Pergamon

Tetrahedron 55 (1999) 943–954

TETRAHEDRON

An Efficient Synthesis of 4-Aryl Kainic Acid Analogs

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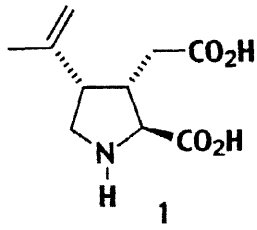
Received 20 May 1998; accepted 19 November 1998

Abstract

A synthesis of 4-aryl kainic acid analogs was achieved using a highly stereoselective Michael addition reaction of dimethyl 2-oxoglutarate with a nitrostyrene. Nitro group reduction, deoxygenation and epimerization complete the synthetic route.

The search for neuroexcitatory compounds has been an active area of research.[1] Of the various natural products containing a glutamic acid subunit, the kainic acid family has seen significant interest, from both a synthetic and a toxicological perspective.[2] Both kainic acid (**1**) and domoic acid (**2**) may be viewed as conformationally constrained glutamic acid analogs. Kainic acid has been used as an anthelmintic agent.



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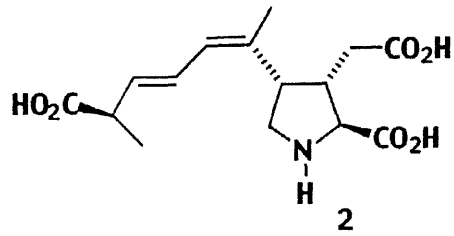

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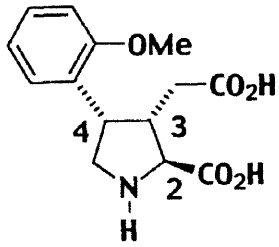

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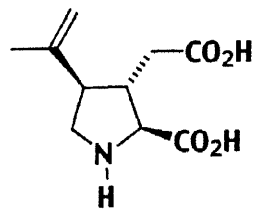

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Many modifications of the kainic acid skeleton have been synthesized and tested. Certain structural features have emerged as crucial for biological activity. Testing results have shown that the substituent at C-4 must be an aryl (as in analog **3**) or an alkenyl group (as

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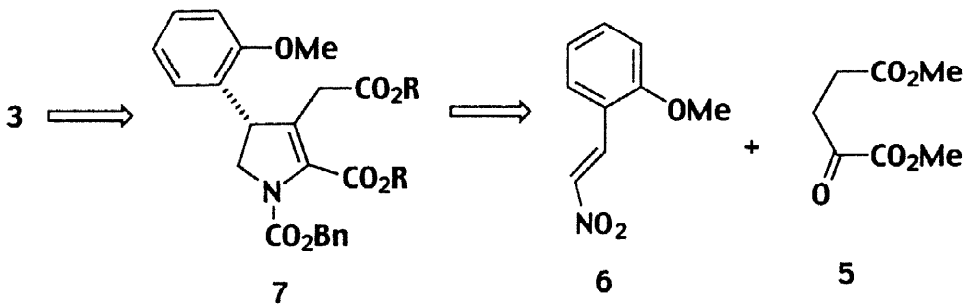
0040-4020/99/$ - see front matter
PII: S0040-4020(98)01101-6

in **1** or **2**). Reduction of the unsaturation in **1** led to loss of activity.[3] The substituents at C-3 and C-4 must be cis. Compounds bearing the trans-relationship such as allokainic acid (**4**), have greatly diminished activity. The trans-relationship between substituents at C-2 and C-3 is also important, although some cis- compounds have been reported to exhibit useful biological activity.[4]

In 1992 Shirahama and coworkers reported the synthesis and biological activity of the aryl kainoid **3**.[5] Compound **3** exhibits more potent neuroexcitatory activity than domoic acid or kainic acid. Since that report, four syntheses of 4-aryl kainoids have been reported. Baldwin and coworkers synthesized **3** by an enantioselective route beginning with 4-hydroxyproline.[6] They employed a directed hydrogenation of a dihydropyrrole as the key step. Shirahama also reported a photochemical approach to the aryl kainoids.[7] This work featured a clever tandem photoenolization reaction-intramolecular Diels-Alder reaction sequence. Lubell and coworkers communicated a novel synthesis using organopalladium chemistry in the key step.[8] We recently communicated a direct synthetic route in 1997.[9] This paper describes a full account of this work.

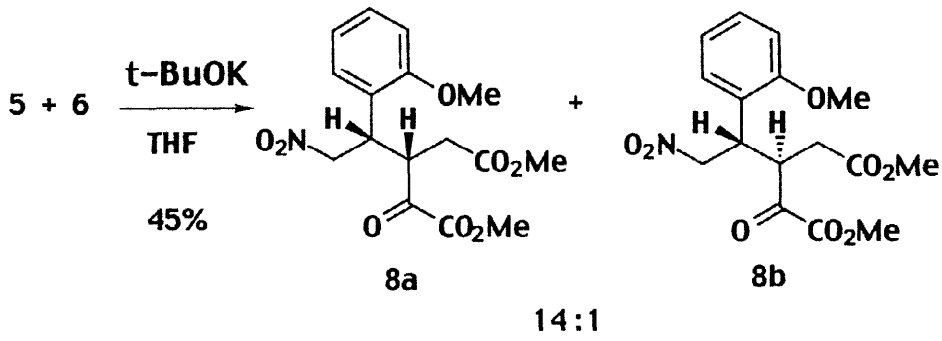
Our approach to the aryl kainoids began with the dimethyl ester of 2-keto glutaric acid (**5**) and nitro styrene **6**. This seemed to be a logical starting point since both carboxylic acid functional groups could be introduced at the desired oxidation state, thus avoiding the sequence of protection, deprotection, and oxidation typical of most syntheses of kainic acid derivatives. The requisite cis relationship between substituents at C-3 and C-4 was to be secured by reduction of an enamide such as **7**. The trans- relationship between C-2 and C-3 could be achieved by epimerization at C-2 under basic reaction conditions. We had previously accomplished such an epimerization in our racemic synthesis of allokainic acid (**4**).[10]



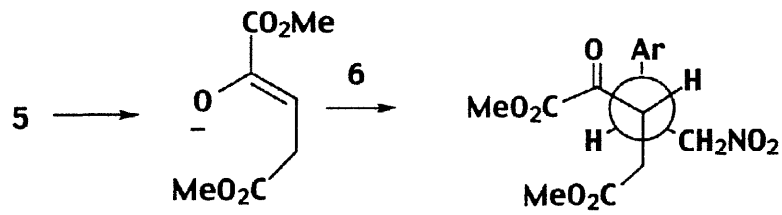
A literature search showed that the chemistry of a-keto glutaric acid or analogous diesters had been little studied. There were no examples of aldol or Michael addition reactions. The reaction of **5** with nitro styrene **6** using a variety of bases and solvents led to a 45% isolated yield of adducts **8a** and **8b** under the optimal conditions involving the use of

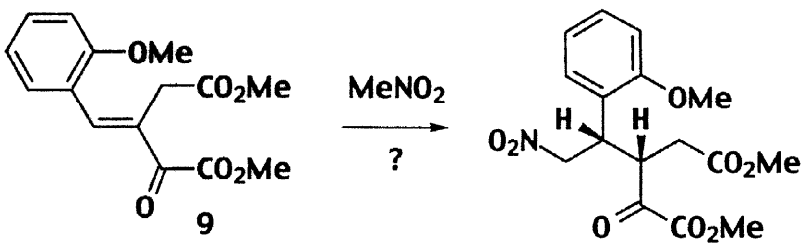
potassium tert-butoxide in THF. Addition of lithium diisopropylamide (LDA) to a mixture of **5** and **6** at -78 °C produced a modest yield of **8a** and **8b** with recovered **6**.

Using the potassium tert-butoxide conditions, adducts **8a** and **8b** could be reproducibly produced on a multigram scale as a 14:1 mixture of stereoisomers. In major isomer **8a** the methylene α-to the nitro group was a doublet, while in the minor isomer the methylene appeared as a doublet of doublets. Seebach and coworkers determined the stereochemistry of adducts produced by the reaction of nitro alkenes with ketone enolates.[11] In many cases they observed that the methylene α- to the nitro group in the anti- isomers appeared as a doublet, while the syn- isomers exhibited doublets of doublets. This result prompted us to tentatively assign the major stereoisomer **8a** as the anti-isomer. This was eventually confirmed by synthesis of **17** and **18**.[12]

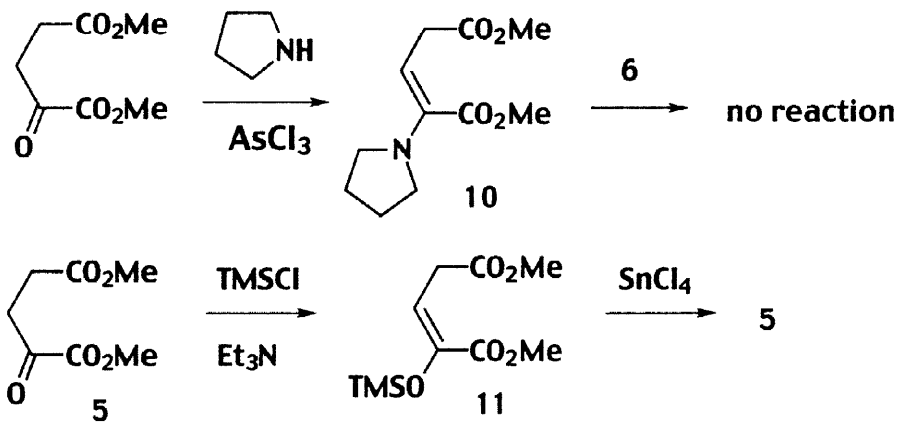


Our rationale for the production of the major stereoisomer is shown below. An extended transition state with the aryl group and the acetic acid group as far apart as possible provides an explanation for the observed selectivity. An alternative approach to the synthesis of **8a** and **8b** involves the addition of the anion of nitromethane to unsaturated ketone **9**. If the facial selectivity of the protonation of the resulting anion is determined by $A^{1,3}$ strain, then **8a** would be expected to be the major isomer. Surprisingly, we were unable to generate **9** by the reaction of 2-methoxy-benzaldehyde with **5**. Under several conditions (t-BuOK, LDA, MeONa), keto diester **5** was destroyed and 2-methoxybenzaldehyde was recovered.



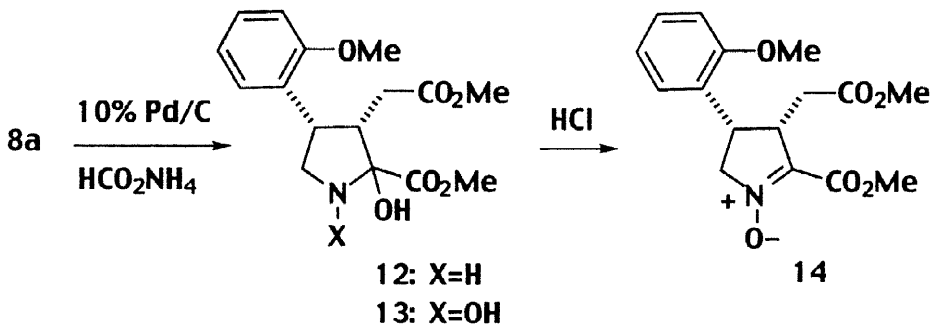


The modest yield of **8a** plus our inability to prepare **9** prompted us to search for nucleophilic alternatives. Enamine **10** was examined as a possible Michael addition donor. It could not be prepared by treatment of **5** with pyrrolidine under conditions where water was removed either by azeotropic distillation or with molecular sieves. The method using titanium tetrachloride also failed.[13] Fortunately, the use of arsenic trichloride afforded enamine **10** in good yield.[14] Enamine **10** was produced as a single stereoisomer. Unfortunately, this enamine was remarkably stable and did not react with either nitro styrene **6** or 2-methoxybenzaldehyde at temperatures ranging from ambient temperature to boiling toluene. Enol silyl ether **11** was prepared from **5** using triethylamine and trimethylchlorosilane. It was formed as a single stereoisomer. The stereochemistry was not determined. The reaction of **11** with nitro styrene **6** using either stannic chloride or boron trifluoride etherate as catalysts led simply to the recovery of **5** and **6**. Similar results with **11** were obtained using either benzaldehyde or its dimethyl acetal.

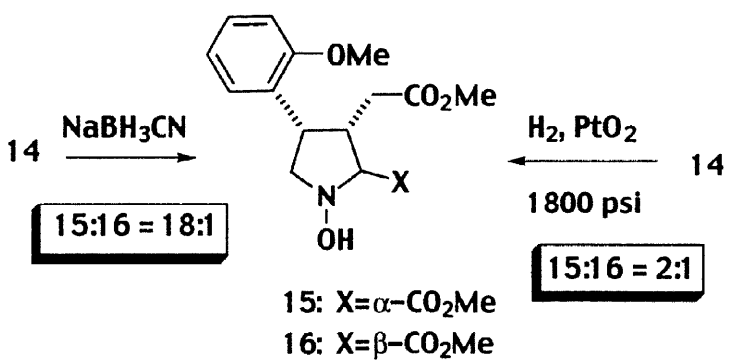


With gram quantities of compound **8a** readily available, the reduction of the nitro group was pursued. Although some precedent for the production of cyclic imines from nitro ketones was available, Reissig and coworkers had shown that nitrones could also be prepared in good yields.[15] Attempted reduction of **8a** using Raney nickel in methanol produced a complex mixture. Reduction using ammonium formate and palladium on carbon (Reissig

conditions) afforded a product in 89% yield whose structure was initially assigned as the amino alcohol **12** based on proton and carbon NMR and the infrared spectrum. Specifically, the carbon NMR showed a resonance at 93 ppm which supported the presence of a carbinol amine unit. Surprisingly, its reaction with benzyl chloroformate did not provide a urethane. This result plus a chemical ionization mass spectrum prompted its reassignment as **13**. This compound was not very stable to storage. Reaction with $POCl_3$ and triethylamine generated a stable nitrone **14** in 42% yield. More conveniently, nitrone **14** could be prepared in 73% yield by treatment of **13** with hydrochloric acid in methanol.

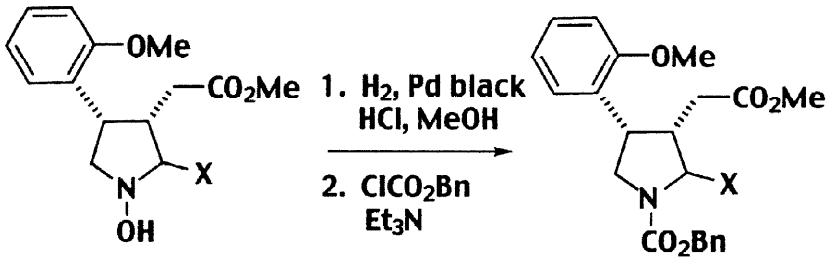


Reduction of nitrone **14** with sodium borohydride in methanol produced multiple products. Reduction with sodium cyanoborohydride in methanol containing hydrochloric acid produced a 18:1 ratio of **15** to **16** in a combined yield of 75%. Based on analogy with chemical shift data published by Shirahama for several aryl kainoid analogs, the C-2 C-3 stereochemistry of the major isomer was assigned as cis.[16] Reduction of **14** using hydrogen and platinum oxide at ambient pressure returned starting material. However, reduction of **14** with hydrogen and PtO_2 in ethanol at 1800 psi for 45 hours gave **15** and **16** in a 2:1 ratio. Attempted reduction of **14** from the face of the molecule cis to the ester using an iridium catalyst returned recovered starting material, even at 1800 psi for two days.[17]



Both isomers were subjected to hydrogenation using palladium black catalyst in methanol. These were conditions used by Murahashi for the conversion of hydroxylamines to amines.[18] Initial experiments afforded recovered starting material. After some experimentation, we found that aqueous hydrochloric acid was essential for reduction. Reaction of the resulting amines with benzyl chloroformate and triethylamine led to carbamates **17** and **18** in 87% and 89% yields, respectively. In an attempt to reduce nitrone **14** directly to a mixture of **17** and **18**, nitrone **14** was treated with hydrogen and PtO_2 in MeOH with a drop of HCl at 1800 psi. Interestingly, amine corresponding to **17** was obtained. There were also products derived from reduction of the aromatic ring.

Compounds **17** and **18** contain two rotamers in a 1:1 ratio. In **18**, the methine proton at C-2 appears as two doublets at 4.13 and 4.17 with J = 5.7 Hz. In **17**, the methine proton at C-2 appears as two doublets at 4.62 and 4.65 with J = 7.2 Hz. Professor Shirahama provided a NMR spectrum which confirmed the structure of **18**.



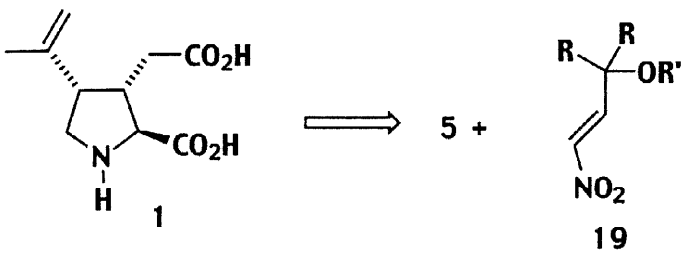
15: X=α-CO_2Me
16: X=β-CO_2Me

17: X=α-CO_2Me
18: X=β-CO_2Me

The final stage involved epimerization of the ester at C-2. We had previously reported a similar epimerization in our synthesis of allokainic acid.[10] Despite many efforts with mild bases, epimerization to **4** was possible only with KOH at 155 °C. Since such high temperature epimerization seemed of limited value for the present situation, the reaction of carbamate **17** with LDA was studied. The methylene in the acetic acid side chain might be expected to be more acidic than the methine proton at C-2. The deprotonation and quenching experiments were therefore conducted with 1.5 to 3 equivalents of LDA. The resulting dianion was quenched with acetic acid dissolved in methylene chloride. The use of 2.6 equivalents of LDA in THF at -78 °C led to a **18**:**17** ratio of 7:1. Our rationale for the observed selectivity is that it involves an "internal return" type process wherein the acetic acid initially protonates the diisopropylamine which then in turn quenches the enolate. This may be related to the observation that the dianion of toluic acid undergoes successful aldol reactions but cannot be

deuterated.[19] Compound **18** has already been transformed into **3** by Shirahama by ester hydrolysis and deprotection of the amine.[12]

In principle, this route should also be applicable to the synthesis of kainic acid (**1**) by use of an aliphatic nitroalkene such as **19a** (R=H, R'=TBS) or **19b** (R=Me, R'=Bn). Compound **19a** had been previously reported[20] and **19b** could be prepared from the reaction of 2-benzyloxy isobutyraldehyde with nitromethane. The reaction of keto diester **5** with **19a** in the presence of potassium tert-butoxide in THF afforded polymer-like products, probably the result of the competitive deprotonation of **19a** followed by polymer formation. The reaction of **19b**, a compound wherein competitive deprotonation was not possible, with **5** gave what appeared to be a Michael adduct in only 5% yield. In view of the poor yield, this approach was abandoned.



The route to **3** described herein (eight steps from nitromethane) provides a direct and flexible route to 4-aryl kainoids. It will make available quantities of these compounds for further biological studies.

Experimental Section

H:EA refers to hexanes:ethylacetate solvent mixture for thin layer chromatography and silica gel flash chromatography (sgc). Infrared spectra (IR) were recorded on a BIO FTS-7 spectrophotometer. Proton NMR spectra were measured at 300 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz. High resolution mass spectra (HRMS) were obtained by a Kratos MS 50 magnetic sector mass spectrometer. Chemical ionization (CI) mass spectra were recorded by a Finnigan TSQ 700 mass spectrometer.

anti-Methyl 4-(2-Methoxyphenyl)-5-nitro-3-carbomethoxymethyl-2-oxopentanoate (8a)

To a stirred solution of potassium *tert*-butoxide (1.16 g, 10.4 mmol) in anhydrous THF (30 mL) was added a solution of dimethyl α-ketoglutarate (**5**) and 2-methoxy-β-nitrostyrene (**6**) in THF (20 mL) at -30 °C, and the reaction mixture was stirred for 20 min at the same temperature. In order to quench the reaction mixture, ice and AcOEt were added. The

aqueous layer was separated and extracted with AcOEt. The combined organic portions were washed with H_2O, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by sgc (H:EA = 5:2) to afford 1.83 g (45%) of a mixture of **8a** and its diastereomer **8b** (14:1) as a syrup. Pure **8a** was obtained by a recrystallization from MeOH as a colorless solid : mp 91-92 °C; Rf = 0.27 (H:EA = 5:2); IR (nujol) 1742, 1723, 1554, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) d 2.65 (dd, J = 17.1 and 4.5 Hz, 1H), 2.92 (dd, J = 17.1 and 10.8 Hz, 1H), 3.63 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 3.95 (brq, J = 7.2 Hz, 1H), 4.29-4.40 (m, 1H), 4.91 (d, J = 7.2 Hz, 2H), 6.85 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 7.05 (dd, J = 7.5 and 1.7 Hz, 1H), 7.27 (dt, J = 8.3 and 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) d 35.0, 42.8, 43.6, 52.1, 52.9, 54.9, 76.1, 111.2, 120.9, 122.8, 129.8, 130.7, 157.0, 160.6, 171.8, 193.0; HRMS exact mass calcd for $C_{16}H_{19}NO_8$ 353.11107, found 353.11108. Anal. Calcd for $C_{16}H_{19}NO_8$:C 54.39, H 5.42, N 3.97. Found: C 54.31, H 5.55, N 3.89.

Methyl 1,2-Dihydroxy-3α-carbomethoxymethyl-4α-(2-methoxyphenyl) pyrrolidine-2-carboxylate (13)

To a stirred suspension of **8a** (300 mg, 0.85 mmol) and 10% palladium on carbon (60 mg) in MeOH (5 mL), ammonium formate (320 mg, 5.1 mmol) was added and the mixture was stirred at rt for 1 h. The reaction mixture was filtrated and the filtrate was evaporated to give a residue. To the residue were added H_2O and AcOEt. The aqueous layer was separated and extracted with AcOEt. The combined organic portions were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a light yellow syrupy oil **13**. This oil was used for the next reaction without further purification; Rf 0.59 (H:EA = 1:2); IR (neat) 3465 (br), 1734 cm^{-1}; ^1H NMR ($CDCl_3$) d 1.79 (dd, J = 17.1 and 4.8 Hz, 1H), 2.13 (dd, J = 17.1 and 11.4 Hz, 1H), 3.30-3.60 (m, 2H), 3.50 (s, 3H), 3.80 (s, 3H), 3.75-3.90 (m, 1H), 3.91 (s, 3H), 4.03-4.18 (m, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 7.22 (dt, J = 7.8 and 1.5 Hz, 1H), 7.34 (dd, J = 7.5 and 1.5 Hz, 1H); ^{13}C NMR (CDCl3) d 31.4, 33.0, 41.1, 51.3, 53.3, 55.3, 57.8, 92.8, 110.1, 120.5, 126.5, 128.0, 128.8, 157.3, 172.7, 173.0; *m/z* (CI, NH3) 339 (M^+, 29%), 321 (M^+-H2O, 81%), 306 (100%).

Methyl Dihydro-4α-carbomethoxymethyl-3α-(2-methoxyphenyl)-2H-pyrrole-5-carboxylate-1-oxide (14)

To a solution of **13** (256 mg, 0.76 mmol) in anhydrous MeOH (3 mL), 2N HCl in anhydrous MeOH (0.57 mL, 1.13 mmol) was added at -10 °C and the mixture was stirred at 0 °C for 20 min. After quenching the reaction mixture with ice and AcOEt, the aqueous layer was separated and extracted with AcOEt. The combined organic portions were washed with H_2O, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (H:EA = 1:2) to afford 178 mg (78%) of **14** as a colorless syrup;

Rf 0.29 (H:EA = 1:2); IR (neat) 1732, 1696, 1552 cm^{-1}; ^1H NMR ($CDCl_3$) d 2.33 (dd, J = 16.5 and 7.8 Hz, 1H), 2.46 (dd, J = 16.5 and 4.8 Hz, 1H), 3.38 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.08-4.33 (m, 3H), 4.58-4.73 (m, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.94 (dd, J = 7.5 and 1.2 Hz, 1H), 7.07 (dd, J = 7.5 and 1.5 Hz, 1H), 7.29 (dt, J = 7.8 and 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) d 32.6, 35.5, 42.0, 51.3, 52.1, 55.2, 68.3, 110.4, 120.4, 123.6, 128.7, 129.1, 135.5, 157.6, 159.9, 171.3; HRMS exact mass calcd for $C_{16}H_{19}NO_6$ 321.12124, found 321.12128.

Reduction of nitrone 14

To a stirred mixture of **14** (126 mg, 0.39 mmol) in anhydrous MeOH (2.5 mL), 2N HCl in anhydrous MeOH (0.39 mL, 0.79 mmol) was added at 0 °C, and then $NaBH_3CN$ (20 mg, 0.32 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 20 min. In order to quench the reaction mixture, ice, saturated aqueous $NaHCO_3$ solution, and AcOEt were added. The aqueous layer was separated and extracted with AcOEt. The combined organic portions were washed with H_2O, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (H:EA = 2:3) to afford 90 mg (71%) of 1-hydroxy-2α-methoxycarbonyl-3α-methoxycarbonylmethyl-4α-(2-methoxyphenyl)pyrrolidine (**15**) as a colorless syrup and 13.5 mg (4%) of 1-hydroxy-2β-methoxycarbonyl-3α-methoxycarbonylmethyl-4α-(2-methoxyphenyl)pyrrolidine (**16**) as a colorless solid, respectively. **15**: Rf 0.51 (H:EA = 2:3); IR (neat) 3420 (br), 1739 cm^{-1}; ^1H NMR ($CDCl_3$) d 1.95 (dd, J = 16.8 and 6.6 Hz, 1H), 2.08 (dd, J = 16.8 and 8.4 Hz, 1H), 3.32 (dd, J = 10.5 and 9.9 Hz, 1H), 3.39 (s, 3H), 3.40-3.60 (m, 1H), 3.70 (s, 3H), 3.65-3.80 (m, 1H), 3.81 (s, 3H), 4.07 (d, J = 7.5 Hz, 1H), 4.20-4.33 (m, 1H), 6.41 (d, J = 8.1 Hz, 1H), 6.92 (brt, J = 7.5 Hz, 1H), 7.21 (dt, J = 7.8 and 1.5 Hz, 1H), 7.34 (dd, J = 7.8 and 1.5 Hz, 1H), ^{13}C NMR ($CDCl_3$) d 32.5, 36.8, 38.4, 51.2, 51.7, 55.2, 60.3, 73.6, 110.0, 120.4, 126.9, 127.9, 128.5, 157.4, 171.7, 172.3; HRMS exact mass calcd for $C_{16}H_{21}NO_6$ 323.13689, found 323.13704. **16**: mp 161-162 °C (from $CHCl_3$-hexane); Rf = 0.31 (H:EA = 2:3); IR (nujol) 3245 (br), 1738 cm^{-1}; ^1H NMR ($CDCl_3$) d 2.11 (dd, J = 16.2 and 6.9 Hz, 1H), 2.24 (dd, J = 16.2 and 7.8 Hz, 1H), 3.06-3.20 (m, 1H), 3.38-3.52 (m, 1H), 3.44 (s, 3H), 3.57 (dd, J = 9.3 and 6.9 Hz, 1H), 3.66 (d, J = 8.4 Hz, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 3.84-3.98 (m, 1H), 6.60-6.75 (br, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.91 (t, J = 7.2 Hz, 1H), 7.11 (dd, J = 7.5 and 1.5 Hz, 1H), 7.24 (dt, J = 8.2 and 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) d 35.2, 37.8, 38.9, 51.3, 52.1, 55.1, 59.9, 74.6, 110.2, 120.3, 125.9, 128.3, 129.3, 157.5, 172.3, 172.5; HRMS exact mass calcd for $C_{16}H_{21}NO_6$ 323.13689, found 323.13613. Anal. Calcd for $C_{16}H_{21}NO_6$: C 59.43, H 6.55, N 4.33. Found:C 59.09, H 6.64, N 4.27.

1-Benzyl-2-methyl 3α-methoxycarbonylmethyl-4α-(2-methoxyphenyl) pyrrolidine-1,2β-dicarboxylate (18)

A mixture of **16** (55 mg, 0.17 mmol), Pd-black (15 mg), and 2N HCl (5 drops) in MeOH (2 mL) was stirred at rt for 1.5 h under hydrogen (1 atm). The reaction mixture was filtrated and the filtrate was evaporated to give a residue. To the residue were added aqueous NaCl solution, saturated aqueous $NaHCO_3$ solution, and AcOEt. The aqueous layer was separated and extracted with AcOEt. The combined organic portions were dried over $MgSO_4$ and concentrated in vacuo to give a syrup. To a solution of this syrup and triethylamine (0.024 ml, 0.177 mmol) in anhydrous CH_2Cl_2 (2 mL), benzyl chloroformate (0.025 ml, 0.175 mmol) was added at 0 °C and stirred at the same temperature for 30 min. After quenching the mixture with ice and AcOEt, the aqueous layer was separated and extracted with AcOEt. The combined organic portions were washed with 5% $KHSO_4$ solution, saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (H:EA = 3:2) to afford 63 mg (89%) of **18** as a colorless syrup; Rf 0.55 (H:EA = 3:2); IR (neat) 1740, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) (contains two rotamers) d 2.06 (dd, J = 16.8 and 6.6 Hz, 1H), 2.16 (dd, J = 16.8 and 7.8 Hz, 1/2H), 2.19 (dd, J = 16.8 and 7.8 Hz, 1/2H), 3.15-3.27 (m, 1H), 3.59 (s, 3H), 3.60 (s, 3/2H), 3.75 (s, 3/2H), 3.76 (s, 3/2H), 3.80 (s, 3/2H), 3.79-4.09 (m, 3H), 4.13 and 4.17 (2d, J = 5.7 Hz, 1H), 5.06 (d, J = 12.3 Hz, 1/2H), 5.15 (d, J = 12.3 Hz, 1/2H), 5.25 (d, J = 12.3 Hz, 1H), 6.82-7.04 (m, 3H), 7.19-7.43 (m, 6H); ^{13}C NMR ($CDCl_3$) d 33.0, 33.1, 37.9, 38.7, 42.1, 43.1, 49.6, 49.8, 51.5, 52.1, 52.4, 55.1, 63.3, 63.6, 67.2, 110.11, 110.13, 120.6, 120.7, 125.8, 125.9, 127.29, 127.31, 127.78, 127.81, 127.9, 128.0, 128.3, 128.4, 136.3, 136.5, 154.1, 154.7, 157.2, 171.9, 172.0, 172.2, 172.4; HRMS exact mass calcd for $C_{24}H_{27}NO_7$ 441.17875, found 441.17983.

1-Benzyl-2-methyl 3α-methoxycarbonylmethyl-4α-(2-methoxyphenyl) pyrrolidine-1,2α-dicarboxylate (17)

The procedures used to prepare **16** were applied to **15** (80 mg, 0.25 mmol). Compound **17** (95 mg, 87%) was obtained as a colorless syrup; Rf 0.55 (H:EA = 3:2); IR (neat) 1746, 1707 cm^{-1}; ^1H NMR ($CDCl_3$) (contains two rotamers) d 2.05 (dd, J = 17.1 and 5.4 Hz, 1/2H), 2.08 (dd, J = 17.1 and 5.4 Hz, 1/2H), 2.21 (dd, J = 17.1 and 9.6 Hz, 1/2H), 2.25 (dd, J = 17.1 and 9.6 Hz, 1/2H), 3.44 (s, 3/2H), 3.47 (s, 3H), 3.51-3.64 (m, 1H), 3.68 (s, 3/2H), 3.81 (s, 3H), 3.84-3.99 (m, 3H), 4.62 and 4.65 (2d, J = 7.2 Hz, 1H), 5.04 (d, J = 12.3 Hz, 1/2H), 5.12 (d, J = 12.3 Hz, 1/2H), 5.22 (d, J = 12.3 Hz, 1/2H), 5.23 (d, J = 12.3 Hz, 1/2H), 6.84 (brd, J = 8.4 Hz, 1H), 6.91 (brq, J = 6.6 Hz, 1H), 7.10-7.42 (m, 7H); ^{13}C NMR ($CDCl_3$) d 30.7, 30.8, 39.0, 39.4, 40.1, 40.2, 48.1, 48.8, 51.3, 51.5, 51.8, 55.1, 62.1, 62.5, 67.1, 67.2, 109.98, 110.03, 120.2, 120.3, 124.8, 125.0, 127.79, 127.88, 127.94, 128.0, 128.3, 128.4, 136.1, 136.4, 154.4,

154.8, 157.30, 157.33, 170.7, 171.0, 172.2, 172.3; HRMS exact mass calcd for $C_{24}H_{27}NO_7$ 441.17875, found 441.17936.

Epimerization of 17

To a stirred solution of **17** (53 mg, 0.12 mmol) in ahnydrous THF (1.5 mL), a solution of LDA (0.31 mmol) in THF (1 mL) was added at -78 °C, and the mixture was stirred at the same temperature for 1 h. After quenching the reaction mixture with ice and 5% $KHSO_4$ solution, the aqueous layer was separated and extracted with AcOEt. The combined organic portions were washed with saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (H:EA = 3:2) to afford 38 mg (72%) of a mixture of **18** and **17** (7:1) as a syrup according to the integration of the α-protons in the ^1H NMR spectrum.

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