SYNTHESIS OF FERRULACTONE I AND ITS DIMER

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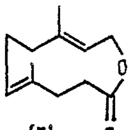
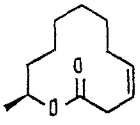
The syntheses of ferrulactone I (the principal component of the aggregational pheromone of the short-antennaed meal beetle), and of is dimer having a 22-membered ring, from the readily available geraniol, have been accomplished in seven and five stages, respectively.

The aggregational pheromone of the short-antennaed meal beetle Cryptolestes ferrugineus (Stephen), which is a serious pest of grain and products derived therefrom, contains the two macrocycles (I) and (II), known as ferrulactone I and ferrulactone II, respectively [1]. The greatest attractant activity is shown by a mixture of (I) and (II) in a ratio of 9:1 [2], so that access to the principal isoprenoid component (I) is of considerable interest. This compound has been obtained by lactonization of the α, ω-hydroxyacid (III), obtained in turn by a multistage procedure from geraniol [3] or farnesol [4]. We here described two new approaches to the construction of the 11-membered lactone (I) from the former, more readily available terpenol.


(I)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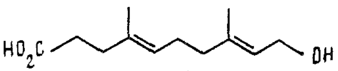
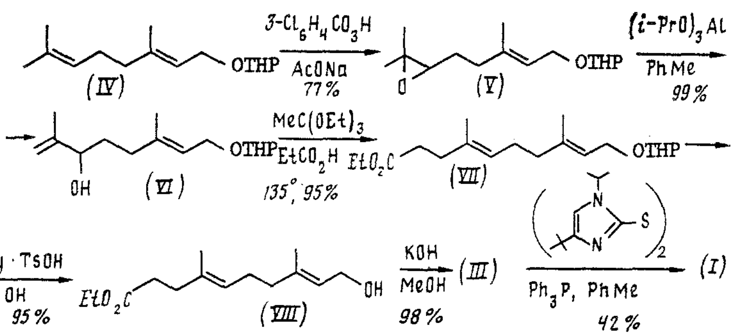

(III)

Bearing in mind earlier work [3, 4], the orthoester version of the Claisen rearrangement of the allyl alcohol (VI) was initially selected as the key step, leading directly to the trisnorfarnesane structure (VII). The required intermediate (VI) is readily obtained by selective epoxidation of the tetrahydropyranyl (THP) ether (IV) of geraniol, followed by isomerization of the monoepoxide (V) with aluminum isopropoxide, rather than the previously employed but much less effective lithium diisopropylamide [5].

Treatment of the alcohol (VI) with ethyl orthoacetate in the presence of catalytic amounts of propionic acid at 135°C proceeds stereospecifically to give near- quantitative yields of the ester (VII), in which the E,E-isomer constitutes, according to GLC, more than 99% of the total reaction mixture. This result is in agreement, in particular, with the integral intensities of the signals for $CH_3{-}C^4$ and $CH_3{-}C^8$, seen at 1.56 and 1.62 ppm, respectively, which are characteristic of E-trisubstituted olefins [6].

Subsequent conversion of the ester (VII) into the key compound (III) was accomplished in high yield by successive removal of first the THP protection, then hydrolysis of the



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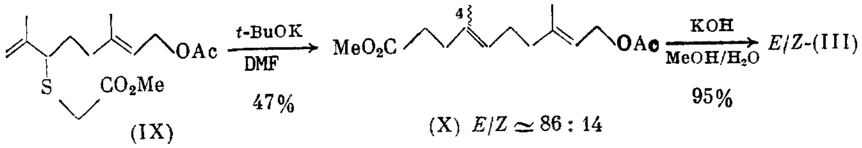
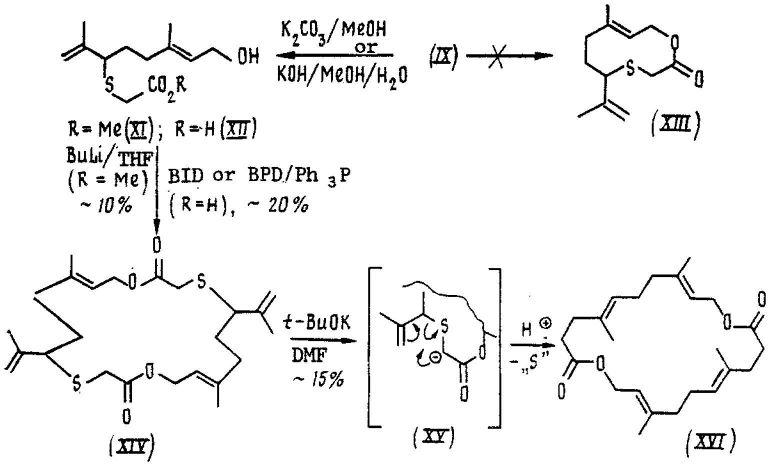
intermediate hydroxyester (VIII). Macrolactonization of the hydroxyacid (III) was effected with bis(3-isopropyl-5-tert-butyl-2-imidazolyl) disulfide (BID) and Ph_3P under conditions similar to those described previously [3, 4], with slightly better results than those obtained previously. The overall yield of (I) was >28% over these six stages, which is in excess of the mean statistical standards for such substances.

The structures of the previously unreported compounds (VII) and (VIII) were established from their spectra and elemental analyses. The structures of the known compounds (III) [3, 4], (V) and (VI) [5] were confirmed spectrally, and the physicochemical properties of the ferrulactone I (I) obtained were close to those reported [3, 4], the purity of the distilled product being, according to GLC, ~100%.

The other approach to the synthesis of (I) which we have examined was based on the sigmatropic rearrangement of activated allyl sulfides [2, 3]. The starting material selected in this case was the readily accessible (IX), obtained by the ene reaction of geranyl acetate with the sulfenyl chloride derivative of methyl thioglycollate [7]. The strong base-catalyzed rearrangement of the thioester (IX) gave a mixture of diesters (X), cf. [7]. Subsequent exhaustive hydrolysis of the mixture gave an overall yield of ~45% of the hydroxyacid (III) as a mixture of stereoisomers in which E/Z = 85:15, as shown by measurement of the integral intensity of the signals for CH_3–C^4 in the PMR spectrum (δ = 1.63 and 1.68 ppm).



Hence, this approach is much less efficient than the one described above, mainly in respect of its stereochemistry. Yet another possibility for the use of the thioester (IX) in the synthesis of (I) was therefore examined, involving its initial cyclization to the 10-membered thialactone (XIII), followed by [3,2]-rearrangement of the latter. The hydroxyester (XI) and hydroxyacid (XII) required for this purpose were obtained quantitatively by the partial and complete hydrolysis, respectively, of the diester (IX). It was found that boiling the lithium alkoxide obtained from the hydroxyester (XI) in THF (cf. [8]) gave a low yield of the 20-membered dithiadiolide (XIV) in place of the expected (XIII). The structure of this previously unreported compound was confirmed spectrally. Its mass spectrum showed an M^+ peak, and the PMR spectrum contained, in particular, signals for the CH_3–C=C group (δ 1.58 and 1.72 ppm), CHS (δ 3.35 ppm), and CH_2O (δ 4.57-4.80 ppm). The same diolide (XIV) was obtained in double the yield by macrolactonization of the hydroxyacid (XII) with BID or bis(2-pyridyl) disulfide (BPD) and Ph_3P using the high-dilution technique. It must be specially emphasized that in neither case was the monomeric lactone (XIII) detected in the reaction mixture. The reasons for the formation of the diolide (XIV) as the pure stereoisomer, as shown by its PMR spectrum, have not been specially studied.



Treatment of the dithiadiolide (XIV) with strong bases such as t-BuOK resulted in the formation of the sulfur-free 22-membered diolide (XVI), which is a dimer of ferrulactone I

(I), and was of interest as a possible meal beetle attractant. The formation of (XVI) from (XIV), apparently via the intermediate (XV), apparently provides the first example of a [3,2]-sigmatropic reaction in macrocyclic allyl sulfides, leading to intramolecular desulfurization.

The spectral properties of the diolide (XVI) were in full agreement with the literature values [3] for this compound. The structures of the novel sulfides (XI) and (XII) were confirmed by their spectra and elemental analyses.

Ferrulactone I (I) and its dimer (XVI) can thus be quite simply obtained from the readily available geraniol.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument in chloroform. The PMR spectra of solutions in $CDCl_3$ were measured relative to TMS on a Bruker WM-250 spectrometer. Mass spectra were obtained with an ionizing voltage of 70 eV on a Varian MAT CH-6 spectrometer. GLC was carried out on an LKhM-80 instrument (3 m × 3 mm column with 15% Carbowax 20M on Chromatone N-AW-HMDS). TLC was carried out on plates with bound layers of Silufol silica.

Epoxyether (V). To a suspension of 4.76 g (20 mmoles) of (IV) [9] and 2.05 g (25 mmoles) of sodium acetate in 45 ml of dichloromethane was added with stirring at 0°C over 5 min 3.97 g (23 mmoles) of m-chloroperbenzoic acid. The mixture was stirred for 30 min at 0°C and 1.5 h at 20°C, then filtered. The filtrate was washed with saturated solutions of sodium bicarbonate and sodium chloride, dried over magnesium sulfate, evaporated, and the residue (~5 g) chromatographed on 250 g of silica. Gradient elution from hexane to ether (up to 25% of the latter) gave 3.92 g (77%) of (V) [5] as a colorless oil, R_f 0.35 (hexane—ether, 1:1). PMR spectrum (δ, ppm, J, Hz): 1.21 and 1.26 s (6H, CH_3—C^2), 1.4-1.8 m (8H, CH_2), 1.65 s (3H, CH_3—C=C), 2.13 m (2H, HC^5), 2.67 t (1H, HC^3, J = 6), 3.4-4.3 m (4H, CH_2O), 4.59 t (1H, OCHO, J = 4), 5.37 t (1H, HC=C, J = 7).

Hydroxyether (VI). To a solution of 1.78 g (7 mmoles) of (V) in 30 ml of toluene was added all at once with stirring at 25°C 3.3 ml of a 50% solution of aluminum isopropoxide (8 mmoles) in toluene. The mixture was boiled for 6 h, diluted with ether, neutralized with 1% HCl, washed with saturated sodium chloride solution, dried over magnesium sulfate, evaporated, and the residue (~2 g) chromatographed on 150 g of silica. Elution with a mixture of hexane and ether (7:3) gave 1.77 g (99%) of (VI) [5], bp 125°C (0.06 mm), n_D^{17} 1.4911. PMR spectrum (δ, ppm; J, Hz): 1.4-1.8 m (8H, CH_2), 1.62 and 1.68 s (6H, CH_3), 2.03 m (2H, HC^5), 3.4-4.2 m (5H, HC^3, CH_2O), 4.58 t (1H, OCHO, J = 4), 4.78 and 4.88 s (2H, H_2C=C), 5.33 t (1H, HC^7, J = 7).

Ethyl 4,8-Dimethyl-10-(2-tetrahydropyranyloxy)-4E,8E-decadienoate (VII). A mixture of 0.5 g (1.97 mmoles) of (VI), 2.23 g (13.8 mmoles) of triethyl orthoformate, and 8 mg (0.11 mole) of propionic acid was heated at 125-135°C for 1.5 h, then evaporated under reduced pressure, and the residue (~0.7 g) chromatographed on 50 g of silica. Gradient elution from hexane to ether (up to 20% of the latter) gave 0.61 g (95%) of (VII) as a colorless oil, R_f 0.39 (hexane—ether, 3:2). IR spectrum (ν, cm^{-1}): 810, 860, 905, 1020, 1035, 1050, 1075, 1115, 1130, 1160, 1180, 1210, 1235, 1265, 1300, 1360, 1370, 1445, 1670, 1720, 2850, 2950, 3010. PMR spectrum (δ, ppm; J, Hz): 1.21 t (3H, CH_3, J = 7), 1.4-1.8 m (6H, CH_2), 1.56 and 1.62 s (6H, CH_3C=C), 2.0 m (4H, HC^6, HC^7), 2.2-2.4 m (4H, HC^2, HC^3), 3.4-4.2 m (6H, CH_2O), 4.58 t (1H, OCHO, J = 4), 5.10 t (1H, HC^5, J = 7), 5.32 t (1H, HC^9, J = 7). Mass spectrum (m/z, %): M^+ 324 (15), 306 (15), 256 (20), 240 (40), 239 (25), 223 (25), 222 (50), 210 (15), 209 (25), 196 (15), 195 (20), 177 (75), 165 (15), 155 (100), 154 (50). Found, %: C 70.76, H 9.57. $C_{19}H_{32}O_4$. Calculated, %: C 70.33, H 9.94.

Ethyl 4,8-Dimethyl-10-hydroxy-4E,8E-decadienoate (VIII). A solution of 0.44 g (1.36 mmoles) of (VII) and 33 mg (0.13 mmole) of Py·TsOH [9] in 20 ml of ethanol was heated at 50-55°C for 4 h, then evaporated under reduced pressure, and the residue (~0.4 g) chromatographed on 50 g of silica. Gradient elution from hexane to ether (up to 40% of the latter) gave 0.31 g (95%) of (VIII), bp 112°C (1 mm), n_D^{20} 1.4801. IR spectrum (ν, cm^{-1}): 860, 990, 1030, 1095, 1160, 1210, 1230, 1265, 1300, 1345, 1375, 1450, 1670, 1720, 1735, 2920, 2940, 2985, 3500, and 3605. PMR spectrum (δ, ppm; J, Hz): 1.19 t (3H, CH_3, J = 7), 1.55 and 1.60 t (6H, CH_3C=C), 2.0 m (4H, HC^6, HC^7), 2.2-2.4 m (4H, HC^2, HC^3), 4.0-4.1 m (4H, CH_2O), 5.07 t (1H, HC^5, J = 7), 5.32 t (1H, HC^9, J = 7). Mass spectrum (m/z, %): M^+ 240 (15), 222 (20), 209 (15), 196 (20), 194 (15), 178 (40), 167 (50), 154 (75), 150 (100). Found, %: C 69.54, H 10.03. $C_{14}H_{24}O_3$. Calculated, %: C 69.94, H 10.06.

Hydroxyacid (III). To a solution of 1.8 g (7.5 mmoles) of (VIII) in 40 ml of methanol was added in one portion with stirring at 25°C a 25% aqueous solution of KOH (12 ml, 75 mmoles). After 1 h, the mixture was evaporated, the residue acidified with 5% HCl to pH $\leq$ 3, and extracted with ether. The extract was washed with saturated sodium chloride solution, dried over magnesium sulfate, evaporated under reduced pressure, and the residue (1.6 g) chromatographed on 150 g of silica. Gradient elution from hexane to ether (up to 50% of the latter) gave 1.56 g (98%) of (III) [3, 4] as a colorless oil, R_f 0.33 (hexane—ether, 1:4). PMR spectrum (δ, ppm; J, Hz): 1.63 br. s (6H, CH_3), 2.1 m (4H, HC^6, HC^7), 2.30 t (2H, HC^3, J = 7.5), 2.43 t (2H, HC^2, J = 7.5), 4.17 d (2H, CH_2O, J = 7), 5.10 t (1H, HC^5, J = 7), 5.35 t (1H, HC^9 , J = 7).

Ferrulactone I (I). To a solution of 0.25 g (1.18 mmoles) of (III) and 0.7 g (1.78 mmoles) of BID [10] in 30 ml of toluene was added in a single portion with stirring at −75°C under argon 0.47 g (1.79 mmoles) of Ph_3P. After 30 min, the mixture was warmed to −10°C, stirred at this temperature for 1.5 h, then cooled to −60°C, diluted with 350 ml of toluene, and 0.25 g (0.63 mmole) of BID added to the resulting solution. After 1 h, the mixture was brought to the boil, boiled for 2 h, concentrated to a volume of ~100 ml, and filtered through a layer (~5 cm) of silica. The filtrate was evaporated, and the residue (0.3 g) chromatographed on 50 g of silica. Gradient elution from hexane to ether (up to 3% of the latter) gave 97 mg (42%) of (I) [3, 4], bp 63°C (1 mm), n_D^{22} 1.5011. PMR spectrum (δ, ppm; J, Hz): 1.58 and 1.66 s (6H, CH_3), 2.10 m (4H, HC^6, HC^7), 2.33 m (4H, HC^2, HC^3), 4.3-4.8 m (2H, CH_2O), 4.84 t (1H, HC^5, J = 7), 5.57 t (1H, HC^9, J = 7).

E/Z-Hydroxyacid (III) from Diester (X). As described above for (VIII), from 0.2 g (0.75 mmole) of (X) [7] in 5 ml of methanol and 3 ml of 30% aqueous KOH, following purification of the product on silica there was obtained 0.15 g (95%) of (III), E/Z ≈ 85:15, R_f 0.33 (hexane—ether, 1:4).

3,7-Dimethyl-6-methoxycarbonylmethylthio-2E,7-octadien-1-ol (XI). A suspension of 0.2 g (0.66 mmole) of (IX) and 50 mg (0.36 mmole) of potassium carbonate in 5 ml of methanol was stirred at 25°C for 30 min, then diluted with hexane and water, and extracted with a mixture of hexane and ether (4:1). The extract was dried over magnesium sulfate, evaporated under reduced pressure, and the residue (0.2 g) chromatographed on 20 g of silica. Gradient elution from hexane to ether (up to 45% of the latter) gave 0.17 g (99%) of (XI) as a colorless oil, R_f 0.30 (hexane—ether, 1:4). IR spectrum (ν, cm^{-1}): 675, 790, 840, 905, 1005, 1105, 1140, 1165, 1200, 1240, 1290, 1375, 1385, 1410, 1440, 1640, 1670, 1730, 2895, 2955, 3015, 3085, 3530, and 3615. PMR spectrum (δ, ppm; J, Hz): 1.65 and 1.70 s (6H, CH_3), 1.6-1.8 m (2H, HC^5), 2.05 br. t (2H, HC^4, J = 7), 3.11 AB q (2H, CH_2S, J_{AB} = 14, δ_A = 3.14, δ_B = 3.08), 3.42 t (1H, HC^6, J = 7), 3.69 s (3H, CH_3O), 4.13 d (2H, HC^1, J = 7), 4.81 and 4.91 s (2H, HC^8), 5.42 t (1H, HC^2, J = 7). Mass spectrum (m/z, %): M^+ 258 (10), 240 (10), 186 (25), 185 (100), 174 (25), 173 (10), 172 (20), 167 (75), 154 (10), 153 (25), 152 (75). Found, %: S 12.32. $C_{13}H_{22}O_3S$. Calculated, %: S 12.40.

3,7-Dimethyl-6-carboxymethylthio-2E,7-octadien-1-ol (XII). As described above for (VIII), from 0.25 g (0.83 mmole) of (IX) [7] in 4 ml of methanol and 5 ml of 25% aqueous potassium hydroxide there was obtained 0.2 g (98%) of (XII) as colorless crystals, mp 65-66°C (from hexane). IR spectrum (ν, cm^{-1}): 660, 725, 905, 985, 1130, 1160, 1205, 1295, 1375, 1435, 1640, 1715, 2360, 2570, 2670, 2860, 2940, 3005, 3085, 3610. PMR spectrum (δ, ppm; J, Hz): 1.64 and 1.75 s (6H, CH_3), 1.6-1.8 m (2H, HC^5), 2.0-2.3 m (2H, HC^4), 3.09 AB q (2H, CH_2S, J_{AB} = 14, δ_A = 3.12, δ_B = 3.06), 3.48 t (1H, HC^6, J = 7), 4.1-4.3 m (2H, HC^1), 4.85 and 4.91 s (2H, HC^8), 5.48 t (1H, HC^2, J = 7), 6.6 br. s (2H, OH). Mass spectrum (m/z, %): M^+ 244 (17), 226 (17), 185 (100), 171 (15), 167 (90), 152 (100). Found, %: C 59.41, H 8.38, S 12.74. $C_{12}H_{20}O_3S$. Calculated, %: C 58.99, H 8.25, S 13.12.

2,12-Dioxa-9,19-dithia-5,15-dimethyl-8,18-diisopropenyl-4E,14E-cycloeicosadiene-1,11-dione(XIV). To a solution of 0.17 g (0.66 mmole) of (XI) and 1 ml of HMPA in 380 ml of THF at −60°C under argon was added dropwise with stirring over 10 min a 0.23 N solution of BuLi in hexane (2.9 ml, 0.67 mmole). After 2 h, the mixture was brought to the boil for 5 h, and concentrated under reduced pressure. The residue was diluted with ether, neutralized with 1% HCl, washed with saturated sodium chloride solution, dried over magnesium sulfate, and the residue (~0.2 g) chromatographed on 5 g of silica. Gradient elution from hexane to ether (up to 10% of the latter) gave 13 mg (9%) of (XIV) as colorless needles, mp 61.5-63°C (from hexane), R_f 0.42 (hexane—ether, 7:3). IR spectrum (ν, cm^{-1}): 640, 665, 735, 905, 965, 1105, 1125, 1160, 1205, 1275, 1340, 1375, 1415, 1440, 1450, 1640, 1730, 2860, 2940, 2980, 3005, 3080.

PMR spectrum (δ, ppm; J, Hz): 1.58 and 1.72 s (12H, CH_3), 1.5-1.8 m (4H, HC^7, HC^{17}), 2.0-2.2 m (4H, HC^6, HC^{16}), 3.05 br. s (4H, HC^{10}, HC^{20}), 3.35 t (2H, HC^8, HC^{18}, J = 7), 4.68 AB portion of an ABX system (4H, HC^3, HC^{13}, $J_{AB} = 12$, $J_{AX} = J_{BX} = 7$, $\delta_A = 4.72$, $\delta_B = 4.64$), 4.87 and 4.90 s (4H, $H_2C{=}C$), 5.38 br. t (2H, HC^4, HC^{14}, J = 7). Mass spectrum (m/z, %): M^+ 452 (15), 394 (15), 362 (15), 361 (20), 296 (15), 295 (30), 294 (100), 293 (75), 262 (25), 261 (25), 228 (25), 227 (75), 226 (25), 215 (25), 185 (75), 184 (25), 183 (100), 167 (40), 152 (25).

To a solution of 0.5 g (2.05 mmoles) of (XII) in 25 ml of acetonitrile was added with stirring at 25°C under argon 0.9 g (4.09 mmoles) of BID, followed after 30 min by 1.07 g (4.08 mmoles) of Ph_3P. The mixture was stirred at 25°C for 1.5 h, then diluted with 150 ml of p-xylene, and after 5 h this solution was added dropwise to 350 ml of boiling p-xylene. The mixture was boiled for a further 2 h, then concentrated under reduced pressure to a volume of ~50 ml, filtered through a layer (~5 cm) of silica, the filtrate evaporated, and the residue (~0.25 g) chromatographed on 50 g of silica as described above to give 100 mg (22%) of the diolide (XIV), identical with the sample of this compound obtained above.

The macrocyclization of (XII) with BID was carried out by a method similar to that described above for the conversion of (III) into (I). In this way, from 0.17 g (0.69 mmole) of (XII), 0.54 g (1.37 mmoles) of BID, and 0.27 g (1.03 mmoles) of Ph_3P in 260 ml of toluene there was obtained 31 mg (20%) of the diolide (XIV) with the properties given above.

Diolide (XVI). To a solution of 0.12 g (0.265 mmole) of (XIV) in 5 ml of DMF was added with stirring at 25°C under argon, portionwise over 5 min, 40 mg (0.357 mmole) of t-BuOK. The mixture was stirred for 4 h at 25°C and 6 h at 55°C, then neutralized with 1% HCl and extracted with hexane. The extract was washed with saturated sodium chloride solution, dried over magnesium sulfate, evaporated under reduced pressure, and the residue (~100 mg) chromatographed on 25 g of silica. Gradient elution from hexane to ether (up to 5% of the latter) gave 15 mg (15%) of (XVI) [3] as a colorless oil, R_f 0.45 (hexane—ether, 1:1). PMR spectrum (δ, ppm; J, Hz): 1.60 and 1.68 s (12H, CH_3), 2.0-2.2 m (8H, HC^6, HC^7, HC^{17}, HC^{18}), 2.2-2.5 m (8H, HC^{10}, HC^{11}, HC^{21}, HC^{22}), 4.58 br. d (4H, CH_2O, J = 7), 5.0-5.4 m (4H, $HC{=}C$). Mass spectrum (m/z, %): M^+ 388 (15), 370 (15), 320 (15), 303 (20), 296 (25), 295 (100), 294 (100), 293 (100), 288 (15), 270 (75), 262 (75), 261 (80), 217 (20), 215 (80), 202 (20), 186 (40), 185 (100), 184 (75), 183 (100), 175 (70), 177 (70), 58 (50), 152 (50).

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