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AN ASYMMETRIC SYNTHESIS OF VIGABATRIN

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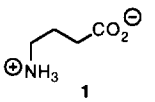
Summary: Enantiomerically pure vigabatrin is available in four steps and 59% overall yield from butadiene monoepoxide.

The biochemical mechanisms responsible for epilepsy, a disease characterized by convulsive seizures resulting from repetitive and excessive electrical neuronal discharges, are not fully understood.[1] It is known that convulsions do occur when GABA (**1**) levels diminish below a certain threshold level in the brain.[2] The low



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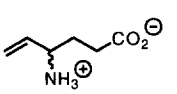

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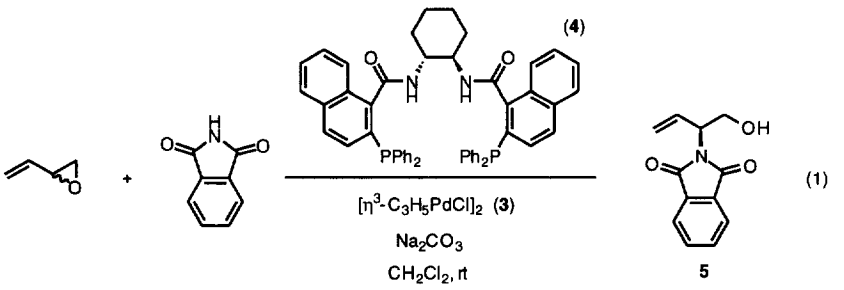
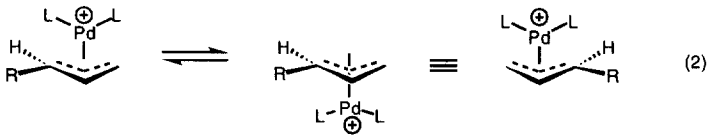
lipophilicity of GABA presumably prevents it from crossing the blood-brain barrier and thereby prevents its administration as a therapy for epilepsy. GABA deficiency is also associated with Parkinson's[3] and Huntington's diseases.[4] An anticonvulsant effect may derive from a lipophilic compound capable of crossing the blood-brain barrier which would inhibit GABA transaminase (GABA-T), the enzyme that degrades GABA.[5] 4-Amino-5-hexenoic acid (γ-vinyl GABA or vigabatrin) is a highly selective irreversible inhibitor of GABA-T with the net effect of increasing GABA levels.[6] Vigabatrin is therefore useful for treating disorders associated with depletion of GABA levels in the central nervous system such as tardive dyskinesia, schizophrenia and epilepsy.[7]

In conjunction with our program on asymmetric allylic alkylations,[8] we developed a catalytic system that permitted efficient deracemization of butadiene monoepoxide, a commercially available compound obtained by the direct silver-catalyzed epoxidation of butadiene with oxygen,[9] as shown in eq. 1.[10] The remarkable features of this reaction include 1) a regioselectivity of 75:1 favoring **5** over attack at the primary

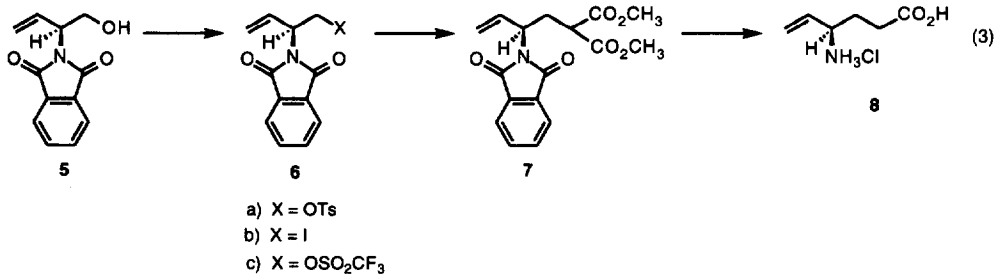


terminus of the allylic system and 2) an enantiomeric ratio (er) of 99:1 at 100% conversion (i.e., it is not a kinetic resolution). This requires that the intermediate π-allylpalladium complex undergoes enantioface exchange (eq. 2) faster than the nucleophilic attack of phthalimide. In scaling up this reaction, we decided to



explore the effect of reducing the quantities of Pd(0) complex **3** and ligand **4** from the amounts originally used (2.5 mol% **3** and 7.5 mol % **4**). We discovered that the ee did show some dependence on the amount of catalyst. Surprisingly, the ee dropped as the amount of catalyst decreased. Originally, we envisioned that the ability of both enantiomers of the starting material to give the same enantiomeric product arose from an equilibration (eq. 2) of the intermediate π-allylpalladium complex by an η^3-η^1-η^3 mechanism. It is unclear how such a mechanism should promote a decrease in ee with decreasing catalyst concentration. On the other hand, if a Pd-Pd substitution contributed to the equilibration,[11] then there would exist a second order dependence on Pd(0) concentration. It appears possible that a combination of both of these mechanisms is required to assure an equilibration more rapid than the nucleophilic attack. Synthetically, we find it convenient to employ 0.4 mol % **3**, 1.2 mol % **4**, 5 mol % sodium carbonate, 1.0 equiv. butadiene monoepoxide, and 1.1 equiv. of phthalimide at 0.125 M (in butadiene monoepoxide) in methylene chloride to give **5** with a 98% yield and 98:2 er (96% ee). Recrystallization from diisopropyl ether gives phthalimide **5** of >99:1 er (>99% ee) as a crystalline solid, mp 62 °C, $[\alpha]_D^{28}$ = -72.2 (c = 2.02, CH_2Cl_2).

The availability of enantiomerically pure vinylglycinol in protected form, in one step, makes it an attractive intermediate for the synthesis of vigabatrin,[6c,12] as outlined in eq. 3. Surprisingly, substitution of the primary alcohol by an acetate equivalent proved difficult due to the reactivity of the phthalimide group. For



example, exposure of the tosylate **6a** to the lithium enolate of t-butyl acetate led only to addition to the carbonyl group of the phthalimide. On the other hand, iodide **6b** does form by a displacement reaction (Ph_3P, I_2, imidazole) in excellent yield (85%) but, again, does not participate in subsequent substitutions. Since the formation of the iodide **6b** indicates that the alkoxyphosphonium leaving group is substituted by iodide, we explored C-alkylations under Mitsunobu conditions, but to no avail.

The key was to boost the reactivity of the alcohol-derived leaving group in order to enhance the rate of alkylation compared to the rate of carbonyl addition. The triflate **6c** is formed in 96% yield under standard conditions [$(CF_3SO_2)_2O$, $(C_2H_5)_3N$, CH_2Cl_2, 0°]. The somewhat unstable but crystalline triflate undergoes substitution with the sodium salt of dimethyl malonate (THF, rt) in 64% yield. Heating malonate **7** in 6N aqueous hydrochloric acid at 100° effects removal of the phthalimide, hydrolysis of the diester, and decarboxylation to give a 96% yield of *R*-vigabatrin, mp 165 °C (lit.[12d] mp 164-5 °C) and $[\alpha]_D^{26}$ = -12.12 (c = 2.35, H_2O) lit.[12d] $[\alpha]_D^{25}$ = -12.0 (c = 2.5, H_2O). Furthermore, the ^1H and ^{13}C nmr spectral data are fully in accord with that previously recorded.

While we performed our synthesis with the *R,R*-ligand **4**, which produces *R*-vigabatrin, this route provides equivalent access to *S*-vigabatrin by using the *S,S*-ligand ***ent*-4**. This strategy which requires 4 steps from two readily available inexpensive building blocks, butadiene monoepoxide and phthalimide, provides either enantiomer in at least 59% overall yield. This efficient strategy derives from the availability of the Pd(0)-catalyzed deracemization reaction.

An experimental procedure for the asymmetric alkylation to form **5** follows: Dichloromethane (80 mL) was added to a solid mixture of 14.6 mg (0.04 mmol) of π-allylpalladium chloride, 94.6 mg (0.12 mmol) of ligand **4**, 53.0 mg (0.05 mmol of sodium carbonate and 1.47 g (10.0 mmol) of phthalimide which was purged under nitrogen for 1 h. After 10 min. at room temperature, 810 μL (10.0 mmol) of racemic butadiene monoepoxide was added and the mixture stirred at room temperature for 14 h. The reaction mixture was concentrated *in vacuo* and directly flash chromatographed (gradient ether:hexanes, 4:6 to 6:4) to give 2.1 g

(98% yield) of crystalline material, mp 62°C (diisopropyl ether).

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