1-(Arylthio)cyclopropanecarboxaldehydes. Conjunctive Reagents for Secoalkylation

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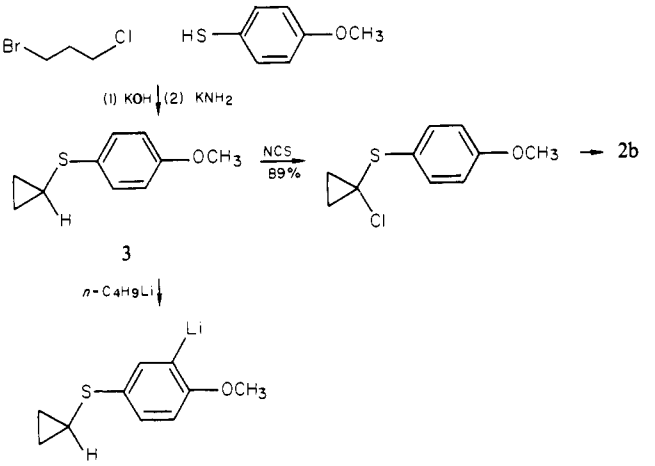
Abstract: The aldol products from 1-(arylthio)cyclopropanecarboxaldehydes and ketones undergo dehydration and addition of nucleophiles to the carbonyl group. The products are vinylogues of cyclopropylcarbinol systems that have previously been rearranged to cyclobutanones. The key for the successful rearrangement here is the employment of 2,6-dimethoxyphenyl as the aryl group. The generated vinylcyclobutanones add a range of nucleophiles to the carbonyl group and suffer base-induced fragmentation after epoxidation. This secoalkylation sequence creates a versatile functionalized chain at the α position of a carbonyl compound. The utility of this methodology in cyclopentane ring formation is particularly noted.

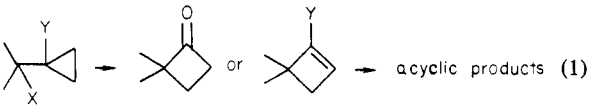
The extension of a carbon chain with functionalization by four or more carbon atoms α to a carbonyl group is a classic problem in organic chemistry.[1] The importance lies not only in the necessity of having efficient methods for extending carbon chains but also the desirability of forming carbocycles via chain-extension techniques, cf. the Robinson annulation. The ability to add carbon chains where one or more of the carbon atoms introduced is activated by various functional groups, as well as maintaining chemodifferentiation of these groups, are important aspects of this problem.

Use of strained rings as building blocks for molecular construction allows the release of strain energy to provide the driving force for molecular rearrangement. The uniqueness of this feature creates the ability to carry reactive functionality along in a masked form and then to achieve the unravelling chemoselectively.[2-4] Great interest has focused around cyclopropane conjunctive reagents culminating in a number of notable applications, especially in terpene and alkaloid synthesis.[5,6] In these applications, the full strain energy of the cyclopropane is released by conversion to acyclic systems or relatively unstrained rings (e.g., five or seven).

Scheme I

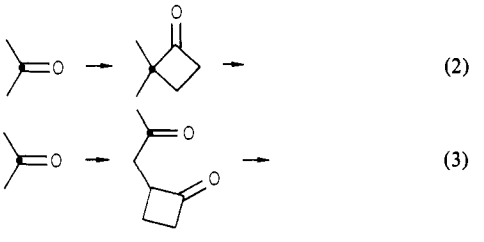


An alternative strategy to capitalize on such systems involves a timed release of strain energy. As represented in eq 1, ring



(1)

enlargement from the three- to four-membered ring, a system of only slightly less strain energy, and subsequent release of the strain of the latter ring expands the flexibility of this strategy for structural elaboration.[2c-h,3] Indeed, cyclobutanones and cyclobutenes are exciting synthetic intermediates for a whole host of applications including cyclopentanone and cyclohexanone formation, olefin and diene synthesis, geminal alkylation, reductive acylation, among others. One approach to such systems employed nucleophilic conjunctive reagents to add to carbonyl groups or in conjugate fashion to α,β-unsaturated carbonyl systems. Our previous work exploited the utility of two such reagents, diphenylsulfonium cyclopropylide and 1-lithiocyclopropyl phenyl sulfide.[2c-h,3] Complementary behavior would evolve from electrophilic conjunctive reagents. For example, instead of elaboration occurring at the carbonyl carbon (eq 2), it would occur at the α-carbon via the enol or enolate (eq 3). Intermediates such as



(2)

(3)

that in eq 3 are particularly exciting because of the flexibility they

(1) For some reviews see: House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1972; Chapters 9 and 10. Caine, D. In "Carbon-Carbon Bond Formation"; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979. Jung, M. E. *Tetrahedron* **1976**, *32*, 3. Gawley, R. E. *Synthesis* **1976**, 777. D'Angelo, J. *Tetrahedron* **1976**, *32*, 2979. Martin, S. F. *Synthesis* **1979**, 633.

(2) For some recent general methodology see: (a) Dolfini, J. E.; Menich, K.; Corliss, P.; Cavanaugh, R.; Danishefsky, S.; Chakrartly, S. *Tetrahedron Lett.* **1966**, 4421; (b) Danishefsky, S.; Rounyak, G.; Cavanaugh, R. *Chem. Commun.* **1969**, 636; (c) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3088; (d) Trost, B. M.; Keeley, D. E.; Rigby, J.; Bogdanowicz, M. J. *Ibid.* **1977**, *99*, 3080; (e) Trost, B. M.; Rigby, J. *J. Org. Chem.* **1976**, *41*, 3217; (f) Trost, B. M.; Scudder, P. H. *J. Am. Chem. Soc.* **1977**, *99*, 7601; (g) Trost, B. M.; Kurozumi, S. *Tetrahedron Lett.* **1974**, 1929; (h) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5307, 5311, 5321; (i) Miller, R. D.; McKean, D. R. *Tetrahedron Lett.* **1979**, 583, 587. (j) Danheiser, R. L.; Martinez-Davila, C.; Morin, J. M., Jr. *J. Org. Chem.* **1980**, *45*, 1340; (k) Mueller, L. G.; Lawton, R. G. *Ibid.* **1979**, *44*, 4741; (l) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360.

(3) For reviews see: Trost, B. M. *Acc. Chem. Res.* **1974**, *7*, 85; *Pure Appl. Chem.* **1975**, *43*, 563; Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

(4) Trost, B. M.; Bogdanowicz, M. J.; Frazee, W. J.; Salzmann, T. N. *J. Am. Chem. Soc.* **1978**, *100*, 5512. Trost, B. M.; Frazee, W. J. *Ibid.* **1977**, *99*, 6124. Trost, B. M.; Bogdanowicz, M. J. *Ibid.* **1972**, *94*, 4777.

(5) (a) Trost, B. M.; Hiroi, K.; Holy, N. *J. Am. Chem. Soc.* **1975**, *97*, 5873. (b) Trost, B. M.; Keeley, D. E. *J. Org. Chem.* **1975**, *40*, 2013. (c) Trost, B. M.; Latimer, L. H. *Ibid.* **1978**, *43*, 1031. (d) Trost, B. M.; Rigby, J. H. *Ibid.* **1978**, *43*, 2938. (e) Trost, B. M.; Nishimura, Y.; Yamamoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 1328.

(6) (a) Danishefsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 7711, 4783. (b) Stevens, R. V.; Luh, Y. *Tetrahedron Lett.* **1977**, 979. (c) Wender, P. A.; Eissenstat, M. A.; Filosa, M. P. *J. Am. Chem. Soc.* **1979**, *101*, 2196. (d) Wenkert, E.; Berges, D. A.; Golob, N. F. *Ibid.* **1978**, *100*, 1263. (e) Wenkert, E.; Buckwalter, B. L.; Craveiro, A. A.; Canchez, E. L.; Sathe, S. S. *Ibid.* **1978**, *100*, 1267. (f) Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *Ibid.* **1978**, *100*, 4893. (g) Hiyama, T.; Kanakura, A.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1978**, 3047, 3051. (h) Piers, E.; Banville, J. *Chem. Commun.* **1979**, 1138. (i) Piers, E.; Ruediger, E. H. *Ibid.* **1979**, 166.

(7) In parallel independent work, Stevens developed the use of (1-phenylthio)cyclopropanecarboxaldehyde. See ref 6b.

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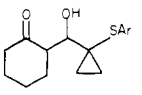
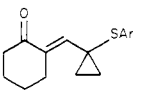
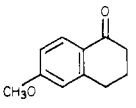
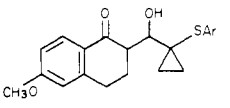
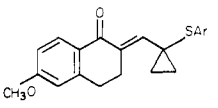
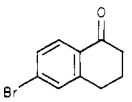
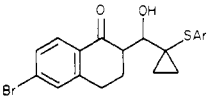
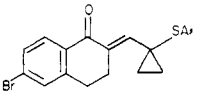
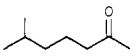
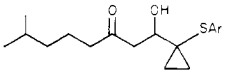
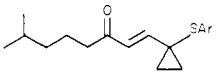
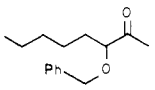
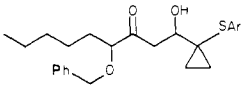
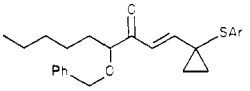
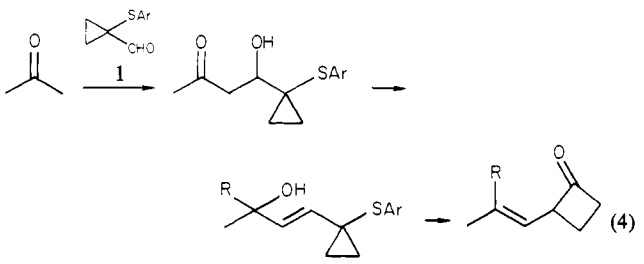
Table I. Aldol Condensation and Dehydration

entry	ketone	aldehyde	aldol product[a]	yield	dehydration, product	yield
1						
			6		7	
		1a	6a	86	7a	76
		1b	6b	83	7b	76
		1c[b]	6c	83	7c	71
2						
			8		9	
		1a	8a	90	9a	87
		1c[b]	8c	96[c]	9c	91
3						
			10		11	
		1a	10a	72	11a	24[d]
		1c[b]	10c	99[c]	11c	81
4						
		1c[b]	12c	94	13c	68
		1c[b]				
5						
		1c[b]	14c	70	15c	98

[a] In the "a" series, Ar = Ph; "b" series, Ar = 4-$CH_3OC_6H_4$; "c" series, Ar = 2,6-$(CH_3O)_2C_6H_3$. [b] A solution of anhydrous zinc chloride in ether was added prior to the addition of the aldehyde. [c] Crude yield; compound used directly in dehydration without further purification. [d] For this reaction, a stoichiometric amount of HMPA in pyridine as a solvent was employed instead of the normal conditions. The dehydration was not attempted via the normal pathway which would be the method of choice.

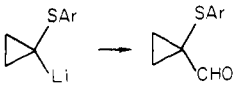
hold for introduction of functionalized chains α to a carbonyl group. For this purpose, we undertook an investigation of the synthesis and reactions of 1-(arylthio)cyclopropanecarboxaldehyde (**1**), for which we envisioned a sequence as outlined in eq 4.



(4)

Synthesis of Conjunctive Reagents

Three routes to the requisite reagents were employed. In the first, 1-lithiocyclopropyl phenyl sulfide (**2**), generated by direct deprotonation of cyclopropyl phenyl sulfide,[2d] was formylated by quenching with DMF. 1-Lithiocyclopropyl 4′-anisyl sulfide (**2**, Ar = 4-$CH_3OC_6H_5$) was similarly quenched with DMF to give **1b**. Since direct metalation of cyclopropyl 4-anisyl sulfide (**3**)



2 **1a**, Ar = Ph
1b, Ar = 1-$CH_3OC_6H_4$

led only to ring lithiation ortho to the methoxy group, chlorination with NCS at the cyclopropyl carbinyl position[8] followed by metal–halogen exchange[9] was required to smoothly give the requisite cyclopropyllithium compound **2b** (Scheme I).[10] This alternative synthetic approach to net lithiation should serve to greatly expand the availability of substituted lithiocyclopropyl aryl sulfides as a general class of conjunctive reagents. The desired conjunctive reagent **1b** was available in 35% overall yield from *p*-anisylthiol, the precursor to the cyclopropyl sulfide **3**.

The third reagent, 1-(2,6-dimethoxyphenyl)cyclopropanecarboxaldehyde (**1c**), was synthesized by a different approach as outlined in Scheme II. This route is patterned after that employed by Stevens in his studies of 1-(phenylthio)cyclopropanecarboxaldehyde.[6b] We found the interesting thiol **4**[11] to be conveniently available via direct metalation chemistry.[12] The requisite conjunctive reagent **1c** was available in 47% overall yield from **4** or 33% overall yield from 1,3-dimethoxybenzene.

Aldol Condensation. The initial step in the chain extension is the directed aldol condensation of a ketone enolate with the aldehydes **1a–c**. For **1a,b**, simple quenching of the lithium enolates by rapid addition of the aldehyde at −78 °C gave the adducts normally in 70% yields (see Table I). On the other hand, quenching with the more hindered aldehyde **1c** required prior addition of anhydrous zinc chloride to the lithium enolates[13] and a temperature of −10 °C to give the desired adducts normally in

(8) Oae, S.; Masuda, T.; Furukawa, N. *Chem. Lett.* **1977**, 1103.

(9) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785. Also see: Miller, R. B.; McGarvey, G. *Synth. Commun.* **1979**, *9*, 831.

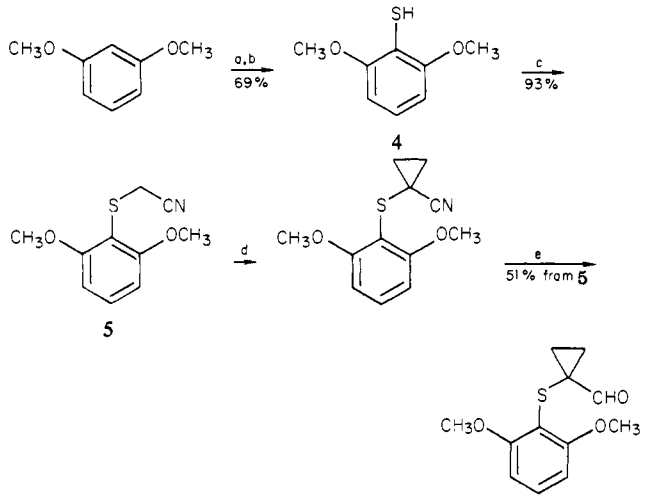
(10) For an alternative indirect generation from 1,1-bis(phenylthio)-cyclopropanes, see: Cohen, T.; Matz, J. R. *Synth. Commun.* **1980**, *10*, 311; Cohen, T.; Daniewski, W. M.; Weisenfeld, R. B. *Tetrahedron Lett.* **1978**, 4665.

(11) (a) Baliah, V.; Rangarajan, T. *J. Indian Chem. Soc.* **1961**, *38*, 33. (b) Hirota, M.; Hoshi, R. *Tetrahedron* **1969**, *25*, 5953.

(12) Shirley, D. A.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 217.

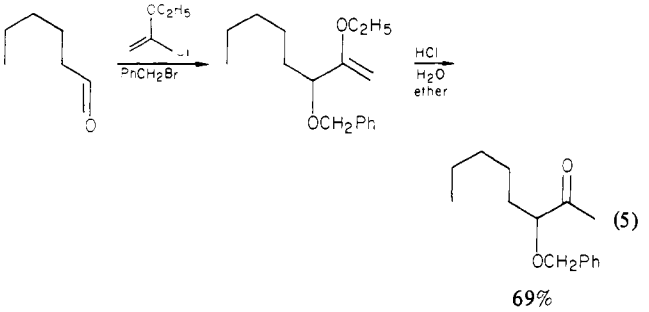
(13) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

Scheme II



90% yields. Table I summarizes the results. The aldol products are characterized by infrared absorptions at 3500 ± 50 (OH) and 1700 ± 10 (C=O) or 1660 ± 10 cm^{-1} (ArC=O). Characteristic NMR signals appear between δ 4.6–3.6 (d or t, 1 H, J = 4–5 Hz) for *H*COH and δ 1.0–0.8 (m, 4 H) for the cyclopropyl protons.

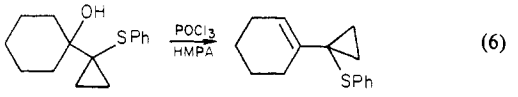
6-Bromo-3,4-dihydronaphthalen-1(2*H*)-one (Table I, entry 3) was synthesized by diazotisation of 6-amino-1-tetralone[14] with *tert*-butyl nitrite followed by decomposition of the diazonium salt with anhydrous cupric bromide in acetonitrile.[15] 2-Benzyloxyoctan-2-one was available in 69% overall yield by addition of 1-ethoxyvinyllithium[16] to hexanal, in situ quenching with benzyl bromide and HMPA and aqueous acid hydrolysis (eq 5).



(5)

69%

Dehydration Step. Dehydration of the aldol products was anticipated to be complicated by retroaldol reaction and ring enlargement. Indeed, typical dehydration conditions were unsatisfactory. Earlier in these laboratories, a mixture of $POCl_3$ in HMPA (eq 6) proved particularly effective for dehydrating



(6)

the adducts of 1-lithiocyclopropyl phenyl sulfide to carbonyl partners without concommitant rearrangement.[17] There is some question as to what is the actual reagent. Addition of $POCl_3$ to a solution of the alcohol in HMPA results in the immediate formation of a white precipitate which gradually redissolves. It has been reported that a redistribution of groups occurred (eq 7) and recent evidence suggested the intermediacy of a salt, **16**, which is stable at room temperature.[18] Either the salt **16** or *N*,*N*,*N*′,*N*′-tetramethylphosphordiamidic chloride (**17**) can participate in activating the hydroxyl group toward elimination.

$$O{=}PCl_3 + 2O{=}P[N(CH_3)_2]_3 \rightarrow 3[(CH_3)_2N]_3PCl^+\ PO_2Cl_2^- \rightarrow 3O{=}P(Cl)[N(CH_3)_2]_2 \quad (7)$$

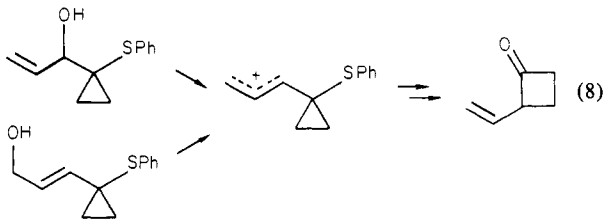
16 **17**

This new dehydration method proved very effective in the current case as the examples summarized in Table I show. The initial reaction involves treating the alcohol in HMPA with $POCl_3$ with slow heating to 50 °C. After formation of a homogeneous solution, pyridine is added and the dehydration completed at 100 °C. An attempt to use pyridine as solvent and stoichiometric amounts of HMPA with $POCl_3$ led to a substantially reduced yield (see Table I, entry 3a). Assignment of the *E* geometry is based upon the chemical shift of the olefinic proton between δ 7.14 and 6.52 (b s, 1 H; for *Z* isomer expected at $\delta \sim 5$) and the 15-Hz coupling in the cases of **13c** and **15c**. The IR spectra reveal a conjugated carbonyl stretch at 1680 ± 15 cm^{-1}.

Formation of Vinyl Cyclobutanones. The alcohols derivable from the ketones of Table I serve as the precursors for the ring expansion to cyclobutanones. Formation of the secondary alcohol with minimization of conjugate reduction was achieved with DIBAL for the phenylthio series ("**a**" series) and with lithium diisobutyl-*n*-butylaluminum hydride[5c,19] (the ate complex from *n*-butyllithium and DIBAL) for the 2,6-dimethoxyphenyl series ("**c**" series). The latter reagent appears to be a very selective source of nucleophilic hydride in a number of reactions. Table II summarizes the results. The infrared spectra of the desired alcohols generally showed hydroxyl stretching vibrations at 3600 and 3500–3400 cm^{-1}. The methine proton on carbon bearing the hydroxyl group appeared between δ 3.92 and 3.84 as either a broad singlet or multiplet, except in the tetralone series where this proton is also benzylic and thus appears between δ 4.78 and 4.62. The vinyl protons shift upfield (relative to the enones) to δ 6.5–5.7.

Tertiary alcohols are available by addition of Grignard reagents to the ketones. For simplicity, *n*-butylmagnesium bromide was employed with the results also summarized in Table II.

We envisioned the formation of cyclobutanones from our allylic alcohols in a fashion similar to our earlier studies,[2c] only in a vinylogous sense (eq 8). Slow addition of an ether solution of

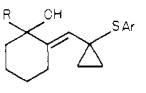
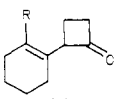
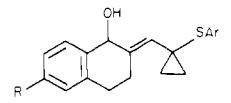
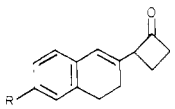
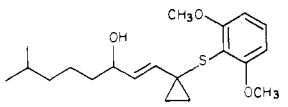
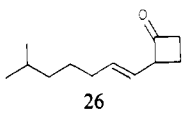
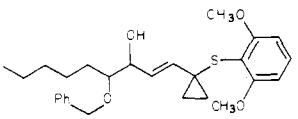
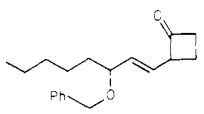


(8)

the allyl alcohols in the "**a**" series (i.e., Ar = Ph) to a mixture of ether and 48% fluoboric acid gave rise to the desired cyclobutanones in moderate yields (see Table II). That the cyclobutanone had been formed was indicated by the carbonyl stretching vibration at 1775 ± 5 cm^{-1} and the NMR absorption for H_a which appeared between δ 4.30 and 3.76 as either a triplet or multiplet. Unfortunately, the formation of many byproducts made isolation of pure products tedious. Typically, the crude residue was subjected to Kugelrohr distillation followed by a fractional distillation or chromatography. It is interesting to note that an inverse relationship existed between the yield and the stability of the presumed intermediate carbonium ion, the more stable the carbonium ion the lower the yield: i.e., **18a**, 60%; **19a**, 48%; **12a**, 36%; **20a**, 28%. Use of trimethyloxonium fluoborate gave yields comparable to that of fluoboric acid. Stannic chloride,

(14) Allinger, N. L.; Jones, E. S. *J. Org. Chem.* **1962**, *27*, 70.
(15) Doyle, M. P.; Siegfried, B.; Dellaria, J. F., Jr. *J. Org. Chem.* **1977**, *42*, 2426.
(16) Schollkopf, V.; Hanssle, P. *Justus Liebigs Ann. Chem.* **1972**, 763, 208. Baldwin, D. E.; Hofle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974** *96*, 7125.
(17) Caldwell, C., unpublished observations in these laboratories.
(18) Dormoy, J. R.; Castro, B. *Tetrahedron Lett.* **1979**, 3321. Pianka, B.; Owen, B. D. *J. Appl. Chem.* **1955**, *5*, 525. Lester, P. U.S. Patent 2678335; *Chem. Abstr.* **1954**, *49*, 6300. Also see: Normant, H. *Russ. Chem. Rev. (Engl. Transl.)* **1970**, *39*, 457.
(19) Trost, B. M.; Rivers, G. T.; Gold, J. *J. Org. Chem.* **1980**, *45*, 1835. Kovaco, G.; Galamba, G.; Juvancz, A. *Synthesis* **1977**, 171.
(20) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100.

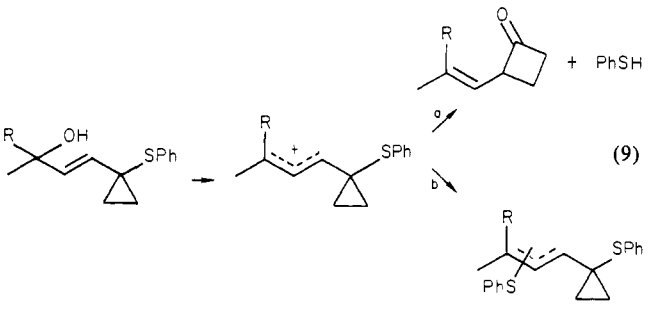
Table II. Formation of Vinylcyclobutanones

entry	ketone	addition reagent	alcohol	yield	cyclobutanone	yield
						
			18, R = H; 19, R = n-C_4H_9		24	
1	7a	DIBAL	18a, Ar = Ph	83	24a, R = H	60
2	7c	DIBAL	18c, Ar = 2,6-$(CH_3O)_2C_6H_3$	89	24a, R = H	70
3	7a	C_4H_9MgBr	19a, Ar = Ph	66	24b, R = C_4H_9	48
4	7b	C_4H_9MgBr	19b, Ar = 1-$(CH_3O)C_6H_4$	70	24b, R = C_4H_9	44
5	7c	C_4H_9MgBr	19c, Ar = 2,6	100	24c, R = C_4H_9	61 (40)[b]
						
			20, R = OCH_3; 21, R = Br		25	
6	9a	DIBAL	20a, Ar = Ph	59	25a, R = CH_3O	20
7	9c	LiAlH(n-C_4H_9), (s-C_4H_9)$_2$	20c, Ar = 2,6-$(CH_3O)C_6H_3$	86	25a, R = CH_3O	46[a]
8	11a	DIBAL	21a, Ar = Ph	70	25b, R = Br	36
9	11c	LiAlH(n-C_4H_9), (s-C_4H_9)$_2$	21c, Ar = 2,6-$(CH_3O)C_6H_3$	97	25b, R = Br	62 (44)[b]
						
10	13c	LiAlH(n-C_4H_9), (s-C_4H_9)$_2$	22c	87	26	58 (44)[b]
						
11	15c	LiAlH(n-C_4H_9), (s-C_4H_9)$_2$	23c	98	27	(32)[b]

[a] The initial yield was 57% but the material was only ~90% pure by NMR. Additional chromatography gave 46% pure product. [b] Yield in parentheses represents the overall yield from starting cyclopropanecarboxaldehydes 1 and ketones without purifying intermediates.

p-toluenesulfonic acid, and p-toluenesulfinic acid gave inferior results.

In searching for a source of the complexity of the reaction, we attempted to purify the byproducts. In several instances a relatively nonpolar side product was partially purified. Its NMR spectrum revealed the presence of the cyclopropane ring and two phenylthio groups. Since the formation of cyclobutanone liberates thiophenol (eq 9a), this byproduct might involve trapping the intermediate cation by the liberated thiophenol (eq 9b). The fact

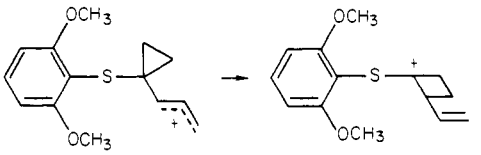


(9)

that the more stabilized carbonium ion led to a lower yield of the desired cyclobutanone reinforced this interpretation. Attempts to encapsulate thiophenol to preclude such an undesirable side reaction were to no avail—apparently the carbonium ion is a better trap than the alternatives.

In order to improve the ring enlargement, we needed to increase the rate of migration of the cyclopropyl bond and/or to decrease the rate of trapping by the thiol. Our initial approach focused on increasing the rate of ring enlargement by increasing the push by sulfur. However, when we switched from phenylthio to 4-methoxyphenylthio (cf. Table II, entries 3 and 4), virtually no change occurred. Apparently, while an increased rate of rearrangement might have occurred, a corresponding increase in rate of trapping of the intermediate carbonium ion by the thiol accompanied it since the p-methoxy group would also increase the nucleophilicity at sulfur of the p-methoxythiophenol. The net effect is for the two phenomena to balance each other, leading to no change.

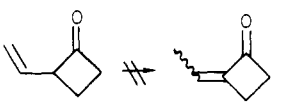
Being unconvinced that our reasoning was faulty, we carried our thinking one step further. We needed a substitution pattern that provided electronic acceleration for the bond migration but also steric bulk to inhibit the nucleophilicity of the thiol. Our choice of 2,6-dimethoxyphenyl (eq 10) was motivated not only



(10)

by these considerations but also from the point of view that bis ortho substitution may provide a steric as well as an electronic acceleration for the bond migration. We were most gratified by the experimental results. Not only did the yields improve in every case, but also the tremendous increase in the cleanliness of the reaction mixtures allowed isolation of the pure cyclobutanones by simple distillation or, on small scale, a simple chromatography. The facility of the reaction is highlighted by the fact that one can synthesize the desired cyclobutanones from the conjunctive reagent **1c** and starting ketone in about 40% overall yield from starting ketone without purifying any intermediates (see Table II, entries 5, 9, 10, 11).

It is interesting to note that we only obtained the vinylcyclobutanones and we did not see the alkylidene isomers (eq 11). The

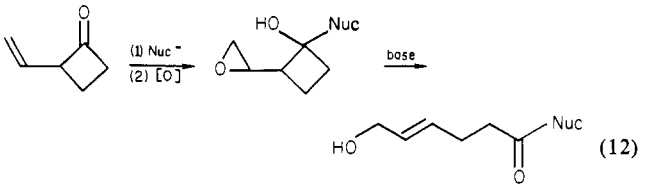


(11)

two dihydronaphthalene derivatives, **25a** and **25b**, were obtained as amorphous solids, but all the rest were obtained as colorless sweet smelling oils. The 270-MHz NMR spectra of **26** and **27**

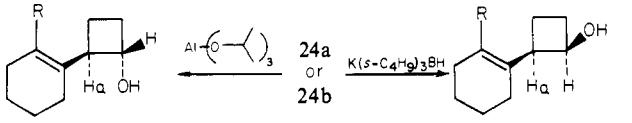
verified the E geometry of the olefin (**26**, δ 5.57, dtd, J = 15.8, 6.5, 1.2 Hz, and δ 5.43, ddt, J = 15.8, 6.5, 1.2 Hz; **27**, δ 5.65, dd, J = 15.5, 6.2 Hz, and 5.47, ddm, J = 15.5, 7.75 Hz).

Fragmentation Sequence. Unravelling the functionalized carbon chain focused on the nucleophilically triggered fragmentation of epoxycyclobutanones.[4] Addition of a nucleophile to the cyclobutanone followed by epoxidation primes the system for the fragmentation with base as outlined in eq 12. Three types of nucleophiles were employed, hydride, alkyl and aryl organometallic reagents, and ester enolates.



(12)

Reduction of the cyclobutanones **24a** and **24b** with potassium selectride gave a single cyclobutanol; similarly, reduction with aluminum isopropoxide under Meerwein–Ponndorf–Verley conditions gave an isomeric cyclobutanol (eq 13).[21] Considering the



29a, R = H
29b, R = n-C_4H_9

28a, R = H
28b, R = n-C_4H_9

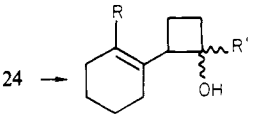
(13)

former conditions should lead to that isomer involving attack of hydride from the least hindered face and the latter conditions should reflect thermodynamic considerations, we assigned the Z (i.e., **28**) and E[22] (i.e., **29**) configuration, respectively. Sodium borohydride gave a 2:1 mixture of **29** and **28**, respectively.

With the assignment of the stereochemistry utilizing mechanistic considerations, several trends which proved useful for stereochemical assignment in later cases were noted. Chromatographically, the E isomers **29** were more polar than their Z counterparts **28**.[23] The NMR shift for the allylic proton (labeled H_a in **28** and **29**) of the E isomers **29** appeared upfield compared to the Z isomers of **28**. The shielding of a proton by a hydroxyl group cis to it was also observed in the NMR spectrum of cyclobutanol itself.[24] The line shapes for H_a were strikingly different in the two isomers; the E isomers showed H_a either as a triplet (J = 7–9 Hz), a broad quartet, or multiplet, while the Z isomers only showed a multiplet with no observable splittings for this absorption. Finally, the vinyl proton of the E isomer absorbed at higher field than that in the corresponding Z isomer. These same trends were observed for all the subsequent cyclobutanols and thus formed the basis of their stereochemical assignment (see Experimental Section).

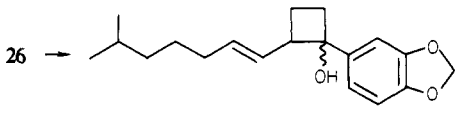
At −78 °C in ether, Grignard and alkyl- and aryllithium reagents added nicely to the cyclobutanones to give **30a,b,c** and **31** without complications from enolization (eq 14 and 15). Mixtures of diastereomers usually resulted, the major isomer arising from attack on the presumably less hindered face, the side opposite the C-2 substituent. Use of spectral and chromatographic data as above supported this assignment. In general, the diastereomers were readily separated by chromatography.

Most exciting was the ready addition of ester enolates to give cyclobutanols **32**, **33a–d**, **34**, and **35** as shown in eq 16–19. With

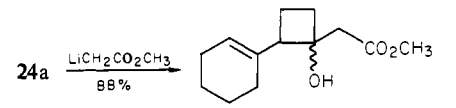


(14)

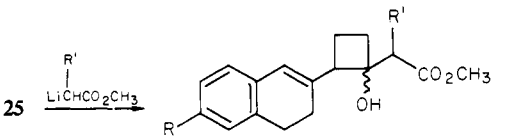
C_2H_5MgBr 30a, R = H, R' = C_2H_5 (96%)
n-C_4H_9Li 30b, R = R' = n-C_4H_9 (86%)
n-$C_5H_{11}MgBr$ 30c, R = n-C_4H_9, R' = n-C_5H_{11} (79%)



31 (58%) (15)

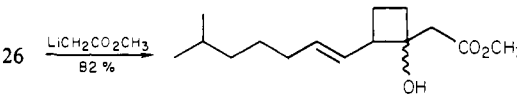


32 (16)

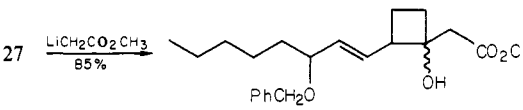


(17)

33a, R = OCH_3, R' = H (65%)
33b, R = OCH_3, R' = CH_3 (94%)
33c, R = Br, R' = H (73%)
33d, R = Br, R' = CH_3 (95%)



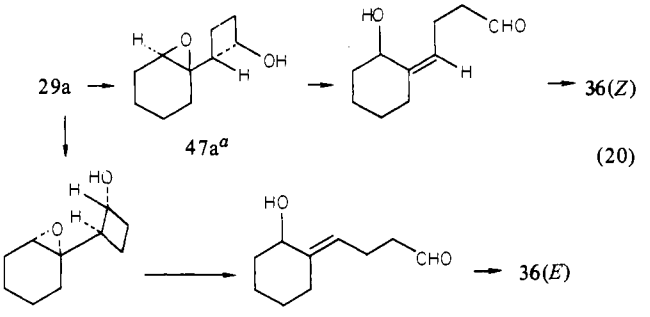
34 (18)



35 (19)

use of the same chromatographic and spectral criteria summarized above, the major isomers were assigned the E configuration (vicinal hydroxyl and alkyl groups trans). Separation of these cyclobutanols into their pure diastereomers was difficult.

Cyclobutanols **30a–c**, **31**, **32**, and **33c,d** smoothly epoxidized with buffered MCPBA in methylene chloride at 0 °C (for all cases except **35**) or room temperature (for **35**).[25] Generally, the epoxides were directly fragmented by treatment with base. Table III summarizes the results. It had been established that methanolic sodium methoxide effects a stereospecific anti elimination.[4] Thus, the stereochemistry of the epoxidation can be correlated with the stereochemistry of the fragmented products and, at times, verified by independent direct spectral examination of the epoxides. For example, the crude epoxide from cyclobutanol **29a** was determined to be a 2:1 mixture of diastereomers as determined by NMR absorptions at δ 3.08 (b s, ~0.67 H) and 2.88 (b s, ~0.33 H) (see eq 20 and Table III). Treatment of this crude epoxide



(20)

[a] A 2:1 mixture of 47a–47b.

(21) Wilds, A. L. *Org. React.* (*N.Y.*) **1944**, *2*, 178. Also see: Moriarty, R. M. *Top. Stereochem.* **1974**, *8*, 273.

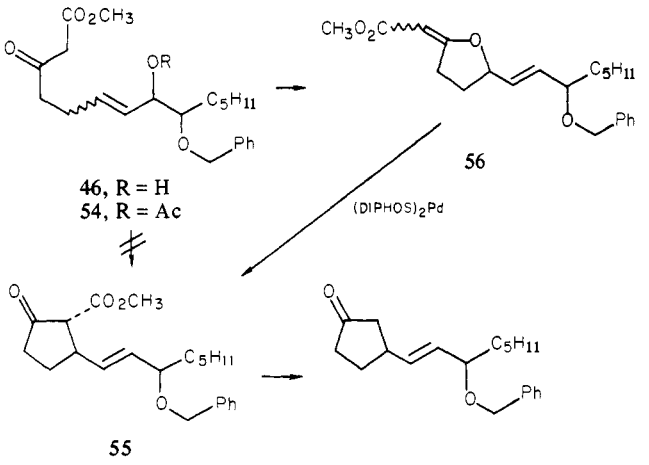
(22) The E configuration has been shown to be thermodynamically more stable in the cyclobutyl system. Fonkin, G. J.; Shiengthong, S. *J. Org. Chem.* **1963**, *28*, 3435.

(23) Cf.: Wagner, P. J.; Kelso, P. A.; Kemppainen, A. E.; McGrath, J. M.; Schott, H. N.; Zepp, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 7506.

(24) Wiberg, K. B.; Barth, D. E. *J. Am. Chem. Soc.* **1969**, *91*, 5124. Also see: Yang, N. C.; Morduchowitz, A.; Yang, D. D. H. *Ibid.* **1963**, *85*, 1017; Yang, N. C.; Elliot, S. P.; Kim, B. *Ibid.* **1969**, *91*, 7551.

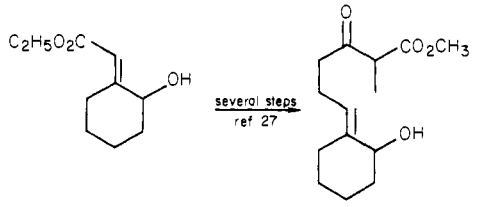
(25) Anderson, W. K.; Veysoglw, T. *J. Org. Chem.* **1973**, *38*, 2267.

Scheme III



mixture with methanolic sodium methoxide containing sodium borohydride gave the desired allylic alcohols as a 2:1 mixture of *Z* and *E* olefins as determined by NMR absorptions at δ 5.20 (t, J = 7 Hz, ~0.64 H) and δ 5.44 (t, J = 7 Hz, ~0.33 H). Not only did the ratio of olefin stereoisomers fully reflect the ratio of epoxide diastereomers, but also the stereochemistry of the olefins (vide infra) allowed assignment of the stereochemistry of the epoxides as **47a,b** (eq 20). Similar arguments apply to all the remaining cases.

Stereochemical assignment of the trisubstituted olefins rests on NMR arguments. The allylic alcohols **36**, **38**, **42**, **43**, and **44** showed a typical pattern for the olefinic proton H_a and the hydroxyl methine H_b in which the signals for *E* and *Z* isomers were clearly discernible. These assignments were confirmed by isolation of the pure *E* isomer of **36** and the pure *Z* isomer of **38** and europium-induced shifts. A Eu(fod)$_3$ shift study on **38**(*E*,*Z*) shifted the olefinic proton at δ 5.02 by 0.78 ppm to δ 5.80 while the absorption at δ 5.30 shifted by 1.36 ppm to δ 6.66. In both isomers, the methine proton geminal to the hydroxyl group shifted by ~1.7 ppm, indicating that the above differential shifts were not due to preferential coordination of the europium reagent with one of the two isomers. The known selectivity of the europium reagent to coordinate to a hydroxyl group more strongly than a carbonyl group[26] allowed the signal at δ 5.02 to be assigned to the *Z* olefinic proton and that at δ 5.30 to the *E* olefinic proton. Independent evidence derived from an unequivocal synthesis of **48** whose spectral data closely paralleled that for **42**(*E*) (eq 21).



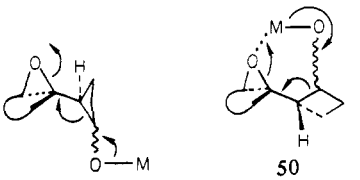
(21)

48

Assignment of olefin geometry to alcohols **37**, **39**, and **40** utilized the chemical shift difference of the olefinic protons as the primary criterion—the shift of this proton for the *E* isomer again appearing at lower field than that for the *Z* isomer. Addition of Eu(fod)$_3$ to **40**(*E*,*Z*) caused the olefinic triplet at δ 5.43 to shift to δ 6.16 while the doublet of doublets at δ 5.01 shifted only to δ 5.31—an observation which verifies the above trend. Parenthetically, we noticed that the *E* isomers of this series were the more polar isomers by TLC on silica gel than the corresponding *Z* isomers.

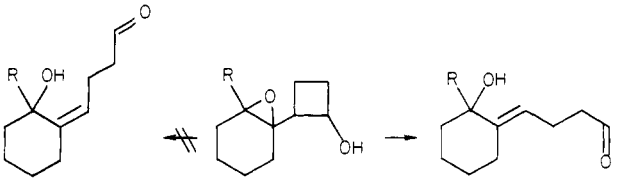
Assignments for allylic alcohols **41**, **45**, and **46** were relatively simple since they all contained a disubstituted double bond. The NMR spectrum of allyl alcohol **41** showed a vinyl coupling constant of 15.5 Hz for the major isomer and thus assigned the *E* configuration. Similarly, a 15-Hz coupling constant was observed for the major isomer of **45**. The presence of diastereomers in addition to olefin stereoisomers complicated the interpretation of the spectrum of **46**. However, the presence of two complex multiplets at δ 4.21 and 4.01 in a 1:1 ratio, assigned to the hydroxyl methine protons of the two olefinic isomers, suggested a 1:1 ratio of *E* and *Z* olefins.

While sodium methoxide induced a stereospecific anti fragmentation, (i.e., **49**), the high strain energy of the epoxycyclobutanols (~50–55 kcal/mol)[28] and the possibility for a transition state in which the hydroxyl and epoxide oxygens chelate a metal ion suggest the difference between a syn (i.e., **50**) and anti pathway



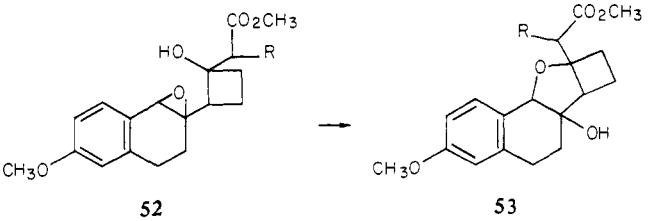
49 50

may be reduced or even reversed by switching from sodium to magnesium methoxide. Indeed, treating the 2:1 mixture of epoxide diastereomers from cyclobutanol **29a** with methanolic magnesium methoxide containing sodium borohydride gave the allylic alcohol **36** in 80% with a 1:1 ratio of *E*–*Z* olefin isomers. The dramatic effect of the magnesium counterion on the stereochemical course of the reaction was repeated in the cases of entries 2, 8, 10, 13–17, 24, and 25 in Table IV. Temperature plays a role (Table III, entries 13–15) with the lower temperature giving higher stereoselectivity. It is important to note that virtually complete stereoselectivity for the *E* isomer is observed in fragmentations of tetrasubstituted epoxides of general structure **51** (R = alkyl or aryl) because of the severe steric congestion in the *Z* isomer (eq 22). When R = H, the steric congestion of the *Z* isomer is sufficiently diminished that both isomers can be seen although a strong preference still exists for the *E* isomer under the magnesium methoxide conditions.



(22)

In only one case did we fail to achieve the secoalkylation sequence. Epoxide **52** opened at the benzyllic position to give the tetrahydrofuran **53** rather than fragment (eq 23). Assessing the source of the opening as, in part, arising from the electron-releasing methoxyl group, we switched to the bromo derivative **33** and returned to clean fragmentation.



(23)

Synthesis of Cyclopentane Derivatives. Many applications of this functionalized carbon chain elongation procedure can be

(26) Martin, G. S.; Martin, M. L. *Prog. Nucl. Magn. Reson. Spectrosc.* **1972**, *8*, 163.
(27) Runge, T., unpublished work in these laboratories.
(28) Cox, J. D. *Tetrahedron* **1963**, *19*, 1175.

Table III. Fragmentation

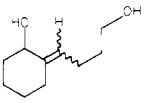
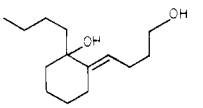
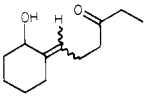
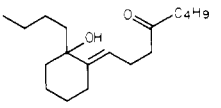
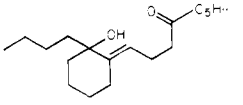
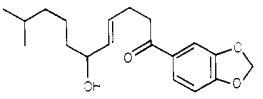
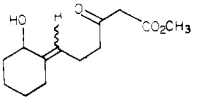
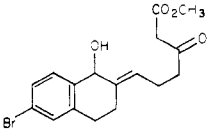
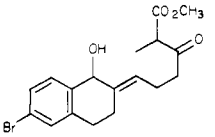
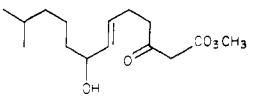
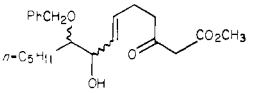
entry	vinyl cyclobutanol	epoxide[a] ratio	base[b]	product	E–Z
1	28a	3:2[d]	$NaOCH_3$[c]	 36	3:2[c]
2	28a	3:2[d]	$Mg(OCH_3)_2$[c]	36	2:3[e]
3	29a	2:1[b]	$NaOCH_3$[c]	36	1:2[e]
4	29a	2:1[b]	$Mg(OCH_3)_2$[c]	36	>10:<1[e]
5	28b	100:0[d]	$NaOCH_3$[c]	 37	100:0[b]
6	29b	1:1[d]	$NaOCH_3$[c]	37	1:1[g]
7	29b	1:1[d]	$NaOCH_3$[c]	37	1:1[g]
8	29b	1:1[d]	$Mg(OCH_3)_2$[c]	37	100:0[g]
9	30a(Z)	3:2[h]	$NaOCH_3$	 38	3:2[i]
10	30a(Z)	3:2[h]	$Mg(OCH_3)_2$	38	2:3[i]
11	30a(E)	95:5[x]	$NaOCH_3$	38	<7:>93[i]
12	30a(E)	95:5[x]	$Mg(OCH_3)_2$	38	16:84[i]
13	30b		$Mg(OCH_3)_2$[j]	 39	3:2[i]
14	30b		$Mg(OCH_3)_2$[l]	39	3:1[r]
15	30b		$Mg(OCH_3)_2$[l]	39	94:6[r]
16	30c		$Mg(OCH_3)_2$[m]	 40	95:5[h]
17	31		$Mg(OCH_3)_2$[o]	 41	3:1[p]
18	32(Z)	1:1[q]	$NaOCH_3$	 42	~1:1[r]
19	32(Z)	1:1[q]	$Mg(OCH_3)_2$	42	2:3[r]
20	32(Z)	1:1[q]	$PhCH_2N^+(CH_3)_3O^-CH_3$	42	3:2[r]
21	32(E)	4:1[s]	$NaOCH_3$	42	>1:5[r]
22	32(E)	4:1[s]	$Mg(OCH_3)_2$	42	1:3[r]
23	32(E)	4:1[s]	$PhCH_2N^+(CH_3)_3O^-CH_3$	42	
24	33c		$Mg(OCH_3)_2$[u]	 43	>1:5[r]
25	33d		$Mg(OCH_3)_2$[u]	 44	>1:1[t]

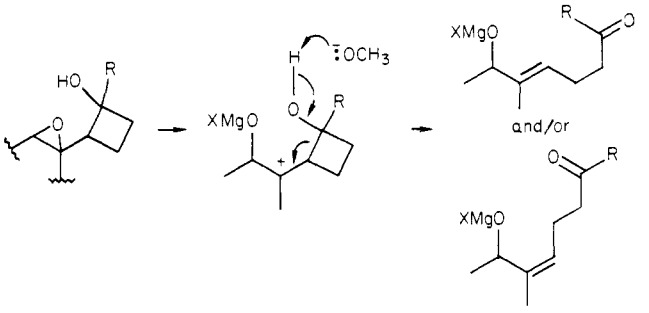
Table III (*Continued*)

entry	vinyl cyclobutanol	epoxide[a]/ratio	base[b]	product	*E*–*Z*
26	34		$Mg(OCH_3)_2$[o]	 45	>1:1[v]
27	35[w]		$Mg(OCH_3)_2$[m]	 46	

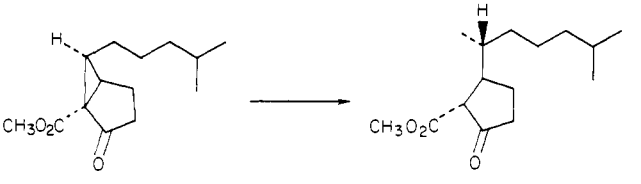
[a] In virtually all cases, MCPBA in the presence of $NaHCO_3$ was used for epoxidation. [b] Typically 2–3 molar equiv of base at room temperature overnight were employed to effect cleavage. [c] In this case, 1 equiv of sodium borohydride was added to reduce the first formed aldehyde to the alcohol. [d] Assigned by assuming that sodium methoxide catalyzes a concerted anti fragmentation. [e] Determined by NMR integration of the olefinic signals at δ 5.44 (t) and 5.20 (t). [f] Determined by NMR integration of the signals at δ 3.08 (p) and 2.88 (p). [g] Determined by NMR integration of the olefinic signals at δ 5.44 (t) and 5.04 (dd). [h] Determined by NMR integration of signals at δ 3.2 and 2.8. [i] Determined by NMR integration of olefinic signals at δ 5.30 (t) and 5.02 (t). [j] Reaction performed for 22 h at room temperature. [k] Determined by NMR integration of the olefinic signals at δ 5.38 (t) and 4.88 (dd). [l] Reaction performed for 20 min at 65 °C. [m] Reaction performed for 72 h at +2 °C. [n] Determined by NMR integration of the olefinic signals at δ 5.43 (dd) and 5.01 (dd). [o] Reaction performed for 24-h at +2 °C. [p] Determined by NMR integration of the olefinic signals at δ 5.71 and 5.5. [q] Determined by NMR integration of signals at δ 3.2 and 2.8. [r] Determined by NMR integration of olefinic signals at δ 5.26 (t) and 5.00 (t). [s] Determined by NMR integration of new signal at δ 3.0 relative to the signal for the methyl ester. [t] Determined by NMR integration of olefinic signals at δ 5.56 (t) and 5.34 (m). [u] Reaction performed 15–30 min at room temperature. [v] See text. [w] Epoxidation performed with unbuffered MCPBA at room temperature. [x] Determined by NMR integration of epoxide methine proton at δ 3 relative to methyl ester signal.

envisioned. We concentrated our initial studies on cyclopentane synthesis, an area of intense interest in both physical organic and natural product studies. For example, **46** served as an intermediate toward PG's.[29–31] Cyclized of β-ketoesters related to **46** have been noted for their tendency to O-alkylate—an observation we confirmed.[30] Even cyclization of **54** with a catalytic amount of tetrakis(triphenylphosphine)palladium (**57**) in THF led to O-alkylation product **56** rather than the C-alkylation product **55**.[32] The O-alkylation product **56** was more conveniently available by direct reaction of **46** with boron trifluoride etherate in methylene chloride at 0 °C. Smooth isomerization of **56** occurred with bis(1,2-diphenylphosphinoethane)palladium in refluxing dioxane in the presence of *O,N*-bis(trimethylsilyl)acetamide (Scheme III).[32a] In the absence of the silylating agent, decarbomethoxylation accompanied rearrangement. The *E* stereochemistry of the 2,3-substituents is expected on thermodynamic grounds and verified by an 11-Hz coupling constant between the 2,3 protons.[30,33] Since **55** is the benzyl ether of the Roussel-Uclaf intermediate to PGA_2[30] and has served toward the PGE family,[31] this sequence is a formal synthetic entry into PG's. Further a lactone related to **55** has been found to have hypotensive activity.[34] Bicyclo[2.1.0]hexanes related to **57** have proven useful as an entry into the ring D of steroids (eq 24).[33,35] Such a system, **58**, is readily available in 44% overall yield from **45** after silylation of the alcohol by diazo transfer (TsN_3, CH_3CN, $(C_2H_5)_3N$, room temperature)[36]

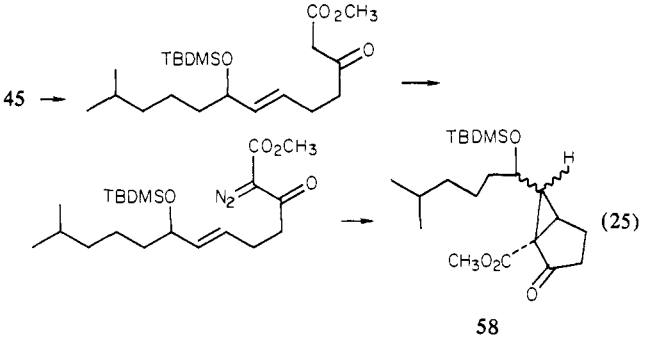
Scheme IV



followed by copper–bronze-catalyzed intramolecular carbene addition (eq 25). Further reaction of **58** in a fashion analogous to that shown for **57** would generate the D ring of the insect-molting hormone, ecdysone.



57 (24)



58 (25)

Alternatively, the 2′-carboalkoxy 3-substituted cyclopentanone system can be constructed from **46** by an intramolecular Michael reaction. Oxidation of the allylic alcohol **46** with pyridinium dichromate in DMF gave quantitative conversion to the crude

(29) For a review see: Bindra, J. S.; Bindra, R. "Prostaglandin Synthesis"; Academic Press: New York, 1977.

(30) Martel, J.; Blade-Font, A.; Marie, C.; Vivat, M.; Toromanoff, E.; Buenida, J. *Bull. Chim. Soc. Fr.* **1978**, II, 131. Buenida, J.; Nierat, J.; Vivat, M. *Ibid.* **1979**, II 614.

(31) Taber, D. F. *J. Am. Chem. Soc.* **1977**, *99*, 3513. Toru, T.; Kurozumi, S.; Tanaka, T.; Muira, S. *Tetrahedron Lett.* **1976**, 4087. Kondo, K.; Umemoto, T.; Takahatake, Y.; Tunemoto, D. *Ibid.* **1977**, 113.

(32) (a) Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 2840. (b) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, 1475.

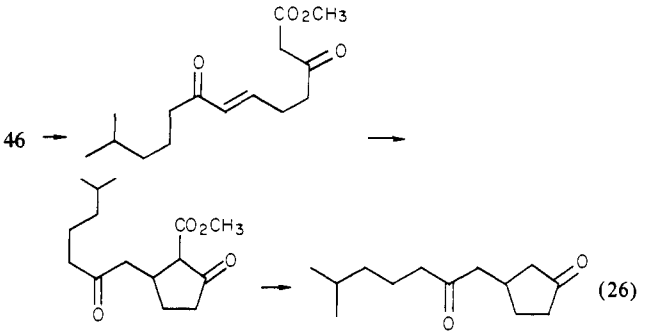
(33) Trost, B. M.; Taber, D. F.; Alper, J. B. *Tetrahedron Lett.* **1976**, 3857. Also see: Trost, B. M.; Vladuchick, W. C. *J. Org. Chem.* **1979**, *44*, 148.

(34) Roussel-Vclaf. Fr. Demande 2 383 936; *Chem. Abstr.* **1979**, *91*, 389984.

(35) Cf.: Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1975**, 529.

(36) Regitz, M.; Hocker, J.; Liedhegener, A. "Organic Syntheses"; Wiley: New York, 1973, p 179.

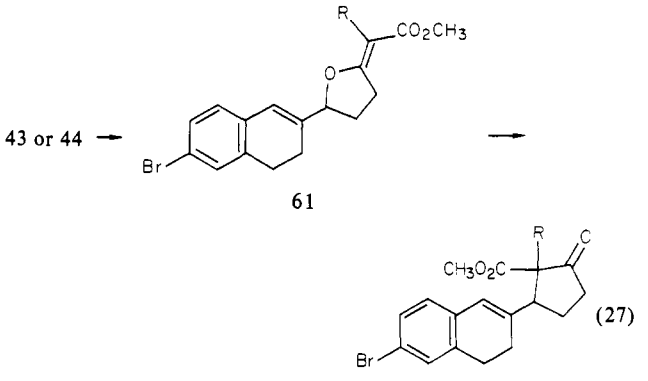
enone which was directly cyclized to **59** by reaction with 10 mol % of sodium methoxide in methanol (~95% overall yield). Further characterization of **59** was achieved by decarbomethoxylation with lithium chloride in wet Me_2SO[37] to give cyclopentanone **60** as a sweet smelling oil in 66% overall yield from **46** (eq 26).



(26)

59 60

In ancillary work, the keto esters **43** and **44** were directly cyclized to their corresponding crystalline (alkylidene)tetrahydrofurans **61** (R = H or CH_3) with boron trifluoride etherate in ether at −78 °C to room temperature in 33–55% overall yield from cyclobutanols **33c,d** (eq 27). These O-alkylated compounds have been smoothly isomerized to the desired cyclopentanones **62**[32] as an entry into the steroid family.[38]

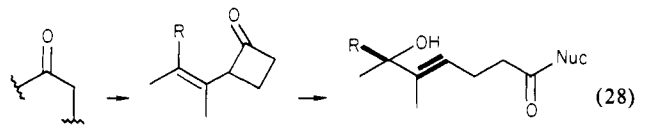


(27)

61 62

Discussion and Conclusions

1-((2′,6′-Dimethoxyphenyl)thio)cyclopropanecarboxaldehyde represents a very useful chain elongation conjunctive reagent (eq 28). As shown by the emboldened bonds in **63**, a C–C or C–H

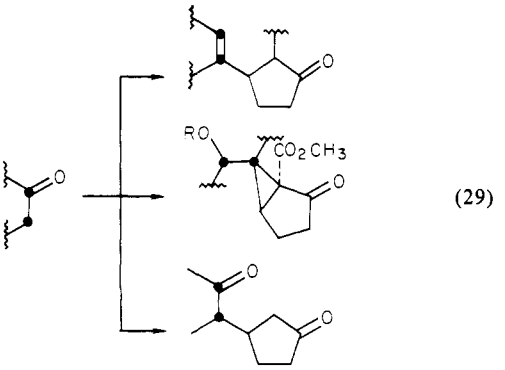


(28)

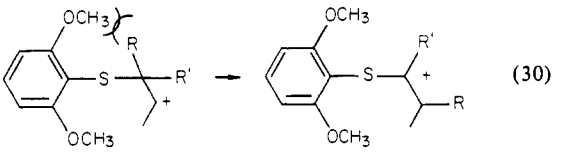
63

bond can be introduced at the former carbonyl carbon and an alkylidene group at the alpha carbon. The juxtaposition of the functionality is particularly advantageous as demonstrated by the variety of approaches to make cyclopentanones as shown in eq 29.

Two key points merit particular attention. First, the role of the (2,6-dimethoxyphenyl)thio ring appears unique. Electron donation by the methoxyl groups increases the ability of sulfur to stabilize an adjacent carbonium ion. Further steric congestion in the sulfide **64** is somewhat relieved in the Wagner–Meerwein shifted product **65** (eq 30). Both of these effects should contribute



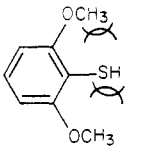
(29)



(30)

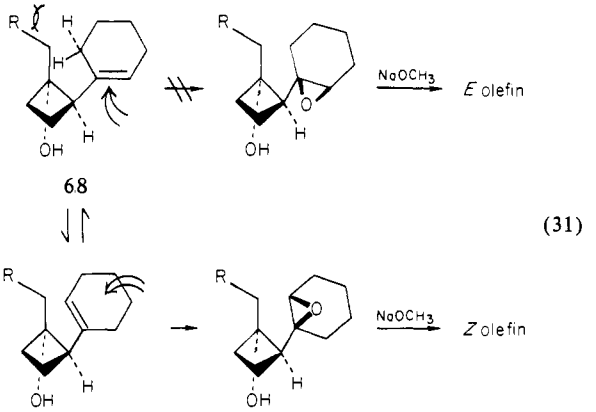
64 65

to an increased rate of alkyl shift. As previously noted, this steric shielding of the sulfur should also decrease the nucleophilicity of the thiol **66**. Second, the fragmentation induced by magnesium



66

methoxide can involve either a mixture of syn and anti fragmentations (i.e., **49** and **50**) or, more likely, a carbonium ion reaction (Scheme IV).[4,39] Thus the stereochemistry of the olefin can be attributed to thermodynamic considerations which, in many instances, led to high selectivity for the *E* isomer. Further, to the extent that the epoxidation can yield a single stereoisomer, then sodium methoxide can be used for fragmentation to a single olefin stereoisomer. The *E*-cyclobutanols of **30a** and **32** show such high selectivity compared to their *Z* counterparts. As previously pointed out (vide supra), we can assign the major to exclusive isomer to be **67** deduced from the stereochemistry of the fragmentation product. Of the two conformers of starting olefins **68** and **69**, the latter has smaller nonbonded eclipsing interactions than the former (eq 31). Approach of the epoxidizing agent from the least



68 69 67

(31)

hindered face of the olefin (distal from the quaternary cyclobutyl

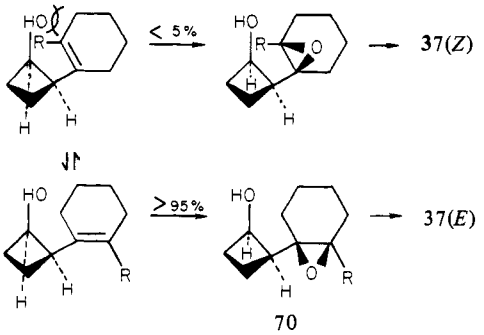
(37) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.
(38) Cf.: Posner, G. H.; Chapdelaine, M. J.; Lentz, C. M. *J. Org. Chem.* **1979**, *44*, 3661.
(39) Abenhaim, D.; Borreaw, G.; Narny, J.-L. *Bull. Soc. Chim. Fr.* **1972**, 985. House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070, 5083. Nawvi, S. M.; Horwitz, J. P.; Filler, R. *Ibid.* **1957**, *79*, 6284. Hudrlik, P. F.; Misia, R. N.; Withers, G. P.; Hudrlik, A. M.; Rona, R. J.; Arioles, J. P. *Tetrahedron Lett.* **1976**, 1453.

Table IV. Experimental Details for Fragmentation Reactions

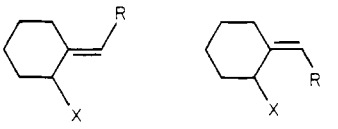
vinyl cyclobutanol, mg (mmol)	epoxidation: mg (mmol)	epoxidation: temp, °C	epoxidation: time, h	fragmentation: CH_3OH, mL	fragmentation: base (mmol)	fragmentation: $NaBH_4$, mg	product[a] (mg, % yield)
				28a			
48 (0.30)	65 (0.32)	0	5	5	$Mg(OCH_3)_2$ (2)	12	36 (45, 86)[b]
33 (0.21)	65 (0.32)	0	5	2	$NaOCH_3$ (0.3)	9	36 (21, 59)[c]
				29a			
45 (0.29)	65 (0.32)	0	5	2	$Mg(OCH_3)_2$ (1)	12	36 (40, 80)
45 (0.29)	65 (0.32)	0	5	3	$NaOCH_3$ (0.6)	12	36 (50, Q)[c]
				28b			
82 (0.39)	87 (0.43)	0	4	4	$Mg(OCH_3)_2$ (2)	15	37 (58, 66)[b]
				29b			
82 (0.39)	87 (0.43)	0	4	3	$NaOCH_3$ (0.9)	15	37 (54, 61)[d]
82 (0.39)	87 (0.43)	0	4	3	$Mg(OCH_3)_2$ (2)	15	37 (54, 61)[b]
				30a			
50 (0.27)[l]	62 (0.31)	0	5	3	$NaOCH_3$ (0.45)		38 (57, Q)[e]
45 (0.25)[l]	62 (0.31)	0	5	3	$Mg(OCH_3)_2$ (1)		38 (46, 94)[c]
50 (0.27)[m]	62 (0.31)	0	5	3	$NaOCH_3$ (0.45)		38 (40, 75)[c]
45 (0.25)[m]	62 (0.31)	0	5	3	$Mg(OCH_3)_2$ (1)		38 (50, Q)[c]
				30b			
528 (2)	440 (2.2)	0	5	20	$Mg(OCH_3)_2$ (10)[g]		39 (391, 69)[f]
132 (0.5)	110 (0.55)	0	5	5	$Mg(OCH_3)_2$ (2)[h]		39 (99.5, 71)[c]
132 (0.5)	110 (0.55)	0	5	5	$Mg(OCH_3)_2$ (2)[i]		39 (75.6, 54)[b]
				30c			
176 (0.63)	150 (0.75)	0	5	6	$Mg(OCH_3)_2$ (2)[i]		40 (90, 49)[b]
				31			
140 (0.46)	140 (0.69)	0	4	3	$Mg(OCH_3)_2$ (1.5)[i]		41 (102, 69)[b]
				32			
50 (0.22)[l]	49 (0.25)	0	5	3	$NaOCH_3$ (0.45)		42 (50, 95)[b]
50 (0.22)[l]	49 (0.25)	0	5	3	$Mg(OCH_3)_2$ (1)		42 (56, Q)[b]
49 (0.22)[l]	49 (0.25)	0	5	3	$PhCH_2N(CH_3)_3OCH_3$ (0.3)		42 (45, 85)[b]
50 (0.22)[m]	49 (0.25)	0	5	3	$NaOCH_3$ (0.45)		42 (46, 87)[b]
50 (0.22)[m]	49 (0.25)	0	5	3	$Mg(OCH_3)_2$ (1)		42 (60, Q)[b]
80 (0.35)[m]	78 (0.39)	0	5	4	$PhCH_2N(CH_3)_3OCH_3$ (0.5)		42 (75, 89)[b]
				33c			
350 (1)	240 (1.2)	0	5	6	$Mg(OCH_3)_2$ (3)		43 (184, 50)
				33d			
110 (0.30)	78 (0.39)	0	5	3	$Mg(OCH_3)_2$ (1)		44 (47, 41)
				34			
719 (3.0)	800 (4.0)	0	8	20	$Mg(OCH_3)_2$ (9)[i]		45 (469, 58[j])
				35			
556 (1.48)	370 (1.85)	RT[n]	12	10	$Mg(OCH_3)_2$ (4.5)[i]		46 (320, 57[k])

[a] Product ratio listed in Table IV. [b] Essentially only *E* olefin. [c] Product mixture analyzed by NMR without separating isomers. [d] Preparative TLC (40% C_2H_5OAc in hexane) gave 18 mg of *E* isomer (R_f = 0.14) and 36 mg of *Z* isomer (R_f = 0.29). [e] Essentially only *Z* olefin. [f] Preparative TLC (10% acetone in hexane) gave 331 mg of *E* isomer (R_f = 0.2) and 60 mg of *Z* isomer (R_f = 0.3). [g] Reaction performed at room temperature for 22 h. [h] Reaction performed at 65 °C for 20 min. [i] Reaction performed at +2 °C for 72 h. [j] Overall yield from cyclobutanone 26. [k] Overall yield from cyclobutanone 27. [l] *E* isomer. [m] *Z* isomer. [n] Room temperature.

carbon) generates the observed stereochemistry. The relative differences between the corresponding conformers of the *Z* series, where the eclipsing interaction is between the OH rather than the RCH_2 and the cyclohexenyl group, is sufficiently smaller that little stereoselectivity is seen in the epoxidation. Similar reasoning rationalizes the preferred formation of **70** from **28b** and thus the *E* olefin as summarized in eq 32. Thus, this method also represents a stereocontrolled approach to trisubstituted olefins of general structure **71** and **72**, a most difficult task.



70 (32)



71 72

Experimental Section

General Data. All reactions were run under a positive pressure of dry nitrogen. Infrared spectra were obtained as solutions in the indicated solvent on a Beckman Acculab and/or Perkin-Elmer 267 spectrophotometer and are reported in cm^{-1}. NMR spectra were determined in the indicated solvent on a JEOLCO MH-100 (100 MHz) or a Brucker WH270 (270 MHz) instrument; chemical shifts are reported in ppm downfield from tetramethylsilane (Me_4Si). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet); addition of b indicates a broadened pattern. Coupling constants are given in hertz. CMR spectra were recorded on a JEOLCO FX-60 spectrometer. Mass spectra were recorded on an AE1-MS-902 high-

resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 100 mA unless otherwise specified. Melting points were obtained on a Thomas Hoover apparatus, in open capillary tubes, and are uncorrected. Boiling points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI. Thin layer or preparative layer (1.5-mm) plates were made of E. Merck AG Darmstadt silica gel PF-254 or Brinkman silica gel P/UV-254 no. 66 and activated by drying at 140 °C for 2 h. Eluting solvents are indicated in the text. Removal of material from silica gel was accomplished by successive washings with ether or ethyl acetate.

Apparatus for experiments requiring anhydrous conditions were flamed dry under a stream of nitrogen. In experiments requiring dry solvents, ether, tetrahydrofuran (THF), dioxane, and toluene were distilled from sodium benzophene ketyl. Methylene chloride, benzene, acetonitrile, hexane, methyl acetate, ethyl acetate, dimethylformamide (DMF), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride. Alcoholic solvents were distilled from magnesium turnings.

1-Chlorocyclopropyl *p*-Methoxyphenyl Sulfide. To a room temperature solution of cyclopropyl *p*-methoxyphenyl sulfide[40] (36.3 g, 0.2 mol) in 1 L of benzene was added 24.3 mL of pyridine followed by 32.3 g (0.3 mol) of *N*-chlorosuccinimide. The mixture was stirred at room temperature for 23 h and then washed with 5% aqueous sodium thiosulfate solution, 5% aqueous hydrochloric acid solution, and brine. The organic phase was dried ($MgSO_4$), and the solvent evaporated in vacuo. Kugelrohr distillation (bath temperature 90 °C (0.05mmHg)) gave 38.5 g (89%) of the title compound as an oil. NMR (CS_2): δ 7.3 (d, 2 H, J = 9 Hz), 6.72 (d, 2 H, J = 9 Hz), 3.73 (s, 3 H), 1.36 (m, 4 H). Mass spectrum was in accord with structure. Calcd for $C_{10}H_{11}ClOS$: 214.0219. Found: 214.0210.

1-((*p*-Methoxyphenyl)thio)cyclopropane-1-carboxyaldehyde (1b). To a −78 °C solution of 1-chlorocyclopropyl *p*-methoxyphenyl sulfide (37.4 g, 0.17 mol) in 800 mL of ether was added over a 20-min period *tert*-butyllithium in pentane (294 mL, 0.35 mol, 1.19 M; Lithcoa). The mixture turned milky before complete addition of the *tert*-butyllithium. After being stirred for 2 h at −78 °C, dimethylformamide (20 mL) was added as rapidly as possible and stirring continued for 30 min. The cold mixture was poured into 10% aqueous hydrochloric acid solution, the phases were separated, the organic phase was washed with brine and dried ($MgSO_4$), and the solvent was evaporated in vacuo. Reduced pressure distillation through a 15-cm glass-packed column, bp 99–100 °C (0.1 mmHg), gave 20.59 g (56%) of the title compound as a yellow oil which was pure by NMR criteria. IR (CCl_4): 1705, 1590, 1490, 690 cm^{-1}. NMR (CCl_4): δ 9.4 (s, 1 H), 7.14 (d, 2 H, J = 9 Hz), 6.68 (d, 2 H, J = 9 Hz), 3.66 (s, 3 H), 1.2 (m, 4 H). Mass spectrum was in accord with structure. Calcd for $C_{11}H_{12}O_2S$: 208.0557. Found: 208.0554.

2,6-Dimethoxybenzenethiol (4). To a refluxing solution of *m*-dimethoxybenzene (138 g, 1 mol; Aldrich) in hexane (500 mL) was added over a 30-min period a solution of *n*-butyllithium in hexane (689 mL, 1 mol, 1.4 M). The resulting yellow slurry was refluxed for 2 h, then transferred via polyethylene tubing to a 5-L Morton flask equipped with a mechanical stirrer, cooled to 0 °C, and charged with a slurry of tetramethylthiuram disulfide (240 g, 1 mol; Aldrich, recrystallized from $CHCl_3$) in 600 mL of THF. After transfer was complete, the resulting slurry was stirred as rapidly as possible for 2 h. The slurry was dissolved in chloroform and washed with 10% aqueous hydrochloric acid solution and brine. The organic phase was dried ($MgSO_4$) and the solvent evaporated in vacuo to give 249 g of crude *N,N*-dimethylthiocarbamate as a yellow solid.

To a 0 °C slurry of the crude *N,N*-dimethylthiocarbamate (1 mol theoretical) in ether (1.5 L) was added in portions lithium aluminum hydride (38 g, 1 mol). After the initial exotherm had ceased, the mixture was refluxed for 20 h, then cooled, and *carefully* quenched by dropwise addition of 10% hydrochloric acid solution. The resulting slurry was stirred with 1 L of ethyl acetate and the organic phase decanted. After this procedure was repeated twice, the combined organic extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo to give ca. 170 g of a yellow solid. Recrystallization from aqueous ethanol gave a first crop of 117 g (68%) of the title compound as a yellow tinted amorphous solid, mp 82–83 °C (lit.[11a] 85–86 °C). NMR spectrum was identical with an authentic sample.[11b]

((2,6-Dimethoxyphenyl)thio)acetonitrile (5). To a slurry of 2,6-dimethoxybenzenethiol (23 g, 0.135 mol) in 400 mL of methanol was added a solution of potassium carbonate (18.7 g, 0.135 mol) in 30 mL of water. After 30 min, chloroacetonitrile (8.54 mL, 0.135 mol) was added and stirring continued for 3 h. The solvent was removed in vacuo and the residue partitioned between water and ethyl acetate. The organic phase was washed with brine and dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was triturated with 50 mL of ether to give 26.5 g (93%) of **5**, mp 52.5–53.5 °C (heptane–toluene), as an amorphous solid. IR (CCl_4): 2250, 1575, 1465, 1110, 710 cm^{-1}. NMR (CCl_4): δ 7.18 (t, 1 H, J = 8 Hz), 6.15 (d, 2 H, J = 8 Hz), 3.81 (s, 6 H), 3.46 (s, 2 H). Calcd for $C_{10}H_{11}NO_2S$: 209.0511. Found: 209.0513.

1-((2,6-Dimethoxyphenyl)thio)cyclopropanecarbonitrile. To a −78 °C solution of lithium diisopropylamide (1 mol) in 1.5 L of THF was added 150 mL of HMPA followed by a solution of ((2,6-dimethoxyphenyl)-thio)acetonitrile (81 g, 0.387 mol) in THF (300 mL). The mixture was warmed slowly to −20 °C, and 1,2-dichloroethane (158 mL, 2 mol) was added dropwise. The mixture was recooled to −78 °C and allowed to warm gradually to room temperature overnight. The solvent was removed in vacuo and the residue partitioned between water and toluene. The organic phase was washed with brine and dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was filtered through 150 g of silica gel by using ether as eluant and then evaporated in vacuo to give 82 g (90%) of the title compound as a light brown solid. An analytical sample was crystallized from methanol (mp 94–96 °C, colorless prisms). IR (CCl_4): 2240, 1580, 1465 cm^{-1}. NMR: δ 7.68 (t, 1 H, J = 8 Hz), 6.57 (d, 2 H, J = 8 Hz), 3.89 (s, 6 H), 1.43 (m, 4 H). Mass spectrum was in accord with structure. Calcd for $C_{12}H_{13}NO_2S$: 235.0667. Found: 235.0662.

1-((2,6-Dimethoxyphenyl)thio)cyclopropanecarboxaldehyde (1c). To a 0 °C solution of 1-((2,6-dimethoxyphenyl)thio)cyclopropanecarbonitrile (82 g, 0.348 mol) in 800 mL of toluene was added a solution of DIBAL-H in hexane (475 mL, 0.41 mol, 0.88 M). After 3 h, during which time it was allowed to warm to room temperature, the mixture was carefully poured into 4 L of 6% aqueous sulfuric acid and stirred for 1 h. The phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with 6% aqueous sulfuric acid solution and brine and dried ($MgSO_4$), and solvent was evaporated in vacuo. The crude residue was crystallized from hexane–ethyl acetate to give 47.6 g (51% from **5**) of the title compound as colorless prisms, mp 78–79 °C. IR ($CHCl_3$): 1695, 1580, 1460 cm^{-1}. NMR ($CDCl_3$): δ 10.17 (s, 1 H), 7.28 (t, 1 H, J = 8 Hz), 6.61 (d, 2 H, J = 8 Hz), 3.84 (s, 6 H), 1.36 (m, 4 H). Mass spectrum was in accord with structure. Anal. ($C_{12}H_{14}O_3S$): C, H, S, mol wt.

6-Bromo-3,4-dihydronaphthalen-1(2*H*)-one. Following the procedure of Doyle et al.,[15] 87.6 g (0.34 mol) of anhydrous cupric bromide and 50.6 g (0.49 mol) of *tert*-butyl nitrite in 1.3 L of acetonitrile was reacted with 52 g (0.32 mol) of 6-amino-1-tetralone[14] at 0 °C for 2 h and at room temperature for 17 h to give, after reduced pressure distillation at 115–116 °C (0.05mmHg) through a 20-cm Vigreux column, 32.1 g (44%) of the title compound which solidified upon standing, mp 44–45 °C (methanol). IR (CCl_4): 1690, 1590, 1480 cm^{-1}. NMR (CCl_4): δ 7.7 (d, 1 H, J = 9), 7.32 (m, 2 H), 2.92 (t, 2 H, J = 6 Hz), 2.55 (t, 2 H, J = 7 Hz), 2.08 (m, 2 H). Mass spectrum was in accord with structure. Anal. ($C_{10}H_9BrO$): C, H, Br, mol wt.

3-(Benzyloxy)octan-2-one. To a −78 °C solution of 38.2 mL (0.4 mol) of vinyl ether in 60 mL of THF was added dropwise 66.6 mL of *tert*-butyllithium in pentane (0.1 mol, 1.5 M). The cooling bath was removed for 45 min until the solution changed from an opaque yellow to a clear pale yellow solution. The solution was recooled to −78 °C, and 12 mL (0.1 mol) of hexanal was added. The solution turned colorless, and the cooling bath was removed. After 20 min 17.4 mL of HMPA (0.1 mol) followed by 11.9 mL (0.1 mol) of benzyl bromide was added, and the mixture was refluxed overnight. The mixture was partitioned between hexane and water. The organic phase was washed with brine and dried ($MgSO_4$) and the solvent evaporated in vacuo.

The residue was dissolved in THF (100 mL), and 0.5 M hydrochloric acid solution (50 mL) was added and the mixture stirred for 24 h. The mixture was partitioned between saturated aqueous sodium bicarbonate solution and ether. The organic phase was dried ($MgSO_4$) and the solvent evaporated in vacuo. Fractional distillation, bp 114–116 °C (0.4mmHg), gave 14.9 g (63%) of the title compound as a colorless oil. IR (CCl_4): 1710, 1600, 1495 cm^{-1}. NMR (CCl_4): δ 7.19 (s, 5 H), 4.2 (AB, 2 H, J = 12 Hg), 3.56 (t, 1 H, J = 6 Hz), 2.04 (s, 3 H), 1.8–0.7 (m, 11 H). Mass spectrum was in accord with structure. Calcd for $C_{15}H_{22}O_2$: 234.1620. Found: 234.1620.

2-[(1-((2,6-Dimethoxyphenyl)thio)cyclopropyl)hydroxymethyl]cyclohexanone (6c). At −78 °C, cyclohexanone (6.3 g, 64.2 mmol) in 20 mL of THF was added to 67.5 mmol of lithium diisopropylamide in 90 mL of THF. After being stirred 30 min, the enolate was quenched with 1-((2,6-dimethoxyphenyl)thio)cyclopropanecarboxaldehyde (15.3 g, 64.2 mmol) in 55 mL of THF. After an additional 30 min the reaction was poured into saturated aqueous ammonium chloride solution. Extraction

(40) Truce, W. E.; Hollister, K. R.; Lindy, L. B.; Parr, J. E. *J. Org. Chem.* **1968**, *33*, 43.

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with ether, drying of the combined organic extracts with $MgSO_4$, and evaporation in vacuo gave 21.4 g (99%) of crude aldol product which contained ~10% of starting aldehyde by NMR; mp 116–117.5 °C (methanol). On a 10-mmol scale, the yield was 62% (88% based on aldehyde recovered by TLC; 619 mg, 26%). IR ($CHCl_3$): 3460, 1690, 1580, 1430 cm^{-1}. NMR ($CDCl_3$): δ 7.34 (t, 1 H, J = 8 Hz), 6.64 (d, 2 H, J = 8 Hz), 3.9 (s, 6 H), 3.22 (m, 1 H), 2.5–1.1 (m, 10 H), 0.84 (m, 4 H). Mass spectrum was in accord with structure. Calcd for $C_{18}H_{24}O_4S$: 336.1395. Found: 336.1405.

1-((2,6-Dimethoxyphenyl)thio)-1-(1-hydroxy-7-methyl-3-oxooctan-1-yl)cyclopropane (12c). As above, 6-methylheptan-2-one (256 mg, 2 mmol) in 1 mL of THF was added to 2.1 mmol of lithium diisopropylamide in 2 mL of THF followed by quenching with **1c** (476 mg, 2 mmol) to give, after TLC (25% ethyl acetate in hexane), 690 mg (94%) of the title compound as an amorphous solid, mp 54–57 °C (hexane–ethyl acetate). On a 15-mmol scale, 5.5 g (100%) of crude material was obtained and used without purification. IR ($CHCl_3$): 3460, 1700, 1580, 1460, 1100 cm^{-1}. NMR ($CDCl_3$): δ 7.33 (t, 1 H, J = 8 Hz), 6.64 (d, 2 H, J = 8 Hz), 3.90 (s, 6 H), 4.04 (b s, 1 H), 3.64 (t, 1 H, J = 5), 2.86 (d, 2 H, J = 5 Hz), 2.48 (t, 2 H, J = 8 Hz), 1.8–0.7 (m, 9 H), with 0.9 (d, 6 H, J = 6 Hz) superimposed. Mass spectrum was in accord with structure. Calcd for $C_{20}H_{30}O_4S$: 366.1865. Found: 366.1866.

1-((2,6-Dimethoxyphenyl)thio)-1-(4-(benzyloxy)-1-hydroxy-3-oxononan-1-yl)cyclopropane (14c). As above, 3-(benzyloxy)octan-2-one (4.68 g, 20 mmol) in 10 mL of THF was added to 21 mmol of lithium diisopropylamide, followed by quenching with **1c** (4.76 g, 20 mmol) in 20 mL of THF to give 9.5 g (100%) of the crude title compound. This material contained ~10% of starting aldehyde plus ketone by NMR and was used without purification. On a 1-mmol scale, 331 mg (70%) was obtained after TLC (25% ethyl acetate in hexane). IR ($CHCl_3$): 3460, 1725, 1590, 1470, 1110 cm^{-1}. NMR ($CDCl_3$): δ 7.4–7.12 (m, 6 H), 6.51 (d, 2 H, J = 8 Hz), 4.48 (AB, 2 H, J = 12 Hz), 3.77 (s, 6 H), 3.58 (m, 2 H), 2.92 (m, 2 H), 1.8–0.6 (m, 16 H). Mass spectrum was in accord with structure. Calcd for $C_{27}H_{36}O_5S$: 472.2283. Found: 472.2304.

2-[(1-((2,6-Dimethoxyphenyl)thio)cyclopropyl)hydroxymethyl]-6-bromo-3,4-dihydronaphthalen-1(2*H*)-one (10c). As above 6-bromo-1-tetralone (2.25 g, 10 mmol) in 10 mL of THF was added to lithium diisopropylamide (10.5 mmol) in 15 mL of THF, followed by warming to −10 °C and addition of anhydrous zinc chloride (1.36 g, 10 mmol) in 20 mL of ether, and quenching with **1c** (2.38 g, 10 mmol) in 10 mL of THF gave 4.6 g (99% crude) of the title compound which contained a trace of starting aldehyde but was used without purification. An analytical sample was purified by TLC (40% ethyl acetate in hexane) to give a colorless foam, mp 128–132 °C. IR ($CHCl_3$): 3460, 1660, 1570, 1420, 825 cm^{-1}. NMR ($CDCl_3$): δ 7.91 (d, 1 H, J = 8 Hz), 7.44 (m, 2 H), 7.31 (t, 1 H, J = 8 Hz), 6.65 (d, 2 H, J = 8 Hz), 4.26 (d, 1 H, J = 4 Hz), 3.88 (s, 6 H), 3.6–0.7 (m, 10 H). Anal. ($C_{22}H_{23}BrO_4S$): C, H.

(*E*)-2-[(1-((2,6-Dimethoxyphenyl)thio)cyclopropyl)methylene]cyclohexanone (7c). To a solution of **6c** (21.4 g of unpurified material, 64.2 mmol theoretical) in 150 mL of HMPA was added dropwise phosphorous oxychloride (6.85 mL, 75 mmol). A white precipitate formed which gradually dissolved. After the solution was stirred 1 h at room temperature and 1 h at 50 °C, 12.1 mL (150 mmol) of pyridine was added and heating continued at 50 °C for 1 h, 75 °C for 30 min, and 100 °C for 45 min. After being cooled, poured into water, extracted with toluene, and filtered through a pad of silica gel, 16.26 g (79%) of the title compound was obtained as an amorphous solid. On a 5-mmol scale with purification by TLC (40% ethyl acetate in hexane), 1.21 g (71%) was obtained; mp 124–125 °C (methanol). IR ($CHCl_3$): 1680, 1580, 1460 cm^{-1}. NMR ($CDCl_3$): δ 7.28 (t, 1 H, J = 8 Hz), 6.65 (b s, 1 H), 6.58 (d, 2 H, J = 8 Hz), 3.86 (s, 6 H), 2.33 (m, 4 H), 1.9–1.2 (m, 6 H), 0.9 (m, 2 H). Mass spectrum was in accord with structure. Calcd for $C_{18}H_{22}O_3S$: 318.1290. Found: 318.1297.

1-((2,6-Dimethoxyphenyl)thio)-1-(7-methyl-3-oxooctan-1-(*E*)-en-1-yl)cyclopropane (13c). As above, **12c** (5.5 g crude, 15 mmol) in 40 mL of HMPA was treated with phosphorous oxychloride (2.05 mL, 22.5 mmol) and 3.65 mL (45 mmol) of pyridine to give, after extraction with toluene and filtration through a pad of silica gel, 4.9 g (93% crude) of the title compound as an oil. On a 1.61-mmol scale with purification by TLC (25% ethyl acetate in hexane), 383 mg (68%) was obtained. IR (CCl_4): 1675, 1615, 1580, 1470 cm^{-1}. NMR (CCl_4): δ 7.10 (t, 1 H, J = 8 Hz), 6.62 (d, 1 H, J = 15 Hz), 6.44 (d, 2 H, J = 8 Hz), 6.12 (d, 1 H, J = 15 Hz), 3.77 (s, 6 H), 2.32 (t, 2 H, J = 7 Hz), 1.68–0.96 (m, 9 H), 0.86 (d, 6 H, J = 6 Hz). Mass spectrum was in accord with structure. Calcd for $C_{20}H_{28}O_3S$: 348.1759. Found: 348.1760.

1-((2,6-Dimethoxyphenyl)thio)-1-(4-(benzyloxy)-3-oxonon-1(*E*)-en-1-yl)cyclopropane (15c). As above **14c** (9.5 g crude, 20 mmol) in 60 mL of HMPA was treated with phosphorous oxychloride (2.74 mL, 30 mmol) and 4.84 mL (60 mmol) of pyridine to give, after extraction with hexane, 8.9 g (89% crude) of the title compound as an oil. On a 0.68-mmol scale with isolation by TLC (25% ethyl acetate in hexane), 166 mg (53%) was obtained. IR ($CHCl_3$): 1695, 1610, 1590, 1500, 1470 cm^{-1}. NMR ($CDCl_3$): δ 7.4–7.07 (m, 6 H), 6.77 (m, 2 H), 6.48 (d, 2 H, J = 7 Hz), 4.32 (AB, 2 H, J = 12 Hz), 3.76 (m, 1 H), with 3.77 (s, 6 H) superimposed, 1.7–0.7 (m, 15 H). Mass spectrum was in accord with structure. Calcd for $C_{27}H_{34}O_4S$: 454.2177. Found: 454.2177.

2-[(1-((2,6-Dimethoxyphenyl)thio)cyclopropyl)methylene]-6-methoxy-3,4-dihydronaphthalen-1-one (9c). As above, **8c** (4 g, 10 mmol theoretical) in 40 mL of HMPA was treated with phosphorous oxychloride (1.37 mL, 15 mmol) and 2.4 mL (30 mmol) of pyridine to give, after extraction with toluene and filtration through a pad of silica gel, 3.61 g (91%) of the title compound as an amorphous solid, mp 111–112 °C (hexane–ethyl acetate; needles). IR ($CHCl_3$): 1675, 1600, 1505, 1475, 1440, 860 cm^{-1}. NMR ($CDCl_3$): δ 8.07 (d, 1 H, J = 8 Hz), 7.25 (t, 1 H, J = 8 Hz), 7.08 (b s, 1 H), 6.76 (m, 2 H), 6.53 (d, 2 H, J = 8 Hz), 3.82 and 3.97 (two s, 9 H), 2.52 (m, 4 H), 1.36 (m, 2 H), 0.95 (m, 2 H). Mass spectrum was in accord with structure. Anal. ($C_{23}H_{24}O_4S$): C, H, S, mol wt.

2-[(1-((2,6-Dimethoxyphenyl)thio)cyclopropyl)methylene]-6-bromo-3,4-dihydronaphthalen-1-one (11c). As above, **10c** (4.6 g, 10 mmol theoretical) in 55 mL of HMPA was treated with phosphorous oxychloride (1.37 mL, 15 mmol) and 2.4 mL (30 mmol) of pyridine to give, after extraction with toluene and dry column chromatography (250 g silica gel, 4.5 × 40 cm, eluting with 20% ethyl acetate in hexane), 3.75 g (81%) of the title compound as an amorphous solid, mp 106–109 °C (hexane–ethyl acetate). IR ($CHCl_3$): 1660, 1580, 1430 cm^{-1}. NMR ($CDCl_3$): δ 7.89 (d, 1 H, J = 8 Hz), 7.36 (m, 3 H), 7.14 (b s, 1 H), 6.56 (d, 2 H, J = 8 Hz), 3.8 (s, 6 H), 2.5 (m, 4 H), 1.36 (m, 2 H), 0.96 (m, 2 H). Mass spectrum was in accord with structure. Anal. ($C_{22}H_{21}BrO_3S$): C, H, Br, S, mol wt.

2-[(1-((2,6-Dimethoxyphenyl)thio)cyclopropyl)methylene]cyclohexanol (18c). At −78 °C, 318 mg (1 mmol) of **7c** in 5 mL of toluene was treated with 1.36 mL (1.2 mmol, 0.88 M) of DIBAL-H. After being stirred 30 min at −78 °C and 2 h at 0 °C, the reaction was quenched by addition of methanol and allowed to warm to room temperature. Saturated aqueous sodium sulfate solution was added followed by ether. The resulting slurry was dried (Na_2SO_4) and filtered through a pad of celite. After TLC (40% ethyl acetate in hexane), 287 mg (89%) of the title compound was obtained as an amorphous solid, mp 101–104 °C. On a 7-mmol scale, 2.25 g (99% crude) was obtained and used without purification. IR ($CHCl_3$): 3600, 3490, 1570, 1430 cm^{-1}. NMR ($CDCl_3$): δ 7.21 (t, 1 H, J = 8 Hz), 6.56 (d, 2 H, J = 8 Hz), 5.68 (b s, 1 H), 3.92 (b s, 1 H), 3.86 (s, 6 H), 2.3–0.7 (m, 13 H). Mass spectrum was in accord with structure. Calcd for $C_{18}H_{24}O_3S$: 320.1446. Found: 320.1439.

1-((2,6-Dimethoxyphenyl)thio)-1-(3-hydroxy-7-methyloct-1(*E*)-en-1-yl)cyclopropane (22c). To a stirred 0 °C solution of 21.3 mL of DIBAL-H in hexane (18.7 mmol, 0.88 M) was added dropwise a solution of 12.9 mL of *n*-butyllithium in hexane (18.7 mmol, 1.45 M). After 10 min the resulting white slurry was dissolved by addition of 10 mL of THF and the solution cooled to −78 °C. A solution of 4.9 g (15 mmol) of crude **13c** in 20 mL of THF was added dropwise and stirring continued at −78 °C for 2 h. The reaction was quenched at −78 °C with 1 mL of methanol and warmed to room temperature; saturated aqueous sodium sulfate solution (1 mL) was added followed by toluene (40 mL) and ether (40 mL). After the suspension of aluminum salts formed, the mixture was dried (Na_2SO_4) and filtered through a pad of celite and the solvent evaporated in vacuo to give 4.6 g (87% crude) of the title compound which was used without purification. On a 1.35-mmol scale with isolation by TLC (25% ethyl acetate in hexane), 308 mg (82%) was obtained. IR ($CHCl_3$): 3605, 3490, 1575, 1460, 1100 cm^{-1}. NMR ($CDCl_3$): δ 7.21 (t, 1 H, J = 8 Hz), 6.51 (d, 2 H, J = 8 Hz), 5.73 (d, 1 H, J = 16 Hz), 5.33 (dd, 1 H, J = 16, 6 Hz), 3.92 (m, 1 H), 3.81 (s, 6 H), 1.7–0.9 (m, 12 H), 0.8 (d, 6 H, J = 6 Hz). Mass spectrum was in accord with structure. Calcd for $C_{20}H_{30}O_3S$: 350.1916. Found: 350.1914.

1-((2,6-Dimethoxyphenyl)thio)-1-(4-(benzyloxy)-3-hydroxynon-1-(*E*)-en-1-yl)cyclopropane (23c). As above, 8.9 g (20 mmol) of crude **15c** in 35 mL of THF was added to a mixture of DIBAL-H (28.4 mL, 25 mmol, 0.88 M) and *n*-butyllithium (17.2 mL, 25 mmol, 1.45M) in 20 mL of THF to give 9.0 g (98% crude) of the title compound as an oil which was used without purification. On a 0.19-mmol scale with isolation by TLC (40% ethyl acetate in hexane), 65 mg (73%) was obtained. IR ($CHCl_3$): 3560, 1585, 1500, 1460 cm^{-1}. NMR ($CDCl_3$): δ 7.42–7.08 (m, 6 H), 6.52 (d, 2 H, J = 8 Hz), 5.85 (d, 1 H, J = 15 Hz), 5.38 (dd, 1 H, J = 15, 6 Hz), 4.42 (AB, 2 H, J = 12 Hz), 3.92 (m, 1 H), 3.8 (s, 6 H), 3.11 (m, 1 H), 2.28 (m, 1 H), 1.6–0.7 (m, 15 H). Mass spectrum was in accord with structure. Calcd for $C_{27}H_{36}O_4S$: 456.2334. Found: 456.2354.

2-[(1-((2,6-Dimethoxyphenyl)thio)cyclopropyl)methylene]-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (20c). As above, 3.0 g (7.57 mmol)

of **9c** in 15 mL of THF was added to a mixture of DIBAL-H (9.47 mL, 8.33 mmol, 0.88 M) and *n*-butyllithium (5.4 mL, 8.33 mmol, 1.5 M) in 15 mL of THF to give, after TLC (40% ethyl acetate in hexane), 2.61 g (86%, 78% overall from 6-methoxy-1-tetralone) of the title compound. IR ($CHCl_3$): 3600, 3500, 1615, 1590, 1510, 1475, 830 cm^{-1}. NMR ($CDCl_3$): δ 7.24 (m, 2 H), 6.6 (m, 4 H), 5.92 (b s, 1 H), 4.78 (b s, 1 H), 3.76 (s, 9 H), 2.3 (m, 4 H), 1.92 (b s, 1 H), 1.24 (m, 2 H), 0.85 (m, 2 H). Mass spectrum was in accord with structure. Calcd for $C_{23}H_{26}O_4S$: 398.1552. Found: 398.1540.

2-[(1-((2,6-Dimethoxyphenyl)thio)cyclopropyl)methylene]-6-bromo-1,2,3,4-tetrahydronaphthalen-1-ol (21c). As above, 2.0 g (4.49 mmol) of **11c** in 8 mL of THF was added to a mixture of DIBAL-H (6.13 mL, 5.4 mmol, 0.88 M) and *n*-butyllithium (3.7 mL, 5.4 mmol, 1.45 M) in 4 mL of THF to give, after TLC (20% ethyl acetate in hexane), 1.95 g (97%) of the title compound. On a 15-mmol scale, 6.65 g (98% crude) was obtained and used without purification. IR ($CHCl_3$): 3470, 1565, 1425 cm^{-1}. NMR ($CDCl_3$): δ 7.26 (m, 4 H), 6.52 (d, 2 H, J = 8 Hz), 5.95 (b s, 1 H), 4.76 (b s, 1 H), 3.88 and 3.76 (two s, 6 H), 2.28 (m, 5 H), 1.24 (m, 2 H), 0.84 (m, 2 H). Mass spectrum was in accord with structure. Calcd for $C_{22}H_{23}{}^{79}BrO_3S$: 446.0551. Found: 446.0554.

(*E*)-2-[(1-((2,6-Dimethoxyphenyl)thio)cyclopropyl)methylene]-1-*n*-butylcyclohexanol (19c). A solution of 16.2 g (52 mmol) of **9c** in 125 mL of THF was added to 52 mL of *n*-butylmagnesium bromide in ether (78 mmol, 1.5 M) at 0 °C and then stirred for 4 h at room temperature. Addition of saturated aqueous ammonium chloride quenched the reaction. The mixture was extracted with ether, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give 19.7 g (100% crude) of the title compound which was of sufficient purity to be used directly. IR ($CHCl_3$): 3600, 3480, 1580, 1430 cm^{-1}. NMR ($CDCl_3$): δ 7.24 (t, 1 H, J = 8 Hz), 6.56 (d, 2 H, J = 8 Hz), 5.76 (b s, 1 H), 3.86 (s, 6 H), 2.2 (m, 2 H), 1.8–0.6 (m, 20 H). Mass spectrum was in accord with structure. Calcd for $C_{22}H_{32}O_3S$: 376.2072. Found: 376.2065.

Preparation of Cyclobutanones. 2-(1-Cyclohexenyl)cyclobutanone (24a). A solution of 5.3 g (20.3 mmol) of **18a** in 100 mL of ether was added dropwise over a 1-h period to a rapidly stirred mixture of 25 mL of 48% aqueous fluoboric acid and 100 mL of ether. After an additional 10 min the acid was carefully quenched with sodium bicarbonate and diluted with additional ether. The organic phase was washed with 1 M aqueous potassium hydroxide solution and brine and dried ($MgSO_4$) and the solvent removed via distillation through a 30-cm Widmer column. Reduced pressure distillation via a short path gave a yellow oil, bp RT–80 °C (1mmHg). This oil was subjected to Kugelrohr distillation (bath temperature 60 °C (1mmHg)) to give 1.81 g (60%) of the title compound as a clear sweet smelling oil.

As above, a solution of 1.7 g (5.3 mmol) of **18c** in 45 mL of ether was added to 6.7 mL of 48% fluoboric acid in 20 mL of ether to give, after Kugelrohr distillation (bath temperature 50 °C (0.1mmHg)), 561 mg (70%). IR (CCl_4): 1780, 1435, 915 cm^{-1}. NMR (CCl_4): δ 5.48 (b s, 1 H), 3.76 (t, 1 H), J = 8 Hz), 3.0–2.7 (m, 2 H), 2.6–1.4 (m, 10 H). Mass spectrum was in accord with structure. Anal. ($C_{10}H_{14}O$): C, H, mol wt.

2-(2-*n*-Butylcyclohexen-1-yl)cyclobutanone (24b). As above, 75 mg (0.23 mmol) of **19a** in 2 mL of ether was added to 0.3 mL of 48% fluoboric acid in 2 mL of ether to give, after TLC (5% ethyl acetate in hexane), 23.7 mg (48%) of the title compound as a clear sweet smelling oil. On a large scale run 12 g of crude material gave after Kugelrohr distillation (90 °C bath temperature at (0.1mmHg)) ca. 3 g of volatile material. Purification of this by TLC (10% acetone in hexane) gave 2.2 g (28% overall from ene–one **7a**).

To a solution of 158 mg (0.5 mmol) of **19a** in 5 mL of methylene chloride was added 92 mg (0.62 mmol) of trimethyloxonium tetrafluoborate. After 1 h at room temperature, 1.5 mL of 0.5 M sodium hydroxide was added, and after an additional 1.5 h, the mixture was partitioned between water and ether. The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. Preparative TLC (10% acetone in hexane) gave 48 mg (46%) of the title compound.

As above, 400 mg (1.15 mmol) of **19b** in 5 mL of ether was added to 1.5 mL of 48% fluoboric acid in 5 mL of ether to give, after TLC (10% acetone in hexane), 104 mg (44%) of cyclobutanone which had extraneous signals in the NMR at δ 7.35 (d), 6.76 (d), and 3.8 (s).

As above, 376 mg (1 mmol) of **19c** in 6 mL of ether was added to 1.25 mL of 48% fluoboric acid in 3 mL of ether to give, after TLC (chloroform), 127 mg (61%) of the pure cyclobutanone. On a 52-mmol scale after Kugelrohr distillation (bath temperature 60 °C (0.01mmHg)), 5.29 g (40% overall from cyclohexanone) was obtained. IR (CCl_4): 1790 cm^{-1}. NMR (CCl_4): δ 4.3 (t, 1 H, J = 9 Hz), 3.2–2.7 (m, 2 H), 2.4–1.1 (m, 16 H), 0.9 (b t, 3 H). Mass spectrum in accord with structure. Calcd for $C_{14}H_{22}O$: 206.1670. Found: 206.1666.

2-(6-Methylhept-1(*E*)-en-1-yl)cyclobutanone (26). As above, 4.6 g (15 mmol theoretical) of crude **13c** in 50 mL of ether was added to 18 mL of 48% fluoboric acid in 50 mL of ether to give, after Kugelrohr distillation (bath temperature 70 °C (1mmHg)), 1.20 g (44% overall from 6-methylheptan-2-one) of the title compound as a sweet smelling oil. On a 0.85-mmol scale 90 mg (58%) was obtained. IR (CCl_4): 1790, 965 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 5.57 (dtd, 1 H, J = 15.8, 6.5, 1.25 Hz), 5.43 (ddt, 1 H, J = 15.8, 6.5, 1.25), 3.9 (m, 1 H), 3.12–2.84 (m, 2 H), 2.26 (dtd, 1 H, J = 11, 10, 5 Hz), 1.99 (b q, 2 H, J = 7 Hz), 1.86 (m, 1 H), 1.52 (septet, 1 H, J = 7 Hz), 1.36 (m, 2 H), 1.18 (m, 2 H), 0.86 (d, 6 H, J = 7 Hz). ^{13}C NMR: δ 208.4, 133.2, 124.4, 63.0, 44.6, 38.6, 32.8, 27.9, 27.0, 22.6, 17.2. Anal. ($C_{12}H_{20}O$): C, H.

2-(3-(Benzyloxy)oct-1(*E*)-en-1-yl)cyclobutanone (27). As above, 9.0 g of crude material (20 mmol theoretical) of **23c** in 100 mL of ether was added to 20 mL of 48% fluoboric acid in 50 mL of ether to give, after being filtered through a silica gel column (150 g silica gel, 9% ethyl acetate in hexane), 2.4 g (41%) of cyclobutanone which was further purified by Kugelrohr distillation (bath temperature 100 °C (0.02mmHg)) to give 1.83 g (32% overall from 3-(benzyloxy)octan-2-one) of the title compound. IR (CCl_4): 1795, 1460, 860 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 7.30 (m, 5 H), 5.65 (dd, 1 H, J = 15.5, 6.25 Hz), 5.47 (ddt, 1 H, J = 15.5, 7.75, 1.6 Hz), 5.47 (ddt, 1 H, J = 15.5, 7.75, 1.6 Hz), 4.55 (two d, total 1 H, J = 12 Hz), 3.98 (m, 1 H), 3.70 (m, 1 H), 3.17–2.86 (m, 2 H), 2.28 (ddt, 1 H, J = 16.5, 10.5, 5.5 Hz), 1.89 (m, 1 H), 1.62 (m, 1 H), 1.54–1.16 (m, 7 H), 0.87 (t, 3 H, J = 6.5). ^{13}C NMR: 138.8, 133.2, 128.2, 127.6, 79.8, 70.0, 62.5, 44.9, 35.6, 31.7, 25.0, 22.6, 17.0, 14.0. Mass spectrum was in accord with structure. Calcd for $C_{19}H_{26}O_2$: 286.1933. Found: 286.1924.

2-(2-Cyclobutanonyl)-6-methoxy-3,4-dihydronaphthalene (25a). As above, 27.4 g (81 mmol) of **20a** in 150 mL of ether was added to 105 mL of 48% fluoboric acid in 750 mL of ether to give, after dry column chromatography on silica gel (2 × 300 g, 4.5 × 35 cm; 10% acetone in hexane), 5.1 g (28%) of the title compound as an oil.

As above, 1.21 g (3.04 mmol) of **20c** in 20 mL of ether was added to 4 mL of 48% fluoboric acid in 20 mL of ether to give, after TLC (20% ethyl acetate in hexane), 321 mg (46%) as a waxy solid, mp 29–30 °C (isopentane). IR (CCl_4): 1785, 1600, 1495, 860 cm^{-1}. NMR (CCl_4): δ 7.2–6.3 (m, 3 H), 6.14 (s, 1 H), 3.92 (t, 1 H, J = 8 Hz), 3.66 (s, 3 H), 3.04–1.8 (m, 8 H). Mass spectrum was in accord with structure. Anal. Calcd ($C_{15}H_{16}O_2$): C, H, mol wt.

2-(2-Cyclobutanonyl)-6-bromo-3,4-dihydronaphthalene (25b). As above, 450 mg (1.16 mmol) of **21a** in 4 mL of ether was added to 1.5 mL of 48% fluoboric acid in 2 mL of ether to give, after TLC (10% acetone in hexane), 115 mg (36%) of the title compound as an oil.

As above, 1.9 g (4.25 mmol) of **21c** in 50 mL of ether was added to 5.3 mL of 48% fluoboric acid in 20 mL of ether to give, after TLC (chloroform), 735 mg (62%) as an amorphous solid, mp 75–77 °C (hexane). On a 15-mmol scale without purification of any intermediates, 1.85 g (44% overall from 6-bromo-1-tetralone) was obtained. IR (CCl_4): 1780, 1650, 1590, 1480, 870 cm^{-1}. NMR (CCl_4): δ 7.44–6.68 (m, 3 H), 6.18 (s, 1 H), 3.96 (t, 1 H, J = 9 Hz), 3.2–2.6 (m, 4 H), 2.6–1.8 (m, 4 H). Mass spectrum was in accord with structure. Anal. Calcd ($C_{14}H_{13}BrO$): C, H, mol wt.

Preparation of Cyclobutanols. Reductions. (*Z*)-2-(1-Cyclohexenyl)-cyclobutanol (28). To a 0 °C solution of 110 mg (0.73 mmol) of **24a** in 1 mL of ether was added 2 mL of K-Selectride (1 mmol; Aldrich, 0.5 M in THF). After 30 min, 0.75 mL of 20% aqueous sodium hydroxide and 0.75 mL of 30% aqueous hydrogen peroxide solutions were carefully added. The mixture was stirred for 30 min, then poured into ether, and washed with 5% aqueous sodium thiosulfate solution and brine. The organic phase was dried (Na_2SO_4) and solvent removed via distillation through a 15-cm Vigreux column. Preparative TLC (30% ether in hexane) gave 90 mg (80%) of the title compound as an oil (R_f = 0.5). IR (CCl_4): 3490, 1450, 1100, 920 cm^{-1}. NMR (CCl_4): δ 5.6 (b s, 1 H), 4.28 (b s, 1 H), 3.0 (b s, 1 H), 2.6–1.2 (m, 13 H). Mass spectrum was in accord with structure. Calcd for $C_{10}H_{16}O$: 152.1201. Found: 152.1196.

(*E*)-2-(1-Cyclohexenyl)cyclobutanol (29a). To a solution of 340 mg (2.2 mmol) of **24a** in 10 mL of 2-propanol was added 1.3 g of aluminum isopropoxide (6.4 mmol; Alfa). The mixture was refluxed for 22 h, then cooled, diluted with ether, and washed with 5% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, and brine. The ether extracts were dried ($MgSO_4$), and the solvent was removed via distillation through a 30-cm Widmer column. The residue was dissolved in pentane and washed with water. The organic phase was dried ($MgSO_4$) and solvent removed via distillation to give 340 mg (98%) of the title compound as an oil which was one spot by analytical TLC (30% ether in hexane, R_f = 0.4). IR (CCl_4): 3600, 3400, 1435, 1090 cm^{-1}. NMR (CCl_4): δ 5.3 (b s, 1 H), 3.8 (q, 1 H, J = 7 Hz), 3.64 (b s, 1 H), 2.5 (m, 1 H), 2.2–1.2 (m, 12 H). Mass spectrum was in accord with

structure. Calcd for $C_{10}H_{16}O$: 152.1201. Found: 152.1198.

(Z)-2-(2-n-Butylcyclohexen-1-yl)cyclobutanol (28b). As above, a solution of 400 mg (1.9 mmol) of **24b** in 2 mL of ether was reacted with 5 mL of K-Selectride (2.5 mmol; Aldrich, 0.5 M in THF). After the same workup, preparative TLC (40% ether in hexane) gave 257 mg (65%) of the title compound as an oil (R_f = 0.48). IR (CCl_4): 3560, 110, 860 cm^{-1}. NMR (CCl_4): δ 4.28 (m, 1 H), 3.44 (m, 1 H), 3.4–1.0 (m, 19 H), 0.9 (b t, 3 H). Mass spectrum was in accord with structure. Calcd for $C_{14}H_{24}O$: 208.1827. Found: 208.1827.

(E)-2-(2-n-Butylcyclohexen-1-yl)cyclobutanol (29b). As above, a solution of **24b** in 6 mL of 2-propanol was reacted with 1.22 g of aluminum isopropoxide (6 mmol; Alfa). After the same workup, preparative TLC (40% ether in hexane) gave 325 mg (78%) of the title compound as an oil (R_f = 0.35). IR (CCl_4): 3630, 3400, 1100, 860 cm^{-1}. NMR (CCl_4): δ 4.06 (m, 1 H), 3.58 (b s, 1 H), 3.1 (m, 1 H), 3.4–1.0 (m, 18 H), 0.9 (b t, 3 H). Mass spectrum was in accord with structure. Calcd for $C_{14}H_{24}O$: 208.1827. Found: 208.1827.

Addition of Organometallics to Cyclobutanones. 2-(1-Cyclohexenyl)-1-ethylcyclobutanol (30a). To 2.6 mL of a −78 °C solution of ethylmagnesium bromide (6.5 mmol, 2.5 M in ether) in 20 mL of ether was added dropwise a solution of 400 mg (2.6 mmol) of **24a** in 2 mL of ether. After the mixture was stirred at −78 °C for 5.5 h, saturated aqueous ammonium chloride solution (2 mL) was added and the mixture poured into ether. The organic phase was washed with brine and dried ($MgSO_4$) and solvent removed via distillation through a 15-cm Vigreux column to give 460 mg (96% crude) of the title compound as a 3:2 mixture of *Z*–*E* isomers as determined by NMR integration of the olefinic protons: δ 5.6 (b s, ~0.67 H) and 5.3 (b s, ~0.33 H). For stereochemical assignment see the discussion section. The isomers were separated by TLC (30% ether in hexane): R_f = 0.7, *Z* isomer; R_f = 0.5, *E* isomer. **36(E)**: IR (CCl_4) 3610, 3400, 1020 cm^{-1}; NMR (CCl_4) δ 5.24 (m, 1 H), 2.67 (t, 1 H, J = 9 Hz), 2.43 (s, 1 H), 2.2–1.1 (m, 14 H), 0.88 (t, 3 H, J = 7 Hz); mass spectrum in accord with structure; calcd for $C_{12}H_{20}O$ 180.1514; found 180.1508. **36(Z)**: IR (CCl_4) 3400, 1020 cm^{-1}; NMR (CCl_4) 5.54 (m, 1 H), 3.61 (m, 1 H), 2.3–1.2 (m, 15 H), 0.88 (t, 3 H, J = 7 Hz); mass spectrum in accord with structure; calcd for $C_{12}H_{20}O$ 180.1514, found 180.1516.

(E)- and (Z)-2-(2-n-Butylcyclohexen-1-yl)-1-n-butylcyclobutanol (30b). To 5 mL of a −78 °C solution of *n*-butyllithium in hexane (7.5 mmol, 1.5 M) in 10 mL of ether was added dropwise a solution of 1.03 g (5 mmol) of **24b** in 10 mL of ether. The mixture was stirred at −78 °C for 5 h, then quenched with saturated aqueous ammonium chloride solution, diluted with ether, and washed with brine. The organic phase was dried ($MgSO_4$) and solvent evaporated in vacuo. Kugelrohr distillation (bath temperature 60 °C (0.01mmHg)) gave 1.14 g (86%) of the title compound as an oil. IR (CCl_4): 3540, 1150, 1055, 860 cm^{-1}. NMR (CCl_4): δ 3.16 (m, 1 H), 2.7–1.0 (m, 25 H), 0.92 (b t, 6 H). A small triplet at δ ~2.7 ($J \approx$ 7 Hz) seen in a 270-MHz spectrum of crude material may be due to a minor diastereomer. Mass spectrum was in accord with structure. Calcd for $C_{18}H_{32}O$: 264.2453. Found: 264.2455.

(E)- and (Z)-2-(2-n-Butylcyclohexen-1-yl)-1-n-pentylcyclobutanol (30c). To 9.5 mL of a −78 °C solution of *n*-pentylmagnesium bromide in ether (12.3 mmol, 1.3M) in 30 mL of ether was added dropwise a solution of 1.7 g (8.25 mmol) of **24b** in 10 mL of ether. The mixture was allowed to warm gradually over a 3-h period to room temperature and worked up as above. Kugelrohr distillation (bath temperature 90 °C (0.05mmHg)) gave 1.83 g (79%) of the title compound as an oil. IR (CCl_4): 3620, 3550, 1450, 1100 cm^{-1}. NMR (CCl_4): δ 3.26 (m, ~1 H) (a small multiplet at δ 2.6 is assigned to a minor diastereomer), 2.4–1.1 (m, 27 H), 0.93 (b t, 6 H). Mass spectrum was in accord with structure. Calcd for $C_{19}H_{34}O$: 278.2609. Found: 278.2599.

(E)- and (Z)-2-(6-Methylhept-1(E)-en-1-yl)-1-[3,4-(methylenedioxy)phenyl]cyclobutanol (31). To 201 mg (1 mmol) of a −78 °C solution of 4-bromo-1,2-(methylenedioxy)benzene in 2 mL of ether was added 1.25 mL of *tert*-butyllithium in pentane (2 mmol, 1.59 M), and the mixture turned immediately to a cloudy yellow color. After 20 min a solution of 150 mg (0.833 mmol) of **26** in 2 mL of ether was added dropwise. The mixture was stirred for 1.5 h at −78 °C, then warmed gradually to room temperature over a 1-h period, and quenched with 10% aqueous ammonium chloride solution. The mixture was partitioned between ether and brine, the organic phase dried ($MgSO_4$), and solvent evaporated in vacuo. Preparative TLC (25% ethyl acetate in hexane) gave 147 mg (58%) of the title compound as an oil along with recovered cyclobutanone and 1,2-(methylenedioxy)benzene. IR (CCl_4): 3550, 1610, 1490, 1100, 940, 860 cm^{-1}. NMR (CCl_4): δ 6.73 (m, 3 H), 5.81 (s, 2 H), 5.52 (m, 2 H), 3.08 (m, 1 H), 2.4–1.0 (m, 12 H), 0.82 (d, 6 H, J = 6 Hz). Mass spectrum was in accord with structure. Calcd for $C_{19}H_{26}O_3$: 302.1882. Found: 302.1881.

Addition of Ester Enolates to Cyclobutanones. (E)- and (Z)-2-(1-Cyclohexenyl)-1-((carbomethoxy)methyl)cyclobutanol (32). To a −78 °C solution of lithium diisopropylamide (3.2 mmol) in 12 mL of ether was added 0.25 mL (3.2 mmol) of methyl acetate. After 30 min, a solution of 400 mg (2.67 mmol) of **24a** in 2 mL of ether was added dropwise and stirring continued at −78 °C for 2 h. The mixture was quenched with saturated aqueous ammonium chloride solution at −78 °C and then partitioned between ether and brine. The organic phase was dried ($MgSO_4$) and solvent evaporated in vacuo. NMR integration of the olefinic protons at δ 5.32 (m, ~0.5 H) and 5.48 (m, ~0.5 H) indicated the presence of a 1:1 mixture of diastereomers. For assignment of stereochemistry see the discussion section. Preparative TLC (5% ether in chloroform; multiple elutions) gave 184 mg ($R_f \approx$ 0.8) of pure *Z* isomer, 140 mg of a mixture, and 204 mg ($R_f \approx$ 0.7) of pure *E* isomer (88%). 40(*E*): IR (CCl_4) 3510, 1720, 1440, 110 cm^{-1}; NMR (CCl_4) δ 5.32 (m, 1 H), 3.66 (s, 3 H), 2.76 (t, 1 H, J = 8 Hz), 2.34 and 2.32 (two internal lines of AB, 2 H), 2.2–1.4 (m, 13 H); mass spectrum in accord with structure; calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1399. 40(*Z*): IR (CCl_4) 3620, 1720, 1435, 1100 cm^{-1}; NMR (CCl_4) δ 5.48 (m, 1 H), 3.65 (s, 3 H), 2.8 (m, 1 H), 2.56 and 2.54 (two internal lines of AB, 2 H), 2.2–1.5 (m, 13 H); mass spectrum in accord with structure; calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1405.

(E) and (Z)-2-(6-Bromo-3,4-dihydronaphthalen-2-yl)-1-(carboxymethyl)cyclobutanol (33c). As above, 8 g (28.9 mmol) of **25b** in 60 mL of ether was added to the ester enolate prepared from 39 mmol of lithium diisopropylamide and 3.1 mL (39 mmol) of methyl acetate in 40 mL of ether to give, after dry column chromatography (400 g silica gel, 4.5 × 50 cm; 15% ethyl acetate in hexane), 7.4 g (73%) of the title compound as a mixture of diastereomers. NMR shows two olefinic absorptions at δ 6.17 and 6.02 and two methyl ester absorptions at δ 3.64 and 3.56. NMR (CCl_4): δ 7.4–6.68 (m, 3 H), 6.17 and 6.02 (two s, total 1 H), 3.84 (m, 1 H), 3.64 and 3.56 (two s, total 3 H), 3.2–1.5 (m, 11 H). Mass spectrum was in accord with structure. Calcd for $C_{17}H_{19}BrO_3$: 350.0517. Found: 350.0504.

(E)- and (Z)-2-(6-Methylhept-1(E)-en-1-yl)-1-((carbomethoxy)methyl)cyclobutanol (34). As above, 190 mg (1.05 mmol) of **26** in 2 mL of ether was added to a −78 °C solution of the ester enolate prepared from 1.58 mmol of lithium diisopropylamide and 0.12 mL (1.58 mmol) of methyl acetate to give, after TLC (20% ethyl acetate in hexane), 219 mg (82%) of the title compound as a mixture of diastereomers which were not separated. On a 3-mmol scale, 719 mg (94% crude) was obtained and used without purification. IR (CCl_4): 3510, 1720, 960 cm^{-1}. NMR (CCl_4): δ 5.66–5.20 (m, 2 H), 3.92 (m, 1 H), 3.81 (s, 3 H), 3.0–2.8 (m, 2 H), 2.53 and 2.40 (two s, total 2 H), 2.18–1.03 (m, 10 H), 0.9 (d, 6 H, J = 6 Hz). Mass spectrum was in accord with structure. Calcd for $C_{15}H_{26}O_3$: 254.1882. Found: 254.1873.

(E)- and (Z)-2-(3-(Benzyloxy)oct-1(E)-en-1-yl)-1-((carbomethoxy)methyl)cyclobutanol (35). As above, 572 mg (2 mmol) of **27** in 4 mL of ether was added to a −78 °C solution of the ester enolate prepared from 3 mmol of lithium diisopropylamide and 0.24 mL (3 mmol) of methyl acetate in 5 mL of ether to give, after TLC (25% ethyl acetate in hexane), 613 mg (85%) of the title compound as a mixture of diastereomers which were not separated. IR (CCl_4): 3520, 1740, 1500, 1460 cm^{-1}. NMR (CCl_4): δ 7.20 (s, 5 H), 5.88–5.10 (m, 2 H), 4.38 (two AB, total 2 H, J = 12 Hz), 4.0–3.6 (m, 1 H) with 3.61 and 3.60 (two s, total 3 H) superimposed, 3.06–2.7 (m, 1 H), 2.51 and 2.42 (two s, total 2 H), 2.2–0.72 (m, 16 H). Mass spectrum was in accord with structure. Calcd for $C_{22}H_{32}O_4$: 360.2301. Found: 360.2301.

(E)- and (Z)-2-(6-Bromo-3,4-dihydronaphthalen-2-yl)-1-(1-((carbomethoxy)ethyl)cyclobutanol (33d). To a −78 °C solution of 3.9 mmol of lithium diisopropylamide in 8 mL of ether was added dropwise 0.38 mL (3.9 mmol) of methyl propionate. After 30 min a solution of 363 mg (1.3 mmol) of **25b** in 8 mL of ether was added dropwise. After 3 h at −10 °C the mixture was poured into saturated aqueous ammonium chloride solution and extracted with ether. The organic phase was washed with brine and dried ($MgSO_4$) and solvent evaporated in vacuo. Preparative TLC (20% ethyl acetate in hexane) gave 450 mg (94%) of the title compound as a 3:2 mixture (more polar–less polar) of diastereomers by NMR integration of the methyl ester signals at δ 3.68 and 3.61. Preparative TLC (20% ethyl acetate in hexane, multiple elutions) gave 31 mg of the less polar isomer, 35 mg of a mixture, and 56 mg of the more polar isomer. Less polar isomer: IR (CCl_4) 3520, 1725, 1485, 1460, 1440, 865 cm^{-1}; NMR (CCl_4) δ 7.22 (m, 2 H), 6.83 (d, 1 H, J = 8 Hz), 6.18 (b s, 1 H), 3.61 (s, 3 H), 3.0–1.8 (m, 11 H), 1.17 (d, 3 H, J = 7 Hz); mass spectrum in accord with structure; calcd for $C_{18}H_{21}{}^{79}BrO_3$ 364.0674, found 364.0666. More polar isomer: IR (CCl_4) 3530, 1725, 1640, 1590, 1485, 870 cm^{-1}; NMR (CCl_4) δ 7.18 (m, 2 H), 6.83 (d, 1 H, J = 8 Hz), 6.24 (b s, 1 H), 3.68 (s, 3 H), 3.0–1.7 (m, 11 H), 1.21 (d, 3 H, J = 7 Hz). Mass spectrum was in accord with structure. Calcd for $C_{18}H_{21}{}^{79}BrO_3$: 364.0674. Found: 364.0666.

Preparation and Fragmentation of Epoxycyclobutanols. (E)- and (Z)-2-(4-Hydroxybutylidene)cyclohexanol (36). To a 0 °C mixture of

45 mg (0.29 mmol) of **29a** in 2 mL of methylene chloride (2 mL) was added 1.5 mL of a 0.5 M sodium bicarbonate solution and 65 mg (0.32 mmol; Aldrich, 85% pure) of MCPBA. After being stirred at 0 °C for 5 h the mixture was poured into ether and washed with 1 N aqueous potassium hydroxide solution and brine. The organic phase was dried ($MgSO_4$) and the solvent evaporated in vacuo. NMR of the residue showed absorptions at δ 3.1 (b s, ~0.67 H) and 2.9 (b s, ~0.33 H), indicating a 2:1 mixture of epoxide isomers was present.

The crude epoxide was dissolved in 2 mL of methanol and added to 1 mL of a freshly prepared solution of 1 M magnesium methoxide in methanol which contained 12 mg of sodium borohydride. The mixture was stirred at room temperature overnight, then diluted with ether, and washed with saturated aqueous ammonium chloride solution and brine. The organic phase was dried (Na_2SO_4) and solvent evaporated in vacuo. NMR of this residue showed at least a 10:1 mixture of olefin isomers present (δ 5.44 t, *E* isomer and δ 5.2 t, *Z* isomer). Column chromatography on silica gel in a disposable pipette column (50% ether in hexane) gave 40 mg (80%) of essentially pure *E* isomer as an oil. The remaining examples are summarized in Table IV. IR ($CHCl_3$): 3600, 3440 cm^{-1}. NMR ($CDCl_3$): δ 5.44 (t, 1 H, J = 7 Hz; *E* isomer), 5.2 (t, J = 7 Hz; *Z* isomer), 4.14 (m, 1 H; *E* isomer), 3.64 (t, 2 H, J = 6 Hz), 2.8–1.2 (m, 14 H). Mass spectrum was in accord with structure. Calcd. for $C_{10}H_{18}O_2$: 170.1306. Found: 170.1305.

(*E*)- and (*Z*)-2-(4-Hydroxybutylidene)-1-*n*-butylcyclohexanol (37). The details for the individual runs are summarized in Table IV. *E* isomer: IR ($CHCl_3$) 3610, 3450 cm^{-1}; NMR ($CDCl_3$) δ 5.44 (t, 1 H, J = 7.5 Hz), 3.64 (t, 2 H, J = 6 Hz), 3.7–1.0 (m, 21 H), 0.9 (t, 3 H, J = 6 Hz); mass spectrum in accord with structure; calcd for $C_{14}H_{26}O_2$ 226.1932, found 226.1933. *Z* isomer: IR ($CHCl_3$) 3600, 3420, 1450, 890 cm^{-1}; NMR ($CDCl_3$) δ 5.04 (dd, 1 H, J = 9, 6 Hz), 3.64 (t, 2 H, J = 4 Hz), 2.92 (m, 4 H), 2.2–1.0 (m, 16 H), 0.9 (b t, 3 H); mass spectrum in accord with structure; calcd for $C_{14}H_{26}O_2$ 226.1932, found 226.1937.

(*E*)- and (*Z*)-2-(4-Oxohexylidene)cyclohexanol (38). The details for the individual runs are summarized in Table IV. IR (CCl_4): 3600, 3400, 900 cm^{-1}. NMR (CCl_4) for the *Z* isomer: δ 5.02 (m, 1 H), 4.68 (m, 1 H), 2.9 (s, 1 H), 2.7–1.2 (m, 14 H), 1.03 (t, 3 H, J = 8 Hz). When the *E* isomer is present, additional signals appear at δ 5.3 (t, J = 7.5 Hz), 3.92 (m), and 1.04 (t, J = 8 Hz). Mass spectrum: *m/e* (%) 196 (13), 179 (4), 178 (29), 149 (13), 121 (60), 107 (26), 106 (23), 93 (36), 79 (73), 57 (100), 55 (50). Calcd for $C_{12}H_{20}O_2$: 196.1463. Found: 196.1462.

(*E*)- and (*Z*)-2-(4-Oxo-*n*-octylidene)-1-*n*-butylcyclohexanol (39). The experimental details for each run are listed in Table IV. *Z* isomer: IR (CCl_4) 3620, 3490, 1710, 865 cm^{-1}; NMR (CCl_4) δ 4.88 (dd, 1 H, J = 8, 6 Hz), 3.62 (s, 1 H), 3.3 (m, 1 H), 2.6–2.2 (m, 4 H), 2.0–1.0 (m, 19 H), 0.92 (b t, 6 H); mass spectrum, *m/e* (%) 280 (0.3), 262 (10), 223 (15), 177 (21), 167 (21), 121 (51), 95 (16), 91 (14), 85 (100), 79 (21), 57 (64), 41 (46); calcd for $C_{18}H_{32}O_2$ 280.2402, found 280.2401. *E* isomer: IR ($CHCl_3$) 3610, 1705, 1030 cm^{-1}; NMR ($CDCl_3$) δ 5.38 (t, 1 H, J = 7 Hz), 2.8–2.1 (m, 6 H), 2.0–1.0 (m, 19 H), 0.88 (b t, 6 H); mass spectrum, *m/e* (%) 280 (0.1), 262 (8), 177 (14), 162 (11), 135 (13), 121 (31), 95 (16), 91 (41), 79 (38), 51 (83), 41 (100); calcd for $C_{18}H_{32}O_2$ 280.2402, found 280.2407.

(*E*)- and (*Z*)-2-(4-Oxo-*n*-nonylidene)-1-*n*-butylcyclohexanol (40). The experimental details for each run are listed in Table IV. One preparation using the epoxide prepared from crude cyclobutanol (2.95 g) in methanol (40 mL) containing magnesium methoxide (25 mmol) gave, after 4 days at +2 °C, 1.19 g (41% overall from cyclobutanone **27**) of the pure *E* isomer, plus 240 mg (8%) of epoxide recovered by TLC. This recovered epoxide was fragmented in methanol (6 mL) containing magnesium methoxide (3 mmol) at room temperature for 20 h to give, after TLC (10% acetone in hexane), 59 mg of pure *E* isomer (R_f = 0.2), and 138 mg of pure *Z* isomer (R_f = 0.3). *E* isomer: IR (CCl_4) 3605, 3500, 1710, 850 cm^{-1}. NMR (CCl_4) δ 5.43 (t, 1 H, J = 6 Hz), 2.4 (m, 6 H), 2.0–1.1 (m, 21 H), 0.93 (b t, 6 H); mass spectrum, *m/e* (%) 294 (1), 276 (7), 177 (18), 167 (16), 121 (42), 99 (65), 79 (21), 71 (39), 67 (29), 57 (40), 55 (46), 43 (100); calcd for $C_{19}H_{34}O_2$ 294.2558, found 294.2566. *Z* isomer: IR (CCl_4) 3470, 1710, 1040 cm^{-1}; NMR (CCl_4) δ 5.01 (dd, 1 H, J = 9, 6 Hz), 3.66 (b s, 1 H), 3.3 (m, 1 H), 2.67–1.1 (m, 25 H), 0.92 (b t, 6 H), 3.3 (m, 1 H), 2.67–1.1 (m, 25 H), 0.92 (b t, 6 H); mass spectrum, *m/e* (%) 294 (1), 276 (35), 237 (21), 177 (75), 167 (27), 162 (43), 135 (36), 121 (63), 107 (20), 99 (100), 91 (24), 71 (51), 57 (29), 55 (39), 43 (80); calcd for $C_{19}H_{34}O_2$ 294.2558, found 294.2548.

1-[3,4-(Methylenedioxy)phenyl]-3-hydroxy-10-methyl-1-oxoundec-4-(*E*,*Z*)-ene (41). The details for this run are listed in Table IV. IR ($CHCl_3$): 3600, 3500, 1720, 1680, 1600, 1490 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 7.55 (dd, 1 H, J = 8, 1.5 Hz), 7.42 (dd, 1 H, J = 1.5, 0.75 Hz), 6.83 (dd, 1 H, J = 8, 0.75 Hz), 6.03 (s, 2 H), 5.71 (dtd, ~0.74 H, J = 15.5, 6.5, 0.75 Hz), 5.50 (m, 1.26 H), 4.52 (m, 0.26 H), 4.04 (q, 0.74 H, J = 6.5 Hz), 2.97 (b t, 2 H, J = 7.5 Hz), 2.45 (b q, 2 H, J = 7 Hz). Mass spectrum: *m/e* (%) 318 (1), 300 (5), 164 (19), 149 (100), 127 (18), 111 (13), 98 (15), 96 (12), 95 (11), 85 (23), 81 (20), 57 (24), 55 (53), 43 (60). Calcd for $C_{19}H_{26}O_4$: 318.1831. Found: 318.1813.

(*E*)- and (*Z*)-2-(4-Oxo-5-(carbomethoxy)pentylidene)cyclohexanol (42). The details for these runs are summarized in Table IV. IR (CCl_4): 3450, 1715, 1650, 985 cm^{-1}. NMR (CCl_4): δ 5.26 (t, J = 6 Hz, *E*) and 5.0 (t, J = 8 Hz, *Z*) (total 1 H), 4.64 (m, *Z*), and 3.92 (m, *E*) (total 1 H), 3.72 (s, 3 H), 3.36 (s, 2 H), 2.8–1.0 (m, 13 H). Mass spectrum, *m/e* (%) 240 (0.3), 222 (18), 149 (13), 148 (19), 125 (51), 124 (47), 116 (36), 111 (40), 107 (25), 105 (22), 98 (27), 97 (29), 95 (24), 81 (47), 69 (34), 55 (100). Calcd for $C_{13}H_{20}O_4$: 240.1361. Found: 240.1355.

(*E*)- and (*Z*)-2-(4-Oxo-5-(carbomethoxy)pentylidene)-6-bromo-1,2,3,4-tetrahydronaphthalen-1-ol (43). The details for this run are summarized in Table IV. On a 21-mmol scale, 7.1 g (92%) of the title compound was obtained and used without purification. IR (CCl_4): 3460, 1740, 1710, 1650, 1620, 1590, 1470 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 7.48–7.13 (m, 3 H), 5.57 (t, J = 7.5 Hz) and 5.35 (m) (total 1 H), 5.4 and 4.93 (two m, total 1 H), 3.72 and 3.70 (two s, total 3 H), 3.45 (s, 2 H), 3.0–2.18 (m, 9 H). Mass spectrum: *m/e* (%) 366 (0.1), 350 (3), 348 (2), 322 (23), 234 (20), 232 (15), 206 (25), 205 (100), 204 (19), 203 (18), 168 (19), 167 (17), 153 (16), 128 (32), 110 (30), 91 (18), 69 (27), 57 (26), 55 (39). Calcd for $C_{17}H_{19}{}^{79}BrO_4$: 366.0467. Found: 366.0455.

(*E*)- and (*Z*)-2-(4-Oxo-5-(carbomethoxy)hexylidene)-6-bromo-1,2,3,4-tetrahydronaphthalen-1-ol (44). The details for this run are summarized in Table IV. On a 3-mmol scale, 1.0 g (88% crude) of the desired product was obtained as a 1:1 mixture of olefin isomers and was of sufficient purity to be used without purification. IR ($CHCl_3$): 3600, 3500, 1750, 1720, 1600, 1480 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 7.3 (m, 3 H), 5.56 (t, ~0.55 H, J = 7 Hz), 5.41 (b s, ~0.45 H), 5.34 (m, ~0.45 H), 4.91 (b s, ~0.55 H), 3.72 and 3.69 (s, 3 H), 3.06 (overlapping q, 1 H), 2.39–2.09 (m, 9 H), 1.33 (d, J = 7 Hz) and 1.32 (d, J = 7 Hz) (total 3 H). Mass spectrum: *m/e* (%) 382 (5), 380 (5), 364 (17), 362 (16), 253 (53), 252 (86), 251 (58), 250 (98), 249 (31), 247 (27), 239 (60), 237 (70), 155 (21), 153 (41), 128 (100). Calcd for $C_{18}H_{21}{}^{79}BrO_4$: 380.0623. Found: 380.0618.

Methyl 8-Hydroxy-12-methyl-6(*E*,*Z*)-en-3-oxotridecanoate (45). The details for this run are summarized in Table IV. IR ($CHCl_3$): 3620, 3500, 1750, 1730 cm^{-1}. NMR (270 MHz, $CHCl_3$): δ 5.44 (m, 2 H), 4.40 (m, ~0.45 H), 3.98 (b q, ~0.55 H, J = 6 Hz), 3.67 (s, 3 H), 3.40 (s, 2 H), 2.61 (m, 2 H), 2.30 (b q, 2 H, J = 6 Hz), 2.1–1.0 (m, 8 H), 0.85 (d, 6 H, J = 6 Hz). ^{13}C NMR: δ 201.9, 201.7, 134.7, 134.5, 129.1, 128.9, 72.6, 67.3, 52.2, 49.0, 42.6, 42.4, 39.0, 37.6, 27.9, 26.1, 23.2, 22.6, 21.8. Mass spectrum: *m/e* (%) 270 (0.1), 252 (5), 193 (8), 167 (49), 153 (49), 135 (40), 116 (53), 111 (50), 109 (24), 107 (25), 101 (79), 95 (71), 83 (60), 69 (83), 55 (57), 43 (100). Calcd for $C_{15}H_{26}O_4$: 270.1831. Found: 270.1832.

Methyl 9-(Benzyloxy)-8-hydroxy-6(*E*,*Z*)-en-3-oxotetradecanoate (46). The details for this run are summarized in Table IV. IR (CCl_4): 3550, 1755, 1730 cm^{-1}. NMR (CCl_4): δ 7.16 (b s, 5 H), 5.68–5.16 (m, 2 H), 4.86 (s, 1 H), 4.7–4.2 (m, 2 H), 4.06–3.7 (m, 1 H), 3.62 (b s, 3 H), 3.4–3.1 (m, 1 H), with 3.23 (b s, 2 H) superimposed, 2.7–2.1 (m, 6 H), 1.7–1.1 (m, 7 H), 0.87 (b t, 3 H, J = 5 Hz). Mass spectrum: *m/e* (%) 376 (0.1), 191 (43), 185 (39), 168 (12), 167 (59), 153 (53), 141 (11), 135 (50), 111 (46), 107 (25), 101 (36), 99 (28), 93 (57), 92 (56), 91 (100). Calcd for $C_{22}H_{32}O_5$: 376.2250. Found: 376.2254.

Methyl 8-Acetoxy-9-(benzyloxy)-6(*E*,*Z*)-en-3-oxotetradecanoate (54). To a solution of ~300 mg (0.83 mmol theoretical) of **46** in 5 mL of methylene chloride was added 0.41 mmol of 4-(dimethylamino)-pyridine followed by 0.1 mL of acetic anhydride. After 90 min at room temperature the mixture was diluted with ether and washed with 1% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, and brine. The organic phase was dried ($MgSO_4$) and the solvent evaporated in vacuo. Preparative TLC (25% ethyl acetate in hexane) gave 150 mg (43% overall from cyclobutanol **35**) as an oil. IR (CCl_4): 1750, 1740, 1670, 1635 cm^{-1}. NMR (CCl_4): δ 7.16 (b s, 5 H), 5.7–5.1 (m, 2 H), 4.8–4.2 (m, 2 H), 3.6 (m, 1 H) with 3.64 (s, 3 H) superimposed, 3.34 (m, 1 H), 3.25 (s, 2 H), 2.64–2.2 (m, 4 H), 1.96 and 1.94 (two s, total 3 H), 1.7–1.1 (m, 8 H), 0.86 (b t, 3 H, J = 5 Hz). Mass spectrum: *m/e* (%) 4.8 (1), 359 (11), 358 (16), 327 (6), 287 (4), 227 (22), 195 (5), 191 (16), 187 (18), 185 (27), 167 (59), 157 (55), 153 (37), 132 (21), 99 (75), 91 (100), 43 (74). Calcd for $C_{24}H_{34}O_6$: 418.2356. Found: 418.2354.

2-((Carbomethoxy)methylidene)-5-(3-(benzyloxy)oct-1-en-1-yl)tetrahydrofuran (56). Method A. To a solution of 92 mg (0.22 mmol) of **54** in 4 mL of THF was added 8.4 mg of sodium hydride (0.22 mmol; 63% oil dispersion). The mixture was stirred at room temperature for 45 min until hydrogen evolution ceased. Tetrakis(triphenylphosphine)palladium (15 mg, 6 mol %) was added and the mixture placed in a hot oil bath to

reflux for 4.5 h. The mixture was cooled, diluted with ether, and washed with brine. The organic phase was dried ($MgSO_4$) and the solvent evaporated in vacuo. Preparative TLC (30% ethyl acetate in hexane) gave 33 mg (42%) of the title compound as an oil.

Method B. To a −78 °C solution of 79 mg (0.21 mmol) of **46** in 2 mL of methylene chloride was added 29 μL (0.23 mmol) of boron trifluoride etherate. After 1 h at −78 °C and 2 h at 0 °C the reaction mixture was partitioned between ether and saturated aqueous sodium bicarbonate solution. The organic phase was dried (Na_2SO_4) and solvent evaporated in vacuo. Preparative TLC (30% ethyl acetate in hexane) gave 31 mg (45%) of the desired O-alkylated product. IR ($CHCl_3$): 1700, 1640 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 7.30 (s, 5 H), 5.67 (m, 2 H), 5.35 (b s, 1 H), 4.86 (m, 1 H), 4.56 (two d, total 1 H, J = 12 Hz), 4.35 (d, 1 H, J = 12 Hz), 3.77 (m, 1 H), 3.67 (s, 3 H), 3.29 (dddd, 1 H, J = 18.5, 9, 4.5, 1.5 Hz), 3.02 (m, 1 H), 2.27 (m, 1 H), 1.921.16 (m, 9 H), 0.87 (b t, 3 H, J = 6 Hz). Mass spectrum: m/e (%) 358 (0.1), 252 (4), 235 (1), 205 (2), 19 (4), 149 (4), 105 (42), 99 (12), 91 (100), 77 (19), 71 (12), 69 (11), 57 (14), 55 (12), 43 (16). Calcd for $C_{22}H_{30}O_4$: 358.2144. Found: 358.2144.

2-(Carbomethoxy)-3-(3-(benzyloxy)oct-1(*E*)-en-1-yl)cyclopentanone (55). A solution of 33 mg (0.092 mmol) of **56**, 10 mg (11 mol % of bis[1,2-bis(diphenylphosphino)ethane]palladium(0), and 0.1 mL (0.38 mmol) of *O,N*-bis(trimethylsilyl)acetamide in 0.5 mL of dioxane was degassed by bubbling argon through the solution for 20 min. The mixture was placed in a 110 °C oil bath to reflux for 5 h, then cooled, poured into water, and extracted with ether. The organic extracts were washed with brine and dried (Na_2SO_4), and the solvent was evaporated in vacuo. Preparative TLC (30% ethyl acetate in hexane) gave 23 mg (69%) of the title compound as an oil (R_f = 0.53). IR ($CHCl_3$): 1755, 1725, 1655 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 7.31 (m, 5 H), 5.63 (dd, 1 H, J = 15, 6.7 Hz), 5.5 (dd, 1 H, J = 15, 7.5 Hz), 4.56–4.28 (m, 2 H), 3.75 and 3.74 (two s, total 3 H), 3.70 (m, 1 H), 3.24 (m, 1 H), 3.02 (d, J = 11 Hz) and 3.00 (d, J = 11 Hz) (total 1 H), 2.09 (m, 4 H), 1.79–1.16 (m, 8 H), 0.87 (t, 3 H, J = 6 Hz). Mass spectrum: m/e (%) 358 (0.1), 287 (31), 252 (19), 235 (3), 191 (7), 179 (7), 167 (9), 154 (4), 141 (17), 105 (22), 91 (100), 77 (20), 65 (14), 55 (13), 43 (16). Calcd for $C_{22}H_{30}O_4$: 358.2144. Found: 358.2154.

3-(3-(Benzyloxy)oct-1(*E*)-en-1-yl)cyclopentanone. As above, a solution of the tetrahydrofuranylidene derivative **56** (27 mg, 0.075 mmol) and bis[1,2-bis(diphenylphosphine)ethane]palladium(0) (5 mg, 7 mol %) in dioxane (0.4 mL) was degassed with argon and refluxed for 10 h to give, after TLC (30% ethyl acetate in hexane), 10 mg (44%) of the title compound as an oil. IR ($CHCl_3$): 1740, 1660 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 7.32 (m, 5 H), 5.65 (dd, 1 H, J = 15, 6.7 Hz), 5.44 (dd, 1 H, J = 15, 8 Hz), 4.56 (two d, 1 H, J = 12 Hz), 4.37 (two d, 1 H, J = 12 Hz), 3.71 (q, 1 H, J = 6.5 Hz), 2.73 (m, 1 H), 2.5–1.85 (m, 6 H), 1.79–1.16 (m, 8 H), 0.87 (t, 3 H, J = 6 Hz). Mass spectrum: m/e (%) 300 (1), 230 (10), 229 (38), 109 (2), 107 (2), 99 (14), 97 (43), 91 (100), 83 (3), 81 (6), 77 (5), 65 (11), 55 (13), 43 (25). Calcd for $C_{20}H_{28}O_2$: 300.2090. Found: 300.2074.

1-(Carbomethoxy)-6-(1-((*tert*-butyldimethylsilyl)oxy)-5-methyl-*n*-hex-1-yl)-2-oxobicyclo[3.1.0]hexane (58). To a solution of 90 mg (0.33 mmol) of **45** in 0.5 mL of dimethylformamide was added 45 mg (0.66 mmol) of imidazole followed by 55 mg (0.36 mmol) of *tert*-butyldimethylsilyl chloride. After 5 h at room temperature the mixture was partitioned between pentane and water. The organic phase was dried ($MgSO_4$) and solvent evaporated in vacuo. Kugelrohr distillation (bath temperature 120 °C (0.03mmHg)) gave 97 mg (76%) of the silyloxy protected compound. IR (CCl_4): 1750, 1725, 1660, 1630 cm^{-1}. NMR ($CDCl_3$): δ 5.28 (m, 2 H), 4.80 (s, <1 H), 4.28 (m, 0.45 H), 3.9 (m, 0.55 H), 3.58 (s, 3 H), 3.21 (s, <2 H), 2.43 (m, 2 H), 2.18 (m, 2 H), 1.6–0.98 (m, 7 H), 0.76 (m, 15 H), −0.1 (m, 6 H).

The above silyl protected compound (93 mg, 0.24 mmol) in 2 mL of acetonitrile containing 0.034 mL (9.24 mmol) of ethylamine (0.034 mL, 0.24 mmol) was treated with a solution of 48 mg (0.24 mmol) of tosyl azide in 0.5 mL of acetonitrile. After 18 h at room temperature the mixture was diluted with ether and washed with saturated aqueous ammonium chloride solution, cold 1 N aqueous potassium hydroxide solution, and brine. The organic phase was dried (Na_2SO_4) and solvent removed in vacuo to give 104 mg of crude diazo compound. IR (CCl_4): 2140, 1725, 1660 cm^{-1}. NMR (CCl_4): δ 5.3 (m, 2 H), 4.3 (m, ~0.45 H), 3.90 (m, ~0.55 H), 3.68 (s, 3 H), 2.74 (t, 2 H, J = 8 Hz), 2.22 (m, 2 H), 1.6–0.9 (m, 7 H), 0.72 (m, 15 H), −0.12 (m, 6 H).

To 104 mg of the crude diazo compound in 4 mL of toluene was added 40 mg of copper bronze powder and the mixture refluxed for 1.5 h. After being cooled, the mixture was filtered through celite and the cake washed with ether. Evaporation of solvent in vacuo and TLC (25% ethyl acetate in hexane) gave 39 mg (42%) of the title compound as an oil (R_f = 0.3). IR ($CHCl_3$): 1710, 1660 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 3.93 (q, J = 8 Hz) and 3.81 (m) and 3.65 (t, J = 9 Hz) and 3.45 (m) (total 1 H), 3.77, 3.76, 3.75, and 3.74 (four s, total 3 H), 2.8–1.0 (m, 13 H), 0.82 (m, 15 H), 0.08 (m, 6 H). Mass spectrum: m/e (%) 382 (0.1), 325 (71), 297 (13), 293 (12), 200 (56), 172 (20), 155 (67), 109 (25), 107 (20), 91 (100), 75 (36), 65 (38), 43 (10). Calcd for $C_{21}H_{38}O_4Si$: 382.2539. Found: 382.2538.

3-(6-Methyl-2-oxo-*n*-heptyl)cyclopentanone (60). To a solution of 125 mg (0.46 mmol) of **46** in 3 mL of dimethylformamide was added 522 mg (1.38 mmol) of pyridinium dichromate. After 7 h at 0 °C the mixture was partitioned between ether and water. The organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo to give the crude enone (120 mg) as an oil. IR (CCl_4): 1750, 1725, 1700, 1660, 1630 cm^{-1}. NMR (CCl_4): δ 6.66 (dt, ~0.6 H, J = 16, 6 Hz), 5.98 (m, ~1.4 H), 4.92 (s, <1 H), 3.61 (s, 3 H), 3.31 (s, <2 H), 3.0–2.2 (m, 6 H), 1.8–1.0 (m, 5 H), 9.88 (d, 6 H, J = 6 Hz).

The ketone (120 mg) was dissolved in 4 mL of methanol containing 10 mol % of sodium methoxide. After 20 h at room temperature the mixture was poured into water and extracted with ether. The organic phase was washed with brine and dried ($MgSO_4$) and the solvent evaporated in vacuo to give the crude 2-(carbomethoxy)-3-(6-methyl-2-oxo-*n*-heptyl)cyclopentanone **59** (118 mg) as an oil. IR ($CHCl_3$): 1755, 1725, 1705, 1660, 1640 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 4.3 (m, <1 H), 3.76 and 3.69 (two s, total 3 H), 3.66 (d, J = 4 Hz) and 3.24 (d, J = 6 Hz) (total 1 H), 3.02–2.03 (m, 9 H), 1.55 (m, 3 H), 1.16 (m, 2 H), 0.88 (d, 6 H, J = 6 Hz). Mass spectrum: m/e (%) 268 (3), 237 (2), 236 (3), 183 (7), 151 (12), 141 (86), 140 (21), 109 (51), 95 (68), 69 (31), 43 (100). Calcd for $C_{15}H_{24}O_4$: 268.1675. Found: 268.1665.

The crude 2-(carbomethoxy)cyclopentanone **59** was dissolved in 2 mL of Me_2SO containing 10 μL of water and 58 mg (1.4 mmol) of lithium chloride. This mixture was placed in a preheated 120 °C oil bath for 1.5 h, then cooled, and partitioned between ether and water. The organic phase was washed with water and dried ($MgSO_4$) and solvent removed via distillation through a 15-cm glass-packed column. Kugelrohr distillation (bath temperature 60 °C (0.3mmHg)) gave 64 mg (66% overall) of the title compound as a sweet smelling oil. IR (CCl_4): 1745, 1720 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 2.73–2.09 (m, 7 H) with 2.39 (t, 2 H, J = 7.5 Hz) superimposed, 1.78 (dd, 1 H, J = 18, 10 Hz), 1.64–1.45 (m, 4 H), 1.16 (m, 2 H), 0.88 (d, 6 H, J = 7 Hz). Anal. ($C_{13}H_{22}O_2$): C, H.

2-(2′-Tetrahydrofuranyl-5′(*E*)-carbomethoxymethylidene)-6-bromo-3,4-dihydronaphthalene (61, R = H). To a −78 °C solution of 7.5 g (21 mmol) of **43** in 100 mL of ether was added 21 mmol of boron trifluoride etherate. The mixture was allowed to warm gradually to room temperature over a 1-h period and then partitioned between ether and saturated aqueous sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and the solvent evaporated in vacuo to give, after TLC (30% ethyl acetate in hexane), 2.44 g (33% overall for 3 steps from cyclobutanol **33c**) of the title compound as colorless needles, mp 93–94.5 °C (methanol). IR ($CHCl_3$): 1695, 1635, 1590, 1555, 1470 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 7.26 (m, 2 H), 6.90 (d, 1 H, J = 8 Hz), 6.41 (b s, 1 H), 5.39 (t, 1 H, J = 1.5 Hz), 4.95 (t, 1 H, J = 7.2 Hz), 3.68 (s, 3 H), 3.33 (dddd, 1 H, J = 17.5, 8.7, 4.5, 1.5 Hz), 3.05 (m, 1 H), 2.81 (t, 2 H, J = 8 Hz), 2.35–1.88 (m, 4 H). Anal. ($C_{17}H_{17}BrO_3$): C, H.

2-[5′-Tetrahydrofuranyl-2′-(1″-(*E*)-carbomethoxypropylidene)]-6-bromo-3,4-dihydronaphthalene (61, R = CH_3). To a −78 °C solution of 1.09 g (3 mmol) of crude **44** in 25 mL of ether was added 0.37 mL of boron trifluoride etherate. The mixture was allowed to warm gradually to room temperature over a 1-h period and then partitioned between ether and saturated aqueous sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and the solvent evaporated in vacuo to give, after TLC (30% ethyl acetate in hexane), 517 mg (47% overall from cyclobutanol **33d**) of the title compound as an amorphous solid, mp 72–74 °C (methanol). On a 0.4-mmol scale, 82 mg (55% overall) was obtained. IR (CCl_4): 1700, 1638, 1595, 1485 cm^{-1}. NMR (270 MHz, $CDCl_3$): δ 7.27 (m, 2 H), 6.90 (d, 1 H, J = 7.7 Hz), 6.39 (s, 1 H), 4.93 (t, 1 H, J = 7.5 Hz), 3.70 (s, 3 H), 3.26 (dddq, 1 H, J = 18, 9, 5, 1.5 Hz), 3.01 (m, 1 H), 2.81 (t, 2 H, J = 8.2 Hz), 2.25 (m, 3 H), 1.93 (m, 1 H), 1.88 (t, 3 H, J = 1.5 Hz). Mass spectrum was in accord with structure. Anal. ($C_{18}H_{19}BrO_3$): C, H, mol wt.

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Supplementary Material Available: The experimental details for use of **1a** and **1b** (7 pages). Ordering information is given on any current masthead.