The Angular Trifluoromethyl Group. Part 4.[1] Synthesis of the 9,9,9-Trifluoro Analogue of the Wieland–Miescher Ketone

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The 9,9,9-trifluoro analogue of the Wieland–Miescher ketone **15**, intended to serve as a precursor of 19,19,19-trifluoro steroids, has been prepared from 2-trifluoromethyl-1,4-benzoquinone **1** *via* a Diels–Alder reaction as the key step.

The often beneficial alteration of properties brought by the selective introduction of fluorine atoms into strategically chosen positions of biologically active molecules has recently been highlighted in an extensive review.[2]

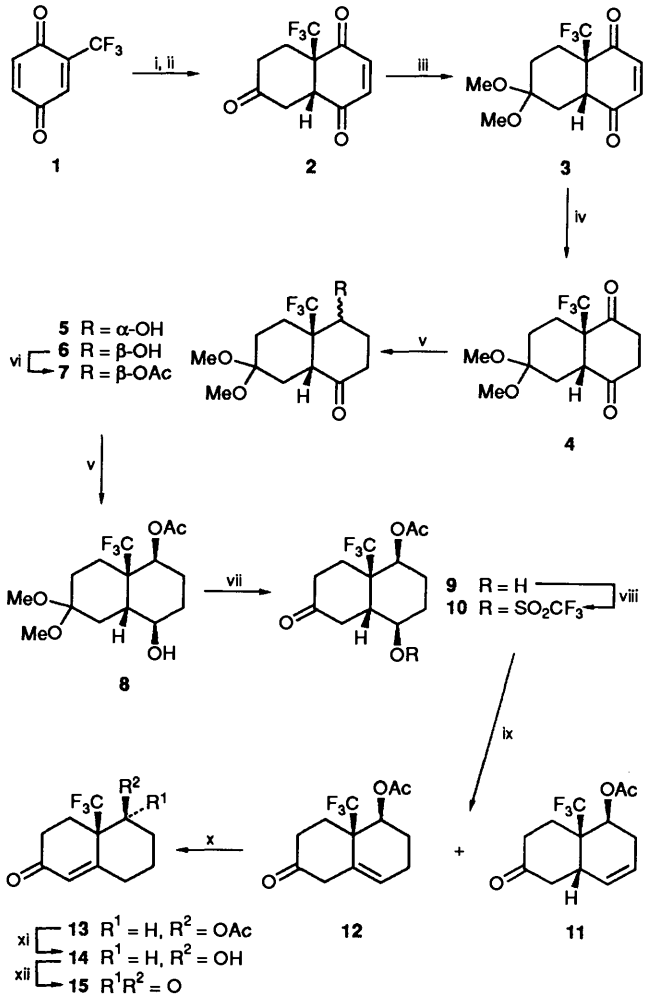
In our earlier work on fluorinated steroids,[3] we demonstrated that the incorporation of an angular trifluoromethyl group, in place of the methyl group, at the CD ring junction of some steroidal estrogens, while preserving the binding affinity of the host molecule towards its elected receptor, might also give new antagonist properties to the fluorinated molecules. On the other hand, it has been shown that 19,19-difluoroandrostenedione may act as an irreversible inhibitor of human cytochrome P-450 aromatase.[4] Since this enzyme is involved in estrogen biosynthesis, this fluorinated compound could find use in the treatment of estrogen-dependent breast cancer.[5] Bringing all these facts together encouraged us to embark on a program directed towards the synthesis of steroidal androgens bearing a trifluoromethyl group at the AB ring junction.

We selected the trifluoroanalogue **15** of the Wieland–Miescher ketone as a pivotal compound in our planned synthesis because this ketone has already been used for the elaboration of steroids[6] and terpenes.[7]

Results and Discussion

Robinson annulation of the Michael adduct between methyl vinyl ketone and 2-methylcyclopentane-1,3-dione is the customary path to the Wieland–Miescher ketone.[8] Although the lower homologue 7a-trifluoromethylindene-1,5-dione could be obtained using this route,[9] lack of the requisite 2-trifluoromethylcyclohexane-1,3-dione† at the present time precludes preparation of the title compound using this approach.

Some years ago, we described a convenient preparation of the quinone **1** by chlorous acid oxidation of 3-trifluoromethylphenol.[10] The ready availability of this fluorinated material led us to consider a Diels–Alder reaction as an attractive means of introducing the angular trifluoromethyl group (Scheme 1). We were pleased to find, therefore, that condensation of 2-trimethylsiloxybuta-1,3-diene and the quinone **1** proceeded easily in dichloromethane at room temperature to furnish a single adduct **2** in good isolated yield (89%) after methanolysis. The high regioselectivity observed in this reaction is noteworthy; earlier Diels–Alder condensations of the quinone **1** with simple dienes[11] gave ambiguous results,‡ whilst poor regioselectivity was observed by using the same siloxy diene with other trifluoromethyl-bearing dienophiles.[12]



Scheme 1 *Reagents and conditions:* i, 2-trimethylsiloxybuta-1,3-diene, CH_2Cl_2; ii, MeOH; iii, $HC(OMe)_3$, Amberlyst-15; iv, H_2/10% Pd-C; v, $NaBH_4$, MeOH, THF; vi, Ac_2O, DMAP, 2,6-lutidine, CH_2Cl_2; vii, 1 mol dm^{-3} HCl, THF; viii, $(CF_3SO_2)_2O$, 2,6-Bu^t_2-4-Me-pyridine, CH_2Cl_2; ix, toluene, 120 °C; x, toluene-*p*-sulphonic acid, benzene, 80 °C; xi, K_2CO_3, MeOH; xii, Jones reagent, acetone

The trione **2** possesses, besides some essential features of the target enone **15**, *i.e.* the angular trifluoromethyl group and the 1,6-dione system, an unwanted 4-keto group. The main synthetic problem to achieve our goal was thus the transformation of this carbonyl function into an endocyclic double bond and this, in turn, involved chemical discrimination between the three keto groups in the adduct **2**.

The more reactive 6-keto group was selectively protected as

† Until now, our own attempts to synthesize this fluorinated dione have met with poor yields. Unpublished results of this laboratory.

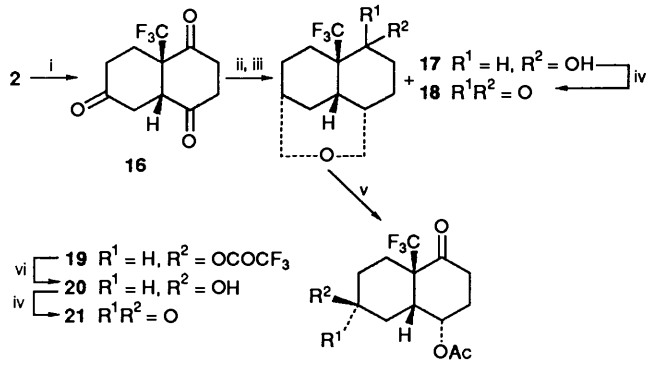
‡ When we repeated the experiment described in ref. 11*b* with 2,3-dimethylbutadiene but using dichloromethane as solvent we observed a 85:15 ratio in favour of the adduct with the angular trifluoromethyl group (76% isolated yield).

its dimethyl ketal **3** (92% yield) with methyl orthoformate using Amberlyst-15 as the catalyst[13] (Nafion catalyst[14] works as well).

Reduction of the conjugated double bond in the ketal **3** proceeded readily (H_2/Pd-C, diethyl ether) affording the homoannular dione **4** (97% yield). At this stage we hoped that the less encumbered 4-keto group might be reduced preferentially over the 1-carbonyl function shielded by the trifluoromethyl group. Unfortunately, this was not the case; using sodium borohydride in a THF–methanol mixture as the reducing agent,[15] we observed the formation of the epimeric alcohols **6** and **5** in a 87:13 ratio, the former being isolated in 75% yield after column chromatography. The same compounds were also obtained upon reduction of the enedione **3**, but in this case the reaction was less clean and the yield lower. Attempted use of bulkier reducing agents proved unsatisfactory: DIBAL[16] reacted sluggishly with the dione **4** and no reaction was observed with K-Selectride[17] after 2 h at room temperature. This unexpected regioselectivity in the reduction may perhaps be ascribed to an enhanced reactivity of the 1-carbonyl function induced by the electron attracting power of the vicinal trifluoro methyl group. In any event, distinction between the two carbonyl groups in the ketal **4** was accomplished and this was secured by converting the β alcohol **6** into its derived acetate **7** (95% yield).

Further reduction of the last carbonyl group of the acetate **7** (Scheme 2) was effected by using the same borohydride based reducing agent as before, but with a longer reaction time, to give the unstable (towards deketalisation) ketal **8**. This compound was not isolated but instead converted directly with acid into the keto alcohol **9** (90% yield from the acetate **7**).

As an alternative to this synthetic scheme, we also investigated the preparation of the diketone **21** cognate to the acetate **9** (Scheme 2). Reduction of the double bond of the



Scheme 2 *Reagents and conditions:* i, H_2/10% Pd-C; ii, poly(methylhydrosiloxane), CF_3CO_2H; iii, 4 mol dm^{-3} KOH; iv, Jones reagent; v, $CF_3C(O)OAc$; vi, pH 7, phosphate buffer, MeOH

primary Diels–Alder adduct **2** either with zinc in acetic acid or *via* catalytic hydrogenation gives the saturated triketone **16**. Exhaustive reduction of this ketone with triethylsilane, or more conveniently polymethylhydrosiloxane, in trifluoroacetic acid[18] afforded a mixture containing variable amounts from run to run of the epoxy ketone **18** and its derived epimeric alcohols **17**. Jones oxidation of the crude mixture thus obtained furnished the ketone **18** in *ca.* 60% overall yield.

Ether formation during ionic reduction with silanes is not unprecedented.[18] In our case, this side reaction may have been favoured by the close spatial proximity between the 4- and 6-keto groups induced by the *cis*-ring junction in the triketone **16**.

The tetrahydrofuran ring in the epoxy-ketone **18** was then regio-and stereo-selectively opened using the mixed anhydride acetyl trifluoroacetate.[19] This reaction could either be run with prior preparation of the mixed anhydride or more simply, but with a lower yield, by stirring the ketone **18** in a 1:1 mixture of acetic and trifluoroacetic anhydride. The intermediate trifluoroacetate **19** was not isolated, instead it was directly converted into the 6-alcohol **20** by selective hydrolysis in phosphate buffer. The overall yield of alcohol **20**, was 74% starting from the ketone **18**. The ketone **21** itself was obtained in 89% yield by Jones oxidation of the precursor alcohol **20**.

Although this route seems attractive, the 1-keto group being present in **21**, it gave rise to both lower and less consistent yields during attempted scale-up of the silane reduction step. For this reason, we selected the acetate **9** as the starting compound for completion of the synthesis.

Thermal elimination of a triflate group was selected as the means of introducing the alkene functionality in the target compound **15**. For this purpose, the alcohol **9** was converted into the triflate **10** (Scheme 1) using 2,6-di-*tert*-butyl-4-methylpyridine as the base. When heated in refluxing toluene, this triflate was smoothly converted into an inseparable 1:2 mixture of the alkenes **11** and **12**. Using this mixture, the conjugation of the $\Delta^{8,8a}$ double bond of the alkene **12** with the keto group proceeded readily with toluene-*p*-sulphonic acid in benzene to furnish the enone **13** and leaving unchanged the $\Delta^{7,8}$ alkene **11**.* Although this mixture too was not easy to separate, selective formation of the enol acetate from the ketone **11**, leaving the enone **13** unchanged allowed isolation of the latter in 56% yield starting from alcohol **9**. We also investigated use of the adduct between triphenylphosphine and trifluoromethanesulphonic anhydride as the dehydrating agent.[21] Although this reagent works equally well, its use does not give any improvement over the triflate route. No dehydration was observed using the Martin sulphurane reagent.[22]

The final steps of the synthesis were straightforward: saponification of the acetate **13** furnished the alcohol **14** (95%) which upon Jones oxidation gave the title ketone **15** (90%). The overall yield of trifluoromethyl Wieland–Miescher ketone **15** was thus *ca.* 20% from the quinone **2**.

Experimental

M.p.s were determined on a Mettler FP-61 apparatus. IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. NMR spectra were taken on Bruker AC-200 E (^{1}H, ^{13}C, ^{19}F), Bruker AM-300 (^{1}H), Varian CFT-20 (^{13}C) and Varian EM-360 L (^{19}F) spectrometers. The reference was $SiMe_4$ for ^{1}H and ^{13}C spectra and $CFCl_3$ for ^{19}F NMR spectra. *J* Values are recorded in Hz. Mass spectra were taken on AEI MS30 mass spectrometer operating at 70 eV. Silica gel refers to silica gel 60, 70–230 Mesh (Merck).

4aβ,5,8,8aβ-Tetrahydro-8a-trifluoromethylnaphthalene-1,4,6(7H)-trione **2**.—A solution of 2-trifluoromethyl-1,4-benzoquinone **1** (12 g, 68 mmol) and 2-trimethylsiloxybuta-1,3-diene (10 g, 70 mmol) in dichloromethane (100 ml) was stirred under an argon atmosphere for 24 h. The solvent was removed under reduced pressure and the crude product was dissolved in methanol (100 ml) and the solution stirred overnight. After removal of solvent, the *unsaturated ketone* **2** was obtained in four crops from ether (15 g, 89%), m.p. 111.5–112 °C (from ether) (Found: C, 53.6; H, 3.7; F, 23.4. $C_{11}H_9F_3O_3$ requires C, 53.7; H, 3.7; F, 23.15%); $\nu_{max}(CCl_4)/cm^{-1}$ 1700 and 1735; δ_H(200 MHz; $CDCl_3$) 6.95 (1 H, 2-H, d, $J_{2\text{-H},3\text{-H}}$ 10.5), 6.87 (1 H, 3-H, dd, $J_{3\text{-H},4a\text{-H}}$ 1.2), 3.55 (1 H, 4a-H, ddd, $J_{4a\text{-H},5\alpha\text{-H}}$ 12.8 and $J_{4a\text{-H},5\beta\text{-H}}$ 5.7), 2.84 (1 H, 8α-H, ddd, $J_{8\alpha\text{-H},8\beta\text{-H}}$ 13.9 and $J_{8\alpha\text{-H},7\text{-H}}$ 4.8, 5.2),

* This alkene was reluctant to conjugate with the carbonyl group even with the more powerful rhodium chloride reagent.[20]

2.65 (1 H, 5β-H, dd, $J_{5\beta\text{-H},5\alpha\text{-H}}$ 15.4), 2.46 (1 H, 5α-H, dd), 2.3–2.5 (2 H, 7α and 7β-H, complex m) and 2.08 p.p.m. (1 H, 8β-H, ddd, $J_{8\beta\text{-H},7\alpha\text{-H}}$ 6.5); δ_C(20 MHz, $CDCl_3$) 25.5 (C-8), 35.8, 40.7 (C-5, -7), 49.3 (C-4a), 56.4 (C-8a, J_{CF} 24), 124.8 (C-9, J_{CF} 286), 139.8 (C-2 and -3), 191.3 (C-1), 194.1 (C-4), and 204.0 p.p.m. (C-6); δ_F(56 MHz, $CDCl_3$) −71.3 p.p.m.; *m/z* 246 (M^+, 20), (*M* −28, 73), 190 (82) and 82 (100%).

4aβ,5,8,8aβ-Tetrahydro-8a-trifluoromethylnaphthalene-1,4,6(7H)-trione 6,6-Dimethyl Ketal **3**.—A solution of the *enone* **2** (8 g, 32.5 mmol) in trimethyl orthoformate (20 ml) containing Amberlyst-15 (1.3 g) was stirred overnight. The mixture was filtered and evaporated and the residue was eluted through a column of silica gel (CH_2Cl_2). The *ketal* **3** (8.7 g, 92%) was obtained as crystals which had m.p. 87–88 °C (from ether) (Found: C, 53.6; H, 5.2 $C_{13}H_{15}F_3O_4$ requires C, 53.4; H, 5.2%); $\nu_{max}(CCl_4)/cm^{-1}$ 1680; δ_H(200 MHz; $CDCl_3$) 6.81 (1 H, 2-H, d, $J_{2\text{-H},3\text{-H}}$ 10.4), 6.77 (1 H, 3-H, dd, $J_{3\text{-H},4a\text{-H}}$ 1.2), 3.24 (1 H, 4a-H, ddd, $J_{4a\text{-H},5\alpha\text{-H}}$ 13.6 and $J_{4a\text{-H},5\beta\text{-H}}$ 4.8), 3.18 and 3.17 (6 H, OMe, s), 2.54 (1 J, 8α-H, ddd, $J_{8\alpha\text{-H},8\beta\text{-H}}$ 13.6 and $J_{8\alpha\text{-H},7\text{-H}}$ 3.2, 3.9), 2.25 (1 H, 7β-H, ddd, $J_{7\beta\text{-H},7\alpha\text{-H}}$ 13.8), 2.05 (1 H, 5β-H, ddq, $J_{5\beta\text{-H},5\alpha\text{-H}}$ 13.8), 1.73 (1 H, 8β-H, ddd, $J_{8\beta\text{-H},7\alpha\text{-H}}$ 13.7 and $J_{8\beta\text{-H},7\beta\text{-H}}$ 4.1) 1.43 (1 H, 5α-H, dd) and 1.28 (1 H, 7α-H, td); δ_C(40 MHz, $CDCl_3$), 22.1 (C-8, J_{CF} 3), 27.6, 34.8 (C-5, -7), 47.6 (OMe), 47.8 (OMe and C-4a), 57.0 (C-8a, J_{CF} 23), 97.4 (C-6), 124.8 (C-9, J_{CF} 286), 139.4, 139.8 (C-2, -3), 191.9 (C-1), and 197.2 p.p.m. (C-4); δ_F(56 MHz, $CDCl_3$) −71.0 p.p.m.; *m/z* 292 (M^+, 17), 261 (30) and 101 (100%).

2,3,4aβ,5,8,8aβ-Hexahydro-8a-trifluoromethylnaphthalene-1,4,6(7H)-trione 6,6-Dimethyl Ketal **4**.—A solution of the *enone* **3** (2 g, 6.8 mmol) in ether (25 ml) was hydrogenated at atmospheric pressure over 10% Pd-C. The mixture was filtered through Celite, the filtrate evaporated and the residue crystallised from ether to give the *ketal*, (1.95 g, 97%) m.p. 68–69 °C (Found: C, 53.1; H, 5.8. $C_{13}H_{17}F_3O_4$ requires C, 53.1; H, 5.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1700; δ_H(200 MHz; $CDCl_3$) 3.11 and 3.09 (6 H, OMe, s, s), 2.99 (1 H, 4a-H, dd, $J_{4a\text{-H},5\alpha\text{-H}}$ 13.8 and $J_{4a\text{-H},5\beta\text{-H}}$ 4.4), 2.6–2.9 (4 H, 2α-, 2β-, 3α- and 3β-H), 2.35 (1 H, ddd, 8α-H, $J_{8\alpha\text{-H},8\beta\text{-H}}$ 13.4, $J_{8\alpha\text{-H},7\alpha\text{-H}}$ 3.8 and $J_{8\alpha\text{-H},7\beta\text{-H}}$ 3.3), 2.10 (1 H, 7β-H, ddd, $J_{7\beta\text{-H},7\alpha\text{-H}}$ 13.6 and $J_{7\beta\text{-H},8\beta\text{-H}}$ 4.1), 1.94 (1 H, 5β-H, ddq, $J_{5\beta\text{-H},5\alpha\text{-H}}$ 13.7 and $J_{5\beta\text{-H,F}}$ 2.3), 1.57 (1 H, 8β-H, ddd, $J_{8\beta\text{-H},7\alpha\text{-H}}$ 13.6), 1.38 (1 H, 5α-H, dd) and 1.30 p.p.m. (1 H, 7α-H, td); δ_C(50 MHz, $CDCl_3$) 22.3 (C-8), 27.4, 32.4, 33.9, 36.6 (C-2, -3, -5, -7), 47.2 (OMe), 47.3 (OMe), 48.1 (C-4a), 56.3 (C-8a, J_{CF} 23), 97.3 (C-6), 125.0 (C-9, J_{CF} 285), 201.0 (C-1) and 205.4 p.p.m. (C-4); δ_F(56 MHz, $CDCl_3$) −70.7 p.p.m.; *m/z* 294 (M^+, 33), 263 (44), 262 (42) and 101 (100%).

3,4,4aβ,5,6,8aβ-Hexahydro-4β-hydroxy-4a-trifluoromethylnaphthalene-1,7(2H,8H)-dione 7,7-Dimethyl Ketal **6**.—$NaBH_4$ (90 mg, 2.4 mmol) was added portionwise to a stirred solution of the ketone **4** (1 g, 3.4 mmol) in a mixture of THF (25 ml) and methanol (2.5 ml) cooled in an ice-bath. After 20 min crushed ice was added and the solution extracted with ether. The extract was dried ($MgSO_4$) and evaporated and the residue was separated on silica gel (20% ether, dichloromethane) to give the 4β-*alcohol* **6** (760 mg, 75%), m.p. 118–119 °C (from ether) (Found: C, 53.05; H, 6.5. $C_{13}H_{19}F_3O_4$ requires C, 52.7; H, 6.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 3580 and 1700; δ_H(200 MHz; $CDCl_3$) 4.43 (1 H, 4-H, ddq, $J_{4\text{-H},3\alpha\text{-H}}$ 5.1, $J_{4\text{-H},3\beta\text{-H}}$ 10.2 and $J_{4\text{-H,F}}$ 2.5), 3.13 (3 H, OMe, s), 3.10 (3 H, OMe, s), 2.72 (1 H, 8a-H, dd, $J_{8a\text{-H},8\beta\text{-H}}$ 13.3 and $J_{8a\text{-H},8\alpha\text{-H}}$ 3.9) and 1.5–2.6 (11 H); δ_C(50 MHz; $CDCl_3$) 21.8 (C-5), 26.1, 29.2, 31.8, 35.0 (C-2, -3, -6, -8), 47.2 (OMe), 47.5 (C-8a and OMe), 48.1 (C-4a, J_{CF} 21), 64.1 (C-4), 97.8 (C-7), 128.4 (C-9, J_{CF} 286 Hz) and 209.2 p.p.m. (C-1); δ_F(56 MHz, $CDCl_3$) −68.0 p.p.m.; *m/z* 296 (M^+, 25), 264 (50) and 101 (100%). A pure sample of the faster eluting 4α-*alcohol* **5** could be obtained after chromatography of the earlier fractions collected on several experiments during purification of the precedingly described isomer; it had m.p. 115.5–116.5 °C (from ether) (Found: C, 52.8; H, 6.6. $C_{13}H_{19}F_3O_4$ requires C, 52.7; H, 6.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 3540 and 1680. This compound is sensitive to acid catalysed epimerization at the 8a centre and all the NMR spectra were run in $CDCl_3$ containing traces of [$^2H_5$]-pyridine; δ_H(200 MHz) 4.22 (1 H, 4-H, unresolved t), 3.21 (1 H, OH, s), 3.11 (6 H, OMe, s), 2.5–2.9 (2 H), and 1.7–2.3 (9 H); δ_C(50 MHz) 24.8 (C-5), 28.6, 30.6, 32.1, 32.7 (C-2, -3, -6, -8), 46.8 (C-8a), 47.5 (OMe), 47.6 (OMe), 48.3 (C-4a, J_{CF} 21), 69.3 (C-4), 99.0 (C-7), 130.9 (C-9, J_{CF} 286) and 211.6 p.p.m. (C-1); δ_F(188 MHz) −71.8 p.p.m.; *m/z* 296 (M^+, 73) and 101 (100%).

4β-Acetoxy-3,4,4aβ,5,6,8aβ-hexahydro-4a-trifluoromethylnaphthalene-1,7-(2H,8H)-dione 7,7-Dimethyl Ketal **7**.—A solution of the *alcohol* **6** (1 g, 34 mmol) in dichloromethane (25 ml) containing acetic anhydride (350 μl, 38 mmol), 2,6-lutidine (400 μl, 34 mmol) and a catalytic amount of DMAP was stirred for 1 h at room temperature. The solvent was removed and the residue after elution through a column of silica gel using dichloromethane gave the *acetate* **7** (1.08 g, 95%), m.p. 94.5–95.5 °C (from ether) (Found: C, 53.4; H, 6.25. $C_{15}H_{21}F_3O_5$ requires C, 53.25; H, 6.3%); $\nu_{max}(CCl_4)/cm^{-1}$ 1700 and 1720; δ_H(200 MHz; $CDCl_3$) 5.68 (1 H, 4-H, tq, $J_{4\text{-H},3\alpha\text{-H}}$ 8.6, $J_{4\text{-H},3\beta\text{-H}}$ 8.6 and $J_{4\text{-H,F}}$ 2), 3.12 (3 H, OMe), 3.08 (3 H, OMe, s), 2.72 (1 H, 8a-H, ddd, $J_{8a\text{-H},8\beta\text{-H}}$ 13.4, $J_{8a\text{-H},8\alpha\text{-H}}$ 3.6 and $J_{8a\text{-H},2\beta\text{-H}}$ 1.5), 2.59 (1 H, 2α-H, ddd, $J_{2\alpha\text{-H},2\beta\text{-H}}$ 16.2, $J_{2\alpha\text{-H},3\beta\text{-H}}$ 11.3 and $J_{2\alpha\text{-H},3\alpha\text{-H}}$ 9.3), 2.38 (1 H, 2β-H, dtd, $J_{2\beta\text{-H},3\beta\text{-H}}$ 3.7 and $J_{2\beta\text{-H},3\alpha\text{-H}}$ 3.7), 1.5–2.2 (8 H) and 2.06 (OAc, s); δ_C(50 MHz, $CDCl_3$) 20.6 (OCO*Me*), 22.1 (C-8), 25.7 (C-2), 26.3, 31.6, 34.4 (C-3, -5, -6), 47.2 (OMe), 47.5 (OMe), 47.7 (C-4a, J_{CF} 22), 47.9 (C-8a), 64.7 (C-4), 97.6 (C-7), 127.4 (C-9, J_{CF} 286), 170.0 (*O*COMe) and 207.5 (C-1); δ_F(56 MHz, $CDCl_3$) −68.7 p.p.m.; *m/z* 338 (M^+, 10) and 101 (100%).

5β-Acetoxy-8β-hydroxy-3,4,4aβ,5,6,7,8,8aβ-octahydro-4a-trifluoromethylnaphthalen-2(1H)-one **9**.—The ketone **7** (1 g, 30 mmol) was reduced in the same way as the ketal **4** using $NaBH_4$ (0.12 g, 32 mmol) for 1.5 h. The crude product thus obtained was dissolved in THF (20 ml) containing hydrochloric acid (1 mol dm^{-3}; 2 ml) and stirred for 3 h. The mixture was then diluted with dichloromethane (50 ml) and washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated and the residue crystallized from ether to give the alcohol **9** (780 mg, 90%), m.p. 154–155 °C (Found: C, 52.9; H, 5.8. $C_{13}H_{17}F_3O_4$ requires C, 53.1; H, 5.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 3600, 1730 and 1710; δ_H(200 MHz; $CDCl_3$) 4.96 (1 H, 5α-H, unresolved t), 3.40 (1 H, 8-H, td, $J_{8\text{-H},8\alpha\text{-H}}$ 12.6 $J_{8\text{-H},7\beta\text{-H}}$ 12.6 and $J_{8\text{-H},7\alpha\text{-H}}$ 4.0), 1.5–2.9 (11 H) and 2.02 (OAc, s); δ_C(50 MHz; $CDCl_3$) 20.9 (OCO*Me*), 24.8, 25.1, 28.7, 36.9 ($J_{C,F}$ 2), 38.0, 39.9 (C-1, -3, -4, -6, -7), 46.7 (C-4a, J_{CF} 22), 67.9 (C-8), 69.6 (C-5, $J_{C,F}$ 3), 128.0 (C-9, J_{CF} 287), 169.4 (OCOMe) and 210.6 p.p.m. (C-2); δ_F(188 MHz, $CDCl_3$) −67.3 p.p.m.; *m/z* 294 (M^+, 5) and 215 (100%).

5β-Acetoxy-4,4aβ,5,6,7,8-hexahydro-4a-trifluoromethylnaphthalen-2(3H)-one **13**.—Trifluoromethanesulphonic anhydride (1.29 ml, 77 mmol) was slowly added to a stirred solution of the alcohol **9** (1.13 g, 38 mmol) in dichloromethane (50 ml), containing 2,6-di-*tert*-butyl-4-methylpyridine (3.16 g, 154 mmol), cooled in an ice bath and under an argon atmosphere. The solution was allowed to come to room temperature and stirred for additional 12 h. The solvent was then distilled off and replaced by dry toluene (50 ml) and the mixture was refluxed for 4 h. The toluene was removed under reduced pressure and the resulting solid was taken up in pentane and the solution filtered. The residue obtained after removal of the pentane was eluted on

a column of silica gel (dichloromethane) to give a 1:2 mixture of the alkenes **11** and **12** (980 mg) [δ_F(56 MHz; $CDCl_3$) −69.7 and 66.0 p.p.m. respectively]. This mixture was dissolved in benzene (50 ml) containing a few mg of toluene-*p*-sulphonic acid and refluxed for 1 h. After chromatography over silica gel (5% ether–dichloromethane) the unsaturated ketone **13** (180 mg) was isolated together with a mixture containing **11** and **13** (730 mg). This mixture was dissolved in an acetylating solution (100 ml)[2,3] and allowed to stand for 45 min. After work-up, column chromatography of the residue using the same eluent as before gave the ketone **13** (410 mg) (total yield 590 mg, 56%) which had m.p. 57–58 °C (from ether) (Found: C, 56.4; H, 5.3. $C_{13}H_{15}F_3O_3$ requires C, 56.5; H, 5.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 1650 and 1710; δ_H(200 MHz; $CDCl_3$) 6.04 (1 H, 1-H, s), 4.79 (1 H, 5α-H, complex m), 2.3–2.6 (5 H), 2.06 (OAc, s), 1.8–2.0 (4 H) and 1.48 p.p.m. (1 H, complex m); δ_C(50 MHz; $CDCl_3$) 20.8 (OCO*Me*), 22.5 (C-7), 27.6 (C-6, $J_{C,F}$ 2), 29.5 (C-4, $J_{C,F}$ 2), 32.7, 33.0 (C-3, -8), 48.5 (C-4a, J_{CF} 23), 77.0 (C-5), 126.2 (C-9, J_{CF} 288), 130.4 (C-1), 155.1 (C-8a), 169.9 (*O*COMe) and 197.1 p.p.m. (C-2); δ_F(56 MHz; $CDCl_3$) −60.7 p.p.m.; *m/z* 276 (M^+, 100%).

4,4*aβ*,5,6,7,8-*Hexahydro-5β-hydroxy-4a-trifluoromethylnaphthalen*-2(3H)-*one* **14**.—Potassium carbonate (20 mg) was added to a stirred solution of the acetate **13** (210 mg, 0.76 mmol) in a mixture of methanol (9 ml) and water (1 ml). After 2 h the solution was diluted with dichloromethane (50 ml), washed with hydrochloric acid (1 mol dm^{-3}; 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated. Crystallization of the residue from ether gave the *alcohol* **14** (170 mg, 95%), m.p. 76.5—77.5 °C (Found: C, 56.45; H, 5.6. $C_{11}H_{13}F_3O_2$ requires C, 56.4; H, 5.6%); $\nu_{max}(CCl_4)/cm^{-1}$ 3600 and 1650; δ_H(200 MHz; $CDCl_3$) 6.01 (1 H, 1-H, unresolved d), 3.54 (1 H, 5α-H, complex m), 2.81 (1 H, ddd, $J_{H,H}$ 14.3, 5.0 and 3.2), 2.2–2.6 (4 H), 1.9–2.0 (3 H), 1.84 (1 H, OH, s) and 1.42 (1 H, complex m); δ_C(50 MHz, $CDCl_3$) 22.7 (C-7), 29.4 (C-4), 30.6 (C-6), 33.0, 33.2 (C-3, -8), 49.5 (C-4a, J_{CF} 22), 78.0 (C-5), 126.6 (C-9, J_{CF} 288), 129.7 (C-1), 157.5 (C-8a) and 198.6 p.p.m. (C-2); δ_F(56 MHz, $CDCl_3$) −59.3 p.p.m.; *m/z* 234 (M^+, 100%).

3,4,8,8*a*-*Tetrahydro-8a-trifluoromethylnaphthalene*-1,6(2H,7H)-*dione* **15**.—The alcohol **14** (280 mg, 1.2 mmol) in acetone (30 ml) was oxidized with Jones reagent (8 mol dm^{-3}; 350 μl) for 20 min. The mixture was diluted with methanol and evaporated and the residue was taken in water (20 ml) extracted with dichloromethane. The extract was dried ($MgSO_4$) and evaporated and the residue crystallized from ether to afford the *diketone* **15** (250 mg, 90%), m.p. 52–53 °C (Found: C, 57.0; H, 4.6 $C_{11}H_{11}F_3O_2$ requires C, 56.9; H, 4.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1660, 1675 and 1720; δ_H(200 MHz; $CDCl_3$) 6.08 (1 H, 5-H, d, $J_{5\text{-H},7\beta\text{-H}}$ 1.9), 2.2–2.9 (7 H), 2.0–2.2 (2 H) and 1.70 (1 H, complex m); δ_C(50 MHz, $CDCl_3$) 22.2 (C-3), 25.7 (C-8), 32.7, 33.2 (C-4, -7), 40.0 (C-2), 57.2 (C-8a, J_{CF} 24), 124.3 (C-9, J_{CF} 288), 130.8 (C-5), 154.6 (C-4a), 196.5 (C-6) and 201.9 p.p.m. (C-1); δ_F(56 MHz, $CDCl_3$) −64.7 p.p.m.; *m/z* 232 (M^+, 12), 231 (16) and 93 (100%).

4*aβ*,5,8,8*aβ*-*Tetrahydro-8a-trifluoromethylnaphthalene*-1,4,6-(2H,3H,7H)-*trione* **16**.—A solution of the enone **2** (4 g, 16 mmol) in THF (100 ml) was hydrogenated at atmospheric pressure with 10% palladium on charcoal for 24 h. The mixture was filtered and evaporated and the residue was sublimed (50 °C, 5 × 10^{-2} mmHg) to give the *diketone* **16** (3.8 g, 94%), m.p. 65–66 °C (from ether) (Found: C, 53.4; H, 4.4. $C_{11}H_{11}F_3O_3$ requires C, 53.2; H, 4.5%); $\nu_{max}(CCl_4)/cm^{-1}$ 1730; δ_H(200 MHz; $CDCl_3$) 3.60 (1 H, dd, 4a-H, $J_{4a\text{-H},5\alpha\text{-H}}$ 8.3 and $J_{4a\text{-H},5\beta\text{-H}}$ 6.2) and 2.0–3.4 (10 H); δ_C(20 MHz, $CDCl_3$) 25.2 (C-8), 35.1, 35.9, 37.2, 38.0 (C-2, -3, -5, -7), 49.3 (C-4a), 55.3 (C-8a, J_{CF} 24), 125.6 (C-9, J_{CF} 286), 201.4 (C-1), 204.0 (C-6) and 205.2 p.p.m. (C-4); δ_F(56 MHz, $CDCl_3$) −71.0 p.p.m.; *m/z* 248 (M^+, 24) and 56 (100%).

4α,6α-*Epoxy*-3,4,4*aβ*,5,6,7,8,8*aβ*-*octahydro-8a-trifluoromethylnaphthalen*-1-(2H)-*one* **18**.—To a solution of the trione **16** (2 g, 8.1 mmol) in trifluoroacetic acid (50 ml) was added poly(methylhydrosiloxane) (3 ml) and the mixture was stirred for 2 days. After removal of the solvent, the residue was stirred with aqueous potassium hydroxide (2 mol dm^{-3}; 50 ml), with occasional crushing of the resulting solid mass, until the solution turns from blue to red (*ca.* 48 h). After filtration, the aqueous phase was extracted with dichloromethane (3 × 20 ml) and the extract dried (Na_2SO_4) and evaporated. The residue (1.3 g) was dissolved in acetone and oxidized by addition of Jones reagent (8 mol dm^{-3}; 2 ml). Methanol (10 ml) was then added followed by water (50 ml). The mixture was then extracted (CH_2Cl_2) and the extract dried and eluted through silica gel (CH_2Cl_2) to give the *ketone* **18** (1.1 g, 58%) as a colourless oil (Found: C, 56.45; H, 5.7. $C_{11}H_{13}F_3O_2$ requires C, 56.4; H, 5.6%); $\nu_{max}(CCl_4)/cm^{-1}$ 1725; δ_H(200 MHz; $CDCl_3$) 4.41 (1 H, 6-H, br quint, *J ca.* 4), 4.08 (1 H, 4-H, q, *J* 3.2), 2.6–2.8 (2 H), 2.15–2.3 (2 H) and 1.5–2.1 (6 H); δ_C(20 MHz, $CDCl_3$) 19.7 (C-8), 26.6, 29.7, 32.3, 33.9 (C-2, -3, -5, -7), 40.1 (C-4a), 55.8 (C-8a, J_{CF} 22), 73.5 and 74.4 (C-4 and -6), 126.9 (C-9, J_{CF} 284), and 205.9 p.p.m. (C-1); δ_F(56 MHz, $CDCl_3$) −74.7 p.p.m.; *m/z* 234 (M^+, 11) and 85 (100%).

4α-*Acetoxy*-6*β*-*hydroxy*-3,4,4*aβ*,5,6,7,8,8*aβ*-*octahydro-8a-trifluoromethylnaphthalen*-1(2H)-*one* **20**.—A solution of the ketone **18** (300 mg, 1.3 mmol) in acetyl trifluoroacetate (4 ml) was stirred overnight. The mixture was evaporated and the residue, dissolved in methanol (5 ml), was twice treated with phosphate buffer (pH 7; 2 ml) for 8 h. The mixture was then evaporated to dryness with the aid of methanol. Chromatography of the residue on silica gel (ether gradient, dichloromethane) afforded the alcohol **20** (280 mg, 74%), m.p. 112.5–113 °C (from hexane–ether in the cold) (Found: C, 53.2; H, 5.8 $C_{13}H_{17}F_3O_4$ requires C, 53.1; H, 5.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 3640, 1720 and 1745; δ_H(300 MHz; $CDCl_3$) 5.65 (1 H, 4-H, dt $J_{4\text{-H},3\alpha\text{-H}}$ 11.6, $J_{4\text{-H},3\beta\text{-H}}$ 4.7 and $J_{4\text{-H},4a\text{-H}}$ 4.7), 4.12 (1 H, 6α-H, br quint, *J ca.* 2.5), 2.97 (1 H, dt, *J* 13.0, 4.1 and 4.1), 2.4–2.8 (2 H), 1.6–2.4 (6 H), 2.02 (3 H, OAc, s), 1.80 (1 H, OH, s), 1.49 (1 H, tdd, *J* 13.8, 13.8, 4.2 and 2.6) and 1.31 (1 H, td, *J* 13.7, 13.7 and 2.2); δ_F(56 MHz, $CDCl_3$) −67.7 p.p.m.; *m/z* 294 (M^+, 10) and 252 (100%).

4α-*Acetoxy*-3,4,4*aβ*,5,8,8*aβ*-*hexahydro-8a-trifluoromethylnaphthalen*-1,6(2H,7H)-*dione* **21**.—Jones reagent (8 mol dm^{-3}; 500 μl) was added to a solution of the alcohol **20** (295 mg, 1.0 mmol) in acetone (30 ml). After 10 min, excess of reagent was destroyed with methanol, and the mixture evaporated. The residue was dissolved in the minimum amount of water and extracted (CH_2Cl_2). The extract was dried ($MgSO_4$) and evaporated and the *ketone* **21** so obtained was crystallized from ether (260 mg, 89%); it had m.p. 127.5–128 °C (Found: C, 53.5; H, 5.1. $C_{13}H_{15}F_3O_4$ requires C, 53.4; H, 52.%); $\nu_{max}(CCl_4)/cm^{-1}$ 1720 and 1750; δ_H(300 MHz; $CDCl_3$) 5.24 (1 H, 4-H, q, *J* 3.8), 3.13 (1 H, dt, *J* 7.1, 3.9 and 3.9), 2.5–2.8 (4 H), 2.41 (1 H, dt, *J* 18.1, 4.8 and 4.8), 2.15–2.35 (4 H), 2.01 (1 H, ddd, *J* 14.0, 11.7 and 5.0) and 1.95 (3 H, OAc, s); δ_F(56 MHz, $CDCl_3$) −72.0 p.p.m.; *m/z* 292 (M^+, 7) and 250 (100%).

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