fumarate (3).—A solution of *N*-carbobenzoxyglycine[14] (0.23 g, 1.1 mmol) in anhydrous THF (1.5 ml) was added dropwise to a solution of *N,N'*-carbonyldiimidazole (CDI, Aldrich Chemical Co., 0.17 g, 1.1 mmol) in THF (2.5 ml) and stirred for 1 hr. To this was then added in one portion, a solution of **2a** (0.50 g, 1.1 mmol) in 2 ml of THF. After 3 days the solution was concentrated to dryness, redissolved in $CHCl_3$, washed twice with 5% HCl solution, saturated $NaHCO_3$ solution, and water and dried. Evaporation of the solvent afforded a syrup (0.61 g) whose tlc ($CHCl_3$) showed three spots. Preparative tlc ($CHCl_3$) of an aliquot (75 mg) of the syrup separated the three components; the one of lowest R_f was shown by comparison ir to be recovered **2a** (10 mg), the middle R_f compound was tentatively assigned (by physical data) as **4a** (10 mg, 11%), and the upper R_f product was identified as the unsaturated **3** (20 mg, 32%). Compound **3** could not be induced to crystallize but an analytical sample was obtained by rechromatographing (1% CH_3OH–$CHCl_3$) on thin layer plates, and the extracted product was washed through a 1:1 charcoal–Celite column with $CHCl_3$. Evaporation of the solvent left a very pale yellow gum (**3**), uv λ_{max} 212 mμ (ε 18,400) and 270 (13,900) with a shoulder at 259; mass spectrum *m/e* 445 (M^+), 430, 354 ($-CH_2C_6H_5$), 310 ($-CO_2CH_2C_6H_5$), 248, 140, 107 ($C_6H_5CH_2O^+$), 91 (base peak).

Anal. Calcd for $C_{26}H_{23}NO_6$: C, 70.11; H, 5.20; N, 3.14. Found: C, 70.10; H, 5.27; N, 3.07.

Dibenzyl *O*-(*N*-Carbobenzoxyglycyl-*N*-carbobenzoxy-*erythro*-β-hydroxy-DL-aspartate (4b) and Dibenzyl 2-Carbobenzoxyaminofumarate (3).—The above procedure was followed using CDI (2.30 g, 14.2 mmol) in 10 ml of THF, *N*-carbobenzoxyglycine[14] (2.96 g, 14.2 mmol) in 10 ml of THF, and **2b** (3.30 g, 7.1 mmol) in 10 ml of THF. The reaction mixture was worked up after 2.5 hr, as described above, to give a pale yellow oil (4.4 g). Tlc (1% MeOH–$CHCl_3$) of the oil indicated one major spot, tentatively assigned as **4b**, and traces of starting material (**2b**) and unsaturated **3**. From several purifications by preparative tlc (1.5% MeOH–$CHCl_3$, 0.21 g/three plates) we obtained a fairly pure (not analytical grade) sample of **4b** (0.18 g, 81% yield). Further attempts at purifying **4b** only led to some decomposition to the unsaturated **3**. By the above preparative tlc we obtained a sample of **3** (8 mg, 5%) which was identical in the ir, nmr, and uv with compound **3** as isolated from the reaction with **2a**.

Dibenzyl 2-Carbobenzoxyaminofumarate (3) and Dibenzyl 2-Carbobenzoxyaminomaleate (5).—A solution of **4a** (10 mg), contaminated with a small amount of **3**, in 1 ml of $CHCl_3$ was divided in half and a few crystals of imidazole were added to one portion. After both portions were stirred overnight a tlc examination indicated no change in the ratio of **4a** to **3** in the absence of imidazole, but about a 60–70% conversion to **3** in the presence of imidazole. Similarly, when **4b** contaminated with only a trace of **3** was stirred overnight with imidazole there was only a 20–30% increase in intensity of the spot on tlc corresponding to **3**, whereas in the absence of imidazole there was no change.

A pure sample of **3** (0.22 g), when allowed to remain in a refrigerator for about 3 months, was slowly converted to approximately 5% of the cis isomer **5**. Preparative tlc afforded 10 mg of **5**, which could not be induced to crystallize. An analytical sample of **5** was obtained by chromatography as reported above for **3**, uv λ_{max} 211 mμ (ε 20,900) and 267 (14,000). Compound **3** (75 mg) was more readily converted to **5** by dissolving it in 1 ml of CH_2Cl_2, diluting with 15 ml of isooctane, and exposing it to daylight for 7 days. The solvent was removed by evaporation, and tlc of the resulting oil indicated a 25–35% enrichment of **5**: mass spectrum of **5** *m/e* 445 (M^+), 430, 354 ($-CH_2C_6H_5$), 310 ($-CO_2CH_2C_6H_5$), 248, 140, 107 ($C_6H_5CH_2O^+$), 91 (base peak).

Anal. Calcd for $C_{26}H_{23}NO_6$: C, 70.11; H, 5.20. Found: C, 69.92; H, 5.48.

DL-Aspartic Acid from Dibenzyl 2-Carbobenzoxyaminofumarate (3).—To a solution of **3** (0.10 g, 0.22 mmol) in 50% ethanol–dioxane (4 ml) was added 50 mg of PtO_2. The mixture was hydrogenated at 1 atm pressure for 70 min, during which the calculated amount of H_2 was consumed. Removal of the catalyst by filtration and concentration of the filtrate gave a residue which was crystallized from H_2O–ethanol, yielding 12 mg (41%) of DL-aspartic acid (identical in the ir with an authentic sample).

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Registry No.—**2a**, 16712-81-5; **2b**, 34910-00-4; **3**, 34910-01-5; **5**, 34910-02-6; L-asparagine, 70-47-3.

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Reaction of 3β-Acetoxy-8α,9α-oxido-5α-lanostane with Grignard Reagents[1]

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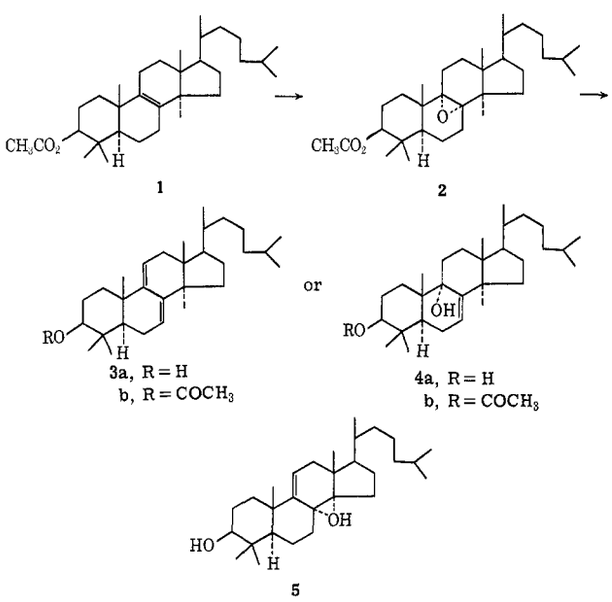
Synthetic degradation of lanosterol has been used to prepare otherwise difficultly accessible 14α-methyl steroids.[2] With the prospect of readily obtaining B/C ring juncture modifications of lanosterol for similar purposes, we decided to explore the oxirane ring opening reactions of an 8α,9α-oxidolanostane with methyl and allyl Grignard reagents. For this purpose dihydrolanosterol acetate (**1**) was oxidized in excellent yield to 3β-acetoxy-8α,9α-oxido-5α-lanostane (**2**).[3]



Methyllithium in ether did not attack the oxirane ring over a period of 19 days. With methylmagnesium iodide in refluxing toluene the product was dihydroagnosterol (**3a**). Allylmagnesium bromide[4] in ether at 25° reacted completely in a few hours with epoxy

(1) Steroids and Related Natural Products. 79. For Part 78 see G. R. Pettit and Y. Kamano, *Experientia*, **28**, in press. This investigation was supported by Public Health Service Research Grants RO1 CA08705-01, R01 CA08705-02, and R01 CA11451-01.

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(3) J. Fried, J. W. Brown, and M. Applebaum, *Tetrahedron Lett.*, 849 (1965); I. G. Guest and B. A. Marples, *J. Chem. Soc. C*, 1468 (1971).

(4) H. Felkin and G. Roussi, *Tetrahedron Lett.*, 4153 (1965). The reactivity of allyl Grignard reagents toward epoxide ring-opening is much greater than that of methyl or isopropyl Grignard reagents. The stereochemical course leads to trans diaxial products.

acetate **2**. The sole product was formulated as 3β,9α-dihydroxy-5α-lanost-7-ene (**4a**) on the following basis.

Acetylation with pyridine and acetic anhydride under the usual conditions gave a monoacetyl derivative **4b** which still contained a hydroxyl function. Very brief treatment with a trace of mineral acid converted the alcohol **4b** into dihydroagnosteryl acetate (**3b**). The nmr spectrum of alcohol **4a** showed the presence of a trisubstituted olefin. Further support for the olefin was provided by the mass spectrum, which displayed an *m/e* 426 fragment (M − 18). The foregoing would allow the product to be assigned structure **4a** or **5**, of which **4a** is preferred. In this respect the lithium in ethylamine reduction of epoxide **2** gives the α alcohol.[3] Also, the strong vicinal 14α-methyl-8α-hydroxy steric interaction in **5** is absent in **4**.

When no products involving alkylation of the lanostane skeleton were detected the Grignard study was not pursued further. However, the new syntheses of dihydroagnosterol and alcohol **4** were considered potentially useful in approaches to natural products such as batracheotoxinin A.

Experimental Section[5]

Dihydroagnosteryl Acetate (3b).—To a solution of 3β-acetoxy-8α,9α-oxido-5α-lanostane (0.65 g) in dry ether (25 ml) was added (during 5 min) the Grignard reagent (in ether) derived from magnesium turnings (4.9 g) and methyl iodide (28 g). After 20 hr at 25° dry toluene (75 ml) was added and the ether was removed by distillation. The solution was heated under reflux for 11 days, cooled, and poured over crushed ice. The product was isolated using ether to afford a brown grease which slowly solidified. Adsorption on activated alumina (22 g) from solution in benzene and elution with benzene–chloroform (4:1) gave dihydroagnosterol (**3a**, 0.60 g): mp 150–154°; λ_{max}^{EtOH} 236, 243, and 252 mμ. Acetylation gave dihydroagnosteryl acetate, plates from ethanol: mp 167–169°; λ_{max}^{EtOH} 236, 243, and 252 mμ. Acetate **3b** was identical[5] with an authentic specimen.

Reaction between Allylmagnesium Bromide and Oxide 2.—Allylmagnesium bromide was prepared[6] and stored at 0° in a narrow-necked bottle fitted with a septum cap. The assay[7] was 0.66 *M* and 15 ml of the reagent was added to oxide **2** (0.71 g) in dry ether (20 ml, under an atmosphere of dry nitrogen). The reaction mixture was kept at 22° and monitored by tlc upon removal of 0.5-ml aliquots. After 14 hr the mixture was poured into 5% ammonium sulfate (100 ml) at 5°. Ether (25 ml) was used for isolation. The product (0.69 g) was a clear oil which showed one component on tlc. Crystallization from methanol containing one drop of pyridine gave fine needles (0.30 g), mp 132–133°, of a compound formulated as **4a**: ν_{max}^{KBr} 3500–3200 cm^{-1}; pmr (pyridine) δ 0.8, 0.88, 0.93, 1.03, 1.12 (ring and side-chain methyl groups), 2.06 (s, 3 protons), 3.5 (broad, 1 proton), 4.25 (1 proton), 5.18 and 5.47 ppm (broad, 1 proton); mass spectrum *m/e* 426 (M^+ − 18).

Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 80.77; H, 11.64.

The product (0.18 g) in pyridine (1.5 ml)–acetic anhydride (1 ml) was kept at 22° for 19 hr. Ether (30 ml) was added and the solution was washed with 2 *N* sodium bicarbonate until effervescence ceased (5 × 15 ml). Drying and solvent removal furnished a colorless solid (0.18 g), one component on tlc, which crystallized as needles from methanol containing one drop of pyridine. The alcohol weighed 0.13 g: mp 170–175° (raised to 171–175° by further recrystallization from the same solvent system); ν_{max}^{KBr} 3580, 1724, and 1230 cm^{-1}; pmr δ 0.675 (C-13 Me), 0.86 (d, *J* = 6.5 Hz, C-26, 27 methyl groups), 0.90, 0.99, 1.18 (C-4, 10, 14α, and 20 methyl groups), 2.03 (3β-OAc), 4.5 (broad, 3α-H), 5.33 ppm (broad, 7-H).

Anal. Calcd for $C_{32}H_{54}O_3$: C, 78.63; H, 11.55. Found: C, 78.98; H, 11.64.

Conversion of Alcohol 4a to Dihydroagnosterol (3a).—Concentrated hydrochloric acid (1 drop) was added to alcohol **4a** (30 mg) in ethanol (5 ml). The ethanol was removed *in vacuo* and the residue was partitioned between ether (15 ml) and water (15 ml). The ether phase was washed with 2 *N* sodium bicarbonate, dried, and evaporated to a white solid (28 mg) which crystallized from ethanol as needles of dihydroagnosterol (**3a**), mp and mp with an authentic sample 150–154°, λ_{max}^{EtOH} 236, 243, and 252 mμ.

Registry No.—**3a**, 2644-75-9; **3b**, 5600-01-1; **4a**, 34910-26-4; **4b**, 34910-27-5.

(5) The introduction to the Experimental Section of an earlier contribution provides a summary of general methods and reagents employed here; see J. C. Knight, G. R. Pettit, and P. Brown, *J. Org. Chem.*, **35**, 1415 (1970).

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The Camptothecin δ-Lactone[1a]

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As part of an approach to total synthesis of the antineoplastic agent[2a–c] camptothecin (**1**),[2d,e] it became necessary to investigate synthesis of the terpenoid unit,[3] or an appropriate subunit, of the alkaloid. Synthesis of camptothecin by combination of appropriate fragment molecules, involving formation of the pyridone amide bond and condensation with the pyrroloidinoquinoline entity, would require an eight-carbon unit. A δ-lactone precursor of the type depicted by

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