Registry No. 1, 85956-82-7; 2, 85956-83-8; 3, 85956-84-9; 4, 85956-85-0; 5, 85956-86-1; 7, 85956-77-0; 9, 85956-87-2; 10, 85956-79-2; 12, 85956-81-6; 15 (epimer 1), 85956-88-3; 15 (epimer 2), 85944-22-5; 16 (epimer 1), 85994-23-6; 16 (epimer 2), 85994-24-7; 19, 85956-89-4; 20, 85994-25-8; 23, 85956-90-7; 24a, 85956-91-8; 24b, 85994-26-9; 25a, 85956-92-9; 25b, 85994-27-0; 26, 85956-93-0; 27, 85956-94-1; MeBr, 74-83-9; *t*-BuBr, 507-19-7; PhBr, 108-86-1; (+)-camphenylallene, 38996-68-8; 4-(3-oxo-1-cyclohexenyl)butanol, 78877-14-2; 4-(3-oxo-1-cyclohexenyl)butyl acetate, 85956-95-2; 4-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)butyl acetate, 85956-96-3; 4-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)butanol, 85956-97-4; 4-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)butanal, 85956-98-5; lithium acetylide, 1111-64-4; 6-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)-1-hexyn-3-ol, 85956-99-6; 3-methyl-1,2-butadiene, 598-25-4.

Regiospecific Homologation of Unsymmetrical Ketones[1-3]

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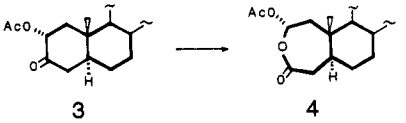
Received December 28, 1982

A method has been developed for the regiospecific homologation of unhindered unsymmetrical ketones. The procedure consists of preparation of a pure α-halo ketone, reaction of this derivative with ethyl diazoacetate and boron trifluoride etherate, removal of the halogen by zinc reduction, and finally decarbethoxylation with water at 230 °C or with $CaCl_2 \cdot 2H_2O$ in dimethyl sulfoxide at 150 °C. The method depends on the electron-withdrawing power of the α-halogen to prevent the migration of the attached carbon. *A*-Homo steroid ketones are most conveniently prepared by this method. The reaction of α-acetoxy ketones with ethyl diazoacetate also leads mainly to migration of the unsubstituted α'-carbon atom.

Although the regiospecific homologation of ketones is a potentially valuable synthetic operation, there is no convenient general method for achieving this transformation. Homologation of ketones by diazoalkanes,[4-6] diazoacetic esters,[7,8] or the Tiffeneau–Demjanov reaction[9] proceeds in good yields, but with unsymmetrical ketones these reactions usually give both regioisomers.[4-6,8-13] Some more recently developed procedures also suffer from the disadvantage of giving two isomeric homo products.[14] Even for unsymmetrical ketones which happen to give a single homo product, it might be desirable to prepare the other isomer. Therefore, we have devised a simple method for regiospecific homologation which is applicable to unhindered cyclic and noncyclic ketones.

The stumbling block in the homologation reactions mentioned above is the closely matched migratory aptitudes of the α- and α'-carbon atoms of the ketones. If the migratory tendencies could be further differentiated by the introduction of an α-substituent that could be removed later, a way would be opened to overcome the migratory problem. Recent observations along these lines were encouraging. Thus, while the Baeyer–Villiger oxidation of 5α- and 5β-cholestan-3-one gave nearly equimolar mixtures of both *A*-homo lactones,[10] the oxidation of several α-bromo- and α-chlorocholestan-3-ones, although slower, gave a single α-halo lactone from each reaction, e.g., **1** → **2**.[15,16] Apparently, the electron-withdrawing effect of the α-halogen completely suppressed the migration of the carbon bearing it. In complementary fashion, it was noted that Baeyer–Villiger oxidation of 2α- and 2β-acetoxy-5α-cholestan-3-one also afforded a single product each, but in these cases only the α-acyloxy-bearing carbon atom migrated to oxygen, e.g., **3** → **4**.[17] The cation-stabilizing effect of the unshared oxygen electrons had increased the relative migratory aptitude of the attached carbon.[18]

1 X = Br, Cl **2**



3 **4**

(1) This work is respectfully dedicated to Professor William S. Johnson on the occasion of his 70th birthday.

(2) α-Halo Ketones. 10. For part 9, see E. W. Warnhoff and F. W. Yerhoff, *Heterocycles*, **15**, 777 (1981).

(3) Presented in part at the 64th Canadian Chemical Conference, Halifax, Nova Scotia, June 3, 1981.

(4) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions", Academic Press, New York, 1968, Chapter 4.

(5) J. S. Pizey, "Synthetic Reagents", Ellis Horwood Ltd., Chichester, U.K., 1974, Vol. 2, pp 102–108.

(6) H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Am. Chem. Soc.*, **82**, 4099 (1960).

(7) W. T. Tai and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964).

(8) W. L. Mock and M. E. Hartman, *J. Org. Chem.*, **42**, 459 (1977).

(9) P. A. S. Smith and D. R. Baer, *Org. React.*, **11**, 157 (1960).

(10) V. Dave, J. B. Stothers, and E. W. Warnhoff, *Can. J. Chem.*, **57**, 1557 (1979).

(11) J. Levisalles, G. Teutsch, and I. Tkatchenko, *Bull. Soc. Chim. Fr.*, 3194 (1969).

(12) J. B. Jones and P. Price, *Tetrahedron*, **29**, 1941 (1973).

(13) H. J. Liu and S. P. Majumdar, *Synth. Commun.*, **5**, 125 (1975).

(14) (a) T. Cohen, D. Kuhn, and J. R. Falck, *J. Am. Chem. Soc.*, **97**, 4749 (1975); (b) S. Knapp, A. F. Trope, and R. M. Ornaf, *Tetrahedron Lett.*, 4301 (1980); (c) H. Takaguchi, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **96**, 6510 (1974); (d) Y. M. Saunier, R. Danion-Bougot, D. Danion, and R. Carrié, *J. Chem. Res. Synop.*, 436 (1978); (e) K. Ogura, M. Yamashita, and G. Tsuchihashi, 177th National Meeting of the American Chemical Society, Honolulu, 1979, ORGN 459; (f) P. J. Calabretta, *Int. Congr. Essent. Oils [Pap.]*, 6th 131 (1974); *Chem. Abstr.*, **84**, 121242y (1976); (g) N. Hashimoto, T. Aoyama, and T. Shioiri, *Tetrahedron Lett.*, **21**, 4619 (1980); (h) Y. Hoyano, V. Patel, and J. B. Stothers, *Can. J. Chem.*, **58**, 2730 (1980); (i) J. Villieras, P. Perriot, and J. F. Normant, *Synthesis*, 968 (1979); (j) H. Taguchi, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, 2617 (1976); (k) K. Nagao, M. Chiba, and S. W. Kim, *Synthesis*, 197 (1983).

(15) J. E. Bolliger and J. L. Courtney, *Aust. J. Chem.*, 17, 440 (1964).

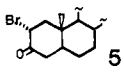
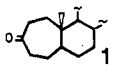
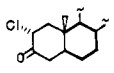
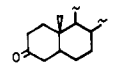
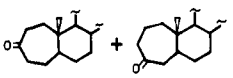
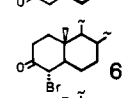
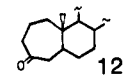
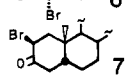
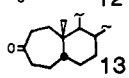
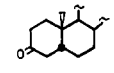
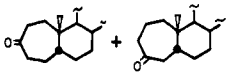
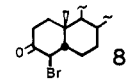
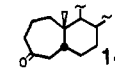
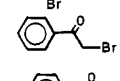
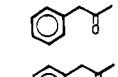
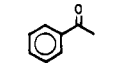
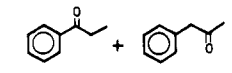
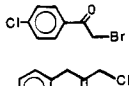
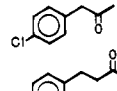
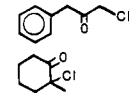
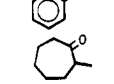
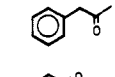
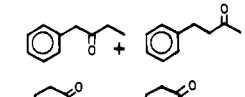
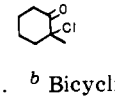
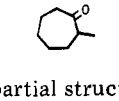
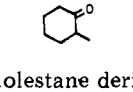
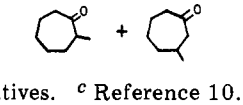
(16) V. Dave, J. B. Stothers, and E. W. Warnhoff, *Can. J. Chem.*, **58**, 2666 (1980).

(17) D. Bijelic, M. J. Gašić, and Z. Darmati, *Glas. Hem. Drus. Beograd*, **44**, 393 (1979).

(18) The acetoxy group is overall electron donating toward a cationic center with a σ_p^+ of −0.08 and σ_R^+ of −0.48. D. Calvert, P. B. D. De La Mare, and N. S. Isaacs, *J. Chem. Res. Synop.*, 156 (1978).

0022-3263/83/1948-2590$01.50/0

Table I. Products of EDA Homologations

reactant[a,b]	product[a,b]	yield, %[a]	reactant[b]	products[b]	product ratio	total yield, %
 5	 11	75				
	"	57			46:54[c]	83[c]
 6	 12	63				
 7	 13	68			47:53[c]	92[c]
 8	 14	62				
		98			90:10[d]	78[d]
		61				
		69			62:38[d]	96[d]
		67			85:15[d]	96[d]

[a] Present work. [b] Bicyclic partial structures are cholestane derivatives. [c] Reference 10. [d] Reference 8.

Since these directing effects of the α-substituent would carry over to other 1,2-shift reactions, it seemed worth testing whether the reaction of a diazo compound with α-halo and α-acetoxy ketones would permit regiospecific homologation. If so, the problem of competitive migrating abilities could be reduced to the simpler task of preparing pure α- (or α′-) substituted ketones. Fortunately, for one reason or another, with most unsymmetrical ketones there is sufficient selectivity in the α- vs. α′-enolization, either in a kinetically controlled or in an equilibrium-controlled situation, that a pure α- (or α′-) substituted derivative is readily prepared. Since both halogenation and acetoxylation with $Pb(OAc)_4$ proceed via the enol, both possible homologation products might be obtainable from selective enolization of a ketone in either direction.

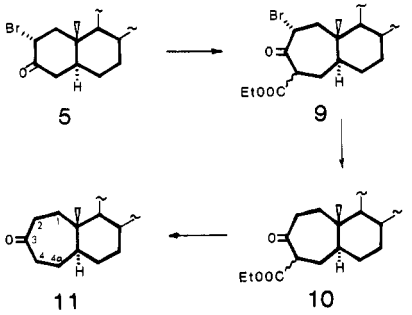
The only pertinent examples known to us were promising. The reaction of 2-chlorocyclohexanone with diazomethane had originally been thought to give both 2- and 3-chlorocycloheptanone together with chloro epoxide,[19] but reexamination showed only 2-chlorocycloheptanone and the chloro epoxide.[20] More recently, the reaction of diazoacetic ester/triethyloxonium tetrafluoroborate with 2-chlorocyclohexanone was presumed to give 7-chloro-2-carbethoxycycloheptanone as at least 98% of the product isolated because its basic treatment afforded *trans*-1,2-cyclohexanedicarboxylic acid.[8] Finally, the ring expansion of several 2,2-dichlorocyclobutanones with diazomethane gave 2,2-dichlorocyclopentanones.[21]

Therefore, we have examined the reaction of diazo compounds with some α-bromo, α-chloro, and α-acetoxy ketones. Initial studies were done with ethyl diazoacetate (EDA) because with simple ketones it has been found to give clean monohomologation[7,8,10,22-24] and rarely any epoxide.[7,8,13,22] Furthermore, unlike diazoalkanes, ethyl diazoacetate is stable for the longer reaction periods required for the Lewis acid catalyzed reaction of the less basic α-substituted ketones. However, the greater stability of the diazo ester is also accompanied by lesser inherent reactivity and a greater steric requirement relative to a diazoalkane such as diazomethane.

In practice, the reactions were slow but clean. The first compounds tested were the four α-bromocholestan-3-ones **5–8** whose two parent unhalogenated ketones **5** and **7** (H instead of Br) were known to give 1:1 ratios of both possible *A*-homo ketones with EDA–$Et_3O^+BF_4^-$.[10] Treatment of **5–8** with 4 equiv of both EDA and $BF_3{\cdot}Et_2O$ (apparently optimum for reasonable reaction time) in CH_2Cl_2 at reflux gave complete reaction within 1–2 days.[25] It was clear from the continued presence of the BrCHC=O signal in the ^1H NMR spectra of the products that the unbrominated carbon had migrated, e.g., **5** → **9**. Reductive removal of the α-bromo substituent was accomplished by the standard treatment with Zn–HOAc at room temperature. The resulting β-keto esters, e.g., **10**, were then hydrolyzed and decarboxylated by Mock and Hartman's method of heating with water in a sealed tube at 230 °C.[8] For the 2α-bromo 5α-3-ketone **5** the intermediate bromo keto ester **9** and keto ester **10** were purified and characterized. For the other three bromo ketones **6–8**, as well as **5**, the three-reaction sequence was carried out without complete purification of intermediates to yield the *A*-homo ketones **11–14** in 62–75% *overall* yields after chromatography (Table I). The homologation of 2α-chloro-5α-cholestan-3-one (**1**, X = Cl) was more sluggish but gave about the same overall yield.

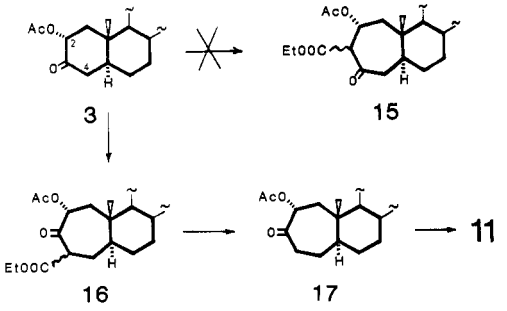
The purity of the *A*-homo ketones was assessed from their ^{13}C NMR spectra.[10,26] For **11** and **13** no trace (<~

(19) C. D. Gutsche, *J. Am. Chem. Soc.*, **71**, 3513 (1949).
(20) Reference 4, p 88, footnote 271a. Also, J. Jacques and A. Bruylants, *Bull. Cl. Sci., Acad. R. Belg.*, **54**, 1015 (1968); *Chem. Abstr.*, **71**, 70164*W* (1969).
(21) (a) A. E. Greene and J. P. Deprês, *J. Am. Chem. Soc.*, **101**, 4003 (1979); (b) J. P. Deprês and A. E. Greene, *J. Org. Chem.*, **45**, 2036 (1980). See also more recently (c) A. E. Greene, M. J. Luche, and J. P. Deprês, *J. Am. Chem. Soc.*, **105**, 2435 (1983); (d) G. Mehta and M. S. Nair, *J. Chem. Soc., Chem. Commun.*, 439 (1983).
(22) V. Dave and E. W. Warnhoff, *J. Org. Chem.*, **43**, 4622 (1978).
(23) In the reactions catalyzed by $BF_3{\cdot}Et_2O$, monohomologation may result from complexation of the enolized β-keto ester by BF_3 as has been observed for α-hydroxymethylene ketones.[24] The enol complex would be more resistant to reaction with diazoacetic ester.
(24) R. A. J. Smith and T. A. Spencer, *J. Org. Chem.*, **35**, 3220 (1970).
(25) For these homologations we found $BF_3{\cdot}Et_2O$ to be more convenient than Et_3O^+ BF_4^- and equal or superior for product yield, although the latter catalyst gave faster reaction.

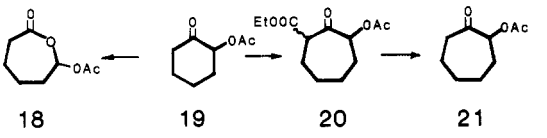


1%) of the contaminating isomeric *A*-homo ketones (**12** and **14**) could be detected. However, **12** and **14** were contaminated by ~5–8% of the corresponding isomeric *A*-homo ketone (**11** and **13**, respectively). These small amounts of impurity arose from traces of the isomeric bromo ketone (**5** and **7**) present in the starting materials **6** and **8**, and not from migration of the brominated carbon in **6** or **8** (see the Experimental Section). In the case of **12** the contaminant was readily removed by recrystallization. Thus, high regiospecific purity of the homologated ketone depends on the starting material being free of both unhalogenated ketone and the other α-halo ketone isomer, but given a pure starting α-halo ketone, the convenient three-step procedure and the good overall yields make this the preferred method of preparation of pure *A*-homo steroid ketones. If the sequence is interrupted after the debromination reaction, the method also serves for the preparation of regiochemically pure homo β-keto esters.

After finding that the four test bromo ketones **5–8** only allowed migration of the unhalogenated α-methylene group, we examined the behavior of α-acyloxy ketones. The original hope had been that the homologation of α-acetoxy ketones would complement the α-halo ketone reactions by leading to migration of the oxygenated carbon (**3** → **15**) in accord with the earlier quoted Baeyer–Villiger precedent.[17] Elimination, reduction, and decarbethoxylation would then be expected to give the other homologated ketone. In fact, we repeated the Baeyer–Villiger oxidation of **3** with *m*-chloroperbenzoic acid and found that the crude product did consist almost entirely of **4** as previously reported.[17] However, although the reaction of 2α-acetoxy-5α-cholestan-3-one (**3**) with EDA–BF_3·Et_2O was faster than the α-halo ketone reactions, it led mainly to migration of the unsubstituted C-4 to produce **16**. This result was evident from the multiplet at δ 5.25 due to the AcOCHC=O proton in the ^1H NMR spectrum. Confirmation that the product was **16** was provided by decarbethoxylation to **17** followed by Li/NH_3 reduction to *A*-homo-5α-cholestan-3-one (**11**; see the Experimental Section).

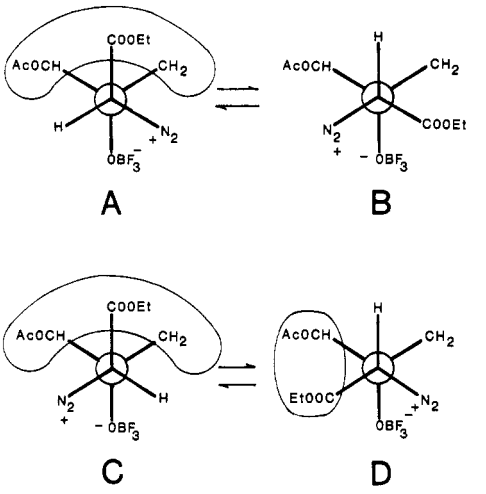


To find whether this result was general, the EDA–BF_3·Et_2O homologation of 2-acetoxycyclohexanone (**19**) was carried out. Again the unsubstituted carbon C-6 migrated (exclusively) to give homo keto diester **20** which was cleanly decarbethoxylated by $CaCl_2$·$2H_2O$–Me_2SO[27] to pure 2-acetoxycycloheptanone (**21**) identical with a sample prepared by lead tetraacetate oxidation of cycloheptanone. On the other hand, Baeyer–Villiger oxidation of 2-acetoxycyclohexanone proceeded with exclusive migration of the acetoxy-substituted carbon to afford lactone **18**. Thus **19** had behaved in the same manner as **3**.



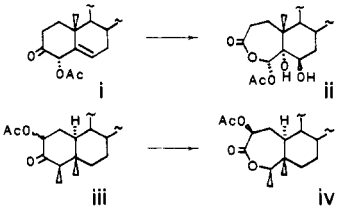
Since Baeyer–Villiger oxidation of both 2-acetoxy ketones **3** and **19** had occurred with migration of C-2, in the EDA–BF_3·Et_2O homologation reactions the *electronic* effect of the acetoxy group would have favored migration of C-2 also.[18] Therefore, in the homologation reactions the electronic effect must have been overridden by steric factors, and the observed migration of the unsubstituted carbon in **3** and **19** probably has the same cause that leads to preferential migration of the less alkyl substituted α-carbon (instead of the electronically favored more alkyl substituted α-carbon) in EDA reactions with simple ketones.[13,28–31]

The rationalization proposed[28,32] for this outcome considers the relative energies of conformations available for anti migration in the diastereomeric EDA addition products. These conformations also keep the oppositely charged groups as close to each other as possible. Of the conformers A–D from attack of EDA on the β-face of the



(26) V. Dave and J. B. Stothers, *Can. J. Chem.*, **57**, 1550 (1979).

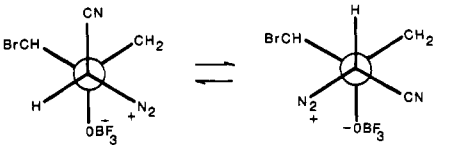
(27) Y. Tsuda and Y. Sakai, *Synthesis*, 119 (1981).
(28) W. L. Mock and M. E. Hartman, *J. Org. Chem.*, **42**, 466 (1977).
(29) H. J. Liu and T. Ogino, *Tetrahedron Lett.*, 4937 (1973).
(30) Even with Baeyer–Villiger reactions of α-acetoxy ketones, migratory tendencies are finely balanced. Thus, while the product of peracid treatment of **i** is the expected **ii**,[31] the product of peroxidation of **iii** is **iv**.[15]

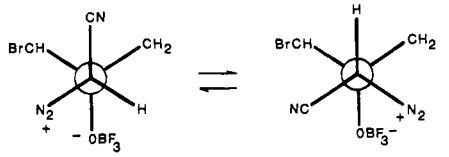


(31) M. S. Ahmad, M. Asif, and M. Mushfiq, *Indian J. Chem., Sect. B*, **16**, 426 (1978).
(32) H. J. Liu, University of Alberta, personal communication, 1974.

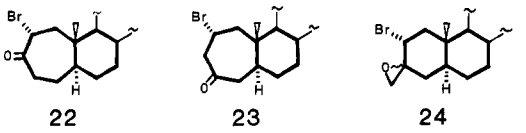
carbonyl group,[33] A and C are the least stable because three bulky groups (encircled) are adjacent. Conformer D having the two bulkiest groups (COOEt and CHOAc) contiguous will be of somewhat higher energy than B which has COOEt abutting only on CH_2. Provided that the transition state for anti migration reflects the energy differences of conformers A–D, then the lowest energy path will have the less substituted CH_2 group of B migrate as N_2 leaves to produce **16**.[34]

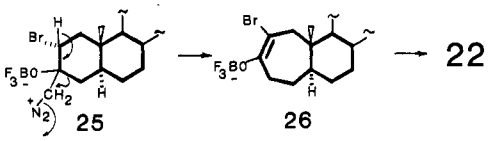
With α-halo ketones this steric effect would operate to reinforce the selectivity expected from the electron-withdrawing nature of the halogen. Therefore, it must be considered whether the effect of halogen itself could be solely steric and not electronic. This possibility was proved not to be the case by two experiments. First, the 2α-bromo 5α-3-ketone **5** was homologated by diazoacetonitrile in which the cyano and diazo groups have the same size and shape, thus making the lower energy conformers F and H essentially identical in energy. If the effect of bromine were only steric, then a mixture of both possible homologation products would be expected. Instead, reductive removal of bromide and hydrolytic removal of the nitrile gave pure *A*-homo-5α-cholestan-3-one (**11**).





Secondly, it was found that **5** could be monohomologated with CH_2N_2–BF_3·Et_2O. Others have noted[6] that the major product from the action of CH_2N_2 on a ketone is often the epoxide. In the case of bromo ketone **5**, without the Lewis acid the major product was epoxide **24**. However, with CH_2N_2–BF_3·Et_2O mono homo ketone was formed.[35,36] The absence of polyhomologation was not caused by sequestration of the product as an enol derivative, e.g., **25** → **26**, because quenching of the reaction with D_2O gave no D incorporation into the homo ketone. In fact, a control experiment showed that the homo bromo ketone was merely unreactive under the homologation conditions. In the CH_2N_2 ring expansion of **5**, there are only two conformers E and F (H for CN) of the β-face adduct to be considered,[37] and a mixture of **22** and **23** would be expected as the product if the effect of bromine were solely steric. However, the product was only **22** since reductive removal of bromide gave pure *A*-homo 3-ketone **11**. Therefore, in both of these reactions it is clearly the *electronic* effect of the 2α-bromine that has completely prevented the migration of C-2.





Even though an α-acetoxy group controls migration in the same sense as α-halogen in ketone reactions with diazo compounds, albeit for different reasons, the basic idea of substituent-controlled regiospecific homologation is still feasible so long as both α- and α'-halo ketones can be prepared, as illustrated by examples **5**–**8**. For those ketones which give different kinetically and thermodynamically controlled enolates, the preparation of both halogenated ketones presents no problem. If only a single enol(ate) is attainable, it is possible to prepare the halo ketone not directly accessible from the enol(ate) by first making the α,α-dihalo ketone, then rearranging it to the α,α'-dihalide,[38] and removing reductively the remaining α-halogen to produce the α'-halo ketone.

A more serious problem is the steric limitation on EDA reactions with ketones. It has been noted previously that hindered ketones such as camphor[13] and methyl *tert*-butyl ketone[8] are sluggish in their catalyzed reactions with EDA, and that 2,2,6-trimethylcyclohexanone[13] did not react under the usual conditions. Therefore, a number of halogenated derivatives of ketones, whose reaction with EDA had been examined,[8] were subjected to the homologation conditions. For those which underwent homologation the regioselectivity was complete, whereas the parent nonhalo ketone gave both isomeric homologation products (see Table I). The overall yields for the three-step sequence are again fair to good.

However, α-bromopropiophenone, α-bromobutyrophenone, α-bromoisobutyrophenone, 4-bromo- (and 4-chloro) menthone, 3-*endo*-bromocamphor, and 3-*exo*-bromonorbornan-2-one were not homologated during extended periods under the usual conditions. The failure of 3-*exo*-bromonorbornanone to react is rather surprising since norbornanone reacts readily;[28] presumably the steric effect of bromine and its carbonyl base-weakening effect combined to decrease the reactivity of bromonorbornanone drastically. Escalation of the reaction conditions by raising the temperature from that of boiling CH_2Cl_2 (~40 °C) to 80 °C (sealed tube) gave dark-colored products from these halo ketones but no appreciable homologation (<5%). Nor did the change to more powerful Lewis acid catalysts such as $Et_3O^+BF_4^-$, $AlCl_3$, $SbCl_5$, or SbF_5 produce homologation with these unreactive halo ketones.

(33) Another equivalent set of four conformers would arise by attack at the carbonyl α-face. The argument presented holds equally well for this second set.

(34) An attempt was made to test this explanation by homologation with CH_2N_2 to determine whether the product ratio **16**/**15** (H for COOEt) would change. The experiment was not pursued further when it was found that mono-, di-, tri-, and tetrahomologation had occurred.

(35) There is no reason to think that **17** is formed by BF_3-catalyzed opening of an epoxide; the methylene epoxide **24** should open to give different products.

(36) In contrast, A. J. C. van Seters, M. Buza, A. J. H. Klunder, and B. Zwanenburg [*Tetrahedron*, **37**, 1027 (1981)] have recently found that an α-bromohomocubanone was regiospecifically homologated by ethereal CH_2N_2. The addition of BF_3·Et_2O had no effect.

(37) Another equivalent pair of conformers would arise by attack at the carbonyl α-face.

(38) E. W. Warnhoff, M. Rampersad, P. Sundara Raman, and F. W. Yerhoff, *Tetrahedron Lett.*, 1659 (1978).

In another effort to circumvent the steric impasse, the spatial requirement of the diazo component was decreased by the substitution of diazoacetonitrile at room temperature for EDA. Although N_2CHCN worked well with the unhindered 2α-bromo ketone **5** as mentioned earlier, it failed to give homologation with α-bromoacetophenone, α-bromoisobutyrophenone, and 3-bromonorbornanone. 2-Bromocamphor gave the cyanomethyl enol ether of camphor. Hence N_2CHCN appeared to be less satisfactory than EDA. A further decrease in the size of the diazo compound to diazomethane, the smallest possible reactant, was tested because it had unexpectedly given clean monohomologation of **5** in the presence of $BF_3{\cdot}Et_2O$ in spite of its usual tendency toward multiple homologation. However, with CH_2N_2–$BF_3{\cdot}Et_2O$ under conditions suitable for **5**, such compounds as α-bromoacetophenone, α-bromo-*p*-chloroacetophenone, and 3-*exo*-bromonorbornanone gave no homologation. Thus although $BF_3{\cdot}Et_2O$ catalyzes diazo additions to α-halo ketones, it speeds up the polymerization of diazomethane to an even greater extent.[6] Without Lewis acid, CH_2N_2–MeOH did react with these halo ketones, but it gave mixtures from multiple homologation. Preliminary experiments with the more nucleophilic anions of EDA[39] and diazomethane[40] were also unpromising. It appears that extension of regiospecific homologation by diazo compounds to more hindered α-halo ketones must await new developments.

Experimental Section

General Procedures. Melting points were determined on a Reichert-Kofler microscope hotstage and are corrected. IR spectra were recorded on a Beckman Acculab 4 instrument with $CHCl_3$ solutions. The ^1H NMR spectra were recorded on Varian T-60 and XL-100 spectrometers with $CDCl_3$ solutions containing Me_4Si; only relevant peaks from spectra are given. The ^{13}C NMR spectra were run with $CDCl_3$ solutions on a Varian XL-100 or XL-200 instrument. Abbreviations in descriptions of proton spectra are the following: br = broad, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, and m = multiplet. Exact masses were determined on a MAT 311A mass spectrometer. Optical rotations were determined with $CHCl_3$ solutions on a Rudolph Model 80 polarimeter.

Camag DF-5 silica gel was used for thick- and thin-layer chromatography. Unless otherwise specified, preparative plates were 20 × 20 cm and contained 20 g of silica gel. Reactions were worked up by partitioning between water and ether or CH_2Cl_2. The organic solution was washed to neutrality ($NaHCO_3$ solution and saturated aqueous NaCl solution) and dried with anhydrous $MgSO_4$ before being evaporated at aspirator vacuum on a rotating evaporator.

Ethyl diazoacetate was prepared by the diazotization of ethyl glycinate.[41] Commercial $BF_3{\cdot}Et_2O$ was redistilled. CH_2Cl_2 was dried over 3-Å molecular sieves and contained no more than 5 μg of H_2O/mL.

***A*-Homo-5α-cholestan-3-one (11). (a) From Bromo Ketone.** To a solution of 250 mg (0.54 mmol) of 2α-bromo-5α-cholestan-3-one (**5**),[42] which had been chromatographed on silica gel to remove residual 5α-cholestan-3-one, in 2 mL of CH_2Cl_2 at 5 °C was added a solution of 310 mg (2.2 mmol) of redistilled $BF_3{\cdot}Et_2O$ in 2 mL of CH_2Cl_2 followed by a solution of 250 mg (2.2 mmol) of EDA in 2 mL of CH_2Cl_2. The reaction mixture was then refluxed for 2 days, cooled, stirred with water for 0.5 h, and then extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, dried, and concentrated to leave the ***A*-homo-2α-bromo keto ester 9** as a brown oily solid.

[A specimen of **9** from another reaction was purified by thick-layer chromatography to give a colorless oil, single TLC spot (R_f 0.56 in benzene); IR 1742 (ester C=O), 1720 cm^{-1} (ketone C=O); ^1H NMR δ 1.37 (t, CH_3CH_2O), 4.01 (dd, 1 H, O=CCHC=O), 4.22 (q, 2 H, OCH_2CH_3), 4.43 (dd, 1 H, BrCHC=O); molecular ion calcd for $C_{31}H_{51}O_3{}^{79}Br$ 550.3021, found 550.3022.]

The crude bromo keto ester **9** was dissolved in 25 mL of ether containing 2.5 mL of HOAc and stirred at room temperature with 1.25 g of Zn dust. After 1 h when the reduction was complete (TLC showed a single, more polar spot), the reaction mixture was filtered through sintered glass. The filtrate was washed with water, dried, concentrated, and chromatographed on a 20-g silica gel plate developed in benzene–ether (96:4). The band at R_f 0.64 yielded 200 mg of ***A*-homo-4ξ-carbethoxy-5α-cholestan-3-one (10)** as an oily solid.

[A specimen of **10** from another reaction was purified by thick-layer chromatography to give a colorless oil, single TLC spot (R_f 0.66 in benzene–ether, 95:5); IR 1735 (ester C=O), 1700 cm^{-1} (ketone C=O); ^1H NMR δ 1.25 (t, CH_3CH_2O), 3.51 (dd, J = 0.8 Hz, O=CCHC=O), 4.17 (q, 2 H, OCH_2CH_3); molecular ion calcd for $C_{31}H_{52}O_3$ 472.3916, found 472.3917 (base peak).]

The keto ester **10** was heated with 0.5 mL of distilled water in a sealed glass tube at 230 °C for 2.5 h. The 185 mg of ether-soluble material from the opened tube was chromatographed on a 20-g plate of silica gel developed in benzene–ether (96:4). Extraction of the band at R_f 0.46 gave 163 mg (75% overall from **5**) of crystalline ***A*-homo 5α-3-ketone 11**. Two recrystallizations from MeOH gave 110 mg of colorless granules: mp 81.5–83.5 °C (lit.[43] mp 82–83 °C); IR 1690 cm^{-1} (ketone C=O); ^{13}C NMR 28 peaks only, identical with the reported spectrum.[26] There was no detectable peak from the isomeric *A*-homo 5α-4-ketone **12** (<1%). Molecular ion calcd for $C_{28}H_{48}O$, 400.3705; found, 400.3705.

(b) From Chloro Ketone. To a solution of 100 mg (0.24 mmol) of pure 2α-chloro-5α-cholestan-3-one (**1**, X = Cl)[44] in 1 mL of CH_2Cl_2 at 5 °C was added a solution of 136 mg (0.96 mmol) of $BF_3{\cdot}Et_2O$ in 1 mL of CH_2Cl_2 followed by a solution of 110 mg (0.96 mmol) of EDA in 1 mL of CH_2Cl_2. The reaction mixture was then refluxed for 7 days and worked up as described in (a) to give viscous brown oily **9** (Cl for Br).

To a stirred (magnetic bar) solution of chloro keto ester in 7 mL of ether containing 0.5 mL of HOAc was added 500 mg of Zn dust. After 3.5 h when the reduction was complete (TLC showed a single, more polar spot), the mixture was filtered and concentrated. The residual brown oil was chromatographed on a column of 650 mg of silica gel. Elution with 40 mL of ether and evaporation of the eluate left pale yellow oily **10**.

The keto ester **10** was heated with 0.3 mL of distilled water at 230 °C in a sealed glass tube for 4 h. The 84 mg (87% crude yield from **1**, X = Cl) of ether-soluble hydrolysate was chromatographed on a 10-g plate developed in benzene–ether (96:4). Extraction of the band at R_f 0.44 gave 55 mg (57% overall) of ***A*-homo-5α-cholestan-3-one (11)** as a colorless crystalline solid.

4α-Bromo-5α-cholestan-3-one (6). This bromo ketone was prepared by the selective reduction of 250 mg (0.46 mmol) of 2α,4α-dibromo-5α-cholestan-3-one[45] with 117 mg (0.45 mmol) of Ph_3P in 3.5 mL of benzene plus 1 mL of MeOH at 8 °C for 0.5 h (method of Borowitz and Grossman[46]). Workup and preparative TLC afforded 123 mg (57%) of crystalline **4α-bromo 5α-3-ketone 6**, which after two recrystallizations from ether–MeOH gave colorless needles: mp 143–145 °C (lit.[47] mp 144–146 °C, lit.[48] mp 146–147.5 to 154.8–155.3 °C); ^1H NMR δ 4.50 (d, J = 11 Hz, 1 H, BrCHC=O). The 26 peaks (all except C=O) of the ^{13}C NMR spectrum were identical with the reported spectrum.[26] In addition

(39) (a) E. Wenkert and C. A. McPherson, *J. Am. Chem. Soc.*, **94**, 8084 (1972); (b) U. Schöllkopf, B. Bânhidal, H. Frasnelli, R. Meyer, and H. Beckhaus, *Justus Liebigs Ann. Chem.*, 1767 (1974).

(40) (a) E. Müller and W. Rundel, *Chem. Ber.*, **90**, 1299 (1957); (b) E. Müller and D. Ludsteck, *ibid.*, **88**, 921 (1955).

(41) N. E. Searle, "Organic Syntheses", Wiley, New York, 1963, Collect. Vol. IV, p 424.

(42) L. F. Fieser and X. A. Dominguez, *J. Am. Chem. Soc.*, **75**, 1704 (1953).

(43) N. A. Nelson and R. N. Schut, *J. Am. Chem. Soc.*, **81**, 6486 (1959).

(44) J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 3500 (1953).

(45) A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1712 (1946).

(46) I. J. Borowitz and L. I. Grossman, *Tetrahedron Lett.*, 471 (1962).

(47) R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker, and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956).

(48) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

there were weak signals in the spectrum indicating up to ~5% contamination with the 2α-bromo 5α-3-ketone **5**.

***A*-Homo-5α-cholestan-4-one (12).** The three-reaction sequence was carried out as for the homologation of the 2α-bromo ketone **5** with 250 mg (0.54 mmol) of 4α-bromo-5α-cholestan-3-one (**6**), 310 mg (2.2 mmol) of redistilled BF_3·Et_2O, 250 mg (2.2 mmol) of EDA, and 6 mL of CH_2Cl_2. The crude bromo keto ester had the following: IR 1730 (ester C=O), 1710 and 1700 cm^{-1} (ketone C=O); ^1H NMR δ 1.28 (t, CH_3CH_2O), 4.03 (d, J = 10 Hz, 1 H, BrCHC=O), 4.07 (dd, O=CCHC=O), 4.23 (q, 2 H, OCH_2CH_3); molecular ion calcd for $C_{31}H_{51}O_3{}^{79}Br$ 550.3021, found 550.3016.

Debromination with 1.25 g of Zn, 2.5 mL of HOAc, and 25 mL of ether followed by chromatography afforded 180 mg of keto ester: IR 1735 (ester C=O), 1700 cm^{-1} (ketone C=O); ^1H NMR δ 1.26 (t, CH_3CH_2O), 3.40 (m, <1 H, O=CCHC=O), 4.16 (q, 2 H, OCH_2CH_3); molecular ion calcd for $C_{31}H_{52}O_3$ 472.3916, found 472.3913 (base peak).

Decarbethoxylation with 0.5 mL of distilled water in a sealed glass tube at 230 °C for 2.5 h followed by chromatography gave 136 mg (63% overall from **6**) of crystalline ***A*-homo 5α-4-ketone 12**, IR 1690 cm^{-1} (ketone C=O). The 27 peaks of the ^{13}C NMR spectrum (all except C=O) were identical with the reported spectrum.[26] In addition weak signals for C-1, C-5, C-6, C-8, and C-9 of the *A*-homo 3-keto isomer **11** were apparent, and these amounted to <5% of contamination. Two recrystallizations from methanol removed the impurity **11** completely (^{13}C spectrum) to yield 94 mg of colorless plates of **12**: mp 94–96 °C (lit.[10] mp 96–97.5 °C); molecular ion calcd for $C_{28}H_{48}O$ 400.3705, found 400.3705. That the impurity arose from either 5α-cholestan-3-one or isomeric bromo ketone **5** in the starting material **6** was shown when the homologation reaction was run on a purer sample of **6** prepared from 5α-cholestane 3α,4α-oxide (HBr followed by CrO_3 oxidation). The *A*-homo 5α-4-ketone **12** produced contained only ~2% of **11** as impurity (^{13}C spectrum).

2β-Bromo-5β-cholestan-3-one (7). This bromo ketone was prepared by the selective reduction of 400 mg (0.74 mmol) of 2β,4β-dibromo-5β-cholestan-3-one[49] with 190 mg (0.73 mmol) of Ph_3P in 6 mL of benzene plus 2 mL of MeOH at 8 °C for 0.5 h.[46] Workup and preparative TLC afforded 210 mg (61%) of crystalline 2β-bromo 5β-3-ketone **7**, which after two recrystallizations from $CHCl_3$–MeOH gave 150 mg of colorless needles of **7**: mp 133–136 °C (lit.[50] mp 138–140 °C); ^1H NMR δ 4.70 (dd, 1 H, BrCHC=O).

***A*-Homo-5β-cholestan-3-one (13).** The three-reaction homologation sequence was carried out as on **5** with 280 mg (0.60 mmol) of 2β-bromo-5β-cholestan-3-one (**7**), 330 mg (2.3 mmol) of redistilled BF_3·Et_2O, 280 mg (2.4 mmol) of EDA, and 6 mL of CH_2Cl_2. The crude bromo keto ester had the following: IR 1740 (ester C=O), 1715 cm^{-1} (ketone C=O); ^1H NMR δ 1.27 (t, CH_3CH_2O), 3.96 (dd, 1 H, O=CCHC=O), 4.21 (q, 2 H, OCH_2CH_3), 4.46 (dd, 1 H, BrCHC=O); molecular ion calcd for $C_{31}H_{51}O_3{}^{79}Br$ 550.3021, found 550.3011.

Debromination with 1.25 g of Zn, 3.0 mL of HOAc, and 25 mL of ether followed by chromatography gave 213 mg of keto ester: IR 1730 (ester C=O), 1700 (ketone C=O), 1640 + 1610 cm^{-1} (enolized β-keto ester); ^1H NMR δ 1.27 (t, CH_3CH_2O), 3.17 (dd, 1 H, O=CCHC=O), 4.21 (q, 2 H, OCH_2CH_3); molecular ion calcd for $C_{31}H_{52}O_3$ 472.3916, found 472.3917 (base peak).

Decarbethoxylation with 0.5 mL of distilled water in a sealed glass tube at 230 °C for 2.5 h followed by chromatography gave 163 mg (68% overall from **7**) of crystalline ***A*-homo 5β-3-ketone 13**, IR 1690 cm^{-1} (ketone C=O). The 26 peaks of the ^{13}C NMR spectrum (all except C=O; the 56.3-ppm peak contained the absorption of two carbon atoms) were identical with the reported spectrum.[26] There was no detectable peak from the isomeric *A*-homo 5β-4-ketone **14** (<1%). Recrystallization from ether–MeOH gave 133 mg of colorless granules: mp 54–55 °C (lit.[10] mp 55.5–56 °C); molecular ion calcd for $C_{28}H_{48}O$ 400.3705, found 400.3701.

***A*-Homo-5β-cholestan-4-one (14).** The three-reaction homologation sequence was carried out as on **5** with 250 mg (0.54 mmol) of 4β-bromo-5β-cholestan-3-one (**8**),[51] 310 mg (2.2 mmol) of redistilled BF_3·Et_2O, 250 mg (2.2 mmol) of EDA, and 5.0 mL of CH_2Cl_2. The crude bromo keto ester had the following: IR 1740 (ester C=O), 1715 cm^{-1} (ketone C=O); ^1H NMR δ 1.28 (t, CH_3CH_2O), 4.21 (m, 1 H, O=CCHC=O), 4.24 (q, 2 H, OCH_2CH_3), 4.61 (d, J = 12 Hz, 1 H, BrCHC=O); molecular ion calcd for $C_{31}H_{51}O_3{}^{79}Br$ 550.3021, found 550.3022.

Debromination with 1.25 g of Zn, 2.5 mL of HOAc, and 25 mL of ether followed by chromatography gave 193 mg of keto ester which was apparently a mixture of α- and β-carbethoxy epimers: IR 1735 (ester C=O), 1700 cm^{-1} (ketone C=O); ^1H NMR δ 1.24 (t, CH_3CH_2O), 1.26 (t, CH_3CH_2O), 3.02 (dd, O=CCHC=O), 3.41 (m, O=CCHC=O), 4.16 (q, OCH_2CH_3), 4.18 (q, OCH_2CH_3); molecular ion calcd for $C_{31}H_{52}O_3$ 472.3916, found 472.3914 (base peak).

Decarbethoxylation with 0.5 mL of distilled water at 230 °C in a sealed glass tube for 2.5 h followed by chromatography gave 135 mg (62% overall from **8**) of crystalline ***A*-homo 5β-4-ketone 14**, IR 1690 cm^{-1} (ketone C=O). The 27 peaks of the ^{13}C NMR spectrum (all except C=O) were identical with the reported spectrum.[26] In addition weak signals for C-1, C-2, C-5, C-6, C-7, C-13, and C-19 of the *A*-homo 5β-3-ketone were apparent, and these amounted to ~8% of contamination (not completely removed by recrystallization). Recrystallization from ether–MeOH gave 118 mg of colorless plates: mp 108–110 °C; $[\alpha]^{22}_D$ +30.8° (*c* 1.17, $CHCl_3$); molecular ion calcd for $C_{28}H_{48}O$ 400.3705, found 400.3705.

Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.07. Found: C, 83.83; H, 12.03.

Reaction of 2α-Bromo-5α-cholestan-3-one (5) with Diazoacetonitrile. Diazoacetonitrile was prepared from 450 mg of CH_2=NCH_2CN trimer by the procedure of McCullough and Manning.[52] The CH_2Cl_2 solution (3 mL) of the diazo compound was added at 0 °C over 20 min to a stirred (magnetic bar) solution of 135 mg (0.29 mmol) of 2α-bromo 5α-3-ketone **5** and 165 mg (1.16 mmol) of freshly distilled BF_3·Et_2O in 2 mL of CH_2Cl_2. A brown solid precipitated. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 4 h. The precipitate dissolved slowly. Then 5 mL of water was added, and stirring was continued for 0.5 h more. Extraction with CH_2Cl_2 gave 143 mg of amber viscous oil. TLC (hexanes–EtOAc, 80:20) examination showed the absence of **5** and the presence of a single more polar compound **bromo keto nitrile 9** (CN for COOEt): IR 2260 (CN), 1730 cm^{-1} (ketone C=O); ^1H NMR δ 3.66 (m, O=CCHCN), 4.33 (dd, BrCHC=O); molecular ion calcd for $C_{29}H_{46}ON^{79}Br$ 503.2763, found 503.2760.

The bromo keto nitrile in 10 mL of ether containing 0.5 mL of HOAc was stirred (magnetic bar) with 500 mg of Zn dust for 2.5 h. Filtration, washing with water, drying, and concentration gave 86 mg of **4ξ-cyano-*A*-homo-5α-cholestan-3-one (10**, CN for COOEt) as a viscous oil which gave a single TLC spot: IR 2250 (CN), 1715 cm^{-1} (ketone C=O); ^1H NMR δ 3.66 (m, O=CCHCN); molecular ion calcd for $C_{29}H_{47}ON$ 425.3658, found 425.3659.

A solution of 80 mg of keto nitrile in 2 mL of HOAc containing 0.2 mL of concentrated aqueous HCl was refluxed for 48 h with the addition of a further 0.2 mL of HCl every 12 h. The hydrolysate was evaporated in a stream of N_2, and the residue was extracted with ether. Preparative TLC of the extract on a 20-g plate developed in hexanes–EtOAc (84:16) gave 39 mg (34% overall from **5**) of colorless crystalline homo ketone whose ^{13}C NMR spectrum (28 peaks) was identical with that of ***A*-homo-5α-cholestan-3-one (11)**. There was no signal from the isomeric homo ketone **12** in the ^{13}C spectrum (<1%).

Reaction of 2α-Bromo-5α-cholestan-3-one (5) with Diazomethane–Boron Trifluoride. (a) A solution of undistilled CH_2N_2 in 15 mL of ether was prepared from 1.2 g (11.6 mmol) of methylnitrosourea. A separate solution of 130 mg (0.91 mmol) of BF_3·Et_2O in 0.4 mL of CH_2Cl_2 was also prepared. These solutions were added with stirring (magnetic bar) in one-fifth portions (catalyst first, CH_2N_2 second) to a solution of 130 mg (0.28 mmol) of bromo ketone **5** in 5 mL of CH_2Cl_2 at intervals

(49) H. H. Inhoffen, G. Kolling, G. Koch, and I. Nebel, *Chem. Ber.*, **84**, 361 (1951).
(50) J. Y. Satoh, K. Misawa, T. T. Takahashi, M. Hirose, C. A. Horiuchi, S. Tsuji, and A. Hagitari, *Bull. Chem. Soc. Jpn.*, **46**, 3155 (1973).
(51) A Butenandt and A. Wolff, *Chem. Ber.*, **68**, 2091 (1935).
(52) J. J. McCullough and C. Manning, *J. Org. Chem.*, **43**, 2839 (1978). **Caution**: Diazoacetonitrile can be explosive.

of 10 min. During the additions there was brisk evolution of N_2 and precipitation of polymethylene. After a further 0.5 h the reaction mixture was filtered, concentrated, and partitioned between ether and water to yield 155 mg of viscous oil. Chromatography on two preparative plates developed twice in hexanes–benzene (50:50) afforded 66 mg of oily solid **2α-bromo-*A*-homo-5α-cholestan-3-one (22)**: IR 1710 cm^{-1} (ketone C=O); ^1H NMR δ 4.31 (dd, BrCHC=O); molecular ion calcd for $C_{28}H_{47}O^{79}Br$ 478.2810, found 478.2806.

The bromo ketone in 10 mL of ether containing 0.6 mL of HOAc was stirred with 300 mg of Zn dust for 2 h. Filtration and workup gave 57 mg of oily solid which was chromatographed on a 10-g preparative TLC plate developed in benzene–ether (96:4). The band at R_f 0.41 gave 43 mg (38% overall from **5**) of colorless crystalline **homo ketone 11**: mp 79–81 °C (lit.[43] mp 82–83 °C) after recrystallization from ether–MeOH; IR 1690 cm^{-1} (ketone C=O); mass spectrum, *m/e* 400 (molecular ion, base peak). The ^{13}C NMR spectrum (28 peaks) was identical with that of ***A*-homo-5α-cholestan-3-one (11)**.[26] There was no signal from the isomeric homo ketone **12** in the ^{13}C spectrum (<1%).

(b) The reaction in (a) was repeated on 10 mg of bromo ketone **5** in 0.3 mL of CH_2Cl_2 with 10 mg of redistilled $BF_3{\cdot}Et_2O$ and the undistilled CH_2N_2 from 150 mg of methylnitrosourea in 2 mL of ether. After 0.5 h the reaction was quenched by the addition of 1 mL of D_2O. After a further 0.25 h mixture was worked up and chromatographed on a 5-g plate developed twice in hexanes–benzene (50:50). The band at R_f 0.34 gave 3 mg of recovered undeuterated (mass spectrum) starting material **5**, IR 1725 cm^{-1} (ketone C=O). The band at R_f 0.57 gave 2 mg of **2α-bromo-*A*-homo-5α-cholestan-3-one (22)**, IR 1710 cm^{-1} (ketone C=O), whose $M + 1^+/M^+$ ratio in its mass spectrum gave no indication of D incorporation in comparison with the spectrum of **22** from (a).

(c) A 10-mg sample of the 2α-bromo *A*-homo ketone **22** in 0.2 mL of CH_2Cl_2 was treated with 10 mg of redistilled $BF_3{\cdot}Et_2O$ and the undistilled CH_2N_2 from 125 mg of methylnitrosourea in 2 mL of ether. Workup after 2 h gave 7 mg of product whose mass spectrum showed that no more than 5% homologation had taken place.

Reaction of 2α-Bromo-5α-cholestan-3-one (5) with Diazomethane–Methanol. A solution of 150 mg (0.32 mmol) of 2α-bromo ketone **5**, 3 mL of MeOH, and the distilled CH_2N_2 from 1.0 g of Diazald in 15 mL of ether was allowed to stand at 0 °C for 15 days. The reaction mixture was blown to dryness in a stream of nitrogen, and the residue was chromatographed on two plates developed eight times in hexanes–benzene (75:25). The less polar band at R_f 0.62 gave 76 mg (50%) of oily solid which was rechromatographed on another plate in the same solvent to yield 58 mg of colorless solid. Two recrystallizations from ether–EtOAc gave colorless granules of bromo epoxide **24**: mp 146–147 °C; IR no C=O; ^1H NMR δ 2.43 and 3.01 (AB, J = 5 Hz, CH_2O), 4.43 (dd, BrCHCO); ^{13}C NMR δ 50.4 (CHBr), 52.2 (OCH_2), 59.0 (OC-3); molecular ion calcd for $C_{28}H_{47}O^{79}Br$ 478.2810, found 478.2808.

The more polar TLC band (R_f 0.50) yield 39 mg (25%) of almost colorless oily **homologated bromo ketone 22**: IR 1710 cm^{-1}; ^1H NMR δ 4.27 (dd, CHBrC=O); molecular ion calcd for $C_{28}H_{47}OBr$ 478 and 480, found 478 and 480.

2α-Acetoxycholestan-3-one (3) and 2-Carbethoxy-*A*-nor-5α-cholestane. A solution of 1.0 g (2.6 mmol) of 5α-choelstan-3-one, 2.2 g (15 mmol) of redistilled $BF_3{\cdot}Et_2O$, and 1.3 g (2.9 mmol) of $Pb(OAc)_4$ in 30 mL of dry benzene was stirred at room temperature for 2 h according to the procedure of Henbest et al.[53] After workup, the crude product was chromatographed on three preparative plates developed twice in benzene–ether (96:4). Extraction of the band moving with the solvent front gave 146 mg (13%) of pale yellow oily **2-carbethoxy-*A*-nor-5α-cholestane**[54] which was rechromatographed on a single plate developed in benzene. Extraction of the band at R_f 0.61 gave 116 mg of colorless oil: IR 1730 cm^{-1} (ester C=O); ^1H NMR δ 1.25 (t, J = 7 Hz, CH_3CH_2O), 2.85 (m, 1 H, O=CCH), 4.13 (q, J = 7 Hz, 2 H, CH_3CH_2O); molecular ion calcd for $C_{29}H_{50}O_2$ 430.3810, found 430.3813.

Extraction of the band at R_f 0.48 on the three plates gave 707 mg (61%) of an off-white solid. One recrystallization from MeOH gave 560 mg of colorless granules of **2α-acetoxycholestan-3-one (3)**: mp 118–121 °C (lit.[53] mp 123–125 °C); IR 1745 (ester C=O), 1725 cm^{-1} (ketone C=O); ^1H NMR δ 2.15 (s, CH_3C=O), 5.29 (dd, 1 H, O=CCHOAc); molecular ion calcd for $C_{29}H_{48}O_3$ 444.3603, found 444.3600.

A solution of 100 mg of the ester (from the band at the solvent front) and 100 mg of KOH in 5 mL of 95% ethanol was refluxed for 2 h. Evaporation of the alcohol, acidification with aqueous HCl, and extraction with ether gave 80 mg of colorless solid. Two recrystallizations from MeOH gave 60 mg of colorless granules of ***A*-nor-5α-cholestane-2α(?)-carboxylic acid**: mp 163–170 °C (lit.[54] mp 177–181 °C); IR 3600–2400 (broad carboxyl OH), 1700 cm^{-1} (carboxyl C=O); ^1H NMR δ 2.92 (br dd, 1 H, CH carboxyl); molecular ion calcd for $C_{27}H_{46}O_2$ 402.3497, found 402.3502. The ^{13}C NMR spectrum (25 resolved signals) showed the acid to be a single pure epimer.

Homologation of 2α-Acetoxy-5α-cholestan-3-one with Ethyl Diazoacetate. To a stirred (magnetic bar) solution of 380 mg (0.86 mmol) of **3** and 497 mg (3.5 mmol) of $BF_3{\cdot}Et_2O$ in 4.5 mL of CH_2Cl_2 at 5 °C was added a solution of 399 mg (3.5 mmol) of EDA in 1 mL of CH_2Cl_2. After the cooling bath had warmed to room temperature, the reaction solution was refluxed for 5 h at which time 5 mL of water was added, and stirring was continued for 3 h. The organic layer was washed with water, dried, and concentrated to leave 630 mg of amber oil (mostly **16**): ^1H NMR, complex overlapping of epimeric and enolic forms of **16**; molecular ion calcd for $C_{33}H_{54}O_5$ 530.3971, found 530.3971.

The β-keto ester **16** was decarbethoxylated by stirring (magnetic bar) with 265 mg (1.8 mmol) of $CaCl_2{\cdot}2H_2O$ and 2 mL of Me_2SO under nitrogen for 6 h at 150 °C.[27,55] After distillation of most of the Me_2SO at aspirator vacuum, the residue was acidified with 10% aqueous HCl and extracted with pentane. The water-washed and dried pentane solution was evaporated to leave 383 mg (97%) of amber oily **2α-acetoxy-*A*-homo-5α-cholestan-3-one (17)** which exhibited essentially a single TLC spot more polar than **16**: IR 1740 (ester C=O), 1720 cm^{-1} (ketone C=O); ^1H NMR δ 2.12 (s, 3 H, CH_3C=O), 5.32 (dd, 1 H, O=CCHOAc); molecular ion calcd for $C_{30}H_{50}O_3$ 458.3759, found 458.3758.

To insure that no ketol from deacetylation was present for the next step, the crude **17** was treated with 1 mL of Ac_2O and 2 mL of Py for 12 h at room temperature. Workup afforded 372 mg of amber oily **17** for the next step.

Reductive removal of acetate was done according to the procedure of Pardo et al.[56] A solution of 350 mg (0.76 mmol) of the acetoxy ketone in 5 mL of anhydrous ether was added to a stirred (magnetic bar) blue solution of 90 mg (12.8 g atom) of freshly cut Li metal in 25 mL of liquid NH_3 cooled in a dry ice–acetone bath. Additional Li (45–90 mg) was added whenever the blue color faded (15–30 min) until 3 h had passed. Solid NH_4Cl was added and the ammonia was allowed to evaporate. Partition of the residue between ether and 10% aqueous HCl, and evaporation of the dried ether solution left 230 mg of amber colored oil (several TLC spots) which was chromatographed on two plates developed in benzene–ether (90:10). Elution of the band at R_f 0.52 gave 55 mg (16% overall) of ***A*-homo-5α-cholestan-3-one (11)**, molecular ion 400, all 28 of whose ^{13}C NMR signals were identical with the reported chemical shifts.[26] The product was contaminated with up to ~5% of the *A*-homo 4-ketone **12**.

Homologation of 2-Acetoxycyclohexanone with Ethyl Diazoacetate. To a stirred (magnetic bar) solution of 200 mg (1.28 mmol) of 2-acetoxycyclohexanone[57] and 738 mg (5.2 mmol) of $BF_3{\cdot}Et_2O$ in 4 mL of CH_2Cl_2 at 5 °C was added a solution of 593 mg (5.2 mmol) of EDA in 2 mL of CH_2Cl_2 over a period of 5 min. The ice bath was allowed to warm to room temperature, and the reaction solution was then refluxed for 2 h. After the

(53) H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc.*, 4472 (1961).

(54) H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc. C*, 756 (1967).

(55) Decarbethoxylation with distilled water in a sealed glass tube at 230 °C led to hydrolysis of the acetate and isomerization of the resulting ketol.

(56) S. N. Pardo, S. Ghosh, and R. G. Salomon, *Tetrahedron Lett.*, **22**, 1885 (1981).

(57) G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, 4426 (1955).

addition of 4 mL of water the mixture was stirred for 4 h more. The organic layer was washed with water, dried, concentrated, and distilled bulb-to-bulb at 200 °C (2.5 torr) to give 263 mg (85%) of almost colorless liquid **2-acetoxy-7-carbethoxycycloheptanone (20)**: IR 1740 (ester C=O), 1720 cm^{-1} (shoulder, ketone C=O); ^1H NMR δ 1.28 (unresolved triplets, CH_3CH_2O), 2.07 (s, CH_3C=O), 3.50 (br dd, O=CCHC=O), 4.1 (br m, OCH_2CH_3), 5.10 (br dd, O=CCHOAc); molecular ion calcd for $C_{12}H_{18}O_5$ 242.1153, found, 242.1155.

The TLC in benzene–ether (88:12) showed the absence of starting material and the presence of two less polar spots, presumably corresponding to stereoisomers of or keto/enol tautomers of **20**.

2-Acetoxycycloheptanone (21). A solution of 150 mg (0.62 mmol) of β-keto ester **20** and 228 mg (1.6 mmol) of $CaCl_2 \cdot 2H_2O$ in 1 mL of Me_2SO was stirred (magnetic bar) under nitrogen and heated at 150 °C for 7 h.[27] After cooling, the solution was acidified with 10% aqueous HCl and extracted with pentane. The washed and dried pentane solution was evaporated to leave 43 mg (40%) of liquid **2-acetoxycycloheptanone (21)**: IR 1740 (ester C=O), 1720 cm^{-1} (ketone C=O); ^1H NMR δ 2.17 (s, 3 H, CH_3C=O), 5.23 (m, 1 H, O=CCHOAc); ^{13}C NMR δ 20.7 (CH_3), 23.0, 26.5, 28.5, 30.3 (C-3–C-6), 40.7 (C-7), 78.5 (C-2), 170.2 (OC=O), 207.5 (C-1); molecular ion calcd for $C_9H_{14}O_3$ 170.0942, found 170.0942.

The infrared and ^1H NMR spectra and all nine peaks of the ^{13}C spectrum were identical with those of an authentic specimen prepared by the lead tetraacetate oxidation of cycloheptanone according to the procedure of Cavill and Solomon for cyclohexanone.[57] Likewise the retention time (8.2 min) on a 1.8 m × 3.4 mm column of 2.5% Carbowax 20 M on silanized Chromosorb P at 150 °C was the same as for the authentic specimen.

Baeyer–Villiger Cleavages of 2-Acetoxy Ketones. (a) 2α-Acetoxy-5α-cholestan-3-one (3). A 75-mg sample of **3** was oxidized with *m*-chloroperbenzoic acid according to the procedure of Bijelic et al.[17] The crude product (72 mg, 93%) was at least 95% lactone **4**: IR 1750 cm^{-1} (ester + lactone C=O); ^1H NMR δ 2.13 (s, CH_3C=O), 6.52 (d, J = 8 Hz, OCHO); ^{13}C NMR δ 92.0 (AcOCO), 168.6 (lactone C=O), 171.1 (acetate C=O), no peaks between 56.2 and 92.0 ppm; molecular ion calcd for $C_{29}H_{48}O_4$ 460.3552, found 460.3554. Minor peaks in the ^{13}C spectrum indicated the presence of up to ~5% of an unknown contaminant.

(b) 2-Acetoxycyclohexanone (19). To a stirred (magnetic bar) solution of 33 mg (0.22 mmol) of **19** in 0.5 mL of $CHCl_3$ at 0 °C was added a cold (~0 °C) solution of 93 mg (0.41 mmol of oxidant) of *m*-chloroperbenzoic acid (Aldrich, 75%) in 1 mL of $CHCl_3$ during 30 s. The cooling bath was allowed to warm to room temperature, and the reaction solution was stirred for 2.5 h more. The solution was then diluted with $CHCl_3$ and extracted successively wtih 5% aqueous NaI, 5% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and water. The dried organic layer was evaporated to leave 33 mg (86%) of residual oily **lactone 18**: IR 1745 cm^{-1} (ester + lactone C=O); ^1H NMR δ 2.13 (s, CH_3C=O), 6.41 (dd, OCHO); ^{13}C NMR δ 20.8 (CH_3), 22.6, 24.4, 33.1, 36.1 (4 CH_2), 93.6 (OCO), 168.5 (lactone C=O), 172.1 (acetate C=O); there were no traces of other peaks in the ^{13}C spectrum; molecular ion calcd for $C_8H_{12}O_4$ 172.0735, found 172.0731.

α-Bromoacetophenone → Phenylacetone. A solution of 100 mg (0.50 mmol) of phenacyl bromide, 284 mg (2.0 mmol) of redistilled $BF_3 \cdot Et_2O$, and 228 mg (2.0 mmol) of EDA in 4 mL of CH_2Cl_2 was refluxed for 2 days. Workup gave 172 mg of crude bromo keto ester: molecular ion calcd for $C_{12}H_{13}O_3{}^{79}Br$ 284.0048, found 284.0048. Debromination with 500 mg of Zn dust in 10 mL of ether containing 1 mL of HOAc, filtration, and workup gave crude **ethyl 2-phenylacetoacetate**. Decarbethoxylation of the above keto ester by heating at 230 °C with 2.5 mL of distilled water afforded 66 mg (98% overall) of pure **phenylacetone**: IR 1725 cm^{-1} (ketone C=O); ^1H NMR δ 2.08 (s, CH_3C=O), 3.60 (s, $PhCH_2C$=O), 7.10 (br s, Ar H); molecular ion calcd for $C_9H_{10}O$ 134.0732, found 134.0731.

α-Bromo-*p*-chloroacetophenone → (*p*-Chlorophenyl)acetone. A solution of 100 mg (0.43 mmol) of *p*-chlorophenacyl bromide, 244 mg (1.7 mmol) of redistilled $BF_3 \cdot Et_2O$, and 196 mg (1.7 mmol) of EDA in 3.5 mL of CH_2Cl_2 was refluxed for 5 days. Workup and debromination with 500 mg of Zn dust in 10 mL of ether containing 1.5 mL of HOAc gave crude **ethyl 2-(*p*-chlorophenyl)acetoacetate** which amounted to 72 mg of colorless oil after chromatography: molecular ion calcd for $C_{12}H_{13}O_3{}^{35}Cl$ 240.0553, found 240.0550. Decarbethoxylation by 0.3 mL of distilled water at 230 °C afforded 50 mg of a pale-yellow oil which by GLC was a mixture of 23% of *p*-chloroacetophenone and 77% of **(*p*-chlorophenyl)acetone**: IR 1710, 1690 cm^{-1} (ketone C=O); ^1H NMR δ 2.15 (s, CH_3C=O), 3.66 (s, CH_2C=O), 7–8 (m, Ar H).

3-Chloro-1-phenylacetone → 4-Phenyl-2-butanone. A solution of 100 mg (0.59 mmol) of 3-chloro-1-phenylacetone (prepared by the reaction of phenylacetyl chloride and diazomethane[58]), 340 mg (2.4 mmol) of redistilled $BF_3 \cdot Et_2O$, and 273 mg (2.4 mmol) of EDA in 3 mL of CH_2Cl_2 was refluxed for 2 days. Debromination with 500 mg of Zn dust in 10 mL of ether containing 1.5 mL of HOAc, filtration, workup, and chromatography on a thick plate gave 95 mg (73%) of **ethyl 2-benzylacetoacetate**: IR 1735 (ester C=O), 1710 cm^{-1} (ketone C=O); molecular ion calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1098. Decarbethoxylation with 0.3 mL of distilled water at 230 °C afforded 60 mg (69% overall) of amber colored oily **4-phenylbutan-2-one** (containing about 7% of phenylacetone from unhomologated starting material): IR 1710 cm^{-1} (ketone C=O); ^1H NMR δ 2.13 (s, 3 H, CH_3C=O), 2.82 (sym octet, 4 H, CH_2CH_2), 7.0–7.4 (m, 5 H, Ar H); mass spectrum, m/e 148 (molecular ion).

2-Chloro-2-methylcyclohexanone → 2-Methylcycloheptanone. To a solution of 4.8 g (33 mmol) of 2-chloro-2-methylcyclohexanone[59] in 40 mL of CH_2Cl_2 at 5 °C was added with stirring (magnetic bar) 14 g (99 mmol) of $BF_3 \cdot Et_2O$ followed by a solution of 11.3 g (99 mmol) of EDA in 15 mL of CH_2Cl_2 over a period of 35 min. The cooling bath was allowed to warm to room temperature, and the reaction mixture was stirred for 2.5 h more. TLC (hexanes–benzene, 75:25) showed the absence of starting material and the presence of a more polar product. To the reaction solution was added 40 mL of water, and stirring was continued for 2 h. The organic layer was separated, washed with water, saturated aqueous $NaHCO_3$, dried, and concentrated. Distillation gave 6.9 g (88%) of pale-yellow liquid mixture of epimeric **6-carbethoxy-2-chloro-2-methylcycloheptanones**: bp 110–112 °C (0.8 torr); IR 1740 cm^{-1} (br C=O); ^1H NMR δ 1.28 (doubled t, CH_3CH_2O), 1.70 and 1.77 (2 s of approximately equal intensity, $CH_3C(Cl)C$=O), 3.63 (br m, O=CCHC=O), 4.17 (doubled q, OCH_2CH_3); molecular ion calcd for $C_{11}H_{17}O_3{}^{35}Cl$ 232.0866, found 232.0861.

Dechlorination was carried out by stirring the chloro keto ester with 10 g of Zn dust in 50 mL of ether containing 5 mL of HOAc for 12 h. The reaction solution was filtered through sintered glass, and the Zn was washed with ether. The filtrate was washed with water, saturated $NaHCO_3$, and water and dried. Distillation afforded 4.4 g (76%) of **6-carbethoxy-2-methylcycloheptanone**: bp 85–93 °C (0.75 torr); IR 1730 (ester C=O), 1700 cm^{-1} (ketone C=O); molecular ion calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1259.

The keto ester was decarbethoxylated by heating with water (4 mL of distilled water/g of compound) in several heavy wall Pyrex tubes (16 mm o.d. × 30 cm) at 230 °C for 4 h. Extraction of the hydrolysate with ether gave 2.8 g (67% overall for the three steps) of brown liquid **2-methylcycloheptanone** (~95% pure by TLC and ^1H NMR). Distillation afforded 1.8 g of colorless liquid ketone: bp 101–103 °C (53 torr); IR 1700 cm^{-1} (ketone C=O); ^1H NMR δ 1.07 (d, J = 6.5 Hz, CH_3CHC=O), 2.2–2.7 (br m, 3 H, $CH_2C(=O)CH$); molecular ion calcd for $C_8H_{14}O$ 126.1045, found 126.1042. GLC on a 1.8 m × 3.4 mm column of 2.5% Carbowax 20M on silanized Chromosorb P at 80 °C gave a single peak of retention time 5.5 min. Injection of a larger sample gave a trace peak (<~1% of total off-scale 5.5-min peak) of retention time 6.5 min presumably corresponding to the isomeric 3-methylcycloheptanone.

A solution of 5 mg of the 2-methylcycloheptanone in 0.2 mL of a solution of 10 mg of Na in 1 ml of D_2O was sealed in a glass tube and heated at 80 °C for 1 h. Workup gave 4.8 mg of colorless oil: ^1H NMR δ 1.06 (br s, CH_3CDC=O) and the δ 2.2–2.8 m was missing. Deuterium analysis by mass spectroscopy gave 3% d_0, 7% d_1, 25% d_2, 65% d_3, and less than 1% d_4.

(58) W. D. McPhee and E. Klingsberg, "Organic Syntheses", Wiley, New York, 1955, Collect. Vol. III, p 119.
(59) E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses", Wiley, New York, 1963, Collect. Vol. IV, p 162.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for Financial support, Heather Schroeder for the 100-MHz ^1H NMR spectra, Doug Hairsine for the mass spectra, and Mary-Ellen Sturgeon and Professor J. B. Stothers for the ^{13}C NMR spectra.

Registry No. 1 (X = Cl), 2516-50-9; **3**, 14161-45-6; **4**, 71766-29-5; **5**, 1452-34-2; **6**, 2042-05-9; **6** bromo keto ester, 86118-83-4; **6** keto ester, 86118-84-5; **7**, 51014-33-6; **7** bromo keto ester, 86118-85-6; **7** keto ester, 86118-86-7; **8**, 4657-43-6; **8** bromo keto ester, 86161-64-0; **8** keto ester (isomer 1), 86161-65-1; **8** keto ester (isomer 2), 86161-66-2; **9**, 86118-87-8; **9** Cl derivative, 86118-88-9; **9** CN derivative, 86118-89-0; **10**, 86118-90-3; **10** CN derivative, 86118-91-4; **11**, 13914-51-7; **12**, 5885-22-3; **13**, 71557-24-9; **14**, 71557-26-1; **16**, 86118-92-5; **17**, 86118-93-6; **18**, 86118-94-7; **20**, 86118-95-8; **21**, 19347-07-0; **22**, 86118-96-9; **24**, 86118-97-0; EDA, 623-73-4; $BF_3{\cdot}Et_2O$, 109-63-7; 2α,4α-dibromo-5α-cholestan-3-one, 2239-57-8; 2β,4β-dibromo-5β-cholestan-3-one, 4575-78-4; 2-carbethoxy-*A*-nor-5α-cholestane, 86118-98-1; *A*-nor-5α-cholestan-2-carboxylic acid, 86161-67-3; ethyl 2-phenylacetoacetate, 5413-05-8; ethyl 2-(*p*-chlorophenyl)acetoacetate, 30186-24-4; ethyl 2-benzylacetoacetate, 620-79-1; *cis*-6-carbethoxy-2-chloro-2-methylcycloheptanone, 86118-99-2; *trans*-6-carbethoxy-2-chloro-2-methylcycloheptanone, 86119-00-8; 6-carbethoxy-2-methylcycloheptanone, 86119-01-9; 2-acetoxycyclohexanone, 17472-04-7; diazoacetonitrile, 13138-21-1; diazomethane, 334-88-3; 5α-cholestan-3-one, 566-88-1; phenacyl bromide, 70-11-1; phenylacetone, 103-79-7; *p*-chlorophenacyl bromide, 536-38-9; (4-chlorophenyl)acetone, 5586-88-9; 3-chloro-1-phenylacetone, 937-38-2; 4-phenylbutan-2-one, 2550-26-7; 2-chloro-2-methylcyclohexanone, 10409-46-8; 2-methylcycloheptanone, 932-56-9.

Notes

Thiol–Disulfide Interchange Reaction between Ellman's Reagent (5,5′-Dithiobis(2-nitrobenzoic acid)) and Functionalized Thiol Vesicles

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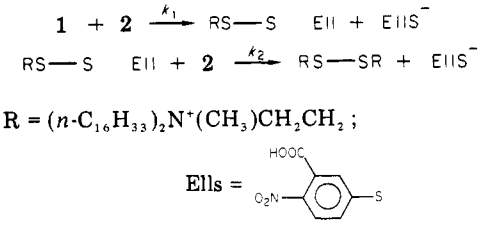
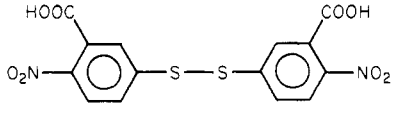
Received November 22, 1982

There has recently been much attention focused on the behavior of chemical reactions in synthetic surfactant vesicles.[2] Studies of reactions of fully functionalized thiol vesicles[3] and of organic thiols noncovalently bound to "inert" surfactant vesicles[4] have been particularly interesting. Large rate enhancements have been observed in the thiolyses of activated esters,[3a,4a,b] and the diastereoselectivity of peptide ester cleavages was lower in thiol-functionalized vesicles than in comparable micelles.[3b] Perhaps the most interesting were observations of kinetically distinct exovesicular, endovesicular, and transvesicular reactions.[3a,c,4c] This very interesting and unusual pattern of reactivity was a direct result of the vesicle structure.[3c]

Ellman's reagent,[5] 5,5′-dithiobis(2-nitrobenzoic acid) (1), reacts with a variety of thiols and is widely used in their analysis.[6] Several groups have carefully examined the thiol–disulfide interchange reactions of 1.[7] Other investigations have characterized the reactivity of 1 toward other nucleophiles such as aqueous hydroxide ion,[8] cyanide ion,[9] and organic amines.[10] More recently, the reaction of 1 with poly(ethylenimine),[11] the reaction of cyanide ion and 1 in polysoaps,[12] and the hydroxide ion cleavage of 1 in micellar[13] and vesicular[13b] solutions have been studied. This paper describes the thiol–disulfide interchange re-

Scheme I





1

$(n\text{-}C_{16}H_{33})_2N^+(CH_3)X,Y^-$

2, X = CH_2CH_2SH; Y = Cl
3, X = CH_3; Y = Br

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(2) Reviews: (a) Fendler, J. H. *Acc. Chem. Res.* **1980**, *13*, 7. (b) T. Kunitake, T.; Shinkai, S. *Adv. Phys. Org. Chem.* **1980**, *17*, 435. (c) Fendler, J. H. "Membrane Mimetic Chemistry"; Wiley: New York, 1982.

(3) (a) Moss, R. A.; Bizzigotti, G. O. *J. Am. Chem. Soc.* **1981**, *103*, 6512. (b) Moss, R. A.; Taguchi, T.; Bizzigotti, G. O. *Tetrahedron Lett.* **1982**, *23*, 1985. (c) Moss, R. A.; Bizzigotti, G. O.; Ihara, Y. In "Biomimetic Chemistry"; Yoshida, Z.-i., Ise, N., Eds.; Kodansha, Ltd.: Tokyo, 1983; p 189.

(4) (a) Cuccovia, I. M.; Aleixo, R. M. V.; Mortara, R. A.; Filho, P. B.; Bonilha, J. B. S.; Quina, F. H.; Chaimovich, H. *Tetrahedron Lett.* **1979**, 3065. (b) Cuccovia, I. M.; Quina, F. H.; Chaimovich, H. *Tetrahedron* **1982**, *38*, 917. (c) Moss, R. A.; Bizzigotti, G. O. *Tetrahedron Lett.* **1982**, *23*, 5235.

(5) Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70.

(6) Habeeb, A. F. S. A. *Methods Enzymol.* **1972**, *25*, 457.

(7) (a) Whitesides, G. M.; Lilburn, J. E.; Szajewski, R. P. *J. Org. Chem.* **1977**, *42*, 332. (b) Wilson, J. M.; Bayer, R. J.; Hupe, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 7922. (c) Ozawa, T.; Haraki, A. *Chem. Pharm. Bull.* **1981**, *29*, 1101. (d) Snyder, G. H.; Cennerazzo, M. J.; Karalis, A. J.; Field, D. *Biochemistry* **1981**, *20*, 6509.

(8) (a) Danehy, J. P.; Parameswaran, K. N. *J. Org. Chem.* **1968**, *33*, 568. (b) Donovan, J. W.; White, T. M. *Biochemistry* **1971**, *10*, 32. (c) Danehy, J. P. *Int. J. Sulfur Chem., Part B* **1971**, *6*, 17. (d) Danehy, J. P.; Elia, V. J.; Lavelle, C. J. *J. Org. Chem.* **1971**, *36*, 1003. (e) Riddles, P. W.; Blakeley, R. L.; Zerner, B. *Anal. Biochem.* **1979**, *94*, 75.

(9) Humphrey, R. E.; Hinze, W. L. *Talanta* **1974**, *6*, 326.

(10) Al-Raivi, H.; Stacey, K. A.; Weatherhead, R. H.; Williams, A. *J. Chem. Soc., Perkin Trans. 2*, **1978**, 663.

(11) Weatherhead, R. H.; Stacey, K. A.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1978**, 802.

(12) Ueda, T.; Haroda, S.; Ise, N. *Polym. J.* **1974**, *6*, 326.

(13) (a) Hiramatsu, K. *Biochim. Biophys. Acta* **1977**, *490*, 209. (b) Fendler, J. H.; Hinze, W. L. *J. Am. Chem. Soc.* **1981**, *103*, 5439.

0022-3263/83/1948-2598$01.50/0