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THE ANGULAR TRIFLUOROMETHYL GROUP. PART 3. SYNTHESIS OF A RING D PRECURSOR OF TRIFLUOROMETHYLATED STEROIDS

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SUMMARY

A trifluoromethylated cyclopentanoid aldehyde 7, intended to serve as a ring D precursor of trifluoromethylated steroids, is obtained in four steps starting from 2-trifluoromethylcyclopentane-1,3-dione 1.

INTRODUCTION

In our continuous interest in the synthesis of trifluoromethylated steroids [1, 2], we needed quantities of a derivative of the diketo aldehyde 3, with masked ketonic carbonyl groups, as a precursor of the ring D part of the steroid skeleton.

The availability of 2-trifluoromethylcyclopentane-1,3-dione 1 [3, 4] led us to investigate the preparation of the target aldehyde 3 itself, or a protected version, via ozonolysis of an allylated precursor of type 2 (scheme 1).

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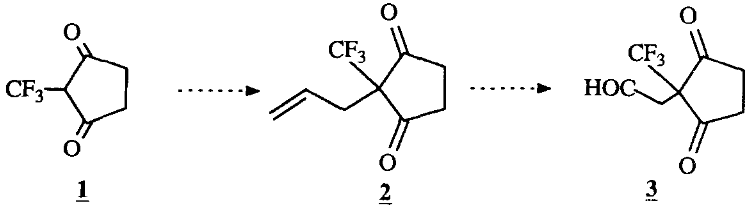


Scheme 1.

We were thus faced with the allylation of the base sensitive trifluoromethyl ketone 1.

RESULTS AND DISCUSSION

We initially considered the direct allylation of the trifluoromethyldione 1 with allyl bromide in the presence of cesium fluoride [5], since this system has proved very valuable in the alkylation of dimethyl trifluoromethylmalonate, a closely related congener of the starting ketone 1.

However, in our case, these reaction conditions led to the total destruction of the starting dione 1, without production of the desired allylated product 2, which may reflect a higher sensitivity of compound 1 toward a basic medium.

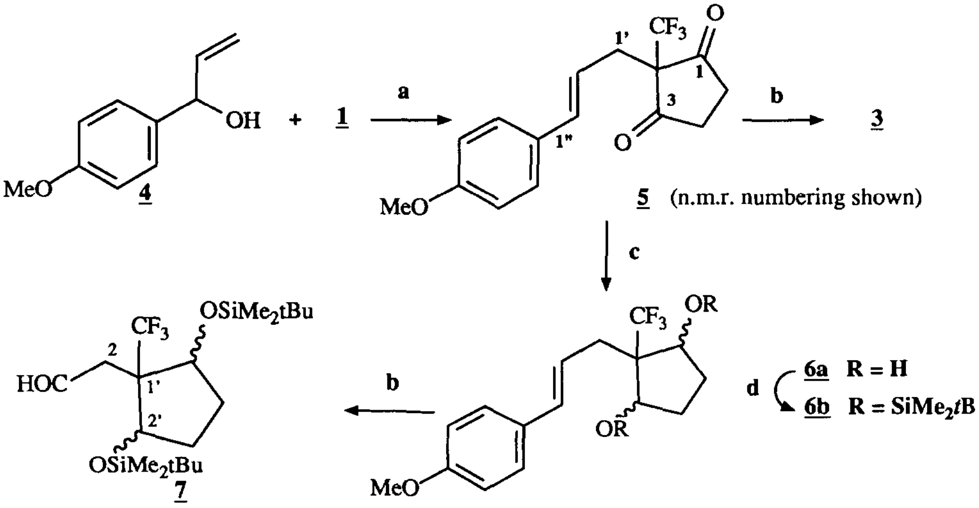
We next tried the palladium catalysed allylation of 1, since this kind of reaction could usually be performed under neutral conditions. Among the systems we investigated ($Pd(PPh_3)_4$ / allyl acetate / 1,8-diazabicyclo[5.4.0]undec-7-ene [6], $Pd(PPh_3)_4$ / diallyl carbonate [7], $Pd(dba)_2$ [dba : dibenzylideneacetone] / *O*-allyl-*N*,*N*-dicyclohexyl isourea / dppe [dppe: 1,2-bis(diphenylphosphino)ethane] [8], $Pd(dba)_3.CHCl_3$ / allyl-*N*,*N*-diisopropyl carbamate / dppe [9], bis(acetylacetonate)palladium / allyl acetate / PPh_3 [10]), only the first two ones gave positive results with best yields of *ca.* 20 % of the allylated adduct 2 on a 3 mmol scale.

These results are far from satisfactory, suffering from a severe drawback: the best yields could only be achieved in two instances, these experiments being highly irreproducible since most runs gave no product at all.

We have no clear cut explanation for this fact, but a possibility is the poisoning of the palladium based catalyst by released fluoride ions which may originate in some decomposition of the trifluoromethylketone 1.

Knowing that the dione 1 readily enters Torgov type condensation with allylic alcohols [1], we noticed that the primary condensation product 5, obtained in such a reaction, is in fact a substituted derivative of the requisite diketone 2.

Thus the condensation of 2-trifluoromethylcyclopentane-1,3-dione 1 with the allylic alcohol 4 proceeded readily in refluxing benzene, under azeotropic separation of water, to furnish the substituted styrene 5 in 72 % isolated yield (scheme 2), as the single *E* isomer.



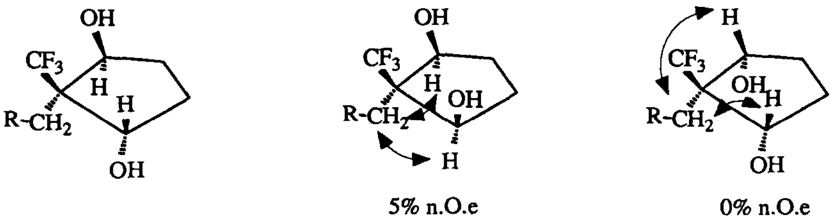
Reagents: a) benzene reflux. b) O_3, MeOH, -78°C. c) $LiAlH_4$, Et_2O, R.T.
d) *t* $BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0°C.

Scheme 2.

Although the unprotected ketone 3 could be obtained after ozonolysis of the unsaturated precursor 5, its separation from *p*-anisaldehyde which is also formed proved difficult and a pure sample could only be obtained after preparative g.l.c..

Since, for our planned synthesis, the carbonyl groups of the cyclopentanedione 3 should be protected in some way, we find it more convenient to reduce them first before the ozonolysis step. This reduction was effected by $LiAlH_4$ in diethyl ether and the resulting diol 6a was obtained in 90 % yield as a (*ca.* 4:10:1) mixture of diastereoisomers. Although this lack of stereoselectivity was not inconvenient, at this stage, for the following of our synthesis, we were interested in the assignment of the structure of each isomer, since this information could help us in the achievement of a, planned, more stereoselective reduction at a later stage. With this goal in mind, samples of each diastereoisomer were obtained by p.t.l.c. and subjected to n.m.r. analysis.

The trans diol structure 6a-1 (scheme 3) was readily assigned to the major isomer (δ_F -66.2 p.p.m.), based on the presence of signals for two distinct -CHOH- groupings both in the ^1H and ^{13}C n.m.r. spectra, as compared to only one for each of the two other isomers. The fact that the trans isomer was the major one could probably be explained by an intramolecular reduction of the second carbonyl function by the oxygen bonded reducing agent produced by the attack on the first carbonyl group and by a favourable statistical ratio. The second abundance isomer (δ_F -61.3 p.p.m.) was assigned the cis diol structure 6a-2 resulting from the incoming of the reducing agent on the opposite side of the bulky trifluoromethyl group. This assignment was based on the deshielding of ca. 2 to 7 p.p.m. observed for a trifluoromethyl groups cis to a hydroxyl function as compared to the trans analogue [11] (the less abundant isomer 6a-3 had δ_F -70.9 p.p.m.). This assignment was confirmed by a n.O.e. experiment. We observed an intensity enhancement of ca. 5% for the signal of the allylic hydrogen atoms upon irradiation of the CHOH fragment in the 6a-2 isomer with the two groups in close spatial proximity and 0% for the 6a-3 one with more distant groupings.



6a-1 *major* 6a-2 6a-3 *minor*

Scheme 3.

In the next step, we selected the *tert*-butyldimethylsilyl group for the protection of the hydroxyl functions. This group, while meeting our own requirements, has a good stability toward ozonolysis [12] and was readily introduced (94 % yield) *via* the corresponding silyl triflate, using 2,6-lutidine as the base. The bis-silyl ether 6b showed essentially the same diastereoisomeric distribution as the starting diol 6a.

The target aldehyde 7 was ultimately obtained (85 % yield) after ozonolytic cleavage (MeOH, -78°C) of the alkene part of silyl ether 6b. In this compound the diastereoisomeric ratio was somewhat altered, the minor isomer being partly lost during the workup.

The preceding reaction sequence constitutes thus a convenient synthesis of the aldehyde 7 with protected oxygen functionalities, the total yield being 50 % over four steps, starting from the trifluoromethyl dione 1.

EXPERIMENTAL

M.p.s. were determined on a Mettler FP-61 apparatus. I.r. spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. N.m.r. spectra were taken, in $CDCl_3$, on a Bruker AC-200 E spectrometer. The reference was $SiMe_4$ for ^1H and ^{13}C spectra and $CFCl_3$ for ^{19}F n.m.r. spectra. All chemical shifts were reported downfield from the reference [13]. Mass spectra were taken on AEI MS30 mass spectrometer operating at 70 eV. Silica gel refers to silica gel 60, 70-230 Mesh (Merck). Preparative g.l.c. was performed on a Varian Aerograph 920 chromatograph (10 ft x 3/8 in column of 30 % SE 30 on Chromosorb PAW 45–60 mesh operating at 200 °C.

2-Allyl-2-trifluoromethylcyclopentane-1,3-dione

This experiment is typical of all experiments done with palladium catalysts. A solution of tetrakis(triphenylphosphine)palladium (200 mg, 0.17 mmol) in dry THF (5 ml), was added via a syringe to a stirred solution of 2-trifluoromethylcyclopentane-1,3-dione 1 [3,4] (500 mg, 3 mmol) in dry THF (5 ml) cooled in an ice bath and maintained under an argon atmosphere. Allyl acetate (1 ml, 9 mmol) was then added, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (450 µl, 3 mmol) giving an exothermic reaction. After 24 h, more palladium catalyst (200 mg, 0.17 mmol) was added and the mixture was stirred for additional 24h. After removal of the solvent, short path distillation of the residue (60°C, 0.13 Pa) afforded 570 mg of crude material which was purified by g.l.c. to give 120 mg (19%) of the allylated dione 2 as a semi-solid (**m.p.** ca. 25-30°C); **Analysis** Found: C, 51.2; H, 4.2 $C_9H_9F_3O_2$ requires C, 52.4; H, 4.4%. υ_{max}($CHCl_3$) 1720 and 1620 cm^{-1}; δ_F -68.5 p.p.m; δ_H 2.5-3.1 (6H, *ring H* and $H_{1'}$), 5.0-5.12 (2H, $H_{3'}$) and 5.3-5.5 p.p.m. (1H, $H_{2'}$); δ_C 33.2 (C1', J_{CF} 2 Hz), 36.4 (C4 and C5), 61.5 (C2, J_{CF} 24 Hz), 121.5 (CF_3, J_{CF} 284 Hz), 121.9 (C2'), 128.4 (C3') and 205.8 p.p.m. (C1 and C3); **m/z** 206 ($M^{+\cdot}$, 3%) and 179 (100%).

2-{3-[4-Methoxyphenyl]prop-2-enyl}-2-trifluoromethylcyclopentane-1,3-dione

A mixture of the dione 1 (2.0 g, 0.12 mol) and 1-(4-methoxyphenyl)prop-2-en-1-ol 4 [14] (2.0 g, 0.12 mol) in benzene (100 ml) was refluxed for 1 h in a Dean-Stark apparatus. The resulting suspension was allowed to cool and more allylic alcohol (2.0 g) was added.

After 1 h refluxing all the solid dissolved. The solvent was removed under vacuum, and the residue was eluted on a column of silica gel (CH_2Cl_2) to give the dione 5 (2.70 g, 72%) as a white solid which had **m.p.** 86-87 °C (isopropanol); **Analysis:** Found: C, 61.6; H, 4.9 $C_{16}H_{15}F_3O_3$ requires C, 61.5; H, 4.8%. $\upsilon_{max}(CHCl_3)$ 1720 and 1600 cm^{-1}; δ_F -88.1 p.p.m; δ_H 2.7-2.9 (6H), 3.70 (3H, *OMe*), 5.59 (1H, $H_{2'}$, $J_{2',3'}$ 15.8, $J_{2',1'}$ 7.8 Hz), 6.32 (1H, $H_{3'}$), 6.69-6.82 and 7.08-7.27 p.p.m. (4H, *Aromatic* H); δ_C 32.7 (C1'), 36.6 (C4 and C5), 55.0 ($O\underline{C}H_3$), 61.9 (C2, J_{CF} 24 Hz), 113.9 (C3" and C5"), 116.8 (C2'), 121.6 ($\underline{C}F_3$, J_{CF} 284 Hz), 127.4 (C2" and C6"), 128.6 (C1"), 136.1 (C3'), 159.6 (C4") and 206.0 p.p.m. (C1 and C3); **m/z** 312 ($M^{+\cdot}$,43 %) and 47 (100%).

[1-Trifluoromethylcyclopentyl-2,5-dione]acetaldehyde

A solution of the unsaturated dione 5 (1g, 3.2 mmol) in methanol (30 ml) was treated with ozone (2g per hour) at -78°C until the solution became blue. Excess ozone was then removed by a stream of argon. Methyl sulphide (0.8 ml, 11 mmol) was added and the solution was stirred for additional 10 min at -78°C. The mixture was diluted with water (50 ml) and extracted with ether. After removal of the solvent, the residue was dissolved in methanol (5 ml) and treated with a 20 ml solution of 37% hydrogen sulphite for one hour. The resulting suspension was filtered and the solid washed with ether. The ethereal layer was washed with water and dried ($MgSO_4$) to give 400 mg of a crude product which was mainly the methyl acetal of the required aldehyde. Treatment of this material, dissolved in 2% aqueous acetonitrile (5 ml), with lithium tetrafluoroborate [15] (150 mg, 1.6 mmol) for 24 h afforded the free aldehyde 3 (300 mg, 45%) which still contained ca. 20% impurities. The analytical sample obtained by preparative g.l.c. had (after sublimation at 50°C, 40 Pa) **m.p.** 86-86°C; **Analysis:** Found: C, 46.1; H, 3.4 $C_8H_7F_3O_3$ requires C, 46.2; H, 3.4%; v_{max} (CCl_4) 1695 and 1715 cm^{-1}; δ_F -67.8 p.p.m.; δ_H 2.90-3.05 (4H, *ring H*), 3.48 (2H, H_2), and 9.36 p.p.m. (1H, H_1); δ_C 36.2 (C3' and C4'), 46.0 (C2), 57.3 (C1', J_{CF} 25 Hz), 121.5 ($\underline{C}F_3$, J_{CF} 283 Hz), 196.9 (C1) and 205.1 p.p.m. (C2' and C5'); **m/z** 208 ($M^{+\cdot}$, 60%) and (179, 100%).

2-{3-[4-Methoxyphenyl]prop-2-enyl}-2-trifluoromethylcyclopentane-1,3-diol

A solution of the dione 5 (2.0 g, 6.4 mmol) in dry ether (40 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (970 mg, 25.5 mmol) in ether (80 ml) cooled in an ice bath. After completion of the addition, the mixture was stirred 2 h at room temperature. Water (1 ml) was then added followed by 15% NaOH (1 ml) and additional water (3 ml). The whole reaction mixture was dried over Na_2SO_4. After removal of the solvent, the crude diol 6a (2.02 g) was distilled in a Buchi apparatus (1.3 Pa, oven temperature 230-250°C) to give 1.82g

(90%) of pure **6a** as an oily mixture of diastereoisomers; **Analysis:** Found: C, 60.9; H, 6.1 $C_{16}H_{19}F_3O_3$ requires C, 60.75; H, 6.05%. υ_{max}($CHCl_3$) 3340 and 1600 cm^{-1}; δ_F -61.3 (29%), - 66.2 (65%) and -70.9 p.p.m (6%); **m/z** 316 ($M^{+\cdot}$,22%), 146 (70%) and 121 (100%). Samples of each diastereoisomer could be obtained by p.t.l.c. (SiO_2, 20% ether/ dichloromethane). The major isomer **6a-1** had δ_H 1.3-1.6 (2H, *ring H*), 1.9-2.15 (2H, *ring H*), 2.25 (1H, $H_{1'A}$, $J_{1'A,1'B}$ 15.0, $J_{1'A,2'}$8.1 Hz), 2.37 (2H, *OH*), 2.60 (1H, $H_{1'B}$, $J_{1'B,2'}$ 6.5 Hz), 3.69 (3H, *OMe*), 4.17 (1H, H_1 or H_3, *t*, J 6.3 Hz), 4.52 (1H, H_3 or H_1, *t*, J 8.0 Hz), 6.07 (1H, $H_{2'}$, $J_{3',2'}$ 15.8 Hz), 6.33 (1H, $H_{3'}$), 6.7-6.8 and 7.1-7.2 p.p.m. (4H, *Aromatic H*); δ_C 29.9 (C4 or C5), 30.2 (C5 or C4), 32.2 (C1'), 55.3 ($O\underline{C}H_3$), 55.7 (C2, J_{CF} 20 Hz), 73.8 (C1 or C3), 75.6 (C3 or C1), 114.0 (C3" and C5"), 122.5 (C2'), 127.3 (C2" and C6"), 128.6 ($\underline{C}F_3$, J_{CF} 287 Hz), 129.6 (C1"), 133.5 (C3') and 159.0 p.p.m. (C4"). The second isomer **6a-2** had δ_H 1.86-2.10 (4H, *Ring H*), 2.19 (2H, $H_{1'}$, $J_{1',2'}$ 7.4 Hz), 2.50 (2H, *OH*), 3.72 (3H, *OMe*), 4.13 (2H, H_1 and H_3), 5.98 (1H, $H_{2'}$, $J_{3',2'}$ 15.7 Hz), 6.75 (1H, $H_{3'}$), 6.74-6.80 and 7.16-7.23 p.p.m.(4H, *Aromatic H*); δ_C 31.5 (C4 and C5), 35.6 (C1'), 55.2 ($O\underline{C}H_3$), 57.2 (C2, J_{CF} 21 Hz), 76.7 (C1 and C3), 113.9 (C3" and C5"), 121.2 (C2'), 127.3 (C2" and C6"), 127.8 ($\underline{C}F_3$, J_{CF} 287 Hz), 129.4 (C1"), 133.4 (C3') and 159.1 p.p.m. (C4"). The minor isomer **6a-3** had δ_H 1.7-2.1 (6H, *Ring H* and *OH*), 2.68 (2H, $H_{1'}$, $J_{1',2'}$ 6.9 Hz), 3.72 (3H, *OMe*), 4.28 (2H, H_1 and H_3), 6.29 (1H, $H_{2'}$, $J_{3',2'}$ 15.9 Hz), 6.47 (1H, $H_{3'}$), 6.73-6.81 and 7.18-7.26 p.p.m. (4H, *Aromatic H*).

2-{3-[4-Methoxyphenyl]prop-2-enyl}-2-trifluoromethylcyclopentane-1,3-diol bis(*tert*-butyldimethylsilyl ether)

t-Butyldimethylsilyl triflate (5g, 19 mmol) was added via a syringe through a septum to a stirred solution of the diol **6a** (2g, 6.4 mmol) and 2,6-lutidine (2.72g, 25 mmol) in dichloromethane (50 ml) cooled in an ice bath. The mixture was stirred for 1h. After removal of the solvent (high vacuum), the residue was eluted through a column of silica gel (CH_2Cl_2) to give the bissilyl ether **6b** (3.28g, 94%) as a low melting solid; **Analysis**: Found: C, 61.8; H, 8.9 $C_{28}H_{47}F_3O_3Si_2$ requires C, 61.7; H, 8.7%; v_{max} ($CHCl_3$) 1590 cm^{-1}; δ_F -62.2 (28%), -66.5 (66%) and -72.3 p.p.m. (6%); δ_H 0.00-0.09 (12H, *SiMe*), 0.86-0.93 (18H, *SiBu^t*), 1.4-2.2 (*Ring H*), 2.4-2.7 (2H, $H_{1'}$), 3.8 (3H, *OMe*), 4.0-4.6 (2H, H_1 and H_3), 5.8-6.42 (2H, $H_{2'}$ and $H_{3'}$), 6.80-6.9 and 7.2-7.3 (4H, *Aromatic* H); **m/z** 544 ($M^{+\cdot}$, 1%) and 73 (100%).

[1-Trifluoromethylcyclopentyl-2,5-diol bis(*tert*-butyldimethylsilyl ether)]acetaldehyde

A stream of ozone (2g per hour) was bubbled into a solution of the bissilyl ether **6b** (3.0g, 5.5 mmol) in methanol (30 ml) cooled to -78°C. When the solution became blue (ca.

10 min), the ozone was replaced by a stream of argon until a white precipitate appeared. Methyl sulphide (1.4 ml, 19 mmol) was then added and the mixture was stirred for additional 10 min at -78°C. After removal of the solvent, purification was effected by column chromatography on silica gel (40% dichloromethane/ petroleum ether). The aldehyde 7 (2.06g, 85%) was obtained as a solid **m.p.** 45-47°C; **Analysis:** Found: C, 54.6; H, 8.95 $C_{20}H_{39}F_3O_3Si_2$ requires C, 54.5; H, 8.9%; $\mathbf{v_{max}}$ ($CHCl_3$) 1700 cm^{-1}; δ_F -61.6 (29%), -67.7 (69%) and -73.9 p.p.m. (2%); δ_H (major isomer) 0.00 and 0.03 (12H, *SiMe*), 0.83 (18H, $SiBu^t$), 1.3 - 2.2 (*ring H*), 2.52 (2H, H_2, d J 2.6 Hz), 4.38 (1H, $H_{2'}$ or $H_{5'}$), 4.50 (1H, $H_{5'}$ or $H_{2'}$) 9.8 (1H, H_1); (2nd isomer) -0.03 and -0.01 (12H, *SiMe*), 0.83 (18H, $SiBu^t$), 1.3 - 2.2 (*ring H*), 2.55 (2H, H_2, d J 2.8 Hz), 4.22 (2H, $H_{2'}$ and $H_{5'}$) and 9.8 p.p.m. (1H, H_1); δ_C (major isomer) -5.0 and -4.7 ($Si\underline{C}H_3$), 17.4 ($Si\underline{C}(CH_3)_3$), 20.4 ($SiC(\underline{C}H_3)_3$), 31.1 (C3' or C4'), 31.3 (C4' or C3'), 42.2 (C2), 56.0 (C1', J_{CF} 21 Hz), 76.2 (C2' or C5'), 76.3 (C5' or C2'), 127.3 ($\underline{C}F_3$, J_{CF} 286 Hz), 200.1 (C1); (2nd isomer) -3.3 ($Si\underline{C}H_3$), 17.5 ($Si\underline{C}(CH_3)_3$), 25.3 ($SiC(\underline{C}H_3)_3$), 30.9 (C3' and C4'), 47.1 (C2), 55.3 (C1', J_{CF} 21 Hz), 73.5 (C2' and C5'), 126.5 ($\underline{C}F_3$, J_{CF} 286 Hz), and 199.8 p.p.m. (C1); **m/z** 440 ($M^{+\cdot}$, 2%), 398 (70%) and 73 (100%).

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