A Ring Expansion Procedure Based on the Tandem Dealkoxycarbonylation–Michael Addition Reaction

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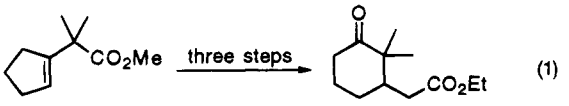
A three-step ring expansion procedure has been developed to convert methyl α,α-dialkyl-1-cyclopenteneacetates to highly functionalized cyclohexaneacetic esters. The procedure involves (1) ozonolytic double bond cleavage, (2) chemoselective Wittig olefination of the aldehyde carbonyl of the resulting keto aldehyde, and (3) tandem dealkoxycarbonylation–Michael addition to close the ring. The transformation proceeds best when the α-carbon of the starting acetate is quaternary, and thus, the method is unique in yielding hindered 2,2-dialkyl-3-oxocyclohexaneacetic esters. The reaction sequence is easily performed, and overall yields of 40–50% are readily achieved. The synthetic and mechanistic details of this process as well as optimization studies are presented. An analogous five-membered cyclization process was also investigated. Tandem dealkoxycarbonylation–Michael addition of 1-ethyl methyl (*E*)-7,7-dimethyl-6-oxo-2-octenedioate was found to afford a 24% isolated yield of ethyl 2,2-dimethyl-3-oxocyclopentaneacetate by a disfavored 5-[*enolendo*]-*exo-trig* process.

Introduction

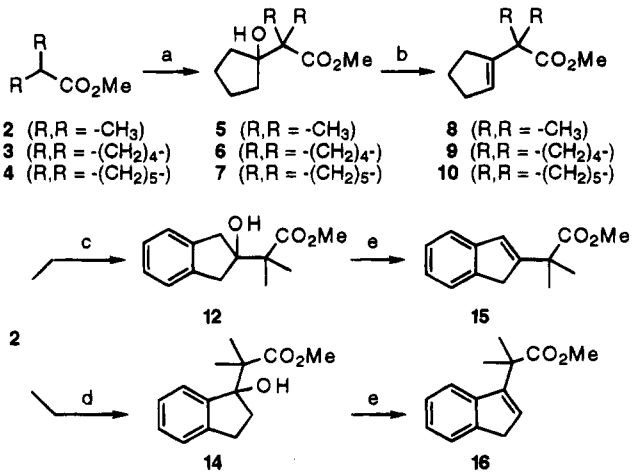
Ring expansion is an important and widely used transformation in organic synthesis.[1] One common strategy for ring enlargement is the one-atom carbon insertion, where a side chain carbon becomes part of the expanded ring. Among the most prevalent of these are the pinacol[2] and Tiffeneau–Demjanov[3] rearrangements which involve oxygen-assisted migration of a ring carbon to a side chain electron deficient center. A third method for inserting side chain carbons into a ring employs cyclic ketones doubly substituted at C-2 by an electron-withdrawing group and a side chain incorporating an anion or radical precursor. Attack on the carbonyl by the side chain reactive center followed by oxygen-assisted ring opening of the central bond in the resulting bicyclic structure affords products ring-expanded by 1–4 carbons.[4] As part of our studies on tandem reactions, we wish to report the use of a tandem dealkoxycarbonylation–Michael addition process in a novel anionic one-carbon ring expansion procedure for the synthesis of highly functionalized cyclohexaneacetic esters under neutral conditions (eq 1).



(1)

Previous work in this laboratory has demonstrated the utility of the tandem dealkoxycarbonylation–Michael addition reaction for the preparation of five- and six-membered carbocycles.[5] In this earlier report, methyl esters, activated toward decarboxylation by a C-2 electron-withdrawing group and tethered to an acrylate (Michael acceptor) moiety by a three- or four-carbon chain, were used as the cyclization substrates. The current work employs methyl esters activated by a carbonyl group in the chain linking the two reacting centers such that the dealkoxycarbonylation–Michael addition reaction produces a cyclic ketone. Since the easiest synthetic approach to these substrates starts with the readily available methyl α,α-dialkyl-1-cyclopenteneacetates, the procedure constitutes a novel and potentially valuable ring expansion protocol. This paper describes the application of this strategy to the preparation of monocyclic, spirocyclic, and hydroaromatic systems and evaluates stereoelectronic requirements in the ring closure step.

Scheme 1[a]



[a] Key: (a) LDA, THF, −78 °C, cyclopentanone (**1**); (b) $SOCl_2$, pyridine, 0 °C; (c) LDA, THF, −78 °C, 2-indanone (**11**); (d) LDA, THF, −78 °C, 1-indanone (**13**); (e) $POCl_3$, pyridine, 110 °C.

Synthesis of Cyclization Substrates. The synthesis of the ring expansion substrates is illustrated in Scheme 1. Addition of the anions derived from methyl isobutyrate, methyl cyclopentanecarboxylate, or methyl cyclohexanecarboxylate (LDA, −78 °C) to cyclopentanone[6] provided the hydroxy esters in 70–85% yield. Dehydra-

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1995.

(1) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: New York, 1991.

(2) See, for example: Gutsche, C. D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*; Academic Press: New York, 1968; pp 64–73.

(3) See, for example: Smith, P. A.; Baer, D. R. *Org. React.* **1960**, *11*, 157–188.

(4) See, for example: (a) Nakashita, Y.; Hesse, M. *Helv. Chim Acta* **1983**, *66*, 845–860. (b) Xie, Z.-F.; Suemune, H.; Sakai, K *J. Chem. Soc., Chem. Commun.* **1988**, 1638–1639. (c) Dowd, P.; Choi, S.-C. *Tetrahedron* **1989**, *45*, 77–90.

(5) Bunce, R. A.; Dowdy, E. D.; Jones, P. B; Holt, E. M. *J. Org. Chem.* **1993**, *58*, 7143–7148.

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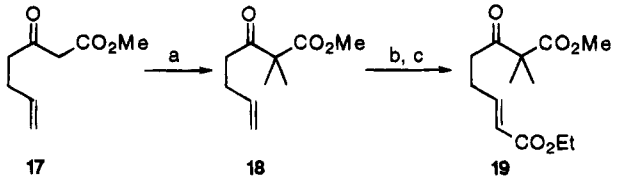
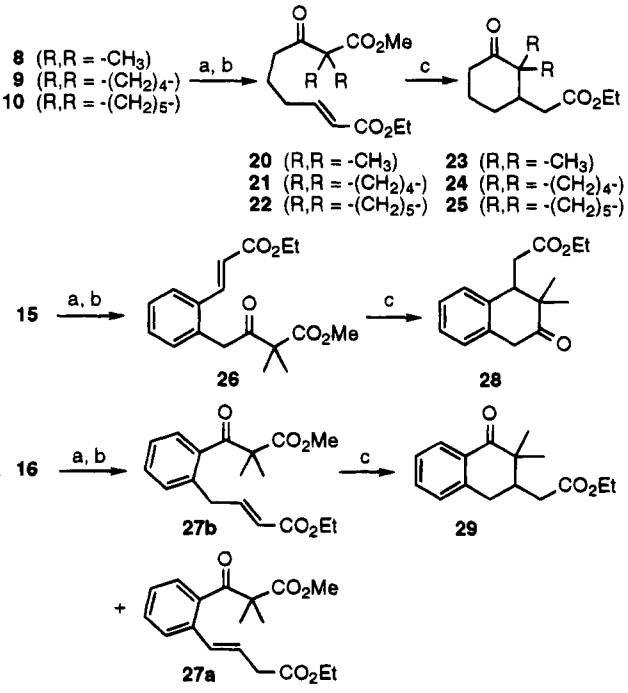
Scheme 2[a]



[a] Key: (a) NaH, DMF, CH_3I, 20–50 °C (2x); (b) O_3, CH_2Cl_2, −78 °C, Me_2S, −78° → 0 °C; (c) $Ph_3P{=}CHCO_2Et$, PhH, 80 °C.

Scheme 3[a]



[a] Key: (a) O_3, CH_2Cl_2, −78 °C, Me_2S, −78 → 0 °C; (b) $Ph_3P{=}CHCO_2Et$, PhH, 80 °C; (c) LiCl, HMPA, 120 °C.

tion using thionyl chloride in pyridine[6] then afforded 70–90% of the 1-cyclopenteneacetic ester derivatives. A similar approach was used to generate the α,α-dimethyl-1*H*-indeneacetic esters except that the final dehydration was carried out using phosphorus oxychloride in pyridine.[7] Overall yields for the aromatic substrates were 45–65%.

The synthesis of a five-membered ring precursor for evaluation of ring size effects is outlined in Scheme 2. Stepwise dimethylation (NaH, DMF, CH_3I)[8] of the known methyl 3-oxo-6-heptenoate (**17**)[9] afforded the *gem* dimethyl keto ester **18** in 87% yield. Ozonolysis followed by reductive workup and Wittig olefination[5] then gave 58% of 1-ethyl methyl (*E*)-7,7-dimethyl-6-oxo-2-octenedioate (**19**).

Results and Discussion

The results of our ring expansion study are given in Scheme 3 and Table 1. The three-step sequence involves

Table 1. Ring Expansion of a,a-Dimethyl-1-cyclopenteneacetates

susbtrate	ozonolysis-Wittig (yield, %)[a]	cyclohexaneacetate (yield, %)[a]
8 (R, R = $-CH_3$)	**20** (58)	**23** (74)
9 (R, R = $-(CH_2)_4-$)	**21** (75)	**24** (63)
8 (R, R = $-(CH_2)_5-$)	**22** (60)	**25** (60)
15	**26** (78)	**28** (63)
16	**27b** (19)[b]	**29** (46)[c]

[a] Yields refer to isolated purified products. [b] Product accompanied by 52% of **27a**. [c] Product accompanied by 22% of **27a**.

(1) ozonolytic cleavage of the double bond in the α,α-dialkyl-1-cyclopenteneacetic ester, (2) chemoselective Wittig olefination of the aldehyde carbonyl in the resulting keto aldehyde, and (3) tandem dealkoxycarbonylation–Michael addition to close the ring.[5] The optimized reaction conditions for cyclization (step 3) involve heating the keto diester with 4 equiv of LiCl in dry HMPA at 120 °C (±5 °C) for 4 h. Other solvents, such as DMF,[5] DMSO,[5] 1-methyl-2-pyrrolidinone,[5] and 1,3-dimethylindolizidinone,[10] were explored as substitutes for HMPA, but the results proved less satisfactory. Optimum yields of cyclized products were achieved using reaction scales of 1–5 mmol and substrate concentrations of ≤0.1 M.

Typical yields for the three-step sequence were generally in the 40–50% range. The method allows for rapid synthesis of cyclohexaneacetic esters bearing a substitution pattern that would be difficult to achieve using conventional synthetic methodology. Additionally, when the C-8 *gem* dialkyl substitution in the starting substrate is a ring, the procedure permits the synthesis of highly functionalized spiranes. The method can also be used to prepare fused hydroaromatic systems, but this approach is limited when double bond migration is possible. Thus, while cinnamic ester **26** was prepared and cyclized in good yield, synthesis and reaction of **27b** resulted in the isolation of a significant quantity of **27a** (20–55%, GC) resulting from migration of the acrylate double bond into conjugation with the aromatic ring.

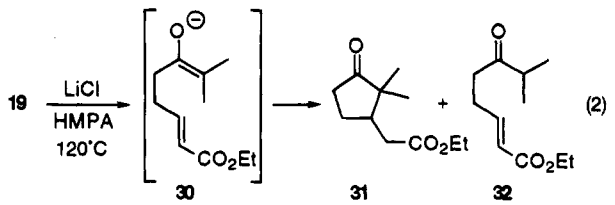
The cyclized product structures were confirmed by spectroscopic methods. IR indicated the loss of the acrylate double bond. ^1H NMR showed diastereotopic geminal methyls and a complex pattern for the acetate side chain; it also confirmed the absence of the acrylate moiety and the methyl ester. ^{13}C NMR exhibited the correct number of carbons and corroborated the IR and ^1H NMR structural assignments. Finally, HRMS established the exact molecular weights to within ± 2 ppm of those expected, and satisfactory elemental analyses were obtained for each final product.

The mechanism involves selective attack by chloride ion at the methyl ester in an S_N2-type reaction. This step produces gaseous methyl chloride, along with an α-keto carboxylate anion. At 120 °C, this intermediate undergoes spontaneous loss of carbon dioxide to afford a ketone-stabilized anion which adds in Michael fashion to the pendant acrylate ester. In all cases, the cyclizations were carried out on substrates which react via tertiary carbanions which tend to cyclize in higher yield with fewer side products.[5,11] The method works best for the preparation of six-membered rings; one attempt at a five-membered ring closure proceeded in low yield.

Further consideration of the transition states for cyclization shows that the 2,2-dialkyl-3-oxocyclohexane-

(6) Engel, P. S.; Schexnayder, M. A. *J. Am. Chem. Soc.* **1975**, *97*, 145–153.
(7) (a) Allen, W. S.; Bernstein, S. *J. Am. Chem. Soc.* **1955**, *77*, 1028–1032. (b) Rinehart, K. L., Jr.; Perkins, E. G. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 444–450. (c) Bunce, R. A.; Childress, R. S. *Org. Prep. Proc. Int.* **1995**, *27*, 122–125.
(8) Inomata, K.; Aoyama, S.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 930–932.
(9) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087.
(10) Barker, B. J.; Rosenfarb, J.; Caruso, J. A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 503–507.

acetic esters form by a favorable 6-[*enolendo*]-*exo-trig* closure while five-membered rings must close by a disfavored 5-[*enolendo*]-*exo-trig* process.[12] The difficulty in 5-[*enolendo*]-*exo-trig* closures (i.e., via **30**) derives from stereoelectronic effects where the planarity of the enolate restricts the reacting centers from obtaining the optimum geometry for cyclization.[12] In the current reaction, this process is further impeded by steric hindrance and the reversibility of the Michael reaction.[13] Previous work by others has demonstrated that 5-[*enolendo*]-*exo-trig* cyclizations proceed only in systems where reversibility is precluded by elimination of a leaving group following cyclization.[14,15] Additionally, by analogy with 5-[*enolendo*]-*exo-tet* alkylations,[16] several cases of cyclization by Michael addition of the enolate oxygen[17] have been reported. In the current study, we have found that five-membered ring closure by dealkoxycarbonylation–Michael addition of 1-ethyl methyl 7,7-dimethyl-6-oxo-2-octenedioate (**19**) proceeds to give **31** in 24% yield indicating that cyclization is not totally disfavored in reversible systems. The balance of the product proved to be ethyl (*E*)-7-methyl-6-oxo-2-octenoate (**32**), the uncyclized dealkoxycarbonylation product (eq 2).



In summary, we have developed and optimized a ring expansion strategy using a tandem dealkoxycarbonylation–Michael addition reaction. The three-step method is simple to perform and furnishes the final products in good overall yield. The procedure is novel in providing hindered 2,2-dialkyl-3-oxocyclohexaneacetic esters which would be difficult to obtain by conventional means. It has also been demonstrated that the disfavored 5-[*enolendo*]-*exo-trig* cyclization reaction proceeds for the preparation of five-membered rings though yields are not synthetically useful. Efforts are continuing to extend this technology to the preparation of heterocyclic ring structures.

Experimental Section

Solvents were purified in the following manner: DMF and HMPA were stored under nitrogen over 4-Å molecular sieves, THF was distilled from $LiAlH_4$, and diisopropylamine was distilled from CaH_2. Other reagents were used as received. All reactions were run under dry N_2. Unless otherwise indicated, the saturated NH_4Cl, saturated $NaHCO_3$, 5% $Na_2S_2O_3$, saturated NaCl, and 0.5–1.0 M HCl used in workup procedures refer to aqueous solutions. Reactions were monitored by one of the following methods: (1) TLC on hard-layer silica gel GF plates (Analtech) visualized using UV light, phosphomolybdic acid, or I_2 vapor or (2) capillary GC with FI detection (SE-30 column, 6-m × 0.25-mm i.d., 0.25-μm film thickness) programmed between 50 and 300 °C. Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm × 20-cm silica gel GF plates[18] (Analtech), (2) flash chromatography[19] on silica gel (Grace, grade 62, 60–200 mesh) containing UV-active phosphor (Sylvania no. 2282), or (3) flash vacuum chromatography[20] on silica gel (60–200 mesh). Band elution, where appropriate, was monitored using a hand-held UV lamp. Melting points are uncorrected. IR spectra are referenced to polystyrene. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively, and are referenced to internal $(CH_3)_4Si$. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV. Elemental analyses are ± 0.3%.

Methyl α,α-dimethyl-1-cyclopenteneacetate (**8**) was prepared in 82% yield according to the procedure of Engel.[6] This same procedure was adapted for the preparation of methyl 1-(1-cyclopentenyl)cyclopentanecarboxylate (**9**), methyl 1-(1-cyclopentenyl)cyclohexanecarboxylate (**10**), methyl 2,3-dihydro-2-hydroxy-α,α-dimethyl-1*H*-indene-2-acetate (**12**), and methyl (±)-2,3-dihydro-1-hydroxy-α,α-dimethyl-1*H*-indene-1-acetate (**14**). The spectral data were as follows:

Methyl 1-(1-cyclopentenyl)cyclopentanecarboxylate (9): 7.53 g (38.8 mmol, 74%); IR (thin film) 1730, 1640 cm^{-1}; ^1H NMR δ 5.50 (quintet, 1 H, J = 2.1 Hz), 3.67 (s, 3 H), 2.33 (m, 2 H), 2.26 (m, 2 H), 2.22 (m, 2 H), 1.86 (quintet, 2 H, J = 7.5 Hz), 1.77 (m, 2 H), 1.63 (m, 4 H); ^{13}C NMR δ 176.5, 145.4, 124.6, 56.4, 52.0, 34.8, 32.8, 32.3, 24.0, 23.5; HRMS m/e for $C_{12}H_{18}O_2$ calcd 194.1307, found 194.1302.

Methyl 1-(1-cyclopentenyl)cyclohexanecarboxylate (10): 6.97 g (33.5 mmol, 70%); IR (thin film) 1731, 1630 cm^{-1}; ^1H NMR δ 5.51 (quintet, 1 H, J = 2.1 Hz), 3.67 (s, 3 H), 2.31 (m, 2 H), 2.26 (m, 2 H), 2.17 (d, 2 H, J = 13.3 Hz), 1.82 (quintet, 2 H, J = 7.4 Hz), 1.62–1.47 (complex, 5 H), 1.40–1.21 (complex, 3 H); ^{13}C NMR δ 175.5, 146.5, 125.1, 51.7, 49.4, 33.2, 32.4, 31.8, 25.7, 23.4, 23.1; HRMS m/e for $C_{13}H_{20}O_2$ calcd 208.1463, found 208.1458.

Methyl 2,3-dihydro-2-hydroxy-α,α-dimethyl-1*H*-indene-2-acetate (12): 9.22 g (39.4 mmol, 52%); IR (thin film) 3510, 1730, 1390, 1370, 741 cm^{-1}; ^1H NMR δ 7.20–7.14 (complex, 4 H), 3.74 (s, 3 H), 3.38 (s, 1 H), 3.27 (A of ABd, 1 H, J = 16.7 Hz), 2.92 (B of ABd, 1 H, J = 16.7 Hz), 1.32 (s, 6 H); ^{13}C NMR δ 178.4, 140.9, 126.5, 124.7, 85.2, 52.1, 48.9, 43.2, 22.0; HRMS m/e for $C_{14}H_{18}O_3$ calcd 234.1256, found 234.1252.

(11) The synthesis of substrates without a quaternary center α to the acetate is complicated by double bond migration out of the five-membered ring and into conjugation with the ester. Methyl (1-cyclopentenyl)acetate is available, however; see: Masamune, T.; Sato, S.; Abiko, A.; Ono, M.; Murai, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2895–2904. Conversion of this substrate to 1-ethyl methyl 7-oxo-2-nonenedioate and treatment with LiCl in HMPA yielded a complex mixture of products.

(12) (a) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939–2947. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: New York, 1992; p 50.

(13) (a) Bergman, E. D.; Ginsberg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179–555. (b) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227–407.

(14) For examples of 5-[*enolendo*]-*exo-trig* anion cyclizations involving eliminations, see; (a) Bennett, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878–880. (b) Beak, P.; Wilson, K. D. *J. Org. Chem.* **1987**, *52*, 218–225. (c) Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940–949. (d) Ager, D. J.; Mole, S. J. *Tetrahedron Lett.* **1988**, *29*, 4807–4810. (e) Beak, P.; Burg, D. A. *J. Org. Chem.* **1989**, *54*, 1647–1654. (f) Thebtaranoth, C.; Thebtaranoth, Y. *Tetrahedron* **1990**, *46*, 1385–1487. (g) Mathew, J. *J. Org. Chem.* **1991**, *56*, 713–716. (h) Brandänge, S.; Leijonmarck, H.; Novacic, Z. *J. Chem. Soc., Chem. Commun.* **1992**, 569–570. (i) Padwa, A.; Filipkowski, M. A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. *J. Org. Chem.* **1994**, *59*, 588–596.

(15) One possible 5-[*enolendo*]-*exo-trig* ring closure has been observed from a β-keto ester metal chelate; see: Stork, G.; Winkler, J. D.; Saccomano, N. A. *Tetrahedron Lett.* **1983**, *24*, 465–468. This cyclization can also be viewed as proceeding through a 5-[*enolexo*]-*exo-trig* transition state.

(16) (a) Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977**, 233–235. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 3rd ed.; Plenum Press: New York, 1990; pp 25–26.

(17) For examples of 5-[*enolendo*]-*exo-trig* O-addition, see: (a) Jones, R. C. F.; Jones, R. F. *Tetrahedron Lett.* **1990**, *31*, 3363–3366. (b) Lamothe, M.; Fuchs, P. L. *J. Am. Chem. Soc.* **1993**, *115*, 4483–4496.

(18) For non-UV active compounds, PTLC plates were visualized with I_2 vapor and the separated bands were cut from the plates and extracted with ether. The ether extract was washed with 5% $Na_2S_2O_3$ and NaCl, dried ($MgSO_4$), and concentrated.

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(20) Leopold, E. J. *J. Org. Chem.* **1982**, *47*, 4592–4594.

Methyl (±)-2,3-dihydro-1-hydroxy-α,α-dimethyl-1*H*-indene-1-acetate (14): 13.8 g (59.1 mmol, 78%); IR (thin film) 3480, 1725, 1705, 1390, 1370, 763 cm^{-1}; ^1H NMR δ 7.26–7.16 (complex, 4 H), 4.77 (s, 1 H), 3.77 (s, 3 H), 2.99 (m, 1 H), 2.82 (m, 1 H), 2.42 (m, 1 H), 2.17 (m, 1 H), 1.22 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR δ 179.4, 144.4, 144.0, 128.3, 126.4, 124.1, 86.9, 52.3, 50.2, 37.7, 30.7, 21.4, 20.8; HRMS *m/e* for $C_{14}H_{18}O_3$ calcd 234.1256, found 234.1257.

Representative Procedure for the Preparation of 1*H*-Indeneacetate Esters: Methyl α,α-Dimethyl-1*H*-indene-2-acetate (15).[7] To a stirred 0 °C solution of 8.5 g (36.3 mmol) of **12** in 75 mL of pyridine was added 11.1 g (6.8 mL, 72.6 mmol) of phosphorus oxychloride dropwise during 30 min. The mixture was heated to reflux for 2 h, cooled to rt, poured onto 250 g of crushed ice, and ether extracted (3 × 100 mL). The combined ether extracts were washed with 1 M HCl (3 × 150 mL), H_2O, $NaHCO_3$, and NaCl and then dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by chromatography on a 30 cm × 2 cm silica gel column eluted with increasing concentrations of ether in hexane. Concentration of the major band gave 6.48 g (30.0 mmol, 83%) of **15** as a clear yellow oil which crystallized to a yellow solid: mp 27–28 °C; IR (thin film) 1738, 1610, 1388, 1369, 752 cm^{-1}; ^1H NMR δ 7.39 (d, 1 H, *J* = 7.4 Hz), 7.31 (d, 1 H, *J* = 7.4 Hz), 7.25 (m, 1 H), 7.14 (m, 1 H), 6.68 (s, 1 H), 3.67 (s, 3 H), 3.41 (s, 2 H), 1.53 (s, 6 H); ^{13}C NMR δ 176.5, 152.3, 144.5, 143.1, 126.7, 126.3, 123.5, 120.7, 52.2, 44.7, 38.7, 25.7; HRMS *m/e* for $C_{14}H_{16}O_2$ calcd 216.1150, found 216.1145.

Methyl α,α-dimethyl-1*H*-indene-3-acetate (16): 5.58 g (25.8 mmol, 78%); mp. 35–36 °C; IR (thin film) 1740, 1608, 1385, 1365, 768 cm^{-1}; ^1H NMR δ 7.45 (d, 1 H, *J* = 6.9 Hz), 7.27–7.20 (complex, 2 H), 7.18 (t, 1 H, *J* = 7.2 Hz), 6.37 (quintet, 1 H, *J* = 2.1 Hz), 3.62 (s, 3 H), 3.35 (d, 2 H, *J* = 2.1 Hz), 1.59 (s, 6 H); ^{13}C NMR δ 177.2, 147.6, 144.8, 143.3, 127.6, 126.0, 124.4, 123.9, 120.2, 52.2, 43.3, 37.3, 25.3; HRMS *m/e* for $C_{14}H_{16}O_2$ calcd 216.1150, found 216.1152.

Methyl 2,2-Dimethyl-3-oxo-6-heptenoate (18). This compound was prepared by treating 7.67 g (49.2 mmol) of methyl 3-oxo-6-heptenoate[9] twice with 1 equiv of NaH and 1.1 equiv of MeI according to the procedure described previously.[5,8] The crude product was chromatographed on a silica gel column eluted with increasing concentrations of ether in hexane to give 7.52 g (40.9 mmol, 83%) of **18** as a light yellow oil: IR (thin film) 3085, 1752, 1725, 1648, 1395, 1375, 1000, 920 cm^{-1}; ^1H NMR δ 5.78 (ddt, 1 H, *J* = 17.0, 10.3, 6.7 Hz), 5.03 (d, 1 H, *J* = 17.0 Hz), 4.98 (d, 1 H, *J* = 10.3 Hz), 3.73 (s, 3 H), 2.55 (t, 2 H, *J* = 7.1 Hz), 2.32 (m, 2 H), 1.37 (s, 6 H); ^{13}C NMR δ 207.1, 174.1, 137.0, 115.3, 55.5, 52.4, 37.2, 27.8, 21.9; HRMS *m/e* for $C_{10}H_{16}O_3$ calcd 184.1099, found 184.1104.

Representative Ozonolysis–Wittig Procedure: 1-Ethyl Methyl (*E*)-8,8-Dimethyl-7-oxo-2-nonenedioate (20).[5] A 300-mL CH_2Cl_2 solution of 13.1 g (71 mmol) of **8** was cooled to −78 °C and treated with ozone until the solution turned light blue. The reaction was quenched at −78 °C with 8.83 g (10.4 mL, 142 mmol) of dimethyl sulfide, warmed to rt, stirred for 3 h, and concentrated in vacuo. To the resulting yellow oil was added 150 mL of benzene and 35.5 g (102 mmol) of ethyl (triphenylphosphoranylidene)acetate.[21] The solution was refluxed for 12 h and then cooled and concentrated to afford a tan semisolid mass. The residue was loaded onto a 10 cm × 10 cm plug of silica gel in a sintered glass frit, and 1 L of 15% ether in hexanes was poured through under aspirator vacuum.[20] Concentration of the filtrate afforded the crude diester as a light yellow oil. The crude product was flash chromatographed[19] on a silica gel column eluted with increasing concentrations of ether in hexane to give 11.2 g (41.5 mmol, 58%) of **20** as a light yellow oil: IR (thin film) 1750, 1730, 1718, 1660, 1390, 1372 cm^{-1}; ^1H NMR δ 6.91 (dt, 1 H, *J* = 15.6, 6.9 Hz), 5.81 (d, 1 H, *J* = 15.6 Hz), 4.18 (q, 2 H, *J* = 7.2 Hz), 3.72 (s, 3 H), 2.48 (t, 2 H, *J* = 7.2 Hz), 2.19 (m, 2 H), 1.77 (quintet, 2 H, *J* = 7.2 Hz), 1.37 (s, 6 H), 1.29 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 207.3, 174.1, 166.5, 148.0, 122.0, 60.2, 55.5, 52.5, 36.9, 31.2, 22.0 (3), 14.2; HRMS *m/e* for $C_{14}H_{22}O_5$ calcd 270.1467, found 270.1469.

Other compounds prepared using this procedure, though on different scales, are given below. The compounds were purified by silica gel column chromatography eluted with increasing concentrations of ether in hexanes.

Ethyl (*E*)-7-(1-(methoxycarbonyl)cyclopentyl)-7-oxo-2-heptenoate (21): 5.78 g (19.5 mmol, 75%); IR (thin film) 1744, 1723, 1668 cm^{-1}; ^1H NMR δ 6.90 (dt, 1 H, *J* = 15.6, 6.9 Hz), 5.82 (d, 1 H, *J* = 15.6 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.72 (s, 3 H), 2.45 (t, 2 H, *J* = 7.1 Hz), 2.19 (m, 2 H), 2.10 (m, 4 H), 1.77 (m, 2 H), 1.64 (m, 4 H), 1.29 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 205.5, 173.9, 166.5, 148.0, 121.9, 66.6, 60.2, 52.5, 37.7, 33.1, 31.2, 25.5, 22.2, 14.2; HRMS *m/e* for $C_{16}H_{24}O_5$ calcd 296.1624, found 296.1617.

Ethyl (*E*)-7-(1-(methoxycarbonyl)cyclohexyl)-7-oxo-2-heptenoate (22): 5.80 g (18.7 mmol, 60%); IR (thin film) 1740, 1729, 1710, 1668 cm^{-1}; ^1H NMR δ 6.90 (dt, 1 H, *J* = 15.6, 6.9 Hz), 5.81 (d, 1 H, *J* = 15.6 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.72 (s, 3 H), 2.47 (t, 2 H, *J* = 7.1 Hz), 2.19 (m, 2 H), 2.08 (m, 2 H), 1.74 (m, 4 H), 1.58–1.27 (complex, 6 H), 1.29 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 206.8, 172.8, 166.4, 147.9, 121.9, 61.1, 60.1, 52.2, 36.8, 31.1, 30.6, 25.1, 22.7, 21.8, 14.2; HRMS *m/e* for $C_{17}H_{26}O_5$ calcd 310.1780, found 310.1773.

Ethyl (*E*)-3-(2-(3-(methoxycarbonyl)-3-methyl-2-oxobutyl)phenyl) propenoate (26): 6.11 g (19.2 mmol, 78%); IR (thin film) 1750, 1720, 1639, 1391, 1371, 767 cm^{-1}; ^1H NMR δ 7.73 (d, 1 H, *J* = 15.7 Hz), 7.61 (m, 1 H), 7.33–7.27 (complex, 2 H), 7.10 (m, 1 H), 6.36 (d, 1 H, *J* = 15.7 Hz), 4.24 (q, 2 H, *J* = 7.1 Hz), 3.97 (s, 2 H), 3.80 (s, 3 H), 1.49 (s, 6 H), 1.33 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 204.5, 174.0, 166.7, 141.6, 134.2, 133.5, 131.2, 129.9, 127.7, 126.7, 120.2, 60.4, 55.6, 52.7, 42.2, 22.3, 14.3; HRMS *m/e* for $C_{18}H_{22}O_5$ calcd 318.1467, found 318.1461.

Methyl (*E*)-3-(2-(3-(ethoxycarbonyl)-1-propenyl)phenyl)-2,2-dimethyl-3-oxopropanoate (27a): 4.96 g (15.6 mmol, 52%); IR (thin film) 1740, 1698, 1387, 1369, 965 cm^{-1}; ^1H NMR δ 7.59 (d, 1 H, *J* = 7.8 Hz), 7.38 (m, 1 H), 7.25 (m, 2 H), 6.58 (d, 1 H, *J* = 15.8 Hz), 6.25 (dt, 1 H, *J* = 15.8, 7.1 Hz), 4.17 (q, 2 H, *J* = 7.1 Hz), 3.65 (s, 3 H), 3.24 (dd, 2 H, *J* = 7.1, 1.5 Hz), 1.49 (s, 6 H), 1.28 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 204.3, 174.2, 171.3, 137.1, 135.6, 130.9, 130.2, 127.0, 126.7, 125.4, 124.7, 60.8, 55.8, 52.4, 38.4, 23.5, 14.2; HRMS *m/e* for $C_{18}H_{22}O_5$ calcd 318.1467, found 318.1463.

Methyl (*E*)-3-(2-(3-(ethoxycarbonyl)-2-propenyl)phenyl)-2,2-dimethyl-3-oxopropanoate (27b): 1.82 g (5.72 mmol, 19%); IR (thin film) 1740, 1721, 1695, 1655, 1385, 1368 cm^{-1}; ^1H NMR δ 7.37 (m, 2 H), 7.25 (m, 2 H), 7.07 (dt, 1 H, *J* = 15.7, 6.7 Hz), 5.75 (d, 1 H, *J* = 15.7 Hz), 4.16 (q, 2 H, *J* = 7.1 Hz), 3.63 (m, 2 H), 3.61 (s, 3 H), 1.50 (s, 6 H), 1.26 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 203.1, 174.6, 166.4, 147.0, 137.4, 137.2, 131.5, 130.9, 126.3, 126.2, 122.5, 60.2, 55.3, 52.4, 36.1, 24.0, 14.2; HRMS *m/e* for $C_{18}H_{22}O_5$ calcd 318.1467, found 318.1466.

1-Ethyl methyl (*E*)-7,7-dimethyl-6-oxo-2-octenedioate (19): 4.82 g (18.8 mmol, 58%); IR (thin film) 1751, 1735, 1720, 1663, 1392, 1374 cm^{-1}; ^1H NMR δ 6.90 (dt, 1 H, *J* = 15.7, 6.8 Hz), 5.83 (d, 1 H, *J* = 15.7 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.73 (s, 3 H), 2.63 (t, 2 H, J = 6.8 Hz), 2.49 (m, 2 H), 1.38 (s, 6 H), 1.28 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 206.2, 173.8, 166.3, 146.8, 122.1, 60.1, 55.3, 52.4, 36.1, 26.1, 21.8, 14.3; HRMS *m/e* for $C_{13}H_{20}O_5$ calcd 256.1311, found 256.1309.

Representative Procedure for the Tandem Dealkoxycarbonylation–Michael Reaction: Ethyl (±)-2,2-Dimethyl-3-oxocyclohexaneacetate (23). The general procedure of Bunce and co-workers[5] was used. To a flame-dried three-necked round-bottomed flask, equipped with magnetic stirring, a reflux condenser, and a rubber septum, was added 170 mg (4 mmol) of dry LiCl and 270 mg (1 mmol) of **20**. HMPA (10 mL) was added via syringe, and the reaction mixture was stirred at rt to dissolve the LiCl. Once homogeneous, the reaction was heated for 4 h in an oil bath which had been preheated to 120 °C (± 5 °C). The reaction was cooled, added to 1.0 M HCl, and extracted with ether (2×). The combined organic layers were washed with 1.0 M HCl, H_2O, and NaCl, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by PTLC,[18] eluting with increasing concentrations

(21) (a) Maercker, A. *Org. React.* **1965**, *14*, 270–490. (b) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, pp 112–114.

of ether in hexanes, to afford 157 mg (0.74 mmol, 74%) of **23**: IR (thin film) 1745, 1720, 1390, 1375 cm^{-1}; ^1H NMR δ 4.14 (q, 2 H, J = 7.1 Hz), 2.47 (m, 2 H), 2.38 (m, 1 H), 2.16 (m, 2 H), 1.98 (m, 1 H), 1.84 (m, 1 H), 1.80–1.55 (complex, 2 H), 1.26 (t, 3 H, J = 7.1 Hz), 1.14 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR δ 215.0, 173.0, 60.5, 48.3, 44.1, 37.8, 35.7, 27.0, 22.9, 20.1, 15.3, 14.2; HRMS m/e for $C_{12}H_{20}O_3$ calcd 212.1412, found 212.1417.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 68.03; H, 9.40.

Other compounds prepared using this procedure, though on different scales, are given below. The compounds were purified by silica gel column chromatography or PTLC[18] eluted with increasing concentrations of ether in hexanes.

Ethyl (±)-10-oxospiro[4.5]decane-6-acetate (24): 150 mg (0.63 mmol, 63%); IR (thin film) 1738, 1705 cm^{-1}; ^1H NMR δ 4.13 (q, 2 H, J = 7.1 Hz), 2.51 (m, 1 H), 2.42–2.13 (complex, 5 H), 1.94 (m, 2 H), 1.80 (m, 1 H), 1.57 (m, 6 H), 1.37–1.23 (complex, 2 H), 1.25 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 213.8, 172.9, 60.6, 60.4, 44.1, 38.0, 35.3, 34.9, 31.8, 27.3, 25.5 (2), 23.3, 14.2; HRMS m/e for $C_{14}H_{22}O_3$ calcd 238.1569, found 238.1564.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.58; H, 9.24. Found: C, 70.55; H, 9.22.

Ethyl (±)-5-oxospiro[5.5]undecane-1-acetate (25): 151 mg (0.58 mmol, 60%); IR (thin film) 1740, 1710, 1380 cm^{-1}; ^1H NMR δ 4.12 (q, 2 H, J = 7.1 Hz), 2.48 (m, 2 H), 2.35 (m, 2 H), 2.06 (m, 4 H), 1.92 (m, 1 H), 1.84 (m, 1 H), 1.65–1.12 (complex, 9 H), 1.25 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 216.1, 173.2, 60.5, 52.6, 44.0, 38.0, 34.2, 33.6, 29.7, 26.0, 25.0, 24.4, 22.6, 22.3, 14.2; HRMS m/e for $C_{15}H_{24}O_3$ calcd 252.1725, found 252.1728.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.43; H, 9.52. Found: C, 71.37; H, 9.55.

Ethyl (±)-1,2,3,4-tetrahydro-2,2-dimethyl-3-oxo-1-naphthaleneacetate (28): 163 mg (0.63 mmol, 63%); IR (thin film) 1740, 1718, 1390, 1375, 760 cm^{-1}; ^1H NMR δ 7.23–7.10 (complex, 4 H), 4.04 (m, 2 H), 3.68 (A of ABd, 1 H, J = 21.0 Hz), 3.61 (B of ABd, 1 H, J = 21.0 Hz), 3.33 (m, 1 H), 2.68 (dd, 1 H, J = 15.1, 4.8 Hz), 2.26 (dd, 1 H, J = 15.1, 9.9 Hz), 1.16 (s, 3 H), 1.15 (t, 3 H, J = 7.1 Hz), 1.06 (s, 3 H); ^{13}C NMR δ 213.1, 172.1, 138.0, 132.4, 128.4, 128.1, 127.1, 126.8, 60.6, 48.1, 46.9, 42.2, 37.1, 25.5, 20.8, 14.1; HRMS m/e for $C_{16}H_{20}O_3$ calcd 260.1412, found 260.1406.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.85; H, 7.69. Found: C, 73.78; H, 7.66.

Ethyl (±)-1,2,3,4-tetrahydro-3,3-dimethyl-4-oxo-2-naphthaleneacetate (29): 120 mg (0.46 mmol, 46%); IR (thin film) 1735, 1680, 1600, 1382, 740 cm^{-1}; ^1H NMR δ 8.02 (dd, 1 H, J = 7.8, 1.2 Hz), 7.45 (t, 1 H, J = 7.5 Hz), 7.31 (t, 1 H, J = 7.1 Hz), 7.21 (d, 1 H, J = 7.2 Hz), 4.16 (q, 2 H, J = 7.1 Hz), 3.12 (dd, 1 H, J = 17.1, 4.3 Hz), 2.84 (dd, 1 H, J = 17.1, 8.7 Hz), 2.57 (m, 2 H), 2.23 (m, 1 H), 1.29 (s, 3 H), 1.27 (t, 3 H, J = 7.1 Hz), 1.10 (s, 3 H); ^{13}C NMR δ 201.9, 172.7, 141.2, 133.3, 130.8, 128.8, 127.9, 126.8, 60.6, 45.0, 40.5, 35.4, 31.3, 23.1, 19.4, 14.2; HRMS m/e for $C_{16}H_{20}O_3$ calcd 260.1412, found 260.1412.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.85; H, 7.69. Found: C, 73.69; H, 7.71.

Ethyl (±)-2,2-dimethyl-3-oxocyclopentaneacetate (31): 48 mg (0.24 mmol, 24%); IR (thin film) 1740, 1390, 1372 cm^{-1}; ^1H NMR δ 4.17 (q, 2 H, J = 7.1 Hz), 2.49–2.36 (complex, 2 H), 2.30–2.14 (complex, 4 H), 1.55 (m, 1 H), 1.28 (t, 3 H, J = 7.1 Hz), 1.05 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR δ 222.4, 172.6, 60.6, 47.5, 43.7, 36.1, 35.1, 25.1, 22.5, 18.1, 14.2; HRMS m/e for $C_{11}H_{18}O_3$ calcd 198.1256, found 198.1255.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.41; H, 9.21.

Ethyl (*E*)-7-methyl-6-oxo-2-octenoate (32): 103 mg (0.52 mmol, 52%); IR (thin film) 1730, 1710, 1660, 1390, 1372, 975 cm^{-1}; ^1H NMR δ 6.94 (dt, 1 H, J = 15.6, 6.8 Hz), 5.83 (d, 1 H, J = 15.6 Hz), 4.18 (q, 1 H, J = 7.1 Hz), 2.61 (m, 3 H), 2.47 (q, 2 H, J = 6.8 Hz), 1.28 (t, 3 H, J = 7.1 Hz), 1.11 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 212.7, 166.4, 147.4, 121.9, 60.2, 40.8, 38.1, 26.0, 18.1, 14.2; HRMS m/e for $C_{11}H_{18}O_3$ calcd 198.1256, found 198.1251.

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Supplementary Material Available: High-field ^1H NMR and ^{13}C NMR spectra for **8–10**, **12**, **14–16**, **18–29**, **31**, and **32** (44 pages). This material is contained in 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.

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