Electronic Supplementary Information

Sustainable synthesis of 1,2,3,4-cyclohexanetetracarboxylate from sugar-derived carboxylic acids

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Materials

All chemicals were of analytical grade and used as received unless otherwise indicated. *trans,trans*-Muconic acid (*tt*MA, 98 %) and dimethyl fumarate (99 %) were purchased from Tokyo Chemical Industry Co., Ltd.. Pd/C (5 wt%) was provided by Aladdin industrial Inc. Raney Ni (RTH-2110) was purchased from Dalian Tongyong Chemical Co., Ltd.. 1,2,4,5-Tetramethylbenzene (99.0%) was purchased from Acros Organics. Concentrated sulfuric acid (98 wt%) and *n*-octane were purchased from Tianjin Kemiou Chemical Reagent Co., Ltd.. Anhydrous methanol, ethanol and 1,4-dioxane were purchased from Shanghai Chemical Reagent, Inc. of the Chinese Medicine Group.

Experiments

Synthesis of dimethyl *trans,trans*-muconate (*tt*DMM): The mixture of *tt*MA (0.50 g), absolute methanol (50 mL) and concentrated sulfuric acid (0.2 mL, 1.86 g mL^{-1}) were added into a 100 mL round-bottom flask and the reaction system was kept refluxing for 24 hours. As soon as the reaction stopped, the solution was cooled down to room temperature and stayed overnight. The white crystal was precipitated out and washed with cold water several times. The solid product was obtained after filtration. The part of filter liquor was concentrated by rotary evaporation to give dark yellow liquid and diluted with ethyl acetate. Saturated NaCl solution was used to extract sulfuric acid, anhydrous sodium sulfate was introduced to absorb the small amount of water followed by solvent removed. After collecting the two parts of solid product and vacuum drying at 40 °C for 24 h, the yield of *tt*DMM was more than 95%. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37-7.29 (m, 2H), 6.26-6.17 (m, 2H), 3.79 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.27, 140.88, 128.03, 51.92 ppm.

Diels-Alder reaction of *tt*DMM with dimethyl fumarate: A mixture of *tt*DMM (0.05 mmol), dimethyl fumarate (0.15 mmol) and 1,4-dioxane (0.5 mL) was added into a 15 mL glass vial. The

vial was purged with argon for 15 min in glovebox and immersed into a preheated oil bath. After reacting for 4 h at 500 rpm, the reactor was cooled to room temperature and a certain amount of internal standard 1,2,4,5-tetramethylbenzene was added. The sample was diluted with 1,4-dioxane and then uniformized the solution by ultrasonic dispersion. Qualitative and quantitative analysis were analyzed by GC-MS and GC, respectively.

Synthesis of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate: In a 15 mL glass vial, a mixture of dimethyl *trans,trans*-muconate (1.0 mmol), dimethyl (3.0 mmol) and *n*-octane (0.5 mL) was added. The vial was purged with argon for 15 min in glovebox and immersed into a preheated oil bath. After reacting at 180 °C for 4 h at 500 rpm, the reactor was cooled to room temperature. And part of product was precipitated out and dissolved completely with 1,4-dioxane. After removing the solvent by rotary evaporation, the solid product was redissolved by a small amount of ethyl acetate and isolated by column chromatography (Gradient eluent, hexane/ethyl acetate (v/v) = 100/20-100/40). The yields of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate were 95.5%. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.03 (ddd, J=10.1, 4.8, 2.6, 1H), 5.91 (dt, J=10.1, 2.4, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.60 (dt, J=7.3, 2.4, 1H), 3.59-3.54 (m, 1H), 3.48 (dq, J=8.2, 2.6, 1H), 3.23 ppm (dd, J=9.7, 5.6, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 174.37, 171.79, 171.72, 171.18, 125.30, 124.47, 52.43, 52.36, 52.31, 52.23, 44.75, 42.10, 41.41, 40.66 ppm.

Simultaneous dehydrogenation and hydrogenation of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate: In a 15 mL glass vial, tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate (0.1 mmol), 5% Pd/C (5 mol% to substrate) and *n*-octane (0.5 mL) were added. The dehydrogenation was conducted at under argon atomosphere. After reacting at 220 °C for a definite time, the vial was cooled to room temperature and a certain amount of internal standard was added. The sample was diluted with 1,4-dioxane and then uniformized the solution by ultrasonic dispersion. Qualitative and quantitative analysis were analyzed by GC-MS and GC, respectively.

Hydrogenation of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate: A mixture of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate (0.1 mmol), Raney Ni (0.02 g) and 1,4-dioxane (1.0 mL) were added into a 5 mL stainless steel autoclave. The reactor was purged with argon and hydrogen, respectively. The hydrogenation reaction was conducted at room temperature for 24 h under 10 bar hydrogen. A certain amount of internal standard was added and then diluted with 1,4-dioxane. Qualitative and quantitative analysis were analyzed by GC-MS and GC, respectively. In another batch of experiments, the reaction solution was vapored to remove solvent after catalyst separation and the obtained solid mixtures were also identified by NMR. **Qualitative and quantitative analysis**: The identification of individual liquid product was carried by gas

chromatograph-mass spectra (Agilent 7890A/5975C) system (70 eve electron-impact ion source) equipped with an Agilent 19091s-433 capillary column (30 m × 250 μm × 0.25μm). The separated products were also analyzed by NMR. The liquid products were quantified by a gas chromatograph (Agilent 7890A) system equipped with an Agilent 19091j-323 hp-5 capillary column (30 m × 250 μm × 0.25 μm) on the basis of internal standard calibration curve and 1,2,4,5-tetramethylbenzene was used as the internal standard. The conversion of substrates and the selectivity of products were calculated as below:

$$\text{Conversion of substrate} = \frac{\text{the amount of substrate unreacted}}{\text{the amount of substrate loaded}} \times 100\%$$

$$\text{Selectivity of product} = \frac{\text{the amount of product detected}}{\text{the amount of substrate reacted}} \times 100\%$$

$$\text{Yield of product} = \frac{\text{the amount of product detected}}{\text{the } theoretical \text{ amount of product}} \times 100\%$$
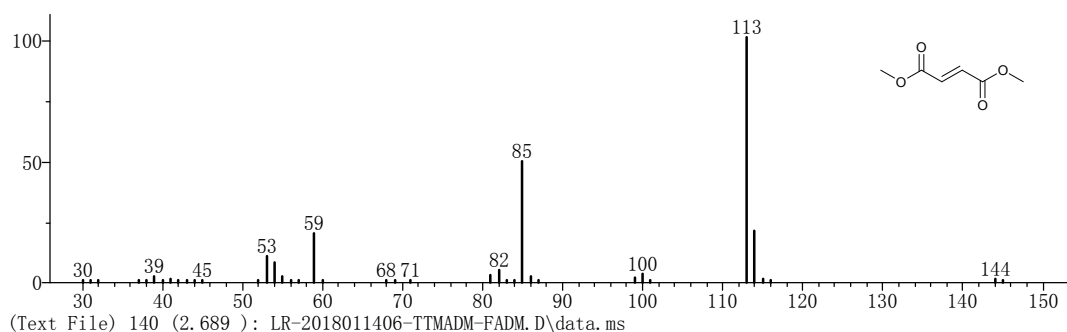
Experimental results

The GC-MS analysis for the Diels-Alder reaction of dimethyl *trans,trans*-muconate and dimethyl fumarate

The Diels-Alder reaction of dimethyl *trans,trans*-muconate (*tt*DMM) and dimethyl fumarate was detected by GC-MS. Tetramethyl cyclohexene-1,2,3,4-tetracarboxylate was the main product and a small amount of isomers of cycloadduct were also detected (Fig. S1). The mass spectra of dimethyl fumarate, *tt*DMM and tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate were presented in Fig. S2, Fig. S3 and Fig. S4, respectively.
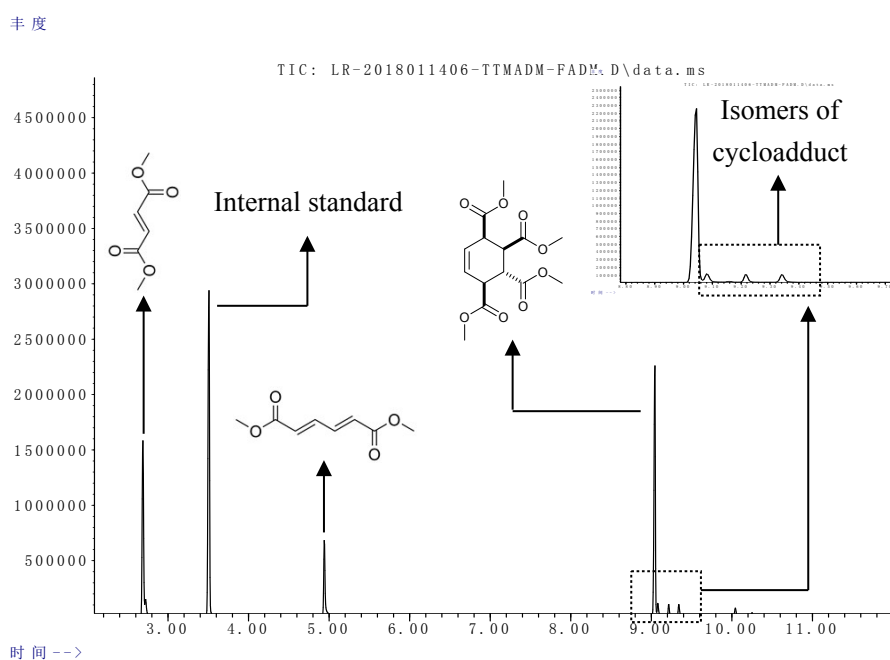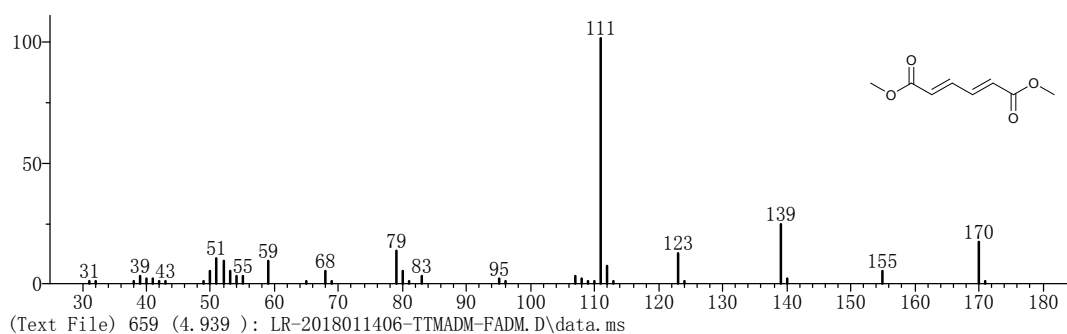

**Fig. S1** Typical total ion chromatogram (TIC) spectrum for the Diels-Alder reaction of dimethyl

trans,trans-muconate and dimethyl fumarate.

(Text File) 140 (2.689): LR-2018011406-TTMADM-FADM.D\data.ms

Fig. S2 Mass spectrum of dimethyl fumarate. MS (70 eV): m/z (%) 144 (1) [M$^+$], 114 (21), 113 (100), 85 (49), 59 (20), 53 (11), 39 (2).

(Text File) 659 (4.939): LR-2018011406-TTMADM-FADM.D\data.ms

Fig. S3 Mass spectrum of dimethyl *trans,trans*-muconate. MS (70 eV): m/z (%) 170 (17) [M$^+$], 155 (5), 139 (34), 123 (12), 111 (100), 79 (13), 59 (9), 51 (10), 39 (3).


(Text File) 1606 (9.045): LR-2018011406-TTMADM-FADM.D\data.ms
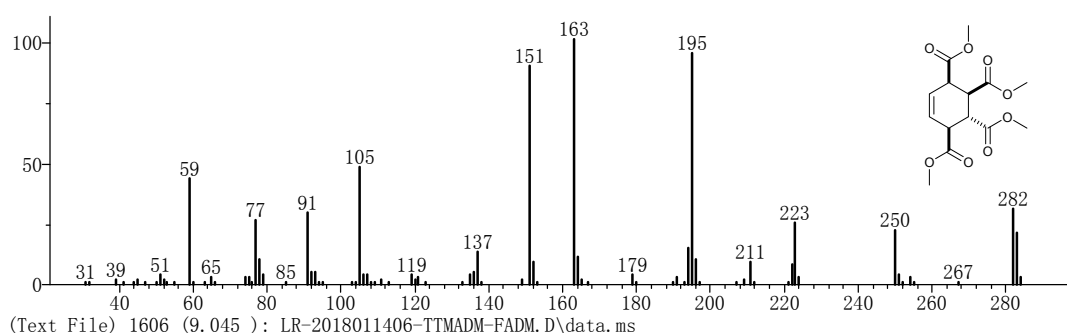
Fig. S4 Mass spectrum of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate. MS (70 eV): m/z (%) 314 (0) [M$^+$], 283 (21), 282 (31), 250 (22), 223 (25), 195 (94), 163 (100), 151 (69), 137 (13), 105 (48), 91 (29), 77 (26), 59 (43), 39 (2).

The effect of atomosphere on the Diels-Alder reaction of dimethyl *trans,trans*-muconate and dimethyl fumarate
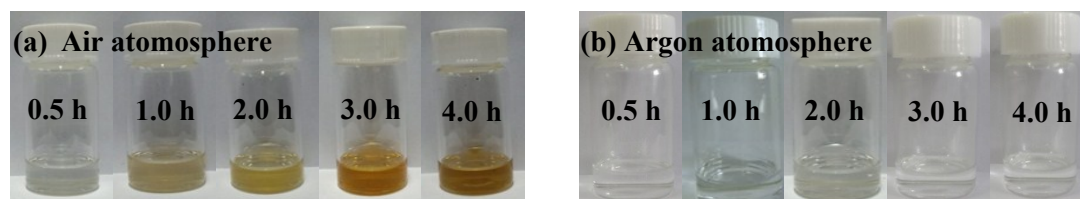
Fig. S5 The reaction solutions of Diels-Alder reaction of dimethyl *trans,trans*-muconate and dimethyl fumarate in air (**a**) and argon (**b**) atomosphere.

Fig. S5 showed the reaction solutions of Diels-Alder reaction of dimethyl *trans,trans*-muconate and dimethyl fumarate in air (**a**) or argon (**b**) atomosphere, respectively. As reaction time was prolonged, the color of solution changed from colorless to brown after reacting in air while kept almost unchanged in argon. Combined with the final results, some side reactions such as oligomerization reaction of the substrates might exist in air atomosphere.
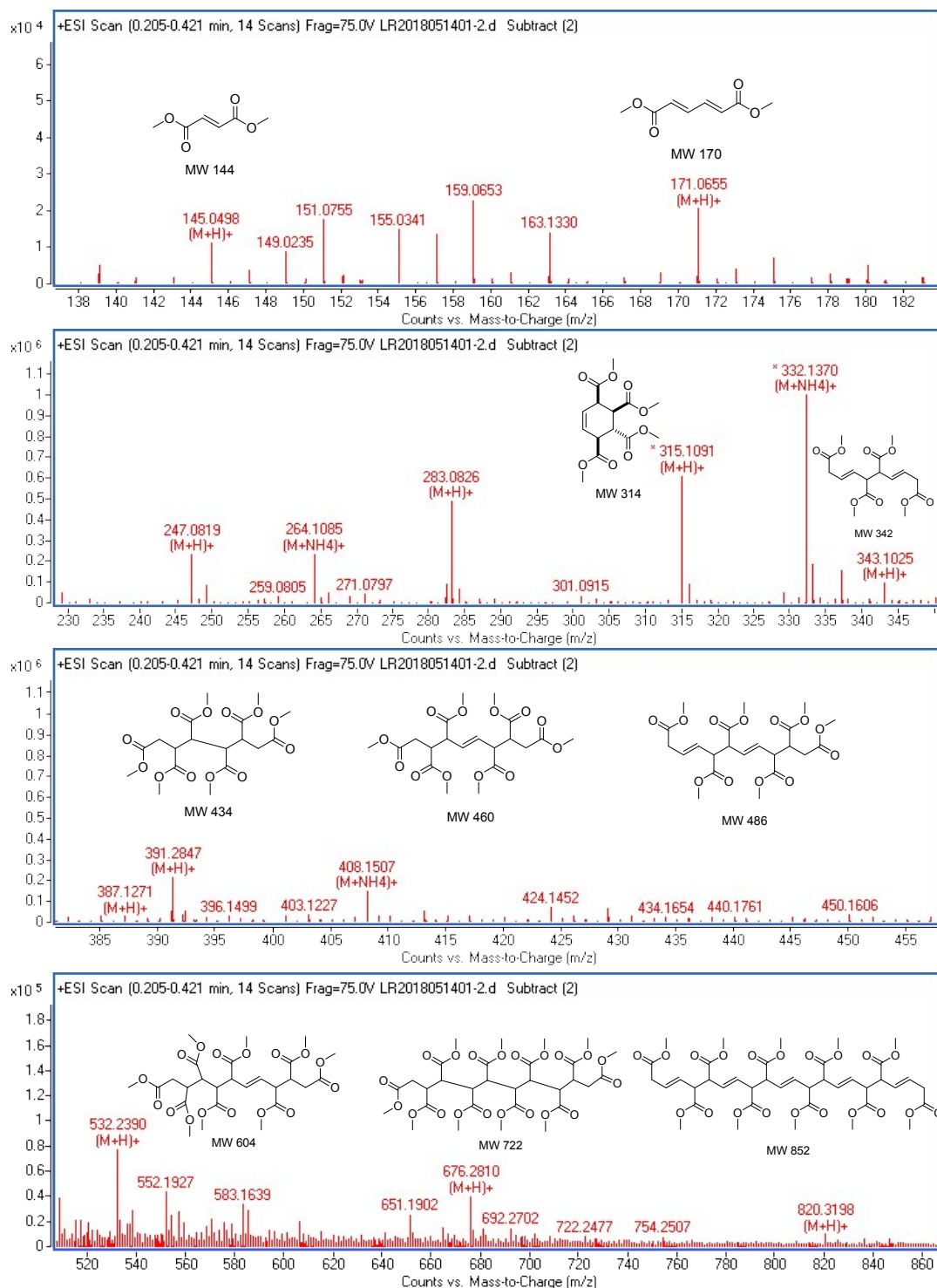
Fig. S6 The LC-QTOF-MS analysis for the reaction solution of Diels-Alder reaction between dimethyl *trans,trans*-muconate and dimethyl fumarate in air for 4 h.

It was clear to see that the color of solution turned brown after reacting for 4 h in air atomosphere. The reaction solution was analyzed by UHPLC-Q-TOF/MS and some unreacted substrates and cycloadduct were detected. It could be predicted that some oligomers were formed based on the fragments and possible structure were also provided in Fig. S6. There have also been some reports on the radical polymerization of muconate[1] and fumarate[2] in the literatures to support us speculation.

NMR spectra of dimethyl *trans,trans*-muconate
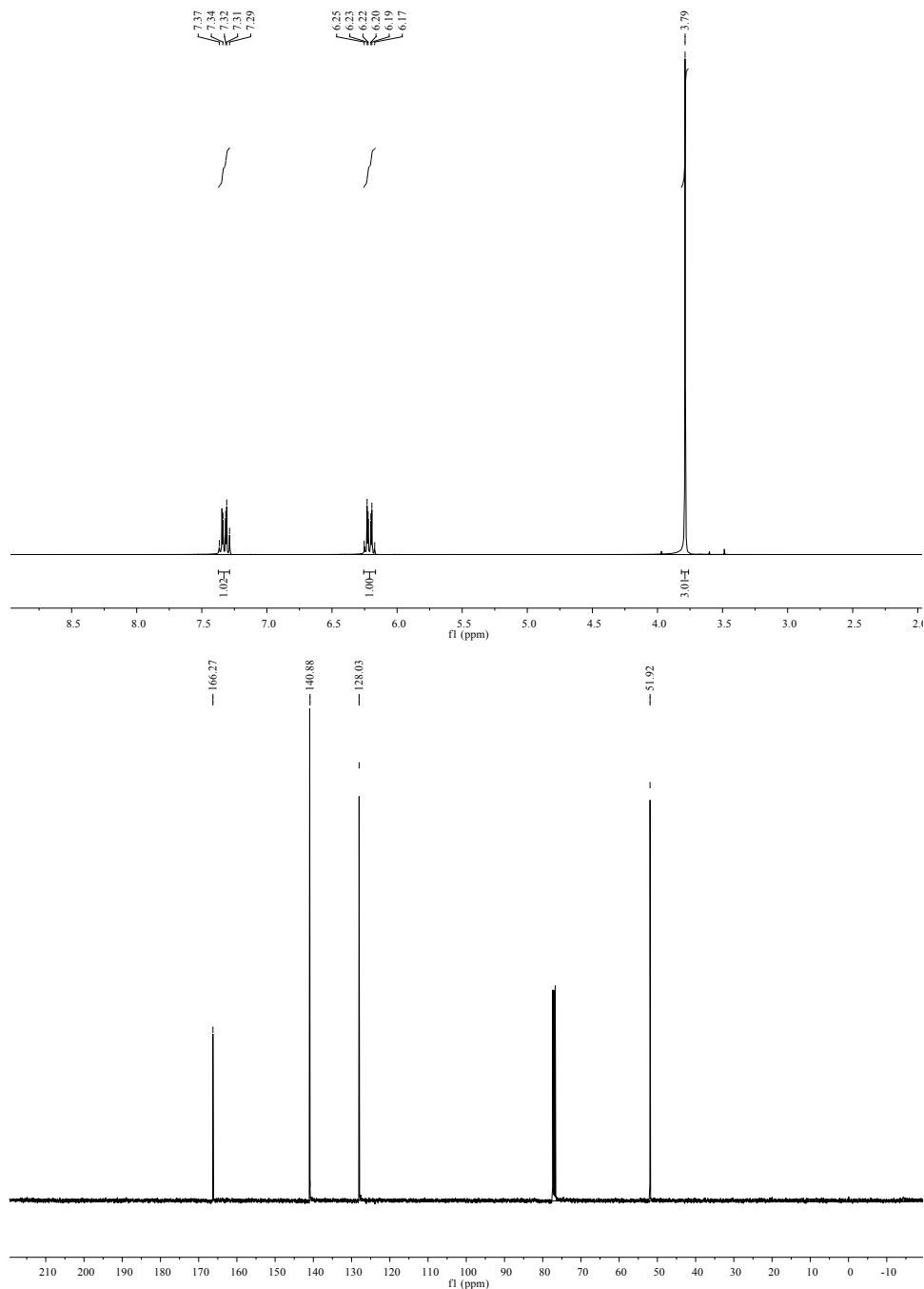
Fig. S7 The ^{1}H and ^{13}C NMR spectra of dimethyl *trans,trans*-muconate in CDCl$_3$ (400 M)

NMR spectra of cycloadduct tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate
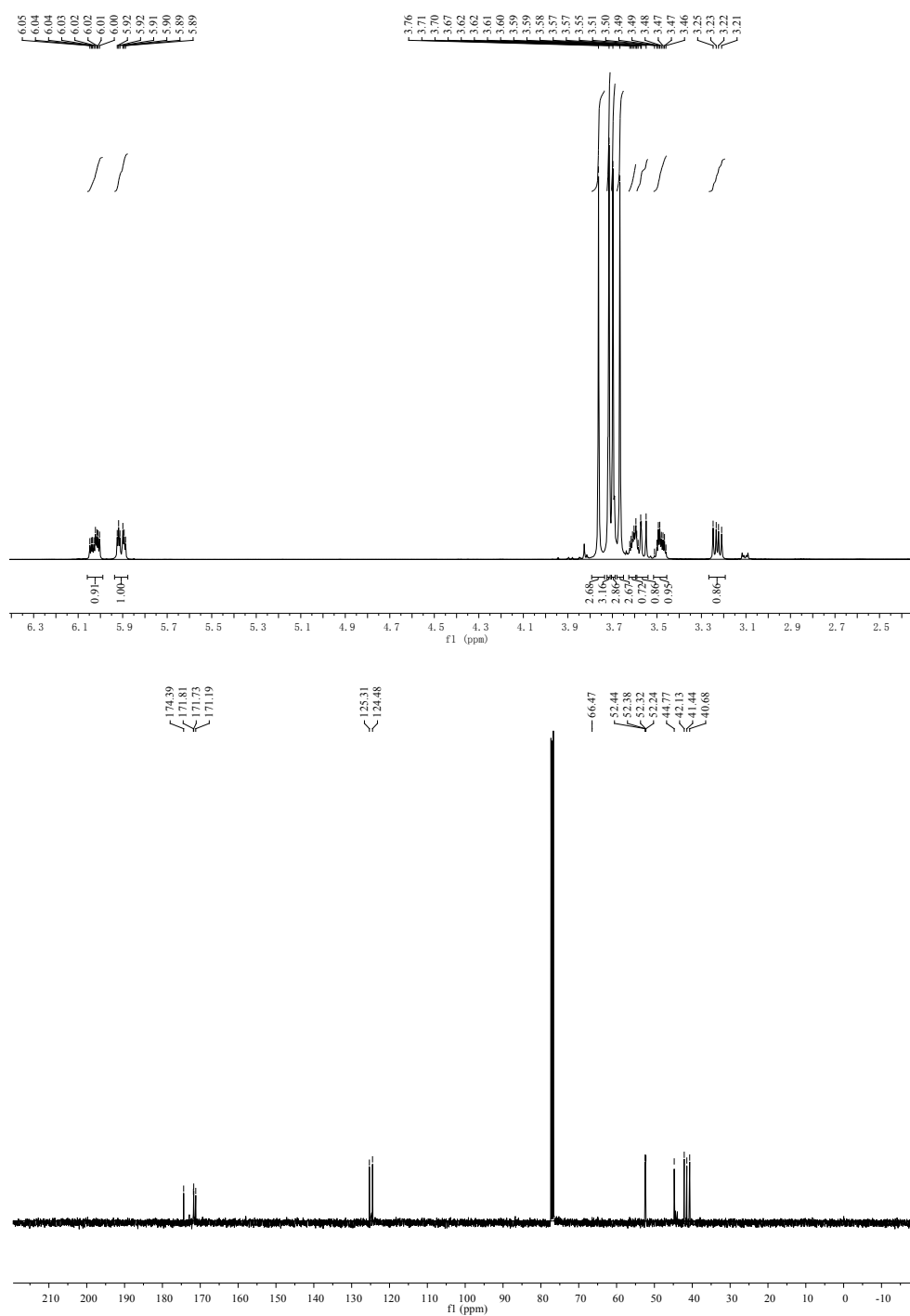
Fig. S8 The ^1H and ^{13}C NMR spectra of cycloadduct tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate CDCl$_3$ (400 M)

The NMR spectra of dimethyl *trans,trans*-muconate and tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate were illustrated in Fig. S7 and Fig. S8, respectively.

Table S1 The Diels-Alder reaction of dimethyl *trans,trans*-muconate (*tt*DMM) and dimethyl fumarate in deionized water and methanol[a]

Entry	Solvent	Conversion of *tt*DMM (%)	Selectivity of cycloadduct[b] (%)	Yield of cycloadduct[b] (%)
1	Deionized water	86.2	5.0	4.3
2	Methanol	80.3	59.4	47.7

[a] Reaction condition: *tt*DMM (0.05 mmol), dimethyl fumarate (0.015 mmol), solvent (0.5 mL), 150 °C, 4 h, argon atomosphere. [b] The selectivity of cycloadduct was calculated according to the input amount of *tt*DMM and the yield of cycloadduct was based on the molar ratio of the detected amount to the theoretical value.

The selectivity of the target cycloadduct in such solvents as deionized water and methanol was much lower. So 1,4-dioxane and *n*-octane were selected as solvent in the work.

Simultaneous synthesis of tetramethyl 1,2,3,4-cyclohexanetetracarboxylate and tetramethyl 1,2,3,4-prehnitate catalyzed by Pd/C
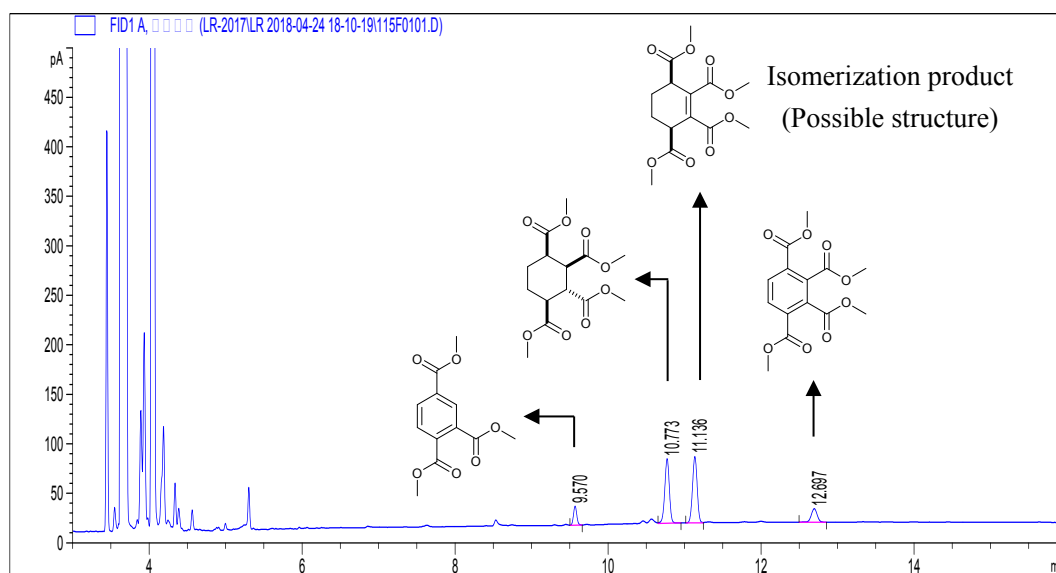
Fig. S9 The GC spectrum for the reaction of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate catalyzed by Pd/C under argon atomosphere. Reaction condition: 15 mL glass vial, substrate (0.1 mmol), 5% Pd/C (5 mol% to substrate), *n*-octane (0.5 mL), 220 °C, 4 h, argon atomosphere.
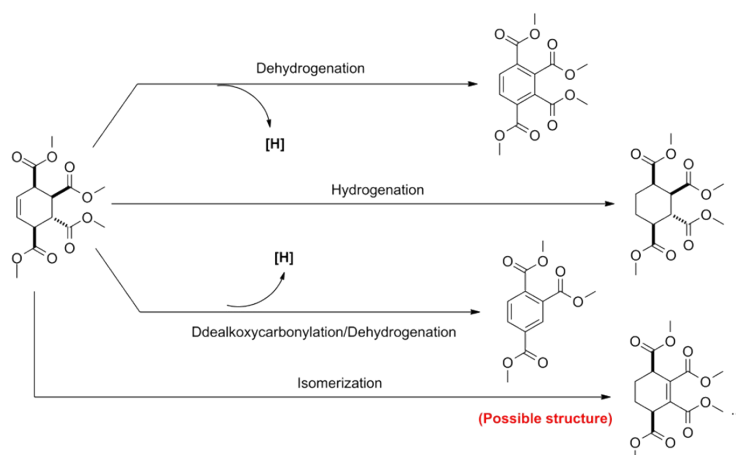
Fig. S10 The predicted reaction path for the reaction of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate catalyzed by Pd/C under argon atomosphere.

From the spectrum in Fig. S9, the products also included isomerization product of substrate and trimethyl trimellitate except tetramethyl 1,2,3,4-cyclohexanetetracarboxylate and tetramethyl 1,2,3,4-prehnitate. Therefore, the reaction path could be predicted as follows: the C=C isomerization reaction of substrate might proceed easily and another part of the substrate underwent dehydrogenation to tetramethyl 1,2,3,4-prehnitate. The dealkoxycarbonylation reaction of part substrate was also existed and trimethyl trimellitate was obtained through subsequent dehydrogenation. The hydrogen generated from dehydrogenation reaction could be added to C=C bond of the substrate again and tetramethyl 1,2,3,4-cyclohexanetetracarboxylate was formed.

Hydrogenation reaction of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate catalyzed by commercial Raney Ni
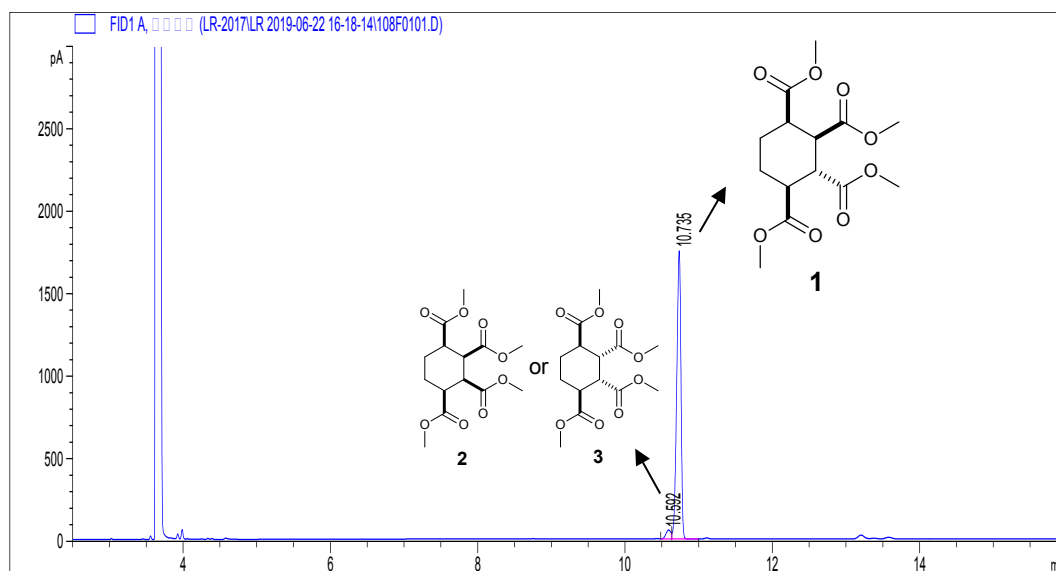

Fig. S11 The GC spectrum for hydrogenation of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate. Reaction condition: 5 mL stainless steel autoclave, substrate (0.1 mmol), Raney Ni (0.02 g), 1,4-dioxane (1.0 mL), room temperature, 24 h, 10 bar H_2.

The hydrogenation of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate was conducted under 10 bar H_2 catalyzed by Raney Ni under room temperature. The liquid products were quantified by GC analysis (Fig. S11). The main product was tetramethyl 1,2,3,4-cyclohexanetetracarboxylate (**1**)

and a small amount of other products could be detected. In another batch of experiments under the same condition, the obtained solid mixtures were analyzed directly by ^{1}H and ^{13}C NMR after the reaction solution was vapored to remove solvent after catalyst separation (Fig. S12).
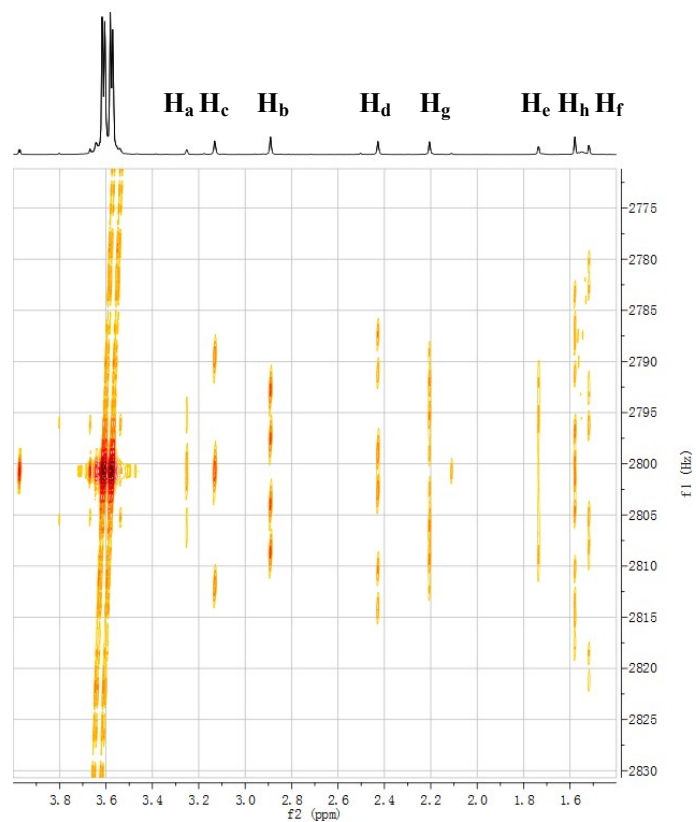
NMR spectra of the hydrogenated products
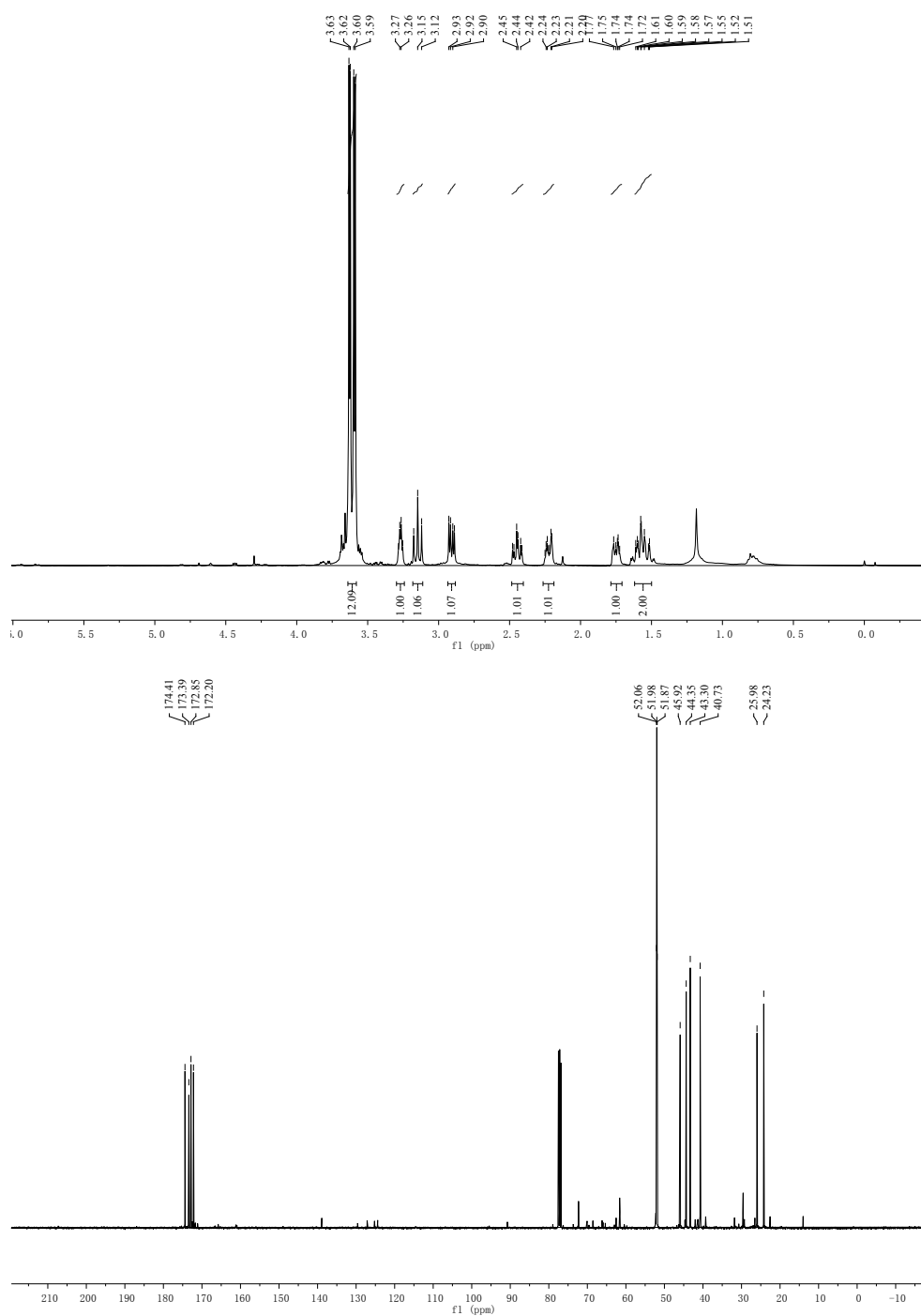
Fig. S12 The ^{1}H and ^{13}C NMR spectra of solid mixtures obtained from tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate hydrogenation reaction in CDCl$_3$ (400 M)
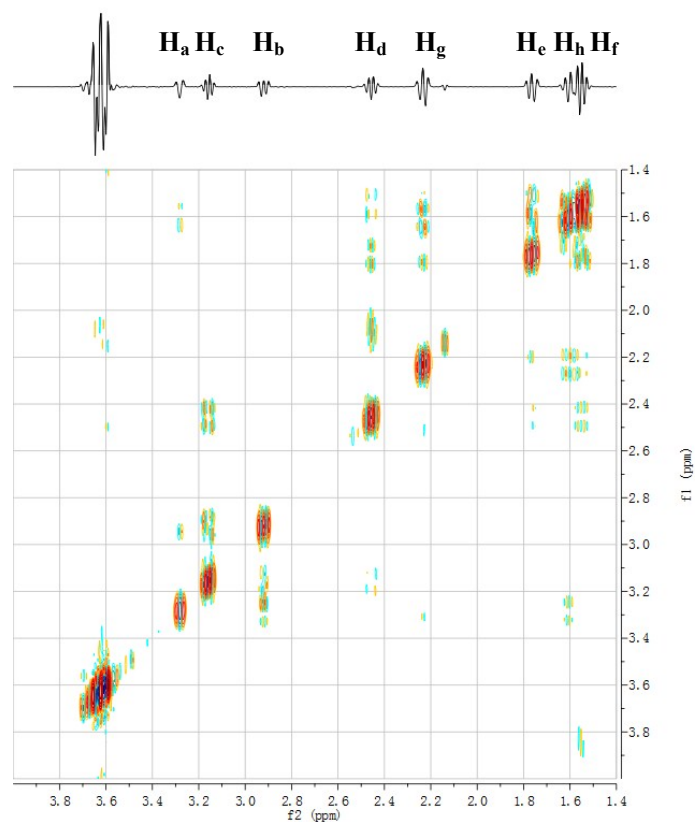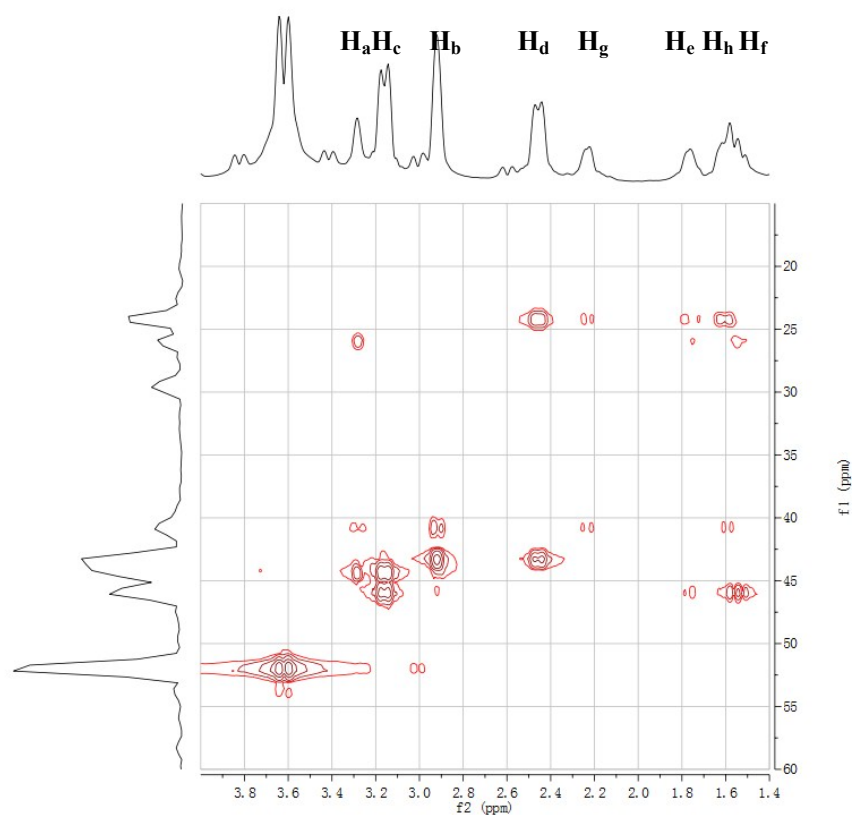
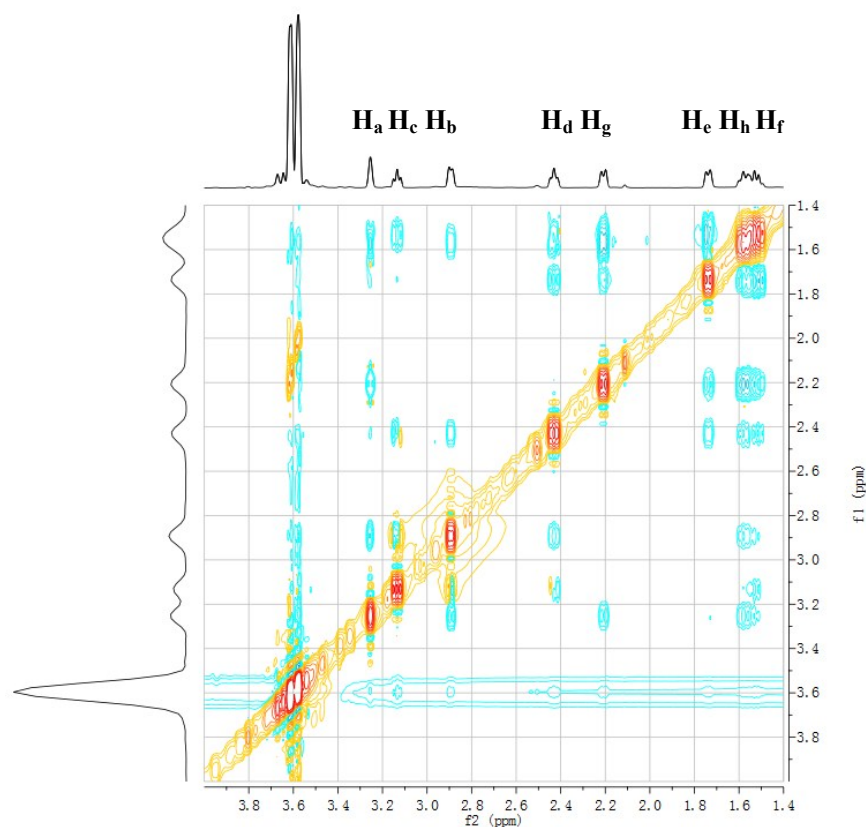**Fig. S13** The DQF-COSY analysis of the main hydrogenated product in CDCl$_3$ (700 M)

Fig. S14 The homonuclear 2D J-Resolved ^{1}H NMR spectrum of the main hydrogenated product in CDCl$_3$ (700 M)
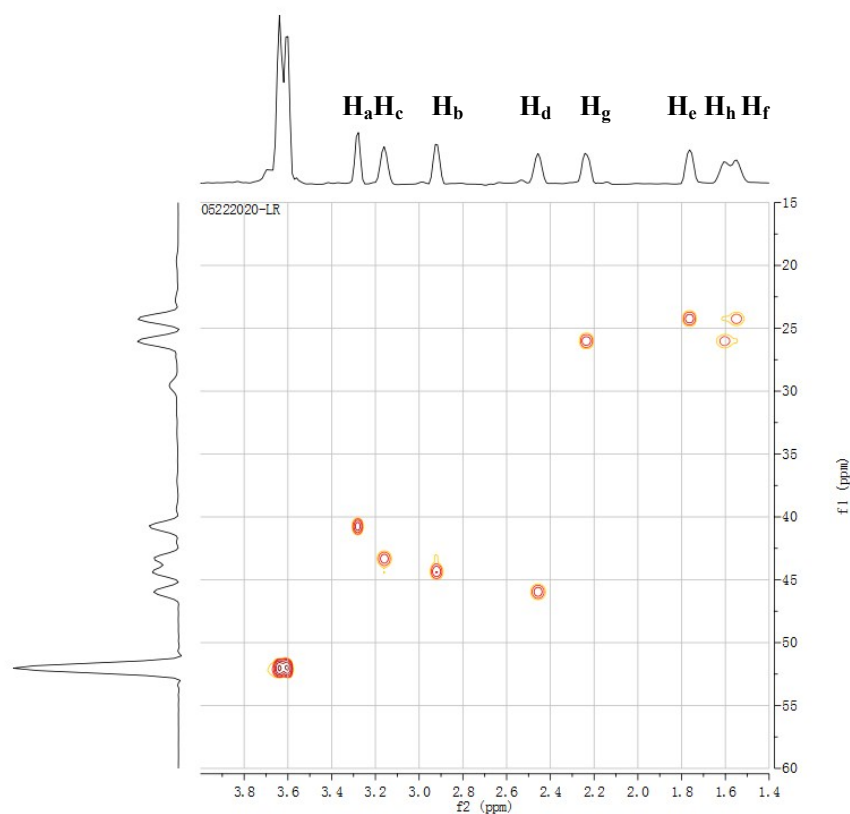
**Fig. S15** The C-H HSQC analysis of the main hydrogenated product in CDCl₃ (700 M)

**Fig. S16** The C-H H2BC analysis of the main hydrogenated product in CDCl₃ (700 M)

Fig. S17 The 2D NOESY analysis of the main hydrogenated product in CDCl$_3$ (700 M)

And several 2D NMR methodologies have also been conducted to confirm the structure of the main hydrogenated product. Combined the 1D NMR, 2D DQF-COSY, homonuclear 2D J-Resolved 1H NMR, C-H HSQC and C-H H2BC analysis, the assignments of the individual proton were given in Fig. S18 except for the protons of four methoxyl groups. The spectra of 2D NOESY illustrated that there existed NOE signals among H$_a$-H$_b$, H$_b$-H$_d$, H$_c$-H$_f$ and H$_d$-H$_e$ (Fig. S17). And no signal was detected between H$_a$ and H$_c$. It was consistent with the proposed stereochemistry of the hydrogenated product. The spectra also revealed NOE signals between H$_c$ and H$_b$ or H$_d$ and it might be that the protons of adjacent carbon had close spatial distance.
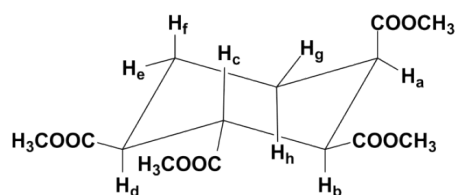
Fig. S18 The relative configuration of the main hydrogenated product

From the GC and NMR analysis, we predicted that the stereoisomers of **1** (**2** and **3**) might be formed via the hydrogenation of intermediate **4** which was formed via the C=C bond isomerization of cycloadduct (Fig. S19). All of the three hydrogenated products were important cyclohexyl monomers and the total yield was nearly 100% after reacting for 24 h at room temperature. Considering their extremely similar structures and properties, it is difficult to isolate to obtain single component product by common methods and further research needed to be explored.
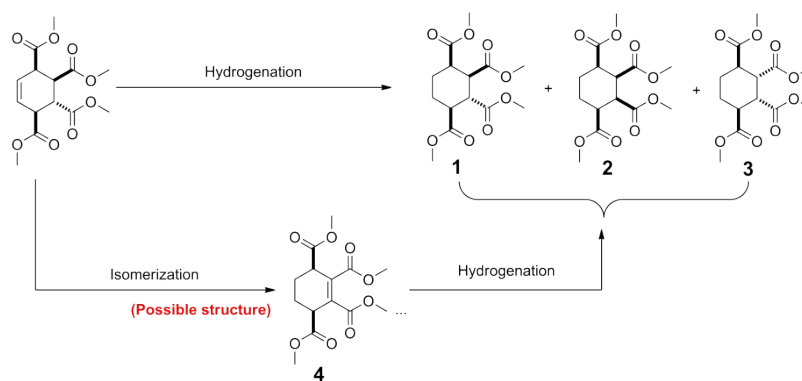
Fig. S19 The possible reaction path for the hydrogenation reaction of tetramethyl 5-cyclohexene-1,2,3,4-tetracarboxylate catalyzed by Raney Ni

References

1 (a) Y. Bando, T. Dodou and Y. Minoura, *J. Polym. Sci., Polym. Chem. Ed.*, 1977, **15**, 1917-1926; (b) A. Matsumoto, K. Katayama, T. Odani, K. Oka, K. Tashiro, S. Saragai and S. Nakamoto, *Macromolecules*, 2000, **33**, 7786-7792; (c) I. Khalil, G. Quintens, T. Junkers and M. Dusselier, *Green Chem.*, 2020, **22**, 1517-1541.

2 (a) M. Z. Elsabeé and S. G. Ibrahim, *Polym. Test.*, 2001, **20**, 173-178; (b) H. Alkassiri, *Radiat. Phys. Chem.*, 2005, **73**, 61-63; (c) M. Susana Cortizo, *J. Appl. Polym. Sci.*, 2007, **103**, 3785-3791.