

Supporting Information

Preparation of 4-Allylisoindoline via a Kumada Coupling with Allylmagnesium Chloride

Michael J. Zacuto, C. Scott Shultz, and Michel Journet*

Department of Process Research, Merck and Co., Inc. P.O. Box 2000 Rahway, NJ 07065

michael_zacuto@merck.com

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General Methods

Reagents and solvents were obtained from commercial sources and were used as received. Chromatography was performed using silica gel (70-230 mesh), using reagent grade solvents which were used as received. ¹H NMR spectra were recorded at 400 MHz using Bruker Avance 400 NMR spectrometers unless otherwise noted, using the *d*₆-dmsO resonance as an internal standard measured at 2.50 ppm. ¹³C NMR spectra were recorded on 100 or 125 MHz using Bruker Avance NMR spectrometers unless otherwise noted, using the *d*₆-dmsO resonance as an internal standard measured at 39.5 ppm. All manipulations were carried out under an inert atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. Allyl-MgCl was purchased from Acros and was used as received. Pd(OAc)₂ and (neopentyl)(*t*-Bu₂)P•HBF₄ were purchased from Strem Chemicals and used as received. All other reagents were purchased from Aldrich Chemical Co. unless otherwise noted.

4-Allylisoindoline•HCl. A 3 L flask equipped with overhead stirring, an addition funnel and a thermocouple was purged with N₂, then charged under positive N₂ pressure with **2•HCl** (100 g, 0.426 mol), Pd(OAc)₂ (0.48 g, 2.13 mmol) and (neopentyl)*t*Bu₂P•HBF₄ (1.3 g, 4.3 mmol). The flask was then charged with toluene (1.8 L, which had been previously de-oxygenated *via* N₂ subsurface sparging). Allylmagnesium chloride (800 mL, 1.36 mol, 1.7 M in THF) was charged to the addition funnel and then added to the slurry, with external cooling, over 1 h such that T_i ≤ 25 °C.¹ The resulting solution was then heated to and maintained at T_i = 45-50 °C for 16 h. After cooling to ambient temperature, the reaction was inverse-quenched by slow transfer, with external cooling and at a rate such that T_i < 35 °C, into a 3 L jacketed flask (equipped with a drop valve and overhead stirring) that had been charged with a solution of 15 wt% citric acid (1.1 L). The organic phase, which contained 1.2 g of **1** by assay, was rejected. The aqueous phase was assayed for 61.3 g of **1** (90% yield in organic phase, corresponding to a 92% end of reaction assay yield, along with 2.6% AY of **3**). The aqueous phase was transferred to an extractor, to which was charged fresh toluene (650 mL) and the resulting biphasic mixture was stirred. Ammonium hydroxide (28-30% in water, 650 mL) was added at a rate such that T_i ≤ 30 °C, resulting in a pH 10 aqueous phase. The phases were separated, and the aqueous phase (which contained 1.8 g of **1** by assay, 1.0 g/L) was extracted with 200 mL of toluene (0.3 g of **1** remained in the aqueous phase after extraction, or 0.18 g/L). The combined organic phases were then washed with 160 mL of 15 wt% aqueous NaCl. The toluene solution was dried via azeotropic distillation with toluene under "constant volume" conditions, then concentrated to a 650

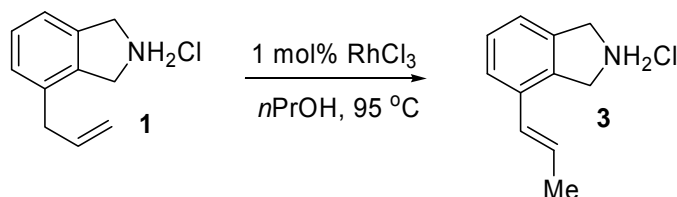
¹ Evolution of propene occurs during the exothermic addition of allylmagnesium chloride at a rate proportional to the rate of addition. A mild N₂ sweep efficiently removed any residual propene that was observed to evolve upon heating to T_i = 45 °C.

mL total volume solution (KF = 500 ppm H₂O). The solution was assayed by wt/wt% to contain 59.4 g of **1** (87.5% AY after workup).

The toluene solution of **1** was transferred to a 1 L flask equipped with overhead stirring, an addition funnel and a thermocouple. A solution of HCl in *i*PrOH (5.1 M) was transferred to the addition funnel, and then added slowly over 1 hour to the solution of **1** in toluene, at a rate such that $T_i \leq 40\text{ }^{\circ}\text{C}$. The resulting slurry was aged for 6 hours, with gradual cooling to ambient temperature. The slurry was then slowly cooled to $T_i = 0\text{ }^{\circ}\text{C}$ over 1 hour, then maintained at this temperature for an additional hour. The slurry was filtered, with loss to the supernatant assayed at 7.6 g/L of **1**•HCl (4.12 g total, along with 1.6 g of **3**•HCl). The cake was washed with 175 mL of 9:1 toluene:IPA (pre-cooled to $T_i = 0\text{ }^{\circ}\text{C}$), then dried with vacuum/N₂ sweep. **1**•HCl was isolated as an off white solid (69.5 g) that was assayed at 96 wt% (97.6 area % by HPLC), corresponding to an isolated yield of 80%. ¹H NMR (400 MHz, *d*₆-dmsO) δ 9.95 (br s, 2H), 7.32 (t, $J = 7.4\text{ Hz}$, 1H), 7.25 (d, $J = 7.4\text{ Hz}$, 1H), 7.16 (d, $J = 7.4\text{ Hz}$, 1H), 5.96-5.84 (m, 1H), 5.10-5.04 (om, 2H), 4.48 (s, 2H), 4.45 (s, 2H), 3.37 (d, $J = 6.5\text{ Hz}$, 2H); ¹³C NMR (100 MHz, *d*₆-dmsO) δ 135.6, 135.1, 134.6, 133.8, 128.7, 128.3, 120.8, 116.4, 49.8, 48.7, 36.9; HRMS [M+H]⁺ for C₁₁H₁₃N calc'd 160.1126, found 160.1128.

Compound 3:

The identity of **3** was initially determined using LCMS. In an effort to independently verify the structure, an authentic sample was prepared from pure **1**.



A flask was charged with **1**•HCl salt (0.5 g, 3.14 mmol) and RhCl_3 hydrate (6 mg, 0.03 mmol), then $n\text{PrOH}$ (15 mL). The flask was sealed under an N_2 atmosphere and heated to $T_i = 95\text{ }^\circ\text{C}$ for 10 h. The solution was gradually cooled to ambient temperature, whereupon a slurry formed. The product was filtered, and the cake was washed with $n\text{PrOH}$. Drying afforded 300 mg of **3**•HCl. ^1H NMR (400 MHz, d_6 -dmso) δ 9.56 (br s, 2H), 7.45 (d, $J = 7.7$ Hz, 1H), 7.32 (t, $J = 7.7$ Hz, 1H), 7.24 (d, $J = 7.7$ Hz, 1H), 6.44 (dd, $J = 15.8, 1.5$ Hz, 1H), 6.29 (dq, $J = 15.8, 6.6$ Hz, 1H), 4.53 (s, 2H), 4.47 (s, 2H), 1.89 (dd, $J = 6.6, 1.5$ Hz, 3H); ^{13}C NMR (125 MHz, d_6 -dmso) δ 135.5, 132.6, 131.8, 128.8, 128.6, 127.6, 124.6, 121.1, 49.8, 49.3, 18.5; HRMS $[\text{M}+\text{H}]^+$ for $\text{C}_{11}\text{H}_{13}\text{N}$ calc'd 160.1126, found 160.1130.

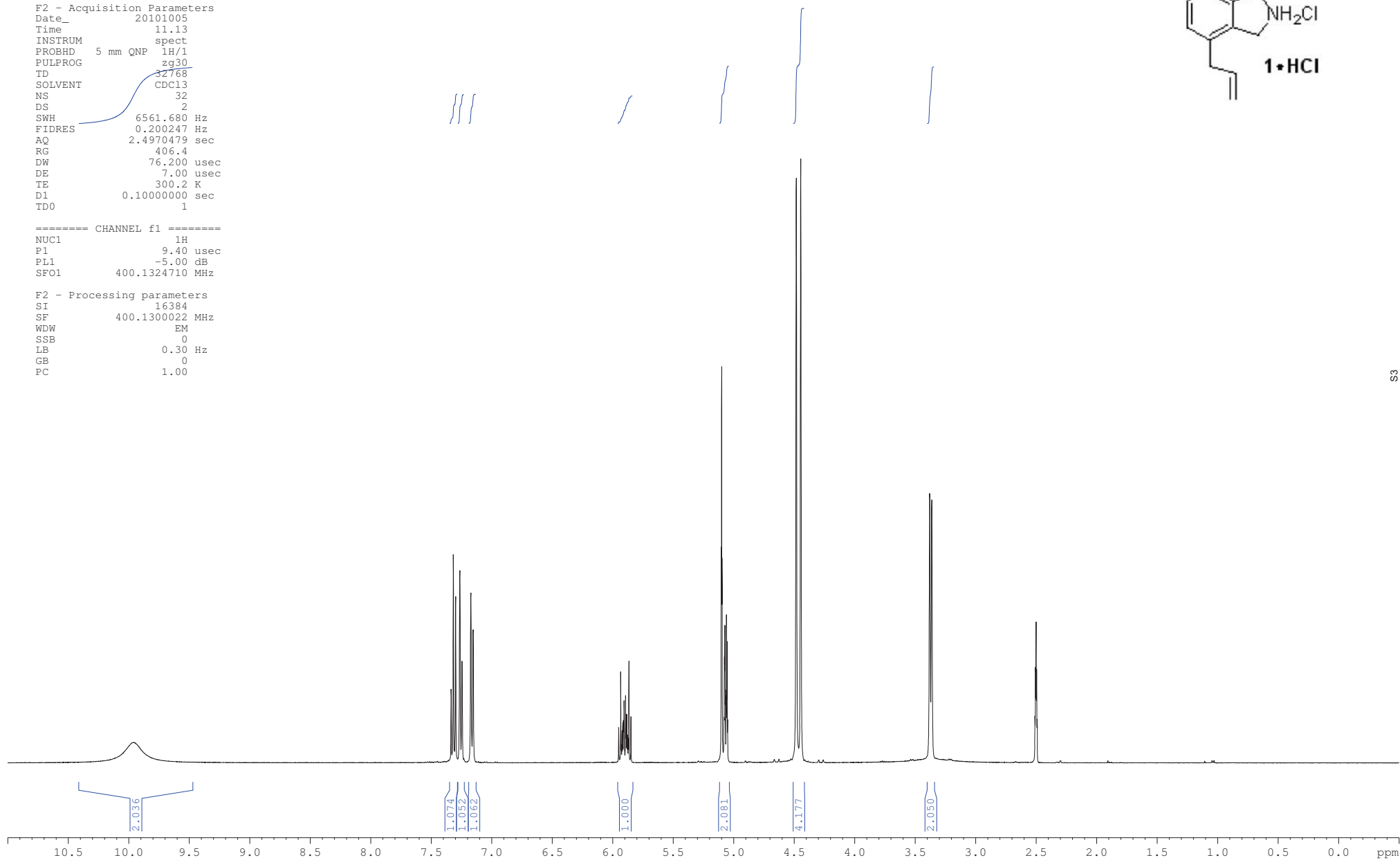
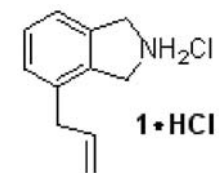
isolated 4-allylisoindoline HCl salt (d6-dmsO)

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PROCNO 1

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PROCNO 1

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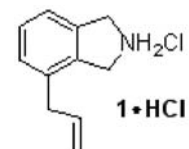
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49.84
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36.94

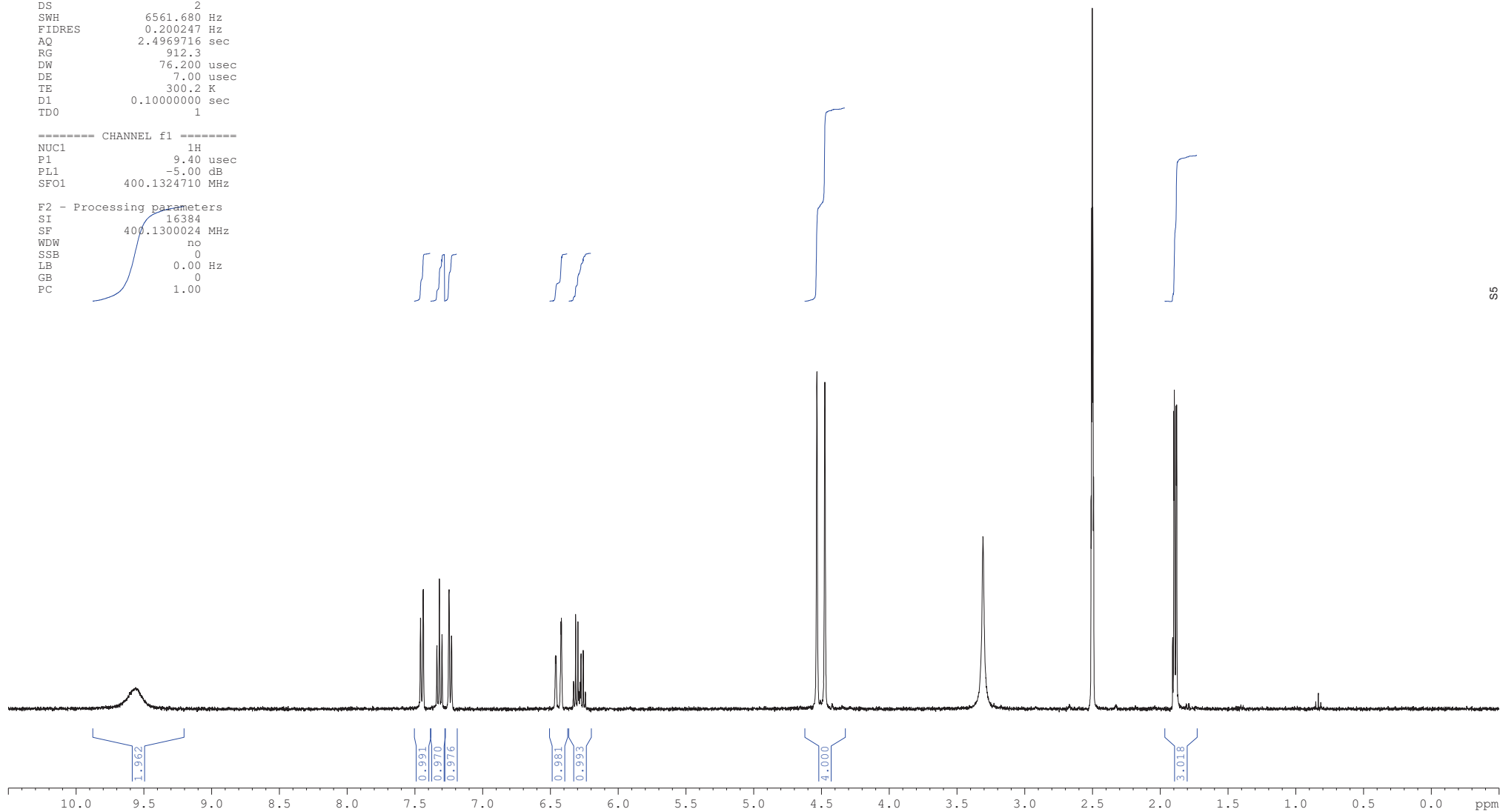
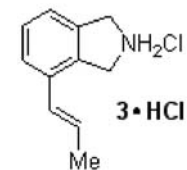


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PROCNO 1

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FIDRES 0.200247 Hz
AQ 2.4969716 sec
RG 912.3
DW 76.200 usec
DE 7.00 usec
TE 300.2 K
D1 0.10000000 sec
TD0 1

===== CHANNEL f1 =====
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P1 9.40 usec
PL1 -5.00 dB
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F2 - Processing parameters
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SF 400.1300024 MHz
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LB 0.00 Hz
GB 0
PC 1.00



Current Data Parameters
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EXPNO 1
PROCNO 1

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PULPROG zgdc
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39.00

18.54

