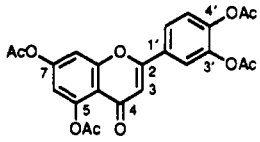
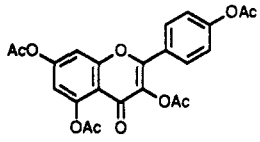
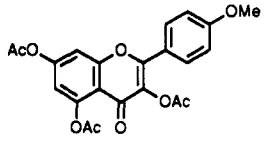
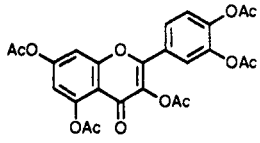
Table I. Alcoholysis of Compounds 1, 2, 3, and 4 Catalyzed by *Pseudomonas cepacea* Lipase in THF[a]

substrate	enzyme, mg/mL	conversion, %[b]	products	fraction, %[c]
 1	2	64	5,7,3′-triacetoxy-4′-hydroxyflavone (5) 5,7-diacetoxy-3′,4′-dihydroxyflavone (6)	90 10
 2	20	81	3,5,7-triacetoxy-4′-hydroxyflavone (7) 3,5-diacetoxy-7,4′-dihydroxyflavone (8)	52 48
 3	50	72	3,5-diacetoxy-7-hydroxy-4′-methoxyflavone (9) 3-acetoxy-5,7-dihydroxy-4′-methoxyflavone (10)	75 25
 4	20	80	3,5,3′,4′-tetraacetoxy-7-hydroxyflavone (11) 3,5,3′-triacetoxy-7,4′-dihydroxyflavone (12) 3,3′,4′-triacetoxy-5,7-dihydroxyflavone (13) 3-acetoxy-5,7,3′,4′-tetrahydroxyflavone (14)	49 28 13 10

[a] Substrate (200 mg) was dissolved in anhyd THF to 20 mM concentration (15 mM for 1). 1-Butanol (5 equiv) and *P. cepacea* lipase (Amano PS), "straight from the bottle" were added. The suspension was shaken (300 rpm) at 42 °C for 24 h. [b] Determined by HPLC analysis. [c] For the isolated yields, see the Experimental Section.

= 2.0 Hz, 6 H), 3.83 (s, 4′ OMe), 2.28 (s, 2 × Ac); UV (abs EtOH) λ_{max} 317 (ε 18100), 257 nm (ε 15500). Anal. Calcd for $C_{20}H_{16}O_8$: C, 62.50; H, 4.17. Found: C, 62.70; H, 4.25. **3-Acetoxy-5,7-dihydroxy-4′-methoxyflavone (10)**: ^{1}H NMR [$(CD_3)_2SO$] δ 7.82 (d, J = 8.8 Hz, 2′ H and 6′ H), 7.13 (d, J = 8.8 Hz, 3′ H and 5′ H), 6.49 (d, J = 2.0 Hz, 8 H), 6.24 (d, J = 2.0 Hz, 6 H), 3.84 (s, 4 OMe), 2.32 (s, Ac); UV (abs EtOH) λ_{max} 325 nm (ε 16000), 267 nm (ε 22000). Anal. Calcd for $C_{18}H_{14}O_7$: C, 63.16; H, 4.09. Found: C, 63.28; H, 4.17.

Alcoholysis of 3,5,7,3′,4′-Pentaacetoxyflavone (Quercetin Acetate, 4). Chromatography of the crude reaction mixture using solvent 1 gave 11 (63 mg), 12 (31 mg), 13 (14 mg), and 14 (9 mg). **3,5,3′,4′-Tetraacetoxy-7-hydroxyflavone (11)**: ^{1}H NMR [$(CD_3)_2SO$] δ 7.82 (dd, J = 2.1, 8.2 Hz, 6′ H), 7.79 (d, J = 2.1 Hz, 2′ H), 7.50 (d, J = 8.2 Hz, 5′ H), 6.91 (d, J = 2.0 Hz, 8 H), 6.62 (d, J = 2.0 Hz, 6 H), 2.32 (s, 2 × Ac), 2.27 (s, 2 × Ac); UV (abs EtOH) λ_{max} 304 nm (ε 12800), shifted to 314 on addition of fused sodium acetated, 254 nm (ε 17800), shifted to 304 on addition of fused sodium acetate. Anal. Calcd for $C_{23}H_{18}O_{11}$: C, 58.73; H, 3.83. Found: C, 58.83; H, 3.95. **3,5,3′-Triacetoxy-7,4′-dihydroxyflavone (12)**: ^{1}H NMR [$(CD_3)_2SO$] δ 7.28 (d, J = 2.2 Hz, 2′ H), 7.23 (dd, J = 2.2, 4 Hz, 6′ H), 6.89 (d, J = 8.4 Hz, 5′ H), 6.84 (d, J = 1.8 Hz, 8 H), 6.57 (d, J = 1.8 Hz, 6 H), 2.29 (s, Ac), 2.27 (s, 2 × Ac); UV (abs EtOH) λ_{max} 330 nm (ε 19550), shifted to 354 on addition of fused sodium acetate, 226 nm (ε 20800), shifted to 236 on addition of sodium acetate. Anal. Calcd for $C_{21}H_{16}O_{10}$: C, 58.88; H, 3.74. Found: C, 59.01; H, 3.84. **3,3′,4′-Triacetoxy-5,7-dihydroxyflavone (13)**: ^{1}H NMR [$(CD_3)_2SO$] δ 7.82 (d, J = 9.1 Hz, 6′ H), 7.81 (s, 2′ H), 7.51 (d, J = 9.1 Hz, 5′ H), 6.52 (s, 8 H), 6.28 (s, 6 H), 2.32 (s, 3 × Ac); UV (abs EtOH) λ_{max} 265 nm (ε 22000), shifted to 275 on addition of fused sodium acetate. Anal. Calcd for $C_{21}H_{16}O_{10}$: C, 58.88; H, 3.74. Found: C, 59.05; H, 3.82. **3-Acetoxy-5,7,3′,4′-tetrahydroxyflavone (14)**: ^{1}H NMR [$(CD_3)_2SO$] δ 7.32 (d, J = 2.1 Hz, 2′ H), 7.27 (dd, J = 2.1, 8.4 Hz, 6′ H), 6.90 (d, J = 8.4 Hz, 5′ H), 6.46 (s, 8 H), 6.23 (s, 6 H), 2.32 (s, Ac); UV (abs EtOH) λ_{max} 350 nm (ε 21300), shifted to 360 on addition of fused sodium acetate and to 378 on addition of sodium acetate/boric acid mixture, 256 nm (ε 25000), shifted to 266 on addition on fused sodium acetate. Anal. Calcd for $C_{17}H_{12}O_8$: C, 59.31; H, 3.49. Found: C, 59.12; H, 3.58.

Synthesis of Ombuin (3,5,3′-Trihydroxy-7,4′-dimethoxyflavone, 16). An ethereal solution of CH_2N_2 was added to a solution of 12 (20 mg) in CH_2Cl_2 (4 mL). After 1 h excess CH_2N_2 was destroyed by addition of acetic acid, the solvent removed, and the residue chromatographed on LiChroprep Si-gel DIOL using a gradient of ether in hexane to yield 15 mg of 3,5,3′-triacetoxy-7,4′-dimethoxyflavone (15): ^{1}H NMR [$(CD_3)_2SO$] δ 7.86 (dd, J = 2.0, 8.9 Hz, 6′ H), 7.70 (d, J = 2.0 Hz, 2′ H), 7.34 (d, J = 8.9 Hz, 5′ H), 7.29 (d, J = 2.2 Hz, 8 H), 6.85 (d, J = 2.2 Hz, 6 H), 3.87 (s, OMe), 3.79 (s, OMe), 2.30 (s, 3 × Ac). Hydrolysis of 15 according to Deulofeu and Schopflocher[22] gave ombuin 16, identified by comparison of its spectral properties with those reported in the literature.[20]

Acknowledgment. This work was financially supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST, Roma). We wish to express our thanks to Dr. Mario Foti who performed the AM1 calculations.

(22) Deulofeu, V.; Schopflocher, N. *Gazz. Chim. Ital.* **1953**, *83*, 449.

Acceleration of the Ortho Ester Claisen Rearrangement by Clay-Catalyzed Microwave Thermolysis: Expeditious Route to Bicyclic Lactones

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The Claisen rearrangement and its variants enjoy widespread use in synthesis,[1a-g] in part due to the sim-

Table I. Catalysis of the Johnson Ortho Ester Rearrangement of Cycloalkenols

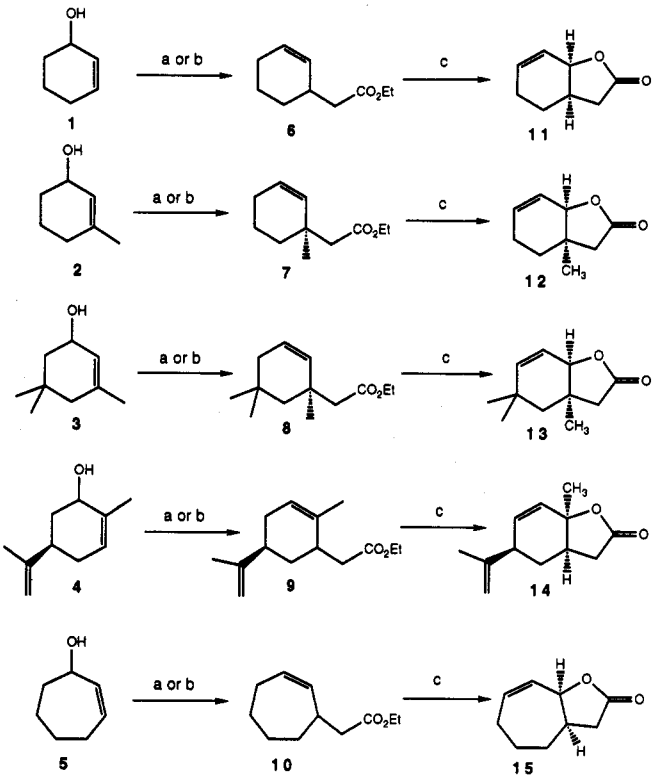
alcohol	product	% yield (% acetate A) conventional	microwave
1	6	73 (18)	80 (–)
2	7	53 (20)	78 (–)
3	8	47 (32)	66 (–)
4	9	83 (8)	85 (–)
5	10	68 (32)	100 (–)

plicity of the transformation and also the high degree of stereocontrol attainable by careful consideration of the transition-state assembly.[2,3] In connection with studies toward natural product total synthesis we desired an expeditious route to unsaturated fused bicyclic lactones and reasoned that the Johnson ortho ester Claisen rearrangement[1e] of a cycloalkenol would provide easy access to the desired frameworks by utilizing the emergent endocyclic alkene moiety from the rearrangement in a selenolactonization sequence with the (unmasked) carboxylate function.

Results and Discussion

To test the efficiency of the above mentioned strategy, a number of allylic cycloalkenols were prepared from the corresponding ketones using the method of Luche,[4] thence the alcohols could be subjected to the Johnson ortho ester rearrangement. One drawback with such rearrangements using the traditional method of thermolysis (excess triethyl orthoacetate (TEOA), propionic acid (0.1 equiv), 140 °C, with distillative removal of ethanol) has been the extended times required to drive the reaction to completion, frequently giving moderate to low yields of product. Indeed as we initially observed using the traditional catalyst approach with alcohols 1–5 (method a, Scheme I) on optimization only moderate yields of product were recovered (Table I), contaminated with varying amounts of starting alcohol and their derived acetates[14] even after forcing conditions (12 h, 180 °C) and repeated addition of more catalyst to the reaction.[5] We therefore decided to pursue an alternative means of (accelerated) thermolysis and chose to examine the effect of microwave heating[6] in conjunction with acid catalysis provided by montmorillonite KSF clay.[7]

Scheme I. Formation of Bicyclic Lactones via Ortho Ester Claisen Rearrangement[a]



[a] Conditions: (a) TEOA (7.0 equiv), propionic acid (0.1 equiv), reflux 0–12 h/140 °C; (b) TEOA (7.0 equiv), DMF, KSF clay, microwave thermolysis 9 min/500 W; (c) (i) LiOH/THF–H_2O, (ii) PhSeCl/Et_3N/CH_2Cl_2, (iii) H_2O_2/THF.

The alcohols 1–5 were placed in a sealed tube with TEOA and dissolved in dry DMF with the addition of a catalytic amount of KSF clay. Microwave thermolysis (9 min, 500 W) and subsequent workup gave the rearranged product esters 6–10 *cleanly and in high yield* in all cases examined (Table I, method b).

Increasing the amount of KSF clay in the reaction had little effect on rate or yield, but the use of DMF as solvent was essential, avoiding the formation of intractable tars.[8] Of added benefit was the complete absence on workup of any of the derived acetates[14] of the alcohols typically found using conventional thermolysis/catalysis conditions, making purification of the product esters a trivial operation. The use of microwave heating with propionic acid as catalyst gave no improvement over the conventional thermal conditions, save for a reduction in reaction time (<10 min to achieve moderate conversion). Conventional thermolysis conditions using KSF as the catalyst failed to give any of the desired products with large quantities of unconsumed starting alcohol recovered even after forcing conditions.

Having successfully executed an expeditious high-yielding route to the required Claisen products, it remained to (i) expose the carboxylate function, (ii) effect selenolactonization,[10] and then (iii) form and eliminate the derived selenoxides. Using the protocol shown (Scheme I, method c) the transformations proceeded without incident to afford cleanly in all cases the desired cis bicyclic unsaturated lactones in good yield.[11] The 5,7 fused lactone

(1) (a) Claisen, L. *Chem. Ber.* **1912**, *45*, 3157. (b) Burgstahler, A. W.; Nordin, I. C. *J. Am. Chem. Soc.* **1961**, *83*, 198. (c) Carroll, M. F. *J. Chem. Soc.* **1940**, *704*, 1266. (d) Marbet, R.; Saucy, G. *Helv. Chim. Acta* **1967**, *50*, 1158. (e) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (f) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (g) Felix, D.; Steen, K. G.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.

(2) Ziegler, F. E.; *Acc. Chem. Res.* **1977**, *10*, 227.

(3) Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*, 3896.

(4) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(5) All new compounds gave satisfactory spectroscopic and analytical data.

(6) Microwave thermolysis has been used successfully to effect a number of important synthetic transformations. For a recent review of microwave accelerated reactions, see: Abramovitch, R. A. *Org. Prep. Proc. Int.* **1991**, *23*, 683. Also see: Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945. By surrounding the reaction vessel with vermiculite beads, extremely rapid heating of the substrate can be achieved since the beads absorb energy in the microwave range (2450 MHz)–thermal energy is then transferred to the DMF solution via conduction. A rough indication of the internal temperature of the reaction medium achieved during such thermolyses was obtained using the sealed capillary method. A number of solids of known melting point were sealed in glass capillaries which were inserted into a typical reaction run for careful observation. Using the microwave heating conditions reported herein (500 W, 9 min) it was determined that the DMF solution reaches a temperature of ca. 280 °C.

(7) KSF clay has been shown to catalyze the thermal allyl ether claisen rearrangement, presumably by the way of acidic cavities on its surface. See: Dauben, W. G.; Cogen, J. M.; Behar, V. *Tetrahedron Lett.* **1990**, *31*, 3241.

(8) Srikrishna, A.; Nagaraju, S. *J. Chem. Soc. Perkin Trans. 1* **1992**, 311.

(9) Gonzalez, F. B.; Bartlett, P. A. *Org. Synth.* **1986**, *64*, 175–181.

(10) Nicolaou, K. C.; Lysenko, Z. *J. Am. Chem. Soc.* **1977**, *99*, 3185.

15 is of interest in that it represents the core nucleus of a number of members of the guaianolide family, e.g. Hysterin.[12]

The above protocol gives access to complex unsaturated bicyclic lactones in a total of five steps from commercially available enones. The method is noteworthy in that using the modified catalysis conditions superior yields of the Johnson ortho ester rearranged products are attainable in a trivial operation which combines high yields with *very short reaction times* and no contamination of the rearranged product with the usual acetate byproduct. Exploitation of this key process in the total synthesis of natural products is currently underway in this laboratory.

Experimental Section

Unless noted all operations were performed under an atmosphere of dry nitrogen gas, using flame-dried glassware. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C spectra were recorded at 75 MHz as solutions in $CDCl_3$.

The following experimental sequence is typical and details the preparation of lactone 15 from commercially available 2-cyclohepten-1-one.

2-Cyclohepten-1-ol (1). 2-Cyclohepten-1-one (Aldrich) (2.0 g, 18.2 mmol) was added to a solution of cerium trichloride heptahydrate (6.76 g, 18.2 mmol) in methanol (45 mL). $NaBH_4$ (0.687 g, 18.2 mmol) was added over 5 min, and the resulting mixture was stirred for a further 5 min at 25 °C. The mixture was diluted with water until a clear solution was evident (ca. 60 mL), and the mixture was then neutralized (10% HCl) and extracted with ether. The ethereal extracts were washed with brine (1 × 20 mL), dried over Na_2SO_4, and then filtered and condensed in vacuo to give pure **2-cyclohepten-1-ol** (1) (2.03 g, 100%) as a clear colorless oil: ^{1}H NMR δ 5.73 (m, 2 H), 4.37 (d, 1 H, J = 6.8 Hz), 2.13 (m, 1 H), 2.13–1.3 (m, 8 H); ^{13}C NMR δ 137.9, 130.0, 72.0, 36.7, 28.56, 26.8, 26.7.

2-Cycloheptene-1-acetic Acid Ethyl Ester (10). Microwave Thermolysis (Method b). Montmorillonite KSF clay (ca. 0.04 g) was suspended in dry DMF (1.0 mL) in a flame-dried sealed tube (Teflon screw cap type). 2-Cyclohepten-1-ol (0.200 g, 1.78 mmol) was added under a stream of nitrogen, followed by triethyl orthoacetate (2.30 mL, 2.0 g, 12.5 mmol). The tube was purged with nitrogen, sealed, and packed in vermiculite. Following microwave irradiation (9 min, 500-W commercial oven, 2450 MHz),[13] the crude mixture was diluted with ethyl acetate (25 mL) and washed with HCl solution (10%, 20 mL) followed by saturated sodium bicarbonate solution (20 mL). The combined organic extracts were concentrated in vacuo, to ca. 5 mL, filtered through a short plug of silica gel, and then concentrated to dryness to give essentially pure **2-cycloheptene-1-acetic acid ethyl ester (10)** (0.324 g, 100%) as a colorless oil: ^{1}H NMR δ 5.75 (m, 1 H), 5.49 (dd, J = 10.9, 3.9 Hz, 1 H), 4.11 (q, 2 H, J = 7.1 Hz), 2.73 (m, 1 H), 2.33 (m, 2 H), 2.11 (m, 2 H), 1.90 (m, 1 H), 1.62 (m, 4 H), 1.31 (m, 1 H), 1.24 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 172.8, 135.8, 131.9, 60.1, 41.4, 36.6, 33.3, 30.1, 28.6, 26.7, 14.2.

Conventional Thermolysis (Method a). A flame-dried three-necked round-bottomed flask (25 mL) was fitted with a thermometer, septum, and a Claisen head to which was attached a receiver flask at one port and a water-cooled condenser at the other. The assembly was flushed with dry nitrogen gas, and then triethyl orthoacetate (10.0 mL, 54.55 mmol) was introduced followed by 2-cyclohepten-1-ol (0.960 g, 8.56 mmol) and finally propionic acid (0.06 g, 0.81 mmol). The thermometer was lowered such that the mercury bulb was suspended immediately above the reaction medium, and then the contents were heated slowly using an oil bath to 140 °C (internal temperature). Heating was continued until the theoretical yield of ethanol was recovered on distillation (0.5 mL) and all 2-cyclohepten-1-ol had been consumed (12.5 h by TLC). The mixture was cooled to 25 °C and diluted with ethyl acetate (20 mL); hydrochloric acid (2 N, 15 mL) was added and the mixture extracted into ethyl acetate; the organic extracts were washed with $NaHCO_3$ (sat. 15 mL), dried ($MgSO_4$), and condensed in vacuo to give 1.49 g of a chromatographically inseparable 68:32 mixture of **2-cycloheptene-1-acetic acid ethyl ester (10)** and the **acetate A**[14] **(n = 7)**, respectively. In a separate experiment, the reaction was run exactly as above but using a solvent (xylene, 10 mL). In order to achieve good conversion it was found necessary to add additional propionic acid (0.06 g) every 3 h, to make up for distillative losses and thereby resume effective catalysis of the reaction. In this investigation the yields of the product esters (using conventional thermolysis conditions) were generally higher when the thermolyses were conducted in the absence of a solvent, instead using a large excess of TEOA. All attempts to improve the conversion to the product ester in such reactions by adding more catalyst during the course of the reaction were unsuccessful.

2-Hydroxy-3-cycloheptene-1-acetic Acid Lactone (15). The ester (10) (0.9424 g, 5.17 mmol) was dissolved in THF (10 mL), and LiOH (0.6 g, 14.3 mmol) was added with water (4.0 mL). The reaction mixture was stirred at reflux for 4 h, diluted with water (10 mL) and ether (10 mL), and acidified with HCl (1 N, 20 mL). The product was extracted into ether, and the ethereal extracts were washed with brine (10 mL) and concentrated in vacuo to give **2-cycloheptene-1-acetic acid** as a clear colorless oil (0.79 g, 99%) (^{13}C NMR δ 179.0, 135.5, 132.2, 41.2, 36.4, 33.3, 30.1, 28.7, 26.7). The above acid (0.445 g, 2.89 mmol) was dissolved in dry CH_2Cl_2 (20 mL) in a flame-dried round-bottomed flask. Triethylamine (0.40 mL, 0.292 g, 2.89 mmol) was added, and the resulting solution was stirred at 25 °C for 30 min and then cooled to −78 °C. A solution of phenylselenenyl chloride (0.608 g, 3.17 mmol) in CH_2Cl_2 (6 mL) was added via syringe pump over a 30-min period. The reaction mixture was maintained at this temperature for 3 h, warmed to 25 °C, filtered through a plug of silica gel, and then concentrated in vacuo to give a pale yellow oil which was purified by silica gel chromatography ($CHCl_3$ eluent) to give **2-hydroxy-3-(phenylselenenyl)cycloheptane-1-acetic acid lactone** (0.665 g, 89%) as a colorless oil (^{13}C NMR δ 175.8, 135.3, 129.0, 128.4, 128.0, 86.0, 45.6, 39.7, 38.0, 32.0, 30.7, 29.9, 27.7). The selenide (0.631 g, 2.04 mmol) was dissolved in THF (10 mL) and the solution cooled to 0 °C for the dropwise addition of H_2O_2 (30%, 0.285 mL, 3.06 mmol). After addition was complete, the resulting solution was stirred at 25 °C for 12 h, diluted to 30 mL with water, and extracted with ethyl acetate (3 × 10 mL). The organic extracts were washed with $NaHCO_3$ (1 × 10 mL) and then dried over molecular sieves (4A) before being concentrated in vacuo. The resulting residue was purified by chromatography (9:1 hexane–ethyl acetate eluent) to give **2-hydroxy-3-cycloheptene-1-acetic acid lactone (15)** (0.280 g, 90%) as a colorless oil: ^{1}H NMR δ 5.70 (m, 1 H), 5.58 (m, 1 H), 5.33 (m, 1 H), 2.71 (m, 2 H), 2.20 (m, 3 H), 1.66 (m, 4 H); ^{13}C NMR δ 176.3, 129.7, 126.2, 81.4, 38.0, 36.2, 28.3, 27.5, 22.0.

Acknowledgment. We would like to thank Professor William S. Johnson for helpful suggestions, Professors R. A. Abramovitch and G. Majetich for useful discussions concerning microwave technology, and Dr. Dan Bearden for performing 2D NMR experiments on the product lactones.

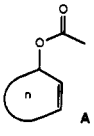
Supplementary Material Available: ^{1}H NMR spectra of 6–15 (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Yields for lactones 11–15 over three steps: 11 (75%), 12 (74%), 13 (61%), 14 (84%), and 15 (80%).

(12) Vandewalle, M. *J. Org. Chem.* **1979**, *44*, 4863.

(13) In the present study an inexpensive household microwave oven (Sanyo 500 W, approximate cost $80 from K mart) was used without any modifications.

(14) A major byproduct of the Johnson ortho ester rearrangement of cyclic allylic alcohols with TEOA is the simple acetate **A**, derived from hydrolysis (on workup) of the intermediate ortho ester. In order to minimize its formation, consumption of all of the intermediate ortho ester can be encouraged by sequential addition of more acid catalyst at intervals.[9]



A