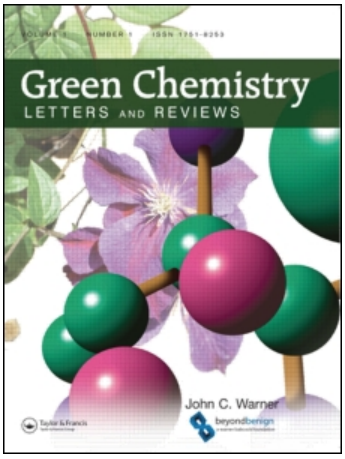

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ORIGINAL ARTICLE

Enzymatic synthesis of chiral heteroaryl alcohols using plant fragments as the only biocatalyst and reducing agent

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The enzymatic reduction of prochiral heterocyclic ketones by carrot (*Daucus carota*) root in water afforded the corresponding *S*-alcohols in accordance with the Prelog's rule. The reaction was performed under various conditions in order to optimize the procedure of bioreduction regarding reaction time, yield, and optimal mass of carrot. The optimized procedure was used to test the ability of other plants to carry out the reaction. In the latter experiment, it was observed that, with regard to stereospecificity, most vegetables tested were poorer reducing agents compared to *D. carota*.

Keywords: Enantioselective reductions; heteroaryl ketones; biocatalysis; *Daucus carota*

Introduction

The transfer of chirality from an optically active catalyst to a prochiral reagent in a chemical reaction ranks among the most fascinating and challenging chemical transformations. Technology developed in this field has been at the forefront of science for several years, and brilliant chemists have been recognized and honored for inventing chemical catalysts capable of efficiently performing the task (*1–3*).

Due to their homochiral nature, biocatalysts are efficient chirality deliverers. Examples of such use of biocatalysts can be traced back to the Baker's yeast (BY) reduction of ketones (*4*), the lipase catalyzed resolution and desymmetrization (*5*), and the aromatic dihydroxylation (*6*), among other applications that have contributed extensively to enrich the available asymmetric toolbox.

Traditionally, biocatalyzed reactions have been sharply divided into two classes – "isolated enzyme catalysis" and "whole-cell biotransformations." Each procedure presents advantages and disadvantages, and the method of choice relies on the particular reaction type to be performed or catalyzed. The isolated enzyme methods make use of biocatalysts obtained from all kinds of living organisms. Therefore, technologically useful enzymes have been isolated from animals, plants, and microorganisms, including bacteria and fungi. On the other hand, whole-cell biotransformations are performed mainly with microorganisms, while other organisms or their parts are not commonly used. Exceptions to this trend are reactions carried out by cultured plant cells, but the method is of limited practical application, or at least not appealing for the chemist not fully trained in culturing techniques. As a matter of fact, at least part of the success of BY among organic chemists is that reactions catalyzed by *Saccharomyces cerevisiae* can be run without any microorganism preculture, and aseptic conditions are not required. Therefore, chemists make use of BY similar to any chemical reagent, adding it directly into the reaction, which is possible because the required biomass is already adequately grown avoiding culture contamination.

Over the 20th century, the fact that plants themselves are an excellent source of biocatalysts has passed mainly unnoticed. Only after 2000, reports on the utilization of crude plant parts for the enzymatic reduction of ketones appeared in the chemistry literature (*7–9*). In particular, the common carrot plant (*Daucus carota*) has been mentioned repeatedly as a valid alternative to the BY reduction of several aryl and aliphatic ketones (*7*,*8*,*10–20*). Although the acting reductase has not been characterized, the reaction is an attractive alternative that can be used in the preparation of several optically pure alcohols, with minimum cost and environmental impact.

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Optically pure building blocks are in continuous demand for the construction of more selective drugs and materials of defined properties. Particularly, heterocyclic compounds are common fragments found in several natural and unnatural bioactive compounds. Herein, we present studies on the reduction of a series of methyl heteroaryl ketones in order to prepare optically enriched alcohols, and generate a small library of optically pure building blocks in a green fashion. We have also tested the ability of other common plants to perform the reduction, and compared the results observed with the corresponding "carrot-catalyzed" reaction.

Results and discussion

Reduction of heteroaryl ketones with D. carota

We previously observed the facile reduction of 2-acetylbenzofurane (**10**) by *D. carota* root fragments (*21*). This ketone is transformed into the corresponding chiral alcohol (**10a**) in <2 h without any starting material remaining in the reaction mixture (Figure 1). The result prompted us to test the ability of carrot and other plants for the reduction of related substrates.

There are a wide variety of reported conditions for the reduction of ketones catalyzed by plant fragments with the majority of the reactions run at room temperature. However, conditions as high as 32°C have been reported (*17*). The media for the reaction is typically water (*7*,*11*,*13*,*14*,*17*), and to a minor extent phosphate buffer (*12*,*20*). The enantioselectivity of the reaction is often high, with reported values of enantiomeric excess close or above those obtained with BY catalyzed reductions. The reported carrot to substrate mass ratio varies from 100/1 to 1000/1, and the addition of sparingly soluble substrates is often performed as a solution in a polar organic solvent. Research on the use of other plants has shown that *D. carota* is often the best reducing agent, but other vegetables can also perform the reaction (*8*,*11*,*12*). Our initial purpose was to study the influence of temperature and amount of reductive agent, in order to optimize the reaction conditions for heterocyclic substrates.

The incubation of ketones **1–11** (Figure 1) with fresh carrot fragments in water furnished, in most cases, the corresponding alcohols, in very good (ee $>$ 93%) to excellent (ee $>$98%) enantiomeric excess. Exceptionally, 2-acetylthiophene (**5**) afforded **5a** in only 28% ee, as determined by chiral GC analysis of the purified reaction products. The high ee values determined for the conversion of most substrates contrasted with the modest results of isolated yield. A standard work-up and isolation procedure of five extractions with ethyl acetate (total volume doubling the water extract) provided a maximum yield of 47% even when total conversion was observed by gas chromatography. Exhaustive extraction of the water solution with organic solvent until no product could be detected in the aqueous phase was performed on the biotransformation of pyridine **1**. By means of this procedure, the isolated yield was raised to 60% (Table 1). The absence of an adequate mass balance suggests that further metabolization of the product or a different reaction on the substrate may be occurring in the reaction media.

We studied the behavior of the reaction as a function of the temperature. Our results showed that running the reaction above 25°C resulted in lower isolated yields. For good substrates such as pyridine **3**, the yield decreased from 47 to 10% when the reaction temperature was raised from 25 to 40°C. For

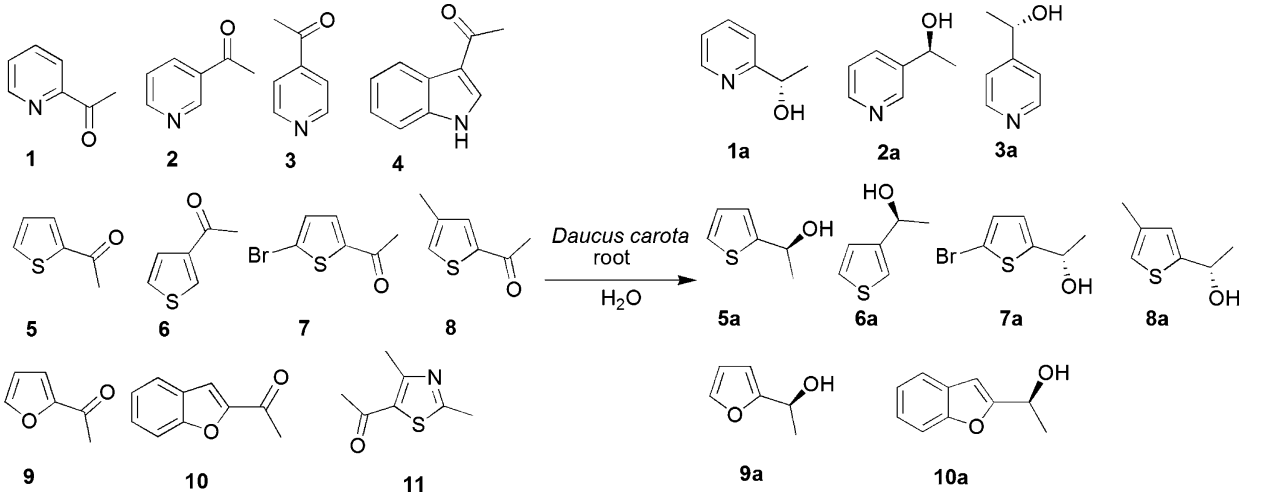

Figure 1. Examples of heteroaryl methyl ketones reduced by plants.

Table 1. Isolated yield and enantiomeric excess of the metabolites.

Entry	Substrate (No.)	Product	Isolated yield (%)	ee (%)†	$(\alpha]_D$ (lit. value)
1	2-Pyridinyl (**1**)	**1a**	47 (60)*	>99	−25 (−25.1) (*22*)
2	3-Pyridinyl (**2**)	**2a**	37	>99	−49 (−39.0) (*23*)
3	4-Pyridinyl (**3**)	**3a**	47	>99	−52.1 (−40.8) (*24*)
4	3-Acetylindol (**4**)	–	–	–	–
5	2-Thienyl (**5**)	**5a**	30	>28	−15.1 (−24.2) (*23,25*)
6	3-Thienyl (**6**)	**6a**	15	>92	−§
7	2-(5-Bromothienyl) (**7**)	**7a**	21	>97	–25.6
8	2-(4-Methylthienyl) (**8**)	**8a**	20	>99	−§
9	2-Furanyl (**9**)	**9a**	10	>93	−§
10	2-Benzofuranyl (**10**)	**10a**	47	>95	−16 (−16.6) (*26*)
11	5-(2,4-Methylthiazolyl) (**11**)	–	–	–	–

†%ee as determined by chiral GC and/or comparison of optical rotation data; ‡isolated yield obtained after exhaustive extraction of the aqueous solution; §insufficient amount of sample for precise [α]D determination. The absolute configuration was assigned by coinjection of the product with an authentic sample of the *S* alcohol obtained by lipase desymmetrization ($[\alpha]_D^{22}$ =–27.3, lit. $[\alpha]_D^{20}$ =–44.7) (*24*).

poor substrates, such as thiophene **5**, the reaction stopped above 30°C (entries 1–6, Table 2). Regarding the carrot/substrate mass ratio, we observed that increasing the amount of *D. carota* increased the reaction rate for all substrates. We tested the reaction of pyridine **3** at three different w/w ratios, and found that the reaction time required to observe complete disappearance of the starting material decreased from 24 to 6 h when the carrot/substrate ratio increased from 100/1 to 500/1 (entries 7–9). For other substrates such as thiophene **5**, the reaction was never completed even after 24 h. Nevertheless, a positive effect on the isolated yield of the reaction was noticed when the carrot/substrate ratio was increased. At 100/1 ratio, the final yield after 24 h was only 5%, while higher ratios increased the yield up to 30% (entries 10–13). Further increasing of the ratio is not practical under laboratory experimental conditions, and also increases the amount of water and organic solvent required.

Screening of reductase activity on various plants

Having optimized these parameters, we investigated the potential of other plants for the reduction of heteroaryl ketones. A similar study has been reported recently by Andrade et al. describing the ability of several plants to reduce acetophenone in moderate yield and good to excellent enantiomeric excess (*8*). Previously, a report by Bruni et al. reported that *D. carota*, *Foeniculum vulgare*, and *Cucurbita pepo* were able to reduce acetophenone in very high enantiomeric excess and diverse yield (*11*). Very recently, Lemos et al. described the use of *Manihot esculenta* and *M. dulcis*, two species of a tropical plant grown in Brazil, for the reduction of several ketones and aldehydes including furfural (*9*). We were

Table 2. Optimization of the reduction of acetyl-heteroaryl ketones under different reaction conditions and carrot/substrate ratios.

Entry	Substrate	Carrot/substrate ratio (w/w)	Temp (°C)	Reaction time (h)	Isolated yield (%)
1	4-Pyridyl (**3**)		25	24	47
2		500/1	30		15
3			40		10
4	2-Thienyl (**5**)	500/1	25	24	10
5			30		5
6			40		0
7	4-Pyridyl (**3**)	100/1	25	24	47
8		200/1		10	47
9		500/1		6	47
10	2-Thienyl (**5**)	100/1	25	24	5
11		200/1			10
12		500/1			10
13		1000/1			30

interested in expanding these studies to heteroaromatic ketones, exploring not only other plants, but also identifying the plant parts (tuber, stem, and fruit) with stronger activity. We chose plants from various genus and families and tested them using the reaction conditions optimized for *D. carota* and 4-acetylpyridine (**3**) as substrate, since it was efficiently reduced by carrot root.

The best results regarding enantioselectivity were provided by the fruit of *C. maxima,* commonly known as pumpkin, and the stem of *F. vulgare* (entries 1 and 4 in Table 3). Both plants rendered the corresponding 4-pyridylethanol (**3a**) in essentially optically pure state. However, the isolated yield of the reactions was lower than that observed by the reaction promoted by carrot root. Interestingly, another variant of the species *C. maxima*, the common marrow plant, did perform the reaction in quite good yields albeit with very poor enantiomeric excess (37% yield, >60% ee). A similar result was observed for the fruit of the related species *C. peppo* (zucchini), which rendered the product in 13% yield and 66% ee (entries 2 and 3). The tuber of *Beta vulgaris* (beet) performed the reaction in acceptable yield, but with modest enantioselectivity, while two plants from the Solanaceae family provided different results. The tuber of *Solanum tuberosum* (potato) reduced the pyridine with very low yield and low stereoselectivity, but the fruit of *S. melongena* (eggplant) did not perform the reaction in detectable yield (entries 5–7). Other plants tested from the Convolvulaceae, Rutaceae and Alliaceae families did not furnish the desired alcohol (entries 8–10).

These primary results indicate that there is not an obvious taxonomic relationship between the reducing power and the plant family. The results are diverse and suggest that *D. carota* possess a differential capacity of performing this reduction. There remains the question about the nature of the actual catalyst, and more detailed studies are needed in this area. Moreover, the role of endophytic microorganisms in these plant-mediated biocatalytic reactions should be further investigated, since microorganisms isolated from carrot root have exhibited remarkable biocatalytic activity (*27*).

Conclusion

The enzymatic reduction of ketones effected by intact plant fragments, and particularly carrot root, is a general reaction and was successfully applied for the first time to a series of methyl heteroaryl ketones rendering, in all the cases, the corresponding *S* alcohol in high ee and moderate isolated yield. To date, all the plant-mediated reductions tested have yielded the Prelog reduction product. A wider screening in order to possibly identify anti-Prelog behavior in other plants remains necessary. We have demonstrated that for the reduction of these types of ketones, the optimal results are obtained at room temperature, and that both the yield and reaction time are strongly dependant on the relative amount of carrot used in the reaction. Other plants tested also exhibited reducing power, but according to these results, only *Curcubita maxima* and *F. vulgare* measure up to *D. carota* regarding enantiomeric excess, and did not render the alcohol in comparable yield.

Experimental section

General methods

Commercial grade ethyl acetate and hexane were purified prior to use. Optical rotations were measured on a Zuzi 412 automatic polarimeter using a 7-ml cell (concentration c given as g/100 ml). Nuclear magnetic resonance spectra were recorded on Bruker Advance DPX-400 instrument with Me_4Si as the internal standard and chloroform-d as solvent unless otherwise indicated. Analytical TLC was performed on silica gel 60F-254 plates and visualized with UV light

Table 3. Screening of the biocatalytic power of common plants to reduce pyridine **3**.

Entry	Family	Plant (common name, part used)	Isolated yield	ee (%)
1	Cucurbitaceae	*Curcubita maxima* (pumpkin, fruit)	27	>98
2	Cucurbitaceae	*Cucurbita maxima* (marrow, fruit)	37	60
3	Cucurbitaceae	*Cucurbita pepo* (zucchini, fruit)	13	66
4	Apiaceae	*Foeniculum vulgare* (fennel, stem)	33	>98
5	Amaranthaceae	*Beta vulgaris* (beet, tuber)	24	80
6	Solanaceae	*Solarium tuberosum* (potato, tuber)	7	50
7	Solanaceae	*Solarium melongena* (eggplant, fruit)	–	–
8	Convolvulaceae	*Ipomoea batatas* (sweet potato, tuber)	–	–
9	Rutaceae	*Citrus X limon* (lemon, fruit)	–	–
10	Alliaceae	*Allium cepa* (onion, tuber)	–	–

(254 nm) and/or anisaldehyde-H_2SO_4-EtOH as the detecting agent. Flash column chromatography was performed using silica gel (Kieselgel 60, EM Reagents, 230–400 mesh). Chiral chromatographic analyses were performed in a HP 5890SII gas chromatograph equipped with a Cyclodex beta 30 m; 0.25 mm ID; 0.25 df column. Conditions: 70°C (2 min) to 130°C (5 min) at 1°C/min, then 10°C/min to 180°C (10 min) using He as the carrier gas.

Optimized procedure of biotransformation

The corresponding ketone (100 mg) was added to a previously prepared suspension of freshly sliced carrot root (10–100 g) in water (30–100 ml). The carrot was prepared as follows: the external layer was removed; the peeled root was washed with sodium hypochlorite (5%), and distilled water. Then it was fractioned into pieces of approximately 3 mm^3 with a food processor. The reaction mixture was incubated in an orbital shaker (150 rpm) at room temperature (otherwise stated) until the conversion was achieved (6–24 h). The suspension was then filtered and centrifuged (10 min, 5000 rpm). The supernatant was extracted with ethyl acetate (3×25 ml); the organic layer was dried (anh. Na_2SO_4), and the solvent was removed under reduced pressure. For the pyridinyl derivatives, the supernatant was acidified (pH = 3) with 10% HCl, and the β-carotene was extracted with ethyl acetate (3×25 ml). Then, the aqueous layer was treated with 10% NaOH until pH = 11, and the product was recovered from the basic aqueous solution with ethyl acetate (3×25 ml). Final purification was performed by flash column chromatography on silica gel using mixtures of ethyl acetates/hexanes as eluent. Identity of compounds was confirmed by analysis of the respective 1H and 13C NMR spectra, chiral GC analysis and optical rotation data.

(1S)-1-pyridin-2-yl-ethanol (1a) (*22*). Yield: 47–60%; GC retention time: 13.41 min; $[\alpha]_D^{22} = -25$ (c 0.60), 1H RMN (400 MHz, $CDCl_3$) $\delta = 1.53$ (d, J = 6.6 Hz, 3H), 3.81 (bs, 1H), 4.92 (q, J = 6.5 Hz, 1H), 7.27 (dd, J = 5.5, 7.0 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.71 (ddd, J = 1.6, 7.7, 7.7 Hz, 1H), 8.55 (d, J = 4.7 Hz, 1H) ppm. 13C RMN (100 MHz, $CDCl_3$): $\delta = 24.6$, 69.2, 120.2, 122.6, 137.3, 148.4, 163.5 ppm.

(1S)-1-pyridin-3-yl-ethanol (2a) (*23*). Yield: 37%; GC retention time: 26.40 min; $[\alpha]_D^{22} = -49$ (c 0.84, $CHCl_3$), 1H RMN (400 MHz, $CDCl_3$) $\delta = 1.49$ (d, J = 6.5 Hz, 3H), 3.90 (bs, 1H), 4.90 (q, J = 6.5 Hz, 1H), 7.25 (dd, J = 4.9, 7.7 Hz, 1H), 7.73 (ddd, J = 1.7, 1.7, 7.9 Hz, 1H), 8.38 (dd, J = 1.6, 4.8 Hz, 1H), 8.47 (d, J = 2.1 Hz, 1H) ppm. 13C RMN (100 MHz, $CDCl_3$): $\delta = 25.6$, 68.0, 123.9, 133.9, 142.0, 147.5, 148.5 ppm.

(1S)-1-pyridin-4-yl-ethanol (3a) (*24*). Yield: 30%; GC retention time: 27.70 min; $[\alpha]_D^{22} = -52.1$ (c 2.9, $CHCl_3$), 1H RMN (400 MHz, $CDCl_3$) $\delta = 1.46$ (d, J = 6.6 Hz, 3H), 4.59 (bs, 1H), 4.86 (q, J = 6.5 Hz, 1H), 7.29 (d, J = 5.8 Hz, 2H), 8.40 (d, J = 4.2, Hz, 2H) ppm. 13C RMN (100 MHz, $CDCl_3$): $\delta = 25.4$, 68.7, 121.0, 149.5, 156.3 ppm.

(1S)-1-thien-2-yl-ethanol (5a) (23,25). Yield: 47%; GC retention time: 17.84 min; $[\alpha]_D^{22} = -15.1$ (c 2.9, $CHCl_3$), 1H RMN (400 MHz, $CDCl_3$) $\delta = 1.63$ (d, J = 6.4 Hz, 3H), 2.00 (bs, 1H), 5.16 (q, J = 6.4 Hz, 1H), 7.26 (dd, J = 1.4, 4.8 Hz, 1H) ppm. 13C RMN (100 MHz, $CDCl_3$): $\delta = 25.7$, 66.6, 123.6, 124.8, 127.1, 150.3 ppm.

(1S)-1-thien-3-yl-ethanol (6a) (*24*). Yield: 15%; GC retention time: 17.84 min; $[\alpha]_D^{22} = -27.3$ (c 1.1, $CHCl_3$),, 1H RMN (400 MHz, $CDCl_3$) $\delta = 1.55$ (d, J = 6.4 Hz, 3H), 1.73 (bs, 1H), 5.00 (q, J = 6.4 Hz, 1H), 7.12 (dd, J = 5.0, 1.0 Hz, 1H), 7.21 (bd, J = 3 Hz, 1H), 7.32 (dd, J = 5.0, 3.0 Hz, 1H) ppm. 13C RMN (100 MHz, $CDCl_3$): $\delta = 147.7$, 126.5, 126.1, 120.6, 67.0, 24.9 ppm.

(1S)-1-(5-bromothien-2-yl)-ethanol (7a). Yield: 20%; GC retention time: 21.19 min; 1H RMN (400 MHz, $CDCl_3$) $\delta = 1.59$ (d, J = 6.4 Hz, 1H), 1.88 (bs, 1H), 5.06 (q, J = 6.5 Hz, 1H), 6.74 (dd, J = 0.8, 3.7 Hz, 2H), 6.92 (d, J = 3.7, Hz, 1H) ppm. 13C RMN (100 MHz, $CDCl_3$): $\delta = 25.5$, 66.9, 111.7, 123.8, 129.8, 151.9 ppm.

(1S)-1-(4-methylthien-2-yl)-ethanol (8a). Yield: 20%; GC retention time: 19.08 min; 1H RMN (400 MHz, $CDCl_3$) $\delta = 1.61$ (d, J = 6.4 Hz, 3H), 1.63 (bs, 1H), 2.25 (s, 3H), 5.09 (q, J = 6.4 Hz, 1H), 6.82 (m, 2H) ppm. 13C RMN (100 MHz, $CDCl_3$): $\delta = 16.1$, 25.5, 66.7, 119.9, 126.0, 137.7, 150.0 ppm.

(1S)-1-(2-furyl)-ethanol (9a). Yield: 10%; GC retention time: 9.58; 1H RMN (400 MHz, $CDCl_3$) $\delta = 1.55$ (d, J = 6.4 Hz, 3H), 1.73 (bs, 1H), 5.00 (q, J = 6.4 Hz, 1H), 7.13 (dd, J = 1.1, 5.0 Hz, 1H), 7.22 (d, J = 2.8, 1H); 7.33 (dd, J = 3.0, 5.0 Hz, 1H) ppm. 13C RMN (100 MHz, $CDCl_3$): $\delta = 24.9$, 66.0, 119.9, 120.6, 126.0, 126.5, 147.7 ppm.

(1S)-1-(1-benzofuran-2-yl)-ethanol (10a) [26]. Yield = 39%; $[\alpha]_D^{22} = -16$ (c = 1.0, $CHCl_3$); *1H NMR (400 MHz, $CDCl_3$)* $\delta = 7.54$ (dd, J = 1.2, 7.4 Hz, 1H), 7.46 (bd, J = 7.5 Hz, 1H), 7.27 (m, 1H), 7.22 (dt, J = 1.1, 7.4 Hz, 1H), 6.60 (s, 1H), 5.01 (q, J = 6.6 Hz, 1H), 2.30 (s, 1H), 1.64 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 160.2$, 154.8, 128.1, 124.1, 122.7, 121.0, 111.2, 101.7, 64.1, 21.4 ppm.

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