Efficient Route to (S)-Azetidine-2-carboxylic Acid

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A new and efficient route to (S)-azetidine-2-carboxylic acid (>99.9% ee) in five steps and total yield of 48% via malonic ester intermediates was established. As the key step, efficient four-membered ring formation (99%) was achieved from dimethyl (S)-(1’-methyl)benzylaminomalonic acid by treating with 1,2-dibromoethane (1.5 eq) and cesium carbonate (2 eq) in DMF. Krapcho dealkoxy-carbonylation of dimethyl (1’S)-1-(1’-methyl)benzylazetidine-2,2-dicarboxylate, the product of this cyclization procedure, proceeded with preferential formation (2.7:1, 78% total yield) of the desired (2S,1’S)-monoester, with the help of a chiral auxiliary which was introduced on the nitrogen atom. The undesired (2R,1’S)-isomer could be converted to that with proper stereochemistry, by a deprotonation and subsequent re-protonation step. Finally, lipase-catalyzed preferential hydrolysis of the (2S,1’S)-monoester and subsequent deprotection provided enantiomerically pure (S)-azetidine-2-carboxylic acid in a 91% yield from the mixture of (2S,1’S)- and (2R,1’S)-isomers.

Key words: cyclic amino acid; azetidine-2-carboxylate; azetidine-ring formation; Krapcho dealkoxy-carbonylation; diastereofacially selective protonation

(S)-Azetidine-2-carboxylic acid (1a), a non-proteogenic cyclic amino acid, is the key component of deoxymugineic acid and nicotianamine, which are potent plant-origin promoters for the uptake of iron from soil.1–3) Acid 1a also works as the starting material for a nicotinic receptor tracer.4) Preparation of the pure (S)-enantiomer has been achieved by synthesis from chiral pools5–7) optical resolution,8,9) and enzymecatalyzed kinetic resolution.10,11) Among these, Sumitomo’s group has reported the separation of diastereomers (2S,1’S)- and (2R,1’S)-2a,9) which had been prepared in an equimolar ratio from racemic methyl 2,4-dibromobutanoate. Our synthesis, inspired by the forementioned situation was improved (78%) by the combined use of tert-butyl-4-methylphenol (BHT) as a proton source. The yields of

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It was found from systematic studies that the proper combination of the amine and haloester, in regard to steric hindrance, nucleophilicity, electrophilicity, and stability, was very important. For example, an attempt to directly prepare 4a from (S)-α-methylbenzylamine and dimethyl bromomalonate only resulted in very low yield. An α-methyl substituent in the benzylamine moiety increased the nucleophilicity, in spite of the steric hindrance. Indeed, benzylamine16) itself showed much lower reactivity toward alkylation.

The first key step, azetidine ring formation, was successful (99%) by applying 1,2-dibromoethane (1.5 eq) and cesium carbonate (2 eq) in DMF. The only detected by-product was an eight-membered ring compound (5). Steric hindrance of the diester moiety affected the rate of cyclization. When the substrate was changed to diethyl ester 4b, C-alkylated intermediate 6 was isolated in a substantial amount, and the addition of tetra-n-butylammonium iodide (TBAI) was necessary to ensure cyclization to azetidine 3b (95%). Efficient deprotonation of the malonic ester was also essential to promote the first step of cyclization. When a weaker base, potassium carbonate, was applied to 4b, the only isolable product was imine 7, which originated from the initial attack of the amine lone-pair electron on the bromine atom of 1,2-dibromoethane, accompanied with ethylene formation and subsequent dehydrobromination of the resulting N-bromo intermediate.

Conventional Krapcho dealkoxy-carbonylation on 3a by applying sodium chloride in aqueous DMSO12) at as high a temperature as 160 °C only resulted in a moderate yield of 2a (65%), probably due to undesired hydrolysis of either the starting material or the product. The attempted dealkoxy-carbonylation of more stable diethyl ester 3b under similar conditions was very slow. This situation was improved (78%) by the combined use of lithium chloride in DMSO17) under strictly anhydrous conditions in the presence of molecular sieves 3A. Instead of water, 2,6-di-tert-butyl-4-methylphenol (BHT) was added as a proton source. The yields of
(S)-Azetidine-2-carboxylate

2a and (2R,1'S)-2a were 57% and 21%, respectively, and both could be easily separated by silica gel column chromatography. On the other hand, attempts at selective hydrolysis18,19) of one of the two esters prior to decarboxylation of the α-alkoxycarbonyl acid only resulted in a complex mixture of highly polar, water-soluble materials.

We have some comments on the preferential formation (2.7:1) of desired (2S,1'S)-2a. The intermediate from dealkoxycarbonylation was an enolate, and two possible stable conformers, A and B, which are postulated by means of the Newman projection, are shown in Fig. 1. Protonation from the less sterically hindered sides, the re-face on A and the si-face on B, would provide (2S,1'S)-2a and (2R,1'S)-2a, respectively. Gauche repulsion between the phenyl group in the α-methylbenzyl chiral auxiliary and the α-oriented hydrogen atom at the azetidine C-4 position would reduce the stability of conformer B, and protonation would then preferentially proceed on conformer A. As a high

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\text{Scheme 1. Reagents: a) DBU, MeOH, 86%; b) Cs}_2\text{CO}_3 (2.0 eq), \text{BrCH}_2\text{CH}_2\text{Br (1.5 eq), 99%; c) LiCl (3.2 eq), BHT (3.2 eq), 140°C, 78%; d) 1) LDA, THF, –78°C; 2) aq. NH}_4\text{Cl, –78°C, 82%.}
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temperature was required for the dealkoxycarbonylation (160 °C), the difference between the foregoing two pathways is rather small (2.7:1). However, when the same enolate was independently generated20) by the action of LDA in THF on product 2a, protonation with an aqueous ammonium chloride solution proceeded in a 6:1 ratio at 0 °C. This ratio was further improved to 6.7:1 under a lower (−78 °C) temperature. In turn, by treating with sodium methoxide or DBU in refluxing methanol, no interconversion between the two dealkoxycarbonylation products, (2S,1′S)-2a and (2R,1′S)-2a, occurred. This means that re-abstraction of the α-proton from the resulting products in the presence of a proton source was not feasible, even under basic conditions at high temperature. The combined results suggest that the ratio of the two products was determined under kinetic control, and not under thermodynamic control, as Krapcho dealkoxycarbonylation proceeded under nearly neutral conditions.

Based on the foregoing comments, the property of the proton source would be important under non-aqueous conditions. Among such bulky and hydrophobic candidates as BHT, 2,4,6-trichlorophenol and Amberlyst-15, only BHT worked well as was shown before. The similar phenol, (S)-binaphthol, also promoted the reaction (23%), but the existing chirality of the proton source21) did not affect the product ratio (2.8:1).

Product (2S,1′S)-2a isolated by chromatography was hydrolyzed with Candida antarctica lipase B (Chirazyme L-2)5) under neutral conditions to provide acid (2S,1′S)-2b in a 75% yield. Finally, catalytic hydrolysis of the chiral auxiliary enabled (S)-azetidine-2-carboxylic acid (1a) to be obtained in quantitative yield (Scheme 2). Its high ee (>99.9%) was confirmed by an HPLC analysis of corresponding ester (S)-1b, to which a benzyl group had been introduced on the free amine. Lipase-catalyzed hydrolysis also worked in a diastereoselective manner on the 2.7:1 mixture of (2S,1′S)- and (2R,1′S)-2a to give (2S,1′S)-2b with some contamination by (2R,1′S)-2b (ca. 3%). This was eventually converted to (S)-1 (91% from the mixture of 2a) with >99.9% ee, after recrystallization at the final stage.10) As already stated, undesired (2R,1′S)-2a was epimerized into a 6.7:1 mixture of (2S,1′S)- and (2R,1′S)-2a in an 82% yield.

In conclusion, a new and efficient route to (S)-azetidine-2-carboxylic acid (1a) via the malonic ester intermediates, 3a and 4a, was established.

Experimental

All boiling point (bp) and melting point (mp) data are uncorrected. IR spectra were measured as films for oil and as KBr disks for solids with a Jasco FTIR-410 spectrometer. 1H- and 13C-NMR spectra were measured with a Jeol JNM GX-270 or GX-400 spectrometer. High-resolution mass spectra were recorded by a Jeol JMS-700 spectrometer. HPLC data were recorded by an SSC-5410 liquid chromatograph (Senshu Scientific Co., Ltd.). Optical rotation data were recorded on a Jasco DIP 360 polarimeter. Silica gel 60 (spherical, 100–210μm) from Kanto Chemical Co. was used for column chromatography. Preparative TLC was performed with E. Merck silica gel 60 F256 plates (0.5 mm thickness, No. 5744).

Dimethyl (1′S)-(1′-methyl)benzyaminomalonate (4a). Known crude diester 4b14) (1.30 g, 4.68 mmol) was dissolved in MeOH (65 ml), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 70 μl, 0.47 mmol) was added dropwise at room temperature, before the mixture was stirred under reflux for 3 h. The reaction mixture was concentrated in vacuo. The residue was poured into a phosphate buffer (0.1 M, pH 8.0, 100 ml), and the mixture was extracted three times with ethyl acetate. The extracts were combined, washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo to give 4a (1.01 g, 86%, from diethyl bromomal-
Dimethyl (1'S)-1-((1'-methyl)benzylazetidin-2,2-dicarbonylate (3a). Cesium carbonate (140 mg, 0.41 mmol) was added to a solution of 4a (45.7 mg, 0.18 mmol) in DMF (0.7 mL), and the mixture was stirred for 10 min at room temperature. 1,2-Dibromoethane (23 μL, 0.267 mmol) was added, and the reaction mixture was stirred for 14 h at room temperature and then for 2 h at 40 °C. The reaction mixture was then diluted with a phosphate buffer (0.1 M, pH 7.5) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give a crude product. Purification by preparative TLC [developed with hexane–EtOAc (4:1) with a trace of triethylamine]. δ H (270 MHz, CDCl₃): 1.33 (3H, d, J = 6.6 Hz, 2.18 (1H, br), 3.62 (3H, s), 3.69 (3H, s), 3.71 (1H, q, J = 6.6 Hz), 3.87 (1H, s), 7.15–7.29 (5H, m); δ C (65.7 MHz, CDCl₃): 24.46, 52.67 (x2), 56.41, 62.54, 126.70 (x2), 127.24, 128.36 (x2), 143.47, 168.42, 169.33. The IR and NMR spectra were in good accordance with those of the racemate reported previously.¹⁴

Methyl (2S,1'S)-1-((1'-methyl)benzylazetidin-2,2-dicarbonylate (2a) and methyl (2R,1'S)-1-((1'-methyl)benzylazetidin-2,2-dicarbonylate (2a). Lithium chloride (23 mg, 0.54 mmol), BHT (120 mg, 0.55 mmol) and molecular sieves 3Å (150 mg) were added to a solution of 3a (47 mg, 0.17 mmol) in DMSO (0.25 mL), and the mixture was stirred for 1 h at room temperature. The reaction mixture was then heated at 140 °C for a further 2 h and, after cooling, was diluted with a phosphate buffer (pH 6.0, 0.1 M) and extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography [developed with hexane–EtOAc (2:1) with a trace of triethylamine] to afford a mixture of (2S,1'S)-2a and (2R,1'S)-2a (total 27.2 mg, 78%) as a pale yellow oil. The diastereomeric ratio (2:1) was estimated from the 1H-NMR spectra as shown next. These two components were further purified by the same preparative TLC and subsequent bulb-to-bulb distillation.

(2S,1'S)-2a (Rf 0.40): Bp 150–170 °C at 0.18 mmHg (bath temp.). [α]D²⁵ −118.7° (c 1.1, EtOH); IR νmax cm⁻¹: 1753, 1730, 1196, 1174; δ H (270 MHz, CDCl₃): 1.21 (3H, d, J = 6.6 Hz), 2.16 (1H, ddd, J = 2.8, 8.0, 8.4, 8.6 Hz), 2.25 (1H, ddd, J = 8.0, 8.0, 8.4, 8.6 Hz), 2.78 (1H, ddd, J = 8.0, 8.0, 8.0 Hz), 3.09 (1H, ddd, J = 2.8, 8.0, 8.0 Hz), 3.43 (1H, q, J = 6.6 Hz), 3.74 (3H, s), 3.74 (1H, d, J = 8.4, 8.4 Hz), 7.18–7.33 (5H, m); δ C (67.5 MHz, CDCl₃): 20.85, 20.99, 49.62, 51.87, 63.89, 67.21, 127.04, 127.30 (x2), 128.14 (x2), 142.27, 173.44. Anal. Found: C, 71.26; H, 7.74; N, 6.35%. Calcd for C₁₃H₁₈N₂O₃Na: C, 71.12; H, 7.74; N, 6.39%. The 1H-NMR spectrum was identical with that reported previously.⁹

(2R,1'S)-2a (Rf 0.15): Bp 150–170 °C at 0.18 mmHg (bath temp.). [α]D²⁵ +48.9° (c 1.1, EtOH); IR νmax cm⁻¹: 1761, 1732, 1252, 1101; δ H (270 MHz, CDCl₃): 1.26 (6H, t, J = 7.1 Hz), 1.28 (3H, d, J = 6.4 Hz), 2.39–2.55 (2H, m), 3.00 (1H, ddd, J = 3.0, 6.5, 7.9 Hz), 3.14 (1H, ddd, J = 7.4, 7.4, 7.9 Hz), 3.73 (1H, q, J = 6.4 Hz), 4.06–4.39 (4H, m), 7.14–7.34 (5H, m).

When the reaction was quenched prior to cyclization under a low dose of TBAI, the C-alkylated form (6) was isolated as an intermediate: δ H (270 MHz, CDCl₃): 1.10 (3H, t, J = 7.1 Hz), 1.22 (3H, t, J = 7.1 Hz), 1.34 (3H, d, J = 6.8 Hz), 2.14–2.26 (1H, m), 2.43–2.54 (1H, m), 3.05–3.17 (2H, m), 3.73 (1H, q, J = 6.8 Hz), 7.17–7.26 (5H, m).

Another by-product with an imine structure (7): δ H (270 MHz, CDCl₃): 1.47 (3H, d, J = 6.4 Hz), 1.23 (3H, t, J = 7.3 Hz), 1.24 (3H, t, J = 7.3 Hz), 4.24 (2H, q, J = 7.3 Hz), 4.27 (2H, q, J = 7.3 Hz), 4.58 (1H, q, J = 6.6 Hz), 7.10–7.28 (5H, m).

A small portion was purified by preparative TLC [developed with hexane–EtOAc (4:1) with a trace of triethylamine]. [α]D²⁵ −64.5° (c 1.1, EtOH); IR νmax cm⁻¹: 3338, 1757, 1739, 1225, 1153; δ H (270 MHz, CDCl₃): 1.33 (3H, d, J = 6.6 Hz, 2.18 (1H, br), 3.62 (3H, s), 3.69 (3H, s), 3.71 (1H, q, J = 6.6 Hz), 3.87 (1H, s), 7.15–7.29 (5H, m); δ C (65.7 MHz, CDCl₃): 24.46, 52.67 (x2), 56.41, 62.54, 126.70 (x2), 127.24, 128.36 (x2), 143.47, 168.42, 169.33. The IR and NMR spectra were in good accordance with those of the racemate reported previously.¹⁴
cm\(^{-1}\); 1745, 1196, 1173; NMR \(\delta_H\) (270 MHz, CDCl\(_3\)): 1.27 (3H, d, \(J = 6.6\) Hz), 2.12 (1H, dddd, \(J = 3.0, 8.1, 8.8, 9.2\) Hz), 2.28 (1H, dddd, \(J = 9.2, 9.2, 9.2, 9.2\) Hz), 2.99 (1H, dd, \(J = 8.1, 8.1, 9.2\) Hz), 3.31 (3H, s), 3.34 (1H, q, \(J = 6.6\) Hz), 3.56 (1H, ddd, \(J = 3.0, 8.1, 9.2\) Hz), 3.56 (1H, dd, \(J = 8.8, 9.2\) Hz), 7.17–7.27 (5H, m); NMR \(\delta_C\) (67.5 MHz, CDCl\(_3\)): 19.74, 20.85, 50.74, 51.45, 64.40, 68.09, 127.31, 127.79 (\(x_2\)), 127.86 (\(x_2\)), 141.42, 172.38. Anal.: C, 71.13; H, 7.78; N, 6.30%. Calcd. for C\(_{13}\)H\(_7\)NO\(_2\): C, 71.21; H, 7.81; N, 6.39%. The NMR spectrum was identical with that reported previously.\(^9\)

**Isomerization of (2R,1'S)-2a.** An LDA solution was prepared by adding n-butyllithium (2.7 M in hexane, 150\(\mu\)l, 0.41 mmol) to a solution of disopropylamine (117\(\mu\)l, 0.83 mmol) in THF (0.5 ml) at 0°C. After cooling to \(-78\)°C, a solution of (2R,1'S)-2a (45.4 mg, 0.21 mmol) in THF (0.5 ml) was added, and the mixture was stirred for 2h. The reaction was quenched by adding MeOH at \(-78\)°C, and the conventional workup and purification already described to give a mixture of (2S,1'S)- and (2R,1'S)-2a (37.1 mg, 82%, 6.7:1).

(2S,1'S)-1-(1'-Methyl)benzazetidin-2-carboxylic acid (2b) from pure (2S,1'S)-2a. Chiralazine L-2 (c-f, 40 mg) was added to (2S,1'S)-2a (36.4 mg, 0.12 mmol) in water (1.5 ml), which had been ultrasonically emulsified in advance. The mixture was stirred for 2h at 40°C. The reaction mixture was then filtered, and the filtrate was extracted with diethyl ether. The aqueous layer was extracted with diethyl ether. The aqueous layer was then evaporated in vacuo to give (2S,1'S)-2b (38.7 mg, quant) as a pale yellow amorphous solid. [\(\alpha\)]\(^{20}\)D = \(-48.9\)° (c 1.0, EtOH); IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3411, 1626, 1404; NMR \(\delta_H\) (270 MHz, CDCl\(_3\)): 1.69 (3H, d, \(J = 6.9\) Hz), 2.40 (1H, ddd, \(J = 3.6, 9.3, 9.6, 9.9\) Hz), 2.66 (1H, ddd, \(J = 9.3, 9.3, 9.6\) Hz), 3.34 (1H, ddd, \(J = 9.3, 9.3\) Hz), 3.89 (1H, ddd, \(J = 3.6, 9.3, 9.3\) Hz), 4.25 (1H, q, \(J = 6.9\) Hz), 4.42 (1H, dd, \(J = 9.6, 9.6\) Hz), 7.34–7.52 (5H, m); NMR \(\delta_C\) (67.5 MHz, CDCl\(_3\)): 18.57, 21.04, 47.43, 65.12, 66.86, 121.94, 129.08 (\(x_2\)), 129.13 (\(x_2\)), 135.38, 170.84; FAB-HRMS (M\(^+\) + Na\(^+\), m/z): 228.0974; calcd. for C\(_{12}\)H\(_7\)NO\(_2\)Na, 228.1001. The \(^1\)H-NMR spectrum was identical with that reported previously.\(^9\)

(S)-Azetidine-2-carboxylic acid (1a). N-Protected amino acid 2b (112 mg, 0.55 mmol) was dissolved in a mixture of water and ethanol (1:1, 2.5 ml). Palladium on carbon (10%, 120 mg) was added, and the mixture was vigorously stirred under hydrogen for 46 h. The resulting suspension was filtered, and the solid residue was washed with water. The solvent was evaporated in vacuo, and the solid residue (41.8 mg, 75%) was ultrasonically suspended in methanol (0.5 ml), before the mixture was left to stand overnight at \(-20\)°C. The solid was recovered and washed with methanol to afford 1a (30.0 mg, 54%) as colorless fine needles. Mp above 200°C (dec.). [\(\alpha\)]\(^{20}\)D = \(-121.7\)° (c 0.5, H\(_2\)O); IR \(\nu_{\text{max}}\) cm\(^{-1}\): 2976, 2688, 2517, 1637, 1593, 1410, 1306, 1288, 1254; NMR \(\delta_H\) (270 MHz, D\(_2\)O): 2.28–2.44 (1H, m), 2.54–2.69 (1H, m), 3.75 (1H, dd, \(J = 6.0, 10.0, 10.0\) Hz), 3.91 (1H, dd, \(J = 8.8, 10.0, 10.0\) Hz), 4.62 (1H, dd, \(J = 8.3, 10.2\) Hz). All the physical and spectral properties were coincident with those of a commercially available authentic sample (Sigma, A0760).

A small portion of (S)-1a was converted to corresponding N-benzoyl methyl ester 1b by successively treating with benzoyl chloride in an aqueous sodium hydroxide solution and then with diazomethane in diethyl ether in the conventional manner to determine its enantiomeric excess (ee). HPLC: column, Daicel Chiralcel OD, 0.46 cm × 25 cm; eluent, hexane-isopropyl alcohol = 7/1; flow rate, 0.5 ml/min; Rt 63.4 min for (S)-1b as a single peak. Rt 56.7 min for (R)-1b.

(S)-Azetidine-2-carboxylic acid (1a) from a mixture of (2S,1'S)- and (2R,1'S)-2a. Chiralazine L-2 (c-f, 117 mg) was added to a mixture of 2a (115 mg, total 0.52 mmol, (2S,1'S)/(2R,1'S) = 2.7:1 by NMR) in water (2.5 ml), which had been ultrasonically emulsified in advance. The mixture was stirred for 10 h at 17°C. The reaction mixture was filtered, and the resulting filtrate was extracted several times with toluene to remove the unreacted materials. Concentration of the combined organic layer and purification by preparative thin-layer column chromatography yielded 2a (23.4 mg, 20% recovery). Its NMR spectrum showed that the unreacted material was the pure (2R,1'S)-isomer.

The aqueous layer was concentrated in vacuo to give (2S,1'S)-2b (108 mg, quant.) as a pale yellow amorphous solid. This contained (2R,1'S)-2b (ca. 3%), judging from its NMR spectrum with the signal at \(\delta_H\) 3.54 (1H, ddd, \(J = 8.9, 8.9, 8.9\) Hz). This was hydrogenated in a similar manner to that just described to give crude 1a (51.1 mg, quant.). Preferential crystallization from methanol (0.5 ml) afforded (S)-1a (35.2 mg, 91% from mixture of 2a), whose ee was >99.9% after conversion to 1b as already described. The acid (S)-1a recovered from the mother liquor of the final crystallization showed 87.5% ee.

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