action depend on the metal used to promote the reaction. With platinum the induction period observed with a nonpresaturated catalyst is probably due merely to the removal of adsorbed oxygen and not to any long term interaction of the olefin with the catalyst surface. Over palladium, if hydrogen is not present, reaction with even a very small amount of olefin results in a distinct change in the reaction characteristics of the catalyst as compared with what takes place if the catalyst is treated first with hydrogen. The data in Figure 1 for solution-phase hydrogenations are in agreement with these conclusions.

Presaturation of these catalysts with hydrogen results in the storage of relatively large amounts of hydrogen in the support material by the process of spillover. With these presaturated catalysts, reactions with olefins are more straightforward because of this hydrogen "reservoir" in intimate contact with the active sites. Here, too, there appear to be some differences between platinum and palladium. The reverse spillover to the metal particles of a supported palladium catalyst seems to be occurring at a slower rate than it does with similar platinum catalysts. This is indicated by the observation that there was virtually no contact time dependence on the amount of saturation taking place on an olefin pulse passing over a presaturated palladium catalyst while over a platinum catalyst the extent of saturation depends on the time the olefin pulse is in contact with the catalyst. This comparison is somewhat tenuous, though, and more work is obviously needed to determine the validity of this conclusion.

Acknowledgment. We thank the Ameron Corp. for their support of this work and Johnson Matthey, Inc., for supplying the chloroplatinic acid and palladium chloride through their Platinum Group Metals Loan Program.

Registry No. Pentane, 109-66-0; *cis*-2-pentene, 627-20-3; *trans*-2-pentene, 646-04-8; 1-pentene, 109-67-1; butane, 106-97-8; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; 1-butene, 106-98-9.

Reductive Cyclizations Involving Attack of Radical Anions Derived from Ketones, Aldehydes, and Enones on Isolated Carbon–Carbon Triple and Double Bonds. Application of Frontier Molecular Orbitals

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Reductive cyclization to tertiary alcohols was carried out with 4.5-secocholestan-5-one in which the 10α side chain was varied from $(CH_2)_2C{\equiv}CH$ (**1a**), to $(CH_2)_2C{\equiv}CCH_3$ (**1b**), $(CH_2)_3C{\equiv}CH$ (**1d**), and $(CH_2)_2CH{=}CH_2$ (**4**) by using Na/NH_3/THF (method B) and Na/THF (method C), and the results were compared with those obtained previously by using $C_{10}H_8Na$/THF (method A). Cyclization was the sole product with methods A and C but was accompanied by reduction to secondary alcohol when method B was used. Cyclization was regiospecific (formation of a smaller ring) and stereoselective (with only 5β-ol being produced). With **1b** initial syn attack by the ketyl radical anion across acetylene was further confirmed. The final product was predominantly the *E* isomer with methods A and B but the *Z* isomer with method C. Reductive cyclization was extended to 16,17-secopregn-5-enes whose side chains at 13α and 14β were varied, respectively, from $C{\equiv}CCH_3$ and CH_2CHO (**31**) to $C{\equiv}CCH_3$ and CH_2COCH_3 (**40**), $CH{=}CHCH_3$ and CH_2CHO (**44**), and $CH{=}CHCH_3$ and CH_2COCH_3 (**45**). Comparative studies were carried out and all products fully characterized except alkylnaphthalenes from **45**. Thus **31** gave a mixture of the four stereoisomers of 16-hydroxypregna-5,17(20)-dienes. This reaction was still regiospecific but no longer very stereoselective. The 16β-ols predominated as did the *Z* isomers. Results were markedly similar with all three methods, confirming the similarity in mechanisms. Rapid isomerization of vinyl radicals formed by syn addition is suggested. Method B gave no reduction products. From both **44** and **45** this method gave only two cyclized products differing in the configuration at position 16, with 16α-ols predominating. For an explaination of the lack of steric effect in replacement of the hydrogen of aldehyde by methyl on the 16α/16β raios an FMO argument has been advanced which uses an SOMO–HOMO interaction between radical and olefin instead of the presently accepted SOMO–LUMO for radical cyclizations. Application of FMO methods was justified by showing that 7α-methyl substitution in **1a** does not prevent C–C bond formation at the 5α-position. Stereoselective formation of the equatorial 5β-ols in these cases is ascribed to a dissymetric FMO for the ketyl radical ion, with the orbital at C-5 being extended in the axial direction. Reductive cyclization of α,β-unsaturated ketones was more likely to occur at the β-position because of the larger FMO coefficient. This was confirmed when $C_{10}H_8Na$ caused reductive cyclization of 4,5-secocholest-5-en-3-yn-7-one (**7**) whereas the isomeric 6-en-5-one (**8**) failed to cyclize. The product was unambiguously characterized as 3-methylene-*A*-nor-5β-cholestan-7-one (**20**).

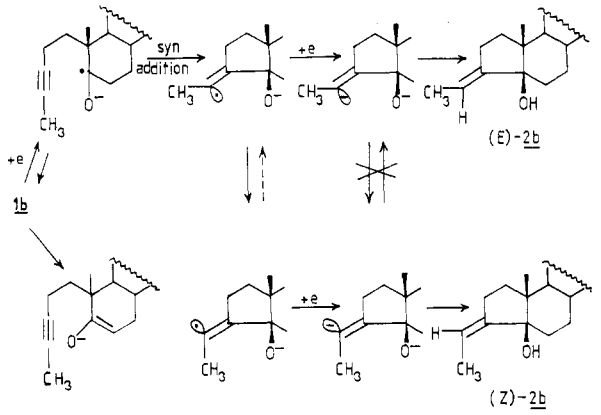
For several years we have been engaged in an in-depth study of reductive cyclization using alkali metals directly or through the derived aromatic radical ions.[1-3] Whereas cyclization of **1a** under the Stork conditions[4] gave the "overreduction" product 3-methyl-*A*-norcholest-3(5)-ene, use of *t*-BuOH gave a mixture of this and **2a** while naphthalene sodium yielded the latter exclusively. The mechanism given in Scheme I was established for the reaction of **1b** with naphthalene sodium in THF.

The stereoselective formation of A:B cis steroids and the initial syn[5] addition across the acetylene noted in the

(1) S. K. Pradhan and V. M. Girijavallabhan, *Steroids*, 13, 11-20 (1969).
(2) S. K. Pradhan, T. V. Radhakrishnan, and R. Subramanian, *J. Org. Chem.*, 41, 1943-52 (1976).
(3) Preliminary observations presented at the Colloque International CNRS Sur les Radicaux Libres Organiques, July, 1977, Aix-en-Provence, France.
(4) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Am. Chem. Soc.*, 87, 1148-9 (1965).

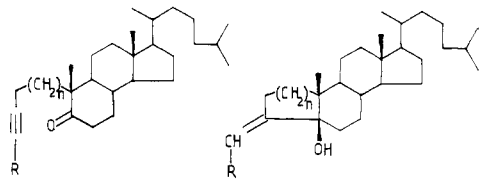
0022-3263/81/1946-2622$01.25/0

Scheme I



previous paper were observations confined to only a few compounds which were all 5-oxo-4,5-secocholestane derivatives (see Scheme I). The need was felt to examine a wider spectrum of compounds, particularly in view of the results obtained by Shono[6] using electrochemical methods. It was also necessary to settle the issue of whether alkali metal/NH_3 reactions follow the same path in spite of the ability of this reagent to reduce isolated acetylenes.[7] A comparative study of reductive cyclizations by the two reagents of a number of substrates was desirable to settle this. Since the primary tool for this study consisted of comparing the stereochemistry of the reaction, results with substrates capable of giving a larger number of stereoisomers were expected to be more conclusive. The choice fell on nonterminal γ-ethynyl aldehydes and methyl ketones derived from pregnanes.

In the course of this work, it was noticed that whereas cyclization was never accompanied by simple reduction of the ketone or aldehyde if $C_{10}H_8Na$ was used, such was not the case in the reaction of Na/liquid NH_3 with 5-oxo compounds such as **1a,b,d** etc. Seeking an explanation

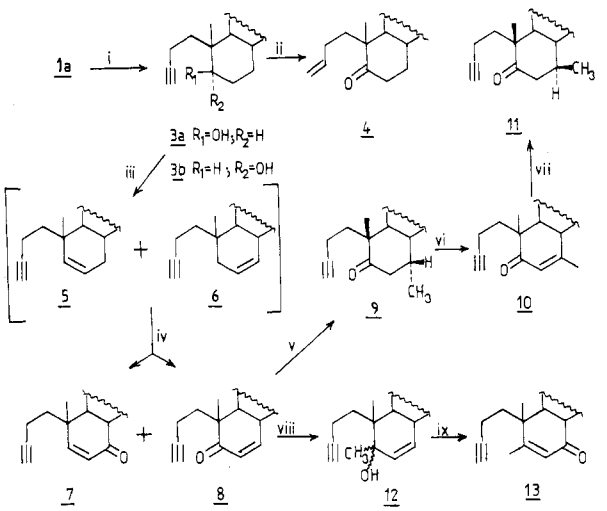


1a	n=1, R=H	2a	n=1, R=H
b	n=1, R=CH_3	b	n=1, R=CH_3
c	n=1, R=D	c	n=1, R=D
d	n=2, R=H	d	n=2, R=H
e	n=2, R=D	e	n=2, R=D

27 Dihydro 2a

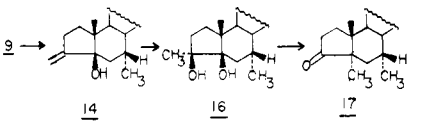
for this resulted in work which amounts to a significant contribution to the mechanism of reduction of ketones by Na in anhydrous ammonia. For the sake of clarity the relevant observations are presented in a separate paper immediately following this one. The cyclization aspects

Scheme II[a]



[a] (i) $NaBH_4$; (ii) Na/EtOH, CrO_3/Py; (iii) $POCl_3$/Py; (iv) *tert*-butyl chromate; (v) $(CH_3)_2CuLi$; (vi) Br_2/AcOH, $CaCO_3$/DMF; (vii) Li/NH_3; (viii) CH_3Li; (ix) pyridine chlorochromate.

Scheme III



are, however, dealt with here.

A major objective was to try and explain the exclusive formation of 5β-hydroxy sterols in reductive cyclizations of a variety of 5-oxo compounds. It was suspected that the key factor governing the stereoselectivity might be the same as that responsible for the observed regiospecificity. In the previous paper,[2] it had been suggested that the latter could be accounted for if the transition state closely resembled the starting material. From the stereochemical results of cyclization of the 7α-methyl derivative of **1a**, definitive evidence has now been obtained which justifies application of frontier molecular orbitals (FMO's). FMO considerations explained as well as prompted a variety of observations.

Results

Preparation and Reactions of 4,5-Secocholestane Derivatives. The substrates required included some prepared earlier,[2] their deuterated derivatives,[8] and a group of new ones. Synthesis of the latter is presented in Scheme II.

The stereochemistry assigned to **9** is not on the basis of its method of preparation but on its conversion to its stereoisomer **11**. The product of Li/NH_3 reduction of **10** can be assigned structure **11** in which the methyl group at the 7-position is equatorial[9] and hence β. Additional evidence was obtained by comparing the results of $NaBH_4$ reductions of **1a**, **9**, and **11**. Whereas **1a** and **11** gave mixtures of epimeric alcohols in which the equatorial 5β-ols predominated,[10] **9** gave exclusively the axial 5α-ol. Thus, the presence of the axial methyl at the 7-position desta-

(5) By "syn" addition or "syn" attack by a radical R· is meant an attack which gives a bent radical with the radical lobe at a dihedral angle of 0° relative to the C–R bond. Subsequent reduction etc. can give a "syn" *product* only if there is no isomerization. See also the footnotes to Table I.

(6) T. Shono, I. Nishiguchi, and H. Omizu, *Chem. Lett.* 1233–6 (1976), report that electroreduction of octan-6-yn-2-one gives the (*E*)- and (*Z*)-2-ethylidene-1-methylcyclopentanols in a ratio close to 1:2. This could be the result of equilibration.

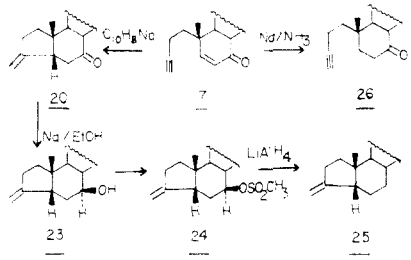
(7) H. O. House and E. F. Kinlock, *J. Org. Chem.*, **39**, 747–55 (1974), and references cited therein.

(8) Deuteration procedures and the results of cyclization of **1c** and **1e** are given in the Experimental Section.

(9) H. O. House, R. W. Giese, K. Kranberger, J. P. Kaplan, and J. P. Sumeone, *J. Am. Chem. Soc.*, **92**, 2800–10 (1970).

(10) Individual alcohols were isolated and their configurations assigned on the basis of the $w_{1/2}$ values of the hydrogen at C-5.

Scheme IV



bilizes the transition state for α attack by the hydride at the 5-position[11] in **9**.

Reductive Cyclizations of 9 and 11. Addition of **9** to naphthalene sodium in THF gave only one product in 85% yield, the remainder being starting material. From NMR[12] data, it could be assigned the structure and stereochemistry depicted in **14**. NBS gave 3α-(bromomethyl)-3β,5β-epoxy-7α-methyl-*A*-norcholestane (**18**), having a 19-CH_3 chemical shift comparable to that of a similar derivative of **2a**. Since the stereochemistry at the 5-position in **14** was crucial, additional confirmation was obtained by the transformation outlined in Scheme III.

The stereochemistry of the ketone **17** was confirmed by CD measurements. Its ΔE = 2.21 (294 nm) in methanol compares well with ΔE = 2.8 (294 nm) for *A*-nor-5α-methylcholestan-3-one in MeOH and with the CD of hexahydroindanone types.[13]

The isomeric compound **11** also underwent reductive cyclization readily to give 7β-methyl-3-methylene-*A*-norcholestan-5β-ol (**19**) in 60% yield. Here the 5β stereochemistry has been assigned on the basis of the 19-CH_3 chemical shift. It was noted that compound **19** was identical with a byproduct of the Li/NH_3 reduction of **10** possibly formed because a proton donor was used to destroy the excess metal.

Reductive Cyclization of Enones 7, 8, 10 and 13. These were undertaken to test an FMO-based prediction that reductive cyclization linking C-3 and C-5 should occur with **7**. The structures assigned to **7** and **8** are based on UV and NMR spectra and on the conversion of **8** to **1a** by standard methods. Reaction of **8** with $C_{10}H_8Na$ failed to give any compounds having an *exo*-methylene group. Dihydro dimers and steroid naphthalene adducts were formed in 15% and 60% yields, respectively.

Reaction of **7** also gave dihydro dimers and naphthalene steroid adducts in yields of 60% and 5%, respectively. Accompanying these was a compound of melting point 111 °C. This was consistently obtained in 20–25% yield. The presence in the IR of an *exo*-methylene group (890 and 1660 cm^{-1}) and a saturated six-membered ketone (1700 cm^{-1}) was a clear indication of the occurrence of a *rare type* of *reductive cyclization*. Structure **20** was assigned to it on the basis of its spectra and transformations summarized in Scheme IV.

In the mass spectrum, besides the molecular ion at *m/e* 384, an intense peak was noted at *m/e* 247 and a lesser one at *m/e* 289. This is readily accounted for in structure **20**, as the cleavage of the bond between C-5 and C-6 is to be expected. Subsequent cleavage at C(9)–C(10) followed by hydrogen transfer explains *m/e* 289. Loss of ketene then completes the picture. Reduction with $NaBH_4$ of **20** gave exclusively 3-methylene-*A*-nor-5β-cholestan-7α-ol (**21**). Ozonolysis of **21** gave a cyclopentanone derivative **22** having a peak at 1735 cm^{-1} in the IR. Reductive removal of oxygen from either **20** or **21** was expected to yield either **25** or its 5α isomer. The latter has been prepared by Levisalles:[14] mp 46–47 °C; $[\alpha]_D$ +13°. It follows that the 3-methylene-*A*-norcholestane (mp 91–92 °C; $[\alpha]_D$ 88°) prepared earlier by Dauben[15] must be the 5β compound **25**. Several attempts at converting **20** or **21** to **25** failed. Finally, the route via **23** and **24** succeeded, giving **25** in high yields. Examination of the crude product confirmed the absence of any stereoisomer of **25**. This unusual reductive cyclization of **7** does not take place if alkali metal/NH_3 is used, nor was this product detected when alkali metal in THF was used. Reaction of **7** with sodium in anhydrous liquid NH_3/THF followed by quenching with sodium benzoate after 5 min gave the saturated acetylenic 7-oxo compound **26** in 94% yield.

Since the main products obtained by $C_{10}H_8Na$ treatment of **7** and **8** were suspected to be hydrodimerization or Michael addition products, it was worthwhile to attempt reactions with **10** and **13** as substrates since the presence of a methyl substituent at the β-position could be expected to provide hindrance to the hydrodimerization process. The results were instructive.

Compound **13** gave a cyclization product analogous to **20** in 20% yield. Compound **10** failed to cyclize or hydrodimerize. A significant amount of reduction of the enone system occurred. Formation of **11** in 26% yield is probably linked with 32% recovery of starting material. Enolate formation from **7** or **8** requires the removal of the relatively inaccessible proton at C-8. In these cases no compound with the double bond reduced was detected. In the light of this, the finding that compound **7** with the stronger reducing agent, Na/NH_3, gives only the dihydro compound can be explained either by assuming proton donation by NH_3 to a weakly basic radical anion or by postulating the rapid formation of a dianion. The results described in the accompanying paper strongly support the latter possibility.

Reductive Cyclization of 4. Though cyclizations by radical attack on double bonds are well-known, reports of attack by a radical anion behaving as a radical are very limited.[16] Only one of these deals with the stereochemistry of the reaction. Shono reductively cyclized[16b] 6-hepten-2-one to 1,2-dimethylcyclopentanol using an electrochemical method. The isomer having the 2-methyl trans to the hydroxyl was the sole product. Mixtures were obtained by using Na/HMPA/THF whereas Na/NH_3 and Na/wet ether failed to cause cyclization. It was therefore not surprising that **4** was almost quantitatively recovered after treatment with $C_{10}H_8Na$. Less than 3% of another product was detected. Cyclization product was obtained in 8% yield by using Na/NH_3/THF. In this reaction, the accountability was 94%, with the remaining 86% being divided almost equally between **4** and the corresponding secondary alcohol. The new compound could be readily characterized after it was produced in 58% yield (accompanied by recovery of **4** to the extent of 35%) when **4** was stirred with metallic Na in dry THF for 70 h, followed by removal of excess unreacted metal by filtration. Similar

(11) It also confirms that **9** reacts in the chair conformation as β attack would be impossible in the boat conformation.
(12) All NMR data in this paper refers to ^1H NMR.
(13) D. N. Kirk and W. Klyne, *J. Chem. Soc., Perkin Trans. 1*, 762–70 (1976).
(14) J. Levisalles and I. Tkatchenko, *Bull. Soc. Chim. Fr.*, 1287–92 (1966).
(15) W. G. Dauben and J. N. Ross, *J. Am. Chem. Soc.*, 81, 6521–2 (1959).
(16) (a) J. M. Greenwood, I. H. Qureshi, and J. K. Sutherland, *J. Chem. Soc.*, 3154–9 (1965). (b) T. Shono, I. Nishiguchi, H. Ohmizu, and M. Mitani, *J. Am. Chem. Soc.*, **100**, 545–50 (1978). (c) A. F. Sowinski, and G. M. Whiteside, *J. Org. Chem.*, 44, 2369 (1979). These authors report the intermolecular counterpart.

Table I. Reductive Cyclization of 4,5-Secocholestane Compounds

compd	method[a]	% cyclization[b,c]	% reduction[b]	% recovery[b]	syn/anti[d] ratio
1a	A	74		20	
	B	64	14	16	
	C	89		5	
	C (Li)[e]	74		20	
1b	A	60		32	70:30
	A (low temp)	55		40	92:8
	B	16	40	40	65:35
	B (*t*-BuOH)[f]	26	31	35	71:29
	C	90		10	3:97
1d	A	81		10	
	B	47	21	23	
4	A[g]			95	
	B	8	45	41	
	C	58		35	
	C (Li)[e]	50		44	

[a] A = $C_{10}H_8Na$, B = Na/NH_3/THF, and C = Na/THF. [b] Percentage yield with reference to starting ketone in terms of amounts actually isolated by chromatography. [c] All four compounds gave exclusively 5β-ols. [d] In this case syn/anti is actually *E*/*Z*. Only the former terms signify that the two new bonds formed by addition to acetylene are at dihedral angles of 0° or 180°. [e] Li replaces Na. [f] 20:4:1 of NH_3/THF/*t*-BuOH. [g] 3–5% of unidentified products.

results were obtained with Li. The most remarkable feature of this reaction was the complete absence of side products.

The product obtained has been assigned structure **27** (see below, **2e**). It was shown to be a cyclized product by dehydration with thionyl chloride/pyridine to 3-methyl-*A*-norcholest-3(5)-ene. The same olefin was produced along with **27** when **2a** was catalytically hydrogenated. Thus there can be no doubt about the 5β-ol configuration. The 3α-methyl configuration is tentative and is based on the assumption that the catalyst would approach **2a** preferentially from the β face.

Standarization of Methods of Reductive Cyclization and Application to Secocholestanes. As stated at the outset, a comparative study of reductive cyclization by $C_{10}H_8Na$ in THF and Na in liquid NH_3/THF was to be undertaken. The two methods are henceforth referred to as methods A and B, respectively. In view of the experience with compound **4**, a third method was included. Method C consists of stirring the compound for up to 70 h at room temperature with excess Na in THF. This was included to see what stereochemical differences would emerge between reactions on the metal surface and in homogeneous solution. Unlike method C, reactions using methods A and B are over in minutes if not in seconds. Hence, it was desirable to avoid variations as much as possible. Thus method A was restricted to "inverse addition"; i.e., a solution of the compound in THF was added to a 2.5 molar excess of an approximately 0.4 N solution of naphthalene–sodium in THF. At end of 2–15 min, excess reagent was destroyed by air, methanol, or water. This made little difference in the overall result. Method B, on the other hand, was a far more difficult proposition. The important question was whether to add proton donors with acidity equal to or greater than that of *t*-BuOH. No reductive cyclizations have been reported so far with alkali metal in anhydrous liquid NH_3 free of proton donors other than NH_3 or substrate. With *t*-BuOH as an additive, the formation of overreduction product in the Stork[4] reductive cyclization was minimal but unavoidable. In the presence of this product, the relative amounts of cyclized isomers actually isolated can no longer be assumed to be the same as those initially formed. It was felt that if cyclization could be achieved without added proton donors, then not only would the overreduction be avoided but comparison with the aprotic conditions of the other two methods also would be more meaningful. Cyclization was achieved by adding the compound **1a** in THF to an approximately 0.1 N solution of Na in anhydrous ammonia. But attempts to avoid overreduction altogether were initially unsuccessful. The lack of anhydrous conditions and the presence of "acidic" impurities during the reaction or at the time of quenching were responsible. Refinement in technique to the extent of adding alkali metal without opening the reaction vessel and use of sodium benzoate for quenching led consistently to **2a** free of overreduction product. This method then became a standard procedure and is referred to henceforth as method B.

Results obtained by treating 4,5-secocholestane derivatives by the three methods and some variations thereof are given in Table I. In order to focus attention on the mode of addition, the words "syn" and "anti" are used to describe the *E* and *Z* isomers, respectively. Irrespective of the method used, all the compounds underwent cyclization stereoselectively and regiospecifically to give 5β-ols. Over 90% of the material was accounted for. By use of method B, the reductive cyclization product was accompanied by a compound formed by simple reduction of the 5-ketone to 5β-alcohol. The ratio of reduction to recovery was close to 1:1. No secondary 5β-alcohol was detected when methods A and C were used. Strong additional support for initial syn addition,[5] as proposed in Scheme I, has been obtained from the results of lowering the temperature for the $C_{10}H_8Na$ reaction. The substantial increase in the amount of syn compound formed from **1b** on lowering of the temperature below −40 °C is consistent with the expectation that the rate of isomerization of the "syn" vinyl radical to the "anti" radical is slowed down, but the rate of electron transfer, leading to trapping by reduction to a vinyl carbanion, is not appreciably affected. This device has been used before in related problems.[17] The overall data are consistent with the identity of mechanism of cyclization step between $C_{10}H_8Na$ and Na/NH_3/THF.

One interesting finding remains to be pointed out. The deuterated compound **1e** was cyclized by using $C_{10}H_8Na$ to give a mixture of **2d** and **2e** estimated to contain 50% of the latter from the NMR spectrum of the corresponding methyl ether. It could be seen that **2e** was not a mixture of *E* and *Z* isomers. To decide between the two possibilities, we converted it to the corresponding epoxide and compared its NMR with that of the epoxide from **2d** re-

(17) (a) S. J. Cristol and R. V. Barbour, *J. Am. Chem. Soc.*, **88**, 4262–3 (1966); (b) G. D. Sargent and M. W. Browne, *J. Am. Chem. Soc.*, **89**, 2788–90 (1967).

Table II. Reductive Cyclization of 16,17-Secopregnane Compounds[i]

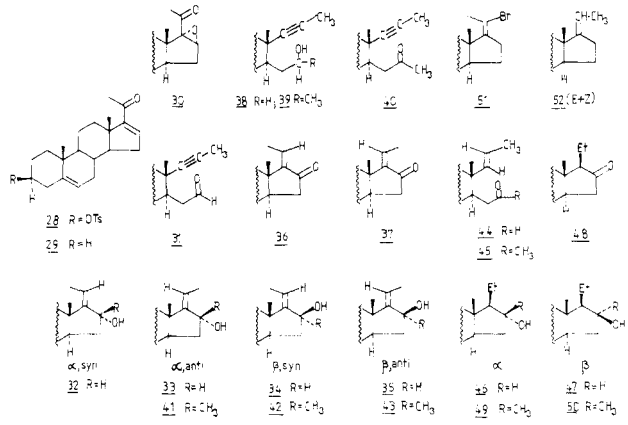
compd	method[a]	% cyclization[b,c]	% recovery[b]	ratio α/β (16-OH)	α syn/anti[d] ratio	β syn/anti[d] ratio
31	A	43	39	44:56	34:66	41:59
	B	75	20	38:62	18:82	29:71
40	A	56	34	38:62	0:100	21:79
	A (low temp)	46	44	26:74	0:100	20:80
	B	75	16	20:80	0:100	5:95
	B (ether)[h]	76	10	22:78	0:100	8:92
	B (*t*-BuOH)[f]	88	5	20:80	0:100	6:94
	C	89	5	19:81	0:100	7:93
44	B[g]	61	28	57:43		
45	B	73	19	59:41		
	B (*t*-BuOH)[f]	91	3	72:28		
	B (Li)[e]	80	15	67:33		
	C	73	20	25:75		

[a] A = $C_{10}H_8Na$, B = Na/NH_3/THF, and C = Na/THF. [b-g] As for Table I. [h] Ether in place of THF. [i] No reduction products obtained.

ported previously.[2] The two geminal hydrogens attached to the carbon bearing the oxygen were reported to have δ 2.69 (d, J = 5 Hz) and 3.12 (dd, J = 5, 1.5 Hz). In **2e** the signal at δ 3.12 disappeared while that at δ 2.69 was observed as a singlet. Thus the particular hydrogen in **2d** which has the additional long-range coupling of 1.5 Hz is being replaced by deuterium in **2e**. Examination of models shows a relationship approximating a W between the hydrogen (deuterium) cis to C-5 and the 3β-hydrogen. No such relationship is seen between the hydrogen cis to *C-3* and any other hydrogen. Similar long-range coupling has been observed in *meso*-2,3-epoxybutane but not in *dl*-2,3-epoxybutane.[18] A W relationship is possible in the former but not in the latter. It follows that **2e** must be the *Z* isomer formed by anti addition across the acetylene.

Preparation and Reductive Cyclization of 16,17-Secopregnanes and Related Compounds. Readily available 16-dehydropregnenolone was converted into the 3-deoxy derivative **29** by Zn/NaI/DME reduction of the corresponding tosylate (**28**). Epoxidation to **30** followed by fragmentation gave the required aldehyde **31**. Reductive cyclization of **31** using $C_{10}H_8Na$ gave a mixture of cyclized products. It was soon realized that all four possible stereoisomers were being produced, out of which two could not be separated. Hence, the four possible isomers **32–35** were synthesized by methods which also established their stereochemistry. Thus reaction of **30** with hydrazine gave a mixture of **32** and **33**, oxidation of which gave **36** and **37**, shown to be *E* and *Z*, respectively, by NMR. $NaBH_4$ reduction converted **36** to **34** and **37** to **35**. Chemical shifts of the methyl groups in all the isomers were as expected from the corresponding 3β-hydroxy compounds whose stereochemistry has already been established.[19] Since all the four isomers were produced in cyclization of **31**, a special method of describing them has been adopted in Chart I and in Table II. α and β refer to the configuration of the hydroxyl at C-16. Syn and anti refer to mode of addition across the alkyne. If Scheme I is considered applicable, then it follows that two simultaneous cyclizations are taking place, one leading to total α products (**32** plus **33**) and the other leading to total β products (**34** plus **35**). The relative distribution of syn to anti isomers within each pair is then considered as occurring subsequently to the cyclization step and is expected to be dependent on whether the syn or anti vinyl radical is produced first and on the efficiency of trapping the

Chart I



radical as a carbanion before equilibration. To obtain an insight into this, we found it necessary to determine the relative proportions of the four isomers formed in cyclization. Two were obtained pure by chromatography. The remaining two had identical R_f values and were hence isolated together, and the relative proportions were estimated on the basis of their specific rotations after the NMR of the mixture was checked. Results of comparative studies using the three methods of reductive cyclization are given in Table II. For FMO considerations, it was desirable to study the effect of substituting the aldehydic hydrogen by a methyl group. Hence **31** was converted to **40** via **39**. Reductive cyclization of **40** gave a mixture of **41–43**. Treatment of **36** and **37** with methyllithium gave **42** and **43**, respectively, thus confirming the structure and stereochemistry of the latter pair. It follows that **41** must have a 16α-hydroxy group. The *Z* configuration assigned to it is on the basis of NMR. The formation of predominantly anti products from both **31** and **40** could mean encroachment of a cyclization step involving carbanion attack onto acetylene. To probe into this, we subjected **40** to variants of the three methods, and, in addition, a study of the corresponding ethylenes was taken in hand as the latter are much less, if at all, reactive to nucleophiles. Information was also required as to the effect of substituting an aldehyde hydrogen by methyl in this series. The required compound **45** with $C_{10}H_8Na$ gave complicated mixtures containing steroid naphthalene (or dihydronaphthalene) adducts. Careful NMR examination of partially separated crudes from the reaction of **45** revealed the absence of methyl attached to either ethylene or ketone. Thus reaction with naphthalene radical ion must occur after cyclization of the ketyl radical ion to give a

(18) M. Kainosho, A. Ajisaka, W. H. Pirkle, and S. D. Beare, *J. Am. Chem. Soc.*, **94**, 5924–6 (1972).
(19) S. V. Kessar and A. L. Rampel, *Tetrahedron*, **24**, 887–92 (1968).

radical at C-20. Such a radical but not the corresponding carbanion can be expected to couple with $C_{10}H_8Na$ itself.[20] It appears that naphthalene/dihydronaphthalene adduct formation is restricted to alkyl radicals only. Thus, in reductive cyclizations involving acetylenes, failure to obtain such adducts is because of the apparent *inability of naphthalene radical ion to couple with vinyl radicals or with the ketyl radical anions*. This defines the circumstances in which a naphthalene radical anion can be used as a substitute for alkali metals in electron-transfer reactions. Reaction of **44** with Na/liquid NH_3/THF led to the isolation of two cyclized products, denoted **46** and **47**. These were independently prepared by $NaBH_4$ reduction of **48** which, in turn, was obtained by metal/NH_3 reduction of the enones **36** and **37** followed by reoxidation. From its method of preparation **48** was assumed to have a 17β-ethyl group. The major product obtained from it by $NaBH_4$ reduction was tentatively assumed to be formed by α attack and was assigned the structure **47**. The validity of these assumptions was confirmed when **46** was obtained from **32** on catalytic hydrogenation. Reductive cyclization of **45** gave **49** and **50**. Structures were assigned to these on the basis of NMR comparisons with **46** and **47**, respectively. Further confirmation was obtained when **50** was obtained from **48** by the action of CH_3MgI.

After settling the stereochemical assignments, reductive cyclizations were carried out by using the different methods, and the results are given in Table II. Where applicable, methods A and B give comparable results while method C shows substantial departure at times. The discussion below is limited to methods A and B. Unlike in 5-oxo-4,5-secocholestanes, no simple reduction of the carbonyl function is observed even when method B (Na/NH_3/THF) is used. Another difference is the absence of "total stereoselectivity". Thus both 16α- and 16β-ols are produced. Regiospecificity is, however, maintained in that bond formation occurs exclusively at the 17-position. The acetylenes **31** and **40** give a predominance of *Z* isomers corresponding to "anti addition" across the triple bond. This could be the result of nucleophilic carbanion attack by either a dianion or a monoanion. This was at first considered unlikely because these species would have been expected to give rise to simple reduction products (reduction of CO to CHOH) in the case of the ethylenes **44** and **45** wherein cyclization would be denied to them.[21] Hence, three alternatives appeared to be left. The ketyl radical ion could attack the acetylene as a nucleophile[22] to give a vinyl carbanion. Alternatively, the ketyl radical ion may attack as a radical to give either an anti or a syn vinyl radical. If the first alternative was exclusively operative, then no syn product should have been formed. This is not so. It is more difficult to rule out the simultaneous operation of this mechanism. But even this is unlikely in view of the results obtained from compound **51** which are discussed below. Attack as a radical, on the other hand, could proceed exclusively by the anti or syn mode, followed by isomerization, to yield the observed ratio. Such isomerization was observed to be slow enough with the 4,5-secocholestane derivative **1b** so that the initially formed syn vinyl radical could be trapped to a greater extent at low temperatures. In the case of **40**, lowering of the temperature for the $C_{10}H_8Na$ reaction made no difference to the syn/anti ratio. This failure could be understood if there was a considerable destabilization of the initially produced vinyl radical because of steric effects. This is indeed true of the syn vinyl radical but not of the anti. In the former, there is considerable steric repulsion of the 21-methyl by methylene at position 12 as is manifested in deshielding of this methyl in compound **42** as compared with 1-methyl-2-ethylidenecyclopentanol.[23] Though initial formation of syn vinyl radical would be in conformity with what had been established for the secocholestanes there was still doubt as to whether such extensive isomerization to the anti configuration would occur prior to trapping as carbanion. Fortunately, as a result of a related study[24] we had available to us the closely related "syn" vinyl bromide **51** correctly designated as (20*E*)-17(20)-bromopregna-5,17(20)-diene. This could be quantitatively converted to the corresponding hydrocarbon **52** by treatment with either $C_{10}H_8Na$ or Na/NH_3/THF. The former reagent gave a syn/anti ratio of 24:76 while the latter gave a ratio of 19:81. Thus, it appears that overall anti addition leading to high yields of compounds **35** and **43** in the cyclization of **31** and **40**, respectively, is due to rapid isomerization of a vinyl radical produced predominantly by syn attack.

The overall similarity in syn/anti ratios as well as α/β ratios with either $C_{10}H_8Na$ or Na/NH_3/THF is an indication that similar mechanisms are operating. But this may not be the whole story in view of the syn/anti radio of 5:95 observed for method B as compared to 20:80 for method A in the case of compound **40**. Either the nature of ion pairing on oxygen causes sufficient disparity between the position of equilibrium or an additional simultaneous anti attack on acetylene is taking place in NH_3 by a carbanionic species which is not produced in $C_{10}H_8Na$ reductions. The latter process is not occurring in secocholestanes, but this may be because the particular species gets diverted into producing a secondary alcohol. The failure to detect primary or secondary alcohols in Na/NH_3/THF reaction of **31** and **40**, respectively, is then readily understood. But similar failure in the case of **44** and **45** is not. A clear decision between the possibilities must await definitive work on carbanion addition to unconjugated olefins.

When the α/β ratios are compared, it is seen that whereas the β products predominate in the case of the acetylenic compounds **31** and **40**, the reverse is observed with the ethylenic compounds. Both **44** and **45** gave more 16α-hydroxy compounds than 16β-hydroxy ones. On the basis of a proposal by Shono,[16b] the above observations are readily accounted for in terms of repulsion between alkoxide and C-20, thereby favoring transition states corresponding to the conformation shown in structures A and B. The α/β ratio can be expected to be sensitive to subtle factors such as whether the counterion is associated with the alkoxide in the form of a contact or solvent-separated ion pair. The effect of lowering the temperature and of changing from sodium to lithium may be ascribed to this. But more work is necessary. Hence, the effect of changing from R = H to R = CH_3 can be judged only when the same method is used for reductive cyclization. On steric grounds, the conformations shown in structures A and B should be destabilized on changing from R = H to R = CH_3, and, hence, a decrease in the proportion of the major products (16β-ols from the acetylenes and 16α-ols from the

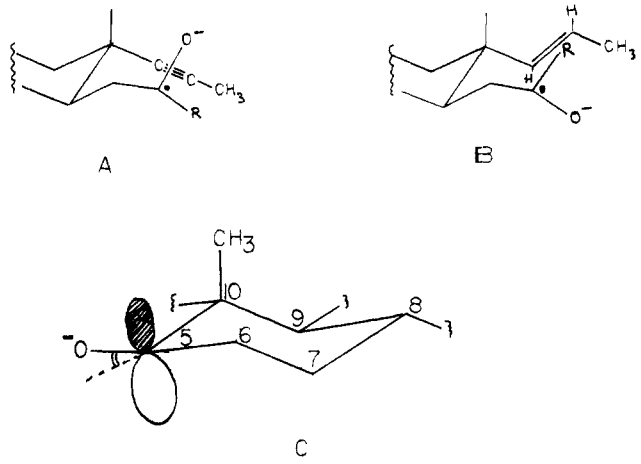
(20) Generation of 5-hexenyl radicals by using $C_{10}H_8Na$ is accompanied by formation of an alkylnaphthalene before as well as after rearrangement or cyclization.

(21) Competitive experiment established that cyclization of the ethylenic ketone **45** is slower than that of the acetylenic ketone **40**.

(22) P. T. Lansbury, T. R. Demmin, G. E. Dubois, and V. R. Haddon, *J. Am. Chem. Soc.*, **97**, 394–403 (1975).

(23) Reference 6 gives a chemical shift of δ 1.27 for the methyl on the double bond in (*E*)-2-ethylidene-1-methylcyclopentanol whereas in the syn isomer **42** it is at δ 1.68, i.e., deshielded by 0.41 ppm.

(24) J. N. Kolhe, unpublished work.



ethylenes) was to be expected. This does not occur in either set. Hence, a compensatory attractive force between the CH_3 groups at C-16 and the radical developing at C-20 must be present. This was precisely what was expected with FMO considerations which are presented below.

Application of FMO's to Various Facets of These Reductive Cyclizations. FMO concepts have afforded an insight into a number of reactions[25] and their regio- and stereoselectivity.[26] Particularly for those reactions which are highly exothermic and hence have a transition state resembling the starting materials, these concepts are providing an invaluable tool. The cyclization of **1a** and related compounds involves a rate-determining step in which a radical anion attacks an alkyne function to generate a vinyl radical and an alkoxide ion. This step can be expected to be quite exothermic and is indeed quite fast. In our previous paper,[2] we suggested an explanation for the regiospecific formation of exo compounds in terms of a transition state resembling starting material. Models show that in certain conformations of **1a**, C-3 and C-5 come within a distance of 2.0 Å. At this distance the 7α-methyl provides practically no hindrance to α attack at C-5. Hence, provided the energy barrier is crossed when the C-3,C-5 bond distance is close to this value, the cyclization of **9** should not only be as equally facile as of **1a** but, in addition, it should also give an A:B cis product, just as in the latter. On the other hand, requirement of a shorter bond distance (between C-5 and an approaching reagent) in the transition state could deter α attack. The soundness of this reasoning has been dramatically confirmed by the results of $NaBH_4$ reduction of **9** relative to **11**.[27]

Hence the present finding that cyclization of **9** gave **14** opened the way for application of FMO's. The total stereoselectivity observed in cyclization of 5-oxo compounds of the 4,5-secocholestane series can be regarded as being *a consequence of a preference for axial bond formation by the ketyl radical anion* derived from the ketone at C-5. To explain this preference in the FMO-controlled process, one finds it necessary to refer to the explanations given by Fukui[28] for preferential "exo" reactions of the norbornyl radical and axial reactions of cyclohexyl radicals,[26] instances of which have been cited by Klein.[29] Fukui has calculated that the single electron occupies an unsymmetrical orbital extended in the appropriate direction. ESR studies[30] have confirmed that such pyramidalization also persists in compounds having a hydroxyl attached to the carbon in question. Even greater pyramidalization can be expected[30b] when an alkoxide, rather than a hydroxyl group, is present, but preference for exo extension of the radical lobe at C-2 should remain, unless strong steric factors intervene.

Hence the ketyl radical anions derived from 5-oxo-4,5-secocholestanes can be represented as shown in structure C. The SOMO at C-5 is regarded as being unsymmetrically disposed relative to the plane containing C-10, C-5, and C-6. Dissymmetry in the mixing of the s and p orbitals at C-5 is primarily the result of perturbation by the 6–7 and 9–10 bond orbitals and causes an extension in the α (axial) direction. Hence, the minimal overlap necessary for reaching the transition state in this FMO-controlled reaction is achieved at a longer distance from C-5 in the α direction than in the β. Nonbonded interactions in addition to those in the appropriate conformation of the starting material are relatively less at the longer distance. The deviation from planarity of the carbon–oxygen bond is nowhere near the 54.5° corresponding to the equatorial linkage. About half this value appears nearer the mark.[31] Steric factors inhibiting the alkoxide from taking up the appropriate position are not likely to be encountered in cyclohexanones and β-decalones but could be present in *trans*-α-decalones having equatorial substituents at the 8-position.

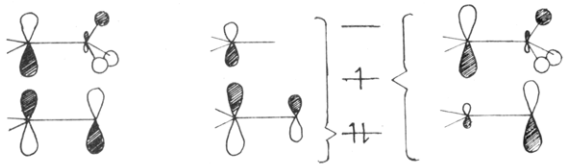
Thus, both the regiospecificity and stereoselectivity observed with 4,5-secocholestane derivatives can be understood.

In the 16,17-secopregnanes free rotation around the 15–16 bond permits formation of both 16α- and 16β-alcohols. Preferential formation of 16α-alcohols from **44** and **45** and of 16β-alcohols from **31** and **40** has already been explained. We are concerned here primarily with the possibility of an attractive force between the 16-methyl and the radical at C-20 in the cyclization of **45**, leading to **49**. For the analogous example of preferential formation of *cis*-1,2-dimethylcyclopentanes by the cyclization of hept-6-en-2-yl radical, Beckwith[32] has given an explanation involving secondary orbital interactions along the lines proposed by Hoffmann.[33]

Beckwith's proposal suffers from a serious drawback. It assumes an SOMO–LUMO interaction. This is quite unlikely. Ionization potential values,[34] calculations by Fukui[35] of the reaction of methyl radical with ethylene, and MINDO-3 calculations by Dewar[36] of the same reaction all indicate that the primary interaction must be SOMO–HOMO. We propose that for cyclization involving radical attack on an isolated olefin, Beckwith's explanation, sum-

(25) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, London, 1976.
(26) K. Fukui, "Theory of Orientation and Stereoselection", Springer-Verlag, West Berlin, 1975.
(27) Reductions of ketones by $NaBH_4$ need no longer be regarded as having a transition state resembling the starting material: W. T. Wipke and P. Gund, *J. Am. Chem. Soc.*, **98**, 8107–18 (1976).
(28) (a) H. Fujimoto and K. Fukui, *Tetrahedron Lett.*, 5551–4 (1966); (b) ref 26, pp 79–80.
(29) J. Klein, *Tetrahedron*, **30**, 3349 (1974).
(30) (a) Y. Ellinger, R. Subra, and G. Berthier, *J. Am. Chem. Soc.*, **100**, 4961–3 (1978); (b) T. Kawamura, T. Koyama, and T. Yonezawa, *ibid.*, **95**, 3220–8 (1973); (c) J. Gloux, M. Guglielmi, and H. Lemaire, *Mol. Phys.*, **17**, 425–7 (1961); (d) T. Kawamura, Y. Sugiyama, and T. Yonezawa, *ibid.*, **33**, 1499–501 (1977).
(31) Y. Ellinger, R. Subra, A. Rassat, J. Doudy, and G. Bertheir, *J. Am. Chem. Soc.*, **97**, 476–9 (1975), and references cited therein.
(32) A. L. J. Beckwith, I. Blair, and G. Phillipon, *J. Am. Chem. Soc.*, **96**, 1613–4 (1974).
(33) R. Hoffmann, C. C. Levin, and R. A. Moss, *J. Am. Chem. Soc.*, **95**, 629–31 (1973).
(34) The ionization potential for the CH_3 radical is given as 9.82 eV by T. Koenig, T. Balls, and W. Snell, *J. Am. Chem. Soc.*, **97**, 662–3 (1975), while that for $CH_2{=}CH_2$ is given as 10.5 eV by Houk.[37]
(35) H. Fujimoto, S. Yamabe, T. Manato, and K. Fukui, *J. Am. Chem. Soc.*, **94**, 9205–10 (1972).
(36) M. J. S. Dewar and S. Olivella, *J. Am. Chem. Soc.*, **100**, 5290–5 (1978).

marized in structure D, be replaced by a three-electron interaction as given in structure E. The latter is seen to have an equally favorable secondary interaction between the developing radical and a methyl group.

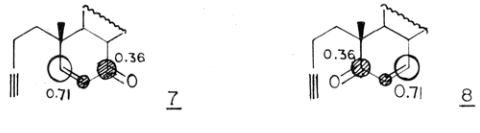


D E

In radical anion attack on acetylene there was a distinct possibility of a more significant involvement of the SOMO–LUMO interaction also. It was hoped that some indication of this would be seen in the stereochemistry of cyclization. Thus if Houk's[37] conclusions about nucleophilic attack on acetylenes were equally applicable to nucleophilic radicals,[25] then initial formation of an "anti" vinyl radical may be expected. In the cyclization of γ-ethynyl ketones, initial "syn" attack has been established for the secocholestanes and shown to be likely for the secopregnanes. Models show that in the former case the angle of approach necessary[37] for nucleophilic attack on acetylene is impossible. Thus only the SOMO–HOMO component can come into play. Approach in the latter case would correspond to that proposed by Baldwin.[38] The restriction no longer applies in the case of the terminal δ-ethynyl ketones.

Reaction of **1e** with $C_{10}H_8Na$ is seen to give, besides undeuterated **2d**, a monodeuterated compound rich in the product of anti addition. In the absence of additional data it seems inadvisable to use this in support of an SOMO–LUMO interaction.

The final and most satisfying application of FMO theory is in connection with reductive cyclization of enones. The radical anion derived from addition of an electron to an α,β-unsaturated ketone is expected to be almost planar, and the coefficient calculated for the LUMO of the parent enone should present a fair picture of the distribution of spin densities. The much larger coefficient at the β-position relative to the carbonyl carbon has been used for explaining hydrodimerization.[39] ESR studies[40] on radical anions derived from substituted cyclohexenones confirm the large coefficient at the β-position. The spin density distribution given in that paper has been assumed for the SOMOs from **7** and **8** and is depicted in structures F and G, respectively. It is emphasized that the values apply to the unprotonated radical anions. Protonation leads to a reversal in the size of the coefficients.[41]



7 **8**

F G

Thus it could be anticipated that the cyclization by radical attack on acetylene should be much more facile for the radical ion derived from **7** than from **8**, provided protonation does not precede cyclization. Since naphthalene sodium is a proton scavenger, no such protonated species were expected. With this reagent it was gratifying to note that compared to a 20% yield of cyclization product from **7** no cyclization products could be detected in the reaction with **8**.

Experimental Section

General Methods. Infrared spectra were obtained with a Perkin-Elmer Model 297 and a Perkin-Elmer Model 397 double beam spectrophotometer. UV spectra were recorded on a Beckman DB spectrophotometer. NMR spectra were recorded on Varian A-60, Varian EM-360L, and Varian XL-100 (100 MHz) spectrometers in CCl_4 or $CDCl_3$ with Me_4Si as an internal standard. Optical rotations were determined in $CHCl_3$ at room temperature with a Carl-Zeiss Winkel spectropolarimeter. Melting points were determined in a VEB Analytic Dresden HMK melting point apparatus and are uncorrected. THF was purified for all purposes by being refluxed initially with sodium followed by another distillation from $C_{10}H_8Na$. Sodium benzoate was dried at 110 °C under vacuum (2.5 mmHg) for 3 h before use. This was used for quenching reactions with alkali metal in liquid NH_3 unless stated otherwise. All reactions using naphthalene–sodium were done under nitrogen. All reactions as well as column chromatography were followed by TLC using microslides with detection by exposure to iodine vapor. Unless otherwise stated, reactions were worked up as follows. The mixtures were poured into water and extracted twice with ether, and the combined ether extract was washed with dilute HCl followed by water and dilute bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was subjected to column chromatography over standard grade alumina or silica gel.

4,5-Secocholest-3-yn-5α- and -5β-ols from 1a. To a solution of 384 mg (1 mmol) of **1a** in 15 mL of 1:1 methanol–ether was added 114 mg (3 mmol) of $NaBH_4$ in one portion. After 30 min, 10% acetic acid was added dropwise until the solution became slightly acidic. The usual workup and chromatography on alumina with 1:1 hexane–benzene gave initially 136 mg of 4,5-secocholest-3-yn-5α-ol (**3b**): mp 90–91 °C; $[\alpha]_D$ +47° (*c* 0.12); IR (Nujol) 3475 (OH), 3300 (≡CH), 2105 (C≡C), 1050, 1000, 620 cm^{-1}; NMR (CCl_4) δ 0.63 (3 H, s, C-18 methyl), 0.92 (3 H, s, C-19 methyl), 3.73 (H, s, $w_{1/2}$ = 6 Hz, C-5 H). Anal. Calcd for $C_{27}H_{46}O$: C, 84.31; H, 11.53. Found: C, 83.94; H, 11.31. Later fractions gave 223 mg of 4,5-secocholest-3-yn-5β-ol (**3a**): mp 62 °C; $[\alpha]_D$ +21° (*c* 0.12); IR (Nujol) 3400 (OH), 3310 (≡CH), 2120 (C≡C), 1090, 1050, 640 cm^{-1}; NMR (CCl_4) δ 0.65 (3 H, s, C-18 methyl), 0.93 (3 H, s, C-19 methyl), 3.4 (1 H, m, $w_{1/2}$ = 18 Hz, C-5 H). Anal. Calcd for $C_{27}H_{46}O$: C, 84.31; H, 11.53. Found: C, 84.08; H, 11.12.

Preparation of 4,5-Secocholest-5-en-3-yn-7-one (7) and 4,5-Secocholest-6-en-3-yn-5-one (8) from a Mixture of 3a and 3b via 5 and 6. To an ice-cooled solution of 386 mg (1 mmol) of a mixture of acetylenic alcohols **3a** and **3b** in 5 mL of dry pyridine was added dropwise 0.4 mL of $POCl_3$ with stirring. The reaction mixture was stirred for 1 h, heated on a water bath for 5 h, and allowed to cool to room temperature. Dilute NH_4OH solution was then added followed by the usual workup and chromatography on alumina. Elution with hexane gave 230 mg of an inseparable mixture of unsaturated hydrocarbons **5** and **6**. To a solution containing 184 mg (0.5 mmol) of the above mixture of **5** and **6** in 4 mL of dry CCl_4 was added *tert*-butyl chromate reagent[42] (prepared from 0.55 g of chromium trioxide), and the reaction mixture was refluxed for 10 h. It was then allowed to cool to room temperature, diluted with water, and extracted with CCl_4. The organic layer was washed several times with water, dried, and concentrated, and the residue was chromatographed on silica gel. Elution with 1:1 hexane–benzene gave 40 mg of 4,5-secocholest-5-en-3-yn-7-one (**7**) as an oil: $[\alpha]_D$ −32° (*c* 0.15); UV (EtOH) λ_{max} 227 nm (ε 9500); IR (neat) 3315 (≡CH), 2120 (C≡C), 1665 (C=O), 1450, 1370, 1190, 1010, 920, 630 cm^{-1}; NMR ($CDCl_3$) δ 0.7 (3 H, s, C-18 methyl), 1.1 (3 H, s, C-19 methyl), 5.81 and 6.53 (2 H, AB q, sharp, *J* = 10 Hz, CH=CH). Anal. Calcd for $C_{27}H_{42}O$: C, 84.74; H, 11.08. Found: C, 84.92; H, 11.45.

(37) R. W. Strozier, P. Caramell, and K. N. Houk, *J. Am. Chem. Soc.*, **101**, 1340–2 (1979).
(38) J. E. Baldwin, *Chem. Commun.*, 734–6 (1976).
(39) Reference 25, p 199.
(40) G. A. Russell and G. R. Stevenson, *J. Am. Chem. Soc.*, **93**, 2432–7 (1971).
(41) A. Imamura and T. Hirano, *J. Am. Chem. Soc.*, **97**, 4192–8 (1975).
(42) D. Gunsburg and R. Pappo, *J. Chem. Soc.*, 516–9 (1951).

Further elution gave 35 mg of 4,5-secocholest-6-en-3-yn-5-one (8) as an oil: $[\alpha]_D$ −56° (c 0.12); UV (EtOH) λ_{max} 227 nm (ε 9500); IR (neat) 3315 (≡CH), 2120 (C≡C), 1670 (C=O), 1465, 1380, 1245, 1015, 975, 630 cm^{-1}; NMR (CCl_4) δ 0.73 (3 H, s, C-18 methyl), 0.95 (3 H, s, C-19 methyl), 5.73 and 6.6 (2 H, AB q, br, J = 10.5 Hz, CH=CH). Anal. Calcd for $C_{27}H_{42}O$: C, 84.74; H, 11.08. Found: C, 84.76; H, 11.16.

Reduction of 8 with Sodium Borohydride–Pyridine[43] to 1a. To a solution of 382 mg (1 mmol) of acetylenic enone 8 in 4 mL of anhydrous pyridine was added 100 mg (2.6 mmol) of $NaBH_4$, and the reaction mixture was stirred for 5 h at room temperature. It was then worked up as usual. The residue (380 mg) in CH_2Cl_2 (10 mL) was oxidized by addition to an ice-cooled solution of CrO_3 (400 mg) in pyridine (4 mL). After the mixture was allowed to stand overnight, it was worked up and chromatographed on silica gel. Elution with benzene gave 236 mg of an oil which was identical in all respects with 4,5-secocholest-3-yn-5-one (1a).

Action of Lithium Dimethylcuprate[44] on 8. To 12.5 mL of an ice-cooled solution of 0.1 N lithium dimethylcuprate was added a solution of 382 mg (1 mmol) of the acetylenic enone 8 in 5 mL of dry ether under nitrogen with stirring. Aqueous NH_4Cl was added after 15 min followed by ether extraction and chromatography on silica gel. Elution with benzene gave 335 mg of 7α-methyl-4,5-secocholest-3-yn-5-one (9) isolated as an oil: $[\alpha]_D$ +27° (c 0.15); IR (neat) 3300 (≡CH), 2100 (C≡C), 1710 (C=O), 1465, 1385, 1240, 1085, 630 cm^{-1}; NMR (CCl_4) δ 0.75 (3 H, s, C-18 methyl), 1.07 (3 H, s, C-19 methyl); mass spectrum, m/e 398.3 (M^+), 346.3 (base peak). Anal. Calcd for $C_{28}H_{46}O$: C, 84.33; H, 11.63. Found: C, 84.46; H, 11.83.

Reduction of 9 with Sodium Borohydride. A 200-mg (0.5 mmol) sample of acetylenic ketone 9 was reduced by sodium borohydride as for 1a. Workup and chromatography on alumina gave 175 mg of 7α-methyl-4,5-secocholest-3-yn-5α-ol after elution with 1:1 hexane–benzene. It was crystallized from hexane–methanol: mp 75–76 °C; $[\alpha]_D$ +18° (c 0.14); IR (neat) 3500 (OH), 3225 (≡CH), 2100 (C≡C), 1466, 1385, 1060, 1030, 630 cm^{-1}; NMR ($CDCl_3$) δ 0.65 (3 H, s, C-18 methyl), 0.85 (3 H, s, C-19 methyl), 0.93 and 1.02 (d, 3 H, C-7 methyl), 3.64 (1 H, s, $w_{1/2}$ = 8 Hz, C-5 H). Anal. Calcd for $C_{28}H_{48}O$: C, 83.90; H, 12.07. Found: C, 84.23; H, 12.21.

Action of Naphthalene Sodium on 7α-Methyl-4,5-secocholest-3-yn-5-one (9). To 12.6 mL (5.25 mmol) of preformed naphthalene sodium in THF[2] was added 1.0 g (2.5 mmol) of acetylenic ketone 9 in 10 mL of THF with stirring. The green color of the reaction mixture was allowed to discharge by itself. Then water was added followed by ether extraction and chromatography on alumina. Initial elution with hexane removed all naphthalene. Elution with benzene/hexane gave 122 mg of starting material followed by 800 mg of an oil, which was identified as 7α-methyl-3-methylene-A-norcholestan-5β-ol (14): $[\alpha]_D$ +32° (c 0.12); IR (neat) 3400 (OH), 1645 (C=C), 1475, 1385, 1060, 895 (=CH_2) cm^{-1}; NMR (CCl_4) δ 0.67 (3 H, s, C-18 methyl), 0.92 (3 H, s, C-19 methyl), 4.99 and 5.17 (2 H, s, =CH_2). Anal. Calcd for $C_{28}H_{48}O$: C, 83.90; H, 12.07. Found: C, 83.49; H, 12.42.

To a stirred solution of 300 mg (0.75 mmol) of 9 in 5 mL of THF was added a solution of naphthalene sodium in THF until a faint green end point was observed. Workup and chromatography on alumina gave 75 mg of starting material and 210 mg of the tertiary allylic alcohol 14.

β-Epoxide of 7α-Methyl-3-methylene-A-norcholestan-5β-ol. To 300 mg (0.75 mmol) of the tertiary allylic alcohol 14 was added 2.0 mL of 0.6 N perbenzoic acid in chloroform, and the reaction mixture was kept at 5 °C for 8 h. The solution was extracted with chloroform after dilution with water and washed with solutions of potassium iodide, sodium thiosulfate, and sodium bicarbonate and finally with water. The residue obtained after removal of the chloroform was chromatographed on alumina. Elution with benzene gave 230 mg of the desired epoxy alcohol 15. It was crystallized from chloroform–methanol: mp 65–67 °C; IR (Nujol) 3540 (OH), 1460, 1390, 912 cm^{-1}; NMR (CCl_4) δ 0.68 (3 H, s, C-18 methyl), 0.81 (d, C-7 methyl, J = 5 Hz), 0.93 (C-19 methyl), 1.83 and 3.1 (2 H, AB q, J = 5 Hz, CH_2(O)). Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 81.01; H, 11.84.

3α,7α-Dimethyl-A-norcholestane-3β,5β-diol (16). To a solution of 200 mg (0.5 mmol) of the epoxy alcohol 15 in 20 mL of dry ether was added 200 mg (5 mmol) of $LiAlH_4$ in small portions, and the reaction mixture was stirred for 3 h at room temperature. After the excess $LiAlH_4$ was destroyed with ethyl acetate, a saturated aqueous solution of sodium potassium tartarate was added, and the product was worked up and crystallized from methanol to give the diol 16: 155 mg; mp 115–116 °C; $[\alpha]_D$ −46° (c 0.12); IR (Nujol) 3540 (OH), 3400 (OH), 1160, 1070 cm^{-1}; NMR (CCl_4) δ 0.66 (3 H, s, C-18 methyl), 0.835 (d, J = 7 Hz, C-7 methyl), 1.03 (3 H, s, C-19 methyl), 1.61 (3 H, s, C-3 methyl). Anal. Calcd for $C_{28}H_{50}O_2$: C, 80.32; H, 12.03. Found: C, 80.42; H, 12.18.

5α,7α-Dimethyl-A-norcholestan-3-one (17). To 90 mg (0.22 mmol) of the diol 16 was added 5 mL of 5% methanolic HCl, and the mixture was refluxed for 15 min. Neutralization by addition of dilute bicarbonate, workup, and chromatography on alumina with 1:1 hexane–benzene as eluent gave 45 mg of 5α,7α-dimethyl-A-norcholestan-3-one (17). It was crystallized from ethanol; mp 105–107 °C. The CD spectrum of 17 shows one negative maximum at 294 nm (ΔE = −2.29): IR (KBr) 1745 (C=O), 1465, 1385, 1260, 1010 cm^{-1}. Anal. Calcd for $C_{28}H_{48}O$: C, 83.90; H, 12.07. Found: C, 83.56; H, 12.14.

Action of Naphthalene Sodium on 4,5-Secocholest-6-en-3-yn-5-one (8). A solution of naphthalene sodium was added to a well-stirred solution of 400 mg (1 mmol) of acetylenic enone 8 in 10 mL of THF until a faint green end point was observed. It was worked up as usual and chromatographed on alumina. Elution with hexane gave initially 22 mg of a compound in which an exocyclic methylene group was found to be absent as evidenced by its IR and NMR spectra. Later fractions gave 230 mg of a naphthalene–steroid adduct isolated as an oil: $[\alpha]_D$ +11° (c 0.11); IR (neat) 3330 (≡CH), 3030, 2130 (C≡C), 1710 (C=O), 1475, 1380, 780, 630 cm^{-1}; NMR ($CDCl_3$) δ 0.74 (3 H, s, C-18 methyl), 1.1 (3 H, s, C-19 methyl), 2.0 (2 H, dd, J = 18, 2.5 Hz, CH_2CO), 7.14 (m, aromatic protons). Further elution with 1:1 hexane–benzene gave 50 mg of the starting material followed by 40 mg a dihydro dimer: mp 65–67 °C; $[\alpha]_D$ −19° (c 0.12); IR (Nujol) 3300 (≡CH), 2120 (C≡C), 1700 (C=O), 1015, 630 cm^{-1}; NMR (CCl_4) δ 0.72 (3 H, s, C-18 methyl), 1.04 (3 H, s, C-19 methyl); mass spectrum, m/e 766 (M^+), 714 (base peak). Anal. Calcd for $(C_{27}H_{43}O)_2$: C, 84.53; H, 11.30. Found: C, 84.47; H, 11.67.

To 15.6 mL of preformed naphthalene sodium was added 1.0 g (2.5 mmol) of 8 in 15 mL of THF with stirring. Workup and chromatography gave 40 mg of the compound in which the exocyclic methylene group was absent; 435 mg of naphthalene–steroid adduct, 60 mg of starting material, and 255 mg of the dihydro dimer were obtained.

Reductive Cyclization of 4,5-Secocholest-5-en-3-yn-7-one (7) with Naphthalene Sodium. To 4.7 mL of preformed naphthalene sodium was added 285 mg (0.75 mmol) of acetylenic enone 7 in 10 mL of THF. The green color of the reaction mixture was allowed to discharge by itself, and the mixture was worked up as described earlier. It was chromatographed on alumina. Elution with hexane gave 16 mg of a dihydronaphthalene adduct as an oil: IR (neat) 3560, 3210, 2120, 1705, 1600, 1575, 1460, 1380, 785, 745, 630 cm^{-1}. It was found to be unstable.

Later fractions gave 69 mg of a new compound identified as 3-methylene-A-nor-5β-cholestan-7-one (20). A NMR spectrum of the compound isolated was found to be identical with that of the crystalline sample described below. It was crystallized from methanol: 111 °C; $[\alpha]_D$ +9° (c 0.15); IR (CCl_4) 1700 (C=O), 1660 (C=C), 1460, 1385, 1020, 965, 890 (=CH_2) cm^{-1}; NMR (CCl_4) δ 0.66 (3 H, s, C-18 methyl), 1.26 (3 H, s, C-19 methyl), 2.53 (2 H, s, CH_2CO), 4.95 (2 H, s, =CH_2); mass spectrum, m/e 384.3 (M^+), 289, 247 (base peak). Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.21; H, 11.60. Further elution with 1:1 hexane–benzene gave 134 mg of a dihydro dimer. It was crystallized from methanol: mp 68–70 °C; $[\alpha]_D$ −28° (c 0.12); IR (KBr) 3215 (≡CH), 2120 (C≡C), 1710 (C=O), 1420, 1380, 1125, 1020 cm^{-1}; NMR ($CDCl_3$) δ 0.65 (3 H, s, C-18 methyl), 1.08 (3 H, s, C-19 methyl); mass spectrum, m/e 510, 383 (base peak). Anal. Calcd for $(C_{27}H_{43}O)_2$: C, 84.53; H, 11.30. Found: C, 84.20; H, 11.10. The

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dihydro dimer was further characterized by preparation of its dioxime and reduction with $NaBH_4$. The dioxime was found to be sparingly soluble in all organic solvents; mp 250 °C. Its mass spectrum gave a molecular ion peak at m/e 796. The major diol obtained from borohydride reduction gave a molecular ion peak at m/e 770: IR (Nujol) 3590, 3455 (OH), 3320 (≡CH), 2130 (C≡C), 1280, 1250, 1050 cm^{-1}.

Action of Sodium/Liquid Ammonia on 4,5-Secocholest-5-en-3-yn-7-one (7). To 20 mL of anhydrous redistilled ammonia was added 46 mg (2 mmol) of sodium, and the mixture was allowed to react completely. To this stirred solution was added a solution of 250 mg (0.65 mmol) of acetylenic enone **7** in 5 mL of THF. The reaction mixture was stirred for 5 min. Workup and chromatography on alumina with benzene as eluent gave 235 mg of 4,5-secocholest-3-yn-7-one (**26**) as an oil: $[\alpha]_D$ −30° (*c* 0.15); IR (neat) 3320 (≡CH), 2120 (C≡C), 1715 (C=O), 1375, 635 cm^{-1}; NMR (CCl_4) δ 0.61 (3 H, s, C-18 methyl), 1.12 (3 H, s, C-19 methyl). Anal. Calcd for $C_{27}H_{44}O$: C, 84.30; H, 11.53. Found: C, 83.95; H, 11.72.

Preparation of 4,5-Secocholest-3-yn-7-one (26). The acetylenic enone **7** (382 mg), on reduction with $NaBH_4$ and pyridine followed by reoxidation as described for **8**, gave 228 mg of a compound found to be identical with acetylenic ketone **26** prepared as above.

4,5-Secocholest-3-en-5-one (4). To a warm solution of 386 mg (1 mmol) of acetylenic alcohol **3a** in 15 mL of absolute ethanol was added 460 mg (20 mmol) of sodium. The reaction mixture was refluxed until all the sodium had reacted. Workup and chromatography on alumina with benzene as eluent gave 360 mg of 4,5-secocholest-3-en-5β-ol. It was crystallized from aqueous methanol: mp 57–58 °C; $[\alpha]_D$ +40° (*c* 0.12); IR (Nujol) 3450 (OH), 3100, 1640 (C=C), 1060, 1020, 1010, 910 (CH=CH_2) cm^{-1}; NMR (CCl_4) δ 0.65 (3 H, s, C-18 methyl), 0.93 (3 H, s, C-19 methyl), 3.33 (1 H, m, $w_{1/2}$ = 19 Hz, C-5H), 4.92 (2 H, m, CH=CH_2), 5.7 (1 H, m, CH=CH_2). Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.21; H, 12.51. A 360-mg sample of 4,5-secocholest-3-en-5β-ol on oxidation with pyridine–CrO_3 in methylene chloride (as in 8 → **1a**) gave, after workup and chromatography on silica gel, 290 mg of 4,5-secocholest-3-en-5-one (**4**) as an oil: $[\alpha]_D$ +45.7° (*c* 0.12); IR (neat) 3095 (C=C), 1710 (C=O), 1645 (C=C), 1430, 1380, 910 (CH=CH_2) cm^{-1}; NMR (CCl_4) δ 0.66 (3 H, s, C-18 methyl), 0.98 (3 H, s, C-19 methyl), 4.9 (2 H, m, CH=CH_2), 5.67 (1 H, m, C**H**=CH_2). Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.75; H, 11.95.

Reductive Cyclization of 4 with Sodium in THF. To a stirred solution of 394 mg (1 mmol) of ethylenic ketone **4** in 8 mL of THF, under a nitrogen atmosphere, was added 94 mg (4 mmol) of freshly cut sodium pieces. The mixture was stirred at room temperature for 70 h. Unreacted sodium was filtered, and the filtrate was worked up and chromatographed on alumina. Elution with benzene gave initially 137 mg of the starting material, followed by 228 mg of 3α-methyl-*A*-norcholestan-5β-ol (**27**). It was crystallized from methanol: mp 48–49 °C; $[\alpha]_D$ +27° (*c* 0.12); IR (Nujol) 3615 (OH), 3500 (OH), 1100, 1080, 1060, 1040 cm^{-1}; NMR (CCl_4) δ 0.66 (3 H, s, C-18 methyl), 0.9 (3 H, s, C-19 methyl). Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.20; H, 12.40.

Comparative Study of Reductive Cyclizations. Standard procedures were established and followed for reductive cyclization of substrates under three different conditions. The application of these is typified by the descriptions given below for reactions with **1b**. The data given in the tables have been obtained by following identical procedures for all the substrates. (The precautions taken for ensuring anhydrous conditions in reductions carried out by liquid NH_3 are described in detail in the accompanying paper.)

Action of Naphthalene Sodium on 1b. Method A. A solution of 350 mg (0.88 mmol) of 4-methyl-4,5-secocholest-3-yn-5-one (**1b**) in 7 mL of THF was added to 5.6 mL of freshly prepared standard naphthalene sodium in THF with stirring. After 2 min the reaction was allowed to discharge its color by itself. It was extracted in ether, and the ether layer was washed by dilute HCl, water, and dilute bicarbonate solution and finally dried over anhydrous sodium sulfate. Removal of the solvent and chromatography on alumina with 1:1 benzene–hexane as eluent gave after naphthalene 110 mg of the unreacted starting material. Finally, 208 mg of 3-ethylidene-*A*-norcholestan-5β-ol (**2b**) was obtained as oil. Epoxidation of **2b** as reported earlier gave 55 mg of the β-epoxide of the *Z* allylic alcohol and 127 mg of the β-epoxide of the *E* allylic alcohol.

A low-temperature reaction of **1b** was carried out by using 0.23 N naphthalene sodium cooled with acetone–solid CO_2. Results are given in Table I.

Action of Na/NH_3/THF on 1b. Method B. To a stirred solution of 100.43 mg (4.367 mmol) of Na in 40 mL of anhydrous ammonia (freshly distilled from Na) was added a solution of 300 mg (0.75 mmol) of 4-methyl-4,5-secocholest-3-yn-5-one (**1b**) in 10 mL of dry THF. After the mixture was stirred for 4 min, the reaction was quenched by addition of sodium benzoate. The ammonia was evaporated, and the residue was extracted with ether. The ether layer was washed with dilute bicarbonate solution followed by water. It was dried over anhydrous sodium sulfate. Removal of ether and chromatography on silica gel with 1:1 benzene–hexane as eluent gave initially 120 mg of starting material followed by 49 mg of (*E*)- and (*Z*)-3-ethylidene-*A*-norcholestan-5β-ols (**2b**).

Finally, 121 mg of 4-methyl-4,5-secocholest-3-yn-5β-ol was obtained: mp 78–80 °C; $[\alpha]_D$ +12° (*c* 0.10); IR (Nujol) 3560 and 3300 (OH), 1085, 1040 cm^{-1}; NMR (CCl_4) δ 0.6 (3 H, s, C-18 methyl), 0.9 (3 H, s, C-19 methyl), 1.7 (3 H, s, C≡CCH_3) 3.4 (1 H, m, $w_{1/2}$ = 18 Hz, C-5H).

Epoxidation of the **2b** as reported earlier gave 16 mg of the β-epoxide of the *Z* allylic alcohol and 30 mg of the β-epoxide of the *E* allylic alcohol.

Action of Na/THF on 1b. Method C. To a solution of 400 mg (1 mmol) of 4-methyl-4,5-secocholest-3-yn-5-one (**1b**) in 8 mL of dry THF was added 96.13 mg (4.18 mmol) of freshly cut sodium in eight pieces under nitrogen, and the mixture was stirred for 70 h. The reaction mixture was filtered from unreacted sodium and extracted with ether. The ether layer was washed with dilute HCl, water, and dilute bicarbonate solutions and finally dried over anhydrous sodium sulfate. Removal of ether and chromatography on silica gel with 1:1 benzene–hexane as eluent gave 40 mg of starting ketone followed by 355 mg of cyclized stereoisomeric allylic alcohols **2b**.

Epoxidation of **2b** by a previously reported method gave 330 mg of the β-epoxide of the *Z* allylic alcohol and 10 mg of the β-epoxide of the *E* allylic alcohol.

Preparation of 4-Deuterio-4,5-secocholest-3-yn-5-one (1c). To a solution of 1 mL of D_2O in 10 mL of dry THF was added 10 mg of sodium. After all the sodium had reacted, a solution of 1 g of a mixture of acetylenic alcohols **3a** and **3b** in 5 mL of THF was added and the mixture refluxed for 4 h. Dry hexane was added to the reaction mixture, and it was filtered through anhydrous sodium sulfate under a nitrogen atmosphere; removal of the solvent in vacuo gave a product. By repetition of the process a couple of times, complete deuterium exchange, as determined by the disappearance of IR absorption bands at 3310 (≡CH), 2120 (C≡C), and 630 cm^{-1}, was achieved to give 900 mg of a mixture of 4-deuterio-4,5-secocholest-3-yn-5-ols; IR (neat) 2600 cm^{-1} (C≡CD).

The mixture of deuterated alcohols obtained above was oxidized by pyridine–chromium trioxide reagent in dry dichloromethane and subsequently chromatographed on activated silica gel. Elution with benzene gave 680 mg of 4-deuterio-4,5-secocholest-3-yn-5-one (**1c**): IR (neat) 2590 (C≡CD), 1700 (C=O) cm^{-1}.

Reductive Cyclization of 1c with Sodium in THF. Reductive cyclization of **1c** (384 mg) by using method C gave **2a** (332 mg). Treatment of **2a** obtained above with CH_3I/NaH in THF gave the corresponding methyl ether. The ratio of the vinylic protons to the methoxy group was found to be 2:3; hence, total absence of deuterium at the vinylic position was ascertained.

4a-Deuterio-4a,5-seco-*A*-homocholest-4(4a)-yn-5-one (1e). A 125-mg sample of acetylenic ketone **1d** on sodium borohydride reduction (as in **1a**), workup, and chromatography on alumina gave 110 mg of an isomeric mixture of 4a,5-seco-*A*-homocholest-4(4a)-yn-5-ols.

The isomeric mixture of these acetylenic alcohols (110 mg) was deuterated as in the preparation of **1c**. Complete deuterium exchange, as determined by the disappearance of IR absorption bands at 3320 cm^{-1} (≡CH), was achieved to give 100 mg of deuterated acetylenic alcohol. It was oxidized by pyridine–chromium trioxide reagent (as for **1c**) to yield 65 mg of 4a-

deuterio-4a,5-seco-*A*-homocholest-4(4a)-yn-5-one (**1e**): IR (neat) 2600 (≡CD), 1710 (C=O) cm^{-1}.

Action of Naphthalene Sodium on 1e. Reductive cyclization of **1e** (64 mg) by using method A gave 7 mg of **1d** and 52 mg of a mixture of reductively cyclized, partially deuterated alcohols (**2d** plus **2e**). Mass spectra showed approximately 30% d_2, 50% d_1, and 20% d_0. Epoxidation of 31 mg of this with 0.6 N perbenzoic acid gave 26 mg of the corresponding β-epoxide:[2] NMR (CCl_4) δ 0.8 (3 H, s, C-18 methyl), 1.17 (3 H, s, C-19 methyl), 2.69 (0.5 H, s, superimposed on weak d), 3.12 (0.3 H, m, band width same as that for undeuterated compound). The allylic tertiary alcohols **2d** and **2e** were converted to their corresponding methyl ethers on treatment with CH_3I/NaH in THF. The combined integration of the vinyl protons was observed to be 0.9 protons as compared to the 3 protons of the methoxy group.

16,17-Secopregn-5-en-17(20)-yn-16-al (31). To an ice-cooled solution of 1.6 g (5 mmol) of epoxide **30** in 34 mL of methylene chloride and 12 mL of acetic acid was added 950 mg (5 mmol) of tosyl hydrazine, and the mixture was allowed to stand at 0 °C for 36 h. The deep yellow solution was slowly warmed to 42 °C and kept at that temperature for 10 min. The reaction mixture was worked up as usual but with $CHCl_3$ for the extraction. The crude product was chromatographed on silica gel with benzene as eluent to give 900 mg of 16,17-secopregn-5-en-17(20)-yn-16-al (**31**) as an oil: $[\alpha]_D$ −98.77°; IR (neat) 2674 (CHO), 1724 (C=O) cm^{-1}; NMR (CCl_4) δ 0.93 (3 H, s, C-18 methyl), 1.07 (3 H, s, C-19 methyl), 1.73 (3 H, s, C≡CCH_3), 9.63 (1 H, t, CHO). Since this compound was unstable, it was not analyzed.

16,17-Secopregn-5-en-17(20)-yn-16-ol (38). Sodium borohydride reduction of 298 mg of aldehyde **31** as described in the reduction of **1a** gave 262 mg of 16,17-secopregn-5-en-17(20)-yn-16-ol (**38**): mp 120–121 °C; $[\alpha]_D$ −108.2° (*c* 0.12); IR (KBr) 3400 (OH), 1450, 1435, 1375, 1050 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (3 H, s, C-18 methyl), 1.10 (3 H, s, C-19 methyl), 1.78 (3 H, s, C≡CCH_3), 3.70 (2 H, m, CH_2OH), 5.23 (1 H, m, C-6 H). Anal. Calcd for $C_{21}H_{32}O$: C, 83.92; H, 10.74. Found: C, 84.03; H, 10.80.

Reductive Cyclization of Aldehyde 31 by Naphthalene Sodium. A solution of 300 mg (1 mmol) of aldehyde **31** in 6 mL of THF was added to 6.3 mL of naphthalene sodium in THF, and the reaction was worked up as usual. Chromatography on alumina and elution with 1:1 benzene–hexane gave initially 120 mg of starting aldehyde, followed by 35 mg of (*Z*)-pregna-5,17(20)-dien-16α-ol (**33**): mp 101–103 °C; $[\alpha]_D$ −98° (*c* 0.10); IR (Nujol) 3350 (OH), 1460, 1380, 1250, 1060 cm^{-1}; NMR ($CDCl_3$) δ 0.75 (3 H, s, C-18 methyl), 1.01 (3 H, s, C-19 methyl), 1.79 (3 H, d, *J* = 7 Hz, C-21 methyl), 4.83 (1 H, br, C-16 H), 5.38 (2 H, m, q due to C-20 H masked by C-6 H). Anal. Calcd for $C_{21}H_{32}O$: C, 83.92; H, 10.74. Found: C, 83.53; H, 10.50. Further elution gave 62 mg of a mixture of (*E*)-pregna-5,17(20)-dien-16α-ol (**32**) and (*Z*)-pregna-5,17(20)-dien-16β-ol (**35**), $[\alpha]_D$ −77°. Since pure **32** and **35** obtained by a different route had $[\alpha]_D$ −121° and −61°, respectively, the composition of the mixture could be estimated. Finally, 30 mg of (*E*)-pregna-5,17(20)dien-16β-ol (**34**) was obtained: mp 92–93 °C; $[\alpha]_D$ −46° (*c* 0.10); IR (Nujol) 3320 (OH), 1250, 1170, 830 cm^{-1} NMR ($CDCl_3$) δ 1.01 (3 H, s, C-18 methyl), 1.05 (3 H, s, C-19 methyl), 1.73 (3 H, dd, *J* = 7, 1.5 Hz, C-21 methyl), 4.33 (1 H, br, C-16 H), 5.26 (1 H, br, C-6 H), 5.25 (1 H, q, *J* = 7 Hz, each limb of q is split into d, *J* = 2 Hz, C-20 H). Anal. Calcd for $C_{21}H_{32}O$: C, 83.92; H, 10.74. Found: C, 83.82; H, 10.67.

16-Methyl-16,17-secopregn-5-en-17(20)-yn-16-one (40). To 144 mg (6 mmol) of freshly activated magnesium in 20 mL of anhydrous ether was added with stirring 852 mg (6 mmol) of CH_3I in 10 mL of anhydrous ether dropwise under nitrogen. After the mixture was stirred for 10 min, a solution of 596 mg (2 mmol) of acetylenealdehyde **31** in 10 mL of anhydrous ether was added with stirring. The reaction mixture was stirred for 20 minutes and then quenched with water. Workup and chromatography on alumina gave 540 mg of a mixture of the two epimeric alcohols **39**. A 540-mg sample of **39** was oxidized by being stirred for 2 h with pyridinium chloromate (556 mg) in dry methylene chloride (27 mL). The usual workup and column chromatography on alumina gave 494 mg of 16-methyl-16,17-secopregn-5-en-17-(20)-yn-16-one (**40**). It was crystallized from methanol: mp 111–112 °C; $[\alpha]_D$ −122.3° (*c* 0.1); IR (Nujol) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 0.9 (3 H, s, C-18 methyl), 1.0 (3 H, s, C-19 methyl), 1.72 (3 H, s, C≡CCH_3), 2.1 (3 H, s, $COCH_3$), 5.15 (1 H, m, C-6 H). Anal. Calcd for $C_{22}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.20; H, 10.6.

Reductive Cyclization of 16-Methyl-16,17-secopregn-5-en-17(20)-yn-16-one (40) with Naphthalene Sodium. A solution of 624 mg (2 mmol) of **40** in 5 mL of THF was reacted with naphthalene sodium as usual. Chromatography on alumina with benzene/hexane as eluent gave 207 mg of starting material. Elution with benzene gave initially 133 mg of (*Z*)-16β-methylpregna-5,17(20)-dien-16α-ol (**41**). It was crystallized from methanol: mp 111–113 °C; $[\alpha]_D$ −100° (*c* 0.1); IR (Nujol) 3400 (OH), 1650 (C=C), 1195, 930 cm^{-1}; NMR (CCl_4) δ 0.77 (3 H, s, C-18 methyl), 0.98 (3 H, s, C-19 methyl), 1.43 (3 H, s, C-16 methyl), 1.8 (3 H, d, *J* = 7 Hz, C-21 methyl), 5.15 (2 H, m, q due to C-21 H masked by C-6 H). Anal. Calcd for $C_{22}H_{34}O$: C, 84.01; H, 10.9. Found: C, 84.31; H, 11.12. Later fractions gave 172 mg of (*Z*)-16α-methylpregna-5,17(20)-dien-16β-ol (**43**). It was crystallized from benzene–petroleum ether: mp 145–147 °C; $[\alpha]_D$ −33.67° (*c* 0.1); IR (Nujol) 3360 (OH), 1664 (C=C), 1170, 1022 cm^{-1}; NMR (CCl_4) δ 0.9 (3 H, s, C-18 methyl), 1.0 (3 H, s, C-19 methyl), 1.38 (3 H, s, C-16 methyl), 1.78 (3 H, d, *J* = 7 Hz, C-21 methyl), 5.15 (2 H, m, q due to C-21 H masked by C-6 H). Anal. Calcd for $C_{22}H_{34}O$: C, 84.01; H, 10.9. Found: C, 84.21; H, 11.05. Last fractions gave 47 mg of (*E*)-16α-methyl-pregna-5,17(20)-dien-16β-ol (**42**). It was crystallized from benzene–petroleum ether: mp 120–121 °C; $[\alpha]_D$ −64° (*c* 0.1); IR (Nujol) 3350 (OH), 1660 (C=C), 1110, 1025 cm^{-1}; NMR (CCl_4) δ 1.0 (3 H, s, C-19 methyl), 1.05 (3 H, s, C-18 methyl), 1.23 (3 H, s, C-16 methyl), 1.68 (3 H, d, *J* = 7 Hz, C-21 methyl), 5.15 (1 H, m, C-6 H), 5.4 (1 H, q, C-20, *J* = 7 Hz). Anal. Calcd for $C_{22}H_{34}O$: C, 84.01; H, 10.9. Found: C, 83.94, H, 11.2.

A low-temperature reaction of **40** (312 mg) was carried out by using 0.27 N naphthalene sodium cooled with acetone–solid CO_2. Workup and chromatography on alumina with benzene as an eluent gave 137 mg of **40**, 37 mg of **41**, 85 mg of **43**, and 21 mg of **42**.

(*E*)-16,17-Secopregna-5,17(20)-dien-16-al (44). To 30 mL of liquid ammonia was added 210 mg (30 mmol) of freshly cut lithium pieces, and the solution was stirred for 1 min. To this was added 600 mg (2 mmol) of 16,17-secopregn-5-en-17(20)-yn-16-ol (**38**) in 8 mL of THF containing 0.8 mL of *tert*-butyl alcohol over a period of 5 min. Stirring was continued for an additional 15 min. The excess reagent was then destroyed by dropwise addition of MeOH. Workup and chromatography on alumina gave 546 mg of an oil.

This was oxidized by pyridine–CrO_3 in dichloromethane (as described for **8** → **1a**). Workup and chromatography on alumina with 1:1 hexane–benzene gave 365 mg of **44**. It was crystallized from methanol: mp 83–85 °C; $[\alpha]_D$ −115° (*c* 0.1); IR (Nujol) 2720 (CHO), 1720 (C=O), 980 (CH=CH, trans) cm^{-1}; NMR (CCl_4) δ 0.9 (3 H, s, C-18 methyl), 0.95 (3 H, s, C-19 methyl), 1.63 (3 H, d, *J* = 5 Hz, C-21 methyl), 5.2 (3 H, m, C-6, C-17, and C-20 H), 9.58 (1 H, t, *J* = 1.5 Hz, CHO). Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 84.05; H, 10.89.

(*E*)-16-Methyl-16,17-secopregna-5,17(20)-dien-16-one (45). Compound **39** (628 mg), on being reduced with Li/NH_3 and then oxidized as in the previous experiment, gave 355 mg of **45**. It was crystallized from methanol: mp 80–81 °C; $[\alpha]_D$ −100.2° (*c* 0.1); IR (Nujol) 1715 (C=O), 1670 (C=C), 1170, 980 (CH=CH, trans) cm^{-1}; NMR (CCl_4) δ 0.87 (3 H, s, C-18 methyl), 0.95 (3 H, s, C-19 methyl), 1.63 (3 H, d, *J* = 5 Hz, C-21 methyl), 2.02 (3 H, s, $COCH_3$), 5.15 (3 H, m, C-6, C-17, and C-20 H). Anal. Calcd for $C_{22}H_{34}O$: C, 84.01; H, 10.9. Found: C, 84.04; H, 10.96.

Naphthalene Sodium Reaction with (*E*)-16-Methyl-16,17-secopregna-5,17(20)-dien-16-one (45). A solution of standard naphthalene sodium was added to a well-stirred solution of 650 mg (2 mmol) of the ethylenic ketone **45** in 5 mL of THF until a faint green end point was observed. The faint color discharged by itself after 10 min. Workup and chromatography on alumina gave 362 mg of the starting material. The rest was separated into a number of fractions. Examination of each by UV, IR, NMR, and mass spectra showed them to be mixtures. NMR and UV indicated that all contained an aromatic ring; NMR further indicated the absence of CH_3 at δ 1.6 and 2.0.

Action of Sodium/Liquid Ammonia on (*E*)-16,17-Secopregna-5,17(20)-dien-16-al (44). To a stirred solution of 55 mg (2.4 mmol) of sodium in 20 mL of anhydrous and redistilled

ammonia was added a solution of 150 mg (0.5 mmol) of the ethylenic aldehyde **44** in 5 mL of THF. After 4 min, workup and chromatography on alumina with benzene as an eluent initially gave 42 mg of the starting material **44**. Later fractions gave 39 mg of pregn-5-en-16β-ol (**47**). It was crystallized from methanol: mp 97–99 °C; $[\alpha]_D$ –60° (*c* 0.1); IR (Nujol) 3430 (OH), 1030, 1005, 830 cm^{-1}; NMR (CCl_4) δ 0.75 (3 H, s, C-18 methyl), 1.0 (3 H, s, C-19 methyl), 4.23 (1 H, m, C-16 H), 5.17 (1 H, m, C-6 H). Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.67; H, 11.59. Further fractions gave 52 mg of pregn-5-en-16α-ol (**46**). It was crystallized from chloroform/methanol: mp 174–176 °C; $[\alpha]_D$ –103.33° (*c* 0.1); IR (Nujol) 3300 (OH), 1340, 1060, 835 cm^{-1}; NMR ($CDCl_3$) δ 0.57 (3 H, s, C-18 methyl), 0.98 (3 H, s, C-19 methyl), 3.97 (1 H, m, C-16 H), 5.27 (1 H, m, C-6 H). Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.52; H, 11.44. The last fraction gave 7 mg of a product which was not characterized.

Action of Sodium/Liquid Ammonia on (*E*)-16-Methyl-16,17-secopregna-5,17(20)-dien-16-one (45). To a stirred solution of 55 mg (2.4 mmol) of sodium in 20 mL of anhydrous and redistilled ammonia was added 150 mg (0.48 mmol) of ethylenic ketone **45** in 5 mL of THF. After 4 min, workup and chromatography on alumina with benzene as eluent initially gave 45 mg of the starting material **45**. Later fractions gave 39 mg of 16α-methylpregn-5-en-16β-ol (**50**). It was crystallized from methanol: mp 99–101 °C; $[\alpha]_D$ –58.4° (*c* 0.1); IR (Nujol) 3400 (OH), 1340, 1070, 940, 895 cm^{-1}; NMR (CCl_4) δ 0.77 (3 H, s, C-18 methyl), 0.98 (3 H, s, C-19 methyl), 1.25 (3 H, s, C-16 methyl), 5.16 (1 H, m, C-6 H). Anal. Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.47. Found: C, 83.24; H, 11.38. The last fractions gave 55 mg of 16β-methylpregn-5-en-16α-ol (**49**). It was crystallized from methanol: mp 145–147 °C; $[\alpha]_D$ –77.43° (*c* 0.1); IR (Nujol) 3400 (OH), 1310, 1120, 920, 875 cm^{-1}; NMR (CCl_4) δ 0.57 (3 H, s, C-18 methyl), 0.97 (3 H, s, C-19 methyl), 1.2 (3 H, s, C-16 methyl), 5.16 (1 H, m, C-6 H). Anal. Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.47. Found: C, 83.50; H, 11.80. Compound **45** (150 mg, 0.48 mmol) was reacted with 165 mg (7.17 mmol) of Na in NH_3 for 15 min as above. The reaction gave 28 mg of starting material, 45 mg of **50**, and 65 mg of **49**. TLC showed complete absence of **39**.

Results of addition of *t*-BuOH and of replacement of Na by Li are given in Table II.

Relative Reactivities of 40 and 45. To a stirred solution of 97 mg of sodium in 40 mL of NH_3 was added a mixture of 200 mg each of **40** and **45** in 10 mL of THF. Workup after 1 min followed by column chromatography yielded 61 mg of **45**, 30 mg of **40**, and 275 mg of a mixture of more polar compounds, excluding **40** and **45**. Thus **40** appears to react twice as fast as **45**.

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Registry No. 1a, 21489-86-1; **1b**, 58502-98-0; **1c**, 77081-48-2; **1d**, 58503-18-7; **1e**, 77081-49-3; **2a**, 21489-85-0; (*E*)-**2b**, 58503-11-0; (*E*)-**2b** β-epoxide, 58503-14-3; (*Z*)-**2b**, 58503-12-1; (*Z*)-**2b** β-epoxide, 58503-13-2; **2d**, 58503-19-8; **2e**, 77081-50-6; **3a**, 32232-84-1; **3b**, 32232-85-2; **4**, 77071-08-0; **5**, 77081-51-7; **6**, 77081-52-8; **7**, 77081-53-9; **8**, 77081-54-0; **9**, 77081-55-1; **10**, 77081-56-2; **11**, 77081-57-3; **12**, 77081-58-4; **13**, 77081-59-5; **14**, 77081-60-8; **15**, 77081-61-9; **16**, 77081-62-0; **17**, 77081-63-1; **18**, 77081-64-2; **19**, 77081-65-3; **20**, 77081-66-4; **20** tosyl hydrazone, 77081-67-5; **21**, 77081-68-6; **22**, 77081-69-7; **23**, 77081-70-0; **24**, 77081-71-1; **25**, 77081-72-2; **26**, 77081-73-3; **27**, 77071-10-4; **28**, 6996-36-7; **29**, 60069-43-4; **30**, 77081-74-4; **31**, 26538-48-7; **32**, 77081-75-5; **33**, 77081-76-6; **34**, 77081-77-7; **35**, 77097-77-9; **36**, 77081-78-8; **37**, 77081-79-9; **38**, 77081-80-2; **39** (isomer 1), 77111-00-3; **39** (isomer 2), 77111-01-4; **40**, 77081-81-3; **41**, 77081-82-4; **42**, 77081-83-5; **43**, 77081-84-6; **44**, 77097-02-0; **45**, 77081-85-7; **46**, 77081-86-8; **47**, 77081-87-9; **48**, 77081-88-0; **49**, 77081-89-1; **50**, 77081-90-4; 7α-methyl-4,5-secocholest-3-yn-5α-ol, 77081-91-5; 4,5-secocholest-3-en-5β-ol, 77071-09-1; 4-methyl-4,5-secocholest-3-yn-5β-ol, 58503-16-5; 4-deuterio-4,5-secocholest-3-yn-5α-ol, 77081-92-6; 4-deuterio-4,5-secocholest-3-yn-5β-ol, 77081-93-7; 4a,5-seco-*A*-homocholest-4(4a)-yn-5α-ol, 77081-94-8; 4a,5-seco-*A*-homocholest-4(4a)-yn-5β-ol, 77071-07-9; 5β-methyl-3-methylene-*A*-norcholestan-7-one, 77081-95-9; 5β-methyl-4,5-secocholest-3-yn-7-one, 77081-96-0; 3-methyl-*A*-norcholest-3(5)-ene, 6908-07-2.

Supplementary Material Available: Preparation and melting point, $[\alpha]_D$, IR, and NMR data for **10–13**, **19**, **21–25**, **29**, **30**, **32**, **35–37**, and **48** as well as C and H analysis of all except **22**, **24**, and **25**; unsuccessful attempts at conversion of **20** to **25**; details of naphthalene–sodium reaction on **10** and **13**; structure and stereochemistry determinations for **27**; alternative preparations of **33**, **34**, **42**, **43**, **46**, **47**, and **50** (8 pages). Ordering information is given on any current masthead page.

Mechanism of Reduction of Enolizable Saturated Ketones and α,β-Unsaturated Ketones by Sodium in Liquid Ammonia

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The ratios of reduction product to (reductive) cyclization product obtained from the reactions of 4-methyl-4,5-secocholest-3-yn-5-one (**1b**) and 4,5-secocholest-3-en-5-one (**4**) with Na/NH_3/THF were found to be directly proportional to the initial concentration of sodium/electrons taken in excess but independent of ketone concentration. It followed that the intermediate undergoing cyclization was simultaneously taking up another Na/e to eventually give the secondary alcohol. This crucial evidence taken in conjunction with (i) the 1:1 reduction/recovery ratio found at the same time, (ii) the failure of these compounds to give reduction products with $C_{10}H_8Na$/THF and Na/THF, and (iii) the formation of 5α,6,6-trideuterated 4,5-secocholestan-5β-ol from 6,6-dideuterated 4,5-secocholestan-5-one on treatment with Na/NH_3/THF has been used to distinguish between alternative mechanisms of alkali metal/NH_3 reductions of enolizable ketones. All except the vicinal dianion stand excluded. Two alternatives are proposed for its subsequent behavior. Alkali metal/NH_3 reductions of α,β-unsaturated ketones are also considered as proceeding via dianions. By extending the study to 4,5-secocholest-3-yn-5-one (**1a**) and 4a,5-seco-*A*-homocholest-4(4a)-yn-5-one (**1c**) the reactivity to cyclization via a 5-ketyl has been shown to be **1a** > **1c** > **1b** > **4**.

The mechanism of reduction of ketones by alkali metals in alcohols, ethers, and ammonia undoubtedly involves the formation of a radical anion in the first step. No agreement exists as to the sequence of addition of the remaining

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