(d, 1 H), 8.05 (d, 1 H), 10.15 (s, 1 H); MS, m/e 319 (M^+), 318, 304, 276, 275.

7-(Benzyloxy)-8-methoxybenzo[*c*]phenanthridine (7g). Amine **4d** (0.45 g, 1.04 mmol) was treated with potassium amide (from 0.273 g, 7.00 mmol, of potassium metal) in liquid ammonia/ethyl ether for 25 min. The solid obtained on workup was recrystallized from methanol to give **7g** (0.180 g, 49%): mp 138–139 °C; 1H NMR (CCl_4) δ 4.00 (s, 3 H), 5.30 (s, 2 H), 7.30–8.00 (m, 10 H), 8.25 (d, 1 H), 8.40 (d, 1 H), 9.40 (d, 1 H), 9.85 (s, 1 H); MS, m/e (relative intensity) 365 (M^+, 100), 274 (96), 246 (80). Anal. Calcd for $C_{25}H_{19}NO_2$: C, 82.19; H, 5.20; N, 3.83. Found: C, 82.60; H, 5.23; N, 3.85.

An identical reaction quenched after 3 h furnished a mixture of **7g** and **7f**. Recrystallization from methanol gave pure **7f**: MS, m/e 275 (M^+), 260, 232. Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.54; H, 4.72; N, 5.09. Found: C, 78.32; H, 4.70; N, 5.06.

***N*-Methylation of 7-(Benzyloxy)-8-methoxybenzo[*c*]phenanthridine (7g).** A solution of **7g** (0.080 g, 0.22 mmol) in xylene (2 mL) containing freshly neutralized[31] dimethyl sulfate (0.6 mL) was refluxed for 45 min. The mixture was cooled, and the yellow solid thus formed was centrifuged and washed with benzene (3 × 1 mL) and petroleum ether (40–60 °C, 3 × 2 mL). The solid was warmed with water and the insoluble part centrifuged out. The clear aqueous solution was basified with a few drops of ammonia and extracted with chloroform (2 × 5 mL). The solvent was evaporated to yield **17b** (single spot on TLC) as a dark violet solid (0.015 g, 23.6%): mp >310 °C; 1H NMR (CF_3COOH) δ 3.80 (s, 3 H), 4.70 (s, 3 H), 9.5 (s, 1 H); MS, m/e (relative intensity) 289 (M^+, 39), 274 (100), 259 (56), 231 (31).

2,3-(Methylenedioxy)-8,9-dimethoxybenzo[*c*]phenanthridine (7i). Treatment of **4f** (0.5 g, 1.2 mmol) with potassium amide (from 0.4 g, 12 mmol, of potassium metal) in liquid ammonia/ethyl ether for 3 h, followed by MnO_2 oxidation, gave a dark solid (0.4 g). It was repeatedly recrystallized from ethanol to yield pure **7i** (0.04 g, 10%), mp 274–276 °C (lit.[32] mp 277–279 °C). Its identity was confirmed by admixture melting point (274–276 °C) and TLC comparison with an authentic sample.[32] Similar cyclization of **4e** gave **7h** in a comparable yield.

2,3:8,9-Bis(methylenedioxy)benzo[*c*]phenanthridine (7h). Reduction of **17** (0.1 g, 0.3 mmol) with $LiAlH_4$ (0.15 g) in refluxing dioxane (100 mL) afforded **7h** (0.07 g, 73%) identical with the earlier prepared sample.

LDA/THF Cyclization of 4g. Reaction of **4g** (0.083 g, 0.2 mmol) with LDA (0.6 mmol) in THF at −78 °C for 3 h and then at 40 °C for 18 h, followed by MnO_2 oxidation, gave a light brown solid (0.055 g). It was recrystallized from ethanol to yield pure **7i** in 75% yield.

8,9-Dimethoxybenzo[*c*]phenanthridine (7h): from LDA/THF cyclization of **4h** in 83% (14%)[33] yield; mp 225–226 °C.

8,9-(Methylenedioxy)benzo[*c*]phenanthridine (7l): from LDA/THF cyclization of **4i** in 91% (11%) yield; mp 227–228 °C (lit.[34] mp 223–225 °C).

8,9-(Methylenedioxy)phenanthridine (23a): from LDA/THF cyclization of **22a**[4b] in 80.7% (13%) yield; mp 137–138 °C (lit.[4b] mp 138–139 °C).

Phenanthridine (23b): from **22b**[4a] by treatment with LDA/THF at 25 °C for 48 h in 75% (>90%) yield; mp 104–105 °C (lit.[4a] mp 103–105 °C).

Registry No. **1a**, 89-98-5; **1b**, 53811-50-0; **1c**, 95712-55-3; **1d**, 113250-72-9; **1e**, 20035-41-0; **1** ($R^1 = R^4 = H$, $R^2 + R^3 = OCH_2O$, X = Cl), 15952-61-1; **1** ($R^1 = R^4 = H$, $R^2 = R^3 = OMe$, X = Cl), 18093-05-5; **1** ($R^1 = R^4 = H$, $R^2 = R^3 = OMe$, X = Br), 5392-10-9; **1** ($R^1 = R^2 = R^4 = OMe$, $R^3 = H$, X = Br), 64108-61-8; **1** ($R^1 = R^4 = H$, $R^2 + R^3 = OCH_2O$, X = I), 58343-53-6; **2a**, 134-32-7; **2b**, 53811-49-7; **3a**, 113250-73-0; **3b**, 53811-51-1; **3c**, 113250-74-1; **3d**, 113250-75-2; **3e**, 113250-76-3; **3f**, 113250-77-4; **3g**, 113250-78-5; **3h**, 113250-79-6; **3i**, 56516-98-4; **3j**, 113250-94-5; **4a**, 113250-80-9; **4b**, 53811-52-2; **4c**, 95712-58-6; **4d**, 113250-81-0; **4e**, 113250-82-1; **4f**, 113250-83-2; **4g**, 113250-84-3; **4h**, 113250-85-4; **4i**, 113250-86-5; **4j**, 113250-93-4; **6a**, 113250-95-6; **7a**, 218-38-2; **7b**, 6900-99-8; **7c**, 54354-62-0; **7e**, 3895-92-9; **7f**, 113250-91-2; **7g**, 113250-90-1; **7h**, 217-52-7; **7i**, 18034-03-2; **7l**, 214-06-2; **8b**, 3895-92-9; **9**, 41303-44-0; **10**, 41303-45-1; **11**, 53811-53-3; **12**, 24677-78-9; **13a**, 86734-60-3; **13b**, 86734-59-0; **13c**, 95712-56-4; **13d**, 113250-88-7; **13** ($R^1 = H$, $R^2 = Me$), 148-53-8; **14a**, 95712-57-5; **14b**, 95712-54-2; **14b** (dimethyl acetal), 113250-87-6; **14c**, 113250-89-8; **16a**, 51059-64-4; **17b**, 113250-92-3; **17h**, 113250-96-7; **22a**, 41001-82-5; **22b**, 41001-24-5; **23a**, 224-11-3; **23b**, 229-87-8.

(31) Zee-Cheng, K. Y.; Cheng, C. C. *J. Heterocycl. Chem.* **1973**, *10*, 85.
(32) Sample kindly provided by Prof. T. R. Govindachari, Amrutanjan Ltd., Madras, India.
(33) The number in parentheses refers to the yield obtained in the corresponding KNH_2/NH_3 reaction.
(34) Narula, S. Ph.D. Dissertation, Panjab University, Chandigarh, India, 1978.

Acid-Catalyzed Isomerization of 7-Dehydrocholesterol Benzoate. A Revised Mechanism and an Improved Synthetic Procedure

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A revised mechanism has been proposed for the low-temperature HCl-catalyzed isomerization of 3β-(benzoyloxy)cholesta-5,7-diene to 3β-(benzoyloxy)-5α-cholesta-7,14-diene. Two byproducts, 3β-(benzoyloxy)-5β-cholesta-7,14-diene and 3β-(benzoyloxy)-5β-cholesta-8,14-diene, and a new intermediate, 3β-(benzoyloxy)-6α-chloro-5α-cholest-7-ene, were isolated from this reaction. An improved procedure for the synthesis of 3β-(benzoyloxy)-5α-cholesta-7,14-diene minimizes the levels of these and other contaminants in the reaction product. All new sterols were characterized by 1H and 13C NMR.

3β-Hydroxy-5α-cholest-8(14)-en-15-one (1) is a potent inhibitor of sterol synthesis in cultured mammalian cells.[1] Oral administration of 1 to Rhesus monkys resulted in marked decreases in serum low density lipoprotein cholesterol levels and substantial increases in high density lipoprotein cholesterol levels.[2] These changes are generally considered to be beneficial for the treatment and/or prevention of atherosclerosis. For the completion of investigations concerning the effects of 1 in primates, several kilograms of 1 were required. A critical step in the most attractive route[1,3] for the large-scale preparation of 1 is the

(1) Schroepfer, G. J., Jr.; Parish, E. J.; Chen, H. W.; Kandutsch, A. A. *J. Biol. Chem.* **1977**, *252*, 8975–8980.
(2) Schroepfer, G. J., Jr.; Sherrill, B. C.; Wang, K.-S.; Wilson, W. K.; Kisic, A.; Clarkson, T. B. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 6861–6865.

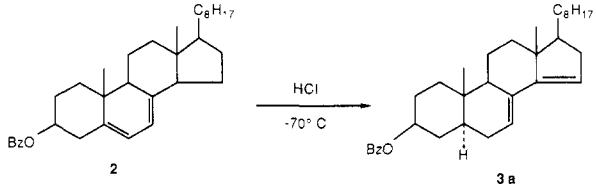
0022-3263/88/1953-1713$01.50/0

Table I. Relative Concentration of Diene Intermediates and Products[a]

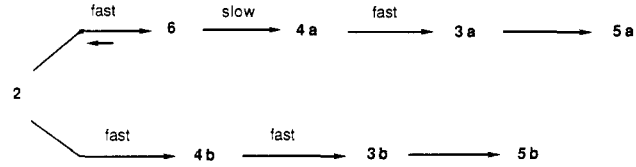
	time (min)										
compd	0	2	6	17[b]	26	55	75	115	160	220	300[c]
2	98	0.5	0.1	0.2	0	0	0	0	0	0	0
6	0	46	49	24	5	0	0	0	0	0	0
4a	0	2	2	2	3	2	3	2	4	2	2
8	0	1	2	0.5	0	0	0	0	0	0	0
3a	0	27	26	54	76	78	70	75	73	76	34
5a	0	0	0	0	0	0	3	2	2	4	19
4b	0	3	0	5	5	0	0	0	0	0	0
3b	0	15	18	8	0	2	0	0	0	0	0
5b	0	0	0	5	9	14	13	15	14	16	16
d	0	4	2	1	0		6	3	7	2	2
e	2	1	2	2	2		3	2	2	2	2

[a] Concentrations (±5% absolute for values ≥10%, ±2% absolute for values <10%) determined on quenched reaction aliquots by a combination of ^1H and ^{13}C NMR. [b] Sample partially decomposed during workup. Measured values of **6**, **4a**, **3a**, **5a**, **3b**, and **5b** were 16%, 10%, 43%, 11%, 0%, and 13%. Values shown were estimated by postulating that **6**, **3a**, and **3b** were partially converted to **4a**, **5a**, and **5b** during decomposition. [c] The reaction was allowed to warm to 15 °C during the last hour. Because the product was only partially soluble in $CDCl_3$ and contained several minor impurities, the percentage compositions were normalized to give **5b** a value of 16%. [d] Unknown substance having a ^1H NMR singlet at δ 0.74. [e] Cholesterol benzoate (see ref 3b).

Scheme I



Scheme II



HCl-catalyzed isomerization of the $\Delta^{5,7}$-diene system of **2** (Scheme I). This reaction has been studied by numerous investigators,[3a,c,4] and mechanisms have been proposed to explain the products observed.[5] Although a mixture of products is usually obtained, reaction conditions can be adjusted so as to favor the formation of either the 5α-$\Delta^{6,8(14)}$ isomer,[4i] the 5α-$\Delta^{7,14}$ isomer **3a**,[3a,4c,g,h,j,k] or the 5α-$\Delta^{8,14}$ isomer **5a**.[4d-f] By carrying out the isomerization in $CHCl_3$ at −50 °C, the 5α-$\Delta^{7,14}$ sterol **3a** has been obtained as a 3:1 mixture with a substance believed to be the 5α-$\Delta^{8,14}$ isomer **5a**.[3a,4k] In our hands, the reported procedures for the HCl-catalyzed isomerization of **2** gave highly variable yields of **3a** contaminated with unknown side products.

We report here the isolation and identification of new intermediates and side products of the diene isomerization and discuss their mechanistic implications. An improved understanding of the isomerization reaction has enabled us to devise a procedure to obtain **3a** in consistently better yield and purity than previously reported.

Results and Discussion

Conversion of the $\Delta^{5,7}$ sterol **2** to the 5α-$\Delta^{7,14}$ isomer **3a** initially proved to be highly variable in yield (30–70%) and product purity (30–85%). Moderate variation of such factors as reaction temperature, purity of the starting material and solvents, duration of reaction, and temperature of quenching of the reaction had little or no discernible effect on product composition. Isolation and identification of the major intermediates and side products in the reaction clarified this matter. In addition to the expected minor species **4a** and **5a**, the principal intermediate was found to be 3β-(benzoyloxy)-6α-chloro-5α-cholest-7-ene (**6**). The principal side product was found to be the 5β-$\Delta^{8,14}$ isomer **5b**. The 5β-$\Delta^{7,14}$ isomer **3b** was also isolated as a minor side product. The structures of **3b**, **5b**, and **6** were determined by ^1H and ^{13}C NMR, and the structures of **5b**[6a] and **6**[6b] have been confirmed by X-ray crystallography.

Once the various species in the diene isomerization had been identified and characterized by ^1H and ^{13}C NMR, the course of the reaction was followed by periodically analyzing[7] aliquots of the reaction. The results of this analysis, shown in Table I, indicate that **2** reacts very rapidly to form **6**.[8a] The slow step of the reaction appears to be the dehydrohalogenation of **6**, which bears a pseudoequatorial chlorine. At low temperatures, this elimination requires a rather high concentration of HCl, suggesting the intermediacy of a sterol having a pseudoaxial chlorine. The consistently low levels of the 5α-$\Delta^{6,8(14)}$ isomer **4a** as the reaction progressed indicate that conversion of **4a** to **3a** is much faster than the dehydrohalogenation of **6**. The

(3) (a) Parish, E. J.; Spike, T. E.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids* **1977**, *18*, 233–239. (b) Wilson, W. K.; Wang, K.-S.; Kisic, A.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids*, in press. (c) Barton, D. H. R.; Laws, G. F. *J. Chem. Soc.* **1954**, 52–63.

(4) (a) Windaus, A.; Dithmar, K.; Murke, H.; Suckfüll, F. *Justus Liebigs Ann. Chem.* **1931**, *488*, 91–110. (b) Schenk, F.; Buchholz, K.; Wiese, O. *Chem. Ber.* **1936**, *69*, 2696–2704. (c) Barton, D. H. R.; Brooks, C. W. *J. Chem. Soc.* **1951**, 257–277. (d) Fieser, M.; Rosen, W. E.; Fieser, L. F. *J. Am. Chem. Soc.* **1952**, *74*, 5397–5403. (e) Fieser, L. F.; Ourisson, G. *J. Am. Chem. Soc.* **1953**, *75*, 4404–4414. (f) Lutsky, B. N.; Schroepfer, G. J., Jr. *J. Biol. Chem.* **1970**, *245*, 6449–6455. (g) Woodward, R. B.; Patchett, A. A.; Barton, D. H. R.; Ives, D. A. J.; Kelly, R. B. *J. Chem. Soc.* **1957**, 1131–1144. (h) Knight, J. C.; Klein, P. D.; Szczepanik, P. A. *J. Biol. Chem.* **1966**, *241*, 1502–1508. (i) Johnston, P.; Sheppard, R. C.; Stehr, C. E.; Turner, S. *J. Chem. Soc. C* **1957**, 1847–1856. (j) Muccino, R. R.; Djerassi, C. *J. Am. Chem. Soc.* **1974**, *96*, 556–570. (k) Dolle, R. E.; Kruse, L. I. *J. Org. Chem.* **1986**, *51*, 4047–4053.

(5) (a) Barton, D. H. R. *J. Chem. Soc.* **1946**, 512–522. (b) Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: New York, 1968; p 293.

(6) (a) Wilson, D. K.; Quiocho, F. A.; Wilson, W. K.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids*, in press. (b) Wilson, D. K.; Quiocho, F. A.; Wilson, W. K.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids*, in press.

(7) We have found that ^{13}C NMR provides the most useful approach for compositional analysis of these reaction mixtures because all of the known components can be resolved without decomposition (Table II). Chromatography (see Table IV) and ^1H NMR (300 MHz) were less suitable for compositional analysis. NMR analyses of mixtures containing **6** should be completed within 10–30 min of dissolution since **6** is unstable in most solvents.

(8) (a) This 1,2 addition of HCl to the $\Delta^{5,7}$ system contrasts with a 1,4 addition proposed much earlier[5a] and with the preferred Markovnikov addition of HCl to Δ^5 of steroids.[8b,c,d] (b) Shoppee, C. W. *J. Steroid Biochem.* **1983**, *19*, 777–781. (c) Tal, D. M.; Keinan, E.; Mazur, Y. *Tetrahedron* **1981**, *37*, 4327–4330. (d) Barton, D. H. R. *Experientia, Suppl. 2* **1955**, 121–136.

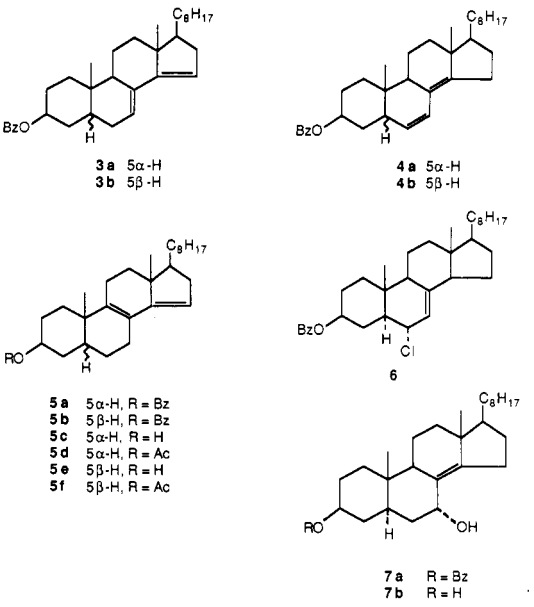
isomerization of **3a** to the 5α-$\Delta^{8,14}$ isomer **5a** appears to be somewhat slower than the dehydrohalogenation of **6**, since the reaction can be quenched at an optimal time when **6** has completely reacted yet only minor amounts of the **5a** isomer have formed.

These results are summarized in Scheme II, which shows a revised[5b] pathway for the diene isomerization. Except for a difference in reaction rates and the absence of a detectable chloro intermediate corresponding to **6**, isomerization of the 5β-dienes appears to follow a pathway similar to that for the 5α-dienes. Analysis of the total reaction product indicated that ~20% of the initial protonation of the $\Delta^{5,7}$ system occurred so as to give 5β-sterols. Because the 5β-dienes constitute the bulk of the impurities in the isomerization reaction, any attempts to increase further the yield of the desired product **3a** would require modifications of conditions to further favor the initial addition of HCl to the α face of the sterol.

The observations described above led to a rational procedure for obtaining consistently good yields and high product purity in the isomerization reaction. The reaction was carried out at the lowest practicable temperature (−70 °C). Low temperature increases the solubility of HCl and retards formation of **5a**, thereby insuring that the time period for optimal quenching of the reaction is not too short. CH_2Cl_2 was added to the $CHCl_3$ solvent to lower the freezing point without adversely affecting solubility of **2**. The HCl gas was introduced rapidly until a concentration of 2.0–2.5 M was obtained in order to counteract the tendency of the starting material to crystallize out at low temperature. The conversion of **6** to **3a** was allowed to proceed at −70 °C,[9] while the reaction was monitored periodically by TLC to determine the optimal quenching time. During workup, pyridine was added to the $CHCl_3$ solution to neutralize any additional HCl released from the dehydrohalogenation of **6**, thus preventing HCl-catalyzed isomerization of **3a** to **5a**.[10] With use of this procedure, 12 consecutive reactions (700–1000-g scale) gave 77–84% yields of **3a** of 83–91% purity (containing 9–17% **5a** and **5b**).[11]

5β sterols have been isolated previously from diene isomerizations: **5f** (prepared by Windaus[12a] by HCl/$CHCl_3$ isomerization of 3β-acetoxy-5β-cholesta-6,8(14)-diene and later identified by Barton[12b]) and 5β-ergosta-6,8(14),22-trien-3β-ol (identified[12c,d] as a minor product of an acid-catalyzed isomerization of ergosterol). Saponification and acetylation of **5b** gave a diene acetate (**5f**) with mp, UV spectrum, and optical rotation virtually identical with those reported by Windaus for **5f**. Whereas the major side product of diene isomerizations in our work was generally **5b**, the major side products of one reaction in CH_2Cl_2 were the 5β-$\Delta^{7,14}$ species **3b** and 3β-(benzoyloxy)-5α-cholest-8(14)-en-7α-ol (**7a**). The structure of **7a** was established by hydrolysis to the known[13] diol **7b** (Chart I).

Chart I



Although chloro intermediates in the diene isomerization of sterols were proposed by Barton[5a] over 40 years ago, **6** is the first such reported intermediate. No 5β epimer of **6** was detected. If 1,2 addition of HCl occurs in a syn manner,[14] then the resulting 6β-chloro substituent would be pseudoaxial and, unlike **6**, capable of facile elimination to the 5β-$\Delta^{6,8(14)}$ species **4b**.[15] Diene **4b** is a postulated intermediate, which we believe to have isolated in impure form.

In methanol or ethanol or in concentrated $CHCl_3$ solution, **6** decomposed within 5 h to a mixture of dienes **2**, **4a**, and a component (**8**), which probably represents 3β-(benzoyloxy)-5α-cholesta-6,8-diene. Pyridine and triethylamine retarded the decomposition of **6** in $CHCl_3$. In dilute (1%) solution in ethyl acetate or benzene, **6** was stable for 12 days. Upon slow heating (10 min) in a capillary tube, **6** melted (with decomposition) 20 °C lower than its normal melting point. These combined observations suggest that HCl promotes the decomposition of **6**; the HCl released then further accelerates the decomposition.

^{1}H and ^{13}C NMR Assignments and Observations. The ^{13}C NMR assignments presented in Table II were made from comparisons with assigned spectra of similar sterols[13,16] as well as from HETCOR (^{13}C–^{1}H shift-correlated 2D NMR) and COSY spectra,[17] acetylation and benzoylation shifts, lanthanide-induced shifts,[18] and the

(9) The reaction is much slower at a 1 M concentration of HCl; once the $CHCl_3$ is nearly saturated with HCl, there is no advantage in continuing to bubble HCl through the reaction mixture.

(10) Use of pyridine has been reported twice previously, once to neutralize HCl released by hypothesized chloro intermediates[3c] and once to neutralize HCl not destroyed in the quenching process.[4k]

(11) The 5β isomers can be separated easily from the 5α isomers by recrystallization but the 5α isomers, especially the 5α-$\Delta^{7,14}$ and 5α-$\Delta^{8,14}$ isomers **3a** and **5a**, are not, on a preparative scale, separated readily by recrystallization or chromatography. Small-scale chromatographic separations of 3β-acetoxy-5α-cholesta-7,14-diene and **5d** have been achieved (a) using silica gel–$AgNO_3$ columns (Lutsky, B. N.; Martin, J. A.; Schroepfer, G. J., Jr. *J. Biol. Chem.* **1971**, *246*, 6737–6744. Schroepfer, G. J., Jr.; Lutsky, B. N.; Martin, J. A.; Huntoon, S.; Fourcans, B.; Lee, W.-H.; Vermilion, J. *Proc. R. Soc. London, B* **1972**, *180*, 125–146), (b) by MPLC on alumina–$AgNO_3$ (Pascal, R. A., Jr.; Farris, C. L.; Schroepfer, G. J., Jr. *Anal. Biochem.* **1980**, *101*, 15–22), and (c) by HPLC (Thowsen, J. R.; Schroepfer, G. J., Jr. *J. Lipid Res.* **1979**, *20*, 681–685).

(12) (a) Windaus, A.; Zühlsdorff, G. *Justus Liebigs Ann. Chem.* **1938**, *536*, 204–216. (b) Barton, D. H. R. *J. Chem. Soc.* **1946**, 1116–1123. (c) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359–363. (d) The reported stability of this species to acid isomerization appears to be inconsistent with our results and those of Windaus.

(13) Tsuda, M.; Parish, E. J.; Schroepfer, G. J., Jr. *J. Org. Chem.* **1979**, *44*, 1282–1289.

(14) Both syn and anti addition of HCl to isolated double bonds of sterols has been observed and rationalized.[8d] Primarily syn addition occurs when simpler alkenes are treated with dichloromethane saturated with HCl at −98 °C: Becker, K. B.; Grob, C. A. *Synthesis* **1973**, 789.

(15) Formation of **6** and its 6β epimer in a 2:1 ratio followed by rapid dehydrohalogenation of the 6β-chloro isomer to **4a** and isomerization to **3a** provides an attractive explanation to account for the presence of the large amounts (27%) of **3a** after 2 min of reaction (Table I).

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(17) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon: Elmsford, NY, 1987.

Table II. ^{13}C NMR Assignments[a,b]

carbon atom	2	6	4a	3a	3b	5d	5a	5e	5f	5b	7a	7b
1	37.9	36.61	35.0	36.5	30.6	35.1	35.2	31.0	31.1	31.3	36.0	36.3
2	28.2	27.4	27.5	27.6	26.0	27.6	27.8	31.1	27.4	27.5	27.6	31.4
3	73.3	73.3	74.2	73.9	71.1	73.3	73.9	67.3	70.6	71.3	74.1	71.0
4	36.7	30.9	32.6	33.9	32.4	34.1	34.3	36.88	32.8	32.7	33.7	37.8
5	138.4	49.2	44.6	39.53	36.2	40.7	40.8	39.3	38.8	38.7	37.1	37.1
6	120.3	62.3	128.9	30.2	29.0	25.2	25.2	24.86*	24.29	24.05*	35.5	35.5
7	116.3	120.5	125.9	119.9	118.4	26.5	26.5	24.90*	24.29	24.13*	66.6	66.7
8	141.6	142.3	125.1	134.4	133.2	123.1	123.2	123.5	123.9	124.0	128.22	128.4
9	46.0	48.5	48.0	49.6	36.05	140.5	140.4	138.9	138.0	137.8	44.1	44.1
10	37.1	36.61	35.7	33.8	33.7	36.5	36.6	36.94	36.94	37.1	36.74	36.7
11	21.0	21.3	19.7	20.9	21.3	21.8	21.8	22.8	22.6	22.59	19.3	19.3
12	39.1	39.1	36.7	40.1	40.7	36.9	36.9	36.88	36.86	36.9	36.74	36.8
13	42.9	43.5	43.7	46.4	46.8	45.0	45.0	45.1	45.0	45.1	42.9	42.9
14	54.4	54.7	147.8	151.9	152.1	151.0	151.0	150.7	150.6	150.7	148.4	148.3
15	23.0	22.78	24.9	119.6	119.3	117.6	117.6	117.6	117.6	117.6	25.1	25.1
16	28.1	27.8	27.4	35.1	35.3	35.9	35.9	35.8	35.8	35.9	26.9	26.8
17	55.8	56.1	55.9	58.6	58.7	57.2	57.3	57.2	57.2	57.1	56.4	56.4
18	11.8	12.0	19.2	16.5	16.6	15.7	15.7	15.3	15.4	15.4	18.0	17.9
19	16.2	13.5	11.3	12.3	24.3	18.2	18.3	25.1	25.9	26.5	11.9	11.9
20	36.14	36.1	34.8	34.1	34.1	34.0	34.1	34.0	34.0	34.0	34.4	34.4
21	18.8	18.8	18.9	18.9	18.9	18.9	18.9	18.8	18.8	18.9	19.0	19.0
22	36.09	36.0	35.9	36.0	36.08	36.1	36.1	36.1	36.1	36.1	35.9	35.9
23	23.9	23.9	23.7	23.7	23.7	23.7	23.7	23.7	23.7	23.7	23.7	23.6
24	39.5	39.5	39.5	39.47	39.5	39.5	39.5	39.5	39.5	39.5	39.5	39.5
25	28.0	28.0	28.0	28.0	28.0	28.0	28.0	28.0	28.0	28.0	28.0	28.0
26	22.6	22.6	22.6	22.5	22.6	22.5	22.6	22.5	22.5	22.56	22.6	22.5
27	22.8	22.81	22.8	22.8	22.8	22.8	22.8	22.8	22.7	22.8	22.8	22.8
Bz-*p*	132.7	132.7	132.7	132.7	132.6		132.6			132.7	132.6	
Bz-*m*	128.2	128.2	128.9	128.2	128.4		128.2			128.3	128.20	
Bz-*o*	129.5	129.5	129.5	129.5	129.5		129.5			129.5	129.5	
Bz-*q*	130.7	130.7	130.8	130.7	131.1		130.9			131.0	130.9	
Bz-CO	165.9	165.9	166.1	165.9	165.8		166.0			166.1	160.0	
Ac-Me						21.4			21.4			
Ac-CO						170.7			170.5			

[a] Chemical shifts in ppm (δ). Spectra obtained in $CDCl_3$ solution. [b] Values marked with an asterisk may be interchanged.

substituent parameters of Blunt and Stothers.[16c] ^1H NMR data, obtained partially from HETCOR spectra,[17,19] are summarized in Table III.

The 5α- and 5β-dienes were readily differentiated by ^1H and ^{13}C NMR. Relative to the 5α-diene benzoate peaks, the 5β-diene benzoate NMR resonances appeared ~0.3 ppm downfield for 3α-H, ~0.1–0.2 ppm downfield for H-19 (as suggested by Zürcher's rules[20]), ~3 ppm upfield for C-3, and 8–12 ppm downfield for C-19. At 75 MHz, C-19 and C-5 (and to a lesser extent C-4, C-6, C-7, and C-9) of the 5β-$\Delta^{8,14}$ species (**5b**, **5e**, and **5f**) were notably broadened at 22 °C. At 75 MHz and 40 °C or at 22.5 MHz and 30 °C, these peaks had normal ^{13}C NMR line widths. These findings suggest slow interconversion (on the NMR time scale) of two conformations[6a] at 22 °C and rapid interconversion at 40 °C; at 22.5 MHz, the NMR peaks of the two interconverting species may not be well enough resolved to result in noticeable line broadening. Only minor line broadening of this kind was observed for the 5β-$\Delta^{7,14}$ species **3b**.

The ^{13}C NMR chemical shifts of 5α sterol benzoates **3a**, **5a**, and **7a** were identical (except for acetylation or benzoylation shifts) with the chemical shifts of the free sterols reported previously.[16a] Likewise, the 5β sterols differed in ^{13}C NMR chemical shift from the 5α sterols only in the expected positions near the AB ring junction.[21] Consequently, none of the dienes reported here underwent epimerization and in particular were not epimerized at C-17,[22,23] as has been observed in some HCl/$CHCl_3$ isomerizations of $\Delta^{8(14)}$ to Δ^{14} sterols. The structure of **3b** was based upon the close similarities of ^1H and ^{13}C NMR spectra of **3a** and **3b** after consideration of the characteristic NMR shifts described above for 5β sterols.

Conclusion. In the course of optimizing the conditions for the diene isomerization, we have isolated and identified the major intermediates and side products in this reaction, findings that have significant implications with respect to the mechanism and use of this reaction. Under conditions developed herein, the 5α-$\Delta^{7,14}$ sterol **3a** can be obtained with only minor amounts of the 5α-$\Delta^{8,14}$ isomer **5a**; the 5–15% $\Delta^{8,14}$ contaminant observed is mainly the 5β-$\Delta^{8,14}$ isomer **5b**, which can be removed by recrystallization.

Experimental Section

Most instrumentation and analytical procedures have been described elsewhere.[16d] Ultraviolet (UV) spectra were recorded in absolute ethanol on an IBM 9430 spectrophotometer. Infrared (IR) spectra were recorded on a Beckman 4230 spectrometer using KBr pellets. Optical rotations were measured on a JASCO DIP-4 digital polarimeter at 589 nm in $CHCl_3$ solution. High resolution MS were recorded by using electron impact on either a CEC/DuPont 21-110B double-focusing high resolution mass spectrometer or a Varian CH-5 spectrometer (courtesy of Professor C. C. Sweeley). ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions on an IBM AF300 spectrometer (300.1 MHz for ^1H, 75.5 MHz for ^{13}C) or a JEOL FX 90Q spectrometer (89.60 MHz for

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(23) The ^{13}C NMR chemical shifts of 17α and 17β sterols differ markedly in chemical shift in the vicinity of C-17.[22a]

Table III. ^{1}H NMR Chemical Shifts[a-c]

carbon atom	2	3a	3b	4a	5a	5b	5d	5e	5f	6	7a	7b
1	1.94	1.91	1.65	1.76		1.73		1.67	1.65		1.75	
	1.42	1.19	1.49	1.24		1.68		1.57	1.61		1.29	
2	2.06	1.98	1.81*	2.03		1.73		1.62	1.56*		2.00	
	1.72	1.64	1.81*	1.72		1.66		1.46	1.56*		1.60	
3	4.96	4.95	5.30	5.03	4.97	5.22	4.71	3.89	4.94	4.97	4.99	3.65
4	2.64	1.88	1.71	1.97		1.88		*d*	1.75	2.54	1.78	
	2.53	1.48	1.60	1.59		1.81		*d*	1.69	1.52*	1.47	
5		1.54	1.85	2.21		1.77		1.66	1.67		1.93	
6	5.61	1.88	2.54	5.26		1.87		1.70*	1.82	4.32[b]	1.56	
		1.82	1.60			1.58*		1.58	1.57		1.44	
7	5.40	5.76[e]	5.70	6.15		2.3*		2.31*	2.31*	5.28	4.54	4.53
						2.0*		1.97*	1.98*			
9	2.03	1.79	2.23	1.97							2.15	
11	1.67	1.66	1.55*	1.68		2.25*		2.24	2.24*		1.65	
	1.60	1.58	1.55*	1.63		2.02		2.07	2.07*		1.48*	
12	2.10	2.05	2.08	2.03		2.03		2.02	2.02		1.96	
	1.25	1.35	1.41	1.27		1.41		1.36	1.39		1.16	
14	1.89											
15	1.70	5.52[e]	5.49[e]	2.37	5.38[e]	5.39[e]	5.37[e]	5.39[e]	5.39[e]		2.37	
	1.39			2.34							2.37	
16	1.93	2.33	2.38*	1.92		2.38		2.36	2.37		1.87	
	1.31	1.93	1.92*	1.43		2.08		2.06	2.07		1.41*	
17	1.22	1.60	1.62	1.20		1.55		1.52	1.53		1.16	
18	0.630	0.839	0.853	0.905	0.830	0.844	0.816	0.829	0.829	0.554	0.861	0.667
19	0.997	0.854	0.946	0.711	1.058	1.174	1.004	1.119	1.126	0.925	0.731	0.851
20	1.39	1.61	1.61	1.48		1.63		1.63	1.63		1.47	
21	0.949	0.930	0.938	0.949	0.947	0.951	0.938	0.941	0.942	0.927	0.937	0.938
22	1.37	1.38	1.38*	1.40		1.39		1.38	1.38		1.38	
	1.02	1.06	1.09	1.07		1.08		1.06	1.07		1.06	
23	1.36	1.36	1.38*	1.34		1.37		1.36	1.36		1.34	
	1.16	1.18	1.17*	1.14		1.18		1.17	1.19		1.17	
24	1.15	1.16	1.15*	1.15		1.17		1.16	1.16		1.13	
	1.11	1.13	1.15*	1.11		1.13		1.13	1.13		1.13	
25	1.53	1.53	1.53	1.53		1.53		1.53	1.53		1.52	
26	0.870	0.871	0.872	0.867	0.873	0.873	0.867	0.870	0.869	0.868	0.869	0.867
27	0.874	0.874	0.875	0.870	0.873	0.875	0.869	0.872	0.871	0.873	0.872	0.871

[a] Values (±0.02 ppm) for methylene and methine protons extracted from HETCOR data. An asterisk indicates less reliable chemical shifts (±0.05 ppm) estimated from a combination of COSY, ^{1}H NMR, and HETCOR power spectra. [b] At 300 MHz, all resonances were multiplets except 18-H (s), 19-H (s), 21-H (d, J = 6.3 ± 0.3 Hz), 26-H and 27-H (d, J = 6.6 ± 0.3 Hz). Also, 6α-H of **6**, br d, J = 9 Hz; 7α-H of **7b**, t, J = 3 Hz. [c] Benzoates **2**, **3a**, **3b**, **4a**, **5a**, **5b**, **6**, and **7a** also showed the following resonances: δ 8.05 (1 H, d, J = 7.1 Hz), 7.55 (2 H, t, J = 7.4 Hz), 7.43 (2 H, t, J = 7.3 Hz). Acetates **5d** and **5f** showed a singlet at δ 2.03. [d] Not observed or poorly defined in HETCOR spectrum. [e] Broad singlet.

Table IV. Chromatographic Characteristics of Diene Benzoates[a]

		chromatographic mobility						
method	eluent	2	4a	4b	3a	3b	5a	5b
TLC–SiO_2	toluene/hexane (1:1)	0.56	0.56	0.51	0.56	0.52	0.56	0.56
TLC–SiO_2/$AgNO_3$	toluene/hexane (1:1)	0.50	0.64		0.52	0.47	0.49	0.54
TLC–SiO_2	ether/hexane (1:19)	0.56	0.56		0.55	0.55	0.56	0.56
TLC–SiO_2/$AgNO_3$	ether/hexane (1:19)	0.10	0.17		0.08	0.08	0.08	0.12
TLC–SiO_2	EtOAc/hexane (1:49)	0.43	0.42	0.42	0.42	0.42	0.42	0.42
TLC–SiO_2/$AgNO_3$	EtOAc/hexane (1:49)	0.15	0.21		0.13	0.13	0.14	0.16
HPLC	2-propanol/MeOH (1:4)	27.6	24.9	17.9	22.2	16.7	22.2	19.3
GC		17.86	18.07		16.82		17.05	13.76

[a] R_f values for TLC (silica gel G), retention volumes for HPLC (Spherisorb ODS-II, 1.7 mL/min); retention times for GC (15 m DBU, 5 psi N_2).

^{1}H and 22.53 MHz for ^{13}C). $AgNO_3$-coated silica gel TLC plates were prepared by dipping the commercial plates in a 10% solution of $AgNO_3$ in methanol/water (2:1 v/v) for 5 s and heating the dried plates at 110 °C for 1 h. HPLC analyses were carried out in the reversed phase mode on a Waters liquid chromatograph with columns (4.6 × 250 mm) packed with Spherisorb ODS-II, 5 μm. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN.

3β-(Benzoyloxy)-5α-cholesta-7,14-diene (3a), Large-Scale Preparation. HCl gas was bubbled through a partially crystallized mixture of 1 kg of **2**, 3 L of $CHCl_3$, and 0.8 L of CH_2Cl_2 cooled to −55 °C. The reaction mixture was further cooled to −70 °C. When the HCl concentration reached 2.0–2.5 M (determined by titration of a reaction aliquot with standard base), the HCl flow was shut off, and the reaction was monitored every 15–30 min by TLC ($AgNO_3$-coated silica gel, toluene/hexane 1:1) until only a single spot was observed at R_f 0.55 from a neutralized, washed aliquot of the reaction mixture. Most of the HCl was then evaporated in vacuo, and the reaction was neutralized by addition to ice/NH_4OH. The neutralized mixtures were combined, and the organic phase was washed with 2 × 2.5 L of water and immediately drained into 120 mL of pyridine. The (often turbid) solution was concentrated to 3 L and crystallized by addition of 6 L of acetone. Filtration gave a white powder (815–841 g) composed of **3a** (83–88% pure) contaminated with **5a** and **5b** (data from 12 consecutive reactions). Further recrystallization from acetone/$CHCl_3$ (2:1) was effective in the removal of **5b** but not **5a**. A second crop obtained from concentration of the filtrate consisted of **3a** and **5b** in a 1:4 ratio. An analytical sample (98% **3a**, 2% **5a**) was obtained by three additional recrystallizations from acetone/$CHCl_3$: mp 154.5–156 °C (lit.[4f] mp 152 °C; lit.[4e] mp 151–152 °C); $[\alpha]^{24}_D$ −159° (*c* 1.1, $CHCl_3$) (lit.[4e] $[\alpha]_D$ −150° (*c*

1-2, $CHCl_3$)); IR (KBr) 3070, 3040, 3020, 3000–2820, 1715, 1630, 1600, 1580, 1110, 710 cm^{-1}; ^1H and ^{13}C NMR: Tables III and II; MS, m/z (rel intensity) 488 (6, M^+), 375 (21), 366 (16), 351 (22), 253 (50), 159 (50), 105 (100); exact mass calcd for $C_{34}H_{48}O_2$ 488.3654, obsd 488.3619.

Concentrations of Diene Intermediates as the Reaction Progresses. A diene isomerization was carried out as described above but using 20 g of **2** in 120 mL of $CHCl_3/CH_2Cl_2$ (4:1). The reaction was cooled to −55 °C, a saturated solution of HCl in $CHCl_3$ (30 mL, −55 °C) was added, and HCl was allowed to bubble through the reaction mixture for 20 min. The HCl was then shut off, and the reaction was held at −65 °C. At various times ~10-mL aliquots were removed from the reaction and poured into cold concentrated NH_4OH. The resulting organic layer was washed with water, evaporated to an oil or solid, and dissolved in $CDCl_3$ immediately prior to ^1H and ^{13}C NMR analysis. The results of the NMR analysis are presented in Table I. An analogous experiment carried out on a 200-g scale gave similar results.

HCl Concentrations in the Diene Reaction Mixture. The HCl concentration in the diene isomerization reaction mixture was determined by quickly transferring 1.0 ± 0.1 mL aliquots of the reaction mixture (using a cooled, calibrated Pasteur pipet) to 50 mL of water and titrating the resulting solution with standard NaOH solution to the phenolphthalein end point. In each case, the HCl concentration was ~0.6 M after 30 min and reached ~2.6 M after 2–3 h.

3β-(Benzoyloxy)-6α-chloro-5α-cholest-7-ene (6). To a solution of 1.6 M HCl in 100 mL of $CHCl_3$ (ethanol-free) at −65 °C was added a solution of 10.0 g of **2** in 100 mL of $CHCl_3$ (ethanol-free) at −58 °C. The resulting amber solution was stirred at −62 °C for 70 s and poured into NH_4OH/ice. The cold organic layer was drained into 5 mL of pyridine, washed with 2 × 150 mL of water, evaporated (after addition of 5 mL of pyridine), and dried in vacuo. The resulting solid (10.74 g, 50% **6**, 25% **3a**, 5% **2**, and 20% **4b** by ^1H NMR) was dissolved in 30 mL of $CHCl_3$; addition of 60 mL of acetone yielded a slowly forming precipitate, which was collected after 30 min by suction filtration. This product (3.38 g) was subjected to five additional recrystallizations to give an analytical sample of **6** (0.37 g): melted over a 2–3° range at 135 °C (slow heating) or 155 °C (normal heating rate); melted with evolution of gas mainly to **4a** (analysis of melted material by ^1H NMR); IR (KBr) 3020, 3000–2820, 1725, 1600, 1580, 1110, 710 cm^{-1}; UV (hexane) λ_{max} (ϵ) 228 (18000); ^1H and ^{13}C NMR, Tables III and II; MS, m/z (rel intensity) (no M^+), 488 (0.5), 375 (1), 366 (4), 351 (3), 253 (27), 199 (10), 158 (17), 143 (22), 105 (35), 37 (34), 35 (100); the reconstructed ion profile of the direct probe sample showed that the m/z 35 ion appeared shortly after the heating was begun; the m/z 488 ions appeared ~10 s later; exact mass calcd for $C_{34}H_{48}O_2$ 488.3654, obsd 488.3679; TLC, decomposes mainly to **4a** when spotted onto silica gel plates; decomposes to a mixture of dienes (**2**, **4a**, **8**) when spotted onto silica gel plates impregnated with $AgNO_3$ (analyses of spotted material by ^1H NMR). Anal. Calcd for $C_{34}H_{49}O_2Cl$: C, 77.75; H, 9.40; Cl, 6.75. Found: C, 77.87; H, 9.60; Cl, 6.86.

Product Obtained from Decomposition of 6 (8). A solution of 60 mg of **6** in 10 mL of $CHCl_3$ containing 0.50 g of Na_2CO_3 was stirred at 20 °C for 3 days. The Na_2CO_3 was removed by filtration, and the filtrate was evaporated to a white solid. ^1H and ^{13}C NMR analysis indicated a mixture of 70% of **8** (possibly 3β-(benzoyloxy)-5α-cholesta-6,8-diene), 15% of **4a**, and 15% of **2**. ^1H NMR of **8** (90 MHz; δ 4–7 region only): δ 8.2–8.0 (1 H, m) and 7.6–7.3 (4 H, m), 5.85 (1 H, dd, J = 11 Hz, 4 Hz), 5.38 (1 H, dd, J = 11 Hz, 2 Hz), 5.0 (1 H, m), 0.59 (3 H, s). Partial ^{13}C NMR of **8** (22.5 MHz): δ 166.0, 138.8, 132.7, 130.8, 129.5, 128.8, 128.2, 125.8, 74.0, 54.8, 50.1, 41.9, 39.5, 36.6, 36.3, 36.2, 35.9, 33.4, 32.2, 28.8, 28.0, 27.6, 23.9, 23.6, 23.2, 22.8, 22.6, 18.8, 12.3, 10.8.

Stability of 6. Solutions of **6** prepared in EtOAc (1%), anhydrous ether (1%), benzene (1%), and acetone (0.5%) showed no decomposition after 24 h. After 12 days, no decomposition was observed for the EtOAc or benzene solutions, but **6** had decomposed completely to **4a** in ether solution and partially to a mixture including **4a** and **2** in acetone solution. A 0.13% solution of **6** in cyclohexane stored at 20 °C for 6 weeks showed no decomposition to **4a** or any other sterol (2% detection limit). After 1 h at 20 °C, 1% solutions of **6** in $CHCl_3$/methanol (1:1) or $CHCl_3$/ethanol (1:1) each containing 0.1 mL of pyridine decomposed completely to a mixture of **2**, **4a**, and **8**. A 20% solution of **6** decomposed rapidly in $CDCl_3$ solution (contained 5% **4a** after 1 h, >95% **4a** and unidentified sterols after 5 h) whereas a 2% solution in $CDCl_3$ decomposed more slowly (~10% each of **4a** and **8** after 3 h), and a 2% solution in $CDCl_3$ containing 10% pyridine or triethylamine showed no detectable decomposition products (<10%) after 3 h at 20 °C. At −20 °C, a 2% solution of **6** in $CDCl_3$ was stable for a month. Stirring a solution of **6** in tetrahydrofuran containing solid $AgNO_3$ resulted in a mixture of **2**, **4a**, and **8**. Heating **6** at 80–120 °C for 10 min in an unsealed tube did not lead to detectable (>10%) decomposition (^1H NMR analysis).

3β-(Benzoyloxy)-5α-cholesta-6,8(14)-diene (4a). A sample was prepared from 2.0 g of **2** as described previously[24a] but using 2,5-dihydrothiophene 1,1-dioxide in place of SO_2.[24b] (In our experience and judging from results from the literature, a better conversion of **2** to **4a** is obtained with free sterols than with benzoate esters.) The crude product (a 2:1 mixture of **4a** and **2**) was separated on an alumina-$AgNO_3$ medium pressure liquid chromatography (MPLC) column[11b] eluted with toluene/hexane (3:10) to give 0.67 g of 97% pure material. An analytical sample was prepared by recrystallization from $CHCl_3$/acetone (1:2): mp 115–116 °C, clearing at 145.5 °C (lit.[25] mp 115 °C); $[\alpha]^{24}_D$ −64.7° (*c* 1.8, $CHCl_3$) (lit.[25] $[\alpha]_D$ −62° (*c* 1.1, $CHCl_3$)); IR (KBr) 3060, 3020, 3000–2820, 1715, 1600, 1580, 1110, 710 cm^{-1}; ^1H and ^{13}C NMR, Tables III and II; MS, m/z (rel intensity) 488 (40, M^+), 473 (12), 375 (72), 366 (40), 351 (45), 253 (100), 227 (34), 211 (18), 199 (54), 105 (42); HPLC (2-propanol/methanol 1:2; 1.7 mL/min) 10.0 mL (0.8%), 12.7 mL (99.2%).

3β-(Benzoyloxy)-5β-cholesta-6,8(14)-diene (4b) (impure). A solution of 10.0 g of **2** in 75 mL of $CHCl_3$ (ethanol-free) was treated with HCl as described for the preparation of **6**. The filtrate from the first recrystallization was evaporated in vacuo to a glassy solid which was taken up in $CHCl_3$, washed with water, and evaporated to a glassy amber solid (1.13 g). ^1H NMR (δ 4–7 region only): δ 6.14 (m, 1 H), 5.54 (m, 1 H), 5.33 (m, 1 H). Partial ^{13}C NMR: δ 165.8, 147.4, 132.7, 131.0, 129.5, 129.2, 128.3, 124.7, 70.2, 55.9, 43.6, 40.1, 39.5, 37.3, 35.9, 34.7, 34.3, 33.7, 29.4, 28.0, 27.4, 25.4, 24.9, 23.7, 23.2, 22.8, 22.5, 19.5, 19.0, 18.9.

Isolation of Side Products 3b and 7a. A diene isomerization was carried out by using the large-scale procedure for preparing **3a** but with 100 g of **2** dissolved in 900 mL of CH_2Cl_2. After 1.3 h, titration indicated an HCl concentration of 1.9 M, and the HCl was turned off. The reaction was neutralized and worked up as usual except that the CH_2Cl_2 was evaporated completely and replaced with $CHCl_3$ for the recrystallization step. A first crop of 57.1 g of sterol consisted of 92% **3a**, 5% **4a**, and 3% $\Delta^{8,14}$ species (**5a** and **5b**). A second crop (recrystallized from hot acetone after washing with water to remove pyridinium salts) of 10.4 g consisted of 40% **3a**, 15% **6**, 15% **4a**, and 30% **7a**. The mother liquor of the second crop was evaporated to a pale brown residue (30.0 g), which was mainly a 1:1 mixture of **3b** and **7a**. A 2.00-g sample of this residue was separated by silica gel column chromatography into a fraction highly enriched in **3b** (eluted with toluene/hexane 1:1) and a fraction highly enriched in **7a** (eluted with EtOAc). The first fraction (80% **3b**, 13% **5b**, and 7% **3a**/**5a**) was purified by semipreparative HPLC (5-μm Spherisorb ODS-II, 2-propanol/methanol 1:5) to give 90 mg of an analytical sample of **3b**. The second fraction, consisting of **7a** and various polar impurities, was recrystallized twice from methanol to give a 99% pure sample of **7a**.

3β-(Benzoyloxy)-5β-cholesta-7,14-diene (3b) prepared above: mp 100.5–101.5 °C; $[\alpha]^{24}_D$ −79.8° (*c* 1.2, $CHCl_3$); IR (KBr) 3070, 3040, 3020, 3000–2820, 1715, 1600, 1580, 1110, 710 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 231 (20900); ^1H and ^{13}C NMR, Tables III and II; MS, m/z (rel intensity) 488 (1, M^+), 375 (21), 366 (16), 351 (22), 253 (50), 239 (13), 105 (99); exact mass calcd for $C_{34}H_{48}O_2$ 488.3654, obsd 488.3619; HPLC (2-propanol/methanol 1:5, 0.8 mL/min) 12.1 mL (99.3%), 13.0 mL (0.3%), 14.2 mL (0.3%), 16.7 mL (0.1%).

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3β-(Benzoyloxy)-5α-cholest-8(14)-en-7α-ol (7a) prepared above: mp 103 °C, clearing at 120 °C; IR (KBr) 3400, 3060, 3000–2820, 1720, 1600, 1580, 1110, 710 cm^{-1}; ^1H and ^{13}C NMR, Tables III and II; MS, m/z (rel intensity) 506 (2, M^+), 488 (M $-H_2O$, 1), 393 (1), 384 (1), 375 (7), 366 (3), 361 (3), 351 (5), 298 (4), 290 (6), 253 (24), 199 (13), 177 (17), 145 (21), 107 (28), 105 (100), 55 (51), 43 (73); HPLC (methanol, 1.2 mL/min) single peak (detection limit 1%) at 8.7 mL.

Hydrolysis of 7a to 7b. A solution of 26.6 mg (0.05 mmol) of **7a** in 0.9 M KOH in absolute ethanol was stirred at 20 °C for 1 h. Standard workup gave a pale yellow solid (19 mg). The ^1H and ^{13}C NMR spectra (Tables III and II) were identical within experimental error with those reported previously.[13]

3β-(Benzoyloxy)-5β-cholesta-8,14-diene (5b). A diene isomerization reaction was carried out on a 500-g scale as described for **3a**. The filtrate from the first crop of crystals (353.6 g, 71% yield of 92% pure **3a**) was evaporated to 2 L and crystallized at 4 °C, giving a product (40 g) consisting of 94% **5b** and 6% **3a** (^1H NMR analysis). Three recrystallizations from $CHCl_3$–acetone yielded an analytical sample (13.2 g) having no ^1H NMR vinyl impurity peaks (detection limit 0.3%): mp 157.5–158.5 °C; $[\alpha]^{24}_D$ −17.5° (*c* 1.2, $CHCl_3$); IR (KBr) 3040, 3000–2820, 1720, 1600, 1580, 1110, 710 cm^{-1}; UV (EtOH) λ_{max} (ε) 237 (26 000); ^1H and ^{13}C NMR, Tables III and II; MS, m/z (rel intensity) 488 (4, M^+), 366 (4), 351 (10), 312 (2), 253 (5), 238 (37), 105 (100); exact mass calcd for $C_{34}H_{48}O_2$ 488.3654, obsd 488.3646. Anal. Calcd for $C_{34}H_{48}O_2$: C, 83.55; H, 9.90. Found: C, 83.48; H, 10.06.

5β-Cholesta-8,14-dien-3β-ol (5e). To a solution of 2 g (4.1 mmol) of **5b** in 200 mL of absolute EtOH was added 13.2 g (200 mmol) of KOH. The reaction mixture was stirred vigorously at 40 °C for 1 h; after 40 min, the sterol had completely dissolved, and TLC analysis showed disappearance of **5b**. Standard workup conditions afforded 1.7 g of white solid, which was recrystallized from hot acetone (5 mL) to give an analytical sample (1.35 g, 86%): mp 93–94 °C (lit.[12a] mp 75 °C); $[\alpha]^{24}_D$ −53.4° (*c* 1, $CHCl_3$) (lit.[12a] $[\alpha]^{20}_D$ −48°); IR (KBr) 3300, 3060, 3000–2820, 1630, 1030 cm^{-1}; UV (EtOH) λ_{max} (ε) 249 (20 600); ^1H and ^{13}C NMR, Tables III and II; MS, m/z (rel intensity) 384 (100, M^+), 369 (82), 351 (82), 325 (23), 312 (11), 238 (71), 57 (60), 55 (65); exact mass calcd for $C_{27}H_{44}O$ 384.3392, obsd 384.3401; TLC, R_f 0.63 (silica gel, EtOAc/hexanes 1:1) and R_f 0.72 (silica gel/$AgNO_3$, EtOAc/hexanes 1:1); GC (3% OV-17 packed column, 250 °C, TMS derivative) single peak at 16.8 min. Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.16; H, 11.23.

3β-Acetoxy-5β-cholesta-8,14-diene (5f). Acetylation of 1.0 g (2.6 mmol) of **5e** in 9.0 g of dry pyridine and 9.0 g of acetic anhydride at 20 °C for 23 h gave a crude product of 0.87 g (95% pure). Chromatography (silica gel, eluted with toluene/hexane 4:6) followed by recrystallization from acetone gave an analytical sample (0.50 g, 45%): mp 81.5–83 °C (lit.[12a] mp 80–81 °C); $[\alpha]^{24}_D$ −46.5° (*c* 2, $CHCl_3$) (lit.[12a] $[\alpha]^{19}_D$ −49.3° (*c* 1.3, $CHCl_3$)); IR (KBr) 3060, 3000–2820, 1745, 1240, 1120, 800 cm^{-1}; UV (EtOH) λ_{max} (ε) 249 (20 300) (lit.[12a] UV 248 (22 000)); ^1H and ^{13}C NMR, Tables III and II; MS, m/z (rel intensity) 426 (67, M^+), 411 (12), 366 (54), 352 (80), 351 (100), 313 (37), 253 (56), 238 (100), 105 (70), 55 (88); exact mass calcd for $C_{29}H_{46}O_2$ 426.3498, obsd 426.3507; TLC, R_f 0.47 (EtOAc/hexane 1:19) and R_f 0.78 (EtOAc/hexane 1:3); HPLC (2-propanol/methanol 1:4) 3.2 mL (0.3%), 7.6 mL (0.3%), 9.5 mL (99.4%). Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.68; H, 10.90.

5α-Cholesta-8,14-dien-3β-ol (5c). The synthesis was carried out as described by Fieser[4d] using 10 g of 7-dehydrocholesterol. A crude product of 5.24 g was obtained and shown by ^{13}C NMR, GC (3% OV-17 packed column), and HPLC to contain 93% **5c**, 5% **5e**, and 2% other compounds. A 99% pure sample was obtained by fractional crystallization from methanol: MS, m/z (rel intensity) 384 (100, M^+), 369 (93), 351 (46), 271 (35), 257 (20), 253 (19), 238 (42), 159 (40); HPLC (methanol, 1.2 mL/min) 7.6 mL (99%), 8.4 mL (1%); GC (3% OV-17, 248 °C) 21.0 min (99%), 19.4 min (1%).

3β-(Benzoyloxy)-5α-cholesta-8,14-diene (5a). A mixture of 0.35 g (0.91 mmol) of **5c**, 2.5 g of pyridine, and 0.55 g (3.9 mmol) of benzoyl chloride was heated at 90 °C for 1 h. To the cooled solution was added 10 mL of water; the precipitated material was filtered, washed (water, saturated Na_2CO_3, acetone), and dried in vacuo, giving 0.39 g (88%) of colorless crystals: mp 146–147 °C (lit.[26] mp 147–148 °C); $[\alpha]^{24}_D$ +2° (*c* 0.5, $CHCl_3$) (lit.[26] $[\alpha]_D$ −6.9° (*c* 0.6, $CHCl_3$)); ^1H and ^{13}C NMR, Tables III and II; MS, m/z (rel intensity) 488 (74, M^+), 473 (6), 375 (10), 366 (9), 351 (100), 253 (14), 239 (24), 105 (50); HPLC (2-propanol/methanol 1:1, 1.1 mL/min) single peak at 7.6 mL (>99%).

3β-Acetoxy-5α-cholesta-8,14-diene (5d). A sample was prepared from 7-dehydrocholesterol using the Fieser procedure.[4d] Repeated recrystallization from ether/methanol to remove **5f** gave a 99% pure sample: mp 101–101.5 °C (lit.[4e] mp 101–102 °C); $[\alpha]^{24}_D$ −26° (*c* 1.5, $CHCl_3$) (lit.[26] $[\alpha]_D$ −22.9° (*c* 0.6, $CHCl_3$)); ^1H and ^{13}C NMR, Tables III and II; MS, m/z (rel intensity) 426 (67, M^+), 411 (21), 366 (8), 351 (100), 313 (18), 253 (15), 238 (32), 159 (20); HPLC (methanol) 14.2 mL (**5f**, 0.5%), 16.3 mL (99%), 18.0 mL (0.5%); GC (3% OV-17, 268 °C) 15.0 min (0.7%, **5f**) 18.6 min (99.3%).

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Highly Selective Photoinduced Dimerization of Alkyl Pyruvates Catalyzed by Cobaloxime

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Alkyl pyruvates with an electron-withdrawing group, an α-methyl group, and a group that can react with hydridocobaloxime were dimerized selectively to dialkyl 4-hydroxy-4-methyl-2-oxopentanedioates in the presence of a catalytic amount of benzyl(pyridine)cobaloxime under irradiation by a tungsten lamp. Hydridocobaloxime is the active species produced by the reaction of photoactivated benzylcobaloxime and alkyl pyruvate in the initiation step. The hydridocobaloxime induced the dimerization reaction catalytically via the insertion of enol pyruvate into the Co–H bond of the hydridocobaloxime to give an intermediate alkylcobaloxime, which, in the catalytic cycle, reacted with the second alkyl pyruvate.

Currently, considerable interest is directed toward alkylcobaloximes as models for vitamin B_{12}[1] and organocobalt reagents.[2] However, their usefulness as catalysts has been little explored.[3] On irradiation, an alkylcobal-

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