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Catalytic Asymmetric Synthesis of Glutamate Analogues

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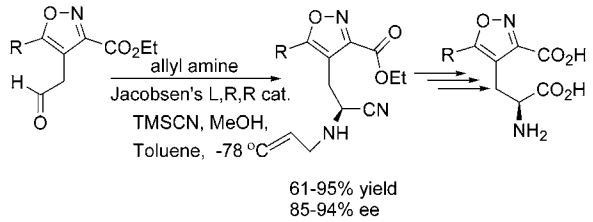
ABSTRACT



Utilizing our lateral metalation coupled with Jacobsen's catalytic asymmetric amino nitrile synthesis, we have demonstrated the ability to synthesize isoxazole-containing amino acid glutamate analogues in high yield and high enantiomeric excesses. Chiral centers α or *β* at the C-5 position do not detract from diastereoselectivity of the Jacobsen–Strecker reaction.

The asymmetric Strecker reaction to produce optically pure amino nitriles is of synthetic and medicinal value since it provides a direct route to chiral amino acids.[1] (*S*)-Glutamic acid is the primary excitatory neurotransmitter of the mammalian CNS.[2] Three classes of heterogeneous ionotropic glutamate receptors (iGluR) named for their respective agonists, (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)-propionic acid (AMPA), *N*-methyl-D-aspartic acid (NMDA), and kainic acid (KA), make up the bulk of excitatory neurotransmission in the human CNS.[3]

These proteins play a significant role in a wide variety of neurological pathways, including cognition, learning, and memory formation, and contain small but significant differences in their subunit composition.[4−6] Excitatory imbalance of these receptors is thought to be a primary culprit in neurological disorders including epilepsy, cerebral ischemia, Parkinson's, Huntington's, and Alzheimer's diseases. The synthesis of subunit selective agonists and antagonists as potential therapeutics is, therefore, of great importance.[7] Structure−activity relationship studies of AMPA analogues show a distinct enantioselectivity of action. C-5 lipophilic aryl and alkyl analogues of AMPA bearing the (*S*)-amino acid configuration are agonists at AMPA receptors whereas their enantiomers are antagonists or are inactive.[8]

The C-5 substituents of analogues bearing the (*R*)-amino acid configuration likely disrupt the interdomain interactions necessary for domain closure and activation of iGluRs resulting in antagonism. The X-ray structure of (*S*)-2-amino-3-(5-*tert*-butyl-3-hydroxy-4-isoxazolyl)propionic acid ((*S*)-ATPA) in complex with the GluR2 subunit reveals this

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(1) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon: Elmsford, 1989; pp 208−229.
(2) Wheal, H. V.; Thomson, A. M. *Excitatory Amino Acids and Synaptic Transmissionp* Academic Press: London, 1995.
(3) Monaghan, D. T.; Wenthold, R. J. *The Ionotropic Glutamate Receptors*; Humana Press: Totowa, NJ, 1997.
(4) Lodge, D.; Ed. *Excitatory Amino Acids in Health and Disease*; Wiley: Chichester, 1988.
(5) Watkins, J. C.; Krogsgaard-Larsen, P.; Honore, T. *Trends Pharmacol. Sci.* **1990**, *11*, 25−33.
(6) Watkins, J. C.; Collingridge, G. L. *The NMDA Receptor*; Oxford University Press: Oxford, 1989. (b) Krogsgaard-Larsen, P. *Pharmacol. Toxicol.* **1992**, *70*, 95−104.
(7) Brauner-Osborne, H.; Egebjerg, J.; Nielsen, E. O.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609−2645.
(8) Sorensen, U. S.; Falch, E.; Stensbol, T. B.; Jaroszewski, J. W.; Madsen, U.; Krogsgaard-Larsen, P. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 62−68.

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unique interaction between the C-5 *tert*-butyl group of ATPA and a group of amino acids which make up a partially lipophillic pocket, giving ATPA a 50-fold selectivity for the GluR5 subunit. The amino acids which describe the lipophillic pocket vary between subunits which make up AMPA (GluR1−4) and kainate (GluR5−7 and KA1−2) receptors, and this makes an attractive target for the design of subunit selective agonists and antagonists. Based on molecular modeling using Gouaux's coordinates,[9] we established a working hypothesis for the receptor's tolerance of C-5 lipophilic groups (Figure 1).

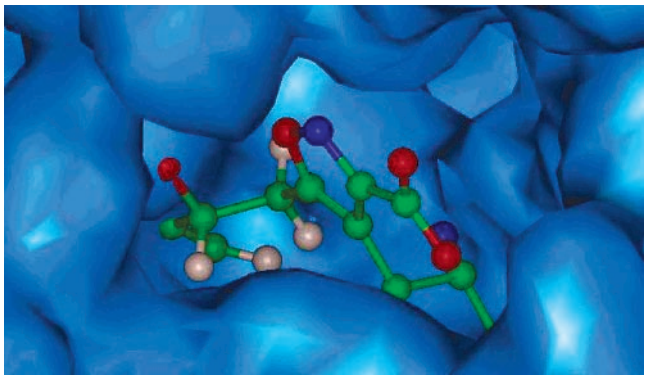


Figure 1. Molecular surface modeling of the ligand binding domain of the apo state of the AMPA receptor, bound with putative ligand, **20**, using the InsightII program. SGI Surface modeling reveals the dimensions of the lipophilic pocket in the GluR2 subunit (see the Supporting Information).

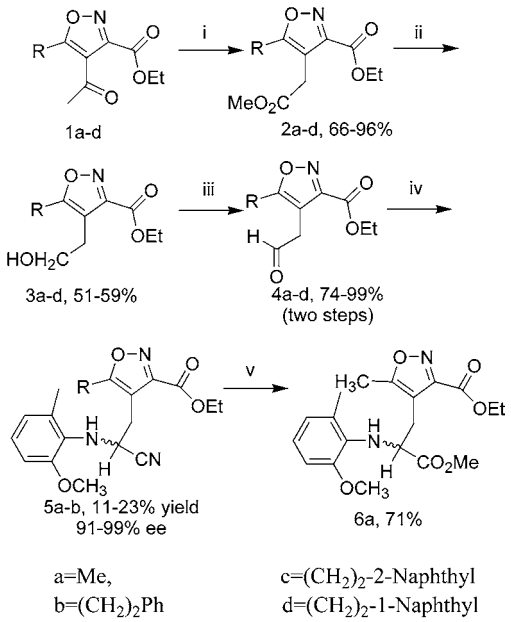
The additional effect of a heteroatom proximal to the isoxazole ring at the C-5 position is also known to enhance activity and binding affinity.[10] We sought to combine these effects in a survey of the role of chirality at the C-5 position of AMPA analogues in search of highly subunit selective compounds using steric bulk and chirality as selectivity filters.

To date, the enantioselective syntheses of AMPA analogues have employed chiral pool techniques with limited application or asymmetric Strecker reactions via chiral auxiliaries, which resulted in poor optical purity.[11,12]

Using the highly potent AMPA agonist (*S*)-2-amino-3-(3-carboxy-5-methyl-4-isoxazolyl)propionic acid (ACPA)[13] as a lead, we report here the first catalytic asymmetric synthesis of ACPA and C-5 analogues. Numerous catalysts for the asymmetric Strecker reaction producing highly enantioenriched amino nitriles, have appeared in recent years.[14−16] The Br-BINOL-zirconium catalyst pioneered by Kobayashi,[17] and the 5-pivaloyl-substituted Schiff base developed by Jacobsen[18] and co-workers, were the most successful with both aryl and alkyl aldehydes. Both catalyst systems were applied to the asymmetric synthesis of ACPA to determine the best method for production of optically active ACPA analogues bearing lipophilic and/or chiral hydroxyl groups at the C-5 position.

For the synthesis of C-5 lipophilic aryl ACPA analogues, lateral metalation of an isoxazolyl acetal,[19] followed by electrophilic quenching produced **1a−d** in good yields (Scheme 1). To achieve the proper carbon framework of ACPA, these compounds were readily homologated to their methyl ester via the modified Willgerodt−Kindler conditions of Ila and Junjappa.[20] Borane-THF selectively reduced the methyl ester of **2a−d** to give alcohols **3a−d** in good yield, followed by Dess−Martin[21] oxidation to produce aldehydes **4a−d**.

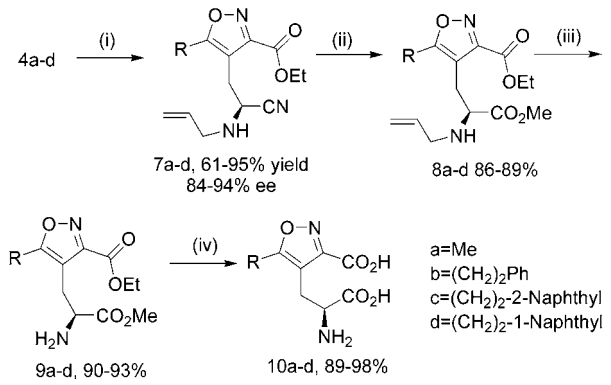
Scheme 1 [a]



[a] Key: (i) BF_3 etherate, MeOH, lead(IV) acetate, benzene; (ii) 5.0 equiv of BH_3 dimethyl sulfide, THF, rt, 30 h; (iii) Dess−Martin periodinane, CH_2Cl_2, rt; (iv) 2-amino-*m*-cresol, HCN, 10 mol % Zr−Br−BINOL, CH_2Cl_2, −45 °C, 60 h, then MeI, acetone; (v) MeOH, HCl, rt, 12 h.

(9) Lunn, M.; Hogner, A.; Stensbøl, T.; Gouaux, E.; Egebjerg, J.; Kastrup, J. S. *J. Med. Chem.* **2003**, *46*, 872−875.
(10) Falch, E.; Brehm. L.; Mikkelsen, I.; Johansen, T. N.; Skjaerbaek, N.; Nielsen, B.; Stensbol, T. B.; Ebert, B.; Krogsgaard-Larsen, P. *J. Med. Chem.* **1998**, *41*, 2513−2523.
(11) Pajouhesh, H.; Curry, K.; *Tetrahedron: Asymmetry* **1998**, *9*, 2757−2760.
(12) Ma, D.; Tang, G.; Tian, H.; Zou, G. *Tetrahedron Lett.* **1999**, *40*, 5753−5756.
(13) Johansen, T. N.; Stensbol, T. B.; Nielsen, B.; Vogensen, S. B.; Frydenvang, K.; Slok, F. A.; J.; Madsen, U.; Krogsgaard-Larsen, P. *Chirality* **2001**, *13*, 523−532.
(14) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910−4911.
(15) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315−5316.
(16) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284−4285.
(17) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762−766.
(18) Sigman, M. S.; Vachal, P.; Jacobsen. E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279−1281.
(19) Burkhart, D.; Zhou, P.; Blumenfeld, A.; Twamley, B.; Natale, N.; *Tetrahedron* **2001**, *57*, 8039−8046.
(20) Ila, H.; Junjappa, H. *Synth. Commun.* **1981**, *81*, 126−127.

Scheme 2 [a]



[a] Key: (i) allylamine, 10% Jacobsen's L,R,R peptide catalyst, TMSCN, MeOH, toluene, −78 °C; (ii) MeOH, HCl, rt, 8 h; (iii) 10 mol % $Pd(PPh_3)_4$, *N*,*N*′-dimethylbarbituric acid, CH_2Cl_2, 35 °C; (iv) 2 M HCl, 74 °C, 22 h.

Since the imines of aldehyde **4a** were found to be unstable, the Kobayashi method offered the advantage of a true three-component Strecker reaction and was applied first. The results of the three component asymmetric Strecker reaction for aldehydes **4a** and **4b**, using 10 mol % of the Kobayashi zirconium-Br-BINOL catalyst and 2-amino-*m*-cresol are summarized in Scheme 1. A high degree of enantioselectivity was observed and extended reaction times improved the yields somewhat, but repeated attempts at deprotection (ceric ammonium nitrate oxidative cleavage)[22] of the α-amino ester product at various temperatures resulted in decomposition, rendering the synthesis impractical in our hands.

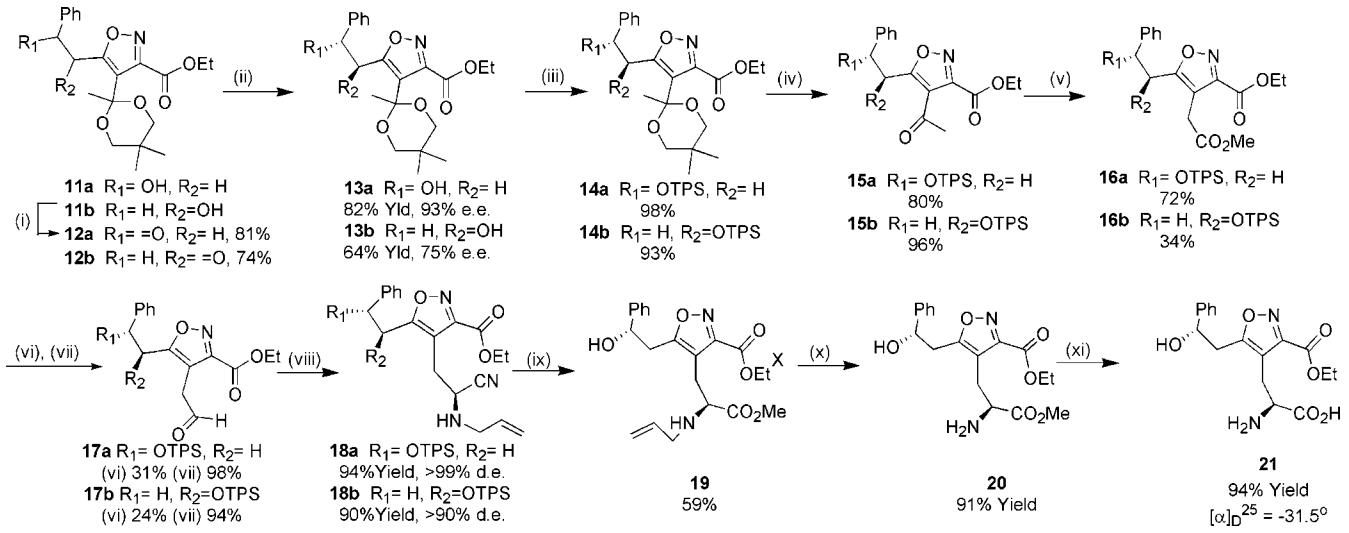
Using in situ Schiff base formation to circumvent the instability of aliphatic imines, the asymmetric Strecker reaction catalyzed by Jacobsen's L,R,R-peptide[23] provided allylamino nitriles in excellent yield (>90%) and in good to excellent optical purity (Scheme 2). A higher catalyst loading (10 mol %) was required to give consistent results with this method, but with the ease of the catalyst synthesis it did not present a problem. Pinner synthesis[24] produced amino esters **8a**−**d**, followed by Pd(0)-deallylation[25] of the amines to give **9a**−**d**. HCl (2 M) hydrolysis gave the final amino acids in good yield with no detectable racemization (Scheme 2). The absolute configuration was established on the basis of the published rotation of (*S*)-ACPA.[13] Optical purity was determined by chiral HPLC analysis of racemic mixtures and asymmetric reaction products for all compounds (see the Supporting Information).

The aldehydes were converted to the amino acids in synthetically useful yields with no chromatography. For the synthesis of ACPA analogues with chiral carbon atoms bearing heteroatoms α and *β* to the isoxazole ring, compounds produced by lateral metalation **11a**,**b** were again employed (Scheme 3).

Over 50 attempts at direct asymmetric induction during the lateral metalation step in the presence of chiral bis-oxazolines, binaphthols, spartaiene, and other chiral catalysts or stoichiometric reagent based adjuvants gave disappointing results: 6−19% ee. Alternatively, Dess−Martin oxidation produced the ketones **12a**,**b** in good yield although compound **12b** was found to be highly light sensitive.

The asymmetric borane reduction using 10 mol % of Corey's 2-methyl-CBS-oxazaborolidine[27] produced α- and *β*-isoxazolyl alcohols **13a**,**b** in good yield and good optical purity. The sense of asymmetric induction (*R* gives *S*) was in agreement with that reported by Corey and co-workers. The *tert*-butyldiphenylsilyl protecting group was thought to

Scheme 3 [a]



[a] Key: Dess−Martin periodinane, CH_2Cl_2, rt; (ii) 10 mol % (*R*)-2-methyl-CBS-oxazoborolidine, CH_2Cl_2, 1 equiv of BH_3−DMS, −45 °C, 18 h; (iii) 2 equiv of imidazole, 10 mol % DMAP, 1.2 equiv of TPS-Cl, CH_2Cl_2; (iv) 1 equiv of TsOH, acetone; (v) $BF_3{\cdot}Et_2O$, MeOH, lead(IV) acetate, benzene; (vi) 5.0 equiv of borane−DMS, THF, rt 30 h; (vii) Dess−Martin periodinane, CH_2Cl_2, rt; (viii) allylamine, 10 mol % Jacobsen L,R,R catalyst, TMSCN, MeOH, toluene, −78 °C; (ix) MeOH, HCl, rt, 8 h; (x) 10 mol % $Pd(PPh_3)_4$, NMDBA,CH_2Cl_2 35 °C; (xi) 2 M HCl, 74 °C, 22 h.

be robust enough to permit the alcohols to be taken through the homologation sequence and the silyl ethers were formed quantitatively.

The *p*-toluenesulfonic acid hydrolysis gave the methyl ketones **15a**,**b** in good yield and these compounds were carried through to the aldehydes **17a**,**b** as before. The chemical yields for the α TPS-ether were dramatically lower, presumably due to the steric bulk proximal to the C-4 position. The modified Jacobsen Strecker conditions used previously were again successful in producing the amino nitriles **18a**,**b** in excellent yield (>90%) and diastereomeric excess (>90%).

A significant degree of double asymmetric induction was observed for the alpha TPS-ethers as the (*S*,*S*) isomer was formed in 99% de versus 90% for the (*R*,*S*) diastereomer. The Pinner reaction produced the amino esters and cleaved the TPS protecting group in a single step in 53% yield. It is noteworthy that the 2 M HCl hydrolysis in the final step did not result in any detectable loss of the C-5 alcohol moiety. This synthetic strategy enables the production of ACPA derivatives containing lipophilic aryl groups at the C-5 position in addition to chiral hydroxyl groups α or *β* to the isoxazole to take advantage of the proximal heteroatom effect at AMPA receptors.

This modification of the Jacobsen asymmetric Strecker reaction permits the facile asymmetric synthesis of optically active ACPA analogues eliminating isomeric ballast and the need for tedious resolution.

The overall yield for our catalytic ACPA synthesis is 32%, compared to the previously reported resolution route of 0.2%.[13] We have examined competitive binding of [^{3}H]-AMPA with (S)-ACPA, **10a**, prepared by our independent route described herein. Figure 2 dramatically illustrates that

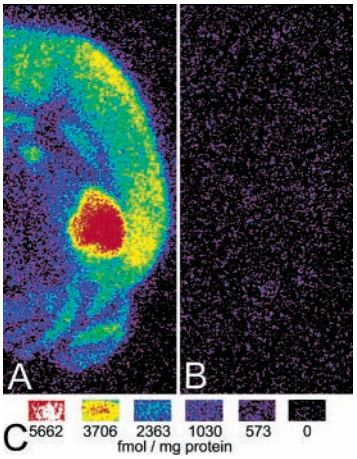


Figure 2. ACPA inhibition of [^{3}H]AMPA binding in mouse brain. (A, B) Pseudocolored computer images of representative autoradiograms of [^{3}H]AMPA binding (50 nM in incubation solution) in the absence (A) and presence (B) of 10 μM (S)-ACPA, **10a**, in horizontal sections of mouse brain. (C) Legend indicates densities (fmol/mg protein) of binding for different pseudocolor levels.[26]

(*S*)-ACPA, **10a**, *completely* displaces [^{3}H]-AMPA from mouse brain within experimental error. The complete biological evaluation of our ACPA analogues will be described in due course. Using this synthetic route, structure based design will permit further lead optimization in pursuit of subunit selective therapeutic agents for neurological disorders.

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Supporting Information Available: Experimental details and full characterization data for all final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(22) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K.; *J. Org. Chem.* **1982**, *47*, 2765−2768.
(23) Su, J. T.; Vachal, P.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 197−200.
(24) Compagnon, P. L.; Miocque, M. *Ann. Chim. (Paris)* **1970**, *14*, 23−37.
(25) Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109−6113.
(26) Magnusson, Kathy R. *Mech Aging Dev.*, **1998**, *104*, 227−248.
(27) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.