−water bath, to diisopropylamine (20.3 mL, 145 mmol) in THF (190 mL). After stirring for an additional 45 min, the mixture was cooled to −78 °C, and then ester **7** (17.5 g, 60.3 mmol) in 60 mL THF was added dropwise at a rate such that the internal temperature did not exceed −65 °C. The mixture was stirred for an additional 18 h with warming to rt and then maintained at 60 °C for 2 h. The mixture was concentrated on the rotary evaporator and then partitioned between 0.1 N aqueous NaOH and EtOAc. The organic layer was discarded. The aqueous layer was acidified with 10% aqueous HCl and extracted with EtOAc (2 × 50 mL). The organic extract was dried ($Na_2SO_4$) and concentrated. The residue was taken up in $CCl_4$ (250 mL), and the solution was maintained at reflux for 4 h. The mixture was concentrated and the residue was chromatographed to yield 9.09 g (36.9 mmol, 61% yield) of ketone **8** as a pale yellow oil: TLC $R_f$ (15% EtOAc/petroleum ether) = 0.43; $^1$H NMR ($\delta$) 1.13 (s, 6H), 2.08 (s, 3 H), 2.24 (s, 2H), 3.99 (dd, $J$ = 6.0 Hz, $J$ = 1.2 Hz, 2H), 4.49 (s, 2H), 5.61 (dt, $J$ = 15.7 Hz, $J$ = 6.1 Hz, 1H), 5.83 (bd, $J$ = 15.7 Hz, 1H), 7.26−7.35 (m, 5H); $^{13}$C NMR ($\delta$) down 27.2, 32.0, 122.9, 127.4, 127.7, 128.3, 142.4; up 35.5, 55.1, 70.8, 71.9, 138.4, 207.6; IR (cm$^{-1}$) 2961, 2870, 1717, 1454, 1361; MS ($m/z$) 231 (6), 188 (6), 164 (2), 91 (100); HRMS calcd for $C_{16}H_{22}O_2$ 246.1620, found 246.1613.

**(*R**,*R**)-2,2-Dimethyl-4-(1,1-dimethyl-3-oxobutyl)-5-[(phenylmethoxy)methyl]-1,3-dioxolane (9).** Ketone **8** (246 mg, 1.00 mmol) was dissolved in ethanol (20 mL), and at 0 °C sodium borohydride (190 mg, 5 mmol) was added. After completion of the reaction (TLC), the mixture was acidified with 10% aqueous HCl. Water (20 mL) was added, and the reaction mixture was extracted with EtOAc. The organic layer was dried ($Na_2SO_4$), concentrated, and filtered through silica gel to give 225 mg (0.91 mmol, 91%) of the corresponding alcohol.

An amount of 8.43 g (34 mmol) of this alcohol was dissolved in *tert*-butyl alcohol (135 mL). This solution was added to a solution of potassium ferricyanide (33.6 g, 102 mmol), potassium carbonate (14.1 g, 102 mmol), and potassium osmate (Colonial Metals; 68 mL of a 0.025 M solution in 1:3 water−*tert*-butyl alcohol, 1.7 mmol) in water (110 mL). The mixture was stirred vigorously at rt for 24 h. Saturated aqueous sodium sulfite was added, and the mixture was stirred for another 1 h. After extraction with EtOAc, the combined organic layers were washed with saturated aqueous sodium sulfite, dried over $Na_2SO_4$, and concentrated. Chromatography yielded the corresponding triol (5.34 g, 18.5 mmol, 56%) as a mixture of diastereomers.

Sodium sulfate (10.2 g, 72 mmol) followed by 10 drops of concentrated sulfuric acid were added to a solution of the mixture of triols (5.04 g, 17.9 mmol) in dry acetone (170 mL). The mixture was stirred for 18 h, after which the acid was neutralized with potassium carbonate. After filtration from the solids, the solvent was removed *in vacuo* to give the crude acetonide (5.41 g) as a mixture of diastereomers.

DMSO (3.05 mL, 43.0 mmol) was added slowly at −60 °C with stirring to a solution of oxalyl chloride (2.03 mL, 23 mmol) in 100 mL of $CH_2Cl_2$. After an additional 30 min, a solution of the mixture of acetonides (5.41 g) in $CH_2Cl_2$ (25 mL) was added dropwise over an additional 30 min. After a further 30 min at −60 °C, triethylamine (12.5 mL, 89.5 mmol) was added dropwise, after which the reaction mixture was allowed to warm slowly to rt. Water (20 mL) was added, the layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic extract was dried ($Na_2SO_4$), concentrated, and chromatographed to give the ketone **9** (4.78 g, 14.9 mmol, 83%, 42% from **8**), TLC $R_f$ (10% EtOAc/petroleum ether) = 0.33, as a light yellow oil: $^1$H NMR ($\delta$) 0.99 (s, 3H), 1.00 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 2.09 (s, 3H), 2.33 (d, $J$ = 15.4 Hz, 1H), 2.52 (d, $J$ = 15.4 Hz, 1H), 3.52−3.55 (m, 2H), 3.81 (d, $J$ = 7.7 Hz, 1H), 4.00−4.07 (m, 1H), 4.55 (d, $J$ = 12.3 Hz, 1H), 4.61 (d, $J$ = 12.3 Hz, 1H), 7.25−7.35 (m, 5H); $^{13}$C NMR ($\delta$) down 22.1, 23.4, 26.9, 27.0, 32.2, 76.6, 83.3, 127.5, 127.6, 128.2; up 35.4, 51.2, 72.5, 73.3, 108.7, 137.9, 208.2; IR (cm$^{-1}$) 2985, 2934, 2876, 1716, 1379, 1368; MS ($m/z$, %) 305 (5), 262 (6), 141 (21), 91 (100); HRMS calcd for $C_{18}H_{25}O_4$ ($M^+ - CH_3$) 305.1752, found 305.1746.

**(*R**,*S**)-3,3,7,9,9,-Pentamethyl-5-[(phenylmethoxy)-methyl]-2,4-dioxaspiro[4.4]non-6-ene (10).** n-BuLi (6.7 mL of 2.38 M in hexanes, 16.0 mmol) was added dropwise over 5 min to (trimethyl)silyldiazomethane (Aldrich, 2.0 M in hexanes, 8.0 mL, 16.0 mmol) in 20 mL of DME at −78 °C. The cooling bath was removed, and the heterogeneous mixture was stirred until it becomes a clear amber. The mixture was chilled in a −40 °C bath, and then ketone **9** (1.23 g, 3.84 mmol) in 4 mL of DME was added dropwise over 5 min. The mixture was stirred and allowed to come to rt over 4 h. Water (10 mL) was added, and the mixture was stirred for an additional 10 min and then partioned between EtOAc and water. The organic extract was dried ($Na_2SO_4$) and concentrated, and the residue was chromatographed to give cyclopentene **10** (876 mg, 2.77 mmol, 72% yield) as a colorless oil: TLC $R_f$ (5% EtOAc/petroleum ether) = 0.35; $^1$H NMR ($\delta$) 0.94 (s, 3H), 1.10 (s, 3H), 1.35 (s, 3H), 1.45 (s, 3H), 1.70 (d, $J$ = 0.9 Hz, 3H), 1.84 (bd, $J$ = 15.9 Hz, 1H), 2.25 (bd, $J$ = 15.9 Hz, 1H), 3.46 (dd, $J$ = 10.6 Hz, $J$ = 2.3 Hz, 1H), 3.54 (dd, $J$ = 10.6 Hz, $J$ = 7.5 Hz, 1H), 4.20 (dd, $J$ = 7.5 Hz, $J$ = 2.3 Hz, 1H), 4.47 (d, $J$ = 12.4 Hz, 1H), 4.68 (d, $J$ = 12.4 Hz, 1H), 5.27 (m, 1H), 7.25−7.34 (m,

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5H); $^{13}C$ NMR (δ) down 17.2, 24.0, 25.7, 26.6, 28.9, 77.6, 125.0, 127.4, 127.6, 128.2; up 43.1, 51.0, 70.6, 73.2, 95.2, 107.1, 138.1, 144.2: IR ($cm^{-1}$) 2983, 2934, 2872, 1453; MS (*m/z*, %) 316 (2), 215 (4), 149 (13), 137 (14), 134 (16), 125 (38), 109 (26), 104 (47), 91 (100); HRMS calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2042.

**(*R**,*S**)-5-[(Phenylmethoxy)methyl]-3,3,10,10-tetramethyl-2,4-dioxaspiro[4.5]dec-6-en-8-one (4).** Ozone in oxygen was bubbled through a solution of cyclopentene **10** (876 mg, 2.77 mmol) in $CH_2Cl_2$ (10 mL) at −78 °C until the solution was faintly blue (15 min). The mixture was flushed with $N_2$ to dispel the blue color, and then triphenylphosphine (800 mg, 3.05 mmol) was added and the mixture was allowed to warm to rt over 18 h. The mixture was concentrated, and the residue was taken up in a solution of KOH (171 mg, 3.05 mmol) in water (10 mL). After the yellow solution had been stirred for 90 min, the mixture was adjusted to pH = 7 by the addition of 1 N aqueous HCl and partioned between EtOAc and water. The organic layer was thoroughly dried ($Na_2SO_4$) and concentrated.

The residue was taken up in DMSO (20 mL), and the resulting solution was maintained at 150 °C for 90 min. After cooling, the mixture was diluted with water (100 mL) and extracted with EtOAc (2 × 20 mL). The organic extract was dried ($Na_2SO_4$) and concentrated, and the residue was chromatographed to give ketone **4** (593 mg, 1.79 mmol, 65% yield) as a colorless oil: TLC $R_f$ (10% EtOAc/petroleum ether) = 0.45. This material crystallized from petroleum ether in the freezer to give colorless needles, mp = 52−53 °C; $^1H$ NMR (δ) 1.01 (s, 3H), 1.14 (s, 3H), 1.43 (s, 3H), 1.49 (s, 3H), 2.29 (d, $J$ = 16.3 Hz, 1H), 2.50 (d, $J$ = 16.3 Hz, 1H), 3.51 (dd, $J$ = 10.5 Hz, $J$ = 3.65 Hz, 1H), 3.64 (dd, $J$ = 10.5 Hz, $J$ = 6.2 Hz, 1H), 4.40−4.42 (m, 1H), 4.47 (d, $J$ = 12.1 Hz, 1H), 4.60 (d, $J$ = 12.1 Hz, 1H), 5.96 (d, $J$ = 10.3 Hz, 1H), 6.62 (d, $J$ = 10.3 Hz, 1H), 7.27−7.34 (m, 5H); $^{13}C$ NMR (δ) down 24.0, 24.7, 26.5, 29.0, 78.1, 127.7, 128.3, 128.7, 146.7; up 38.3, 50.0, 69.6, 73.5, 76.5, 83.7, 108.4, 137.3, 198.6; IR ($cm^{-1}$) 2922, 2872, 1683; MS (*m/z*, %) 330 (1), 315 (4), 216 (4), 183 (13), 180 (24), 123 (24), 91 (100); HRMS calcd for $C_{20}H_{26}O_4$ 330.1831, found 330.1849.

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**Supplementary Material Available:** $^1H$ and $^{13}C$ spectra for compounds **4** and **7−10** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.