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PERFLUOROALKENYL ETHERS OF SIMPLE STEROLS

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SUMMARY

Base-catalyzed addition of simple sterols to perfluoroalkenes, to give a variety of perfluoroalkenyl steroidal ethers, has been investigated. The outcome of the reaction was dependent on the base used for deprotonation of sterols. With potassium hydride, a mixture of 1- and 2-perfluoroalkenyl steroidal ethers was obtained in a low yield, whereas with n-butyllithium, preferential formation of 1-perfluoroalkenyl steroidal ethers was achieved in high yields.

INTRODUCTION

The addition of alcohol to a fluoroalkene to give an ether was first reported in 1946 by Hanford and Rigby [1]. Since then this reaction has been extensively investigated and applied in numerous syntheses [2-6]. As a part of our continuing study to synthesize perfluoroalkyl-substituted steroids and their derivatives [7] as potential surfactants (or co-surfactants) for fluorocarbon-based blood substitutes [8-11], we report the application of the above reaction to the synthesis and characterization of a new class of compounds: steroidal perfluoroalkenyl ethers.

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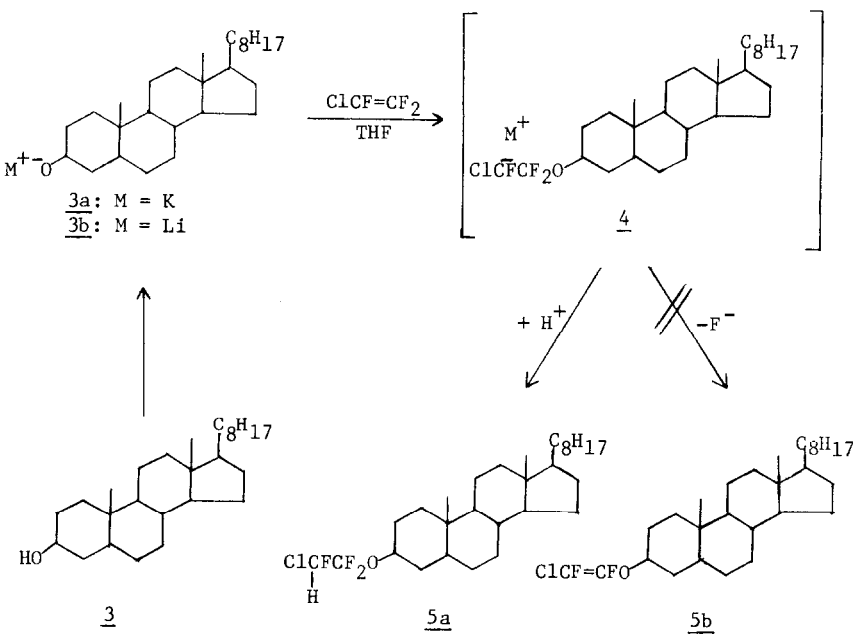
RESULTS AND DISCUSSION

Our initial attempts to synthesize perfluoroalkyl ethers were not successful. Attempts to convert the carbonyl group in steroidal perfluoroalkane carboxylates [12] to a difluoromethylene group using sulfur tetrafluoride [13,14] resulted in either total decomposition at elevated temperatures (180°C) or in a quantitative recovery of the starting ester at room temperature. At intermediate temperatures, a complex mixture arising from opening of the steroid rings resulted. Alkylation, employing phase transfer $S_{RN}1$ conditions [15], also failed. Attempted synthesis of the $R_fCH_2CH_2O$-steroid by Williamson ether synthesis resulted in the facile elimination of HI from $R_fCH_2CH_2I$ [16]; the desired substitution was not observed.

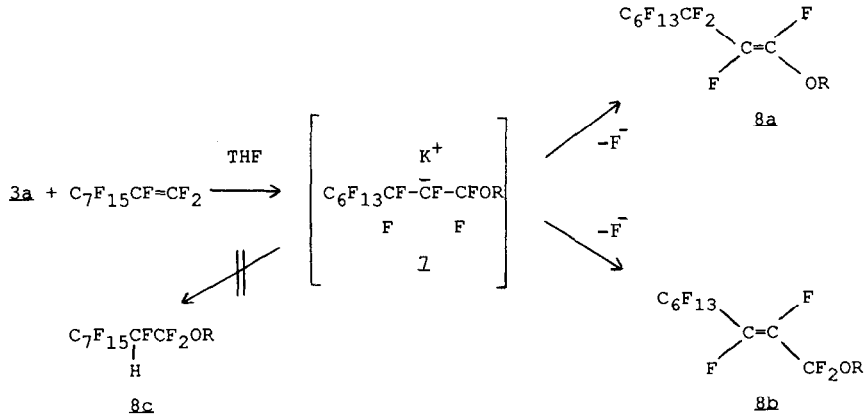


Scheme 1

Perfluoroalkenes were synthesized by decarboxylation of the dry sodium salts at 300°C [17,18]. Perfluoro-1-heptene (1) and perfluoro-1-nonene (2), were obtained in 81% and 77% yields, respectively from de-

carboxylation of sodium perfluorooctanoate and sodium perfluorodecanoate. For our initial studies trifluorochloroethylene and 5α-cholestan-3β-ol (3) were chosen as perfluoroalkene and steroid. 5α-Cholestan-3β-ol (3) was reacted with potassium hydride in tetrahydrofuran (THF) to give potassium cholestanoate (3a) which was then reacted at -20°C with trifluorochloroethylene to give the addition product 5a in 86% yield (Scheme 1). The proton and fluorine-magnetic-resonance spectra of 5a confirmed the structure assigned.

In the base-catalyzed addition of alcohol to perfluoroalkene the first step is the regiospecific addition of alkoxide to the terminal CF_2 as shown by the addition of 3a to trifluorochloroethylene in Scheme 1. The carbanion 4 then abstracts a proton from the alcohol to give the addition product 5a or loses fluoride ion to form the substitution product 5b. When 3a reacted with perfluoro-1-nonene (2), only substitution was observed. The products 8a and 8b, resulting from the loss of the fluoride ion from the intermediate carbanion 7 (Scheme 2), were isolated in 25% yield (ratio of 8a/8b = 1.5, determined by ^{19}F NMR). Efforts to obtain the protonated form 8c by reaction at a lower temperature (0°C), or by use of a weaker base (triethylamine or 4-dimethylaminopyridine), were unsuccessful.

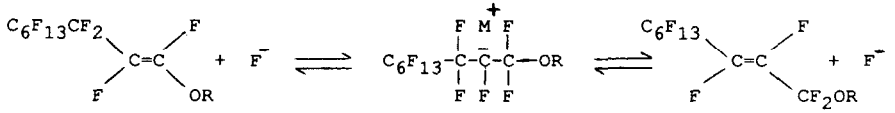


R = 5α-cholestan-3β-yl

Scheme 2

A possible explanation for addition with trifluorochloroethylene and substitution with perfluoro-1-nonene lies with the kinetics and the relative stabilities of the carbanions 4 and 7 [2]. Carbanion 4 is significantly more stable than carbanion 7 with a longer lifetime because of delocalization of charge into the d-orbital of the chlorine. The much less stable carbanion 7 loses fluoride ion faster than it adds a proton to yield the substitution products 8a and 8b. Attempts to optimize the yield by heating the mixture at reflux or stirring the mixture for a longer period were unsuccessful. However, when the base was changed from potassium hydride to n-butyllithium, a much higher yield (65%) of the unsaturated ether 8a was obtained. This change probably results from the difference in the solubility of the metal alkoxides, 3a and 3b, in THF. Lithium alkoxide 3b is soluble in THF, whereas the corresponding potassium alkoxide 3a is not. A possible explanation for the greater solubility of the lithium alkoxide in THF is that the lithium-oxygen bond has a large amount of covalent character, whereas the potassium-oxygen bond is mainly ionic.

Fluorine-magnetic-resonance spectra (^{19}F NMR) showed 8a to contain less than 5% of 8b. This change in the product ratio of 8a/8b from 60/40 with potassium hydride to 95/5 with n-butyllithium is a significant result. We postulate that KF dissociates to a much greater extent than LiF in the solvent THF. As a result, fluoride ion-induced isomerization [19] of 8a to 8b is observed with potassium hydride and no isomerization occurs with n-butyllithium (Scheme 3).

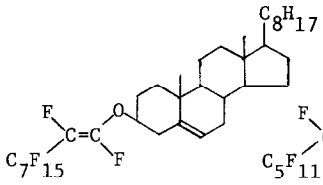


8a 3a: M = K 3b: M = Li 8b

Scheme 3

The progress of the reaction was followed by thin-layer chromatography (TLC). Products were characterized by infrared and ^{1}H NMR. Useful infrared absorption occurred for the carbon-carbon double bond of the perfluoroalkenyl group at ca. 1745 cm^{-1}. ^{19}F NMR spectroscopy was used to assign *'trans'* stereochemistry to the double bond in the perfluoroalkenyl group.

The following additions of steroid and perfluoroalkene were carried out in the yields indicated using n-butyllithium as a base: cholest-5-ene-3β-ol and 2 to give 9 (65%); 5α-cholestan-3β-ol and 1 to give 10 (60%); pregn-5-ene-3β-ol-20-one and 1 to give 11 (62%).



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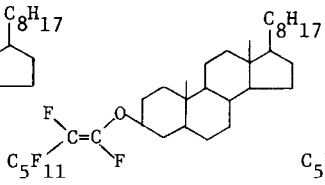

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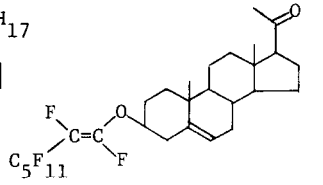

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The results of this study have been extended to bis- and tris-perfluoroalkenyl ethers of bile acids and bile acid derivatives. The results are reported in a subsequent paper.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The infrared (IR) spectra were obtained on a Perkin-Elmer Model 1750 Infrared Fourier Transform Spectrometer. Only principal, sharply defined peaks are reported. The ^{1}H NMR spectra were recorded on a Varian EM-390, 90 MHz, NMR Spectrometer, using tetramethylsilane as an internal standard. The ^{19}F NMR spectra were obtained on a JEOL JNM-PS-100, high resolution NMR Spectrometer. The chemical shifts were recorded in δ units relative to $CFCl_3$ as the reference. 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. Elemental analyses were carried out by Galbraith Laboratories Inc. Solvents used were ACS grade and were distilled just prior to use. Tetra-

hydrofuran (THF) and diethyl ether (DEE) were dried and distilled over sodium/benzophenone. Perfluorodecanoic acid and n-butyllithium (2.6M solution in hexane) were purchased from Aldrich Chemical Co. Perfluorooctanoic acid was purchased from PCR Research Chemical Inc. Perfluoro-1-heptene and perfluoro-1-nonene were prepared from perfluorooctanoic acid and perfluorodecanoic acid, respectively, by following the procedure of Brice et al. [17] as modified by Schechtman [18]. The term "brine" means a saturated sodium chloride solution in water.

Perfluoro-1-heptene (1)

Decarboxylation of the sodium salt of perfluorooctanoic acid (20.0 gm, 48.3 mmol) at 300°C provided 13.6 gm (81.3%) of 1 as a clear, colorless liquid, boiling between 81.5-83.5°C (lit. bp. [21] 80-82°C). On the basis of ^{19}F NMR and gas liquid chromatography it was concluded that the liquid obtained was pure perfluoro-1-heptene (1) and was free of contamination from internal alkenes: IR (thin film): 1790 and 1120-1360 cm^{-1}; ^{19}F NMR (neat): δ84.2 (CF_3CF_2-, 3F), δ92.2 (=CF, 'F' *trans* to 'R_f', 1F), δ107-109.6 (=CF, 'F' *cis* to 'R_f', 1F), δ120.6 (-CF_2CF=, 2F), δ125.4-126.4 (-CF_2-, 4F), δ128.8 (CF_3CF_2-, 2F) and δ190.8-192.4 (R_fCF=, 1F).

Perfluoro-1-nonene (2)

In a similar manner, 25.0 gms (48.6 mmol) of perfluorodecanoic acid afforded 16.9 gm (77.3%) of 2, as a colorless liquid boiling between 115-118°C (lit. bp. [21] 113-118°C); IR (thin film): 1795 and 1100-1370 cm^{-1}; ^{19}F NMR (neat): δ83.8 (CF_3CF_2-, 3F), δ91.8 (=CF, 'F' *trans* to 'R_f', 1F), δ106.4-109.0 (=CF, 'F' *cis* to 'R_f', 1F), δ119.8 (-CF_2CF=, 2F), δ123.0-125.8 (-CF_2-, 8F), δ128.2 (CF_3CF_2-, 2F) and δ188.2-190.8 (R_fCF=, 1F).

Reaction of 5α-cholestan-3β-ol with trifluorochloroethylene (using potassium hydride as base)

A 100-mL, 3-necked, round-bottomed flask fitted with a reflux condenser, a magnetic stirring bar, a glass stopper, rubber septums and a nitrogen inlet/outlet was charged with 181 mg (4.40 mmol) of potassium

hydride and 15 mL of THF. A solution of 1.76 gm (4.52 mmol) 5α-cholestan-3β-ol in 45 mL of THF was added and the mixture stirred at room temperature for 4 hours and under reflux for 1 hour. The reflux condenser was replaced with a cold finger containing dry ice/acetone, and the stopper with a gas inlet adaptor. The contents were cooled to -78°C in a dry ice/acetone bath, and 4.5 mL of liquified trifluorochloroethylene was slowly transferred to the reaction vessel. The mixture was stirred vigorously at -78°C for 10 minutes and allowed to warm gradually to the temperature at which trifluorochloroethylene refluxed slowly. An additional 1.5 mL of liquid trifluorochloroethylene was added and the mixture allowed to warm gradually to room temperature. The resulting brownish-yellow solution was poured into 50 mL of 15% NH_4Cl, the organic layer separated, and the aqueous layer extracted with diethyl ether (2 x 50 mL) and THF (1 x 50 mL). The combined organic extracts were washed with brine (3 x 150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 2.4 gm of a solid, off-white residue. The residue was dissolved in a minimum amount of hexane and loaded onto an alumina column. The column was eluted with hexane. The appropriate fractions were combined and concentrated under reduced pressure to give 1.95 gm (86.0%) of 5a as a white, waxy solid. Recrystallization of the solid from methanol/diethyl ether at room temperature gave 5a as white needles with the following characteristics: mp. 77-91°C; TLC (CH_2Cl_2): R_F 0.82; IR (KBr): 2950, 2860, 1270-1170, 1080 and 1000 cm^{-1}; ^1H NMR ($CDCl_3$): δ6.10 and 5.54 (triplet of doublets, J_{ab} = 49.5 Hz, J_{ac} = 3.0 Hz, $ClFC\underline{H}CF_2O$-) and δ4.17 (m, 1H, C_3-$\underline{H}$); ^{19}F NMR ($CDCl_3$): δ86.2 ($-C\underline{F}_2$-, 2F) and δ150.6 ($ClFC\underline{H}CF_2O$-, 1F); mass spectrum, m/e: 505 (M^+).

Anal. Calcd. for $C_{29}H_{48}F_3OCl$: C, 69.0; H, 9.6; F, 11.3

Found: C, 69.0; H, 9.4; F, 11.2

Reaction of 5α-cholestan-3β-ol with perfluoro-1-nonene

(1) Procedure-A (using potassium hydride as a base)

To a 50-mL, 3-necked, round-bottomed flask fitted with rubber septums, a reflux condenser, a nitrogen inlet/outlet and a magnetic stirring bar was added 140 mg (3.42 mmol) of potassium hydride. THF (5 mL) was added, followed by the dropwise addition of a solution of

5α-cholestan-3β-ol (3, 0.700 gm, 1.81 mmol) in 15 mL of THF. The above mixture was stirred at room temperature for 4 hours, heated under reflux for 1 hour, cooled to 0°C, and treated with 0.60 mL (1.1 gm, 2.4 mmol) of perfluoro-1-nonene. The dissolution of the white insoluble precipitate of 5α-cholestan-3β-ol oxide into a clear, yellowish-green solution marked the completion of the reaction. The progress of the reaction was followed by TLC, which revealed that the reaction was over in less than 10 minutes at 0°C. Stirring the mixture for a longer time at room temperature or even at reflux did not seem to affect the outcome of the reaction. The mixture was diluted with diethyl ether and poured into a flask containing 50 mL of 0.5N HCl. The organic layer was separated, and the aqueous layer further extracted with diethyl ether (2 x 25 mL). The combined extracts were washed with brine (3 x 75 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 1.2 gm of a solid, white residue. Chromatography of the residue over alumina, using hexane as an eluent, gave 0.369 gm (25.0%) of 8a + 8b as an opaque, viscous oil. Crystallization of the oil from methanol/diethyl ether at room temperature gave a mixture of 60% 8a and 40% 8b as white needles: mp. 55-68°C; TLC (30-60 pet-ether): two spots, R_F 0.72 and 0.77; IR (KBr): 2940, 2868, 1746, 1170-1310, 1148, 1068 and 998 cm^{-1}; ^1H NMR ($CDCl_3$): δ4.22 (m, 1H, C_3-H); ^{19}F NMR ($CDCl_3$): δ70.4 (8b, $-CF_2O$), δ81.0 (CF_3CF_2-), δ84.6 (8b, 'F' *cis* to 'R_f', $=CFCF_2O$), δ103.4-105 (8a, 'F' *cis* to 'R_f', =CFO-steroid), δ115.6-118.0 ($-CF_2CF=$), δ122.0-123.4 ($-CF_2-$), δ126.2 (CF_3CF_2-), δ182.4 (8b, $R_fCF=$) and δ187.2-188.4 (8a, $R_fCF=$).

Anal. Calcd for $C_{36}H_{47}F_{17}O$: C, 52.8; H, 5.8; F, 39.4

Found: C, 53.0; H, 5.8; F, 38.8

(2) Procedure-B (using n-BuLi as a base)

A 50-mL, 3-necked, round-bottomed flask fitted with rubber septums, a magnetic stirring bar and a nitrogen inlet/outlet was charged with 1.03 gm (2.66 mmol) of 5α-cholestan-3β-ol (3) and 25 mL of THF. The solution was cooled to 0°C and treated dropwise with 1.20 mL (3.1 mmol) of 2.6M n-BuLi solution in hexane. The mixture was stirred at 0°C for 20 minutes and at room temperature for 3 hours. Perfluoro-1-nonene (0.80 mL, 1.4 gm, 3.2 mmol) was added, and the resulting orange-yellow solution was stirred at room temperature for 3 hours. Periodic analysis

of the reaction mixture by TLC, however, indicated that the reaction was over in 30 minutes. The work-up, as described above (procedure-A), provided 1.95 gm of a pale yellow solid residue. Chromatography of the residue over alumina, using hexane as an eluent, afforded 1.42 gm (65.2%) of 8a as a colorless, viscous oil, which crystallized on standing. Recrystallization from methanol/diethyl ether at room temperature provided pure 8a as white needles: mp. 65-66.5°C; TLC (30-60° pet. ether): R_F 0.72; ^{19}F NMR ($CDCl_3$): δ81.2 ($C\underline{F}_3CF_2$-, 3F), δ103.2-105.4 (=C$\underline{F}$O-Steroid, 'F' *cis* to 'R_f', 1F), δ115.6-116.6 (-$C\underline{F}_2$CF=, 2F), δ122.0-124.2 (-$C\underline{F}_2$-, 10F), δ126.2 ($CF_3C\underline{F}_2$-, 2F) and δ187.2-188.0 ($R_fC\underline{F}$=, 1F).

3β-(Perfluoro-*trans*-1-nonenyl-1-oxy)-cholest-5-ene (9)

To a solution of 1.00 gm (2.57 mmol) of cholest-5-ene-3β-ol in 10 mL of THF cooled in an ice bath was added 1.15 mL (3.0 mmol) of 2.6M n-BuLi solution in hexane. The mixture was stirred for 30 minutes at 0°C and for 3 hours at room temperature whereupon 0.80 mL (1.4 gm, 3.2 mmol) of perfluoro-1-nonene was added. The mixture was then stirred under nitrogen at room temperature for 12 hours. The work-up, as described for 8a + 8b (procedure-A), followed by chromatography of the residue on alumina, with hexane as an eluent, gave 1.36 gm (64.8%) of 9 as a white waxy solid. Recrystallization from methanol/diethyl ether gave pure 9 as a white, cotton-like solid: mp. 77-81°C; TLC (30-60° pet. ether): R_f 0.77; IR (KBr): 2953, 2869, 1747, 1160-1300, 1149, 1104 and 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ5.33 (d, J = 4.5 Hz, 1H, C_6-H), δ4.17 (m, 1H, C_3-H) and δ2.46 (d, 2H, C_4-H_2); ^{19}F NMR ($CDCl_3$): δ81.2 ($C\underline{F}_3CF_2$-, 3F), δ103.4-104.8 (=C$\underline{F}$O-steroid, 'F' *cis* to 'R_f', 1F), δ115.6-116.6 (-$C\underline{F}_2$CF=, 2F), δ122.2-123.8 (-$C\underline{F}_2$-, 8F), δ126.2 ($CF_3C\underline{F}_2$-, 2F) and δ187.0-188.2 ($R_fC\underline{F}$=, 1F).
Anal. Calcd. for $C_{36}H_{45}F_{17}O$: C, 53.0; H, 5.6; F, 39.5
Found: C, 52.8; H, 5.5; F, 39.6

3β-(Perfluoro-*trans*-1-heptenyl-1-oxy)-5α-cholestan (10)

In a manner similar to that described above (procedure-B), a solution of 0.515 gm (1.33 mmol) of 5α-cholestan-3β-ol (3) in 15 mL of THF was treated with 0.60 mL (1.6 mmol) of 2.6M n-butyllithium solution in hexane at 0°C. The mixture was stirred at 0°C for 20 minutes and at

room temperature for 3 hours. Perfluoro-1-heptene (0.40 mL, 0.90 gm, 2.1 mmol) was added and the mixture stirred at room temperature for 12 hours. The work-up, as described previously (procedure-A), followed by chromatography of the residue over silica gel (60-200 mesh), using 5% CH_2Cl_2/hexane as an eluent, gave 0.575 gm (60.2%) of 10. Recrystallization from methanol/diethyl ether at room temperature gave pure 10 as white star-like crystals: mp. 50.5-52°C; TLC (30-60° pet.ether): R_f 0.65; IR (KBr): 2944, 2869, 1741, 1160-1280, 1140, 1108 and 1065 cm^{-1}; ^1H NMR ($CDCl_3$): δ4.26 (m, 1H, C_3-H); ^{19}F NMR ($CDCl_3$): δ81.2 (CF_3CF_2-, 3F), δ103.6-104.8 (=CFOsteroid, 'F' *cis* to 'R_f', 1F), δ116.8 (-CF_2CF=, 2F), δ123.2-124.0 (-CF_2-, 4F), δ126.0 (CF_3CF_2-, 2F) and δ187.2-188.4 (=CF$\dot{R}_f$, 1F).

Anal. Calcd. for $C_{34}H_{47}F_{13}O$: C, 56.8; H, 6.6; F, 34.4
Found: C, 56.9; H, 6.7; F, 34.3

3β-(Perfluoro-*trans*-1-heptenyl-1-oxy)-pregn-5-ene-20-one (11)

In a manner simlar to that described above (procedure-B), a solution of 0.825 gm (2.60 mmol) of pregn-5-ene-3β-ol-20-one in 6 mL of THF was cooled in an ice bath and treated dropwise, over a period of 30 minutes, with 1.00 mL (2.45 mmol) of 2.45M n-BuLi solution in hexane. After stirring the mixture at 0°C for 30 minutes and at room temperature for 45 minutes, the contents were re-cooled and treated with 0.55 mL (1.0 gm, 2.8 mmol) of perfluoro-1-heptene. The mixture was then stirred at room temperature for 1 hour. The work-up, as described previously (procedure-A), followed by chromatography of the residue over silica gel using 50% hexane/CH_2Cl_2 as an eluent, afforded 0.980 gm (62.0%) of 11 as an opaque, viscous oil. Crystallization from methanol/water/diethyl ether at room temperature provided pure 11 as colorless needles: mp. 69.5-71°C; TLC (benzene): R_F 0.29; IR (KBr): 3005, 2971, 2945, 2856, 1743, 1698 (C=0), 1160-1280, 1142, 1107 and 1068 cm^{-1}; ^1H NMR ($CDCl_3$): δ5.41 (d, J = 4.5 Hz, 1H, C_6-H), δ4.22 (m, 1H, C_3-H), δ2.50 (d, J = 7.5 Hz, 2H, C_4-H_2), δ1.04 (s, C_{19}-H_3) and δ0.64 (s, C_{18}-H_3); ^{19}F NMR ($CDCl_3$): δ81.8 (CF_3CF_2-, 3F), δ103.4-104.6 (=CFOR, 'F' *cis* to 'R_f', 1F), δ115.8-116.6 (-CF_2CF=, 2F), δ123.2-124.0 (-CF_2-, 4F), δ126.6 (CF_3CF_2-, 2F) and δ187.2-188.4 (R_fCF=, 1F).

Anal. Calcd. for $C_{28}H_{31}F_{13}O_2$: C, 52.0; H, 4.8; F, 38.0
Found: C, 51.8; H, 4.8; F, 37.7

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