Organocuprate-Mediated Methods for the Stereospecific Introduction of Steroid Side Chains at C-20

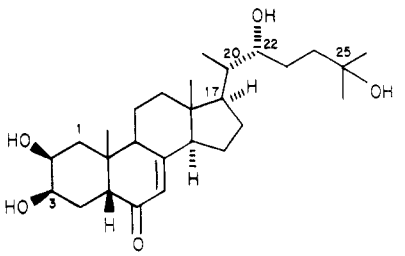
Norman R. Schmuff and Barry M. Trost*

McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

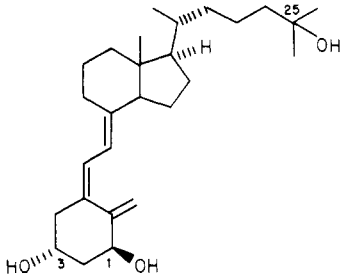
Received August 16, 1982

The reactions of organocuprates with various $\Delta^{17(20)}$-unsaturated steroid substrates leads to the stereocontrolled introduction of the side chain onto the steroid nucleus to give either desired C-20 epimer. The reaction of an E-$\Delta^{17(20)}$-16-keto steroid with lithium diisohexylcuprate leads to α-face attack, giving exclusively a product having the "natural" 20R chirality. This product was then converted to cholesterol. The reactions of either the E-$\Delta^{17(20)}$-16α-pivalyloxy or the corresponding 16β-pivaloyloxy steroid with lithium isohexylcyanocuprate each proceeded in a regio- and stereocontrolled manner. The former (16α) compound gave exclusively the "unnatural" 20S chirality while the latter (16β) compound gave exclusively the "natural" 20R chirality. The 20S compound was converted to 20-epicholesterol, and similarly, the 20R compound was converted to cholesterol. A result complementary to that of the pivalates ensued from the E-$\Delta^{17(20)}$-16α-N-phenylcarbamoyl steroid, which was converted by the action of a presumed internal mixed cuprate to a compound having 20R chirality.

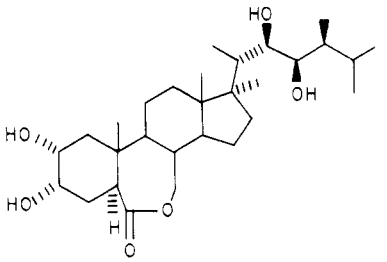
The stereospecific introduction of steroid side chains onto the basic steroid nucleus has attracted a good deal of recent interest,[1-3] particularly as it relates to the ecdysones,[4] vitamin D metabolites,[5] halosterols,[6] and the newly discovered plant-growth regulator brassinolide.[7] We report here two efficient approaches that involve the stereo- and regiocontrolled cuprate addition to an enone and to allylic alcohol derivatives. At a time when our work was essentially complete, a report by Marino[3c] appeared, which described the reactions of $\Delta^{17(20)}$ type steroidal vinyl oxiranes with alkylcyanocuprates, a method that is closely related to one of the methods detailed herein. Our initial approach to side-chain introduction involved the selective α-face addition of the elements of RH to a $\alpha^{17(20)}$ olefin,



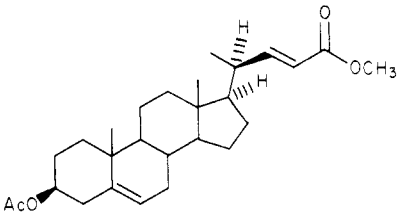
ecdysone



1,25-dihydroxyvitamin D_3



brassinolide



methyl (20R,22E)-3β-acetoxychola-5,22-dienoate

(1) For a review, see: Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199.

(2) For previous palladium-mediated approaches, see: (a) Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435.

(3) For recent references exemplifying C-20 stereocontrol, see: (a) Takahashi, T.; Naito, Y.; Tsuji, J. *J. Am. Chem. Soc.* **1981**, *103*, 5261. (b) Takahaski, T.; Yamada, H.; Tsuji, J. *Ibid.* **1981**, *103*, 5259. (c) Marino, J. P.; Abe, H. *Ibid.* **1981**, *103*, 2907. (d) Kametani, T.; Masayoshi, T.; Nemoto, H. *Tetrahedron Lett.* **1981**, *22*, 2373. (e) Batcho, A. D.; Berger, D. E.; Davoust, S. G.; Wovkulich, P. M.; Uskoković, M. R. *Helv. Chim. Acta* **1981**, *64*, 1682. (f) Batcho, A. D.; Berger, D. E.; Uskokovic, M. R.; Snider, B. B. *J. Am. Chem. Soc.* **1981**, *103*, 1293. (g) Dauben, W. G.; Brookhart, T. *Ibid.* **1981**, *103*, 237. (h) Midland, M. M.; Kwon, Y. C. *J. Org. Chem.* **1981**, *46*, 229. (i) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862. (j) Grieco, P. A.; Takigawa, T.; Moore, D. R. *Ibid.* **1979**, *101*, 4380. (k) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *Ibid.* **1979**, *101*, 4378. (l) Riediker, M.; Schwartz, J. *Tetrahedron Lett.* **1981**, *22*, 4655. (m) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172. (n) Partridge, J. J.; Shivey, S.-J.; Chadha, N. K.; Baggiolini, E. G.; Hennessy, B. M.; Uskokovic, M. R.; Napoli, J. L.; Reinhardt, T. A.; Horst, R. L. *Helv. Chim. Acta* **1981**, *64*, 2138. (o) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1982**, *23*, 2077.

(4) (a) Coudron, T. A.; Law, J. H.; Koeppe, J. K. *Trends Biochem. Sci. (Pers. Ed.)* **1981**, *6*, 248. (b) Hikino, H.; Hikino, Y. *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 256. (c) Nakanishi, K. *Pure Appl. Chem.* **1971**, *25*, 167. For a recent total synthesis of 20-hydroxyecdysone, see: Kametani, T.; Tsubuki, M.; Nemoto, H. *Nippon Kagaku Kaishi* **1981**, 819.

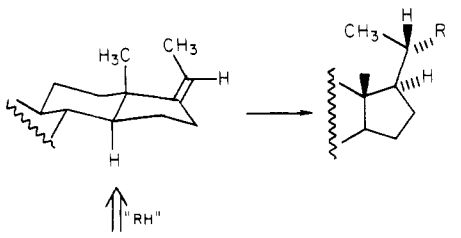
(5) (a) DeLuca, H. F. *Annu. Rev. Physiol.* **1981**, *43*, 199. (b) Uskokovic, M. R.; Partridge, J. J.; Narwid, T. A.; Baggiolini, E. G. In "Vitamin D: Basic and Clinical Nutrition"; Norman, A. W., Ed.; Marcel Dekker: New York, 1980; Vol. 2, p 1 ff. (c) Yakhimovich, R. I. *Russ. Chem. Rev. (Engl. Transl.)* **1980**, *49*, 371. (d) DeLuca, H. F. *Nutr. Rev.* **1980**, *38*, 169. (e) Fraser, D. R. *Physiol. Rev.* **1980**, *60*, 551. (f) Lythgoe, B. *Chem. Soc. Rev.* **1980**, *9*, 449. (g) Monnier, L.; Colette, C.; Mirouze, J. *Diabete Metab.* **1980**, *6*, 159. (h) Stern, P. H. *Pharmacol. Rev.* **1980**, *32*, 47. (i) Norman, A. W.; Henry, H. L. *Trends Biochem. Sci.* **1979**, *4*, 14. (j) Lawson, D. E. M.; Davie, M. *Vitam. Horm. (N.Y.)* **1979**, *37*, 1.

(6) (a) Djerassi, C. *Pure Appl. Chem.* **1981**, *53*, 873. (b) Barbier, M. *Mar. Nat. Prod.: Chem. Biol. Perspect.* **1981**, *4*, 147. (c) Goad, L. J. *Ibid.* **1978**, *2*, 75. (d) Schmitz, F. J. *Ibid.* **1978**, *1*, 241. (e) Nes, W. R.; McKean, M. L. "Biochemistry of Steroids and Other Isopentenoids"; University Park Press: Baltimore, MD, 1977; pp 411-533. (f) Scheurer, P. J. "Chemistry of Marine Natural Products"; Academic Press: New York, 1973; pp 58-87.

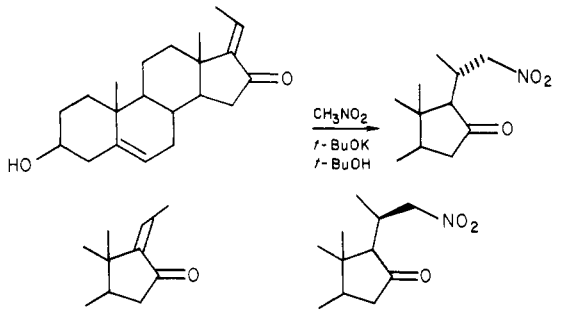
(7) (a) Takatsuto, S.; Ying, B.; Morisaki, M.; Nobuto, I. *Chem. Pharm. Bull.* **1981**, *29*, 903. (b) Wada, K.; Marumo, S.; Ikekawa, N.; Morisaki, M.; Mori, K. *Plant Cell Physiol.* **1981**, *22*, 323. (c) Maugh, T. H. *Science (Washington, D.C.)* **1981**, *212*, 33. (d) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580. (e) Ishiguro, M.; Takatsuto, S.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc. Chem. Commun.* **1980**, 962. (f) Mori, K. *Agric. Biol. Chem.* **1980**, *44*, 1211.

0022-3263/83/1948-1404$01.50/0

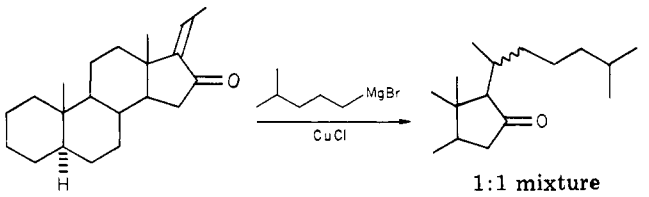
with the Z olefin shown, giving a product with the natural



20α-H chirality. This conceptual approach has been previously recognized by Kessar[8] and Djerassi.[9] Kessar has examined the 1,4-addition of nitro-stabilized carbanions to both E and Z isomers of $\Delta^{17(20)}$-16-oxo steroids and

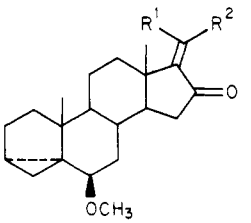


concludes that "predominantly one product is formed in each case",[8d] though the extent of stereocontrol is not further quantitated. In the course of mass spectral studies of labeled steroids, Djerassi conducted copper-catalyzed

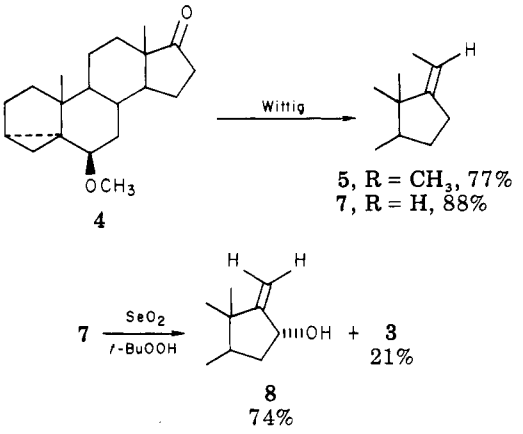


Grignard additions to similar steroidal enones and observed that mixtures of C-20 epimers were produced starting either from the pure E or Z isomer.[9]

In connection with another project,[10] we had prepared steroidal enones **1**, **2**, and **3** from the known ketone **4**,[2a,11] which is derived from dehydroepiandrosterone. Allylic oxidation of olefin **5**[2a,12] to alcohol **6** (Scheme I) using the procedure developed Sharpless[13,14] proved to be superior to the classical selenium dioxide/ethanol procedure employed earlier in these laboratories for a similar oxidation.[15,16] Though enone **3** was obtained initially as an

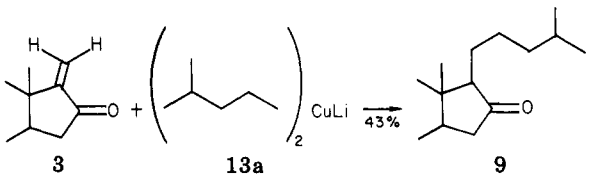


1, $R^1 = CH_3$; $R^2 = H$
2, $R^1 = H$; $R^2 = CH_3$
3, $R^1 = H$; $R^2 = H$



overoxidation product in the allylic oxidation of the corresponding olefin, in general it proved to be more convenient to prepare enone **1** by a two-step procedure via allylic alcohol **6**.[17] This alcohol was oxidized to the E enone **1** by using a modified Moffatt type oxidation[18,19] (note that the E enone **1** has the same double-bond geometry as the starting Z olefin, the change in designation being due to the introduction of the 16-oxygen). It is noteworthy that enone **1** [δ 6.40 (1 H, q, J = 7.5 Hz, CH-20), 1.78 (3 H, d, J = 7.5 Hz, CH_3-20)] was the exclusive oxidation product if the crude product was immediately purified; however, if the crude product was allowed to stand for 48 h prior to purification, enone **1** was found to contain a considerable amount of the Z isomer **2** [δ 5.68 (1 H, q, J = 8.3 Hz, CH-20), 2.05 (3 H, d, J = 8.4 Hz, CH_3-21)].

The reaction of enone **3** with 4 equiv of lithium diisoamylcuprate led to a moderate yield of the dinorcholesterol derivative **9**. Under similar conditions enone **1** gave a



3 **13a** **9**

single product **10** as judged by 270-MHz ^{1}H NMR and 50-MHz ^{13}C NMR. The chirality is assigned as 20R (20α-H), on the basis of an analogy with the homologous compound **11**, whose C-20 chirality was determined with

(8) (a) Kessar, S. V.; Rampal, A. L. *Chem. Ind. (London)* **1963**, 1957. (b) Kessar, S. V.; Rampal, A. L.; Mangat, S.; Gupta, Y. P. *Indian J. Chem.* **1966**, *4*, 501. (c) Kessar, S. V.; Rampal, A. L. *Tetrahedron* **1968**, *24*, 887. (d) Kessar, S. V.; Gupta, Y. P.; Mahajan, R. K.; Rampal, A. L. *Ibid.* **1968**, *24*, 893. (e) Kessar, S. V.; Gupta, Y. P.; Mahajan, R. K.; Joshi, G. S.; Rampal, A. L. *Ibid.* **1968**, *24*, 899. (f) Kessar, S. V.; Rampal, A. L.; Gupta, Y. P. *Ibid.* **1968**, *24*, 905.

(9) (a) Beard, C.; Wilson, J. M.; Budzikiewicz, H.; Djerassi, C. *J. Am. Chem. Soc.* **1964**, *86*, 269. (b) Wyllie, S. G.; Djerassi, C. *J. Org. Chem.* **1968**, *33*, 305.

(10) Trost, B. M.; Schmuff, N. R., unpublished results.

(11) Thoa, H. K.; Procházka, Z.; Budensinski, M.; Kocousky, P. *Collect. Czech. Chem. Commun.* **1978**, *43*, 2305.

(12) Brown, F. J. Ph.D. Thesis, Stanford University, Stanford, CA, 1980.

(13) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

(14) For other recent uses of this procedure, see: (a) Paaren, H. E.; DeLuca, H. F.; Schnoes, H. K. *J. Org. Chem.* **1980**, *45*, 3253. (b) Haruna, M.; Ito, K. *J. Chem. Soc., Chem. Commun.* **1981**, 483.

(15) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435.

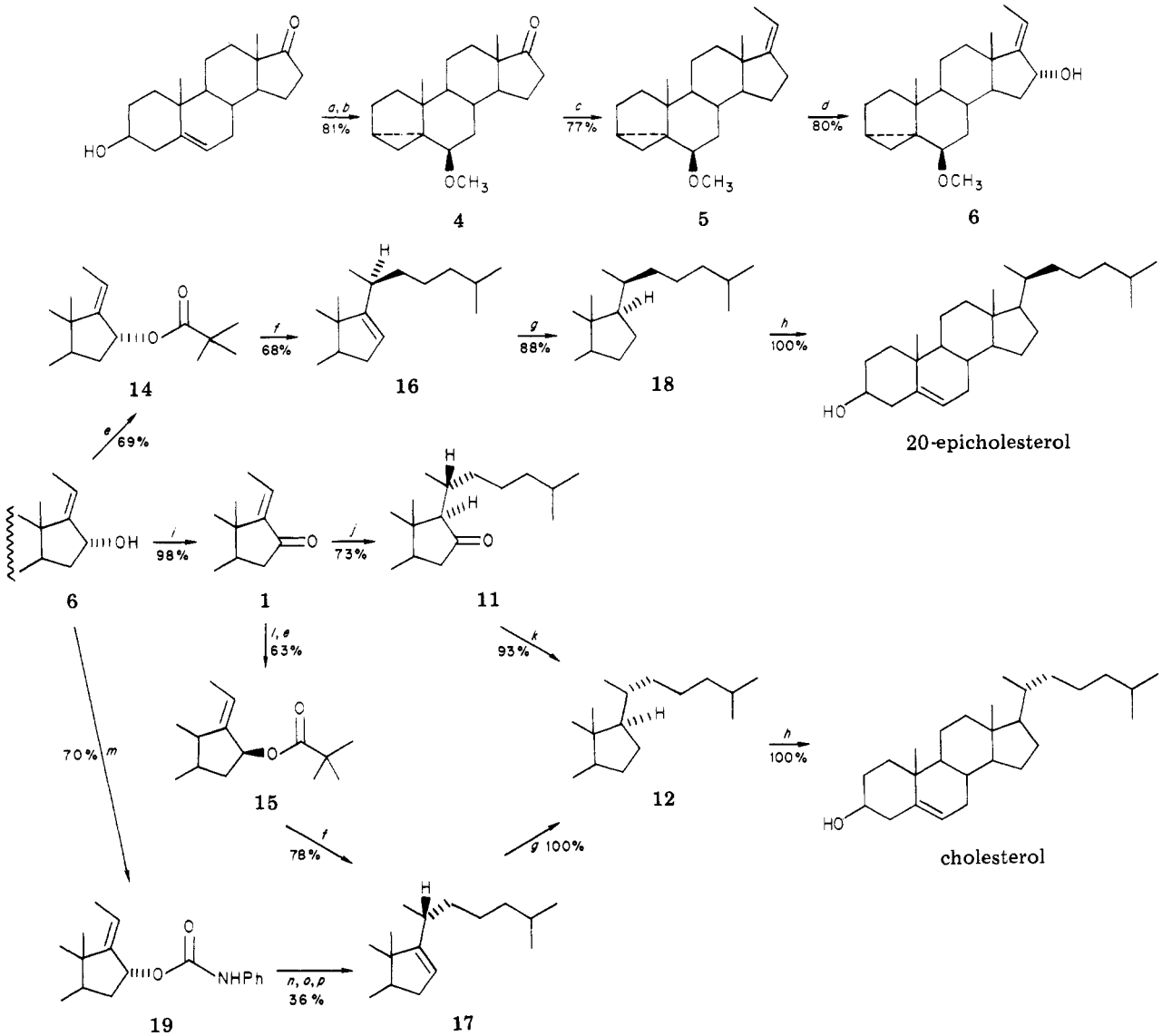
(16) For other reports concerning the selenium dioxide oxidation of $\Delta^{17(20)}$ type steroids, see: (a) Pike, J. E.; Lincoln, F. H.; Spero, G. B.; Jackson, R. W.; Thomson, J. L. *Steroids* **1968**, *11*, 755. (b) Upjohn Co. Neth. 1965; Pat. *Appl.* 6414319, *Chem. Abstr.* **1966**, *64*, 3645b. (c) Upjohn Co. Brit. Pat. 1088160, 1968; *Chem. Abstr.* **1968**, *69*, 10623u.

(17) Alcohol **6** has also been prepared by Wharton reaction of the appropriate epoxy ketone. Both E and Z olefin isomers of the 16α-alcohol are produced.[3i]

(18) Mancuso, A. J; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. For a review of Me_2SO-mediated oxidations, see: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

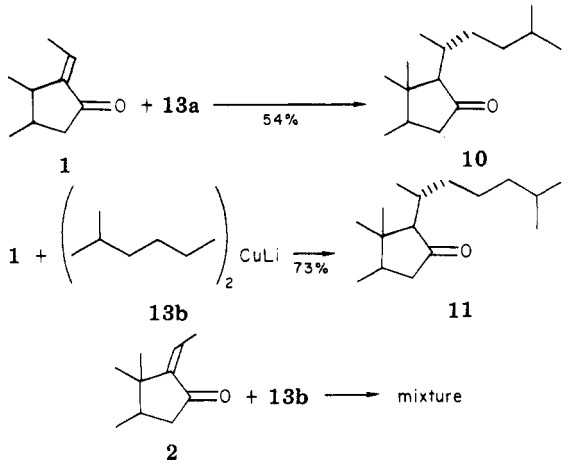
(19) Oxidation of a similar allylic alcohol using chromium-based reagents is reported to give isomeric mixtures.

Scheme I. Alkylcuprate-Mediated Routes to Cholesterol and 20-Epicholesterol



[a] TsCl, pyridine. [b] MeOH, KOAc. [c] $Ph_3PCH_2CH_3^+/Br^-$, *t*-BuOK, THF. [d] SeO_2, *t*-BuOOH. [e] $(CH_3)_3CCOCl$, Et_3N. [f] *i*-$C_6H_{13}CuCN$, Et_2O. [g] H_2, 5% $Pd/BaCO_3$. [h] TsOH, aqueous dioxane. [i] Me_2SO, $(COCl)_2$. [j] $(i\text{-}C_6H_{12})_2CuLi$, Et_2O. [k] N_2H_4, K_2CO_3, triethylene glycol. [l] $LiAlH_4$. [m] PhNCO. [n] *n*-BuLi. [o] CuI. [p] *i*-$C_6H_{13}Li$.

certainty (vide infra). Enone 1 then was reacted with lithium diisohexylcuprate to give cholestanone 11 as the only detectable C-20 isomer. Subsequent Wolff–Kishner



reduction then gave the known iso-cholesterol methyl ether **12**.[20] This material was subsequently converted into cholesterol, which proved to be identical with authentic material as judged by 270-MHz ^1H NMR, ^{13}C NMR, IR, and mixed-melting-point determination. The reaction of lithium diisohexylcuprate with enone **2** appeared to give a mixture of products as judged by NMR, and this material was not further characterized. The foregoing enone-based reactions, then, provide a method for the stereocontrolled preparation of 16-keto steroids having the natural 20α-H chirality.[21]

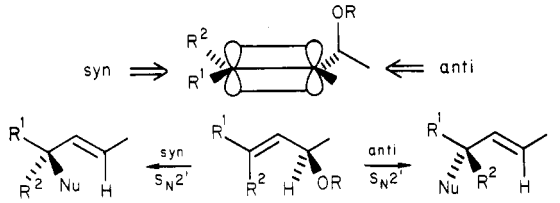
The second approach to side-chain introduction was prompted by recent successful efforts in controlling both the regio- and stereochemistry of nucleophilic attack in various allylic alcohol derivatives.[22-25] Thus, it appears

(20) (a) Nes, W. R.; Varkey, T. E.; Crump, D. R.; Gut, M. *J. Org. Chem.* **1976**, *41*, 3429. (b) Patel, M. S.; Peal, W. J. *J. Chem. Soc.* **1963**, 1544. (c) Riegel, B.; Hager, G. P.; Zenitz, B. L. *J. Am. Chem. Soc.* **1946**, *68* 2562. (d) Ford, E. G.; Wallis, E. S. *Ibid.* **1932**, *59*, 1415. (e) Wagner-Jauregg, T.; Werner, L. *Hoppe-Seyler's Z. Physiol. Chem.* **1932**, *213*, 119. (f) Stoll, W. *Ibid.* **1932**, *207*, 147.

(21) Conceptually this method might also be applicable to the stereocontrolled synthesis of 20β-H type compounds by Wittig olefination to introduce the side chain followed by reaction of the corresponding enone with lithium dimethylcuprate to introduce the 20-CH_3.

(22) Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4256.

that by appropriate selection of a cuprate auxilliary ligand, exclusive S_N2' substitution can be achieved. Furthermore, it is possible to select either the syn-facial or apo-facial (anti) mode of replacement as desired by adjustment of the nucleofuge and reaction conditions. The first of the



allylic alcohol derivatives investigated were the epimeric pivalates **14** and **15**. The 16β-alcohol corresponding to **15** is available as the exclusive epimer resulting from lithiumaluminum hydride reduction of enone **1**. Reaction of each individual epimeric ester[26] with lithium isohexylcyanocuprate[27,28] proceeded in a regio- and stereospecific manner to give **16** and **17**, respectively, products of the expected apo-facial mode of reaction. In each case a trace (~5%) of the corresponding regioisomer could be discerned in the crude 270-MHz ^{1}H NMR [for **16**, δ 5.72 (1 H, br s, CH-16) with a small signal for the presumed regioisomer at δ 5.05 (qd, J = 6.8, 2.2 Hz, CH-20); for **17**, δ 5.25 (1 H, t, J = 1.3 Hz, CH-16) with a small signal for the presumed regioisomer at δ 5.11 (qd, J = 7.5, 2.5 Hz, CH-20)]. Neither **16** nor **17** seemed to be contaminated with the other epimer to any detectable extent on the basis of an examination of the 270-MHz ^{1}H NMR and 15-MHz ^{13}C spectra where it is estimated that 5–10% contamination could be detected in each case. The most definitive distinguishing feature of the two isomers is the ^{1}H NMR chemical shift for the C-21 signals, with that of **16** appearing at δ 1.01 while that of **17** appears at δ 0.96. It is noteworthy that compound **17** of the natural 20*R* chirality has the more upfield shift for this signal, a trend that is opposite to that found in compounds saturated at the 16(17)′ position.[1,29] This reversal of trends for C-21 signals in Δ^{16} type steroids appears to be general.[3c,30]

Compound **16** was then hydrogenated to give **18** whose spectral properties clearly differ from those of the previously prepared **12** [for **12**, δ 0.91 (3 H, d, J = 6.4 Hz, CH_3-21) and for **18** δ, 0.81 (3 H, d, J = 6.5 Hz, CH_3-21)]. Similarly, **17** was hydrogenated to give iso-cholesterol methyl ether **12** identical by spectral comparison with that previously prepared from ketone **11** (vide supra), thereby confirming the 20*R* chirality of **17**. The 20*S* chirality of **16** was then verified by the treatment of **18** with aqueous acid in dioxane to give 20-epicholesterol whose physical constants were in agreement with those previously reported.[3c,i,29,31]

Carbamate **19** was then prepared from alcohol **6**. Reaction of this compound first with 1 equiv of *n*-butyllithium followed by sequential treatment with cuprous iodide and isohexyllithium afforded a 36% isolated yield of the previously identified olefin **17**, a result of the expected syn-facial mode of reaction.[32,33] The reaction of the 16α-carbamate **19** is seen to give a complementary stereochemical result to that from the 16α-pivalate **14**. That is, whereas **14** gave **16**, **15** produces **17**; therefore, either C-20 epimeric product is available from a single alcohol precusor.

There are a number of desirable features of the foregoing protocol for steroid side-chain introduction. First, it begins with a readily available class of compounds, the 17-keto steroids, which can be obtained either from the sapogenins[34] or the soybean sterols (by chemical[35] or microbiological[36] methods). Second, it allows for the synthesis of both C-20 epimers[37] in a predictable manner[38] from common intermediates. Further, the entire intact steroid side chain can be introduced directly in one step with a minimum of superfluous functionality. The approaches' flexibility lies in their potential convergence of variously functionalized 17-keto steroids[40] with the wide assortment of available cuprate side-chain components.[42,43]

From a synthetic viewpoint, the sequence involves relatively few steps (eight to ten from dehydroepiandrosterone to the final products), each of which can be expediently conducted on a large or small scale. The overall yield is good being from 13% to 33% from dehydroepi-

(23) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1981**, *46*, 2144.
(24) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318.
(25) For a review of previous work in the area of cuprate addition to allylic systems, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.
(26) Reaction of the 16α-acetate of alcohol **6** with the mixed cuprate was found to give carbonyl attack at a rate comparable to that of the substitution.
(27) Note that the cuprate species present in solution and responsible for the substitution is assumed to have a stoichiometry of $RCuCN^-$ although in each case more than 1 equiv of cuprous cyanide was used.
(28) For a recent report concerning the use of mixed alkyl cyanocuprates in substitution reactions at unactivated secondary centers, see: (a) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672. (b) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *Ibid.* **1982**, *104*, 2305.
(29) Nes, W. R.; Varkey, T. E.; Krevitz, K. *J. Am. Chem. Soc.* **1977**, *99*, 260.
(30) Schmuff, N. R. Ph.D. Thesis, University of Wisconsin—Madison, 1982.
(31) (a) Koreeda, M.; Koizumi, N. *Tetrahedron Lett.* **1978**, 1641. (b) Sondheimer, F.; Mechoulam, R. *J. Am. Chem. Soc.* **1958**, *80*, 3087.
(32) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035.
(33) Goering, H. L.; Kantner, S. S., unpublished results.
(34) (a) Tendick, F. H.; Lawson, E. J. U.S. Patent 2 335 616, 1943; *Chem. Abstr.* **1944**, *38*, 3095. (b) Rosenkranz, G.; Mancera, O.; Sondheimer, F.; Djerassi, C. *J. Org. Chem.* **1956**, *21*, 520. (c) Wilson, C. O.; Gisvold, O.; Doerge, R. F. "Textbook of Organic Medicinal and Pharmaceutical Chemistry", 7th ed.; Lippencott: Philadelphia, PA; 1977; pp 813–817. (d) Lehmann, P. A.; Boliva, A.; Qunitero, R. *J. Chem. Educ.* **1973**, *50*, 195.
(35) Fieser, L. F.; Fieser, M. "Steroids"; Reinhold: New York, 1959; pp 552–553.
(36) (a) Martin, C. K. A. *Adv. Appl. Microbiol.* **1977**, *22*, 28. (b) Shoemer, U.; Martin, C. K. A. *Biotechnol. Bioeng.* **1980**, *22*, 11.
(37) Steroids having the "unnatural" 20β-H chirality have proved useful in a number of biological studies. See, for example: (a) Teicher, B. A.; Koizumi, N.; Koreeda, M.; Shikita, M.; Talalay, P. *Eur. J. Biochem.* **1978**, *91*, 11. (b) Nes, W. R.; Joseph, J. M.; Landrey, J. R.; Behzadan, S.; Connor, R. L. *J. Lipid. Res.* **1981**, *22*, 770. (c) Nes, W. R; Alder, J. H.; Joseph, J.; Landrey, J. R.; Connor, R. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1977**, *36*, 708. (d) Erickson, K. J.; Nes, W. R., unpublished results cited in: Nes, W. R. "Biogenesis and Function of Plant Lipids"; Mazliak, P., Benveniste, P., Costes, C., Douce, R., Eds.; Elsevier/North-Holland: Amsterdam, 1980; pp 387–394.
(38) The availability of comparison material of known C-20 chirality would be useful in cases where this chirality can be assigned only tentatively. For example, in one case,[39] lack of sufficient natural material permitted assignment of the "unnatural" 20β-H chirality only by inference from an anomalous GC retention time.
(39) Idler, D. R.; Khalil, M. W.; Gilbert, J. D.; Brooks, C. J. W. *Steroids* **1976**, *27*, 155.
(40) For example, either dehydroepiandrosterone[41] or its iso-methyl ether **4**[11] can be microbiologically hydroxylated at the 1-position to give precursors for the therapeutically important vitamin D metabolites containing an oxygen function at this position.
(41) Dodson, R. M.; Goldkamp, A. H.; Muir, R. D. *J. Am. Chem. Soc.* **1960**, *82*, 4026.
(42) (a) Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1. (b) Posner, G. H. *Ibid.* **1975**, *22*, 253. (c) Posner, G. H. "Introductions to Synthesis Using Organocopper Reangets"; Wiley-Interscience: New York, 1980.
(43) For recent examples of functionalized cuprates, see, e.g.: (a) Baldwin, J. E.; Hofle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125. (b) Chavdarian, C. G.; Heathcock, C. H. *Ibid.* **1975**, *97*, 3822. (c) Boeckman, R. K., Jr.; Bruza, K. J.; Baldwin, J. E.; Lever, O. W., Jr. *J. Chem. Soc., Chem. Commun.* **1975**, 519. (d) Baldwin, J. E.; Lever, O. W., Jr.; Tzodikov, N. R. *J. Org. Chem.* **1976**, *41*, 2312. (e) Boeckman, R. K., Jr.; Bruza, K. J. *Ibid.* **1979**, *44*, 4781. (f) Huynh, C.; Linstrumell, G. *Tetrahedron Lett.* **1979**, 1073.

androsterone to cholesterol or 20-epicholesterol. The cuprate reactions, with the exception of that of enone **2**, proceed with near complete (i.e., >90%) regio- and stereocontrol. Of the current solutions to the problem of C-20 stereocontrol, the one detailed above compares quite favorably in terms of flexibility, simplicity, and expediency.

Experimental Section

General Methods. All reactions were run under a positive pressure of dry nitrogen or argon. Reactions requiring anhydrous conditions were performed in flame-dried glassware that was cooled under nitrogen. Anhydrous solvents were transferred by an oven-dried syringe. Solvents were distilled before use: dichloromethane, pyridine, dimethyl sulfoxide, hexane, and pentane from calcium hydride; diethyl ether, tetrahydrofuran (THF), 1,2-dimethoxyethane, and 1,4-dioxane from sodium benzophenone ketyl; acetone from barium oxide; methanol from magnesium. After workup, all organic layers were dried over anhydrous magnesium sulfate. The term "in vacuo" refers to solvent removal via a Büchi Rotoevaporator at water-aspirator pressure, followed by evacuation of the flasks at ~0.1 torr for several hours. Preparative thin-layer chromatography (TLC) was performed on 20 × 20 cm or 20 × 40 cm glass plates coated with 1.5 mm of silica gel (Machery-Nagel, MN-Kieselgel, P/UV_{254} Cat. No. 8163880). Analytical TLC was performed on plastic-backed plates coated with silica gel (Merck 60-PF254). Column chromatography was performed by using silica gel obtained from W. R. Grace (Grade 62, 60–200 mesh). Preparative high-pressure liquid chromatography (HPLC) was performed on a Waters Prep 500A instrument using either a PrepPak-500 cartridge or a homemade semiprep column (2.5 × 30 cm, μPoracil, 37–75 μm). Melting points were obtained on a Thomas-Hoover apparatus using open capillary tubes. Melting points are uncorrected.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Jeol MH-100 (100 MHz) or a Bruker WH-270 (270 MHz) instrument. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; br, broad. In spectra where splitting patterns are or may be non first order, the reported apparent coupling constant (J_{app}) refers to peak separations measured directly from such spectra. Coupling constants are reported in hertz (Hz). Infrared spectra (IR) were determined in the indicated solvents in sodium chloride cavity cells on a Perkin-Elmer 267 or a Beckman AccuLab 7. Carbon-13 nuclear magnetic resonance spectra were determined at 15 MHz on a Jeol FX-60 or at 50 MHz on a Jeol FX-200. Chemical shifts are reported in δ units, parts per million downfield from tetramethylsilane. Mass spectra (MS) were obtained on an AEI-902 instrument at an ionizing current of 98 mA and an ionizing voltage of 70 eV unless otherwise noted. Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI, or Galbraith Laboratories, Knoxville, TN. Optical rotations were performed on a Perkin-Elmer 141 or a Perkin-Elmer 241 polarimeter using a microcell (100 mm, 1 mL) in the indicated solvent and concentration (*c*) in grams of solute per 100 mL of solution.

(17*Z*)-6β-Methoxy-3α,5-cyclo-5α-pregn-17(20)-ene (5). A mixture of ethyltriphenylphosphonium bromide (74.3 g, 200 mmol) and potassium *tert*-butoxide (20 g, 180 mmol) in 100 mL of dry THF was vigorously stirred for 16 h (using an overhead mechanical stirrer). To this solution was added ketone **4**[2a,11] (21.8 g, 72.6 mmol) in 75 mL of the same solvent. This mixture was stirred at reflux for 48 h and then partitioned between 300 mL of hexane and 500 mL of 50% aqueous methanol. The aqueous methanol layer was extracted three additional times with 100-mL portions of hexane. The organic layers were combined, and the solvent was removed in vacuo. To the resulting oil was added 200 mL of methanol and 5 mL (80 mmol) of methyl iodide. This mixture was stirred at room temperature for 2 h, and the solvent and excess methyl iodide were removed in vacuo.[44] This mixture was then partitioned between 500 mL of hexane, and 500 mL of water. The aqueous layer was extracted with another 500 mL of hexane. Most of the solvent was removed from the combined organic layers. The remaining ~100 mL of solution was passed through a 75 mL silica gel column. The column was then washed with 200 mL of hexane. The solvent was removed in vacuo to give 21.1 g (93%) of the product as a yellow oil. Further purification was achieved by HPLC (100% hexane, the product begins to elute with the solvent front) to give 17.5 g (77%) of a colorless oil that solidifies on standing to give a solid of mp 50–53 °C (lit.[2a] 55–56 °C for recrystallized material). A small amount (~5%) of the corresponding *E* olefin was noted in later LC fractions. This minor isomer had ^{1}H NMR signals at δ 0.78 (s, CH_3-18) and δ 5.02 (qt, J = 6.6, 2.5 Hz).

For the *Z* isomer 5: IR ($CHCl_3$) 3045, 2930, 2865, 1430, 1370, 1085, 1070, 1010 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.11 (1 H, qd, J = 7.2, 2.1 Hz, CH-20), 3.35 (3 H, s, OCH_3), 2.79 (1 H, t, J = 2.8 Hz, CH-6α), 1.93 (1 H, dt, J = 13.4, 3.1 Hz, CH-7β), 1.66 (3 H, dt, J = 7.2, 2.0 Hz, CH_3-21), 1.04 (3 H, s, CH_3-19), 0.93 (3 H, s, CH_3-18), 0.66 (1 H, t, J_{app} = 4.5 Hz, CH-4β), 0.44 (1 H, dd, J = 5.0, 7.9 Hz, CH-4α); ^{13}C NMR (15 MHz, C_6D_6) δ 150.4, 113.6, 82.7, 56.9, 56.7, 48.8, 45.1, 44.0, 38.2, 36.0, 35.8, 34.0, 32.1, 30.8, 25.6, 25.0, 23.5, 21.9, 19.7, 17.4, 13.7, 13.5.

(17*E*)-6β-Methoxy-3α,5-cyclo-5α-pregn-17(20)-en-16α-ol (6). To a suspension of selenium dioxide (2.78 g, 25 mmol) in 50 mL of methylene chloride at 0 °C was added dropwise 4.50 mL (4.9 g, 49 mmol) of a 70% solution of *tert*-butyl hydroperoxide (Aldrich) to give a nearly homogeneous solution after stirring for 1 h. A solution of the steroidal olefin **5**[2a] (15.4 g, 49 mmol) in 150 mL of the same solvent was added dropwise at a rate such that the temperature did not exceed 0 °C. After holding the resulting mixture at the indicated temperature for 16 h, it was then stirred at room temperature for ~3 h (note that it probably would have been preferrable to stop the reaction sooner than this, while some starting material still remained) at which time 400 mL of benzene was added. The methylene chloride was removed in vacuo; then 200 mL of ether was added to the remaining benzene solution and the resulting mixture was extracted three times with 100-mL portions of 10% sodium hydroxide, followed by one extraction with brine. The organic layer was dried and the solvent evaporated in vacuo. The crude yellow oil was then purified by HPLC (7% ethyl acetate/hexane) to give 11.17 g (70%) of the 16α-alcohol **6** as a foam and approximately 500 mg (3%) of the 16β-alcohol. In some runs where the starting olefin was contaminated with 5–10% of the isomeric *E* olefin, a corresponding amount of the *Z*-$\Delta^{17(20)}$-16α-alcohol was observed but could be separated from **6** by chromatography. This compound was identified by spectral comparison with data reported by Tanabe[3i] for this material.

In a smaller scale run starting with 310 mg (0.99 mmol) of **5** and using 1 equiv of 70% *tert*-butyl hydroperoxide and the usual 50 mol % of selenium dioxide, the reaction was conducted for 0.5 h at room temperature in 10 mL of methylene chloride. After the usual workup and purification by preparative TLC (3:1 hexane/ethyl acetate), 325 mg (99%) of the alcohol **6** was isolated. An analytical sample of the **6** was obtained by crystallization from an ethyl acetate/hexane mixture, giving a solid of mp 107–108 °C (lit.[3i] mp 108–110 °C): IR ($CHCl_3$) 3600, 3350, 3060, 2990, 2930, 2860, 2820, 1450, 1375, 1105, 1085, 1075 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.56 (1 H, qd, J = 7.0, 1.3 Hz), 4.44 (1 H, br d, J = 4 Hz), 3.34 (3 H, s), 2.80 (1 H, t, J = 2.8 Hz), 2.26 (1 H, td, J = 11.5, 2.8 Hz), 1.91 (1 H, td, J = 12.4, 3.0 Hz), 1.74 (3 H, dd, J = 7.3, 0.9 Hz), 1.04 (3 H, s), 0.92 (3 H, s) 0.66 (1 H, t, J = 4.4 Hz), 0.45 (1 H, dd, J = 7.9, 5.1 Hz); ^{13}C NMR (15 MHz, C_6D_6) δ 156.1, 118.7, 82.7, 74.4, 56.7, 53.0, 48.7, 45.1, 44.0, 38.3, 35.9, 35.7, 35.6, 33.9, 30.1, 25.4, 23.3, 21.8, 19.6, 18.1, 13.6, 13.4; MS (30 eV), *m/e* (%) 330 (43), 316 (12), 315 (65), 298 (100), 296 (6), 280 (24), 275 (98), 273 (23), 265 (2), 214 (28), 145 (3), 135 (3), 121 (8), 120 (6), 119 (9), 118 (8), 109 (2), 107 (2), 105 (18), 95 (9), 93 (2). Anal. Calcd for $C_{22}H_{34}O_2$: 330.2559. Found: 330.2599.

(17*E*)-6β-Methoxy-3α,5-cyclo-5α-pregn-17(20)-en-16-one (1) and (17*Z*)-6β-Methoxy-3α,5-cyclo-5α-pregn-17(20)-en-16-one (2). To a solution of oxalyl chloride (654 μL, 951 mg, 7.5 mmol) in 15 mL of methylene chloride at −78 °C was added a solution of dimethyl sulfoxide (1.67 mL, 1.17 g, 15 mmol) in 5 mL of the same solvent. This solution was stirred at −78 °C for 5 min after which time the initially cloudy solution became clear. A solution

(44) This procedure converts the triphenylphosphine present to methyltriphenylphosphonium iodide, which can then be easily removed by chromatography or aqueous extraction. Triphenylphosphine is otherwise difficult to remove from the olefin **5** by chromatography.

of the 16α allylic alcohol **6** (2.24 g, 6.77 mmol) in 10 mL of methylene chloride was added dropwise to this mixture at −78 °C. After stirring for 15 min, neat triethylamine (2.78 mL, 2.02 g, 20 mmol) was added. The solution was allowed to warm to −20 °C, held at this temperature for 2 h, and then partitioned between 75 mL of chloroform and 25 mL of 10% hydrochloric acid. The organic layer was then extracted with a saturated solution of sodium bicarbonate, separated, and dried. After removal of the solvent in vacuo, the remaining oil was purified by filtration through a short silica gel column (75 mL), eluting with chloroform to give 2.18 g (98%) of the *E* enone as an oil uncontaminated by the corresponding *Z* isomer as judged by ^{1}H NMR. However, approximately 25% of the *Z* isomer was isolated in one run when the crude material was allowed to stand at room temperature before purification (these isomers are easily separable by TLC or HPLC).

For the *E* isomer 1: IR ($CHCl_3$) 3060, 3000, 2940, 2870, 2820, 1715, 1645, 1455, 1380, 1110, 1092, 1088 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.40 (1 H, q, J = 7.5 Hz), 3.30 (1 H, s), 1.78 (3 H, d, J = 7.0 Hz), 1.00 (6 H, s); MS, m/e (%) 328 (5), 313 (9), 296 (7), 273 (25), 174 (7), 159 (13), 135 (15), 107 (17), 105 (14), 95 (14), 93 (10), 91 (14), 85 (57), 83 (100), 79 (22), 55 (30), 47 (26), 44 (33), 43 (53), 41 (34). Anal. Calcd for $C_{22}H_{32}O_2$: 328.2402. Found: 328.2399. Calcd for $C_{22}H_{32}O_2 \cdot 0.5\ H_2O$: C, 78.29; H, 9.86. Found: C, 78.40; H, 9.70.

For the *Z* isomer 2: IR ($CHCl_3$) 3060, 3000, 2950, 2920, 2850, 1710, 1645, 1455, 1380, 1110, 1090, 1085 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.68 (1 H, q, J = 8.3 Hz), 3.32 (3 H, s), 2.05 (3 H, d, J = 8.4 Hz), 1.04 (3 H, s), 0.94 (3 H, s); MS, m/e (%) 328 (65), 313 (49), 296 (17), 273 (85), 191 (23), 164 (21), 149 (13), 135 (29), 107 (26), 105 (37), 95 (28), 93 (42), 91 (73), 83 (6), 81 (35), 79 (66), 77 (33), 71 (24), 69 (22), 67 (37), 55 (72), 45 (21), 44 (17), 43 (54), 41 (100). Anal. Calcd for $C_{22}H_{32}O_2$: 328.2402. Found: 328.2402.

(17*E*)-6β-Methoxy-3α,5-cyclo-5α-pregn-17(20)-en-16β-ol. The ketone **1** (281 mg, 0.86 mmol) was dissolved in 20 mL of cyclohexane and distilled until ~5 mL of solvent remained to remove any water. To this solution was added 20 mL of ether, and this mixture was cooled to −78 °C. To this solution was added lithium aluminum hydride (80 mg, 2.10 mmol), and the cooling bath was removed. After warming the solution to room temperature during 1 h, the excess hydride was quenched by the dropwise addition of ethyl acetate and this mixture was partitioned between 75 mL of ether and 30 mL of 10% sodium bisulfate. The organic layer was then extracted with 30 mL of brine and 30 mL of 10% sodium hydroxide. The organic layer was dried, and the solvent was removed in vacuo. Analysis of the crude product by analytical HPLC (3% ethyl acetate/hexane) indicated the presence of less than 1% of the 16α-isomer **6**. The crude product was purified by preparative HPLC (5% ethyl acetate/hexane) to give 219 mg (77%) of the 16β-alcohol as a foam that solidified on standing unrecrystallized (mp 108–109 °C). An analytical sample was obtained by recrystallization from hexane to give a sample with mp 105–107 °C: IR ($CHCl_3$) 3600, 3440, 3060, 2990, 2930, 2860, 2820, 1460, 1380, 1090, 1075 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.51 (1 H, qd, J = 7.1, 1.8 Hz), 4.35 (1 H, t, J = 7.5 Hz), 3.34 (3 H, s), 2.28 (1 H, m), 2.12 (1 H, ddd, J = 11.5, 7.5, 5 Hz), 1.73 (3 H, dd, J = 792, 1.7 Hz), 1.09 (3 H, s), 1.04 (3 H, s), 0.66 (1 H, t, J = 4.8 Hz), 0.45 (1 H, dd, J = 7.8, 5.1 Hz); MS (27 eV), m/e (%) 330 (85), 316 (15), 315 (65), 298 (32), 296 (18), 280 (31), 275 (63), 273 (32), 265 (26), 216 (37), 215 (87), 214 (100), 199 (36), 159 (56), 145 (43), 135 (43), 121 (64), 130 (37), 119 (45), 109 (34), 107 (49), 105 (44), 95 (36), 93 (41). Anal. Calcd for $C_{22}H_{34}O_2$: M_r, 330.2559; C, 79.95; H, 10.37. Found: M_r, 330.2562; C, 79.73; H, 10.57.

17-Methylene-6β-methoxy-3α,5-cyclo-5α-androstane (7). To a bright yellow mixture of methyltriphenylphosphonium bromide (1.61 g, 4.5 mmol) and potassium *tert*-butoxide (483 mg, 4.3 mmol) in 5 mL of dry THF was added ketone **4** (922 mg, 3.05 mmol) in 25 mL of the same solvent. After refluxing for 16 h, the mixture was partitioned between 60 mL of hexane and 50 mL of water. The organic layer was extracted with 50 mL of 50% aqueous methanol and then with 50 mL of brine. The hexane layer was separated and dried, and the solvent was removed in vacuo. The crude product was purified by filtration through a short silica gel column (hexane) to give 806 mg (88%) of the product as a colorless oil: IR ($CHCl_3$) 3075, 2990, 2930, 2865, 2845, 2820, 1660, 1467, 1450, 1372, 1110, 1085, 1070, 880 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.62 (1 H, m), 3.34 (3 H, s), 2.79 (1 H, t, J = 2.8 Hz), 2.51 (1 H, M of ABMNXY, apparent ddq, J_{app} = 16.5, 9.5, 2.0 Hz, CH-16β), 2.27 (1 H, N of ABMNXY, apparent dtt, J_{app} = 16.4, 8.2, 1.6 Hz, CH-16α), 1.96 (1 H, dt, J_{app} = 12.8, 5.8, CH-7β), 1.05 (3 H, s), 0.83 (3 H, s), 0.66 (1 H, t, J = 4.3 Hz), 0.47 (1 H, dd, J = 7.8, 5.0 Hz); MS, m/e (%) 300 (28), 285 (34), 268 (61), 253 (15), 246 (13), 245 (100), 242 (12), 163 (12), 159 (14), 147 (32), 145 (15), 133 (12), 131 (11), 121 (16), 120 (12), 119 (12), 107 (38), 105 (28), 95 (14), 93 (16), 91 (24). Anal. Calcd for $C_{21}H_{32}O$: M_r, 300.2453; C, 83.94; H, 10.74. Found: M_r, 300.2449; C, 84.04; H, 10.84.

17-Methylene-6β-methoxy-3α,5-cyclo-5α-androstan-16α-ol (8) and 17-Methylene-6β-methoxy-3α,5-cyclo-5α-androstan-16-one (3). To a suspension of selenium dioxide (104 mg, 0.94 mmol) in 4 mL of methylene chloride at room temperature was added 360 μL (339 mg, 3.76 mmol) of a 70% solution of *tert*-butyl hydroperoxide (Aldrich). After stirring this mixture for 1 h at room temperature, a solution of the above steroidal olefin **7** (564 mg, 1.88 mmol) in 10 mL of the same solvent was added. The mixture was stirred at room temperature for 5 h and then partitioned between 100 mL of ether and 100 mL of 10% sodium hydroxide. The organic layer was extracted again with 100 mL of 10% sodium hydroxide, separated, and dried, and the solvent was removed in vacuo. The crude product was purified by preparative TLC (1:1 ethyl acetate/hexane) to give 422 mg (74%) of the alcohol **8** and 127 mg (21%) of the enone **3**.

For alcohol 8: IR ($CHCl_3$) 3590, 3450, 3070, 3000, 2940, 2870, 2830, 1660, 1455, 1380, 1200, 1115, 1095 1080, 1020, 900 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.04 (1 H, d, J = 1.6 Hz), 4.86 (1 H, d, J = 2.1 Hz), 4.68 (1 H, br d, J = 6.5 Hz), 3.34 (3 H, s), 2.80 (1 H, t, J = 2.4 Hz), 1.05 (3 H, s), 0.84 (3 H, s); MS, m/e (%) 316 (45), 301 (36), 284 (45), 266 (12), 261 (100), 179 (18), 145 (11), 123 (13), 107 (23), 105 (36), 95 (25), 93 (20), 91 (43). Anal. Calcd for $C_{21}H_{32}O_2$: 316.2402. Found: 316.2394.

For the enone 3: IR ($CHCl_3$) 3065, 3000, 2960, 2935, 2870, 2825, 1725, 1640, 1460, 1380, 1135, 1105, 1090, 1020, 945 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.79 (1 H, d, J = 1.0 Hz), 5.02 (1 H, d, J = 0.8 Hz), 3.36 (3 H, s), 2.81 (1 H, t, J = 2.7 Hz), 1.09 (3 H, s), 1.01 (3 H, s), 0.69 (1 H, t, J = 4.9 Hz), 0.49 (1 H, dd, J = 7.9, 5.2 Hz); MS, m/e (%) 314 (26), 299 (39), 282 (51), 260 (12), 259 (100), 256 (11), 177 (15), 121 (12), 107 (16), 105 (15), 95 (13), 93 (16), 91 (11). Anal. Calcd for $C_{21}H_{30}O_2$: 314.2246. Found: 314.2236. Calcd for $C_{21}H_3O_2 \cdot H_2O$: C, 75.84; H, 9.70. Found: C, 75.61; H, 9.49.

21,24-Dinor-6β-methoxy-3α,5-cyclo-5α-cholestan-16-one (9). To a stirred suspension of cuprous iodide (99 mg, 0.52 mmol) in 1 mL of ether at −20 °C was added dropwise a 1.2 M solution of 1-lithio-3-methylbutane[45] (830 μL, 1.0 mmol) in ether. After several minutes the solution became clear but contained some black precipitate. This solution was cooled to −78 °C. To the preceeding mixture was added dropwise a solution of 75 mg (0.24 mmol) of enone **3** in 1 mL of ether. This mixture was allowed to warm to −10 °C during 1.5 h and quenched dropwise into a vigorously stirred solution of ice-cold 10% hydrochloric acid (50 mL). After quenching was complete, 50 mL of ether was added; the organic layer was then separated and extracted with saturated aqueous sodium bicarbonate. The organic layer was separated and dried, and the solvent was removed in vacuo. The crude material was then purified by preparative TLC (3:1 hexane/ethyl acetate) to give 40 mg (43%) of the product **9** as a colorless oil: IR ($CHCl_3$) 3080, 3010, 2960, 2940, 2880, 1735, 1460, 1390, 1100 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.34 (3 H, s), 2.25 (1 H, dd, J = 17.5, 7.5 Hz), 1.06 (3 H, s), 0.87 (3 H, d, J = 7.6 Hz), 0.75 (3 H, s); MS, m/e (%) 386 (38), 371 (100), 354 (23), 332 (15), 331 (96), 121 (13), 119 (11), 109 (10), 107 (21), 105 (22), 95 (25), 93 (23), 91 (23), 91 (23), 79 (24), 69 (38), 55 (61). Anal. Calcd for $C_{26}H_{42}O_2$: M_r, 386.3185; C, 80.77, H, 10.95. Found: M_r 386.3195; C, 80.59; H, 11.02.

24-Nor-6β-methoxy-3α,5-cyclo-5α-cholestan-16-one (10). This reaction and subsequent workup were conducted in a manner similar to that described for **9** by using the following amounts of reagents and solvents: enone **1** (159 mg, 0.48 mmol), cuprous

(45) Prepared from the corresponding alkyl bromide and lithium wire, containing 1% sodium, see: Klun, T. P. Ph.D. Thesis, University of Wisconsin—Madison, 1981.

iodide (209 mg, 1.10 mmol), 1-lithio-3-methylbutane[45] (1.67 mL of a 1.2 M solution in ether, 2.00 mmol), ether (2 mL). The mixture was quenched as described previously after stirring for 1 h while warming gradually from −78 ° to −10 °C. The crude material was purified by preparative TLC (3:1 hexane/ethyl acetate) to give 103 mg (54%) of **10** as a colorless oil: IR ($CHCl_3$) 3060, 2950, 2930, 2860, 2820, 1735, 1470, 1390, 1110, 1095, 1075, 935 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 3.16 (3 H, s), 2.54 (1 H, t, J = 2.5 Hz), 2.04 (1 H, dd, J = 17.5, 7.5 Hz), 1.15 (3 H, s), 1.01 (3 H, d, J = 7 Hz), 0.98 (3 H, d, J = 6.4 Hz), 0.97 (3 H, d, J = 6.3 Hz), 0.62 (3 H, s); ^{13}C NMR (50 MHz, C_6D_6) δ 215.5, 82.2, 68.3, 56.6, 50.9, 48.3, 43.8, 43.3, 39.8, 38.9, 37.1, 35.6, 35.7, 34.1, 33.5, 32.1, 29.8, 28.7, 25.3, 23.2, 22.8, 22.5, 21.7, 19.5, 19.0, 13.7, 13.5; MS, m/e (%) 400 (70), 386 (24), 385 (100), 368 (26), 245 (77), 287 (24), 213 (11), 149 (10), 139 (11), 121 (12), 109 (17), 107 (16), 105 (18), 97 (14), 95 (20), 93 (16), 91 (16), 81 (18), 78 (21), 69 (34), 57 (26), 55 (43). Anal. Calcd for $C_{27}H_{44}O_2$: M_r, 400.3341; C, 80.94; H, 11.07. Found: M_r, 400.3329; C, 80.72; H, 11.06.

6β-Methoxy-3α,5-cyclo-5α-cholestan-16-one (11). To a suspension of cuprous iodide (974 mg, 5.12 mmol) in 15 mL of ether at −78 °C was added 5.0 mL (5.0 mmol) of a 1.0 M solution of isohexyllithium[45] in the same solvent. The mixture was stirred for 30 min at this temperature and then for 5 min at −15 °C at which time the mixture turned black. The mixture was then recooled to −78 °C, and a solution of the E enone **1** (408 mg, 1.24 mmol) (containing ~2% of the Z isomer) in 10 mL of ether was added. The mixture was stirred at this temperature for 3 h, between −20 to −10 °C for 45 min, and then transferred via cannula to 50 mL of a rapidly stirred ice-cold solution of saturated aqueous ammonium chloride. To the resulting mixture was then added 50 mL of ether. The organic layer was separated, extracted again with 50 mL of saturated aqueous ammonium chloride, and dried, and the solvent was removed in vacuo. The crude product was then purified on a 10 × 1 cm silica gel column using an ethyl acetate/hexane gradient to give 374 mg (73%) of the ketone **11** as an oil. An analytical sample was obtained by crystallization from methanol, giving needles of mp 56.5–57.5 °C: IR ($CHCl_3$) 3070, 3000, 2960, 2930, 2870, 2830, 1730, 1475, 1460, 1390, 1060, 1040, 1075 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 3.18 (3 H, s, OCH_3), 2.56 (1 H, t, J = 2.7 Hz, CH-6), 1.13 (3 H, s, CH_3-19), 0.98 (3 H, d, J = 6.8 Hz, CH_3-21), 0.94 (3 H, d, J = 6.6 Hz, CH_3-26 or 27), 0.93 (3 H, d, J = 6.6 Hz, CH_3-27 or 26), 0.64 (3 H, s, CH_3-18), 0.61 (1 H, t, J = 4.9 Hz, CH-4β), 0.39 (1 H, dd, J = 8.0, 5.1 Hz, CH-4α); ^{13}C NMR (15 MHz, C_6D_6) δ 215.3, 82.3, 68.5, 56.6, 51.0, 48.4, 43.9, 43.4, 39.9, 39.8, 39.0, 36.5, 35.8, 33.6, 31.9, 29.9, 28.4, 25.6, 25.5, 23.0, 22.9, 22.6, 21.8, 19.6, 19.1, 13.9, 13.6; MS, m/e (%) 414 (23), 400 (21), 399 (100), 382 (18), 360 (15), 359 (75), 287 (20), 213 (20), 164 (11), 145 (12), 137 (12), 121 (14), 119 (12), 109 (16), 107 (22), 105 (25), 97 (20), 95 (29), 93 (24), 91 (22). Anal. Calcd for $C_{22}H_{46}O_2$: M_r, 414.3498; C, 81.10; H, 11.18. Found: M_r, 414.3484; C, 81.17; H, 11.27.

6β-Methoxy-3α,5-cyclo-5α-cholestane (12). A. From Ketone 11. To a solution of ketone **11** (76 mg, 0.18 mmol) in 2 mL of triethylene glycol was added 250 μL of hydrazine hydrate and 240 mg of potassium carbonate. This mixture was heated to 150 °C for 1 h; then the condensor was removed and the temperature was increased to 220 °C. After excess hydrazine and water had boiled off, the condensor was replaced and the bath temperature was maintained at 220 °C for 4.5 h. The mixture was then cooled and partitioned between 50 mL of hexane and 50 mL of 10% hydrochloric acid. The organic layer was then separated, extracted again with 50 mL of 10% hydrochloric acid, followed by extraction with 25 mL of water and 50 mL of saturated aqueous sodium bicarbonate, dried, and the solvent removed in vacuo to give 68 mg (93%) of a colorless oil, homogeneous as judged by TLC, that solidified on standing. An analytical sample was obtained by recrystallization from methanol to give needles of mp 79–80 °C (lit. mp 69–71 °C,[20a] 78–78.5 °C,[20d] 79 °C,[20f] 79–80 °C,[20b] 79.5–80 °C,[20c] 80 °C[20e]): IR ($CHCl_3$) 3075, 3000, 2960, 2910, 2875, 2855, 1472, 1462, 1390, 1380, 1098, 1080 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.32 (3 H, s), 2.76 (1 H, t, J = 2.5 Hz), 1.98 (1 H, dt, J = 12.5, 3.1 Hz, CH-12β), 1.89 (1 H, dt, J = 13.6, 2.8 Hz, CH-7α), 1.02 (3 H, s), 0.91 (3 H, d, J = 6.4 Hz), 0.86 (6 H, d, J = 6.4 Hz), 0.72 (3 H, s), 0.64 (1 H, t, J = 4.6 Hz), 0.42 (1 H, dd, J = 7.8, 5.0 Hz); ^{13}C NMR (50 MHz, C_6D_6) δ 82.68 56.9, 56.6, 48.6, 43.8, 40.8, 40.0, 36.7, 36.2, 35.8, 35.7, 33.8, 31.0, 28.7, 28.4, 25.4, 24.6, 24.4, 23.3, 23.0, 22.8, 21.8, 19.7, 19.0, 13.5, 12.4; $[\alpha]^{22}_D$ +51.9° (c 1.1, $CHCl_3$) (lit. $[\alpha]_D$ +54°,[20b,d] +55°,[20f] +51.8°[20e]).

B. From Olefin 17. To a solution of **17** (105 mg, 0.26 mmol) in 5 mL of ethyl acetate was added 55 mg of 5% palladium on barium carbonate. This mixture was attached to a Parr hydrogenation apparatus and shaken at room temperature under 45 psi (gauge pressure) of hydrogen for 12 h. The mixture was filtered through a pad of Celite, and the pad was washed with 25 mL more of ethyl acetate. Removal of the solvent in vacuo gave a quantitative recovery of a while solid, homogeneous by TLC. This material was identical with the material prepared from ketone **11** as judged by ^1H NMR and ^{13}C NMR. Recrystallization from methanol gave a powder of mp 70.5–71.5 °C.

Cholesterol. To a mixture of steroid **12** (30 mg, 0.075 mmol) in 7 mL of dioxane and 2 mL of water was added d-10-camphorsulfonic acid (20 mg, 0.086 mmol). This mixture was heated to 80 °C for 2 h and then cooled to room temperature and partitioned between 50 mL of ether and 50 mL of saturated sodium bicarbonate. The organic layer was separated and dried, and the solvent was removed in vacuo to give 30 mg (103%) of a white solid, homogeneous as judged by TLC. This material was purified by preparative TLC (3:1 hexane/ethyl acetate) to give 20 mg (70%) of a white solid. Two recrystallizations from methanol gave a solid of mp 144–145 °C (lit.[37] mp 149.5–150 °C), mixed melting point with authentic cholesterol (Aldrich, recrystallized) mp 144–145 °C. The 270-MHz ^1H NMR and IR spectra of the synthetic material were virtually identical with those of an authentic sample. In addition, the observed ^{13}C NMR spectrum was in accord with those previously reported:[46] ^1H NMR (270 MHz, $CDCl_3$) δ 5.35 (1 H, d, J = 5.1 Hz, CH-16), 3.51 (1 H, m, CH-3α), 1.01 (3 H, s, CH_3-19), 0.91 (3 H, d, J = 6.4 Hz, CH_3-21), 0.87 (3 H, d, J = 6.6 Hz, CH_3-26 or -27), 0.86 (3 H, d, J = 6.6 Hz, CH_3-27 or -26), 0.68 (3 H, s, CH_3-18); ^{13}C NMR (15 MHz, $CDCl_3$) δ 140.9, 121.7, 71.9, 56.9, 56.4, 50.4, 42.5, 40.0, 39.7, 37.4, 36.6, 36.3, 35.8, 32.1, 31.9, 28.3, 28.1, 24.4, 24.0, 22.8, 22.6, 21.2, 19.4, 18.8, 11.9.

(17*E*)-16α-(Pivaloyloxy)-6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-ene (14). To a solution of alcohol **6** (1.79 g, 5.42 mmol) in 10 mL of methylene chloride was added pivaloyl chloride (844 mg 7.0 mmol), triethylamine (1.21 g, 12 mmol) and 4-(dimethylamino)pyridine (50 mg, 0.41 mmol). The mixture was stirred overnight at room temperature and partitioned between 100 mL of ether and 50 mL of 10% hydrochloric acid. The organic layer was then extracted with 100 mL of brine and 100 mL of saturated aqueous sodium bicarbonate solution and dried, and the solvent was removed in vacuo. The crude compound was purified by chromatography through a 25 × 2 cm silica gel column (first hexane, then an ethyl acetate/hexane gradient), giving 1.56 g (69%) of the ester as a colorless oil: IR ($CHCl_3$) 3060, 2960, 2940, 2880, 2840, 1715, 1480, 1460, 1285, 1160, 1095 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.46 (1 H, br d, J = 7 Hz), 5.43 (1 H, qd, J = 7, 1.5 Hz), 3.32 (3 H, s), 1.72 (3 H, dd, J = 7.3, 1.4 Hz), 1.19 (9 H, s), 1.04 (3 H, s), 0.95 (3 H, s); MS, m/e (%) 414 (0.4), 315 (0.7), 105 (1), 102 (1), 85 (15), 57 (100), 45 (4), 41 (53). Anal. Calcd for $C_{27}H_{42}O_3$: M_r, 414.3134; C, 78.21; H, 10.21. Found: M_r 414.3134; C, 78.43; H, 10.34.

(17*E*)-16β-(Pivaloyloxy)-6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-ene (15). This material was prepared in a manner similar to that described for the 16α-pivalate **14**, using the following amounts of reagents and solvents: 16β-alcohol (188 mg, 0.57 mmol), triethylamine (200 mg, 1.98 mmol), pivaloyl chloride (82 mg, 0.68 mmol), 4-(dimethylamino)pyridine (70 mg, 0.57 mmol), methylene chloride (2 mL). The reaction was complete in 2 h as judged by TLC. The crude product was purified by preparative TLC (1:4 ethyl acetate/hexane) to give 193 mg (82%) of **15** as a colorless oil: IR ($CHCl_3$) 3060, 2950, 2930, 2860, 2820, 1710, 1480, 1460, 1290, 1170, 1095 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.40 (1 H, qd, J = 7.3, 1.4 Hz), 5.34 (1 H, br t, J = 7.5 Hz), 3.33 (3 H, s), 1.71 (3 H, dd, J = 7.1, 1.2 Hz), 1.17 (9 H, s), 1.07 (3 H, s), 1.04 (3 H, s); MS, m/e (%) 414 (1), 315 (2), 297 (1), 283 (2), 281 (2), 280 (6), 265 (4), 159 (3), 145 (3), 121 (3), 119 (2), 105 (2), 85 (40), 57 (100), 41 (16). Anal. Calcd for $C_{27}H_{42}O_3$: 414.3134. Found: 414.3134.

(46) (a) Blunt, J. W.; Stothers, J. B. *Org. Magn. Reson.* **1977**, *9*, 439. (b) Smith, W. B. *Annu. Rep. NMR Spectrosc.* **1978**, *8*, 199.

(17*E*)-6β-Methoxy-3α,5-cyclo-5α-pregn-17(20)-en-16α-ol Phenylcarbamate (19). To a solution of alcohol **6** (796 mg, 2.40 mmol) and phenyl isocyanate (283 μL, 310 mg, 260 mmol) in 20 mL of methylene chloride was added triethylamine (552 μL, 401 mg, 4.00 mmol) and 4-(dimethylamino)pyridine (53 mg, 0.43 mmol). This mixture was stirred overnight at room temperature and then partitioned between 50 mL of 10% hydrochloric acid and 150 mL of ether. The organic layer was then extracted with 20 mL of water and 100 mL of saturated aqueous sodium bicarbonate, separated, dried, and the solvent removed in vacuo. The crude product was purified by preparative TLC (4:1 hexane/ethyl acetate) to give 799 mg (70%) of the product as a foam: IR ($CHCl_3$) 3440, 3060, 3000, 2960, 2930, 2870, 2830, 1725, 1605, 1520, 1440, 1310, 1090, 1080 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 738 (2 H, m), 7.30 (2 H, m), 7.04 (1 H, tt, J = 7.4, 1.3 Hz), 6.66 (1 H, br s), 3.33 (3 H, s), 2.80 (1 H, t, J = 2.4 Hz), 2.29 (1 H, tt, J = 11.5, 2.5 Hz), 1.75 (3 H, dd, J = 7.0, 1.1 Hz), 1.05 (3 H, s), 0.97 (3 H, s); MS, m/e (%) 405 (9), 330 (11), 315 (20), 298 (26), 281 (25), 280 (11), 275 (37), 214 (22), 159 (16), 121 (18), 119 (100), 93 (33), 91 (19). Anal. Calcd for $C_{31}H_{39}O_3N \cdot 0.5H_2O$: C, 77.14; H, 8.35; N, 2.90. Found: C, 77.30; H, 8.62; N, 2.98.

(20*S*)-6β-Methoxy-3α,5-cyclo-5α-cholest-16-ene (16). To cuprous cyanide (990 mg, 11.0 mmol) at −20 °C was added 9.0 mL (9.0 mmol) of a 1.0 M solution of isohexyllithium in ether. The mixture initially turns a yellow-orange color and then becomes black. After stirring this mixture for 20 min at this temperature, pivalate **14** (1.09 g, 2.62 mmol) in 6 mL of ether was added. The mixture was stirred for 1 h, allowed to stand for 48 h at −23 °C, quenched by addition of a small amount of saturated aqueous ammonium chloride, and then filtered through a short silica gel plug. The mixture was then partitioned between 75 mL of ether and 50 mL of saturated aqueous ammonium chloride. The organic layer was again extracted with 50 mL of saturated aqueous ammonium chloride and 50 mL of saturated sodium bicarbonate and then separated, dried, and the solvent removed in vacuo. The crude product was separated by preparative HPLC (0.5% ethyl acetate/hexane) to give 456 mg (41%) of recovered starting material and 413 mg (68% based on recovered starting material) of the product: IR ($CHCl_3$) 3060, 2990, 2945, 2915, 1465, 1455, 1370, 1185 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.27 (1 H, br s, CH-16), 3.31 (3 H, s, OCH_3), 2.76 (1 H, t, J = 2.4 Hz, CH-6α), 1.03 (3 H, s, CH_3-19), 1.01 (3 H, d, J = 6.6 Hz, CH_3-21), 0.83 (6 H, d, J = 6.6 Hz, CH_3-26, -27), 0.80 (3 H, s, CH_3-18); ^{13}C NMR (15 MHz, C_6D_6) δ 157.6, 121.3, 82.6, 57.7, 56.6, 49.3, 47.8, 44.0, 39.7, 38.1, 36.1, 36.0, 35.7, 33.6, 32.3, 31.6, 29.6, 28.3, 25.78 25.4, 23.0, 21.8, 21.6, 19.6, 17.2, 13.6; MS, m/e (%) 398 (8), 384 (6), 383 (25), 366 (25), 352 (13), 351 (65), 343 (15), 285 (36), 254 (13), 253 (100), 245 (14), 159 (32), 157 (15), 147 (13), 145 (38), 133 (16), 131 (25), 121 (55), 119 (27), 107 (29), 105 (42), 95 (20), 93 (35), 91 (45). Anal. Calcd for $C_{28}H_{46}O$: 398.3548. Found: 398.3547.

In the early LC fractions containing product, a trace of material was observed (estimated at <5% relative to the major isomer) with spectral characteristics corresponding to what is assumed to be a regioisomer of **16** having a ^1H NMR signal at δ 5.05 (qd, J = 6.8, 2.2 Hz, CH-20). This material was not obtainable in pure form.

6β-Methoxy-3α,5-cyclo-5α-cholest-16-ene (17). A. From Pivalate 15. To a slurry of cuprous cyanide (296 mg, 3.0 mmol) in 2 mL of ether at −78 °C was added 2.7 mL (2.7 mmol) of a 1.0 M solution of isohexyllithium[45] in ether. This mixture was allowed to warm to −30 °C and stirred at this temperature for ~40 min. The solution was then recooled to −78 °C, and a solution of pivalate **15** (193 mg, 0.47 mmol) in 6 mL of ether was added. The mixture was then allowed to warm to −30 °C for 5 h, −23 °C for 16 h, and then quenched by the addition of several milliliters of saturated aqueous ammonium chloride and subsequently partitioned between 50 mL of ether and 50 mL of saturated aqueous ammonium chloride. The organic layer was then washed with an additional 50 mL of saturated aqueous ammonium chloride and 50 mL of saturated aqueous sodium bicarbonate, separated, and dried, and the solvent was removed in vacuo. The crude product was purified by HPLC (0.5% ethyl acetate/hexane) to give 145 mg (78%) of the product as a colorless oil: IR ($CHCl_3$) 3060, 2990, 2945, 2915, 2860, 1468, 1455, 1372, 1185 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.25 (1 H, t, J = 1.3 Hz, CH-16), 3.32 (3 H, s, OCH_3), 2.77 (1 H, t, J = 2.5 Hz, CH-6α), 1.04 (3 H, s, CH_3-19), 0.96 (3 H, d, J = 6.8 Hz, CH_3-21), 0.83 (6 H, d, J = 6.6 Hz, CH_3-26, -27), 0.79 (3 H, s, CH_3-18); ^{13}C NMR (15 MHz, C_6D_6) δ 157.7, 121.0, 82.6, 57.9, 56.6, 49.3, 47.6, 44.1, 39.6, 37.4, 36.0, 35.6, 33.6, 32.9, 31.5, 29.7, 28.4, 25.9, 25.4, 23.0, 22.9, 22.3, 21.8, 19.7, 16.9, 13.6; MS, m/e (%) 398 (6), 383 (29), 366 (15), 351 (50), 343 (18), 286 (10), 285 (62), 254 (17), 253 (100), 145 (22), 133 (12), 121 (44), 119 (12), 109 (11), 107 (21), 105 (22), 95 (20), 93 (20), 91 (19). Anal. Calcd for $C_{28}H_{46}O$: 398.3548. Found: 398.3547.

In the early LC fraction containing product, a trace of material was observed (estimated at <5% relative to the major isomer) with spectral characteristics corresponding to what is assumed to be a regioisomer of **17** having a ^1H NMR signal at δ 5.11 (qd, J = 7.5, 2.5 Hz, CH-20). This material was not obtainable in pure form.

B. From Carbamate 19. Carbamate **19** (237 mg, 0.50 mmol) was dissolved in 10 mL of cyclohexane, and the mixture was distilled to near dryness to remove any water. To this solution was added 3 mL of ether. After cooling this mixture to −30 °C, n-butyllithium (333 μL of a 1.5 M solution in hexane, 0.50 mmol) was added dropwise. After warming the solution to room temperature, solid cuprous iodide (95 mg, 0.50 mmol) was added. The previously colorless solution became yellow and then slightly green. This mixture was recooled to −30 °C and iso-hexyllithium[45] was added (2.4 mL of 0.23 M solution in ether, 0.55 mmol). The mixture became very dark brown. After holding this mixture at −20 °C overnight, it was allowed to warm to room temperature and then partitioned between 75 mL of ether and 50 mL of saturated aqueous sodium bicarbonate. The organic layer was separated and dried, and the solvent was removed in vacuo. The crude product was purified by preparative TLC (19:1 hexane/ethyl acetate) to give 71 mg (36%) of the product **17** as identified by spectral comparison (270-MHz ^1H NMR) with the preceeding material. No other regioisomer or stereoisomer could be detected.

(20*S*)-6β-Methoxy-3α,5-cyclo-5α-cholestane (18). The preparation of this material and subsequent workup were conducted in a manner similar to that described for the hydrogenation of olefin **17** leading to **12** by using the following amounts of reagents and solvents: olefin **16** (304 mg, 0.76 mmol), 5% palladium on barium carbonate (150 mg), ethyl acetate (6 mL). The mixture was shaken under 30 psi of hydrogen for 4 h. The crude material was purified by preparative TLC to give 268 mg (88%) of **18** as an oil: IR ($CHCl_3$) 3060, 2950, 2870, 1470, 1455, 1095, 1075 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.29 (3 H, s), 2.76 (1 H, t, J = 2.5 Hz), 1.96 (1 H, dt, J = 12.0, 2.7 Hz, CH-12β), 1.89 (1 H, dt, J = 13.5, 2.8 Hz, CH-7α), 1.01 (3 H, s), 0.85 (6 H, d, J = 6.4 Hz), 0.81 (3 H, d, J = 6.3 Hz), 0.71 (3 H, s), 0.62 (1 H, t, J = 4.3 Hz), 0.42 (1 H, dd, J = 7.5, 4.5 Hz); MS, m/e (%) 400 (28), 385 (29), 369 (13), 368 (57), 345 (64), 164 (31), 145 (20), 121 (21), 109 (15), 107 (24), 105 (27), 95 (37), 93 (25), 91 (24), 81 (39), 79 (23), 71 (25), 69 (33), 57 (56), 56 (27), 55 (64), 43 (100), 41 (81). Anal. Calcd for $C_{28}H_{48}O$: M_r, 400.3705; C, 83.93; H, 12.07. Found: M_r, 400.3707; C, 84.11; H, 11.67.

(20*S*)-Cholesterol (20-Epicholesterol). To a mixture of steroid **18** (189 mg, 0.47 mmol) in 8 mL of dioxane and 2 mL of water was added p-toluenesulfonic acid monohydrate (20 mg, 0.10 mmol). This mixture was heated at 85 °C for 1.5 h, cooled to ambient temperature, and partitioned between 50 mL of ether and 50 mL of saturated sodium bicarbonate. The organic layer was separated and dried, and the solvent was removed in vacuo to give 187 mg (103%) of the product, homogeneous as judged by TLC. An analytical sample was obtained by recrystallization from methanol to give a white solid with mp 152–153 °C (lit. mp 153–154 °C,[29] 152–154 °C,[31] 151–153 °C,[3c] 149–151 °C[3i]). The ^1H NMR spectral data were in accord with that previously reported for this compound.[3i,c,29,31a] The ^{13}C NMR data were in accord with that previously reported by Marino (resonances unassigned). It was possible to assign all the carbon resonances to this compound from the spectrum obtained by using the INEPT pulse sequence described by Ernst[47a] and Doddrell[47b] in conjunction with the assignments previously made for cholesterol:[46] ^1H NMR (270 MHz, $CDCl_3$) δ 5.35 (1 H, d, J = 5.3 Hz, CH-6), 3.51 (1 H, m, CH-3α), 1.01 (3 H, s, CH_3-19), 0.87 (6 H, d, J = 6.4 Hz, CH_2-26, -27), 0.82 (3 H, d, J = 6.6 Hz, CH_3-21), 0.68 (3 H, s, CH_3-18); ^{13}C

(47) (a) Burum, D. P.; Ernst, R. R. *J. Magn. Reson.* **1980**, *3*, 163. (b) Doddrell, D. M.; Pegg, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6388.

NMR (50 MHz, $CDCl_3$) δ 140.9 (C-5), 121.6 (C-6), 71.8 (C-3), 56.9 (C-14), 55.9 (C-17), 50.4 (C-9), 42.4 (C-13), 42.3 (C-4), 39.8 (C-12), 39.5 (C-24), 37.4 (C-1), 36.6 (C-10), 35.9 (C-22), 35.1 (C-20), 32.1 (C-8), 32.0 (C-7), 31.8 (C-2), 28.0 (C-16), 27.9 (C-25), 24.2 (C-15), 24.0 (C-23), 22.7 (C-27), 22.6 (C-26), 21.2 (C-11), 19.4 (C-19), 18.7 (C-21), 12.2 (C-18).

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, and the National Science Foundation for their generous support of our programs. We express special thanks to Roussel-Uclaf for a generous gift of dehydroepiandrosterone. We thank Mr. Stephen S. Kantner and Dr. C. C. Tseng of Professor Goering's group for helpful discussions during the course of this work. In particular we thank Mr. Kantner for providing a modified procedure for the reaction of the *N*-phenylcarbamate. We thank Mr. Bruce Adams for obtaining the ^{13}C NMR spectra of 20-isocholesterol.

Registry No. 1, 84927-48-0; 2, 84927-49-1; 3, 84927-50-4; 4, 14425-92-4; (*Z*)-5, 84985-74-0; (*E*)-5, 84985-75-1; 6, 73668-91-4; 16β-6, 84927-51-5; 7, 84927-52-6; 8, 84927-53-7; 9, 84927-54-8; 10, 84927-55-9; 11, 84927-56-0; 12, 2867-93-8; 13a, 84943-97-5; 13b, 84927-57-1; 14, 84927-58-2; 15, 84927-59-3; 15-ol, 84927-51-5; 16, 84985-76-2; 17, 30270-50-9; 18, 84985-77-3; 19, 84927-60-6; $Ph_3P^+EtBr^-$, 1530-32-1; $Ph_3P^+MeBr^-$, 1779-49-3; $(CH_3)_3CCOCl$, 3282-30-2; PhNCO, 103-71-9; cholesterol, 57-88-5; 20-epicholesterol, 34026-89-6.

Syntheses of [15α-^{2}H]-, [15β-^{2}H]-, and [15-$^2H_2$]Progesterone

Vincent C. O. Njar,† Thangavel Arunachalam, and Eliahu Caspi*

The Worcester Foundation for Experimental Biology, Inc., Shrewsbury, Massachusetts 01545

Received July 20, 1982

[15α- and 15β-^{2}H]Progesterone and [15-$^2H_2$]progesterone were synthesized, and their deuterium NMR spectra were determined. The chemical shifts of the 15α- and 15β-deuterio isomers were separated by 0.47 ppm.

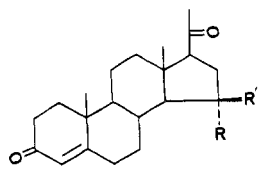
For ongoing biosynthetic studies, we required samples of progesterone stereospecifically labeled with deuterium at C-15. In this paper we describe the synthesis of 15α- and 15β-deuterio- and 15,15-dideuterioprogesterone.

15β-Deuterioprogesterone (**1b**, Chart I) was synthesized as described earlier by us for the synthesis of [15β-^{3}H]-progesterone.[1] Accordingly, 15α-hydroxyprogesterone (**1d**) was converted into the diketal **2a** and treated with *p*-toluenesulfonyl chloride in pyridine to give the 15α-tosylate diketal **2b**. Hydrogenolysis of **2b** with lithium triethylborodeuteride gave [15β-^{2}H]progesterone diketal **2j** which, on acid hydrolysis, provided the desired [15β-^{2}H]progesterone (**1b**). The overall yield was ca. 42%. The assignment of the 15β configuration to the deuterium rests on the proven inversion which occurs in the metal hydride hydrogenolysis of tosyl esters.[2,3]

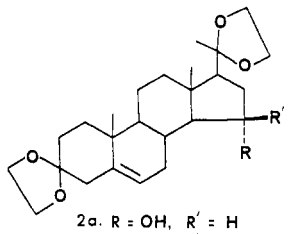
The introduction of deuterium at the 15α-position of progesterone was somewhat more challenging. A logical approach for preparing [15α-^{2}H]progesterone would be via hydrogenolysis of the 15β-tosylate diketal **2d** with lithium triethylborodeuteride. However, exposure of the 15β-alcohol diketal **2c** to *p*-toluenesulfonyl chloride in pyridine led invariably to the dehydration product, pregna-5,14-diene-3,20-dione diethylene diketal (**3a**).[1] Also, the attempted controlled reduction ($LiAlD_4$) of the C-15 tosylhydrazone[4] **2i** failed, and instead the olefin **3a** was obtained. The possibility of introducing the 15α-deuterium by the hydrolysis with propionic acid-*d* of the 15α-alkylborane[5] derived from pregna-5,14-diene-3,20-dione diethylene diketal (**3a**) was considered briefly. However, the approach was abandoned when, in exploratory experiments in which the 15α-alkylborane was refluxed with propionic acid, a mixture of products was obtained, none of which was progesterone.

The procedure finally developed was based on the utilization of the 15-^{2}H olefin diketal **3b**. The 15α-hydroxyprogesterone diketal **2a** was oxidized, and the resulting 15-ketone **2h** was reduced with sodium borodeuteride. The obtained 15β-hydroxy[15α-^{2}H]progesterone diketal **2e** was dehydrated (*p*-toluenesulfonyl chloride-

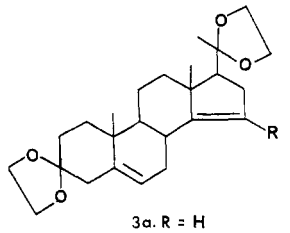
Chart I



1a. R = D, R′ = H
b. R = H, R′ = D
c. R = R′ = D
d. R = OH, R′ = H



2a. R = OH, R′ = H
b. R = OTs, R′ = H
c. R = H, R′ = OH
d. R = H, R′ = OTs
e. R = D, R′ = OH
f. R = OH, R′ = D
g. R = OTs, R′ = D
h. R, R′ = O
i. R, R′ = N_2HTs
j. R = H, R′ = D
k. R = D, R′ = H
l. R = R′ = D



3a. R = H
b. R = D

Table I. Deuterium NMR Spectral Data of 15-Deuterioprogesterone

	chemical shift, ppm	
progesterone	15α-^{2}H	15β-^{2}H
1c	1.66	1.22
1a	1.70	
1b		1.23

† Postdoctoral fellow 1980–1982. Present address: Department of Chemistry, University of Ibadan, Ibadan, Nigeria.

(1) Ramm, P. J.; Caspi, E. *J. Biol. Chem.* **1969**, *244*, 6064.
(2) Helkamp, G. K.; Rickborn, B. F. *J. Org. Chem.* **1957**, *22*, 479.
(3) Burrows, E. P.; Hornby, G. M.; Caspi, E. *J. Org. Chem.* **1969**, *34*, 103.
(4) Tokes, L.; Thorp, L. J. "Organic Reactions in Steroid Chemistry"; Fried, J., Edwards, J. A., Ed,; Van Nostrand-Reinhold: New York, 1972; Vol. I, pp 173–178.
(5) Brown, H. C.; Murray, K. J. *J. Org. Chem.* **1961**, *26*, 631.

0022-3263/83/1948-1412$01.50/0