the reaction mixture, and the solution was extracted with $CHCl_3$ (10 mL × 2). The combined extracts were washed with water and brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure and column chromatography on SiO_2 using $CHCl_3$ as eluent gave 0.21 g of **1a** as a colorless liquid: ^1H NMR δ 7.20–7.30 (m, 5 H), 7.00 (t, 1 H, J = 1.5 Hz), 4.70–5.00 (m, 1 H), 2.65–2.90 (m, 2 H), 1.95–2.25 (m, 2 H), 1.95 (t, 3 H, J = 1.5 Hz); IR (film) 3040, 2950, 1760, 1660, 1500, 1460, 1100 cm^{-1}; HRMS, calcd for $C_{13}H_{14}O_2$ m/e 202.0995, found m/e 202.0966.

5-(*p*-Chlorophenyl)-3-methyl-2(5*H*)-furanone (1b): white crystals; mp 77–79 °C; ^1H NMR δ 7.10–7.45 (m, 5 H), 7.12 (t, 1 H, J = 2 Hz), 5.85 (t, 1 H, J = 2 Hz), 2.00 (t, 3 H, J = 1.5 Hz); IR (film) 1770, 1675, 1500, 1300, 1100, 1050, 840 cm^{-1}; HRMS, $C_{11}H_9ClO$ m/e 208.0342, found m/e 208.0006.

5-*tert*-Butyl-3-methyl-2(5*H*)-furanone (1c): white crystals; mp 56–56 °C; ^1H NMR δ 7.00 (t, 1 H, J = 1.5 Hz), 4.50 (m, 1 H), 1.92 (t, 3 H, J = 2 Hz), 0.97 (s, 9 H); IR (film), 2950, 1760, 1480, 1380, 1240, 1080 cm^{-1}. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.98; H, 9.13.

5-Ethyl-3,4-dimethyl-2(5*H*)-furanone[14] **(1d)**: colorless liquid; ^1H NMR δ 4.60–4.90 (m, 1 H), 1.94 (s, 3 H), 1.80 (s, 3 H), 1.10–1.70 (m, 2 H), 0.90 (t, 3 H, J = 8 Hz); IR (film) 3000, 2900, 1760, 1700, 1450, 1340, 1090, 1000 cm^{-1}; HRMS, calcd for $C_8H_{12}O_2$ m/e 140.0838, found m/e 140.0828.

5-*tert*-Butyl-3-ethyl-2(5*H*)-furanone (1e): colorless liquid; ^1H NMR δ 7.05 (t, 1 H, J = 2 Hz), 4.58 (m, 1 H), 2.20–2.50 (m, 2 H), 1.20 (m, 3 H, J = 7 Hz), 0.98 (s, 9 H); IR (film) 2950, 1750, 1700, 1420, 1050 cm^{-1}; HRMS, calcd for $C_{10}H_{16}O_2$ m/e 168.1151, found m/e 168.1140.

3-Methyl-5-prenyl-2(5*H*)-furanone (1f): colorless liquid; ^1H NMR δ 7.05 (t, 1 H, J = 1.5 Hz), 5.38 (m, 1 H), 5.15 (m, 1 H), 1.90 (t, 2 H, J = 2 Hz), 1.72 (s, 3 H), 1.68 (s, 3 H); IR (film) 2950, 2900, 1750, 1440, 1200, 1080 cm^{-1}; HRMS, calcd for $C_9H_{12}O_2$ m/e 152.0838, Found m/e 152.0837.

Methyl 2,5-dihydro-4-methyl-5-oxofuran-2-acetate[15] **(1g)**: colorless liquid; ^1H NMR δ 7.10 (t, 1 H, J = 1.5 Hz), 5.25 (tt, J = 7.5 Hz, J = 1.5 Hz), 3.70 (s, 3 H), 2.65 (d, 2 H, J = 7 Hz), 1.95 (t, 3 H, J = 2 Hz); IR (film) 2970, 1775, 1755, 1670, 1450, 1180, 1060, 870 cm^{-1}.

Methyl 3-allyl-2,5-dihydro-4-methyl-5-oxofuran-2-acetate (1h): colorless liquid; ^1H NMR δ 5.50–6.15 (m, 1 H), 5.20–5.40 (m, 2 H), 5.10 (m, 1 H), 3.70 (s, 3 H), 3.05–3.30 (m, 2 H), 2.92 (dd, 1 H, J = 15 Hz, J = 4.5 Hz), 2.45 (dd, 1 H, J = 16 Hz, J = 8 Hz), 1.85 (d, 3 H, J = 2 Hz); IR (film) 2930, 1735, 1720, 1660, 1440, 1150, 1150, 1040 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.64; H, 6.66.

Methyl 2,5-dihydro-5-oxo-4-phenylfuran-2-acetate (1i): colorless liquid; ^1H NMR δ 7.00 (t, 1 H, J = 1.5 Hz), 5.15 (tt, J = 8 Hz, J = 1.5 Hz), 3.68 (s, 3 H), 2.70 (d, 1 H, J = 4 Hz), 2.58 (d, 1 H, J = 4.5 Hz), 2.10–2.45 (m, 2 H), 1.15–1.70 (m, 6 H), 0.90 (t, 3 H, J = 5.5 Hz); ^{13}C NMR δ 173.0, 169.5, 147.4, 134.7, 77.1, 51.9, 38.0, 31.4, 27.1, 25.2, 22.4, 13.9.; IR (film) 3000, 2960, 1770, 1455, 1190, 1080 cm^{-1}; HRMS, calcd for $C_{12}H_{18}O_4$ m/e 226.1206, found m/e 226.1195.

1-(4-Chlorophenyl)-4,4-dimethoxy-3-methyl-2-buten-1-one (10). To a stirred solution of **6b** (545 mg, 2.0 mmol) and (dimethylamino)pyridine (20 mg, 0.16 mmol) in pyridine (2 mL) was added acetic anhydride (505 mg, 5 mmol) at room temperature, and the resultant mixture was stirred at room temperature for 3 h. Then the reaction mixture was poured onto ice–water and extracted with ether (10 mL × 2). The combined organic phase was washed with saturated aqueous $CuSO_4$ (30 mL × 2), water, and brine and was dried (Na_2SO_4). Removal of the solvent under reduced pressure and flash column chromatography on SiO_2 using C_6H_{14}/Et_2O (3:1) as eluent gave 127 mg (25%) of **10** as a yellow liquid: ^1H NMR δ 7.83 (d, 2 H, J = 10 Hz), 7.34 (d, 2 H, J = 10 Hz), 6.95 (q, 0.83 H, J = 1.7 Hz, *E* form), 6.60 (q, 0.17 H, J = 2.0 Hz, *Z* form), 4.70 (s, 1 H), 3.82 (s, 6 H), 2.15 (d, 2.49 H, J = 1.7 Hz, *E*), 1.98 (d, 0.51 H, J = 2.0 Hz, *Z*). Anal. Calcd for $C_{13}H_{15}O_3Cl$: C, 61.30; H, 5.94. Found: C, 61.02; H, 5.69.

3-Methyl-5-(2-methylpropylidene)-2(5*H*)-furanone (11). A mixture of **1f** (304 mg, 2.0 mmol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (304 mg, 2.0 mmol) in toluene (5 mL) was refluxed for 3 h and was cooled. Water was added to the reaction mixture, and the mixture was extracted with toluene (10 mL). The organic phase was washed with water and brine and was dried (Na_2SO_4). Removal of the solvent under reduced pressure and flash column chromatography on SiO_2 using C_6H_{14}/Et_2O as eluent gave **11**[13] (218 mg, 72%) as a colorless liquid. Further purification by a preparative thin layer chromatography gave *E* and *Z* isomers as pure compounds. *E* isomer: ^1H NMR δ 7.79 (q, 1 H, J = 1.5 Hz), 6.23 (d, 1 H, J = 7.2 Hz), 2.55 (m, 1 H), 2.10 (d, 3 H, J = 1.5 Hz), 1.65 (d, 6 H, J = 7.0 Hz). Anal. Calcd for $C_9HCl_2O_2$: C, 71.03; H, 7.95. Found: C, 71.22, H, 7.68. *Z* isomer: ^1H NMR δ 7.35 (q, 1 H, J = 1.5 Hz), 5.43 (d, 1 H, J = 8.5 Hz), 2.65 (m, 1 H), 2.15 (d, 3 H, J = 1.5 Hz), 1.65 (d, 6 *H*, J = 7.0 Hz). Anal. Found: C, 70.88; H, 7.85.

Registry No. **1a**, 96250-05-4; **1b**, 85671-08-5; **1c**, 112712-36-4; **1d**, 79379-60-5; **1e**, 112712-37-5; **1f**, 112712-38-6; **1g**, 64198-13-6; **1h**, 112712-39-7; **1i**, 112712-40-0; **3a**, 6342-56-9; **3b**, 6342-57-0; **3c**, 6344-10-1; **4** (R^2 = H, R^3 = $(CH_2)_2Ph$), 59417-89-9; **4** (R^2 = H, R^3 = *p*-Cl-C_6H_4), 58518-76-6; **4** (R^2 = H, R^3 = Bu-*t*), 17510-46-2; **4** (R^2 = Me, R^3 = Et), 17510-47-3; **5** (R^2 = H, R^3 = CH=C(Me)$_2$), 141-79-7; **5** (R^2 = H, R^3 = CH_2CO_2Me), 105-45-3; **5** (R^2 = CH_2-CH=CH_2, R^3 = CH_2CO_2Me), 100636-39-3; **6a**, 112712-27-3; **6b**, 112712-28-4; **6c**, 112712-29-5; **6d** (*R**,*R**), 112712-30-8; **6d** (*R**,*S**), 112712-31-9; **6e**, 112712-32-0; **6f**, 112712-33-1; **6g**, 112712-34-2; **6h**, 92533-59-0; **6i**, 112739-90-9; **10E**, 112712-41-1; **10Z**, 112712-42-2; **11E**, 112712-43-3; **11Z**, 112712-44-4; 1,1-dimethoxy-2-propanone dimethylhydrazone, 62752-81-2; 1,1-dimethoxy-2-heptanone dimethylhydrazone, 112712-35-3.

(14) Hong, P.; Mise, T.; Yamazaki, H. *Chem. Lett.* **1981**, 989.
(15) Scharf, H. D.; Mattay, *Leibigs Ann. Chem.* **1977**, 770.

Studies on the Acid-Catalyzed Homonuclear Steroidal Diene Isomerization

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As a result of our continued interest in the design and synthesis of mechanism based inhibitors of sterol biosynthesis, we required multigram quantities of (3β,5α,22*E*)-ergosta-8,14,22-trien-3-ol acylated derivatives **1a,b** and the corresponding (3β,5α)-cholesta-8,14-dien-3-ol derivatives **2a,b**. Previous preparations of **1a,b** have generally been based on the pioneering work of Windaus,[1] who observed the acid-catalyzed migration of the 5,7-diene of ergosterol to yield a mixture of trienes. In classic early studies, Fieser[2] and Barton[3] have employed this type of acid-catalyzed rearrangement for the synthesis of **1a,b** and **2a,b** from ergosterol **3a** and 7-dehydrocholesterol (**4a**), respectively, with variable success. They have shown that HCl-catalyzed rearrangements of these steroidal dienes are capricious, particularly in the case of **3a** → **1a**, frequently giving low yields of the desired diene as one component in a difficult to separate mixture of isomers of known and unknown structures.[2g] To our knowledge a detailed study of the HCl-catalyzed homonuclear diene isomerization of **3a,b** and **4a,b** to produce **1a,b** and **2a,b**, respectively, has not been conducted. In addition, anomolous undesired isomers generated in the rearrangement have not been isolated nor have their structures been identified. We have

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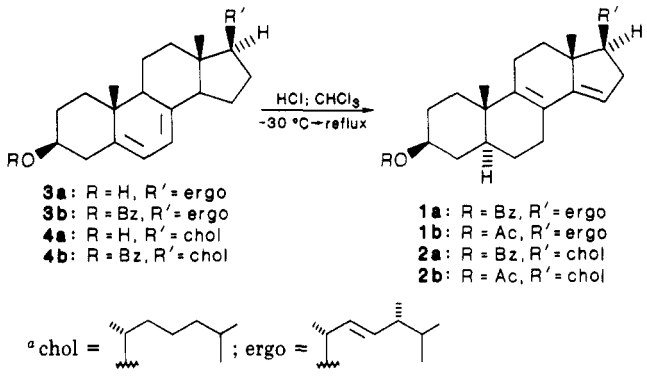
Scheme I[a]



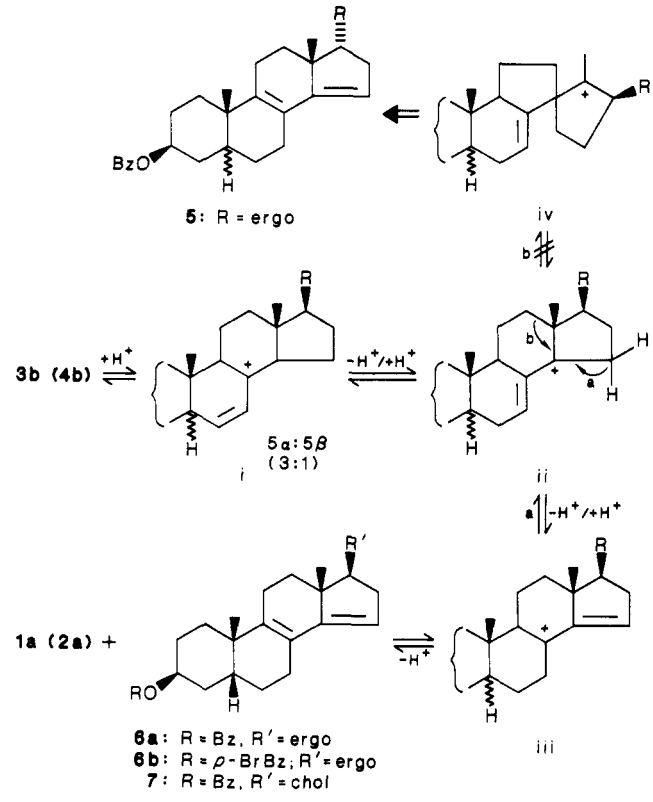
undertaken such a study in an attempt to exploit the HCl-catalyzed rearrangement as a viable route to **1a,b** and **2a,b** on a preparative scale.

As demonstrated previously by us[4a] and others,[4b,c] exposure of benzoate **3b** to HCl gas in $CHCl_3$ at −30 °C for 2 h afforded a 3:1 mixture of (3β,5α,22*E*)-ergosta-7,14,22-trien-3-ol benzoate and **1a**. We have subsequently observed that slow warming of the reaction mixture from −30 °C to 25 °C followed by heating at gentle reflux for 15 min gives good yields of **1a** (Scheme I).

A 90-MHz ^1H NMR spectrum of the crude product appeared consistent with the near exclusive formation of this material. However, further analysis of the crude reaction product by capillary GC revealed a mixture of **1a** (64%), the 7,14,22-triene (4%),[4a] an isomer of unknown structure (22%), and a large number of unidentified products (10%) each of which was present in ≲2%. Recrystallization of the crude product mixture from Et_2O and then EtOAc afforded **1a** in 45% yield (mp 132–134 °C) that was suitable for synthetic use, although still containing up to 7–8% of the unknown isomer. A total of 14 recrystallizations from EtOAc were needed to provide analytically pure crystals (capillary GC, ^{13}C NMR) of **1a** (mp 143–144 °C, lit.[3a] mp 140–142 °C).[5]

Our initial speculation as to the structure of the unknown isomer obtained was influenced by the previous work of Anastasia[6] and Caspi.[7] These workers have independently shown that treatment of 3β-cholestenol acetates possessing unsaturation at C-7(8) or C-8(14), respectively, under thermodynamic conditions with HCl gas in chloroform followed by basic workup, furnished (3β,5α,17α)-cholest-14-en-3-ol acetate, an isomer having inverted stereochemistry at C17. The acid-catalyzed rearrangement of **3b** and **4b** (Scheme II)[8] has been postulated to involve carbocationic intermediates similar to those invoked in the cholesterol acetate rearrangement.[6,7,9] Therefore, we had reason to suspect that the structure of our minor isomer may have been benzoate **5**, a product

Scheme II



(1) Windaus, A.; Dithman, K.; Murke, H.; Suckfull, F. *Liebigs Ann. Chem.* **1931**, *488*, 91. Reindel and co-workers were the first to investigate this reaction. Reindel, F.; Walter, E.; Rauch, H. *Liebigs Ann. Chem.* **1927**, *452*, 134.

(2) (a) Fieser, M.; Rosen, W. E.; Fieser, L. F. *J. Am. Chem. Soc.* **1952**, *74*, 5397. (b) Fieser, L. F.; Ourisson, G. *J. Am. Chem. Soc.* **1953**, *75*, 4404. (c) Fieser, L.; Fieser, M. *Steroids*; Reinhold: New York, 1959; pp 111–222. (d) Adams, W. J.; Petrow, V.; Royer, R. *J. Chem. Soc.* **1951**, 678. (e) Hudgell, A. W. D.; Turnbull, J. H.; Wilson, W. *J. Chem. Soc.* **1954**, 815. (f) Baghos, V. B.; Boulos, A. L.; Youssef, Y. R.; Tadrus, W. *Egypt. J. Chem.* **1980**, 217. (g) Fieser and co-workers reported refinements over the original Windaus procedure for the preparation of acetates **1b** and **2b** in good yield.[2a,b] We experienced difficulty in attempting to scale up (>100 g) these protocols.

(3) (a) Barton, D. H. R.; Corrie, J. E. T.; Widdowson, D. A.; Band, M.; Woods, R. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1326. (b) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359. (c) Barton, D. H. R.; Davies, S. G.; Motherwell, W. B. *Synthesis* **1979**, 265.

(4) (a) Dolle, R. E.; Kruse, L. I. *J. Org. Chem.* **1986**, *51*, 4047. (b) Knight, J. C.; Klein, P. P.; Sczepanik, P. A. *J. Biol. Chem.* **1966**, *241*, 1502. (c) Parish, E. J.; Spike, T. E.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids* **1977**, *18*, 233.

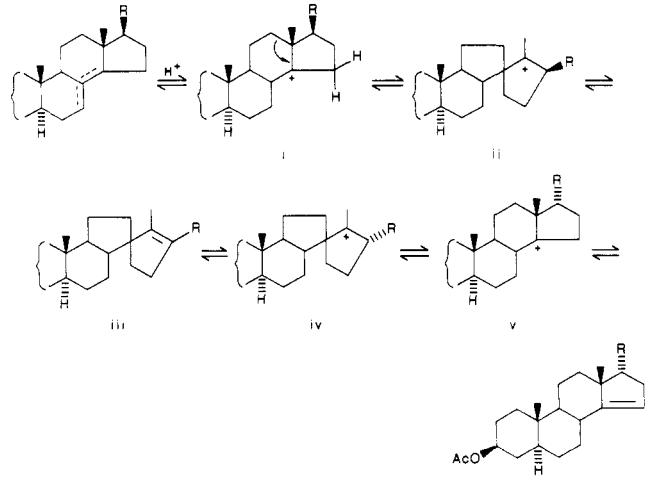
(5) X-ray crystallographic analysis confirmed the structure of major isomer **1a** as the desired (3β,5α,17β,22*E*)-ergosta-8,14,22-trien-3-ol benzoate. See ref 11.

(6) (a) Anastasia, M.; Bologneal, M.; Fiecchi, A.; Ressi, G.; Seola, A. *J. Org. Chem.* **1975**, *40*, 2006. (b) Anastasia, M.; Fiecchi, A.; Scala, M. *J. Org. Chem.* **1978**, *43*, 3505.

(7) (a) Caspi, E.; Duax, W.; Griffen, J. F.; Moreau, J. P.; Wittstuck, T. A. *J. Org. Chem.* **1975**, *40*, 2005. (b) Caspi, E.; Aberhurt, J.; Chan, T. Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 220.

(8) A series of carbocation intermediates are generated upon exposure of **3a,b** to acid. Under thermodynamic conditions the equilibrium **3a,b** ⇄ **1a,b** lies exclusively to the right, the possible driving force being the minimization of the nonbonded interaction of the C18 and C19 methyl groups with the 11β-proton.

(9) The mechanism of C17 epimerization has been unequivocally established to involve the formation of a common carbocation intermediate (i), which under thermodynamic conditions undergoes migration of the C12–C13 bond to yield spiro intermediate ii. Further rearrangement produced the 17α-stereochemistry. See ref 6 and 7.



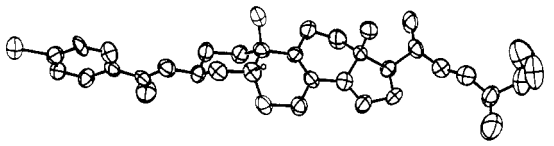


Figure 1. ORTEP drawing of **6b**.

possessing the 8,14 and 22(23) olefins but with 3β,5α,17α stereochemistry.

The minor isomer was isolated in 18% yield via HPLC (silica gel). Examination of the ^1H, ^{13}C, and mass spectra obtained from the unknown indeed suggested a diastereomer of the 8,14,22-triene **1a**. NMR revealed that the C3-H underwent a 0.3 ppm downfield shift while the C3 carbon atom was shifted 2.70 ppm upfield relative to that of **1a**. The carbon resonance at C17 for **1a** and the diastereomer were identical at 57.1 ppm, suggesting inversion had not occurred at this center. Ultimately, the structure of the diastereomer was determined to be (3β,5β,17β,22*E*)-ergosta-8,14,22-trien-3-ol benzoate (**6a**) following X-ray crystallography[10,11] of the corresponding 3β-*p*-bromobenzoate derivative **6b** (Figure 1).

Mechanistically, the absence of a product with 17α stereochemistry (e.g. **5**) may be rationalized by noting that of the two pathways, a and b, available to ii for further rearrangement, route a is preferred exclusively over b. Since carbocation iii is lower in energy relative to iv due to the presence of charge delocalization/stabilization afforded by the π-bond, rearrangement occurs only through tertiary allylic carbocationic intermediates i, ii, and iii.

Treatment of dehydrocholesterol benzoate **4b** (HCl, CH_2Cl_2, −30 °C to reflux), followed by workup with pyridine gave results identical with those found for ergosterol. Pure **2a** (capillary GC) was obtained in 55% yield after two recrystallizations from EtOAc. A ^{13}C NMR of the debenzoylated **2a** showed 27 carbon signals of identical chemical shifts with those previously published.[12]

We have further found that the alcohols **3a** and **4a** may be isomerized with HCl in 4:1 $CHCl_3$/HOAc followed by acetylation or benzoylation in pyridine to produce **1b,2b** or **1a,2a**, respectively. This preferred method for the preparation of these esters, a variation of the isomerization conditions originally reported by Fieser,[2b,13a] eliminates the need for prior preparation/isolation of the acylated derivatives of **3a** and **4a**.[13b]

The syntheses of **1a,b** and **2a,b** described herein are reproducible and amenable to large scale. The stereochemistries of these isomers have been rigorously established. The single major byproduct from the acid-catalyzed rearrangement has been isolated and identified.

Experimental Section

General Methods. Ergosterol and 7-dehydrocholesterol were purchased from Sigma Chemical Co. The corresponding benzoates were prepared as previously described.[5a] HCl gas was used as purchased from Matheson. All other solvents/reagents were reagent grade. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Capillary gas chromatography utilized the Hewlett-Packard 5890A FID and the HP 3392A digital integrator. Capillary GC analyses were performed on saponified steroids only, readily obtained upon treatment of the benzoates/acetates with 5 equiv of NaOMe in MeOH/toluene for 12 h, 25 °C; column, Chrompack, Sil 5, 10 m × 0.24 mm; flow rate, 1 mL/min H_2; oven temperature, 270 °C. HPLC utilized the Rainin Rabbit and the Gilson Holochrome detector (254 nm) fitted with a 2 in. Dynamax silica gel column. Infrared (IR) spectra ($CHCl_3$, thin films) were recorded on a Perkin-Elmer 727 spectrometer. ^1H NMR were recorded at 90 MHz (Varian EM 390) and/or 270 MHz (JEOL GX 270), and ^{13}C NMR spectra[11] were recorded at 67.8 MHz on the latter instrument. Mass spectra were recorded on a Finnigan Model 3625 mass spectrometer equipped with chemical ionization capability. X-ray cystallographic[11] (ENRAF-NONIUS, CAD-4) and elemental analyses were performed in the SK&F Physical and Structural Chemistry Department.

(3β,5α,17β,22*E*)-Ergosta-8,14,22-trien-3-ol Benzoate (1a). HCl gas (ca. 15 g) was passed into $CHCl_3$ (1.1 L) at −30 °C. Ergosterol benzoate **3b**[5a] (100 g, 0.2 mol) was added in one portion. The solution was warmed to room temperature over a 30-min period and then gently refluxed for 15 min. The solvent was removed in vacuo and CH_2Cl_2 (200 mL) containing pyridine (28 mL, 0.4 mol) was added to the residue. The solution was stirred for 5 h and solvents were removed in vacuo. The residue was washed with cold acetone (2 × 200 mL) and the residue was crystallized from Et_2O then EtOAc, giving a 45% yield of **1a**: mp of 132–134 °C. Fourteen recrystallizations from EtOAc gave analytically pure **1a**: mp 143–144 °C (lit.[3a] mp 140–142 °C); lit.[3b] mp 140–141 °C); $[\alpha]^{25}_D$ −28.2° (*c* 0.6, $CHCl_3$) [lit.[3a] $[\alpha]^{25}_D$ −30.3° (*c* 0.89); lit.[3b] $[\alpha]_D$ −31°]; IR 2960, 2880, 1720 cm^{-1}; ^1H NMR δ 8.1 and 7.5 (m, aromatic, 5 H), 5.4 (m, 3 H), 5.00 (m, 1 H, H-3), 2.5–0.8 (m, remaining H); ^{13}C NMR δ 166.1, 150.8, 140.4, 135.5, 132.6, 132.1, 131.0, 129.5, 128.2, 123.3, 117.9, 74.0, 57.1, 44.8, 42.8, 40.9, 38.9, 36.9, 36.7, 36.6, 35.5, 34.3, 33.1, 27.8, 26.6, 25.2, 21.9, 21.0, 19.9, 19.7, 18.4, 17.7, 15.9; mass spectrum, *m/e* 501 (M + H), 379, 374, 255, 125.

Anal. Calcd for $C_{35}H_{48}O_2$: C, 83.95; H, 9.66. Found: C, 83.94; H, 9.71.

A 250-mg portion of the residue obtained after the acetone wash above was chromatographed (HPLC, Dynamax silica gel column; retention time (t_R) for **6a**, 7 min; t_R for **1a**, 9 min; flow rate 30 mL/min, 16% EtOAc/hexane as eluting solvent), to afford benzoate **6a** (45 mg, 18%): mp 114–115 °C; $[\alpha]^{25}_D$ −39.6° (*c* 1, $CHCl_3$), IR 2970, 2950, 1710 cm^{-1}; ^1H NMR δ 8.1 and 7.5 (m, aromatic, 5 H), 5.4 (m, 4 H), 2.5–0.8 (remaining H); ^{13}C NMR δ 166.1, 150.5, 137.7, 135.5, 132.6, 132.1, 131.0, 129.5, 128.2, 124.1, 118.0, 71.3, 57.1, 44.8, 42.8, 38.8, 37.2, 36.7, 36.6, 33.1, 32.8, 31.3, 27.5, 24.1, 22.6, 21.0, 19.9, 19.7, 17.7, 15.6; mass spectrum, *m/e* 501 (M + H), 379, 374, 255, 125.

Anal. Calcd for $C_{35}H_{48}O_2$: C, 83.95; H, 9.66. Found: C, 83.90; H, 9.62.

Benzoate **6a** (100 mg, 0.2 mmol) was saponified with NaOMe (5 equiv) and reacylated with *p*-bromobenzoyl chloride in pyridine under standard conditions. Crystals of *p*-bromobenzoate **6b** suitable for X-ray crystallography[11] were obtained following a single crystallization from EtOAc. **6b**: mp 157–158 °C; $[\alpha]^{25}_D$ −25.7° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{35}H_{47}BrO_2$: C, 72.52; H, 8.17. Found: C, 72.37; H, 7.99.

(3β,5α,17β,22*E*)-Ergosta-8,14,22-trien-3-ol Acetate (1b). HCl gas (10 g) was added to a solution of ergosterol **3a** (100 g, 0.2 mol) in $CHCl_3$ (1 L) containing HOAc (200 mL) at 10 °C. The reaction was refluxed for 30 min and then solvents were removed in vacuo (most of the HOAc was removed). Pyridine (300 mL) was added to the syrupy residue followed by Ac_2O (40 mL, 0.4 mol). The reaction was stirred overnight, poured into water (1.5 L), and

(10) (3β,5β,17β,22*E*)-Ergosta-6,8(14),22-trien-3-ol has been isolated in 21–25% yield from the HCl- or rhodium-catalyzed isomerization of ergosterol in ethanol. This material reportedly proved resistant to further rearrangement under acidic conditions. See ref 3b.

(11) See supplementary material for X-ray crystallographic data.

(12) (a) Tsuda, M.; Parish, E. J.; Schroepfer, G. J., Jr. *J. Org. Chem.* **1979**, *44*, 1282. (b) NMR evidence again showed the formation of an unknown diastereomer to the extent of ca. 20%. The diastereomer was not isolated in this case, but it is assumed to be structurally analogous to that found in the ergosterol isomerization. Windaus, A.; Zuhlsdorff, G. *Liebigs Ann. Chem.* **1938**, *536*, 204. Barton, D. H. R. *J. Chem. Soc.* **1946**, 1116.

(13) (a) This procedure for the synthesis of the steroid dienes **1a,b** and **2a,b** was developed as a result of the difficulty we encountered in reproducing and scaling up of the original Fieser synthesis.[2b] In their preparation of **4a** → **2b**, large volumes of benzene (>2 L per 100 g of **4a**) and freshly distilled Ac_2O (from P_2O_5) must be used. We found this to be prohibitive. Also we found as had Barton[3a] that the EtOH/HCl rearrangement of ergosterol **3a** furnished **1a** in <10% yield. Our modified conditions ($CHCl_3$, HOAc, HCl) are equally applicable to the synthesis of **1** and **2**, reproducible and amenable to large scale. (b) Under these reaction conditions the 5β-diasteromer was formed to the extent of ca. 10%, thus improving the ease of isolation and yield of **1b** and **2b**.

filtered. The residue was washed with acetone and then recrystallized twice from EtOAc to give acetate **1b** in 60% yield contaminated with ca. 4% of the 5β isomer. Acetate **1b**: mp 143–144 °C (lit.[1,2a] mp 148.5–150 °C; lit.[2e] mp 137–138 °C; lit.[2f] mp 143–144 °C; lit.[3c] mp 139–140 °C); $[\alpha]^{25}_D$ −58.2° (*c* 1, $CHCl_3$) [lit.[1] $[\alpha]_D$ −35.0°; lit.[2a] $[\alpha]_D$ −36.0°; lit.[2e,f] −50.0°]; IR 2960, 2880, 1760 cm^{-1}; ^1H NMR δ 5.4 (m, H-15, -22, -23, 3 H), 4.8 (m, H-3, 1 H), 2.5–0.8 (m, remaining H); mass spectrum, *m/e* 439 (M + H), 379, 313, 125.

Anal. Calcd for $C_{30}H_{46}O_2$; C, 82.14; H, 10.57. Found: C, 82.54; H, 10.45.

(3β,5α,17β)-Cholesta-8,14-dien-3-ol Benzoate (2a) and Acetate (2b). 7-Dehydrocholesterol (**4a**) (100 g, 0.2 mol) was isomerized with HCl in the same fashion as in the preparation of **1b** to furnish, following benzoyl chloride/pyridine workup, benzoate **2a** (63 g, 65%) as crystals (EtOAc): mp 146–147 °C (lit.[2d] mp 147–148 °C); $[\alpha]^{25}_D$ −5.5° (*c* 1, $CHCl_3$) [lit.[2d] $[\alpha]^{22}_D$ −6.9°]; IR 2940, 2880, 1720 cm^{-1}; ^1H NMR δ 8.10 and 7.5 (m, aromatic, 5 H); 5.4 (s, 1 H, H-15); 5.00 (m, 1 H, H-3); 2.5–0.8 (m, remaining H); mass spectrum, *m/e* 489 (M + H), 367, 123.

Anal. Calcd for $C_{34}H_{48}O_2$: C, 83.55; H, 9.90. Found: C, 83.53; H, 9.80.

Employing an acetic anhydride/pyridine workup afforded acetate **2b** (55 g, 65%) after two recrystallizations from Et_2O: mp 100–102 °C (lit.[2b] mp 99–100 °C; lit.[2d] mp 101–102 °C); $[\alpha]^{25}_D$ −27.1° (*c* 1, $CHCl_3$) [lit.[2b] $[\alpha]^{25}_D$ −21.0°; lit.[2d] $[\alpha]^{24}_D$ −22.9°]; IR 2940, 2880, 1760 cm^{-1}; ^1H NMR δ 4.8 (m, H-3, 1 H), 2.5–0.8 (m, remaining H); mass spectrum, *m/e* 427 (M + H), 405, 367.

Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.69; H, 10.89.

Registry No. **1a**, 53639-76-2; **1b**, 71242-49-4; **2a**, 74524-23-5; **2b**, 5226-33-5; **3a**, 57-87-4; **3b**, 5035-30-3; **4a**, 434-16-2; **6a**, 113089-06-8; **6b**, 113089-07-9.

Supplementary Material Available: Tables of fractional atomic coordinates, thermal parameters, and interatomic distances and angles for both **1a** and **6b** (45 pages). Ordering information is given on any current masthead page. Tables of observed and calculated structure factors are available from the authors upon request.

Designer Spin Traps with a Cyclic Nitrone Structure[1]

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The technique of spin trapping[2] is now being widely applied to probe for free radicals in biological systems.[3,4] For the method to work well, the traps must be efficient scavengers of transient free radicals and the trapping reaction must lead to persistent spin adducts whose hyperfine splittings point to the identity of the scavenged radical.

While 5,5-disubstituted 1-pyrroline *N*-oxides[5-7] are known to be good spin traps and are widely employed,[3,4,6,8-10] their 3,3,5,5-tetrasubstituted analogues[11,12]

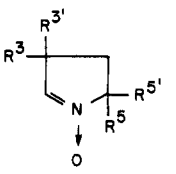
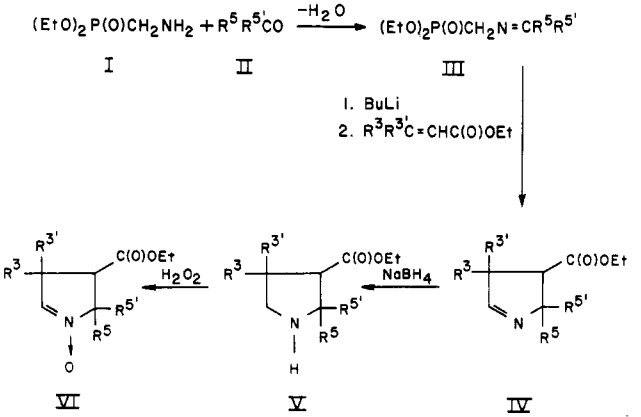


Figure 1.

Scheme I



	R^3	$R^{3'}$	R^5	$R^{5'}$
IVa–VIa	Me	Me	Me	Me
IVb–VIb	Me	Me	Ph	Me
IVc–VIc	Me	Me	$(CH_2)_{11}Me$	Me
IVd–VId	$(CH_2)_5$		$(CH_2)_5$	

Table I. Hyperfine Splittings for Spin Adducts VII Formed in the Reactions of Various Radicals with Spin Traps VI (eq 1)

	X·			
spin trap	*t*-BuO·[a] a^N, a^{H^2}, G	Ph·[b] a^N, a^{H^2}, G	$\dot{C}H_2OH$[c] a^N, a^{H^2}, G	$\dot{O}H$[d] a^N, a^{H^2}, G
VIa	12.9, 4.0	14.0, 21.3[e]	15.4, 18.0	15.5, 15.5
VIb	13.0, 10.5	13.2, 24.0	15.0 25.9	14.4, 19.1
VIc	13.3, 5.4	14.0, 23.5	15.0, 22.0[h]	*f*
VId	*g*	14.3, 25.0	15.0, 25.0[h]	14.7, 14.7

[a] Photolysis of di-*tert*-butyl peroxide in benzene. [b] Photolysis of phenylazotriphenylmethane in benzene. [c] Photolysis of H_2O_2 (1%) in phosphate buffer (pH 6) containing methanol (4%). [d] Photolysis of H_2O_2 (1%) in phosphate buffer (pH 6). [e] 10% of diastereometric spin adduct formed, c.f. ref 12. [f] Spin trap insoluble in buffer. [g] Spin adduct not detected. [h] In 60% methanol.

(Figure 1) are actually far superior since the presence of the additional substituents enhances the lifetimes of the spin adducts but has a minimal effect on the efficiency of the trapping reaction.[11] However, the synthesis of tetrasubstituted traps is not straightforward.[5,12] Three of the substituents have to be incorporated into an unsaturated ketone, which is one of the primary synthons, and the fourth has to be introduced in an alkylation procedure toward the end of the multistep synthesis.[5,12]

We have developed a simple method of making cyclic nitrone spin traps that allows substitutents of choice to be introduced at the critical 3,3- and 5,5-positions. In addition, the synthesis introduces a carbalkoxy group at

(1) Issued as NRCC Publication No. 28633.
(2) Janzen, E. G. *Acc. Chem. Res.* **1971**, *4*, 31.
(3) Janzen, E. G. *Free Radicals in Biology*; Academic: New York, 1980; Vol. IV, p 115.
(4) Rosen, G. M.; Finkelstein, E. *Adv. Free Radical Bio. Med.* **1985**, *1*, 345.
(5) Bonnett, R.; Brown, R. F. C.; Clark, V. M.; Sutherland, I. O.; Todd, A. *J. Chem. Soc.* **1959**, 2094.
(6) Haire, D. L.; Janzen, E. G. *Can. J. Chem.* **1982**, *60*, 1514.
(7) Improvements in nitrone synthesis devised by Huie and Cherry,[7a] have been applied to these compounds.[7b] (a) Huie, R.; Cherry, W. R. *J. Org. Chem.* **1985**, *50*, 1531. (b) Haire, D. L.; Hilborn, J. W.; Janzen, E. G. *J. Org. Chem.* **1986**, *51*, 4298.
(8) Iwamura, M.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 702; **1970**, *43*, 856.
(9) Janzen, E. G.; Liu, J. I.-P. *J. Magn. Reson.* **1973**, *9*, 510; Janzen, E. G.; Evans, C. A.; Liu, J. I.-P. *J. Magn. Reson.* **1973**, *9*, 513.
(10) Marriott, P. R.; Perkins, M. J.; Griller, D. *Can. J. Chem.* **1980**, *58*, 803.
(11) Janzen, E. G.; Shetty, R. V.; Kunanec, S. M. *Can. J. Chem.* **1981**, *59*, 756.
(12) Barker, P.; Beckwith, A. L. J.; Cherry, W. R.; Huie, R. *J. Chem. Soc., Perkin Trans 2* **1985**, 1147.

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