New Synthetic Reactions. Stereoreversed Cyclobutanone Formation Utilizing Selenoxide as a Leaving Group

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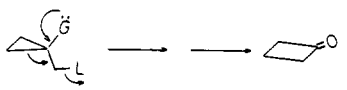
Abstract: Oxaspiropentanes undergo smooth opening with sodium phenylselenide in ethanol to give the β-hydroxyselenides at room temperature. Oxidation with *m*-chloroperbenzoic acid at −78 to −30 °C and rearrangement at −30 °C in the presence of pyridine leads directly to cyclobutanones. A mechanism invoking benzeneselenenate as a leaving group to generate a carbonium ion is presented. The stereochemistry is determined by the rate of ring expansion compared with bond rotation. Indeed, in several cases a high stereospecificity is observed. The stereochemistry obtained is opposite to that normally produced by the acid-catalyzed rearrangement of oxaspiropentanes. Thus, from one oxaspiropentane, either stereoisomeric cyclobutanone may be produced. This represents the first report of a selenoxide serving as a leaving group for formation of a carbonium ion. In ancillary studies, use of ORD, ^{13}C NMR spectroscopy, solvent-induced ^{1}H NMR shifts, and chromatographic properties to assign stereochemistry of spirocyclobutanones is reported. A novel polarization of cyclopropyl ring bonds referred to as a pseudo γ effect is observed in the ^{13}C NMR spectra of oxaspiropentanes.

One of the major methods of forming cyclobutanones is via pinacol and pinacol related ring enlargement of properly activated cyclopropane moieties.[1] Most of the processes are nonselective unless constrained by a ring system into migrating one of the cyclopropyl bonds in preference to the other. The

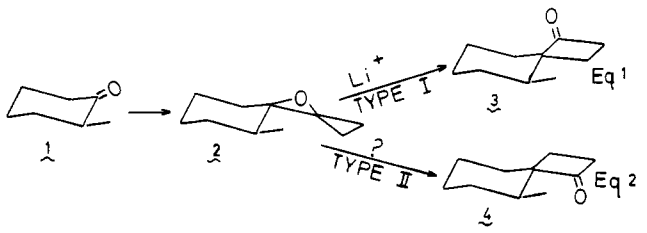


ability to stereoselectively produce spirocyclobutanones in high yield is very important for geminal alkylation,[2-5] spiroalkylation,[6] and secoalkylation[7] of ketones, but the stereoselective methods are few. One of the methods of stereoselectively producing spirocyclobutanones is the attack of 1-lithiocyclopropylphenyl sulfide on ketones and subsequent rearrangement to the spirocyclobutanone.[8]

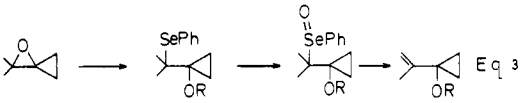
A more stereocontrolled approach to spirocyclobutanones involves the use of the stereospecific rearrangement of oxaspiropentanes to cyclobutanones with lithium salts. The stereoselectivity is limited by the stereohomogeneity of the oxaspiropentane.

Oxaspiropentanes are available through epoxidation of cyclopropylidene compounds[9] and through the nucleophilic addition of 1-lithio-1-bromocyclopropanes to ketones at low temperature.[10] The stereoselectivity of the former process is quite variable, whereas, for the latter, it is unknown.

On the other hand, preparation of oxaspiropentanes utilizing diphenylsulfonium cyclopropylide and carbonyl compounds proceeds with very high stereoselectivity in most cases. The method also has the virtue of controlling the stereochemistry at the carbons alpha to the carbonyl partner as illustrated with 2,6-dimethylcyclohexanone,[6] 2-isopropyl-5-methylcyclopentanone,[4] and Stork's ketone.[3,6] The high stereoselectivity of oxaspiropentane formation translates into a highly stereocontrolled cyclobutanone synthesis of type I as represented in eq 1—i.e., the new carbon-carbonyl carbon bond of the cyclobutanone is introduced on the sterically more hindered face of the ketone. The versatility of cyclobutanones in synthesis suggested that it would be exceedingly important to generate the complementary stereochemistry from the same intermediate (i.e., type II process represented by eq 2) in which the new carbon–carbonyl carbon bond is introduced on the sterically less hindered face.



In conjunction with studies directed at vinylcyclopropane formation, we investigated the route outlined in eq 3. When



we noticed the cyclobutanones were arising from **5** (R = H), we undertook an investigation to optimize the process and to examine its stereochemistry. The intense interest in the chemistry of selenoxides and the general acceptance of the rapidity of olefin formation made such a study particularly important.[11] Indeed, we have uncovered apparently the first case of extremely facile formation of carbonium ions from selenoxides—so facile that elimination does not effectively compete with ionization.[11g]

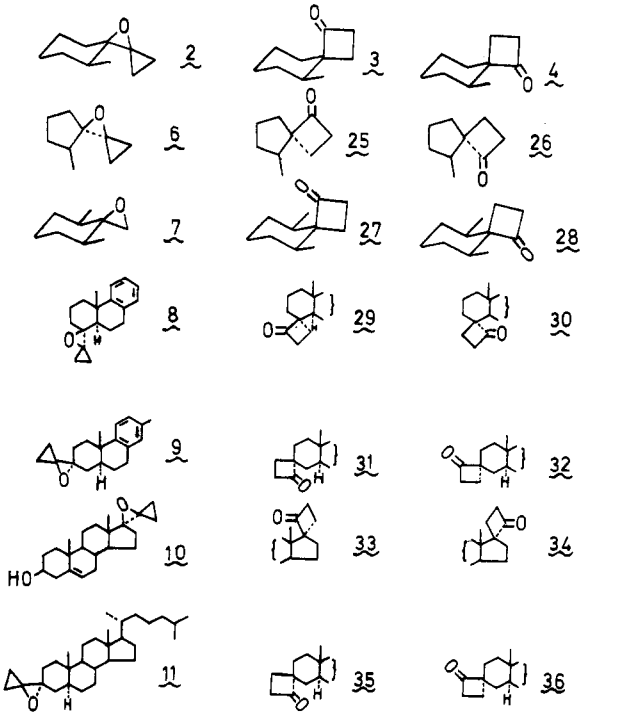
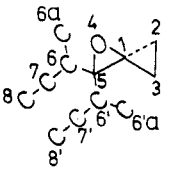


Table I. Type I and II Cyclobutanone Spiroannulation

Oxaspiro-pentane	Cyclobutanone		% yield, type I process, normal	% yield, type II process, relative		Overall isoln yield from starting ketone
	Normal	Reverse		Normal	Reverse	
2	**3**	**4**	80	13	87	85
6	**25**	**26**	61	4	96	48
7	**27**	**28**	88	60,[a] 70[b]	40,[a] 29[b]	85
8	**29**	**30**	80	36	64	68
9	**31**	**32**	75	7	93	75
10	**33**	**34**	67	97	3	57
11	**35**	**36**	51	<2	<98	62

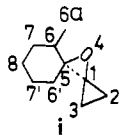
[a] Rearrangement at 25 °C. [b] Rearrangement at −90 °C.

Table II. ^{13}C NMR Data for Oxaspiropentanes[a,b]



Compd	C(1)	C(2)	C(3)	C(4)	C(5)	C(6a)	C(6')	C(6'a)	C(7)	C(7')	C(8)	C(8')
2	62.63	3.96	1.56	67.62	34.91	14.67	32.81		32.02	23.42	24.64	
7	58.48	4.25	4.25	69.04	36.18	15.65	36.18	15.65	33.64	33.64	25.77	
12	61.84	3.33	3.33	72.90	32.19		32.19		25.25	25.25		
13	64.29	3.08	3.08	68.99	37.89	16.87	33.64		32.76	24.50	25.72	29.63
14	62.58	2.79	2.79	66.10	36.18		36.18		18.09	18.09	14.33	14.33
15	61.70	5.86[e]	1.36[e]	68.35	34.32	26.21[f]	17.89[g]					
16[c,d]	58.48	3.28	1.81	58.92	31.29				37.55		38.82	
	58.04		1.71		30.90				37.11			

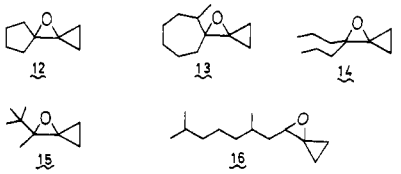
[a] All chemical shifts are given in parts per million downfield from internal TMS. [b] The generalized formula applies to cyclic and noncyclic systems, e.g., i, etc. [c] Additional absorptions seen at 18.65 and 20.09, 24.74, 39.26, 27.97, 22.69, and 22.59 for remaining carbons.



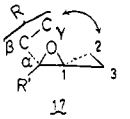
i

[d] The doubling of some peaks arises since a diastereomeric mixture is present. [e] t of t (J = 161, 4.4 Hz). [f] q of h (J = 125.7, 4.7 Hz). [g] q (J = 125.7 Hz).

Selenide Formation. The oxaspiropentanes shown in Table I were prepared in the usual manner.[12] In addition, oxaspiropentanes **2, 7,** and **12–16** were characterized by their ^{13}C NMR spectra as summarized in Table II. The assignments are based upon off-resonance decoupling and chemical shift analogy.[13] The spectra confirm the stereohomogeneity of the oxaspiropentanes for all cases except **16** which is a mixture. The most striking feature of the data is the clear evidence for polarization of the cyclopropane bonds due to a pseudo γ effect. Two trends demonstrate this phenomenon. In **12** and **14,** C(2)



and C(3) appear at 2.9 ± 0.2. Placing additional steric bulk at 6 and 6′ causes a net downfield shift (i.e., **7**). This suggests a polarization of the electrons in the cyclopropyl ring bonds away from C(2) and C(3). Indeed, there is observed a corresponding upfield shift of C(1) due to increased electron density at this carbon. Unsymmetrical substitution at C(6) and C(6′) leads mainly to polarization of the C(2)–C(3) bond (i.e., **2, 15, 16**) as reflected by chemical shift differences of these two carbons of 3.0 ± 1.5. The more deshielded carbon is assigned to the carbon proximal to the larger group R or R′ (i.e., in **17**) in accordance with the effects of steric bulk in the symmetrical cases (vide supra). As the steric bulk difference and the conformational rigidity maximizing eclipsing of R and R′ with the cyclopropyl carbons increase, this chemical shift difference increases. The coupling of the cyclopropyl hydrogens are quite normal. The unusual polarization of the C–C ring bonds is reminiscent of the γ effect on the C–H bonds (cf. **18**) in which



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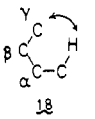
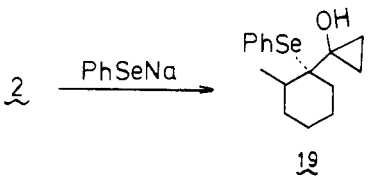


18

electrons in the C–H bond are polarized away from H toward C—increasing the shielding of the carbon. Drawn for comparison in **17** and **18,** we are seeing C(2) deshielded and C(3) or C(1) shielded because of a similar polarization of the C–C bonds. We propose to refer to this phenomenon as a pseudo γ effect.

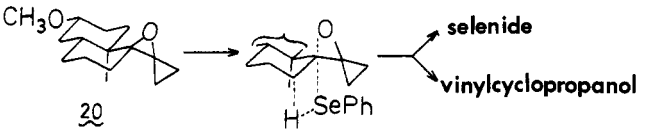
Ring opening by in situ formed sodium phenylselenide normally was performed on the *crude* oxaspiropentanes in the presence of diphenyl sulfide, the by-product of the ylide reaction. The addition of phenylselenide to oxaspiropentanes is highly accelerated by protic solvents which protonate and weaken the C–O bond, thus increasing its tendency toward nucleophilic attack. The reaction to form **19** is incomplete after 70 h at 60 °C in dimethoxyethane, whereas at 25 °C in ethanol it is complete within 40 min. The addition of phenylselenide to normal epoxides has been studied by Sharpless and Lauer[14]



19

and is complete in ethanol at reflux in 0.5–2.0 h for acyclic cases.

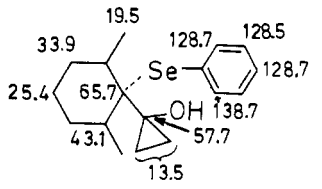
As to be expected for an S_N2 reaction, extreme steric hindrance will preclude the formation of the selenide. Oxaspiropentane **20** was recovered unchanged after 10 days exposure[15] to sodium phenylselenide at 25–30 °C. However, if **20** is heated



20 u

for ~30 h at 60 °C in a concentrated DME solution of sodium phenylselenide, upon workup with saturated aqueous bicarbonate, one isolates in addition to the selenide, the vinylcyclopropanol in ~50% yield.[15] The selenide upon oxidation yields only cyclobutanone and no vinylcyclopropanol. This curious result can be rationalized by invoking a merged substitution-elimination mechanism.[15,16]

In two other examples, sterically hindered selenides **21** and **22** from **7** and **10**, respectively, could be obtained but had to



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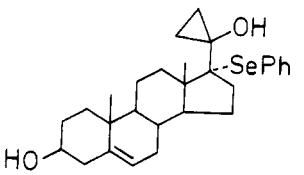
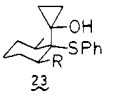


22

be handled carefully and quickly. Their instability was characterized by originally colorless dichloromethane solutions of the selenides turning yellow over an hour or two at 25 °C indicating the formation of diphenyl diselenide. As to be expected from an S_N2 process, the selenide formation is completely stereospecific, for the ^{13}C NMR spectrum of **21** is clean and contains no trace of any other isomers. The ^{13}C assignment based on the off resonance, intensities, and model compounds[17] is as shown. The ^1H NMR of **21** is characterized by two symmetrical multiplets at 0.70 and 1.12 ppm for the cyclopropyl protons, the methyl doublet (J = 6 Hz) at 1.41 ppm and the rest of the protons falling in a complex multiplet between 1.2 and 2.0 ppm. The corresponding sulfides **23a** and **23b** have



23
a) R=H
b) R=CH_3

been formed by the substitution of thiophenoxide as the nucleophile. The proton NMR spectra show only one methyl doublet in each case—supporting the stereohomogeneity of both. The ^1H NMR of **23** is rather unusual, for the cyclopropyl hydrogens form a complex ABCD multiplet between 1.1 and −0.25 ppm.

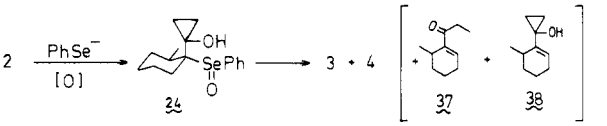
Selenoxide Oxidation. The oxidation of the selenides proceeds smoothly at −78 °C with a variety of oxidizing agents as shown in Table III for the case of **2.** Note that these oxidations are normally performed on the crude products of the previous reaction with no separation at any stage. Thus, it is

Table III

Solvent	Oxidant/base	Temp, °C	Reverse to normal ratio (GLC) of **4:3**
EtOH	H_2O_2/NH_4OH	0	1:1[a]
EtOH	H_2O_2/pyridine	0	2:1[b]
EtOH	H_2O_2/pyridine	60	1.5:1
EtOH	H_2O_2/pyridine	−30	2.45:1
EtOH	O_3/pyridine	−78	2:1
Hexane	O_3/pyridine	−78	3.1:1
Benzene	MCPBA[c]/pyridine	0	2.5:1
CH_2Cl_2	MCPBA[c]/pyridine	−30	3:1
Hexane	MCPBA[c]/pyridine	−30	4:1
Hexane	MCPBA[c]/pyridine	−78	3.7:1

[a] **37** also present by NMR. [b] **38** also present by NMR. [c] *m*-Chloroperbenzoic acid.

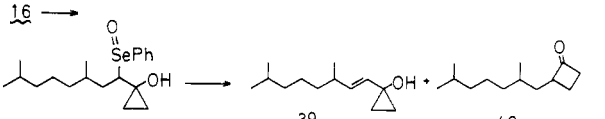
done in the presence of diphenyl sulfide which apparently does not affect the process. When warmed to −20 to −30 °C, rapid decomposition takes place to give a product mixture dependent upon reaction conditions. Added base is necessary for optimal results but too strong a base effects cleavage to **37.** Note that



24 37 38

in all cases cyclobutanone formation is the preferred pathway. Quite unexpectedly, vinylcyclopropane formation (a formal selenoxide elimination[18-21]) is minimized by going to lower temperatures—i.e., the pathway for cyclobutanone formation is of lower energy than the normal selenoxide elimination. Table I summarizes the examples for this new approach to cyclobutanone formation. The yields given in every case are for going from starting ketone to final cyclobutanone without any intermediate purifications.

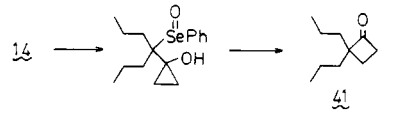
Increasing substitution favors cyclobutanone formation over elimination. In every case, the oxaspiropentanes from ketones gave virtually only the cyclobutanone products under optimum conditions. In the case of the oxaspiropentane from an aldehyde i.e., **16,** the vinylcyclopropane **39** is the major product. It does



39 40

2 : 1

not transform to cyclobutanone under these conditions. The *E* configuration is established by the 15-Hz coupling constant of the vinyl protons.[11b] To show the difference between **16** and the examples in Table I does not reflect a difference in behavior for oxaspiropentanes from acyclic vs. cyclic carbonyl partners, we examined an acyclic ketone **14** and observed only cyclobutanone formation, i.e., **41.** Qualitatively, the rate of the re-



41

action increases as the steric congestion increases as determined by a change from colorless to yellow, the latter associated with the selenium by-products formed as a result of rearrangement. Thus, in the cases of **7, 8,** and **10** reaction proceeded appreciably more rapidly than in the other examples. It should be noted that, in the absence of the cyclopropane ring,

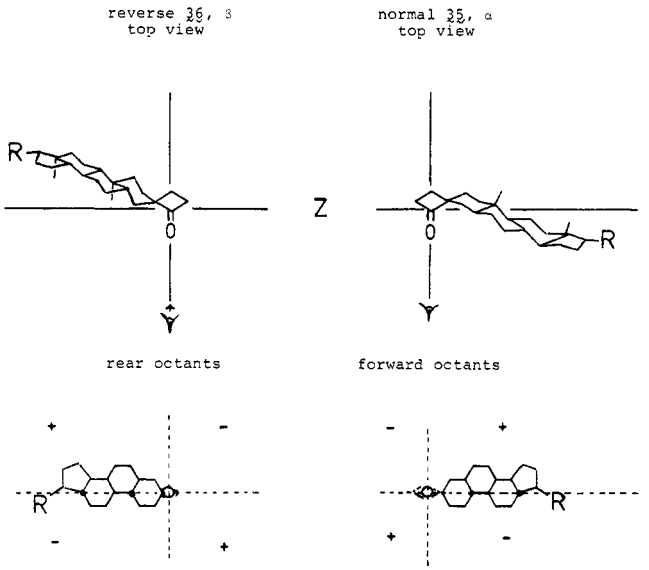
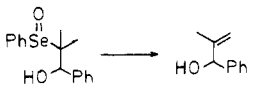


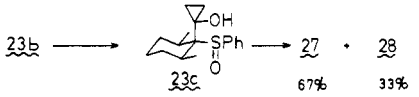
Figure 1.

no pinacol-like rearrangement occurs.[18]



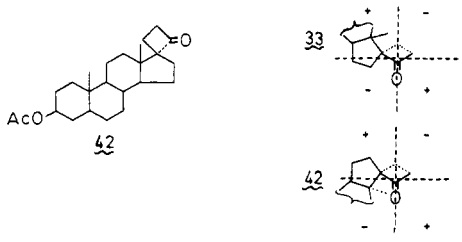
(no carbonyl products)

In an ancillary study, the sulfide **23b** was oxidized. Rearrangement of its sulfoxide **23c** was slower than the selenoxide case, and required 25 °C. The stereochemical results for the two rearrangements were identical.



Stereochemical Assignment of the Cyclobutanones. The stereochemistry of the cyclobutanones formed in the type I process (referred to as normal) can be predicted based upon the known behavior of this spiroannelation reaction[1] and confirmed in several cases by independent spectroscopic data (vide infra). The remarkable finding is that the *type II process produces the cyclobutanone of opposite stereochemistry.* In most cases, it is the major product and in several it is virtually the exclusive product (see Table I). In addition to comparing the cyclobutanone(s) arising from a type II process to that from a type I process for assignment of stereochemistry, four additional methods were developed—solvent induced ^{1}H NMR shifts, ^{13}C NMR spectroscopy, ORD, and chromatographic behavior.

Optical rotary dispersion is useful in the assignments of **33–36** which derive from optically pure starting materials.[18] Utilizing the octant rule, cyclobutanone **42** should show a



negative Cotton effect as it is reported to have. Cyclobutanone **33,** on the other hand, should have a positive Cotton effect as indeed it does. Figure 1 illustrates that, for **35,** the molecular

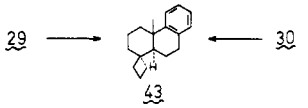
Table IV. Solvent Induced Shifts

Compd	Carbon	δ_{CDCl_3}	δ_{PhH}	$\Delta\delta = \delta_{PhH} - \delta_{CDCl_3}$[a]
Dehydroepiandrosterone	C(18)	0.89	0.63	−0.26
Dehydroepiandrosterone	C(19)	1.04	0,86	−0.18
33	C(18)	0.86	0.86	0
33	C(19)	1.02	0.91	−0.11
29[b,c]		1.24	1.35	+0.11
30[b]		1.09	0.93	−0.16

[a] A positive number indicates a downfield shift and a negative number an upfield shift. [b] CCl_4 utilized as normal solvent. [c] Reference 6.

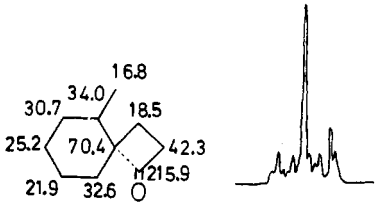
structure puts some of the steroidal A ring in the net zero shift situation while placing the rest of the molecule in the forward positive octant. The Cotton effect is predicted to be small and of the positive sign. Compound **36,** on the other hand, is in the rear positive quadrants which dictate a strong positive Cotton effect. As predicted, the normal cyclobutanone **35** shows a weak positive and the reverse cyclobutanone **36** a strong positive Cotton effect (see Experimental Section).

The benzene-induced solvent shifts have been well studied in steroids,[19] as in other compounds, and indicate that a methyl group will be shifted upfield if it is behind the plane that is perpendicular to and bisecting the C–O bond of the carbonyl group and a downfield shift if it is in front. Table IV lists the relevant data. The C(18) methyl group in dehydroepiandrosterone shows the expected upfield shift. However, in cyclobutanone **33,** this methyl group is about on the zero shift plane and should give a very small, if any, solvent-induced shift. This prediction is confirmed. Cyclobutanones **29** and **30** should



show downfield and upfield shifts, respectively, for the angular methyl group as is observed. To confirm that **29** and **30** represent only different locations of the cyclobutanone carbonyl group, a Wolff–Kishner reduction of each to the identical hydrocarbon **43** was carried out.

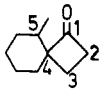
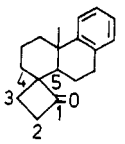
^{13}C NMR spectra appear to be especially valuable for assigning configurations, see Table V. The ^{13}C resonances were assigned using a variety of methods. For example, the carbons in **4** were assigned using single proton decoupling at 3.12 ppm (cyclobutanone α CH_2), single-frequency off-resonance decoupling,[20] and model compounds.[13] The 18.5 carbon resonance was assigned using the characteristic isolated $-CH_2-CH_2-$ off-resonance coupling pattern shown below and discussed by Hagaman.[20] The single frequency off-resonance splitting pattern is shown at right.



All other resonances in the molecule are usually within 1 ppm of the other isomer's, which is especially important in **9** and **10** to establish that the ring juncture is the same, as shown in Table VI.

The ^{13}C NMR shifts of the carbonyl, the α-methylene, the spirocyclic quaternary, and the methyl carbons in most cases

Table V. ^{13}C Shifts of Cyclobutanones[a]

Compd[c]	(C=O)C_1	(CH_2)C_2	(CH_2)C_3	(–C–)C_4	(CH)C_5	CH_3
	N 215.4	41.5[b]	23.0	69.6	36.5	16.7
	R 215.9	42.3[b]	18.5	70.4	34.0	16.8
	N 215.4	42.7	22.8	74.2	43.4	15.3
	R 215.3	42.9	20.0	74.1	38.5	15.7
	N 216.4	42.8	19.0	74.5	37.9	17.5
	R 218.2	44.1	12.9	75.2	36.1	17.1
	N 213.3	41.3	23.4	68.9	47.0	24.5
	R 216.4	44.2	21.1	69.1	43.0	24.2

[a] In parts per million. [b] Located by single proton decoupling at 3.12 ppm. [c] Both isomers of the last compound in the column have high field resonances, 20.8 18.7, (R, reverse), 20.1, and 19.7 (N, normal).

Table VI

10	9	Assignment
216.4	213.3	Carbonyl
147.2	148.4	
134.8	134.3	
129.1	128.9	Aromatic
125.6	125.5	
125.4	125.3	
124.4	123.9	
69.1	68.9	Spiro quaternary
43.0	47.0	C_5 methine
44.4	41.3	C_2 methylene
37.6	37.8	
37.0	37.4	Benzylic quaternary
34.2	35.4	
29.7	29.3	
24.2	24.5	Methyl
21.1	23.4	C_3 methylene
20.8	20.1	
18.8	19.7	

Table VII. Methyl Shifts in Proton NMR Spectra[a]

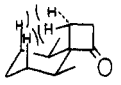
Normal	Reverse
25, δ 1.03	**26,** δ 0.96
3, δ 1.01	**4,** δ 0.88
27, δ 1.02	**28,** δ 0.92
29, δ[b] 1.25	**30,** δ 1.09

[a] In parts per million downfield from internal TMS. [b] Reference 6.

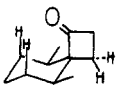
Table VIII. GLC Retention Times of Cyclobutanones

Compd	Time from air, min	Temp, °C
26	2.7	83
25	2.2	
28	5.1	95
27	4.0	
4	3.8	92
3	3.0	

show little variance with the stereochemistry of the cyclobutanone. The 3-methylene and the 5-methine carbons show predictable and consistent trends. In going from the normal (**27**) to the reverse (**28**) stereochemistry, the 3-methylene



28



27

carbon moves upfield 2.3 to 6.2 ppm owing to the 1,3-diaxial interactions shown in the diagram. The 5-methine moves upfield by roughly the same amount (1.8–5.0 ppm). The diaxial interactions in **28** are more severe than in **4** because the additional methyl group further limits the conformational mobility of the cyclohexane ring. The resulting 1,3-diaxial steric compression of the 3-methylene is shown by its 12.86-ppm shift which is 4.3 ppm higher than the methyl resonance!

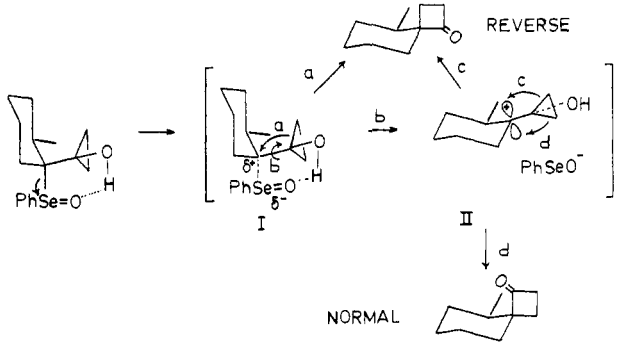
Another trend which is noticeable in the 5-methylspirocyclobutanones is the dependence of the methyl ^1H NMR shift on the stereochemistry of the cyclobutanone. If the carbonyl group is syn to the methyl as in the normal series, the methyl resonance is at lower field than when it is anti as in the reverse series as summarized in Table VII.

The gas chromatographic traces show another trend (see Table VIII). On a UCON Polar column (A), the reverse isomers **4, 28,** and **26** always have a longer retention time than their respective normal isomers. This order presumably reflects the greater accessibility (i.e., lower steric congestion) of the carbonyl group in the reverse isomers.

Mechanistic Discussion

Considering the experimental observations, a composite mechanism clearly implicating carbonium ions appears most reasonable. The selenoxide seems to be playing the role of a leaving group. Control experiments eliminate vinylcyclopropanols as intermediates. As illustrated in Scheme I, **24** would be expected to prefer a conformation in which the selenoxide is hydrogen bonded to the hydroxyl group. This conformation perfectly lines up one of the cyclopropane bonds for back-side migration once the selenoxide leaves. The transition state is represented in I, a benzeneselenenate tight ion pair which can undergo back-side migration or convert to II, a conformationally relaxed ion pair. This second ion pair can collapse to a cyclobutanone by either axial or equatorial migration of a cyclopropane bond. Axial migration yields the reverse cyclobutanone while equatorial migration produces the normal cyclobutanone. The fact that a stereohomogeneous selenide **21** produces a mixture of cyclobutanones (i.e., **27** and **28**)

Scheme I. Mechanistic Rationale



clearly supports this picture. While the stereohomogeneity of the selenides in the other cases has not been established, their stereohomogeneity seems reasonable to presume. First, the oxaspiropentanes are stereohomogeneous as determined by ^{13}C NMR and by their stereospecific rearrangement in the type I process. Second, very high stereospecificity is observed in the type II process in many cases, implying that epoxide opening by selenide is stereospecific. Such openings in simple epoxides are stereospecific. It seems reasonable to conclude that the oxaspiropentane ring opening is stereospecific in all cases and that any loss of stereospecificity arises in the rearrangement step.

This composite mechanism easily explains the effect various solvents have on the stereoselectivity. Any solvent capable of breaking up the internal solvation of I and thereby bringing about conformational relaxation to II or a solvent associated II will produce a drop in stereoselectivity. Solvents that can protonate the selenoxide may bring about its departure and form II directly or a solvent separated ion pair. The net result will be a decrease in the stereoselectivity as shown in Table III.

Higher temperatures would be expected to shorten the lifetime of the tight ion pair and facilitate conformational relaxation to II thereby causing a drop in stereoselectivity. As can be noted in Table III, the best combination of temperature and solvent is −30 °C in hexane; at −78 °C the rearrangement proceeds too slowly to be practical.

The selenoxide is particularly labile toward rearrangement arising from the internal hydrogen bonding and from the partial weaking of the carbon–selenium bond to the ability of a tertiary cyclopropyl carbinyl center to accept a positive charge. As is demonstrated by the cyclic examples, a change of stabilization from tertiary cyclopropyl carbinyl to secondary cyclopropyl carbinyl is enough to retard the rearrangement process to allow the normal concerted selenoxide elimination to compete. Without the cyclopropyl ring, no pinacol-like products are seen.

Scheme I also rationalizes the sensitivity of the rearrangement to steric crowding. If the tight ion pair is destabilized owing to unfavorable steric interactions relative to II, then its lifetime will be shorter and rotation about bond b will be competitive to back-side migration. As a result the stereoselectivity will drop. This trend is easily noticed in Table I, for the degree of stereoselectivity decreases in going from **6** to **2** and finally to **7.** In the case of **10,** both type I and type II processes produce essentially only the normal cyclobutanone **33.** The preference for α migration reflects the steric congestion on the β face owing to the angular methyl group which is well known in this system.

This scheme is reinforced by the observation that switching from a selenoxide to a sulfoxide leaving group does not affect the stereochemistry. The lack of dependence of the stereochemistry upon the nature of the leaving group and upon the rate of reaction (sulfoxide considerably slower than selenoxide) suggests that the rate-determining and product-determining steps are different.

Conclusion

The excellent work of Reich, Sharpless, Jones, and Clive, among others, has exploited the chemistry of selenoxides.[11] The possibility of heterolytic cleavage to carbonium ions has not been heretofore recognized. The observations reported herein demonstrate that under special circumstances such a process can be very favorable indeed—occurring at −30 °C in hydrocarbon solvents. Furthermore, this new arrangement expands the scope of the geminal alkylation procedure and the γ-butyrolactone annelations. The high stereoselectivity for the condensation of the oxaspiropentane formation utilizing dephenylsulfonium cyclopropylide can now translate into a high degree of stereocontrol for formation of either cyclobutanone from a single precursor.

Experimental Section

General. All reactions were carried out under a positive pressure of dry nitrogen; apparatus for anhydrous reactions were flamed out under a stream of dry nitrogen. Ethereal solvents, dimethoxyethane (DME), dioxane, tetrahydrofuran (THF), and diethyl ether (ether), were distilled from sodium benzophenone ketyl. All amines used were distilled from calcium hydride onto fused potassium hydroxide. Dimethyl sulfoxide (Me_2SO), benzene, pyridine, and all halocarbon solvents were distilled from calcium hydride before use. All other solvents were used as obtained commercially. Evaporation of solvents in vacuo was performed at aspirator pressure on a Büchi rotavapor. Residual solvent traces were removed at ambient temperature on an Aldrich Kugelrohr distillation apparatus at 5–10 Torr prior to distillation. General drying of organic fractions was done with anhydrous sodium sulfate. Melting and boiling points are uncorrected; all reaction temperatures were measured externally.

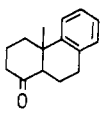
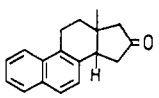
Thin layer chromatography (TLC) used to monitor a reaction was done on microscope slides coated with E. Merck silica gel 60 PF-254 while preparative layer chromatograph (PLC) for purification of products was done on 20 × 40 and 20 × 20 cm plates coated with 2 mm of PF-254 silica gel and activated in an oven at 120 °C for 2 h. Column chromatography was done on Grace grade 62 silica gel.

All ^1H NMR spectra recorded on a JEOL JNM-MH-100 spectrometer fitted with a variable temperature probe. Most ^{13}C NMR spectra were recorded on a JEOL FX-60 spectrometer; all others were recorded on a Varian XL-100.

NMR multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; m, multiplet. The prefix "b" is used to denote a broadened peak. The symbol "tp" is used to denote the five major line pattern generated in off-resonance ^{13}C NMR by an isolated $-CH_2-CH_2-$ group (Chapter IV, ref 66). The prefix "a" will be used to denote an approximate assignment for those patterns between t and tp. Chemical shifts are in δ units and are relative to an internal tetramethylsilane standard. Infrared spectra were recorded on a Perkin-Elmer 267 grating spectrophotometer and are calibrated with the 1601-cm^{-1} peak of polystyrene. Mass spectra were recorded on an AEI-MS-9. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Optical rotatory dispersion spectra were recorded on a Durrum–Jasco Model J-20 spectropolarimeter. GLC evaluations of product mixtures were done on a Varian Aerograph Model 90P-3 with a flow rate fixed at 2 mL/s, injection port at ~280 °C, and detector at 160 °C on the following columns: (A) 12 × ¼ in. 10% UCON 50 HB 2000 Polar on Chrom W Reg. (60/80); (B) 8 ft × ¼ in. 10% UCON 50 HB 2000 Polar on Chrom W Reg. (60/80); (C) 8 ft × ¼ in. 20% Dow-Corning 710 on Chrom P; (D) 11 ft × ¼ in 8% SE-30 on Chrome W; (E) 8 ft × ¼ in. 20% diethyleneglycolsuccinate on Chrome P. GLC traces are reported as minutes from the air peak and not from injection.

Preparation of Normal Cyclobutanones (Type I Process). (4*R,5*S**)-5-Methylspiro[3.5]nonan-1-one (3).** Through a solution of 448 mg (4 mmol) of 2-methylcyclohexanone and 1.35 g (4.3 mmol) of diphenylcyclopropylsulfonium tetrafluoroborate in 12 ml of Me_2SO was passed a stream of nitrogen bubbles for 5 min. To this degassed solution was then added 0.5 g (9 mmol) of powdered potassium hydroxide, the solution again degassed for 5 min and allowed to stir at 25 °C for 7 h. The reaction mixture was poured into 100 ml of hexane

Table IX. Preparation of Normal Cyclobutanones (Type I Process)

Ketone	Wt in mg (mmol)	Wt of ▷—SPh_2BF_4 in mg (mmol)	Wt of KOH in g (mmol)	Me_2SO, ml	Reaction time, h	Reflux time, h	Cyclobutanone, wt in mg (%)
2-Methylcyclohexanone	See text						
4-Heptanone	685 (6.0)	1.94[d] (6.2)	0.73 (13.0)	15	5	4	**41**, 387[a,b] (89.5)
3,7-Dimethyloctanal	1.113[d] (7.15)	2.5[d] (8.0)	0.65 (11.6)	15	21	6.5	**40**, 33.3[a,c] (24)
2-Methylcyclopentanone	495 (5.0)	1.65[d] (5.25)[e]	0.4 (7.1)	12	12	4.5	**25**, 212[a,b] (61.3)
 (ref 21)	1.011[d] (4.7)	1.97[d] (6.3)[e]	0.46 (8.2)	20	10	9	**29**, 996 (80)
Cholestan-3-one	385 (1.0)	321 (1.25)	0.43 (8.4)	17	5.5	2.5	**35**, 98[b] (50.8)
Dehydroepiandrosterone	144 (0.5)	302 (0.96)[e]	0.12 (2.1)	15	9.5	9	**33**, 110 (67)
	121 (0.48)	190 (0.61)	66[h] (1.2)	12	4	17	35.9[f] (77)[g]

[a] Corrected for diphenyl sulfide present (NMR): **41**, 25% by wt; **40**, 34% by wt; **25**, 15% by wt. All IR and mass spectral samples of these compounds were GLC purified. [b] One-half of the oxaspiropentane was used in the rearrangement to the cyclobutanone. [c] Only one-tenth of the oxaspiropentane used. [d] In grams. [e] Added portionwise. [f] Only one-third of the oxaspiropentane used. [g] Determined to be a 1:1 mixture of isomers by planimeter integration of the 270-MHz NMR methyl resonances. [h] In milligrams.

and extracted with 4 × 80 mL of hexane. The combined hexane extracts were washed 2 × 100 mL of saturated aqueous sodium bicarbonate and dried over sodium sulfate. The solvents were removed in vacuo. For the ^{13}C NMR analyses, the oxaspiropentanes were normally isolated by Kugelrohr distillation at this point. For cyclobutanone formation, the crude product was taken directly on. To the resulting oil 10 mL of benzene and ~5 mg of anhydrous lithium tetrafluoroborate were added. The mixture was allowed to reflux for 3 h, whereupon the solvents were removed by distillation and the resulting oil Kugelrohr distilled at 65 °C at 0.1 Torr to yield 683.3 mg of (4*R**,5*S**)-5-methylspiro[3.5]-nonan-1-one (**3**) which by NMR contained 28% by weight of diphenyl sulfide, corrected yield 80.4%. For spectral analysis, a sample was further purified by GLC: IR (CCl_4) 2937, 2855, 1770, 1460, 1443, 1080, 1060, 1040, 1030 cm^{-1}; NMR (CCl_4) δ 1.01 (d, J = 6 Hz, 3 H), 1.10–2.2 (m, 11 H), 2.5–3.1 (m, 2 H); ^{13}C NMR ($CDCl_3$) 215.4 (s), 69.6 (s), 41.5 (tp), 36.5 (bd), 33.1 (atp), 31.2 (at), 24.7 (bt), 23.0 (tp), 16.7 (q) ppm; mass spectrum (MS) (rel intensity) *m/e* 153 (3), 162 (26), 134 (10), 124 (29), 110 (31), 109 (32), 108 (11), 97 (11), 96 (46), 95 (57), 82 (29), 81 (100), 79 (10), 77 (6), 69 (12), 68 (42), 67 (62), 66 (8), 56 (6), 55 (28), 54 (20), 53 (16), 42 (6), 41 (37), 40 (6), 39 (23). Calcd for $C_{10}H_{16}O$: mol wt, 152.12011. Found: mol wt, 152.11966. GLC: column A, 92 °C, 3.0 min. The remaining examples were summarized in Table IX.

Spectral Data for Normal Cyclobutanones. *trans*-4aβ-Methyl-1β(2′-oxospirocyclobutyl)-1,2,3,4,4a,10a,9,10-octahydrophenanthrene (29): IR and NMR compared with those of a known sample;[6] ^{13}C NMR ($CDCl_3$) 213.3 (s), 148.4 (s), 134.3 (s), 128.9 (d), 125.5 (d), 125.3 (d), 123.9 (d), 68.9 (s), 47.0 (d), 41.3 (atp), 37.8 (at), 37.4 (s), 35.4 (at), 29.3 (atp), 24.5 (q), 23.4 (atp), 20.1 (at), 19.7 (at) ppm; PLC (CH_2Cl_2) R_f 0.49.

***trans*-7-Methoxy-4aβ-methyl-2α-(2′-oxospirocyclobutyl)-1,2,3,4,4a,10a,9,10-octahydrophenanthrene (31):** IR and NMR compared with those of a known sample prepared by James H. Rigby.[5]

3α-(2′-Oxospirocyclobutyl)cholestane (35): IR (CCl_4) 2990–2820, 1770, 1465, 1443, 1380, 1365, 1065 cm^{-1}; NMR ($CDCl_3$) δ 0.64 (s, 3 H), 0.76 (s, 3 H), 0.84 (s, 3 H), 0.90 (s, ~6 H), 0.8–2.0 (m, ~33 H); 2.84 (apparent t, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$ 11.20, 12.09, 18.66, 20.98, 22.54, 22.80, 23.85, 24.10, 24.84, 27.99, 28.21, 28.65, 29.04, 31.69, 35.28, 35.50, 35.77, 36.16, 39.53, 39.97, 40.58, 42.25, 53.72, 56.26, 56.27, 64.98, 214.97 ppm; MS (rel intensity) *m/e* 426 (4), 399 (7), 398 (24), 385 (32), 384 (100), 383 (19), 382 (52), 369 (11), 325 (6), 244 (23), 243 (16), 231 (19), 230 (49), 229 (62), 215 (10), 203 (5), 202 (5), 201 (5), 189 (5), 177 (6), 176 (7), 175 (18), 174 (6), 173 (7), 163 (11), 162 (12), 161 (31), 160 (5), 159 (9), 149 (18), 148 (9), 147 (21), 146 (5), 145 (9), 137 (7), 136 (9), 135 (28), 134 (15), 133 (20), 131 (7), 123 (19), 122 (30), 121 (40), 120 (17), 119 (25), 117 (10), 111 (5), 110 (5), 109 (33), 108 (23), 107 (52), 106 (15), 105 (30), 99 (15), 97 (12), 96 (6), 95 (58), 94 (20), 93 (54), 92 (6), 91 (29), 83 (18), 82 (8), 81 (56), 80 (9), 79 (38), 77 (12), 75 (6), 73 (21), 71 (20), 70 (5), 69 (35), 68 (12), 67 (36), 57 (44), 56 (9), 55 (55), 53 (8), 43 (63), 41 (38), 39 (7); mp 153–154 °C; ORD (CH_2Cl_2, 3.99 mM) λ_{NM} [Φ] 590 [+17.5], 400 [+250.6], 315 [+1027.6], 286 [0], 272 [−325.8], 240 [0]. Anal. Calcd. C, 84.43; H, 11.82. Found: C, 84.34; H, 11.88.

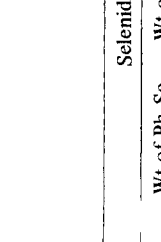
3β-Hydroxy-Δ^5-17β-(2′-oxospirocyclobutyl)androstene (33): IR (CCl_4) 3600, 3460, 3000–2820, 1755, 1480–1430, 1380, 1035, 1010 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (s, 3 H), 1.02 (s, 3 H), 0.8–2.5 (m, ~21 H), 2.89 (apparent t, J = 8 Hz, 2 H), 3.3–3.7 (m, 2 H), 5.35 (m, 1 H); ^{13}C NMR ($CDCl_3$) 15.63, 19.39, 20.72, 23.92, 25.19, 31.60, 31.99, 32.15, 32.43, 33.47, 36.51, 37.34, 42.26, 43.97, 46.18, 49.78, 52.98, 71.43, 77.34, 121.09, 140.93, 214.40 ppm; MS (rel intensity) *m/e* 328 (4), 285 (6), 272 (14), 271 (16), 254 (7), 253 (7), 175 (6), 161 (7), 159 (9), 157 (5), 149 (9), 147 (9), 145 (13), 143 (7), 133 (13), 131 (10), 129 (10), 121 (12), 120 (8), 119 (17), 117 (8), 115 (7), 111 (6), 109 (12), 108 (7), 107 (26), 106 (6), 105 (25), 97 (13), 96 (6), 95 (21), 94 (8), 93 (23), 92 (8), 91 (38), 85 (10), 84 (8), 83 (18), 82 (9), 81 (35), 80 (7), 79 (36), 78 (7), 77 (26), 73 (19), 71 (19), 70 (12), 69 (61), 68 (14), 67 (32), 65 (10), 60 (22), 57 (52), 56 (16), 55 (76), 54 (11), 53 (21), 51 (9), 49 (8), 45 (45), 44 (13), 43 (100), 42 (27), 41 (100), 39 (22); ORD (CH_2Cl_2, 1.22 mM) λ_{NM} [Φ] 590 [0], 400 [+245.9], 311 [+4672.1], 292 [0], 260 [−7745.9], 230 [−7786.9]; softens at 175 °C, melts at 179–182 °C. Calcd for $C_{22}H_{32}O_2$: mol wt, 328.24023. Found: mol wt, 328.24100.

(4*R,5*S**)-5-Methylspiro[3.4]octan-1-one (25):** IR (CCl_4) 2940, 2850, 1775, 1680, 1460, 1395, 1380, 1250, 1050 cm^{-1}; NMR (CCl_4) δ 1.03 (d, J = 7 Hz, 3 H), 1.2–2.2 (m, 9 H), 2.80 (apparent t, J = 9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 215.36 (s), 74.20 (s), 43.45 (d), 42.73 (atp), 34.73 (t), 33.62 (t), 22.91 (atp), 22.80 (atp), 15.29 (q) ppm; MS (rel intensity) *m/e* 138 (5), 95 (4), 82 (4), 81 (9), 67 (5), 48 (46), 43 (100), 42 (7), 39 (5). Calcd for $C_9H_{14}O$: mol wt, 138.10446. Found: mol wt, 138.10434. GLC: column A, 83 °C, 2.2 min.

2-(2′,6′-Dimethylheptyl)cyclobutanone (40): IR (CCl_4) 2990–2820, 1780, 1460, 1380, 1080 cm^{-1}; NMR (CCl_4) δ 0.86 (d, J = 7 Hz, 9 H), 0.9–1.8 (m, ~10 H), 1.9–2.4 (m, 2 H), 2.9–3.1 (m, 2 H), 3.1–3.5 (m, 1 H); MS (rel intensity) *m/e* 196 (5), 152 (8), 126 (6), 125 (5), 124 (7), 117 (5), 113 (10), 112 (100), 111 (12), 109 (7), 98 (8), 97 (19), 95 (6), 94 (7), 91 (7), 85 (5), 84 (17), 83 (28), 82 (7), 81 (8), 77 (5), 71 (47), 70 (29), 69 (27), 68 (8), 67 (9), 57 (73), 56 (28), 55 (58), 53 (7), 44 (8), 43 (54), 42 (12), 41 (52), 39 (18). Calcd for $C_{13}H_{24}O$: mol wt, 196.18271. Found: mol wt, 196.18235. GLC: column A, 95 °C, 14 min.

***cis*-13-Methyl-16-(2′-oxospirocyclobutyl)-11,12,13,14,15,17-hexahydrocyclopenta[*a*]phenanthrene:** IR (CCl_4) 3050, 2990, 2840, 1775, 1468, 1438, 1390, 1375, 1260, 1105, 1060, 860 cm^{-1}; NMR (CCl_4) δ 1.08 (2 s, 3 H), 1.5–2.3 (m, 8 H), 2.5–3.4 (m, 5 H), 7.0–8.0 (m, 6 H); MS (rel intensity) *m/e* 291 (19), 290 (66), 249 (13), 248 (61), 247 (7), 234 (6), 233 (15), 206 (8), 205 (11), 195 (7), 194 (28), 193 (100), 192 (18), 186 (6), 180 (7), 179 (32), 178 (10), 167 (7), 165 (10), 141 (5). Calcd for $C_{21}H_{22}O$: mol wt, 290.16706. Found: mol wt,

Table X. Preparation of Reverse Cyclobutanones (Type II Process)

Ketone	Oxaspiropentanes: Wt in mg (mmol)	Wt of  in mg (mmol)	Wt of SPh_2BF_4 in mg (mmol)	Wt of KOH in mg (mmol)	h	Selenides: Wt of Ph_2Se_2 in mg (mmol)	Wt of $NaBH_4$ in mg (mmol)	h	Cyclobutanones: MCPBA in mg (mmol)	−30 °C, h	0–25 °C, h	Yield in mg (%)	R compd	R:N ratio[a]
2,6-Dimethylcyclohexanone	884 (7.0)	2.25[b] (7.16)	0.94[b] (16.8)	4.3	1.15[b] (3.69)	390 (10.3)	1.6	1.72[b] (8.5)	3	5	975 (84)[c]	28	40:60[d]
2-Methylcyclohexanone	See text													
2-Methylcyclopentanone	490 (5.0)	1.85[b] (5.9)[e]	420 (7.5)[e]	21.5	860 (2.75)	420 (11.1)	7.0	1.03[b] (5.1)	6	1.2	328 (47.5)[c]	26	96:4[d]
	214.5 (1.0)	340 (1.08)[e]	197 (3.5)	21	180 (0.58)	120 (3.3)	5.5	258 (1.28)	5	2.5	172 (68)	30	64:36[f]
	123 (0.51)	193 (0.61)	170 (3.0)	3	102 (0.32)	62 (1.64)	1.1	172 (0.85)	2	0.5	101.2 (71)	32	93:7[g]
Cholestan-3-one	193 (0.5)	226 (0.72)[e]	310 (5.5)	11	176 (0.57)	100 (2.6)	4.1	172[h] (0.85)	7	8	131.2 (61.5)	36	>98.2[i]
Dehydroepiandrosterone	144 (0.5)	295 (0.94)[k]	112 (2.0)	22	96 (0.3)	68 (1.8)	6.0	86[i] (0.43)	4.5	3	94 (57)	34	>3:97[i]

[a] Normal isomers were identified by comparison of their spectra with those of the compounds synthesized using the lithium tetrafluoroborate procedure. [b] In grams. [c] Corrected for diphenyl sulfide present by NMR: 28, 18% by wt; 26, 16% by wt. Samples for spectral analysis were GLC purified. [d] GLC determined ratio. [e] Reaction solvent 1:1 Me_2SO/dichloromethane. [f] Isolated ratio. [g] Ratio determined by integration of δ 1.07 vs. 0.99 in NMR spectrum. [h] Reaction solvent 1:1 hexane/dichloromethane. [i] Other isomer not detectable by NMR. [j] Reaction solvent 4:1 hexane/dichloromethane. [k] Added portionwise.

290.16604.

Preparation of Reverse Cyclobutanones (Type II Process). (4*R,5*R**)-5-Methylspiro[3.5]nonan-one (4).** Through a solution of 786 mg (7.0 mmol) of 2-methylcyclohexanone and 2.25 g (7.16 mmol) of diphenylcyclopropylsulfonium tetrafluoroborate in 20 mL of Me_2SO was passed a stream of nitrogen bubbles for 5 min. To this degassed solution was then added 0.92 g (16.45 mmol) of powdered potassium hydroxide and the solution was degassed for ~3 min and then allowed to stir at 25 °C for 4 h. The reaction mixture was poured into 100 mL of hexane and extracted with 4 × 80 ml of hexane. The combined hexane extracts were washed with 2 × 100 ml of saturated aqueous sodium bicarbonate solution and dried over sodium sulfate.

The solvents were removed in vacuo and the resulting oil added to a *colorless* solution of sodium phenylselenide in ethanol prepared by adding 390 mg (10.3 mmol) of sodium borohydride to a solution of 1.15 g (3.69 mmol) of diphenyl diselenide in 35 mL of commercial anhydrous ethanol. The colorless solution was stirred at 25 °C for 75 min until TLC indicated the disappearance of an iodine visible spot at R_f 0.3 and the appearance of a UV active spot at R_f 0.75. Then ~50 mL of saturated aqueous sodium bicarbonate solution were added to it along with ~10 mL of dichloromethane. The colorless mixture was added to 50 mL of saturated aqueous sodium bicarbonate solution and extracted with 5 × ~50 mL of dichloromethane. The combined dichloromethane extracts were washed with 100 mL of saturated sodium bicarbonate solution and dried over sodium sulfate. The solvents were removed in vacuo, benzene was added, and the solvents were again removed.

The resulting oil was dissolved in 250 mL of hexane and cooled to −30 °C in an aqueous calcium chloride eutectic bath. To this colorless solution was added a solution of 1.72 g (8.5 mmol) of 85% *m*-chloroperbenzoic acid in 20 mL of dichloromethane. Then to this colorless clouding solution was added 2.5 mL of pyridine and the mixture was stirred at −25 to −30 °C for 7 h. The yellow suspension was warmed to 25 °C over 3 h and poured into 100 mL of 3 N hydrochloric acid. The hexane layer was washed with 2 × 100 mL of water and 2 × 100 mL of saturated aqueous sodium bicarbonate solution and dried over sodium sulfate. The bulk of the solvents were removed by distillation at atmospheric pressure and the remainder was removed at ~3 Torr. The remaining oil was Kugelrohr distilled at ~75 °C at 0.25 Torr to yield 1.053 g of 5-methylspiro[3.5]nonan-1-one (**4**), which by NMR contained 14% by weight of diphenyl sulfide, corrected yield 85%. A sample was GLC collected for spectral analysis: IR (CCl_4) 2990–2840, 1778, 1460, 1445, 1390, 1375, 1110, 1060, 1010 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (s, 3 H), 1.0–2.2 (m, ~11 H), 2.5–3.2 (m, 2 H); ^{13}C NMR ($CDCl_3$) 215.9 (s), 70.4 (s), 42.3 (tp), 34.0 (bd), 32.6 (bt), 30.7 (bt), 25.2 (bt), 21.9 (bt), 18.5 (tp), 16.8 (q) ppm; MS (rel intensity) *m/e* 152 (20), 134 (9), 124 (13), 110 (25), 109 (20), 108 (10), 97 (12), 96 (40), 95 (57), 93 (7), 82 (29), 81 (100), 80 (6), 79 (11), 77 (7), 69 (13), 68 (42), 67 (65), 66 (8), 65 (5), 56 (11), 55 (30), 54 (20), 53 (18), 51 (5), 44 (9), 43 (7), 42 (7), 41 (44), 39 (29). Calcd for $C_{10}H_{16}O$: mol wt, 152.12011. Found: mol wt, 152.11981. GLC: column A, 92 °C, 3.8 min.

The remaining examples are summarized in Table X.

***trans*-4a*β*-Methyl-1*α*-(2′-oxospirocyclobutyl)-1,2,3,4,4a,10a,9,10-octahydrophenanthrene (30):** IR (CCl_4) 3060, 3010, 2980, 2930, 2860, 1775, 1480, 1440, 1390, 1373, 1110, 1075, 1062, 720 cm^{-1}; NMR (CCl_4) δ 1.08 (s, 3 H), 1.10–2.40 (m, 11 H), 2.50–3.3 (m, 4 H), 6.85–7.25 (m, 4 H); ^{13}C NMR ($CDCl_3$) 216.4 (s), 147.2 (s), 134.8 (s), 129.1 (d), 125.6 (d), 125.4 (d), 124.4 (d), 69.1 (s), 44.2 (atp), 43.0 (bd), 37.6 (at), 37.0 (s), 34.2 (atp), 29.7 (atp), 24.2 (q), 21.1 (atp), 20.8 (at), 18.8 (at) ppm; MS (rel intensity) *m/e* 255 (6), 254 (34), 239 (19), 226 (22), 213 (7), 212 (58), 211 (5), 198 (27), 197 (100), 184 (6), 183 (35), 170 (8), 169 (16), 167 (5), 165 (7), 158 (21), 157 (15), 156 (13), 155 (27), 144 (19), 143 (26), 142 (18), 141 (43), 131 (9), 130 (22), 129 (38), 128 (33), 127 (7), 117 (26), 116 (9), 115 (31), 105 (8), 91 (27), 81 (11), 79 (7), 77 (16), 69 (5), 67 (14), 65 (9), 55 (25), 53 (13), 51 (8), 42 (17), 41 (46), 39 (27); mp 94–94.5 °C. Calcd for $C_{18}H_{22}O$: mol wt, 254.16706. Found: mol wt, 254.16602.

(4*R,5*R**,9*S**)-5,9-Dimethylspiro[3.5]nonan-1-one (28):** IR (CCl_4) 3000–2840, 1775, 1465, 1455, 1440, 1387, 1378, 1246, 1195, 1184, 1120, 1092, 1052, 1005, 945 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (d, J = 6 Hz, 6 H), 0.95–1.8 (m, 8 H), 1.81 (apparent t, J = 8 Hz, 3 H), 2.72 (apparent t, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 218.21 (s), 75.16 (s), 44.12 (tp), 36.12 (bd), 30.69 (atp), 25.83 (at), 17.09 (q), 12.86 (tp) ppm; MS (rel intensity) *m/e* 167 (3), 166 (30), 151 (15), 148 (8), 138

(20), 133 (7), 124 (15), 123 (33), 122 (15), 110 (31), 109 (79), 107 (7), 97 (12), 96 (25), 95 (100), 93 (8), 91 (6), 83 (9), 82 (80), 81 (51), 79 (13), 77 (9), 70 (5), 69 (17), 68 (64), 67 (55), 65 (6), 56 (10), 55 (35), 54 (9), 53 (20), 43 (10), 42 (7), 41 (51), 40 (7), 39 (25). Calcd for $C_{11}H_{18}O$: mol wt, 166.13576. Found: mol wt, 166.13553. GLC: column A, 95 °C, 5.1 min.

(4*S,5*R**,9*S**)-5,9-Dimethylspiro[3.5]nonan-1-one (27):** IR and NMR compared with those of a known sample prepared by Dr. Margaret Preckel;[3] ^{13}C NMR ($CDCl_3$) 216.39 (s), 74.47 (s), 42.81 (tp), 37.95 (bd), 32.18 (t), 24.95 (bt), 19.03 (tp), 17.54 (q) ppm. GLC: column A, 95 °C, 4.0 min.

***trans*-7-Methoxy-4aβ-methyl-2β-(2′-oxospirocyclobutyl)-1,2,3,4,4a,10a,9,10-octahydrophenanthrene (32):** IR (CCl_4) 2930, 2850, 1775, 1605, 1495, 1463, 1270, 1238, 1143, 1086, 1041 cm^{-1}; NMR (CCl_4) δ 1.07 (s, 3 H), 1.2–2.25 (m, 11 H), 2.7–3.0 (m, 4 H), 3.74 (s, 3 H), 6.36–6.65 (m, 2 H), 6.9–7.1 (m, 1 H); MS (rel intensity) *m/e* 285 (12), 284 (54), 270 (6), 269 (29), 243 (7), 242 (38), 241 (18), 228 (18), 227 (100), 213 (5), 187 (10), 174)9), 173 (14), 171 (10), 159 (9), 158 (5), 147 (25), 129 (5), 128 (6), 121 (6), 115 (9), 91 (7), 77 (5), 55 (6), 42 (6), 41 (9), 39 (5); mp 110–112 °C. Calcd for $C_{19}H_{24}O_2$: mol wt, 284.17763. Found: mol wt, 284.17710.

3β-(2′-Oxospirocyclobutyl)cholestane (36): IR (CCl_4) 2990–2820, 1775, 1465, 1441, 1380, 1365, 1098, 1068 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (s, 3 H), 0.79 (s, 3 H), 0.83 (s, 3 H), 0.90 (s, ~6 H), 0.8–2.1 (m, ~33 H), 2.96 (apparent t, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 11.65, 12.09, 18.71, 20.92, 22.52, 22.80, 23.90, 24.18, 24.73, 27.33, 27.99, 28.21, 28.65, 32.09, 34.06, 34.23, 35.50, 35.61, 35.77, 36.22, 39.33, 41.04, 41.52, 41.96, 42.56, 54.43, 56.37, 66.69, 215.86 ppm; MS (rel intensity) *m/e* 426 (7), 399 (15),398 (47), 384 (57), 369 (17), 316 (5), 271 (7), 262 (9), 258 (6), 245 (11), 244 (43), 243 (24), 232 (5), 231 (36), 230 (100), 229 (62), 216 (7), 215 (16), 203 (6), 202 (6), 201 (7), 196 (6), 189 (7), 188 (6), 187 (6), 177 (7), 176 (10), 175 (22), 174 (9), 173 (7), 163 (18), 162 (20), 161 (47), 160 (5), 159 (8), 149 (27), 148 (11), 147 (21), 145 (8), 135 (34), 134 (18), 133 (18), 131 (7), 123 (29), 122 (90), 121 (49), 120 (22), 119 (23), 118 (6), 111 (10), 110 (9), 109 (41), 108 (29), 107 (54), 106 (18), 105 (26), 97 (20), 96 (11), 95 (76), 94 (25), 93 (55), 92 (7), 91 (22), 85 (6), 83 (30), 82 (15), 81 (76), 80 (12), 79 (41), 77 (9), 71 (26), 70 (8), 69 (53), 68 (17), 67 (46), 57 (64), 56 (13), 55 (82), 54 (5), 53 (8), 45 (9), 44 (5), 43 (75), 42 (6), 41 (47), 39 (5); mp 165–166 °C; ORD (CH_2Cl_2, 5.86 mM), λ_{NM} [Φ] 590 [+59.7], 400 [+349.8], 316 [+1706.5], 290 [0], 270 [−699.7], 230 [−204.8]. Anal. Calcd: C, 84.43; H, 11.82. Found: C, 84.42; H, 11.74.

(4*R,5*R**)-5-Methylspiro[3.4]octan-1-one (26):** IR (CCl_4) 3000–2820, 1780, 1675, 1460, 1400, 1380, 1255, 1110, 1055, 1035 cm^{-1}; NMR (CCl_4) δ 0.96 (d, J = 8 Hz, 3 H), 1.1–2.3 (m, 9 H), 2.5–3.15 (m, 2 H); ^{13}C NMR ($CDCl_3$) 215.31 (s), 74.09 (s), 42.90 (tp), 38.48 (bd), 35.44 (at), 33.46 (at), 22.86 (atp), 20.04, (tp), 15.73 (q) ppm; MS (rel intensity) *m/e* 138 (38), 120 (30), 110 (16), 109 (20), 96 (18), 95 (38), 94 (17), 91 (7), 82 (36), 81 (100), 79 (20), 77 (10), 68 (18), 67 (68), 65 (8), 55 (16), 54 (18), 53 (18), 51 (9), 44 (50), 41 (36), 40 (9), 39 (44). Calcd for $C_9H_{14}O$: mol wt, 138.10446. Found: mol wt, 138.10395. GLC: column A, 83 °C, 2.7 min.

2,2-Di-*n*-propylcyclobutanone (41). In a procedure similar to that used for the synthesis of **4**, exactly half of the oxaspiropentane (~3 mmol) derived from 685 mg (6.0 mmol) of 4-heptanone (see Table IV) was added to a colorless solution of 485 mg (1.66 mmol) of diphenyl diselenide and 280 mg (7.5 mmol) of sodium borohydride in 8 mL of commercial anhydrous ethanol and stirred at 25 °C for 1.5 h. The colorless reaction mixture was worked up according to the procedure outlined for **18** and oxidized with 800 mg (4.0 mmol) of 85% *m*-chloroperbenzoic acid in hexane at −30 °C for 10 h and warmed to 25 °C for 7 h according to the same procedure. The resulting oil was Kugelrohr distilled at ~55 °C at 0.1 Torr to yield 338.8 mg of 2,2-di-*n*-propylcyclobutanone which by NMR contained 4% diphenyl sulfide: corrected yield 75.5% from 4-heptanone; IR (CCl_4) 2950–2840, 1780, 1465, 1390, 1065 cm^{-1}; NMR (CCl_4) δ 0.94 (d, 6 H), 1.0–1.6 (m, 8 H), 1.75 (apparent t, J = 8 Hz, 2 H), 2.84 (apparent t, J = 8 Hz, 2 H); MS (rel intensity) *m/e* 154 (3), 136 (13), 126 (12), 117 (6), 112 (6), 105 (12), 103 (58), 101 (100), 97 (25), 85 (5), 84 (45), 83 (7), 79 (9), 70 (15), 69 (31), 66 (7), 56 (51), 55 (42), 43 (7), 41 (26), 39 (5). Calcd for $C_{10}H_{18}O$: mol wt, 154.13576. Found: mol wt, 154.1363.

3,7-Dimethyl-1-(1′-hydroxycyclopropyl)oct-1-ene (39). To a colorless solution of 100 mg (0.32 mmol) of diphenyl diselenide and 59 mg (1.56 mmol) of sodium borohydride in 5 mL of commercial anhydrous ethanol was added a solution of 102.6 mg (0.33 mmol corrected for 36.4 wt % of diphenyl sulfide) of 2-(2′,6′-dimethylheptyl)-oxaspiropentane and the mixture was stirred for 1.75 h at 25 °C. To the reaction mixture was added ~20 mL of saturated aqueous sodium bicarbonate and the white suspension was extracted with 3 × 12 mL of dichloromethane. The combined organic extracts were washed once with 20 mL of saturated aqueous sodium bicarbonate solution and dried over sodium sulfate. The solvents were removed in vacuo, replaced with dry benzene, and again removed. The residual oil was pumped on at ~1 Torr, taken up in 40 mL of pentane, and cooled to −25 °C. To this colorless solution was added 180 mg (0.89 mmol) of 85% *m*-chloroperbenzoic acid in 2 mL of dichloromethane followed by 180 μL of pyridine. The white suspension was allowed to stir at −25 °C for 4.5 h and at 0 °C for 1 h. The reaction mixture was washed twice with saturated aqueous sodium bicarbonate solution, the aqueous washes were combined and extracted with 2 × 10 mL of dichloromethane, and the combined organic phases were dried over sodium sulfate. The solvents were removed in vacuo at 15–20 °C and the residual oil was taken up in carbon tetrachloride for NMR. This solution was applied to a PLC plate and eluted with dichloromethane containing 5% triethylamine to yield 23 mg (35%) (R_f 0.1–0.3) of oil: IR (CCl_4) 3590, 3600–3300, 3060, 3010–2810, 1775, 1730, 1665, 1620, 1460, 1442, 1380, 1365, 1324, 1294, 1150, 1090, 1037, 964, 833, 685 cm^{-1}; NMR (CCl_4) δ 0.60 (m, 2 H), 0.87 (d, J = 7 Hz, 6 H), 0.96 (d, J = 7 Hz, 3 Hz), 1.0–2.2 (m, ~13 H), 5.1 (d, J = 15 Hz, 1 H), 5.45 (d of d, J = 15, 7 Hz, 1 H); MS (rel intensity) *m/e* 196 (2), 140 (5), 125 (9), 124 (9), 123 (48), 112 (30), 111 (15), 110 (9), 109 (17), 97 (13), 96 (7), 95 (23), 93 (5), 85 (7), 84 (14), 83 (100), 82 (26), 81 (22), 79 (7), 77 (17), 71 (21), 70 (15), 69 (32), 67 (14), 57 (41), 56 (15), 55 (58), 54 (5), 53 (11), 51 (7), 43 (42), 42 (7), 41 (57), 39 (17). Calcd for $C_{13}H_{24}O$: mol wt, 196.18271. Found: mol wt, 196.18286.

2,6-Dimethyl-1-(1′-hydroxycyclopropyl)-1-phenylselenocyclohexane (19). As in the general procedures 659 mg (2.1 mmol) of cyclopropyldiphenylsulfonium tetrafluoroborate, 253 mg (2 mmol) of 2,6-dimethylcyclohexanone, and 198 mg (3.5 mmol) of powdered potassium hydroxide in 12 mL of Me_2SO were allowed to stir at 25 °C for 4 h. After the usual workup, the residual cloudy oil was taken up in ethanol and added to a colorless solution of 321 mg (1.03 mmol) of diphenyl diselenide and 120 mg (3.17 mmol) of sodium borohydride in 10 mL of commercial grade anhydrous ethanol. After stirring at 25 °C for 70 min, the reaction was worked up as in the type II general procedure. The residual colorless oil was applied to a pre-wet dry column and eluted with 1:1 dichloromethane/hexane until the diphenyl sulfide had passed out of the column. The solvent was then changed to pure dichloromethane until a UV-visible band had moved to the center of the column. The column was then cut up and the silica gel containing that UV-visible band extracted with ether and dichloromethane. After solvent removal in vacuo the colorless oil was pumped on at ~1 Torr until it crystallized. The yield of colorless crystals was 545.4 mg: 87%; mp 67.5–69.5 °C (pentane); IR (CCl_4) 3605, 3090, 3040, 2980–2840, 1470, 1460, 1445, 1432, 1368, 1200, 1143, 1023, 950, 920, 690 cm^{-1}; NMR ($CDCl_3$) δ 0.60–0.80 (m, 2 H), 1.08–1.24 (m, 2 H), 1.39 (d J = 6 Hz), ~1.2–2.05 (m, ~12 H), 7.2–7.45 (m, 3 H), 7.5–7.7 (m, 2 H); ^{13}C NMR ($CDCl_4$) 138.66 (d), 128.73 (d), 128.54 (d), 127.85 (s), 65.66 (s), 57.69 (s), 41.31 (bd), 33.93 (atp), 25.42 (t), 19.46 (q), 13.49 (tp) ppm; MS (rel intensity) *m/e* 324 (3), 186 (11), 185 (9), 168 (9), 167 (71), 166 (13), 160 (11), 159 (7), 158 (63), 157 (19), 156 (32), 155 (19), 154 (19), 153 (6), 152 (6), 151 (10), 149 (24), 139 (11), 138 (36), 137 (16), 133 (5), 124 (11), 123 (49), 122 (7), 117 (5), 116 (13), 111 (15), 110 (29), 109 (100), 107 (11), 105 (5), 97 (22), 96 (14), 95 (68), 93 (17), 91 (12), 83 (14), 82 (40), 81 (39), 79 (23), 78 (78), 77 (44), 74 (7), 71 (8), 70 (5), 69 (36), 68 (32), 67 (47), 66 (6), 65 (11), 57 (70), 56 (12), 55 (67), 54 (5), 53 (20), 52 (5), 51 (26), 50 (12), 45 (5), 44 (18), 43 (45), 42 (9), 41 (61), 40 (7), 39 (33). Calcd for $C_{17}H_{24}OSe$: mol wt, 324.09921. Found: mol wt, 324.09903.

Synthesis, Oxidation, and Elimination of 2,6-Dimethyl-1-(1′-hydroxycyclopropyl)-1-phenylthiocyclohexane (23b). In a procedure similar to the synthesis of 2,6-dimethyl-1-(1′-hydroxycyclopropyl)-1-phenylselenocyclohexane (**19**), one-quarter of the oxaspiropentane obtained from 2 mmol of 2,6-dimethylcyclohexanone was added to a solution of 90 mg (2.38 mmol) of sodium borohydride and 71 μL (76 mg, 0.69 mmol) of thiophenol in 6 ml of commercial anhydrous ethanol and the mixture was allowed to stir at 25 °C for 78 min (followed by the appearance on TLC in 1:1 hexane/dichloromethane of a UV-visible spot at R_f 0.45). The mixture was then worked up as for **19** and

the residue taken up in 20 mL of hexane and cooled to −25 °C, and 190 mg (0.94 mmol) of 85% *m*-chloroperbenzoic acid in 2 mL of dichloromethane followed by 150 μL of pyridine was added. The reaction mixture was stirred at −25 °C for 2 h and then warmed to 0 °C and stirred for 4 h. The TLC in 1:1 hexane/dichloromethane indicated that the sulfide **23b** was present but the diphenyl sulfide was gone. To the reaction 430 mg (2.12 mmol) of 85% *m*-chloroperbenzoic acid in 5 mL of dichloromethane was added and the mixture was stirred for another 20.5 h. The mixture was then poured into hexane and washed with 3 × 40 mL of saturated aqueous sodium bicarbonate solution and dried over sodium sulfate. The solvents were removed in vacuo and the residue was triturated with carbon tetrachloride. The NMR and IR indicated the presence of **27** and **28** by comparison with known spectra. GLC on column A at 95 °C followed by planimeter integration yielded a 2:1 **28:27** mixture.

1-(1′-Hydroxycyclopropyl)-2-methyl-1-phenylthiocyclohexane (23a). As in the general procedure, 1.60 g (5.1 mmol) of cyclopropyldiphenylsulfonium tetrafluoroborate, 560 mg (5.0 mmol) of 2-methylcyclohexanone, and 700 mg (12.5 mmol) of powdered potassium hydroxide in 12 mL of Me_2SO were reacted and worked up in the usual fashion to give the crude oxaspiropentane. To 280 μL (2.72 mmol) of thiophenol in 8 mL of DME was added, at 25 °C, 1.7 mL of a 1.45 M solution of *n*-butyllithium in hexane. To this solution of lithium thiophenoxide was added 15% of the above oxaspiropentane the mixture was stirred at 30 °C for 16.5 h and then at 55 °C for 29 h. The mixture was then poured into 1:1 water/saturated aqueous sodium carbonate solution and extracted with 40 mL of chloroform; the extracts were washed with 3 × 40 mL of 1:1 water/saturated aqueous sodium carbonate solution and dried over sodium sulfate. The solvents were removed in vacuo and the residue chromatographed twice on PLC to yield 88 mg (45%) of **25**, R_f 0.3, a viscous gum: IR (CCl_4) 3560, 3500, 3060, 3010–2840, 1770, 1460, 1440, 1350, 1230, 1190, 1020, 920, 690 cm^{-1}; NMR (CCl_4) δ −0.25 to 1.1 (m, 4 H); 1.17 (d, J = 7 Hz, 3 H), 1.2–1.9 (m, ~7 H), 2.0–2.5 (m, ~2 H), 3.0–3.3 (m, 1 H), 7.2–7.45 (m, 3 H), 7.5–7.7 (m, 2 H); MS (rel intensity) *m/e* 262 (0.1), 205 (15), 152 (7), 137 (5), 134 (5), 124 (10), 123 (10), 111 (10), 110 (100), 109 (35), 108 (7), 97 (8), 96 (23), 95 (58), 93 (6), 91 (5), 84 (11), 82 ([6(= —[(49), 79 (10), 78 (5), 77 (16), 69 (15), 68 (20), 67 (41), 66 (28), 65 (14), 57 (12), 56 (7), 55 (29), 54 (11), 53 (12), 51 (12), 50 (7), 45 (7), 43 (10), 41 (26), 39 (23), Calcd for $C_{16}H_{22}OS$: mol wt, 262.13914. Found: mol wt, 262.13930.

***trans*-4a-Methyl-1-(spirocyclobutyl)-1,2,3,4,4a,10a,9,10-octahydrophenanthrene (43).** To 182 mg (3.25 mmol) of potassium hydroxide and 0.25 mL (5.0 mmol) of hydrazine hydrate in 3 mL of diethylene glycol was added 110.3 mg (0.43 mmol) of crystalline *trans*-4aβ-methyl-1α-(2′-oxospirocyclobutyl)-1,2,3,4,4a,10a,9,10-octahydrophenanthrene (**30**). The mixture was heated at 160–170 °C for 1 h and then at 210 °C for 10 h, cooled to 25 °C, diluted with 5 mL of water, and extracted with hexane. After drying, the solvents were removed in vacuo and the residual oil applied to a PLC plate and eluted twice with pentane to yield 47.7 mg (46%) (R_f 0.4) of a colorless oil.

In a procedure similar to the above, 324 mg (1.27 mmol) of *trans*-4aβ-methyl-1β-(2′-oxospirocyclobutyl)-1,2,3,4,4a,10a,9,10-octahydrophenanthrene (**29**), 0.40 mL (8 mmol) of hydrazine hydrate, and 267 mg (4.8 mmol) of potassium hydroxide in 4 mL of diethylene glycol were heated to 160 °C for 2.5 h and then at 210 °C for 5.5 h and then worked up as previously indicated. The yield after PLC purification was 62.0 mg (24.5%) of colorless oil. Spectral data of both oils were identical: IR (CCl_4) 3060, 3000-2820, 1490, 1445, 1387 cm^{-1}; NMR (CCl_4) δ 1.01 (s, 3 H), 1.0–2.4 (m, 15 H), 2.9 (m, 2 H), 6.9–7.2 (m, 4 H); ^{13}C NMR ($CDCl_3$) 148.78 (s), 135.34 (s), 128.98 (d), 125.16 (d), 125.12 (d), 124.58 (d), 47.77 (bd), 42.05 (s), 40.04 (bt), 38.63 (bt), 38.33 (s), 31.10 (at), 30.56 (at), 27.38 (at), 23.91 (q), 19.65 (bt), 19.41 (bt), 15.94 (atp) ppm; MS (rel intensity) *m/e* 242 (6), 240 (32), 228 (15), 227 (5), 226 (14), 225 (72), 213 (7), 212 (44), 198 (18), 197 (100), 183 (13), 170 (10), 169 (35), 168 (26), 167 (12), 165 (11), 158 (24), 157 (33), 156 (18), 155 (30), 154 (7), 153 (13), 152 (10), 145 (8), 144 (28), 143 (80), 142 (29), 141 (66), 131 (36), 130 (42), 129 (65), 128 (61), 127 (15), 118 (9), 117 (44), 116 (15), 115 (48), 105 (10), 97 (6), 95 (8), 91 (43), 83 (6), 82 (6), 81 (21), 29 (16), 78 (7), 77 (20), 69 (8), 67 (20), 65 (11), 58 (7), 55 (33), 53 (20), 51 (6), 43 (7), 41 (55), 39 (24). Calcd for $C_{18}H_{24}$: mol wt, 240.18780. Found: mol wt, 240.18676.

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