Synthesis of Phenylacetic Acids with 2-Oxoalkyl Substituents in the *ortho*-Position from *o*-Phenylenediacetic Acid

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Abstract: A one-step procedure for the synthesis of 2-(2-oxoalkyl)-substituted phenylacetic acids is described. Very slow addition of organolithium compounds to *o*-phenylenediacetic acid is the crucial feature to obtain the desired ε-oxo acids in good yields. The selective formation of the ε-oxo acids from the diacid is explained on the basis of hemiketal anion formation.

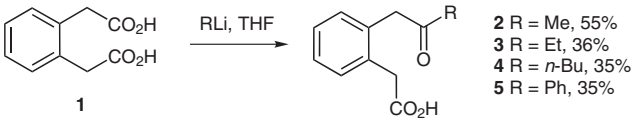
Key words: organometallic reagents, polyanions, carboxylic acids, ketones, nucleophilic addition, heterocycles, ε-oxo acids, hemiketal anions

The γ-, δ-, and ε-oxo acids constitute valuable building blocks for the asymmetric synthesis of several carbo- and heterocycles including substituted naphthalenones,[1] pyrrolidines,[2] piperidones,[3] azepines, and 3-benzazepines.[4] These carbo- and heterocycles are of particular interest in medicinal chemistry. However, the methods described for the synthesis of oxo acids involve several steps and are, thus, rather circumstantial and time-consuming.[1,5,6]

Although the synthesis of ketones by the reaction of carboxylic acids with organolithium reagents is well known, the formation of undesired tertiary alcohols is a problem associated with this transformation.[7–9] Only a few reports in the literature describe the reaction of diacids with organolithium reagents.[10]

In this paper we wish to report on a general method for the synthesis of phenylacetic acid derivatives with various 2-oxoalkyl residues in position 2 of the phenyl ring starting from the diacid *o*-phenylenediacetic acid (**1**). We postulate that the selective formation of ε-oxo acids as the main product is based on the intermediate formation of a hemiketal anion.

At first we concentrated on the production of the phenylacetic acid **2** with a 2-oxopropyl residue in position 2. However, all attempts to transform the dimethyl ester of **1** with methyllithium[8] or Tebbe reagent[11,12] into the corresponding methyl ester of **2** failed. In a further approach we tried to prepare the ε-oxo acid **2** by reaction of *o*-bromophenylacetic acid and active methylene compounds using several palladium/copper catalysts and different bases;[13] this reaction did not result in the formation of the desired phenylacetic acid derivatives.



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Scheme 1

Then we focused our attention on the direct reaction of *o*-phenylenediacetic acid with methyllithium (Scheme 1). Indeed the reaction of diacid **1** with eight equivalents of methyllithium provided the desired oxo acid **2**, albeit in low isolated yield (10%) along with large amounts of unreacted diacid **1**.

Next, the yield of **2** was improved by varying the reaction conditions (Table 1). In order to obtain a rapid result, the ^{1}H NMR spectrum (CD_3OD) of the crude reaction mixture was recorded. Usually the signals for only two compounds (diacid **1** and oxo acid **2**) were observed in the ^{1}H NMR spectrum indicating a clean transformation. The ratio of oxo acid **2** to diacid **1** was calculated by integration of characteristic signals (CH_2CO_2H singlets of **1** and CH_2COR singlets of **2**–**5**, see Figure 1).

At first the solvent diethyl ether was employed instead of tetrahydrofuran. However, due to the low solubility of the anionic intermediates only a very low conversion was observed.

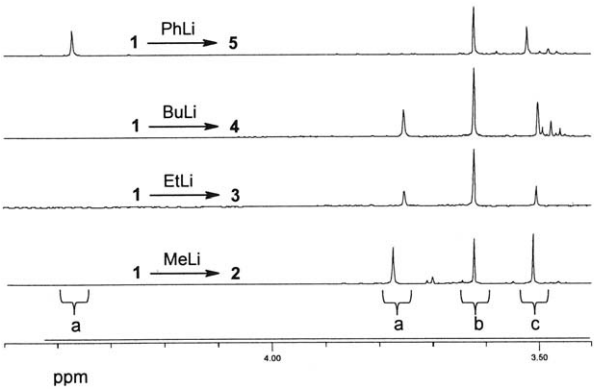

Figure 1 Comparison of characteristic signals of diacid **1** and oxo acids **2**–**5** in the ^{1}H NMR spectra (CD_3OD); (a) CH_2COR of **2**–**5**; (b) CH_2COOH of diacid **1**; and (c) CH_2COOH of oxo acids **2**–**5**.

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Table 1 Optimization of the Reaction of *o*-Phenylenediacetic Acid **1** with Methyllithium

Entry	Temp	Equiv of MeLi[a]	Rate of addition of MeLi	Time (h)	Ratio[b] **2/1**
1	–10 °C	8	>10 mL/min	24	–
2	0 °C	8	>10 mL/min	24	17:83
3	0 °C to r.t.	8	>10 mL/min	24	60:40
4	reflux (66 °C)	8	>10 mL/min	24	35:65[c]
5	0 °C to r.t.	8	>10 mL/min	24	45:55[d]
6	0 °C to r.t.	8	>10 mL/min	6	38:62
7	0 °C to r.t.	8	>10 mL/min	96	47:53[c]
8	0 °C to r.t.	10	>10 mL/min	24	52:48
9	0 °C to r.t.	8	2 mL/h	24	73:27
10	0 °C to r.t.	10	2 mL/h	24	75:25

[a] All reactions used diacid **1** (2.6 mmol) and THF (35 mL), unless otherwise noted.
[b] Determined by integration of characteristic CH_2 singlets in the ^1H NMR spectra.
[c] Side products are observed in the ^1H NMR spectrum in addition to the main components **2** and **1**.
[d] THF (12 mL).

Table 2 Optimization of the Reaction of Ethyllithium, Butyllithium, and Phenyllithium with *o*-Phenylenediacetic Acid (**1**)

Entry	R	Equiv of RLi[a]	Rate of addition of RLi	Ratio[b] **3–5/ 1**
1	Et	8	>10 mL/min	38:62
2	Et	10	>10 mL/min	45:55
3	Et	15	>10 mL/min	40:60
4	Et	10	2 mL/h	58:42
5	Et	10[c]	2 mL/h	69:31
6	Bu	8	>10 mL/min	48:52
7	Bu	8	2 mL/h	51:49
8	Bu	10[c]	2 mL/h	59:41
9	Ph	8	>10 mL/min	45:55
10	Ph	8	2 mL/h	53:47
11	Ph	10[c]	2 mL/h	61:39

[a] All reactions used diacid **1** (2.6 mmol) and THF (35 mL) unless otherwise noted.
[b] Determined by integration of characteristic CH_2 singlets in the ^1H NMR spectra.
[c] Diacid **1** (5.2 mmol), THF (70 mL).

Performing the reaction at –10 °C or lower temperatures (THF) did not lead to any conversion (Table 1, entry 1). At 0 °C only very little formation of the oxo acid **2** was observed (Table 1, entry 2). However, addition of methyllithium at 0 °C and subsequent stirring of the reaction mixture at room temperature for 24 hours provided **2/1** in a ratio of 60:40 (Table 1, entry 3). A further increase in the reaction temperature to 66 °C (THF, reflux) reduced the yield of oxo acid **2** (Table 1, entry 4) due to side reactions induced by the large excess of methyllithium, as observed in the ^1H NMR spectrum.

The amount of solvent (concentration of the reactants) seems to play an important role for this transformation. Increasing the concentration by reducing the amount of solvent afforded a reduced yield of oxo acid **2** (Table 1, cf. entries 3 and 5). Further concentration of the reaction mixture led to a further decrease in the yield due to solubility problems.

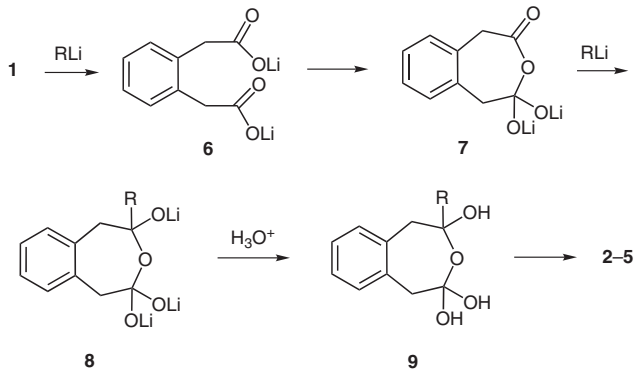
Shortening as well as prolongation of the reaction time from 24 hours to 6 hours or to 96 hours (Table 1, cf. entries 3, 6, and 7) resulted in decreased yields of **2**.

Finally, the addition rate of methyllithium to the reaction mixture turned out to be the crucial feature for high yields of **2**. Very slow addition of methyllithium increased the yield of the oxo acid **2** considerably. Thus, an addition rate of 2 mL/h (syringe pump) provided 73% of oxo acid **2** along with only 27% of unreacted diacid **1** (Table 1, cf. entries 3 and 9). A slight increase in the yield was attained using 10 equivalents of methyllithium with an addition rate of 2 mL/h (Table 1, entry 10).

In summary, performing the transformation in tetrahydrofuran at 0 °C to room temperature and adding 8 equivalents of methyllithium very slowly (2 mL/h) led to the highest conversion of the diacid **1** into the oxo acid **2**, which was isolated in 55% yield after flash chromatography.

After optimization of the reaction of diacid **1** with methyllithium, the organolithium reagents ethyllithium, *n*-butyllithium, and phenyllithium were also investigated. The results are summarized in Table 2. In general, the observations with these organolithium reagents confirm the rules that were found during the optimization cycles with methyllithium: increasing the number of equivalents of organolithium reagent did not lead to complete transformation, but instead resulted in reduced yields of oxo acids (Table 2, cf. entries 1–3). Very slow addition of RLi to the solution of diacid **1** of tetrahydrofuran resulted in considerable improvement of the yields (Table 2, cf. entries 2 and 4, 6 and 7, and 9 and 10). In the case of slow addition, an increase of RLi from eight to ten equivalents together with an increase in scale from 2.6 to 5.2 mmol led to increased yields of oxo acids (Table 2, cf. entries 4 and 5, 7 and 8, and 10 and 11).

After reaction of diacid **1** with various RLi reagents, tertiary alcohols, or diketones were neither isolated nor detected. Therefore, we assume the reaction path depicted in Scheme 2: initially excess RLi deprotonates the diacid **1** to give the dicarboxylate **6**, which is able to form the cyclic ortho acid dianion **7**. The lactone-like structure of **7** reacts with a further molecule of RLi to provide the trianion **8**, which is resistant to further RLi attack. Addition



Scheme 2

of water during workup leads to protonation of **8** to give the hydrate **9**, which results in the oxo acids **2**–**5** upon ring opening.

We assume that the isolation of large amounts of starting diacid **1** is due to α-deprotonation of **6** or **7**. The resulting enolate or enediolate is not able to react with RLi and gives the starting diacid **1** upon workup. The ratio of **1/2**–**5** in the ^{1}H NMR spectra of the crude products (Figure 1) reflects the ratio of α-deprotonation to nucleophilic attack of **7**.

In the case of *ortho*-substitution the lactone-like intermediate **7** is activated for nucleophilic attack of RLi resulting in considerable amounts of oxo acids **2**–**5**. In order to prove this hypothesis of the formation of a hemiketal anion, the *meta*-substituted diacid, *m*-phenylenediacetic acid, and the *para*-substituted diacid, *p*-phenylenediacetic acid, were treated with a large excess of methyllithium using the optimized reaction conditions found for the *ortho* derivative **1**. Neither in the case of *meta*- nor *para*-substituted phenylenediacetic acids were any oxo acids isolated or detected, indicating that α-deprotonation is the predominant process.

In conclusion, a one-step synthesis of phenylacetic acids with various 2-oxoalkyl side chains in the *ortho* position has been elaborated. Although the yields are only in the range of 35–55% the desired 2-[2-(2-oxoalkyl)phenyl]acetic acids are accessible in only one step starting with inexpensive, commercially available starting material. Also the reaction of diacids with organolithium reagents was studied carefully, and the mechanism for the product formation was given on the basis of an intermediate hemiketal anion.

TLC: Silica gel 60 F_{254} plates (Merck). Flash chromatography: silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, eluent, fraction size, R_f value. Melting point: melting point apparatus SMP 3 (Stuart Scientific), uncorrected. MS: MAT GCQ (Thermo-Finnigan). HRMS: MicroTof (Bruker Daltronics, Bremen), calibration with sodium formate clusters before measurement. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury plus 400 spectrometer (Varian); TMS as reference and coupling constants given with 0.5 Hz resolution. Elemental analysis: CHN-Rapid Analysator (Fons-Heraeus). HPLC method for determination of the product purity: Merck Hitachi equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher 60 RP-select B (5 μm); LiCroCART 250–4 mm cartridge; flow rate: 1.000 mL/min; injection volume: 5.0 μL; detection at λ = 210 nm; solvents: A: H_2O with 0.05% TFA; B: MeCN with 0.05% TFA: gradient elution: 0.0 min: 90.0% of A, 10.0% of B; 4.0 min: 90.0% of A, 10.0% of B; 29.0 min: 0.0% of A, 100.0% of B; 31.0 min: 0.0% of A, 100.0% of B; 31.5 min: 90.0% of A, 10.0% of B; 40.0 min: 90.0% of A, 10.0% of B.

Reaction of *o*-Phenylenediacetic Acid (1) with Organolithium Reagents; General Procedure

Under N_2, a soln of *o*-phenylenediacetic acid (**1**, 500 mg, 2.57 mmol) in anhyd THF (35 mL) was cooled to 0 °C. Then a commercially available organolithium reagent (20.6–25.7 mmol, 8–10 equiv) was added at a rate of 2 mL/h through a syringe pump. The mixture was vigorously stirred for 24 h at r.t., cooled to 0 °C, and quenched with 1 M HCl (30 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL), the Et_2O layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo. A ^{1}H NMR spectrum of the crude reaction product was recorded in CD_3OD to determine the ratio of the starting compound **1** and the formed product **2**–**5**. Then the residue was purified by flash chromatography.

2-[2-(2-Oxopropyl)phenyl]acetic Acid (2)

According to the general procedure *o*-phenylenediacetic acid (**1**, 500 mg, 2.57 mmol) was treated with 1.6 M MeLi in Et_2O (12.8 mL, 20.6 mmol). In the crude product the ratio of **1/2** was 24:76. Purification by flash chromatography [2 cm, EtOAc–cyclohexane–HCO_2H, 20:79.5:0.5, 25 cm, 15 mL, R_f = 0.21 (EtOAc–cyclohexane–HCO_2H, 50:49.5:0.5)] led to a pale yellow oil that solidified upon standing at –30 °C, colorless solid; yield: 272 mg (55%); mp 42–44 °C. In ref.[5,6] compound **2** is mentioned. However a preparative procedure and spectroscopic and analytical data are not available.

Purity by HPLC method (see general part): t_R = 13.6 min (99.8%).

FT-IR (ATR, film): 3201 (w, COOH), 3058, 3022 (w, C–H_{arom}), 2970, 2919 (w, C–H_{aliph}), 1701 [s, C=O, C(=O)OH], 1157, 747 cm^{-1} (m, 1,2-disubstituted benzene).

^{1}H NMR ($CDCl_3$): δ = 2.17 (s, 3 H, COCH_3), 3.62 (s, 2 H, CH_2COOH), 3.80 (s, 2 H, CH_2COCH$_3$), 7.16–7.27 (m, 4 H_{arom}), 9.35 (s, 1 H, CO_2H).

^{13}C NMR ($CDCl_3$): δ = 29.7 (1 C, CO*C*H$_3$), 38.9 (1 C, *C*H$_2$COCH$_3$), 48.8 (1 C, *C*H$_2$CO$_2$H), 127.9, 128.2, 131.3, 131.4 (4 C, Ph-CH), 132.8, 133.6 (2 C, Ph-C), 177.2 (1 C, CH$_2$*C*OCH$_3$), 206.6 (1 C, CH$_2$*C*O$_2$H).

MS (EI): *m*/*z* (%) = 192 [M$^+$, 9], 132 [$C_9H_8O^+$ (M$^+$ – CH$_2$COOH – H), 82], 104 [$C_8H_8^+$, 100], 91 [$C_7H_7^+$].

Anal. Calcd for $C_{11}H_{12}O_3$ (192.2): C, 68.74; H, 6.29. Found: C, 68.56; H, 6.25.

2-[2-(2-Oxobutyl)phenyl]acetic Acid (3)

According to the general procedure *o*-phenylenediacetic acid (**1**, 500 mg, 2.57 mmol) was treated with 1.7 M EtLi in Bu_2O (12.1 mL, 20.6 mmol). In the crude product the ratio of **1/3** was 31:69. Purification by flash chromatography [2 cm, EtOAc–cyclohexane–HCO_2H, 20:79.5:0.5, 25 cm, 15 mL, R_f = 0.30 (EtOAc–cyclohexane–HCO_2H, 50:49.5:0.5)] led to a colorless viscous oil that solidified upon standing at –30 °C, colorless solid; yield: 191 mg (36%); mp 44–46 °C.

Purity by HPLC method (see general part): t_R = 14.9 min (98.9%).

FT-IR (ATR, film): 3187 (w, COOH), 3065, 3023 (w, C–H_{arom}), 2977, 2935 (w, C–$H_{aliph.}$), 1703 [s, C=O, C(=O)OH], 1154, 749 cm^{-1} (m, 1,2-disubstituted benzene).

^{1}H NMR ($CDCl_3$): δ = 1.04 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.49 (q, *J* = 7.3 Hz, 2 H, C*H*$_2$CH$_3$), 3.64 (s, 2 H, C*H*$_2$COOH), 3.80 (s, 2 H, C*H*$_2$COEt), 7.16–7.28 (m, 4 H_{arom}), 10.57 (br s, 1 H, CO_2H).

^{13}C NMR ($CDCl_3$): δ = 7.9 (1 C, COCH$_2$*C*H$_3$), 35.7 (1 C, CO*C*H$_2$CH$_3$), 39.1 (1 C, *C*H$_2$COEt), 47.6 (1 C, Ph*C*H$_2$CO), 127.8, 128.1, 131.2, 131.3 (4 C, Ph-CH), 132.9, 133.9 (2 C, Ph-C), 177.5 (1 C, CH$_2$*C*OEt), 209.3 (1 C, CO_2H).

MS (EI): *m*/*z* (%) = 206 [M$^+$, 5], 132 [$C_9H_8O^+$ (M$^+$ – CH_2CO_2H, CH_3), 100], 104 [$C_8H_8^+$, 89], 91 [$C_7H_7^+$, 43].

Anal. Calcd for $C_{12}H_{14}O_3$ (206.2): C, 69.89; H, 6.84. Found: C, 69.75; H, 6.81.

2-[2-(2-Oxohexyl)phenyl]acetic Acid (4)

According to the general procedure *o*-phenylenediacetic acid (**1**, 500 mg, 2.57 mmol) was treated with 1.6 M BuLi in hexane (12.8 mL, 20.6 mmol). In the crude product the ratio of **1/4** was 41:59. Purification by flash chromatography [2 cm, EtOAc–cyclohexane–HCO_2H, 10:89.5:0.5, 25 cm, 15 mL, R_f = 0.39 (EtOAc–cyclohexane–HCO_2H, 50:49.5:0.5)] led to a pale yellow solid that gave a colorless solid upon recrystallization (hexane–CH_2Cl_2); yield: 211 mg (35%); mp 59–61 °C.

Purity by HPLC method (see general part): t_R = 18.9 min (97.8%).

FT-IR (ATR, film): 3023 (w, COOH), 2951, 2931 (w, C–H_{arom}), 2868.8 (w, C–H_{aliph}), 1713 [s, C(=O)OH], 1690 (s, C=O), 1240, 742 cm^{-1} (m, 1,2-disubstituted benzene).

^{1}H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 7.3 Hz, 3 H, $CH_2CH_2CH_2CH_3$), 1.25–1.32 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.50–1.57 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.48 (t, *J* = 7.4 Hz, 2 H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 3.63 (s, 2 H, C*H*$_2$COOH), 3.78 (s, 2 H, C*H*$_2$COBu), 7.14–7.17 (m, 1 H_{arom}), 7.24–7.27 (m, 3 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 14.0 (1 C, $CH_2CH_2CH_2CH_3$), 22.4 (1 C, $CH_2CH_2CH_2CH_3$), 26.0 (1 C, $CH_2CH_2CH_2CH_3$), 39.0 (1 C, *C*H$_2$CO$_2$H), 42.3 (1 C, $CH_2COCH_2CH_2CH_2CH_3$), 47.9 (1 C, Ph*C*H$_2$CO), 127.9, 128.1, 131.2 (4 C, Ph-CH), 132.9, 133.7 (2 C, Ph-C), 176.9 (1 C, CO_2H), 208.9 (1 C, C=O).

MS (EI): *m*/*z* (%) = 234 [M$^+$, 4], 132 [$C_9H_8O^+$ (M$^+$ – CH_2CO_2H – $CH_2CH_2CH_2CH_2$), 100], 104 [$C_8H_8^+$, 68], 91 [$C_7H_7^+$, 40].

Anal. Calcd for $C_{14}H_{18}O_3$ (234.3): C, 71.77; H, 7.74. Found: C, 71.61; H, 7.72.

2-[2-(2-Oxo-2-phenylethyl)phenyl]acetic Acid (5)

According to the general procedure *o*-phenylenediacetic acid (**1**, 500 mg, 2.57 mmol) was treated with 2.0 M PhLi in Bu_2O (10.3 mL, 20.6 mmol). In the crude product the ratio of **1/5** was 39:61. Purification by flash chromatography [2 cm, EtOAc–cyclohexane–HCO_2H, 10:89.5:0.5, 25 cm, 15 mL, R_f = 0.34 (EtOAc–cyclohexane–HCO_2H, 50:49.5:0.5)] led to a pale yellow solid that gave a colorless solid upon recrystallization (hexane–CH_2Cl_2); yield: 229 mg (35%); mp 187–187.7 °C.

Purity by HPLC method (see general part): t_R = 18.9 min (99.2%).

FT-IR (ATR, film): 3202 (w, COOH), 3062, 3019 (w, C–H_{arom}), 2954, 2920 (w, C–H_{aliph}), 1700 (s, C=O), 1684 [s, C(=O)OH], 1206, 746 cm^{-1} (m, 1,2-disubstituted benzene).

^{1}H NMR ($CDCl_3$): δ = 3.64 (s, 2 H, C*H*$_2$COPh), 4.41 (s, 2 H, C*H*$_2$CO$_2$H), 7.15–7.17 (m, 1 H_{arom}), 7.24–7.36 (m, 3 H_{arom}), 7.47 (t, *J* = 7.7 Hz, 2 H_{arom}), 7.58 (t, *J* = 7.4 Hz, 1 H_{arom}), 8.02 (d, *J* = 7.3 Hz, 2 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 39.2 (1 C, *C*H$_2$CO), 43.2 (1 C, *C*H$_2$CO$_2$H), 127.9, 128.1, 128.6, 128.9, 131.2, 131.3, 132.9 (9 C, Ph-CH), 133.6, 134.0, 136.8 (3 C, Ph-C), 177.2 (1 C, CO_2H), 197.9 (1 C, C=O).

MS (EI): *m*/*z* (%) = 254 [M$^+$, 7], 132 [$C_9H_8O^+$, 100], 105 [PhCO$^+$, 86], 91 [$C_7H_7^+$, 8].

Anal. Calcd for $C_{16}H_{14}O_3$ (254.3): C, 75.58; H, 5.55. Found: C, 75.35; H, 5.42.

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