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Efficient syntheses of regioisomers of tiagabine

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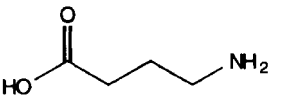
Abstract: The title compounds are being investigated as selective GABA uptake inhibitors that exhibit anti-convulsant effects. Versatile syntheses have been developed for the preparation of these compounds in excellent yields.

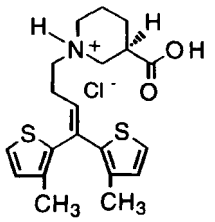
Epilepsy is a disorder characterized by recurrent spontaneous electrical discharges within the brain which are manifested by clinical seizures. Four million patients in the USA are afflicted with this ailment; 20% of these have seizures which cannot be controlled sufficiently with existing medications to permit normal activities of everyday life. Epileptic seizures can be classified as primary epilepsies (35%) and partial epilepsies (65%). Primary epilepsies (generalized convulsions) can be controlled with valproate (Depakote), carbamazepine (Tegretol), phenytoin (Dilantin), or phenobarbitol. Most of the partial epilepsies have resisted control with chemotherapeutic agents.

Current targets for therapeutic intervention with respect to epilepsy are (i) blocking of receptors of excitatory amino acids, (ii) modulating membrane ion channels (sodium and calcium) involved in neuronal membrane excitability and (iii) enhancing the neurotransmittory effect of gamma-aminobutyric acid (GABA) **(I)**.[1,2]

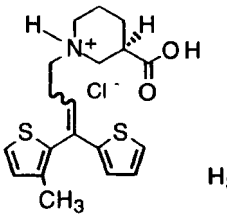


(I)

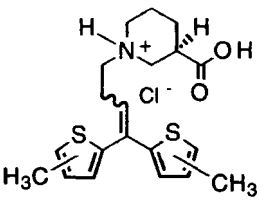
(I) is the principal inhibitory neurotransmitter in the mammalian central nervous system (CNS).[3] It may inhibit mammalian CNS activity in numerous ways:[4] Inhibition of GABA uptake into neuronal and glial cell bodies[5,6] by designing appropriate substrates. This has proved to be the most promising strategy.



(II)



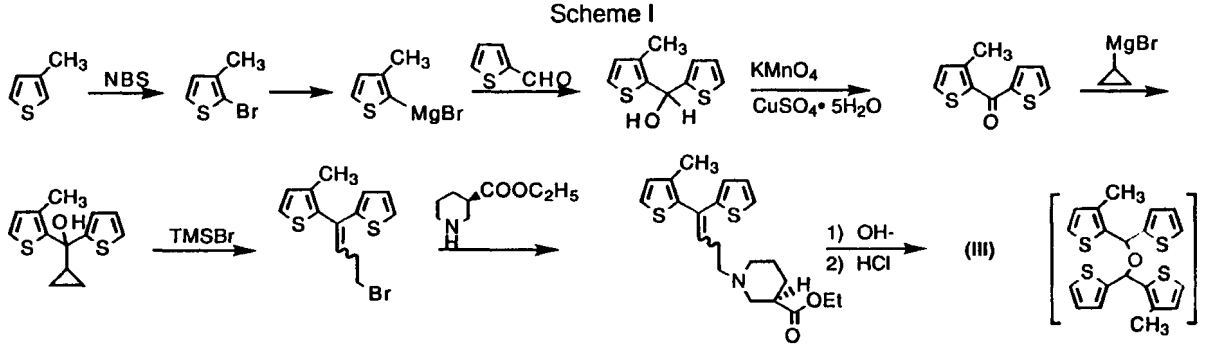
(III)



(IV)

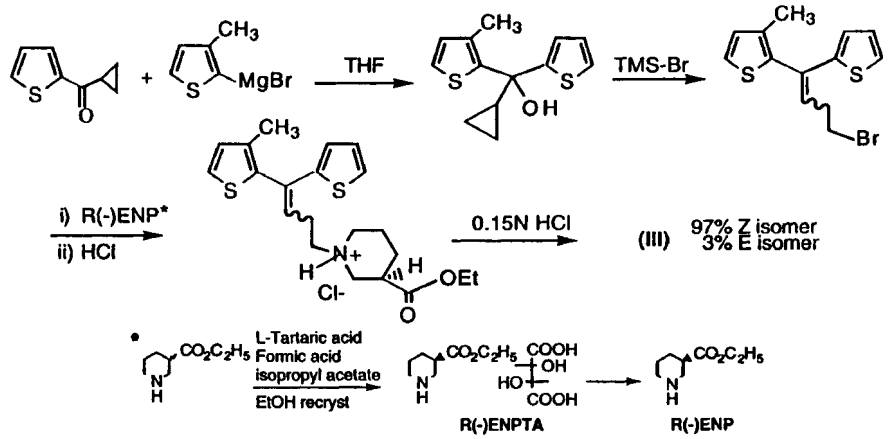
Tiagabine **(II)**,[7] currently in phase III clinical trials, works by retarding the neuronal reuptake of GABA into the presynaptic terminal. Maintaining the extra cellular concentration of GABA leads to calming of excitatory synaptic currents thereby preventing seizures. The synthesis of several novel GABA uptake inhibitors, tiagabine,[8] desmethyltiagabine **(III)**[9] have already been reported. The initial synthesis of desmethyltiagabine is outlined below.

Scheme I



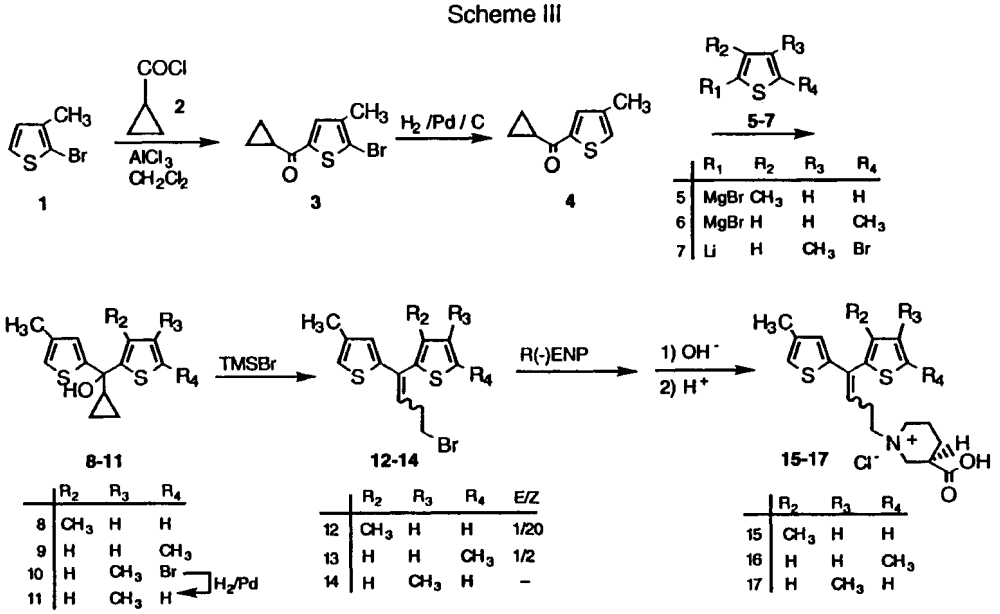
This methodology had some drawbacks: i) The secondary carbinol formed is unstable to storage and is readily converted to the corresponding ether dimer. ii) Dithienyl ketone is obtained in very low yields along with numerous side products and requires a tedious workup procedure. An improved synthesis of desmethyltiagabine, designed by us, is shown in scheme II.

Scheme II



We now report practical syntheses of regioisomers of tiagabine **(IV)** that were amenable to scale up. Scheme III depicts the first of our methods.

Scheme III



	R_1	R_2	R_3	R_4
5	MgBr	CH_3	H	H
6	MgBr	H	H	CH_3
7	Li	H	CH_3	Br

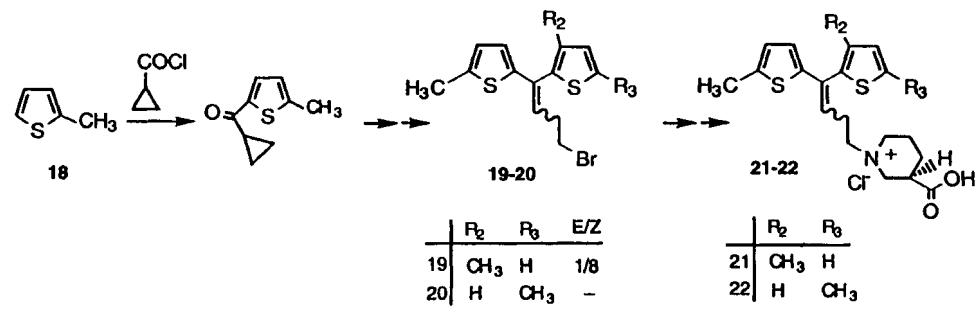
	R_2	R_3	R_4
8	CH_3	H	H
9	H	H	CH_3
10	H	CH_3	Br
11	H	CH_3	H

	R_2	R_3	R_4	E/Z
12	CH_3	H	H	1/20
13	H	H	CH_3	1/2
14	H	CH_3	H	–

	R_2	R_3	R_4
15	CH_3	H	H
16	H	H	CH_3
17	H	CH_3	H

Schemes IV and V detail alternate methods for the synthesis of the desired regioiosmers in reasonable yield. The stereochemistry around the olefinic linkage was determined by nmr.

Scheme IV



	R_2	R_3	E/Z
19	CH_3	H	1/8
20	H	CH_3	–

	R_2	R_3
21	CH_3	H
22	H	CH_3

Scheme V

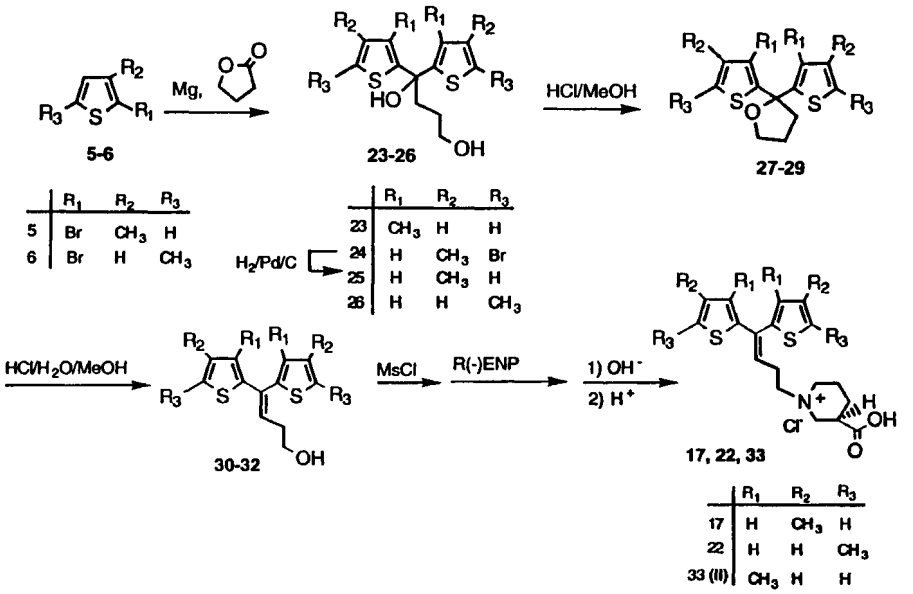
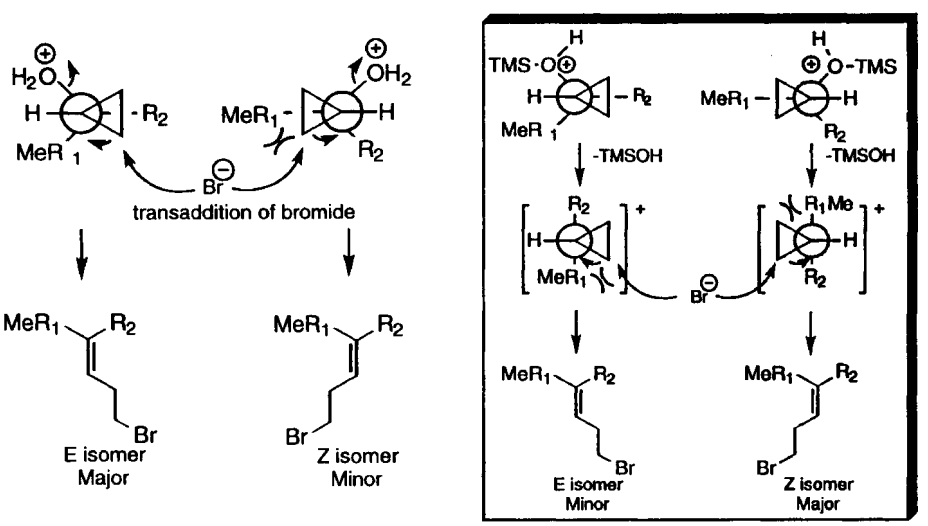


Figure 1 shows the presumed transition state for the Julia-olefination.

Figure 1



Unravelling of the cyclopropyl ring would necessitate S_N2 transaddition of bromide. This would lead to a preponderance of the E-isomer over the Z- derivative. We believe that the reaction on our substrate proceeds by an S_N1, carbonium ion mechanism yielding the Z- isomer as the major product.

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