Synthetic Study of Optically Active 3-Azabicyclo[3.3.0]octane-2,6,8-tricarboxylic Acid

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Received April 30, 2003; accepted June 6, 2003

Synthesis of (1R,2S,5S,6R,8S)-3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylic acid (2) from trans-4-hydroxy-\(\alpha\)-proline (5) was attempted. A Diels–Alder reaction of 3,4-dehydroproline derivative 9 and cyclopentadiene afforded a single stereoisomer 11. The Diels–Alder adduct was smoothly converted to the hydrochloride of 2 (24) via RuO\(_4\) oxidation. Although some racemization of the material or product was observed during the synthetic processes, the amino acid 24 proved to be optically pure.

Key words trans-4-hydroxy-\(\alpha\)-proline; Diels–Alder reaction; ruthenium tetroxide; 3,4-dehydroproline; dicyclopentadiene; (1R,2S,5S,6R,8S)-3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylic acid

During our study on the synthesis of amino acids using Diels–Alder adducts,\(^1\)–\(^3\) we synthesized racemic 3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylic acid (1)\(^1\) as an analog of kainic acid. However, considering its potential biological uses, the optically active compound has more advantages, so we wanted to synthesize optically active 3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylic acid (2). In this paper, we report a synthetic approach to 2 and the related chemistry.

Retro-synthesis of 2 (Chart 1) gave the Diels–Alder adduct 3 and then the derivative of 3,4-dehydroproline 4, which should be derived from readily available trans-4-hydroxy-\(\alpha\)-proline (5). To obtain the derivative of 3,4-dehydroproline 4, selective 3,4-elimination of 5 is needed,\(^4\)–\(^7\) so the hydroxyl group of 5 must be converted to a phenylseleno group, which would cause elimination similar to the Cope elimination reaction after H\(_2\)O\(_2\) oxidation.\(^4\)

The starting 5 was converted to the \(\text{N},\text{C}\)-protected form 6 by usual method\(^8\) in 94% yield. Treatment of 6 with \(p\)-toluenesulfonyl chloride (TsCl) and 4-dimethylaminopyridine (DMAP) in pyridine afforded 7\(^9\) in 91% yield. Compound 7 was allowed to react with sodium phenylselenide,\(^4\)–\(^7\) which was generated from diphenyldiselenide and sodium borohydride in situ, to afford compound 8 in 97% yield. Oxidation of 8 with 30% H\(_2\)O\(_2\) in CH\(_2\)Cl\(_2\) in the presence of pyridine afforded dienophile 9 in 70% yield. Estimation of the optical purity of 9 was difficult on HPLC analysis using a chiral column (DAICEL CHIRALCEL OD), so 9 was hydrogenated to form 10a (Chart 3). Its specific rotation ([\(\alpha\)]\(_D\)\(^{18}\) = \(-96.7\)\(^\circ\)) was compared with that of 10b, which was prepared from 1-\(\alpha\)-proline ([\(\alpha\)]\(_D\)\(^{18}\) = \(-101.7\)\(^\circ\)),\(^10\) and the optical purity of 10a proved to be 95.1%ee.

Next, a Diels–Alder reaction of the dienophile 9 and cyclopentadiene was attempted. When compound 9 was heated with cyclopentadiene in a bomb tube at 90 °C, almost no reaction was observed. Additions of a Lewis acid such as (C\(_5\)H\(_5\))\(_2\)O·BF\(_3\), SnCl\(_4\) or ZnI\(_2\) at \(-70\)–0 °C into the mixture of 9 and the cyclopentadiene were investigated, but they resulted in the formation of polymers (when used (C\(_5\)H\(_5\))\(_2\)O·BF\(_3\) or SnCl\(_4\)) or the decomposition of 9 (when used ZnI\(_2\)). We then tried to employ dicyclopentadiene (cyclopentadiene dimer) as both reagent and solvent at a higher temperature (Chart 4). A solution of 9 in dicyclopentadiene was heated in a bomb tube at 150 °C (oil bath temp., inner temp.: 135 °C), and 9 had completely disappeared after 48 h, giving the desired 11a in 52% yield (after recrystallization). At 170 °C (oil bath temp., inner temp.: 153 °C), 9 had disappeared after 36 h and 11b was obtained in 52% yield. Both products 11a, b had the same specific rotation, [\(\alpha\)]\(_D\)\(^{20}\) = \(-73.2\)\(^\circ\). Although four stereoisomers were expected to form in this reaction, only one isomer 11 was isolated; on analysis of mass spectra (MS) for the other constituents of the reaction mixture, there was no peak of 297 (M\(^+\)), which would have been indicative of the diastereomers. The stereochemistry of 11 was confirmed by differential nuclear Overhauser effect (NOE) experiments of \(^1\)H-NMR; +NOEs were observed between a signal at \(\delta\) 4.58 assigned to the 3-proton and signals at \(\delta\) 6.05, 6.07, 6.27, and 6.36 assigned to olefinic protons (signals split due to the rotamers).

As we feared that racemization would occur under the reaction conditions employed, the following experiments were
attempted. A solution of 9 ([α]_D^20 = -357.8°) in xylene was heated in a bomb tube at 150 °C (oil bath temp.) for 48 h, and the recovered 9 had [α]_D^20 = -292.3°. When heated at 170 °C (oil bath temp.) for 36 h, the recovered 9 had [α]_D^20 = -231.5°. When heated at 170 °C (oil bath temp.) for 48 h, the recovered 9 had [α]_D^20 = -202.4°. Despite exchanging xylene for dicyclopentadiene as a solvent, Diels–Alder adduct 11 obtained from the reaction at 150 °C (oil bath temp.) for 48 h had the same specific rotation [α]_D^20 = -73.2° (after one recrystallization) as that obtained from the reaction at 170 °C (oil bath temp.) for 36 h, or 48 h. Furthermore, when the obtained 11 was heated in dicyclopentadiene at these temperatures, no formation of 9 was observed; the retro-Diels–Alder reaction could not occur under these conditions. These results suggest that the rate of the Diels–Alder reaction is much faster than that of racemization of 9.

To estimate the exact optical purity of the obtained 11 and ratio of the racemization under the reaction conditions, we prepared the enantiomer 17 from cis-4-hydroxy-d-proline (12) and compared the enantiomers on HPLC using a chiral column (DAICEL CHRALCEL OD, 0.46 cm i.d. × 25 cm). Compound 12 was converted to the N,C-protected form 13 by the usual method in 85% yield. Treatment of 13 with p-TsCl in pyridine afforded 14 in 90% yield when DMAP was added to the reaction mixture as a catalyst similar to the conversion of 6 to 7, the yield of the product decreased by ca. 20% with increasing by-products. Compound 14 was treated with sodium phenylselenide to afford 15 in 97% yield. Oxidation of 15 with 30% H_2O_2 in CH_2Cl_2 in the presence of pyridine afforded 16 in 74% yield. Dienophile 16 was subjected to a Diels–Alder reaction similarly to 9, giving 17 in 51% yield. A mixture of enantiomers 11 and 17 were separable under the following condition: solvent, hexane–2-propanol (9:1); flow rate, 1 ml/min; column temperature, 30°C. The retention time for 17 was 9.2 min and that for 11 was 11.9 min. A solid of 11 obtained by separation using silica gel column chromatography from the Diels–Alder reaction mixture was analyzed and proved to be 91.1%. After one recrystallization of the solid from diisopropyl ether, the optical purity increased to 99.8%. After two recrystallizations, 11 did not contain the enantiomer (100%). As such, the once-recrystallized 11 was used as the starting material for the following stage because of the balance between quality and quantity.

However, to avoid racemization under the Diels–Alder reaction conditions, we next chose compound 19 as another dieneophile (Chart 5). Reduction of ester 8 by NaBH_4–LiCl in THF–EtOH followed by treatment with benzoyl chloride (BzCl) afforded benzoate 18 in 91% yield. Oxidation of 18 in a similar manner to that employed for the oxidation of 8 afforded the desired dienophile 19 in 64% yield. Compound 19 was heated with dicyclopentadiene in a bomb tube at 170°C for 48 h, and the Diels–Alder adduct 20 was obtained in 51% yield. The stereochromy of 20 was confirmed by identification of the product 21b at the next step with 21a. Diastereomers of 20 were not detected by MS analysis in the other constituents of the reaction mixture, which had Rf values on TLC similar to that of 19.

Ruthenium tetroxide (RuO_4) oxidation of 1 followed by treatment with diazomethane afforded triester 21a in 83% yield, the specific rotation of which was [α]_D^20 = -35.0°. In contrast, benzoate 20 was first hydrolyzed by 1 M NaOH, oxidized by ruthenium tetroxide, then treated with diazomethane to afford 21b in 71% yield, for which the specific rotation was [α]_D^20 = -33.5°.

We attempted to elucidate the reason for the lower optical purity of 21b than 21a as follows. Compound 19 was hydro-
generated in the presence of 10% Pd/C and converted to compound 23a, for which the specific rotation was \([\alpha]_D^{18} = -157.2^\circ\). This product was then compared with the authentic 23b derived from L-prolinol (22),\textsuperscript{13} for which the specific rotation was \([\alpha]_D^{18} = 168.0^\circ\), and the optical purity of 23a proved to be 93.6%ee. The proportion of partial racemization of 23a was slightly more than that of 10a. Therefore, the lower optical purity of 21b appeared to be due to the purification of 20 by recrystallization not being possible because 20 was obtained as an oil.

Compounds 21a and 21b were heated with 6 M HCl–AcOH at 100 °C for 24 h, respectively, and the salts of the target amino acid 2 (24) were quantitatively obtained by concentration of the aqueous solution washed with benzene. The structure of 24 was confirmed by identification of \(^1\)H- and \(^{13}\)C-NMR data with those of 1. In the case of racemic 1, the hydrochloride salt was desalted simply by being dissolved in water, giving the free amino acid as a crystal. In particular, when the pH of the aqueous solution was adjusted to 4 with NaOH, the crystallization was quantitative. A crude hydrochloride of 2 (from 21a) was treated similarly, but no solid was deposited. When a crude hydrochloride of 2 (from 21b) was treated similarly, a small amount of free amino acid was deposited, but the yield was only 6%; moreover, the crystal did not exhibit optical rotation, consisting only of 1. It turned out that the deposited crystal of the amino acid was a racemate, crude 2 (from 21a) was purified as a hydrochloride; recrystallization of the hydrochloride from water–acetone gave 24 as a white powder in 83% yield.

To evaluate the optical purity of the target amino acid, racemic 1 was esterified with SOCl\textsubscript{2}–MeOH, followed by treatment with \((S)\-(+)\-\alpha\)-methoxy-\(\alpha\)-trifluoromethylphenylacetyl chloride \([(S)\-(+)\-MTPA-Cl, 98\%ee]\),\textsuperscript{14,15} and converted into a comparable mixture of both epimers 25 and 26 in 62% yield. Optically active 24 was treated similarly to 1, giving a mixture of MTPA amides in 61% yield. Mixtures of both epimers were separable on HPLC using a silica gel column [JASCO Finepak SIL, hexane–AcOEt (1 : 1), retention time; 25: 8.70 min, 26: 9.99 min] and the diastereomeric purity from 21a proved to consist of 99% 25 and 1% 26 (or enantiomer 27). \(^1\)H-NMR analysis also supported this result, indicating that the signal of a proton at the 2-position of 25 exists at \(\delta \) 4.41 and that of 26 exists at \(\delta \) 4.68; the component ratio of 25 : 26 (or enantiomer 27) was 99 : 1. The diastereomeric purity of the MTPA amide derived from 24 reflected the optical purity of \((S)\-(+)\-MTPA-Cl (98\%ee). Consequently, the target amino acid 2 proved to be optically pure.

In conclusion, while the free target 2 has not been isolated, we synthesized an optically active \((1R,2S,5S,6R,8S)\-3\-azabicyclo[3.3.0]octane-2,6,8-tricarboxylic acid as hydrochloride 24.

**Experimental**

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Specific rotations were determined with a JASCO DIP-370 polarimeter. NMR spectra, except for the amino acids, were recorded in chloroform-d (CDCl\textsubscript{3}) on a GSX-400 spectrometer using tetramethylsilane as an internal standard. For the amino acids, analysis was performed in 2M deuterium chloride (DCl) using 1,4-dioxane as an internal standard (\(\delta \) 3.7 for \(^1\)H-NMR and \(\delta \) 67.4 for \(^{13}\)C-NMR). Infrared (IR) spectra were recorded on a Hitachi 270-30 spectrophotometer. Mass spectra (MS) were obtained with a JEOL JMS-DX300 instrument. TLC was performed on Silica gel 60 F\textsubscript{254} plates (0.25 mm, Merck). Column chromatography was performed on silica gel (Kieselgel 60, 70—230 mesh, Merck) or alumina (Aluminium oxide 90, 70—230 mesh, Merck). Flash chromatography was performed on silica gel (Silica Gel 60, 230—400 mesh, Nacalai Tesque).

**Fig. 2.** NOE Relationships of Diels–Alder Adduct 11

**Fig. 3**

**Fig. 4**
Methyl (2S,4R)-1-Benzoyl-4-hydroxyprolinol-2-carboxylate (6)
Thionyl chloride (21.8 ml) was added dropwise to MeOH (500 ml) at −10 °C. After 30 min, trans-4-hydroxy-t-proline (5, 26.2 g, 0.20 mol) was added to the solution, and the white solid was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and MeOH (300 ml) was added to the residue, after which the solution was concentrated under reduced pressure to give a white solid. The solid was dissolved in 1,4-dioxane (400 ml), and the solution was cooled in an ice bath. After aqueous NaHCO₃ (50.4 g/450 ml) was added in several portions, the solution was cooled to room temperature. The resulting yellow oil was subjected to column chromatography on silica gel [hexane–AcOEt (4 : 1)] to give 9 (8.10 g, 70%) as colorless needles, mp 100.5—101.5 °C, [α]D₅–18° (c = 1.00, CHCl₃). IR νCO: 1651 (C=O), 1610 (C=O), 1552 (C=C). MS m/z: 369 (M⁺, 100%). Anal. Calcd for C₁₇H₁₉NO₆: C, 58.31; H, 5.91; N, 3.50. M. 360.0.

Methyl (2S,4R)-4-Benzoylselenol-1-prolinol-2-carboxylate (8)
Under argon atmosphere, NaBH₄ (2.04 g, 54 mmol) was slowly added to a solution of 3 (19.4 g, 0.05 mol) and pyridine (8.0 ml, 0.10 mol) in CH₂Cl₂ (100 ml) at −78 °C. After aqueous NaHCO₃ (50.4 g/450 ml) was added in several portions, the solution was cooled to room temperature. The resulting yellow oil was subjected to column chromatography on silica gel [hexane–AcOEt (4 : 1)] to give partially racemized 9, which was then analyzed by optical rotation.

Methyl (1R,2S,5S,6R,7S)-4-Benzoyl-4-azatricyclo[5.2.1.0²,6]dec-8-ene-2-carboxylate (11)
A mixture of compound 9 (3.35 g, 14.5 mmol) and diisopropylamine (20 ml) was heated in a bomb tube at 150 °C (oil bath temp., inner temp.: 135 °C) for 4 h or at 170 °C (oil bath temp., inner temp.: 153 °C) for 3 h. The reaction mixture was subjected to column chromatography on silica gel (hexane–AcOEt (4 : 1)) to recover partially racemized 9, which was then analyzed by optical rotation.
tallization from benzene–hexane gave colorless needles, mp 100—101.5 °C, the whole was then vigorously stirred at room temperature for 2 h. CH₂Cl₂ percent aqueous H₂O₂ solution (4.0 ml) was added dropwise to a solution of (2.73 g, 7.03 mmol) and pyridine (1.12 ml) in CH₂Cl₂ (15 ml) at 0 °C, and 3.58 (2H, m), 3.78—3.93 (1H, m), 4.46—4.78 (3H, m), 7.19—8.06 (15H, s). Anal. Calcd for C₃₄H₄₄N₄O₂S: C, 59.9; H, 5.25; N, 3.47. Found: C, 59.43; H, 5.25; N, 3.64.

Methyl (2R,4S)-1-Benzoyl-4-phenylselenopyrrolidin-2-carboxylate (21a) Derived from Compound 20 A mixture of compound 19 (2.50 g, 8.13 mmol) and diclof pendiadene (15 ml) was heated in a bomb tube at 170 °C for 48 h. The reaction mixture was subjected to column chromatography on silica gel [hexane–AcOEt (1 : 1)] to give 21a (1.08 g, 89%) as a colorless oil.

Methyl (2S,4S)-1-Benzoyl-4-phenylselenopyrrolidin-2-carboxylate (21b) Derived from Compound 20 1st NaOH (5.0 ml) was droppedwise to a solution of 20 (1.87 g, 5.01 mmol) in MeOH (30 ml), and the mixture was stirred at 0 °C for 4 h. Water (100 ml) was added, and the whole was extracted with AcOEt (200 ml×3). The organic layer was washed with water (100 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The precipitated RuO₂ was filtered off, and the solution was dried over anhydrous Na₂SO₄, then concentrated under reduced pressure. The residue was dissolved in MeOH (10 ml) and treated with diazomethane. The solution was concentrated, and the residual white solid was recrystallized from MeOH (10 ml) to give 21b [(1.92 g, 85%) as a colorless needle, mp 73.8—75.0 °C, [α]D25 25.7° (C 1.0, CHCl₃). 1H-NMR, 13C-NMR, IR, and MS data completely coincided with those of the isomer 21a.

Methyl (2S,4R,5S,6R,7R,8)-6-Benzoyl-4-azatricyclo[5.2.1.02,6]dec-8-en-3-ylmethy 1-Benzozyl-4-phenylselenopyrrolidin-2-carboxylate (25) Under argon atmosphere, LiCl (4.16 g, 110 mmol) and NaBH₄ (4.16 g, 110 mmol) were added to a solution of compound 17 (2.5 g, 7.70 mmol) in THF (90 ml), and EtOH (160 ml) was dropwise added to the mixture with stirring at room temperature. The stirring was continued overnight. Water (180 ml) was added, and the whole was extracted with CHCl₃ (150 ml×3). The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was subjected to column chromatography on alumina (AcOEt), and the resulting solid was recrystallized from AcOEt–hexane to give 25 (21.3 g, 91%) as colorless prisms, mp 107—108 °C, [α]D25 −74.3° (c = 1.0, CHCl₃). 1H-NMR (CDCl₃) δ: 2.03—2.11 (1H, m), 2.59—2.64 (1H, m), 3.38—3.59 (2H, m), 3.78—3.93 (1H, m), 4.46—4.78 (3H, m), 7.19—8.06 (15H, s). 13C-NMR (CDCl₃) δ: 39.51 (t), 39.63 (d), 56.15 (d), 57.13 (t), 64.44 (t), 127.09 (d), 127.61 (s), 128.25 (d), 128.37 (d), 128.48 (d), 129.22 (d), 129.61 (d), 129.92 (s), 130.57 (d), 133.06 (d), 135.11 (d), 136.05 (s), 166.23 (s), 169.85 (s). IR νKBr cm⁻¹: 1726 (C=O), 1636 (C=O). MS m/z: 465 (M⁺).

Anal. Calcd for C₃₄H₄₄N₄O₂Se: C, 64.65; H, 4.99; N, 3.02. Found: C, 64.69; H, 4.96; N, 3.00.
presence of 10% Pd/C (50 mg) under a pressure of 3 atm for 6 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give 23a (295 mg, 98%) as a colorless oil. [α]_D^25 −157.2° (c = 1.0, CHCl₃). Authentic 23b was prepared from 22 by the reported procedure. 1) [α]_D^25 −168.0° (c = 1.0, CHCl₃), lit. [α]_D^25 −154.0° (CHCl₃).] Comparison of the specific rotations indicated that the optical purity of 19 was 93.6%ee.

(1R,2S,5S,6R,8S)-3-Azabicyclo[3.3.0]octane-2,6,8-tricarboxylic Acid Hydrochloride (24) Compound 21a (778 mg, 2.00 mmol) was heated in AcOH (40 ml) and 6 M HCl (40 ml) at 100 °C for 24 h. The reaction mixture was concentrated under reduced pressure to give 24 (553 mg, 99%) as a white solid, which was recrystallized from water-acetone to give a white powder (465 mg, 83%), mp 213 °C (dec.), [α]_D^18 23.8° (c = 1.0, 2 M HCl). 1H- and 13C-NMR data completely coincided with those of the racemic 21a, no solid precipitated from the pH 4 solution.

Estimation of the Optical Purity of 24 First, for an authentic sample, racemic 1OH was converted to MTPA amide. Thionyl chloride (33 μl) was added to MeOH (5.0 ml) at −10 °C. After 30 min, compound 1 (24.3 mg, 0.10 mmol) was added to the solution, and the whole was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and MeOH (5.0 ml) was added to the residue, after which the solution was concentrated under reduced pressure to give a white solid (33.0 mg). This product was dissolved in anhydrous pyridine (5.0 ml), and the solution was cooled in an ice bath. (S)-(+)-MTPA-CI (Aldrich, 98%, 27.8 mg, 0.11 mmol) and DMAP (1.2 mg) were added with vigorous stirring at 0 °C, and the stirring was continued for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water (10 ml) was added, and the whole was extracted with benzene (20 ml). The benzene layer was dried with cold 5% HCl (10 ml×2), sat. NaHCO₃ (10 ml), and water (10 ml×3). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (AcOEt) to give a mixture of 25 and 26 (31.0 mg, 62%). The mixture was used in 1H-NMR and HPLC analyses. Second, compound 24 (27.9 mg, 0.10 mmol) was similarly treated to give a mixture of 25 and 26 (or its enantiomer 27) in 61% yield. Analyses on HPLC were done under the condition [JASCO Finepak SIL, 0.46 cm i.d.×25 cm, solvent: hexane–AcOEt (1:1), sample injection: 20 μl (1.00 g/1 CHCl₃ solution, flow rate 1 ml/min, column temp.: 40 °C] and showed that the ratio of the enantiomers derived from 24 was 99 : 1. (retention time: 25: 8.70 min, 26: 9.99 min). 1H-NMR analyses were carried out in CDCl₃ solutions by the comparison of integrated intensities of δ 4.41 (25) and 4.68 (26), and these results supported the HPLC results.

Acknowledgement This work was supported in part by the Special Research Fund of Hokuriku University.

References and Notes
16) Some signals split or broaden due to the rotamers or the conformers.