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An Improved and Practical Synthesis of Tranexamic Acid

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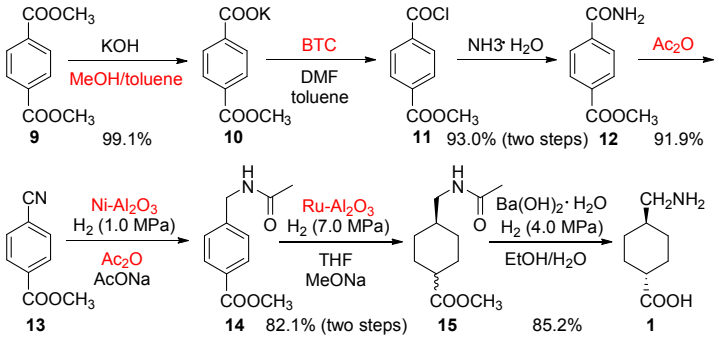

Abstract

Tranexamic acid **1**, a synthetic antifibrinolytic drug with the treatment being considered highly cost effective in many countries, has been included in the WHO list of essential medicines. In this paper, we designed the synthesis of **1** *via* a novel seven-step route from the readily available starting material dimethyl terephthalate, performing with 99.6% purity in 59.2% overall yield. During the process, we successfully developed a direct and efficient method for the preparation of key intermediate methyl 4-(acetamidomethyl)benzoate by one-pot hydrogenation and acylation in acetic anhydride using Ni/Al_2O_3 as catalyst. More importantly, it should be a straightforward and practical way to circumvent the usage of toxic reagents (CrO_3, Cl_2), solvent (CCl_4) and expensive catalyst (PtO_2), etc. that plagued the previous methodologies.

Introduction

Tranexamic acid, (*trans*-4-aminomethylcyclohexane carboxylic acid) **1** (Figure 1), a synthetic ω-amino acid with antifibrinolytic properties, was first approved by the FDA in 1986 as an injection under the brand name of Cyklokapron.[1] With the advantage of causing lesser side effects compared to other antifibrinolytic drugs, **1** is usually used for the treatment of dysfunctional uterine bleeding, and heavy bleeding associated with uterine fibroids.[2] Moreover, **1** is also an important synthetic block for some compounds with potential biological activities.[3]

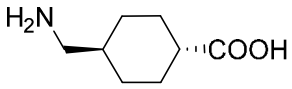

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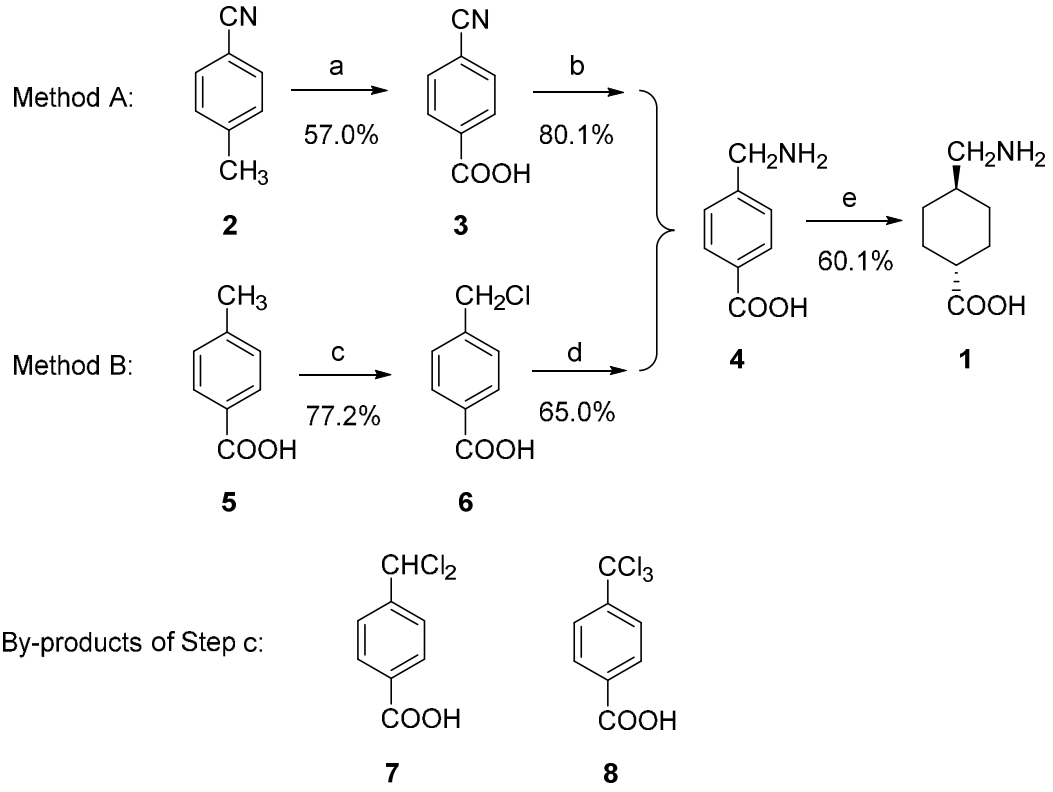
Figure 1. Tranexamic Acid

During recent decades, numerous efforts have been made to find efficient methods to synthesize **1**. A common approach for kilo-scale synthesis involves catalytic hydrogenation of 4-(aminomethyl)benzoic acid **4** over PtO_2 to produce a mixture of *cis*- and *trans*-4-(aminomethyl)cyclohexane-1-carboxylic acid, then converted the resulting *cis*-4-(amino-methyl)cyclohexane-1-carboxylic acid into the desired *trans* isomer **1** by heating the mixture in an aqueous solution of an acid or alkali (Scheme 1).[4] There are two synthetic methods for the preparation of the intermediate **4**. In Method A, 4-methylbenzonitrile **2** was oxidated by CrO_3 gave 4-cyanobenzoic acid **3**, followed by hydrogenation over Raney Cobalt to afford **4** with 45.0% yield.[5] In Method B, 4-methylbenzoic acid **5** was chlorinated with Cl_2 in the presence of UV light or using azodiisobutyronitrile as catalyst. 4-(Chloromethyl)benzoic acid **6** was purified by rectification and it was then ammonolyzed in the presence of urotropine to afford **4** with

23.0% yield. It is worth mentioning that, during Method B, by-products **7** and **8** were formed and they were quite difficult to separate.[6] Additionally, containing both carboxyl and amino group, the success of purification of **4** was highly dependent on the pH value, making the post-process difficult to handle.

Scheme 1. Original Methods for the Synthesis of Tranexamic Acid **1**[a]

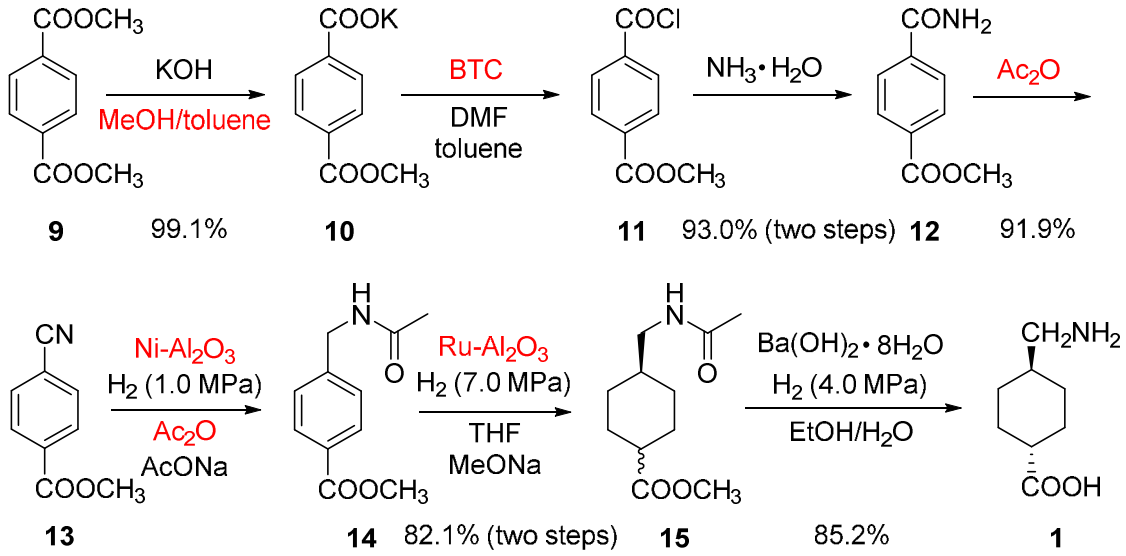


[a]Reactions and conditions: (a) (1) AcOH, H_2SO_4, CrO_3, 5-10 °C, 2 h, 25 °C, 1 h; (2) ice water, $NaHCO_3$; (3) HCl; (b) Raney Cobalt, 28.0% ammonia aqueous, H_2O, H_2 (0.3 MPa), 25 °C, 3 h; (c) UV, Cl_2, 100 °C, 3 h; (d) urotropine, H_2O, NH_3, 50 °C, 4 h; (e) (1) PtO_2, H_2SO_4/H_2O, H_2 (0.15 MPa), 40 °C; (2) 90 °C, $BaCO_3$, H_2O; (3) $Ba(OH)_2$, H_2O/EtOH, H_2 (2.0 MPa), 200 °C, 14 h; (4) H_2SO_4/H_2O.

Those methods mentioned above suffered from disadvantages such as: usage of expensive metal catalysts renders the process economically nonviable and industrially unattractive. Furthermore, some toxic reagents such as CrO_3, Cl_2 and poisonous solvents such as CCl_4 have a detrimental impact on the environment and human health. Although a few other existing approaches have been documented in the literature, they were either cost ineffective or

environment unfriendly, making those methods less easy to implement on a large scale.[7] These triggered our investigation of the process. Herein, we report an improved, seven-step synthesis of **1** from the readily available starting material dimethyl terephthalate (**9**, 1,4-dimethyl benzene-1,4-dicarboxylate), which generates the title compound **1** with 99.6% purity in 59.2% overall yield (Scheme 2).

Scheme 2. Optimized Synthesis of Tranexamic Acid

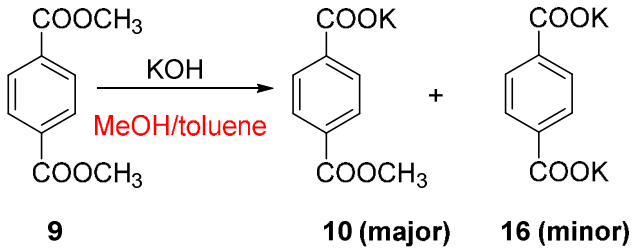


Results and discussion

Preparation of potassium 4-(methoxycarbonyl)benzoate (10).

In the reported procedure for the conversion of **9** to **10**, 1 equiv of potassium hydroxide was added to methanol, the mixture was heated to reflux and gained 73.1-91.0% yield.[8] Nevertheless, we clearly observed a yield decrease of **10** when we increased the loading of **9** (Table 1, entries 1-2). The possible reason is that **10** precipitated from methanol as thick suspension which made the stirring quite inefficient and resulted heat accumulation with increased formation of the by-product potassium terephthalate **16** (Scheme 3).

Scheme 3. Selective Hydrolysis of **9** to Yield **10**



Surprisingly, increasing the volume of methanol had little effect on improving the selectivity. A possible reason is that the excess of methanol dissolved **10** and made it easier to hydrolyse further. Thus, we assumed that adding an antisolvent might work. On the basis of the above-mentioned observations, a trial run was performed on 100 g-scale: a mixture of **9** and 1 equiv of potassium hydroxide in the presence of a mixed solvents of methanol and toluene with 1:1.1 volume ratio (Table 2, entry 3) afforded crude **10** with 97.8% purity in 99.1% yield (containing 2.1% of **16**).

Table 1. Monohydrolysis of Dimethyl Terephthalate **9** in Methanol[a]

Entry	Methanol/mL	Yield of crude **10**[b]/%	Purity of crude **10**[c,d]	
			10/%	**16**/%
1	50[e]	98.8	96.6	2.8
2	1043[f]	98.9	86.3	13.6
3	1143[g]	92.5	87.8	12.0
4	2000[h]	86.8	89.4	10.6

[a]Reaction conditions: **9** (0.52mol), **9**: KOH = 1:1, 45-50 °C. [b]Isolated yield of crude **10**. [c]Crude **10** containing **10** and **16**. [d]The analysis of crude **10** based on HPLC. [e]**9** (0.03mol), **9**: KOH:MeOH = 1:1:50, 45-50 °C. [f]**9**:MeOH = 1: 50. [g]**9**:MeOH = 1: 55. [h]**9**: MeOH = 1: 96.

Table 2. Monohydrolysis of Dimethyl Terephthalate **9** in Methanol and Toluene[a]

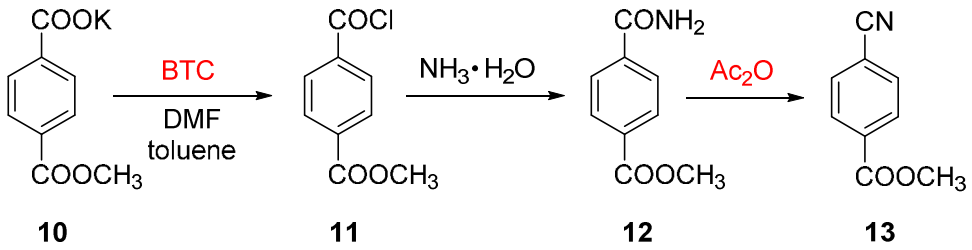
Entry	Methanol/mL	Volume ratio methanol:toluene	Yield of crude **10**[b]/%	Purity of crude **10**[c,d]	
				10/%	**16**/%
1	1043	2:1	97.2	89.9	10.0
2	1043	1:1	97.6	95.8	4.0
3	1043	1:1.1	99.1	97.8	2.1
4	1043	1:1.2	99.4	96.6	3.3

[a]Reaction conditions: **9** (0.52mol), **9**: KOH:MeOH = 1:1:50, 45-50 °C. [b]Isolated yield of crude **10**. [c]Crude **10** containing **10** and **16**. [d]The analysis of crude **10** based on HPLC.

Conversion of the intermediate 10 to methyl 4-cyanobenzoate (13).

The subsequent transformation of intermediate **10** to methyl 4-(chlorocarbonyl)benzoate **11**, methyl 4-carbamoylbenzoate **12** and methyl 4-cyanobenzoate **13** were carried out by conventional chemistry without any difficulties (Scheme 4). The quantitative transformation of **10** to **11** was achieved by using bis(trichloromethyl)carbonate (BTC), which is more environmental friendly than thionyl chloride.[9] Then the resulting solid **11** reacted with aqueous ammonia directly without other solvent to produce **12** in 93.0% yield. Crude **13** was obtained in refluxing acetic anhydride serving both as dehydration agent and as solvent in 91.9% yield from **12**, without using other complicated dehydrating agents.[10] Then our focus shifted to the more troublesome step, the formation of methyl 4-(acetamidomethyl)benzoate **14**.

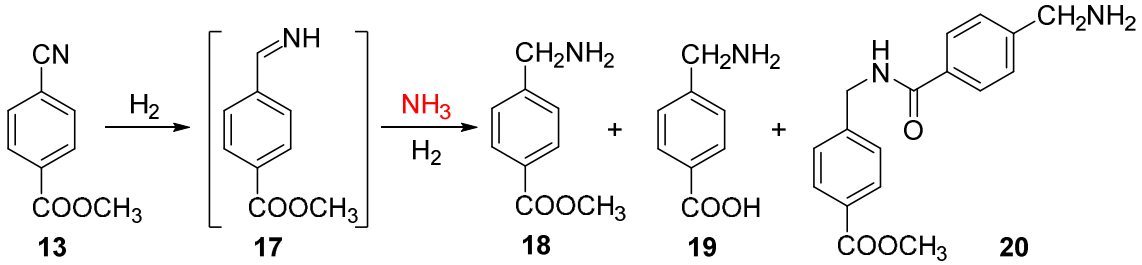
Scheme 4. Preparation of **13** from **10**



Preparation of methyl 4-(acetamidomethyl)benzoate (14).

There have been numerous publications on the methods of hydrogenating nitrile compounds, from which it is known that hydrogenation of **13** to primary amine with good yields always requires some complicated or expensive catalysts such as Pd/C, PtO_2, Rh.[11] The common approach for hydrogenation of nitrile compound over Raney nickel in the presence of ammonia did not work here. The reaction mixture contained 44.3% methyl 4-(aminomethyl)benzoate **18**, 21.9% 4-(aminomethyl)benzoic acid **19**, 6.2% methyl 4-((4-(aminomethyl)benzamido)methyl)benzoate **20** and trace amounts of unidentified side products as detected by LC-MS. We reckoned that under basic condition, the methyl ester group of **13** would be hydrolyzed easily to generate **19**, besides, **20** were formed by the dimerization of **18**. But as we knew that the basic condition was essential to prevent the formation of higher amines (Scheme 5).[12]

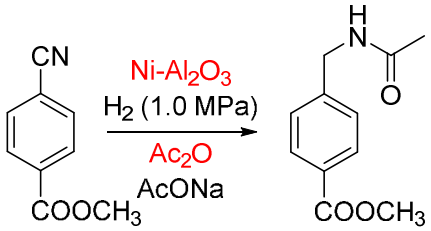
Scheme 5. The Formation of By-products



Facing such a predicament, we turned our attention to acidic condition.[13] The reaction went smoothly using catalyst Ni-Al_2O_3 with anhydrous sodium acetate as cocatalyst and acetic anhydride as solvent at 50 °C under hydrogen pressure of 1.0 MPa (Scheme 6). We attributed the excellent result to the fact that the resulting primary amine was quickly acylated therefore avoided the possible side reactions. Additionally, such an acidic condition also prevented the methyl ester group from hydrolysis. The reaction mixture was distilled under reduced pressure to

recover acetic acid and acetic anhydride, and the residue with a high degree of purity can be used in the next reaction directly.

Scheme 6. Hydrogenation and Acylation of **13** in One Step

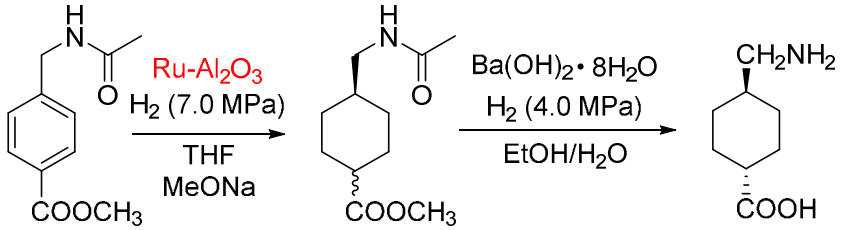


13 **14**

Preparation of *trans*-4-(aminomethyl)cyclohexane-1-carboxylic acid (1).

Compound **14** with acetamide group was stable enough to be efficiently hydrogenated under high pressure (7.0 MPa) with relatively economical catalyst Ru-Al_2O_3 instead of expensive catalysts such as Ru-Rh-Pd/C, Ru/PDMF in 82.1% yield (calculated on **13**) (Scheme 7).[14]

Scheme 7. Preparation of **1**



14 **15** **1**

Based on the reported method of isomerization of *cis* isomer into *trans* isomer,[4b] we attempted to combine hydrolysis and isomeration of **15** in one step. The mixture of **15** and $Ba(OH)_2$ with ethanol and water as solvents was transformed smoothly to **1** at 250 °C and under hydrogen pressure of 4.0 MPa. After adjusting the pH value and clarification, **1** was obtained with 99.6% purity in 85.2% yield.

Conclusions

An improved and cost-efficient synthetic method for practical synthesis of **1** was developed in seven steps with overall yield of 59.2%. One of the key steps involved the transformation of **13** to the corresponding acylated primary amine **14** was accomplished by a process of one-pot hydrogenation and acylation. The resulting intermediate **14** was subsequently hydrogenated with inexpensive catalyst Ru-Al_2O_3 to generate **15** in excellent yield and purity. This novel synthetis route has significant advantages, in terms of low cost, simple downstream processing and environmental friendliness, which make it more attractive for pharmaceutical industry.

Experimental section

General Methods. All solvents and reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The reactions were monitored by analytical thin-layer chromatography (TLC) on silica gel GF254 coated glass plates and visualized under UV light (254 and 365 nm). Melting points (mp) were obtained on a digital melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR were recorded at 400 and 100 MHz, respectively. The chemical shifts are reported as δ ppm relative to tetramethylsilane (TMS). Mass spectra were measured with a HRMS-APCI instrument or a low-resolution MS instrument using ESI ionization. The HPLC analysis data is reported in area %, not adjusted to weight %.

Preparation of potassium 4-(methoxycarbonyl)benzoate 10. To a 2-L round-bottomed flask was added potassium hydroxide (28.8 g, 0.52 mol), methanol (1043 mL, water content 0.27%) and toluene (1147 mL). The mixture was stirred until dissolution, dimethyl terephthalate (**9**, 100.0 g, 0.52 mol) was added at 45 °C, and the mixture was stirred at 45 °C to 50 °C for 5.5 h. Then the mixture was distilled under reduced pressure to cycled solvents, the residue was

washed with dichloromethane (1000 mL) to remove the rest dimethyl terephthalate. The washed filter cake was dried at 50 °C to afford a white solid **10** (112.3 g, yield 99.1%, HPLC > 97.8%).

Preparation of methyl 4-(chlorocarbonyl)benzoate 11. To a stirred mixture of potassium 4-(methoxycarbonyl)benzoate (**10**, 106.8 g, 0.49 mol) and DMF (11.6 g, 0.16 mol) in toluene (750 mL) was added a solution of bis(trichloromethyl) carbonate (BTC, 59.3 g, 0.20 mol) in toluene (150 mL) at 60 °C over a period of 40 min. The reaction mixture was heated to reflux. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, and filtered to remove potassium chloride. The resulting solution was concentrated to dryness under reduced pressure to give **11** as a light brown solid on cooling. This material was used directly in the next step; mp = 53.3-54.1 °C (lit. mp 54-55 °C).[15]

Preparation of methyl 4-carbamoylbenzoate 12. To a stirred solution of conc. aqueous ammonia (453 mL, 6.00 mol) was added the crude methyl 4-(chlorocarbonyl)benzoate (**11**, 97.3 g, 0.49 mol) in portions at 0 °C over a period of 30 min. The mixture was stirred for 1 hour at room temperature and then filtered, the filter cake was washed with brine and crystallized from methanol, and dried at 50 °C to afford a white crystalline solid **12** (81.6 g, yield 93.0%, calculated on **10**, HPLC > 99.8%); mp = 204.6-206.0 °C (lit. mp 201-203 °C);[16] ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (s, 3H), 7.57 (br s, 1H), 7.96-8.02 (q, J = 8.4 Hz, 4H), 8.14 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.3, 127.6 (2C), 128.8 (2C), 131.5, 138.1, 165.4, 166.7; Mass (ESI+) m/z 180.1 $(M+H)^+$.

Preparation of methyl 4-cyanobenzoate 13. To a 500 mL round-bottomed flask was added methyl 4-carbamoylbenzoate (**12**, 86.0 g, 0.48 mol) and acetic anhydride (490.0 g, 4.80 mol). The mixture was stirred at refluxing temperature. After the completion of the reaction (monitored by TLC), the mixture was distilled to recycle acetic acid and the excess acetic anhydride,

respectively. The residue was crystallized from petroleum to give a white crystalline solid **13** (71.1 g, yield 91.9%, HPLC > 99.0%); mp = 62.4-63.1 °C (lit. mp 65-66 °C);[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.73 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7, 116.2, 117.8, 129.9 (2C), 132.0 (2C), 133.7, 165.1; Mass (ESI+) *m/z* 184.0 $(M+Na)^+$.

Preparation of methyl 4-(acetamidomethyl)benzoate 14. A mixture of methyl 4-cyanobenzoate (**13**, 30.6 g, 0.19 mol), Ni-Al_2O_3 (6.0 g, nickel content > 45%), anhydrous sodium acetate (22.1 g, 0.27 mol) and acetic anhydride (220 mL) was stirred at 50 °C under hydrogen pressure of 1.0 MPa for 2.5 hours. Then the mixture was filtered hot and the filtrate was distilled to recycle acetic acid and the excess acetic anhydride, respectively. The residue formed a white solid **14** and was used directly in the next step; mp = 112.5-113.6 °C (lit. mp 110-111 °C);[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 3H), 3.90 (s, 3H), 4.47 (d, J = 5.9Hz, 2H), 6.02 (s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 43.2, 52.1, 127.3 (2C), 129.0, 129.7 (2C), 143.4, 166.5, 169.9; Mass (ESI+) *m/z* 208.1 $(M+Na)^+$.

Preparation of a mixture of *cis*- and *trans*-methyl 4-(acetamidomethyl)cyclohexane-1-carboxylate 15. A mixture of methyl 4-(acetamidomethyl)benzoate (**14**, 33.2 g, 0.16 mol), Ru-Al_2O_3 (3.3 g), sodium methoxide (0.2 g, 0.004 mol) and THF (280 mL) was stirred at 130 °C under hydrogen pressure of 7.0 MPa for 7 hours. Then the mixture was filtered hot and the filtrate was distilled to recycle THF, the residue formed a light yellow oil **15** (33.3 g, yield 82.1%, calculated on **13**, HPLC: *trans*:*cis* = 1:3); Mass (ESI+) *m/z* 236.0 $(M+Na)^+$.

Preparation of trans-4-(aminomethyl)cyclohexane-1-carboxylic acid 1. A mixture of *cis*- and *trans*-methyl 4-(acetamidomethyl)cyclohexane-1-carboxylate (**15**, 29.8 g, 0.14 mol, *trans*:*cis* = 1:3), ethanol (100 mL), water (200 mL) and $Ba(OH)_2$ (97.8 g, 0.31 mol) was stirred at 250°C

under hydrogen pressure of 4.0 MPa for 7.5 hours. Then the reaction mixture was put into a round-bottomed flask with water (200 mL) at 70 °C, the pH was adjusted to 6.3 using carbon dioxide. Then the mixture was cooled to room temperature and filtered to remove barium carbonate. The filtrate pH was adjusted to 5.3 using sulphuric acid, then filtered and washed with water. The filtrate and water were combined and decolorized with activated charcoal (0.5 g) at 100 °C for 1 hour, then cooled to room temperature and filtered. The filtrate was distilled until the liquid volume was concentrated to 50 mL, then ethanol (50 mL) was added to crystallize at 10 °C. The crystals were filtered and washed with ethanol and dried to obtain a white crystalline solid **1** (18.7 g, yield 85.2%, HPLC > 99.6%); mp = 384.1-385.9 °C (decomp.) (lit. mp 384-388 °C (decomp.));[19] ^{1}H NMR (400 MHz, D_2O + DMSO-d_6) δ 0.73-1.35 (m, 4H), 1.41-1.58 (m, 1H), 1.59-1.86 (m, 4H), 1.87-2.01 (m, 1H), 2.69 (d, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, D_2O + DMSO-d_6) δ 29.3 (2C), 29.4 (2C), 35.4, 45.2, 46.7, 185.4; Mass (ESI+) *m/z* 158.0 $(M+H)^+$.

Acknowledgment

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Supporting Information Available

Mass, ^{1}H and ^{13}C NMR spectra, HPLC and LC-MS chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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