

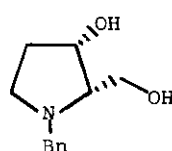
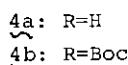
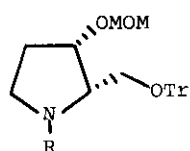
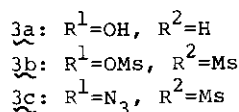
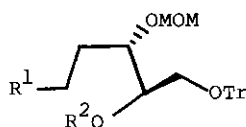
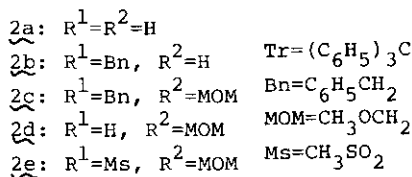
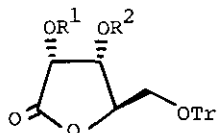
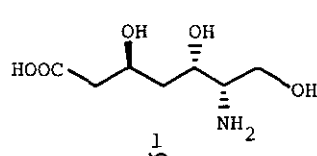
SYNTHESIS OF (-)-GALANTINIC ACID FROM D-RIBONOLACTONE

Nobuo Ikota

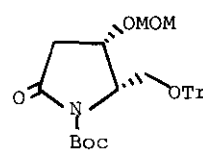
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Abstract — The synthesis of the revised structure of (-)-galantinic acid was achieved from D-ribonolactone.

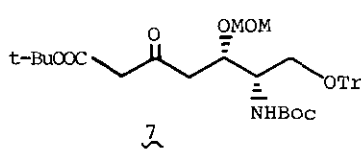
The structure of (-)-galantinic acid, a component of the antibiotic galantin I, was recently revised to 1.¹ The syntheses of the original and revised structure of (-)-galantinic acid from (S)-serine and by asymmetric reaction have been reported.^{1,2} In continuation of our work to utilize the chiral hydroxylated 2-pyrrolidinone derivatives for natural product synthesis³ and asymmetric reaction,⁴ we describe here the synthesis of (-)-galantinic acid (1) and its C-3 epimer using (4S,5S)-4-hydroxy-5-hydroxymethyl-2-pyrrolidinone derivative (6) derived from D-ribonolactone derivative (2a). Mono-O-benzylation of 5-O-trityl-D-ribonolactone (2a)⁵ by Ohno's procedure⁶ afforded 2b selectively. Methoxymethylation of 2b followed by removal of the benzyl group in 2c and subsequent mesylation of 2d gave 2e in 31% yield from 2a. Reduction of 2e with lithium aluminum hydride in tetrahydrofuran (THF)-ether gave the diol (3a), which without purification was converted to the dimesylate (3b) followed by displacement of the primary mesylate in 3b by sodium azide in the presence of 15-crown-5 in dimethylformamide (DMF) to afford the azidomesylate (3c) in 38% yield from 2e. Hydrogenation of the azide group in 3c on palladium black in ethanol gave the pyrrolidine (4a) with intramolecular S_N2 displacement, which was treated with di-tert-butyl dicarbonate to provide the fully protected pyrrolidine (4b) in 71% yield. The structure of 4a was confirmed by the conversion of 4a into (2S,3S)-1-benzyl-3-hydroxy-2-hydroxymethylpyrrolidine (5, [α]_D²⁰ +58.1° (CHCl₃), lit.,^{3d} for (2R,3R)-isomer [α]_D²⁰ -56.5° (CHCl₃)) by N-benzylation (BnBr, K₂CO₃, acetone) followed by acidic hydrolysis. Oxidation of



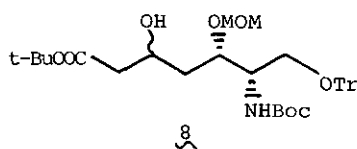
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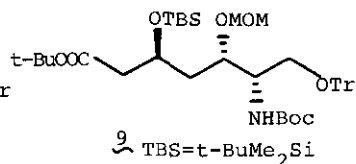
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7



8



9

TBS = $t-BuMe_2Si$

4b by RuO_4 ⁷ provided 2-pyrrolidinone derivative (6)⁸ in 38% yield with 55% recovery of 4b. The two-carbon unit and 3-hydroxy function required for (-)-galantinic acid were introduced by reaction of 6 with lithioacetate⁹ followed by reduction of the resulting β -keto ester. The β -keto ester (7), obtained in 81% yield from 6 by treatment with lithio *tert*-butylacetate in THF at $-78^\circ C$, was reduced with sodium borohydride in the presence of lithium chloride in THF-ethanol at $-40^\circ C$ to give β -hydroxy ester (8) in 75% yield in a ratio of 1.9:1 based on the analysis of 1H nmr spectrum. The two diastereomers were separated by column chromatography on silica gel after the conversion of 8 into the corresponding *tert*-butyldimethylsilyl ether (9) and its C-3 epimer. The major diastereomer (9) was treated with trimethylsilyl bromide¹⁰ in methylene dichloride at $-20^\circ C$ to remove all the protecting groups to afford (-)-galantinic acid (1, mp $128-132^\circ C$ (dec.), $[\alpha]_D^{20} -28.6^\circ$ ($c=1, H_2O$); lit.,¹ mp $125-130^\circ C$ (dec.), $[\alpha]_D^{20} -29.4^\circ$ ($c=0.5, H_2O$)) in 53% yield after treatment with Dowex 50W-X8 (H^+ form). Similarly, C-3 epimer (mp $180-184^\circ C$ (dec.), $[\alpha]_D^{20} -7.1^\circ$ ($c=0.6, H_2O$); lit.,¹ mp $186-188^\circ C$, $[\alpha]_D^{20} -5.8^\circ$ ($c=0.5, H_2O$)) was obtained in 49% yield from the minor diastereomer. 1H Nmr spectra (270 MHz) of synthetic 1

and its C-3 epimer were superimposable with those of previously reported 1 and its C-3 epimer.¹

EXPERIMENTAL

General methods. — Melting points were determined on a hot stage apparatus and are uncorrected. Ir spectra were measured with a JEOL JIR-110 FT-IR spectrophotometer. ¹H and ¹³C Nmr spectra were recorded on a JEOL JNM-FX100 (100 MHz) spectrometer in CDCl₃ unless otherwise mentioned. Data are recorded in parts per million (ppm) downfield from internal tetramethylsilane. Mass spectra were taken on a JEOL JMS-D302 spectrometer. Optical rotations were measured in CHCl₃ solution on a JASCO DIP-360 polarimeter unless otherwise mentioned. The organic solvents were dried over MgSO₄ before vacuum evaporation and a column chromatography was carried out with silica gel (Wakogel C-200).

(+)-2-O-Benzyl-5-O-trityl-D-ribonolactone (2b) This sample was prepared from 2a⁵ in 81% yield according to the reported procedure⁶ after purification by column chromatography (AcOEt-hexane=1:3 as eluant) followed by recrystallization from AcOEt-hexane; mp 64-65 °C (Found: C, 77.22; H, 5.98. C₃₁H₂₈O₅ requires C, 77.48; H, 5.87 %); [α]_D²⁰ +78.7° (c=0.6); ir ν_{max.} (nujol) 3496, 1766, 1089 cm⁻¹; ¹H nmr: 2.93(1H, br s, OH), 3.08(1H, dd, J=2 and 11 Hz, CHOTr), 3.68(1H, dd, J=2.7 and 11 Hz, CHOTr), 3.90(1H, d, J=5.2 Hz, H-2), 4.43(1H, m, CH), 4.64(1H, m, CH), 4.76 and 5.04(2H, AB, J=12 Hz, OCH₂Ph), 7.20-7.40(20H, m, ArH); ¹³C nmr: 62.28 (t), 69.54(d), 73.24(d), 73.78(t), 83.33(d), 87.37(s), 126.99(d), 127.67(d), 128.06(d), 135.91(s), 136.15(s), 173.92(s).

(+)-2-O-Benzyl-3-O-methoxymethyl-5-O-trityl-D-ribonolactone(2c) A solution of 2b (6.4 g, 13.3 mmol), N,N-diethylaniline (7.6 ml, 46.6 mmol), and chloromethyl methyl ether (3.5 ml, 46.6 mmol) in CH₂Cl₂ (60 ml) was stirred at room temperature for 40 h. After dilution with AcOEt, the mixture was washed with 10% aqueous HCl, saturated aqueous NaHCO₃, and water. Drying followed by evaporation gave a residue, which was chromatographed using AcOEt-hexane (1:3) as eluant to give 2c (5.7 g, 82%) as an oil, [α]_D²⁰ +88.1° (c=0.8); ir ν_{max.} (neat) 1789 cm⁻¹; ¹H nmr: 3.20(1H, dd, J=2.5 and 11 Hz, CHOTr), 3.31(3H, s, OCH₃), 3.67(1H, dd, J=3.2 and 11 Hz, CHOTr), 4.08(1H, m, H-2), 4.60(2H, m, 2xCH), 4.66(2H, s, OCH₂O), 4.80 and 5.02(2H, AB, J=12 Hz, OCH₂Ph), 7.20-7.40(20H, m, ArH); ms m/z 524 (M⁺).

(+)-3-O-Methoxymethyl-5-O-trityl-D-ribonolactone (2d) 2c (5.0 g, 9.54 mmol) was hydrogenated on palladium black (700 mg) in EtOH (50 ml) under hydrogen at

atmospheric pressure for 30 h and then the mixture was filtered. The filtrate was concentrated to give a residue, which was chromatographed using AcOEt-hexane (2:1) to give 2d (3.1 g, 75%) as an oil, $[\alpha]_D^{20} +45.2^\circ$ (c=0.7); ir ν_{\max} . (neat) 3442, 1789, 1024 cm^{-1} ; ^1H nmr: 3.26(1H, dd, $\underline{J}=2.8$ and 11 Hz, CHOTr), 3.37(3H, s, OCH₃), 3.65(1H, dd, $\underline{J}=3.4$ and 11 Hz, CHOTr), 4.22(1H, m, CH), 4.55(2H, m, 2xCH), 4.72(2H, s, OCH₂), 4.90(2H, m, CH, OH), 6.95-7.60(15H, m, ArH); ms m/z 434 (M^+).
(+)-3-O-Methoxymethyl-2-O-methanesulfonyl-5-O-trityl-D-ribonolactone (2e)

A mixture of 2d (3.0 g, 6.9 mmol), methanesulfonyl chloride (0.59 ml, 7.6 mmol), and triethylamine (TEA) (1.1 ml, 7.6 mmol) in CH₂Cl₂ (25 ml) was stirred at 0 °C for 15 min. After dilution with ether, the mixture was washed with water, saturated aqueous NaHCO₃, and saturated brine. Drying followed by evaporation gave a solid, which was recrystallized from AcOEt-hexane to afford 2e (2.21 g, 63%) as needles, mp 105-106 °C (Found: C, 63.04; H, 5.44. C₂₇H₂₈O₈S requires C, 63.27; H, 5.51 %); $[\alpha]_D^{20} +53.5^\circ$ (c=1); ir ν_{\max} . (nujol) 1789, 1375, 1182 cm^{-1} ; ^1H nmr: 3.23(3H, s, SO₂CH₃), 3.20-3.30(1H, m, CHOTr), 3.30(3H, s, OCH₃), 3.67(1H, dd, $\underline{J}=2.5$ and 11 Hz, CHOTr), 4.30(1H, m, CH), 4.56(2H, m, 2xCH), 4.65(2H, br s, OCH₂O), 5.82(1H, d, $\underline{J}=6$ Hz, CHOMs), 7.16-7.40(15H, m, ArH).

5-Azido-4,5-dideoxy-2-O-methanesulfonyl-3-O-methoxymethyl-1-O-trityl-D-ribitol (3c) LiAlH₄ (600 mg, 15.8 mmol) was added to a solution of 2e (1.5 g, 2.93 mmol) in 20 ml of THF-ether (1:1) at reflux temperature during a period over 5 min and then the mixture was stirred at reflux for 5 min. After addition of water (0.6 ml), 15% aqueous NaOH (0.6 ml), and water (1.8 ml), the mixture was filtered and the filtrate was dried, followed by evaporation in vacuo to give the crude diol (3a, 0.98 g) as an oil, which was treated with methanesulfonyl chloride (0.45 ml, 5.8 mmol) and TEA (0.81 ml, 5.8 mmol) in CH₂Cl₂ (10 ml) at 0 °C for 30 min. After dilution with AcOEt and washings with water and saturated aqueous NaHCO₃, drying followed by evaporation gave the crude dimesylate (2e, 1.25 g), which was treated with sodium azide (210 mg, 3.23 mmol) in the presence of a catalytic amount of 15-crown-5 in DMF (10 ml) at 80 °C for 30 min. After dilution with AcOEt-benzene (4:1), the mixture was washed with half-saturated brine. Drying followed by evaporation gave a residue, which was chromatographed using AcOEt-hexane (1:3) as eluant to give 3c (585 mg, 38%) as an oil, $[\alpha]_D^{20} -27.2^\circ$ (c=0.3); ir ν_{\max} . (neat) 2100, 1355, 1172 cm^{-1} ; ^1H nmr: 1.49-1.89(2H, m, CH₂), 3.03(3H, s, SO₂CH₃), 3.33(3H, s, OCH₃), 3.12-3.60(4H, m, CH₂, CH₂OTr), 3.97(1H, m, CH), 4.52 and 4.66(2H, AB, $\underline{J}=8$ Hz, OCH₂O), 4.87(1H, m, CH), 7.10-7.56(15H, m,

ArH); ^{13}C nmr: 29.24(t), 38.75(q), 47.22(t), 55.80(q), 62.13(t), 73.58(d), 82.21(d), 87.18(s), 96.00(t), 126.99(d), 127.67(d), 128.28(d), 142.88(s); ms m/z 525 (M^+).

(2S,3S)-1-(tert-Butoxycarbonyl)-3-methoxymethoxy-2-(trityloxymethyl)pyrrolidine

(4b) A solution of 3c (1.0 g, 1.9 mmol) in 20 ml of EtOH-AcOEt (3:1) in the presence of palladium black (200 mg) was stirred under hydrogen at atmospheric pressure for 20 h and then filtered. The filtrate was concentrated in vacuo to give an oily residue, which was dissolved in AcOEt and washed with 10% aqueous NaOH and water. Drying followed by evaporation gave the crude pyrrolidine (4a, 750 mg) as an oil, which was treated with di-tert-butyl dicarbonate (445 mg, 2.05 mmol) and TEA (0.28 ml, 2.05 mmol) in CH_2Cl_2 (8 ml) at 0 °C for 1 h. After removal of the volatiles in vacuo, the residue was chromatographed using AcOEt-hexane (1:3) as eluant to give 4b (683 mg, 71%) as crystals, mp 107-108 °C (Found: C, 74.12; H, 7.45; N, 2.85. $\text{C}_{31}\text{H}_{37}\text{NO}_5$ required C, 73.93; H, 7.41; N, 2.78 %); $[\alpha]_D^{20} +17.9^\circ$ (c=0.6); ir ν_{max} . (nujol) 1690 cm^{-1} ; ^1H nmr: 1.34(9H, br s, tert-butyl), 1.82-2.40(2H, m, CH_2), 3.06-3.68(4H, m, $2\times\text{CH}_2$), 3.22(3H, s, OCH_3), 3.85-4.40(2H, m, $2\times\text{CH}$), 4.45-4.70(2H, br s, OCH_2), 6.96-7.60(15H, m, ArH); ^{13}C nmr: 28.21(q), 29.82(t), 43.47(t), 55.31(q), 57.89(d), 60.86(t), 76.36(d), 79.14(s), 86.69(s), 96.19(t), 126.55(d), 127.38(d), 128.59(d), 143.90(s), 154.23(s).

(4S,5S)-1-(tert-Butoxycarbonyl)-4-methoxymethoxy-5-trityloxymethyl-2-pyrro-

lidinone (6) This sample was obtained as crystals from 4b in 38% yield with 55% recovery of 4b according to the reported procedure⁷ after purification by column chromatography (silica gel, AcOEt-hexane=1:2 as eluant) followed by recrystallization from AcOEt-hexane, mp 132-133 °C (Found: C, 70.43; H, 6.68; N, 2.57. $\text{C}_{31}\text{H}_{36}\text{NO}_6 \cdot 1/2\text{H}_2\text{O}$ required C, 70.70; H, 6.89; N, 2.66 %); $[\alpha]_D^{20} +13.8^\circ$ (c=1.3); ir ν_{max} . (nujol) $1759, 1702\text{ cm}^{-1}$; ^1H nmr: 1.40(9H, s, tert-butyl), 2.59-3.67(4H, m, $2\times\text{CH}_2$), 3.20(3H, s, OCH_3), 4.25(2H, m, $2\times\text{CH}$), 4.51(2H, s, OCH_2), 6.90-7.70(15H, m, ArH); ^{13}C nmr: 27.78(q), 39.62(t), 55.65(q), 59.50(t), 59.70(t), 70.27(d), 82.79(s), 87.27(s), 96.14(t), 126.80(d), 127.53(d), 128.59(d), 143.36(s), 149.12(s), 171.48(s).

tert-Butyl (5S,6S)-6-[(tert-Butoxycarbonyl)amino]-5-methoxymethoxy-3-oxo-7-

(trityloxy)heptanoate (7) A solution of tert-butyl acetate (91 mg, 0.79 mmol) in THF (1 ml) was added to lithium diisopropylamide in THF (1 ml) prepared from diisopropyl amine (88 mg, 0.8 mmol) and butyllithium (0.72 ml of a 1.11 M solution in hexane) at -78 °C. After stirring the mixture for 30 min at -78 °C,

a solution of 6 (323 mg, 0.63 mmol) in THF (2 ml) was added at -78°C . The mixture was stirred at -78°C for 1 h and then quenched with 10% aqueous NH_4Cl (1 ml). After dilution with AcOEt, the mixture was washed with water. Drying followed by evaporation gave a residue, which was chromatographed using AcOEt-hexane (1:3) as eluant to give 7 (320 mg, 81%) as an oil, $[\alpha]_{\text{D}}^{20} +14.5^{\circ}$ ($c=2.2$); ir ν_{max} . (neat) 1732, 1710 cm^{-1} ; ^1H nmr: 1.44(18H, s, 2xtert-butyl), 2.68-2.88(2H, m, CH_2), 3.00-3.33(2H, m, CH_2OTr), 3.11(3H, s, OCH_3), 3.35(2H, s, CH_2COO), 3.75-4.38(2H, m, 2xCH), 4.40(2H, s, OCH_2O), 4.74(1H, d, $J=10$ Hz, NH), 6.96-7.55(15H, m, ArH); ^{13}C nmr: 27.80(q), 28.21(q), 45.27(t), 51.17(t), 53.26(d), 55.55(q), 63.11(t), 73.14(d), 79.19(s), 81.67(s), 86.45(s), 96.88(t), 126.84(d), 127.62(d), 128.45(d), 143.56(s), 155.55(s), 166.02(s), 170.08(s); ms m/z 390 ($(\text{M}-\text{Tr})^+$).

tert-Butyl (3S,5S,6S)-6-[(tert-Butoxycarbonyl)amino]-3-[(tert-butyldimethylsilyl)-oxyl]-5-methoxymethoxy-7-(trityloxy)heptanoate (9) Sodium borohydride

(80 mg, 2.1 mmol) was added to a solution of 7 (200 mg, 0.32 mmol) and lithium chloride (40 mg, 0.94 mmol) in THF (2.5 ml) at -40°C . After addition of EtOH (2.5 ml), the mixture was stirred at -40 -- 50°C for 8 h and then diluted with AcOEt. Washing with half-saturated brine (x4) followed by usual work-up and purification by column chromatography (AcOEt-hexane=1:1 as eluant) provided 8 (150 mg, 75%) as an oil (about 1.9:1 diastereomeric mixture by ^1H nmr: 1.41 and 1.43 (each 9H, each s, 2xtert-butyl), 1.43-1.70(2H, m, CH_2), 2.35(2H, d, $J=7$ Hz, CH_2), 2.80-3.60(3H, m, CH_2OH), 3.13 and 3.19(3H, each s, OCH_3), 3.20-4.21(3H, m, 3xCH), 4.39(2H, s, OCH_2O), 4.68(1H, m, NH), 7.07-7.53(15H, m, ArH)), which was treated with tert-butyldimethylsilyl chloride (71 mg, 0.47 mmol) and imidazole (80 mg, 1.18 mmol) in DMF (3 ml) at room temperature for 40 h. After dilution with AcOEt-benzene (4:1), the mixture was washed with water. Drying followed by evaporation gave a residue, which was chromatographed using AcOEt-hexane (1:1) to give 9 (92 mg, 52%) and its C-3 epimer (50 mg, 28%) as an oil. Less polar diastereomer (9); $[\alpha]_{\text{D}}^{20} +8.8^{\circ}$ ($c=1.4$); ir ν_{max} . (neat) 1714, 1498 cm^{-1} ; ^1H nmr: 0.04(6H, s, 2x CH_3), 0.82(9H, s, tert-butyl), 1.38 (18H, s, 2xtert-butyl), 1.55-1.84(2H, m, CH_2), 2.37(2H, d, $J=6$ Hz, CH_2), 2.82-3.29(2H, m, CH_2OTr), 3.12(3H, s, OCH_3), 3.69-4.03(2H, m, 2xCH), 4.03-4.29(1H, m, CH), 4.38(2H, s, OCH_2O), 4.74(1H, d, $J=9$ Hz, NH), 7.07-7.61(15H, m, ArH); ^{13}C nmr: -4.50(q), 17.88(s), 25.82(q), 28.07(q), 28.36(q), 39.96(t), 44.10(t), 53.41(d), 55.55(q), 63.35(t), 66.47(d), 74.36(d), 78.99(s), 80.26(s), 86.64(s), 96.39(t), 126.84(d), 127.67(d), 128.55(d), 143.75(s), 155.40(s), 170.26(s); ms m/z 506 ($(\text{M}-\text{Tr})^+$). Polar diastereomer (C-3

epimer); $[\alpha]_D^{20} +7.5^\circ$ (c=0.7); ir ν_{\max} . (neat) 1714, 1497 cm^{-1} ; ^1H nmr: 0.05(6H, s, $2\times\text{CH}_3$), 0.82(9H, s, tert-butyl), 1.41 (18H, s, $2\times$ tert-butyl), 1.61-1.90(2H, m, CH_2), 2.39(2H, d, $J=6$ Hz, CH_2), 2.79-3.34(2H, m, CH_2OTr), 3.12(3H, s, OCH_3), 3.62-3.99(2H, m, $2\times\text{CH}$), 3.99-4.29(1H, m, CH), 4.39(2H, s, OCH_2O), 4.78(1H, d, $J=9$ Hz, NH), 6.97-7.68(15H, m, ArH); ^{13}C nmr: -4.58(q), 17.83(s), 25.78(q), 28.12(q), 28.36(q), 39.08(t), 43.51(t), 52.82(d), 55.75(q), 63.74(t), 66.42(d), 74.31(d), 78.99(s), 80.11(s), 86.55(s), 96.14(t), 126.84(d), 127.67(d), 128.55(d), 143.75(s), 155.55(s), 170.36(s); ms m/z 506 ($(\text{M-Tr})^+$).

(-)-Galantinic acid (1) and its C-3 epimer A mixture of 9 (140 mg, 0.19 mmol), trimethylsilyl bromide (0.4 ml, 3 mmol), and molecular sieves 4\AA (120 mg) in CH_2Cl_2 (3 ml) was stirred at -20°C for 1.5 h. After neutralization with aqueous NaHCO_3 , CH_2Cl_2 was removed in vacuo, then the aqueous layer was acidified with 2% aqueous HCl, placed on a Dowex 50W-X8 (H^+ form) column (10 ml), washed with water (25 ml), and eluted with 1N NH_4OH . Lyophilization of the appropriate fractions gave a residue, which was triturated with MeOH-ether to give 1 (19 mg, 53%) as crystals, mp $128-132^\circ\text{C}$ (dec.), $[\alpha]_D^{20} -28.6^\circ$ (c=1.8, H_2O); ^{13}C nmr(D_2O , internal standard: dioxane $\delta=67.4$): 40.49(t), 46.34(t), 58.33(d), 60.23(t), 66.18(d), 180.83(s). C-3 Epimer was obtained in 49% yield in the same manner as described above for the preparation of 1, mp $180-184^\circ\text{C}$ (dec.), $[\alpha]_D^{20} -7.1^\circ$ (c=0.6, H_2O); ^{13}C nmr (D_2O , internal standard: dioxane $\delta=67.4$): 40.45(t), 45.42(t), 57.45(d), 60.96(t), 67.64(d), 180.83(s).

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