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New and Facile Synthesis of Aminobicyclo[2.2.1]heptane-2-carboxylic Acids

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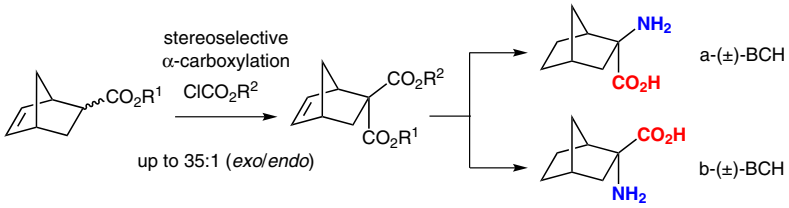

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Abstract A facile approach for the stereoselective synthesis of a- and b-2-aminobicyclo[2.2.1]heptane-2-carboxylic acid is described. Substrate-controlled α-carboxylation of norbonene monoester delivered the asymmetric diester intermediate with high diastereoselectivity (up to 35:1). Sequential chemoselective ester cleavage, Curtius rearrangement, and hydrolysis gave the a- and b-isomers of 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid, respectively.

Key words carbocycles, amino acids, bicyclic compounds, diastereoselectivity, carbonylation

The use of unnatural amino acids as tools for drug discovery research is becoming more important because of their interesting chemical and biological properties.[1] Such compounds have been incorporated into peptides to modify the conformation and enhance the stability of the peptides. Moreover, the modified amino acids and peptides can be more biologically active than the natural analogues. They are capable of acting as enzymatic modulators, by mimicking their natural ligands, while preventing undesired enzymatic reaction by modifying the conformation of the peptide and enhancing resistance to chemical and enzymatic degradation. One of the representative unnatural amino acids is 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (BCH), which bears a norbonane nucleus and α,α-disubstituted α-amino acid. BCH is bulker and more resistant to metabolic enzymes than α-monosubstituted amino acid derivatives. Thus, it is used as an unmetabolizable surrogate for branched-chain amino acids such as valine, leucine, and isoleucine. So far, several potentially useful effects of BCH in biological systems have been reported. It can be used to increase insulin secretion as a selective activator of glutamate dehydrogenase (GDH)[2] and it plays a role in the cell-membrane transport system as an L-amino acid carrier inhibitor.[3]

As shown in Figure 1, there are four stereoisomers of BCH, called a- and b-isomers, in which a- and b- was designated by the group of Christensen according to separation sequence. In pioneering work it was reported that for allosteric activators such as the L-leucine analogue, b-BCH induced insulin release by activating glutamate dehydrogenase. Interestingly, b-(–)-BCH stimulates insulin release from the pancreatic β-cells effectively, whereas their stereoisomers are reported to have weak activity.[4] Given the unique structural features of BCH and its range of biological activities depending on stereochemistry, we sought to develop an efficient and scalable synthetic route to BCH. Herein, we report stereoselective synthesis of a- and b-(±)-BCH through substrate-controlled synthesis of the norbonene diester.

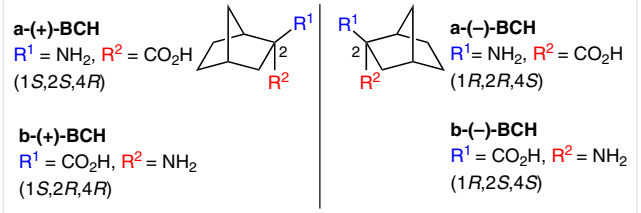
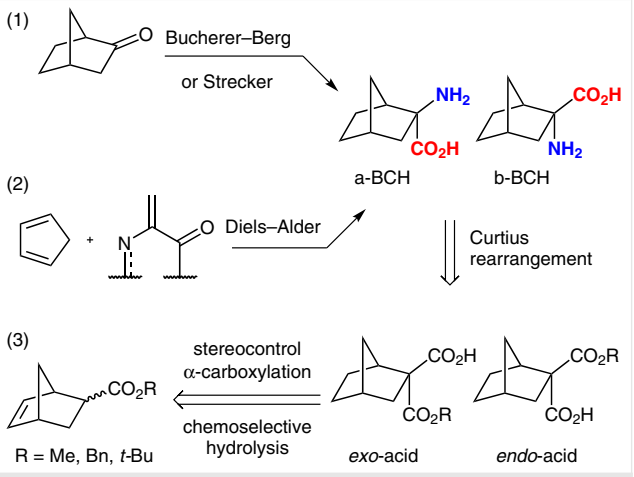


Figure 1 Structures of the four stereoisomers of BCH

Several stereoselective synthetic approaches to 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid and its analogues have been developed. Christensen's group developed the synthesis of both BCH isomers by Bucherer–Berg reaction and Strecker reaction of bicyclo[2.2.1]heptan-2-one.[3a,4d] As evidenced by facile and efficient approaches that have been achieved by using the Diels–Alder reaction with *N*-acyl-α,β-dehydroalaninate and cyclopentadiene,[5]

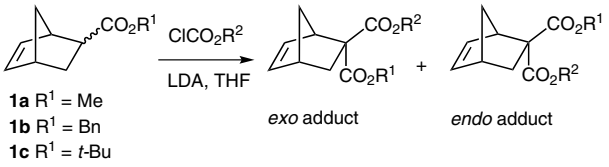
some groups have utilized stereoselective Diels–Alder reactions using a chiral auxiliary and substrate; (i) menthyl 2-acetamidoacrylate,[6] (ii) oxazolone and hydantoin,[7] and (iii) pyrazinone and oxazolidinone[8] along with enantioselective reaction with an organocatalyst.[9] However, separation of the a- and b-isomers of BCH is challenging and the preparation of chiral auxiliaries and catalysts in the previous approaches is not straightforward. In contrast, to our knowledge, fully substrate-controlled direct synthetic methods have not been reported. We envisioned that a- and b-(±)-BCH could be obtained by Curtius rearrangement of the *exo*- and *endo*-acid, respectively, and finally hydrolysis. Our plan for the synthesis of two acid intermediates would be substrate-controlled stereoselective α-carboxylation of 5-norbornene-2-carboxylate, followed by chemoselective hydrolysis of the monoester (Scheme 1).



Scheme 1 Stereoselective synthetic routes to a- and b-BCH

Our study commenced with the preparation of methyl, benzyl, and *tert*-butyl esters **1a**–**c** from commercially available 5-norbornene-2-carboxylic acid under conventional esterification conditions. The resulting esters were obtained as *endo*/*exo* mixtures, and these were used without separation of the stereoisomers. Although it was reported that anionic α-alkylation and acylation in exocyclic compounds such as 5-norbornene-2-carboxylate is *exo*-selective,[10] studies on the stereochemistry and reactivity of substrate-controlled α-carboxylation in which 5-norbornene-2,2-dicarboxylates are generated has not been performed. To differentiate between the two esters chemically and hydrolyze just one ester chemoselectively, electrophiles were selected based on the starting ester **1a**–**c** and thus methyl chloroformate and benzyl chloroformate were chosen as electrophiles. All reactions were carried out by using LDA (1.05 equiv) as base, alkyl chloroformate (1.05 equiv) and anhydrous THF solvent under inert conditions, and two reaction temperatures (–40 and –78 °C) were tested. The results are presented in Table 1. Methyl ester **1a** was transformed into benzyl methyl diester with *exo*/*endo* adduct ratio of 32:1 at –40 °C and 35:1 at –78 °C (entries 1 and 2, respectively). The use of benzyl ester **1b** led to low chemical yield (31 and 38%; entries 3 and 4) compared with methyl ester substrate (77 and 89%; entries 1 and 2), and *tert*-butyl ester **1c** showed relatively low facial selectivity and chemical yields (entries 5–8). Overall, smaller esters gave better chemical yield than bulkier esters, and lower temperature yielded slightly higher chemical yields and increased facial selectivities (*exo*/*endo* ratio).

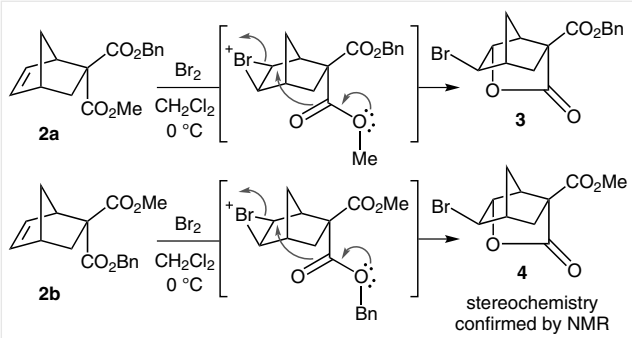
Table 1 Stereoselective Synthesis of Norbornene Diester



Entry	1	R^1	R^2	Temp (°C)	Yield (%)[a]	*exo*/*endo*[b]
1	**1a**	Me	Bn	–40	77	32:1
2	**1a**	Me	Bn	–78	89	35:1
3	**1b**	Bn	Me	–40	31	26:1
4	**1b**	Bn	Me	–78	38	32:1
5	**1c**	*t*-Bu	Me	–40	30	19:1
6	**1c**	*t*-Bu	Me	–78	45	25:1
7	**1c**	*t*-Bu	Bn	–40	23	14:1
8	**1c**	*t*-Bu	Bn	–78	27	22:1

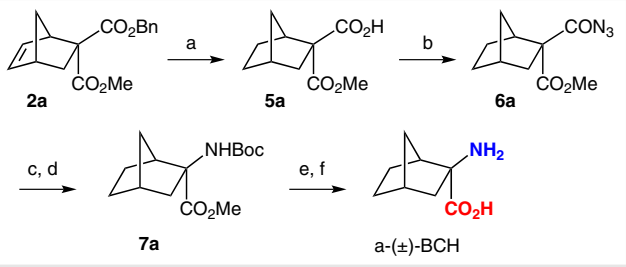
[a] Isolated yield.
[b] Determined by ^{1}H NMR analysis of the total product mixture.

To confirm the stereochemistries of α-carboxylation, the major isolated diester compounds **2a** (*exo* adduct derived from **1a**) and **2b** (*exo* adduct derived from **1b**) were treated with bromine to afford lactones **3** and **4** by bromolactonization.[11] Based on ^{1}H NMR assignment of the resulting lactones, it was concluded that electrophiles favored approach of the upper face of the norbornene enolate to give the *exo* adducts (Scheme 2).

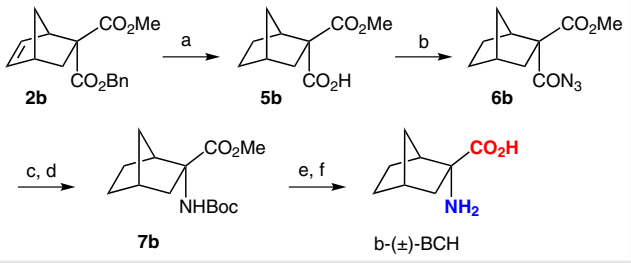


Scheme 2 Stereochemistry confirmation through bromolactonization

With diesters **2a** and **2b** in hand, we turned our attention to the preparation of a-(±)-BCH and b-(±)-BCH, respectively. Stereoselective synthesis of a-(±)-BCH is illustrated in Scheme 3.[12] Under hydrogenation conditions, benzyl methyl diester **2a**, which was prepared through α-carboxylation of methyl ester by using benzyl chloroformate (Table 1, entry 2), was easily converted into the corresponding saturated mono-ester **5a**. Acyl azide **6a** was generated by using DPPA,[13] followed by Curtius rearrangement[14] to afford the isocyanate intermediate, which was used in the next step without further purification. *N*-Boc-protected amino ester compound **7a** was easily generated by treatment with *t*-BuONa/*t*-BuOH in good chemical yield. Finally, hydrolysis of the methyl ester of **7a** followed by Boc-deprotection gave the desired a-(±)-BCH compound. Similarly, b-(±)-BCH was synthesized from **2b** by using the same synthetic process described for a-(±)-BCH (Scheme 4). The concise and scalable synthesis of b-(±)-BCH was thus accomplished in six steps with 64% overall yield.



Scheme 3 Synthesis of a-(±)-BCH from diester **2a**. *Reagents and conditions*: (a) Pd/C, H_2, EtOAc, r.t., 99%; (b) DPPA, Et_3N, anhydrous CH_2Cl_2, r.t., 94% (c) toluene, reflux; (d) *t*-BuONa, *t*-BuOH, r.t. 72% for two steps; (e) KOH, H_2O, reflux; (f) 4 M HCl in 1,4-dioxane, r.t., 81% for two steps.



Scheme 4 Synthesis of b-(±)-BCH from diester **2b**. *Reagents and conditions*: (a) Pd/C, H_2, EtOAc, r.t., 99%; (b) DPPA, Et_3N, anhydrous CH_2Cl_2, r.t., 99%; (c) toluene, reflux; (d) *t*-BuONa, *t*-BuOH, r.t., 76% for two steps; (e) KOH, H_2O, reflux; (f) 4 M HCl in 1,4-dioxane, r.t., 86% for two steps.

In conclusion, we have established a facile and practical synthesis of 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (BCH) from readily available *exo*-predominant (up to *exo*/*endo* ratio 35:1) norbornene diester compounds, which were generated by substrate-controlled stereoselective α-carboxylation. Both high diastereoselectivity and chemical yield make this approach a practical route for the large-scale synthesis of BCH. Further studies on the synthesis of BCH analogues and their biological evaluation are underway and the results will be reported in due course.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378690.

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(12) **Representative procedure for the preparation of a,b-(±)-BCH. (*endo*,*exo*)-Methyl Bicyclo[2.2.1]hept-5-ene-2-carboxylate (1a)**

To a solution of 5-norbornene-2-carboxylic acid (50.67 mmol, 7.00 g; predominantly *endo* mixture) in anhydrous CH_2Cl_2 (150 ml), oxalyl chloride (5.2 mL, 60.80 mmol) and DMF (390 µL, 5.07 mmol) were added at 0 °C under inert conditions. The reaction slowly warm to r.t. and stirred for 12 h at ambient temperature. The resulting solution was maintained at 0 °C and then anhydrous MeOH (4.10 mL, 101.33 mmol) and Et_3N (10.6 mL, 76.00 mmol) were added at 0 °C. The reaction mixture was allowed to ambient temperature and stirred for 6 h. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (1000 mL), washed with H_2O (700 mL), dried over $MgSO_4$, filtered, and the solvent was concentrated in vacuo. The residue was purified by flash column chromatography (hexanes–EtOAc, 20:1) to give ester compound (5.92 g, 77%) as a colorless oil.

***endo*-1a** (major): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.20–6.19 (dd, *J* = 3.6, 6.0 Hz, 1 H), 5.94–5.92 (dd, *J* = 6.0, 3.0 Hz, 1 H), 3.63 (s, 3 H), 3.20–3.20 (d, *J* = 0.6 Hz, 1 H), 2.97–2.94 (td, *J* = 3.6, 9.6 Hz, 1 H), 2.91 (s, 1 H), 1.94–1.89 (m, 1 H), 1.44–1.41 (m, 2 H), 1.28–1.27 (d, *J* = 8.4 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.28, 137.75, 132.37, 51.48, 49.61, 45.66, 43.17, 42.51, 29.25 ppm.

***exo*-1a** (minor): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.15–6.13 (dd, *J* = 5.4, 5.4 Hz, 1 H), 6.11–6.10 (dd, *J* = 5.4, 5.4 Hz, 1 H), 3.69 (s, 3 H), 3.04–3.04 (d, *J* = 0.6 Hz, 1 H), 2.92 (s, 1 H), 2.24–2.22, (dd, *J* = 4.8, 10.8 Hz, 1 H), 1.94–1.91 (m, 1 H), 1.54–1.52 (d, *J* = 9 Hz, 1 H), 1.39–1.35 (m, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.76, 138.05, 135.73, 51.71, 46.57, 46.36, 42.98, 41.62, 29.25 ppm.

2-Benzyl 2-Methyl Bicyclo[2.2.1]hept-5-ene-2,2-dicarboxylate (2a)

To a solution of (endo/exo)-**1a** (8.39 g, 55.13 mmol) in anhydrous THF (150 mL), LDA (2.0 M solution in THF, 28.9 mL, 57.88 mmol) and benzyl chloroformate (8.26 mL, 57.88 mmol) was slowly added at –78 °C and then stirred for 72 h. The reaction mixture was quenched with sat. NH_4Cl and slowly warmed to r.t. The solvent was removed in vacuo and the residue was diluted with EtOAc (1000 mL), washed with H_2O (700 mL), dried over $MgSO_4$ and filtered. The residue was purified by flash column chromatography (hexanes–EtOAc, 100:1) to give diester compound **2a** (14.02 g, 89%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 5 H), 6.27–6.26 (dd, *J* = 3.0, 5.4 Hz, 1 H), 5.99–5.98 (dd, *J* = 3.0, 5.4 Hz, 1 H), 5.23–5.21 (d, *J* = 12.6 Hz, 1 H), 5.16–5.14 (d, *J* = 12.6 Hz, 1 H), 3.60 (s, 3 H), 3.42–3.42 (d, *J* = 0.6 Hz, 1 H), 2.92 (s, 1 H) 2.14–2.12 (dd, *J* = 3.6, 12.6 Hz, 1 H), 2.03–2.00 (dd, *J* = 3.0, 12.6 Hz, 1 H), 1.65–1.64 (d, *J* = 9.0 Hz, 1 H), 1.52–1.51 (dd, *J* = 1.2, 9.0 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.29, 171.31, 139.82, 135.71, 133.45, 128.51, 128.21, 127.84, 66.96, 60.30, 52.28, 49.80, 48.80, 48.77, 42.03, 35.86 ppm.

2-(Methoxycarbonyl)bicyclo[2.2.1]heptane-2-carboxylic acid (5a)

To a solution of diester compound **2a** (300 mg, 1.05 mmol) in EtOAc (5 mL), 10% Pd/C (30 mg, 10 wt.%) was added under an inert atmosphere and the mixture was hydrogenated at 1 atm for 3 h. After completion of the reaction, the catalyst was removed by filtration through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes–EtOAc, 20:1 to 1:1) to give desired compound **5a** (205 mg, 99%) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.75 (s, 3H), 2.86–2.84 (d, *J* = 3.6 Hz, 1 H), 2.31–2.29 (dd, *J* = 3.0, 13.2 Hz, 2 H), 1.93–1.90 (m, 1 H), 1.66–1.65 (m, 1 H), 1.56–1.46 (m, 2 H), 1.41–1.38 (m, 1 H), 1.31–1.27 (m, 1 H), 1.15–1.11 (m, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.81, 171.50, 61.17, 52.68, 43.94, 39.40, 38.55, 36.35, 27.61, 25.23 ppm.

Methyl 2-(Azidocarbonyl)bicyclo[2.2.1]heptane-2-carboxylate (6a)

To a solution of acid compound 5a (205mg, 1.03 mmol) in CH_2Cl_2 (5 mL), diphenylphosphoryl azide (268 µL, 1.24 mmol) and Et_3N (173 µL, 1.24 mmol) were added at ambient temperature and stirred for 12 h. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (120 mL), washed with H_2O (80 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes–EtOAc, 50:1) to give the desired acyl azide **6a** (216 g, 94%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.75 (s, 3 H), 2.89–2.89 (d, *J* = 3.0 Hz, 1 H), 2.32–2.31 (t, *J* = 3.9 Hz, 1 H), 2.26–2.23 (dd, *J* = 3.0, 13.2 Hz, 1 H), 1.83–1.80 (m, 1 H), 1.56–1.46 (m, 3 H), 1.41–1.38 (m, 1 H), 1.30–1.26 (m, 1 H), 1.13–1.09 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.98, 170.74, 63.29, 52.77, 43.46, 39.49, 38.76, 36.55, 27.61, 25.09 ppm.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]bicyclo[2.2.1]heptane-2-carboxylate (7a)

The acyl azide compound **6a** (202 mg, 1.02 mmol) was diluted with anhydrous toluene (4 mL) and refluxed for 1 h. After completion of the reaction, solvent was removed under reduced pressure. The isocyanate intermediate was used in the next step without further purification. To a solution of isocyanate compound in *t*-BuOH (4 mL), NaO*t*-Bu (147 mg, 1.53 mmol) was added and stirred for 30 min at ambient temperature. After completion of the reaction, the reaction mixture was quenched with sat. NH_4Cl solution, and concentrated in vacuo. The reaction mixture was diluted with EtOAc (100 mL), washed with brine (70 mL), dried over $MgSO_4$, filtered, and the solvent was concentrated in vacuo. The residue was purified by flash column chromatography (hexanes–EtOAc, 10:1) to give the desired *N*-Boc amino ester compound **7a** (198 mg, 72% over 2 steps) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.96 (s, 1 H), 3.71 (s, 3 H), 2.45–2.42 (d, *J* = 12.6 Hz, 1 H), 2.34 (s, 1 H), 2.15–2.15 (d, *J* = 3.0 Hz, 1 H), 1.81–1.79 (m, 1 H), 1.69–1.67 (d, *J* = 14.4 Hz, 1 H), 1.53–1.47 (m, 1 H), 1.43–1.37 (m, 1 H), 1.40 (s, 9 H), 1.35–1.30 (m, 2 H),

1.21–1.18 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.86, 154.87, 79.91, 66.50, 52.07, 47.14, 42.82, 38.28, 37.21, 28.24, 27.23, 24.23 ppm.

(±)-2-Aminobicyclo[2.2.1]heptane-2-carboxylic acid (a-(±)-BCH)

To a solution of amino ester compound **7a** in H_2O (5 mL), solid KOH (79 mg, 1.41) was added at ambient temperature and then heated to reflux for 12 h. After cooling the reaction mixture to ambient temperature, the reaction mixture was concentrated in vacuo, treated with 4 M HCl in 1,4-dioxane (5 mL), and stirred at ambient temperature for 12 h. After completion of the reaction, the reaction mixture was concentrated in vacuo, purified by DOWEX®-50WX8 ion-exchange resin column chromatography to give the desired amino acid compound **a-BCH** (90 mg, 81% over 2 steps) as an ivory solid.

^{1}H NMR (600 MHz, D_2O): δ = 2.32 (s, 2 H), 2.06–2.04 (dd, *J* = 1.2, 13.2 Hz, 1 H), 1.59–1.57 (d, *J* = 10.8 Hz, 1 H), 1.48–1.35 (m, 4 H), 1.29–1.25 (m, 1 H), 1.19–1.15 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.87, 68.10, 45.55, 38.77, 37.04, 37.02, 26.15, 23.88 ppm.

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