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A Short Synthesis of GYKI 52466

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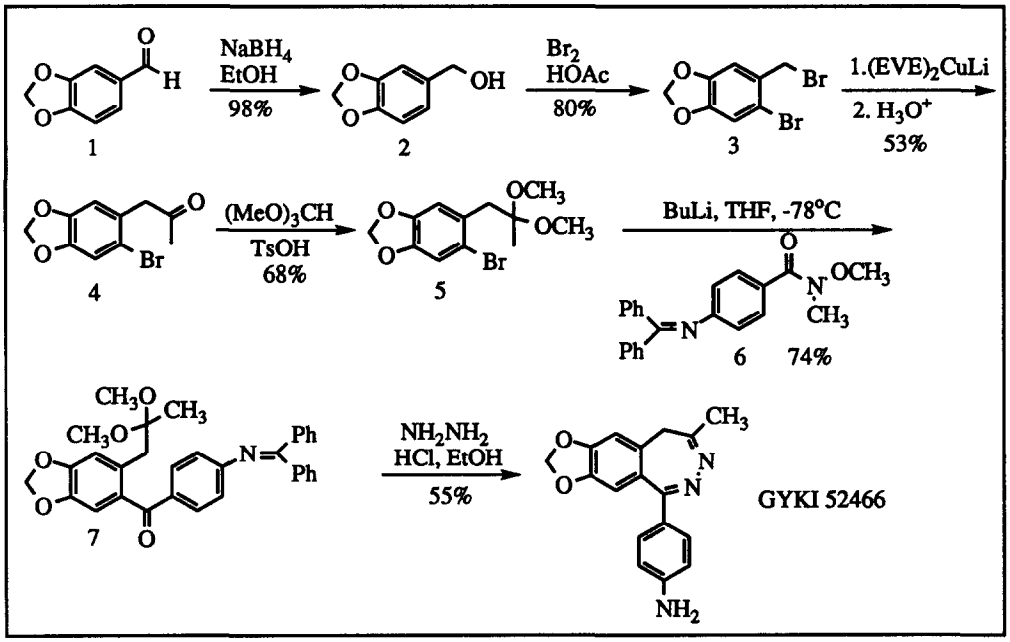
Abstract: *The synthesis of GYKI 52466 has been achieved in a short six step sequence which proceeds in an overall yield of 11.5%.*

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of glutamate receptors has been implicated in the neurodegenerative processes related to several disease states.[1] Most studies of the AMPA receptor have utilized the quinoxalinediones, which competitively inhibit agonist binding.[2] Recently GYKI 52466 has been described as a new ligand which binds to the AMPA receptor in a non competitive fashion.[3] As such, GYKI 52466 has proved to be a useful tool to probe the biological function of the AMPA receptor.[4] Unfortunately, few details relating to the preparation of GYKI 52466 are available.[5] Therefore, we developed an efficient route[6] to the compound in order to more fully characterize its biological actions.



Commercially available piperinal was reduced ($NaBH_4$) and dibrominated (Br_2, HOAc) as previously described to provide 6-bromomethyl-5-bromobenzodioxolane (3) in high yield.[7] The latent acetyl group was introduced by displacement of the benzyl bromide with the lower order cuprate derived from ethyl vinyl ether.[8] Initial attempts to carry out metal halogen exchange reactions on the enol ether were unsuccessful. Therefore, we hydrolyzed the enol ether in the workup of the cuprate reaction. This procedure gave the phenylacetone

derivative **4** in 53% yield and was easily amenable to scale-up (runs on up to 20 grams of **3** consistently produced **4** in comparable yield).[9] The ketone **4** was reprotected as its methyl ketal **5**, converted to the lithium anion (butyllithium, THF, -78°C), and reacted with the diphenylmethylene protected Weinreb amide[10] of 4-aminobenzoic acid (**6**) to afford **7** in 74% yield.[11] Complete deprotection and cyclization was accomplished in a single step upon treatment of **7** with a 1.1:1 mixture of hydrazine dihydrochloride / hydrazine in 9:1 methanol / water (50°C, 4h) to give GYKI 52466 in 55% yield as its free base. The mono hydrochloride salt of GYKI 52466 precipitates from an ethanol solution of the free base upon treatment with 1 equivalent of HCl in ether.[12]

The GYKI 52466 prepared as described above was identical to an authentic sample[13] (tlc, NMR, and elemental analysis) and behaved similarly in a neuroprotection model (protection of cultured rat hippocampal neurons from kainic acid-induced cell death).[14] Thus, this sequence allows the preparation of gram quantities of GYKI 52466 and should facilitate further characterization of its biological actions.

References and Notes

1 Ramakers, G. M.; Peeters, B. W.; Vossen, J. M.; Coenen, A. M. *Epilepsy Res.*, **1991**, *9*, 127-131. Klockgether, T.; Turski, L.; Honore, T.; Zhang, Z. M.; Gash, D. M.; Kurlan, R.; Greenamyre, J. T. *Ann. Neurol.*, **1991**, *30*, 717-723. Choi, D. *Neurobiol. Aging* **1989**, *10*, 605-606. Diemer, N. H.; Jorgensen, M. B.; Johansen, F. F.; Sheardown, M.; Honore, T. *Acta Neurol. Scand.*, **1992**, *86*, 45-49. Judge, M. E.; Sheardown, M. J.; Jacobsen, P.; Honore, T. *Neurosci. Lett.*, **1991**, *133*, 291-294. Nellgard, B.; Wieloch, T. *J. Cereb. Blood Flow Metab.*, **1992**, *12*, 2-11.

2 Sheardown, M. J.; Nielsen, E. O.; Hansen, A. J.; Jacobsen, P.; Honore, T. *Science*, **1990**, *247*, 571-574.

3 Tarnawa, I.; Engberg, I.; Flatman, J. A. in *Aminoacids: Biology, Chemistry, and Medicine*, eds Lubec, G. and Rosenthal, G. A., Lieden: Escom., **1990**, 538-546.

4 Tarnawa, I.; Farkas, S.; Berzsenyi, P.; Pataki, A.; Andrasi, F. *Eur. J. Pharmacol.*, **1989**, *167*, 193. Ouardouz, M.; Durand, J. *Neurosci. Lett.*, **1991**, *125*, 5-8.

5 Lang, T.; Korosi, J.; Andrasi, F.; Hamori, J.; Zolyomi, G.; Elekes, I.; Botka, P.; Sineger, E.; Goldschmidt, K.; Horvath, N.; Balogh, T.; Somogyi, G.; Moravcsik, I. French Patent 2,566,774.

6 All new compounds had acceptable elemental analyses. Melting points for new compounds are as follows: **4**, 97-99°C; **5**, 42.5-43°C; **6**, 124-125°C; **7**, 156-156.5°C ; GYKI 52466 (free base), 237.5-238°C

7 Barthel, W. F.; Alexander, B. H. *J. Org. Chem.*, **1958**, *23*, 1012.

8 Boeckman, R. K., jr.; Braza, K. J.; Baldwin, J. E.; Lever, O. W., jr. *J. Chem. Soc., Chem. Commun.*, **1975**, 519-520. Chavdarian, C. G.; Heathcock, C. H. *J. Amer. Chem. Soc.*, **1975**, *97*, 3822-3823.

9 Note that a dimer of the benzyl bromide was also obtained from this reaction (27%). Also the cuprate coupling reaction could not be carried out efficiently with a higher order cuprate. See: Lipschutz, B. H.; Wilhelm, R., S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.*, **1984**, *49*, 3928-3938.

10 Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.*, **1981**, *22*, 3815-3818.

11 Note that several other amine protecting groups were examined but were found to be unsuitable for this sequence due to inability to completely deprotect (benzyl, 4-methoxybenzyl), decomposition of the product during deprotection (2,5-dimethylpyrrole) or instability of the protecting group (N-1,1,4,4-tetramethyldisilylazacyclopentane adduct). For descriptions and leading references to these and other amine protecting groups see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd Ed., J. Wiley and Sons, New York, 1991,

12 Note that excess HCl yields the dihydrochloride salt.

13 We (F. M., M. A. P., K. E. G. R.) thank Dr. I. Tarnawa (Institute for Drug Research, P. O. Box 82, 1325 Budapest, Hungary) for a sample of GYKI 52466.

14 May, P. C.; Robison, P. M. *Neurosci. Lett.*, **1993**, *152*, 169-172.