Additions of Dihalocarbenes to Steroidal and Related Model Olefins. Studies in Carbenic Selectivity[1]

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CF_2 was added to trimethylethylene (**1**), cyclohexene (**2**), cyclohexen-4-one ethylene acetal (**3**), cyclohexen-3-one ethylene acetal (**4**), 2,2-ethylenedioxy-10-methyl-8-octalin (**5**), 2,2-ethylenedioxy-10-methyl-1(9)-octalin (**6**), 10-methyl-1(9)-octalin (**7**), and cholest-5-en-3-one 3-ethylene acetal (**8**). CCl_2 was also added to **5**, and CFCl to **8**. Stereoselectivities were determined for the various additions: (β/α) for CF_2 additions to **5**, **6**, and **7** were 250, 0.194, and 10.6, respectively. Only β addition could be detected for the addition of CF_2 or CFCl to **8**, and for the addition of CCl_2 to **5**. In the addition of CFCl to **8**, *endo*-F product exceeded *endo*-Cl product by a factor of ~ 3. Reactivities, relative to **2** (= 1.00) were determined for CF_2 additions (80°) to the various substrates: **1**, 49.5; **3**, 0.43; **4**, 0.018; **5**, 0.38; **6**, 0.12; **7**, 0.46. The significance of the quantitative data is discussed.

Reactions of carbenes with steroidal olefins have been of interest for more than a decade.[4-29] Carbenic species of particular interest included CBr_2,[5,8] CCl_2,[6,7,16-18] Simmons–Smith "CH_2",[4c,9-15] and CFCl.[16] Beyond this general concern, the medicinal potential of fluoro steroids has focused attention on the additions of fluorocarbenes to steroidal olefins.[4a,b,19,20] With a few exceptions,[21,22] most of this effort centered on CF_2 additions to ring A and ring B double bonds. Usually the stereoselectivity (α or β) of the difluorocyclopropanation was determined.[20,23-28] Key reports included those of Knox et al.,[27] and of Bond and Cornelia,[29] which indicated that normal steroids with $\Delta^{5,6}$ unsaturation afforded β-CF_2 adducts.

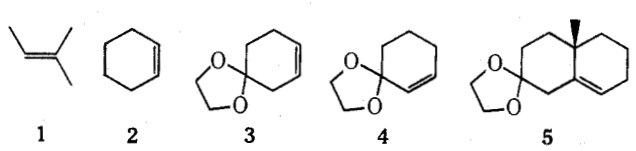
Given the variety and depth of interest, it was striking that systematic studies of carbenic selectivity toward steroidal substrates were nonexistent. Carbenic stereoselectivity has been discussed,[4a,b] but studies of the ability of, e.g., CF_2 to discriminate between different steroidal double bonds, and of how such discrimination related to the larger body of carbenic selectivity data,[30] were missing. Also sparse were discussions of the addition of unsymmetrical carbenes to steroidal olefins, and of the pertinent stereoselectivity,[31] subjects which have been extensively studied with nonsteroidal olefins.[32]

No doubt these lapses partially stemmed from anticipated analytical difficulties which could beset relative reactivity experiments with steroidal olefins. We therefore chose to examine CF_2 selectivities toward model olefins,[1] and then to extend aspects of these studies to steroidal substrates. In these initial efforts, we have restricted ourselves to Δ^4 and $\Delta^{5,6}$ AB model olefins and to a $\Delta^{5,6}$ steroidal olefin. Nevertheless, the results comprise the first integrated mechanistic study from the viewpoint of *carbenic reactivity*, deal with three kinds of carbenic selectivity, establish the utility of model studies in the $\Delta^{5,6}$ series, and should be of importance in future synthetic planning.

Results

Olefins. Primary substrates included olefins **1–8.** Olefin **3**[33] was prepared by the acid-catalyzed ketalization of 2-cyclohexen-1-one, whereas isomeric **4** was obtained from cyclohexanone ethylene acetal by the bromination–dehydrobromination method of Garbisch.[34]

Bicyclic ketals **5** and **6** were both prepared from 10-methyl-1(9)-octal-2-one (**9**), which was itself obtained by condensation of 2-methylcyclohexanone and methyl vinyl ketone under either basic[35] or acidic[36] conditions. The latter procedure was simpler, and it gave a better yield. Conversion of **9** to **5** required ethylene glycol and a catalytic quantity of *p*-toluenesulfonic acid in refluxing benzene.[37] Under similar conditions, the use of adipic acid as the catalyst[38] converted (70%) **9** to a mixture of **6** (87%) and **5** (13%), which provided **6** upon fractional distillation. The isomers could easily be differentiated by NMR; in CCl_4, **6** had a vinyl resonance at δ 5.07 (broad singlet), whereas the vinyl resonance of **5** appeared as a multiplet centered at δ 5.23.[37]



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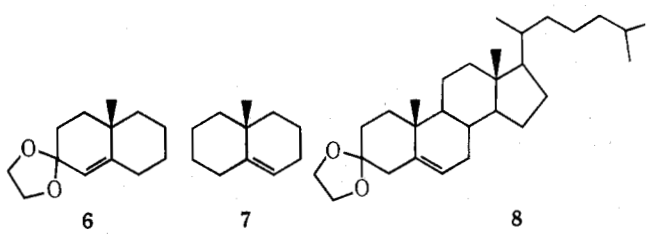

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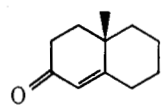

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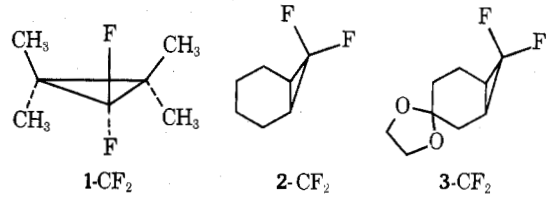
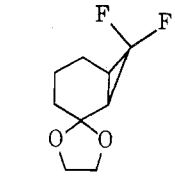
Octalin **7** was prepared from **9** by Marshall's sequence: reduction to the enol with $LiAlH_4$, acetylation with acetic anhydride, and removal of the acetoxyl group with Li–$C_2H_5NH_2$.[39] Finally, cholest-4-en-3-one was converted to **8** by treatment with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene.[40]

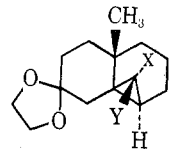
Dihalocarbene Additions. Adducts 1-CF_2–8-CF_2 were obtained by the reaction, with substrates **1–8**, of CF_2 generated from $(CH_3)_3SnCF_3$ and NaI in refluxing 1,2-dimethoxyethane,[41] or from $C_6H_5HgCF_3$ and NaI in refluxing benzene,[42] whereas **5**-β-CCl_2 was prepared by treating **5** with chloroform and 50% aqueous NaOH in the presence of benzyltriethylammonium bromide.[18,43] Adducts **5**-β-CH_2, **5**-α-CH_2, **5**-β-*endo*-F-*exo*-Cl, and **5**-β-*endo*-Cl-*exo*-F were



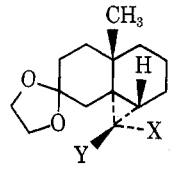
1-CF_2 2-CF_2 3-CF_2



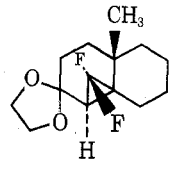
4-CF_2



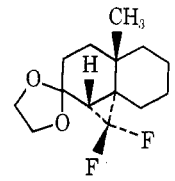
5-β-CF_2, X = Y = F
5-β-CCl_2, X = Y = Cl
5-β-CH_2, X = Y = H
5-β-*endo*-F-*exo*-Cl, X = F; Y = Cl
5-β-*endo*-Cl-*exo*-F, X = Cl; Y = F



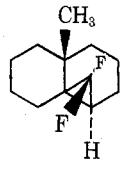
5-α-CF_2, X = Y = F
5-α-CH_2, X = Y = H



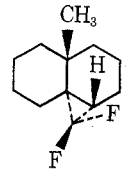
6-β-CF_2



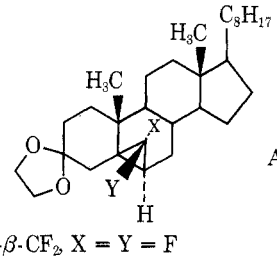
6-α-CF_2



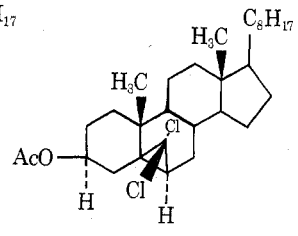
7-β-CF_2



7-α-CF_2



8-β-CF_2, X = Y = F
8-β-*endo*-F-*exo*-Cl, X = F; Y = Cl
8-β-*endo*-Cl-*exo*-F, X = Cl; Y = F



10-β-CCl_2

available from a previous study,[44] and 8-β-*endo*-F-*exo*-Cl and 8-β-*endo*-Cl-*exo*-F were prepared by the reaction of **8** with FCCl generated from $C_6H_5HgCFCl_2$ in refluxing benzene.[45]

The additions of CF_2 to **1** and **2** gave the known[46,47] difluorocyclopropanes in 80 and 70% yields. Ketal olefin **3** afforded **3**-CF_2 in 78% yield, but preparative scale CF_2 addition to **4** was complicated by NaI-catalyzed[48] isomerization of **4** to **3**, and subsequent difluorocyclopropanation of **3**. Adduct **4**-CF_2 was 20–30% of the product mixture and could be isolated by GC on a Carbowax column at 160°.

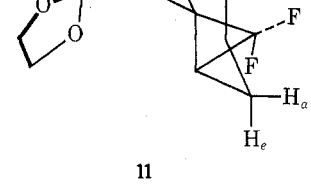
Difluorocyclopropanes **1**-CF_2–**4**-CF_2 were purified by GC (Carbowax), and their structures followed from consistent ir, ^1H and ^{19}F NMR spectra, mass spectral parent ions, and satisfactory elemental analyses. Significant NMR data appear in Table I.

The ^{19}F NMR spectra of **1**-CF_2–**4**-CF_2 are characterized by high-field doublets (*endo*-F), $J_{gem,F-F}$ = 130–150 Hz, and lower field signals for the *exo*-F atoms. The *exo*-F resonances show strong *vic*-H–F coupling to the (cis) cyclopropyl proton(s), $J_{vic,H-F}$ = 10–13 Hz, in addition to the major F–F coupling, and appear as either a doublet of doublets (**1**-CF_2) or a doublet of triplets (**2**-CF_2–**4**-CF_2). In fluorocyclopropanes, *trans*-*vic*-H–F coupling is substantially weaker than its cis counterpart, and the *endo*-F doublets are therefore not further split, although each component is clearly broadened ($W_{1/2} \sim 8$ Hz.)[49] All other CF_2 adducts prepared in this study exhibit ^{19}F NMR spectra similar to those of **1**-CF_2–**4**-CF_2.

Crucial to all structural assignments in this study were the carbene adducts of **5**. From CFCl and **5**, we isolated **5**-β-*endo*-F-*exo*-Cl and a minor isomer, which is now assigned as **5**-β-*endo*-Cl-*exo*-F (see below), in ratios ranging from 4:1 to 9:1.[44] The β configuration of the major adduct followed from its high-field (unsplit) ^{19}F NMR signal (*endo*-F), and from the ^1H NMR observation of long-range coupling (0.6 Hz) between F and the angular methyl protons (Table I). The latter observation is only consistent with a β-*endo*-F configuration: "long-range coupling between angular methyl protons and fluorine five or more σ-bonds apart may occur only when a vector directed along the C–F bond, and originating at the carbon atom converges upon and intersects a vector drawn along an angular methyl C–H bond in the direction of the proton and originating at the methyl carbon".[50] Of the four possible CFCl adducts of **5**, only **5**-β-*endo*-F-*exo*-Cl satisfies this requirement.[44] However, we noted that the extent of coupling was smaller than that usually observed in 5β,6β-difluorocyclopropyl steroids (1–3 Hz),[27] and that the model compound had probably assumed a conformation not well suited to the long-range coupling. This alternative conformation was unavailable to steroidal analogues. (See below.)

CF_2 and **5** gave 68% of **5**-β-CF_2 and **5**-α-CF_2 (ratio 250:1), separable by GC on a SE-30 column at 190°. Both adducts showed parent ions at *m/e* 258, and were void of olefinic protons (NMR). The major product was originally assigned the β configuration by analogy to the apparently exclusive β addition of CFCl to **5**, and because of the experimentally identical chemical shifts of the angular methyl resonances of **5**-β-*endo*-F-*exo*-Cl and the presumed **5**-β-CF_2 (Table I). In addition, calculations[51] of δ values for the angular methyls of **5**-β-CF_2 and **5**-α-CF_2, employing deshielding contributions of 5[27] and 17 Hz[29b] for the β and α CF_2 groups, respectively, indicated that the β adduct should have the higher field resonance.[52]

However, the calculated δ CH_3 values[52] were neither very accurate (cf. Table I) nor very different. Moreover, we could not resolve any long-range splitting of the angular methyl group of **5**-β-CF_2 on 60-, 90-, 100-, or 270-MHz spectrometers.[54] Therefore, crystalline **5**-β-CF_2 was subjected to x-ray analysis. The results not only definitively established the β configuration,[55] but, at least in the crystal, **5**-β-CF_2 was shown to adopt the "nonsteroid" conformation,[51,56] **11**. Were this conformation also preferred in



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solution, then long-range coupling of β-*endo*-F and CH_3 would not be expected; the appropriate vectors[50] do not intersect.[57,58]

Simmons–Smith methylenation of **5** gave **5**-β-CH_2 and **5**-α-CH_2 in a ratio of 45:55; the structures were assigned on the basis of their angular methyl chemical shifts.[44] Literature evidence strongly indicated that the higher field resonance had to belong to the β adduct.[14,29b]

Makosza addition of (excess) CCl_2[43] to **5** gave a single adduct, in nearly quantitative yield, to which we assigned the β configuration by analogy to the overwhelming β-addition preferences of CF_2 and CFCl toward **5**. In verification, re-

Table I
Selected NMR Data[a]

Adduct	^{19}F NMR, ϕ*[b]		^{1}H NMR, δ[c]	
	endo-F (J_{FF}, Hz)[d]	*exo*-F (J_{HF}, Hz)[e]	Ketal	Angular CH_3[f]
1-CF_2	150.4 (d, 134)	138.7 (dd, 10)		
2-CF_2	149.2 (d, 140)	127.5 (dt, 12)[g]		
3-CF_2	150.4 (d, 141)[h]	128.1 (dt, 12)[i]	3.86 (s)	
4-CF_2	148.2 (d, 146)	126.4 (dt, 13)	3.86 (br s)	
5-β-CF_2	146.1 (d, 142)	134.9 (dd, 12)[j]	3.84 (s)	1.13 (s, $W_{1/2}$ = 2)
5-α-CF_2	[k]		4.10 (s)	1.17 (s)
5-β-CCl_2			3.87 (s)	1.23 (s)
5-β-*endo*-F-*exo*-Cl	149.2 (s, $W_{1/2}$ = 8)		3.83 (s)	1.12 (d, J = 0.6)
5-β-*endo*-Cl-*exo*-F		129.8 (d, 20)[l]	3.83 (s)	1.20 (s)
5-β-CH_2			3.78 (s)	1.00 (s)
5-α-CH_2			3.78 (s)	1.11 (s)
6-β-CF_2	[k]		3.86 (s)	1.10 (s, $W_{1/2}$ = 8)
6-α-CF_2	145.6 (d, 144)	124.9 (dd, 13)	4.03 (m)	1.19 (s, $W_{1/2}$ = 2)
7-β-CF_2	143.7 (d, 143)	135.9 (dd, 14)[m]		1.10 (s)
7-α-CF_2	143.9 (d, 142)	133.0 (dd, 14)		1.12 (s)
8-β-CF_2	142.9 (d, 146)	129.8 (dd, 12)	3.88 (m)	1.02 (d, J = 1.5)
8-β-*endo*-F-*exo*-Cl	144.9 (s, $W_{1/2}$ = 10)		3.88 (m)	1.05 (d, J = 2.4)
8-β-*endo*-Cl-*exo*-F		123.4 (d, 17)	3.88 (m)	1.17 (s)
10-β-CCl_2				1.25 (s)[n]

[a] Additional NMR data appear in the Ph. D. Dissertation of D. J. Smudin, Rutgers University, New Brunswick, N.J., 1976. Abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, $W_{1/2}$ = width at half-height. [b] The solvent was CCl_4, containing 15% of $CFCl_3$ and 5% of c-C_4F_8 as internal standards. ϕ* in parts per million to high field of $CFCl_3$. [c] The solvent was CCl_4, with Me_4Si as internal standard. [d] Geminal F–F coupling; the equivalent coupling is not tabulated for the *exo*-F resonance. [e] *cis-vic*-H–F coupling involving the cyclopropyl proton(s). [f] At the A/B ring junction; splittings are due to long range β-*endo*-F–CH_3 coupling. [g] Further splitting (~2 Hz) was observed in the triplet components. [h] Further splitting (~2 Hz) was observed. [i] Further splitting (~3 Hz) was observed. [j] Long-range coupling (4.6 Hz) was also observed. [k] An insufficient quantity of this compound was available for determination of the ^{19}F NMR spectrum. [l] Long-range coupling (5.2 Hz) was also observed. [m] Long-range coupling (3 Hz) was also observed. [n] See ref 18.

duction of 5-β-CCl_2 with Na–NH_3 gave a single product, identical (ir and NMR) with 5-β-CH_2. It is interesting to note that, whereas the Simmons–Smith addition to 5 is nonstereoselective, the CCl_2 addition–reduction sequence is stereospecifically β.

The foregoing now permits the nearly certain designation of the minor adduct of CFCl and 5 as 5-β-*endo*-Cl-*exo*-F.[59] Thus, its angular CH_3 resonance (δ 1.20) is nearly identical with that of 5-β-CCl_2 (δ 1.23), and its *exo*-F ^{19}F NMR resonance exhibits long-range splitting similar to that of the *exo*-F resonance of 5-β-CF_2.[58] The *cis-vic*-H–F coupling of 5-β-*endo*-Cl-*exo*-F (20 Hz), although larger than those of the analogous CF_2 adducts, is similar in magnitude to the couplings of its steroidal analogue, 8-β-*endo*-Cl-*exo*-F (17 Hz), and to those of the *exo*-F CFCl and C_6H_5CF adducts of *cis*-butene (18 and 22 Hz, respectively).[49]

Addition of CF_2[42] to 6 was complicated by NaI-catalyzed[48] isomerization of 6 to 5, and gave 23% of a mixture of 5-β-CF_2, 6-α-CF_2, and 6-β-CF_2 in a ratio of 18:5:1, respectively. Separation was achieved by GC on a SF-96 column at 178°. The β stereochemical assignment for the minor adduct of 6 rests upon its higher field angular methyl resonance, which was also broadened ($W_{1/2}$ = 8 Hz), relative to that of 6-α-CF_2 ($W_{1/2}$ = 2.2 Hz), presumably by long-range coupling[50] to the β-*endo*-F atom. The NMR assignments are buttressed by chemical evidence. Thus 6-α-CF_2 could be converted to the corresponding thioketal by acid-catalyzed transketalization with ethanedithiol in benzene, and thence to 7-α-CF_2 by Raney nickel desulfurization. The material thus obtained was insufficient for NMR characterization, but did have identical retention times with authentic 7-α-CF_2 (see below) on SF-96 and Carbowax 20M GC columns.

Addition of CF_2[42] to 7 afforded 90% of a mixture of 7-β-CF_2 and 7-α-CF_2 (ratio 10.6:1), separable by GC on a SF-96 column at 120°. Stereochemical assignments could not be made with confidence by NMR. Long-range CH_3–F coupling was not detectable in the isomer ultimately designated as 7-β-CF_2, and the chemical shift of its angular methyl group (albeit at higher field) was uncomfortably close to that of 7-α-CF_2 (cf. Table I). The *exo*-F atom of the likely 7-β-CF_2 did, however, exhibit the anticipated[58] long-range coupling (3 Hz).

Conclusive assignments were possible by chemical means. Adduct 5-β-CF_2, the structure of which was firm,[55] could be converted to authentic 7-$\beta$$CF_2$ by the ketal → thioketal interchange–Raney nickel desulfurization sequence. The material thus obtained was identical (ir and NMR) with the major (β) adduct of 7 and CF_2.

Addition of CF_2[42] to cholest-5-en-3-one ethylene acetal (8) gave 33% of purified 8-β-CF_2, the identity of which was established by elemental analysis and mass (M^+) and NMR spectroscopy. Its angular methyl resonance (δ 1.02) was a doublet (J = 1.5 Hz), indicating long-range coupling to the β-*endo*-F atom,[50] and securing the β stereochemistry. Apparently, CF_2 addition to 8 was highly β stereoselective; only the ^{19}F resonances of 8-β-CF_2 were observed in the NMR spectrum of the crude, concentrated reaction mixture.

Addition of CFCl[45] to 8 gave two products (ratio 3:1), as indicated by their ^{19}F NMR resonances, observable in the crude reaction mixture. Extensive purification (see Experimental Section) afforded a pure sample of the major product, 8-β-*endo*-F-*exo*-Cl, in 55% isolated yield. Of particular importance to the structural assignment were the high-field ^{19}F NMR "singlet" (*endo*-F, cf. 5-β-*endo*-F-*exo*-Cl) and the doublet (J = 2.4 Hz) angular methyl ^{1}H NMR resonance at δ 1.05. These features were only consistent with the β-*endo*-F-*exo*-Cl configuration.

The minor reaction product was isolated chromatographically, and can be most reasonably assigned as 8-β-*endo*-Cl-*exo*-F. Its ^{19}F NMR doublet at ϕ* 123.4 (J = 17 Hz) is consistent with this assignment (cf. 5-β-*endo*-Cl-*exo*-F, ϕ* 129.8, J = 20 Hz), as is its strongly deshielded singlet angu-

Table II
Empirical Relative Reactivities toward CF_2[a]

Case	Olefins A/B	Precursor[b]	Solvent	Temp, °C	GC analyt cond[c] Column	GC analyt cond[c] Temp, °C	k_A/k_B	a.d.$_n$, %[d]
1	**1/2**	Hg	C_6H_6	80	A	60–80	49.5	1.1_3
2	**3/2**	Hg	C_6H_6	80	A	83–150	0.43	
3	**3/2**	Hg	DME[e]	90	A	83–150	0.48	
4	**3/2**	Sn	DME	90	A	83–150	0.46	3.5_3
5	**4/2**	Sn	DME	90	A	83–150	0.020	9.1_2
6	**4/2**	Hg	C_6H_6	80	A	83–150	0.018	6.7_2
7	**4/2**	Hg	DME	90	A	83–150	0.020	
8	**3/4**	Sn	DME	90	A	158	25.6	3.5_3
9	**3/4**	Hg	C_6H_6	80	A	158	25.1	
10	**5/4**	Hg	C_6H_6	80	B	160–175	20.9	6.0_2
11	**5/3**	Hg	C_6H_6	80	B	160–175	0.933	
12	**5/6**[f]	Hg	C_6H_6	80	C	178	3.36	
13	**6/4**[f]	Hg	C_6H_6	80	C	178	6.74	
14	**7/2**[g]	Hg	C_6H_6	80	C	60–130	0.46	4.3_2

[a] Further details of each run, including initial reactant concentrations, reaction time, and thermal conductivity detector calibration coefficients, appear in the Ph.D. Dissertation of D.J.S. [b] Sn = [Me_3SnCF_3 + NaI],[41] Hg = [$C_6H_5HgCF_3$ + NaI].[42] [c] GC analyses were done on packed columns with injector and detector temperatures of 235 and 275°, respectively. Column temperatures were generally programmed between the indicated limits. Columns were: A, 12 ft × 0.25 in., 15% Carbowax 20M on 60/80 Gas-Chrom R; B, 20 ft × 0.25 in., 7% Carbowax 20M + 3% SF-96 on 60/80 Gas-Chrom R; C, 20 ft × 0.25 in., 10% SF-96 on 60/80 acid-washed, silylated Chromosorb W. Product peak integrals were determined by cut-and-weigh of Xerox copies, with a Disc integrator, or with a Varian Model 481 electronic integrator. [d] Percent average deviation of n experiments. [e] 1,2-Dimethoxyethane. [f] The isomerization of **6** to **5** was <20% under competition conditions, in which [NaI]/[**6**] was small. For relative reactivity calculations, the effective [**6**] was taken as the mean of its initial and final concentrations as determined by GC. The indicated reactivities are based on the *sum* of β and α CF_2 additions to **6**. [g] The indicated reactivity is based on the *sum* of β and α CF_2 additions to **7**.

lar methyl resonance at δ 1.17 (cf. the analogous resonance of **10**-β-CCl_2[18] at δ 1.25; the latter should be modified[53] to δ 1.22 if the 3β-acetate of **10**-β-CCl_2 were replaced by the 3-ethylene acetal function featured in the adducts of **8**). Careful ^1H NMR analysis of **8**-β-*endo*-Cl-*exo*-F failed to reveal vinylic or allylic resonances, thus excluding ring-opened, rearranged structures. Finally, in view of the very high preferences for β additions of CF_2[27] (see also above) and CCl_2[18] to $\Delta^{5,6}$ steroidal olefins, it seems unreasonable to entertain α-cyclopropyl formulations for the (**8** + CFCl) minor product.

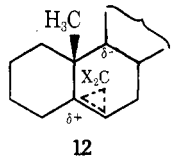
Relative Reactivity Studies. Relative reactivities of olefins **1**–**7** toward CF_2 were determined by the competition method,[30] in which pairs of olefins, present in excess, were permitted to compete for an insufficiency of CF_2. GC analysis of the crude product mixtures permitted calculation of the relative reactivities gathered in Table II. Inspection of the data shows that, within the indicated limits, the choice of carbene precursor, solvent, and reaction temperature had little effect on the olefinic reactivities. With the exception of case 5, reproducibility was within 7%.

Cross-check experiments[30] were performed. From cases 2 and 6, k_3/k_4 is calculated to be 23.9; the observed value (case 9) was 25.1 (deviation, 4.8%). From cases 10 and 11, k_3/k_4 is calculated to be 22.4 (deviation, based on case 9, 11%). From cases 4 and 5, k_3/k_4 is calculated to be 23.0; the observed value (case 8) was 25.6 (deviation, 10%). From cases 10 and 12, k_6/k_4 is calculated to be 6.22; the observed value (case 13) was 6.74 (deviation, 7.7%). The internal consistency of much of the reactivity data is thus verified. We consider the data to be accurate to <±10%. Though not spectacular, these limits are acceptable, especially considering the large spread of reactivities (k_1/k_4 = 2750, cases 1 and 6).

Discussion

Stereoselectivity. Table III summarizes pertinent stereoselectivity data. Patent is the overwhelming preference for β approach of CF_2, CFCl, and CCl_2 during additions at the $\Delta^{5,6}$ positions of both the model substrate **5** and its steroidal analogues **8** and **10**. This basic observation has precedent,[1,27,29,44,60] but there are additional points to be made.

Mechanistic analyses of the carbene–olefin addition reaction require that (1) there be maximum overlap of the carbene's vacant p orbital and an olefinic "p" orbital in the transition state (TS), and (2) that CX_2 approach the π bond in an highly unsymmetrical manner, such that, in the TS, the bulk of the positive charge resides on the carbon atom most capable of supporting it.[61] For a $\Delta^{5,6}$ substrate, (1) and (2) require *axial* attack of CX_2, through a partially charge-separated TS, in which β-attack biased toward C-6 (δ+ at tertiary C-5), **12**, is energetically preferred to α-attack, biased toward C-5 (δ+ at secondary C-6), **13**.



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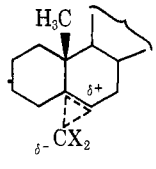

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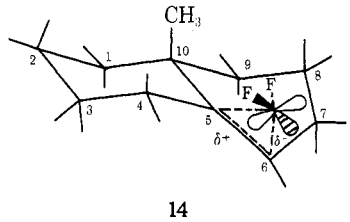
Model olefin **7** can be regarded as the parent $\Delta^{5,6}$ substrate. (For continuity, steroid numbering will be used with **7**.) Therefore, the observed CF_2 stereoselectivity (β/α = 10.6) demonstrates that the β > α preference is innate to the A/B ring system, and is directionally dependent neither on the presence of other substituents nor even of rings C and D of the full steroid. Dreiding models suggest **14** as the



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TS for β addition.[62] The β face of ring B "opens" so that β approach, biased toward C-6, appears to be sterically reasonable as well as electronically favored. Although β ap-

Table III
Stereoselectivies of the Carbene Additions[a]

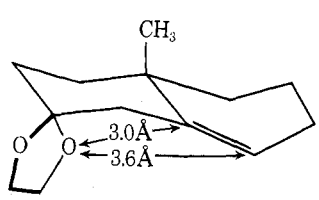
Carbene	Substrate	Stereoselectivity β/α	Stereoselectivity endo-Cl/endo-F
CFCl	1		2.4[b]
CFCl	2		1.2–1.5[c]
CF_2	5	250	
CFCl	5	d	0.11–0.25[e]
CCl_2	5	d	
CF_2	6	0.194[f]	
CF_2	7	10.6[g]	
CF_2	8	d	
CFCl	8	d	0.33
CCl_2	10[h]	d	

[a] Reaction temperature was 80° unless otherwise noted. [b] Reference 49, Moss and Gerstl; temperature −10°. [c] W. Funasaka, T. Ando, H. Yamanaka, H. Kanehira, and Y. Shimokawa, Symposium on Organic Halogen Compounds, Tokyo, Japan, Nov. 29, 1967, Abstracts, p 25 ff; temperature, 35°. [d] Only β addition was detected. [e] Reference 44. The minor adduct (5-β-*endo*-Cl-*exo*-F) was relatively unstable. Presumably, the stereoselectivity is closer to 0.25, [f] Average of three runs; av dev ±0.007. [g] Average of two runs; av dev ±0.08. [h] Reference 18.

proach of CF_2 is opposed by the β angular methyl group, and by β H atoms at C-4 and C-8, α approach (biased toward C-6) appears to be opposed by the α-H atoms at carbons 1, 3, 7, and 9. The relative balance of steric hindrance permits the stereoelectronic preference for β addition to dominate.

Note, however, that peracid epoxidation of 7[39] and $\Delta^{5,6}$ steroidal olefins[63a] affords mainly the α epoxide. The loss of β stereoselectivity may reflect a lesser polarization of the TS for peracid epoxidation, vis-à-vis CF_2 addition, leading to a relaxation of the stereoelectronic control which dominates in the latter reaction. Combined with lower steric hindrance to α (rather than β) approach of the bulkier peracid, α-epoxidation would be expected to prevail. Loss of β stereoselectivity is also encountered in the Simmons–Smith methylenation of $\Delta^{5,6}$ steroidal olefins,[14] and can be similarly explained.

The β preference in CF_2 addition to **5** ($\beta/\alpha = 250$) is 23.6 times more pronounced than in addition to **7**. We attribute the increased selectivity to specific deactivation of **5** at the α face of the $\Delta^{5,6}$ double bond by the 3α ketal oxygen, cf. **15**. This phenomenon is well precedented in various reac-



15

tions of steroidal analogues,[63] and in the β-hydroboration of **5** itself.[37] In this regard, note that the very high β CF_2 stereoselectivity observed in addition to steroid **8** is not a function of the 3-ethylene acetal group. Steroids which lack this functionality also give highly β stereoselective additions of CF_2[27] (and of CCl_2[18]) at $\Delta^{5,6}$.

Originally, it was believed that CCl_2 could not add to $\Delta^{5,6}$ steroidal olefins.[27,29] Granted the necessity for β attack,[64] it was argued that only the smaller CF_2 could add; CCl_2 encountered insurmountable steric hindrance which originated at the 10β methyl group.[27] Although it is now clear that CCl_2 *can* add to both the model, **5**, and actual steroidal substrate, **10**,[18,65] the steric opposition of the 10β methyl to β carbene addition is real, and clearly evident in its effect on CFCl stereoselectivity (Table III). The β addition of CFCl to **5** and **8** occurs predominantly with *endo*-F-*exo*-Cl stereoselectivity, a preference opposite to that exhibited by CFCl with acyclic or simple cyclic alkenes such as **1** or **2** (Table III). There, favorable electrostatic interactions between the carbene's more polarizable Cl atom and the olefinic alkyl substituents (which become partially positive in the addition TS) outweigh any steric deficit due to chlorine's larger size; *endo*-Cl-*exo*-F stereoselectivity commonly results.[66] Note that, in both expressions of stereoselectivity, β/α and endo/exo, the model and steroidal olefins exhibit parallel behavior, underlining the value of the model studies.

Discussion of the α stereoselectivity observed for (CF_2 + **6**) will be considered below, but we note here that **6** can be formally derived from **7** by replacing the 3-allylic protons of the latter with the ethylene acetal function. Because (**7** + CF_2) exhibits β stereoselectivity, the ethylene acetal function of **6** msut be responsible for the changeover to α stereoselectivity.

The stereoelectronic analysis developed to rationalize the β/α selectivity of CX_2 additions to $\Delta^{5,6}$ substrates is reasonably applicable at other sites of steroidal monoene and conjugated diene substrates,[4a,16,27,29,44,60,67] as long as principles 1 and 2 are strictly applied (see above), and due note is taken of any additional substituent-induced steric or electronic perturbations. However, a carbenic addition in which a strongly polarized TS is not involved is excluded from this analysis, and, in the absence of overwhelming steric or specific substituent directive effects, should not exhibit β stereoselectivity (e.g., Simmons–Smith methylenation at the $\Delta^{5,6}$ site[14]).

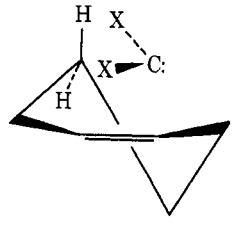
Relative Reactivities. From the empirical data of Table II, we construct a single set of relative reactivities, normalized to cyclohexene, and with CF_2 generated from ($C_6H_5HgCF_3$ + NaI) at 80° (cf. Table IV). In addition, employing the stereoselectivity data of Table III, we can partition the overall reactivities of **5–7** into β- and α-face reactivities.

Table IV
Relative Reactivities toward CF_2 (80°, Benzene[42])

Substrate	Overall rel reactivity	β-Face react.[a]	α-Face react.[a]
1	49.5		
2	1.00		
7	0.46	0.84	0.079
3	0.43		
5	0.38	0.76	0.0030
6	0.12	0.040	0.21
4	0.018		

[a] These values have been multiplied by 2; they are normalized to the cyclohexene scale.

Olefin **1** is 49 times more reactive than **2**. This is mainly due to electronic factors; **1** is trisubstituted whereas **2** is disubstituted, and it is well known that the electrophilic dihalocarbenes strongly discriminate in favor of more highly alkylated olefins.[30,68] For comparison, $(k_1/k_2)_{CCl_2} \sim 16$ (at 0°);[69] CF_2 is more selective than CCl_2, as anticipated.[46,68] The advantage **1** enjoys over **2** is not all electronic, however. Cyclohexene suffers from steric hindrance to addition, compared to acyclic alkenes. Toward CCl_2, for example, **2** is 1.68 times less reactive than *cis*-butene (at 0°);[69] steric interactions between the carbene's "endo" halogen atom and cyclohexene's pseudoaxial H atoms, **16**, probably account for the additional retardation.[70]



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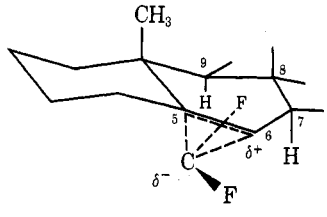
The β face of **7** is comparable in reactivity to **2**, but ought to react considerably faster because it is a trisubstituted "olefin". The problem is clearly steric, and originates at the β angular methyl group. Indeed, if we compare the two trisubstituted olefins, **1** and **7**-β, the reactivity ratio of ~59 can be largely attributed to the alteration of a methyl group in **1** to a *tert*-butyl group in **7**-β, cf. **17** and **18**. With

17 18

CCl_2, alteration of an ethyl group in 1-butene to a freely rotating *tert*-butyl group in 3,3-dimethyl-1-butene leads to a rate retardation of 34.5 (at −10°).[71] In **7**-β (**18**), the "*tert*-butyl moiety" is locked with a methyl group in the most disadvantageous orientation.

The α face of **7** is ~13 times less reactive than **2**. Axial attack[27,29] of CF_2 would here be biased toward C-5, **19**, placing most of the TS δ^+ on secondary C-6. This would make **7**-α and **2** electronically equivalent, but α approach of CF_2 to **7** (according to the Hoffmann model[62]) would encounter steric hindrance from α hydrogen atoms at C-7 and C-9 (as well as C-1 and C-3), cf. **19**. This hindrance would exceed that experienced by CF_2 in addition to **2**, cf. **16**.



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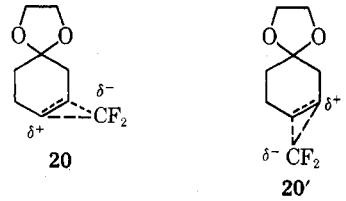
Toward CF_2, olefin **3** is 0.43 times as reactive as **2**, demonstrating inductive deactivation by the ketal group. An identical deactivation was seen in CCl_2 additions to **3** (k_3/k_2 = 0.44 at 80°).[33] A "statistical" explanation was offered: **2** has two equivalent olefinic carbons, but **3** has one site for attack (**20**) which is electronically better than the other

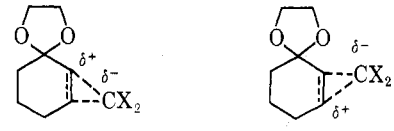


20 20′

(**20′**), i.e., it effectively has one site for attack and should be ca. half as reactive as **2**.

The β-face reactivity of **5** resembles that of **7**; the modest (10%) decrease can be attributed to ketal inductive destabilization of the TS for **5**-β. Addition to the α face of **5** is the slowest process in the entire set, 16500 times slower than addition to **1**, and ~26 times slower than addition to **7**-α. Most of the latter retardation is attributable to specific steric hindrance provided by the 3α ketal oxygen atom, cf. **15**.[63]

Substrate **4** is strongly deactivated toward CF_2 by its allylic ketal substituent, k_2/k_4 = 55.5 and k_3/k_4 = 23.9. The comparable ratios for CCl_2 additions are 83 and 38, respectively.[33] In additions of CX_2 to **4**, TS **21** is destabilized by

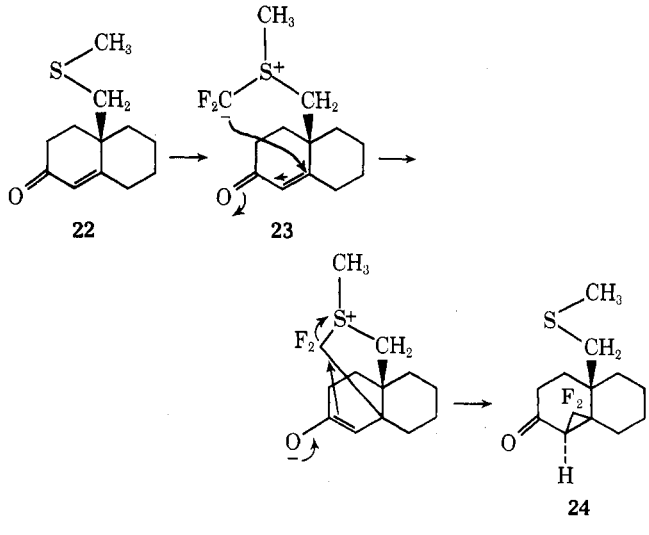


21 21′

the unfavorable inductive effect, whereas alternative **21′** suffers both from steric hindrance at the ketal-bearing carbon and from some inductive destabilization, cf. **20′**. That deactivation here is larger for CCl_2 than for the electronically more selective[68] CF_2 suggests that steric problems, which should be more serious with CCl_2, are quite important in this addition.

Bicyclic olefin **6** combines features of **4** and **7**; however, the ketal function is not tucked beneath ring A, as it is in **9**, but extends away from this ring. Both faces of **6** react with CF_2 more rapidly than does monocyclic analogue **4**, which (superficially) can be attributed to the more favorable trisubstituted alkylation pattern of **6**. However, the behavior of **6** is curious in comparison to that of **7**: $k_{7\text{-}\beta}/k_{6\text{-}\beta}$ = 21, whereas $k_{7\text{-}\alpha}/k_{6\text{-}\alpha}$ ~ 0.4. That is, the α face of **6** appears *activated*, relative to **7**-α, although the reverse is true of the β faces. (The latter observation is readily attributed to ketal deactivation, cf. **21** and relevant discussion.) We dismiss two explanations for the α-face "activation": that ring A of **6** adopts a boat conformation, making **6**-α particularly accessible, and that there is ketal-mediated delivery of CF_2 to **6**-α. Inspection of Dreiding models lends no support to the former idea, and the latter is unpalatable in view of the absence of such synergistic dihalocarbene additions with related substrates.[33,61] We are frankly puzzled by the bizarre reactivity of **6**-α.

Because parent enone **9** did not react with CF_2, and **6** reacted with poor stereoselectivity and concomitant isomerization, we attempted the potentially stereospecific and synergistic transformation of **22** → **24**.



22 23 24

Substrate **22** was prepared as directed by Mathews and Meteyer, who have shown that the methylene ylide corresponding to **23** readily cyclopropanates the enone function from the β face.[72] However, reactions of **22** with CF_2 generated by pyrolysis of ClF_2COONa in glyme, diglyme, or Me_2SO, or from $C_6H_5HgCF_3$ + NaI in glyme, led mainly to the recovery of **22**.[73]

The foregoing results establish the utility of model stud-

ies for contemplated carbene–steroid addition reactions, and constitute the first quantitative study of this kind. These and similar results should prove useful in synthetic planning, as well as in our efforts to understand the selectivity of carbenes toward complicated substrates.

Experimental Section[74]

Olefins. Trimethylethylene (1) and **cyclohexene (2)** were obtained from Aldrich Chemical Co., and were percolated through a column of neutral alumina and Linde 4A molecular sieves before use. **Cyclohex-1-en-4-one ethylene acetal (3)** was prepared by the method of ref 33 in 97% purity.[75]

Cyclohex-1-en-3-one ethylene acetal (4) was prepared from cyclohexanone ethylene acetal by the method of Garbisch.[34] A pure sample was isolated by GC on column A[76] at 165°: NMR (CCl_4) δ 6.00–5.25 (m, 2 H, vinyl), 3.83 (s, 4 H, ketal), 2.71–1.84 (m, 2 H, allyl), 1.84–1.43 (m, 4 H, cyclohexyl).[77]

10-Methyl-1(9)-octal-2-one (9). This ketone was prepared either by the method of Marshall and Fanta[35] or, preferably, by the method of Heathcock and Ellis.[36] According to the latter, 44 g (0.39 mol) of 2-methylcyclohexanone, 41.3 g (0.59 mol) of methyl vinyl ketone, 100 ml of benzene, and 0.3 ml of concentrated H_2SO_4 were refluxed for 24 hr in a flask equipped with a water condenser, topped with a dry ice condenser. The reaction mixture was diluted with 400 ml of *n*-hexane, washed twice with 50-ml portions of 5% KOH solution, twice with 50-ml portions of water, dried over $MgSO_4$, and concentrated under reduced pressure. In our hands, the crude product thus obtained was 66% **9** and 33% uncyclized 2-methyl-2-(3-oxobutyl)cyclohexanone.[73] Therefore, the crude product in 25 ml of anhydrous ethanol was added slowly, with stirring, to 2.0 g of sodium ethoxide in 50 ml of anhydrous ethanol, maintained at 0°. After addition, the reaction temperature was raised to 25°, and stirring was continued for 3 hr. The reaction mixture was added to 250 ml of diethyl ether, washed 4 times with 30-ml portions of brine, dried over $MgSO_4$, and stripped of solvent. Distillation afforded 41 g of **9** (65%), bp 108–110° (3 Torr) [lit. bp[35] 82–83° (0.7 Torr)]. The ir spectrum[77] agreed with that reported by Marshall;[35] NMR (CCl_4) δ 5.23 (s, 1 H, vinyl), 2.67–2.00 (m, 4 H, allyl and CH_2CO), 2.00–1.37 (envelope, 8 H, ring), 1.25 (s, 3 H, methyl).

2,2-Ethylenedioxy-10-methyl-8-octalin (5) was prepared by the method of Marshall.[37]

2,2-Ethylenedioxy-10-methyl-1(9)-octalin (6). Ketone **9**, 10 g (61 mmol), 38 g (610 mmol) of ethylene glycol, and 2 g of adipic acid in 500 ml of benzene were refluxed in a flask equipped with a Dean-Stark trap and a condenser; water was azeotropically removed. The slow reaction was monitored by GC.[78] After 400 hr, about 70% of **9** had been converted to a mixture of **6** and **5**. The benzene phase of the product mixture was washed once with 50 ml of 5% $NaHCO_3$ solution and twice with 50-ml portions of water, and dried over Na_2SO_4. After filtration, solvent was stripped and the residue was chromatographed over neutral alumina, with elution by *n*-pentane. The oily product consisted of 87% of **6** and 13% of **5**.[78] Distillation over a 30-cm Vigreux column gave 4.5 g of 94% pure **6** (6% of **5** was present), bp 92–93° (0.9 Torr). A pure sample, obtained by GC on the SE-30 column,[78] had ir (neat) 1661 cm^{-1} (C=C);[77] NMR (CCl_4) δ 5.07 (broad s, 1 H, vinyl), 3.85 (s, 4 H, ketal), 2.23 –1.23 (envelope, 12 H, major absorption at 1.60, ring), and 1.08 (s, 3 H, methyl). M^+ was observed at *m/e* 208 in the mass spectrum.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.18; H, 9.67.

10-Methyl-1(9)-octalin (7) was prepared from **9** by the method of Marshall.[39]

Cholest-5-en-3-one 3-Ethylene Acetal (8). This olefin was prepared from cholest-4-en-3-one by the method of Antonucci et al.[40] Our material had mp 129–132° (from ether–methanol, lit. mp[40] 133.5–134.5°). NMR showed (CCl_4) 5.16 (broad s, 1 H, vinyl), 3.84 (s, 4 H, ketal), 1.02 (s, 3 H, C-19 methyl), 0.93 (d, J = 6 Hz, 3 H, C-21 methyl), 0.89 (d, J = 6 Hz, 6 H, C-26, C-27 methyls), 0.70 (s, 3 H, C-18 methyl).

Difluorocarbene Adducts.[79] Two procedures were used in CF_2 additions. (A) olefin (1.25 equiv), $(CH_3)_3SnCF_3$ (1 equiv),[41] NaI (1.1 equiv),[48] and 12 ml of 1,2-dimethoxyethane (distilled from sodium onto 3A sieves) were stirred and refluxed together for 16–20 hr under a N_2 atmosphere. The reaction mixture was cooled to 25°, and dry NH_3 was slowly passed in through a gas addition tube, precipitating the ammoniate of $(CH_3)_3SnI$. Filtration afforded a product solution which was worked up as described below. (B) Olefin (1 equiv), $C_6H_5HgCF_3$ (1 equiv),[42] NaI (2.5–3.0 equiv),[48] and 10–15 ml of C_6H_6 were stirred and refluxed together for 16–20 hr under a N_2 atmosphere. After cooling to 25°, the reaction mixture was filtered to remove C_6H_5HgI, NaF, and NaI, and the filtrate was processed as described below.

1,1-Difluoro-2,2,3-trimethylcyclopropane (1-CF_2)[46] was prepared from trimethylethylene by procedure A in 75–80% yield. A pure sample was isolated by preparative GC of the unconcentrated, crude reaction product on column A at 60°.[76] The ^1H NMR (CCl_4) showed multiplets centered at δ 1.20 (3 H) and 1.06 (7 H).

7,7-Difluoronorcarane (2-CF_2)[47] was prepared from cyclohexene in 65–70% yield by either procedure A or B. The pure material was obtained by careful fractional distillation of the crude reaction solution, bp 121–123°. The ir spectrum[77] agreed with that reported.[47] NMR showed (CCl_4) broad multiplets centered at δ 1.67 and 1.37.

7,7-Difluoronorcaran-4-one ethylene acetal (3-CF_2) was prepared from **3** by procedure A in ~78% yield. A pure sample was isolated by GC on column A at 160°.[76,77,80] The mass spectrum showed M^+ at *m/e* 190.

Anal. Calcd for $C_9H_{12}O_2F_2$: C, 56.83; H, 6.36; F, 19.98. Found: C, 57.06; H, 6.61; F, 20.01.

7,7-Difluoronorcaran-3-one ethylene acetal (4-CF_2) was prepared from **4** by either procedure A or B. The crude product mixture contained 20–30% of 4-CF_2, as well as 3-CF_2 (see above). The desired adduct was isolated by preparative GC on column A at 160°.[76,77,80]

Anal. Calcd for $C_9H_{12}O_2F_2$: C, 56.83; H, 6.36; F, 19.98. Found: C, 56.76; H, 6.38; F, 20.46.

8,9-Difluoromethylene-10-methyl-2-decalone 2-Ethylene Acetal (5-β-CF_2 and 5-α-CF_2). These compounds were prepared from **5** by either procedure A or B. They were isolated from the concentrated reaction mixture by GC on a 8 ft × 0.25 in., 20% SE-30 on 80/100 mesh Gas-Chrom RZ column at 190°. The average yield of 5-β-CF_2 (GC) was 68%; the ratio of 5-β-CF_2:5-α-CF_2 was 250:1. The β isomer had mp 51.5–53°.[77,80] The mass spectrum showed M^+ at *m/e* 258.

Anal. Calcd for $C_{14}H_{20}O_2F_2$: C, 65.10; H, 7.81. Found: C, 65.49; H, 7.67.

The α isomer[80] showed M^+ at *m/e* 258 in the mass spectrum.

1,9-Difluoromethylene-10-methyl-2-decalone 2-Ethylene Acetal (6-β-CF_2 and 6-α-CF_2). These compounds were prepared from **6** by procedure B. Because of isomerization of the substrate (see above), all four adducts of **5** and **6** were present in the concentrated reaction mixture. The overall yield was 23%, but the ratio of 5-β-CF_2:6-α-CF_2:6-β-CF_2 was 18:5:1, so that the yield of 6-α-CF_2 was only ~5%. It was isolated by preparative GC on column C at 178°,[76,77,80] and had mp 38–39°. The mass spectrum showed M^+ at *m/e* 258.

Anal. Calcd for $C_{14}H_{20}O_2F_2$: C, 65.10; H, 7.81. Found: C, 64.76; H, 7.92.

Minor adduct 6-β-CF_2 was similarly isolated,[80] and showed M^+ at *m/e* 258 in its mass spectrum.

1,9-Difluoromethylene-10-methyl-2-decalin (7-β-CF_2 and 7-α-CF_2) were prepared from **7** using procedure B in ~90% yield. The β/α ratio was 10.6, and the pure adducts could be isolated by GC on column C at 120°.[76] The β adduct had the shorter retention time, and showed M^+ at *m/e* 200 in its mass spectrum.[77,80]

Anal. Calcd for $C_{12}H_{18}F_2$: C, 71.97; H, 9.06. Found: C, 71.79; H, 9.07.

Adduct 7-α-CF_2[77,80] was subjected to mass spectral analysis.

Exact mass. Calcd for $C_{12}H_{18}F_2$: 200.1376. Found: 200.1355.

5β,6β-Difluoromethylenecholestan-3-one 3-ethylene acetal (8-β-CF_2) was prepared by procedure B, using 4.5 g (10.5 mmol) of **8**, 4.0 g (11.5 mmol) of $C_6H_5HgCF_3$, and 5.2 g (34.5 mmol) of NaI in 50 ml of benzene. After 24 hr of reflux, under N_2, filtration of the reaction mixture afforded a solution which, upon concentration, gave 1.6 g of recovered **8** (mp 132–133°), and a yellow oil. The oil was chromatographed over 80–200 mesh activity I alumina with benzene, benzene–methanol elution. The elutate was monitored by TLC on EM Laboratories F-254 0.25 mm silica gel plates ($CHCl_3$ eluent, visualization by uv or I_2 vapor). The desired product obtained from the column had (TLC) R_f 0.42 and could be crystallized from 95% ethanol.[81] Recrystallization gave 1.6 g (32%) of white needles of 8-β-CF_2, mp 51–53°, M^+ at *m/e* 478 and 479 (34.2% of 478).[80]

Anal. Calcd for $C_{30}H_{48}O_2F_2$: C, 75.27; H, 10.11, F, 7.94. Found: C, 75.07; H, 10.09; F, 7.26.

Other Carbene Adducts. 8,9-Dichloromethylene-10-methyl-2-decalone 2-Ethylene Acetal (5-β-CCl_2). Added to a Morton flask, fitted with a high-speed mechanical stirrer, dropping funnel,

and condenser, were 2.0 g (9.6 mmol) of **5**, 0.6 g of benzyltriethylammonium bromide, and 75 ml of chloroform. With vigorous stirring, 50 ml of 50% aqueous NaOH solution was added dropwise, over 1 hr. Stirring was continued at 25° for 100 hr. The reaction mixture was then diluted with 400 ml of water and extracted thrice with 200-ml portions of chloroform. The total chloroform extract was washed twice with 100-ml portions of water, dried over $MgSO_4$, filtered, and stripped. The residue was chromatographed over a column of neutral, activated alumina (packed in pentane). Elution with pentane, followed by pentane–chloroform, afforded 2.2 g (~78%) of crude 5-β-CCl_2,[82] which was distilled to afford a pure sample, bp 115° (0.04 Torr).[77,80] The mass spectrum showed M^+ at *m/e* 290 and 292 (68% of 290).

A satisfactory elemental analysis could not be obtained; the structure of 5-β-CCl_2 was therefore secured by reduction. Into a three-neck flask equipped with a dry ice condenser capped with a drying tube, dropping funnel, N_2 inlet, and magnetic stirring bar, there was condensed 100 ml of dry NH_3 at −78°. Then 2.6 g (113 mmol) of sodium was added, stirring commenced, and a solution of 1.1 g (3.8 mmol) of 5-β-CCl_2 in 25 ml of dry tetrahydrofuran (THF) was added over 1 hr. Stirring was continued at −78° for 5 hr after addition. Solid NH_4Cl was added to the reaction mixture until its blue color was discharged; stirring was then continued at 25° and the ammonia was allowed to evaporate. The semisolid residue was mixed with 50 ml of THF and filtered. The filtrate was concentrated, and the residue was dissolved in 300 ml of chloroform. This solution was washed thrice with 50-ml portions of $NaHCO_3$ solution and once with brine, and then dried over $MgSO_4$. Filtration and concentration afforded 0.7 g (83%) of an oil, shown by GC on an 8 ft × 0.25 in., 20% SE-30 column (190°) to contain a single product. The GC-purified material had ir and NMR spectra[77,80] identical with those of 5-β-CH_2 prepared from **5** by Simmons–Smith methylenation.[44]

5β,6β-Chlorofluoromethylenecholestan-3-one 3-Ethylene Acetal (8-β-*endo*-F-*exo*-Cl and 8-β-*endo*-Cl-*exo*-F). A solution of 2.0 g (4.67 mmol) of **8** and 2.7 g (7 mmol) of $C_6H_5HgCCl_2F$[45] in 10 ml of dry benzene was refluxed for 15 hr under N_2. Filtration and concentration gave an oil which exhibited two resonances (ϕ^* 144.9 s and 123.4 d, ratio 3:1, see above) in its ^{19}F NMR spectrum. The oil was dissolved in hot, 95% ethanol; cooling returned 0.31 g of substrate **8** (mp 130–133°). The filtrate was concentrated to an oil which was chromatographed on 80–200 mesh, activity I alumina. Elution was with benzene, benzene–chloroform, and chloroform–1% methanol. The initial material obtained from the column crystallized from 95% ethanol, and was shown to be 8-β-*endo*-F-*exo*-Cl, mp 94–95°, 1.26 g (55%), R_f 0.36.[83] In the mass spectrum, a parent ion series was seen at *m/e* 494 (10.6%), 495 (2.9%) and 496 (3.5%).[77,80] The base peak was observed at *m/e* 87.

Anal. Calcd for $C_{30}H_{48}O_2ClF$: C, 72.76; H, 9.77; Cl, 7.15. Found: C, 72.60; H, 9.88; Cl, 7.11.

Further elution of the column afforded a small amount of a product which could be crystallized from ethanol, and which was spectrally identical with the ketone obtained by treating 100 mg of separated this sample into two components. The one with the higher R_f was additional 8-β-*endo*-F-*exo*-Cl (NMR); the other component, 180 mg, was its isomer, 8-β-*endo*-Cl-*exo*-F, which was characterized by NMR (see Results).[80]

Further elution of the column afforded a small amount of a product which could be crystallized from ethanol, and which was spectrally identical with the ketone obtained by treating 100 mg of 8-β-*endo*-F-*exo*-Cl with 5 mg of *p*-toluenesulfonic acid in 0.1 ml of water and 5 ml of methanol, at reflux, for 1 day.[73] These materials were therefore 5β,6β-*endo*-fluoro-*exo*-chloromethylenecholestan-3-one. A pure sample had mp 153–154.5° (from 95% ethanol),[77] and key NMR features (CCl_4) δ 1.15 (d, J = 3.3 Hz, 3 H, C-19 methyl), 0.90 (d, J = 6.6 Hz, 3 H, C-21 methyl), 0.87 (d, J = 6.6 Hz, 6 H, C-26 and C-27 methyls), 0.67 (s, 3 H, C-18 methyl); ϕ^* ($CFCl_3$, CCl_4) 144.5 s. The mass spectrum revealed a parent ion series at *m/e* 450 (45.3%), 451 (14.6%), and 452 (15.3%). The base peak was observed at *m/e* 149.

Anal. Calcd for $C_{28}H_{44}OClF$: C, 74.55; H, 9.83; Cl, 7.85. Found: C, 74.35; H, 9.94; Cl, 8.02.[85]

Further elution of the column afforded 50 mg of an oil [shown by multiple development TLC (see above) to consist of additional 5β,6β-*endo*-fluoro-*exo*-chloromethylenecholestan-3-one and, perhaps, its β-*endo*-Cl-*exo*-F isomer] and, finally, 100 mg of cholest-4-en-3-one.

Conversion of 5-β-CF_2 to 7-β-CF_2. Heated to reflux for 20 hr, under stirring, were 0.15 g (0.58 mmol) of 5-β-CF_2, 0.11 g (1.16 mmol) of ethanedithiol, and 0.01 g of *p*-toluenesulfonic acid in 1 ml of benzene. The cooled reaction mixture was passed through a 3-cm column of 80–200 mesh, neutral activated alumina (packing and elution with benzene), affording 0.14 g of the thioketal analogous to 5-β-CF_2. The NMR spectrum showed the new compound to be ~95% pure, and featured (CCl_4) δ 3.15 (s, 4 H, thioketal) and 1.08 (s, 3 H, methyl).

The thioketal was then stirred with 8.5 g of W-2 Raney nickel[86] in 40 ml of methanol, under reflux for 8 hr. Filtration and concentration afforded 70 mg of an oil which was chromatographed (as above) to afford a product identical (ir, NMR, and retention time on column C[76] at 148°) with 7-β-CF_2.

Conversion of 6-α-CF_2 to 7-α-CF_2. Using an identical procedure, 10 mg (0.04 mmol) of 6-α-CF_2, 10 mg (0.1 mmol) of ethanedithiol, and 5 mg of *p*-toluenesulfonic acid in 1 ml of benzene afforded the thioketal analogue of 6-α-CF_2: NMR (CCl_4) δ 3.17 (m, 4 H, thioketal), 1.11 (s, 3 H, methyl). Again following the previous procedure, this material was treated with 4.3 g of W-2 Raney nickel[86] in 20 ml of methanol to afford, after work-up, 4 mg of an oil which had GC retention times identical with those of 7-α-CF_2 on columns A and C.[76]

Relative Reactivity Experiments. The carbene precursor (100–200 mg) and NaI (dried at 110°, 0.1 Torr, 24 hr, 1–1.1 equiv) were weighed (drybox) into a 10-ml flask which contained a magnetic stirring bar. A solution of olefin A and olefin B (each carefully weighed)[87] in several milliliters of benzene or 1,2-dimethoxyethane (distilled from Na)[79] was added, and the flask was fitted with a condenser which was topped with a N_2 inlet. A positive pressure N_2 atmosphere was maintained throughout the reaction. The flask was lowered into an oil bath, preheated to 80 or 90°, and stirring was begun. After reflux (4–23 hr), the reaction mixture was cooled and filtered through a glass wool plug. The filtrate was immediately assayed by GC.

The competitive cases, precursors, solvents, analytical conditions, and results are summarized in Table II. Relative reactivities were calculated from the standard expression, $k_A/k_B = (O_B/O_A)(P_A/P_B)$, in which O_i represents the initial molar quantity of olefin i, and P_i represents the integrated GC peak of the corresponding carbene adduct.[88]

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Registry No.—**1**, 513-35-9; **1**-CF_2, 823-25-6; **2**, 110-83-8; **2**-CF_2, 823-70-1; **3**, 7092-24-2; **3**-CF_2, 54158-65-5; **4**, 1004-58-6; **4**-CF_2, 54158-66-6; **5**, 3287-60-3; **5**-β-CF_2, 54158-67-7; **5**-β-CF_2 thioketal analogue, 57065-86-8; **5**-α-CF_2, 54165-77-4; **5**-β-CCl_2, 57065-87-9; **5**-β-*endo*-F-*exo*-Cl, 28846-73-3; **5**-β-*endo*-Cl-*exo*-F, 57128-63-9; **5**-β-CH_2, 28846-74-4; **5**-α-CH_2, 28846-75-5; **6**, 50900-97-5; **6**-β-CF_2, 54158-68-8; **6**-α-CF_2, 54165-78-5; **6**-α-CF_2 thioketal analogue, 57065-88-0; **7**, 13943-77-6; **7**-β-CF_2, 57065-89-1; **7**-α-CF_2, 57128-64-0; **8**, 3496-88-6; **8**-β-CF_2, 57090-63-8; 8-β-*endo*-F-*exo*-Cl, 57065-90-4; 8-β-*endo*-Cl-*exo*-F, 57065-91-5; **9**, 826-56-2; CF_2, 2154-59-8; CCl_2, 1605-72-7; CClF, 1691-88-9; ethylene glycol, 107-21-1; 5β,6β-*endo*-fluoro-*exo*-chloromethylenecholestan-3-one, 57065-92-6; ethanedithiol, 540-63-6.

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(73) Details of these experiments appear in the Ph.D. Thesis of D. J. Smudin, Rutgers University, New Brunswick, N.J., 1976.
(74) Ir spectra were recorded on a Perkin-Elmer Model 137 instrument; ^1H NMR spectra were generally recorded on either a Varian T-60 or a Jeolco JNM-MH-100 spectrometer. ^{19}F NMR spectra were recorded on the T-60 instrument (at 56.4 MHz). Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6L spectrometer. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.
(75) The balance was isomer **4**.
(76) Column identifications appear in footnote *c*, Table II.
(77) Complete ir descriptions of *all* compounds appear in the Thesis of D.J.S.[73]
(78) The analysis was by GC on a 12 ft × 0.25 in., 3% SE-30 on 80/100 Gas-Chrom RZ column at 150°.
(79) All olefins were purified just prior to use. They were percolated, in the reaction solvent, through a short column of 80–200 mesh, neutral, activated alumina and Linde 3A molecular sieves. Weighings were done in a N_2-filled drybox, relative humidity 4–5%.
(80) Key features of the NMR spectra of the adducts are described in Table I; additional details appear in the Thesis of D. J. S.[73]
(81) Further elution of the column with benzene–methanol gave 0.5 g of an oil, ir 1718 cm^{-1} (C=O), R_f (CCl_4) 0.20, which was shown to be the deketalized adduct. Control experiments showed that **8**-β-CF_2 partially deketalized during column chromatography, and that the ketone isolated from the reaction of **8** + CF_2 could be reketalized to **8**-β-CF_2. The ketone was not present in the crude reaction product (^{19}F NMR). It could be prepared from **8**-β-CF_2 by deketalization.[73]
(82) Only a single angular methyl resonance (δ 1.23) could be observed in the NMR spectrum of the crude product.
(83) TLC conditions are described under **8**-β-CF_2.
(84) Phosphomolybdic acid was used for visualization.
(85) Control experiments showed that the ketone could be reketalized to **8**-β-*endo*-F-*exo*-Cl, and that its origin was in alumina-induced deketalization of the latter during chromatography.[73]
(86) R. Mozingo, *Org. Synth.*, **21**, 15 (1941).
(87) The molar ratio of the more reactive olefin to carbene precursor was at least 3.3, and usually >5. The less reactive olefin was in excess of the more reactive olefin. Although the former ratio should ideally have been larger (>10), we were limited by substrate availability. The derived *k* values, however, appear to be acceptable; see Results.
(88) For a discussion of this method, see ref 30.