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# PERFLUOROALKENYL ETHERS OF BILE ALCOHOLS

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## SUMMARY

Two synthetic routes are presented for the synthesis of bis- and tris-perfluoroalkenyloxy-substituted bile alcohols with an unsubstituted hydroxyl group in the hydrocarbon side chain. The first route involves selective protection of the 24-hydroxyl group of 3α,7α,12α,24-cholantetrol followed by the attachment of 3α,7α,12α-hydroxyl groups to the perfluoroalkenyloxy linkages and removal of the protecting group. The second pathway is based on the synthesis of the tris-perfluoroalkenyloxy derivative of 3α,7α,12α-trihydroxy-chol-22-ene (or bis-perfluoroalkenyloxy derivative of 3α,12α-dihydroxy-7-deoxy-chol-22-ene), followed by the hydroboration of the double bond.

## INTRODUCTION

Previously [1] we reported the base-catalyzed addition-elimination reaction of sterols with perfluoroalkenes. The mono-perfluoroalkenyl ethers thus obtained are not satisfactory as co-emulsifying agents for the fluorocarbon-based blood substitutes [2]. It was apparent that it would be necessary to synthesize steroids substituted by two or more

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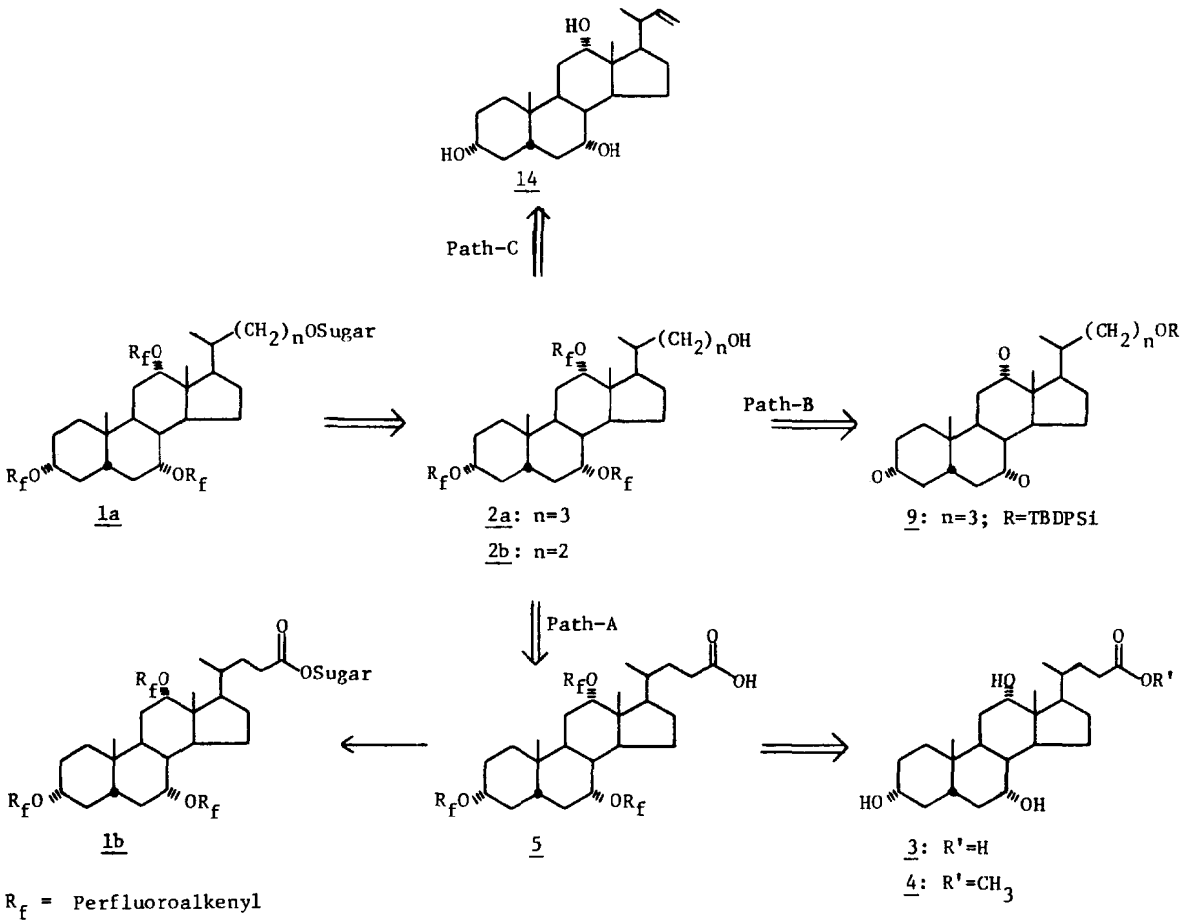
perfluoroalkenyl ether linkages on the *alpha*-side of the molecule if we were to obtain the surfactant properties we desired. We expected that two or three perfluoroalkenyloxy substituents on the *alpha*-side of the steroid would give sufficient fluorocarbon solubility to form stable emulsions in water [3]. Previously, we concentrated on using perfluoroalkyl-substituted steroids and bile acid derivatives as co-emulsifying agents to reduce the interfacial tension between the fluorocarbon ($O_2$-carrier in synthetic blood) and the conventionally used emulsifying agents (Pluronic F-68 or phospholipids) [1,3,4]. It occurred to us that by modifying the hydrocarbon side chain of the perfluoroalkyl-substituted steroid (for example, connecting the side chain to a water-soluble group, e.g., a sugar) we would have compounds that would themselves be emulsifying agents for fluorocarbons in water. In this paper we present the synthesis of bis- and tris-perfluoroalkenyl ethers of bile alcohols and their conversion to derivatives capable of bonding to water-soluble molecules such as sugars or a polyoxyethylene fragment.

## RESULTS AND DISCUSSION

The most practical way to attach a perfluoroalkenyloxy-substituted bile acid to a sugar molecule is by an ether or an ester linkage. This requires a perfluoroalkyl-substituted bile acid substituted by a hydroxyl or a carboxylic acid group in the hydrocarbon side chain. Retrosynthetic analysis of 1a indicated three possible pathways, as outlined in Scheme 1.

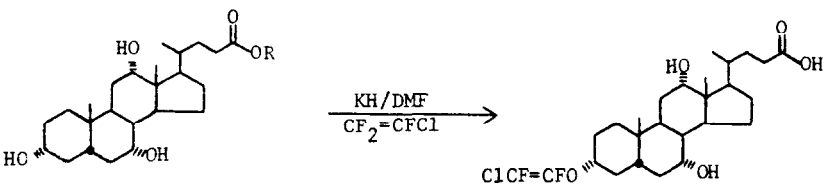
Retrosynthetic path-A seemed the best approach to us. Readily available cholic acid (3) or its methyl ester 4 can be converted to the tris-perfluoroalkenyl ether 5, which, in turn, can be attached to a




$R_f$ = Perfluoroalkenyl

Scheme 1

sugar molecule via an ester linkage to give 1b or reduced to an alcohol (2a) and then attached to the sugar molecule via an ether linkage to give 1a. Our initial synthetic work was with our standard model fluoroalkene, trifluorochloroethylene, and cholic acid (3). Deprotonation of cholic acid (3) with potassium hydride followed by the reaction of the potassium salt with trifluorochloroethylene gave 6 in 4.8% yield (Scheme 2). This unsatisfactory result prompted us to use n-butyl lithium as a base. However, with n-butyl lithium a complex mixture of products was obtained. Similarly, unsatisfactory results were obtained with methyl cholate (4).




3: R=H

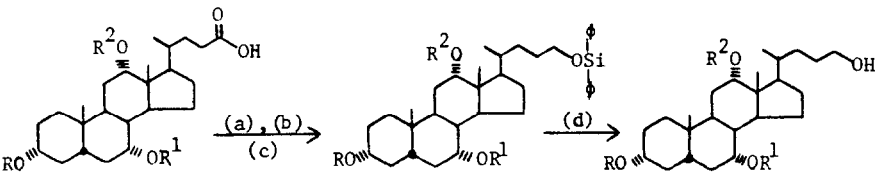
4: R=$CH_3$

6

Scheme 2

These unsatisfactory results and our earlier experimental work with perfluoroalkenes and sterols [1] suggested that in order to obtain a satisfactory conversion of the bile alcohol to the corresponding perfluoroalkenyl ether, we would have to employ n-butyl lithium as a base, which in turn demands a substrate devoid of base labile functional groups. Our experimental work is outlined in Scheme 3 and is derived from path-B of the retrosynthesis of Scheme 1. Cholic acid (3) was reduced with $BH_3$·THF complex in THF to give 5β-cholan-3α,7α,12α-tetrol in 89% yield [5]. The primary alcohol function of 5β-cholan-3α,7α,12α-

tetrol was then selectively protected with *tert*-butyldiphenylchlorosilane to give bile alcohol 9 in 92% yield [6]. Deprotonation of the unsubstituted hydroxyl groups of 9 with n-butyl lithium followed by the reaction of the trilithium salt with perfluoro-1-heptene gave a mixture of tris-perfluoroheptenyl ether 10 and bis-perfluoroheptenyl ethers 11 and 12 in a quantitative yield. The mixture was separated by chromatography to give 10 in 60% yield. An additional 10% of 10 was obtained by the subsequent reaction of bis-perfluoroheptenyl ethers 11 and 12 with perfluoro-1-heptene.



3: R=$R^1$=$R^2$=H

9: R=$R^1$=$R^2$=H

10: R=$R^1$=$R^2$=$R_f$

11: R=$R^1$=$R_f$; $R^2$=H

12: R=$R^2$=$R_f$; $R^1$=H

2a: R=$R^1$=$R^2$=$R_f$

$R_f$=-CF=CF$C_5F_{11}$

(a) $BH_3$·THF/THF

(b) TBDPSi chloride/imidazole/DMF

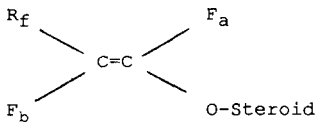
(c) n-BuLi/THF/$C_5F_{11}CF=CF_2$

(d) MeOH/THF/HCl

Scheme 3

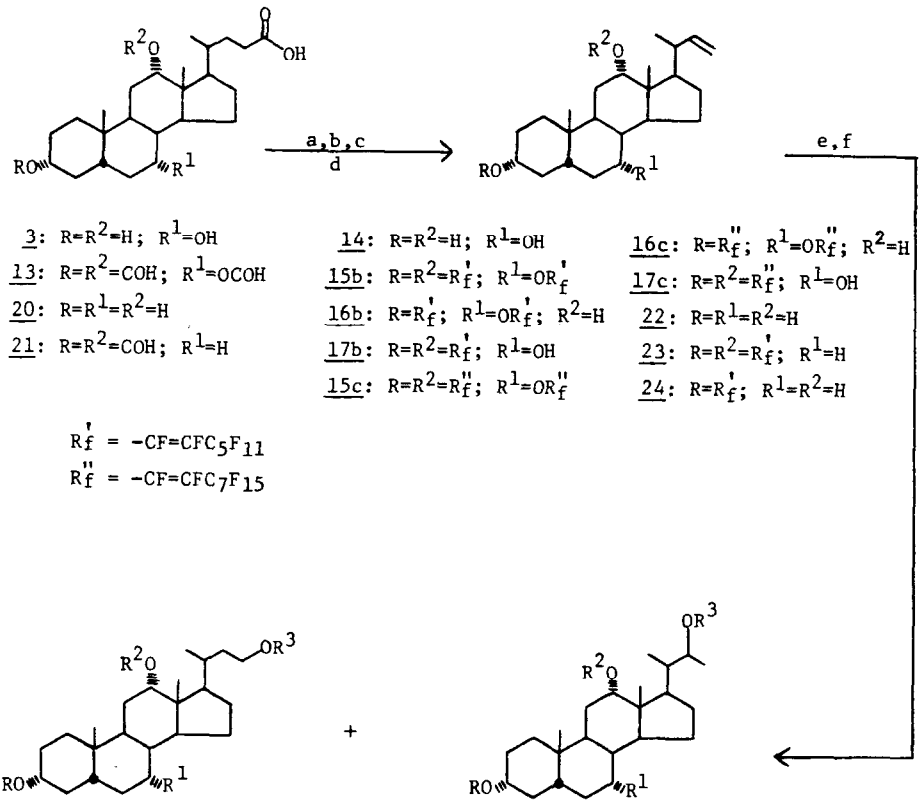
The position and the stereochemistry of the double bond in the perfluoroalkenyloxy side chain of 10 was determined by $^{19}F$ NMR spectroscopy. The signals at δ 104.6 to 109.4 and δ 186.6 to 189.4 were identified as 'F' cis to '$R_f$' ($F_a$) and 'F' cis to 'OR' ($F_b$), respectively. The large coupling constant (J = 118.4 Hz) of $F_a$ with $F_b$ indicated *trans*-stereochemistry of the double bond. The above assignments were based on the chemical shifts of the related compounds reported in the

literature [1,7]. The absence of a $CF_2O$ signal in $^{19}F$ NMR ruled out the possibility of an internal double bond formed by fluoride ion-induced rearrangement [1,8].




Synthesis of the desired compound 2a was achieved by cleaving the *tert*-butyldiphenylsilyl ether function of compound 10 with 5% HCl in methanol or tetra-n-butylammonium fluoride in THF. The use of tetra-n-butylammonium fluoride gave fluoride ion-induced isomerization of the double bond in the perfluoroalkenyloxy side chains [7] and formed a complex mixture of internal alkenes. With 5% HCl no isomerization was observed and the deprotected product 2a was obtained in 75% yield with complete retention of stereochemistry.

Use of Scheme 1 retrosynthesis path-C was our final approach to 2. This approach to 2b and 2c is outlined in Scheme 4. We chose 3α,7α,12α-trihydroxy-chol-22-ene (14) as the starting substrate because of the convenient literature preparation for 14 [9,10]. Using the procedure of Tserng *et al*. [11], cholic acid (3) was converted to 3α,7α,12α-triformyloxy cholic acid (13) in 89% yield. Oxidative decarboxylation of 13 with lead tetraacetate and copper(II) acetate [11], followed by alkaline hydrolysis gave 3α,7α,12α-trihydroxy-24-nor-5β-chol-22-ene (14) in 56% yield. The hydroxyl groups of 14 were then deprotonated with n-butyllithium, and the corresponding trilithium salt was reacted with perfluoro-1-heptene to give a mixture of tris-perfluoroalkenyl ether 15b and bis-perfluoroalkenyl ethers 16b and 17b. Separation of this mixture by column chromatography gave 15b in 56% yield. An additional 10% of 15b was obtained from the conversion of the bis-perfluoroalkenyl ethers 16b



3: R=$R^2$=H; $R^1$=OH
13: R=$R^2$=COH; $R^1$=OCOH
20: R=$R^1$=$R^2$=H
21: R=$R^2$=COH; $R^1$=H

14: R=$R^2$=H; $R^1$=OH
15b: R=$R^2$=$R_f'$; $R^1$=$OR_f'$
16b: R=$R_f'$; $R^1$=$OR_f'$; $R^2$=H
17b: R=$R^2$=$R_f'$; $R^1$=OH
15c: R=$R^2$=$R_f''$; $R^1$=$OR_f''$

16c: R=$R_f''$; $R^1$=$OR_f''$; $R^2$=H
17c: R=$R^2$=$R_f''$; $R^1$=OH
22: R=$R^1$=$R^2$=H
23: R=$R^2$=$R_f'$; $R^1$=H
24: R=$R_f'$; $R^1$=$R^2$=H

$R_f'$ = $-CF=CFC_5F_{11}$
$R_f''$ = $-CF=CFC_7F_{15}$

2b: R=$R^2$=$R_f'$; $R^1$=$OR_f'$; $R^3$=H
2c: R=$R^2$=$R_f''$; $R^1$=$OR_f''$; $R^3$=H
25: R=$R^2$=$R_f'$; $R^1$=$R^3$=H
27: R=$R^2$=$R_f'$; $R^1$=H; $R^3$=$(C=O)CH_3$
29: R=$R^2$=$R_f''$; $R^1$=$OR_f''$; $R^3$=$(C=O)CH_3$

19b: R=$R^2$=$R_f'$; $R^1$=$OR_f'$; $R^3$=H
19c: R=$R^2$=$R_f''$; $R^1$=$OR_f''$; $R^3$=H
26: R=$R^2$=$R_f'$; $R^1$=$R^3$=H
28: R=$R^2$=$R_f'$; $R^1$=H; $R^3$=$(C=O)CH_3$

(a) $H\overset{O}{\overset{\|}{C}}OH/HClO_4/Ac_2O$ (b) $Pb(OAc)_4/Cu(OAc)_2/C_6H_6$ (c) $KOH/CH_3OH$
(d) n-BuLi/THF/$C_5F_{11}CF=CF_2$ or $C_7F_{15}CF=CF_2$ (e) $BH_3$·THF/THF/$H_2O_2$/NaOH
(f) AcOCl/DMAP/$CH_2Cl_2$

**Scheme 4**

and 17b to 15b. The position and the *trans*-stereochemistry of the double bond in the perfluoroalkenyloxy side chain was assigned on the basis of $^{19}F$ NMR, as discussed previously.

The final step in the synthesis of 2b was the incorporation of the alcohol function in the hydrocarbon side chain of 15b. Hydroboration of the $C_{22}$-double bond in 15b with the $BH_3 \cdot THF$ complex in THF, followed by oxidation of the intermediate alkylborane with alkaline hydrogen peroxide, afforded the desired product 2b in 65% yield [12]. A small amount (ca. 6%) of the secondary alcohol 19b was also isolated. Its presence was indicated by a multiplet corresponding to $C_{22}$-H at $\delta$ 3.96 and a doublet due to the adjacent methyl group ($C_{23}$-$H_3$) at $\delta$ 1.12. Further proof was obtained from the irradiation studies. Irradiation of the signal at $\delta$ 3.96 caused the doublet at $\delta$ 1.12 to collapse to a singlet. To avoid formation of the secondary alcohol, 19b, we decided to use a sterically more demanding reagent, 9-borabicylo[3.3.1]nonane (9-BBN) [13]. As expected, hydroboration of 15b with 9-BBN was highly selective (less than 0.5% of 19b), and the desired product 2b was obtained in 86% yield. Similarly, the perfluorononenyl derivative, 2c, was prepared in an overall yield of 14%.

A similar set of reactions was carried out on 7-deoxycholic acid (Scheme 4). 7-Deoxycholic acid (20) was converted to 3α,12α-dihydroxy-7-deoxy-24-nor-5β-chol-22-ene (22) by a literature procedure [10,11,14] in 44% yield. The hydroxy groups of 22 were deprotonated with n-butyl lithium and then reacted with perfluoro-1-heptene to give 23 in 34% yield. Hydroboration of the C-22 double bond gave the desired product 25 in 49% yield. A small amount (ca. 6%) of secondary alcohol 26 was also observed but was easily separated by the converting the mixture of

alcohols to the corresponding acetates, and then separating the acetates by chromatography.

Currently we are testing the ability of 10, 15b, 15c, and 23 to reduce the interfacial tension between perfluorooctyl bromide and the emulsifying agent, Pluronic F-68. Our future goal is to connect 2a, 2b, 2c, and 25 to a sugar molecule. Because perfluoroalkenyl ethers exhibit a high stability under basic conditions, we do not expect serious problems in attaching a sugar group to the above derivatives. We hope these steroidal sugar derivatives will function as emulsifying agents for the fluorocarbon/water system and provide a non-ionic, non-toxic emulsifying agent for the fluorocarbon/water system.

## EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The infrared spectra (IR) were obtained on a Perkin-Elmer Model 1750 Infrared Fourier Transform Spectrometer. Only principal, sharply defined peaks are reported. The proton-nuclear-magnetic resonance spectra ($^{1}H$ NMR) were recorded on a Varian EM-390, 90 MHz, NMR Spectrometer, using tetramethylsilane as an internal standard. The $^{13}C$ NMR were recorded on Magnachem, Model 200, 200 MHz NMR Fourier Transform Spectrometer. The $^{19}F$ NMR spectra were obtained on a Jeol JNM-PS-100, high resolution NMR Spectrometer and the chemical shift is reported in $\delta$ units, relative to $CFCl_3$ as the standard. Thin layer chromatography (TLC) was performed on precoated TLC plates (silica gel-60, F-254, layer thickness 0.2 mm) manufactured by E. Merck and Co. The elemental analyses were carried out by Galbraith Laboratories Inc. Tetrahydrofuran (THF) was dried and distilled over sodium/benzophenone.

Dimethylformamide (DMF), benzene and pyridine were dried and distilled over calcium hydride. n-Butyl lithium was purchased from Aldrich Chemical Co., as a 2.60 M solution in hexane. The exact concentration was determined by titration of n-butyl lithium with diphenylacetic acid in THF [15]. Perfluoro-1-heptene and perfluoro-1-nonene were prepared from perfluorooctanoic acid and perfluorodecanoic acid, respectively, by the procedure of Brice et al. [16] as modified by Schectman [18]. The term 'brine' means a saturated solution of sodium chloride in water. Glass-ware used was dried in an oven, assembled, and flame-dried under argon.

Reaction of Cholic acid with Trifluorochloroethylene

A solution of cholic acid (0.44 g, 1.1 mmol) in DMF (10 mL) was added dropwise to a suspension of potassium hydride (0.20 g, 5.0 mmol) in DMF (5 mL). The mixture was stirred under nitrogen at room temperature for 1.5 hours and then heated under reflux for 3.5 hours. The contents were cooled in a dry ice/acetone bath and then treated with 2.5 mL of liquified trifluorochloroethylene. After stirring at -78°C for 5 minutes, the mixture was allowed to warm to a temperature where a gentle reflux of trifluorochloroethylene was observed. An additional 1.5 mL of trifluorochloroethylene was added and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with diethyl ether (30 mL) and contents poured into a flask containing 50 mL of 0.5 M HCl. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 25 mL). The combined ethereal layers were washed with 0.5M HCl (2 x 75 mL), water (2 x 75 mL) and brine (2 x 75 mL), and

dried over $MgSO_4$. Removal of solvent under reduced pressure gave 0.52 g of an off-white solid consisting of unreacted cholic acid and 6. Product 6 was not isolated, but its amount was calculated from $^1H$ NMR on the basis of the area covered by the $C_3$-H and the proton on the fluorochloromethyl group. In the following spectral data only signals corresponding to 6 are reported: $^1H$ NMR ($CDCl_3$/DMSO) δ 6.50-5.96 (triplet of doublets, J = 48.6 Hz, $-CF_2CHFCl$), 4.23 (m, $C_3$-H), 3.86 (s, $C_{12}$-H) and 3.73 (s, $C_7$-H); TLC (80% $CHCl_3$/methanol) $R_F$ 0.47; $^{19}F$ NMR ($CDCl_3$/DMSO) δ 84.2 ($-OCF_2CHFCl$) and 153.0 ($-OCF_2CHFCl$).

3α,7α,12α-Tris-(perfluoro-*trans*-1-heptenyl-1-oxy)-5β-cholan-24-ol-24-*tert*-butyldiphenysilyl ether (10)

A solution of 9 (0.825 g, 1.30 mmol) in THF (30 mL) was cooled in an ice/water bath and treated dropwise with 1.80 mL (4.32 mmol) of 2.40 M n-butyl lithium solution in hexane. After stirring the mixture at 5°C for 15 minutes and at room temperature for 2 hours, the contents were cooled to 5°C and treated with 0.90 mL (1.6 g, 4.6 mmol) of perfluoro-1-heptene. The mixture was stirred at this temperature for 20 minutes and at room temperature for 42 hours. The contents were poured into a flask containing 50 mL of 0.2 M HCl and 50 mL of diethyl ether. The organic layer was separated and the aqueous layer extracted with two 30-mL portions of diethyl ether. The combined ethereal layers were washed with brine (3 x 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 1.98 g of a colorless oil. Chromatography of this oil over silica-gel (100 g, 60-200 mesh silica-gel), using 85% hexane/$CH_2Cl_2$ as an eluent, gave 1.28 g (60.4%) of 10: TLC (70%

hexane/$CH_2Cl_2$) $R_F$ 0.59; IR (thin film) 3075, 3050, 2950, 2850, 1740, 1575, 1120-1300, 1100, 1065, and 950 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.46 (m, 4H, Ar<u>H</u>), 7.20 (m, 6H, Ar<u>H</u>), 4.63 (m, 1H, $C_{12}$-<u>H</u>), 4.43 (m, 1H, $C_7$-<u>H</u>), 4.07 (m, 1H, $C_3$-<u>H</u>), 3.53 (t, J = 4.8 Hz, 2H, $C_{24}$-$\underline{H}_2$), 1.03 (s, 9H, t-Bu), 0.93 (s, $C_{19}$-$\underline{H}_3$) and 0.73 (s, $C_{18}$-$\underline{H}_3$); $^{13}C$ NMR ($CDCl_3$) δ 135.58, 134.17, 129.49, and 127.55 (aromatic carbons), 84.56 ($C_{12}$), 82.71 ($C_3$), 80.67 ($C_7$) and 64.26 ($C_{24}$); $^{19}F$ NMR ($CDCl_3$) δ 80.6 ($C\underline{F}_3CF_2$-, 9F), 104.6-109.4 (=C<u>F</u>OR, 'F' cis to '$R_f$', $J_{ab}$ = 118.4 Hz, 3F), 116.6 ($C\underline{F}_2CF$=, 6F), 123.4-124.4 (-$CF_2$-, 12F), 126.6 ($CF_3C\underline{F}_2$- 6F) and 186.6-189.4 ($R_FCF$=, 3F).

Anal. Calcd for $C_{61}H_{57}O_4F_{39}Si$: C, 45.14; H, 3.54.

Found: C, 44.88; H, 3.73.

Further elution with 70% $CH_2Cl_2$/hexane provided 0.35 g (21%) of a mixture consisting mainly of bis-perfluoroheptenyl ethers <u>11</u> and <u>12</u>. In a manner similar to one described above, treatment of 0.35 g (0.27 mmol) of a mixture of bis-perfluoroalkenyl ethers (<u>11</u> and <u>12</u>) in 8 mL of THF with 0.28 mL (0.69 mmol) of 2.45 M n-butyl lithium solution in hexane, followed by the addition of 0.20 mL (0.36 g, 1.0 mmol) of perfluoro-1-heptene gave, after chromatography (silica gel, using 80% hexane/$CH_2Cl_2$ as an eluent), 0.22 g (50%) of <u>10</u>. Based on this, the overall yield of <u>10</u> was computed to be 71%.

<u>3α,7α,12α-Tris-(perfluoro-*trans*-1-heptenyl-1-oxy)-5β-cholan-24-ol</u> (<u>2a</u>).

A round-bottomed flask containing a magnetic stirring bar was charged with 0.67 g (0.35 mmol) of <u>10</u>, 5 mL of THF, 3 mL of diethyl ether, 9 mL of methanol and 1.3 mL of conc. HCl. The mixture was stirred

at room temperature for 22 hours, concentrated under reduced pressure, and the residue partitioned between diethyl ether and water. The layers were separated and the aqueous layer extracted with diethyl ether (2 x 30 mL). The combined ethereal layers were washed with water (1 x 75 mL), 5% $NaHCO_3$ (1 x 75 mL), and brine (2 x 75 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel (60-200 mesh), using 98% $CH_2Cl_2$/methanol as eluent, to furnish 0.21 g (68%) of 2a as a colorless, viscous oil: TLC (94% $CH_2Cl_2$/methanol) $R_F$ 0.56; IR (thin film) 3340, 2953, 2874, 1743, 1150-1310, 1142, 1098 and 1039 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.73 (m, 1H, $C_{12}$-H), 4.52 (m, 1H, $C_7$-H), 4.15 (m, 1H, $C_3$-H) and 3.54 (t, J = 5.2 Hz, 2H, $C_{24}$-$H_2$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 83.91 ($C_{12}$), 82.31 ($C_3$), 79.77 ($C_7$) and 63.42 ($C_{24}$); $^{19}F$ NMR ($CDCl_3$) $\delta$ 80.8 ($CF_3CF_2$-, 9F), 103.8-107.8 (=CFOR, 3F), 116.4 ($-CF_2CF=$, 6F), 123.4-124.4 ($-CF_2CF_2-$, 12F), 126.4 ($CF_3CF_2$-, 6F) and 186.8-189.8 ($=CFR_f$, 3F).

Anal. Calcd for $C_{45}H_{39}F_{39}O_4$: C, 39.04; H, 2.84; F, 53.51.

Found: C, 39.44; H, 3.03; F, 53.41.

3α,7α,12α-Tris(perfluoro-*trans*-1-heptenyl-1-oxy)-24-nor-5β-chol-22-ene (15b)

A solution of 0.545 g (1.50 mmol) of 14 in 25 mL of THF was cooled in an ice/water bath and treated with 2.0 mL (4.9 mmol) of 2.45 M n-butyl lithium solution in hexane over a period of 10 minutes. The mixture was stirred at room temperature for 2 hours and then treated dropwise with 1.20 mL (2.16 g, 6.17 mmol) of perfluoro-1-heptene. After stirring at room temperature for 24 hours, the reaction mixture was diluted with diethyl ether and slowly poured into a beaker containing

50 mL $H_2O$ and 2 mL of 6M HCl. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 50 mL). The combined ethereal layers were washed with brine (2 x 150 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 1.81 g of a brownish-red, viscous oil. The oil was dissolved in dichloromethane, impregnated on 3 g of 60-200 mesh silica gel and loaded onto a silica gel column (125 g, 60-200 mesh). The column was eluted with 85% hexane/$CH_2Cl_2$. The fractions containing the least polar component were combined and concentrated under reduced pressure to provide 1.1 g (56%) of 15b as an opaque, viscous oil: TLC (85% hexane/$CH_2Cl_2$) $R_F$ 0.60; IR (thin film) 3078, 2955, 2872, 1744, 1641, 1120-1350, 1108, 1066, 957, and 914 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.66 (m, 1H, $C_{22}$-H), 4.97-4.77 (m, 3H, $C_{23}$-$H_2$ and $C_{12}$-H), 4.57 (br s, 1H, $C_7$-H), 4.18 (m, 1H, $C_3$-H), 1.27 (d, J = 5.7 Hz, $C_{21}$-$H_3$), 0.98 (s, $C_{19}$-$H_3$) and 0.81 (s, $C_{18}$-$H_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 143.99 ($C_{22}$), 112.54 ($C_{23}$), 84.50 ($C_{12}$), 82.84 ($C_3$) and 80.80 ($C_7$); $^{19}F$ NMR ($CDCl_3$) $\delta$ 81.8 ($CF_3CF_2$-, 9F), 103.8-109.0 (=CFOR, 'F' cis to '$R_f$', 3F), 116.6 (-$CF_2CF$=, 6F), 123.4-124.2 (-$CF_2CF_2$-, 12F), 126.6 ($CF_3CF_2$-, 6F) and 185.8-188.6 (=$CFR_f$, 3F).

Anal. Calcd for $C_{44}H_{35}F_{39}O_3$: C, 39.07; H, 2.61; F, 54.78.

Found: C, 39.09; H, 2.66; F, 55.01.

Further elution with 50% hexane/$CH_2Cl_2$ and $CH_2Cl_2$ gave 0.42 g (27%) of a mixture consisting mainly of bis-perfluoroheptenyl ethers 16b and 17b. Treatment of the solution of this mixture (16b + 17b) in 8 mL of THF with 0.25 mL (0.61 mmol) of 2.45M n-butyl lithium solution in hexane, followed by the addition of 0.15 mL (0.27 g, 0.77 mmol) of perfluoro-1-heptene, afforded after chromatography (60-200 mesh silica gel, 80% hexane/$CH_2Cl_2$ as eluent) 0.20 g (36%) of 15b. Based on this, the overall yield of 15b was 66%.

3α,7α,12α-Tris(perfluoro-*trans*-1-nonenyl-1-oxy)-24-nor-5β-chol-22-ene (15c)

The procedure described for 15b was used to prepare 15c in 42% yield: TLC (85% hexane/$CH_2Cl_2$) $R_F$ 0.45; IR (thin film) 3082, 2964, 2877, 1745, 1642, 1115-1300, 1105, 1053 990 and 916 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.66 (m, 1H, $C_{22}$-H), 4.97-4.77 (m, 3H, $C_{23}$-$H_2$ + $C_{12}$-H), 4.57 (m, 1H, $C_7$-H), 4.21 (m, 1H, $C_3$-H), 1.06 (d, J = 5.8 Hz, $C_{21}$-$H_3$), 0.98 (s, $C_{19}$-$H_3$) and 0.81 (s, $C_{18}$-$H_3$); $^{13}C$ NMR ($CDCl_3$) δ 143.99 ($C_{22}$), 112.54 ($C_{23}$), 84.30 ($C_{12}$), 82.70 ($C_3$) and 80.55 ($C_7$); $^{19}F$ NMR ($CDCl_3$) δ 80.2 ($CF_3$-, 9F), 103.4-109.0 (=CFOR, 3F), 116.8 (-$CF_2$CF=, 6F), 122.2-124.2 (-$CF_2CF_2$-, 24F), 126.6 ($CF_3CF_2$-, 6F) and 187.6-190.4 (=CF, 3F).

3α,7α,12α-Tris(perfluoro-*trans*-1-heptenyl-1-oxy)-24-nor-5β-chol-23-ol (2b)

(1) Procedure-A (using $BH_3$·THF)

A solution of 0.40 g (0.30 mmol) of 15b in 8 mL of THF was treated with 1.50 mL (1.50 mmol) of 1M $BH_3$·THF complex in THF. The mixture was stirred at room temperature for 12 hours, diluted with THF, and poured into a flask containing 3 mL of $H_2O$, 1 mL of 3M NaOH, and 1 mL of 30% $H_2O_2$. After stirring the mixture at room temperature for 30 minutes the reaction mixture was diluted with diethyl ether and saturated with potassium carbonate. The layers were separated and the aqueous layer extracted with diethyl ether (2 x 30 mL). The combined ethereal layers were washed with brine (2 x 100 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give 0.46 g of an oily residue. Chromatography of this residue on silica gel (60-200 mesh), using 97% $CH_2Cl_2$/methanol as an eluent, afforded 0.030 g (6.20%) of 15b ($R_F$ 0.60,

85% hexane/$CH_2Cl_2$), 0.028 g (6.80%) of 19b ($R_F$ 0.73, 96% $CH_2Cl_2$/methanol) and 0.268 g (65.4%) of 2b ($R_F$ 0.54, 96% $CH_2Cl_2$/methanol). The product 2b was obtained as a chromatographically pure colorless paste: TLC (96% $CH_2Cl_2$/methanol) $R_F$ 0.73; IR (KBr) 3343, 2952, 2876, 1744, 1120-1320, 1107, 1065 and 1026 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.81 (br s, 1H, $C_{12}$-H), 4.58 (m, 1H, $C_7$-H), 4.23 (m, 1H, $C_3$-H), 3.73 (t, J = 6.0 Hz, 2H, $C_{23}$-$H_2$), 1.03 (s, $C_{19}$-$H_3$ + $C_{21}$-$H_3$) and 0.88 (s, $C_{18}$-$H_3$); $^{13}C$ NMR ($CDCl_3$) δ 84.55 ($C_{12}$), 82.55 ($C_3$), 80.60 ($C_7$), and 60.40 ($C_{23}$); $^{19}F$ NMR ($CDCl_3$) δ 80.6 ($CF_3CF_2$-, 9F), 103.8-109.0 (=CFOR, 3F), 116.2 ($CF_2CF$=, 6F), 123.0-124.2 (-$CF_2CF_2$-, 12F), 126.2 ($CF_3CF_2$-, 6F) and 187.0-190.6 ($R_fCF$=, 3F).

(2) Procedure-B (using 9-BBN)

In a manner similar to that described above, a solution of 0.40 g (0.30 mmol) 15b in 8 mL of THF was reacted with 1.4 mL of 9-BBN solution in THF at room temperature for 17 hours. Work-up, as indicated above, followed by the removal of solvent under reduced pressure gave an oil. The oil was dissolved in dichloromethane, impregnated on 2 g of silica gel and loaded onto a 60-200 mesh silica gel column. Elution of the column with $CH_2Cl_2$, 98% $CH_2Cl_2$/methanol and 95% $CH_2Cl_2$/methanol, followed by the removal of solvent from the appropriate fractions gave 0.36 g (87%) of 2b as a colorless paste. The spectral properties of 2b were identical with 2b prepared by procedure-A.

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*Product 2b was isolated as a chromatographically pure oil. No problems were encountered in the separation of 2b from the reaction mixture and thus conversion of 2b to the corresponding acetate was not required.

3α,7α,12α-Tris(perfluoro-*trans*-1-nonenyl-1-oxy)-24-nor-5β-chol-23-ol (2c)

The procedure described for 2b (Procedure-A) was used to prepare 2c in 68% yield: TLC (95% $CH_2Cl_2$/methanol) $R_F$ 0.55; IR (thin film) 3333, 2949, 2876, 1743, 1120-1300, 1105 and 1025 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.72 (s, 1H, $C_{12}$-H), 4.49 (s, 1H, $C_7$-H), 4.06 (m, 1H, $C_3$-H), 3.63 (t, J = 6.0 Hz, 2H, $C_{23}$-$H_2$), 0.87 (br s, $C_{21}$-$H_3$ + $C_{19}$-$H_3$) and 0.71 (s, $C_{18}$-$H_3$); $^{13}C$ NMR ($CDCl_3$) δ 84.64 ($C_{12}$), 82.99 ($C_3$), 80.65 ($C_7$) and 60.45 ($C_{23}$); $^{19}F$ NMR ($CDCl_3$) δ 80.6 ($CF_3$-, 9F), 103.8-109.8 (=CFOR, 3F), 116.6 (-$CF_2$CF=, 6F), 122.2-124.2 (-$CF_2CF_2$-, 24F), 126.6 ($CF_3CF_2$-, 6F) and 187.0-189.8 ($R_fCF$=, 3F). In order to simplify the separation of 2c from the reaction mixture, the crude product was acetylated* and 2c isolated as its acetate (29). The acetate 29 was obtained as a chromatographically pure colorless oil: IR (thin film) 2948, 2877, 1742 (br), 1080-1310, and 1055 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.74 (m, 1H, $C_{12}$-H), 4.52 (m, 1H, $C_7$-H), 4.04 (br t, J = 6.2 Hz, 3H, $C_{23}$-$H_2$ + $C_3$-H), 1.99 (s, 3H, -OCOC$H_3$), 0.92 (br s, $C_{19}$-$H_3$ + $C_{21}$-$H_3$) and 0.75 (s, $C_{18}$-$H_3$); $^{13}C$ NMR ($CDCl_3$) δ 171.15 (C=O), 84.50 ($C_{12}$), 82.79 ($C_3$), 80.60 ($C_7$) and 62.54 ($C_{23}$); $^{19}F$ NMR ($CDCl_3$) δ 80.2 ($CF_3$-, 9F), 103.8-109.4 (=CFOR, 3F), 116.6 (-$CF_2$CF=, 6F), 121.8-122.6 (-$CF_2CF_2$-, 24F), 126.4 ($CF_3CF_2$-, 6F) and 180.2-183.4 ($R_fCF$=, 3F). Anal. Calcd for $C_{50}H_{39}O_4F_{51}$: C, 36.47; H, 2.29; F, 56.57. Found: C, 37.53; H, 2.76; F, 56.06.

*A solution of 1.0 equivalent alcohol, 2.2 equivalent DMAP, and 1.2 equivalent of triethylamine in dichloromethane, was treated with 2.5 equivalents of acetyl chloride. The mixture was stirred at room temperature for 12 hours and then worked up in the usual mannner to give an oil. Flash chromatography of the oil over silica gel gave the desired product in ca. 80% yield.

3α,12α-Bis(perfluoro-*trans*-1-heptenyl-1-oxy)-24-nor-5β-chol-22-ene (23)

In a manner similar to that described for 15b, a solution of 22 (0.441 g, 1.27 mmol) in 15 mL of THF at 5°C was treated with 1.0 mL (2.45 mmol) of 2.45M n-butyl lithium solution in hexane. The mixture was stirred at room temperature for 30 minutes, cooled, and treated with 0.55 mL (1.0 g, 2.8 mmol) of perfluoro-1-heptene. The resulting mixture was stirred at room temperature for 24 hours. The work-up (as described for 15b), followed by chromatography of the residue (1.05 g) over silica gel, using 85% hexane/dichloromethane as an eluent, gave 0.42 g (34%) of chromatographically pure 23 as a colorless, viscous oil: TLC (75% hexane/dichloromethane) $R_F$ 0.74; IR (thin film) 3079, 2952, 2873, 1744, 1641, 1120-1320, 1107, 1066, 990, and 913 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.53 (m, 1H, $C_{22}$-H), 4.60-4.90 (m, 3H, $C_{23}$-$H_2$ and $C_{12}$-H), 4.22 (m, 1H, $C_3$-H),1.00 (d, J = 5.5 Hz, $C_{21}$-$H_3$), 0.92 (s, $C_{19}$-$H_3$) and 0.78 (s, $C_{21}$-$H_3$). A broad singlet at δ 1.23, due to the hexane trapped in the crystal lattice, was also observed; $^{13}C$ NMR ($CDCl_3$) δ 144.33 ($C_{22}$), 112.30 ($C_{23}$), 85.18 ($C_{12}$) and 83.47 ($C_3$); $^{19}F$ NMR ($CDCl_3$) δ 81.40 ($CF_3CF_2$-, 6F), 103.6-107.8 (=CFOR, 'F 'cis to '$R_f$', 2F), 116.2 (-$CF_2CF$=, 4F), 123.4-124.2 (-$CF_2CF_2$-, 8F), 126.6 ($CF_3CF_2$-, 4F) and 187.2-188.8 ($R_fCF$=, 2F).

Anal. Calcd for $C_{37}H_{36}O_2F_{26}\cdot 2C_6H_{12}$: C, 46.16; H, 4.53; F, 46.30.

Found: C, 45.82; H, 4.11; F, 46.19.

Further elution with 75% hexane/$CH_2Cl_2$, 50% hexane/$CH_2Cl_2$, and $CH_2Cl_2$, afforded 0.35 g (40%) of 24 as a colorless viscous syrup: TLC (50% hexane/$CH_2Cl_2$) $R_F$ 0.62; IR (thin film) 3475,3060, 2930, 2850, 1740, 1635, 1170-1300, 1140, 1100, 1050 and 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.59 (m, 1H, $C_{22}$-H), 4.69-4.92 (m, 2H, $C_{23}$-H), 4.20 (m, 1H, $C_3$-H), 3.93 (s,

1H, $C_{12}$-H), 1.06 (d, J = 5.5 Hz, $C_{21}$-$H_3$), 0.93 (s, $C_{19}$-$H_3$) and 0.73 (s, $C_{18}$-$H_3$); $^{19}$F NMR ($CDCl_3$) δ 81.0 ($CF_3CF_2$-, 6F), 103.4-106.4 (=CFOR, 'F' cis to '$R_f$', 2F), 116.2 (-$CF_2CF$=, 4F), 122.6- 123.6 (-$CF_2CF_2$-, 8F), 126.0 ($CF_3CF_2$-, 4F), 187.1-188.7 (=$CFR_f$, 2F); $^{13}$C NMR ($CDCl_3$) δ 144.77 ($C_{22}$), 111.86 ($C_{23}$), 85.13 ($C_3$) and 73.06 ($C_{12}$).

3α,12α-Bis(perfluoro-*trans*-1-heptenyl-1-oxy)-24-nor-5β-cholan-23-ol (25)

A solution of 0.89 g (0.88 mmol) of 23 in 10 mL of THF was treated with 2.6 mL (2.6 mmol) of 1M $BH_3$·THF complex in THF. The mixture was stirred at room temperature for 12 hours, diluted with THF and poured into a beaker containing 3 mL $H_2O$, 1mL of 3M NaOH, and 1 mL of 30% $H_2O_2$. The resulting mixture was stirred at room temperature for 30 minutes, diluted with diethyl ether, and saturated with potassium carbonate. The layers were separated and the aqueous layer extracted with diethyl ether. The combined ethereal layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale yellow viscous oil. Chromatography of this residue over silica gel, using $CH_2Cl_2$ and 95% $CH_2Cl_2$/methanol as eluents, gave 0.055 g (6.1%) of 26 and 0.440 g (48.9%) of 25. The product 25 had the following characteristics: TLC (94% $CH_2Cl_2$/methanol) $R_F$ 0.71; IR (thin film) 3350, 2950, 2870, 1740, 1120-1350, 1100, 1050 and 950 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.74 (s, 1H, $C_{12}$-H), 4.25 (m, 1H, $C_3$-H), 3.57 (br t, 3H, $C_{23}$-$H_2$ and O-H), 0.92 (br s, 6H, $C_{19}$-$H_3$ and $C_{21}$-$H_3$) and 0.76 (s, 3H, $C_{18}$-$H_3$); $^{13}$C NMR ($CDCl_3$) δ 85.32 ($C_{12}$), 83.43 ($C_3$) and 60.35 ($C_{23}$); $^{19}$F NMR ($CDCl_3$) δ 81.4 ($CF_3CF_2$-, 6F), 104.2-108.4 (=CFOR, 'F' cis to '$R_f$', 2F), 116.6 ($CF_2CF$=, 4F), 123.4-124.2 (-$CF_2CF_2$-, 8F), 126.6 ($CF_3CF_2$- 4F) and 188.0-

190.0 ($R_fC\underline{F}$=, 2F); mass spectra, m/e: 1006 ($M^+ - H_2O$), 677 ($M^+ - C_7F_{13}O$), 659 ($M^+ - C_7F_{13}O - H_2O$).

In order to simplify the separation (and purification) of 25 from the reaction mixture, the crude product was acetylated* and 25 isolated as its acetate 27. The acetate 27 was obtained as a colorless, viscous oil: TLC (65% $CH_2Cl_2$/hexane) $R_F$ 0.58; IR (thin film) 2950, 2865, 1730-1745, 1120-1300, 1100, 1050 and 960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.73 (s, 1H, $C_{12}$-$\underline{H}$), 4.23 (m, 1H, $C_3$-$\underline{H}$), 4.03 (t, J = 4.75 Hz, $C_{23}$-$\underline{H}_2$), 2.04 (s, 3H, $C\underline{H}_3CO_2$-), 0.92 (s, $C_{19}$-$\underline{H}_3$) and 0.76 (s, $C_{18}$-$\underline{H}_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 171.20 (C=O), 85.09 ($C_{12}$), 83.33 ($C_3$) and 62.63 ($C_{24}$); $^{19}F$ NMR ($CDCl_3$) $\delta$ 80.6 ($C\underline{F}_3CF_2$-, 3F), 103.8-109.4 (=$C\underline{F}$OR, 'F' cis to '$R_f$', 2F), 116.6 (-$C\underline{F}_2CF$=, 4F), 123.2-124.2 (-$C\underline{F}_2C\underline{F}_2$-, 8F), 126.6 ($CF_3C\underline{F}_2$-, 4F) and 187.0-190.6 ($R_fC\underline{F}$=, 2F).

Anal. Calcd for $C_{39}H_{40}F_{26}O_4$: C, 43.92; H, 3.98; F, 46.31.

Found: C, 44.17; H, 3.92; F, 46.50.

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REFERENCES

1 A.A. Malik, D.F. Shellhamer, and C.M. Sharts, *J. Fluorine Chem.*, 34 (1987) 409.

2 K. Yokoyama, K. Yamanouchi and T. Suyama, *Life. Chem. Rep.*, 2 (1983), 35; K.C. Lowe, *Pharm. J.*, 232, (1984) 73.

* See footnote on p. 409

3 C.M. Sharts, A.A. Malik, J.C. Easdon, L. Khawli, D.M. Long, D.F. Shellhamer, V.L. Burton, M.K. Porter and L.F. Sprague, *J. Fluorine Chem.*, 34 (1987) 365.

4 A.A. Malik and C.M. Sharts, *J. Fluorine Chem.*, 34 (1987) 395.

5 A.A. Malik and C.M. Sharts, *Org. Prep. & Proc. Intl.*, 19 (1987) 1.

6 A.A. Malik and C.M. Sharts, *Org. Prep. & Proc. Intl.*, 18 (1987) 345.

7 A. Battais, B. Boutevin and P. Moreau, *J. Fluorine Chem.*, 13 (1979) 391.

8 D.J. Burton and J.A. Headley, *J. Fluorine Chem.*, 18 (1981) 323, and references therein.

9 K. Kihira, T. Kuramoto, and T. Hoshita, *Steroids*, 27 (1976) 383.

10 G.L. Carlson, D.T.E. Belobaba, A. F. Hofmann and Y. Wedmid, *Steroids*, 30 (1978) 787.

11 K. Tserng and P.D. Klein, *Steroids*, 29 (1977) 635.

12 H.O. House, Modern Synthetic Reactions, second edition, W.A. Benjamin, Menlo Park, California; p. 106.

13 E.F. Knights and H.C. Brown, *J. Am. Chem. Soc.*, 90 (1968), 5281.

14 A.S. Vaidya, P.N. Chaudhari and A.S. Rao, *Indian J. Chem.*, 11 (1973) 645.

15 W.G. Kofran and L.M. Baclawski, *J. Org. Chem.*, 41 (1976) 1879.

16 T.J. Brice, J.D. Lazerte, L.J. Hob and W.H. Pearlson, *J. Am. Chem. Soc.*, 75 (1953) 2698.

17 W.H. Hoelin and R.B. Moffett, *J. Am. Chem. Soc.*, 67 (1945) 740.

18 L. Schechtman, Master's Thesis, San Diego State University (1979), p. 25.