# Stereospecific Synthesis of Racemic *cis*- and *trans*-6-Trifluoromethylshikimic Acids[1,†]

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Two 'unnatural' derivatives of shikimic acid, *cis*- and *trans*-6-trifluoromethylshikimic acid, have been synthesized in their racemic forms *via* the base-promoted opening of furan Diels–Alder adducts bearing a $CF_3$ group. The relative stereochemistry of the *trans*-diastereoisomer has been confirmed by an X-ray analysis of its t-butyl ester.

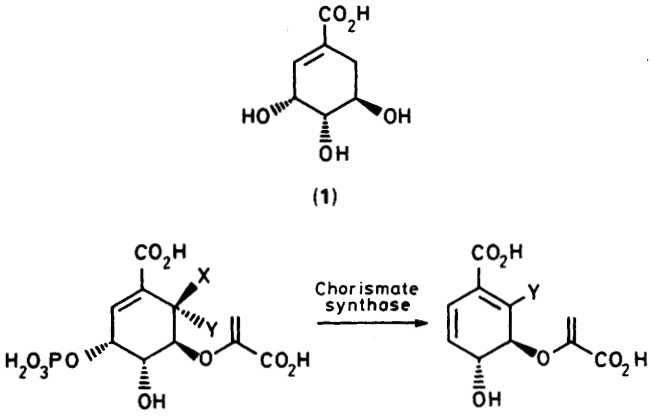


For decades, numerous chemical and biochemical studies have been devoted to (−)-shikimic acid (**1**), a key intermediate in the biosynthesis of aromatic substances in bacteria, fungi, and higher plants.[2] So far, the interest in this compound and its principle metabolites has not weakened, not only because they still are valuable targets for organic synthesis, but also because they are tools for elucidation of unusual enzymatic mechanisms.[3] The success of glyphosate as a herbicide continues to spur on the search for other inhibitors of the various steps of the 'shikimate pathway.' On the other hand, it is now well established that selectively fluorinated biologically significant molecules display modified biochemical reactivity related to, *e.g.* enzyme recognition and activity.[4] Thus, it appeared that 6-fluoroshikimic acids could be useful probes for the study of several steps of the pathway, particularly beyond shikimate itself. With this aim in view, Pilch and Somerville,[5] then Azerad and Le Maréchal,[6] each using chemo-enzymatic procedures, failed to produce 6-fluoroshikimic acids from fluorinated synthons despite extensive studies. In our experience a completely chemical synthesis of such derivatives was dramatically thwarted by aromatization.[7]

Despite creating a drastic change in structure, we felt that the introduction of a trifluoromethyl group at the C-6 position of shikimic acid could also be of interest for mechanistic studies of the enzyme chorismate synthase, after prior phosphorylation then enolpyruvoylation. The conversion of the phosphate (**2**) (EPSP) to chorismate (**3**), which is catalysed by chorismate synthase, was shown to proceed through an overall *trans*-1,4-elimination of phosphate, with abstraction of the C-6 *pro-R* proton (Scheme 1).[8] The stereoselective replacement of one of the two C-6 protons in EPSP (**2**) by a trifluoromethyl group might lead to two quite different types of interaction with chorismate synthase, depending on whether this group is in the β-position normally occupied by the abstracted proton [*i.e.* in (**2**), Scheme 1: X = $CF_3$], or in the α-position [*i.e.* in (**2**), Y = $CF_3$]. In the first instance, a competitive inhibition with the natural substrate could develop, whereas in the second situation, a suicidal-type inhibition of the enzyme, *via* the formation of a transient difluoromethylene moiety, may be expected. A similar process has already been invoked for the suicidal inactivation of thymidylate synthase by 5-trifluoromethyl-2′-deoxyuridylic acid.[9] An alternative evolution could be the formation of the trifluoromethyl derivative of chorismic acid [*i.e.* in (**3**), Y = $CF_3$].

## Results

Among the number of routes developed to prepare shikimic acid, the one initiated by Brion[10] and developed by Campbell *et al.*[11] and Rodrigo *et al.*[12] was well adapted to a stereocontrolled introduction of the trifluoromethyl group.

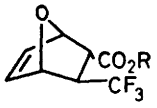



**Scheme 1.**

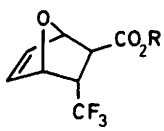
*Synthesis of* (±)-cis-6-*Trifluoromethylshikimic Acid* (**14**).—We previously described[13] the Diels–Alder condensation between ethyl (*E*)-4,4,4-trifluorobutenoate and furan to give a 60:40 to 80:20 mixture of *endo*- and *exo*-epimers‡ of 2-ethoxycarbonyl-3-trifluoromethyl-7-oxabicyclo[2.2.1]hept-5-ene (**4**) and (**7**), in each the trifluoromethyl group being *trans* to the ester group. At this stage, we found it convenient to separate the *trans,endo*-ester (**4**) from its *trans,exo*-isomer (**7**) by stereoselective enzymatic hydrolysis of the *exo*-ester by pig liver esterase (PLE), the *endo*-ester being unaffected. Our initial approach to racemic *cis*-6-trifluoromethylshikimic acid (**14**) was conducted with an ethyl ester group and we ran the synthesis up to (±)-ethyl *cis*-6-trifluoromethylshikimate. This then failed to be saponified cleanly. So, we opted for the acid-removable t-butoxycarbonyl group, introducing it before cleavage of the bicyclic frame. Saponification of (**4**) and esterification of the resulting acid (**5**) (isobutene–Bu$^t$OH–$H_2SO_4$) gave the *trans,endo*-t-butyl ester (**6**) in 74% yield from (**4**). In an alternative procedure, we sought to avoid the separation of the diastereoisomeric adducts (**4**) and (**7**) in effecting a Diels–Alder condensation between furan and (*E*)-

† Since submission of this paper, two closely related reports describing the synthesis of racemic methyl 6α-fluoroshikimate and the synthesis of 6α- and 6β-fluoroshikimic acids *via* the opening of an epoxide with HF–pyridine reagent respectively have been published: see S. Bowles, M. M. Campbell, M. Sainsbury, and G. M. Davies, *Tetrahedron Lett.*, 1989, **30**, 3711; J. K. Sutherland, W. J. Watkins, J. P. Bailey, A. K. Chapman, and G. M. Davies, *J. Chem. Soc., Chem. Commun.*, 1989, 1386.

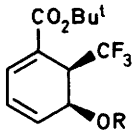
‡ *exo* and *endo* refer to the orientation with respect to the oxygen bridge.



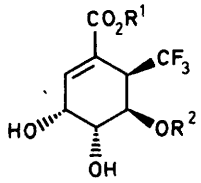
(4) R = Et
(5) R = H
(6) R = Bu$^t$



(7) R = Et
(8) R = H
(9) R = Bu$^t$



(10) R = H
(11) R = Bu$^t$Me$_2$Si



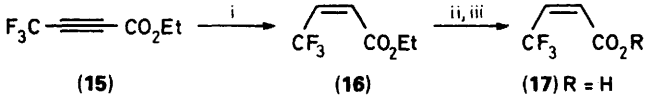
(12) R$^1$ = Bu$^t$, R$^2$ = Bu$^t$Me$_2$Si
(13) R$^1$ = Bu$^t$, R$^2$ = H
(14) R$^1$ = R$^2$ = H

4,4,4-trifluorobutenoic acid since McBee *et al.*[14] obtained an 89% yield of the *trans,endo*-acid (**5**) without noting the presence of the *exo*-form. Surprisingly, in our hands, the same procedure afforded a mixture of the two isomers, the *exo*-form being the most abundant (*ca.* 62%). We believed our assignment was correct on the basis of the characteristic values of the vicinal coupling constant, $J_{1,2}$ = 4.4 or 0.0 Hz, depending on whether 2-H is in an *exo*- or an *endo*-position.[15] We also converted (*E*)-4,4,4-trifluorobutenoic acid[16] into its t-butyl ester (68% yield). Subsequent condensation of this ester with furan (80 °C; 64 h) afforded a mixture of the adducts (**6**) and (**9**) (~80:20) in only a modest yield (41%). So, we used the first procedure.

Finally, on treatment with lithium hexamethyldisilazide (LiHMDS) at *ca.* −70 °C, the *trans,endo*-ester (**6**) underwent a mild β-elimination of the oxygen bridge leading, after hydrolysis, to the cyclohexadienol (**10**), with conservation of the relative *cis*-stereochemistry of the trifluoromethyl group and the oxygenated functionality which is found in (**6**). The stereoselectivity of the *cis*-dihydroxylation of the more reactive C-3–C-4 double bond of the cyclohexadienol (**10**) with osmium tetroxide in diethyl ether was controlled by prior conversion of the C-5 hydroxy group into a bulky dimethyl(t-butyl)silyl ether with dimethyl(t-butyl)silyl trifluoromethanesulphonate in the presence of 2,6-lutidine (93% yield). With the β-face strongly hindered, the resulting ether (**11**) was smoothly osmylated at the α-face with osmium tetroxide (1 equiv.)–pyridine (2 equiv.) in diethyl ether and the resulting complex was reduced with hydrogen sulphide to give the partially protected triol (**12**) in 45% yield after chromatography, without production of any other tractable compound. As osmium tetroxide is expensive, we attempted to use it catalytically. In the presence of hydrogen peroxide as the reoxidant (Milas' reagent), and contrary to Campbell's successful results with (±)-shikimic acid itself,[11] we found no trace of the desired product. On the other hand, only a 15% yield of (**12**) was obtained from (**11**) by catalytic osmylation in the presence of 4-methylmorpholine 4-oxide.[17] Consequently, we employed the non-catalytic procedure. Subsequent mild desilylation of (**12**) with tetrabutylammonium fluoride in tetrahydrofuran (THF), afforded the triol (**13**) in 91% yield. In the final step, release of the carboxylic function in (**13**) was readily performed by treating it with neat trifluoroacetic acid to afford (±)-*cis*-6-trifluoromethylshikimic acid (**14**) in 60% yield after purification. The $^1$H NMR spectrum of (**14**) in $D_2O$ at 500 MHz showed an unresolved narrow signal for 4- and 5-H from which no information could be drawn about their stereochemical relationship. In contrast, in $(CD_3)_2CO$, these protons displayed well separated signals despite their close chemical shifts ($\Delta\delta$ ~0.05 ppm) with $J_{4,5}$ 9.8 Hz, suggesting most probably a *trans*-diaxial relationship between 4- and 5-H as expected.

*Synthesis of* (±)-*trans*-6-*Trifluoromethylshikimic Acid* (**29**).—The above strategy should also apply to the synthesis of the diastereoisomeric (±)-*trans*-6-trifluoromethylshikimic acid (**29**) provided we could start from a bicyclic ester bearing a trifluoromethyl group in an *endo*-position, *i.e. trans* to the C-4–O bond. For this purpose, we esterified with isobutene the *trans,exo*-acid (**8**) which we obtained by enzymatic separation from the isomeric *trans,endo*-ester (**4**). The resulting *trans,exo*-t-butyl ester (**9**), on reaction with LiHMDS under the same conditions as *trans,endo* (**6**), was recovered unchanged. We attributed this lack of reactivity to steric hindrance due to the *endo*-trifluoromethyl group. This hypothesis was strengthened by the successful opening of the adduct *cis,exo* (**24**) with this base to give the known *cis*-cyclohexadienol (**10**) (*vide infra*). On the other hand, when the *trans,exo*-ester (**9**) was allowed to react with an excess of 'anhydrous' Bu$^n_4$NF[18] at 40 °C, we observed only the formation of t-butyl 2-trifluoromethylbenzoate in quantitative yield, probably *via* the expected alkoxide. Curiously, the *trans,endo*-isomer (**6**) did not react with this reagent, even on prolonged heating. This result contrasts with the successful opening of the same molecule with LiHMDS in THF, which formally proceeds *via* a *syn*-elimination of an alkoxide ion (*vide supra*).

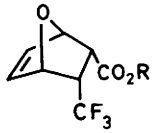
As the *trans,exo*-ester (**9**) could not be opened to give the desired *trans*-cyclohexadienol (**25**), we prepared the bicyclic *cis,endo*-t-butyl ester (**21**) in order to secure easy access to the C-2 proton by the hexamethyldisilazide anion. For this synthesis, we needed the unknown (*Z*)-4,4,4-trifluorobutenoic acid (**17**) and/or its ethyl ester (**16**) (Scheme 2). In contrast with (*E*)-alkenes, methods to prepare their (*Z*)-isomers are scarce, the most common being the partial hydrogenation of the corresponding alkynes.[19] So, we prepared ethyl 4,4,4-trifluorobutynoate (**15**) from trifluoroacetyl chloride and triphenylphosphine.[20] Subsequent controlled partial hydrogenation of this ester ($H_2$–Pd/$BaSO_4$–quinoline) led to the desired ethyl (*Z*)-4,4,4-trifluorobutenoate (**16**) in 55% yield after distillation.



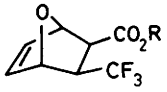
(15) (16) (17) R = H (18) R = Bu$^t$

**Scheme 2.** *Reagents and conditions*: i, $H_2$, Pd/$BaSO_4$, quinoline, MeOH; ii, $HCO_2H$, $H^+$, reflux; iii, $Me_2C{=}CH_2$, Bu$^t$OH, $H^+$, room temp.

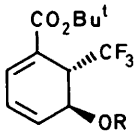
In preliminary experiments, we carried out the thermal, uncatalysed Diels–Alder cycloaddition between (**16**) and furan, and a mixture of *cis,endo*- and *cis,exo*-adducts (**19**) and (**22**) was obtained in low yield (21% from the alkene), in the ratio ~74:26. After separation by column chromatography [PLE did not hydrolyse the *cis,exo*-ethyl ester (**22**) selectively, in contrast with its *trans,exo*-diastereoisomer (**7**)], *saponification of the cis,endo*-ethyl ester (**19**) with refluxing 10% aqueous sodium hydroxide led to the known epimeric *trans,exo*-acid (**8**). Because of this result, we prepared t-butyl (*Z*)-4,4,4-trifluorobutenoate (**18**) in 55% yield from (*Z*)-4,4,4-trifluorobutenoic acid (**17**) and isobutene since Huang's method[20] failed to produce directly this compound because of extensive decomposition at the pyrolysis stage. The acid was itself obtained by acidolysis



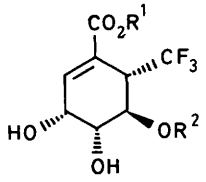
(19) R = Et
(20) R = H
(21) R = Bu$^t$



(22) R = Et
(23) R = H
(24) R = Bu$^t$



(25) R = H
(26) R = Bu$^t$Me$_2$Si



(27) R$^1$ = Bu$^t$, R$^2$ = Bu$^t$Me$_2$Si
(28) R$^1$ = Bu$^t$, R$^2$ = H
(29) R$^1$ = R$^2$ = H

(formic acid–sulphuric acid) of the ethyl ester (**16**) in 64% yield (38% overall yield from trifluoroacetyl chloride). Saponification of (**16**) was not attempted since saponification of ethyl (*E*)-4,4,4-trifluorobutenoate gave an equal proportion of 4,4,4-trifluoro-3-hydroxy butanoic acid and (*E*)-4,4,4-trifluorobutenoic acid.[16] When the t-butyl ester (**18**) was submitted to a Diels–Alder condensation with furan (80 °C; 4 days), only a 17% yield of a mixture of *cis,endo*- and *cis,exo*-adducts (**21**) and (**24**) was obtained (*endo*:*exo* ratio ~77:23, after separation). In contrast, the Diels–Alder reaction of furan with the acid (**17**) (13 days; room temperature) led in high yield (92% of the crude product) to a mixture of *cis,endo*- and *cis,exo*-adducts (**20**) and (**23**) in the ratio 80:20. This mixture was not separated but directly submitted to esterification with isobutene as above and the resulting t-butyl esters were separated by column chromatography. The base-promoted opening of the desired *cis,endo*-isomer (**21**) was successfully achieved with LiHMDS in the same manner as for its *trans,endo*-diastereoisomer (**6**), giving access to the expected *trans*-cyclohexadienol (**25**) in satisfactory yield (83%). As in the *cis*-series, elaboration of (**29**) involved the prior conversion of the hydroxy group of cyclohexadienol (**25**) to the bulky dimethyl(t-butyl)siloxy group with Bu$^t$-Me$_2$SiOSO$_2$CF$_3$ and 2,6-lutidine (78% yield), then *cis*-dihydroxylation of the resulting ether (**26**) with a stoicheiometric amount of osmium tetraoxide in pyridine. A major improvement in yield was obtained using sodium bisulphite ($Na_2S_2O_5$) to reduce the intermediate osmate ester in place of hydrogen sulphide (Baran's procedure[21]), affording the partially protected triol (**27**) in 84% yield from (**26**) after column chromatography. Mild desilylation of the ether moiety was achieved as above with Bu$^n_4$NF in THF, providing the triol (**28**) (89% yield) and the desired free acid (**29**) was obtained, like its isomer (**14**), by acidolysis of the t-butoxycarbonyl group with trifluoroacetic acid at room temperature, in 85% yield from the ester.

Although the $^1$H 500 MHz NMR spectrum of (**29**) was readily assigned, the relative stereochemistry of the substituents could not be firmly established in this way. Moreover, the m.p. of (**29**) (148.8 °C) seemed to us to be abnormally low, compared with that of shikimic acid (**1**) (185–187 °C) and of (**14**) (183.1 °C). In order to confirm definitely the structure of (**29**), an X-ray diffraction analysis was performed on a crystal of the t-butyl ester (**28**), since we failed to produce suitable crystals of the acid. The Figure displays the computer-generated

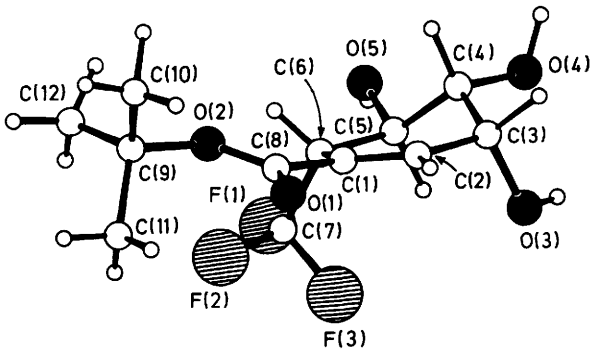



**Figure.** X-Ray crystal structure of (**28**).

perspective drawing of (**28**). The cyclohexene ring is distorted, adopting a half-chair conformation like sodium (−)-shikimate dihydrate in the crystalline state,[22] while the trifluoromethyl group adopts a pseudo-equatorial position. Remarkably, the three hydroxy groups have roughly the same position in (**28**) and sodium (−)-shikimate dihydrate, despite the introduction of the bulky trifluoromethyl group, *i.e.* pseudo-axial for the C(3)-hydroxy group and equatorial for the C(4)- and C(5)-hydroxy groups. Moreover, the relative stereochemistry of the substituents is consistent with our expectations.

## Experimental

M.p.s were determined on a Mettler FP-61 apparatus. IR spectra were recorded using a Perkin-Elmer 1420 spectrophotometer. $^1$H NMR chemical shifts (δ) are reported in ppm, positive downfield relative to internal Me$_4$Si and spectra were recorded at 60 MHz (Varian EM 360L spectrometer equipped with a proton-fluorine probe), and on Bruker WH-90 (90 MHz), WM-250 (250 MHz), AM-300 (300 MHz), and WM-500 (500 MHz) Fourier transform spectrometers. $^{19}$F NMR spectra were obtained at 56.4 MHz and $^{19}$F chemical shifts (δ) are reported in ppm, negative upfield relative to internal $CFCl_3$. Tetrahydrofuran (THF) was refluxed over, and distilled from, lithium aluminium hydride, just prior to use. Silica gel 60 (Merck) was used in classical column chromatography (70–230 mesh) and flash chromatography[23] (230–400 mesh). Analytical TLC was performed on plastic plates coated with silica gel containing a luminescer (254 nm) (Schleicher & Schuell). Chromatograms were visualized either under UV light or with a sulphuric acid–ethanol (30% v/v) spray, then heating. Polyols were revealed with a freshly prepared spray of lead tetra-acetate in benzene (1% solution, w/v), as a white spot. Organic solutions were concentrated using a rotary evaporator under water-pump reduced pressure. Elemental analyses were performed either by the Service Central d'Analyse du CNRS, Vernaison and Gif-sur-Yvette, or by the Service de Microanalyse, Université P. & M. Curie, Paris. High-resolution mass spectra were obtained by the Centre de Spectrométrie de Masse de Lyon, Service Central d'Analyse du CNRS, Lyon, on a AEI MS902 spectrometer. Spinning-band distillations were performed on a Perkin-Elmer 251 Auto Annular Still.

*Ethyl* 3-exo-*Trifluoromethyl*-7-*oxabicyclo*[2.2.1]*hept*-5-*ene*-2-endo-*carboxylate* (**4**) *and* 3-endo-*Trifluoromethyl*-7-*oxabicyclo*[2.2.1]*hept*-5-*ene*-2-exo-*carboxylic Acid* (**8**): *Revised Procedure*.[13]—A mixture of ethyl (*E*)-4,4,4-trifluorobut-2-enoate (15.7 g, 93 mmol) and furan (12.0 ml, 0.165 mol) was stirred in a heavy-walled Pyrex flask at 80 °C for 72 h. The excess of furan was evaporated off (*ca.* 20 mmHg) and the residual oil was distilled (bulb-to-bulb) at 100 °C (0.05 mmHg) to afford a colourless oil (partial crystallization occurred when set aside) [14.7 g, ~73:27 mixture of (**4**) and (**7**), 49% estimated yield,

allowing for the presence of unchanged butenoate (34% by $^{19}F$ NMR)]. This mixture was then submitted to enzymatic hydrolysis by PLE (E.C.3.1.1.1.) as previously described,[13] affording the ester (**4**) (93% recovery) and the acid (**8**) (87% yield).

3-exo-*Trifluoromethyl*-7-*oxabicyclo*[2.2.1]*hept*-5-*ene*-2-endo-*carboxylic Acid* (**5**).—The ester (**4**) (6.0 g, 25.4 mmol) was refluxed with 10% aqueous sodium hydroxide (18 ml) for 2 h. After cooling, water (100 ml) was added and the solution was extracted with dichloromethane (2 × 30 ml). The aqueous fraction was acidified with dilute sulphuric acid and extracted with dichloromethane (4 × 50 ml) with intermediate addition of brine. The combined organic extracts were dried over $MgSO_4$, and concentrated to give the *acid* (**5**) as a white solid suitable for the next step (4.3 g, 82%), m.p. 104.7 °C (from hexane–benzene) (Found: C, 46.1; H, 3.3. $C_8H_7F_3O_2$ requires C, 46.2; H, 3.4%); $\delta_H(CDCl_3$; 90 MHz) 2.65 (1 H, qd, $J_{3,F}$ 9.1 and $J_{3,2}$ 4.4 Hz, 3-H), 3.27 (1 H, t, $J$ ~4.6 Hz, 2-H), 5.16 (1 H, br s, 4-H), 5.31 (1 H, br d, $J_{1,2}$ 4.7 Hz, 1-H), 6.45 (1 H, dd, $J_{5,6 \text{ or } 6,5}$ 5.9 and $J$ 1.5 Hz, 5- or 6-H), 6.59 (1 H, dd, $J_{6,5 \text{ or } 5,6}$ 5.9 and $J$ 1.5 Hz, 6- or 5-H), and 12.0 (1 H, br s, OH); $\delta_F(CDCl_3)$ −68.8 (d, $J_{F,3}$ 9.1 Hz).

*t-Butyl* 3-exo-*Trifluoromethyl*-7-*oxabicyclo*[2.2.1]*hept*-5-*ene*-2-endo-*carboxylate* (**6**).—A mixture of the acid (**5**) (3.0 g, 14.4 mmol), liquified isobutene (~4.5 g, 80 mmol), t-butyl alcohol (1.15 ml), and concentrated sulphuric acid (0.29 ml) was stirred in a thick-walled glass pressure reaction tube for 15 h at room temperature. The mixture was cooled to *ca.* −70 °C before opening and the excess of isobutene boiled off on warming to room temperature. After neutralization with saturated aqueous sodium hydrogen carbonate (25 ml), the mixture was extracted with ether (3 × 40 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a brown solid. Sublimation at 50 °C (0.05 mmHg) afforded the *ester* (**6**) as a white solid (3.4 g, 90%), m.p. 70.4 °C (Found: C, 54.3; H, 5.7; F, 21.9. $C_{12}H_{15}F_3O_3$ requires C, 54.5; H, 5.7; F, 21.6%); $\delta_H(CDCl_3$; 90 MHz) 1.44 (9 H, s, Bu$^t$), 2.63 (1 H, qd, $J_{3,F}$ 9.4 and $J_{3,2}$ 4.4 Hz, 3-H), 3.15 (1 H, t, $J$~4.6 Hz, 2-H), 5.10 (1 H, br s, 4-H), 5.20 (1 H, br d, $J_{1,2}$ 4.7 Hz, 1-H), 6.38 (1 H, dd, $J_{5,6 \text{ or } 6,5}$ 5.7 and $J$ 1.5 Hz, 5- or 6-H), and 6.55 (1 H, dd, $J_{6,5 \text{ or } 5,6}$ 5.7 and $J$ 1.5 Hz, 6- or 5-H); $\delta_F(CDCl_3)$ −68.8 (d, $J_{F,3}$ 9.4 Hz).

*t-Butyl* 5β-*Hydroxy*-6β-*trifluoromethylcyclohexa*-1,3-*diene-carboxylate* (**10**).—To a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (3.3 ml, 15.6 mmol) in anhydrous THF (20 ml), cooled at *ca.* −70 °C under argon, was added dropwise ~1.25M butyl-lithium in hexanes (11.8 ml, 14.8 mmol). The mixture was stirred for 20 min at −70 °C, and the ester (**6**) (3.0 g, 11.4 mmol) in anhydrous THF (20 ml) was added dropwise. After addition was complete, the mixture was allowed to warm to 0 °C during 75 min and was quenched with saturated aqueous ammonium chloride (70 ml). After extraction with chloroform (2 × 130 ml), the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow viscous oil. Column chromatography on silica gel (eluant dichloromethane–ethyl acetate, 80:20) gave the *cyclohexadienol* (**10**) as an off-white solid (2.59 g, 9.8 mmol, 86%), m.p. 66.8–67 °C (Found: C, 54.1; H, 5.8; F, 21.6. $C_{12}H_{15}F_3O_3$ requires C, 54.5; H, 5.7; F, 21.6%); $\nu_{max}(CCl_4)$ 3 620 and 1 708 cm$^{-1}$; $\delta_H(CDCl_3$; 300 MHz) 1.51 (9 H, s, Bu$^t$), ~2.90 (1 H, br s, OH), 3.64 (1 H, quint, $J_{6,F}$ 9.4 and $J_{6,5}$ 8.9 Hz, 6-H), 5.08 (1 H, br d, $J_{5,6}$ 8.9 Hz, 5-H), 6.00 (1 H, ddd, $J_{3,4}$ 9.7, $J_{3,2}$ 5.3, and $J_{3,5}$ 2.9 Hz, 3-H), 6.13 (1 H, dd, $J_{4,3}$ 9.7 and *ca.* 1.8 Hz, 4-H), and 7.13 (1 H, d, $J_{2,3}$ 5.3 Hz, 2-H); $\delta_F(CDCl_3)$ −63.7 (d, $J_{F,6}$ 9.4 Hz).

*t-Butyl* 5β-[*Dimethyl*(*t-butyl*)*silyloxy*]-6β-*trifluoromethyl-cyclohexa*-1,3-*dienecarboxylate* (**11**).—To stirred 2,6-lutidine (1.3 ml, 1.2 g, 11.2 mmol) under argon cooled to 0–5 °C, was added dimethyl(t-butyl)silyl trifluoromethanesulphonate (1.80 ml, 2.07 g, 7.8 mmol). After 30 min, a solution of the diene (**9**) (1.35 g, 5.11 mmol) in dichloromethane (5 ml) was added. The mixture was stirred for 45–50 min at 0 °C with TLC monitoring (dichloromethane), poured into chilled saturated aqueous sodium hydrogen carbonate (20 ml), and extracted with dichloromethane (3 × 20 ml). The combined organic extracts were dried ($Na_2SO_4$) and concentrated under reduced pressure to give a yellow oil. Column chromatography on silica gel, with dichloromethane as eluant, gave the *ether* (**11**) as a viscous colourless oil (1.83 g, 95%) [Found: C, bad (56.0); H, 7.7; $M^+$, 378.1832. $C_{18}H_{29}F_3O_3Si$ requires C, 57.1; H, 7.7%; $M$, 378.1838); $\delta_H(CDCl_3$; 500 MHz) 0.1 (6 H, s, $SiMe_2$), 0.91 (9 H, s, SiBu$^t$), 1.49 (9 H, s, OBu$^t$), 3.43 (1 H, quint, $J_{6,F}$ 9.4 and $J_{6,5}$ 9.0 Hz, 6-H), 4.99 (1 H, br d, $J_{5,6}$ 9.0 Hz, 5-H), 5.91 (1 H, ddd, $J_{3,4}$ 9.6, $J_{3,2}$ 5.3, and $J_{3,5}$ 2.9 Hz, 3-H), 6.01 (1 H, br d, $J_{4,3}$ 9.6 Hz, 4-H), and 7.06 (1 H, d, $J_{2,3}$ 5.3 Hz, 2-H); $\delta_F(CDCl_3)$ −63.8 (d, $J_{F,6}$ 9.4 Hz).

*t-Butyl* 5β-[*Dimethyl*(*t-butyl*)*silyloxy*]-3α,4α-*dihydroxy*-6β-*trifluoromethylcyclohex*-1-*enecarboxylate* (**12**).—To a stirred mixture of osmium tetroxide (1.0 g, 3.93 mmol) and pyridine (0.64 ml, 7.86 mmol) in diethyl ether (20 ml) at 0 °C was added a solution of the diene (**11**) (1.44 g, 3.81 mmol) in ether (15 ml). A brown precipitate developed immediately. The mixture was allowed to warm slowly to room temperature with stirring for *ca.* 15 h. The suspension was cooled to 0–5 °C and hydrogen sulphide was bubbled through, during 15 min. A black precipitate developed immediately. Stirring was continued for 2 h and hydrogen sulphide was introduced again for another 15 min. The suspension was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give a dark-brown viscous oil (1.38 g). Purification by column chromatography on silica gel, with dichloromethane–ethyl acetate (80:20) as eluant, gave the *diol* (**12**) as a brown viscous oil (0.71 g, 45%) (Found: $M^+ - OBu^t$, 339.1233. $C_{14}H_{22}F_3O_4Si$ requires $M - OBu^t$, 339.1239); $\delta_H(CDCl_3$; 500 MHz) 0.12 (6 H, s, $SiMe_2$), 0.92 (9 H, s, SiBu$^t$), 1.47 (9 H, s, OBu$^t$), 2.81 (1 H, br s, OH), 3.25 (1 H, br s, OH), 3.78 (1 H, qd, $J_{6,F}$ 9.7 and $J_{6,5}$ 5.8 Hz, 6-H), 4.08 (1 H, ddq, $J_{5,4}$ 10.1, $J_{5,6}$ 5.8, and $J_{5,F}$ 2.2 Hz, 5-H), 4.14 (1 H, dd, $J_{4,5}$ 10.1 and $J_{4,3}$ 4.8 Hz, 4-H), 4.51 {1 H, t, $J$ 4.6 Hz [= $(J_{3,2} + J_{3,4})/2$], 3-H}, and 6.86 (1 H, d, $J_{2,3}$ 4.4 Hz, 2-H); $\delta_F(CDCl_3)$ −60.8 (d, $J_{F,6}$ 9.7 Hz).

*t-Butyl* 3α,4α,5β-*Trihydroxy*-6β-*trifluoromethylcyclohex*-1-*enecarboxylate* (**13**) [(±)-*t-Butyl* cis-6-*Trifluoromethylshikimate*].—To a stirred solution of the diol (**12**) (1.59 g, 3.86 mmol) in THF (14 ml) cooled to 0–5 °C was added 1.0M tetrabutylammonium fluoride in THF (7.72 ml, 7.72 mmol). The mixture was stirred for *ca.* 1.5 h (TLC monitoring), and concentration under reduced pressure afforded an olive brown oil. Purification by column chromatography on silica gel, with acetone as eluant, afforded the *triol* (**13**) as a green–off-white solid (1.05 g, 91%), m.p. 149.4–149.9 °C (from diethyl ether) (Found: C, 48.2; H, 5.7; F, 19.3. $C_{12}H_{17}F_3O_5$ requires C, 48.3; H, 5.7; F, 19.1%); $\delta_H[(CD_3)_2CO$–$D_2O$; 500 MHz] 1.49 (9 H, s, Bu$^t$), 3.85 (1 H, qd, $J_{6,F}$ 9.9 and $J_{6,5}$ 5.8 Hz, 6-H), 4.05 (1 H, dd, $J_{4,5}$ 9.4 and $J_{4,3}$ 4.9 Hz, 4-H), 4.15 (1 H, ddq, $J_{5,4}$ 9.4 Hz, $J_{5,6}$ 5.8, and $J_{5,F}$ 1.8 Hz, 5-H), 4.47 {1 H, t, $J$ 4.4 Hz [= $(J_{3,2} + J_{3,4})/2$], 3-H}, and 6.81 (1 H, d, $J_{2,3}$ 4.0 Hz, 2-H); $\delta_F[(CD_3)_2CO)]$ −60.3 (d, $J_{F,6}$ 9.9 Hz).

3α,4α,5β-*Trihydroxy*-6β-*trifluoromethylcyclohex*-1-*enecarboxylic Acid* (**14**) [(±)-cis-6-*Trifluoromethylshikimic Acid*].—A solution of the ester (**13**) (0.33 g, 1.11 mmol) in trifluoroacetic acid (3.0 ml) was stirred for 3 h at room temperature. The excess

of acid was evaporated off *in vacuo* (*ca.* 0.05 mmHg) and the glassy residue triturated with diethyl ether (3 ml), giving (**14**) as an off-white solid (0.183 g). Traces of contaminating osmium were removed by dissolution in water (10 ml), addition of decolourizing activated charcoal (Norit, *ca.* 0.1 g), and stirring for 15 min. The suspension was suction-filtered over a glass-microfibre filter and the filtrate lyophilized to give the *acid* (**14**) (0.162 g, 60%) as a fluffy white powder, m.p. 183.1 °C (Found: C, 39.6; H, 3.7; F, 23.6; $M^+$, 242.0404. $C_8H_9F_3O_5$ requires C, 39.7; H, 3.75; F, 23.5%; *M*, 242.0402); $\delta_H$[$(CD_3)_2CO$; 500 MHz] 3.90 (1 H, qd, $J_{6,F}$ 10.0 and $J_{6,5}$ 5.6 Hz, 6-H), ~4.0–4.8 (v br, OH), 4.08 (1 H, ddd, $J_{4,5}$ 9.8, $J_{4,3}$ 4.9, and $J$ 0.6 Hz, 4-H), 4.13 (1 H, ddq, $J_{5,4}$ 9.8, $J_{5,6}$ 5.6, and $J_{5,F}$ 2.0 Hz, 5-H) 4.51 {1 H, t, $J$ 4.4 Hz [= $(J_{3,2} + J_{3,4})/2$], 3-H}, and 6.98 (1 H, d, $J_{2,3}$ 3.9 Hz, 2-H); $\delta_F$[$(CD_3)_2CO$] −60.2 (d, $J_{F,6}$ 10.0 Hz).

*Ethyl* (Z)-4,4,4-*Trifluorobut*-2-*enoate* (**16**).—A 500 ml heavy-walled glass (Pyrex) hydrogenation flask, adaptable for a Parr hydrogenation apparatus, was charged with ethyl 4,4,4-trifluorobutynoate[20] (8.0 g, 48 mmol), methanol (80 ml), 5% palladium on barium sulphate (0.165 g), and synthetic quinoline (8 drops). The flask was placed in the Parr apparatus, evacuated (*ca.* 25–50 mmHg), and filled for a short time with hydrogen (usually *ca.* 1–2 min), then evacuated again. Hydrogen was introduced to *ca.* 54 psi (*ca.* 3.67 atm). The flask was agitated for 40–45 min during which time the pressure decreased from 39–40 psi (*ca.* 2.70 atm) (monitoring of hydrogen uptake by $^{19}F$ NMR spectroscopy proved to be useful in first experiments). After hydrogenation was complete, the suspension was decanted from the catalyst and methanol was distilled off in a spinning-band still. The distillation residues of six identical experiments were gathered and distilled in the auto-annular still, affording the *alkene* (**16**) as a colourless liquid (39.08 g, 80%), b.p. 128–130 °C (Found: C, 42.6; H, 4.2; F, 33.9. $C_6H_7F_3O_2$ requires C, 42.9; H, 4.2; F, 33.9%); $\nu_{max}$ 1 743 and 1 665 $cm^{-1}$; $\delta_H$($CDCl_3$; 90 MHz) 1.32 (3 H, t, $J$ 7.2 Hz, Me), 4.27 (2 H, q, $J$ 7.2 Hz, $CH_2$), 6.05 (1 H, dq, $J_{3,2}$ 12.6 and $J_{3,F}$ 7.6 Hz, 3-H), and 6.29 (1 H, d, $J_{2,3}$ 12.6 Hz, 2-H); $\delta_F$($CDCl_3$) −61.2 (d, $J_{F,3}$ 7.6 Hz).

(Z)-4,4,4-*Trifluorobut*-2-*enoic Acid* (**17**).—A mixture of the ester (**16**) (10.0 g, 59.5 mmol), formic acid (7 ml, 8.54 g), and conc. sulphuric acid (0.25 ml) was heated (oil bath) in a round-bottomed flask fitted with a glass helices-packed column equipped with a variable take-off head. When the reflux had stabilized (head temperature *ca.* 55 °C), ethyl formate was slowly distilled off overnight (>15 h). At the end of the distillation, the pot temperature was allowed gradually to reach 140 °C (head temperature *ca.* 85 °C). Heating was stopped and a short Vigreux column was used to distill off the excess of formic acid. Distillation under reduced pressure (*ca.* 11 mmHg) afforded the *acid* (**17**) as a colourless liquid (5.35 g, 64%), b.p. 66–69 °C (11 mmHg) (Found: C, 34.3; H, 2.4; F, 39.6. $C_4H_3F_3O_2$ requires C, 34.3; H, 2.2; F, 40.7%); $\delta_H$($CDCl_3$; 90 MHz) 6.12 (1 H, dq, $J_{3,2}$ 12.4 and $J_{3,F}$ 7.2 Hz, 3-H), 6.32 (1 H, d, $J_{2,3}$ 12.4 Hz, 2-H), and 10.9 (*ca.* 1 H, s, $CO_2H$); $\delta_F$ −61.2 (d, $J_{F,3}$ 7.2 Hz).

3-endo-*Trifluoromethyl*-7-*oxabicyclo*[2.2.1]*hept*-5-*ene*-2-endo-*carboxylic Acid* (**20**) *and* 3-exo-*Trifluoromethyl*-7-*oxabicyclo*[2.2.1]*hept*-5-*ene*-2-exo-*carboxylic Acid* (**23**).—A mixture of the acid (**17**) (9.40 g, 67 mmol) and furan (10 ml, 9.36 g, 0.137 mmol) was set aside at room temperature for 13 days (monitoring by $^1H$ and $^{19}F$ NMR). The excess of furan was removed under reduced pressure to give a brown viscous oil that was a mixture of the acids (**20**) and (**23**) in the ratio 80:20 (12.86 g, 92%). This mixture was suitable for the next step.

*t-Butyl* 3-*endo*-*Trifluoromethyl*-7-*oxabicyclo*[2.2.1]*hept*-5-*ene*-2-endo-*carboxylate* (**21**) *and t-Butyl* 3-exo-*Trifluoromethyl*-7-*oxabicyclo*[2.2.1]*hept*-5-*ene*-2-exo-*carboxylate* (**24**).—The preceding crude mixture of acids (**20**) and (**23**) (4.95 g, 23.8 mmol) was esterified as described for the acid (**5**) to give the crude esters (5.0 g) as an orange powder. Separation of the isomers by column chromatography on silica gel with dichloromethane as eluant afforded, in order of elution (for two combined identical experiments, *i.e.* 9.9 g of starting material): 3.85 g of (**21**) as a white solid ($R_F$ *ca.* 0.85), 3.34 g of a mixture of the two esters (to be recycled), and 0.91 g of (**24**) as a white solid ($R_F$ ~0.65).

The *ester* (**21**) had m.p. 81 °C (Found: C, 54.2; H, 5.6; F, 21.3. $C_{12}H_{15}F_3O_3$ requires C, 54.5; H, 5.7; F, 21.6%); $\delta_H$($CDCl_3$; 500 MHz) 1.38 (9 H, s, $Bu^t$), 3.29 (1 H, dqd, $J_{3,2}$ 10.0, $J_{3,F}$ 9.2, and $J_{3,4}$ 4.4 Hz, 3-H), 3.33 (1 H, dd, $J_{2,3}$ 10.0 and $J_{2,1}$ 4.0 Hz, 2-H), 5.04 [1 H, dm, $J$ ~4.1 Hz, 1-H (?)], 5.06 [1 H, m, 4-H (?)], 6.36 (1 H, ddq, $J_{5,6}$ 5.8, $J_{5,4}$ 1.7, and $J_{5,F}$ 1.7 Hz, 5-H), and 6.75 (1 H, dd, $J_{6,5}$ 5.8 and $J_{6,1}$ 1.5 Hz, 6-H); $\delta_F$($CDCl_3$) −60.5 (br d, $J_{F,3}$ 9.2 Hz).

The ester (**24**) had m.p. 115 °C; $\delta_H$($CDCl_3$; 300 MHz) 1.45 (s, 9 H, $Bu^t$), *ca.* 2.63 [2 H, m (8 lines), 2-H and 3-H. Calc. spectrum (LAOCOON III[24]): 3-H, 792.14 Hz (δ 2.64), $J_{3,F}$ 9.2 and $J_{3,2}$ 9.0 Hz; 2-H, 797.14 Hz (δ 2.66), $J_{2,3}$ 9.0 Hz. Ethyl ester analogue (**22**): δ(obs.) 2.68 (1 H, quint, $J_{3,F}$ 9.6 and $J_{3,2}$ 9.1 Hz, 3-H), 2.75 (1 H, d, $J_{2,3}$ 9.1 Hz, 2-H)], 5.16 (1 H, s, 1-H or 4-H), 5.27 (1 H, s, 4-H or 1-H), and 6.47 (2 H, ~s, 5-H and 6-H); $\delta_F$($CDCl_3$) −63.3 (~d).

*t-Butyl* 5β-*Hydroxy*-6α-*trifluoromethylcyclohexa*-1,3-*diene*-*carboxylate* (**25**).—The ester (**21**) (4.20 g, 15.9 mmol) was ring-opened with lithium hexamethyldisilazide in THF as described for the ester (**6**), affording an oil. Chromatography on silica gel, with dichloromethane–ethyl acetate (80:20) as eluant afforded the *cyclohexadienol* (**25**) as an oil (3.49 g, 83%) that gave a white solid when set aside in a refrigerator, m.p. 45.7 °C (Found: C, 54.3; H, 5.9; F, 20.9. $C_{12}H_{15}F_3O_3$ requires C, 54.5; H, 5.7; F, 21.6%); $\nu_{max}$($CCl_4$) 3 580 and 1 708 $cm^{-1}$; $\delta_H$($CDCl_3$; 500 MHz) 1.50 (1 H, s, $Bu^t$), 3.85 (1 H, q, $J_{6,F}$ 9.9 Hz, 6-H), 4.47 (1 H, br s, 5-H) [ethyl ester analogue: br d at δ 4.50, $J$ 4.0 Hz], *ca.* 6.28 (2 H, m, 3-H and 4-H), and 7.25 (1 H, ~t, 2-H). Calc. ABXY spectrum: 2-H, 3 626.9 Hz (δ 7.25); 3-H, 3 146.0 Hz (δ 6.29); 4-H: 3 143.0 Hz (δ 6.28); 5-H: 2 250.0 Hz (δ 4.50); $J_{2,3}$ 5.8, $J_{2,4}$ 0.6, $J_{2,5}$ 0.0, $J_{3,4}$ 9.4, $J_{3,5}$ 0.1, and $J_{4,5}$ 5.0 Hz. Calc. frequencies (3-H and 4-H part): 3 132.0, 3 133.9, 3 141.6, 3 143.9, 3 147.0, 3 151.2, 3 153.7, and 3 155.7 Hz. Found: 3 131.6, 3 133.9, 3 141.6, 3 143.8, 3 147.0, 3 151.0, 3 153.4 and 3 155.8 Hz; $\delta_F$($CDCl_3$) −70.5 (d, $J_{F,6}$ 9.9 Hz).

*t-Butyl* 5β-[*Dimethyl*(*t-butyl*)*silyloxy*]-6α-*trifluoromethyl*-*cyclohexa*-1,3-*dienecarboxylate* (**26**).—The cyclohexadienol (**25**) (4.27 g, 16.2 mmol) was converted into its silylated derivative (**26**) with dimethyl(t-butyl)silyl trifluoromethanesulphonate and 2,6-lutidine, following the procedure described for its isomer (**10**). A brown oil was obtained which was chromatographed on silica gel, with dichloromethane–hexane (1:1), as eluant, to give the *ether* (**26**) (4.73 g, 77%) as an oil that crystallized when set aside in a refrigerator, m.p. 40.4 °C (Found: C, 57.5; H, 7.3. $C_{18}H_{29}F_3O_3Si$ requires C, 57.1; H, 7.7%); $\delta_H$($CDCl_3$; 500 MHz) 0.11 (3 H, s, SiMe), 0.14 (3 H, s, SiMe), 0.87 (9 H, s, $SiBu^t$), 1.50 (9 H, s, $OBu^t$), 3.71 (1 H, q, $J_{6,F}$ 10.2 Hz, 6-H), 4.44 (1 H, d, $J_{5,4}$ 5.5 Hz, 5-H), 6.09 (1 H, br dd, $J_{4,3}$ 9.4 and $J_{4,5}$ 5.5 Hz, 4-H), 6.20 [1 H, dd (d on irradiation of 2-H), $J_{3,4}$ 9.4 and $J_{3,2}$ 5.8 Hz, 3-H], and 7.19 (1 H, d, $J_{2,3}$ 5.8 Hz, 2-H); $\delta_F$($CDCl_3$) −70.5 (d. $J_{F,6}$ 10.2 Hz).

*t-Butyl* 5β-[*Dimethyl*(*t-butyl*)*silyloxy*]-3α,4α-*dihydroxy*-6α-*trifluoromethylcyclohex*-1-*enecarboxylate* (**27**).—To a stirred solution of the diene (**26**) (1.0 g, 2.65 mmol) in pyridine (10.2 ml)

**Table.** Fractional co-ordinates for non-hydrogen atoms of (±)-t-butyl *trans*-6-trifluoromethylshikimate (**28**).

| | *x/a* | *y/b* | *z/c* |
|---|---|---|---|
| C(1) | 0.172 0(3) | 0.470 5(4) | 0.418 7(7) |
| C(2) | 0.086 4(3) | 0.466 5(5) | 0.285 5(7) |
| C(3) | 0.019 0(3) | 0.315 6(5) | 0.189 2(8) |
| C(4) | 0.038 0(3) | 0.191 7(5) | 0.342 2(7) |
| C(5) | 0.146 9(3) | 0.166 5(4) | 0.375 3(7) |
| C(6) | 0.217 1(3) | 0.321 4(5) | 0.475 1(8) |
| C(7) | 0.315 1(4) | 0.312 8(5) | 0.392 3(13) |
| C(8) | 0.224 0(3) | 0.629 4(5) | 0.531 5(7) |
| C(9) | 0.349 4(4) | 0.760 3(5) | 0.855 3(9) |
| C(10) | 0.285 5(5) | 0.867 4(7) | 0.963 0(10) |
| C(11) | 0.412 5(4) | 0.840 7(7) | 0.705 9(11) |
| C(12) | 0.411 1(5) | 0.686 1(7) | 1.026 6(12) |
| O(1) | 0.207 0(3) | 0.750 2(3) | 0.458 4(6) |
| O(2) | 0.284 3(2) | 0.620 5(3) | 0.716 7(5) |
| O(3) | 0.038 6(3) | 0.266 2(3) | −0.031 0(5) |
| O(4) | −0.020 0(3) | 0.045 3(3) | 0.240 1(5) |
| O(5) | 0.162 9(2) | 0.056 0(3) | 0.529 4(6) |
| F(1) | 0.352(3) | 0.181 1(4) | 0.427 9(8) |
| F(2) | 0.383 1(3) | 0.432 8(4) | 0.458 1(9) |
| F(3) | 0.304 3(3) | 0.300 5(5) | 0.163 6(9) |

was added osmium tetroxide (0.68 g, 2.68 mmol). After stirring of the mixture for 8 h at room temperature, aqueous sodium bisulphite (1.22 g of $Na_2S_2O_5$ in 20.5 ml of water) and pyridine (13.6 ml) were added successively. After *ca.* 20 min, the mixture, which turned orange, was extracted with chloroform (1 × 80 ml, 2 × 40 ml). The combined organic extracts were dried ($K_2CO_3$) and concentrated under reduced pressure to give an orange oil. Chromatography on silica gel, with dichloromethane–ethyl acetate (70:30) as eluant, gave the *diol* (**27**) as a colourless oil (0.92 g, 84%) (Found: C, 52.45; H, 7.5; F, 14.65. $C_{18}H_{31}F_3O_5Si$ requires C, 52.4; H, 7.6; F, 13.8%); $\delta_H(CDCl_3$; 500 MHz) 0.08 (3 H, s, SiMe), 0.09 (3 H, s, SiMe), 0.83 (9 H, s, SiBu$^t$), 1.45 (9 H, s, OBu$^t$), 2.88 (2 H, br s, OH), 3.38 (1 H, br q, $J_{6,F}$ 9.9 Hz, 6-H), 3.76 [1 H, t, *J* 4.7 Hz, 4-H (?)], *ca.* 4.40 [2 H, m (4 lines), 3-H and 5-H (?)], and 6.75 (1 H, br d, *J* 2.7 Hz, 2-H); $\delta_F(CDCl_3)$ −62.8 (br d, $J_{F,6}$ 9.9 Hz).

*t-Butyl* 3α,4α,5β-*Trihydroxy*-6α-*trifluoromethylcyclohex*-1-*enecarboxylate* (**28**) [(±)-*t-Butyl* trans-6-*Trifluoromethylshikimate*].—The procedure described for (**12**) was followed for (**27**) (2.6 g, 6.31 mmol) with a longer reaction time (*ca.* 7 h at 0–10 °C; TLC monitoring) affording the *triol* (**28**) as a white crystalline solid (1.67 g, 89%), m.p. 129.4 °C (Found: C, 48.55; H, 5.6; F, 18.9. $C_{12}H_{17}O_5F_3$ requires C, 48.3; H, 5.7; F, 19.1%); $\delta_H[(CD_3)_2CO$–$D_2O$; 300 MHz] 1.49 (9 H, s, Bu$^t$), 3.47 (1 H, qd, $J_{6,F}$ 9.8 and $J_{6,5}$ 5.2 Hz, 6-H), 3.59 (1 H, dd, $J_{4,5}$ 8.1 and $J_{4,3}$ 3.7 Hz, 4-H), 4.29 (1 H, dd, $J_{5,4}$ 8.1 and $J_{5,6}$ 5.2 Hz, 5-H), 4.35 {1 H, t, *J* 4.5 Hz [= $(J_{3,2} + J_{4,3})/2$], 3-H}, and 6.80 (1 H, dd, $J_{2,3}$ 5.3 and *J* 1.2 Hz, 2-H). In the absence of $D_2O$, three OH doublets absorb at δ 4.11, 4.27, and 4.57 (*J* 5.2, 5.2, and 4.7 Hz respectively); $\delta_F[(CD_3)_2CO]$ −64.5 (d, $J_{F,6}$ 9.8 Hz).

3α,4α,5β-*Trihydroxy*-6α-*trifluoromethylcyclohex*-1-*enecarboxylic Acid* (**29**) [(±)-trans-6-*Trifluoromethylshikimic Acid*].—A solution of the ester (**28**) (1.13 g, 3.8 mmol) in trifluoroacetic acid (10 ml) was stirred for 3 h at room temperature. After evaporation of the excess of acid (room temperature; *ca*, 0.05 mmHg), the residue was triturated in diethyl ether to give (**29**) by suction filtration, as a white powder (0.78 g, 85%), m.p. 148.8 °C (Found: C, 39.5; H, 3.9; F, 23.3. $C_8H_9F_3O_5$ requires C, 39.7; H, 3.75; F, 23.5%); $\delta_H[(CD_3)_2CO$; 500 MHz] 3.52 [1 H, qdd, $J_{6,F}$ 9.0, $J_{6,5}$ 5.0, and $J_{6,2}$ *ca.* 1.0 Hz (measured at 300 MHz), 6-H], 3.62 (1 H, dd, $J_{4,5}$ 7.8 and $J_{4,3}$ 3.7 Hz, 4-H), 4.35 (1 H, dd, $J_{5,4}$ 7.8 and $J_{5,6}$ 5.0 Hz, 5-H), 4.39 {1 H, t, *J* 4.5 Hz [~ $(J_{3,2} + J_{3,4})/2$], 3-H}, 4.56 (br s, OH), *ca.* 3.8–4.8 (v br, OH), and 6.95 (1 H, dd, $J_{2,3}$ 5.2 and $J_{2,6}$ 0.9 Hz, 2-H); $\delta_F[(CD_3)_2CO]$ −64.5 (d, $J_{F,6}$ 9.0 Hz).

*X-Ray Crystal Structure Analysis of* (**28**).—$C_{12}H_{17}O_5F_3$, $M$ = 298.256; colourless crystal (1 × 0.2 × 0.03 mm) extracted from a mica-like sample, grown from diethyl ether; triclinic, space group $P\bar{1}$, $a$ = 13.689(9), $b$ = 8.606(7), $c$ = 6.100(6) Å, α = 97.22(4), β = 98.73(4), γ = 96.21(4)°, $V$ = 698.74 Å$^3$, $Z$ = 2, $D_c$ = 1.42 g cm$^{-3}$, Cu-$K_\alpha$, λ = 1.5418 Å. From the 2 074 unique reflections, measured on a Philips automated four-circle PW 1100 diffractometer and collected by the θ–2θ scan technique to θ = 60°, 1 792 were considered as observed [$I > 3\sigma(I)$]. The structure was solved by direct methods [25] and refined by full-matrix least-squares minimizing $\Sigma w(\Delta F)^2$. All hydrogen atoms were located on difference Fourier maps and introduced in the calculations, but not refined. Final conventional $R$ 0.0945, the weighting scheme being $w = 1/[\sigma^2(F_o) + 0.0008\,F_o^2]$, using σ from counting statistics. For non-hydrogen atom co-ordinates, see Table. Hydrogen atom co-ordinates, thermal parameters, bond distances, and bond angles have been deposited at the Cambridge Crystallographic Data Centre.*

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