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Synthesis of L-Kynurenine and Homo-L-Kynurenine via an Aza-Fries Rearrangement

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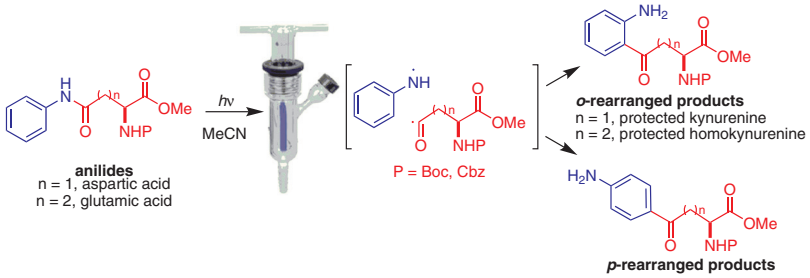

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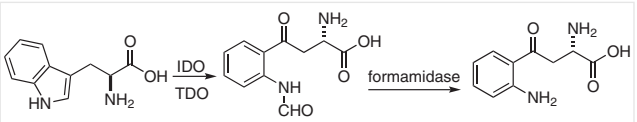
Abstract L-Kynurenine, a non-proteinogenic amino acid, is the primary metabolite of tryptophan via the kynurenine pathway. Kynurenine is involved in a variety of biological processes occurring in the human body, notably in the central nervous system. Thus, the study of this molecule offers multiple opportunities for drug discovery; however, an essential prelude for biological studies is to secure the supply of kynurenine and analogues thereof. A simple synthetic procedure for the efficient preparation of enantiomerically pure L-kynurenine from L-aspartic acid and its implementation to prepare homo-L-kynurenine from L-glutamic acid is presented. The approach relies on a photochemical aza-Fries rearrangement of the corresponding acyl-aniline as the fundamental transformation.

Key words L-kynurenine, homo-L-kynurenine, non-proteinogenic amino acids, aza-Fries, photochemical rearrangement

Kynurenine (**1**), a non-proteinogenic amino acid, is the principal intermediate within the metabolic pathway of tryptophan (**2**). This catabolic pathway, also known as the kynurenine pathway (KP),[1a–c] is responsible for the formation of the essential cofactor nicotinamide adenine dinucleotide (NAD^+)[2] and several neuroactive intermediates. More than 95% of tryptophan is metabolized through KP (Scheme 1)[3] and, collectively, the metabolites of this pathway are designated as kynurenines. Although most of them display neuroactive properties, quinolinic acid, 3-hydroxykynurenine, and kynurenic acid have vital roles in several diseases of the central nervous system (CNS).[4] The kynurenine pathway is involved in the regulation of the immune response and neurodegenerative diseases;[5,6] likewise, kynurenine can act as a vasodilator in inflammation processes. Furthermore, this amino acid has been shown to have endothelial relaxing properties.



Scheme 1 Metabolism of L-tryptophan via the kynurenine pathway (KP)

Age-associated decline in NAD is connected with age-associated diseases, including metabolic and neurodegenerative conditions.[7] Some preclinical studies suggest the involvement of KP in the pathophysiology of stroke and its potential as a pharmacological target for stroke and related complications.[8]

It has been demonstrated that kynurenine is an endogenous ligand for the aryl hydrocarbon (AH) receptor.[9] More recently, it was established that some compounds formed during the KP might have either neuroprotective or neurotoxic properties,[1c] and they have the potential to be used as specific biomarkers for patients diagnosed with amyotrophic lateral sclerosis.[10] One metabolite of the KP (3-hydroxykynurenine-3-*O*-β-glucoside, 3-HKG) functions in the primate lens as a filter of 295–400 nm light, thus protecting the retina from damaging UV radiation.[11] Consequently, the kynurenine pathway has promising potential for drug discovery.[1c,12] For instance, inhibitors of enzymes in the kynurenine pathway may be relevant for the treatment of some of the diseases described above.[13]

Additionally, L-kynurenine has shown a sweetening power 50 times greater than sucrose; however, the D-enantiomer is tasteless and lacks biological activity.[14]

The kynurenine pathway (KP) starts with the conversion of L-tryptophan (**2**) into *N*-formyl-L-kynurenine (**3**, Scheme 1) mediated by the enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO).[1b,4]

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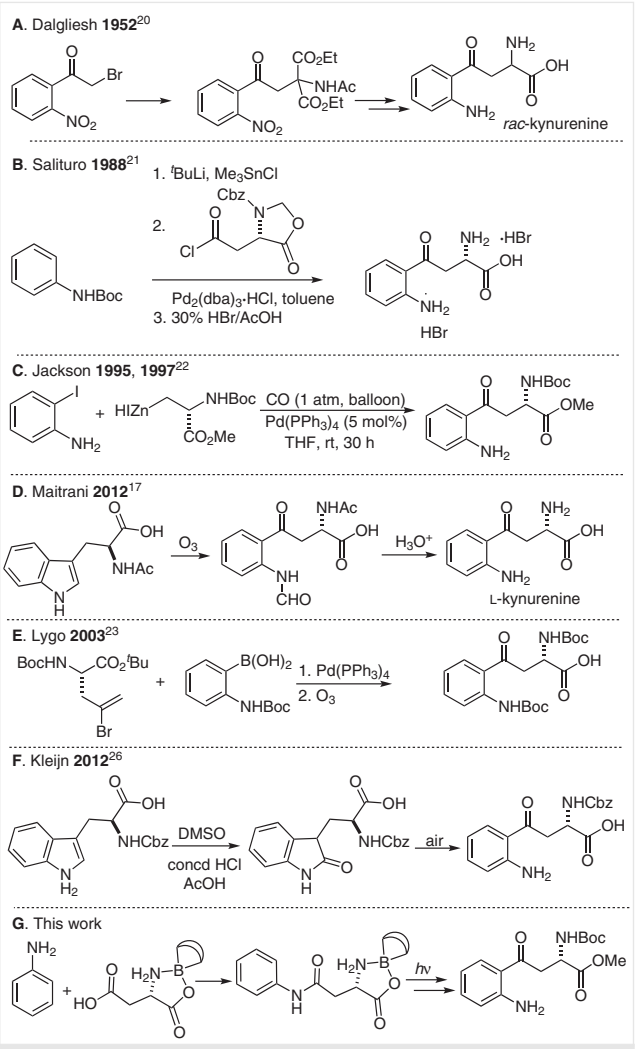


Scheme 2 A–F: previous synthesis of kynurenine; G: this work.

Presumably, this transformation has inspired some reported synthetic procedures to obtain kynurenine either as a racemate or in enantiopure form.

Deuterium labeled kynurenine has been obtained in enantiopure form by acylase catalyzed resolution.[15] Nevertheless, from the synthetic standpoint, the most direct approach to obtain enantiopure kynurenine involves the oxidative rupture of N-protected L-tryptophan derivatives.[16] This approach has been employed to produce enantiopure kynurenine (Scheme 2D)[17] and some peptides containing kynurenine,[18] although using cumbersome purification procedures. Using a related approach, Moriyama reported in 1957 the preparation of kynurenine by reacting tryptophan with ascorbic acid, and Cu_2SO_4, in the presence of air, even though the experimental evidence of kynurenine formation is not well supported.[19]

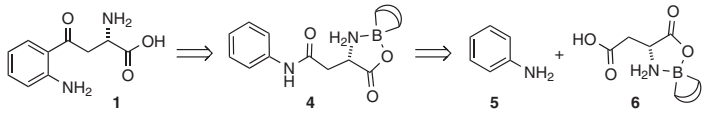
Other strategies have been devised to this end. For instance, the condensation of the sodium salt of diethylacetamidomalonate with *o*-nitrophenacylbromide, followed by reduction of the nitro group and hydrolysis—with the concomitant decarboxylation—afforded kynurenine as a racemate (Scheme 2A).[20] Salituro[21] utilized the *ortho*-metalation of *N*-Boc-aniline, followed by quenching with Me_3SnCl to obtain the stannylated derivative. Subsequent coupling with the chloride derived from protected spartic acid in the presence of $Pd_2(dba)_3$·HCl provided protected kynurenine (Scheme 2B). After removal of the protective groups with 30% HBr/AcOH, kynurenine bis(hydrobromide salt) was obtained in 35% overall yield. Negishi coupling between 2-iodoaniline and a serine-derived organozinc reagent, under a carbon monoxide atmosphere, has also been used to afford protected kynurenine in 52% yield (Scheme 2C).[22]

The use of protected 2-amino-4-bromopent-4-enoic acid in a Suzuki coupling with an aryl boronic acid, followed by ozonolysis of the resulting styrene, allowed the preparation of alanine derivatives such as kynurenine (Scheme 2E).[23] The photocatalytic decomposition of tryptophan has also been reported to produce kynurenine.[24] In 2006, Ferrini et al.[25] reported the preparation of 2-aryl amines in high yields by photochemical rearrangement of aromatic amides when they were irradiated with UV light. Cbz-tryptophan has been used to prepare L-kynurenine upon reaction with the oxidizing mixture of DMSO/HCl in AcOH, followed by additional oxidation with air (Scheme 2F).[26]

Herein, we present a simple procedure for the preparation of the non-proteinogenic amino acid L-kynurenine starting from L-aspartic acid through a photochemical approach, featuring an aza-Fries rearrangement. Furthermore, the developed methodology was implemented to obtain homo-L-kynurenine from L-glutamic acid.

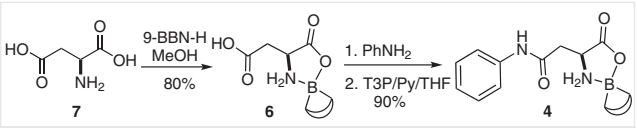
According to our original synthetic strategy, kynurenine (**1**) could be prepared from acyl aniline **4** using a photochemical aza-Fries rearrangement as the critical reaction.[27] Compound **4** would be readily obtained from aniline (**5**) and oxazaborolidinone **6**[28] by using standard peptide chemistry procedures (Scheme 3).

In addition to the carboxy and C-α amino functionalities, α-amino acids can include side chains with additional



Scheme 3 Original synthetic strategy for kynurenine

reactive groups—such as the amino acids aspartic and lysine—imposing chemoselectivity issues.[26] Accordingly, performing chemical reactions on the side chain of those amino acids might be a daunting task, resulting in the formation of side products. Alternatives to address this selectivity issue have been reported. For instance, the temporary installation into the molecule of a group to deter the reactivity of the carboxy and the amino functionalities, such as 9-borabicyclo[3.3.1]nonane (9-BBN-H), has been used to protect both groups in the form of an oxazaborolidinone.[28] Oxazaborolidinone **6** was prepared in good yield by refluxing the corresponding amino acid **7** with 9-BBN-H in MeOH (Scheme 4).



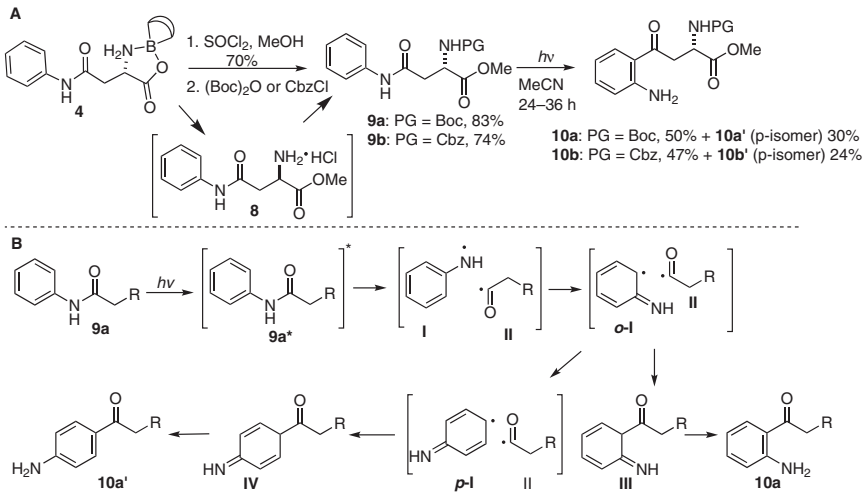
Scheme 4 Preparation acyl aniline **4** from L-aspartic acid

With the carboxy and amino groups masked, the next step was the anilide formation. The use of aniline, pyridine, and T3P proved to be a convenient way to perform this transformation (Scheme 4).[29] This method showed some advantages in handling the product and reaction yield, compared to other methods of activation for the carboxy moiety such as the use of DCC or EDC.[30] Early attempts to carry out the Fries rearrangement were conducted with compound **4**; however, after 12 hours of UV irradiation (254 nm) of a degassed solution of **4** in MeCN, and monitoring the course of the reaction by TLC, only degradation of oxazoborolidinone was observed. To circumvent this obstacle, replacing the 9-BBN protective groups was essential. Removal of the 9-BBN protective group required to prepare compound **9a** and **9b** was accomplished by refluxing an HCl/MeOH solution of **4**,[31] followed by transforming the resulting hydrochloride into a carbamate either with $(Boc)_2O$ or Cbz-Cl in the presence of Et_3N, to provide the aspartic acid derivatives **9a** and **9b** orthogonally protected in 83 and 74% yield, respectively.[32]

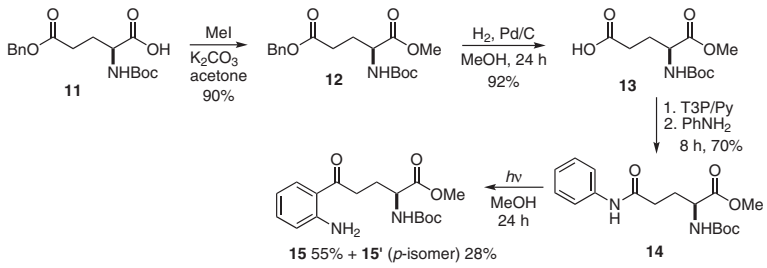
Individual degassed solutions of derivatives **9a** and **9b** in MeCN were irradiated for 12–36 hours at 254 nm. Rearranged products **10a** and **10b** were obtained in 50 and 47% yield, along with the corresponding *p*-isomers **10a′** and **10b′** (20 and 24% yield, respectively), as shown in Scheme 5, plus some unidentified compounds. The mechanism of the photo-Fries rearrangement is known to proceed through the excited state. Thus, the C–N bond in **9a*** undergoes homolytic cleavage giving *N*-radical **I** and acyl radical **II**, which are held in the solvent cage. Recombination of **I** and **II** would provide starting material. However, combination of acyl radical **II** with the mesomeric radical *o*-**I** gives *ortho*-rearranged product **III**, which, upon tautomerization, provides **10a**. Similarly, combination of **II** with the mesomeric radical *p*-**I** gives *para*-rearranged product **IV**, which tautomerizes into the minor isomer **10a′**.[32]

Kynurenine derivatives **10a** and **10b** are reported protected with orthogonal groups to facilitate their manipulation. Accessing free kynurenine would require standard deprotection procedures.[33]

To obtain protected homo-L-kynurenin (**15**), commercially available L-*N*-Boc-(Bn)-Glu-OH (**11**) was used. From this amino acid, methyl ester **12** was obtained by the reaction of **11** with MeI (K_2CO_3, acetone). Compound **12** was selectively deprotected (H_2, Pd/C, MeOH) to unblock the carboxyl group present in the side chain. The formation of amide **14** was achieved with the use of T3P as the coupling reagent. Amide **14** was then irradiated for 24 hours with UV light (254 nm) under anhydrous conditions (degassed MeCN) to provide orthogonally protected homo-L-kynurenine



Scheme 5 A: Preparation of N-protected L-kynurenine via a photochemical aza-Fries reaction. B: Proposed mechanism for the aza-Fries rearrangement.



Scheme 6 Preparation of homo-L-kynurenine from L-glutamic acid

15 in 55% along with the *p*-isomer **15′** in 28% yield (Scheme 6). All the intermediates and final products were satisfactorily characterized.

It is worth mentioning that during the preparation of protected kynurenine (**10a** and **10b**) and protected homokynurenine (**15**), the corresponding *para*-rearranged products **10a′**, **10b′** and **15′** were consistently obtained and fully characterized, albeit in lower yield than the main products. Although these reactions have a detrimental impact on the yield of our methodology, the simplicity, reproducibility, mild reaction conditions, and the ease with which the reaction products can be separated, compensate for the formation of regioisomers. Given the importance of the kynurenine pathway, it might be worth investigating the possible bioactivity of the *para*-isomers reported herein.

Since the existing stereogenic centers in each intermediate subjected to the photochemical rearrangement are not involved in the process, the stereochemical integrity should not experience any change. HPLC analysis for the crude reactions showed no evidence of epimerization during the rearrangement.

In conclusion, the fascinating and growing number of investigations on the paramount role of kynurenine in some essential biological processes occurring in the human body and the opportunities that this molecule offers for drug discovery would benefit from the development of simple and efficient protocols to obtain this remarkable amino acid. Even though several synthetic procedures to prepare kynurenine have been reported, some of them require the use of the hazardous oxidant ozone and cumbersome purification procedures. In other reports, additional steps are required to prepare the starting materials. We have developed a mild synthetic protocol that allows enantiopure kynurenine to be obtained in good yield from readily available starting materials. Our approach relies on the use of a photochemical aza-Fries rearrangement of an arylamide derived from L-aspartic acid. We were delighted to prove that the same protocol can be used to prepare homo-L-kynurenine. We believe that our methodology can be of value for the preparation of kynurenine derivatives required for biological studies.

^{1}H and ^{13}C NMR spectra were recorded with Varian INOVA 300, 400 and 600 MHz spectrometers using $CDCl_3$ as the solvent. ^{1}H NMR data are reported as chemical shift in ppm (δ) with integration, coupling constant in Hz and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet). IR spectra were recorded with a Perkin–Elmer Spectrum 400 FT-IR/FIR spectrophotometer with ATR. Mass spectra were recorded with a JEOL SMX-102a spectrometer. The progress of the reactions was monitored by TLC using glass plates precoated with silica gel 60 F254 (0.5 mm, Machery-Nagel) and 60 F254 (0.5 mm, Merck). The spots were visualized by short/long wavelength lamps and by charring the TLC plate after immersion in a H_2SO_4/H_2O solution of $Ce(SO_4)_2$/phosphomolybdic acid. Column chromatography was performed using 230–400 mesh silica gel.

α-Amino acids, 9-BBN-H, solvents and all other reagents were purchased from Sigma–Aldrich-Chemical Co. and, unless otherwise noted, were used as received. All reactions were performed under nitrogen atmosphere. The photochemical reactions were degassed prior to irradiation. THF was distilled from sodium benzophenone ketyl under nitrogen prior to use. Et_3N was distilled from CaH_2.

(*S*)-4-(Carboxymethyl)-2,2-borabicycle[3.3.1]nonane-1,3,2-oxazaborolidin-5-one (6)

A mixture of amino acid **7** (0.5 g, 3.76 mmol) in MeOH (20 mL) was heated to reflux until the mixture became homogeneous. Afterwards, a 0.5 M solution of 9-BBN-H in THF (7.5 mL, 3.76 mmol) was added dropwise and the heating was continued until the solution became clear. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. The residue was suspended in hot THF (15 mL) and the remnant solid was filtered. The filtrate was concentrated, and the residue was triturated with hot hexanes to provide the oxazaborolidinone.

Yield: 0.76 g (80%); white solid; mp 220 °C (dec).

IR-FT ATR: 3221, 2921, 2842, 1704, 1681, 1216, 960 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.47 (bs, 1 H), 0.59 (bs, 1 H), 1.39–1.78 (m, 12 H), 2.70–2.73 (d, *J* = 6 Hz, 2 H), 3.77–3.81 (m, 1 H), 5.96–5.99 (dd, *J* = 9 Hz, 1 H), 6.43–6.46 (dd, *J* = 9 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.9, 24.3, 25.2, 30.7, 30.9, 31.1, 31.2, 34.2, 51.1, 67.0, 171.6, 172.8.

MS (FAB): *m*/*z* = 254 [M + 1]$^+$, 162, 102, 88, 55.

Amide Preparation; General Procedure

T3P (3.0 equiv) was added dropwise to a solution of the corresponding acid (1 equiv) in THF at 0 °C. The resultant mixture was stirred until it became homogeneous, followed by the slow addition of pyridine (2 equiv) and aniline (2 equiv). The mixture was stirred at r.t. for 8 h,

the solvent (THF) was removed in vacuo, and the residue was redissolved in EtOAc (30 mL), washed with 10% citric acid (2 × 15 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography (silica gel, EtOAc–hexanes 30:70).

(*S*)-4-(*N*-Carboxyphenylamide)-2,2-borabicycle[3.3.1]nonane-1,3,2-oxazaborolidin-5-one (4)

Prepared from **6** (1.0 g, 3.95 mmol).

Yield: 1.08 g (90%); yellow solid; mp 184–186 °C.

IR-FT ATR: 3275, 2919, 2842, 1702, 1659, 1598, 1532, 1298, 1198 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.58 (bs, 1 H), 0.66 (bs, 1 H), 1.41–1.79 (m, 12 H), 2.88 (m, 2 H), 4.00–4.02 (m, 1 H), 6.08 (d, *J* = 12 Hz, 1 H), 6.52 (d, *J* = 9 Hz, 1 H), 7.08 (t, *J* = 7.0 Hz, 1 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.62 (d, *J* = 7.8 Hz, 2 H), 10.15 (s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 20.2, 22.7, 23.3, 25.6, 30.3, 34.77, 51.0, 68.8, 118.9, 123.1, 128.5, 138.7, 168.0, 172.9.

MS (FAB): *m*/*z* = 329 $[M + 1]^+$, 209, 191, 166, 127, 94, 85.

Methyl (*S*)-N^2-[(*tert*-Butoxycarbonylamino)-N^5-phenylamino]-5-oxopentanoate (14)

Prepared from **13** (0.8 g, 3.06 mmol).

Yield: 0.72 g (70%); yellow oil.

IR-FT ATR: 3381, 2919, 1737, 1449, 1409, 1296 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 1.91–1.97 (m, 1 H), 2.28–2.25 (m, 1 H), 2.44 (t, *J* = 6.5 Hz, 2 H), 3.71 (s, 3 H), 4.35 (s, 1 H), 5.43 (d, *J* = 8.0 Hz, 1 H), 7.07 (t, *J* = 7.4 Hz, 1 H), 7.29 (t, *J* = 7.9 Hz, 2 H), 7.57 (d, *J* = 7.9 Hz, 2 H), 8.63 (bs, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 29.9, 33.9, 52.6, 80.5, 119.8, 124.0, 128.9, 138.2, 156.3, 170.4, 172.6.

MS (FAB): *m*/*z* = 337 $[M + 1]^+$, 281, 237.

Cleavage of Amino Acid-9-BBN Complex

$SOCl_2$ (1.0 mL, 12.2 mmol) was slowly added to a flask containing MeOH (10 mL) at 0 °C. The amino acid (1.0 g 2.9 mmol) was then added and the mixture was heated to reflux for 1 h. The solvent was removed in vacuo and the residue was taken up in EtOAc (30 mL) and stirred for 12 h at r.t. to provide a white solid. The mixture was filtered, and the solid residue (**8**) was dried and used without further purification to selectively protect the amino group.

Methyl (*S*)-N^2-[(*tert*-Butoxycarbonylamino)-N^4-phenylamino]-4-oxobutanoate (9a)

Et_3N (0.22 mL, 1.59 mmol) was added dropwise to a mixture of **8** (0.375 g, 1.45 mmol) and $(Boc)_2O$ (0.315 g, 1.45 mmol) in isopropyl alcohol (10 mL). The resultant mixture was stirred for 24 h at ambient temperature and then the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc–hexanes 30:70) to provide the desired product.

Yield: 0.39 g (83%); yellow solid; mp 128–131 °C.

IR-FT ATR: 3298, 1742, 1751, 1698, 1673, 1540, 1293, 1160 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 2.88 (dd, *J* = 16.0, 4.2 Hz, 1 H), 3.07 (dd, *J* = 16.0, 4.1 Hz, 1 H), 3.74 (s, 3 H), 4.56 (dt, *J* = 9.0, 4.7 Hz, 1 H), 5.81 (d, *J* = 8.0 Hz, 1 H), 7.08 (t, *J* = 7.4 Hz, 1 H), 7.27 (t, *J* = 8 Hz, 2 H), 7.47 (d, *J* = 7.7 Hz, 2 H), 7.98 (bs, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 50.3, 52.8, 80.2, 119.9, 124.4, 128.9, 137.6, 155.8, 168.3, 172.0.

MS (FAB): *m*/*z* = 323 $[M + 1]^+$, 267, 223.

Methyl (*S*)-4-N^2-[(Benzyloxycarbonyl)-N^4-phenylamino]-4-oxobutanoate (9b)

Et_3N (0.22 mL, 1.59 mmol) was added dropwise to a mixture of **8** (0.75 g, 1.45 mmol) and benzylchloroformate (0.2 mL, 1.45 mmol) in CH_2Cl_2 (10 mL). The resultant mixture was stirred at r.t. for 24 h. The solvent was removed and the residue was purified by column chromatography (silica gel, EtOAc–hexanes 30:70) to afford the desired product.

Yield: 0.38 g (74%); white solid; mp 148–151 °C.

IR-FT ATR: 3304, 1744, 1712, 1652, 1533, 1286, 1214 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.90 (dd, *J* = 15.9, 3.9 Hz, 1 H), 3.10 (dd, *J* = 16.0, 4.3 Hz, 1 H), 3.75 (s, 3 H), 4.63 (dd, *J* = 8.5, 4.4 Hz, 1 H), 5.11 (s, 2 H), 6.10 (d, *J* = 8.1 Hz, 1 H), 7.09 (t, *J* = 7.4 Hz, 1 H), 7.25–7.31 (m, 6 H), 7.44 (d, *J* = 7.9 Hz, 2 H), 7.70 (dd, *J* = 5.7, 3.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.9, 51.0, 53.0, 67.2, 120.1, 124.7, 127.9, 128.3, 129.0, 129.4, 136.2, 137.6, 156.5, 168.3, 171.9.

MS (FAB): *m*/*z* = 357 $[M + 1]^+$, 313.

Methyl (*S*)-5-Benzyl-(*tert*-butoxycarbonylamino)-5-oxopentanoate (12)

A mixture of **11** (1.0 g, 2.96 mmol), K_2CO_3 (0.41 g, 2.96 mmol) and MeI (0.55 mL, 8.9 mmol) in anhydrous acetone (15 mL) was heated at reflux for 2 h under N_2 atmosphere. The solvent was removed and the residue was taken up in EtOAc (30 mL), washed with 10% citric acid (2 × 15 mL) and dried on Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc–hexanes, 30:70) to afford the desired product.

Yield: 0.94 g (90%); brown oil.

IR-FT ATR: 3374, 2977, 1734, 1711, 1499, 1366, 1156 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 1.90–1.95 (m, 1 H), 2.15–2.16 (m, 1 H), 2.39–2.44 (m, 2 H), 3.67 (s, 3 H), 4.27–4.31 (m, 1 H), 5.08 (s, 2 H), 5.20–5.23 (m, 1 H), 7.30 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9, 28.5, 30.6, 52.6, 53.0, 66.7, 80.2, 128.4, 128.5, 128.8, 135.9, 155.5, 172.7, 172.9.

MS (EI): *m*/*z* = 351 $[M]^+$, 107, 91, 79, 50.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-methoxy-5-oxopentanoic Acid (13)

A mixture of **12** (1.0 g, 2.84 mmol) and Pd/C (0.01 g, 10%w/w) in MeOH (20 mL) was purged and stirred under H_2 atmosphere (balloon) for 5 h. The solution was filtered through a pad of Celite and the solvent evaporated. The residue was purified by column chromatography (silica gel, EtOAc–hexanes, 30:70) to afford the desired product.

Yield: 0.684 g (92%); colorless oil.

IR-FT ATR: 3347, 2978, 1735, 1708, 1513, 1157 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 9 H), 1.76–1.86 (m, 1 H), 1.97–2.02 (m, 1 H), 2.27–2.29 (m, 2 H), 3.58 (s, 3 H), 4.25–4.04 (m, 1 H), 5.59 (d, *J* = 8.2 Hz, 1 H), 7.82 (bs, 1 H).

^{13}CNMR (75 MHz, $CDCl_3$): δ = 27.7, 28.3, 30.1, 51.8, 52.9, 80.0, 155.4, 172.7, 173.2.

MS (EI): *m*/*z* = 260 $[M]^+$, 202, 160, 146, 102, 57.

Photochemical aza-Fries Reaction; General Procedure

Photo-Fries rearrangement was performed using freshly distilled MeCN (P_2O_5) as the solvent, to which a stream of nitrogen was bubbled under sonication for 10 min. The photochemical quartz reactor (Ace Glass Incorporated, Cat. 7825-30) containing the corresponding

arylamide (1 equiv) and a magnetic stirring bar was evacuated and refilled with nitrogen, followed by the addition of degassed MeCN (10 mL). The solution was then irradiated with UV light (254 nm) for 24–36 h. Water was circulated through the condenser, to avoid evaporation of the MeCN. After the irradiation time indicated for each reaction, the solvent was evaporated under reduced pressure and the residue was fractionated by column chromatography (silica gel, gradient), commencing with 20% EtOAc in hexanes to obtain a compound identified as the *ortho*-rearranged product **10a** (R_f = 0.3, 20% EtOAc in hexanes). After recovering unreacted starting material, an increase in the polarity of the eluent (30% EtOAc in hexanes plus 5% of MeOH) allowed the most polar compound to be obtained (R_f = 0.3, 30% EtOAc in hexanes plus 5% of MeOH), identified as the *para*-rearranged product **10a′**. The same procedure was used to purify compounds **10b**, **10b′**, **15** and **15′** with an irradiation time of 24 h.

Methyl (*S*)-4-(2-Aminophenyl)-2-(*tert*-butoxycarbonylamino)-4-oxobutanoato (10a)

Prepared by following the general procedure from **9a** (0.1 g, 0.31 mmol).

Yield: 0.051 g (50%); brown oil.

IR-FT ATR: 3457, 2977, 1699, 1617, 1485, 1365, 1157 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 3.50 (dd, *J* = 17.9, 4.1 Hz, 1 H), 3.70–3.76 (m, 1 H), 3.70 (s, 3 H), 4.64–4.68 (m, 1 H), 5.61 (d, *J* = 15 Hz, 1 H), 6.24 (bs, 2 H), 6.63–6.66 (m, 2 H), 7.26–7.31 (m, 2 H), 7.68 (d, *J* = 7.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 41.4, 49.5, 52.5, 79.9, 115.9, 117.1, 117.3, 131.0, 134.9, 150.6, 155.6, 172.5, 199.3.

MS (FAB): *m*/*z* = 323 $[M + 1]^+$, 223.

Methyl (*S*)-4-(4-Amyinophenyl)-2-(*tert*-butoxycarbonylamino)-4-oxobutanoate (10a′)

Prepared by following the general procedure from **9a** (0.1 g, 0.31 mmol).

Yield: 0.030 g (30%); brown oil.

IR-FT ATR: 3365, 2977, 1696, 1593, 1485, 1366, 1160 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 3.36 (dd, *J* = 17.8, 3.9 Hz, 1 H), 3.59 (dd, *J* = 17.8, 4.1 Hz, 1 H), 3.68 (s, 3 H), 4.60–4.62 (m, 1 H), 5.68 (d, *J* = 8.9 Hz, 1 H), 6.58 (d, *J* = 8.6 Hz, 2 H), 7.70 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 40.1, 49.7, 52.5, 63.6, 79.9, 113.6, 126.1, 130.7, 152.0, 155.7, 172.4, 195.6.

MS (FAB): *m*/*z* = 323 $[M + 1]^+$, 223.

Methyl (*S*)-4-(2-Aminophenyl)-2-(benzyloxycarbonylamino)-4-oxobutanoate (10b)

Prepared by following the general procedure from **9b** (0.1 g, 0.27 mmol).

Yield: 0.047 g (47%); brown oil.

IR-FT ATR: 3456, 3347, 2952, 1705, 1548, 1499, 1337, 1208 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.52 (d, *J* = 20.1 Hz, 1 H), 3.74 (s, 3 H), 4.70–4.72 (m, 1 H), 5.11 (s, 2 H), 5.89 (d, *J* = 8.9 Hz, 1 H), 6.23 (bs, 2 H), 6.62–6.69 (m, 2 H), 7.26–7.32 (m, 6 H), 7.66 (d, *J* = 7.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.3, 50.1, 52.7, 67.0, 116.0, 117.2, 117.4, 128.1, 128.5, 131.0, 135.0, 136.2, 150.5, 156.1, 172.1, 199.1.

MS (EI): *m*/*z* = 357 $[M]^+$, 305, 238, 194.

Methyl (*S*)-4-(4-Aminophenyl)-2-(benzyloxycarbonylamino)-4-oxobutanoate (10b′)

Prepared by following the general procedure from **9b** (0.1 g, 0.27 mmol).

Yield: 0.024 g (24%); brown oil.

IR-FT ATR: 3456, 3347, 2952, 1705, 1548, 1499, 1337, 1208 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.35 (d, *J* = 15 Hz, 1 H), 3.58 (d, *J* = 15 Hz, 1 H), 3.68 (s, 3 H), 4.60–4.62 (m, 1 H), 5.11 (s, 2 H), 5.67–5.69 (d, *J* = 6 Hz, 1 H), 6.57–6.59 (d, *J* = 6 Hz, 2 H), 7.25–7.34 (m, 5 H), 7.68–7.71 (d, *J* = 9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.3, 50.1, 52.7, 67.0, 116.0, 117.2, 117.4, 128.1, 128.5, 131.0, 135.0, 136.2, 150.5, 156.1, 172.1, 199.1.

MS (EI): *m*/*z* = 358 $[M]^+$, 357.

Methyl (*S*)-5-(2-Aminophenyl)-2-(*tert*-butoxycarbonylamino)-5-oxopentanoate (15)

Prepared by following the general procedure from **14** (0.1 g, 0.29 mmol).

Yield: 0.055 g (55%); brown oil.

IR-FT ATR: 3353, 2981, 1747, 1684, 1648, 1514, 1155 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 2.03–2.05 (m, 1 H), 2.23–2.29 (m, 1 H), 2.96–3.01 (m, 1 H), 3.05–3.11 (m, 1 H), 3.73 (s, 3 H), 4.35–4.37 (m, 1 H), 5.17 (d, *J* = 7.9 Hz, 1 H), 6.25 (bs, 1 H), 6.60–6.63 (m, 2 H), 7.22–7.26 (m, 1 H), 7.69 (d, *J* = 11.9 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.3, 28.4, 35.0, 52.4, 53.2, 80.0, 115.9, 117.4, 131.0, 134.5, 150.4, 155.5, 173.1, 201.0.

MS (EI): *m*/*z* = 337 $[M]^+$, 281, 237.

Methyl (*S*)-5-(4-Aminophenyl)-2-(*tert*-butoxycarbonylamino)-5-oxopentanoate (15′)

Prepared by following the general procedure from **14** (0.1 g, 0.29 mmol).

Yield: 0.028 g (28%); brown oil.

IR-FT ATR: 3361, 2962, 1699, 1684, 1593, 1162 cm^1.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 2.03–2.05 (m, 1 H), 2.20–2.27 (m, 1 H), 2.89–3.04 (m, 2 H), 3.72 (s, 3 H), 4.33–4.34 (m, 1 H), 5.17 (d, *J* = 7.8 Hz, 1 H), 6.65 (d, *J* = 8.5 Hz, 2 H), 7.78 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2, 29.9, 33.9, 52.6, 52.7, 80.5, 119.7, 124.0, 128.9, 138.2, 150.9, 156.3, 170.4, 197.0.

MS (EI): *m*/*z* = 337 $[M]^+$, 218, 158, 130, 120, 118.

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