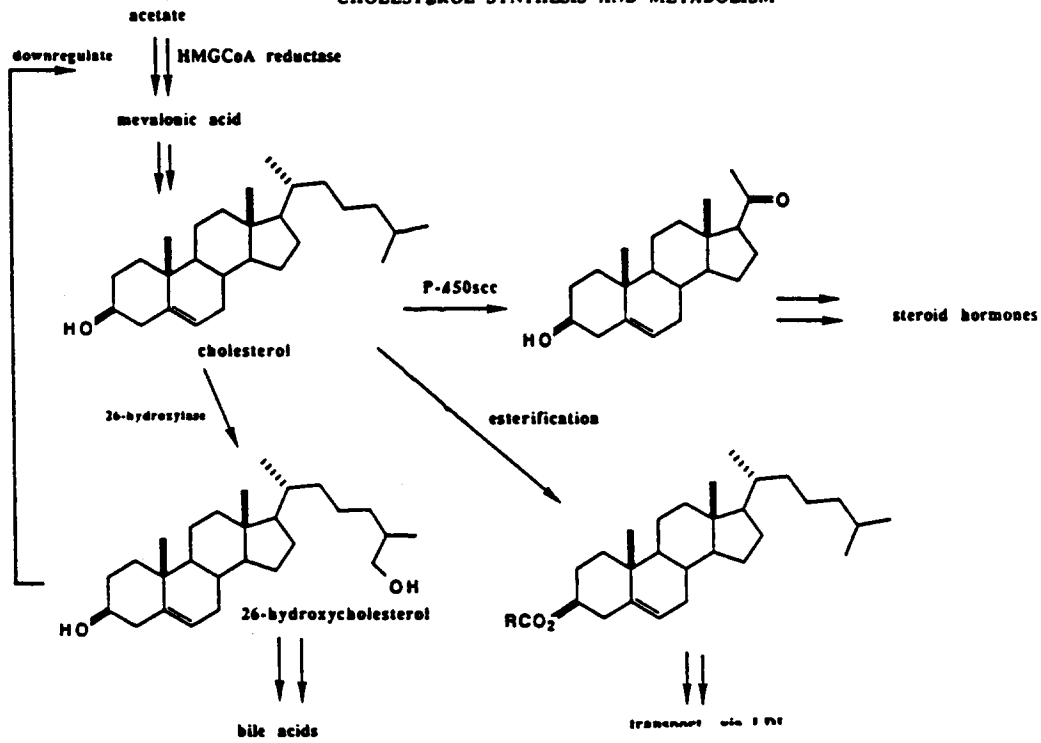
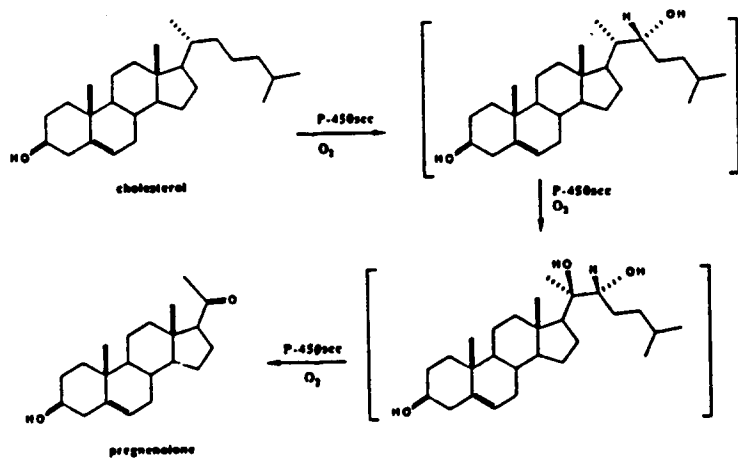


Cytochrome P-450 in Steroid Hormone Biosynthesis

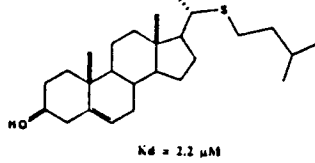
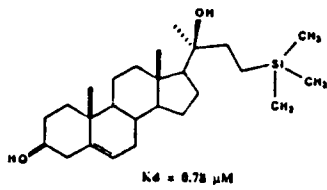
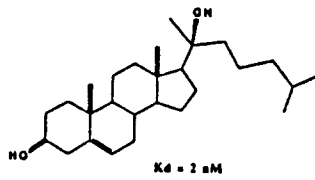
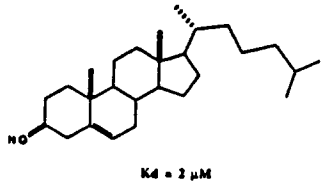
CHOLESTEROL SYNTHESIS AND METABOLISM



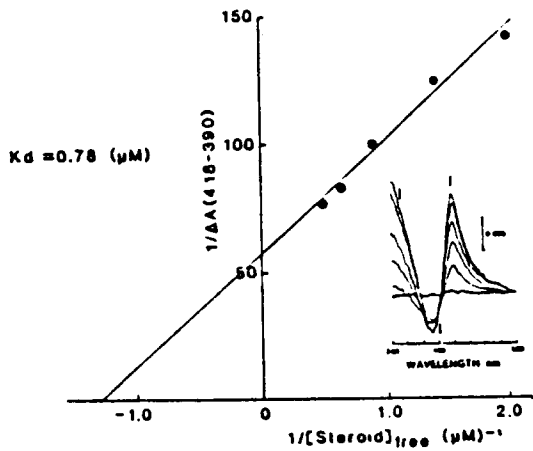
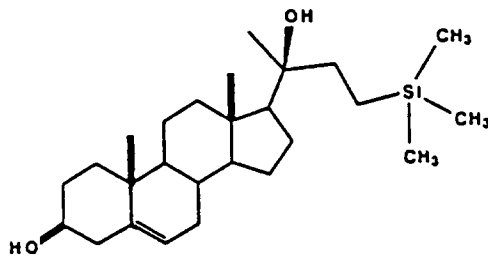
Side-chain Cleavage P-450 from Adrenal Mitochondria



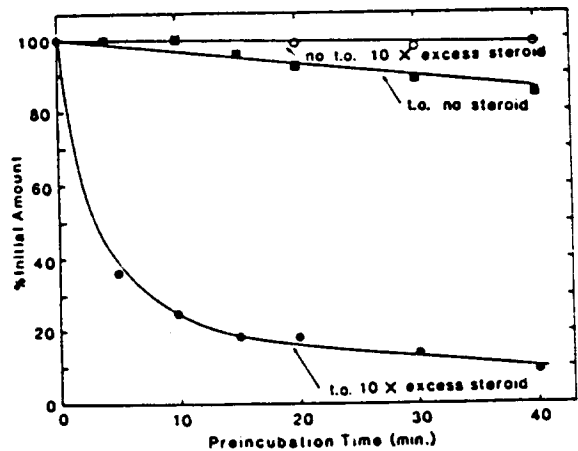
Substrates and Inhibitors for P-450_{sec}



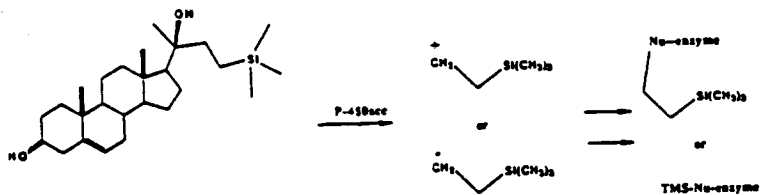
Nagahisa, Orme-Johnson and Wilson
J. Amer. Chem. Soc., 1984, 106, 1166

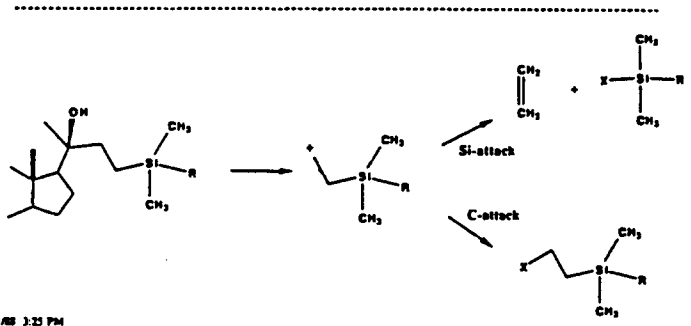
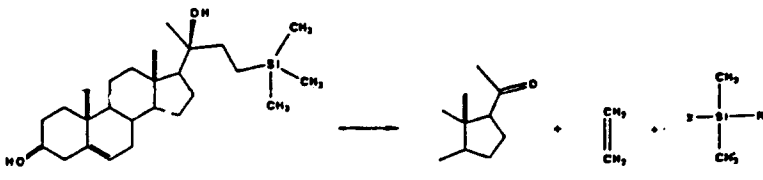


binding



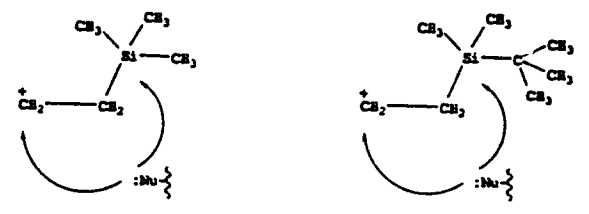
inhibition





de 1 92/108 3:23 PM

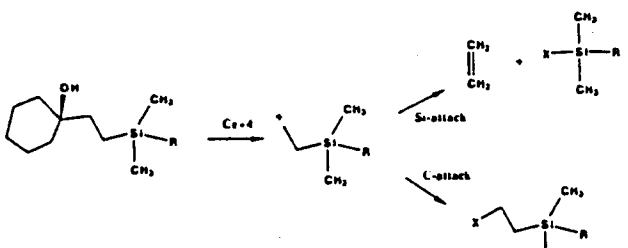
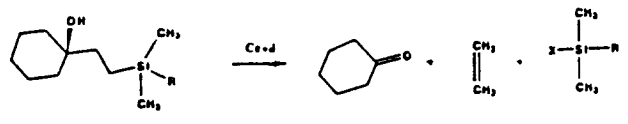
Steric effect on silylation



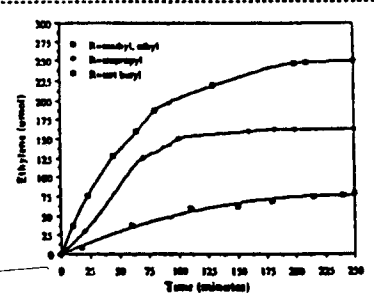
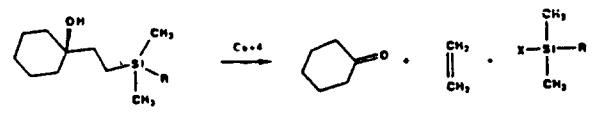
Nu: $\begin{matrix} \text{CH}_3 \\ | \\ \text{R}-\text{Si}-\text{X} \\ | \\ \text{CH}_3 \end{matrix}$

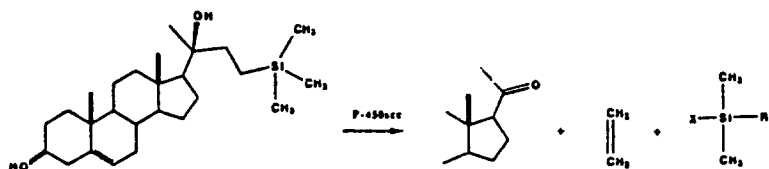
Rate of displacement at the silicon center:

R	rel rate
CH ₃	1
Et	1/10
i-Pr	1/1000
t-Bu	1/20,000

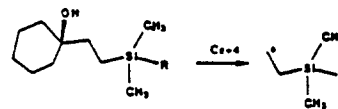
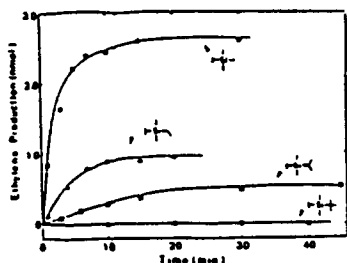
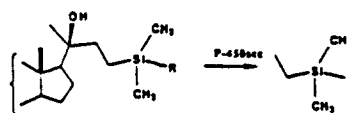


The partitioning of Si vs C attack in the enzymatic and model reaction should be affected by the steric environment around the silicon.





Evidence for a radical pathway?



Free Radical Trap



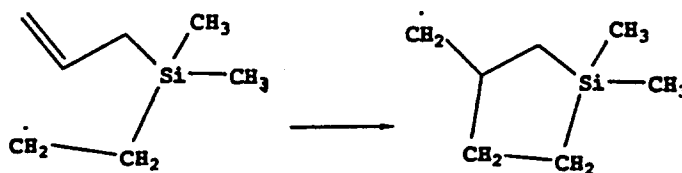
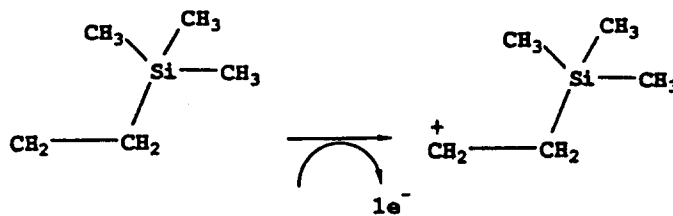
$$k = 1.1 \times 10^5 \text{ sec}^{-1}$$

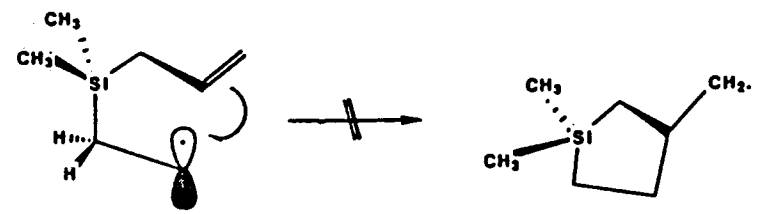
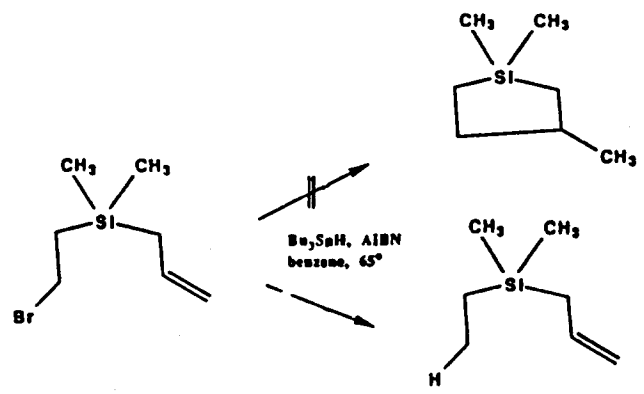
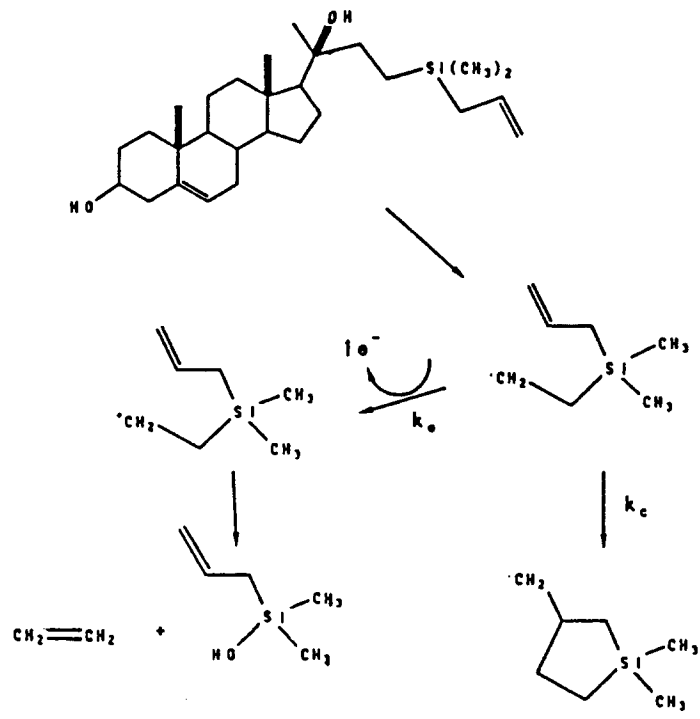


$$k = 0.038 \times 10^5 \text{ sec}^{-1}$$

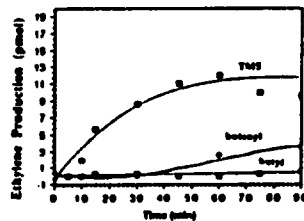
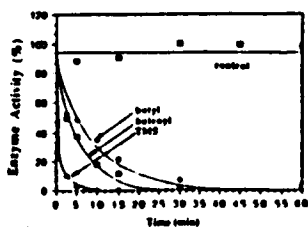
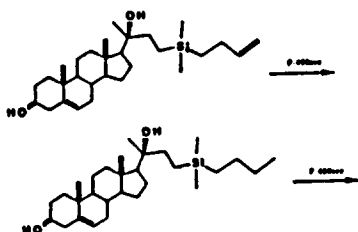
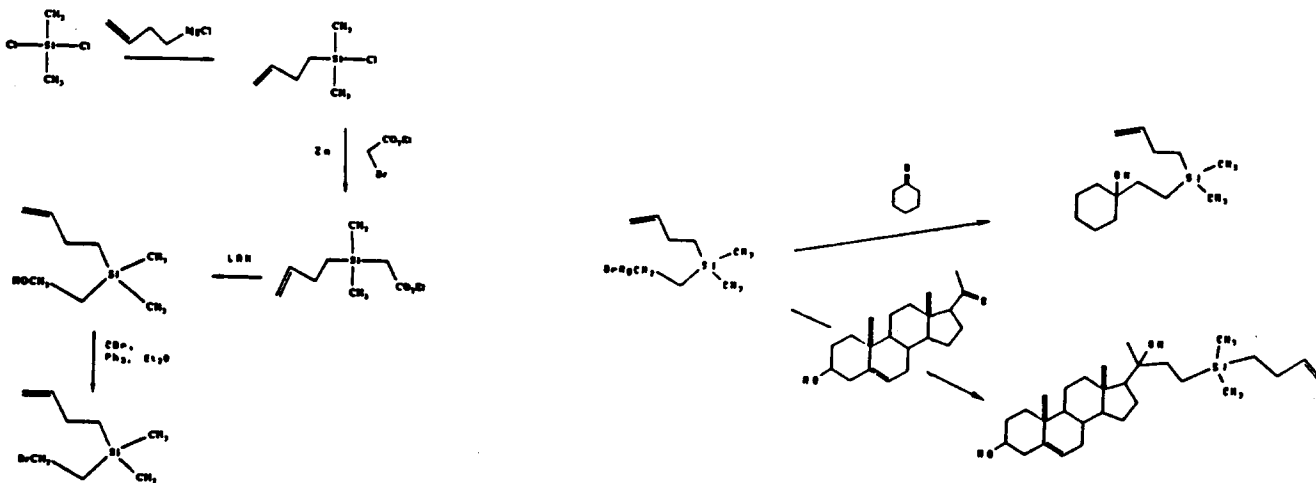
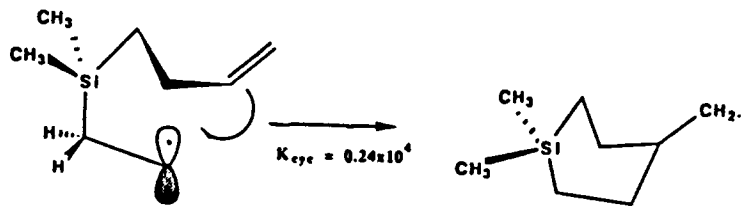
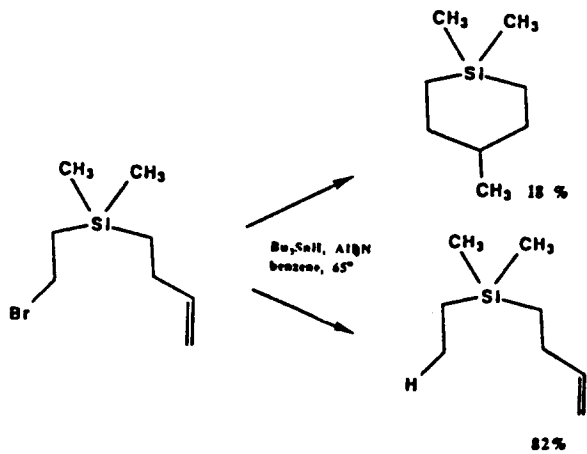
Wilt, J. W., *Tetrahedron*, 19, 3979 (1985).

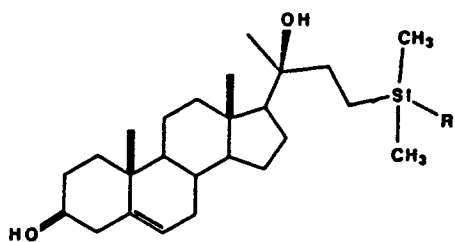
Is a radical involved?



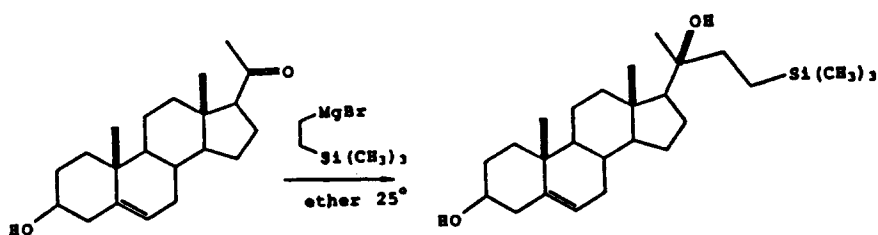


J. Wilt et al., *J. Am. Chem. Soc.*,
 110, 281 (1988)

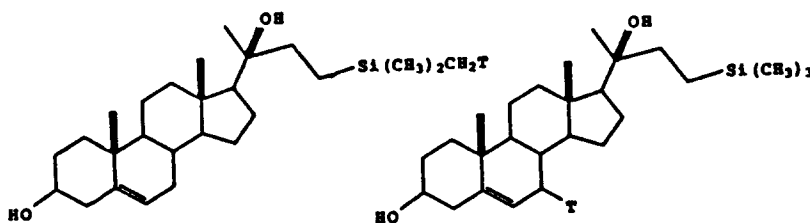




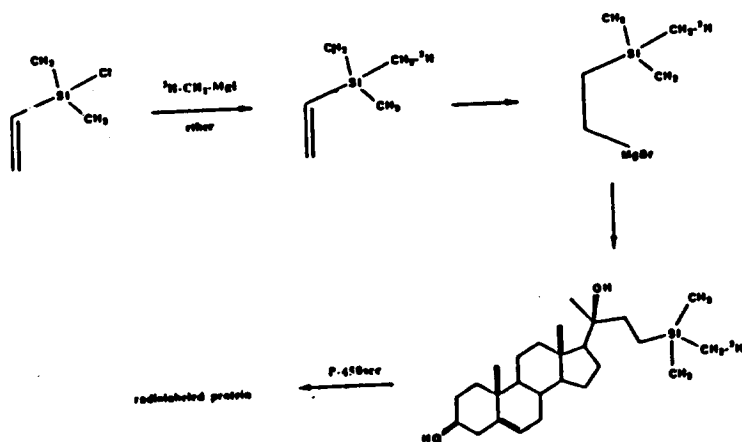
R	Kd (μM)
Methyl	0.70
Ethyl	2.50
i-Propyl	6.3
t-Butyl	-
n-Butyl	30.19
3-Butenyl	10.67



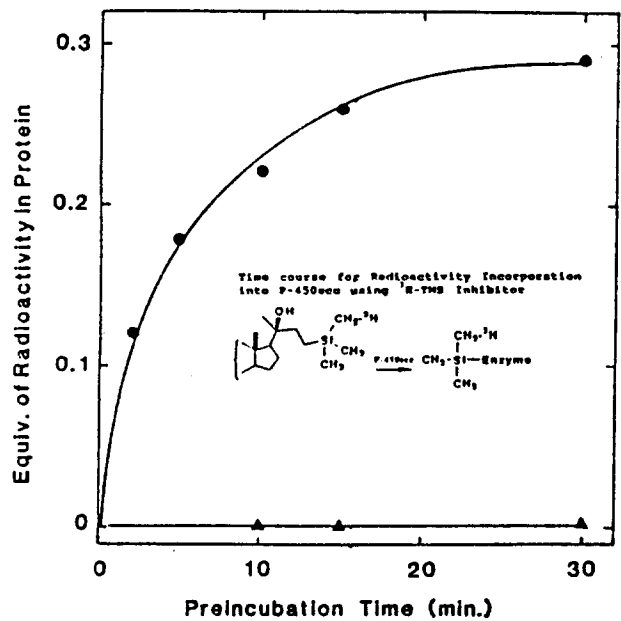
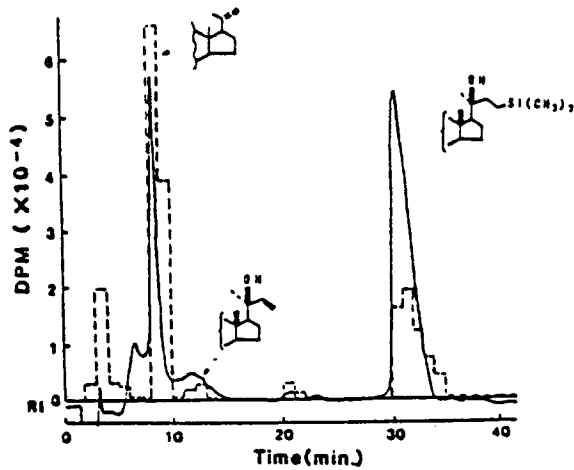
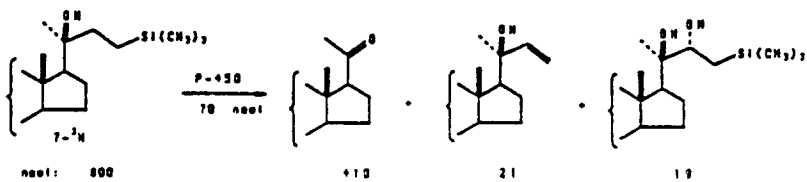
S. R. Wilson and A. Shadrinsky,
J. Org. Chem., 47, 1983 (1982).



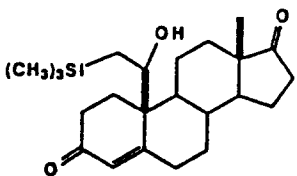
Tracing the fate of the trimethylsilyl group



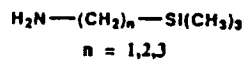
PRODUCT STUDY OF THE TURNOVER OF 7-³H-TMS INHIBITOR WITH CYTOCHROME P-450 PRODUCTS ISOLATED BY HPLC.



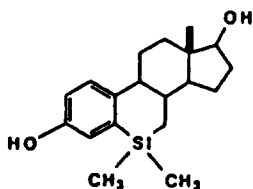
Other Biologically Active Silicon Compounds



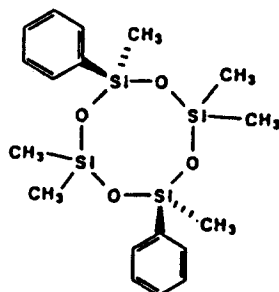
J. P. Burkhart et al., *Steroids*, 45, 357 (1985)



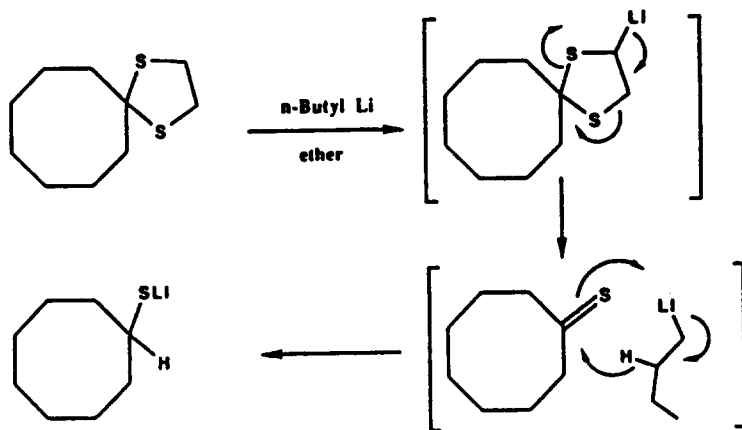
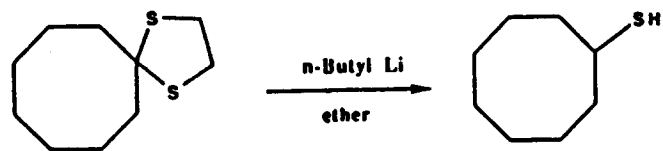
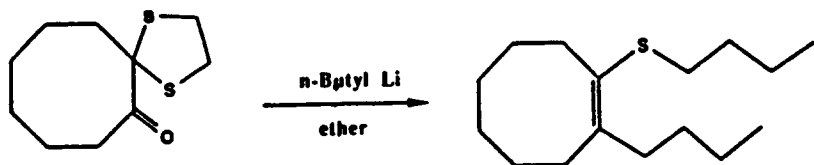
R. B. Silverman, *J. Am. Chem. Soc.*, 109, 2219 (1987)



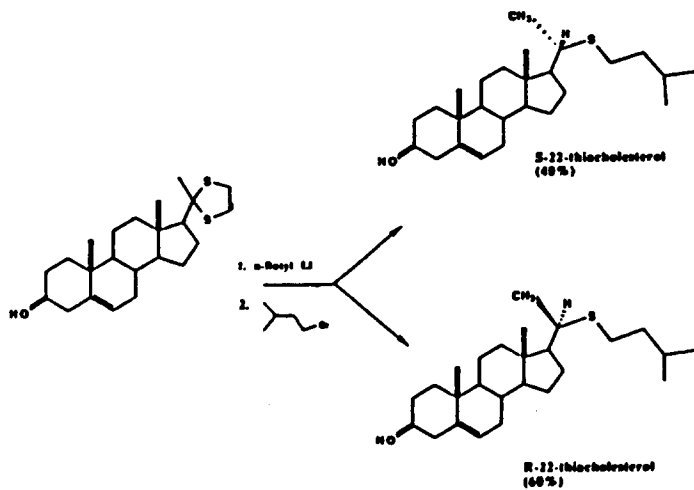
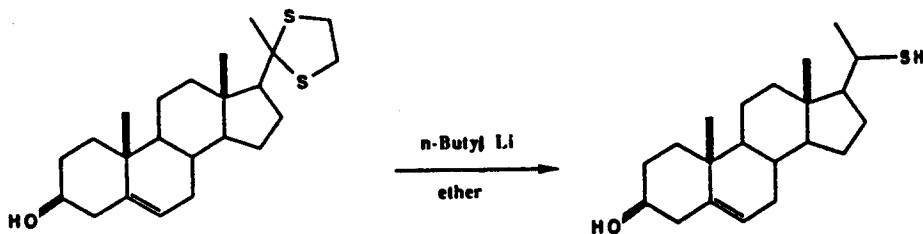
C. G. Pitt et al., *Tetrahedron*, 31, 2369 (1975)

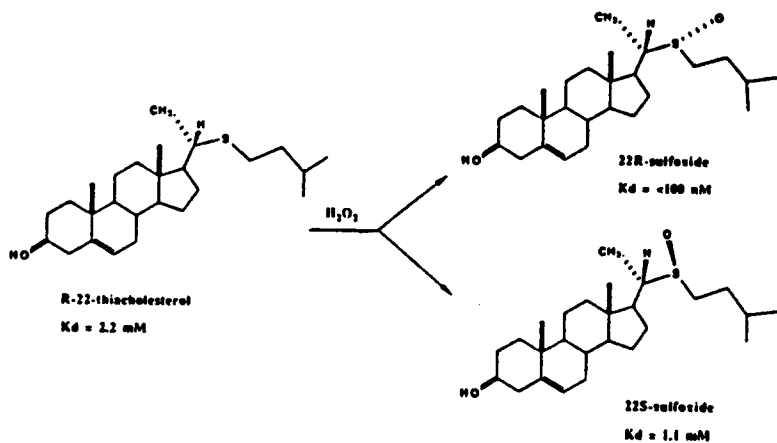
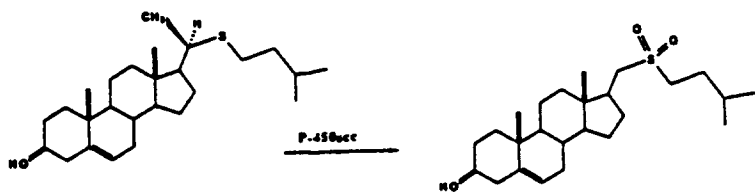
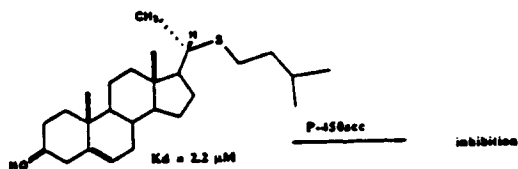


R. R. Le Vier et al., *Toxicol. Appl. Pharm.*, 21, 80 (1972)

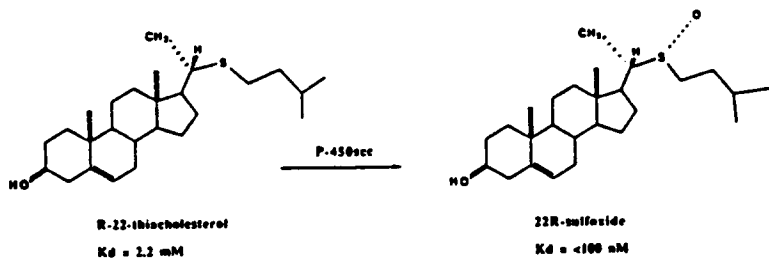


Wilson et. al., *J. Am Chem. Soc.*, 102, 3577 (1980)
 Wilson et. al., *Organic Synthesis*, 61, 74 (1983)





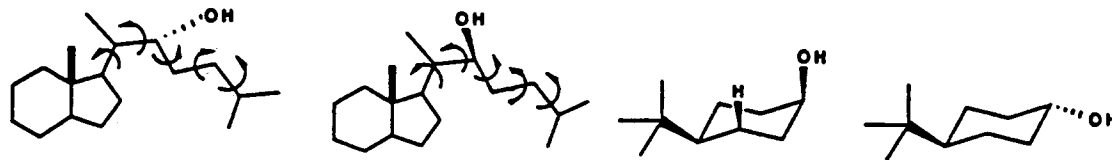
In situ formation of very tight binding inhibitor



Eu+3 shift reagent study



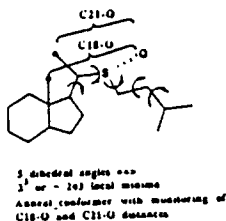
ϕ dihedral angles \Rightarrow
 3° or -243 local minima



ψ dihedral angles \Rightarrow
 3° or -243 local minima

NMR shift reagent study was confounded
 by the flexible nature of the steroid
 chains.....
 Modeling using simulated annealing

Modeling using simulated annealing



22S-sulfoxide conf #1
MM2 energy = 137.17 Kjou/mol



22S-sulfoxide conf #2
MM2 energy = 138.33 Kjou/mol

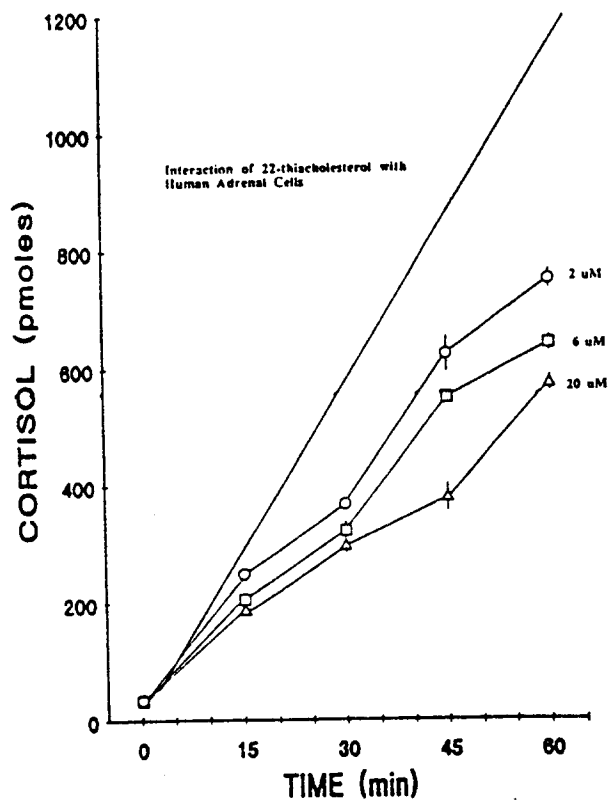
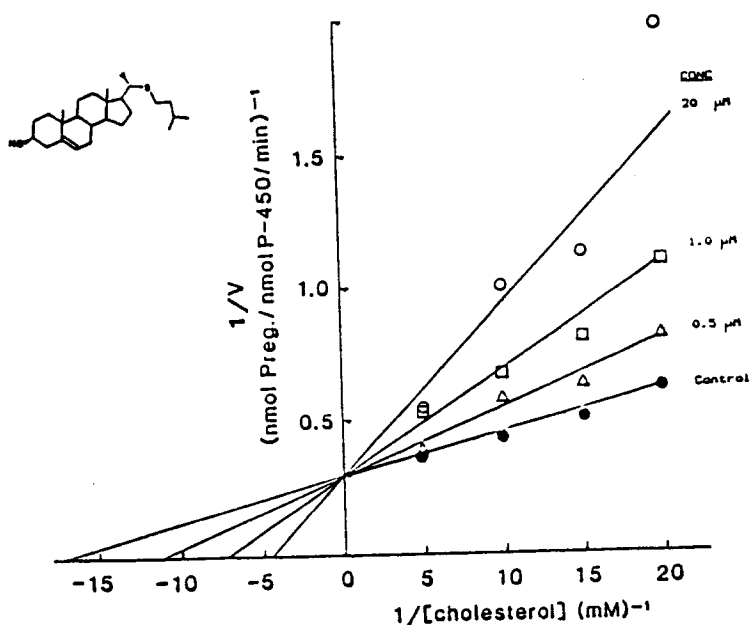


22R-sulfoxide
MM2 energy = 136.38 Kjou/mol

Table I: Distances from the sulfoxide O to Structure C18 C21

Structure	C18	C21
22R-sulfoxide conf #1	5.5703	3.2711
22S-sulfoxide conf #1	5.6389	3.1348
22S-sulfoxide conf #2	5.1650	4.0440
22R-hydroxy	5.2712	3.0110
22S-hydroxy	5.3809	2.9908

Simulated annealing with 250 Monte Carlo steps at 30 different temperatures leads to energy and geometry convergence. The C18-O and the C21-O distance were monitored during the process. Results in table I indicate that because of a major change in the conformation of the R and S isomers, only a small difference in distances in the lowest energy conformations result. The second lowest energy conformer of the 22S-sulfoxide is distinctly different and has a much longer C21 - O distance, consistent with the Eu+3 shift data.



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