Synthesis of Excitatory Amino Acid Analogues

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Abstract: A general route to excitatory amino acid analogues has been developed as exemplified by the synthesis of **A-1** and **A-2**. The key reactions involved were a Negishi coupling of Jackson's organozinc reagent with vinyl bromide **8** and subsequent ring closure of **15** and **16** using the Mitsunobu reaction.

Key words: excitatory amino acids, Claisen rearrangement, Jackson's organozinc reagent, Mitsunobu reaction

Excitatory amino acids (EAA) play an important role in the physiology of higher organisms due to their abilities to trigger synaptic excitation and hence influence neural transmission. Naturally occurring EAA can be found in a variety of organisms; kainic acid (**1**) was isolated from the seaweed *Digenea simplex*,[1] (–)-lycoperdic acid (**2**) was extracted from the mushroom *Lycoperdon perlatum*[2] and (–)-dysiherbaine (**3**) was obtained from the marine sponge *Disidea herbacea*.[3] All of these natural products contain the glutamic acid motif. Glutamic acid (**4**) is one of the principal EAA in the mammalian central nervous system (Figure 1).

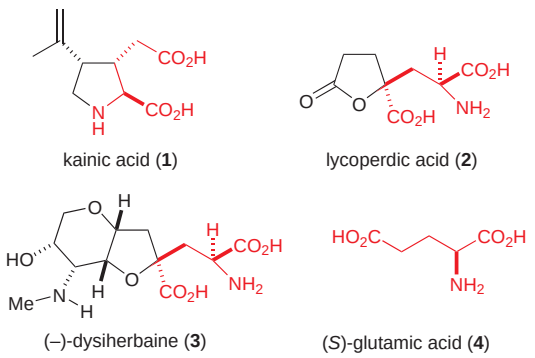


Figure 1 Some naturally occurring excitatory amino acids.

The EAA are considered to be valuable tools for the study of neurophysiology. Hence, much effort is directed towards their synthesis and the preparation of structural analogues in order to understand and establish their structural activities profiles.[4] We report here the synthesis of the general structure **A**, which can be considered as the aromatic analogue of **2** and **3**. Upon completion of our synthetic investigations, Chamberlin et al. disclosed their synthesis of **A-1** and **A-2** from a pyroglutamic acid derivative precursor, together with a biological evaluation of the compounds.[5]

Aiming to achieve maximum structural diversity, we deliberately did not define the absolute stereochemistry of the quaternary centre. Retrosynthetically, general structure **A** could be derived from precursor **9** (Figure 2), the preparation of which is outlined in Scheme 1.

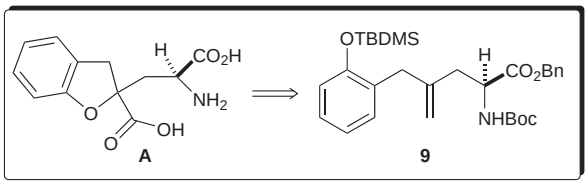
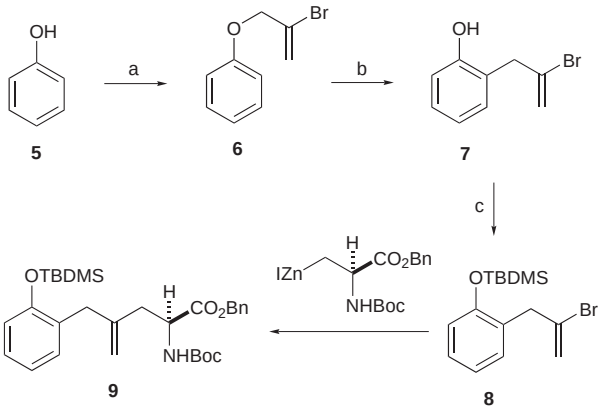


Figure 2 Retrosynthetic analysis of analogue A.



Scheme 1 *Reagents and conditions*: (a) NaH, DMF then 1,2-dibromoprop-2-ene, 91%; (b) *N*,*N*-diethylaniline, sealed tube, 200 °C, 76%; (c) TBDMSCl, imidazole THF, 82%; (d) $[(o\text{-tol})_3P]_2PdCl_2$, THF–*N*,*N*-dimethylacetamide (3:1), ultrasound, 90%.

Phenol (**5**) was deprotonated with sodium hydride in *N*,*N*-dimethylformamide which was followed by alkylation of the resultant phenoxide with 1,2-dibromoprop-2-ene to give ether **6** in 91% yield.[6] Heating **6** in *N*,*N*-diethylaniline effected a thermal Claisen rearrangement and delivered phenol **7** in 76% yield.[7] Compound **7** was protected as its TBDMS ether **8** in 82% yield by the action of TBDMSCl and imidazole. Vinyl bromide **8** was coupled with the L-serine derived Jackson's organozinc reagent[8] under palladium catalysis to afford amino acid derivative **9** in 90% yield. To the best of our knowledge, the coupling of Jackson's reagent with a vinyl bromide has never been reported.

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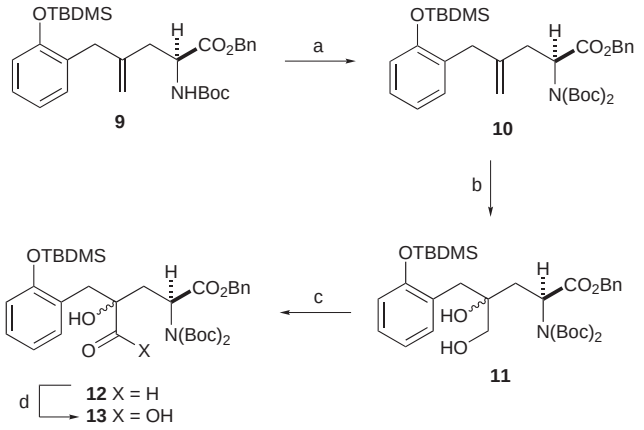
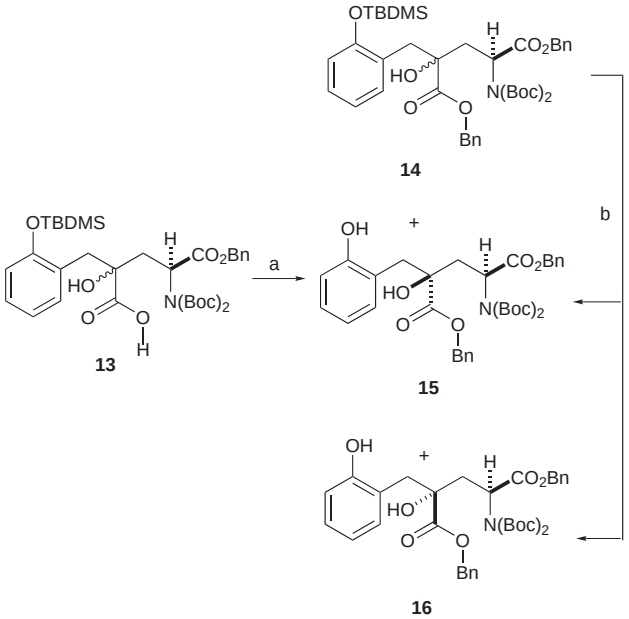
After many exploratory studies the following synthetic route was found to be successful for converting **9** into the desired target molecules **A-1** and **A-2**.



Scheme 2 *Reagents and conditions*: (a) $(Boc)_2O$, DMAP, MeCN, 82%; (b) OsO_4 (cat.), NMO, *t*-BuOH, H_2O, 96%; (c) DMSO, py·SO_3, Et_3N, CH_2Cl_2, 82%; (d) $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, *t*-BuOH, H_2O, 100%.

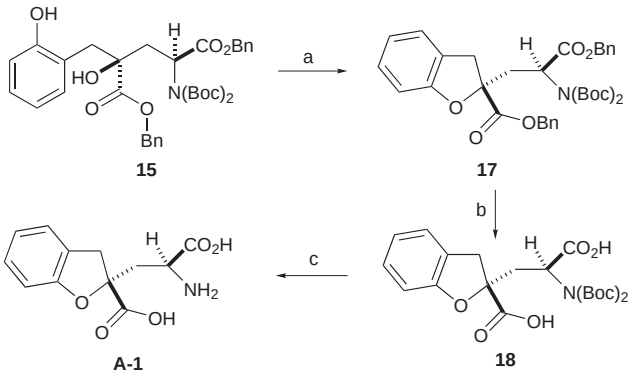
First, **9** was converted to its bis-*tert*-butoxycarbonyl derivative **10** in 56% yield using di-*tert*-butyl dicarbonate and DMAP[9] (Scheme 2). Recovered starting material **9** (34%) was recycled in an iterative fashion, giving a complete conversion of 82% (three cycles). Compound **10** was subjected to catalytic osmium tetroxide dihydroxylation in the presence of *N*-methylmorpholine *N*-oxide[10] to furnish diol **11** as an inseparable mixture of two diastereoisomers in 96% yield. Diol mixture **11** was oxidised to aldehyde **12** in 82% yield by using the Parikh–Doering conditions.[11] Further oxidation of aldehyde **12** by sodium chlorite under buffered conditions delivered acid **13** in quantitative yield.[11]



Scheme 3 *Reagents and conditions*: (a) BnBr, Et_3N, DMF; (b) TBAF, AcOH, THF, 42% for **15** and 31% for **16**.

Acid **13** was treated with benzyl bromide and triethylamine in *N*,*N*-dimethylformamide to give benzyl ester **14** together with phenols **15** and **16**, which resulted from deprotection of the silicon protecting group under the basic conditions. This is inconsequential as both **15** and **16** would be produced in the next step (Scheme 3). These compounds were separated and the *tert*-butyldimethylsilyl group in diastereoisomeric mixture **14** was removed by TBAF buffered with acetic acid[12] to provide more **15** and **16**. The overall yields of **15** and **16** were 42% and 31%, respectively, over two steps from **13**. Compounds **15** and **16** could be separated after repeated flash chromatography. At this stage the absolute configurations of the quaternary centres in **15** and **16** were unknown and the absolute stereochemistries of all the compounds depicted in Schemes 3−5 were later established by chemical correlations (see below).

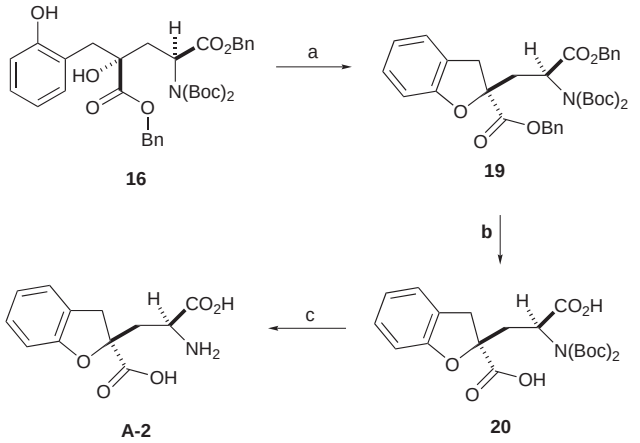
Having obtained pure samples of **15** and **16** we proceeded to convert them individually into their corresponding target molecule.



Scheme 4 *Reagents and conditions*: (a) PBu_3, DIAD, toluene, 0 °C, 85%; (b) Pd/C, H_2, MeOH, 100%; (c) HCO_2H, then ion-exchange chromatography, 100%.

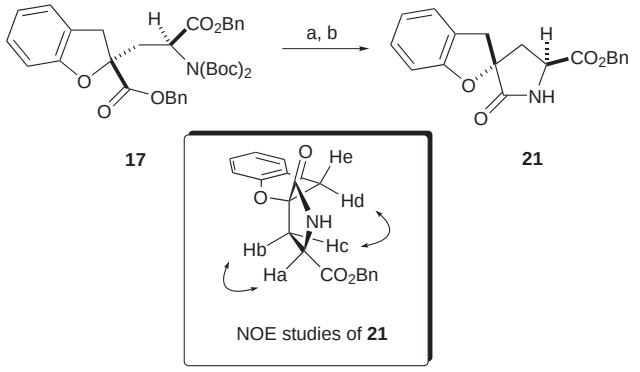
The Mitsunobu ring closure of **15** to **17** required some experimentation (Scheme 4). The optimum conditions for the reaction were to treat **15** with tributylphosphine and diisopropyl azodicarboxylate in toluene at 0 °C. This effected an intramolecular Mitsunobu etherification to afford **17** in 85% yield.[13] This was very gratifying because there are only a small number of literature accounts of such a reaction and all those reactions were performed on simple, uncrowded substrates. Compound **17** was subjected to catalytic hydrogenolysis with palladium on charcoal to deliver dicarboxylic acid **18** in quantitative yield. Amino acid **A-1**[14] was obtained in quantitative yield by removal of the *tert*-butoxycarbonyl groups with formic acid[15] and purification by ion-exchange chromatography.

Similarly, compound **16** was subjected to the Mitsunobu reaction to afford **19** in 88% yield. Removal of the benzyl ester in **19** was effected by hydrogenolysis to deliver dicarboxylic acid **20** in quantitative yield. Finally, treatment of **20** with formic acid followed by purification by ion-exchange chromatography gave **A-2**[16] in quantitative yield (Scheme 5).



Scheme 5 *Reagents and conditions*: (a) PBu_3, DIAD, toluene, 0 °C, 88%; (b) Pd/C, H_2, MeOH, 100%, (c) HCO_2H, then ion-exchange chromatography, 100%.

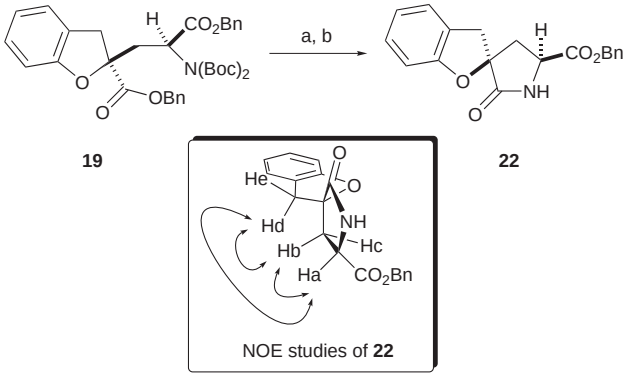
Our next task was to determine the absolute configurations of **15**, **17**, **18** and **A-1**. We decided to make use of the existing α-chiral centre of the amino acid side chain as our reference point. Thus, compound **17** was treated with formic acid, which resulted in removal of the two *tert*-butoxycarbonyl groups. The crude product obtained after neutralisation was heated in xylenes to give lactam **21** in an overall yield of 89% over two steps (Scheme 6).



Scheme 6 *Reagents and conditions*: (a) HCO_2H, then pH 7 buffer; (b) xylenes, 100 °C, 89% for two steps.

The NOE studies of **21** proved to be informative. Irradiation of H_a caused signal enhancement for only H_b but not H_c and H_d. The NOE interaction between H_c and H_d suggested that they are in close proximity. Hence H_c and H_d must be on the opposite face of the lactam ring with respect to H_a and H_b. Therefore this established the absolute configurations of **15**, **17**, **18** and **A-1**. Similarly, compound **19** was deprotected and cyclised to give **22** (Scheme 7).

Lactam **22** was subjected to NOE studies, using H_a as the reference point. NOE interactions were observed between H_a–H_b, H_b–H_d and H_a–H_d. Thus the benzyl methylene group must reside on the same face of the lactam ring with respect to H_a. Hence this established the absolute configurations of compounds **16**, **19**, **20** and **A-2**.



Scheme 7 *Reagents and conditions*: (a) HCO_2H, then pH 7 buffer; (b) xylenes, 100 °C, 89% for two steps.

Analysis of the ^1H NMR spectrum of **A-1** revealed a diastereomeric ratio of 10:1 at the γ-chiral centre. This was consistent upon repetition of the route. We surmised that the slight erosion of the stereochemical integrity of **A-1** probably occurred during the Mitsunobu ring closure of **15** to form **17**. It is possible that the incomplete inversion of the quaternary centre during the Mitsunobu cyclisation is due to some form of anchimeric assistance from various oxygen-containing functional groups near the activated tertiary alcohol. Unexpectedly, the ^1H NMR analysis of **A-2** showed a greater diastereomeric ratio of 19:1. However, this was also consistent upon repetition.

In summary, we have achieved the synthesis of amino acid analogues **A-1** and **A-2** and demonstrated the first example of a coupling reaction between the Jackson organozinc reagent and a vinyl bromide. In addition we have performed the challenging intramolecular etherification of sterically cumbersome substrates using the Mitsunobu reaction.

References and Notes

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(14) **A-1**: white solid; $[\alpha]_D^{21}$ –103.2 (*c* = 0.12, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 2.40 (dd, J_1 = 9.0 Hz, J_2 = 15.5 Hz, 1 H, NCHCH_AH$_B$), 2.56 (dd, J_1 = 3.0 Hz, J_2 = 15.5 Hz, 1 H, NCHCH$_A$$H_B$), 3.29 (d, *J* = 16.5 Hz, 1 H, ArCH_AH$_B$), 3.45 (d, *J* = 16.5 Hz, 1 H, ArCH$_A$$H_B$), 3.84 (dd, J_1 = 3.0 Hz, J_2 = 9.0 Hz, 1 H, NCH), 6.83 (d, *J* = 8.0 Hz, 1 H, Ar), 6.88 (dt, J_1 = 1.0 Hz, J_2 = 7.5 Hz, 1 H, Ar), 7.13 (apparent t, *J* = 7.5 Hz, 1 H, Ar), 7.19 (d, *J* = 7.5 Hz, 1 H, Ar). ^{13}C NMR (125.7 MHz, D_2O): δ = 38.3, 39.5, 51.9, 90.2, 110.2, 121.9, 125.7, 126.4, 128.8, 158.3, 174.4, 180.0. MS (ES, –ve): *m*/*z* (%) = 250.3 (100) [M – H]$^-$. HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{12}H_{13}NO_5$: 250.0715; found: 250.0713.
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(16) **A-2**: white solid; $[\alpha]_D^{21}$ –16.3 (*c* = 0.32, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 2.17 (dd, J_1 = 11.5 Hz, J_2 = 15.5 Hz, 1 H, NCHCH_AH$_B$), 2.67 (dd, J_1 = 2.0 Hz, J_2 = 15.5 Hz, 1 H, NCHCH$_A$$H_B$), 3.16 (d, *J* = 16.5 Hz, 1 H, ArCH_AH$_B$), 3.44 (d, *J* = 16.5 Hz, 1 H, ArCH$_A$$H_B$), 3.70 (dd, J_1 = 2.0 Hz, J_2 = 11.5 Hz, 1 H, NCH), 6.80 (d, *J* = 8.0 Hz, 1 H, Ar), 6.86 (t, *J* = 7.5 Hz, 1 H, Ar), 7.11 (t, *J* = 7.5 Hz, 1 H, Ar), 7.16 (d, *J* = 7.5 Hz, 1 H, Ar). ^{13}C NMR (125.7 MHz, D_2O): δ = 39.0, 40.9, 53.8, 91.7, 110.2, 121.8, 125.7, 126.0, 128.7, 157.9, 174.0, 179.1. MS (ES, –ve): *m*/*z* (%) = 250.3 (100) [M – H]. HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{12}H_{13}NO_5$: 250.0715; found: 250.0721.