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Note

A facile indium-mediated synthesis of protected and unprotected [1-(hydroxymethyl)vinyl]alkanols

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Protected and unprotected [1-(hydroxymethyl)vinyl]alkanols (**7** and **8**) have been synthesized from the homologated γ-hydroxy esters **4** which have been prepared by indium-mediated allylation of the rearranged bromides **3** derived from hydroxyl esters **2** in water medium.

Keywords: Indium-mediated, protected, unprotected, vinylalkanols

Organic reactions that can be carried out in aqueous media or water have become one of the most challenging areas in organic synthesis due to the environmentally benign conditions[1]. Specially, metal-mediated reactions in aqueous media have recently attracted considerable interest in organic synthesis due to a number of advantages[2]. The use of indium for mediating organic reactions in water as the reaction solvent has become the focus of great interest in organic synthesis because of its exceptional stability to air and water compared to other metals. Recently, a review on organic syntheses using indium-mediated and catalyzed reactions in aqueous media has been reported[3]. Additions of allylic bromides to aldehydes under the influence of indium metal in water customarily proceed at convenient rates under ambient temperature conditions to afford homoallylic alcohols. Herein is reported the indium-mediated allylation reaction of formaldehyde with α-(bromomethyl)acrylate derived from 3-hydroxy-2-methylene alkanoates by reacting with N-bromosuccinimide and dimethyl sulfide.

The use of ethyl 2-(bromomethyl)acrylate, instead of allyl halide, with zinc or tin in saturated aqueous NH_4Cl/THF under refluxing conditions, followed by treatment with acid, gave α-methylene-γ-butyrolactones[4,5]. The same products were obtained under much stronger conditions by refluxing bromoacrylic acid and carbonyl compounds with Sn-Al (Ref. 6), $SnCl_2$-AcOH (Ref.7), and $SnCl_2$-Amberlyst 15 (Ref.8) in aqueous media. Benezra *et al*.[9] reported the synthesis of more than thirty lactones, some of which are quite complex using ethyl 2-(bromoethyl)acrylate in presence of zinc. Herein is also reported the synthesis of substituted α-methylene-γ-butyrolactones from the homologated γ-hydroxy-α-methylene esters by acid hydrolysis.

Results and Discussion

3-Hydroxy-2-methylene-alkanoates **2** were prepared by coupling methyl acrylate at the α-position with a variety of aldehydes in the presence of catalytic amounts of DABCO (1,4-diazabicyclo[2.2.2]octane) at RT[10,11]. The IR spectrum of **2a** showed peaks at 3560 and 1690 cm^{-1} due to OH and CO groups, respectively. Its ^1H NMR spectrum showed a singlet at δ 3.74 due to OCH_3 and a doublet at δ 1.34 due to CH_3 protons. The adducts **2** could undergo bromine-tive allylic rearrangement with N-bromosuccinimide and dimethyl sulfide to give (*Z*)-2-(bromomethyl)-2-alkenoic esters **3** (Ref.12). The IR spectrum of **3a** showed peaks at 1700 cm^{-1} due to carbonyl group. Its ^1H NMR spectrum showed a singlet at δ 3.70 due to OCH_3 and a doublet at δ 1.82 due to CH_3 protons. The presence of CO group was confirmed by the presence of a signal at δ 168.2 in its ^{13}C NMR spectrum. Its mass spectrum showed a base peak at *m/z* 212 (M+18).

Formation of the homologated γ-hydroxy-α-methylene esters **4** was carried out by coupling with aqueous formaldehyde in the presence of indium powder[13]. The allylation reaction of carbonyl compounds with allylic halides to afford the homo-allylic alcohols is probably the most widely used of the many indium-mediated reactions in organic synthesis[14]. The IR spectrum of **4a** showed peaks at 3343 and 1711 cm^{-1} due to OH and CO groups, respectively. Its ^1H NMR spectrum showed a broad singlet at δ 2.90 due to hydroxyl and a doublet at δ 1.08 due to methyl protons. Its ^{13}C NMR spectrum showed a signal at δ 166.9 due to carbonyl carbon.

The esters **4** readily cyclized to the corresponding α-methylene-γ-butyrolactones **5** by acid hydrolysis[8,9].

The hydroxyl substituent had been protected as the benzyl ether by using benzyl trichloroacetimidate, and the protected alkanols **6** were reduced with DIBAL-H to give the benzyl protected [1-(hydroxymethyl)-vinyl]-alkanols, **7**. The alkanols **7** were deprotected by hydrogenation in presence of Pd/C to give the debenzylated [1-(hydroxymethyl)vinyl]alkanols **8** (**Scheme I**). The structures of **6**, **7**, and **8** were confirmed by the spectral data shown in the Experimental Section.

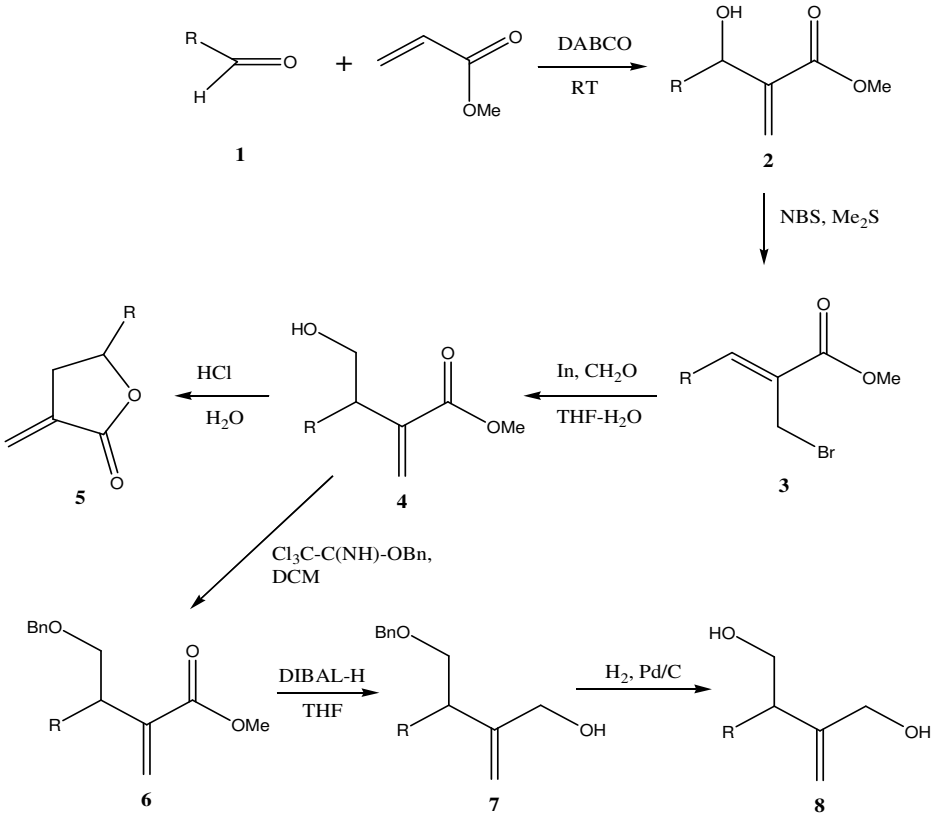
In conclusion, various protected and unprotected [1-(hydroxymethyl)vinyl]alkanols have been synthesized from the homologated γ-hydroxy esters which were prepared by indium-mediated allylation of the rearranged bromides in water medium.

Experimental Section

Infrared (IR) spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. All samples were run as a thin film (produced by evaporation of a chloroform solution) on a sodium chloride plate. Absorption maxima were recorded in wave numbers (cm^{-1}). ^1H NMR spectra were recorded on Varian Unity 500 (500 MHz), Bruker AC-300 and Varian XL (300 MHz) spectrometers. ^{13}C NMR spectra were recorded on Bruker AC-300 and Varian XL (75 MHz) spectrometers. Residual non-deuterated solvent was used as an internal reference and all chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm) downfield from tetramethyl silane (TMS). All samples were run in deutero-chloroform ($CDCl_3$) as solvent unless otherwise stated. Mass spectra were recorded on a Kratas concept-IS mass spectrometer couples to a Mach 3 data system, or on a Jeol-D 300 mass spectrometer.

Synthesis of 3-hydroxy-2-methylene-alkanoates, 2a-d

Acetaldehyde (8.8 g, 11.2 mL, 0.2 mole) was mixed at 0°C with methyl acrylate (25.8 g, 27.0 mL, 0.3 mole) and DABCO (2.25 g, 0.02 mole) was added with dissolution. The reaction mixture was stirred at



a, R = CH_3; **b**, R = C_6H_5;
c, R = *p*-$CH_3C_6H_4$; **d**, R = *p*-Cl-C_6H_4

Scheme I

RT for 7 days; the excess of methyl acrylate was removed *in vacuo*, and the residue was taken up in ether (200 mL). The organic phase was washed with 10% aqueous HCl (2 × 50 mL) and water (2 × 50 mL) and dried (anhyd. Na_2SO_4). Most of the solvent was first removed on a rotary thin film evaporator and traces of solvent were removed with an oil pump to leave a colourless, oily liquid **2a** (14.3 g, 55%); IR (CH_2Cl_2): 3560, 2970, 2850, 1690, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 1.30 (3H, d, *J* = 7.0 Hz, CH_3), 3.74 (3H, s, OCH_3), 4.58 (1H, m, CH), 5.80 (1H, s, =CH), 6.18 (1H, s, =CH).

Similarly, other 3-hydroxy-2-methylene-alkanoates, **2b-d** were prepared[11,15].

Synthesis of (*Z*)-2-(bromomethyl)-2-alkenoic esters, 3a-d

A solution of *N*-bromosuccinimide (10.62 g, 60 mmole) in dry DCM (20 mL) was cooled to 0°C and sequentially treated drop wise with dimethyl sulphide (3.72 g, 4.5 mL, 60 mmole) in dry DCM (10 mL) and a solution of **2a** (5.20 g, 40 mmole) in dry DCM (20 mL). The resulting mixture was stirred overnight at RT, diluted with pentane (100 mL) and poured into cold brine (300 mL). The separated aqueous phase was extracted with pentane (3×150 mL) and the combined organic solution was washed with brine, dried and concentrated. The residue was purified by column chromatography over silica gel by eluting with 10:1 pet. ether/ethyl acetate to give **3a** as a colourless oil (4.40 g, 57%). IR (CH_2Cl_2): 2960, 2900, 1700, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (3H, d, *J* = 7.0 Hz, CH_3), 3.70 (3H, s, OCH_3), 4.98 (2H, s, CH_2), 7.01 (1H, q, *J* = 6.5 Hz, =CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 155.3, 128.1, 53.3, 28.8, 24.1; MS: *m/z* (%) 212 (M + 18, 100), 185 (30), 178 (35), 148 (52).

Following the above procedure, other (*Z*)-2-(bromomethyl)-2-alkenoic esters, **3b-d** were also prepared[13,16].

Synthesis of γ-hydroxy-α-methylene esters, 4a-d

A mixture of **3a** (0.93 g, 4.8 mmole), Indium powder (0.62 g, 5.4 mmole), THF (20 mL) and aqueous formaldehyde (20 mL of 37% excess/40% w/v) was stirred vigorously at RT for 20 hr. The milky-white reaction mixture was diluted with ethyl acetate, and the separated aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers was washed with brine, dried and concentrated. Chromatography of the residue over silica gel (elution with 30% ethyl acetate/pet. ether) gave **4a** as a colouless oil (0.47 g, 68%). IR (CH_2Cl_2): 3343, 1711, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (3H, d, *J* = 7.0 Hz, CH_3), 2.82 (1H, m, CH), 2.90 (1H, br s, OH), 3.45 (1H, m, OCH_2), 3.55 (1H, m, OCH_2), 3.70 (3H, s, OCH_3), 5.55 (1H, s, =CH), 6.20 (1H, s, =CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 142.1, 123.8, 62.8, 51.1, 34.8, 14.9; MS: *m/z* M^+ Calcd 144.0786. Found 144.0791.

Following the above procedure, other γ-hydroxy-α-methylene esters, **4b-d** were prepared[17].

Synthesis of benzylated γ-hydroxy-α-methylene esters, 6a-d

The alcohol, **4a** (0.36 g, 2.5 mmole) was dissolved in dry DCM (5 mL) and cyclohexane (10 mL). Benzyl trichloroacetimidate (1.3 g, 1.7 mL, 5 mmole) was added to the solution with stirring followed by careful dropwise addition (exothermic) of trifluoromethane sulphonic acid (5 drops). The resulting mixture was stirred overnight at RT; pyridine (10 mL) was added to the reaction mixture, which was then diluted with dichloromethane (100 mL) and extracted with water (3 × 100 mL), dried and concentrated. The crude compound was purified by column chromatography by eluting with 4% ethyl acetate/pet. ether to give an yellowish oil, **6a** (0.25 g, 43%). IR (CH_2Cl_2): 1710, 1625, 1365, 1096, 844, 740, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, d, *J* = 7.0 Hz, CH_3), 3.10 (1H, m, CH), 3.42 (1H, m, OCH_2), 3.60 (1H, m, OCH_2), 3.75 (3H, s, OCH_3), 4.58 (2H, s, $PhCH_2$), 5.65 (1H, s, =CH), 6.30 (1H, s, =CH), 7.35 (5H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 138.1, 128.1, 127.8, 127.2, 126.4, 124.4, 70.8, 62.1, 50.6, 35.1, 14.1; MS: *m/z* M^+ Calcd 234.2066. Found 234.2061.

6b: Colourless oil (72%). IR (CH_2Cl_2): 1716, 1636, 1322, 1105, 841, 748, 672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.44 (1H, m, OCH_2), 3.58-3.62 (1H, m, OCH_2), 3.72 (3H, s, OCH_3), 4.06 (1H, t, *J* = 6.5 Hz, CH), 4.52 (2H, s, $PhCH_2$), 5.58 (1H, s, =CH), 6.27 (1H, s, =CH), 7.16-7.38 (10H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 141.2, 128.8, 127.6, 127.4, 126.8, 125.1, 70.2, 63.5, 51.8, 45.6; MS: *m/z* M^+ Calcd 296.0915. Found 296.0917.

6c: Colourless oil (85%). IR (CH_2Cl_2): 1710, 1630, 1355, 1088, 838, 744, 678 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (3H, s, CH_3), 3.38 (1H, m, OCH_2), 3.60 (1H, m, OCH_2), 3.76 (3H, s, OCH_3), 3.98 (1H, t, *J* = 6.5 Hz, CH), 4.56 (2H, s, $PhCH_2$), 5.68 (1H, s, =CH), 6.32 (1H, s, =CH), 7.11-7.32 (9H, m, Ar); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 167.4, 140.7, 138.1, 128.4, 128.2, 127.2, 126.4, 125.6, 70.4, 62.8, 51.2, 48.9, 21.4; MS: *m/z* M^+ Calcd 310.1228. Found 310.1232.

6d: Colourless oil (85%). IR (CH_2Cl_2): 1716, 1625, 1362, 1094, 832, 741, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.32 (1H, m, OCH_2), 3.58 (1H, m, OCH_2), 3.72 (3H, s, OCH_3), 4.02 (1H, t, *J* = 6.5 Hz, CH), 4.51 (2H, s, $PhCH_2$), 5.62 (1H, s, =CH), 6.38 (1H, s, =CH), 7.08-7.28 (9H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 141.2, 140.8, 128.6, 128.2, 127.0, 126.8, 125.8, 65.4, 62.8, 51.8, 48.5; MS: *m/z* M^+ Calcd 331.0858. Found 331.0897.

Synthesis of benzylated [1-(hydroxylmethyl)vinyl]-alkanols, 7a-d

A cold (–78°C), magnetically stirred solution of **6a** (0.23g, 1 mmole) in dry THF (1 mL) was treated dropwise with DIBAL-H (2 mL of 1.0 *M* solution in hexane, 2 mmole). After 3 hr at this temperature and 1 hr at 0°C, saturated Rochelle salt solution (3 mL) was added and the heterogeneous reaction mixture was allowed to warm to RT overnight. The separated aqueous phase was extracted with ethyl acetate, and the combined organic phase was washed with brine, dried and concentrated. Purification of the residue by column chromatography over silica gel (elution with 30% ethyl acetate/ pet. ether) gave **7a** as a colourless oil (0.16 g, 82%). IR (CH_2Cl_2): 3450, 1650, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (3H, d, *J* = 7.0 Hz, CH_3), 2.38 (1H, br s, OH), 2.50 (1H, m, CH), 3.31-3.38 (2H, m, OCH_2), 3.97-4.05 (2H, m, OCH_2), 4.45 (2H, s, $PhCH_2$), 4.87 (1H, s, =CH), 5.03 (1H, s, =CH), 7.18-7.28 (5H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.1, 128.4, 127.9, 127.7, 123.8, 70.4, 63.8, 51.4, 36.3, 14.6; MS: *m/z* M^+ Calcd 206.1993. Found 206.1995.

7b: Colourless oil (98%). IR (CH_2Cl_2): 3448, 1635, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (1H, br s, OH), 3.25-3.38 (2H, m, OCH_2), 3.98-4.04 (2H, m, OCH_2), 4.10 (1H, t, *J* = 6.5 Hz, CH), 4.48 (2H, s, $PhCH_2$), 5.04 (1H, s, =CH), 5.25 (1H, d, *J* = 12.4 Hz, =CH), 7.10-7.32 (10H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.4, 140.9, 128.3, 128.1, 127.8, 126.6, 66.4, 65.8, 50.7, 36.7; MS: *m/z* M^+ Calcd 268.1981. Found 268.2012.

7c: Colourless oil (92%). IR (CH_2Cl_2): 3540, 1661, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, d, *J* = 6.8 Hz, CH_3), 2.36 (1H, br s, OH), 3.16-3.25 (2H, m, OCH_2), 3.92-4.01 (2H, m, OCH_2), 4.17 (1H, t, *J* = 6.5 Hz, CH), 4.42 (2H, s, $PhCH_2$), 5.03 (1H, s, =CH), 5.18 (1H, d, *J* = 12.4 Hz, =CH), 7.16-7.35 (9H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.9, 140.4, 128.8, 128.4, 128.0, 127.1, 66.8, 66.2, 50.8, 37.6, 21.3; MS: *m/z* M^+ Calcd 282.1702. Found 282.1693.

7d: Colourless oil (88%). IR (CH_2Cl_2): 3488, 1635, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.54 (1H, br s, OH), 3.22-3.34 (2H, m, OCH_2), 3.88-4.08 (2H, m, OCH_2), 4.22 (1H, t, *J* = 6.8 Hz, CH), 4.48 (2H, s, $PhCH_2$), 5.12 (1H, s, =CH), 5.25 (1H, d, *J* = 12.4 Hz, =CH), 7.10-7.30 (9H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.3, 140.8, 128.7, 128.4, 128.2, 127.3, 66.6, 66.1, 51.3, 38.2; MS: *m/z* M^+ Calcd 303.2304. Found 303.2321.

Synthesis of debenzylated [1-(hydroxymethyl)vinyl]alkanols, 8a-d

Palladium on charcoal (10%, 10 mg) and 5 drops of acetic acid were added to a solution of **7a** (46 mg, 0.165 mmole) in absolute ethanol (3 mL). The flask was evacuated and flushed with hydrogen four or five times, and then the reaction mixture was allowed to stir under an atmosphere of hydrogen for 72 hr. The mixture was filtered through Celite and the residue washed with ethanol (2 × 10 mL), brine (2 × 10 mL), dried (anhyd. $MgSO_4$) and the solvent removed under reduced pressure to give an oil which was purified by flash chromatography using petrol:ether (1:1) as eluent to yield the unprotected alkanol **8a** as a colourless oil (91%). IR (CH_2Cl_2): 3445, 3430, 1630, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (3H, d, *J* = 7.0 Hz, CH_3), 2.41 (1H, br s, OH), 2.50 (1H, m, CH), 3.28-3.33 (2H, m, OCH_2), 3.44 (1H, br s, OH), 3.86-3.95 (2H, m, OCH_2), 4.25 (1H, t, *J* = 7.0 Hz, CH), 4.87 (1H, s, =CH), 5.03 (1H, s, =CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.3, 110.6, 68.1, 65.0, 39.1, 15.9; MS: *m/z* M^+ Calcd 116.0513. Found 116.0723.

8b: Colourless oil (82%). IR (CH_2Cl_2): 3452, 3443, 1625, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.48 (1H, br s, OH), 3.22-3.25 (2H, m, OCH_2), 3.41 (1H, br s, OH), 3.78-3.84 (2H, m, OCH_2), 4.88 (1H, s, =CH), 5.12 (1H, s, =CH), 7.22-7.30 (10H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.8, 128.4, 127.8, 127.1, 126.8, 126.4, 126.0, 111.1, 68.6, 65.2, 40.4; MS: *m/z* M^+ Calcd 178.1446. Found 178.1422.

8c: Colourless oil (86%). IR (CH_2Cl_2): 3446, 3438, 1630, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (3H, d, *J* = 6.5 Hz, CH_3), 2.42 (1H, br s, OH), 3.18-3.32 (2H, m, OCH_2), 3.416 (1H, br s, OH), 3.88-3.96 (2H, m, OCH_2), 4.94 (1H, s, =CH), 5.08 (1H, s, =CH),

7.16-7.32 (9H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.1, 128.2, 127.8, 127.2, 126.5, 126.1, 125.8, 110.8, 68.2, 65.6, 41.2, 19.8; MS: *m/z* M^+ Calcd 192.1808. Found 192.1786.

8d: Colourless oil (96%). IR (CH_2Cl_2): 3456, 3438, 1632, 1598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (1H, br s, OH), 3.18-3.33 (2H, m, OCH_2), 3.48 (1H, br s, OH), 3.65-3.77 (2H, m, OCH_2), 4.82 (1H, s, =CH), 5.05 (1H, s, =CH), 7.18-7.35 (9H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 128.1, 127.9, 127.4, 127.0, 126.8, 126.4, 110.2, 70.2, 66.4, 39.8; MS: *m/z* M^+ Calcd 213.0954. Found 213.0945.

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