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Some synthetic applications of the reactivity of methyl 2-fluoro-3-(phenylthio)acrylate

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Abstract

The synthetic usefulness of the title compound is demonstrated through its reactivity towards thio and amino nucleophiles as well as tin-centred radicals. The synthesis of a 2-fluoro analogue of a natural fungicide (Sinharine) is reported. We also show that 3-aryl-2-fluoropropenoates could be obtained via Stille coupling between an aryl iodide and a 3-tributylstannyl-2-fluoropropenoate.

Keywords: 2-Fluoro-3-(phenylthio)acrylate; 2-Fluoroacrylate; 2-Fluoroacrylamide; Stille coupling

Owing to the growing applications of fluorinated molecules in agro and pharmaceutical chemistry, several groups have proposed new multifunctional fluorinated synthons which are very useful as building blocks [1]. From this point of view 2-fluoro-3-(leaving group) substituted acrylates **1** are of great interest, since they can be functionalised via a 1,2- or 1,4-nucleophilic addition (path *a* or path *b*, then *c*, respectively) as well as via an addition–elimination process (path *b* then *d*) Scheme 1.

Owing to these possibilities, several fluoroheterocycles have been synthesized by reaction of 1,2- or 1,3-bis nucleophiles on 2,3-difluoroacrylates [2] or 5-fluoro-1,3-dioxin-4-ones [3]. On the other hand, the synthetic potentiality of methyl (*Z*)-3-methoxy-2-fluoroacrylate **1** (R^1=H, R^2=Me, Y=OMe) has been examined by Schlosser and co-workers [4] who also obtained the corresponding 3-phenylthio derivative **1a** (R^1=H, R^2=Me, Y=SPh) upon treatment of 3-methoxy 2-fluoroacrylate with thiophenol and subsequent thermal elimination of MeOH. Having proposed at the same time a general methodology for the synthesis of 2-fluoro-3-phenylthio-2,3-unsaturated carbonyl compounds [5], this result prompts us to report our work about the reactivity of (*Z*)-**1a** and (*Z*)-**1b** (R^1=H, R^2=Et, Y=SPh) towards heteronucleophiles. The utility of these reactions will also be demonstrated suggesting an easy synthetic pathway to a fluorinated analogue of a natural product.

1. Reaction of amines and thiols: synthesis of a fluorinated analogue of a natural fungicide

Whatever the conditions used, nitrogen nucleophiles usually react with alkenoate derivatives through a conjugate addition [6]. However, as observed previously from the 3-methoxy derivative [4], *n*-propylamine and phenethylamine reacted exclusively with (*Z*)-**1a** via an 1,2-addition to afford the fluoroamides (*Z*)-**2a**[1] and (*Z*)-**2a**[2], respectively, as indicated in Scheme 2.

On the other hand, it is also known that the thio-moiety of some vinylsulfides could be stereospecifically exchanged via a vinylic substitution [7]. Interestingly, the fluoroacrylate (*Z*)-**1a** reacted smoothly with sodium thioglycolate in methanol to provide the corresponding sulfide (*Z*)-**1c** (Scheme 3, conditions i). Therefore, the preparation of the 2-fluoro analogue (*Z*)-**2d** of the natural fungicide Sinharine [8] was easily achieved from (*Z*)-**1a** in 56% overall yield, via two 100% regioselective successive reactions [Scheme 3: (*Z*)-**1a** ⇒ (*Z*)-**1d** ⇒ (*Z*)-**2d**]. The phenylthio group of (*Z*)-1a was first exchanged with methanethiolate using preferentially CH_2Cl_2 as solvent (conditions ii). Amidation of (*Z*)-**1d** was then performed by reaction with phenethylamine (conditions iii), as mentioned above.

2. Reaction with tin radicals followed by Stille coupling

Among organometallic species, only mixed organo-cuprates reagents allow the selective substitution of the thio

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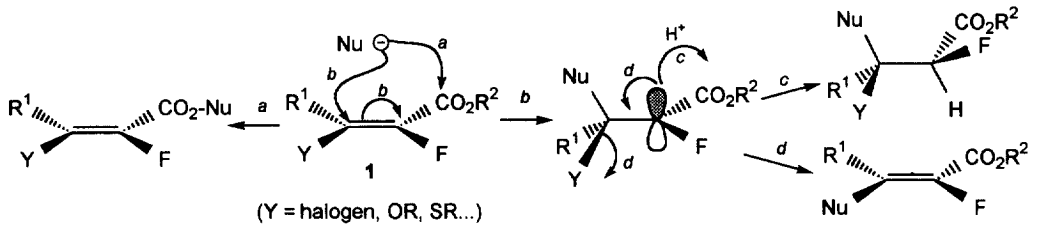
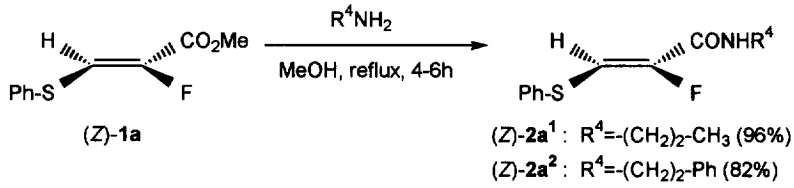
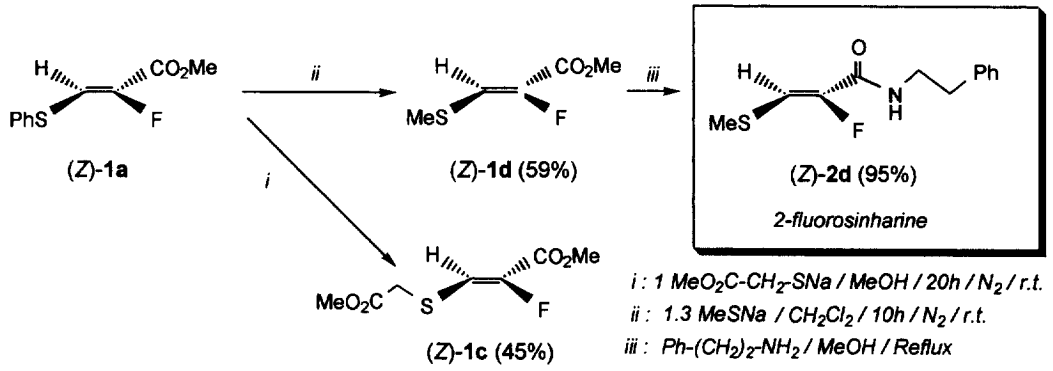


Scheme 1.



Scheme 2.



Scheme 3.

group of 3-alkyl-3-[alkyl(or aryl) thio]alkenoates [9–12]. However, it should be noted that this coupling methodology fails from less bulky 3-monothiosubstituted enoates like ethyl 3-(phenylthio)propenoate (PhSCH=CH–CO_2Et) which gave only a doubly alkylated product by reaction with $(Bu_2CuSCN)Li_2$ in THF at −30°C [10].

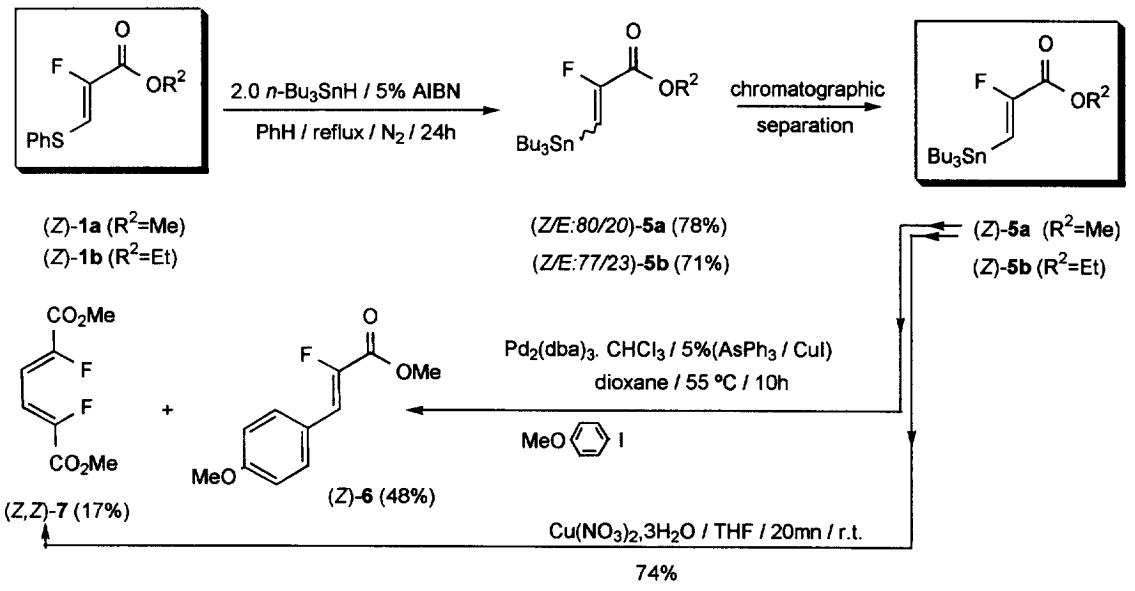
In order to avoid such difficulties, 2-fluoro-3-phenylthioenoates (*Z*)-**1a** and (*Z*)-**1b** were converted [13] under classical conditions, into the new corresponding (2-fluoroacrylyl)stannanes [14–17] (*E*/*Z*)-**5a** and (*E*/*Z*)-**5b**, respectively (Scheme 4). Pure (*Z*)-stereomers were then isolated by flash chromatography on SiO_2 (with petroleum ether as eluent).

Then as depicted in Scheme 4, (*Z*)-**5a** has been stereoselectively coupled with *para*-iodoanisole via a Stille reaction under Farina's conditions to give (*Z*)-**6** [18]. The diene (*Z*,*Z*)-**7**, isolated as minor by-product was also selectively prepared in good yield from treatment of (*Z*)-**5a** with copper (II) nitrate trihydrate in tetrahydrofuran [19,20].

To conclude, the title compound which was easily prepared by one electrofluorination step from their respective-hydrogeno analogues, are very useful as a 2-fluoroacrylate cation equivalent. The thio group can be stereoselectively exchanged via an addition–elimination. Moreover, the substitution of this thio group by a tributyltin one leads to a reversal polarity allowing the Stille reaction to be successfully applied. Finally, such fluoroacrylate moiety synthetic methodology is an alternative towards more classical Horner–Wadsworth–Emmons or Reformatsky reactions involving fluoroacetate anion [21].

3. Experimental

All melting points were uncorrected. ^{1}H NMR spectra (TMS, $CDCl_3$, ppm, Hz) were recorded on a BRUKER AC 200 (200 MHz) spectrometer. ^{19}F NMR ($CFCl_3$, $CDCl_3$) spectra were measured at 188.2 MHz on a BRUKER AC 200 whilst ^{13}CNMR spectra (TMS, $CDCl_3$) were recorded on the same apparatus at 50.3 MHz. Mass spectra were taken on a NERMAG R10-10S (70 eV) coupled with a capillary GC DELSI-DI 700 using DB5 column: 30 m×0.25 nm. Chromatography was carried out on silica gel (Merck, 230–400 mesh).



Scheme 4.

3.1. Preparation of (Z)-1b

3.1.1. Ethyl 2-fluoro-3-(phenylthio)acrylate

It was obtained by electrochemical fluorination of the corresponding 2-hydrogeno analogue as previously described [5]. ^{1}H NMR: 1.34 (t, 3H, $^3J_{HH}$=7.1), 4.30 (q, 2H, $^3J_{HH}$=7.1), 7.07 (d, 1H, $^3J_{HF}$=31.5), 7.37–7.51 (m, 5H$_{arom}$); ^{19}F NMR: −124.4 (d, $^3J_{HF}$=31.5); ^{13}C NMR: 14.2 (s, CH_3), 6.17 (s, CH_2), 121.0 (d, C_3, $^2J_{CF}$=13.5), 128.4 (s, C_p), 129.6 (s, 2 $C_{o/m}$), 130.9 (s, 2 $C_{o/m}$), 132.6 (s, C_i), 144.8 (d, C_2, $^1J_{CF}$=254.2), 159.2 (d, C_1=O, $^2J_{CF}$=32.5).

3.2. Preparation of (Z)-1c and (Z)-1d from (Z)-1a

3.2.1. Methyl 2-fluoro-3-[(methoxycarbonyl)methylthio]-prop-2-enoate (Z)-1c

To a stirred solution of 125 mg (1.18 mmol) of methylthioglycolate and 64 mg (1.18 mmol) of MeONa in 10 ml of MeOH, under nitrogen atmosphere, was slowly added (15 min) a solution of 250 mg (1.18 mmol) of (Z)-**1a** in 7 ml of methanol. The mixture was then stirred at room temperature and its evolution followed by GC. After 20 h, the reaction medium was hydrolysed with water (10 ml) and acidified by 6N HCl up to pH 1. Methanol was then evaporated under reduced pressure and the aqueous phase was extracted with dichloromethane. After drying on $MgSO_4$, evaporation of the solvent gave a crude oil (280 mg) which was purified by column chromatography using petroleum ether (b.p. 45–60°C)/acetone (95/5) as eluent. 90 mg (36%) of starting material (Z)-**1a** and 110 mg (45%) of (Z)-**1c** were isolated. (Z)-1c: ^{1}H NMR: 3.53 (s, 2H), 3.78 (s, 3H), 3.82 (s, 3H), 6.95 (d, 1H, $^3J_{HF}$=31.6); ^{19}F NMR: −125.0 (d, $^3J_{HF}$=31.6) ^{13}C NMR: 34.5 (s, CH_2), 52.5 (s, CH_3), 53.0 (s, CH_3), 119.3 (d, C_3, $^2J_{CF}$=13.5), 145.2 (d, C_2, $^1J_{CF}$=253.7), 169.1 (d, C_1=O, $^2J_{CF}$=32.8).

3.2.2. Methyl 2-fluoro-3-(methylthio)prop-2-enoate (Z)-1d

To a stirred solution of 500 mg (2.35 mmol) of (Z)-**1a** in 5 ml of dichloromethane was added 214 mg (3.06 mmol) of MeSNa. The resulting heterogeneous mixture was then kept under nitrogen for 10 h and the final work-up was carried out as described as (Z)-**1c**. The crude oil (668 mg) was then purified by column chromatography using pure petroleum ether and 207 mg (59%) of (Z)-**1d** was isolated. (Z)-**1d**: ^{1}H: NMR 2.44 (s, 3H), 3.81 (s, 3H), 6.82 (d, 1H, $^3J_{HF}$=31.9); ^{19}F NMR: −128.2 (d, $^3J_{HF}$=31.9); ^{13}C NMR: 16.9 (s, CH_3), 52.3 (d, CH_3, $^4J_{CF}$=0.7), 122.9 (d, C_3, $^2J_{CF}$=13.6), 144.6 (d, C_2, $^1J_{CF}$=251.8), 159.7 (d, C_1=O, $^2J_{CF}$=32.5).

3.3. Preparation of 2-fluoro acrylamides: (Z)-2a[1], (Z)-2a[2] and (Z)-2d

3.3.1. N-phenethyl-2-fluoro-3-(methylthio)prop-2-enamide (Z)-2d

3 ml of dry dichloromethane was placed in a small flask and kept under nitrogen. Then 60 mg (0.4 mmol) of (Z)-**1d** and 55 μl (0.44 mmol) of phenethylamine were introduced. The homogeneous mixture was stirred under reflux for 4 h and the solvent was evaporated under reduced pressure giving 91 mg (95%) of the crystallised product (Z)-**2d**: which was not more purified. (Z)-**2d**: m.p.: 111–112°C; ^{1}H NMR: 2.40 (s, 3H), 2.88 (t, 2H, $^3J_{HH}$=7.0), 3.58 (dt, 2H, $^3J_{HH}$=7.0, $^3J_{HH}$=13.4), 6.18 (s, 1H, NH), 6.73 (d, 1H, $^3J_{HF}$=35.4), 7.20–7.31 (m, 5H$_{arom}$); ^{19}F NMR: −130.8 (d, $^3J_{HF}$=35.4); ^{13}C NMR: 17.0 (s, CH_3), 35.6 (CH_2),

40.5 (CH_2), 117.5 (d, CH=, $^2J_{CF}$=13.4), 126.6 (s, C_p), 128.7 (2×2 $C_{o/m}$), 138,4 (C_i), 147.8 (d, CF, $^1J_{CF}$=261.2), 158.8 (d, CO, $^2J_{CF}$=27.3). MS *m/z* (%): 239 (M^+, 2), 192 (37), 148 (33), 135 (14), 120 (15), 119 (100), 105 (12), 104 (47), 91 (28), 65 (15). *Anal.* Calc. for $C_{12}H_{14}SNOF$: C, 60.23; H, 5.90; S, 13.40; F, 7.54%. Found: C, 60.13; H, 5.92; S, 13.35; F, 7.78%.

3.3.2. *N-propyl-2-fluoro-3(phenylthio)prop-2-enamide (Z)-***2a**[1]

According to the procedure described above for (*Z*)-**2d**, it was isolated as a white solid. (*Z*)-**2a**[1]: m.p.: 62–64°C, ^{1}H NMR: 0.94 (t, 3H, $^3J_{HH}$=7.1), 1.42–1.67 (m, 2H), 3.17–3.39 (m, 2H), 6.31 (s, 1H, NH), 7.01 (d, 1H, $^3J_{HF}$=34.9), 7.14–7.55 (m, 5H_{arom}); ^{19}F NMR: −127.4 (d, $^3J_{HF}$=34.9). MS *m/z* (%): 239 ($M^{+\cdot}$, 84), 182 (10), 181 (100), 161 (12), 153 (10), 152 (15), 133 (18), 130 (15), 110 (10), 109 (33), 93 (18), 89 (11), 65 (14), 51 (10), 43 (10).

3.3.3. *N-phenethyl-2-fluoro-3(phenylthio)prop-2-enamide (Z)-***2a**[2]

According to the procedure described above for (*Z*)-**2d**, it was isolated as a white solid. (*Z*)-**2a**[2]: m.p.: 91–93°C; ^{1}H NMR: 2.89 (t, 2H, $^3J_{HH}$=7.0); 3.62 (dd, 2H, $^3J_{HH}$=7.0, $^3J_{HH}$=13.3); 6.18 (broad s, 1H, NH); 7.01 (d, 1H, $^3J_{HF}$=34.8); 7.22–7.48) (m, 10H); ^{19}F NMR: −127.9 (d, $^3J_{HF}$=34.8). MS *m/z* (%): 301 ($M^{+\cdot}$, 45), 210 (17), 197 (54), 192 (23), 182 (12), 181 (100), 133 (28), 109 (34), 93 (20), 91 (21), 89 (17), 77 (16), 65 (26).

3.4. *Preparation of (Z)-***5a** *and (Z)-***5b** *by stannylation of (Z)-***1a** *and (Z)-***1b**, *respectively*

3.4.1. *Methyl 2-fluoro-3-(tributyltin)prop-2-enoate (Z)-***5a**

A solution of 1074 mg (3.69 mmol) of tributyltinhydride, 380 mg (1.80 mmol) of (*Z*)-**1a** and 36 mg (0.22 mmol, 5%) of azaisobutyronitrile (AIBN) in 15 ml of benzene was refluxed for 6 h, under a nitrogen atmosphere. Then, benzene was evaporated under reduced pressure, giving 1330 mg of crude oil which was purified by column chromatography (petroleum ether). 552 mg of **5a** (*Z*/*E*: 80/20) was firstly isolated and pure (*Z*)-**5a** was obtained after a second column chromatography. (*Z*)-**5a**: ^{1}H NMR: 0.89 (t, 9H, $^3J_{HH}$=7.1), 1.02 (t, 6H, $^3J_{HH}$=8.2), 1.19–1.52 (m, 6H), 1.56–1.69 (m, 6H), 3.82 (s, 3H), 6.56 (d, 1H, $^3J_{HF}$=65.2); ^{19}F NMR: −99.3 (d, $^3J_{HF}$=65.2); ^{13}C NMR: 10.2 (s, 3 CH_2), 13.5 (s, 3 CH_3), 27.1(s, 3 CH_2), 28.9 (s, 3 CH_2-Sn), 52.4 (s, CH_3), 116.6 (d,=CHSnBu_3, $^2J_{CF}$=41.2), 155.7 (d, CF, $^1J_{CF}$=249.5), 159.8 (d, CO, $^2J_{CF}$=46.4). (*E*)-**5a**: ^{1}H NMR: 0.89 (t, 9H, $^3J_{HH}$=7.1), 0.98 (t, 6H, $^3J_{HH}$=8.1), 1.21–1.47 (m, 6H), 1.51–1.67 (m, 6H), 3.83 (s, 3H), 6.01 (d, 1H, $^3J_{HF}$=32.0); ^{19}F NMR: −88.3 (d, $^3J_{HF}$=32.0).

3.4.2. *Ethyl 2-fluoro-3-(tributyltin)prop-2-enoate (Z)-***5b**

Prepared by the same procedure used for (*Z*)-**5a**. (*Z*)-**5b**: ^{1}H NMR: 0.85 (t, 9H, $^3J_{HH}$=7.1), 0.98 (t, 3H, $^3J_{HH}$=7.50), 1.22–1.60 (m, 18H), 4.28 (q, 2H, $^3J_{HH}$=7.50), 6.55 (d, 1H, $^3J_{HF}$=65.1); ^{19}F NMR: −99.1 (d, $^3J_{HF}$=65.1); ^{13}C NMR: 10.2 (s, 3 CH_3), 13.6 (s, 3 CH_3), 14.2 (s, CH_3), 27.2 (s, 3 CH_2), 29.0 (s, 3 CH_2-Sn), 61.7 (s, CH_2), 116.4 (d, $^2J_{CF}$=41.2), 156.1 (d, $^1J_{CF}$=249.8). 159.6 (d, CO, $^2J_{CF}$=45.8). (*E*)-**5b**: ^{19}F NMR: −88.3 (d, $^3J_{HF}$=30.3).

3.5. *Preparation of (Z)-***6** *by Stille coupling*

Under dried nitrogen atmosphere, 132 mg (0.56 mmol) of iodoanisol, 35 mg (0.12 mmol, 20%) of triphenylarsine, 11 mg (10%) of CuI, 27 mg (5%) of Pd_2dba_3, $CHCl_3$ and 220 mg (0.56 mmol) of (*Z*)-**5a** were dissolved in anhydrous degassed dioxane (4 ml). After 10 h at 50°C under stirring, the solvent was evaporated and the crude oil (405 mg) was chromatographed on SiO_2 (petroleum ether/acetone: 95/5) giving 57 mg (0.27 mmol) of (*Z*)-**6** then 10 mg (0.05 mmol) of (*Z,Z*)-**7**.

3.5.1. *Methyl 2-fluoro-3-(4-methoxyphenyl)prop-2-enoate (Z)-***6** *[22]:*

^{1}H NMR: 3.84 (s, 3H), 3.87 (s, 3H), 6.88 (d, 1H, $^3J_{HF}$=35,7), 6.94–7.62 (m, 4H_{arom}); ^{19}F NMR: −129.6 (d, $^3J_{HF}$=35.7). MS *m/z* (%): 210 ($M^{+\cdot}$, 100), 179 (17), 159 (11), 152 (10), 150 (11), 136 (14), 132 (34), 108 (20), 107 (32).

3.6. *Preparation of (Z,Z)-***7** *by intermolecular coupling of (Z)-***5a**

3.6.1. *(Z,Z)-Dimethyl 2,5-difluorohex-2,4-diene-1,6-dioate (Z,Z)-***7**

To a solution of 105 mg (0.43 mmol) of $Cu(NO_3)_2{\cdot}3H_2O$ in 0.5 ml of THF at room temperature was added 170 mg (0.43 mmol) of (*Z*)-**5a**. The resulting mixture was stirred for 20 mn at the same temperature then treated as described in [20]. The purification of the crude oil (250 mg) by column chromatography afforded 65 mg (0.32 mmol, 74%) of (*Z,Z*)-**7**. ^{1}H NMR: 3.88 (s, 6H), 6.87–7.03 (m, 2H); ^{19}F NMR: −118.4 to −118.1 (m); ^{13}C NMR: 52.9 (s, 2 CH_3), 108.5 (dd, $^2J_{CF}$=7.0, $^3J_{CF}$=4.6, 2 CH=) 149.5 (d, $^1J_{CF}$=269.3, 2 CF=), 162.1 (d, $^2J_{CF}$=33.9, 2 CO). MS *m/z* (%): 206 ($M^{+\cdot}$, 21), 175 (10), 147 (100), 59 (15).

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