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Stereoselective Synthesis of Isomers of the Naturally Occurring 13-Hydroxy-2,4,9-tetradecatrienic Acid I

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Summary. The stereoselective synthesis of (*S*,2*E*,4*E*,9*Z*)-13-hydroxy-2,4,9-tetradecatrienic acid is described. Starting from (*S*)-methyloxirane, the carbon chain was built by means of *Wittig* reactions, regioselective oxidation of the resulting dialcohol, and a diastereomerization reaction.

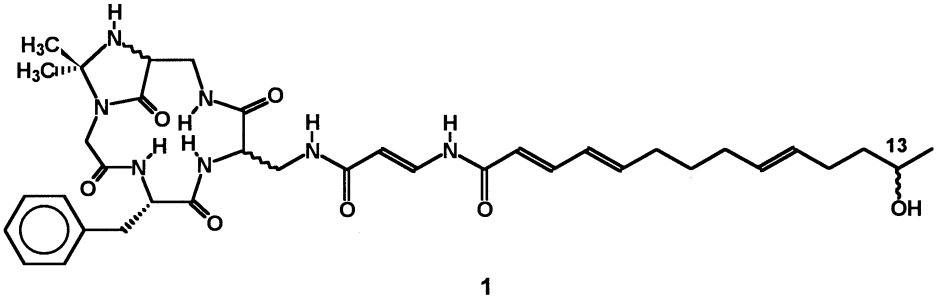
Keywords. Fatty acid; *Wittig* reaction; Oxidation; Diastereomerization.

Stereoselektive Synthese von Isomeren der natürlich vorkommenden 13-Hydroxy-2,4,9-tetradecatriensäure, 1. Mitt.

Zusammenfassung. Ausgehend von (*S*)-Methyloxiran wurde (*S*,2*E*,4*E*,9*Z*)-13-Hydroxy-2,4,9-tetradecatriensäure dargestellt. Die Kohlenstoffkette wurde durch *Wittig*-Reaktionen, regioselektive Oxidation des entstandenen Dialkohols und eine Diastereomerisierungsreaktion aufgebaut.

Introduction

Recently, 13-hydroxy fatty acids have attracted interest because it has been shown that arachidonic and linolenic acids with an OH-group in position 13 increase cell proliferation by activating EGF [1]. The (*S*)-enantiomers are the most effective compounds in this con [2]. In 1995 a new cyclic lipopeptide, enamidonin (**1**), was isolated from the *Streptomyces* sp. 91–75 culture broth [3]. It contains (2*E*,4*E*,9*E*)-13-hydroxy-2,4,9-tetradecatrienic acid which is attached to a side chain of a cyclic tetrapeptide *via* an enamide bridge. The configuration of C-13 has not been determined.



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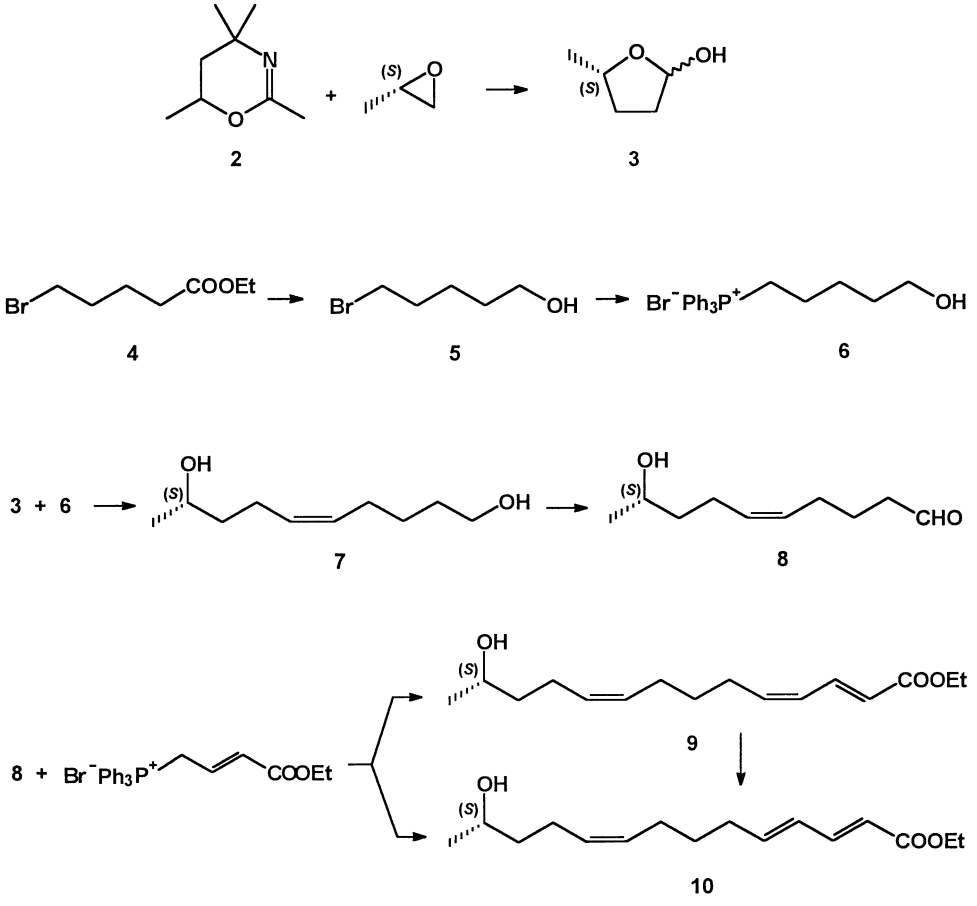
Compound **1** shows an effect contrary to that of the hydroxylated C_{18} and C_{20} fatty acids: it slows down cell proliferation by inhibiting the EGF dependent uptake of [^{3}H]thymidine into Balb/MK cells [3, 4]. Similarly, (*S*,2*E*,4*E*,8*E*)-13-hydroxy-2,4,8-tetradecatrienic acid, isolated from *Valsa ambiens*, has been shown to inhibit the growth of lettuce roots and hypocotyls [5]. The (*E*,*E*,*Z*)-diastereomer displays the same activity [6].

To provide material for biological tests, the synthesis of (*S*,2*E*,4*E*,9*Z*)-13-hydroxy-2,4,9-tetradecatrienic acid (**10**) was approached as an initial goal.

Results and Discussion

As chiral synthon, (*S*)-methyloxirane was used which is available in several steps from *l*-lactic acid [7]. It was used as electrophilic agent in a reaction with 5,6-dihydro-2,4,4,6-tetramethyl-4*H*-1,3-oxazine (**2**). The lithium salt of **2** reacted – analogous to furyl lithium [8, 9] – with C-1 of the epoxide which is less hindered. The resulting crude 2-(3-hydroxybutyl) derivative was reduced to 2-(3-hydroxybutyl)-4,4,6-trimethyl-perhydro-1,3-oxazine with $NaBH_4$ according to the method of *Meyers et al.* [9, 10]. The crude product was hydrolyzed to 2-hydroxy-5(*S*)-



Scheme 1

methyltetrahydrofuran (**3**) which was obtained in an overall yield of 23%. The corresponding 4-methyl analogue, which would result from addition of **2** to C-2 of methyloxirane, was not detected.

Ethyl 4-bromovalerate (**4**) was reduced with $LiAlH_4$ to give 5-bromopentanol (**5**) which was transformed into the triphenylphosphonium salt **6** using the procedure of *Meyers* [10]. After deprotonation with butyl lithium, **6** was converted to its ylide which undergoes a *Wittig* reaction with **3** leading to (9*S*,5*Z*)-decen-1,9-diol (**7**) in 43% yield. Since the chemical shifts of the two olefinic protons 5-H and 6-H in the ^1H NMR spectrum are identical, the configuration of its double bond could not be directly established. However, after oxidation, the (*Z*)-configuration of **8** was determined by means of the small (10.6 Hz) *cis* coupling constant between 5-H and 6-H. The primary OH-group in **7** was then selectively oxidized with oxygen and 2,2,6,6-tetramethylpiperidin-1-oxyl as catalyst [11].

In a further *Wittig* reaction, **8** was coupled to 3-ethoxycarbonyl-2-propenyl-triphenylphosphonium bromide. A mixture of **9** and **10** in a ratio of approximately 4:5 was obtained. By irradiation of this mixture in the presence of diphenyl disulfide, the configuration of the double bond between C-4 and C-5 in **9** was changed from (*Z*) to (*E*) as revealed by the NMR spectra of **10**. In a NOE experiment, irradiation of 3-H gave an intensity enhancement of the resonance of 5-H. Selective decoupling of 3-H and 6-H, respectively, revealed a large *trans* coupling (15.1 Hz) between 4-H and 5-H, and selective decoupling of 8-H and 11-H showed $J_{9,10}$ to equal 10.8 Hz. This confirms a (*Z*)-configuration for the isolated double bond in position 9 of **10**. In conclusion, a synthesis of **10** starting from (*S*)-methyloxirane was achieved which gave a 4% overall yield.

Experimental

Analytical methods

Melting points: Melting point apparatus Dr. Tottoli, uncorrected. Optical rotation: polarimeter 241 MC (Perkin Elmer). MS: Varian MAT 711 spectrometer, 70 eV electron impact. IR spectra: infrared spectrometer System 2000 FT (Perkin Elmer). UV/Vis: UV-160A UV-visible recording spectrophotometer (Shimadzu). NMR spectra: Varian Unity Inova 400 (297 K), 5 mm tubes, solvent resonance as internal standard. ^1H and ^{13}C resonances were assigned using $^1H,^1H$ and $^1H,^{13}C$ correlation spectra. Assignments marked with an asterisk are interchangeable. Before performing NOE experiments, dissolved oxygen was carefully removed by bubbling Ar through the solutions. Elementary analyses were performed by the Laboratory for Microanalysis, Institute of Physical Chemistry, University of Vienna. Their results were in satisfactory agreement with the calculated values. Irradiation: high pressure mercury lamp Hanau-Hochdrucklampe TQ 150 Hg. Materials: Column chromatography (CC): silica: Kieselgel 60 (Merck) (70–230 mesh), pore diameter 60 Å; thin-layer chromatography (TLC): TLC plates (Merck) Kieselgel 60 F_{254}, 0.2 mm, 200×200 mm; the substances were detected in UV light at 254 nm and by spraying with molybdatophosphoric acid and subsequent heating with a heat gun.

5-Bromo-1-pentanol (**5**)

A solution of 8.4 g (40 mmol) **4** in 20 ml abs. Et_2O was added dropwise to a suspension of 2.0 g (53 mmol) $LiAlH_4$ in 200 ml abs. Et_2O and refluxed for 30 min. After cooling to room temp., excess

hydride was carefully destroyed by addition of approx. 5 ml of water. The reaction mixture was acidified with 5 *N* sulfuric acid. The organic layer was separated, and the aqueous phase was extracted with 2×50 ml Et_2O. The combined organic layers were washed with 20 ml of brine, dried over K_2CO_3, and evaporated. Distillation from K_2CO_3 under reduced pressure gave 5.4 g (76%) of **5** as a colourless liquid. Its b.p. of 95°C (12 mbar) agrees with that of **5** synthesized by hydrolysis of 5-bromopentyl acetate [10] (62°C/0.5 mm).

5-Hydroxy-1-pentyltriphenylphosphonium bromide (**6**)

6 was prepared from **5** according to Ref. [10]; m.p.: 188–189°C, (Ref. [10]: 190–191°C).

(5S)-2-Hydroxy-5-methyltetrahydrofuran (**3**)
a) 2-(3-Hydroxybutyl)-5,6-dihydro-4,4,6-trimethyl-4H-1,3-oxazine

4.24 g (30 mmol, 4.7 ml) **2** were dissolved under Ar in 30 ml abs. *THF* and cooled to −78°C. 19.5 ml of a 1.6 *N* solution of BuLi in hexane were added dropwise. After stirring for one hour at −78°C, a yellow solid lithium salt appeared. 1.74 g (30 mmol, 2.10 ml) (*S*)-methyloxirane in 5 ml abs. *THF* were added slowly. The reaction mixture was allowed to warm slowly to room temp. overnight. It was then poured into 30 ml of ice water and acidified with conc. HCl to *pH* 2–3. The organic layer was discarded. The aqueous layer was washed with 3×20 ml petrol ether, alkalized with 40% NaOH, and extracted with 3×180 ml Et_2O. The combined organic layers were dried over K_2CO_3. Evaporation under reduced pressure afforded 5.3 g of crude 2-(3-hydroxybutyl)-5,6-dihydro-4,4,6-trimethyl-4*H*-1,3-oxazine ($R_f = 0.34$ in EtOAc:EtOH = 9:1) as a yellow oil which was used without further purification.

b) 2-(3-Hydroxybutyl)-4,4,6-trimethyl-perhydro-1,3-oxazine

The crude 2-(3-hydroxybutyl)-5,6-dihydro-4,4,6-trimethyl-4*H*-1,3-oxazine (5.3 g, approx. 0.03 mol) was dissolved in a mixture of 30 ml *THF* and 30 ml EtOH, cooled to −35 to −40°C, and neutralized with conc. HCl. 1.13 g (30 mmol) $NaBH_4$ were dissolved in a mixture of 2 ml water and a drop of 40% NaOH. This solution was added simultaneously with conc. HCl to the reaction mixture taking care that the *pH* was maintained at 6–8 and that the temperature remained between −35 and −40°C. After addition of the $NaBH_4$ solution the mixture was stirred for two hours at −35 to −40°C and for a further hour during warm up to room temperature. During this time the *pH* was kept between 6 and 8 by addition of conc. HCl. The reaction mixture was poured into 30 ml water, alkalized with 40% NaOH, and extracted with 4×100 ml Et_2O. The combined extracts were washed with 20 ml brine and dried over K_2CO_3. Evaporation under reduced pressure gave crude 3.9 g (approx. 65%) of 2-(3-hydroxybutyl)-4,4,6-trimethyl-perhydro-1,3-oxazine as a yellow oil which was used without further purification. $R_f = 0.27$ (EtOAc:EtOH = 9:1).

c) (S)-2-Hydroxy-5-methyltetrahydrofuran (**3**)

15 g (0.14 mol) oxalic acid monohydrate and 3.9 g (approx. 0.02 mmol) of the crude 2-(3-hydroxybutyl)-4,4,6-trimethyl-perhydro-1,3-oxazine in 30 ml H_2O were refluxed for two hours under argon. After cooling to room temp., the mixture was extracted with 4×100 ml CH_2Cl_2. The combined extracts were treated with 5 g of solid $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed; subsequent distillation under reduced pressure gave 710 mg (23%) of **3** as a colourless liquid. Its b.p. of 80°C (30 mbar) is in agreement with that of *l*-2-hydroxy-5-methyltetrahydrofuran derived from *l*-6-hydroxy-2-methyl-2-hepten *via* ozonolysis [12] (43–46°/1–2 mm).

(9S,5Z)-Decen-1,9-diol (**7**; $C_{10}H_{20}O_2$)

2.4 ml of a 1.6 *N* solution of BuLi in hexane were added dropwise to a solution of 858 mg (2.0 mmol) **6** in 20 ml abs. *THF* under argon. The mixture was stirred for 30 min, and 204 mg (2.0 mmol) **3** in 2 ml abs. *THF* were added slowly. After stirring for another hour, the reaction mixture was evaporated under reduced pressure, diluted with 30 ml of H_2O, and extracted with 4×50 ml CH_2Cl_2. The combined organic phases were washed with 15 ml brine, dried over Na_2SO_4, and evaporated. CC over 100 g silica with EtOAc afforded 160 mg (47%) of **7** as a colourless oil.

$R_f = 0.33$ (EtOAc); $[\alpha]_{20}^{D} = +7.24°$ ($c = 0.46$ in CH_2Cl_2); IR (neat): $\nu = 3335$ (s), 2932 (s), 1457 (m), 1437 (m), 1374 (m), 1121 (m), 1069 (m), 723 (m) cm^{-1}; ^1H NMR (400 MHz, δ, $CDCl_3$): 1.14 (d, $J = 6.1$ Hz, 3H, 10-H), 1.39 (quint, $J = 7.7$ Hz, 2H, 3-H), 1.46 (m, 2H, 8-H), 1.52 (m, 2H, 2-H), 2.04 (m, 2H, 4-H), 2.09 (m, 3H, 7-H), 2.09 (s br, 2H, OH), 3.58 (t, $J = 6.5$ Hz, 2H, 1-H), 3.75 (sext, $J = 6.1$ Hz, 1H, 9-H), 5.35 (m, 2H, 5-H, 6-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 23.5 (q, C-10), 23.6 (t, C-7), 25.7 (t, C-3), 26.7 (t, C-4), 32.1 (t, C-2), 39.0 (t, C-8), 62.5 (t, C-1), 67.6 (d, C-9), 129.5 (d, C-6*), 130.1 (d, C-7*) ppm; MS (70 eV): *m/z* (%) = 172 (1.5) [M^+], 154 (1.5) [M^+-H_2O], 139 (1.3) [154-CH_3], 136 (1.5) [M^+-2 H_2O], 121 (3.1) [136-CH_3], 107 (7.0) [136-C_2H_5], 95 (12.8) [136-C_3H_5], 93 (12.3) [136-C_3H_7], 81 (20.8), 79 (100) [136-C_4H_9], 67 (49.8) [136-C_5H_7], 31 (7.6) [CH_2OH].

(9S,5Z)-9-Hydroxy-5-decenal (**8**; $C_{10}H_{18}O_2$)

140 mg (0.81 mmol) **7**, 25 mg (0.16 mmol) 2,2,6,6-tetramethylpiperidin-1-oxyl (*TEMPO*), 221 mg (1.65 mmol) dry $CuCl_2$, and 102 mg (2.43 mmol) CaH_2 in 5 ml abs. CH_3CN were stirred vigorously under O_2 in a 25 ml round bottom flask overnight. The reaction mixture was evaporated under reduced pressure, diluted with 8 ml of water, and extracted with 4×25 ml CH_2Cl_2. The combined organic phases were washed with 5 ml brine, dried over Na_2SO_4, evaporated to 2 ml and filtered over 2 g alumina. The alumina was washed with CH_2Cl_2, and the product containing fractions were combined and evaporated. CC over 50 g silica (EtOAc) gave 90 mg (65%) of **8** as a colourless oil.

$R_f = 0.50$ (EtOAc); $[\alpha]_{20}^{D} = +14.4°$ ($c = 2.0$ in CH_2Cl_2); IR (neat): $\nu = 3422$ (s), 3007 (m), 2929 (s), 2721 (m), 1719 (s), 1651 (w), 1457 (m), 1374 (m), 1129 (m), 723 (m) cm^{-1}; ^1H NMR (400 MHz, δ, $CDCl_3$): 1.18 (d, $J = 6.3$ Hz, 3H, 10-H), 1.51 (m, 2H, 8-H), 1.67 (quint, $J = 7.3$ Hz, 2H, 3-H), 1.74 (s br, 1H, OH), 2.08 (m, 4H, 2-H, 4-H), 2.42 (t, $J = 7.3$ Hz, 2H, 2-H), 3.79 (sext, $J = 6.3$ Hz, 1H, 9-H), 5.33 (m, 1H, 5-H), 5.38 (m, 1H, 6-H), 9.74 (t, $J = 1.5$ Hz, 1H, 1-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 21.2 (t, C-3), 22.8 (q, C-10), 22.9 (t, C-7), 25.7 (t, C-4), 38.2 (t, C-8), 42.5 (t, C-2), 66.8 (d, C-9), 128.1 (d, C-5), 129.8 (d, C-6), 201.9 (d, C-1) ppm; MS (70 eV): *m/z* (%) = 152 (0.9) [M^+-H_2O], 137 (1.1) [152-CH_3], 123 (3.7) [152-CHO], 108 (13.3) [152-C_2H_4O], 93 (17.0) [108-CH_3], 79 (100) [$C_6H_7^+$], 31 (2.1) [CH_2OH].

(S)-Ethyl-13-hydroxy-2,4,9-tetradecatrienoate (mixture of (4*Z*)- and (4*E*)-isomer; **9**+**10**)

228 mg (0.50 mmol) 3-ethoxycarbonyl-2-propenyl-triphenylphosphonium bromide and 300 mg K_2CO_3 were heated to 120°C in 10 ml abs. *DMF* under Ar. A solution of 85 mg (0.50 mmol) **8** in 1 ml abs. DMF was added, and stirring at 120°C was continued for 1.5 hours. After cooling to room temp., the reaction mixture was poured into 20 ml of water and extracted with 4×25 ml Et_2O. The combined extracts were washed with 20 ml brine, dried over Na_2SO_4, and evaporated under reduced pressure. CC over 50 g silica with EtOAc afforded 95 mg (71%) of a (*Z*/*E*)-mixture of **9** as a colourless oil.

$R_f = 0.63$ (EtOAc); IR (neat): $\nu = 3420$ (s), 2930 (s), 2860 (s), 1718 (s), 1641 (s), 1617 (m), 1456 (s), 1368 (s), 1304 (s), 1269 (s), 1183 (s), 1136 (s), 1095 (m), 1039 (s), 1001 (s), 872 (m), 714 (m) cm^{-1}; UV (CH_2Cl_2): λ_{max} (lgε) = 262.5 (4.28) nm.

(S,2E,4E,9Z)-Ethyl-13-hydroxy-2,4,9-tetradecatrienoate (**10**; $C_{16}H_{26}O_3$)

60 mg (0.226 mmol) of the above (*Z*/*E*) mixture (**9**+**10**) and 98 mg (0.451 mmol) of diphenyl disulfide were dissolved in 5 ml of abs. benzene. The solution was filled into two 5 mm NMR tubes, and Ar was bubbled through for five minutes. The tubes were closed, placed in an irradiation apparatus, and irradiated for 14 h at room temp. with a high pressure mercury lamp with a 1% potassium chromate filter in a thickness of 1 cm. The reaction mixture was evaporated under reduced pressure. CC over 15 g silica with EtOAc gave 50 mg (83%) of **10** as a colourless oil.

$R_f = 0.63$ (EtOAc); $[\alpha]_{20}^{D} = -2.43°$ ($c = 0.62$ in CH_2Cl_2); IR (neat): $\nu = 3412$ (s), 2930 (s), 2860 (s), 1715 (s), 1642 (s), 1617 (m), 1457 (s), 1368 (s), 1303 (s), 1246 (s), 1136 (s), 1095 (m), 1039 (s), 1001 (s), 874 (w), 723 (w) cm^{-1}; UV (CH_2Cl_2): λ_{max} (lgε) = 262.5 (4.26) nm; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 1.19 (d, $J = 6.2$ Hz, 3H, 14-H), 1.29 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 1.50 (m, 4H, 7-H, 12-H), 1.78 (s br, 1H, OH), 2.04 (quint, $J = 6.6$ Hz, 2H, 8-H), 2.07 (m, 2H, 11-H), 2.17 (quint, $J = 6.6$ Hz, 2H, 6-H), 3.81 (sext, $J = 5.9$ Hz, 1H, 13-H), 4.20 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 5.38 (m, 1H, 10-H), 5.42 (m, 1H, 9-H), 5.78 (d, $J = 15.4$ Hz, 1H, 2-H), 6.12 (m, 1H, 5-H), 6.18 (m, 1H, 4-H), 7.25 (dd, $J = 15.4$, 10.0 Hz, 1H, 3-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 14.2 (q, OCH_2CH_3), 23.5 (q, C-14), 23.7 (t, C-11), 26.6 (t, C-8) 28.6 (t, C-7), 32.4 (t, C-6), 39.0 (t, C-12), 60.1 (t, OCH_2CH_3), 67.7 (d, C-13), 119.2 (d, C-2), 128.5 (d, C-4), 129.5 (d, C-9*), 129.8 (d, C-10*), 144.1 (d, C-5), 144.9 (d, C-3), 167.2 (s, C-1) ppm; MS (70 eV): *m*/*z* (%) = 266 (0.9) [M^+], 248 (2.3) [M^+-H_2O], 220 (10.2) [248-C_2H_4], 206 (3.0) [248-C_3H_6], 192 (7.3) [220-CO or C_2H_4], 175 (12.0) [120-COOH], 147 (16.3) [175-C_2H_4], 133 (31.7) [175-C_3H_6], 119 (56.1) [147-C_2H_4], 79 (100) [$C_6H_7^+$], 31 (24.5) [CH_2OH].

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