solution in CH_2Cl_2; 2.4 mmol), 1 h, −78 °C. The crude reaction product was purified by HPLC on silica and eluted with 1:3 hexane/EtOAc to yield acetal **107** in 63% yield: ^1H NMR ($CDCl_3$) δ 4.9 (t, J = 5.6 Hz, 1 H), 3.8 (bs, 2 H), 3.7 (m, 2 H), 3.5 (m, 2 H), 2.5 (ol m, 5 H), 1.15 (t, J = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 208.2, 99.6, 62.2, 57.5, 47.7, 46.0, 15.0; IR (neat) 3464, 1705, 1295, 1222, 1123 cm^{-1}; HRMS calcd $C_9H_{18}O_4$ 190.1205, found 190.1202.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and to the National Institutes of Health (GM38243). F.P. thanks the Toyota Corporation and Wayne State University for graduate fellowships. We thank Professor Robert Bach for helpful discussions.

Registry No. **15**, 763-32-6; **17a**, 109553-12-0; **17b**, 109553-16-4; **18a**, 135695-69-1; **18b**, 135695-70-4; **19a**, 135695-71-5; **19b**, 135695-72-6; **20a**, 109553-13-1; **20b**, 109553-17-5; **21**, 109553-14-2; **22a**, 109553-15-3; **22b**, 109553-18-6; **23**, 31080-83-8; **24a**, 135695-73-7; **24b**, 135720-62-6; **25**, 135695-76-0; **26a**, 135695-74-8; **26b**, 135695-75-9; **27a**, 135695-77-1; **27b**, 135695-78-2; **37**, 110589-84-9; **38**, 135695-79-3; **39**, 19788-92-2; **42**, 135695-80-6; **43**, 135695-81-7; **44**, 135695-82-8; **45**, 135695-83-9; **46**, 135695-84-0; **47**, 135695-85-1; **52**, 497-02-9; **53**, 23009-73-6; **54**, 135695-86-2; **55**, 1594-24-7; **56**, 135720-63-7; **58**, 135695-87-3; **60**, 2004-67-3; **61**, 135695-88-4; **62**, 1708-93-6; **63**, 135695-89-5; **64**, 627-27-0; **65**, 6559-36-0; **71**, 86341-37-9; **72**, 135695-90-8; **76**, 71885-98-8; **78**, 135695-91-9; **79**, 135759-64-7; **80**, 135759-65-8; **81**, 135759-66-9; **85**, 127841-27-4; **86**, 135695-92-0; **91**, 117201-93-1; **92**, 113195-06-5; **93**, 117201-94-2; **94a**, 127841-28-5; **94b**, 127841-29-6; **95**, 127841-24-1; **96a**, 127841-32-1; **96b**, 127841-30-9; **96c**, 127841-33-2; **96d**, 127841-31-0; **97**, 117202-11-6; **98a**, 127841-34-3; **98b**, 127841-35-4; **99**, 127841-26-3; **100a**, 127841-36-5; **100b**, 127841-37-6; **101**, 127841-25-2; **102**, 127841-38-7; **103**, 117201-96-4; **104**, 127841-39-8; **105**, 60068-17-9; **106**, 127841-40-1; **107**, 135695-93-1; **108**, 135695-94-2; $(MeO)_3CH$, 149-73-5; $(EtO)_3CH$, 122-51-0; (*i*-ArO)Me_2SiCH_2MgCl, 122588-50-5; $Ph_3PCH_3^+Br^-$, 1779-49-3.

Supplementary Material Available: Details on the stereochemical assignments of compounds **18a**, **22a**, **22b**, **56**, **42–47**, and **78–81** and ^1H and ^{13}C NMR spectra of all new compounds (56 pages). Ordering information is given on any current masthead page.

Regioselective Conversion of Cycloalkanones to Vinyl Bromides with 1,2-Functionality Transposition. A General Stratagem

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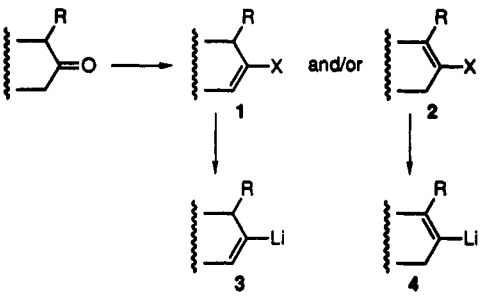
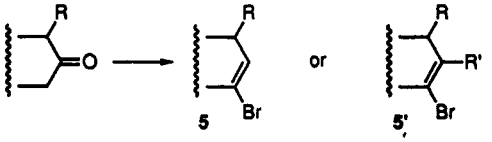
Cyclic β-keto esters, available by regioselective acylation of cycloalkanone enolates, are rapidly transformed to α,β-unsaturated acids. This functionality transposition allows the derived 3-hydroxy-4-methylthiazole-2-(3*H*)-thione derivatives to serve as precursors to synthetically useful vinyl bromides. The process involves heating the hydroxamate ester with AIBN in bromotrichloromethane solution. Alkylative and ring contractive variants of the methodology are highlighted. The short sequence makes available precursors to vinyl anions that are not otherwise conveniently accessible.

In recent years, cycloalkenyllithiums have been used with increasing frequency as nucleophiles to achieve carbon–carbon bond construction. The requirement that this class of reactive intermediates be routinely available has been met with the development of increasingly sophisticated methods of preparation. In those specific cases where electronic and strain effects are appropriate, direct deprotonation of a cyclic olefin precursor can be utilized satisfactorily. Cyclic enol ethers[2-4] and cyclopropenes[5] fall into this category. More commonly, reliance is placed upon umpolung of a cycloalkanone carbonyl group as shown in Scheme I. The classical method involving the reaction of a ketone with PCl_5 to produce vinyl chlorides[6] is ineffective.

Scheme I



Scheme II



(1) (a) Procter and Gamble Fellow, 1990–1991. (b) National Science Foundation Undergraduate Research Participant, Summer 1990. (c) Postdoctoral Fellow, Wigner-Stifung der Technischen Universität Berlin (1989–1990) and Deutsche Forschungsgemeinschaft (1990–1991).

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fective at controlling double-bond regiochemistry (viz., 1-Cl versus 2-Cl) in unsymmetrical cases. The more recently discovered halogenative deoxygenation of 1,3-benzodioxoles with BBr_3[7] suffers from the same regiochemical limitation, as does the oxidation of hydrazones with iodine[8] discovered by Barton,[9] the generation and reductive lithiation of enol phenyl thioethers,[10] and those procedures based on 1,2-addition of $Bu_3SnMgCl$ and subsequent elimination of the derived tosylate (K_2CO_3 treatment)[11] or acetate (via pyrolysis).[12]

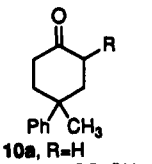
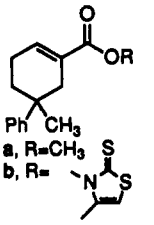
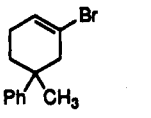
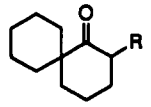
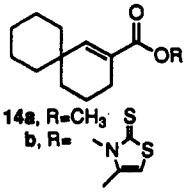
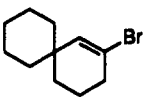
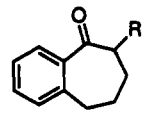
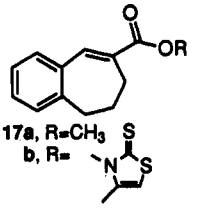
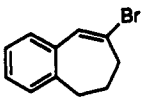
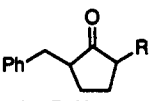
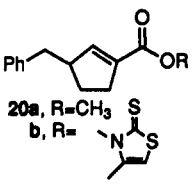
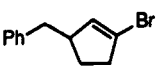
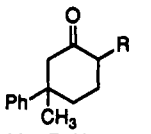
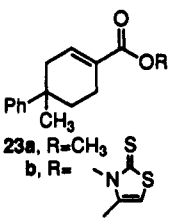
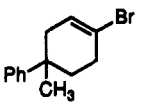
The less substituted isomers **3** can be prepared cleanly by means of the Shaprio reaction.[13] Quenching of **3** generated in this manner with cyanogen bromide[14] or preferably 1,2-dibromotetrafluoroethane[15] provides **1** (X = Br) that can be metalated subsequently[15,16] for a broader range of synthetic applications. Regiocontrolled access to either **3** or **4** is possible by Wulff's scheme,[17] which rests upon preparation of either the "kinetic" (1-OTf) or "thermodynamic" enol triflate (2-OTf), independent conversion of either to the vinylstannane,[18] and transmetalation with an alkyl- or aryllithium.[19]

The utility of cycloalkenyllithiums would be augmented by the availability of a mild, position-selective method for the conversion of cycloalkanones to vinyl bromides such as **5** and **5′** (Scheme II). This permutation positions the nucleophilic site α' to the original carbonyl group and provides an opportunity to develop nucleophilic reagents that have not previously been part of synthetic practice. This paper describes a practical solution to this synthetic transform.

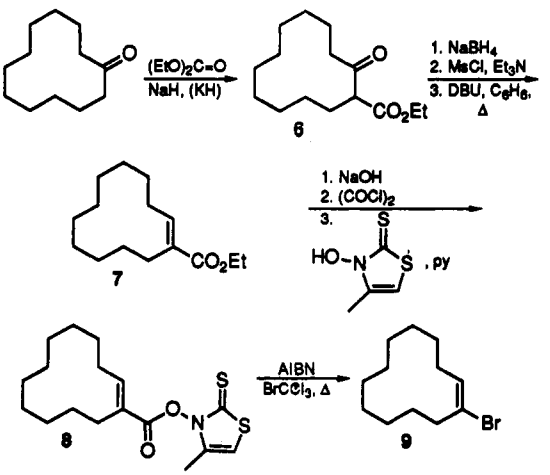
Results and Discussion

The 1,2-functionality transposition was contemplated to involve regioselective conversion to a β-keto ester, reductive elimination of the ketone carbonyl, and halodecarboxylation of the resultant α,β-unsaturated acid. For

Table I. Conversion of Cycloalkanones to 1,2-Transposed Vinylic Bromides

ketone/keto ester	α,β-unsaturated acyl derivatives	vinyl bromide
 **10a**, R=H; **b**, R=CO_2CH_3	 **11a**, R=CH_3; **b**, R=	 **12**
 **13a**, R=H; **b**, R=CO_2CH_3	 **14a**, R=CH_3; **b**, R=	 **15**
 **16a**, R=H; **b**, R=CO_2CH_3	 **17a**, R=CH_3; **b**, R=	 **18**
 **19a**, R=H; **b**, R=CO_2CH_3	 **20a**, R=CH_3; **b**, R=	 **21**
 **22a**, R=H; **b**, R=CO_2CH_3	 **23a**, R=CH_3; **b**, R=	 **24**

determination of the workability of this plan, cyclododecanone was first converted to **6** by the Deslongchamps variant,[20] subjected to sodium borohydride reduction, and transformed into **7** by β-elimination of the mesylate.[21]



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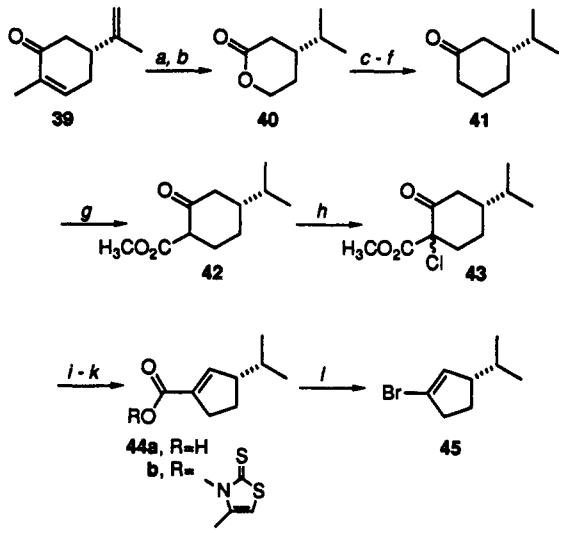
Scheme III[a]



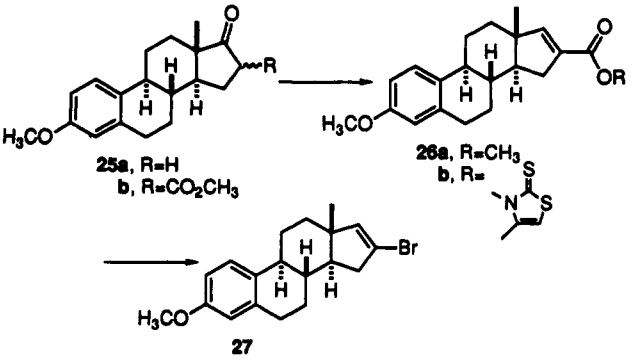
[a] (a) H_2, Pt; O_3, EtOAc; (b) $NaBH_4$, aqueous NaOH; H_3O^+; (c) HBr, C_2H_5OH; (d) $CH_2(COOC_2H_5)_2$, NaOEt, EtOH; (e) NaOEt, EtOH; toluene, Δ; (f) H_3O^+, Δ; (g) $(CH_3O)_2C{=}O$, NaH; (h) SO_2Cl_2, CH_2Cl_2; (i) Na_2CO_3, mesitylene, Δ; aqueous KOH; (j) $(COCl)_2$; (k) $H_3CC{=}CHSC(=S)NOH$, py, DMAP, ether; (l) AIBN, $BrCCl_3$, Δ.

After investigation of several bromodecarboxylation options, the most reliable and effective intermediate was found to be the thiohydroxamic ester 8.[22] Slow addition of 8 to a refluxing solution of AIBN in bromotrichloromethane produced 9 in 82% yield after 1 h. Since the need exists for separation of the vinyl bromide from excess $BrCCl_3$, a problem would be expected to arise with this procedure if the product boiling point is comparable to that of the solvent. Otherwise, the methodology works quite well as gauged by the examples given below.

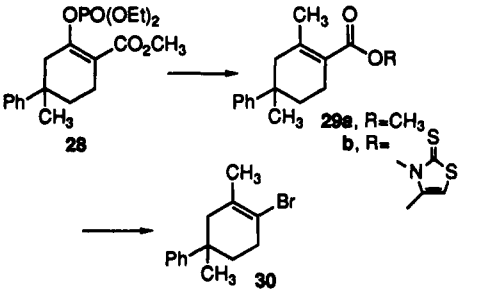
The symmetrically substituted cyclohexanone **10a**[23] (Table I) proved to be an exemplary system, ultimately giving rise to **12** in 96% isolated yield from **11b**. When the α site of the starting ketone is not enolizable as in **13a**[24] and **16a**,[25] regioselectivity during conversion to the β-keto esters is not an issue, **15** and **18** being formed without the possbility of isomeric contamination. Relevantly, excellent experimental control over the site of carbomethoxylation persists when the cycloalkanone is 2-substituted as in **19** or 3,3-disubstituted as in **22** (Table I). This utilitarian selectivity undoubtedly stems from the reversible nature of Claisen condensations when product enolization is not possible[26] and the sensitivity of these acylations to steric factors, respectively.

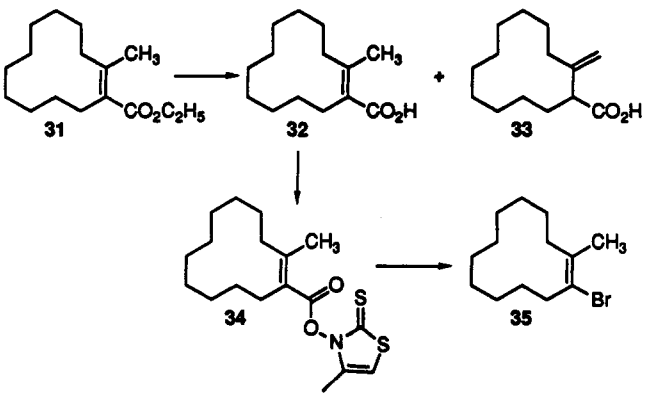
Since the overall process results in the introduction of a double bond, stereoselectivity is not of concern. As expected, stereochemical markers present in the starting ketone are preserved during the several stages of the sequence. For example, estrone methyl ether (**25a**)[27] lends itself well to conversion to **27**.

The alkylative option represented by generic formula **5′** has been examined in three representative cases. Enol



phosphate **28** is the sole product formed by reaction of **22b** with sodium hydride and diethyl phosphorochloridate.[28] Coupling of **28** to lithium dimethylcuprate[29] at low temperature produced **29a** in good yield. Once thiohydroxamic ester **29b** was in hand, free radical decomposition in the presence of $BrCCl_3$ resulted in smooth conversion to **30** (92%). Equal success was met in the conversion of **6** to methyl homologue **31**. However, the saponification of





this ester gave rise to a 3:1 mixture of the α,β- and β,γ-unsaturated carboxylic acids **32** and **33**. Purified samples of **32** could be obtained by recrystallization from petroleum ether. The subsequent conversion to **34** was accomplished in quantitative fashion, setting the stage for ultimate conversion to **35** (74%).

It did not prove possible to coax enol phosphate **36** into formation of the β-methyl-substituted ester by dialkylcuprate coupling. Reduction to give **37a** was encountered instead,[30] presumably caused by steric inaccessibility to the reaction center. This finding provided the opportunity to effect the overall conversion of *D*-camphor to optically pure bicyclic vinyl bromide **38**.

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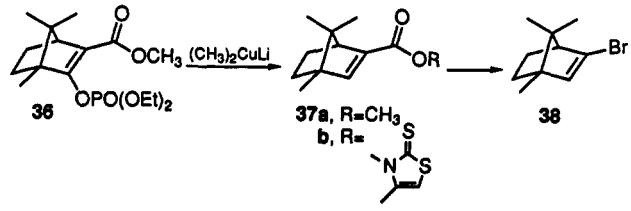

Finally, (*R*)-(−)-carvone (**39**) has served as a starting point for a ring concentration variant of this general type of transformation. The conversion of **39** to lactone **40**[31] was followed by reincorporation of a ring carbon atom to give (*R*)-(+)-3-(1-methylethyl)cyclohexanone (**41**) (Scheme III). Exposure of **41** to the usual carbomethoxylation conditions provided **42**, chlorination of which[32] furnished **43** exclusively. Favorskii ring contraction[33] of **43** was effected with sodium carbonate in hot mesitylene, yielding after saponification cyclopentenecarboxylic acid **44a**. This acid was converted via **44b** into the optically enriched (>96% ee) vinyl bromide **45**.

The methodology described above has established the feasibility of regiocontrolled vinyl bromide formation with 1,2-functionality transposition. The substitution patterns that contribute to regioselectivity are defined and steric limitations to the alkylative alternative have been clarified, at least for cyclic systems. Although acyclic analogues were not examined, equivalently good regiocontrol should be possible for open-chain compounds. Current efforts are focused on the application of this stratagem to a variety of synthetic problems. In this connection, the bromine substituent provides for uncomplicated halogen–metal exchange and ready access to the structurally related vinyl anions.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 or 20 MHz on $CDCl_3$ solutions unless noted. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The column chromatographic purifications were performed with Woelm silica gel (63–200 mesh). Solvents were reagent grade and in many cases dried prior to use. The organic extracts were dried over anhydrous $MgSO_4$. The purity of all compounds was shown to be ≥95% by TLC and high field ^{1}H NMR analyses.

Representative Procedure for Carbalkoxylation: Methyl 3-Benzyl-2-oxocyclopentanecarboxylate. A slurry of 50% NaH in oil was washed with pentane to leave 3.75 g (0.156 mol) of active reagent. (If KH is to be added, its introduction is most readily accomplished at the outset; on the present scale, 50 mg of KH is adequate.) The hydride was covered with anhydrous THF (30 mL), treated with dimethyl carbonate (11.26 g, 0.125 mol), and heated to reflux while being magnetically stirred under N_2. A solution of **19a**[34] (8.71 g, 0.05 mol) in THF (25 mL) was added dropwise, and the reaction mixture was refluxed for 8 h, cooled to 0 °C, and treated with 3 M acetic acid (50 mL) in advance of being poured into brine (100 mL). The product was extracted into $CHCl_3$ (4 × 125 mL), dried, filtered, and evaporated. Column chromatography (elution with 20% ether in petroleum ether) gave **19b** as a colorless oily mixture of keto and enol tautomers (11.2 g, 97%).

This procedure afforded the following β-keto esters in the indicated yields: **6** (68%, use of diethyl carbonate), **10b** (72%), **13b** (84%), **16b** (82%), **22b** (93%, for the preparation of **22a** see ref 35), and **25b** (95%, mp 146–152 °C).

Representative Procedure for Conversion to the α,β-Unsaturated Esters: Methyl 3-Benzylcyclopentene-1-carboxylate. Solid $NaBH_4$ (1.50 g, 39.5 mmol) was added to a cold (0 °C), magnetically stirred solution of **19b** (9.17 g, 39.5 mmol) in methanol (100 mL), and the reaction mixture was stirred for 4 h at 0–20 °C, treated with 5% HCl (30 mL), and extracted with ether (2 × 100 mL). The combined ethereal layers were washed with water (100 mL), dried, filtered, and evaporated. Column chromatography (elution with 10–50% ether in petroleum ether) gave 7.03 g (76%) of the β-hydroxy ester that was used directly.

A solution of the above product (3.68 g, 15.7 mmol) in dry CH_2Cl_2 (80 mL) was blanketed with nitrogen and treated dropwise with freshly distilled triethylamine (2.26 g, 22.3 mmol) and then methanesulfonyl chloride (1.90 g, 16.6 mmol). The reaction mixture was stirred overnight and washed with water (80 mL), saturated $NaHCO_3$ solution (80 mL), and brine (80 mL) prior to drying. Solvent evaporation gave 4.62 g (98%) of unpurified β-mesyloxy ester.

The crude product from above was dissolved in benzene (60 mL), treated with DBU (4.68 g, 30.8 mmol), and refluxed under N_2 for 6 h. The cooled reaction mixture was washed with 5% HCl (70 mL), brine (70 mL), and saturated $NaHCO_3$ solution. Following drying and solvent removal, pure ester **20a** was obtained by chromatography (elution with 2% ether in petroleum ether): 2.80 g (84%); IR (neat, cm^{-1}) 1720, 1630; ^{1}H NMR δ 7.30–7.14 (m, 5 H), 6.66 (d, J = 1.9 Hz, 1 H), 3.70 (s, 3 H), 3.11 (m, 1 H), 2.75–2.49 (m, 4 H), 2.09 (m, 1 H), 1.64 (m, 1 H); ^{13}C NMR ppm 165.7, 146.5, 140.1, 136.0, 128.7, 128.3, 126.0, 51.2, 48.0, 40.9, 30.7, 29.7; MS m/z (M^+) calcd 216.1150, obsd 216.1195.

For **7**: the methyl ester is known;[36] good spectral comparison (^{1}H and ^{13}C NMR) was seen; MS m/z (M^+) calcd 238.1933, obsd 238.1950.

For **11a**: IR (neat, cm^{-1}) 1705, 1650; ^{1}H NMR δ 7.30 (m, 4 H), 7.18 (m, 1 H), 3.69 (s, 3 H), 2.67 (m, 1 H), 2.33 (m, 2 H), 2.16–1.74 (m, 3 H), 1.27 (s, 3 H); ^{13}C NMR ppm 167.5, 148.2, 138.2, 129.5, 125.8, 125.4, 51.3, 38.0, 35.9, 34.5, 28.5, 22.1; MS m/z (M^+) calcd 230.1307, obsd 230.1326.

For **14a**: IR (neat, cm^{-1}) 1705, 1640; ^{1}H NMR δ 6.84 (s, 1 H), 3.72 (s, 3 H), 2.21 (td, J = 6.2, 1.8 Hz, 2 H), 1.80–1.30 (series of m, 14 H); ^{13}C NMR ppm 168.2, 147.9, 128.3, 51.3, 37.1, 35.1, 32.9, 26.1, 24.8, 21.3, 18.5; MS m/z (M^+) calcd 208.1463, obsd 208.1476.

For **17a**: this ester is a known compound.[37]

For **23a**: IR (neat, cm^{-1}) 1705, 1650; ^{1}H NMR δ 7.30 (m, 4 H), 7.18 (m, 1 H), 7.05 (m, 1 H), 3.69 (s, 3 H), 2.67 (s, 3 H), 2.33 (m, 2 H), 2.16–1.74 (m, 3 H), 1.27 (s, 3 H); ^{13}C NMR ppm 167.5, 148.2, 138.3, 129.5, 128.1, 125.8, 125.4, 51.3, 38.0, 35.9, 34.5, 28.5, 22.1; MS m/z (M^+) calcd 230.1307, obsd 230.1326.

For **26a**: IR ($CHCl_3$, cm^{-1}) 1710; ^{1}H NMR δ 7.18 (br d, J = 8.5 Hz, 1 H), 6.91 (dd, J = 2, 0.5 Hz, 1 H), 6.71 (br dd, J = 8.5, 2.5 Hz, 1 H), 6.64 (br d, J = 2.5 Hz, 1 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.00–2.81 (br m, 2 H), 2.56 (br dd, J = 15, 6 Hz, 1 H), 2.39–2.24 (br m, 2 H), 2.26 (ddd, J = 15, 11, 2 Hz, 1 H), 2.00–1.89 (m, 2 H), 1.76–1.38 (m, 5 H), 0.87 (s, 3 H); ^{13}C NMR ppm 166.4, 157.5, 154.7, 137.8, 132.5, 125.9, 113.9, 111.5, 55.2, 55.0, 51.3, 47.1, 44.2, 37.3, 35.0, 31.2, 29.6, 27.7, 26.3, 16.1; MS m/z (M^+) calcd 326.1882, obsd 326.1867.

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 76.99; H, 8.06.

The above esters were fully characterized as their crystalline carboxylic acids following conventional saponification.

3-Benzylcyclopentene-1-carboxylic acid: colorless crystals, mp 105–106 °C (from ether–petroleum ether); ^{1}H NMR δ 7.22 (m, 5 H), 6.81 (dd, J = 4.0, 2.0 Hz, 1 H), 3.15 (m, 1 H), 2.71 (m, 2 H), 2.56 (m, 2 H), 2.12 (ddt, J = 13.2, 8.4, 4.8 Hz, 1 H), 1.66 (m, 1 H); ^{13}C NMR ppm 170.7, 149.4, 139.9, 135.7, 128.7, 128.3,

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126.0, 48.1, 40.7, 30.3, 29.6; MS m/z (M^+) calcd 202.0994, obsd 202.0989.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.23; H, 7.00.

(*E*)-Cyclododecene-1-carboxylic acid: colorless crystals, mp 115–118 °C (from ethyl acetate–petroleum ether); ^1H NMR δ 6.92 (t, J = 8.2 Hz, 1 H), 2.37 (t, J = 6.7 Hz, 2 H), 2.28–2.20 (dt, J = 8.0, 7.4 Hz, 2 H), 1.65–1.50 (m, 4 H), 1.42–1.20 (series of m, 12 H); ^{13}C NMR ppm 173.8, 145.7, 131.6, 26.3, 26.0, 25.9, 25.2, 24.9, 24.8, 23.6, 23.3, 23.0, 22.1; MS m/z (M^+) calcd 210.1620, obsd 210.1651.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 73.97; H, 10.65.

5-Methyl-5-phenylcyclohexene-1-carboxylic acid: colorless crystals, mp 156–159 °C (ethyl acetate–petroleum ether); ^1H NMR δ 7.35–7.18 (m, 5 H), 7.10 (m, 1 H), 2.88 (br d, J = 17.7 Hz, 1 H), 2.37 (br d, J = 17.8 Hz, 1 H), 2.34–2.24 (m, 1 H), 2.09–1.98 (m, 2 H), 1.82–1.72 (m, 1 H), 1.31 (s, 3 H); ^{13}C NMR ppm 172.8, 147.8, 142.1, 128.7, 128.2, 125.8, 125.6, 36.5, 35.4, 33.8, 29.4, 24.2; MS m/z (M^+) calcd 216.1150, obsd 216.1154.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.47; H, 7.39.

Spiro[5.5]undec-1-ene-2-carboxylic acid: colorless crystals, mp 95.5–97.0 °C (from ether–petroleum ether); ^1H NMR δ 11.15 (br s, 1 H), 6.99 (s, 1 H), 2.22 (td, J = 6.1, 1.7 Hz, 2 H), 1.67–1.33 (series of m, 14 H); ^{13}C NMR ppm 173.6, 150.6, 128.0, 37.0, 35.4, 32.9, 26.1, 24.5, 21.3, 18.5; MS m/z (M^+) calcd 194.1306, obsd 194.1272.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.09; H, 9.26.

6,7-Dihydro-5*H*-benzocycloheptene-8-carboxylic acid: colorless crystals, mp 137–139 °C (from ethyl acetate–petroleum ether); ^1H NMR δ 11.90 (br s, 1 H), 7.85 (s, 1 H), 7.40–7.10 (m, 4 H), 2.85 (m, 2 H), 2.66 (t, J = 7.0 Hz, 2 H), 2.12–2.00 (m, 2 H); ^{13}C NMR ppm 174.3, 143.4, 141.8, 134.0, 133.2, 131.5, 129.4, 129.2, 126.2, 35.3, 30.0, 27.3; MS m/z (M^+) calcd 188.0837, obsd 188.0858.

4-Methyl-4-phenylcyclohexene-1-carboxylic acid: colorless crystals, mp 173.5–175 °C (from CH_2Cl_2–petroleum ether); ^1H NMR δ 10.35 (br s, 1 H), 7.31 (m, 4 H), 7.20 (m, 2 H), 2.70 (m, 1 H), 2.32 (m, 2 H), 2.11–1.76 (m, 3 H), 1.28 (s, 3 H); ^{13}C NMR ppm 172.5, 148.1, 141.1, 129.2, 128.2, 125.9, 125.5, 38.2, 36.0, 34.5, 28.5, 21.8; MS m/z (M^+) calcd 216.1151, obsd 216.1151.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.43; H, 7.40.

3-Methoxyestra-1,3,5(10),16-tetraene-16-carboxylic acid (26, R = H): white powder, mp 218–224 °C (unrecrystallized); ^1H NMR δ 7.19 (br d, J = 8.5 Hz, 1 H), 7.07 (br d, J = 2 Hz, 1 H), 6.73 (br dd, J = 8.5, 2.5 Hz, 1 H), 6.66 (br d, J = 2.5 Hz), 3.79 (s, 3 H), 3.01–2.82 (br m, 2 H), 2.58 (br dd, J = 15, 6 Hz, 1 H), 2.41–2.25 (br m, 2 H), 2.28 (ddd, J = 15, 11, 2 Hz, 1 H), 2.01–1.90 (m, 2 H), 1.80–1.40 (series of m, 5 H), 0.90 (s, 3 H); ^{13}C NMR ppm 171.1, 157.5, 157.4, 137.8, 134.6, 132.5, 125.9, 113.9, 111.5, 55.2, 55.0, 47.4, 44.2, 37.3, 34.9, 30.9, 29.6, 27.7, 26.3, 16.0; MS m/z (M^+) calcd 312.1725, obsd 312.1732.

Representative Procedure for Vinyl Bromide Synthesis: 3-Benzyl-1-bromocyclopentene (21). A suspension of 3-benzylcyclopentenecarboxylic acid (6.06 g, 30.0 mmol) in benzene (50 mL) was cooled to near 0 °C, at which point oxalyl chloride (4.57 g, 3.1 mL, 36.0 mmol) was introduced slowly via syringe. As the reaction mixture was allowed to warm to rt, 20 mL of CH_2Cl_2 was added prior to stirring overnight at 20 °C. The excess oxalyl chloride was removed under reduced pressure, and 4-(dimethylamino)pyridine (0.18 g, 1.47 mmol) and pyridine (3.27 g, 41.3 mmol) were added. The resulting solution was cooled to 0 °C and 3-hydroxy-4-methylthiazole-2(3*H*)-thione[22] (4.68 g, 31.8 mmol) was introduced as a solid. After overnight stirring, the solvent was removed under reduced pressure and the residue was purified by chromatography (elution with ether–petroleum ether, 1:1) to give 7.30 g (73%) of **20b**, which was used without further purification.

The yields in the other examples studied were 8 (81%); **11b** (93%); **14b** (84%); **17b** (92%); **23b** (98%); **26b** (91%).

To refluxing bromotrichloromethane (5 mL) contained in a two-necked 100-mL round-bottomed flask was added via syringe pump during 3 h a solution of hydroxamate ester **20b** (2.05 g, 6.18 mmol) and AIBN (0.34 g, 2.05 mmol) in bromotrichloromethane (20 mL). Following completion of the addition, the reaction mixture was heated for an additional 30 min, cooled, and chromatographed directly on silica gel (elution with petroleum ether) to give **21** (0.54 g, 37%) as a colorless oil: ^1H NMR δ 7.29–7.11 (m, 5 H), 5.76 (m, 1 H), 2.94 (m, 1 H), 2.70–2.46 (m, 4 H), 2.09 (m, 1 H), 1.64 (m, 1 H); ^{13}C NMR ppm 140.2, 134.6, 128.8, 126.0, 121.5, 47.5, 41.8, 39.1, 29.9; MS m/z (M^+) calcd 238.0182, obsd 238.0205.

(*E*)-1-Bromocyclododecene (9): pale yellow liquid (82%); ^1H NMR δ 5.83 (t, J = 8.2 Hz, 1 H), 2.50–2.46 (t, J = 6.5 Hz, 2 H), 2.14–2.06 (m, 2 H), 1.70–1.00 (series of m, 16 H); ^{13}C NMR ppm 133.4, 126.7, 31.7, 26.7, 26.6, 25.6, 24.7, 24.3, 24.0, 23.9, 22.4, 22.1; MS m/z (M^+) calcd 246.0806, obsd 246.0782.

(3-Bromo-1-methyl-3-cyclohexen-1-yl)benzene (12): colorless liquid (96%); ^1H NMR δ 7.40–7.30 (m, 4 H), 7.26–7.21 (m, 1 H), 6.02–5.99 (m, 1 H), 2.92 (br d, J = 17.7 Hz, 1 H), 2.59 (br d, J = 17.7 Hz, 1 H), 2.19–1.70 (m, 4 H), 1.34 (s, 3 H); ^{13}C NMR ppm 147.4, 128.2, 128.1, 126.0, 125.5, 120.6, 46.9, 39.5, 33.7, 28.8, 25.2; MS m/z (M^+) calcd 252.0336, obsd 252.0350.

2-Bromospiro[5.5]undec-1-ene (15): colorless oil (74%); ^1H NMR δ 5.99 (s, 1 H), 2.38 (t, J = 6.3 Hz, 2 H), 1.71 (m, 2 H), 1.56–1.28 (series of m, 12 H); ^{13}C NMR ppm 137.3, 121.6, 38.0, 37.6, 35.6, 32.8, 26.0, 21.5, 20.6; MS m/z (M^+) calcd 230.0494, obsd 230.0467.

8-Bromo-6,7-dihydro-5*H*-benzocycloheptene (18): colorless liquid (87%); ^1H NMR δ 7.18–7.07 (m, 4 H), 6.98 (t, J = 1.5 Hz, 1 H), 2.93 (td, J = 6.6, 1.5 Hz, 2 H), 2.88–2.85 (m, 2 H), 2.02–1.94 (m, 2 H); ^{13}C NMR ppm 141.0, 134.3, 133.1, 130.9, 129.2, 128.4, 127.3, 126.2, 42.9, 35.1, 27.2; MS m/z (M^+) calcd 224.0023, obsd 224.0028.

(4-Bromo-1-methyl-3-cyclohexen-1-yl)benzene (24): colorless liquid (81%); ^1H NMR δ 7.44–7.22 (m, 5 H), 6.14 (m, 1 H), 2.59–2.38 (m, 2 H), 2.27–2.16 (m, 2 H), 2.09–2.00 (m, 1 H), 1.91–1.82 (m, 1 H), 1.29 (s, 3 H); ^{13}C NMR ppm 147.9, 128.2, 127.4, 125.9, 125.4, 121.4, 39.5, 36.6, 35.6, 33.1, 28.2; MS m/z (M^+) calcd 252.0336, obsd 252.0283.

16-Bromo-3-methoxyestra-1,3,5(10),16-tetraene (27): colorless crystals (36%), mp 124–125 °C (from petroleum ether); ^1H NMR δ 7.18 (br d, J = 8.5 Hz, 1 H) 6.72 (br dd, J = 8.5, 2.5 Hz, 1 H), 6.65 (br d, J = 2.5 Hz, 1 H), 6.05 (dd, J = 2, 1 Hz, 1 H), 3.79 (s, 3 H), 3.00–2.80 (m, 2 H), 2.49 (ddd, J = 14.5, 11, 2 Hz, 1 H), 2.41 (ddd, J = 14.5, 7, 1 Hz, 1 H), 2.39–2.26 (m, 2 H), 1.94–1.80 (m, 3 H), 1.69–1.39 (m, 4 H), 0.90 (s, 3 H); ^{13}C NMR ppm 157.5, 143.1, 137.7, 132.5, 125.8, 121.4, 113.9, 111.5, 55.7, 55.2, 47.3, 44.2, 39.8, 36.8, 35.4, 29.6, 27.8, 26.3, 16.8; MS m/z (M^+) calcd 348.0912, obsd 348.0921.

Anal. Calcd for $C_{19}H_{23}BrO$: C, 65.71; H, 6.68. Found: C, 65.69; H, 6.77.

Methyl 2-[(Diethoxyphosphinyl)oxy]-4-methyl-4-phenyl-1-cyclohexene-1-carboxylate (28). Keto ester **22b** (19.5 g, 79.2 mmol) in dry ether (50 mL) was added dropwise to a cold (0 °C), magnetically stirred slurry of NaH (2.30 g of 97%, 95.8 mmol) in ether (25 mL). After 1 h, diethyl chlorophosphate (13.0 mL, 90 mmol) was added dropwise. After 4 h, the mixture was filtered through a pad of Celite (ether rinse) and the filtrate was evaporated to give 31.8 g of **28** as a clear, viscous oil that was used without further purification: IR (CCl_4, cm^{-1}) 1725, 1655, 1285, 1040, 700; ^1H NMR δ 7.34–7.24 (m, 4 H), 7.24–7.14 (m, 1 H), 4.32–4.15 (m, 4 H), 3.64 (s, 3 H), 2.97 (br d, J = 18 Hz, 1 H), 2.58 (br dddd, J = 18, 2, 2, 2 Hz, 1 H), 2.47–2.33 (br m, 1 H), 2.20–2.05 (br m, 1 H), 1.95 (dddd, J = 13, 6.5, 5.5, 1 Hz, 1 H), 1.76 (br ddd, J = 13, 7.5, 5.5 Hz, 1 H), 1.36 (m, 6 H), 1.32 (s, 3 H); MS m/z (M^+) calcd 382.1545, obsd 382.1583.

Methyl 2,4-Dimethyl-4-phenylcyclohexene-1-carboxylate (29a). A 6.60-g portion of **28** in dry ether was added dropwise to a cold (−50 °C), stirred slurry of lithium dimethylcuprate [from CuI (9.60 g, 50.4 mmol) and methyllithium (65 mL of 1.5 M in ether, 97.5 mmol)]. The resulting mixture was slowly warmed to 0 °C during 3 h, quenched with 5% HCl, and filtered through Celite. The organic phase was washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel to give pure **29a** as a colorless oil (3.37 g, 84% from **22b**): IR (CCl_4, cm^{-1}) 1715, 1645; ^1H NMR δ 7.35–7.24 (m, 4 H), 7.24–7.15 (m, 1 H), 3.69 (s, 3 H), 2.60 (br d, J = 18 Hz, 1 H), 2.42–2.30 (br m, 1 H), 2.27 (br d, J = 18 Hz, 1 H), 2.15–2.20 (br m, 1 H), 2.14 (br s, 3 H), 1.96 (dddd, J = 13, 6.5, 5.5, 1 Hz, 1 H), 1.76 (dddd, J =

13, 7.5, 5.5, 1 Hz, 1 H), 1.28 (s, 3 H); ^{13}C NMR ppm 168.8, 148.3, 145.5, 128.1 (2 C), 125.7, 125.4 (2 C), 123.2, 51.0, 46.0, 36.4, 34.6, 28.6, 24.2, 21.9; MS m/z (M^+) calcd 244.1463, obsd 244.1460.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.75; H, 8.19.

(4-Bromo-1,3-dimethyl-3-cyclohexen-1-yl)benzene (30). The saponification of **29a** to give the carboxylic acid, mp 95–97 °C, was accomplished in 97% yield. The subsequent conversion of **29b** was achieved via the acid chloride in 96% overall yield. Application of the general procedure to **29b** (2.76 g, 7.68 mmol) afforded 1.87 g (92%) of **30** after silica gel chromatography: colorless oil; ^{1}H NMR δ 7.36–7.26 (m, 4 H), 7.24–7.17 (m, 1 H), 2.57–2.42 (br m, 1 H), 2.55 (br d, J = 17 Hz, 1 H), 2.34–2.18 (br m, 1 H), 2.23 (br d, J = 17 Hz, 1 H), 2.01 (dddd, J = 13, 6.5, 5.5, 1.5 Hz, 1 H), 1.90 (br s, 3 H), 1.84 (dddd, J = 13, 7, 6, 1 Hz, 1 H), 1.29 (s, 3 H); ^{13}C NMR ppm 148.0, 130.6, 128.2 (2 C), 125.8, 125.4 (2 C), 117.7, 44.8, 37.1, 36.9, 34.2, 28.4, 23.2; MS m/z (M^+) calcd 266.0494, obsd 266.0540.

Ethyl (*E*)-2-Methylcyclododecene-1-carboxylate (31). To a suspension of NaH (1.25 g, 52 mmol) in dry ether (150 mL) was added dropwise a solution of **6** (12.0 g, 47 mmol) in the same solvent (50 mL), followed by an ethereal solution (50 mL) of diethyl dichlorophosphate (9.04 g, 52 mmol). After 12 h, the reaction mixture was processed as described above to leave 12.3 g (70%) of the enol phosphate as a pale yellow oil.

A cold (−5 °C) ethereal suspension (500 mL) of CuI (17.2 g, 93 mmol) was treated slowly under N_2 with methyllithium in hexanes (125 mL of 1.5 M, 187 mmol) below 0 °C. This mixture was cooled to −40 °C, treated with the enol phosphate (12.0 g, 31 mmol) in ether (50 mL) via cannula, and worked up 4 h later in the predescribed manner. Purification by flash chromatography (elution with petroleum ether–ether 1:1) afforded 6.2 g (79%) of **31** as a colorless oil: IR (neat, cm^{-1}) 1710; ^{1}H NMR δ 4.20 (q, J = 7 Hz, 2 H), 2.36 (t, J = 7 Hz, 2 H), 2.16 (t, J = 7.5 Hz, 2 H), 1.85 (s, 3 H), 1.62–1.51 (m, 2 H), 1.54–1.20 (series of m, 14 H), 1.29 (t, J = 7 Hz, 3 H); ^{13}C NMR ppm 170.2, 142.1, 129.2, 59.7, 31.3, 26.4, 26.1, 25.2, 24.9, 24.63, 24.61, 24.3, 22.5, 22.3, 20.1, 14.2; MS m/z (M^+) calcd 252.2089, obsd 252.2090.

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.92; H, 11.11.

(*E*)-2-Methylcyclodecene-1-carboxylic Acid (32). Ester **31** (2.35 g, 9.31 mmol) was refluxed with excess 10% aqueous KOH for 24 h, at which time a homogeneous solution resulted. After ether extraction, the aqueous phase was acidified and reextracted with $CHCl_3$. After drying and evaporation of the combined $CHCl_3$ layers, a colorless, viscous syrup that soon solidified was obtained (1.94 g, 93%). ^{1}H NMR analysis showed this material to consist chiefly of a 3:1 mixture of **32** and **33**. Pure **32** could be obtained in 35% yield (unoptimized) by recrystallization from petroleum ether: colorless crystals, mp 98–100 °C; ^{1}H NMR δ 2.42 (br t, J = 7 Hz, 2 H), 2.22 (br t, J = 7.5 Hz, 2 H), 2.00 (br s, 3 H), 1.65–1.20 (m, 16 H); MS m/z (M^+) calcd 224.1776, obsd 224.1792.

(*E*)-1-Bromo-2-methylcyclododecene (35). Carboxylic acid **32** (730 mg, 3.25 mmol) was converted to its acid chloride by treatment with oxalyl chloride (0.50 mL, 5.73 mmol) in dry benzene at rt for 6 h. After evaporation of all volatiles, condensation with 3-hydroxy-4-methylthiazole-2(3*H*)-thione (600 mg, 4.08 mmol) was effected in the usual way and **34** was purified by flash chromatography on silica gel (1.17 g, 100%). This material was transformed into the vinyl bromide according to the general procedure. Isolation by flash chromatography (elution with petroleum ether) afforded pure **35** (623 mg, 74% overall) as a colorless oil: IR (CCl_4, cm^{-1}) 1640; ^{1}H NMR δ 2.56 (br t, J = 7 Hz, 2 H), 2.19 (br t, J = 7.5 Hz, 2 H), 1.85 (t, J = 1 Hz, 3 H), 1.74–1.47 (m, 4 H), 1.47–1.23 (m, 12 H); ^{13}C NMR ppm 134.7, 124.7, 33.9, 31.1, 26.6, 25.4, 24.9, 24.6, 24.2, 24.0, 23.0, 22.9, 22.3; MS m/z (M^+) calcd 260.0963, obsd 260.0967.

Enol Phosphate 36. (1*R*)-(+)-Camphor was carbomethoxylated according to the general procedure to give a 4:1 endo/exo mixture of β-keto esters in 87% yield: bp 120–125 °C/2 Torr; IR (CCl_4, cm^{-1}) 1765, 1735; ^{1}H NMR δ (major) 3.70 (s, 3 H), 3.32 (dd, J = 5, 2 Hz, 1 H), 2.40 (br dd, J = 5, 4 Hz, 1 H), 1.90–1.42 (series of m, 4 H), 0.99 (s, 3 H), 0.91 (s, 3 H), 0.85 (s, 3 H); (minor) 3.71 (s, 3 H), 2.85 (s, 1 H), 2.62 (br d, J = 4 Hz, 1 H), 2.08–1.31 (series of m, 4 H), 0.95 (s, 3 H), 0.92 (s, 3 H), 0.76 (s 3 H); ^{13}C NMR ppm (major) 211.2, 169.9, 58.3, 55.4, 51.9, 47.0, 45.6, 29.3, 22.4, 19.4, 18.7, 9.4; (minor) 210.8, 168.1, 58.3, 57.4, 52.2, 46.6, 45.9, 30.0, 27.2, 20.6, 19.3, 9.3; MS m/z (M^+) calcd 210.1256, obsd 210.1262.

The enol phosphate was prepared as before from NaH (1.25 g, 52 mmol), 10.9 g (48 mmol) of the keto ester, and 9.9 g (57.1 mmol) of diethyl chlorophosphate in 72% yield and obtained as a colorless oil: IR (CCl_4, cm^{-1}) 1730, 1635, 1285, 1035; ^{1}H NMR δ 4.21–4.09 (m, 4 H), 3.63 (s, 3 H), 2.64 (d, J = 3.5 Hz, 1 H), 1.86 (ddddd, J = 12, 8.5, 4, 3.5, 2 Hz, 1 H), 1.60 (ddd, J = 12, 8.5, 4 Hz, 1 H), 1.44 (ddd, J = 12, 9, 4 Hz, 1 H), 1.29 (td, J = 7, 1 Hz, 3 H), 1.27 (td, J = 7, 1 Hz, 3 H), 1.18 (ddd, J = 12, 9, 4 Hz, 1 H), 1.00 (s, 3 H), 0.84 (s, 3 H), 0.71 (s, 3 H); MS m/z (M^+) calcd 346.1545, obsd 346.1512.

Methyl (1*S*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-ene-3-carboxylate (37a). Lithium dimethylcuprate was prepared as usual from CuI (11.4 g, 61.5 mmol) and methyllithium (102.5 mL of 1.5 M in hexanes, 158 mmol) in dry ether, cooled to −35 °C, and treated with an ethereal solution of **36** (8.0 g, 23.1 mmol). After 3 h, the reaction mixture was quenched and worked up in the predescribed manner. Purification by flash chromatography (elution with petroleum ether–ether 9:1) afforded 2.79 g (62%) of **37a** as a colorless oil: IR (CCl_4, cm^{-1}) 1715; ^{1}H NMR δ 6.63 (br s, 1 H), 3.70 (s, 3 H), 2.71 (br d, J = 3.5 Hz, 1 H), 1.92–1.84 (m, 1 H), 1.71–1.62 (m, 1 H), 1.12–0.95 (m, 2 H), 1.07 (s, 3 H), 0.80 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR ppm 165.6, 151.0, 138.9, 57.0, 55.1, 52.0, 51.2, 31.6, 19.3, 19.1, 12.8; MS m/z (M^+) calcd 194.1307, obsd 194.1260.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.17; H, 9.35. Found: C, 74.26; H, 9.40.

Saponification of **37a** gave the known carboxylic acid[38] (92%) as colorless crystals: mp 110–111 °C; IR (CCl_4, cm^{-1}) 1680; ^{1}H NMR δ 10.95 (br, 1 H), 6.79 (br s, 1 H), 2.72 (br d, J = 3.5 Hz, 1 H), 1.95–1.85 (m, 1 H), 1.73–1.64 (m, 1 H), 1.14–0.96 (m, 2 H), 1.08 (s, 3 H), 0.81 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR ppm 170.6, 153.8, 138.6, 57.2, 55.5, 51.7, 31.5, 24.2, 19.3, 19.1, 12.7; MS m/z (M^+) calcd 180.1150, obsd 180.1162.

(1*S*,4*S*)-3-Bromo-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (38). The above acid was converted to its acid chloride and reacted with 3-hydroxy-4-methylthiazole-2(3*H*)-thione in the usual manner to give **37b** in 88% yield: colorless solid, mp 125 °C dec; IR (KBr, cm^{-1}) 1765; ^{1}H NMR δ 7.15 (br s, 1 H), 6.18 (q, J = 0.7 Hz, 1 H), 2.9 (d, J = 3.5 Hz, 1 H), 2.15 (d, J = 0.7 Hz, 3 H), 2.00 (td, J = 8.6, 3.6 Hz, 1 H), 1.79 (t, J = 8.7 Hz, 1 H), 1.25–1.15 (m, 2 H), 1.15 (s, 3 H), 0.90 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR ppm 181.1, 159.8, 157.6, 137.3, 134.1, 101.9, 57.7, 56.1, 52.6, 31.3, 24.3, 19.2, 19.0, 13.2, 12.4; MS m/z (M^+) calcd 309.0857, obsd 309.0885.

Conversion of **37b** to **38** in the predescribed manner afforded the volatile colorless liquid in 36% yield: ^{1}H NMR δ 5.73 (s, 1 H), 2.35 (d, J = 3.5 Hz, 1 H), 1.82–1.78 (m, 1 H), 1.65–1.56 (m, 1 H), 1.22–1.11 (m, 2 H), 1.04 (s, 3 H), 0.93 (s, 3 H), 0.77 (s, 3 H); ^{13}C NMR ppm 138.0, 124.5, 60.7, 57.1, 55.6, 32.6, 24.2, 19.2, 19.0, 13.0; MS m/z (M^+) calcd 216.0336, obsd 216.0307.

(*R*)-(+)-4-(1-Methylethyl)valerolactone (40).[31] (*R*)-(−)-Carvone (220 g, 1.46 mol, $[\alpha]_D^{20}$ −60.0° (neat), ≥96% ee) was hydrogenated at 50 psi over PtO_2 (500 mg) in a Parr apparatus without external cooling to give 209 g (94%) of colorless liquid, bp 72–76 °C/0.9 Torr, which contained ca. 15% of the fully saturated ketone. A solution of this material (121.9 g) in ethyl acetate (750 mL) was ozonolyzed at −78 °C and reduced by careful addition of $NaBH_4$ (30.0 g, 793 mmol) in 5% aqueous NaOH (300 mL) with vigorous stirring below 35 °C. After being recooled to 0 °C, the reaction mixture was made strongly alkaline with 10% KOH solution, extracted with ether, acidified with 20% HCl, and continuously extracted with ether overnight. The residual material after solvent evaporation was heated with *p*-toluenesulfonic acid (2.0 g) in benzene (500 mL) under a Dean–Stark trap overnight. Workup and distillation afforded 56.2 g (46% overall) of **40** as a colorless liquid: bp 108–110 °C at 1.5 Torr; $[\alpha]^{20}_D$ +26.6° (*c* 1.4, $CHCl_3$); IR (CCl_4, cm^{-1}) 1745; ^{13}C NMR ppm 171.6, 68.2, 37.4, 33.6, 31.9, 25.9, 18.9, 18.7; MS m/z (M^+) calcd 142.0994, obsd 142.1001.

Ethyl (*R*)-5-Bromo-3-(1-methylethyl)pentanoate. A solution of **40** (56.2 g, 0.395 mol) in dry ethanol (350 mL) was treated

(38) (a) Bredt, J. *Ann.* **1909**, *366*, 16. (b) Bredt, J.; Perkin, W. H., Jr. *J. Chem. Soc.* **1913**, *29*, 2182.

with a stream of gaseous HBr, the temperature being kept below 35 °C. After saturation (ca 6 h), the reaction mixture was stirred at 25 °C for 12 h, treated with an equal volume of ether, and diluted with water. With ice cooling, the mixture was neutralized by slow addition of 20% NaOH and repeatedly extracted with ether. The dried ethereal layers were combined and concentrated. Distillation of the residue afforded 92.1 g (93%) of the bromo ester as a colorless liquid, bp 100–105 °C/1.4 Torr. An analytical sample was obtained by flash chromatography (elution with petroleum ether–ether 5:1) and Kugelrohr distillation: $[\alpha]^{20}_D$ −4.2° (c 1.7, $CHCl_3$); IR (CCl_4, cm^{-1}) 1735; ^1H NMR δ 4.11 (q, J = 7 Hz, 2 H), 3.41 (ddd, J = 10, 8, 6.5 Hz, 1 H), 3.36 (ddd, J = 10, 8, 7 Hz, 1 H), 2.30 (dd, J = 15, 5.5 Hz, 1 H), 2.13 (dd, J = 15, 7.5 Hz, 1 H), 2.00–1.75 (m, 3 H), 1.73 (dqq, J = 4, 7, 7 Hz, 1 H), 1.24 (t, J = 7 Hz, 3 H), 0.97 (d, J = 7 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H); ^{13}C NMR ppm 173.1, 60.2, 39.7, 35.5, 34.7, 31.4, 29.8, 19.2, 18.4, 14.1; MS m/z (M^+), calcd 252.0548, obsd 252.0592.

Anal. Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.63. Found: C, 47.85; H, 7.61.

(*R*)-(+)-3-(1-Methylethyl)cyclohexanone (41). Neat diethyl malonate (61.3 g, 0.383 mol) was added during 10 min to an ethanolic sodium ethoxide solution [from sodium (8.7 g, 0.378 mol) and 400 mL of dry ethanol]. The reaction mixture was stirred at 40 °C for 30 min, treated with the above bromo ester (90.7 g, 0.361 mol), and refluxed for 2.5 h. A solution of sodium (10.8 g, 0.470 mol) in dry ethanol (300 mL) was introduced and ethanol was distilled from the mixture through a short Vigreux column, being replaced by portionwise addition of dry toluene, until the distillate consisted of pure toluene. The cyclization was completed by overnight heating. After the distillation of more solvent, the mixture was cooled, acidified (10% HCl), and partitioned between ether and water. The organic phase was washed with water and brine, dried, and evaporated to leave the oily keto diester, which was refluxed with 20% H_2SO_4 (1 L) with efficient mechanical stirring for 24 h, saturated with NaCl, and partitioned between ether and water. After drying and concentration, the residue was distilled to give 31.2 g (62%) of **41** as a colorless liquid: bp 68–75 °C/1.3 Torr; $[\alpha]^{20}_D$ 17.3° (c 6.3, $CHCl_3$); IR (CCl_4, cm^{-1}) 1715; ^1H NMR δ 2.38–2.27 (m, 2 H), 2.21 (dddd, J = 13.5, 12.5, 6, 1 Hz, 1 H), 2.03 (dd, J = 13, 12 Hz, 1 H), 2.10–1.98 (m, 1 H), 1.89–1.78 (m, 1 H), 1.65–1.46 (m, 3 H), 1.33 (dddd, J = 13, 12, 11, 3.5 Hz, 1 H), 0.87 (d, J = 7 Hz, 3 H), 0.86 (d, J = 7 Hz, 3 H); ^{13}C NMR ppm 212.4, 45.3, 45.2, 41.3, 32.4, 28.2, 25.4, 19.4, 19.2; MS m/z (M^+) calcd 140.1201, obsd 140.1221.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.86; H, 11.48.

The distillation residue was saponified (5% KOH in 200 mL of H_2O–CH_3OH, 1:1, 30 h, 25 °C), acidified, freed of CH_3OH in vacuo, and resubjected to decarboxylation (200 mL of 35% HCl, reflux 30 h) to afford an additional 7.1 g of **41** (total yield 87%).

(*R*)-Methyl 4-(1-Methylethyl)-2-oxocyclohexane-6-carboxylate (42). Neat **41** (10.0 g, 71.3 mmol) was added to a suspension of oil-free sodium hydride (from 6.7 g of 60% oil dispersion, 167 mmol) in dry dimethyl carbonate (100 mL) and dry THF (200 mL). The mixture was refluxed overnight and processed as previously described to give 12.7 g (90%) of **42** as a pale yellowish oil, which was almost completely enolized in $CDCl_3$ solution: IR (CCl_4, cm^{-1}) 1745, 1720, 1660, 1620; ^1H NMR δ 12.08 (s, 1 H), 2.37 (ddddd, J = 14.5, 5.5, 2.5, 1.5, 1.5 Hz, 1 H), 2.27 (dddd, J = 17.5, 5, 1.5, 1.5 Hz, 1 H), 2.10 (ddddd, J = 14.5, 11.5, 5, 2.5, 1.5 Hz, 1 H), 2.02 (dddd, J = 17.5, 10.5, 2.5, 1.5 Hz), 1.79 (dddd, J = 13, 5, 2.5, 2.5 Hz, 1 H), 1.52 (dqq, J = 6.5, 6.5, 6.5 Hz, 1 H), 1.40 (ddddd, J = 11.5, 10.5, 6.5, 5, 2.5 Hz, 1 H), 1.14 (dddd, J = 13, 11.5, 11.5, 5.5 Hz, 1 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 3 H), 3.74 (s, 3 H); ^{13}C NMR ppm 172.7, 172.0, 97.1, 51.0, 39.7, 39.7, 32.5, 31.8, 25.9, 22.5, 19.6, 19.2; MS m/z (M^+) calcd 198.1256, obsd 198.1262.

(*S*)-3-(1-Methylethyl)cyclopentene-1-carboxylic Acid (44a). A solution of freshly distilled sulfuryl chloride (66 mL, 0.815 mol) in dry CH_2Cl_2 (200 mL) was added during 30 min to a cold (0 °C) solution of **42** (79.0 g, 0.398 mol) in dry CH_2Cl_2 (1.0 L). The reaction mixture was stirred at 20 °C for 1 h and then evaporated. The residue was diluted with CCl_4 and again evaporated to leave **43** as a pale yellow oil: IR (CCl_4, cm^{-1}) 1770, 1745, 1725; ^1H NMR δ 3.84 (s, 3 H), 2.81 (dd, J = 13.5, 12 Hz, 1 H), 2.65–2.53 (m, 1 H), 2.37 (ddd, J = 13.5, 3.5, 1 Hz, 1 H), 2.32 (ddd, J = 15, 3.5, 3.5 Hz, 1 H), 1.86–1.76 (m, 2 H), 1.73–1.52 (m, 2 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H); ^{13}C NMR ppm 201.2, 167.9, 72.2, 53.4, 45.1, 40.0, 36.9, 32.2, 23.6, 19.3, 19.2; MS m/z (M^+) calcd 234.0837, obsd 234.0874.

This oil was added to a slurry of Na_2CO_3 (160 g, 1.51 mol) in dry mesitylene (1.2 L) and refluxed under N_2 while being mechanically stirred for 20 h, cooled, treated with 10% KOH (1.2 L) and methanol (600 mL), and reheated for 24 h to effect saponification. The usual workup furnished 60.8 g (99%) of **44a** as a viscous oil. This material was routinely carried forward without further purification. An analytical sample was obtained by flash chromatography and Kugelrohr distillation: IR (CCl_4, cm^{-1}) 3300–2300, 1690, 1625; ^1H NMR δ 6.90 (ddd, J = 2, 2, 2 Hz, 1 H), 2.71–2.43 (m, 3 H), 2.08 (dddd, J = 13, 8.5, 8.5, 4.5 Hz, 1 H), 1.73–1.56 (m, 2 H), 0.94 (d, J = 7 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H); ^{13}C NMR ppm 171.0, 149.3, 135.9, 53.9, 32.2, 30.8, 27.4, 20.5, 20.4; MS m/z (M^+) calcd 154.0994, obsd 154.1001.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.97; H, 9.18.

(*R*)-(+)-1-Bromo-3-(1-methylethyl)cyclopentene (45). Reaction of **44a** (60.8 g) with oxalyl chloride (45 mL, 0.516 mol) in the predescribed manner afforded the acid chloride, from which hydroxamate ester **44b** was obtained as usual (100.3 g, 89% overall from **42**). Conversion of 5–10-g portions of **44b** to the volatile vinyl bromide **45** was accomplished according to the general procedure except for a modified workup that proved essential in order to effect complete separation of $BrCCl_3$ from the highly volatile bromide **45**. First, partial evaporation of $BrCCl_3$ and elution with petroleum ether through a pad of silica gel removed polar materials. The petroleum ether solution was then treated (−78 °C to rt) with an appropriate amount of hexamethylphosphorous triamide to destroy any remaining $BrCCl_3$ by phosphonium salt formation. When GC indicated this process to be complete, isolation of **45** was effected by aqueous workup followed by flash chromatography (elution with petroleum ether). Pure **45** was isolated in yields ranging from 25 to 40%: colorless oil; $[\alpha]^{20}_D$ +65.5° (c 1.1, $CHCl_3$); ^1H NMR δ 5.63 (ddd, J = 2, 2, 2 Hz, 1 H), 2.60–2.52 (m, 2 H), 2.52–2.40 (m, 1 H), 2.06 (dddd, J = 12.5, 8.5, 6.5, 6.5 Hz, 1 H), 1.64 (dddd, J = 12.5, 8, 8, 6 Hz, 1 H), 1.55 (dqq, J = 6.5, 6.5, 6.5 Hz, 1 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 6.5 Hz, 3 H); ^{13}C NMR 133.9, 121.1, 52.6, 39.6, 32.6, 27.7, 20.2, 20.0; MS m/z (M^+) calcd 190.0181, obsd 190.0211.

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Registry No. **6**, 75232-70-1; **7**, 135615-88-2; **7** acid, 63657-97-6; **8**, 135615-89-3; **9**, 51306-72-0; **10a**, 18932-33-7; **10b**, 135616-16-9; **11a**, 135615-90-6; **11b**, 135616-17-0; **11** (R = H), 135616-27-2; **12**, 135615-91-7; **13a**, 1781-33-5; **13b**, 135616-18-1; **14a**, 135615-92-8; **14b**, 135616-19-2; **14** (R = H), 135616-28-3; **15**, 135615-93-9; **16a**, 826-73-3; **16b**, 135616-20-5; **17a**, 83303-60-0; **17b**, 135616-21-6; **17** (R = H), 135616-29-4; **18**, 135615-94-0; **19a**, 69815-13-0; **19b**, 135616-22-7; **20a**, 135615-95-1; **20b**, 135616-23-8; **20** (R = H), 135616-26-1; **21**, 135615-96-2; **22a**, 135615-97-3; **22b**, 135616-24-9; **23a**, 135615-98-4; **23b**, 135616-25-0; **23**, 135616-30-7; **24**, 135615-99-5; **25a**, 1624-62-0; **25b**, 135682-91-6; **26a**, 135616-00-1; **26b**, 135615-85-9; **26** (R = H), 135616-31-8; **27**, 135616-01-2; **28**, 135616-02-3; **29a**, 135616-03-4; **29b**, 135615-86-0; **30**, 135616-04-5; **31**, 89462-80-6; **32**, 135616-05-6; **33**, 135616-06-7; **34**, 135616-07-8; **35**, 135616-08-9; **36**, 135616-09-0; **36** (*endo*-keto ester), 135682-92-7; **36** (*exo*-keto ester), 135682-93-8; **37a**, 135616-10-3; **37b**, 135615-87-1; **37** (R = H), 135758-00-8; **38**, 135616-11-4; **39**, 6485-40-1; **40**, 37147-17-4; **41**, 74006-76-1; **42**, 135616-12-5; **43**, 135616-13-6; **44a**, 135616-14-7; **44b**, 135616-15-8; **45**, 120264-20-2; (*R*)-$(CH_3)_2CHCH(CH_2CO_2CH_3)(CH_2)_2Br$, 135616-32-9; $CH_2(CO_2C_2H_5)_2$, 105-53-3; cyclododecanone, 830-13-7; 3-hydroxy-4-methylthiazole-2(3*H*)-thione, 49762-08-5; (+)-camphor, 464-49-3.

Supplementary Material Available: ^1H NMR spectra (300 MHz) of those compounds for which combustion analyses are not provided (37 pages). Ordering information is given on any current masthead page.