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Fluorine-Decoupled Carbon Spectroscopy for the Determination of Configuration at Fully Substituted, Trifluoromethyl- and Perfluoroalkyl-Bearing Carbons: Comparison with $^{19}F-^{1}H$ Heteronuclear Overhauser Effect Spectroscopy

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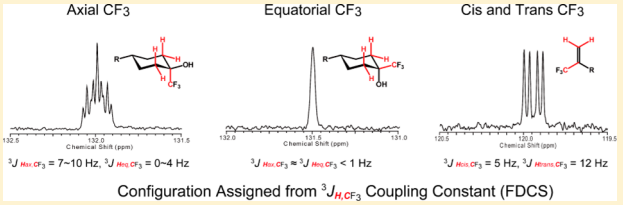
Supporting Information

ABSTRACT: The synthesis of a series of α-trifluoromethylcyclohexanols and analogous trimethylsilyl ethers by addition of the Ruppert–Prakash reagent to substituted cyclohexanones is presented. A method for the assignment of configuration of such compounds, of related α-trifluoromethylcyclohexylamines and of quaternary trifluoromethyl-substituted carbons is described based on the determination of the $^{3}J_{CH}$ coupling constant between the fluorine-decoupled $^{13}CF_3$ resonance and the vicinal hydrogens. This method is dubbed fluorine-decoupled carbon spectroscopy and abbreviated FDCS. The method is also applied to the configurational assignment of substances bearing mono-, di-, and perfluoroalkyl rather than trifluoromethyl groups. The configuration of all substances was verified by either $^{19}F-^{1}H$ heteronuclear Overhauser spectroscopy (HOESY) or X-ray crystallography. The relative merits of FDCS and HOESY are compared and contrasted. $^{2}J_{CH}$, $^{3}J_{CH}$, and $^{4}J_{CH}$ coupling constants to ^{19}F decoupled CF_3 groups in alkenes and arenes have also been determined and should prove to be useful in the structural assignment of trifluoromethylated alkenes and arenes.



INTRODUCTION

The long-appreciated beneficial properties of the trifluoromethyl group in medicinal chemistry[1−6] and the imperatives of green chemistry provide the impetus for the current resurgence of interest in the development of trifluoromethylation methods.[7−36] The ability to produce ever more complex trifluoromethylated substances gives rise to the need for efficient methods to unambiguously assign their constitution, configuration, and conformation. Current projects in our laboratory necessitated the synthesis and configurational assignment of pairs of diastereomeric α-trifluoromethylcyclohexanols and related compounds. While such compounds may be readily accessed by reaction of the Ruppert–Prakash reagent[37,38] or other systems delivering a nucleophilic CF_3 moiety[39−45] with cyclohexanones, it became apparent that assigning the configuration relative to an existing stereogenic center in such compounds is not straightforward in the absence of crystals suitable for X-ray analysis. Thus, in previous work, the relative configuration of diastereomeric pairs of α-trifluoromethyl tertiary alcohols, if assigned at all, was based on considerations of relative polarities, differences in IR stretching frequencies of the OH group, NMR chemical shift differences of the tertiary alcohols or of their derivatives, NOE measurements of derivatives, and considerations of inherent face selectivity in the precursors.[46−51] To address this problem, we considered two potential solutions: (i) the application of heteronuclear NOE-type experiments (HOESY) between the CF_3 group and proximal substituents and (ii) the Karplus-type correlation[52−55] of the dihedral angle (φ) subtended by the CF_3 group and axial or equatorial hydrogen atoms at the vicinal position (**H**-C-C-**C**F_3) with the $^{3}J_{CH}$ heteronuclear coupling constants (Figure 1). Heteronuclear $^{3}J_{CH}$ coupling constants are widely applied in carbohydrate chemistry for the determination of glycosidic bond and hydroxymethyl group torsion angles[56−62] and also enable the determination of torsion angles about CC–OH bonds.[63] However, with the exception of their use for the configurational assignment of sialic acid

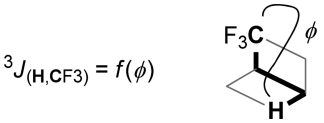


Figure 1. Variation of vicinal ^{3}J heteronuclear $^{13}C-^{1}H$ couplings with the dihedral angle.

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glycosides,[64−68] heteronuclear $^3J_{CH}$ coupling constants do not find wide application in the conformational analysis of cyclic systems.[69−72] We report here on the successful development of a straightforward $^3J_{CH}$ heteronuclear coupling method for the determination of configuration in trifluoromethylated tertiary alcohols and related compounds that we believe will also be of use in determining the relative configuration of a broad range of CF_3-bearing quaternary centers. We also report related vicinal $^{13}C-^1H$ coupling constants in olefinic systems, which should apply in the assignment of configuration of trifluoromethyl alkenes.

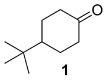
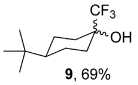
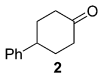
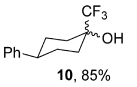
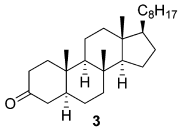
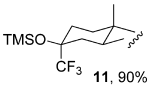
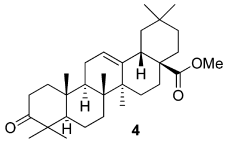
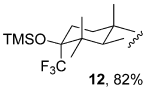
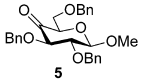
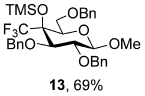
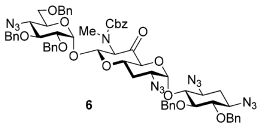
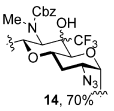
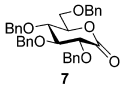
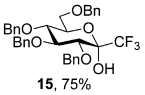
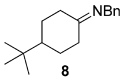
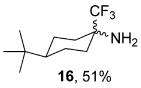
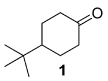
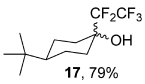
RESULTS AND DISCUSSION

Synthesis. Reaction of the Ruppert−Prakash reagent with a series of representative cyclohexanones **1**−**6** in the presence of either tetrabutylammonium fluoride or cesium fluoride gave rise to the α-trifluoromethylated cyclohexanols or the corresponding trimethylsilyl ethers **9**−**14** with the yields and selectivities listed in Table 1, entries 1−6. Similarly, reaction of the Ruppert−Prakash reagent with gluconolactone **7** gave ketose **15** (Table 1, entry 7). Reaction of the Ruppert−Prakash reagent with imine **8**, formed in situ from 4-*tert*-butylcyclohexanone and benzylamine[73,74] followed by hydrogenolysis, gave diastereoisomeric α-trifluoromethylamines **16** (Table 1, entry 8). Reaction of pentafluoroethyltrimethylsilane[75] with 4-*tert*-butylcyclohexanone catalyzed by tetrabutylammonium fluoride gave α-pentafluoroethyl 4-*tert*-butylcyclohexanols **17** (Table 1, entry 9).

In addition, a diastereomeric mixture of two steroids **19** containing a quaternary carbon, in which one of the four ligands is a trifluoromethyl group, was prepared as described by Blazejewski and co-workers[47] by radical reaction of allyltrimethylstannane[76] with *S*-methyl xanthate ester **18** derived from tertiary trimethylsilyl ether **11** (Scheme 1).

Stereoselectivity in the Addition of the Trifluoromethide Anion to Cyclohexanones and 1,5-Lactones. Although it is not the primary focus of this Article, it is noteworthy and bears comment that kinetically controlled reaction of the Ruppert−Prakash reagent with five of the six cyclohexanones studied is selective for the formation of the axial trifluoromethyl derivatives. The use of both 4-*tert*-butyl and 4-phenylcyclohexanone as substrate gave approximate 4:1 mixtures of adducts favoring introduction of the CF_3 group syn to the remote substituent, with the products retaining essentially undistorted chair conformations in the solution phase, as determined by analysis of the ^1H NMR spectra, despite the axial location of the bulky CF_3 group. Previously, the major product from the reaction with 4-phenylcyclohexanone was assigned the opposite configuration (CF_3 trans to phenyl) on the basis of chemical shift differences in the derived xanthate esters of the two isomers.[48] In view of this discrepancy and in support of the FDCS NMR method discussed below, we obtained an X-ray crystal structure of the major isomer from reaction with 4-phenylcyclohexane (Supporting Information and CCDC 1032684), which confirms its chair conformation and the axial location of the CF_3 group. The CF_3−C1 bond adopts a perfectly staggered conformation in this structure. This assignment corrects the earlier literature,[48] focuses attention on the ambiguities arising from the assignment of configuration in such α-trifluoromethyl tertiary alcohols on the basis of chemical shift arguments alone, and underlines the need for unambiguous methods for assignment of configuration that are preferably based on the analysis of coupling constants.

Table 1. Synthesis of α-Trifluoromethylated Cyclohexanols, Amines, Trimethylsilyl Ethers, and Related Substances by Reaction of Perfluoroalkyl Trimethylsilanes with Ketones and an Imine

Entry	Substrate	Product,[a] yield	ax CF_3:eq CF_3
1[b]	 **1**	 **9**, 69%	4:1
2[b]	 **2**	 **10**, 85%	4:1
3[c]	 **3**	 **11**, 90%	ax only
4[c]	 **4**	 **12**, 82%	ax only
5[d]	 **5**	 **13**, 69%	eq only
6[d]	 **6**	 **14**, 70%	3:1
7[d]	 **7**	 **15**, 75%	eq only
8[e]	 **8**	 **16**, 51%	1:1
9[f]	 **1**	 **17**, 79%	7:3

[a]All reactions, with the exception of entry 9, were conducted with 2.0 equiv of $TMSCF_3$ in THF in the presence of 0.1 equiv of either TBAF or CsF. [b]Promoted with TBAF and worked up with 6 N HCl. [c]Promoted with TBAF. [d]Promoted with CsF and worked up with 2 equiv of TBAF. [e]Promoted with 0.8 equiv of KHF_2 and 1.5 equiv of $TMSCF_3$ in acetonitrile, followed by hydrogenolysis over Pd/C in MeOH. [f]3.0 equiv of $TMSCF_2CF_3$ in THF in the presence of 0.3 equiv TBAF was employed.

In their original report on the reaction of trifluoromethyltrimethysilane with aldehydes and ketones, Prakash and coworkers noted the formation of a single, but unassigned, diastereomeric product in the reaction with cholestanone **3**.[38] Subsequent workers reported a 96:4 ratio of isomers favoring the 3α-CF_3 epimer, but they did not provide any basis for the attribution of configuration.[47] In our hands, a single diastereomer **11** was formed (Table 1, entry 3), to which we assign the 3α-CF_3 configuration on the basis of the FDCS method discussed below and which is further confirmed by

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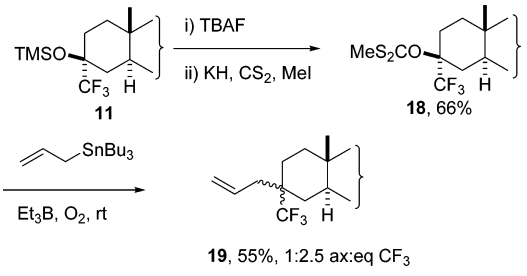
Scheme 1. Preparation of a CF_3-Bearing Quaternary Center



HOESY. Similarly, triterpenoid methyl ester **4** gives a single isomer of adduct **12** with an axial CF_3 group (Table 1, entry 4), as determined by FDCS and confirmed by the HOESY relationship of the CF_3 group to a single of the two vicinal methyl groups. The glucopyranose-4-one derivative **5** reacts in a highly selective manner with the Ruppert–Prakash reagent, but it affords galacto-configured trimethylsilyl ether **13** with the equatorial CF_3 group (Table 1, entry 5). The configuration of this derivative was assigned by the FDCS method below and is confirmed by NOESY correlations between the trimethylsilyl methyl groups and the axial hydrogen at position 2 as well as by HOESY correlations between the CF_3 group and the axial hydrogens at positions 3 and 5. With apramycinone derivative **6**, as reported previously,[77] a return to axial selectivity is observed (Table 1, entry 6), as confirmed by HOESY measurements.

The axial selectivity observed for the introduction of the CF_3 group into cyclohexanones **1**–**4** and **6** is interesting in view of the steric bulk of the CF_3 group itself (Steric A value 2.37)[78] and, more pertinently, of the presumed pentacoordinate species (R_2CO-$SiMe_3$-CF_3^- or F-$SiMe_3$-CF_3^-)[38,79] that transfers the CF_3 group to the ketone. Presumably, this selectivity arises from the coordination/activation of the ketone to the trimethylsilyl group of the Ruppert–Prakash reagent, as suggested by Prakash and Yudin;[79] in much the same way, the facial selectivity of alkyllithium attack on cyclohexanones can be reversed from the equatorial face to the axial face by complexation of the ketone with sterically bulky Lewis acids.[80] The equatorial selectivity observed in the formation of **13** is consistent with that observed for the addition of the bulky trichloromethide anion to **13** and it is α-anomer[81] and for the reduction of the permethyl analogue of **13** by sodium borodeuteride.[82] Less hindered acetylide nucleophiles, on the other hand, are axial selective in their reactions with **13**.[83] The single diastereomer observed in the formation of the six-membered cyclic β-trifluoromethyl hemiacetal **15** presumably is due to mutarotation subsequent to the initial attack and so reflects both the steric bulk of the CF_3 group[78] and the influence of the anomeric effects.[84]

The reduced selectivity observed in the trifluoromethylation of the *N*-benzylimine **8**, as compared to reaction with the corresponding ketone **1** (Table 1, entries 1 and 8), presumably arises from the weaker coordination of the imine nitrogen than the ketone oxygen to the reagent, resulting in a smaller effective bulk and more facile accommodation of the C–N bond in the axial position. Consistent with the greater steric bulk of the pentafluoroethyl group (Steric A value 2.67),[78] reaction of 4-*tert*-butylcyclohexanone **1** with pentafluoroethyltrimethylsilane[75] (Table 1, entry 9) was less selective than that with trifluoromethyltrimethylsilane (Table 1, entry 1), resulting in a greater proportion of adduct **17** with the equatorial fluoroalkyl group.

Fluorine-Decoupled Carbon Spectroscopy (FDCS) Method and Assignment of Configuration. In the sialic acids, the measurement of $^3J_{CH}$ coupling constants between the anomeric carboxyl carbon and the axial H3 is a rapid and reliable method for the determination of anomeric configuration (Figure 2).[64−68] Such experiments, which we dub single

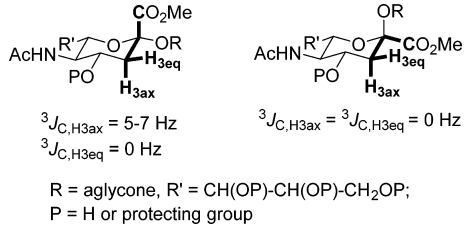


Figure 2. Diagnostic vicinal CH couplings in the sialic acid glycosides.

frequency off-resonance decoupling (SFORD) and which are a variation on standard,[85−88] off-resonance decoupling methods, are usually conducted on the methyl esters and are carried out with selective low-power decoupling of the methoxycarbonyl protons to facilitate identification of the desired residual $^3J_{CH}$ coupling constant in the ^{13}C NMR spectrum, as illustrated in Figure 3A. An axial CO_2Me group, with its antiperiplanar relation to the axial H3, typically displays a vicinal coupling constant of 5–7 Hz, whereas its equatorial counterpart, flanked by two gauche hydrogens, is usually devoid of coupling (Figure 2).

Inspired by this method, we developed an analogous protocol for the determination of $^3J_{CH}$ coupling constants between the carbon of a CF_3 group and its vicinal hydrogen atoms, which we dub the ^{13}C–^1H fluorine-decoupled spectroscopy (FDCS) method. In this experiment, a fully ^1H-coupled, ^{13}C-observed spectrum was acquired with selective ^{19}F irradiation, as illustrated in Figure 3B. In this manner, the $^{13}CF_3$ resonance is observed to be free of $^1J_{CF}$ coupling, thereby revealing the diagnostic $^3J_{CH}$ couplings in an unobstructed manner.

Application of the FDCS method to the various α-trifluoromethyl cycloalkanols or their trimethylsilyl ethers displayed in Table 2 supports the initial premise that the ^{13}C–^1H heteronuclear coupling constant is a function of the torsion angle. Thus, an axial CF_3 group exhibits a coupling constant of 7.3–9.8 Hz with vicinal axial hydrogen atoms (φ 180°) (Table 2, entries 1, 3, 5, 6, and 8). The vicinal coupling constant between an axial CF_3 group and an equatorial hydrogen atom (φ 60°) is typically ≤1 Hz, but it ranges as high as 4.2 Hz in the steroidal and triterpenoid examples (Table 2, entries 1, 3, 5, 6, and 8). An equatorial CF_3 group exhibits a vicinal coupling constant of ≤1 Hz with vicinal axial and equatorial hydrogen atoms (φ 60°) in the systems studied (Table 2, entries 2, 4, 7, 9, and 10). In the case of both the 180° and 60° dihedral angles, the larger coupling constants in the observed ranges are found in the conformationally more rigid systems (Table 2, entries 5 and 6). This suggests that the smaller coupling constants observed in the simple cyclohexyl systems are the result of an appreciable population of nonchair conformers at room temperature, consistent with the most recent estimates of the steric A value for the CF_3 group, which suggest that it is more bulky than an isopropyl group but less so

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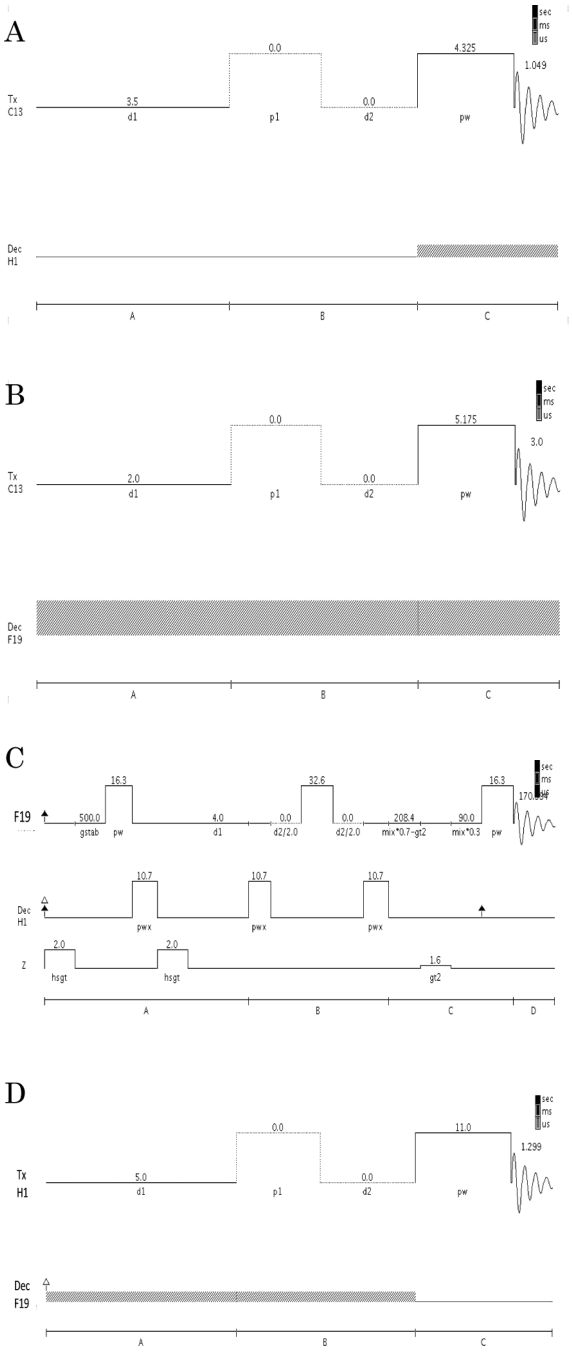

Figure 3. Pulse sequences employed in the SFORD and FDCS determinations and in the confirmatory HOESY experiments. (A) Pulse sequence for single frequency off-resonance decoupling (SFORD) experiment. ^{13}C was the observed nucleus, and the desired ^{1}H was irradiated with low-power single frequency continuous wave (CW) pulse. (B) Pulse sequence for the $^{13}C-^{1}H$ FDCS experiment. ^{13}C spectrum was the observed nucleus, and ^{19}F signal was selectively decoupled with a Waltz-16 composite decoupling scheme. (C) Pulse sequence for the $^{19}F-\{^{1}H\}$ 2D HOESY experiment. The standard pulse sequence from the VNMRJ 3.2 software library was used, with 0.3 s mixing time and 4.0 s relaxation delay. The acquisition time was 0.17 s, with 16 or 32 scans for each of 128 increments. (D) Pulse sequence for the $^{1}H-\{^{19}F\}$ 1D HOESY experiment. The standard pulse sequence from the VNMRJ 3.2 software library was used. For the H−F NOE difference experiment, two FIDs were recorded: one with ^{19}F selective low-power irradiation and the second FID without ^{19}F irradiation. The resulting two spectra were subtracted digitally to observe the H−F NOE spectrum.

than a *tert*-butyl group.[78] Although the present data set is not sufficiently extensive for careful calibration, we note that, as is well-appreciated in homonuclear $^{3}J_{H,H}$ coupling[54] and as has been demonstrated in other heteronuclear $^{3}J_{CH}$ systems,[72,89] the general Karplus-type relationship correlating the magnitude of F_3**C**-C-C-**H** coupling constant with torsion angle will be modulated by the nature and orientation of substituents.

The FDCS method is readily extended from trifluoromethylcyclohexanols to trifluoromethylcyclohexylamines and allows the assignment of axial and equatorial CF_3 groups in the α-trifluoromethyl amines **16** (Table 2, entries 11 and 12). By way of example, Figure 4 shows the ^{13}C resonances of the two CF_3 groups in a mixture of the diastereomeric amines **16** before (Figure 4A) and after (Figure 4B) decoupling of the ^{19}F atoms.

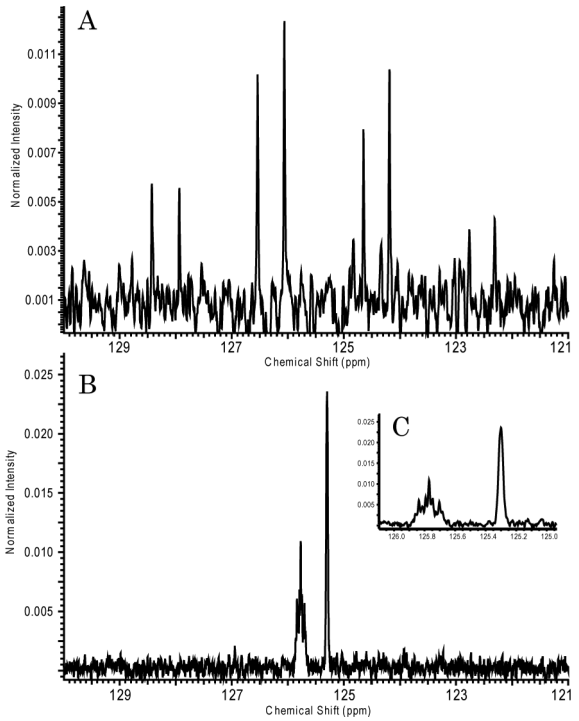

Figure 4. $^{13}CF_3$ Resonances in a diasteromeric mixture of trifluoromethylamines **16** before (A) and after (B) ^{19}F decoupling with a partial expansion (C).

The analysis of the FDCS spectra of the inseparable diastereomeric trifluoromethylated steroid derivatives **19**, in which the trifluoromethyl group is appended to a quaternary carbon, were complicated by the additional $^{3}J_{CH}$ coupling of the $^{13}CF_3$ resonances to the allylic methylene protons in addition to the diagnostic couplings to the vicinal hydrogens in the steroidal A ring (Table 2, entries 15 and 16; Figure 5). Nevertheless, application of the standard FDCS sequence to the standard ^{13}C spectrum (Figure 5A) gave a simplified spectrum (Figure 5B) displaying a downfield CF_3 resonance as a broad multiplet for one isomer and a narrower more upfield multiplet for the second isomer. The broader multiplet, expanded in Figure 5C, clearly represents the axial CF_3 group with its diaxial couplings to the axial hydrogens at the vicinal 2- and 4-positions, whereas the narrower multiplet lacks such large couplings to the vicinal hydrogens in the steroidal A ring. Although both multiplets are convoluted with additional $^{3}J_{CH}$ couplings to the two allylic hydrogens, which renders actual

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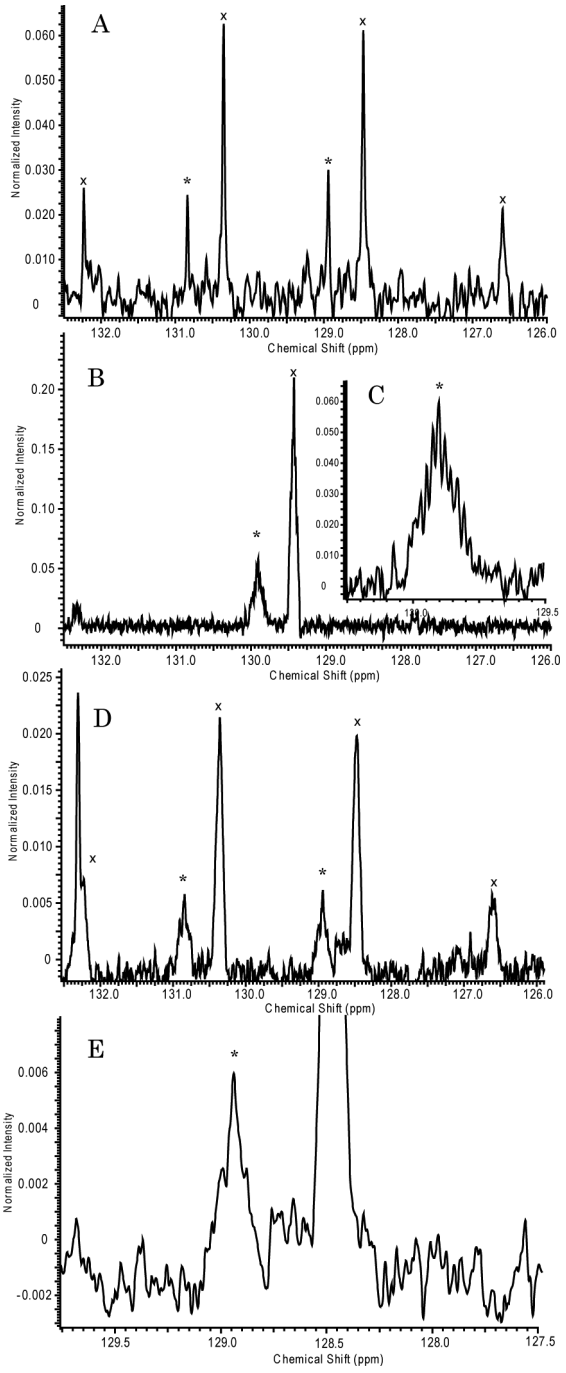

Figure 5. $^{13}CF_3$ resonances in a diasteromeric mixture of trifluoromethylsteroids **19**: (A) before ^{19}F decoupling, (B) after ^{19}F decoupling, (C) expansion of panel B. (D) ^{13}C SFORD experiment, and (E) expansion of panel D.

measurement of the diagnostic $^3J_{CH}$ couplings constants difficult, the clear difference in the width at half height of the two multiplets ($w_{1/2}$ = 17.2 and 26.3 Hz) allows relative configuration to be assigned. To confirm this assignment, a SFORD experiment was conducted in which the allylic hydrogens were selectively decoupled, giving rise to the partial spectrum in Figure 5D. The signals in this SFORD experiment retain the quartet due to coupling to the $C^{19}F_3$ resonances and also display coupling to the vicinal hydrogens at positions 2 and 4 in the A ring. The lines that make up the more downfield quartet are broader than those in the upfield quartet, as they display the larger $^3J_{CH}$ couplings to the axial hydrogens at the 2- and 4-positions, which is observable on the expansion (Figure 5E). Further confirmation of these assignments was achieved by NOESY experiments showing the spatial proximity of the vinylic hydrogens with the axial hydrogen at the 1-position in the A ring of the major isomer.

The FDCS method is not limited to $^{13}CF_3$ groups, as demonstrated by its application to the diastereomeric α-pentafluoroethyl cyclohexanols **17** (Table 2, entries 13 and 14) involving observation of the $^{13}CF_2$ resonance. The FDCS spectra of the two isomers of **17** contain an additional $^2J_{CF}$ quartet coupling to the CF_3 group, but as the extra coupling constant is significantly larger, it is of no consequence and does not complicate interpretation. The FDCS method was also applied to the known α-mono-[90] and di-[91] fluoromethylcyclohexanols **20** and **21** (Table 2, entries 17−20), which were donated by Drs. Lewis Mtashobya and Bruno Linclau at the University of Southampton. The spectra of **20** and **21** are complicated by convolution of the vicinal coupling constants with the $^1J_{CH}$ couplings, but spectral interpretation is not difficult, as the vicinal coupling constants are more than an order of magnitude smaller. Commercially available α-trifluoromethyl ethanol **22** allowed the determination of the $^{13}C-^1H$ vicinal coupling constant between a hydrogen atom and a CF_3 group in a freely rotating acyclic system (Table 2, entry 21).

Comparison of FDCS with HOESY. As discussed above (Table 2), the configuration of a number of the samples employed in this study was confirmed by heteronuclear Overhauser effect (HOESY)[92−95] measurements between CF_3 groups and spatially proximal hydrogen atoms. These measurements enable a comparison of the FDCS and HOESY methods. HOESY spectra were acquired using an autotriple resonance broadband probe (ATB), which is simultaneously tuned to ^1H and ^{19}F on the high-band RF coil. 2D HOESY experiments used the manufacturer supplied FH-HOESY pulse sequence implemented in VNMRJ 3.2 software (Figure 3C). ^1H-observed, ^{19}F-irradiated 1D HOESY experiments used the FH decoupling pulse sequence from the VNMRJ 3.2 software (Figure 3D). The main limitation of the HOESY method, as implemented in these experiments, is the requirement for the three channel or ATB type probe and of a spectrometer with three channel capabilities. When such hardware is on hand, the HOESY method, 1D or 2D, provides a rapid means of assessing the spatial proximity of the CF_3 and adjacent protons and therefore of inferring configuration and/or conformation. Because the 1D HOESY sequence is observed by the proton channel and the 2D HOESY sequence by the ^{19}F channel, sensitivity is correspondingly high and data acquisition times are relatively short. The FDCS sequence, on the other hand, employs a standard two-channel probe and can be implemented on any modern spectrometer. It gives direct information on the dihedral angle subtended by the coupled ^1H and $^{13}CF_3$ spins and therefore on the conformation and/or configuration of the substance under investigation. The FDCS spectrum is acquired through the ^{13}C channel, and data acquisition is correspondingly slow. Overall, FDCS and HOESY provide complementary information, and the combination of the two is a powerful tool for studying the configuration and conformation of CF_3 and other fluoroalkyl-containing molecules.

Application of FDCS to Alkenes and Arenes. Although the primary focus of this investigation is the development of the

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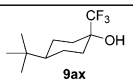
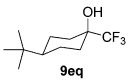
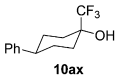
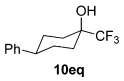
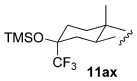
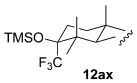
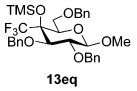
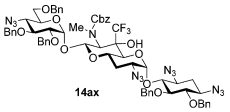
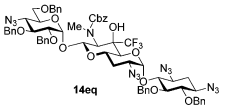
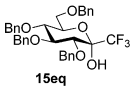
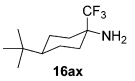
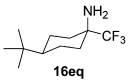
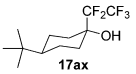
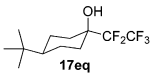
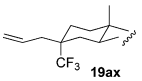
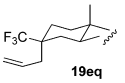
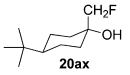
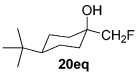
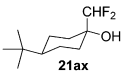
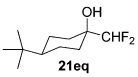
Table 2. Multiplicity and Coupling Constants of ^{19}F-Decoupled $^{13}CF_3$ Resonances and Method of Confirmation of Configuration

Entry[a]	Compound[b]	^{13}CF Signal Multiplicity and Coupling Constants (Hz)	Method of Confirmation of Configuration
1	 **9ax**	Triplet, $^3J_{CF3,2Hax}$ = 9.0 Hz, $^3J_{CF3,2Heq}$ <1 Hz	HOESY
2	 **9eq**	Broad singlet, $^3J_{CF3,2Hax}$ <1 Hz, $^3J_{CF3,2Heq}$ <1 Hz	HOESY
3	 **10ax**	Triplet, $^3J_{CF3,2Hax}$ = 7.3 Hz, $^3J_{CF3,2Heq}$ <1 Hz	HOESY, X-ray
4	 **10eq**	Broad singlet, $^3J_{CF3,2Hax}$ <1 Hz, $^3J_{CF3,2Heq}$ <1 Hz	HOESY
5	 **11ax**	Triplet of triplet, $^3J_{CF3,2Hax}$ = 9.6 Hz, $^3J_{CF3,2Heq}$ = 4.2 Hz	HOESY
6	 **12ax**	Doublet of doublet, $^3J_{CF3,Hax}$ = 9.8 Hz, $^3J_{CF3,Heq}$ = 3.1 Hz	HOESY
7	 **13eq**	Triplet, $^3J_{CF3,2Hax}$ = 1.1 Hz	HOESY, NOESY
8[c]	 **14ax**	Triplet, $^3J_{CF3,2Hax}$ = 8.1 Hz	HOESY
9[c]	 **14eq**	Broad singlet, $^3J_{CF3,2Hax}$ <1 Hz	HOESY
10	 **15eq**	Broad singlet, $^3J_{CF3,Hax}$ <1 Hz	HOESY
11[d]	 **16ax**	Triplet of triplets, $^3J_{CF3,2Hax}$ = 10.4 Hz, $^3J_{CF3,2Heq}$ = 3.4 Hz	HOESY
12[d]	 **16eq**	Broad singlet, $^3J_{CF3,2Hax}$ <1 Hz, $^3J_{CF3,2Heq}$ <1 Hz	HOESY
13	 **17ax**	Quartet of triplet of triplet,[e] $^2J_{CF2,CF3}$ = 28.4 Hz, $^3J_{CF2,2Hax}$ = 7.3 Hz, $^3J_{CF2,2Heq}$ = 3.3 Hz	HOESY
14	 **17eq**	Broad quartet,[e] $^2J_{CF2,CF3}$ = 33.4 Hz, $^3J_{CF2,2Hax}$ <1 Hz, $^3J_{CF2,2Heq}$ <1 Hz	HOESY
15	 **19ax**	Broad multiplet[f]	HOESY
16	 **19eq**	Narrow multiplet[f]	HOESY, NOESY
17	 **20ax**	Triplet of triplet of triplet, $^1J_{CF,CH2F}$ = 150 Hz, $^3J_{CF,2Hax}$ = 7.6 Hz, $^3J_{CF,2Heq}$ = 3.1 Hz	NOESY
18	 **20eq**	Triplet of quintet[f] $^1J_{CF,CH2F}$ = 150 Hz, $^3J_{CF,2Hax}$ = 1.5 Hz, $^3J_{CF,2Heq}$ = 1.5 Hz	NOESY
19	 **21ax**	Doublet of triplet of triplet, $^1J_{CF2,CHF2}$ = 180.7 Hz, $^3J_{CF2,2Hax}$ = 8.1 Hz, $^3J_{CF2,2Heq}$ = 3.1 Hz	NOESY
20	 **21eq**	Broad doublet, $^1J_{CF2,CHF2}$ = 186.3 Hz, $^3J_{CF2,2Hax}$ = <1 Hz, $^3J_{CF2,2Heq}$ = <1 Hz	NOESY
21	 **22**	Quartet of doublet, $^3J_{CF3,CH3}$ = 4.8 Hz, $^2J_{CF3,CH}$ = 3.6 Hz	

[a]Unless otherwise stated, spectra were recorded in $CDCl_3$. [b]The descriptors ax and eq refer to the axial or equatorial location of the fluoroalkyl groups and of the vicinal hydrogens to which they are coupled, respectively. [c]All NMR experiments of **14** were recorded in D_2O after complete deprotection.[77] [d]Recorded in CD_3OD. [e]Multiplicity of the $^{13}CF_2$ resonance. [f]Owing to complications arising from convolution with additional ^{13}CF coupling to the allylic hydrogens, multiplicity and coupling constants are difficult to assign for **19ax** and **19eq** (see text for clarification).

FDCS method for the assignment of configuration in saturated systems carrying CF_3 groups, using commercially available compounds, we also briefly investigated its application to unsaturated molecules. Thus, as illustrated in Figure 6, the FDCS method allows distinction of regioisomers in trifluoromethylated arenes, as the CF_3 group exhibits a measurable $^{13}C-^1H$ coupling only to an *ortho*-hydrogen. Likewise, the FDCS method may be applied to the determination of configuration of trifluoromethyl-substituted alkenes, as the *trans*-$^3J_{CH}$ coupling constant is more than double that of the corresponding *cis* coupling constant; $^2J_{CH}$ couplings are even smaller and should not complicate assignment of configuration (Figure 6).

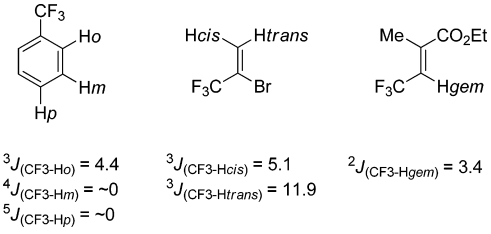


Figure 6. Fluorine-decoupled carbon spectroscopy in sp^2-hybridized systems.

■ CONCLUSIONS

The fluorine-decoupled carbon spectroscopy method is readily implemented on standard two-channel NMR spectrometers

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and provides a facile method for the determination of the configuration and/or conformation of CF_3- and other fluoroalkyl-substituted molecules. Based on the Karplus-type relation of the ^{1}H-C-C-$^{13}CF_3$ torsion angle to the coupling constant, the method is an alternative to ^{1}H,^{19}F HOESY. Earlier methods for the assignment of configuration of CF_3-substituted tertiary alcohols based on chemical shift differences in derived xanthate esters are unreliable and should be succeeded by the FDCS and/or HOESY methods.

EXPERIMENTAL SECTION

General Experimental. All reactions were performed using oven-dried glassware under an atmosphere of argon. All reagents and solvents were purchased from commercial suppliers and were used without further purification unless otherwise specified. All organic extracts were dried over sodium sulfate and concentrated under vacuum. Chromatographic purifications were carried out over silica gel (230−400 mesh). Reactions were monitored by analytical thin-layer chromatography on precoated glass-backed plates (w/UV 254) and visualized by UV irradiation (254 nm) or by staining with 25% H_2SO_4 in EtOH or ceric ammonium molybdate solution. Specific rotations were obtained using a digital polarimeter in the solvent specified. High-resolution mass spectra were recorded with an electrospray source coupled to a time-of-flight mass analyzer. ^{1}H, ^{13}C, ^{19}F, HOESY, and FDCS spectra were recorded on a 400 or 600 MHz spectrometer using VNMRJ 3.2 as processing software. Commercial NMR solvents were used without more purification. Chemical shifts are given in ppm (δ), and coupling constants J are given in Hz.

4-*trans*-*tert*-Butyl-1-trifluoromethyl-*r*-1-cyclohexanol (9ax) and 4-*cis*-*tert*-Butyl-1-trifluoromethyl-*r*-1-cyclohexanol (9eq). Compounds **9ax** and **9eq** were prepared according to a literature protocol[48] using 4-*tert*-butylcyclohexanone (400 mg, 2.6 mmol) and (trifluoromethyl)trimethylsilane (740 mg, 5.2 mmol) in tetrahydrofuran (3.0 mL) at room temperature with a catalytic amount of tetrabutylammonium fluoride (0.25 mL, 1.0 M in tetrahydrofuran). Chromatographic purification (gradient elution of diethyl ether/pentane: 2 to 10%) gave **9eq** (70 mg, 12%, mp 48.0−49.5 °C) as an off-white solid and **9ax** (290 mg, 50%, mp 94.5−95.5 °C) as a white solid.

9eq: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.82 (dd, J = 14.3, 2.2 Hz, 2H), 1.73 (br s, 1H), 1.67 (m, 2H), 1.59 (dt, J = 13.5, 4.0 Hz, 2H), 1.36 (m, 2H), 1.00 (tt, J = 12.1, 2.9 Hz, 1H), 0.88 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 126.0 (q, $^1J_{CF}$ = 284.4 Hz, CF_3), 72.2 (q, $^2J_{CF}$ = 28.1 Hz, C_1), 47.0, 32.3, 30.2, 27.3, 21.1; ^{19}F NMR (564 MHz, $CDCl_3$): δ −87.4 (s, CF_3); FDCS (150) MHz, $CDCl_3$): δ 131.5 (br s).

9ax: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.20 (m, 3H), 1.70 (d, J = 13.5 Hz, 2H), 1.48 (dt, J = 13.9, 2.2 Hz, 2H), 1.30 (q, J = 12.4 Hz, 2H), 1.08 (tt, J = 12.1, 2.9 Hz, 1H), 0.84 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 126.8 (q, $^1J_{CF}$ = 286.1 Hz, CF_3), 71.8 (q, $^2J_{CF}$ = 27.5 Hz, C_1), 46.3, 33.3, 32.2, 27.4, 23.0; ^{19}F NMR (564 MHz, $CDCl_3$): δ −80.4 (s, CF_3); FDCS (150 MHz, $CDCl_3$): δ 131.5 (tt, J = 8.9, 3.6 Hz).

4-*trans*-Phenyl-1-trifluoromethyl-*r*-1-cyclohexanol (10ax) and 4-*cis*-Phenyl-1-trifluoromethyl-*r*-1-cyclohexanol (10eq). Compounds **10ax** and **10eq** were prepared according to a literature protocol[48] using 4-phenylcyclohexanone (1.0 g, 5.7 mmol) and (trifluoromethyl)trimethylsilane (1.6 g, 11.2 mmol) in tetrahydrofuran (5.0 mL) at room temperature with a catalytic amount of tetrabutylammonium fluoride (0.6 mL, 1.0 M in tetrahydrofuran). The residue was purified by column chromatography (eluting with dichloromethane) followed by recrystallization from 2-propanol/water (7:1) to give **10eq** (90 mg, 8%, mp 75.0−76.5 °C) as an off-white solid, **10ax** (356 mg, 24%, mp 70.5−71.3 °C) as a white solid, and a mixture of both isomers (750 mg, 52%).

10eq: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (t, J = 7.7 Hz, 2H), 7.25 (m, 3H), 2.55 (tt, J = 11.7, 4.0 Hz, 1H), 1.93 (m, 3H), 1.85 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 146.1, 125.5, 126.7, 126.6 (q, $^1J_{CF}$ = 284.4 Hz, CF_3), 126.3, 72.0 (q, $^2J_{CF}$ = 28.1 Hz, C_1), 43.2, 30.1, 27.7; ^{19}F NMR (564 MHz, $CDCl_3$): δ −87.3 (s, CF_3); FDCS (150 MHz, $CDCl_3$): δ 131.5 (br s).

10ax: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (m, 2H), 7.26 (m, 3H), 2.77 (br s, 1H), 2.18 (m, 3H), 1.96 (m, 4H), 1.69 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.7, 128.5, 126.8, 126.7 (q, $^1J_{CF}$ = 285.5 Hz, CF_3), 126.1, 72.0 (q, $^2J_{CF}$ = 25.8 Hz, C_1), 40.4, 31.0, 28.0; ^{19}F NMR (564 MHz, $CDCl_3$): δ −82.2 (s, CF_3); FDCS (150 MHz, $CDCl_3$): δ 124.2 (t, J = 7.3 Hz).

3α-Trifluoromethyl-3β-trimethylsilanoxycholestane (11ax). To a stirred solution of cholestan-3-one (400 mg, 1.0 mmol) in tetrahydrofuran (3.0 mL) were added (trifluoromethyl)trimethylsilane (300 mg, 2.1 mmol) and a catalytic amount of tetrabutylammonium fluoride (27 mg, 0.1 mmol, 1.0 M in tetrahydrofuran) at room temperature. The resulting reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane (5.0 mL), washed with water followed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/hexanes (2 to 10%) to afford **11ax**[38] (482 mg, 90%, mp 103−104 °C) as a white solid. $[\alpha]_D^{20}$ = +20.4 (c = 3.7, dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.08 (td, J = 14.6, 1.8 Hz, 1H), 1.95 (td, J = 12.8, 2.9 Hz, 1H), 1.85−1.77 (m, 2H), 1.65 (m, 2H), 1.61−1.42 (m, 6H), 1.39−1.29 (m, 6H), 1.28−1.20 (m, 3H), 1.20−0.94 (m, 11H), 0.89 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 2.6 Hz, 3H), 0.83 (s, 3H), 0.67 (dd, J = 12.4, 4.0 Hz, 1H), 0.64 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 126.6 (q, $^1J_{CF}$ = 287.2 Hz, CF_3), 75.2 (q, $^2J_{CF}$ = 26.9 Hz, C_3), 56.3, 56.2, 53.9, 42.6, 41.8, 39.9, 39.5, 36.8, 36.1, 35.8, 35.4, 35.2, 34.8, 31.7, 30.1, 28.6, 28.2, 27.9, 24.1, 23.8, 22.8, 22.6, 21.1, 18.6, 12.0, 11.7, 2.2; ^{19}F NMR (564 MHz, $CDCl_3$): δ −80.3 (s, CF_3); FDCS (150 MHz, $CDCl_3$) δ: 131.5 (tt, J = 9.6, 4.1 Hz).

Methyl 3α-Trifluoromethyl-3β-trimethylsilanoxy-olean-12-en-28-oate (12ax). A solution of methyl 3-ketoolean-12-en-28-oate[96] (40 mg, 0.08 mmol) and (trifluoromethyl)trimethylsilane (66.2 mg, 0.46 mmol) in tetrahydrofuran (1.5 mL) was treated with a catalytic amount of tetrabutylammonium fluoride (4.4 mg, 0.02 mmol, 1.0 M in tetrahydrofuran) at room temperature. The resulting reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane (2.0 mL), washed with water followed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (gradient elution of EtOAc/hexanes: 2 to 20%) to afford **12ax** (42 mg, 82%, mp 178−179 °C) as a white solid. $[\alpha]_D^{20}$ = +62.1 (c = 1.4, dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.26 (t, J = 3.6 Hz, 1H), 3.60 (s, 3H), 2.84 (dd, J = 13.9, 4.4 Hz, 1H), 1.99−1.78 (m, 5H), 1.70−1.54 (m, 5H), 1.51 (m, 2H), 1.44 (m, 2H), 1.31 (m, 3H), 1.24 (m, 2H), 1.18 (t, J = 12.2 Hz, 2H), 1.12 (m, 1H), 1.11 (s, 3H), 0.96 (br s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H), 0.71 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 178.2, 143.8, 127.2 (q, $^1J_{CF}$ = 291.7 Hz, CF_3), 122.1, 81.0 (q, $^2J_{CF}$ = 24.6 Hz, C_3), 51.4, 51.2, 47.5, 46.7, 45.8, 41.7, 41.6, 41.3, 39.2, 36.3, 35.4, 33.8, 33.0, 32.8, 32.3, 30.6, 27.7, 24.1, 23.5, 23.3, 23.0, 21.1, 19.1, 16.9, 15.5, 2.1; ^{19}F NMR (564 MHz, $CDCl_3$): δ −69.5 (s, CF_3); FDCS (150 MHz, $CDCl_3$): δ 124.6 (dd, J = 9.8, 3.1 Hz); ESIHRMS calcd for $C_{35}H_{57}O_3F_3SiNa$ ([M + Na]$^+$), 633.3916; found, 633.3927.

Methyl 2,3,6-Tri-*O*-benzyl-4-trifluoromethyl-4-*O*-trimethylsilyl-β-D-galactopyranoside (13eq). To a solution of methyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[97] (296 mg, 0.54 mmol) in anhydrous dichloromethane (2.5 mL) was added Dess-Martin periodinane (296 mg, 0.69 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 3 h, quenched with saturated aqueous $NaHCO_3$ (3.0 mL), and washed with water (3.0 mL) and brine (3.0 mL). The solvent was evaporated under reduced pressure to give the 4-ketone as yellow oil, which was taken forward to the next step without further characterization. To a solution of this ketone (220 mg, 0.47 mmol) in anhydrous tetrahydrofuran (4.0 mL) was added a catalytic amount of cesium fluoride (7.0 mg, 0.04 mmol) followed by (trifluoromethyl)trimethylsilane (700 mg, 4.90 mmol) at room temperature. The resulting reaction mixture was

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stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane (5.0 mL), washed with water (5.0 mL) followed by brine (5.0 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 10% EtOAc in hexanes to give **13eq** (198 mg, 69%) as an oil. $[\alpha]_D^{25}$ = +36.5 (*c*= 4.9, dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38−7.25 (m, 15H), 4.97 (dd, *J* = 9.9, 5.1 Hz, 2H), 4.74 (d, *J* = 10.6 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 9.9 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.33 (d, *J* = 7.7 Hz, 1H), 3.96 (dd, *J* = 11.4, 2.2 Hz, 1H), 3.81 (dd, *J* = 7.3, 2.2 Hz, 1H), 3.74 (d, *J* = 9.5 Hz, 1H), 3.69 (dd, *J* = 11.3, 7.7 Hz, 1H), 3.65 (d, *J* = 9.2 Hz, 1H), 3.64 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.3, 138.1, 137.5, 128.7, 128.4, 128.3, 128.2, 128.1, 127.7, 127.7, 127.6, 127.6, 124.6 (q, $^1J_{CF}$ = 291.1 Hz, CF_3), 104.5, 80.3, 79.5, 78.5 (q, $^2J_{CF}$ = 25.2 Hz, C_4), 76.4, 75.6, 74.8, 73.7, 69.3, 57.2, 1.8; ^{19}F NMR (564 MHz, $CDCl_3$): δ −64.7 (s, CF_3); FDCS (150 MHz, $CDCl_3$): δ 122.1 (d, *J* = 1.1 Hz); ESIHRMS calcd for $C_{32}H_{39}O_6F_3SiNa$ ([M + Na]$^+$), 627.2366; found, 627.2341.

2,3,4,6-Tetra-*O*-benzyl-1-trifluoromethyl-α-D-glucopyranose (15eq). To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[98] (200 mg, 0.47 mmol) in anhydrous tetrahydrofuran (4.0 mL), was added a catalytic amount of cesium fluoride (6.0 mg, 0.04 mmol) followed by (trifluoromethyl)trimethylsilane (1.0 g, 7.40 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane (4.0 mL), washed with water (4.0 mL) followed by brine (4.0 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (3.0 mL) and was treated with tetrabutylammonium fluoride (170 mg, 0.65 mmol, 1.0 M in THF) at room temperature. The resulting reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography eluting with 10% EtOAc in hexanes to give **15eq** (142 mg, 65%) as an oil. $[\alpha]_D^{25}$ = +50.3 (*c*= 8.0, dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40−7.27 (m, 17H), 7.26−7.22 (m, 3H), 4.97 (d, *J* = 11.0 Hz, 1H), 4.90 (d, *J* = 2.9 Hz, 1H), 4.87 (br s, 1H), 4.85 (d, *J* = 10.6 Hz, 1H), 4.75 (d, *J* = 9.9 Hz, 1H), 4.69 (dd, *J* = 10.6, 7.7 Hz, 1H), 4.59 (d, *J* = 12.5 Hz, 1H), 4.05 (d, *J* = 9.9 Hz, 1H), 3.94 (br s, 1H), 3.93 (d, *J* = 5.1 Hz, 1H), 3.92 (br s, 1H), 3.85 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.81 (m, 1H), 3.76 (dd, *J* = 11.7, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.2, 138.1, 137.9, 136.9, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 122.4 (q, $^1J_{CF}$ = 287.2 Hz, CF_3), 94.3 (q, $^2J_{CF}$ = 31.9 Hz, C_1), 83.4, 78.3, 76.8, 75.9, 75.7, 75.1, 73.4, 72.9, 67.8; ^{19}F NMR (564 MHz, $CDCl_3$): δ −85.8 (s, CF_3); FDCS (150 MHz, $CDCl_3$): δ 122.1 (br s); ESIHRMS calcd for $C_{35}H_{35}O_6F_3Na$ ([M + Na]$^+$), 631.2283; found, 631.2264.

4-*trans*-*tert*-Butyl-1-trifluoromethyl-*r*-1-cyclohexylamine (16ax) and 4-*cis*-*tert*-Butyl-1-trifluoromethyl-*r*-1-cyclohexylamine (16eq). A suspension of 4-*tert*-butylcyclohexanone (1.0 g, 6.49 mmol), benzylamine (1.0 g, 9.71 mmol), and dry powdered magnesium sulfate (4.0 g, 33.3 mmol) in dichloromethane (10 mL) was stirred at room temperature for 48 h. The reaction mixture was filtered through Celite and washed with water, the solvent was removed under reduced pressure, and the residue was directly subjected to the next reaction without further purification. To a stirred solution of the crude intermediate imine in acetonitrile (10 mL) were added trifluoroacetic acid (0.8 mL, 10.0 mmol), potassium bifluoride (405.0 mg, 5.19 mmol), and *N*,*N*-dimethylformamide (2.0 mL) at 0 °C. The reaction mixture was stirred for 10 min and was then treated with (trifluoromethyl)trimethylsilane (1.4 g, 9.8 mmol) at 0 °C, and the mixture was stirred at room temperature for 48 h. The reaction mixture was quenched with saturated aqueous Na_2CO_3 solution (3 mL), and diluted with water (25.0 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in MeOH (10.0 mL), and the solution was stirred for 36 h with Pd/C (10 mg, 10% mol) under 1 atm of hydrogen (balloon). After completion, the reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The residue was dissolved in 2 M HCl/MeOH and then concentrated to dryness. The resulting hydrochloride salt was crystallized from acetonitrile (3.0 mL), filtered, and washed with diethyl ether to afford the HCl salts of **16ax** and **16eq** (154 mg, 68%, mp 240−242 °C) in a 1:1 ratio as a white solid. ^{1}H NMR (600 MHz, CD_3OD): δ 2.37 (d, *J* = 14.3 Hz, 2H), 2.06 (d, *J* = 12.8 Hz, 2H), 1.95−1.83 (m, 6H), 1.75 (t, *J* = 13.5 Hz, 2H), 1.40−1.27 (m, 4H), 1.16 (m, 2H), 0.92 (s, 9H), 0.88 (s, 8H); ^{13}C NMR (150 MHz, CD_3OD): δ 125.5 (q, $^1J_{CF}$ = 284.9 Hz, CF_3), 125.2 (q, $^1J_{CF}$ = 282.2 Hz, CF_3), 58.4 (q, $^2J_{CF}$ = 25.8 Hz, C_1), 57.2 (q, $^2J_{CF}$ = 28.0 Hz, C_1), 46.5, 45.5, 31.7, 31.6, 29.6, 27.6, 26.3, 26.2, 22.0, 20.3; ^{19}F NMR (564 MHz, CD_3OD): δ −73.4 (s, CF_3), −80.8 (s, CF_3); FDCS (150 MHz, CD_3OD): δ 125.3 (tt, *J* = 10.4, 3.4 Hz), 124.9 (br s); ESIHRMS calcd for $C_{11}H_{21}NF_3$ ([M + H]$^+$), 224.1626; found, 224.1629.

4-*trans*-*tert*-Butyl-1-pentafluoroethyl-*r*-1-cyclohexanol (17ax) and 4-*cis*-*tert*-Butyl-1-pentafluoroethyl-*r*-1-cyclohexanol (17eq). To a stirred solution of (pentafluoroethyl)trimethylsilane (507 mg, 2.6 mmol) in tetrahydrofuran (1.5 mL) were added 4-*tert*-butylcyclohexan-1-one (136 mg, 0.88 mmol) and tetrabutylammonium fluoride (0.26 mL, 0.26 mmol, 1.0 M tetrahydrofuran) at room temperature. After 2 h of stirring, 6 M HCl (1 mL) was added, and the reaction mixture was stirred for 1 h at room temperature. The aqueous layer was separated and extracted with diethyl ether (3 × 3.0 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10.0 mL) and brine (10.0 mL) and dried over $MgSO_4$. The crude products were purified by flash column chromatography (gradient elution with *n*-pentane/diethyl ether = 98:2, 96:4, 94:6, 92:8) to give a white solid **17ax** (116 mg, 54%; mp 74 °C) as the major isomer and a colorless oil **17eq** (54 mg, 25%) as the minor isomer. Neither **17ax** nor **17eq** was amenable to ionization by either electrospray or electron impact mass spectrometry.

17ax: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.37−2.30 (m, 2H), 2.26 (br s, 1H, O*H*), 1.73−1.66 (m, 2H), 1.48 (td, *J* = 13.8, 4.2 Hz, 2H), 1.35 (tdd, *J* = 14.3, 8.3, 2.8 Hz, 2H), 1.17−1.09 (m, 1H), 0.84 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 119.4 (qt, $^1J_{CF}$ = 280 Hz, $^2J_{CF}$ = 31.9 Hz, CF_3CF_2), 116.3 (tq, $^1J_{CF}$ = 260 Hz, $^2J_{CF}$ = 28.4 Hz, CF_3CF_2), 72.2 (t, $^2J_{CF}$ = 22.7 Hz, C_1), 46.0, 34.0, 32.3, 27.4, 22.8; ^{19}F NMR (564 MHz): δ −81.4 (s, 3F, CF_3CF_2), −121.9 (s, 2F, CF_3CF_2); FDCS (150 MHz, $CDCl_3$): δ 116.3 [qtt, *J* = 28.4 Hz (from fluorine), 7.3 Hz (from axial hydrogen), 3.3 Hz (from equatorial hydrogen)].

17eq: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.91−1.85 (m, 2H), 1.76 (s, 1H, O*H*), 1.71−1.59 (m, 4H), 1.38 (m, 2H), 1.00 (tt, *J* = 12.4, 3.1 Hz, 1H), 0.86 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 119.5 (qt, $^1J_{CF}$ = 288.0 Hz, $^2J_{CF}$ = 31.9 Hz, CF_3CF_2), 114.8 (tq, $^1J_{CF}$ = 258.0 Hz, $^2J_{CF}$ = 33.4 Hz, CF_3CF_2), 73.2 (t, $^2J_{CF}$ = 22.7 Hz, C_1), 47.0, 32.3, 30.3, 27.3, 21.1; ^{19}F NMR (564 MHz): δ −80.9 (s, 3F, CF_3CF_2), −129.5 (s, 2F,CF_3CF_2); FDCS (150 MHz, $CDCl_3$): δ 119.5 broad quartet [*J* = 33.4 Hz (from fluorine)].

***S*-Methyl 3-(Trifluoromethyl)-3β-cholestanyl xanthate (18).** A solution of **11ax** (350 mg, 0.66 mmol) in tetrahydrofuran (3.0 mL) was treated with 2 N HCl (0.6 mL) and stirred for 5 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (5.0 mL), washed with saturated aqueous $NaHCO_3$ solution (5.0 mL) and water (5.0 mL) followed by brine (5.0 mL), dried over Na_2SO_4, and concentrated under reduced pressure afford the 3-(trifluoromethyl)-3β-cholestanol,[38] which was taken forward to the next reaction without further purification. A suspension of 3-(trifluoromethyl)-3β-cholestanol (135 mg, 0.29 mmol) and potassium hydride (24 mg, 0.60 mmol) in tetrahydrofuran (6.0 mL) was stirred for 10 min at room temperature followed by addition of carbon disulfide (115 mg, 1.47 mmol) and then methyl iodide (420 mg, 2.95 mmol) at 65 °C. The resulting reaction mixture was stirred for 1 h at 65 °C, cooled to 0 °C, and quenched with water (5.0 mL). After extraction into dichloromethane (2 × 8 mL), the combined organic layers were washed with water (10.0 mL) followed by brine (10.0 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography eluting with hexanes to give **18** (119 mg, 74%, mp 95.5−96.0 °C) as a white solid. $[\alpha]_D^{25}$ =

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+25.4 (c= 0.7, dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.34 (dt, J = 14.3, 5.5 Hz, 1H), 3.14 (t, J = 14.3 Hz, 1H), 2.45 (s, 3H), 1.99 (td, J = 14.3, 2.2 Hz, 1H), 1.95 (td, J = 12.8, 3.3 Hz, 1H), 1.83−1.75 (m, 2H), 1.71 (dd, J = 13.5, 4.4 Hz, 1H), 1.66 (m, 1H), 1.57−1.40 (m, 5H), 1.38−1.18 (m, 9H), 1.16−1.00 (m, 6H), 1.00−0.93 (m, 5H), 0.88 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 2.9 Hz, 3H), 0.84 (d, J = 2.9 Hz, 3H), 0.69 (dt, J = 12.5, 4.0 Hz, 1H), 0.64 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 211.4, 125.7 (q, $^1J_{CF}$ = 286.7 Hz, CF_3), 91.6 (q, $^2J_{CF}$ = 27.5 Hz, C_3), 56.3, 56.2, 53.5, 42.5, 42.5, 39.8, 39.4, 36.1, 35.7, 35.4, 35.3, 35.1, 31.7, 28.8, 28.5, 28.2, 27.9, 24.1, 23.8, 22.8, 22.5, 22.4, 21.2, 19.0, 18.6, 12.6, 12.1; ^{19}F NMR (564 MHz, $CDCl_3$): δ −76.7 (s, CF_3).

3β-(2-Propenyl)-3α-(trifluoromethyl)cholestane (19ax)[47] and 3α-(2-Propenyl)-3β-(trifluoromethyl)cholestane (19eq).[47] To a stirred solution of xanthate **18** (102 mg, 0.18 mmol) in allyltributyltin (433.0 mg, 1.30 mmol) was added triethylborane (20.0 mg, 0.20 mmol) at −30 °C. The resulting reaction mixture was stirred for 1 h at −30 °C, quenched with diisopropyl azodicarboxylate (DIAD) (452.0 mg, 2.23 mmol), and stirred for 3 h at room temperature. Column chromatography of the reaction mixture (silica gel, pentane) afforded a mixture of **19ax** and **19eq** along with allyltributyltin. The residue was dissolved in anhydrous dichloromethane (2.0 mL), and propionaldehyde (84 mg, 1.44 mmol) was added. The reaction mixture was cooled to 0 °C, and boron trifluoride diethyl etherate (205 mg, 1.44 mmol) was added; the resulting reaction mixture was stirred at 0 °C for 1 h, quenched with saturated aqueous $NaHCO_3$ solution (2.0 mL), and washed with water (2.0 mL) and brine (2.0 mL). The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography eluting with hexanes to obtain a mixture of **19ax** and **19eq** (49.2 mg, 55%, mp 51−52 °C) in a 1:2.5 ratio as a white solid. $[\alpha]_D^{25}$ = +16.4 (c= 2.2, dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.71 (m, 2H), 5.11 (dd, J = 10.3, 2.2 Hz, 1H), 5.07 (dd, J = 13.9, 1.8 Hz, 1H), 2.37 (d, J = 7.3 Hz, 2H), 2.16 (m, 1H), 1.96 (m, 2H), 1.81 (m, 2H), 1.72 (dd, J = 13.9, 4.4 Hz, 1H), 1.67 (m, 2H), 1.62−1.41 (m, 11H), 1.40−1.17 (m, 17H), 1.17−1.03 (m, 9H), 1.03−0.94 (m, 4H), 0.91−0.88 (m, 7H), 0.88−0.85 (m, 8H), 0.79 (s, 3H), 0.66−0.63 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 133.7, 132.8, 129.8 (q, $^1J_{CF}$ = 286.1 Hz, CF_3), 129.3 (q, $^1J_{CF}$ = 283.3 Hz, CF_3), 111.8, 117.7, 56.5, 56.4, 56.3, 56.2, 54.3, 54.0, 42.5, 41.0, 40.1, 39.9, 39.5, 36.1, 35.8, 35.5, 35.5, 35.4, 34.9, 34.6, 32.9, 31.9, 31.7, 30.0, 29.2, 28.5, 28.2, 28.0, 27.4, 25.2, 24.1, 23.8, 23.4, 22.8, 22.5, 20.9, 18.6, 13.7, 12.0, 11.7, 8.7; ^{19}F NMR (564 MHz, $CDCl_3$): δ −73.1 (s, CF_3), −79.3 (s, CF_3); FDCS (150 MHz, $CDCl_3$): δ **19eq**, 128.5 (narrow multiplet), **19ax**, 129.0 (broad multiplet).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details and copies of ^{1}H and ^{13}C NMR spectra of all compounds and of all FDCS and HOESY spectra. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 1032684 contains the supplementary crystallographic data for compound **10** and can be obtained from the Cambridge Crystallographic Data Center via www.ccdc.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

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