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INSECT CHEMISTRY—VI[1]

TRIFLUOROMETHYL ANALOGS OF JUVENILE HORMONES

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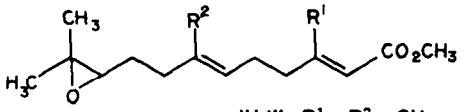
Abstract—Preparation of two trifluoromethyl analogs of JH-III, methyl 10,11-epoxy-7,11-dimethyl-3-trifluoromethyldodeca-2,6-dienoate (**1a**) and methyl 10,11-epoxy-3,11-dimethyl-7-trifluoromethyldodeca-2,6-dienoate (**1b**) is described. The stereochemistry of trisubstituted double bonds, bearing one trifluoromethyl substituent, could be assigned easily by ^{19}F NMR spectroscopy. Some peculiarities of the Wittig reactions of trifluoromethyl ketones are indicated.

Substitution of fluorine for hydrogen to modify the bioactivity of certain molecules by enhancement of their lipophilicity, associated with the corresponding change of both steric and electronic properties, is a well established practice in medicinal chemistry.[2] However, although numerous studies on relationships between chemical structure and insect juvenile hormone mimicking activity of different types of compounds have been reported in the literature,[3] the above effect had so far not been investigated in this particular area. Consequently, to fill this gap, recently we undertook a program devoted to the synthesis of fluorinated analogs of natural insect juvenile hormones.

In a previous communication,[4] we reported our preliminary results on the synthesis of a trifluoromethyl (TFM) analog of natural insect juvenile hormone JH-III,[5] **1a**. In the present paper, full experimental details for this synthesis are given and the preparation of a new TFM analog of this hormone, **1b**, is also described.



JH-III: $R^1 = R^2 = CH_3$
1a: $R^1 = CF_3$; $R^2 = CH_3$
1b: $R^1 = CH_3$; $R^2 = CF_3$

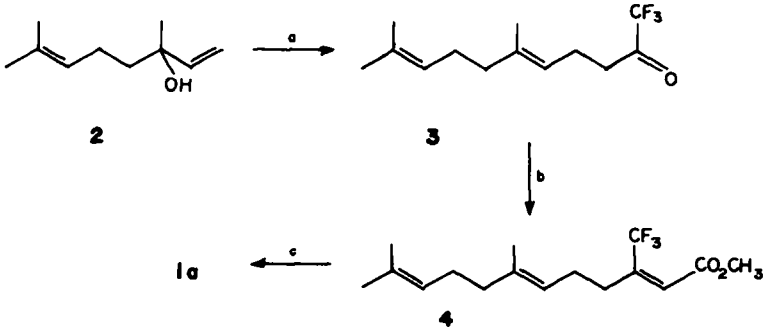
RESULTS AND DISCUSSION

Synthesis of **1a**. As depicted in Scheme 1, synthesis of TFM analog **1a** was accomplished by a nonstereoselective sequence, previously developed by Mori *et al.*[6] for preparation of juvenoids.

Treatment of linalool (**2**) with an excess of ethyl 4,4,4-trifluoroacetoacetate in a Carroll reaction, 15 h at 150° and 3 h at 180°, in the presence of sodium acetate as catalyst, resulted in the formation of a 40:60 *Z*:*E* isomer mixture of trifluorogeranylacetone **3** in 84% yield. Enriched samples of both isomers, containing up to 80% *Z* or 96% *E*, could be obtained by careful column chromatography on silica gel. Configurational assignment was made by comparison of *GLC* relative retention times of both isomers with those of a synthetic isomeric mixture of geranylacetone of known composition, prepared by the same procedure.

Although the methoxycarbonylmethylenation of TFM alkyl ketones had been previously described[7] in the reaction of 1,1,1-trifluoroacetone with methoxycarbonylmethylenetriphenylphosphorane to give only the corresponding *E* isomer (likewise, in our hands, this reaction afforded a 5:95 *Z*:*E* isomer ratio), however, in the present case, being the *Z* isomer of **1a**, the required trifluoroanalogue of JH-III, an alternative procedure of olefination was necessary.

As a model, reaction of 1,1,1-trifluoroacetone with dimethyl (methoxycarbonyl)methylphosphonate was studied under various conditions to achieve stereochemical control.[8] Thus, treatment of this ketone with a 50% excess of the above phosphonate in n-pentane solution afforded a 22:78 *Z*:*E* isomer mixture of methyl 4,4,4-trifluoro-3-methylbut-2-enoate in 95% yield, whereas this ratio was shifted to 41:59 *Z*:*E* when the reaction was carried out in ether solution. A similar reaction of the



(a) $CF_3COCH_2CO_2C_2H_5$, NaOAc, Δ
(b) $(CH_3O)_2P(O)CH_2CO_2CH_3$, NaH, benzene, r.t.
(c) MCPBA, CH_2Cl_2, r.t.

Scheme 1.

above 40:60 $Z:E$ isomer mixture of TFM-ketone **3** in benzene solution 5 h at room temperature resulted in the formation of a 38:62 $Z:E$ isomer mixture at C-2 of the four unsaturated esters **4**, in 92% yield.

As depicted in Table 1, the stereochemistry of trisubstituted double bonds, bearing one TFM group as substituent, could be easily assigned by ^{19}F NMR spectroscopy, Z isomer absorptions throughout the series appearing at fields 6–8 ppm lower than those of the corresponding E isomer.

Table 1. ^{19}F NMR chemical shifts of CF_3 groups†

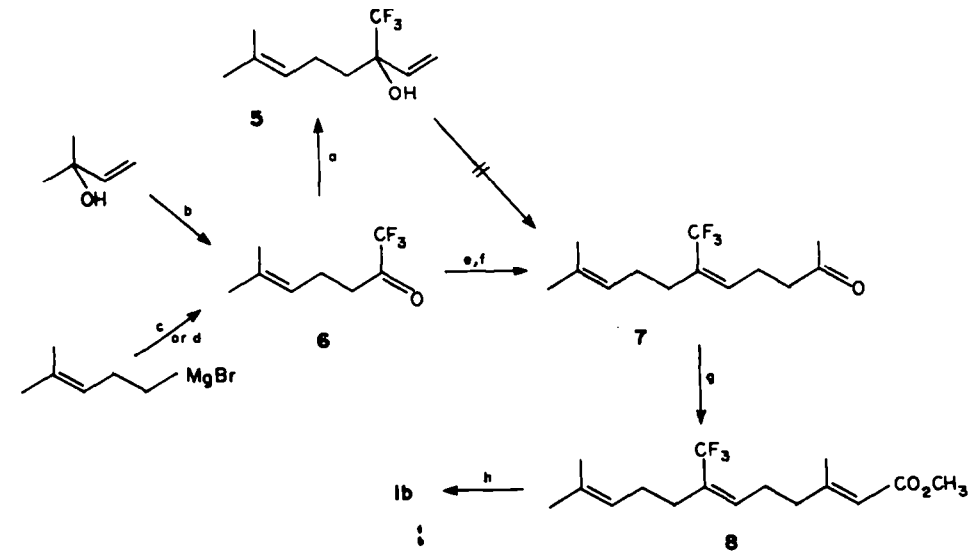
Compound	ppm
5	−2.7
3 (*Z*)	−0.98
(*E*)	−0.75
6	−1.3
6 (Tosylhydrazone)	9.2
Methyl 4,4,4-trifluoro-3-methylbut-2-enoate (*Z*)	13.2
(*E*)	6.8
4 (*Z*)-2, (*Z*)-6	15.9
(*Z*)-2, (*E*)-6	15.9
(*E*)-2, (*Z*)-6	9.8
(*E*)-2, (*E*)-6	10.0
1a (*Z*)-2, (*Z*, *E*)-6	15.9, 16.0
(*E*)-2, (*Z*, *E*)-6	9.9, 10.0
7 (*Z*)	19.9
(*E*)	12.1
8 (*Z*)-2, (*Z*)-6	19.6
(*Z*)-2, (*E*)-6	12.5
(*E*)-2, (*Z*)-6	19.4
(*E*)-2, (*E*)-6	12.5
1b (*Z*)-2, (*Z*)-6	20.2
(*Z*)-2, (*E*)-6	12.6
(*E*)-2, (*Z*)-6	20.0
(*E*)-2, (*E*)-6	12.6

†Measured at 33° as CCl_4 solutions, using trifluoroacetic acid as external reference in a sealed capillary.

Epoxidation of both isomers at C-2 of **4**, previously separated by column chromatography on silica gel, with m-chloroperbenzoic acid in methylene chloride 4 h at room temperature afforded the corresponding terminal epoxides **1a**. Further separation of isomers at C-6 was not pursued due to the lack of activity exhibited by these compounds in morphogenetic tests on *Tribolium confussum* Duv., when compared to a synthetic JH-III mixture with the same 40:60 $Z:E$ isomer ratio at C-6. Presumably, as suggested by ester carbonyl IR absorptions of isomers of **1a** (2*Z* 1742 and 2*E* 1730 cm^{-1}), this result can be attributed to a deconjugative effect of the strong withdrawing TFM group on the α,β-unsaturated ester moiety, an important feature for activity in juvenoids.[3]

Synthesis of **1b**. As shown in Scheme 2, the synthesis of **1b** was first attempted by a sequence analogous to that described above. However, reaction of trifluorolinalool **5**, easily available from condensation of vinylmagnesium bromide with trifluoromethyl 4-methyl-3-pentenyl ketone (**6**) in 79% yield, with ethyl acetoacetate or diketene under a variety of conditions failed to give trifluorogeranylacetone **7**. In this reaction, although the formation of a small amount of the intermediate acetoacetate of **5** was detected by ^{19}F NMR spectroscopy (absorptions at 1.5 and 1.6 ppm, tentatively assigned respectively to enol and keto forms), this compound reversed rapidly to the starting alcohol.

Therefore, alternative routes for preparation of **7** from TMF-ketone **6** were investigated. This ketone was easily available in 80% yield by straightforward condensation of 4-methylpent-3-enylmagnesium bromide with lithium trifluoroacetate.[9] In our hands, this procedure afforded higher yields than the succesive addition of the above Grignard reagent and trifluoroacetic anhydride onto disodium tetracarbonylferrate[10] and was more reliable than

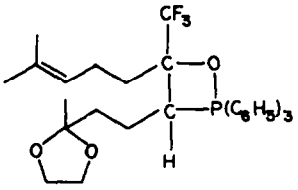


(*a*) CH_2=$CHMgBr$; (*b*) $CF_3COCH_2CO_2C_2H_4$, NaOAc, Δ; (*c*) $Na_2Fe(CO)_4$, $(CF_3CO)_2O$; (*d*) CF_3CO_2Li; (*e*) $CH_3C(CH_2)_3\overset{+}{P}Ph_3Br^-$, $NaNH_2$, diglyme, 100°; (*f*) CH_3COCH_3, *p*-TsOH; (*g*) $(CH_3O)_2P(O)CH_2CO_2CH_3$, NaH, benzene; (*h*) MCPBA, CH_2Cl_2, r.t.

Scheme 2.

our previous described procedure,[4] using 2-methyl-3-buten-2-ol and ethyl 4,4,4-trifluoroacetoacetate.

Reaction of TFM-ketone **6** with a 50% excess of (4,4 - ethylenedioxy) - pentyltriphenylphosphorane in diglyme solution 2 h at 100° and 20 h at room temperature, followed by acid cleavage of the ketal group, resulted in the formation of a 75:25 *Z*:*E* isomer mixture of the desired ketone **7** in 79% overall yield. It is worth pointing out that, in this reaction, despite instant decoloration of the ylide solution upon addition of TFM-ketone **6**, only negligible amounts of trifluorogeranylacetone **7** were obtained when warming up to 100° was skipped. This anomalous behaviour could be plausibly rationalised by formation of intermediate **9**, stabilised by the TFM-electron-withdrawing effect, which would require warming to decompose and to complete the Wittig sequence, by analogy with that observed in oxaphosphenate **10**, isolated in the reaction of hexafluoroacetone with hexaphenylcarbodiphosphorane.[11]



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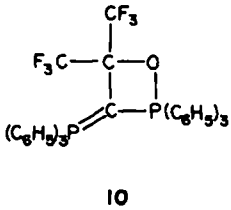

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Wittig–Horner olefination of the 75:25 *Z*:*E* isomer mixture of ketone **7**, under the same conditions described above for TFM-ketone **3**, afforded a 30:70 *Z*:*E* isomer mixture at C-2 of the four unsaturated esters **8** in 89% yield. Finally, regioselective epoxidation of **8** with m-chloroperbenzoic acid, under the usual conditions, resulted in the formation of a mixture of 10,11-epoxides **1b**, from which by preparative thin layer chromatography on silica gel, pure samples of epoxides 2*E*, 6*Z* and 2*Z*, 6*E* could be isolated. The former of these compounds exhibited a juvenile activity considerably greater than that of synthetic JH-III. A full account of the corresponding biological assays will be published elsewhere.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra were recorded as CCl_4 solutions on a Perkin-Elmer 457 Infrared Spectrophotometer. GC-MS analyses were performed on a Hewlett-Packard 5930 A Mass Spectrometer (70 ev) coupled with a Hewlett-Packard 5700 A Gas Chromatograph (1 m × 1/4 in 5% DEGS on Chromosorb G column). ^1H and ^{19}F NMR spectra were recorded on a Perkin-Elmer R-12B NMR spectrometer, operating at 60 and 56.4 MHz, and using TMS (internal) and trifluoroacetic acid (external) respectively, as references. Chemical shifts are reported in ppm downfield from both references. GLC analyses were performed on Perkin-Elmer 900, Perkin-Elmer F-21 and Carlo Erba Fractovap 2200 gas chromatographs.

1,1,1 - *trifluoro* - 6,10 - *dimethylundeca* - 5,9 - *dien* - 2 - *one* **3**. A mixture of linalool **2** (3.85 g, 25 mmole), ethyl 4,4,4-trifluoroacetoacetate[12] (5.98 g, 33 mmole) and NaOAc (0.04 g) was heated 15 h at 150° and 3 h at 180°. Distillation of the crude afforded 5.2 g (b.p. 114–19°/22 torr; 84%) of an isomer mixture of ketone **3** in a 40:60/*Z*:*E* ratio (GLC). Samples of 80:20 and 4:96 *Z*:*E* ratio were isolated by column chromatography on silica gel. IR: ν_{max} 1762, 1210 and 1150 cm^{-1}; ^1H NMR: δ, 2.20–2.80 (4 H, complex abs., $=C-CH_2-CH_2-CO-CF_3$); ^{19}F NMR: −0.98 (*Z*), −0.75 (*E*) ppm. GC-MS: *m/e* (%): (*Z*): 248 (M^+)(3), 136(12), 81(8), 69(100); (*E*): 248(M^+) (2), 136(13), 81(8), 69(100). (Found: C, 63.20; H, 7.52. $C_{13}H_{19}F_3O$ requires: C, 62.87; H, 7.71%).

Methyl 4,4,4 - *trifluoro* - 3 - *methylbut* - 2 - *enoate*.[7] A solution of 1,1,1-trifluoroacetone (11 g, 98 mmole) in Et_2O (25 ml) was added to a vigorously stirred suspension of sodium salt of dimethyl (methoxycarbonyl)methylphosphonate [from NaH (3.84 g, 157 mmole) and dimethyl (methoxycarbonyl)-methylphosphonate (29.1 g, 157 mmole)] in Et_2O (250 ml). Then the mixture was stirred for 1.5 h at 0° and 2.5 h at room temp. The crude was treated with 0.4N HCl (100 ml), the aqueous layer was decanted and extracted with Et_2O. The joined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to give a 41:59/*Z*:*E* isomer mixture (16 g, 95%) of the α,β-unsaturated esters. Analytical samples of each isomer were obtained by column chromatography on silica gel. (*Z*)-isomer: IR: ν_{max} 1748, 1675(m), 1270, 1178 and 1140 cm^{-1}; ^1H NMR: δ, 1.98 (3H, d (J = 1.5 Hz), CH_3–C=C), 3.68 (3H, s, $-COOCH_3$), 6.02 (1H, q, (J = 1.5 Hz), –C=C–H), ^{19}F NMR: 13.2 ppm. (*E*)-isomer: IR: ν_{max} 1735, 1680(m), 1208, 1190, 1140 and 1100 cm^{-1}; ^1H NMR: δ, 2.23 (3H, d(J = 1.5 Hz), CH_3–C=C–), 3.70 (3H, s, $-COOCH_3$), 6.28 (1H, m, –C=C–H); ^{19}F NMR: 6.8 ppm (d, $J_{H,F}$ = 1.5 Hz).

Methyl 7,11 - *dimethyl* - 3 - *trifluoromethyldodeca* - 2,6,10 - *trienoate* (**4**). A solution of **3** (0.98 g, 3.9 mmole, 40:60/*Z*:*E*) in benzene (10 ml) was added dropwise to a vigorously stirred suspension of sodium salt of dimethyl (methoxycarbonyl)methylphosphonate [from NaH (0.12 g, 5 mmole) and dimethyl (methoxycarbonyl)methylphosphonate (0.91 g, 5 mmole)] in benzene (20 ml). Then the mixture was stirred for 5 h at room temp. The crude was treated with 0.4 N HCl (5 ml), the aqueous layer was decanted and extracted with Et_2O. The joined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give 1.023 g of a 34:66/*Z*:*E* isomer mixture at C-2 of α,β-unsaturated esters **4** (92% yield). Pure samples of C-2 isomers were obtained by column chromatography on silica gel. (*Z*)-2: IR: ν_{max} 1750, 1672(m), 1270, 1180 and 1145 cm^{-1}; ^1H NMR: δ, 5.90 (1H, s, $=CHCOOCH_3$); ^{19}F NMR: 15.9 ppm. (Found: C, 62.95; H, 7.75. $C_{16}H_{23}F_3O_2$ requires: C, 63.15; H, 7.62). GC-MS: *m/e* (%) (*Z*)-2,(*Z*)-6: 304(M^+)(< 1), 81(21), 69(100), 41(26); (*Z*)-2, (*E*)-6: 304(M^+)(<1), 81(22), 69(100), 41(25). (*E*)-2: IR ν_{max} 1740, 1675(m), 1210, 1195, 1170 and 1142 cm^{-1}; ^1H NMR: δ, 2.50–2.85 (2H, complex absorption, $-CH_2-C=CO_2CH_3$), 6.20 (1 H, m, $=CHCO_2CH_3$); ^{19}F NMR: 9.8 and 10.0 ppm for the corresponding (*Z*)-6 and (*E*)-6 isomers. (Found: C, 63.50; H, 7.90. $C_{16}H_{23}F_3O_2$ requires: C, 63.15; H, 7.62%). GC-MS: *m/e*(%) (*E*)-2,(*Z*)-6: 304(M^+)(2), 81(32), 69(100), 41(29); (*E*)-2,(*E*)-6: *m/e* (%), 304(M^+)(2), 81(33), 69(100), 41(34).

Methyl 10,11 - *epoxy* - 7,11 - *dimethyl* - 3 - *trifluoromethyldodeca* - 2,6 - *dienoate* (**1a**). A mixture of ester **4** (0.184 g, 0.6 mmole, (*E*)-2, (*Z*:*E*/40:60)-6) and m-chloroperbenzoic acid (0.139 g, 85%, 0.69 mmole) in CH_2Cl_2 (4 ml) was allowed to stand 4 h at room temp. The reaction mixture was worked up in the usual manner to give, after solvent removal, a residue which was purified by preparative TLC on silica gel (CH_2Cl_2:hexane/8:5) to yield **1a** (0.1 g, 52%). IR: ν_{max} 1730, 1670(m), 1310, 1205, 1175, 1152 and 1130 cm^{-1}; ^1H NMR: δ, 1.21 (3 H, s, CH_3–  –), 1.23 (3 H, s,  –), 5.15 (1H, t(J = 7 Hz), $=CH-CH_2-$), 6.27 (1H, m, $=CH-CO_2CH_3$); ^{19}F NMR: 9.9 and 10.0 ppm. (Found: C, 60.40; H, 7.67. $C_{16}H_{23}F_3O_3$ requires: C, 60.00; H, 7.24). In a similar way was obtained the epoxide corresponding to ester **4** (*Z*)-2, (*Z*:*E*/40:60)-6. IR: ν_{max} 1742, 1660(m), 1265, 1170 and 1135 cm^{-1}; ^1H NMR: δ, 1.23 (6 H, br. $(CH_3)_2$–  –), 2.50 (1 H, t (J = 6 Hz), – ), 5.08 (1 H, br., $=CH-CH_2-$), 5.95 (1H, br., $=CH-CO_2CH_3$); ^{19}F NMR: 15.9 and 16.0 ppm. (Found: C, 59.60; H, 7.47. $C_{16}H_{23}F_3O_3$ requires: C, 60.00; H, 7.24%). MS: *m/e* (%): 320 (M^+)(3), 81(100), 69(64), 43(83), 41(92).

7 - *Methyl* - 3 - *trifluoromethylocta* - 1,6 - *dien* - 3 - *ol* **5**. A solution of **6** (3.59 g, 20 mmole) in THF (5 ml) was added dropwise to a solution of vinylmagnesium bromide [prepared from Mg (0.96 g, 40 matg) and vinyl bromide (5.25 g, 40 mmole)] in

THF (15 ml). The mixture was stirred 3 h at room temp. and then treated with a saturated solution of NH_4Cl (3.4 g, 60 mmole), neutralised with 2N HCl and extracted with Et_2O. The joined organic extracts were dried ($MgSO_4$) and concentrated to give a residue which was distilled to yield **5** (3.27 g, 79% yield) b.p. 87–91°/25 torr. IR: ν_{max} 3540(m), 1182 and 1172 cm^{-1}; ^1H NMR: δ, 5.20–5.90 (3 H, complex absorption, –CH=CH_2); ^{19}F NMR: –2.7 ppm. MS: *m/e* (%): 208(M^+)(1), 69(48), 55(100) and 41(83). (Found: C, 57.53; H, 7.52. $C_{10}H_{15}F_3O$ requires: C, 57.75; H, 7.27%).

1,1,1 - *Trifluoro* - 6 - *methylhept* - 6 - *en* - 2 - *one* **6**. A solution of 4 - methylpent - 3 - enylmagnesium bromide [prepared from magnesium (2.1 g, 90 matg) and 4-methylpent-3-enyl bromide[13] (15.2 g, 93 mmole)] in Et_2O (50 ml) was added to a stirred solution of lithium trifluoroacetate (10.2 g, 85 mmole) in Et_2O (80 ml) at 0°. The mixture was allowed to warm up to room temp. and stirred for 5 h, then was cooled, 10% H_2SO_4 (34 ml) added and decanted. The aqueous layer was extracted with n-pentane and the combined organic extracts dried ($MgSO_4$) and evaporated to give a residue which was distilled to afford **6** (12 g, 80% yield), b.p. 128–32°. IR: ν_{max} 1765, 1210, 1160, 1140 and 1070 cm^{-1}; ^1H NMR: δ, 1.65, 1.67 (6 H, s, CH_3), 2.10–2.55 (2 H, m, =C–CH_2–), 2.55–2.90 (2H, m, –CH_2–CO–CF_3), 5.03(1 H, br.t (J ≈ 6 Hz), –C=CH); ^{19}F NMR: −1.3 ppm. MS: *m/e* (%), 180 (M^+)(17), 68(81), 55(33) and 41(100). Tosylhydrazone: m.p. 100–2°. ^{19}F NMR: 9.2 ppm. (Found: C, 51.75; H, 5.75; N, 8.01; S, 9.02. $C_{15}H_{19}F_3N_2O_2S$ requires: C, 51.71; H, 5.50; N, 8.05; S, 9.21%).

10 - *Methyl* - 6 - *trifluoromethylundeca* - 5,9 - *dien* - 2 - *one* **7**. (4,4-Ethylenedioxy)pentyltriphenylphosphonium bromide (8.57 g, 18.2 mmole) was added to a magnetically stirred suspension of $NaNH_2$ (0.623 g, 16 mmole) in diglyme (70 ml) under N_2 atmosphere. The mixture was heated for 1.5 h at 80°, developing an intense red coloration. To this solution, cooled to room temp., was added dropwise a solution of **6** (2.16 g, 12 mmole) in diglyme (15 ml). The reaction mixture was heated for 2 h at 100° and was allowed to proceed at room temp., with stirring, 20 h, and then was carefully neutralised with diluted H_2SO_4 to pH 5. The aqueous layer was extracted with pentane, the joined organic extracts were dried ($Mg SO_4$) and evaporated to give a residue which was treated with anhydrous acetone (25 ml) and a catalytic amount of p-toluenesulphonic acid, 1 h at room temp. The mixture was neutralised with solid Na_2CO_3, filtered and concentrated *in vacuo*. The residue was redisolved in water, extracted with pentane and the joined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and filtered through a short silica gel column to afford a 75:25/*Z*:*E* mixture of **7** (2.25 g, 79% yield). IR: ν_{max} 1718, 1160, 1145 and 1115 cm^{-1}; ^1H NMR: δ, 2.04 (3 H, s, CH_3–CO–), 5.00 (1 H, br., $(CH_3)_2$–C=CH), 5.45–6.10 (1 H, complex absorption, CF_3–C=CH–); ^{19}F NMR: (*Z*)-isomer 19.9 and (*E*)-isomer 12.1 ppm. (Found: C, 62.70; H, 7.83. $C_{13}H_{19}F_3O$ requires: C, 62.87; H, 7.71%). GC-MS: *m/e* (%) (*Z*)-isomer: 248 (M^+)(1), 69(100), 43(35) and 41(39); *m/e* (%) (*E*)-isomer: 228(2), 69(100), 43(34) and 41(37).

Methyl 3,11 - *dimethyl* - 7 - *trifluoromethyldodeca* - 2,6,10 - *trienoate* (**8**). A solution of **7** (0.43 g, 1.7 mmole, 73:27/*Z*:*E*) in benzene (5 ml) was added dropwise to a vigorously stirred suspension of sodium salt of dimethyl (methoxycarbonyl)methylphosphonate [from NaH(0.163 g, 6.8 mmole) and dimethyl (methoxycarbonyl)methylphosphonate (1.25 g, 6.8 mmole)] in benzene (10 ml). Then the reaction was allowed to proceed at 50°, with stirring, 20 h and the crude was treated in the usual manner. Bulb to bulb distillation (190°, 20 torr) of the residue afforded a 30:70/*Z*:*E* isomer mixture at C-2 of **8** (0.46 g, 89% yield). A sample (0.220 g) was purified by preparative TLC on silica gel (cyclohexane: Et_2O/7:1) to yield fractions of (*Z*)-isomer (0.060 g): IR: ν_{max} 1725, 1650 (m), 1225, 1150 and 1125 cm^{-1}; ^1H NMR: δ, 1.90 (3H, S, CH_3–C=C–CO_2CH_3), 5.05 (1 H, br., $(CH_3)_2$–C=CH), 5.66 (1 H, br. s, =CH–CO_2CH_3), 5.78 (1 H, br., CF_3–C=CH–); ^{19}F NMR: 19.6 and 12.5 ppm for the corresponding (*Z*)-6 and (*E*)-6 isomers. (Found: C, 63.34; H, 7.25. $C_{16}H_{23}F_3O_2$ requires: C, 63.15; H, 7.62%). GC-MS: *m/e* (%), (*Z*)-2, (*Z*)-6: 304 (M^+)(1), 114(100), 69(86) and 41(31); *m/e*(%) (*Z*)-2, (*E*)-6: 304 (M^+)(1), 114(36), 69(100) and 41(36), and of (*E*)-isomer (0.145 g): IR: ν_{max} 1720, 1650(m), 1220, 1150 and 1120 cm^{-1}; ^1H NMR: δ, 2.15 (3 H, s, CH_3–C=C–CO_2CH_3), 5.05 (1 H, br., $(CH_3)_2$–C=CH), 5.65 (2 H, complex absorption, =CH–CO_2CH_3 and CF_3–C=CH–); ^{19}F NMR: 19.4 and 12.5 ppm for the corresponding (*Z*)-6 and (*E*)-6 isomers. (Found: C, 62.75; H, 7.66. $C_{16}H_{23}F_3O_2$ requires: C, 63.15; H, 7.62%). GC–MS: *m/e* (%) (*E*)-2, (*Z*)-6: 304 (M^+) (<1), 114 (45), 69(100) and 41(39); *m/e* (%) (*E*)-2, (*E*)-6: 304 (M^+)(1), 114(36), 69(100) and 41(41).

Methyl 10,11 - *epoxy* - 3,11 - *dimethyl* - 7 - *trifluoromethyldodeca* - 2,6 - *dienoate* (**1b**). A mixture of ester **8** (0.50 g, 1.5 mmole), (14:86/*Z*:*E*)-2, (50:50/*Z*:*E*)-6), and m-chloroperbenzoic acid (0.370 g, 85%, 1.6 mmole) in CH_2Cl_2 (10 ml) was allowed to stand 4 h at room temperature. The mixture was worked up in the usual manner to give, after solvent removal, a residue (0.386 g, 89% yield), which was purified by preparative TLC on silica gel (hexane: Et_2O/7:1, eluted threefold) to afford (*E*)-2, (*Z*)-6 isomer (0.170 g): IR: ν_{max} 1725, 1650 (m), 1250, 1152, 1125 and 825 cm^{-1}; ^1H NMR: δ 1.15 (6 H, br., $(CH_3)_2$–C(O)–C–), 5.50–5.85 (2 H, complex absorption, =CH–CO_2CH_3 and CF_3–C=CH–); ^{19}F NMR: 20.0 ppm. MS: *m/e* (%), 85 (100), 59(78), 43(75) and 41(73). (Found: C, 60.31; H, 7.42. $C_{16}H_{23}F_3O_3$ requires: C, 60.00; H, 7.24%), a mixture of four isomers (0.150 g) and (*Z*)-2, (*E*)-6 isomer (0.040 g): IR: ν_{max} 1720, 1650(m), 1250, 1170, 1120 and 870 cm^{-1}; ^1H NMR: δ, 1.20 (6 H, br., $(CH_3)_2$–C(O)–C–), 5.65 (1 H, br. s, =CH–CO_2CH_3), 6.05 (1 H, br., CF_3–C=CH–); ^{19}F NMR: 12.6 ppm. MS: *m/e* (%), 85(90), 59(100), 43(81) and 41(91). (Found: C, 59.80; H, 7.38. $C_{16}H_{23}F_3O_3$ requires: C, 60.00; H, 7.24%).

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