A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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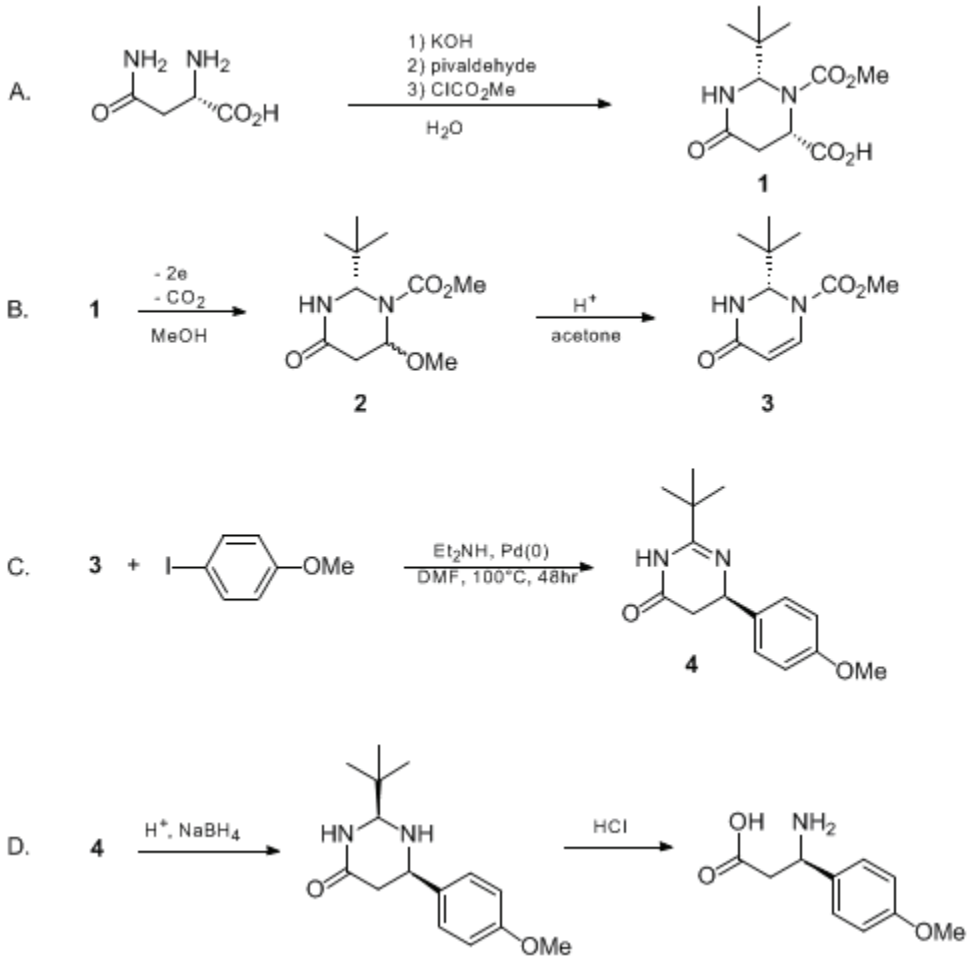
ENANTIOMERICALLY PURE β-AMINO ACIDS FROM 2-*tert*-BUTYL-1-CARBOMETHOXY-2,3-DIHYDRO-4(1H)-PYRIMIDINONE: (R)-3-AMINO-3-(p-METHOXYPHENYL) PROPIONIC ACID

[1(2H)-Pyrimidinecarboxylic acid, 2-(1,1-dimethylethyl)-3,4-dihydro-4-oxo-, methyl ester, (R)- or (S)-]



Submitted by F. J. Lakner, K. S. Chu, G. R. Negrete, and J. P. Konopelski[1].
Checked by Pradeep B. Madan, George P. Yiannikouros, and David L. Coffen.

1. Procedure

A. *(S,S)-2-tert-Butyl-1-carbomethoxy-6-carboxy-2,3,5,6-tetrahydro-4(1H)-pyrimidinone*, **1**. An Erlenmeyer flask equipped with a magnetic stirring bar is charged with 21.8 g of potassium hydroxide (KOH, 85% assay, 0.33 mol) and 500 mL of deionized water. A 50-g portion of L-asparagine monohydrate (0.33 mol) is added with stirring, followed by the addition of 43.6 mL of pivalaldehyde (34.4 g, 0.4 mol) with vigorous stirring, after which the mixture becomes homogeneous (Note 1). At the end of 6 hr, the solution is chilled in an ice bath and 28.0 g of sodium bicarbonate ($NaHCO_3$, 0.33 mol) is added, followed by 25.8 mL of methyl chloroformate (0.33 mol) (Note 1). After 1 hr of vigorous stirring at ice temperature, an additional 8.5 g of $NaHCO_3$ (0.11 mol) and 7.5 mL of methyl chloroformate (0.11 mol) are added. The ice bath is removed and the solution is allowed to warm to

room temperature for 2 hr. Precipitation of heterocycle **1** is accomplished by slow addition of 125 mL of 10% hydrochloric acid (0.44 mol). The resulting solids are collected by vacuum filtration, rinsed with 225 mL of ice water and dried in a vacuum desiccator yielding 62.1–67.1 g (72–79%) of heterocycle **1** as a white solid, mp 201°C (dec), $[\alpha]_D$-108.5° (CH_3OH, *c* 2.05) (Note 2).

B. *(S)-2-tert-Butyl-1-carbomethoxy-2,3-dihydro-4(1H)-pyrimidinone*, **3**. A 1-L, three-necked, round-bottomed flask is equipped with two electrodes, a thermometer, and a magnetic stirring bar (Note 3). The flask is charged with a solution of 60.0 g of heterocycle **1** (0.232 mol) in 620 mL of methanol (Note 4) and 3.2 mL (2.34 g, 23.2 mmol) of triethylamine (Note 5). The temperature is maintained at ≤ 20°C with a circulating water bath, while 0.60 amp is applied for 26 hr (Note 6). After transfer to a suitable vessel, the solvent is evaporated under reduced pressure providing heterocycle **2** as a clear, colorless syrup (Note 7). The residue is dissolved in 425 mL of acetone (Note 4), 20 g of cation exchange resin (Note 8) is added, and the suspension is then heated at reflux for 1 hr. The resin catalyst is collected by filtration and rinsed with an additional 100 mL of acetone, and the filtrate is concentrated under reduced pressure affording heterocycle **3** as a light yellow gum. The crude material is dissolved in 150 mL of ethyl acetate and washed twice with 50-mL portions of saturated aqueous sodium bicarbonate. The organic layer is dried with magnesium sulfate ($MgSO_4$), filtered, and crystallization is allowed to occur by slow evaporation of the solvent. The crystals are collected affording 30–46.8 g (48–68% from asparagine) of large, clear, colorless crystals of heterocycle **3**, mp 142–143°C, $[\alpha]_D$+416.6° (EtOAc, *c* 1.70) (Note 9).

C. *(R)-2-tert-Butyl-6-(4-methoxyphenyl)-5,6-dihydro-4(1H)-pyrimidinone*, **4**. Compound **3** (5.00 g, 23.6 mmol), 4-iodoanisole (5.52 g, 23.6 mmol), diethylamine (Et_2NH) (2.68 mL, 26.0 mmol), and tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] (273 mg, 0.24 mmol) are dissolved in 25 mL of dimethylformamide (Note 10). The yellow-colored solution is transferred to a thick-walled Pyrex pressure tube and purged with argon. The tube is then sealed and suspended in a boiling water bath for 48 hr in the dark (Note 11). The tube is cooled in liquid nitrogen before opening (***Caution: pressure has developed***). The contents of the tube are transferred with the aid of 250 mL of ethyl acetate (EtOAc) to a wet packed approx. 40-mm × 50-mm bed of 17.5 g silica gel that is then rinsed with an additional 200 mL of EtOAc. After the solvent is removed under vacuum, the residue is dissolved in a mixture of 80 mL of water, 21.0 mL of 1.0 N hydrochloric acid solution, and 50 mL of ether. The resulting solution is transferred to a 500-mL separatory funnel, washed twice with 100-mL portions of ether, and the ethereal washings are discarded. The aqueous layer is transferred to an Erlenmeyer flask, cooled in an ice bath, and ~11.5 mL of 2 N aqueous sodium hydroxide solution is added in one portion with stirring to bring the solution to a pH of 8–9. The resulting precipitate (Note 12) is collected by suction filtration and air dried to give **4** as a yellowish solid (3.33–4.50 g, 55–75%), mp 118–120°C, $[\alpha]_D$ −20° ($CHCl_3$, *c* 3.3) (Note 13).

D. *(R)-3-Amino-3-(p-methoxyphenyl)propionic acid*.[2] A 125-mL Erlenmeyer flask containing a magnetic stirring bar is charged with 20 mL of tetrahydrofuran, 20 mL of 95% ethanol, and heterocycle **4** (2.39 g, 9.2 mmol). The mixture is stirred and cooled to −35°C to −45°C with an acetone-dry ice bath. About 0.6 mL of aqueous 9 N hydrochloric acid is added dropwise until a pH of approximately 7 is obtained as determined by pH paper. A solution of sodium borohydride, prepared by dissolving 0.5 g of sodium borohydride (13.0 mmol) in approximately 1.5 mL of water (minimum amount) containing 1 drop of 30% aqueous sodium hydroxide solution, is added dropwise alternately with 9 N hydrochloric acid to the stirred solution of **4** such that a pH of 6–8 is maintained. During the addition, the bath temperature should be maintained between −35°C and −45°C. After the addition of sodium borohydride solution is complete, the reaction mixture is stirred at −35°C for 1 hr. During this time, the reaction mixture is maintained at a pH of 7 by occasional addition of 9 N hydrochloric acid (about 0.4 mL additional is required). The reaction mixture is then stored at −20°C overnight. After warming to room temperature, the reaction mixture is transferred to a separatory funnel and the pH is raised to 9 by addition of aqueous 40% sodium hydroxide (1.5 mL). After dilution with 30 mL of water, the mixture is extracted three times with 20-mL portions of ether, and the combined ether extracts are washed with 10 mL of saturated sodium chloride. After the organic layer is dried over potassium carbonate, the solution is concentrated under reduced pressure giving 2.01 g (85%) of the acyl aminal as a slightly yellow solid that is used without further purification (Note 14).

An 0.80-g (3.0 mmol) portion of the crude aminal above is dissolved in 8 mL of 4.5 N hydrochloric acid solution and heated to 100°C in a boiling water bath for 2.5 hr. The clear liquid reaction mixture is transferred to an evaporating dish and left to evaporate in a fume hood. The residue is dissolved in 2 mL of 2 N hydrochloric acid solution and the pH of the solution is adjusted to 7 by slow addition of 30% aqueous sodium hydroxide with swirling, at which time the whole mixture solidifies. The solid mixture is kept at −20°C overnight, followed by addition of 10 mL of water and stirring with a glass rod. The solids are collected by suction affording 0.38–0.41 g (63–69%) of the β-amino acid of ~85% purity as a slightly yellow crystalline solid, mp 235°C (dec); $[\alpha]_D$ −4° (1 N HCl, *c* 1.86) (Note 15).

2. Notes

1. L-Asparagine monohydate, pivalaldehyde, and methyl chloroformate were purchased from the Aldrich Chemical Company, Inc. and used without purification.
2. An extra 8.0 g may precipitate by saturation of the filtrate with sodium chloride and storing the solution in a refrigerator overnight. This material is of significantly inferior chemical and diastereomeric purity. The initial precipitate, however, is usually 92% optically pure as compared to the material obtained by recrystallization from 1:4 ethanol/water, and exhibits constant rotation upon further recrystallization. The rotation for twice recrystallized **1** is $[\alpha]_D$ −115° (CH_3OH, *c* 2.05). However, this purification procedure (recrystallization) is not necessary, since heterocycle **3** is easily crystallized to ≥ 99% ee as the final isolation step. Spectral characteristics for pure **1** are: ^{1}H NMR (400 MHz, D_2O/K_2CO_3, 10 mg/mL) δ: 1.16 (s, 9 H), 2.87–2.96 (m, 2 H), 3.83 (s, 3 H), 4.58 (m, 1 H), 5.33 (s, 1 H); IR (KBr) cm^{-1}: 3283, 2966, 1719, 1631, 1314, 1220, 1090, 779.
3. The flask possesses three vertical side necks of equal height. The middle neck and one side neck were fitted with 1-hole septa pierced by 1-cm diameter cylindrical graphite electrodes (Sargent Welch). The electrodes were inserted 7 cm into the solution, supplying a working electrode surface of 23 cm^2, and were 5 cm apart. A thermometer was inserted through the third neck with room to vent gases. A power supply (Southwest Technical Products Corp.) is attached to the electrodes with alligator clips. These conditions provide 34–37 V at 0.60 A.
4. Methanol was purchased from Fisher Scientific Company and used without further purification.
5. Triethylamine was purchased from the Aldrich Chemical Company, Inc., distilled, and stored over KOH pellets.
6. This represents the time necessary to pass 2.5 F/mol for the quantity stated at 0.60 A.
7. Methoxylated product **2** consists of diastereomers in a 3:1 ratio, the main proton resonances [^{1}H NMR (400 MHz, $CDCl_3$)] being δ: 0.95 and 1.02 (s, 9 H), 2.6–2.9 (m, 2 H), 3.35 and 3.39 (s, 3 H), 3.77 (s, 3 H), 5.17–5.29 (m, 1 H), 8.07–8.1 (s (br), 1 H).
8. Dowex 50W-X8 cation exchange resin, 200–400 mesh, in the hydrogen form was purchased from J. T. Baker Chemical Company. It was placed in a sintered-glass funnel and washed with three bed-volumes each of 10% hydrochloric acid, water, methanol, and acetone, and then dried under vacuum. The checkers recommend Soxhlet extraction of the resin for complete recovery of product **3**.
9. Product **3** has the following spectral properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.95 (s, 9 H), 3.83 (s, 3 H), 5.15–5.45 (m, 2 H), 7.2–7.5 (m, 1 H), 8.0–8.5 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 25.5, 40.7, 54.0, 72.0, 104.8, 137.5, 153.3, 164.6; IR (thin film) cm^{-1}: 3201, 2966, 1731, 1666, 1443, 1331, 1249. The submitters report an optical rotation for **3** of $[\alpha]_D$ +434° (EtOAc, *c* 1.70). Enantiomeric purity of **3** has been established by acylation of **3** with (s)-O-methylmandelic acid chloride followed by ^{1}H NMR analysis. Integration of the GC traces reveals that the resulting diastereomeric purity is equivalent to the enantiomeric purity of the mandelate (99%).
10. All glassware was oven dried at 120°C prior to use. Diethylamine was distilled from calcium hydride. Palladium(II) acetate, $Pd(OAc)_2$ (53 mg, 0.24), (cancer suspect agent), without added triarylphosphine, gave **4** at a slightly lower yield as compared to $Pd(PPh_3)_4$.
11. During the course of the reaction, the solution is black. When the reaction is complete, the solution is clear brown with some black precipitate.
12. Some decomposition of the product, which appeared to be the major side reaction in this procedure, may occur in this step. The submitters found that decomposition is significant when the temperature is ≥ 20°C, and the desired material is left in contact with the basic solution for extended periods of time. This procedure is the most efficient for larger amounts of material. For smaller amounts, base can be added to the aqueous layer in a separatory funnel and the resulting solution can be extracted with methylene chloride. In many cases the submitters have obtained material directly from this extraction

that was suitable for further transformations.
13. The compound appears to be capable of isolation by sublimation, but this has not been checked. The submitters report obtaining **4** having mp 123–125°C and $[\alpha]_D$ −47° ($CHCl_3$, *c* 3.3). The reasons for the discrepancy in rotation have not been determined. The spectral properties of pure **4** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (s, 9 H), 2.35 (dd, 1 H, J = 16.5, 12.0), 2.72 (dd, 1 H, J = 16.5, 5.7), 3.80 (s, 1 H), 4.71 (dd, 1 H, J = 12.0, 5.7), 6.89 (d, 2 H, J = 9), 7.3 (d, J = 9), 8.66 (s (br), 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.7, 37.6, 55.4, 56.7, 114.0, 127.5, 134.8, 158.8, 160.2, 171.7; IR (KBr) cm^{-1}: 3237, 3000, 1702, 1662, 1508 1254, 1135, 920, 832.
14. The properties of pure saturated heterocycle are as follows: mp 136–138°C, $[\alpha]_D$ +27.67° (CH_2Cl_2, *c* 1.2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.99 (s, 9 H), 2.33–2.72 (m, 2 H), 3.82 (s, 3 H), 3.97–4.04 (m, 1 H), 4.12 (s, 1 H), 6.03 (s (br), 1 H), 6.9 (d, 2 H, J = 10), 7.3 (d, 2 H, J = 10); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.9, 34.5, 39.8, 55.0, 55.4, 76.0, 114.1, 127.4, 134.2, 159.2, 171.6; IR (KBr) cm^{-1}: 3190, 2954, 1655, 1514, 1472, 1243, 1173.
15. Further purification including removal of the slight yellow color could be effected by recrystallization from boiling water. Physical properties of the purified amino acid product are as follows: mp 239°C (dec), $[\alpha]_D$ −4.35° (1 N HCl, *c* 1.86); ^{1}H NMR (400 MHz, D_2O) δ: 3.02–3.25 (m, 2 H), 3.83 (s, 3 H), 4.90 (m, 1 H), 7.03 (d, 2 H, J = 10), 7.45 (d, 2 H, J = 10); ^{13}C NMR (100 MHz, D_2O) δ: 38.7, 52.1, 56.6, 115.9, 128.7, 129.8, 160.8, 174.5; IR (KBr) cm^{-1}: 2960, 2364, 2150, 1615, 1518, 1404, 1250, 1184.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Chemical methods for the production of enantiomerically pure α-amino acids have been extensively investigated in recent years.[3] Conversely, there are relatively few methods for the synthesis of chiral, nonracemic β-amino acids,[4 5] although there is considerable interest in these compounds as precursors to β-lactams,[6 7 8 9 10,11 12] as components of natural products,[13 14 15 16 17] and as reactive molecules in their own right.[18]

The procedure given here stems from our synthetic effort toward (+)-jasplakinolide[19 20 21,22,23 24 25 26] that contains the β-amino acid (R)-β-tyrosine.[27] This protocol permits the introduction of the desired *carbon substitutent* at the β-site in an enantioselective manner. This approach contrasts with previous methodologies, which develop the chiral center via conjugate addition of an amine to an α,β-unsaturated system,[28 29 30 31 32 33 34 35 36] reduction of a C=C or C=N functionality,[37 38 39 40 41] or C-C bond formation involving imines and enolate derivatives.[42 43 44 45 46 47 48 49 50 51 52]

The key element in this technology is heterocycle **3**. Although asparagine has been cyclized with acetone,[53] cyclocondensation with aldehydes has not been described in detail, except for tetrahydropyrimidinone formation using formaldehyde.[54] Electrochemical oxidative decarboxylation, on the other hand, is a well-known procedure[55] with broad applicability.[56] Our initial synthesis of **3** was accomplished with lead(IV) acetate;[57,58] the two-step method described here is cleaner and the cost and hazards of using and disposing of lead are precluded. Furthermore, the acid catalyst is easily recyclable. The two enantiomers of **3** are easily prepared from the corresponding enantiomers of asparagine which are readily available and inexpensive. The intermediate **3** and analogues are highly crystalline, stable, and possess large specific rotations which allows determination of the enantiomeric purity.

In addition, the protocol for the transformation of **3** to **4** has been modified from our original publication. We have found that the use of Et_2NH instead of triethylamine (Et_3N) as base gives a more reproducible reaction and, at the same time, all but eliminates the formation of biaryl material as a side product. The synthesis of **4** with Et_3N as base has been the subject of a mechanistic study and our results have been communicated.[58] Whether or not the mechanism is as we propose when Et_2NH is employed is not known.

Recently, we have demonstrated that **3** functions as an attractive chiral auxiliary for the synthesis of

scalemic α-substituted carboxylic acids.[59] In addition, we have extended the scope of the β-amino acid synthesis to include alkyl groups through a protected derivative of heterocycle **3**.[60] Thus, a unified approach to the synthesis of enantiomerically pure β-amino acids has been developed from **3**. Recent efforts by Seebach, Juaristi, and co-workers[61] [62] [63] on a saturated analog of **3** have developed routes to products substituted at C_5 (α to the carbonyl).

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

amine

β-AMINO ACIDS

1(2H)-Pyrimidinecarboxylic acid, 2-(1,1-dimethylethyl)-3,4-dihydro-4-oxo-, methyl ester, (R)- or (S)-

β-amino acid

L-Asparagine monohydate

β-amino acid (R)-β-tyrosine

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid, HCl (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

formaldehyde (50-00-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

acetone (67-64-1)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

diethylamine (109-89-7)

methylene chloride (75-09-2)

amino (15194-15-7)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

methyl chloroformate (79-22-1)

dimethylformamide (68-12-2)

asparagine (70-47-3)

triethylamine (121-44-8)

argon (7440-37-1)

calcium hydride (7789-78-8)

sodium borohydride (16940-66-2)

pivalaldehyde (630-19-3)

palladium(II) acetate (3375-31-3)

tetrakis(triphenylphosphine)palladium(0) (14221-01-3)

lead(IV) acetate (546-67-8)

2-tert-Butyl-1-carbomethoxy-2,3-dihydro-4(1H)-pyrimidinone (131791-81-6)

(R)-3-Amino-3-(p-methoxyphenyl)propionic acid (131690-57-8)

(S,S)-2-tert-Butyl-1-carbomethoxy-6-carboxy-2,3,5,6-tetrahydro-4(1H)-pyrimidinone (138723-45-2)

L-asparagine monohydrate (5794-13-8)

(S)-2-tert-Butyl-1-carbomethoxy-2,3-dihydro-4(1H)-pyrimidinone (131791-75-8)

(R)-2-tert-Butyl-6-(4-methoxyphenyl)-5,6-dihydro-4(1H)-pyrimidinone (131791-77-0)

4-iodoanisole (696-62-8)

(S)-O-methylmandelic acid chloride

tetrahydropyrimidinone (1852-17-1)