Tetrahedron Vol. 49, No. 2, pp. 369-380, 1993
Printed in Great Britain

0040-4020/93 $5.00+.00

The Claisen Rearrangement in Synthesis: Acceleration of the Johnson Orthoester Protocol *en route* to Bicyclic Lactones [1]

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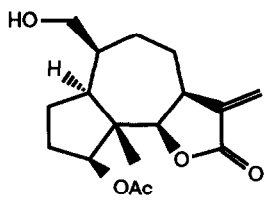
(*Received in USA* 5 *October* 1992)

Abstract: Catalysis of the Claisen orthoester rearrangement of triethyl orthoacetate and a number of 2-cycloalken-1-ols has been achieved using acidic catalysis and brief microwave thermolysis in DMF. Unlike conventional methods of thermolysis, very high yields of rearranged products are typically obtained in less than ten minutes, and the Claisen products themselves require no further purification. The synthetic utility of the products so obtained is demonstrated in a general synthesis of functionalized bicyclic lactones.

Bicyclic lactones are abundant in a wide variety of biologically active natural product systems. As part of an ongoing program concerned with new methods for the synthesis of natural products, we became interested in the guainolide family of which hysterin **1** ambrosin **2** and stramonin B **3** are representative examples. Analysis of



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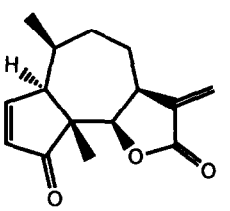

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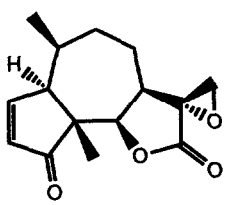

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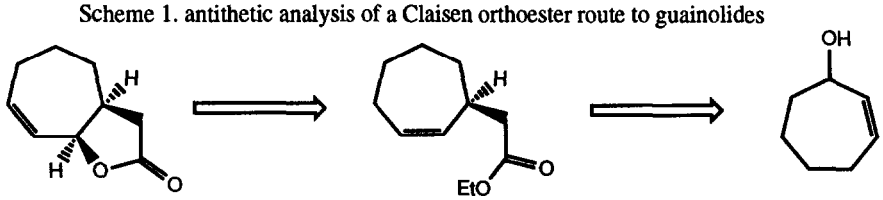
the fused cis bicyclic lactone core (Scheme 1) suggested that the Johnson orthoester rearrangement of a cycloheptenol **4** with triethyl orthoacetate [3] would furnish the desired intermediate cycloalkenyl ester **5**, which could be processed by means of a selenolactonisation / oxidative elimination sequence on the derived acid to furnish the cis 7,5 model system **6**.

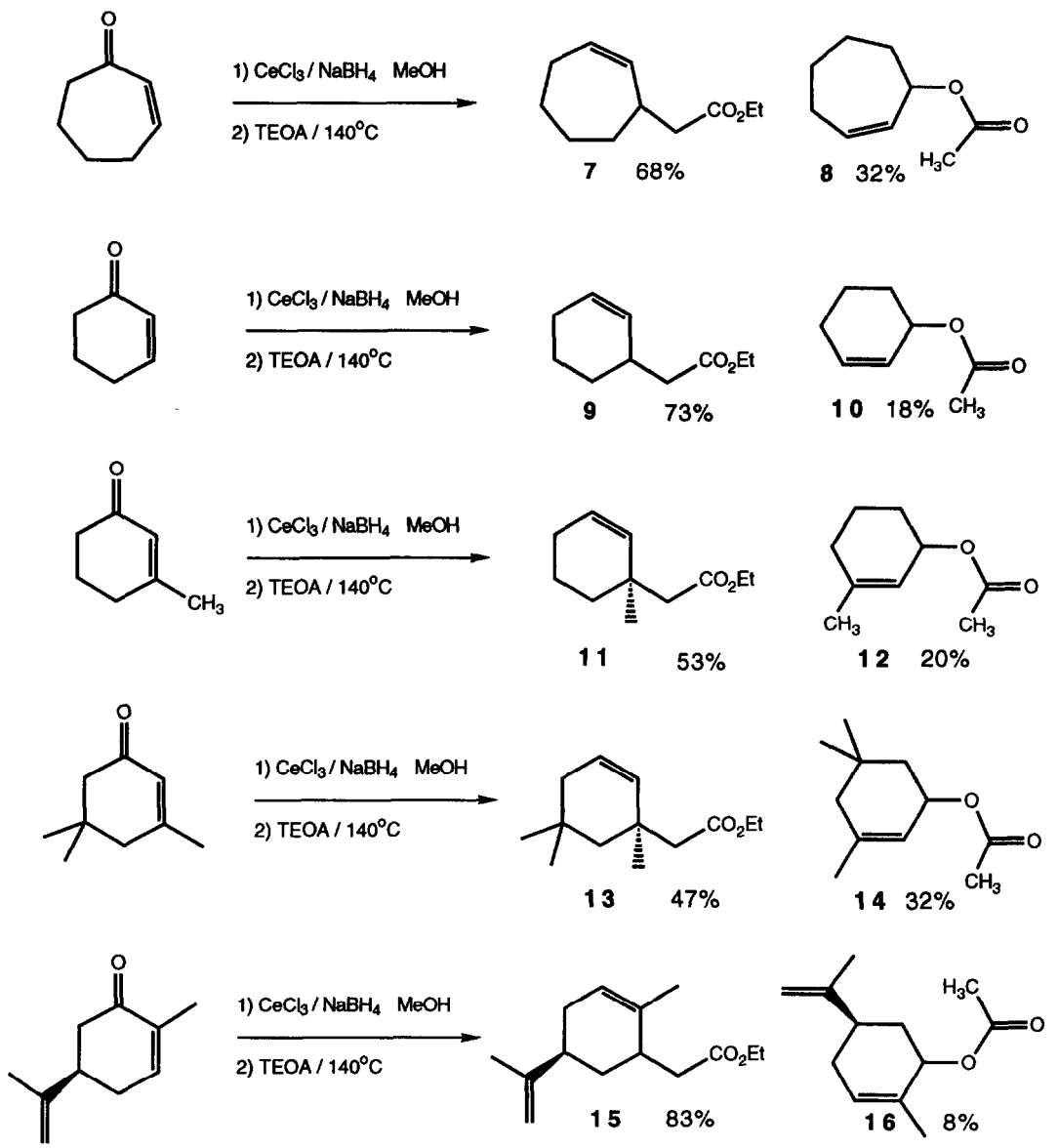
Scheme 1. antithetic analysis of a Claisen orthoester route to guainolides



6 **5** **4**

In order to investigate the scope and efficiency of such a Claisen based strategy, a number of cycloalkenols including **4** were prepared using the method of Luche (Scheme 2).[4] The resulting alcohols were then subjected

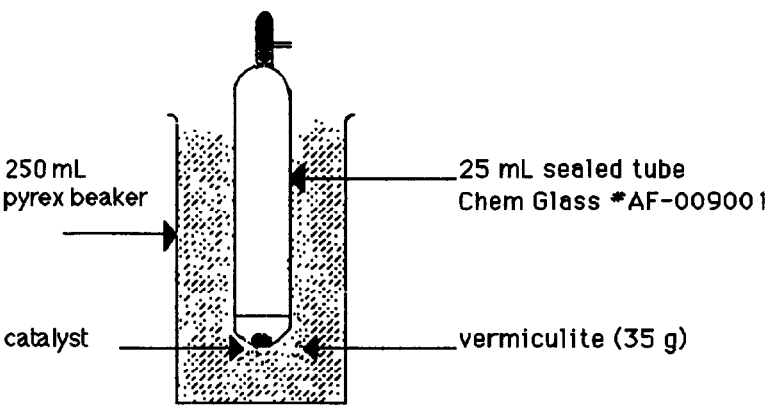
Scheme 2 conversion of cycloalkenones to alkenyl esters *via* Luche reduction followed by Claisen rearrangement



to the Johnson orthoester rearrangement conditions, using triethyl orthoacetate (TEOA). Thermolyses were carried out in the absence of a solvent, heating the alcohol with TEOA (7 equivs.) and propionic acid (0.1

equivs.) at 140°C with distillative removal of ethanol. In order to effect efficient catalysis, it was necessary to add additional propionic acid during the course of the reaction, to counteract distillative losses.[5] Typically, the rearrangements occurred in 3-12 h at 140°C, and the yields of product cycloalkenyl esters ranged from moderate to good, together with varying amounts of the derived acetates of the starting alcohols (Table 2).[6] The formation of the acetates was presumably a consequence of ineffective catalysis of the reaction, and arose *via* hydrolysis on work up of the *intermediate* orthoesters. The yields shown in Scheme 2 are optimised for mininal formation of the undesired acetate, best achieved by sequential addition of more acid catalyst every 1h. Unfortunately, chromatographic and distillative separation of the required esters from the undesired acetates proved problematic, severely hindering rapid evaluation of the proposed sequence. For this reason, coupled with the fact that the rearrangement reactions required constant monitoring over a 12h period, we decided to investigate an alternative means of thermolysis and reasoned that the use of microwave energy with a suitable solvent and catalyst would provide rapid heating in a minimal time frame.[7] It was decided to employ a commercially available Teflon screw cap type sealed tube vessel containing the reactants and surround this with vermiculite beads so that the beads (which absorb micowave energy at 2450 MHz) would be rapidly heated and transfer thermal energy to the solution *via* conduction (Fig. 1).[8]

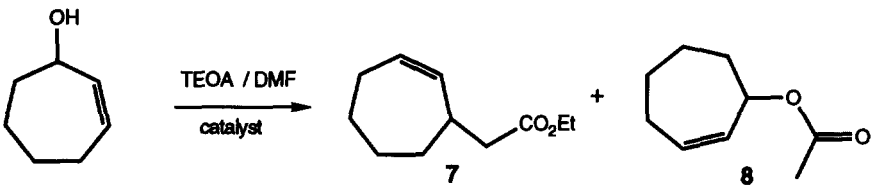
Figure 1. Apparatus used for microwave thermolyses (placed in center of oven)



The choice of both catalyst and solvent were likely to be important, and in order to investigate these variables, a control transformation (2-cyclohepten-1-ol -> **7** / **8**) was used with TEOA (7 equivs.) as a solution in DMF. Table 1 shows the results of the effect of differing catalysts, for a 9 min reaction conducted in an unmodified commercially available 450W oven. Montmorillonite KSF clay (entry 1) proved very effective for the conversion giving slightly better yields than the similar K10 clay (entry 2) with the noticeable absence of any of the unwanted acetate **8**.[9] Propionic acid catalysis (entry 3) resulted in a similar product composition ratio as obtained using the optimized conventional thermolysis conditions. Molecular sieves proved to be ineffective for catalysis, and in one experiment an explosion (**CAUTION!**) resulted destroying the sealed tube. Acidic alumina (entry 5) also proved to be an effective catalyst, but traces of the unwanted acetate remained even after prolonged thermolysis. On the basis of these observations KSF clay was chosen as the catalyst of choice and it was decided

to investigate its use further with a variety of solvents, and thermolysis parameters since work up simply involved filtration and hydrolysis of remaining TEOA.

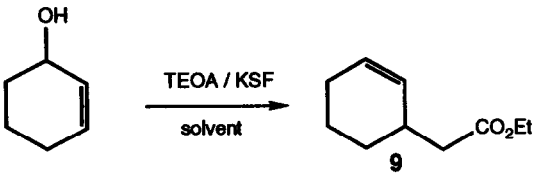
Table 1. Effect of Different Catalysts for the Microwave Thermolysis of 2-Cyclohepten-1-ol with TEOA in DMF



entry	catalyst	yield prod. **7**	yield acetate **8**
1	montmorillonite KSF	100%	0%
2	montmorillonite K10	95%	0%
3	propionic acid	76%	10%
4	4A molecular sieves	-	-
5	acidic alumina	72%	3%

The initial choice of DMF as the solvent proved fortuitous, as indicated in Table 2, which illustrates our results obtained for different solvents in the microwave accelerated Claisen rearrangement of 2-cyclohexen-1-ol with TEOA to give **9**. In order to absorb microwave energy effectively, the solvent must ideally posses an appreciable dielectric constant. However, aside from DMF, the only solvents that gave reasonable yields of products were those with relatively low ε values (entries 4, 5, 8 & 12). It is therefore reasonable to suppose that for the greater part, heating of the solvent occurs via conduction from the vermiculite, and one could speculate that solvent-surface interactions on the clay catalyst play a most important role.[10] In order to prove that traces of dimethylamine were not involved in the catalytic sequence, a reaction was performed using a DMF solution doped with a trace of dimethylamine / water solution (Table 2, entry 6). Detonation of the vessel was again observed, within a matter of seconds at 450W, inferring that using dry distilled DMF as a solvent, dimethylamine is neither present nor generated during the thermolysis. It was important for us to try and establish precisely what internal temperature was reached in the sealed tube during the microwave thermolysis. An experiment was run in a tube which was identical in all respects to a typical reaction (Table 1, entry 1) save for the inclusion of a number of sealed capillary tubes containing solids of known melting point. Thermolysis was carried out with close observation of the tubes, and at the termination of the reaction (9 mins, 450W) ***the internal temperature was judged to be close to 285°C***. Finally, the effects of the actual thermolysis time were examined using cycloalken-1-ol / TEOA combinations with KSF catalysis as test reactions (Table 3). Early experiments suggested that all 2-cyclohexen-1-ol was consumed within 9 mins using a 450W oven (entry 1). Reducing this time as expected lowered the conversion rate (entry 3). However using a 4+4 min thermolysis time with an intermediate cooling period of 5 min, a very high conversion was observed (entry 5), indicating product decomposition under prolonged thermolysis conditions was possible using this substrate.

Table 2. Solvent effects on the Microwave Thermolysis of 2-Cyclohexen-1-ol with TEOA using KSF Catalyst [a]



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entry	solvent	dielectric constant ε	yield product **9**
1	DMF	36.7	80 %
2	DMSO	49.0	<1 %
3	hexane	1.9	<1 %
4	THF	7.3	68 %
5	morpholine	7.3	44 %
6	DMF / (Me_2N)	(5.3)	-
7	DMF / (H_2O)	(78 5)	0 %
8	DME	3.49	65 %
9	CH_3CN	36 2	30 %
10	CH_2Cl_2	8.9	<1 %
11	PhCl	5.6	<1 %
12	EtOAc	6.0	46 %

[a]: thermolyses were carried out using 4+4 mins heating at 450W

Table 3. Effect of Time on Conversion to Product for Reaction of 2-Cycloalkenols with TEOA in DMF with KSF Catalysis for Different Power Output of Microwave Ovens

entry	oven power	cycloalkenol	thermolysis time	product , %
1	450W	2-cyclohexen-1-ol	9.0 min	**9**, 36%
2	600W	2-cyclohexen-1-ol	6.75 min	**9**, 38%
3	450 W	2-cyclohexen-1-ol	5.3 min	**9**, 19%
4	600W	2-cyclohexen-1-ol	4.0 min	**9**, 18%
5	450W	2-cyclohexen-1-ol	4+4 mins	**9**, 80%
6	450W	isophorol	10 min	polymers
7	450W	isophorol	3+3+3 min	**13**, 44%
8	450W	isophorol	2+2+2+2+2 min	**13**, 66%

We had also noticed on several occasions small amounts of brown polymeric deposits forming on the wall of the tube towards the end of some of the 9 min / 450W thermolysis runs (e.g. using isophorol, entry 6) but it was

discovered that if the sequence was interrupted (e.g. using 3 x 3 min bursts) with a 5 min cooling period between each, the amount of polymeric material formed could be reduced (entries 7&8). The conversion compatabilty of the thermolysis time using a different microwave oven was also investigated: using a 600W oven, a 9 min / 450W control thermolysis (entry 1) was complete as expected in 6.75 min (entry 2), and a 5.3 min / 450W reaction (entry 3) translated to 4.0 min / 600W (entry 4).With this intitial study completed, we decided to demonstrate the scope of the procedure, and effect Claisen rearrangement of all of the 2-cycloalken-1-ols detailed in Scheme 2. In all cases now, optimum thermolysis conditions could be found to give excellent conversion to the product esters, with no contamination of the acetates previously encountered using conventional thermolysis conditions. The optimized results are shown in Table 4. Some substrates were more sensitive to thermolysis conditions than others since product **7** could be formed quantitatively with a straight run comprising 10 min thermolysis at 450W (entry 1), but to form ester **13** in good yield, intermediate cooling was necessary (entry 4).

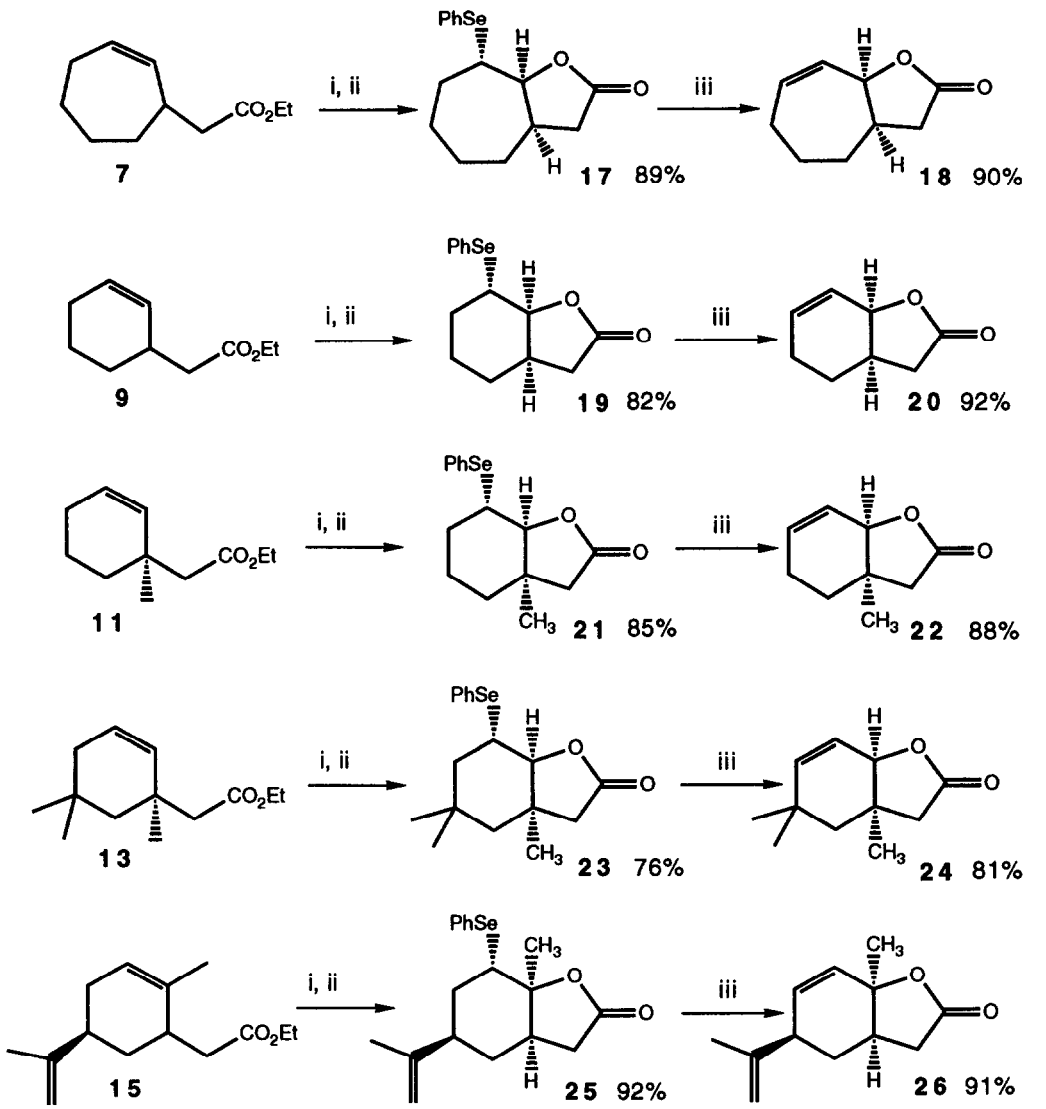
Table 4. Microwave Thermolysis of 2-Cycloalkenols with TEOA in DMF Using KSF Catalysis and Optimized Microwave Thermolysis Periods at 450W.

entry	thermolysis time	product ester (%)		byproduct acetate (%)	
1	10 min	**7**	(100%)	**8**	(0%)
2	4+4	**9**	(80%)	**10**	(0%)
3	10 min	**11**	(78%)	**12**	(0%)
4	2+2+2+2+2 min	**13**	(66%)	**14**	(0%)
5	4+4 min	**15**	(85%)	**16**	(0%)

With a high yielding, highly versatile and simply performed Claisen rearrangement route to the envisioned cycloalkenyl esters secured, we then turned our attention to our secondary goal - the synthesis of functionalized lactones. The esters were saponified using LiOH / THF (Scheme 3), to give the derived acids in nearly quantitative yield. The cycloalkenoic acids were then subjected to selenolactonization [11] to furnish the desired cis selenolactones in good yield in all cases examined. Oxidative elimination to give the bicyclic alkenyl lactones was then accomplished using H_2O_2, which proceeded without incident to secure a concise, high yielding route to functionalized lactones from 2-cycloalken-1-ols. In particular since lactone **18** can now be accessed in such high yield from 2-cyclohepten-1-one, this route offers an attractive entry to the guainolide model framework.

Summary:
The chemistry described herein represents a high yielding expeditious route to functionalized lactones starting from easily accesible cycloalkenols. The critical microwave accelerated Claisen rearrangement sequence proceeds smoothly and in high yield with a thermolysis time of less than 10 min, and would seem to be the method of choice for small scale reactions of this nature. Utilization of this procedure using enantiomerically pure cycloalkenols *en route* to the synthesis of complex chiral bi and tricyclic lactone containing natural products is a potential application and is the subject of an ongoing investigation in this laboratory.

Scheme 3. Formation of bicyclic unsaturated lactones from saponified products of the Claisen rearrangement via selenolactonization / oxidative elimination



Legend for Scheme 3: (i) LiOH / THF (ii) PhSeCl / Et_3N / CH_2Cl_2 (iii) H_2O_2 / THF

Acknowledgments

We thank the National Science Foundation (CHE-9100387) for partial support of this work and Professor William S. Johnson for useful suggestions.

EXPERIMENTAL PROCEDURES

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 NMR spectra were recorded at 75 MHz as solutions in $CDCl_3$. Montmorillonite KSF and K10 clay were used as received from Aldrich. The microwave thermolyses reported herein were conducted using either a Sanyo 450W or Panasonic 600W commercial oven, used without any modification. Solvents were purified using standard laboratory practise.

Claisen rearrangements using conventional thermolysis conditions:

(R)-(+)-Carveol ethyl ester (**15**). 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, then triethyl orthoacetate (10.0 mL, 54.55 mmol) was introduced followed by R-(+) carveol (1.00 g, 6.57 mmol)[4] and propionic acid (0.06 g, 0.81 mmol). The thermometer was lowered such that the mercury bulb was suspended immediately above the reaction medium, then the contents heated slowly using an oil bath to 140°C (internal temp.). Heating was continued until the theoretical yield of ethanol was recovered on distillation (0.5 mL) and all R-(+) carveol had been consumed (12.5 h by TLC). The mixture was cooled to 25°C and diluted with ethyl acetate (20 mL); hydrochloric acid (2N, 15 mL) was added and the mixture extracted into ethyl acetate, the organic extracts were washed with $NaHCO_3$ (sat. 15 mL) then dried ($MgSO_4$) and condensed in vacuo to give an 83:8 mixture of carveol ethyl ester (**15**) and the acetate (**16**) respectively, separated chromatographically (10:1, hexane : ethyl acetate eluent) to give **15** (1.22 g, 83%) and **16** (0.102 g, 8%) both as colorless oils.

(1S, 5R) 2-Methyl-5-isopropenyl-2-cyclohexen-1-acetic acid, ethyl ester (15). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 (m, 1H), 4.69 (s, 2H), 4.12 (q, J=7.1 Hz, 2H), 2.61 (dd, J=16.0, 4.7 Hz, 2H), 2.19-2.00 (m, 3H), 1.89 (m, 2H), 1.71 (s, 3H), 1.64 (s, 3H), 1.24 (t, J=7.1 Hz, 3H), 1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 149.7, 134.7, 123.5, 108.6, 60.2, 41.3, 38.9, 37.3, 35.0, 31.0, 20.9, 20.6, 14.2; FTIR (neat) 2919, 1733, 1644, 1167 cm^{-1}; MS (EI) *m/z* 222, 207 (loss of CH_3), 134, 119; $[\alpha]_D^{23}$ +39.0° (c=3.30, $CHCl_3$); Analysis calc'd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97; found: C, 75.74; H, 10.01.

(1R, 5S) Carvyl acetate (16). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (t, J=1.7 Hz, 1H), 5.44 (broad, 1H, C<u>H</u>-O), 4.71 (m, 2H), 2.29 (m, 1H), 2.22-2.15 (m, 1H), 2.10 (m, 1H), 2.07 (s, 3H), 1.97 (m, 1H), 1.71 (s, 3H), 1.63 (s, 3H), 1.54-1.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 148.3, 132.8, 125.9, 109.3, 73.2, 40.3, 34.0, 30.7, 21.1, 20.4, 18.8; $[\alpha]_D^{23}$ -56.2° (c=8.99, $CHCl_3$).

2-Cyclohexen-1-acetic acid, ethyl ester (9). Compound **9** was produced in 73% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (m, 1H), 5.49 (m, 1H), 4.12 (q, J=7.1 Hz, 2H), 2.54 (m, 1H), 2.22 (m, 2H), 1.96 (m, 2H), 1.82-1.57 (m, 4H), 1.24 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 130.1, 128.0, 60.1, 40.8, 32.2, 28.7, 24.9, 20.9, 14.2; FTIR (thin film) 2934, 1735, 1160 cm^{-1}; MS (EI) *m/z* 168.

1-Methyl-2-cyclohexen-1-acetic acid, ethyl ester (11). Compound **11** was produced in 53% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (m, 1H), 5.50 (d, J=10.1 Hz, 1H), 4.11 (q, J=7.1 Hz, 2H), 2.24 (s, 2H), 1.92 (m, 2H), 1.65 (m, 3H), 1.45 (m, 1H), 1.23 (t, J=7.1 Hz, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 135.0, 126.1, 59.9, 46.7, 35.1, 34.1, 27.3, 24.9, 19.0, 14.3; FTIR (neat) 2926, 1734, 1164 cm^{-1}; MS (EI) *m/z* 182, 95.

1,5,5-Trimethyl-2-cyclohexen-1-acetic acid, ethyl ester (13). Compound **13** was produced in 47% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (m, 1H), 5.49 (d, J=10.3 Hz, 1H), 4.11 (q, J=7.1 Hz, 2H), 2.27 (s, 2H), 1.76 (s, 2H), 1.64 (d, J=13.9 Hz, 1H), 1.34 (d, J=13.9 Hz, 1H), 1.25 (t, J=7.1 Hz, 3H), 1.12 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 133.7, 124.4, 59.8, 47.7, 47.4, 38.5, 34.8, 30.6, 29.8, 29.5, 28.3, 14.3; FTIR (neat) 2951, 1734, 1195 cm^{-1}; MS (EI) *m/z* 210, 123.

2-Cyclohepten-1-acetic acid, ethyl ester (7). Compound **7** was produced in 68% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.49 (dd, J=10.9, 3.9 Hz, 1H), 4.11 (q, J=7.1 Hz, 2H), 2.73 (m, 1H), 2.33 (m, 2H), 2.11 (m, 2H), 1.90 (m, 1H), 1.62 (m, 4H), 1.31 (m, 1H), 1.24 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 135.8, 131.9, 60.1, 41.4, 36.6, 33.3, 30.1, 28.6, 26.7, 14.2; FTIR (film) 2920, 1734, 1177 cm^{-1}; MS (EI) *m/z* 182, 95; Analysis calc'd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95; found: C, 72.23; H, 9.88.

Claisen rearrangements using microwave thermolysis conditions:

Typical procedure: **2-Cyclohepten-1-acetic acid ethyl ester (7).** Montmorillonite KSF clay (c.a. 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 (0.20 g, 1.78 mmol) was added under a stream of nitrogen, followed by triethyl orthoacetate (2.0 g, 12.5 mmol). The tube was purged with nitrogen then sealed, and packed in vermiculite. Following microwave irradiation (10 min , 450W commercial oven, 2450 MHz), 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, then concentrated to dryness to give essentially pure **2-cyclohepten-1-acetic acid ethyl ester (7)** (0.324 g, 100%) as a colorless oil spectroscopically identical to a sample obtained from conventional thermolysis, but free of any of ester (**8**).

2-Cyclohepten-1-acetic acid. The ester (**7**) (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 refluxed for 4h, then diluted with water (10 mL) and ether (10 mL) and acidified with HCl (1N, 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-cyclohepten-1-acetic acid** as a colorless oil (0.79 g, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (broad, 1H), 5.76 (m, 1H), 5.52 (dd, J=3.8, 10.9 Hz, 1H), 2.74 (m, 1H), 2.40 (m, 2H), 2.13 (m, 2H), 1.91 (m, 2H), 1.63 (m, 2H), 1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 135.5, 132.2, 41.2, 36.4, 33.3, 30.1, 28.6, 26.7; FTIR (neat) 3040, 2920, 2680, 1707, 1027 cm^{-1}; MS (EI) *m/z* 154, 94; Analysis calc'd for $C_9H_{14}O_2$: C, 70.10; H, 9.15; found: C, 70.03; H, 9.22.

2-Cyclohexen-1-acetic acid was produced from ester **9** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (broad, 1H), 5.74 (m, 1H), 5.57 (m, 1H), 2.60 (m, 1H), 2.35 (m, 2H), 1.99 (m, 2H), 1.86 (m, 1H), 1.70-1.52 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 129.7, 128.3, 40.4, 31.9, 28.7, 24.9, 20.8; FTIR (thin film) 3068, 2928, 2670, 1732, 1161 cm^{-1}; MS (EI) *m/z* 140, 122 (-H_2O), 81, 80.

1-Methyl-2-cyclohexen-1-acetic acid was produced from ester **11** in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (broad, 1H), 5.64 (m, 1H), 5.53 (d, J=10.1 Hz, 1H), 2.31 (s, 2H), 1.94 (m, 2H), 1.66 (m, 3H), 1.50 (m, 1H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 134.7, 126.4, 46.4, 35.1, 34.0, 27.2, 24.9, 18.9; FTIR (neat) 3065 (broad), 2930, 1705 cm^{-1}; MS (EI) *m/z* 154, 136 (loss of H_2O), 94.

1,5,5-Trimethyl-2-cyclohexen-1-acetic acid was produced from ester **13** in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.22 (broad, 1H), 5.61 (m, 1H), 5.51 (d, J=10.1 Hz, 1H), 2.32 (s, 2H), 1.76 (s, 2H), 1.64 (d, J=13.9 Hz, 1H), 1.38 (d, J=13.9 Hz, 1H), 1.16 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 133.5, 124.7, 47.7, 47.5, 38.5, 34.7, 30.5, 29.8, 29.7, 28.2; FTIR (neat) 3067, 2952, 2674, 1705, 942 cm^{-1}; MS (EI) *m/z* 182, 123, 122.

2-Methyl-5-isopropenyl-2-cyclohexen-1-acetic acid was produced from ester **15** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (broad, 1H), 5.50 (m, 1H), 4.71 (s, 2H), 2.72 (dd, J=14.7, 4.6 Hz, 1H), 2.63 (m, 1H), 2.15 (dd, J=14.7, 8.9 Hz, 1H), 2.14 (m, 1H), 2.04-1.90 (m, 3H), 1.72 (s, 3H), 1.67 (s, 3H), 1.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 149.6, 134.3, 123.9, 108.8, 41.3, 38.6, 37.1, 35.0, 31.1, 21.0, 20.6; FTIR (KBr) 3085, 2914, 1715, 1648, 1190 cm^{-1}; MS (EI) *m/z* 194, 134; $[\alpha]_D^{23}$ +36.6° (c=1.87, $CHCl_3$).

2-Hydroxy-3-phenylselenenylcycloheptane-1-acetic acid lactone (17). 2-Cyclohepten-1-acetic 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 stirred at 25°C for 30 min, 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 3h, then warmed to 25°C, filtered through a plug of silica gel, then concentrated in vacuo to give a pale yellow oil which was purified by silica gel chromatography ($CHCl_3$ eluent) to give **(17)** (0.665 g, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.30 (m, 3H), 4.64 (dd, J=9.0, 6.6 Hz, 1H), 3.44 (m, 1H), 2.88 (dd, J=17.6, 9.2 Hz, 1H), 2.64 (m, 1H), 2.26 (dd, J=17.6, 2.4 Hz, 1H), 2.17 (m, 1H), 1.76 (m, 2H), 1.64 (m, 3H), 1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 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; FTIR (KBr) 2926, 1776, 732 cm^{-1}; MS (EI) *m/z* 310, 308, 153 (loss of SePh).

2-Hydroxy-3-phenylselenenylcyclohexane-1-acetic acid lactone (19). 2-Cyclohexen-1-acetic acid gave selenide **19** in 82% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.31 (m, 3H), 4.48 (t, J=4.2 Hz, 1H), 3.69 (q, J=4.2 Hz, 1H), 2.75 (m, 1H), 2.58 (dd, J=16.8, 6.8 Hz, 1H), 2.27 (dd, J=16.8, 3.0 Hz, 1H), 2.01 (m, 1H), 1.89 (m, 1H), 1.75 (m, 1H), 1.56 (m, 2H), 1.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6,

134.3, 129.3, 128.3, 128.0, 81.3, 41.7, 37.2, 32.7, 26.7, 20.1; FTIR (neat) 2936, 1781, 1245 cm^{-1}; MS (EI) *m/z* 296, 294, 139 (loss of SePh).

1-Methyl-2-hydroxy-3-phenylselenenylcyclohexan-1-acetic acid lactone (21). 1-Methyl-2-cyclohexen-1-acetic acid gave selenide **21** in 85% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.28 (m, 3H), 4.20 (d, J=5.5 Hz, 1H), 3.43 (m, 1H), 2.42 (d, J=16.8 Hz, 1H), 2.23 (d, J=16.8 Hz, 1H), 2.00 (m, 1H), 1.71-1.44 (m, 5H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 134.9, 129.2, 128.3, 128.1, 86.4, 42.9, 42.2, 39.2, 33.2, 28.4, 25.5, 19.5; FTIR (KBr) 2931, 2251 (w), 1781, 1146, 733 cm^{-1}; MS (EI) *m/z* 310, 308, 153 (loss of ·SePh).

2-Hydroxy-1,5,5-trimethyl-3-phenylselenenylcyclohexan-1-acetic acid lactone (23). 1,5,5-Trimethyl-2-cyclohexen-1-acetic acid gave selenide **23** in 76% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.32 (m, 3H), 4.06 (d, J=9.5 Hz, 1H), 3.21 (m, 1H), 2.77 (d, J=17.4 Hz, 1H), 2.15 (d, J=17.4 Hz, 1H), 1.82 (m, 1H), 1.61 (dd, J=14.8, 2.1 Hz, 1H), 1.43 (m, 1H), 1.25 (m, 1H), 1.17 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 135.9, 129.1, 128.2, 127.3, 88.6, 45.5, 45.3, 43.4, 41.3, 39.9, 33.1, 32.0, 30.1, 27.4; FTIR (KBr) 2958, 1778, 1021, 742 cm^{-1}; MS (EI) *m/z* 338, 336, 181 (loss of ·SePh).

2-Hydroxy-2-methyl-5-isopropenyl-3-phenylselenenylcyclohexan-1-acetic acid lactone (25). 2-Methyl-5-isopropenyl-2-cyclohexen-1-acetic acid gave selenide **25** in 92% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.30 (m, 3H), 4.69 (s, 1H), 4.61 (s, 1H), 3.79 (t, J=4.1 Hz, 1H), 2.89 (dd, J=17.3, 6.8 Hz, 1H), 2.44 (m, 2H), 2.23 (d, J=17.3 Hz, 1H), 1.90 (m, 3H), 1.63 (s, 3H), 1.55 (s, 3H), 1.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 147.9, 134.8, 129.3, 129.1, 128.1, 109.6, 87.2, 49.0, 38.7, 38.1, 37.9, 33.5, 32.5, 26.0, 20.9; FTIR (KBr) 2936, 1760, 1149 cm^{-1}; MS (EI) *m/z* 350, 348, 193 (loss of SePh), 133; $[\alpha]_D^{23}$ +54.2° (c=1.14, $CHCl_3$).

2-Hydroxy-3-cyclohepten-1-acetic acid lactone (18). The selenide **17** (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 12h, then diluted to 30 mL with water and extracted with ethyl acetate (3 x 10 mL). The organic extracts were washed with $NaHCO_3$ (1 x 10 mL) 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-cyclohepten-1-acetic acid lactone (**18**) (0.280 g, 90%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.59 (m, 1H), 5.33 (m, 1H), 2.76-2.66 (m, 2H), 2.32-2.10 (m, 3H), 1.78-1.52 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 129.7, 126.2, 81.4, 38.0, 36.1, 28.3, 27.5, 22.0; FTIR (film) 2931, 1775, 1173 cm^{-1}; MS (EI) *m/z* 152; Analysis calc'd for $C_9H_{12}O_2$: C, 71.03; H, 7.95; found: C, 70.87; H, 7.95.

2-Hydroxy-3-cyclohexen-1-acetic acid lactone (20). Selenide **19** gave lactone **20** in 92% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (m, 1H), 5.78 (m, 1H), 4.72 (t, J=4.0 Hz, 1H), 2.65 (dd, J=17.1, 8.1 Hz, 1H), 2.51 (m, 1H), 2.24 (dd, J=17.1, 3.7 Hz, 1H), 2.13-1.89 (m, 2H), 1.67 (m, 1H), 1.36 (m, 1H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 176.4, 133.9, 122.8, 75.2, 34.8, 33.2, 23.2, 22.4; FTIR (film) 2931, 1775, 1173 cm^{-1}; MS (EI) *m/z* 138, 110 (loss of CO).

1-Methyl-2-hydroxy-3-cyclohexen-1-acetic acid lactone (22). Selenide **21** gave lactone **22** in 88% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (m, 1H), 5.77 (m, 1H), 4.38 (d, J=3.7 Hz, 1H), 2.36 (q, J=17.1 Hz, 2H), 2.09 (m, 2H), 1.67-1.47 (m, 2H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 132.9, 122.8, 80.9, 41.9, 37.0, 29.3, 23.2, 21.6; FTIR (film) 2927, 1778, 1155 cm^{-1}; MS (EI) *m/z* 152, 137 (loss of $\cdot CH_3$).

2-Hydroxy-1,5,5-trimethyl-3-cyclohexen-1-acetic acid lactone (24). Selenide **23** gave lactone **24** in 81% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, J=10.1 Hz, 1H), 5.63 (dd, J=10.1, 4.0 Hz, 1H), 4.40 (d, J=4.0 Hz, 1H), 2.52 (d, J=17.0 Hz, 1H), 2.27 (d, J=17.0 Hz, 1H), 1.57 (d, J=14.4 Hz, 1H), 1.46 (d, J=14.4 Hz, 1H), 1.20 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 142.8, 119.0, 80.6, 43.9, 43.3, 37.4, 31.8, 31.4, 30.0, 25.9; FTIR (neat) 2956, 1782, 1001 cm^{-1}; MS (EI) *m/z* 180, 165 (loss of $\cdot CH_3$), 138.

2-Hydroxy-2-methyl-5-isopropenyl-3-cyclohexen-1-acetic acid lactone (26). Selenide **25** gave lactone **26** in 91% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (d, J=10.1 Hz, 1H), 5.80 (dd, J=10.1, 2.5 Hz, 1H), 4.76 (d, J=13.0 Hz, 2H), 2.96 (dd, J=17.6, 8.0 Hz, 1H), 2.71 (m, 1H), 2.30 (m, 1H), 2. 28 (d, J=17.6 Hz, 1H), 1.77 (m, 1H), 1.70 (s, 3H), 1.41 (s, 3H), 1.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 147.1, 135.1, 128.2, 111.2, 81.6, 41.9, 39.3, 36.2, 31.7, 26.5, 20.4; FTIR (KBr pellet) 2931, 1775, 1644, 1197 cm^{-1}; MS (EI) *m/z* 192, 177 (loss of CH_3), 132; $[\alpha]_D^{23}$ +40.3° (c=5.82, $CHCl_3$).

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