length is needed to move the benzophenone oxygen from the center of the C-5/C-5′ bond so as to allow attack at C-4. Attack on substrate **4** is more demanding, since only a half-bond-length shift brings the attacking group in a position to abstract hydrogen from C-4 as well as C-5. Thus the poor selectivity in the reaction of **5** with **4** is not surprising, and the rather good selectivity of the **1**:**4** reaction is particularly striking.

As a control substrate **2** was photolyzed in CH_2Cl_2 with 3-carboxylbenzophenone, which is **7** with only one of the binding carboxylate groups. Here no attack on the chain was observed, the benzophenone reagent forming only products from attack on the solvent (identical with those formed if **2** was omitted). Furthermore, **2** was quantitatively (±2%) recovered unchanged. As a second control, the one-to-one salt of [3-(phenylcarbonyl)-phenyl]trimethylammonium cation (**1** with only one X group) and the monoanion of **4** was prepared and photolyzed in H_2O as above. Here too no functionalization of the chain could be detected, by ^{13}C NMR of the crude reaction mixture. While these experiments thus do not reveal how random the attack on **2** would be with only one coordination, they do show that both binding groups are needed for reaction and thus that two coordinations are undoubtedly present, as shown in **5** and **8**.

Electronic effects should make the central carbons of **2**–**4** the most reactive.[13] While such effects may be contributing to our results, we are clearly seeing geometric control as well. Some of the data in Table I, particularly the decreased reactivity at C-6 compared with C-5 in one case, can only be explained on a geometrical basis. The requirement for *two* binding groups for reaction makes it clear that geometrical control *should* be present. Further work will be needed to establish whether such double coordination of a flexible chain furnishes a general solution to the problem of producing complete selectivity in synthetically useful reactions.[14]

(13) Russell, G. A. *Free Radicals* **1973**, *1*, 273.

(14) Support of this work by the National Science Foundation is gratefully acknowledged.

A New Stereospecific Approach to Steroid Side Chains: Conversion of Dehydroepiandrosterone to Cholesterol, Isocholesterol, and Their 15β-Hydroxy Derivatives

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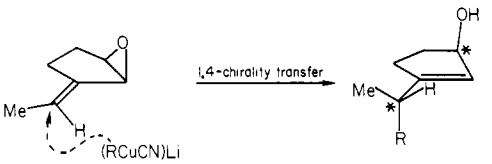
The stereocontrolled formation of carbon–carbon bonds in cyclic and acyclic systems presents a continuing challenge for synthetic chemists. Recently, we reported the regiospecific and stereospecific 1,4 addition of alkyl cyanocuprates to cyclic vinyloxiranes.[1,2] In this communication we wish to report that similar reactions may be applied to the stereospecific construction of side chains from substituted exo-methylene epoxycycloalkanes.[3,4] Our previous work revealed that mixed cyanocuprates can selectively generate *trans*-4-alkylcyclohex-2-enols. If this methodology is extended to a chiral alkylideneoxirane of known configuration there exists the possibility for a 1,4-chirality transfer[5] in which two asymmetric centers are generated in a 1,4 relationship. This overall transformation is depicted below for ethylidenecyclopentene oxide.



In order to demonstrate our approach, we tested its stereochemical efficacy in sterol side-chain synthesis. With the recent discoveries of many new sterols from marine and animal sources, as well as the active metabolites of vitamin D, there is a compelling need to develope general and stereospecific methods for the construction of the 20*R* configuration in naturally occurring sterols. Furthermore, the recent isolation by McMorris[6] of the naturally occurring 15β-hydroxysterol, oogoniol, and its partial synthesis by Djerassi[7] presented the additional incentive for introduction of 15β-hydroxy groups in sterols.

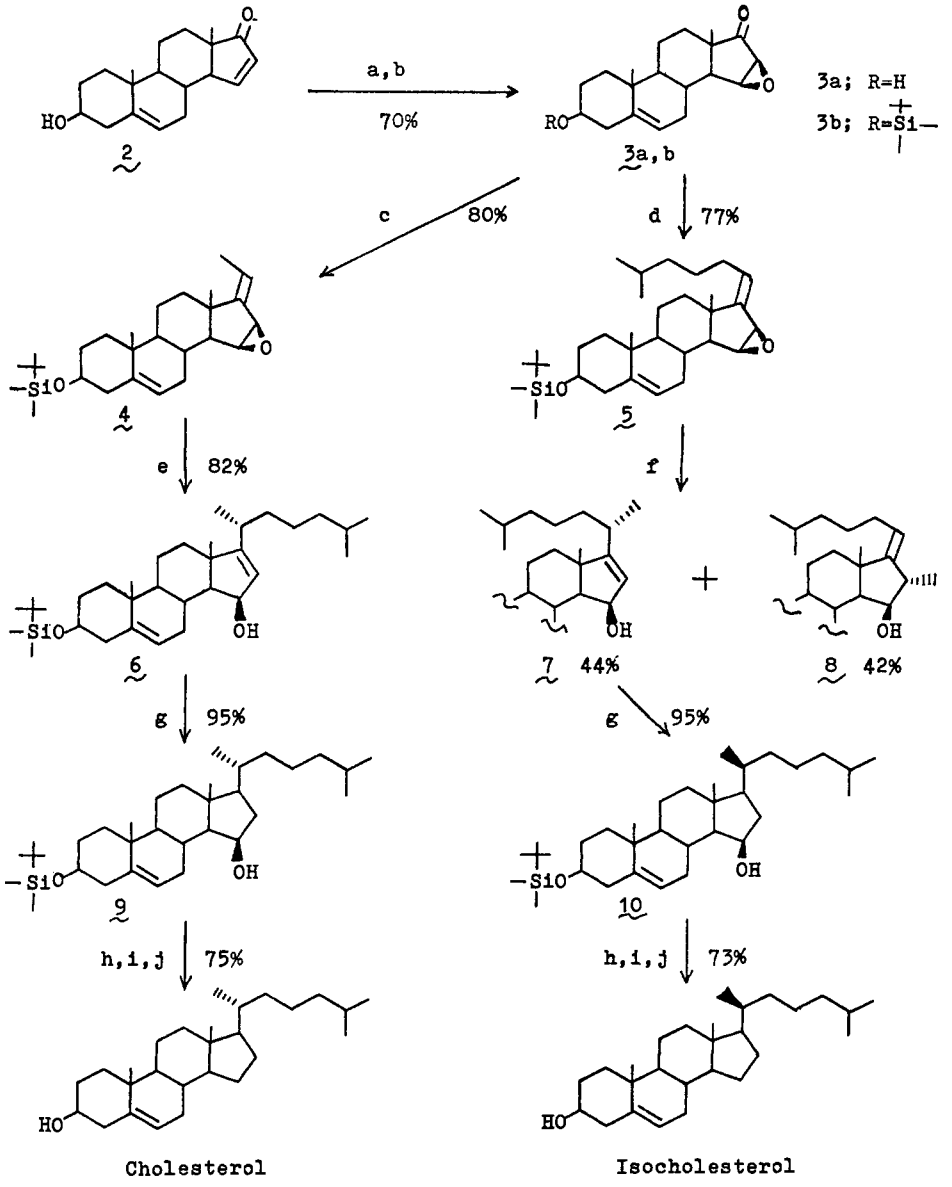
In this communication, we describe the stereospecific conversion of dehydroepiandrosterone (**1**) to cholesterol, isocholesterol, and their 15β-hydroxy derivatives, which possess the same configuration at C-15 as found in oogoniol.[7b] Our synthesis begins with 3β-hydroxyandrosta-5,15-dien-17-one (**2**) which is readily available from **1** in high yield.[8] Scheme I outlines the overall synthetic plan. Stereospecific epoxidation of the 15,16 double bond of **2** occurs regiospecifically,[9] and subsequent protection of the 3β-hydroxy group of **3a** with the *tert*-butyldimethylsilyl (TBDMS) group[10] leads to keto epoxide **3b** in an overall yield of 70%.[11]

The keto epoxide **3b** serves as a precursor to both cholesterol and isocholesterol. While a number of Wittig reactions have been carried out on 17-keto steroids,[12] no reports of such reactions on the 15,16-epoxy-17-keto sterols have come to our attention. The

(1) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.*, **1979**, 675.
(2) Marino, J. P.; Hatanaka, N. *J. Org.Chem.* **1979**, *44*, 4467.
(3) For reactions of *exo*-methylenecyclohexene oxides, see: Marino, J. P.; Abe, Hiroyuki *Synthesis* **1980**, *11*, 872.
(4) In a recent report, some reactions of dialkyl cuprates with alkylidene spiroepoxides are described: Ziegler, F. E.; Cady, M. A. *J. Org. Chem.* **1981**, *46*, 122.
(5) In recent years, there have been many elegant applications of 1,3-chirality transfer in steroid side-chain synthesis. Most notable are those that involve a Claisen rearrangement or π-allylpalladium intermediates. For some recent examples of the Claisen reaction, see: (a) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862. (b) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172. (c) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. For some leading references involving organopalladium intermediates, see: (d) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435. Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. (f) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976**, *98*, 630. (g) Dauben, W. G.; Brookhart, T. *Ibid.* **1981**, *103*, 237.
(6) McMorris, T. C.; Seshadri, R.; Weihe, G. R.; Arsenault, G. P.; Barksdale, A. W.; *J. Am. Chem. Soc.* **1975**, *97*, 2544.
(7) (a) Taylor, E. J.; Djerassi, C. *J. Org. Chem.* **1977**, *42*, 3571. (b) Wiersig, W. R.; Waespe-Sarcevic, N.; Djerassi, C. *Ibid.* **1979**, *44*, 3374.
(8) Kelly, R. W.; Sykes, P. J. *J. Chem. Soc. C* **1968**, 416.
(9) For the epoxidation of 5α-androst-15-en-17-one, see: Djerassi, C.; Von Mutzenbecher, G.; Fajkos, J.; Williams, D. H.; Budzikiewicz, H. *J. Am. Chem. Soc.* **1965**, *87*, 817. (b) Clark, I. M.; Denny, W. A.; Jones, E. H. R.; Meakins, G. D.; Pendlebury, A.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2765. All new compounds gave satisfactory elemental analyses and had spectral properties (IR, ^1H NMR, and ^{13}C NMR) consistent with the assigned structures.
(10) Hosoda, H.; Fukushima, D. K.; Fishman, J. *J. Org. Chem.* **1973**, *38*, 4209.
(11) **3a**: mp 165–166 °C (ether–petroleum ether); $[\alpha]^{27}_D$ −139° (*c* 0.54, $CHCl_3$); ^1H NMR (360 MHz) δ 1.05 (s, 3 H, H-18), 1.15 (s, 3 H, H-19), 3.28 (d, 1 H, *J* = 2.93 Hz, H-15), 3.80 (d, 1 H, *J* = 2.93 Hz, H-16), 3.45–3.48 (m, 1 H, H-3), 5.35–5.42 (br, 1 H, H-6); ^{13}C NMR (22.5 MHz) δ 213.0, 141.7, 120.2, 71.5, 55.6, 53.4, 53.2, 51.3, 42.3, 42.0, 37.1, 36.9, 32.9, 31.6, 30.3, 28.7, 20.0, 19.3, 19.0; IR ($CHCl_3$) 1745 cm^{-1}. **3b**: mp 138–140 °C (petroleum ether); $[\alpha]^{27}_D$ −99° (*c* 0.63, $CHCl_3$).
(12) Drefahl, G.; Ponsold, K.; Schick, H. *Chem. Ber.* **1965**, *98*, 604.

0002-7863/81/1503-2907$01.25/0

Scheme I



reaction of **3b** with the ylide generated from ethyltriphenylphosphonium bromide (LDA in THF) produced only the *E* diastereomer (**4**).[13] In a similar manner, the Wittig reaction of **3b** with the larger isohexyl-substituted methylide yielded only the *E* diastereomer (**5**).[14] Both of these alkenes are the kinetic products that result from the enantioselective approach of the ylides on the 17-keto functionality. The alkylidene epoxides **4** and **5** represent the required chiral molecules for testing the stereospecificity of the 1,4-chirality transfer reaction of organocuprates.

When oxirane **4** was treated with a twofold excess of lithium isohexylcyanocuprate[15] in ether at −78 °C, the isomerically pure 1,4-adduct **6**[16] was produced in 82% yield. The allylic alcohol **6** could be selectively and stereospecifically hydrogenated[17] over PtO_2 to the 15β-hydroxycholesterol[18] (**9**). Utilizing the steric environment of the steroid skeleton, the conversion of **4** into **9** extends the 1,4-chirality transfer process over three asymmetric centers. As a final check on the stereochemical assignments made for intermediates **4**, **6**, and **9**, 15β-hydroxycholesterol was dehydroxylated by a series of well-known transformations. Conversion of **9** to its bis(dimethylamino)phosphoramidate (mp 152–154 °C) and subsequent reductive cleavage with lithium metal in ethyl-

(13) **4**: mp 181–183 °C (petroleum ether); $[\alpha]^{27}_D$ −55° (*c* 0.65, $CHCl_3$); ^1H NMR (360 MHz) δ 1.03 (s, 3 H, H-18), 1.12 (s, 3 H, H-19), 1.73 (d, 3 H, *J* = 7.10 Hz, H-21), 3.42–3.54 (br, 1 H, H-3), 3.46 (d, 1 H, *J* = 3.17 Hz, H-15), 3.59 (d, 1 H, *J* = 3.17 Hz, H-16), 5.32–5.38 (br, 1 H, H-6), 5.68 (q, 1 H, *J* = 7.1 Hz, H-20); ^{13}C NMR (22.5 MHz) δ 150.0, 146.2, 121.7, 120.2, 72.4, 58.8, 57.8, 56.9, 51.1, 42.7, 39.4, 38.0, 37.1, 36.8, 31.9, 31.2, 28.1, 25.8, 22.3, 28.8, 19.1, 18.1, 13.4.

(14) **5**: $[\alpha]^{27}_D$ −14.3° (*c* 0.39, $CHCl_3$); ^1H NMR (360 MHz) δ 1.03 (s, 3 H, H-18), 1.11 (s, 3 H, H-19), 3.42–3.52 (br, 2 H, H-15) and H-3), 3.57–3.61 (br, 1 H, H-16), 5.32–5.36 (br, 1 H, H-6), 5.58 (t, 1 H, *J* = 7.4 Hz, H-20).

(15) This cuprate was made from isohexyl bromide and *tert*-butyllithium.

(16) **6**: $[\alpha]^{27}_D$ −113° (*c* 0.34, $CHCl_3$). ^1H NMR (360 MHz) δ 1.06 (s, 3 H, H-18), 1.10 (s, 3 H, H-19), 0.97 (d, 3 H, J = 6.84 Hz, H-21), 3.42–3.53 (br, 1 H, H-3), 4.40–4.46 (br, 1 H, H-15), 5.34–5.37 (br, 1 H, H-6), 5.50 (br, 1 H, d, H-16).

(17) Hydrogenation of compounds (**6** and **7**) were selective for the 16,17 double bond, an event with little precedence in the literature.

(18) **9**: mp 144–145 °C (ether–petroleum ether); $[\alpha]^{27}_D$ −52.2° (*c* 0.835, $CHCl_3$); ^1H NMR (360 MHz) δ 0.91 (d, 3 H, *J* = 6.59 Hz, H-21), 0.93 (s, 3 H, H-18), 1.01 (s, 3 H, H-19), 3.40–3.50 (br, 1 H, H-3), 4.10–4.22 (br, 1 H, H-15), 5.28–5.38 (br, 1 H, H-6).

amine[19] produced the silyl ether of cholesterol. Deprotection of the 3β-hydroxyl group yielded cholesterol which was spectroscopically identical with an authentic sample (^{13}C NMR, 360-MHz ^1H NMR, and IR).

The alkylideneoxirane **5** provided the complementary proof for our methodology. Addition of lithium methylcyanocuprate to **5** resulted in the formation of equal amounts of 1,4 and 1,2 adducts, **7**[20] and **8**,[21] respectively. The unanticipated 1,2 adduct (**8**) can only be rationalized this time by the differences in the steric bulk of the alkylidene substituents (i.e., methyl vs. isohexyl). Comparison of the 360-MHz ^1H NMR spectra of the enantiomeric adducts **6** and **7** revealed a clear distinction in the absorptions for the respective C-21 methyl groups (0.97 for **6** and 1.11 for **7**). Intermediate **7** was then converted to the known isocholesterol[22] by the same sequence of steps used for the preparation of cholesterol.

As a final check on the purity of the C-20 epimers produced in this study, we subjected the dimethyl ethyl silyl (DMES) ethers of compounds **6**, **7**, **9**, **10**, cholesterol, and isocholesterol to GC analysis.[23] While the retention times for the DMES ethers of **6** and **7** were very close, the ethers of compounds **9**, **10**, cholesterol, and isocholesterol separated well enough that it was possible to detect less than 1% epimeric contaminants. The GC analyses[24] confirmed that our synthetic products, **6**, **7**, **9**, **10**, cholesterol, and isocholesterol were >99.5% pure epimers at C-20.

In conclusion, the 1,4-trans addition of alkyl cyanocuprates to alkylideneoxiranes of sterols provides the only stereospecific methodology for the concomitant introduction of the C-21 asymmetric center and the 15β-hydroxyl group. This synthetic strategy should be applicable to a wide variety of functionalized sterol side chains and functionalized D rings of steroids.

Acknowledgment. We are pleased to acknowledge support of this research from the National Cancer Institute (NIH) under Grant CA 22237. The National Science Foundation is acknowledged for providing funds to purchase a Bruker 360-MHz NMR spectrometer. We also thank the G. D. Searle Co. for a generous gift of dehydroepiandrosterone.

Supplementary Material Available: Experimental details and characterization data for compounds **2–10** are available upon request (11 pages). Ordering information is given on any current masthead.

(19) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

(20) **7**: $[\alpha]^{27}_D$ −87.6° (*c* 0.21, $CHCl_3$); ^1H NMR (360 MHz) δ 1.06 (s, 3 H, H-18) 1.11 (s, 3 H, H-19), H-21 overlapped with 1.11, 3.43–3.52 (m, 1 H, H-3), 4.44–4.48 (br, 1 H, H-15), 5.30–5.38 (br, 1 H, H-6), 5.53 (d, 1 H, *J* = 2.20 Hz).

(21) **8**: $[\alpha]^{27}_D$ −66.9° (*c* 0.22, $CHCl_3$); ^1H NMR (360 MHz) δ 1.03 (s, 3 H, H-18), 1.05 (d, 3 H, *J* = 7.32 Hz, H-16CH_3), 1.18 (s, 3 H, H-19), 3.42–3.52 (m, 1 H, H-3), 3.80 (d, 1 H, *J* = 4.39 Hz, H-20), 5.00–5.08 (br, 1 H, H-20), 5.28–5.36 (br, 1 H, H-6).

(22) Nes, W. E.; Varkey, T. E.; Krevitz, K. *J. Am. Chem. Soc.* **1977**, *99*, 260. Koreeda, M.; Koizumi, N. *Tetrahedron Lett.* **1978**, 1641. See also **5a**. Isocholesterol: mp 151–153 °C; ^1H NMR (360 MHz) δ 0.66 (s, 3 H, H-18), 0.80 (d, 3 H, *J* = 6.59 Hz, H-21), 0.99 (s, 3 H, H-19); ^{13}C NMR (90 MHz) 140.83, 121.70, 71.86, 56.90, 55.91, 50.32, 42.43, 39.81, 39.53, 37.37, 36.62, 35.82, 35.23, 32.05, 31.80, 28.10, 28.00, 24.27, 24.03, 22.75, 22.66, 21.21, 19.43, 18.72, 12.18.

(23) For GC analysis of 20*R* and 20*S* steroidal acetates, see: Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760.

(24) The DMES ethers of **6**, **7**, **9**, **10**, cholesterol, and isocholesterol were prepared at room temperature with neat (dimethylethylsilyl)imidazole (Miyazaki, H.; Ishibashi, M.; Itoh, M.; Nambura, T. *Biomed. Mass Spectrom.* **1977**, *4*, 23). GC analyses were carried out on a Shimadzu TP-MI gas chromatograph (FID) with a 1.8-m (5-mm o.d.) column of 3% SE-30. Column temperature: 320 °C for ethers of **6**, **7**, **9**, **10**; 300 °C for ethers of cholesterol and isocholesterol. Gas flow: nitrogen 40 mL/min; hydrogen 40 mL/min. Retention times relative to THF solvent: DMES ether of **6**, 9.6 min; **7**, 9.4 min; **9**, 8.2 min; **10**, 11.2 min; cholesterol, 10.6 min; isocholesterol, 9.8 min.

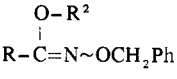
Additions and Corrections

Studies on the Reaction Mechanism of the Photocyclization of *N*-Aryl Enamines. Dependence of Quantum Yields on Back and Side Reactions. [*J. Am. Chem. Soc.* **1980**, *102*, 6098]. THOMAS WOLFF* and REINHARDT WAFFENSCHMIDT, Gesamthochschule Siegen, Physikalische Chemie, D-5900 Siegen 21, West Germany.

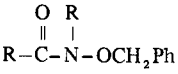
Page 6099, column 1, first paragraph: The NMR data for 1-(*N*-methylanilino)-1-phenyl-1-propene (**3**) should read: ^1H NMR ($CDCl_3$) 1.7 (3 H, doublet), 3.1 (3 H, singlet), 6.1 (1 H, quartet), 6.6–7.4 ppm (10 H, multiplet). The authors are indebted to Professor H. Ahlbrecht, Giessen, for detecting and communicating the error.

Synthesis of β-Lactams from Substituted Hydroxamic Acids [*J. Am. Chem. Soc.* **1980**, *102*, 7026]. M. J. MILLER,* P. G. MATTINGLY, M. A. MORRISON, and J. F. KERWIN, JR., Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556.

The products from the intermolecular *N*-alkylation of *O*-benzyl hydroxamates ($RCONHOCH_2Ph$) with alcohols (R^2OH) in the presence to DEAD/PPh_3 (last four entries in Table I) have been subsequently shown to be the *O*-alkyl isomers



and *not* the *N*-alkyl isomers



as reported. The products from the intermolecular alkylation of *O*-acylhydroxamates and the intramolecular alkylations to give β-lactams are correctly assigned.

^{15}N Nuclear Magnetic Resonance Spectroscopy. Products and Rearrangements in the Reaction of *p*-Toluenesulfonyl Azide-3-^{15}N with the Sodium Salt of *p*-Toluenesulfonamide. An *in Situ* ^{15}N NMR Study [*J. Am. Chem. Soc.* **1980**, *102*, 2364]. CARLA CASEWIT and J. D. ROBERTS,* Contribution No. 6112 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91125

Page 2365, column 2: Figure 1a should appear as shown below.