Selective Epoxidation of Olefins by Perfluoro-*cis*-2,3-dialkyloxaziridines[1]

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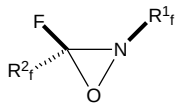
Alkyl-substituted olefins are epoxidized by perfluoro-*cis*-2,3-dialkyloxaziridines under particularly mild conditions. Electron deficient substrates (e.g. α,β-enones) can also be epoxidized, and the more electron poor the double bond is, the more severe the reactions conditions become. The epoxidation is chemoselective (secondary alcohols and their ethers do not interfere), site selective (the monoepoxide of a diene can be obtained), and stereoselective (*cis*-alkenes afford *cis*-epoxides). Various complex and polyfunctional substrates of natural origin (monoterpenes, sesquiterpenes, steroids) have been transformed effectively.

Introduction

The epoxidation of olefins is a particularly useful reaction from the synthetic point of view. Two carbon atoms are oxygenated in a single step, and high chemo-, regio-, and diastereoselectivities are often obtained.[2] Peroxides[3] and peracids[4] are classical epoxidizing reagents. Some metal peroxides and hydroperoxides (Mo, V, Ti, ...),[4,5] dioxiranes,[6] and *N*-sulfonyloxaziridines[7] are more recent epoxidizing agents which have emerged for their effectiveness, versatility, and selectivity. A common feature of these latter agents is that the active oxygen is part of a three-membered ring.

We are involved in an on going study of the oxidative properties of some new members of this class of reagents, namely perfluoro-*cis*-2,3-dialkyloxaziridines **1a,b**.[8] We



	R^1_f	R^2_f
1a	*n*-C_3F_7	*n*-C_4F_9
1b	*n*-C_5F_{11}	*n*-C_6F_{13}

have already reported how they can be usefully employed for the oxidation of various heteroatoms. Sulfides are transformed into sulfoxides or sulfones under mild conditions and with complete chemoselectivity,[9] pyridine derivatives afford corresponding *N*-oxides,[10] and silanes give silanols with very high enantioselectivity.[11] Also the oxidation of some carbon functionalities has already been described. For instance, both secondary alcohols[12] and their ethers[13] afford corresponding ketones in good yields, and more interestingly, nonactivated tertiary hydrocarbon sites are oxyfunctionalized with very high selectivities and in preparative scale.[14] With the aim to further test the synthetic usefulness of perfluoro-*cis*-2,3-dialkyloxaziridines, we have studied their reactivity toward several and structurally different carbon−carbon double bonds. We have already reported that enol ethers are epoxidized under particularly mild conditions, and this reaction has been used to obtain glycoconjugates starting from glycals.[15] Here we describe that less electron rich

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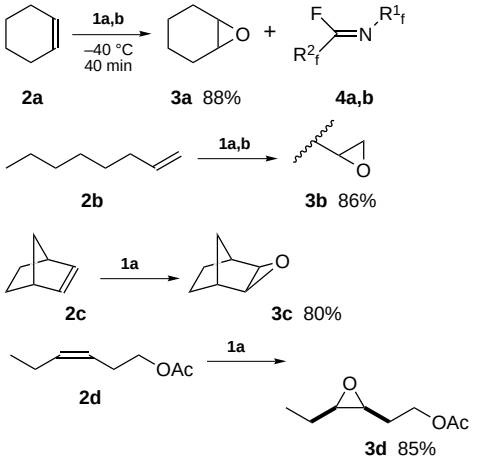
Scheme 1



olefins, such as those bearing alkyl or acyl residues, can also be epoxidized under mild conditions and the reaction can be successfully performed not only on simple, model compounds but also on complex, polyfunctional substrates of biological interest.

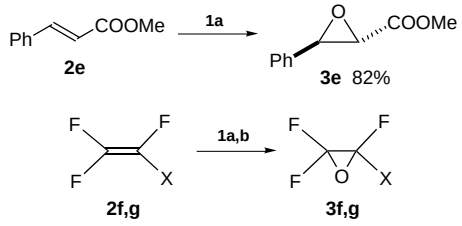
Results and Discussion

Synthetic Aspects. When cyclohexene (**2a**) and 1-octene (**2b**) are treated with a slight excess of perfluoro-*cis*-2-butyl-3-propyloxaziridine (**1a**) in dichloropentafluoropropane (HCFC-225ca,cb)/chloroform (1:1 mixture, −40 °C, 40 min), corresponding epoxides **3a,b** are isolated in 88% and 86% yield, respectively (Scheme 1). This solvent system has been preferred to the $CFCl_3/CHCl_3$ mixture commonly employed in previous studies[8−15] as it is more convenient from the environmental point of view. In fact, hydrochlorofluorocarbons have a definitively lower ozone-depleting effect than chlorofluorocarbons. Moreover, both oxaziridines **1a,b** and a wide range of olefins **2** have a good solubility in the HCFC-225ca,cb/$CHCl_3$ system so that epoxidations are performed under homogeneous conditions. Perfluorinated oxaziridines **1a,b** are not highly soluble in chlorinated solvents (CH_2Cl_2, $CHCl_3$, CCl_4, ...), and the same holds for hydrocarbon substrates **2** and chlorofluorocarbon solvents ($CFCl_3$, $CFCl_2CF_2Cl$, ...). When these solvents are employed, reaction mixtures are heterogeneous. Longer reaction times are thus required, but formed products are strictly similar to those obtained with the HCFC-225ca,cb/$CHCl_3$ system. When trifluoroacetic acid is used as a solvent, epoxidation occurs under homogeneous conditions, but in this case formed epoxides undergo *in situ* solvolyses and vicinal diols are isolated after a basic aqueous workup.

In the epoxidation of alkenes **2a,b** perfluoro-*cis*-2-hexyl-3-pentyloxaziridine (**1b**) behaved similarly to **1a** so that in all other experiments, unless otherwise stated, the oxaziridine **1a** has been employed. Through the monitoring of reactions performed in HCFC-225ca,cb/$CHCl_3$ solution with ^1H and ^{19}F NMRs, it has been possible to establish that (*Z*)-azaalkenes **4a,b** are the only formed "coproducts", similarly to what has already been observed in the oxidation of hydrocarbons,[14a] alcohols,[12] ethers,[13] and sulfides.[9a]

Epoxidation of norbornylene (**2c**) and *cis*-hexenyl acetate (**2d**) with **1a** is completely diastereoselective and

Scheme 2

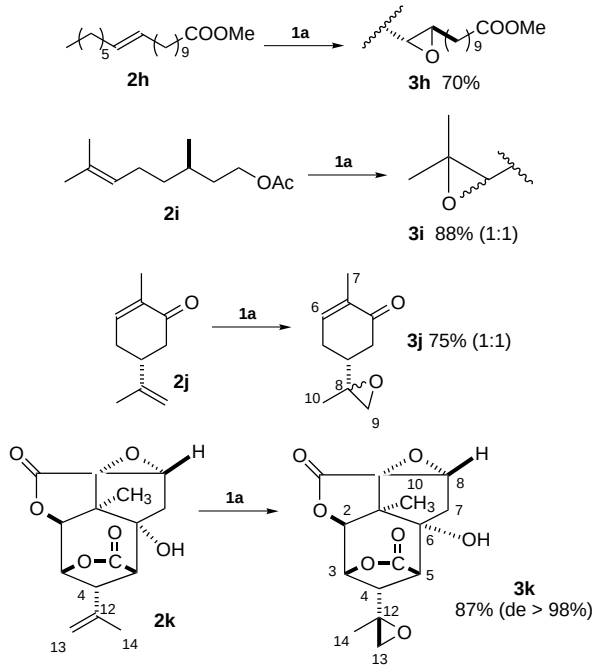


	X	Oxaziridine	Conditions	Yield (%)
2f	$(CH_3)_3Si$	**1b**	neat/rt/20 min	82
2g	Cl	**1a**	neat/100 °C/16 h	60

gives exclusively the *exo*-epoxide[16] **3c** and the *cis*-epoxide **3d** in good yields.

The presence of electron-withdrawing groups on the double bond does not prevent the epoxidation. *trans*-Methyl cinnamate (**2e**) gives diastereoselectively the corresponding *trans*-epoxide **3e** in 82% yield after 16 h at room temperature in CFC-11 solution and trifluoro-(trimethylsilyl)ethylene (**2f**) affords epoxide **3f** in 82% yield when reacted with an equimolar amount of the oxaziridine **1b** and without solvent (rt, 20 min) (Scheme 2). Even the particularly electron deficient chlorotrifluoroethylene oxide (**3g**) could be prepared (60% yield) but olefin **2g** had to be heated with a 30% molar excess of **1a** without solvent in a sealed tube at 100 °C for 16 h.

Scheme 3



After the ability of oxaziridines **1** to perform the epoxidation reaction of simple compounds had been shown, several polyfunctional substrates of natural origin were used in order to prove the synthetic usefulness of the reaction and to test selectivities and functional groups compatibilities. The methyl ester (**2h**) of *trans*-vaccenic

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(16) The two epoxide protons of **3d** exhibited the same chemical shift and the $^3J_{H-3,H-4}$ was established resorting to the ^{13}C satellite peaks. The value of the 4.2 Hz proves a *cis* configuration. By using the same methodology, the oxirane protons H-11 and H-12 of compound **3h** showed a coupling constant of 2.3 Hz, which indicates a *trans* relationship.

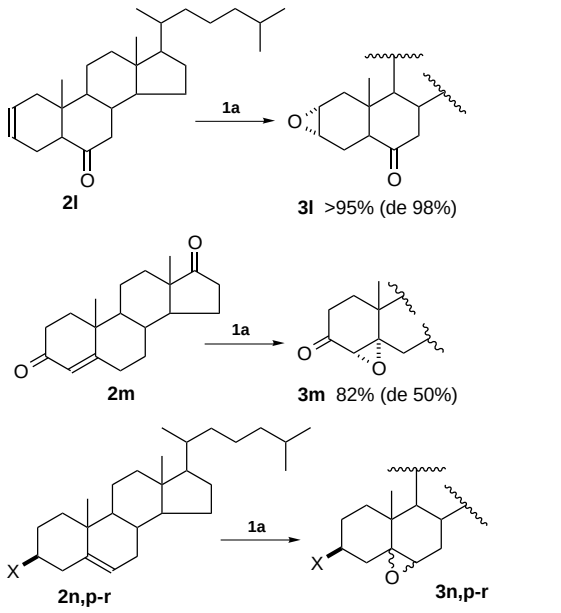
acid gives stereoselectively the *trans*-epoxide[16,17] **3h** in 5 min at −50 °C (Scheme 3). Starting from the monoterpenes (*R*)-*β*-citronellol acetate (**2i**) and (*R*)-carvone (**2j**), equimolar mixtures of two epimers are formed.[18,19] For this last substrate it is worth noting that when 1 equiv of oxaziridine **1a** at −40 °C was used, only the double bond of the isopropenyl chain reacts and the α,*β*-enone moiety remains unaffected. Oxaziridine **1a** attacks selectively the *si* face of the double bond of picrotoxinin (**2k**) and the epoxide having the (*R*) absolute configuration at the newly formed stereogenic centre is formed exclusively in 87% isolated yield.[20,21]

The epoxidation of several steroids has been performed successfully (Scheme 4). 2-Cholesten-6-one (**2l**) affords the α-epoxide[22,23] **3l** in quantitative chemical yields and with complete stereoselection when reacted at −45 °C for 5 min. A double bond is present in the A ring also of 4-androstene-3,17-dione (**2m**), and less mild reaction conditions are necessary for its epoxidation due to the fact it is a deactivated double bond. The corresponding oxiranes **3m** are obtained (α/*β* ratio 74:26)[24] when a molar excess of oxaziridine **1a** is used and the reaction is run at room temperature for 24 h.

Oxidation of several steroids having a double bond in the B ring has been studied. Cholesterol (**2n**) can in principle be oxidized at either the hydroxyl group[12] or the olefin double bond. However when the reaction has been performed at −40 °C with an equimolar amount of **1a**, the 5,6-epoxides **3n**[25,26] were isolated in 76% yield as a 67:33 mixture of α and *β* isomers. In stigmasterol (**2o**) an additional olefin double bond is present (Scheme 5), but the preferential attack of the C_5-C_6 double bond remains unchanged, and by interrupting the oxidation at 75% conversion, the 5,6-epoxides[26,27] could be isolated as major reaction products (44% yield, α/*β* ratio 63:37). As expected, cholesteryl acetate,[25,26] benzoate,[26,28] and chloride[26,29] (**2p**,**q**,**r**, respectively) gave cleaner reactions and the diastereoface selectivity is opposite to that observed with cholesterol and stigmasterol, epoxidation occurring preferentially from the *β* face. A similar behavior was shown by diosgenin acetate (**2s**) which afforded the 5,6-epoxides[26,30] in 80% isolated yield and as a 5:95 mixture of α and *β* isomers.

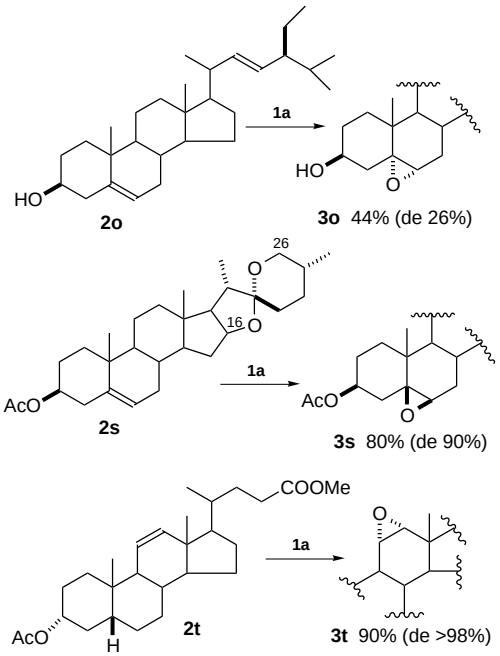
Oxidation of a steroid having a double bond in the C ring was finally studied. The 5*β*-$\Delta^{11,12}$-cholenic acid derivative **2t** was epoxidized in high yields, and the α-epoxide was exclusively obtained.[23]

Scheme 4



	X	Yield (%)	Solvent	α/β ratio
3n	OH	76	HCFC-225ca,cb	67:33
3p	AcO	84	HCFC-225ca,cb/$CHCl_3$ = 1:1	17:83
3q	BzO	81	$CHCl_3$	7:93
3r	Cl	92	CH_2Cl_2	32:68

Scheme 5



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(21) The absolute configuration and preferred conformation of picrotoxinin epoxide **3k** were established with NOE evidence (experimental). In fact, irradiation of H_3-14 enhanced both H-2 and H-3 (1.5%) but not H-5 and OH-6, indicating that the methyl is positioned on the left side of the molecule as depicted in Scheme 3. Moreover, NOEs were observed between H-13*β* and H-4 (1%), H-5 (4.5%), and OH-6 (7.5%), but not with H_3-10, and this shows that the 13-methylene group points to the front side of the molecule. The downfield shift experienced by OH-6 ($\Delta\delta = 2.5$) in comparison with the corresponding resonance in the starting compound **2k** reveals the presence of a hydrogen bond between the hydroxy proton and the newly formed epoxide oxygen, and this observation further supports the conformational assignments made through NOEs data. Differently, in compound **2k** the preferred conformation around the C-4 and C-12 bond was evidenced as depicted in Scheme 3 by the mutual NOEs observed between H-2 and H-13b (3.5 and 5%) and between H-5 and H_3-14 (4.5%) together with the lack of sizeable NOEs between H-5 and H_2-13 and between H-2 and H_3-14.
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(26) The stereochemistry of 5,6-epoxy steroids **3n**−**s** was established from the behavior of the H-6 resonance, which is known to appear as a doublet at 2.9 ppm ca. ($J \simeq 4$ Hz) in the α isomer and as a doublet at 3.1 ppm ca. ($J \simeq 2$ Hz) in the *β* isomer (refs 28, 29).
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Considerations on Selectivity. Some general comments can be made on moving from the above described results. In general the reactivity of perfluorooxaziridines recalls that of dioxiranes and sulfonyloxaziridines.[8] No quantitative comparison has been performed on the relative reactivity of the three types of reagents in epoxidations, nevertheless the set of performed experiments allows us to state that methyl(trifluoromethyl)-dioxirane[31] seems to require milder epoxidizing conditions than perfluorinated oxaziridines **1**, and the opposite is true for dimethyldioxirane and *N*-sulfonyloxaziridines. For instance, cyclohexene **2a**[32] and norbornene **2c**[33] are oxidized by *in situ* generated dimethyldioxirane at 0−5 °C in 2 h, and oxide **3b** is obtained in 42% yield when 1-octene **2b** is reacted with 2-(phenylsulfonyl)-3-(4-nitrophenyl)oxaziridine for 72 h at 60 °C.[34] These three substrates are epoxidized by perfluorinated oxaziridines **1** at −40 °C in less than 40 min.

It is not surprising that the presence of tertiary hydroxy groups (**2k**), of ketone and ester residues (**2d,e,h−m,p,q,s,t**), and of halogen and oxirane functionalities (**2k,r**) does not interfere with the epoxidation reaction. It is more interesting to observe that while oxaziridine **1a** is able to oxidize 3-hydroxy steroids into corresponding ketones,[12] the 3β-hydroxy group of cholesterol **2n** and stigmasterol **2o** remains unaffected during the epoxidation reaction. Moreover, several 5β-steroids have been oxyfunctionalized to the corresponding 5β-hydroxy products.[14b] This has been described also for 3α-hydroxy-5β-cholanic acid 3-acetate, but the $\Delta^{11,12}$ derivative of this compound (**2t**) gives the corresponding 11α,12α-epoxide **3t**, with no concomitant attack at C-5 being observed. The transformation of ethers of secondary alcohols into corresponding ketones has been reported in different classes of steroids,[13] but C-16 and C-26 positions have not been attacked during the epoxidation of diosgenin acetate **2s**. In general, it can therefore be concluded that oxidation of a secondary alcohol and oxyfunctionalization of a nonactivated tertiary hydrocarbon site or an ether moiety do not interfere with the epoxidation of a double bond as this last reaction occurs usually at definitively lower temperature.

Differently, oxaziridines **1** transform vinyl and allyl sulfides into corresponding alkenyl sulfoxides,[9a,c] and alkenyl-substituted nitrogen heteroaromatics give alkenyl *N*-oxides.[10a] In these cases oxidation at the heteroatomic site is preferred over epoxidation.

Mono-, di-, and trialkyl-substituted olefins can all be epoxidized, and the reaction is stereospecific with retention as shown by cinnamic and vaccenic esters **2e** and **2h**. When the double bond bears electron-withdrawing residues, as is the case with **2e−g** and **2m**, epoxidation reaction is retarded. This behavior is a further[9a,c,13] argument for an electrophilic O atom transfer by oxaziridines **1**. Epoxidation of carvone **2j** shows how this electrophilic character can be exploited for the selective attack of an isolated double bond in the presence of an α,β-enone moiety. Another particularly interesting example of selective attack of one double bond in a diunsaturated substrate is epoxidation of stigmasterol **2o**. The C_5-C_6 position of this compound is attacked with preference to the $C_{22}-C_{23}$ position, and this behavior might be rationalized, suggesting that epoxidation with **1a** is sensitive enough to the electron density of the double bond to show a clear preference for the more electron rich trialkyl-substituted olefin with respect to the dialkyl-substituted one. Alternatively, we think that several different parameters can control the selective epoxidation of a poly-unsaturated substrate, and the selectivity observed on **2o** results from the complex stereoelectronic effects associated with the overall structure of the steroid.

In general the diastereoselectivity of epoxidation depends on the conformational and configurational constrain of the substrate. When stereogenic centers are far away from the double bond and free rotation is possible, as in citronellol **2i** and carvone **2j**, the two possible epimers are formed in equimolar amounts. Differently, when access to the double bond is biased by the rigidity of the system, complete diastereoselection can be obtained. The fused polycyclic array of picrotoxinin **2k** prevents free rotation of the isopropenyl chain around the C_4-C_{12} bond, and the preferred conformation is that reported in Scheme 3 as determined through ^{1}H NOE experiments. In this conformation the *si* face of the double bond of the isopropenyl chain is directed toward the *exo* part of the polycyclic system and is definitively more accessible to an incoming reagent than the *re* face. Oxaziridine **1a** attacks only this face, and the (*R*)-epoxide is formed exclusively. It is worth noting that *m*-chloroperbenzoic acid (MCPBA) gave a 5:2 mixture of the two epimers.[20] This lower diastereoselection can be due to the fact that **1a** is more sterically demanding than MCPBA and it is thus unable to attack the double bond from the *re* face which is directed toward the concave side of the molecule.

Both 2-cholesten-6-one **2l** and 5β-$\Delta^{11,12}$-cholenic ester **2t** afford only α-epoxides **3l,t**, and this may be attributed to the shielding of the β side by CH_3-18 and CH_3-19.

Many reagents have been tested in the oxidation of cholesterol **2n** and its derivatives **2p−s**, and quite different results have been obtained. The α-epoxide of cholesterol **2n** is formed in 60% excess when magnesium monoperoxyphthalate (MMPP)[3d] is employed, while it is the only formed isomer by using MCPBA[35] or urea−hydrogen peroxide in the presence of anhydrides.[36] Differently, the β isomer is formed preferentially or exclusively when oxygen is used under catalyses of manganese complexes (de 64%)[28] and nickel[37] and ruthenium[38] porphirines (de 26% and quantitative, respectively). Finally, dimethyldioxirane gives an equimolar mixture of the two epimers.[39] The same overall trends have been described for cholesterol acetate and benzoate **2p,q**.[3d,28,36−40] The diversity of results summarized above imply that ob-

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served diastereoselection is the subtle balance of several factors.[41] A distinctive feature of the behavior of oxaziridines **1** is the unique difference of diastereoface selectivity changing from 3-hydroxysteroids **2n,o**, affording preferentially the α-epoxide, to their analogues **2p**−**r**, which bear an ester or chloride residue in the same position and give mainly the β epimer.

A pronounced influence of solvent on diastereoselectivity of epoxide formation by dimethyldioxirane has been described,[41] and we have therefore studied this influence on some of our substrates. No change of diastereoselectivity is observed with carvone **2j**. The β-epoxide **3q** is obtained in 86 and 74% excess when benzoyl cholesterol **2q** is reacted in chloroform and methylene chloride, respectively. The β-epoxide **3r** is formed in 36 and 14% excess when methylene chloride and trichlorotrifluoroethane are used with cholesteryl chloride **2r**. Other solvents and solvent mixtures have been tested, and results are reported in the Experimental Section.

Conclusions

Perfluoro-*cis*-2,3-dialkyloxaziridines **1** are shown to epoxidize effectively several and structurally different olefins. Alkyl-substituted double bonds react under particularly smooth conditions (−40 °C, 30 min). Mildly and strongly electron deficient substrates can also be oxidized, and the more electron poor the double bond is, the more severe the reaction conditions become. The reaction occurs stereoselectively as *cis*- and *trans*-olefins afford corresponding *cis*- and *trans*-epoxides, respectively.

Both aprotic (halogenated hydrocarbons) and protic solvents (trifluoroethanol and *tert*-butyl alcohol and their mixtures) can be used, and this allows a wide range of substrates to be oxidized in homogeneous reaction conditions. The presence of some functional groups which are known to be oxidized by oxaziridines **1**, notably secondary alcohols and their ethers, does not interfere with epoxide formation. The selective transformation of a single double bond in a di-unsaturated substrate is also possible. On some substrates the diastereoselectivity obtained with oxaziridines **1** was higher than that obtained by using hydrogen peroxide,[36] MCPBA,[20,28] or dioxiranes,[39] and this is probably related to the higher steric requirements of these reagents.

Experimental Section

Oxaziridines **1a,b** have been prepared in two steps from perfluorotri-*n*-butyl- and -tri-*n*-hexylamine.[42] Dichloropentafluoropropane was a 43:56 mixture of HCFC-225ca and HCFC-225cb ($CF_3CF_2CHCl_2$ and $CClF_2CF_2CHClF$, respectively), purchased from PCR Incorporated. Analytical instruments employed and spectral data format are described in ref 9a. New compounds gave correct analytical data (C ± 0.3; H ± 0.4).

General Procedure for the Preparation of Cyclohexene Oxide (3a) with Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (1a). To a solution of cyclohexene (100 mg, 1.2 mmol) in $CHCl_3$ was added, under nitrogen, a solution of the oxaziridine **1a** (647 mg, 1.4 mmol) in HCFC-225ca,cb at −40 °C. After the mixture was stirred for 40 min at the same temperature, the reaction was quenched by the addition of saturated aqueous solution of ammonium chloride. The mixture was stirred and then allowed to warm to room temperature. The aqueous layer was extracted with CH_2Cl_2, and combined organics were evaporated. The residue was distilled to give the corresponding epoxide **3a** (106 mg, 88% yield), which was identified through comparison of its spectral and physical data with those reported in the literature.[43]

1,2-Cyclohexanediol. To a solution of cyclohexene (100 mg, 1.2 mmol) in trifluoroacetic acid (2 mL) was added dropwise at −40 °C a solution of **1a** (647 mg, 1.4 mmol) in the same solvent. After 30 min of stirring at the same temperature, the reaction mixture was evaporated, the residue was dissolved in methanol (2 mL), and sodium methylate (45 mg) was added. The reaction mixture was stirred for 3 h at room temperature, one drop of trifluoroacetic acid was then added, and the mixture was evaporated under reduced pressure. Flash chromatography of the residue afforded 114 mg of 1,2-cyclohexane diol (82% yield).

1-Octene oxide (3b):[44] reaction conditions, $CHCl_3$/HCFC-225ca,cb = 1:1, −40 °C, 40 min; 86% yield.

***exo*-Norbornylene oxide (3c):**[33] reaction conditions, $CHCl_3$/HCFC-225ca,cb = 1:1, −40 °C, 40 min; 80% yield.

***cis*-3,4-Epoxyhexan-1-ol acetate (3d):** reaction conditions, $CHCl_3$/HCFC-225ca,cb = 1:1, −60 °C, 20 min; 85% yield; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, *J* = 7.4), 1.40−2.00 (m, 4H), 2.07 (s, 3H), 2.92 and 3.03 (dt, 2H, *J* = 4.2, 6.1), 4.10−4.40 (m, 2H); IR (KBr) 1041, 1241, 1744, 2973; MS (EI) *m*/*z* 158 (M).

***trans*-Methyl cinnamate oxide (3e):**[45] reaction conditions, CFC-11, rt, 16 h; 82% yield.

Trifluoro(trimethylsilyl)ethylene oxide (3f): reaction conditions, neat, rt, 20 min; 82% yield; ^{19}F NMR ($CDCl_3$) δ −147.8 (dd, 1F, *J* = 26, 9), −114.8 (dd, 1F, *J* = 50, 26), −104.9 (dd, 1F, *J* = 50, 9); IR (gas) 756, 853, 911, 1030, 1110, 1262, 1499, 2974; MS (EI) *m*/*z* 170 (M).

Chlorotrifluoroethylene oxide (3g): reaction conditions, 30% molar excess of **1a**, neat, 100 °C, 16 h; 60% yield; ^{19}F NMR ($CDCl_3$) δ −114.2 (dd, 1F, *J* = 32, 15), −109.6 (dd, 1F, *J* = 32, 19), −94.3 (dd, 1F, *J* = 19, 15); MS (EI) *m*/*z* 132.5 (M).

***trans*-Vaccenic acid methyl ester 11,12-oxide (3h):** reaction conditions $CHCl_3$/HCFC-225ca,cb = 1:1, −50 °C, 5 min; 70% yield; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 6.7), 1.25−1.65 (m, 26H), 2.30 (t, 2H, *J* = 7.5), 2.66 (m, 2H, $J_{11,12}$ = 2.3, H-11 and -12), 3.67 (s, 3H); IR (KBr) 1741, 2854, 2930; MS (CI, CH_4) *m*/*z* 313 (M + 1).

***(R)*-Citronellol acetate oxides (3i):**[18] reaction conditions, HCFC-225ca,cb, −40 °C, 20 min; 88% yield; diastereoisomer ratio 1:1 by GC (SPB-1 fused silica capillary column, 30 m × 0.25 mm (id), df 1 μm, 20 min, 140 °C).

Carvone 8,9-oxides (3j): reaction conditions, HCFC-225ca,-cb, −40 °C, 30 min; 75% yield; diastereoisomer ratio 1:1 by GC (OV-1 fused silica capillary column, 25 m × 0.25 mm (id), df 0.25 μm, 110 °C); ^{1}H NMR ($CDCl_3$) δ 1.31 and 1.33 (broad s, 2 × 3H), 1.78 (broad s, 2 × 3H), 2.58 and 2.60 (d, 2 × 1H, *J* = 4.5), 2.67 and 2.71 (broad d, 2 × 1H, *J* = 4.5), 6.73 (m, 1H); IR (film) 1674, 2927, 3461; MS (EI), *m*/*z* 166 (M). Other solvents ($CFCl_3$, CH_2Cl_2, CCl_4, $CHCl_3$, $CHCl_3$:*t*-BuOH = 1:1, $CF_2ClCFCl_2$) required similar reaction conditions and gave similar yields.

Picrotoxinin oxide (3k): reaction conditions, $CHCl_3$/HCFC-225ca,cb = 1:1, rt, 1 h; 87% yield; de > 98%; mp 189−191 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H, H_3-10), 1.55 (s, 3H, H_3-14), 2.11 (broad d, 1H, *J* = 15.3, H-7α), 2.61 (d, 1H, *J* = 4.2, H-5), 2.84 (d, 1H, *J* = 3.8, H-13α), 2.86 (dd, 1H, *J* = 15.3, 3.5, H-7β), 2.99 (broad d, 1H, *J* = 3.8, H-13β), 3.39 (dd, 1H, *J* = 5.3, 4.2, H-4), 3.71 (d, 1H, *J* = 3.5, H-8), 4.59 (d, 1H, *J* = 3.2, H-2), 4.75 (broad s, 1H, OH-6), 5.02 (dd, 1H, *J* = 5.3, 3.2, H-3); NOEs irradiation of H-2 enhanced H-3 (4%), H_3-10 (1.5%), and H_3-14 (1.5%); {H-3} enhanced H-2 (5%), H-4 (3.5%), and H_3-14 (1.5%); {H-4} enhanced H-3 (5%), H-5 (4.5%), H-13β (1%), and H_3-14 (1%); {H-5} enhanced H-4 (4%), H-7β (3%), H-13β (3%), and OH-6 (2%); {H-13β} enhanced H-4 (1%), H-5 (4.5%), H-13α (20.5%), and OH-6 (7.5%); {OH-6} enhanced H-5

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(2.5%), H-7α (1%), H-13β (5.5%), and H_3-10 (1.5%); IR (KBr): 1797, 3405; MS (CI, CH_4) *m/z* 309 (M + 1); $[\alpha]^{25}_D$ (*c* 1, $CHCl_3$) −73.9.

Picrotoxinin (2k): NOEs, irradiation of H-2 enhanced H_3-10 (1.5%) and H-13b (3.5%); {H-13b} enhanced H-3, H-13a (13.5%) and H-2 (5%); {H_3-14} enhanced H-4 (3.5%), H-5 (4.5%), and H-13a (2.5%).

2,3-Epoxy-5α-cholestan-6-one (3l): reaction conditions, HCFC-225ca,cb, −45 °C, 5 min; >95% yield; de > 98%; mp 128−130 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.65 (s, 3H, H_3-18), 0.71 (broad s, 3H, H_3-19), 1.73 (broad d, 1H, *J* = 15.2, H-1α), 1.95 (dd, 1H, *J* = 15.2, 5.8, H-1β), 2.01 (ddd, 1H, *J* = 15.9, 11.6, 2.0, H-4β), 2.10 (ddd, 1H, *J* = 15.9, 4.7, 2.0, H-4α), 2.36 (broad dd, 1H, *J* = 11.6, 4.7, H-5α), 3.11 (broad dd, 1H, *J* = 5.8, 4.0, H-2), 3.26 (broad ddd, 1H, *J* = 4.0, 2.0, 2.0, H-3); IR (KBr) 1712, 2951, 3448; MS (EI) *m/z* 400 (M); $[\alpha]^{25}_D$ (*c* 1, $CHCl_3$) −1.8.

4,5-Epoxyandrostane-3,17-diones (3m):[24] reaction conditions, HCFC-225ca,cb/$CHCl_3$ = 1:1, rt, 24 h; 82% yield, α/β = 74:26.

5,6-Epoxycholestan-3β-ols (3n):[28,46] reaction conditions, HCFC-225ca,cb, −40 °C, 30 min; 76% yield, α/β = 67:33.

5,6-Epoxystigmasterols (3o): reaction conditions, $CHCl_3$/HCFC-225ca,cb = 1:1, −40 °C, 30 min; 44% yield; α/β = 63:37; ^{1}H NMR ($CDCl_3$) δ 2.90 and 3.06 (d, 2 × 1H, *J* = 4.4, 2.2, H-6β and -6α), 3.69 and 3.91 (m, 2 × 1H, H-3α), 5.01 and 5.20 (dd, 2H, *J* = 15.2, 8.1, H-22 and -23); IR (KBr) 1460, 2956, 3436; MS (EI), *m/z* 428 (M).

5,6-Epoxycholestan-3β-ol acetates (3p):[47] reaction conditions, $CHCl_3$/HCFC-225ca,cb = 1:1, −40 °C, 30 min; 84% yield, α/β = 17:83.

5,6-Epoxycholestan-3β-ol benzoates (3q):[28] reaction conditions, HCFC-225ca,cb, −10 °C, 30 min; 81% yield; α/β = 8:92. Other solvents required similar reaction conditions and gave similar yields ($CHCl_3$, α/β = 7:93; $CHCl_3$:*t*-BuOH = 9:1, α/β = 8:92; $CFCl_2CF_2Cl$, α/β = 9:91; CH_2Cl_2, α/β = 13:87).

3β-Chloro-5,6-epoxycholestanes (3r):[29] reaction conditions, $CHCl_3$/HCFC-225ca,cb = 1:1, −10 °C, 30 min; 92% yield; α/β = 42:58. Other solvents required similar reaction conditions and gave similar yields (CH_2Cl_2, α/β = 32:68; $CHCl_3$, α/β = 38:62; $CFCl_2CF_2Cl$, α/β = 43:57).

(25*R*)-5,6-Epoxy-3β-acetoxyspirostanes (3s): reaction conditions, HCFC-225ca,cb, −40 °C, 30 min; 80% yield; α/β = 5:95; ^{1}H NMR ($CDCl_3$) δ 2.88 (d, 1H, *J* = 4.4, H-6β), 3.07 (d, 1H, *J* = 2.3, H-6α), 3.36 and 3.46 (m, 2H, H_2-26), 4.39 (m, 1H, H-16), 4.78 and 4.94 (m, 2 × 1H, H-3α); IR (KBr) 1243, 1731, 2954; MS (EI) *m/z* 472 (M).

11α,12α-Epoxy-3α-hydroxy-5β-cholanic acid acetate methyl ester (3t): reaction conditions; HCFC-225ca,cb, 0 °C, 20 min; 90% yield; de > 98%; mp 130−131 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.77 (s, 3H, H_3-18), 0.99 (s, 3H, H_3-19), 2.02 (s, 3H), 2.94 (broad d, 1H, H-11β), 3.12 (broad d, 1H, H-12β), 3.66 (s, 3H), 4.72 (m, 1H); IR (KBr) 1209, 1733, 2870, 2951; MS (CI, CH_4) *m/z* 447 (M + 1).

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