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(28) Relative ratios determined from $M^+ - 60$ peaks in the mass spectra.

Synthesis of *dl*-Gabaculine Utilizing Direct Allylic Amination as the Key Step

Stephen P. Singer and K. Barry Sharpless*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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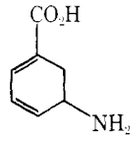
Racemic gabaculine (2,3-dihydro-*m*-anthranilic acid) was synthesized from 3-cyclohexene-1-carboxylic acid in 23% overall yield (seven steps). The key reaction was a direct allylic amination of the *tert*-butyl 3-cyclohexene-1-carboxylate using bis(*N*-*p*-toluenesulfonyl)sulfodiimide. The positional selectivity could be influenced by steric factors with the *N*,*N*-dicyclohexylamine derivative giving amination almost exclusively in the 5 position. The effect of N-substitution on the electrochemical cleavage of allylic *p*-toluenesulfonamide compounds was investigated. While *N*-alkyl groups had little effect, *N*-acyl groups lowered the reduction potential by as much as 0.3 V.

An important aspect of the chemistry of sulfur(IV) and selenium(IV) imido compounds is the allylic amination of alkenes by bis(*N*-*p*-toluenesulfonyl)sulfodiimide[1,2] and bis(*N*-*p*-toluenesulfonyl)selenodiimide.[3] These reagents directly introduce a nitrogen, protected as the *N*-*p*-toluenesulfonyl derivative, in an allylic position. In the past, the strategies used to create this type of functionality have relied on indirect, multistep operations. In view of the potential scope of this new reaction, it was decided to apply the allylic amination sequence to a total synthesis in order to demonstrate its overall utility.

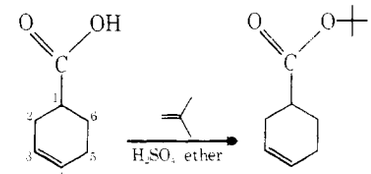
Gabaculine (1) was first isolated from a culture filtrate of *Streptomyces toyocaenis* subspecies 1039 by Mishima and co-workers in 1976.[4] It was an optically active amorphous powder and was assigned the structure 1 on the basis of



1

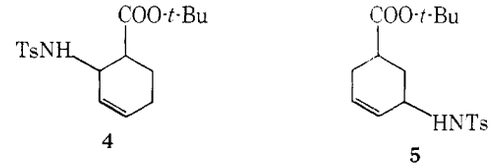
physical and chemical data. This structure was confirmed by the total synthesis of the racemic compound (seven steps from methyl 2,5-dihydrobenzoate, approximately 20% overall yield).[4] Gabaculine is a subject of current biochemical interest since it is an inhibitor of γ-aminobutyrate aminotransferase.[4] This enzyme,[5,6] a member of the general class of aminotransferases,[7] is directly involved in the metabolism of γ-aminobutyric acid (GABA), an important inhibitory transmitter substance in the nervous system.[8,9] Recently, 1 was shown to be a specific irreversible inhibitor of γ-aminobutyrate aminotransferase.[10]

The allylic amine moiety in gabaculine (1) was an obvious attraction for us since it suggested that 1 might be easily constructed by a route involving direct allylic amination of a suitable cyclohexenyl precursor. According to this plan, our synthesis begins with 3-cyclohexene-1-carboxylic acid (2). Acid 2 is commercially available and contains the complete carbon skeleton of gabaculine. It has two different allylic positions (carbons 2 and 5), but only amination at the 5 position will lead to 1. It was felt that the positional selectivity could be controlled by esterification of the acid with a large, bulky group. Hopefully, this would disfavor the approach of the reagent toward the 2 position. Preliminary experiments involving the allylic amination reaction were carried out using the *tert*-butyl ester 3,[11] synthesized in 79% yield by the reaction of 2 with isobutylene under acidic conditions.



2 3

When 3 was added to a solution of TsN=S=NTs in CH_2Cl_2 at 25 °C,[1] a slow reaction took place (5 days). Workup using K_2CO_3 in aqueous MeOH afforded a white solid in yields ranging from 50% to 70%. Although homogeneous by TLC, NMR spectra of this crude product showed two multiplets (δ 3.9 and 4.1 in the ratio of 3:1) in the region where allylic hydrogens α to a *p*-toluenesulfonamido group are observed, as well as resonances due to two different tosyl groups in the aromatic region (δ 7.2–7.9). The minor isomer (δ 4.1, mp 120–121 °C) was isolated by repeated careful fractional recrystallization from $CHCl_3$/hexanes. In the same manner, the major isomer (δ 3.9, mp 83–84 °C) was isolated from the mother liquors. The minor isomer was assigned the structure 4 since irradation of the olefinic protons (in the presence of



4 5

0.1 N NaOD/D_2O) caused collapse of the δ 4.1 multiplet to a doublet (J = 3.4 Hz). The major isomer was assigned the structure 5. The analogous reaction using TsN=Se=NTs[3] also gave a mixture of 4 and 5 (45% yield) in the ratio of 1:1 (by NMR).

* Address correspondence to this author at the Department of Chemistry, Stanford University, Stanford, California 94305.

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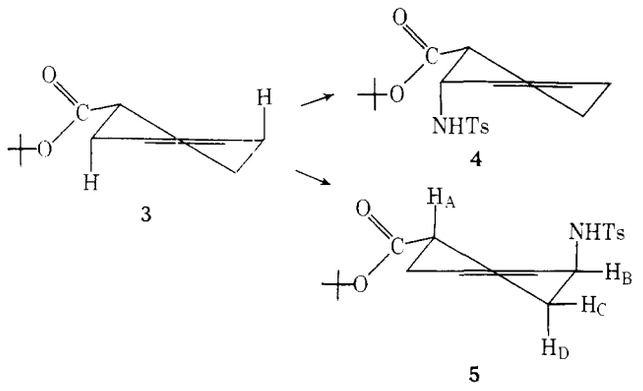
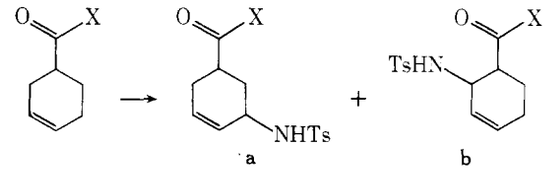


Although the relative stereochemistry of **4** and **5** are unimportant in terms of this particular synthesis, it is important from a mechanistic point of view and for general application to other complex cyclohexenyl systems. Allylic oxidation of conformationally fixed systems by the ene/(2,3) rearrangement pathway preferentially involves the replacement of a pseudoaxial hydrogen by a pseudoaxial substituent. For example, reaction of either SeO_2[12] or TsN=Se=NTs[3] with cholesterol results in the formation of the 4β (axial) alcohol or sulfonamide, respectively. This preference for pseudoaxial hydrogens is a consequence of the need for maximum orbital overlap in the transition state of the ene reaction.[13] Using this reasoning, the allylic sulfonamide **4** is predicted to be the cis and **5** the trans isomer.

The cis relationship in **4** was evident from the NMR decoupling experiments previously mentioned. The observed coupling constant (J = 3.4 Hz) is only consistent with the cis isomer; the corresponding trans compound should have J = 10 Hz at the minimum. When **4** was treated with strong base (potassium *tert*-butoxide in THF) in an attempt to epimerize it to the presumably more stable diequatorial (trans) isomer, only *p*-toluenesulfonamide was isolated, probably originating from an antiperiplanar elimination of the axial sulfonamide moiety. The trans relationship in **5** was demonstrated by both NMR and chemical correlations. High-field NMR (270 MHz)[14] showed a symmetrical eight-line AB portion of an ABXX′ pattern (centered at approximately δ 2.1 in benzene-d_6) for the H_C/H_D methylene group in **5**. Irradiation at δ 4.05 (the allylic proton α to sulfonamido group) caused a collapse of the multiplet to an "AB quartet" (J_{AB} = 11.77 Hz) and J_{BC} and J_{BD} was determined as 6.62 Hz and 8.09 Hz, respectively. These values indicated that H_B is pseudoequatorial and therefore, the sulfonamido group is pseudoaxial. The coupling constants involving H_A could not be determined because of obscuring signals. Similar coupling constants were found in the assignment of stereochemistry for the products of Pd-catalyzed allylic alkylation of *trans*-3-acetoxy-5-carbomethoxycyclohexene.[15] In an attempt to epimerize **5** to the diequatorial (cis) isomer, it was treated with excess potassium *tert*-butoxide in THF. However, the only product isolated (74% yield, mp 162–165 °C) was not the expected *tert*-butyl ester, but rather a carboxylic acid (**6**). This acid (**6**) was completely different from the carboxylic acid (**7**) formed from **5** by treatment with trifluoroacetic acid (76%, mp 174–175 °C). However, treatment of **7** with excess potassium *tert*-butoxide in THF gave **6** in 61% isolated yield. When **6** was heated in *t*-BuOH with a catalytic amount of H_2SO_4, (150 °C, combustion tube) a *tert*-butyl ester different from **5** was formed; however, the extremely poor yield did not allow for complete purification and characterization of this compound.

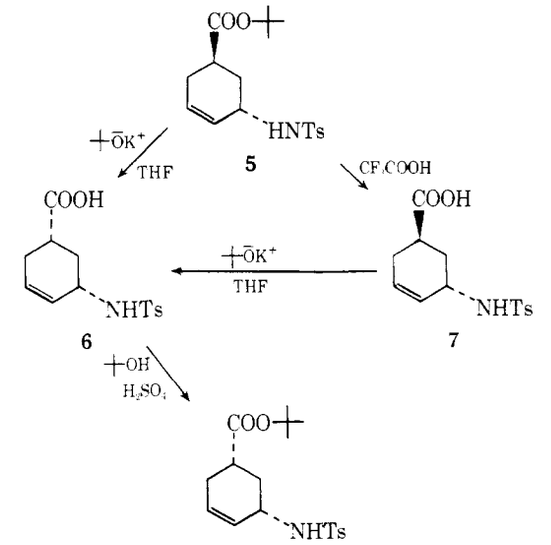
The hydrolysis of **5** to the carboxylic acid **6** under these conditions is not without precedent. Hydrolysis of hindered esters by potassium *tert*-butoxide has been known for many years, although the conditions needed are usually quite vigorous.[16] A possible mechanism is base-catalyzed elimination of *t*-BuOH to form a ketene which is then trapped by KOH (normally found as an impurity in commercial potassium *tert*-butoxide).[17]

Table I

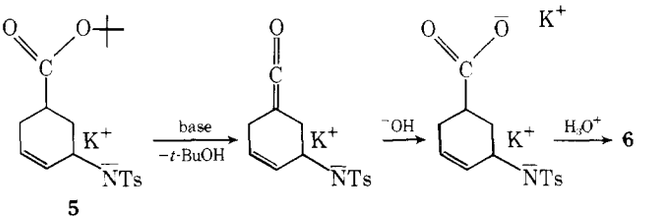


X	Registry no.	Reagent	Equivalents	Total yield	Ratio (b:a)[a]
-OCH_3	49543-03-5	S	1.2	80%	2:3[b]
		Se	1.25	49%	1:1[b]
-O-*tert*-Butyl	65121-09-7	S	1.25	70%	1:3
		Se	1.25	45%	1:1
-$OCHPh_2$	65121-10-0	S	5	50%	1:4
		Se	5	---[c]	----
-2,4,6-Trimethylphenol	65121-11-1	S	5	40%	1:6
		Se	5	---[c]	----
-*N*,*N*-Dicyclohexylamine	65121-12-2	S	5	32%	1:20

[a] Ratio determined by NMR integration. [b] Ratio confirmed by GLPC. [c] No allylic sulfonamide could be isolated.



In order to improve the positional selectivity of the allylic amination reaction, a survey of different ester derivatives was undertaken (Table I). The compounds listed in Table I were all (except for the methyl ester) prepared by reaction of the acid chloride with the appropriate alcohol or amine. The isomer ratio in the product mixture (isolated by chromatography) was determined by NMR integration of the allylic sulfonamide protons (generally found around δ 4.0). By analogy with compounds **5** and **6**, the signal at lower field was assigned



to the 2-*p*-toluenesulfonylamido isomer (b) and the upper field signal to the 5 isomer (a). Two trends can be observed in Table I; first, the sulfur-based reagent is more sensitive to steric factors than the selenium reagent, and secondly, the

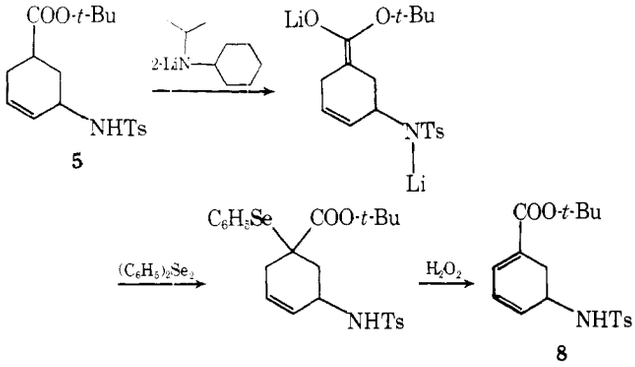
Table II. Methods for Cleavage of Sulfonamide Groups

Method	Ref
Electrochemical	23
(a) Tetramethylammonium amalgam/MeOH	24
(b) Pb cathode/NaOH in aqueous methanol	25
(c) DMF/$R_4N^+X^-$ (controlled potential)	23
(d) $CH_3CN/R_4N^+X^-$ (controlled potential)	26
Sodium napthalene	27, 28
Sodium bis(2-methoxyethoxy)aluminum hydride	29
Sodium–ammonia	30
HBr–phenol	31
Pyridine hydrochloride	31
50% Sodium amylate	31
Concentrated HCl	31

isolated yield of product is reduced when the steric bulk is increased. In the case of the *N,N*-dicyclohexylamine derivative, the allylic amination can be directed almost exclusively to the 5 position; however, the yield of product is low. Because of this and potential difficulties with the hydrolysis of these very hindered compounds, it was decided to continue the synthesis with the *tert*-butyl ester **5**.

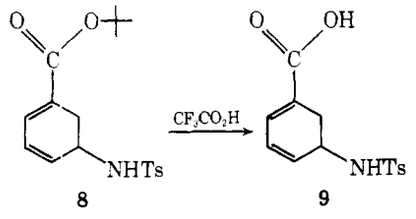
Having **5** in hand, the next step was the introduction of α,β-unsaturation in order to form the dienoic ester system. The classical and still widely used procedure for this type of transformation is halogenation–dehydrohalogenation. However, in recent years alternative methods, based on phenyl selenoxide eliminations[18,19] and on the related phenyl sulfoxide and methyl sulfoxide eliminations,[20] have been developed.

The dianion of **5** was generated with a slight excess of lithium cyclohexylisopropylamide in THF at −78 °C.[21] After quenching the enolate with 2 equiv of dry diphenyl diselenide, the resulting crude phenyl selenide (which was not isolated) was directly oxidized in THF at 0 °C with H_2O_2. From the reaction, the *tert*-butyl ester of *N*-*p*-toluenesulfonylgabaculine (**8**) was isolated in 82% yield as a white crystalline solid



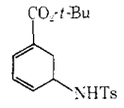
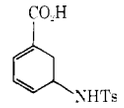
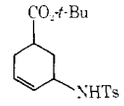
(mp 90–92 °C). Only traces of aromatic compounds were found.

Removal of the *tert*-butyl ester from **8** was accomplished by treatment with trifluoroacetic acid for 5 min at room temperature.[22] Removal of volatile material under high vacuum gave *N*-*p*-toluenesulfonylgabaculine (**9**) as a gummy



semisolid in quantitative yield. Unfortunately, all attempts at the recrystallization of **9** failed. In addition, **9** was somewhat thermally sensitive, decomposing to a dark, tarry material after about 1 day at room temperature. It was generally prepared as needed and used in crude form.

Table III. Comparison of Reduction Potentials

Compounds	Registry no.	$E_{1/2}$ (measd in 0.2 M TEAB[a] in MeOH)[b]
 8	65121-13-3	−1.73 V, −2.5 V
 9	65121-14-4	−2.12 V, −2.5 V
 5	65121-15-5	−2.34 V

[a] TEAB = tetraethylammonium bromide. [b] Vs. calomel reference electrode.

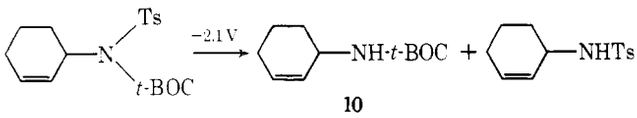
Only the cleavage of the *N*-*p*-toluenesulfonyl group of **9** remained in order to complete the synthesis of **1**. However, the lack of facile methods for the cleavage of sulfonamide groups has been a long-standing problem and many different approaches have been tried. Table II lists some of the methods. Because of the sensitive nature of the desired product, only the first two methods, electrochemical and sodium naphthalene, were considered worth trying.

When **9** was subjected to deprotection by either of these two methods under various conditions, no gabaculine was found. The only products which were isolated (in low yields) seemed by NMR to have one or both of the double bonds reduced. Similar treatment of **8** gave approximately the same results. The *tert*-butyl ester in **8** was stable to these reductive conditions.

In order to clarify the situation, the reduction potentials of **8** and **9**, as well as the saturated derivative **5**, were measured by polarography (Table III). The results indicate that the α,β-double bond is the most easily reducible function present ($E_{1/2}$ ranging from −1.73 to −2.12 V). The sulfonamide group is apparently not reduced until much higher potentials (approximately −2.4 V). This left two alternatives: (1) removal of the Ts group before the introduction of the α,β double bond and reprotection of the resulting amino group, or (2) lowering the reduction potential of the sulfonamide group below that of the double bond.

It is known[26,32] that electron-withdrawing substituents on aromatic sulfonamide groups lower the reduction potential. Alternatively, almost nothing is known about the effects of substitutions on the nitrogen of a primary sulfonamide. Using *N*-*p*-toluenesulfonylcyclohex-2-enamine[3] as a model substrate, the reduction potentials of a number of N-substituted derivatives were measured (Table IV). The compounds were prepared by alkylation (or acylation) of the sodium salt (prepared from the allylic sulfonamide plus NaH) in DMF with the appropriate reagent.

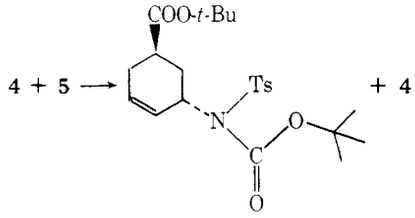
The use of an electron-withdrawing acyl group clearly reduces the reduction potential of the sulfonamide. The fact that the reduction wave is due to reduction of the Ts group was demonstrated by a preparative scale electrolysis of the *N*-tosyl-*tert*-butoxycarbonyl derivative at −2.1 V (0.2 M TEAB in MeCN). The only products isolated were the carbamate **10** (78% yield) and the starting allylic sulfonamide (22%). Unfortunately, the reduction potential of the sulfonamide was



10

still higher than the α,β double bond, so it became necessary to remove the protecting group before the unsaturation was introduced.

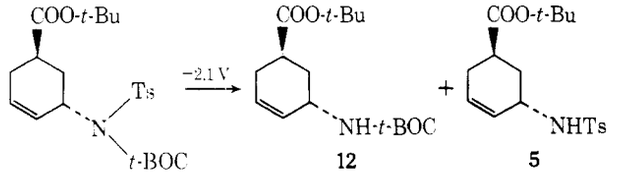
In an attempt to prepare the *t*-BOC derivative of **5**, a 20% 4/80% **5** mixture was subjected to 1.2 equiv of NaH in DMF, followed by 1.5 equiv of *tert*-butoxycarbonyl azide.[33] After heating at 70 °C for a few hours, the only product formed was **11** (100% based on **5**) while **4** was recovered (90% based on **4**).



11

These products were easily separated by column chromatography and so allowed for a convenient method of removing the "wrong" isomer without the need for a fractional recrystallization (and consequent loss of material).

The *N*-tosyl carbamate **11**, a yellow oil, had an $E_{1/2} = -2.06$ V. Preparative scale controlled potential electrolysis at −2.1 V (0.2 M TEAB/MeCN) gave, in analogy to the model compound, two products: the desired allylic carbamate **12** and the



11 12 5

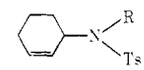
starting allylic sulfonamide **5**. The isolated yields depended on concentration and time of reaction, ranging from 76% **12** and 12% **5** (2.4 g of **11** in 100 mL of electrolyte, 3 h) to 64% **12** and 28% **5** (15.0 g **11** in 300 mL of electrolyte, 15 h). Although the origin of **5** was uncertain, one possible explanation was that the strong bases generated during the reduction cause the hydrolysis of the *tert*-butoxycarbonyl group. Addition of excess phenol (5 equiv) to act as a proton source[26] during the electrolysis prevented the formation of **5** and improved the yield of **12**. However, the isolated yields were still variable, ranging from 80% (4.8 g of **11** in 100 mL of electrolyte, 6 h) to 92% (0.6 g of **11** in 100 mL of electrolyte, 1.5 h).

The advantage of using a *tert*-butoxycarbonyl derivative in the previous reactions lies in its facile hydrolysis under mild acidic conditions, which allows it to be removed at the same time as the *tert*-butyl ester. Because of their acid sensitivity, *t*-BOC protecting groups have found much use in peptide chemistry.[34]

When **12** was subjected to the same reaction sequence (phenyl selenoxide elimination[18,19]) employed to dehydrogenate **5** to **8**, none of the corresponding diene **13** was found. The problem did not lie in the formation of the dianion (formed at −60 to −65 °C) nor in the quenching with diphenyl diselenide since the selenylated product was formed in good yield. Oxidation of the crude α-phenyl seleno ester by various methods (H_2O_2 in THF, H_2O_2 in CH_2Cl_2/pyridine, $NaIO_4$ in CH_3OH and Chloramine-T under phase transfer conditions) gave only complex mixtures of products.

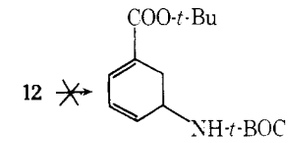
Since the phenyl selenoxide route did not seem viable for the formation of **13**, the dianion was alternatively quenched

Table IV. Effect of N-Substitution on Reduction Potentials

	Registry no.	$E_{1/2}$ (0.2 M TEAB[a] in MeCN)[b]
-H	65121-16-6	−2.31 V
$-CH_3$	65149-42-0	−2.30 V
$-CH_2Ph$	65120-92-5	−2.29 V
$-C(=O)CH_3$(Ac)	65120-93-6	−1.91 V
$-C(=O)OC(CH_3)_3$ (*t*-BOC)	65120-94-7	−2.06 V

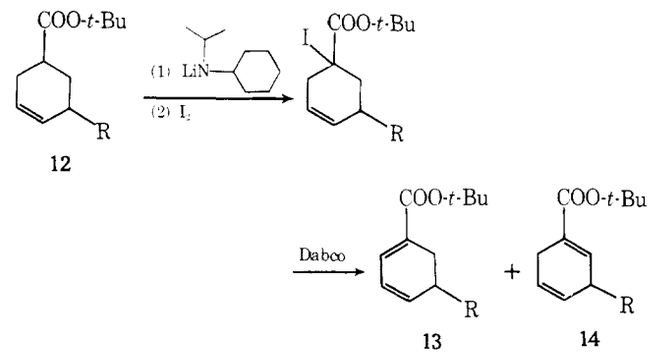
[a] TEAB = tetraethylammonium bromide. [b] Vs. calomel reference electrodes.

with iodine by the method of Rathke and Lindert.[35] The resulting crude α-iodo ester was then treated with base in benzene at room temperature to give **13** in 90% isolated yield. The



13

only other product isolated (9%) was the 2,5-dihydrobenzene derivative **14**, which was unstable in the presence of air and

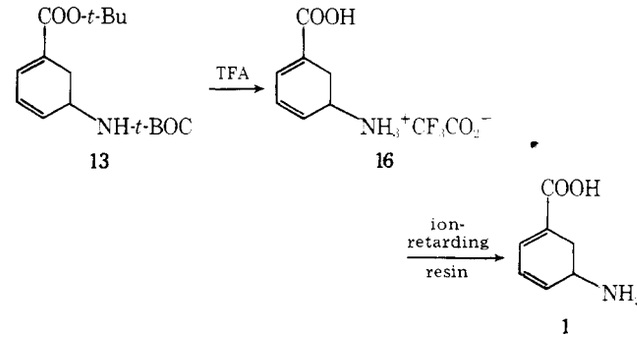


12 13 14

R = NH-*t*-BOC

quickly (10 min at room temperature) aromatized to the corresponding *m*-anthranilate ester **15**. Of the various bases tried (DBU, Dabco, and Et_3N), Dabco (diazobicyclo[2.2.2]octane) gave the highest yield and cleanest product mixture. GLPC analysis showed less than ½% of **5** present in **13**, which was a white crystalline solid, mp 99–101 °C.

The protecting groups of **13** were best removed by distilled trifluoroacetic acid under strictly oxygen-free conditions for 2 min followed by removal of the volatile material under high vacuum. The residue **16** (the trifluoroacetate salt of **1**) was

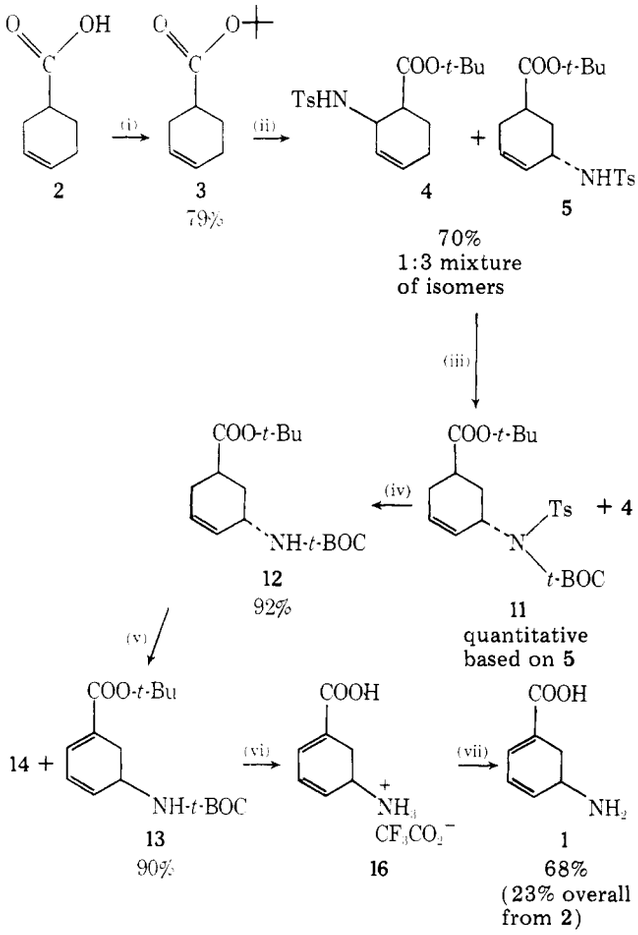


13 16 1

generally not isolated, but dissolved in H_2O and directly eluted through an ion-exchange resin. Use of undistilled CF_3CO_2H under the same conditions caused some aromatization to *m*-anthranilic acid.

Use of the cation-exchange resin SP Sephadex C-25 (used

Scheme I[a]



[a] (i) Isobutylene, H_2SO_4, ether, 25 °C; (ii) (a) 1.2 equiv of TsN=S=NTs, CH_2Cl_2, 25 °C; (b) K_2CO_3 in 60% CH_3OH–H_2O, (iii) (a) NAH, DMF, 25 °C; (b) *tert*-BOC azide; (iv) electrolysis (−2.1 V) in 0.2 M TEAB in MeCN; (v) (a) 3.6 equiv of lithium cyclohexylisopropylamide, THF, −78 °C; (b) I_2, THF, −78 °C; (c) DABCO, benzene, 25 °C; (vi) CF_3CO_2H; (vii) ion-retarding resin.

by Mishima to isolate **1** from the HCl salt[4]) or the related Dowex AG50W-X8 (Bio-Rad Laboratories) to isolate **1** was not totally satisfactory. When a solution of 2% NH_4OH was added in order to remove **1** from the resin, a dark brown, fluorescent impurity was formed which was difficult to separate from the gabaculine. The amount of this impurity was probably small since no peaks other than those of **1** were visible in the NMR spectra. The use of AG11A8 ion-retardation resin (Bio-Rad Laboratories)[36] gave much better results, since ammonium hydroxide was not necessary to remove **1** from the resin. Lyophilization of the appropriate fractions (identified by TLC with visualization by UV and ninhydrin test) gave *dl*-gabaculine (**1**) as an amorphous off-white powder in 68% yield from **13**. This material, mp 194–196 °C dec (after recrystallization from aqueous MeOH, lit.[4] mp 196–197 °C dec) gave NMR, IR, and UV data consistent with the published values. The TLC behavior was identical with an authentic sample. A small sample of **1** was treated with HCl gas in MeOH at 0 °C to give *dl*-gabaculine hydrochloride salt, mp 195–199 °C dec (lit.[4] mp 198–200 °C dec) which gave an undepressed melting point upon admixture with an authentic sample of the racemic hydrochloride obtained from Mishima.

A summary of the exact route used to synthesize *dl*-gabaculine (**1**) is shown in Scheme I. This synthesis is comparable to Mishima's[4] both in terms of length and overall yield. Neither is without fault, particularly in the area of positional selectivity. However, one advantage of this synthesis is that the starting material, 3-cyclohexene-1-carboxylic acid, has been resolved via the brucine salt into the *R* and *S* enantiomers.[37] Although this has not been done, use of the optically active cyclohexene carboxylic acid **2** should lead to optically active gabaculine. Since only *l*-gabaculine is active toward γ-aminobutyrate aminotransferase,[4] this will have the effect of increasing the overall yield of the active agent.

Experimental Section

General Comments. Elemental microanalyses were performed by Midwest Microlab, Ltd. (Indianapolis, Ind.) and by Robertson Laboratory (Florham Park, N.J.). Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected, as are the boiling points.

In general, reagent grade solvents were used without further purification. Tetrahydrofuran and benzene were always freshly distilled from purple sodium–benzophenone solutions under nitrogen. Chlorinated solvents (methylene chloride, chloroform, carbon tetrachloride) were used after passage through alumina and storage over 4 Å molecular sieves. All oxygen or water sensitive reactions were carried out under a dry nitrogen atmosphere in flame-dried glassware (this will be called "anhydrous" conditions). Organic extracts of reaction mixtures were dried over anhydrous magnesium sulfate unless noted otherwise. Evaporation refers to removal of solvent under water aspirator pressure on a roto-vac (bath temperature <30 °C).

The following abbreviations will be used: t_r = GLC retention time under the specified conditions and R_f = TLC mobility relative to the solvent front (= 1).

Tetraethylammonium bromide (Eastman Organic Chemicals) was recrystallized from $CHCl_3/CCl_4$ and dried at 110 °C under vacuum for 12 h. Spectra-grade acetonitrile (stored over 4 Å sieves) was used for the electrochemical experiments (approximately the same results were found using acetonitrile which had been distilled first from CaH_2 and then from P_2O_5).

All ion-exchange resins were washed and prepared according to the manufacturer's instructions before use.

Polarographic measurements were made using a Princeton Applied Research Model 174A Polarographic Analyzer and a standard divided polarographic cell. Connection with the reference electrode (Corning Calomel catalog 476000) was by an Agar bridge (3–5% Difco Bacto-Agar in 1:1 saturated KCl/distilled H_2O). Solutions (generally 10^{-2} to 10^{-3} M) were deaerated by a N_2 stream for at least 3 min. Using 0.2 M TEAB in MeCN, the solvent discharge potential was −2.9 V.

Controlled potential electrolysis was performed using a Princeton Applied Research Model 371 potentiostat–galvanostat. Triply distilled Hg was used for the working electrode (cathode) and either a graphite rod or a Pt wire wrapped with Pt gauze for the counterelectrode (anode). The cell was divided by means of an unglazed, porous porcelain cup (Coors No. 70004) which had been previously extracted with refluxing acetone and then dried at 110 °C under vacuum. The electrolysis cell was flushed with a slow stream of N_2 and, before the addition of substrate, preelectrolyzed at a potential 100 mV more negative than the desired potential.

***tert*-Butyl 3-Cyclohexene-1-carboxylate (3).** Isobutylene was condensed at −78 °C (dry ice/isopropyl alcohol bath) in a 100-mL three-necked round-bottomed flask equipped with a dry ice condenser. Approximately 30–40 mL was transferred by cannula to a precooled Fisher-Porter pressure bottle containing 10.0 g (79.4 mmol) of 3-cyclohexene-1-carboxylic acid (Frinton Labs.) and 1 mL of concentrated H_2SO_4 in 20 mL of ether. The reaction vessel was sealed and allowed to warm to room temperature. After 14 h of stirring (magnetic), the pressure bottle was opened slightly (caution!) and the excess isobutylene was allowed to evaporate. After neutralizing the residue with $NaHCO_3$ (cooling was necessary), it was taken up in ether, which was washed twice with bicarbonate and once with brine, and dried. Filtration and evaporation afforded 13.94 g of a yellowish oil which was distilled (bp 44–46 °C at 0.6 Torr) to give 11.38 g (79%) of *tert*-butyl 3-cyclohexene-1-carboxylate as a clear oil: IR (film) 3030, 2980, 2930, 1730 (ester), 1475, 1455, 1435, 1390 (*tert*-butyl), 1370 (*tert*-butyl), 1310, 1230, 1160 (ester), 1000, 850 and 650 cm^{-1}; NMR ($CDCl_3$) δ 5.65 (2 H, broad s, olefinic), 2.4–1.8 (7 H. m, ring H) and 1.45 (9 H, s, *tert*-butyl). This reaction has been run on scales up to 35 g (0.28 mol) of acid with comparable results.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.40; H, 10.10.

Preparation of Bis(*N*-*p*-toluenesulfonyl)sulfodiimide

(TsN=S=NTs) from *N*-Sulfinyl-*p*-toluenesulfonamide (TsN=S=O). The *N*-sulfinyl-*p*-toluenesulfonamide used here was prepared by a modification of Kresze's[38] procedure; the details of our modified method are given in the accompanying paper[39] in this issue.

The following preparation of TsN=S=NTs follows Kresze's procedure.[38] *N*-Sulfinyl-*p*-toluenesulfonamide (98 g, 0.45 mol) was dissolved in 100 mL of dry benzene under a dry nitrogen atmosphere in a glovebag (due to the great moisture sensitivity of the product all of the following operations should be carried out under a dry atmosphere in a glovebag or a drybox). Dry pyridine (0.75 mL) was added, and the loosely stoppered (to allow for SO_2 evolution) flask was allowed to stand overnight in the glovebag with a slight flow of nitrogen passing through the bag. The sulfodiimide precipitated and was collected by filtration (in the glovebag). The yellow solid was washed twice with small portions of dry carbon tetrachloride and then dried under high vacuum to afford 75 g (90%) of bis(*N*-*p*-toluenesulfonyl)sulfodiimide, mp 40–45 °C (lit.[38] mp 48–50 °C). This compound is extremely sensitive to moisture and should be stored in a desiccator and handled only in the dry atmosphere of a glovebag or a drybox.

Reaction of TsN=S=NTs with 3. Preliminary Experiment. *tert*-Butyl 3-cyclohexene-1-carboxylate (0.91 g, 5 mmol) was added to a stirred solution of 3.45 g (9.3 mmol) of TsN=S=NTs in 15 mL of CH_2Cl_2 in a 50-mL round-bottomed flask under anhydrous conditions. After 3 days at room temperature, the dark reaction mixture was concentrated to a thick oil which was redissolved in 25 mL of 60% CH_3OH containing 3.0 g of K_2CO_3. After stirring overnight, the yellowish solution was taken up in 1:1 EtOAc/ether which was washed once with 1:1 4% NaOH/brine and brine, and dried. Filtration and evaporation left 2.02 g of yellowish oil which was purified by column chromatography (75 g of silica gel; eluted with EtOAc/hexane mixtures). After concentration of the appropriate fractions, 1.1 g (63%) of a pale yellow oil [R_f (35% EtOAc/hexanes) = 0.56] was recovered. NMR showed the product to consist of a mixture of two compounds (see text).

Repeated recrystallization from $CHCl_3$/hexanes produced a pure sample of one of the isomers which was identified as *cis-tert*-butyl 2-(*p*-toluenesulfonamido)-3-cyclohexene-1-carboxylate (**4**), mp 120–121 °C: IR (KBr) 3170 (N–H), 2980, 1695 (H-bonded ester), 1595, 1455, 1390 (*tert*-butyl), 1370 (*tert*-butyl), 1340 (SO_2), 1310, 1160 (SO_2), 1075 and 920 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.9 (4 H, q, aromatic), 5.4 and 5.75 (2 H, m, olefinic), 4.95 (1 H, d, N–H), 4.1 (1 H, m, allylic R_2CHN), 2.45 (3 H, s, aromatic $-CH_3$), 1.8–2.4 (5 H, m, ring H) and 1.45 (9 H, s, *tert*-butyl). When the olefinic proton at δ 5.4 was irradiated ($CDCl_3$ containing 0.1 N NaOD/D_2O), the δ 4.1 multiplet collapsed to a doublet, J = 3.4 Hz. Irradiation at approximately δ 2.4 caused the same multiplet to collapse to a doublet, J = 7 Hz.

Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.98. Found: C, 61.41; H, 7.16; N, 3.70.

Concentration of the mother liquors from above and further recrystallization ($CHCl_3$/hexanes) gave the second isomer which was identified as *trans-tert*-butyl 5-(*p*-toluenesulfonamido)-3-cyclohexene-1-carboxylate (**5**), mp 83–84 °C: IR (KBr) 3280 (NH), 2980, 1710 (ester), 1595, 1450, 1390 (*tert*-butyl), 1370 (*tert*-butyl), 1340 (SO_2), 1310, 1160 (SO_2), 1080 and 820 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.9 (4 H, q, aromatic), 5.35 and 5.75 (2 H, m, olefinic), 5.0 (1 H, d, NH), 3.9 (1 H, m, allylic R_2CHN), 2.45 (3 H, s, aromatic $-CH_3$), 1.8–2.4 (4 H, m, ring H) and 1.45 (9 H, s, *tert*-butyl).

Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.98. Found: C, 61.63; H, 7.24; N, 3.88.

Reaction of TsN=Se=NTs with 3. Preliminary Experiment. The selenium diimide reagent (7.5 mmol) was prepared by stirring a mixture of 0.69 g of selenium metal (8.7 mmol) and 3.42 g of anhydrous chloramine-T (15 mmol) in 20 mL of CH_2Cl_2 at room temperature for 20 h. *tert*-Butyl 3-cyclohexene-1-carboxylate (0.91 g, 5 mmol) was added to the resulting white slurry. After 2 days, the dark reaction mixture was quenched with 1:1 4% NaOH/brine. EtOAc/ether (1:1) was added and both phases were filtered through Celite. The organic phase was separated, washed once with 1:1 4% NaOH/brine and brine, and dried. Filtration and evaporation afforded about 3 g of crude product which was purified by column chromatography (as previously described) to give 790 mg (after 2 h in vacuo, 45%) of a slightly yellow oil. NMR integration of the multiplets at δ 4.1 and δ 3.9 showed an approximate (±10%) 1:1 mixture of **4** and **5**.

Allylic Amination of *tert*-Butyl 3-Cyclohexene-1-carboxylate (3). Best Conditions. *tert*-Butyl 3-cyclohexene-1-carboxylate (**3**) (27.5 g, 0.151 mol) was added to a stirred solution of 80.0 g of TsN=S=NTs (0.216 mol) in 300 mL of CH_2Cl_2 in a 500-mL round-bottomed flask under anhydrous conditions. After 8 days at room temperature, the reaction mixture was concentrated and the residue was redissolved in 300 mL of CH_3OH. Water (200 mL) was added followed by 70 g of K_2CO_3 in three portions. After 16 h, the reddish solution was taken up in 350 mL of 1:1 EtOAc/ether which was washed twice with 1:1 4% NaOH/brine and once with brine, and dried. Filtration and evaporation gave a dark red-yellow oil which was passed through a plug of silica gel (80 g) with 15% EtOAc/hexanes. Concentration of the filtrate gave 49.6 g of crude product. Trituration with 200 mL of cyclohexane while cooling (crystallization was usually induced by scratching or with seed crystals) afforded 33.33 g (after drying in vacuo) of a mixture of **4** and **5** (63%; by NMR, 20% **4** and 80% **5**), mp 89–95 °C.

The mother liquors from above were concentrated and chromatographed on 200 g of silica gel (packed with hexanes; eluted with 500 mL of hexanes, 5% EtOAc/hexanes, then 2 L of 10% EtOAc/hexanes; 100 mL fractions). Combination of appropriate fractions and evaporation afforded 5.9 g of a red-yellow oil. Recrystallization from cold cyclohexane as above gave an additional 4.03 g of the same mixture of **4** and **5** (total overall yield of the mixture of isomers 70%).

Reaction of 5 with Potassium *tert*-Butoxide. Potassium *tert*-butoxide (360 mg, 3.2 mmol, Aldrich Chemical Co.) was added to a stirred solution of 200 mg (0.57 mmol) of **5** in 10 mL of THF in a two-necked, round-bottomed flask under anhydrous conditions. After 36 h at room temperature, water was added and the reaction mixture acidified with 1 N HCl (to pH ~1) and extracted with 1:1 EtOAc/ether. The organic phase was washed once with brine and dried. Filtration and evaporation gave a yellowish oil which was recrystallized from $CHCl_3$/hexanes to give *cis*-5-(*p*-toluenesulfonamido)-3-cyclohexene-1-carboxylic acid **6** (124 mg, 74%), R_f (10% EtOH/EtOAc) = 0.1, mp 162–165 °C: IR (KBr) 3600–3000 (broad band, carboxylic acid OH), 3250 (NH), 1735 and 1705 (carboxylic acid), 1595, 1450, 1400, 1325 (SO_2), 1295, 1250, 1235, 1150 (SO_2), 1075, 930, and 815 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 11.5 (1 H, broad s, exchangeable with D_2O, CO_2H), 7.2–7.9 (4 H, q, aromatic), 6.9 (1 H, d, NH), 5.2–5.8 (2 H, broad m, olefinic), 3.95 (1 H, m, allylic R_2CHN), 2.45 (3 H, s, aromatic $-CH_3$) and 1.8–2.5 (5 H, m, ring H). Equivalent results were obtained if the reaction mixture was refluxed for 1 h instead of stirring 36 h at room temperature.

Reaction of 5 with Trifluoroacetic Acid. One gram of **5** (2.85 mmol) was dissolved in 4.0 mL of trifluoroacetic acid. After 15 min, the volatile material was removed by high vacuum and the residue recrystallized ($CHCl_3$/hexanes). *trans*-5-(*p*-Toluenesulfonamido)-3-cyclohexene-1-carboxylic acid (0.64 g, 76%) **7**, R_f (10% EtOH/EtOAc) = 0.65, was obtained: mp 174–175 °C; IR (KBr) 3600–3000 (broad band, carboxylic acid), 3360 (NH), 1740 and 1705 (carboxylic acid), 1595, 1455, 1405, 1325 (SO_2), 1295, 1250, 1235, 1150 (SO_2), 1075, 930, 885, and 815 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 11.0 (1 H, broad s, CO_2H), 7.2–7.9 (4 H, q, aromatic) 7.05 (1 H, d, NH), 5.6 and 5.35 (2 H, m, olefinic), 3.95 (1 H, m, allylic R_2CHN), 2.45 (3 H, s, aromatic $-CH_3$) and 1.8–2.5 (5 H, m, ring H). While the spectra of **6** and **7** were similar, they were not superimposable.

Isomerization of 7 to 6 with Potassium *tert*-Butoxide. A stirred mixture of 75 mg of **7** (0.25 mmol) and 200 mg (1.8 mmol) of potassium *tert*-butoxide in 5 mL of THF was refluxed for 3 h in a 25-mL round-bottomed flask fitted with a reflux condenser under anhydrous conditions. After cooling, the mixture was quenched with H_2O, acidified with 1 N HCl, and then extracted with EtOAc. The organic phase was washed once with brine and dried. Filtration and evaporation gave a yellowish oil (82 mg) which was recrystallized twice from $CHCl_3$/hexanes to give a white solid (46 mg, 61%) which was identical (TLC, NMR, and IR) with **6**.

***tert*-Butyl 3-(*p*-Toluenesulfonamido)-2,3-dihydrobenzoate (8).** *trans-tert*-Butyl 5-(*p*-toluenesulfonamido)-3-cyclohexene-1-carboxylate **5** (1.05 g, 2.99 mmol) was added to a stirred and cooled (−78 °C, dry ice/isopropyl alcohol) solution of lithium cyclohexylisopropylamide (prepared at −78 °C by the addition of 3.0 mL of 2.4 M (7.2 mmol) *n*-BuLi in hexanes to 1.38 mL (7.6 mmol) of cyclohexylisopropylamine in a 100-mL three-necked, round-bottomed flask under anhydrous conditions). After ½ h, a precooled (−78 °C) solution of 2.34 g (7.5 mmol) diphenyl diselenide (recrystallized from hexanes and dried in vacuo) in 10 mL of THF was added quickly by cannula using positive N_2 pressure. After 2.5 h with gradual warming to room temperature, the reaction was quenched with water (25 mL) and extracted twice with 1:1 EtOAc/ether. The organic phase was washed once with H_2O, 1 N HCl, bicarbonate and brine, and then dried. Filtration and evaporation afforded a yellow oil, which was redissolved in 50 mL of THF, cooled to 0 °C (ice bath), and 3.4 g of 30% H_2O_2 (30 mmol) added in three portions over 1.5 h. After another 1.5 h at room temperature, the colorless reaction mixture was taken up in 1:1 ether/EtOAc which was washed once with bicarbonate and brine, and dried. Filtration and evaporation gave 1.45 g of a light yellowish oil.

This material, although fairly pure by TLC, was best purified by column chromatography (60 g of alumina activity III, eluted with EtOAc/hexane mixtures). Concentration of the appropriate fractions gave 960 mg of a slightly yellow oil, which upon trituration with cyclohexane gave *tert*-butyl 3-(*p*-toluenesulfonamido)-2,3-dihydrobenzoate **8** (840 mg, 82%) as a white crystalline solid, R_f (35% EtOAc/hexanes) = 0.63, mp 90–92 °C; IR (KBr) 3250 (NH), 2980, 1725, and 1705 (ester), 1595, 1580, 1440, 1370, 1330 (SO_2), 1160 (SO_2), 1095, and 810 cm^{-1}; NMR ($CDCl_3$) δ 7.25–7.9 (4 H, q, aromatic), 6.95 (1 H, d, α-hydrogen), 5.8–6.2 (2 H, m, olefinic), 5.0 (1 H, d, exchangeable with 0.1 N NaOD/D_2O, NH), 4.1 (1 H, m, collapses to d of d in base, allylic R_2CHN), 2.6 (2 H, d of d, $-CH_2-$), 2.45 (3 H, s, aromatic $-CH_3$) and 1.5 (9 H, s, *tert*-butyl); UV_{max}(MeOH) 239 nm (log ϵ 4.07) and 283 nm (ϵ 4225).

Anal. Calcd for $C_{18}H_{23}NO_4S$: C, 61.86; H, 6.63; N, 4.00. Found: C, 61.92; H, 6.80; N, 3.78.

***N*-(*p*-Toluenesulfonyl)gabaculine (9).** The diene **8** (50 mg, 0.14 mmol) was dissolved in 1 mL of CF_3CO_2H under N_2. After 5 min, the solvent was removed under high vacuum to afford a gummy residue. This material (42 mg, 100%) was temperature sensitive and could not be recrystallized (CCl_4, $CHCl_3$/hexanes, aqueous EtOH): NMR ($CDCl_3$) δ 8.05 (1 H, d, α-hydrogen), 7.2–7.8 (6 H, m, aromatic and olefinic), 5.15 (1 H, m, allylic R_2CHN), 5.00 (1 H, d, NH), 2.8 (2 H, m, $-CH_2-$) and 2.45 (3 H, s, aromatic $-CH_3$). Cleavage of the *tert*-butyl ester with HCl gas in CH_2Cl_2 at −10 °C (1 h), followed by concentration by high vacuum, gave the same material. Because of its gummy nature and instability, **9** was generally not isolated.

***trans*-*tert*-Butyl 5-(*N*-*tert*-Butoxycarbonyl-*p*-toluenesulfonamido) 3-cyclohexene-1-carboxylate (11).** The allylic sulfonamide mixture obtained by allylic amination of **3** (20% **4**/80% **5**, 25 g, 71.2 mmol) was added in small portions with stirring and cooling (ice bath) to a suspension of 4.3 g of NaH (50% in oil, 89.6 mmol) in 250 mL of DMF in a 500-mL round-bottomed flask under anhydrous conditions. After warming to room temperature (1 h), *tert*-butoxycarbonyl azide[33] (15.3 g, 106.9 mmol) was added. After heating at 60–70 °C for 13 h, the reaction was cautiously quenched with small pieces of ice. EtOAc/ether (1:1, 250 mL) was added and the organic phase washed three times with H_2O and once with brine, and dried. Filtration and evaporation afforded 43.4 g of yellowish oil.

Column Chromatography (400 g of Silica Gel, Eluted with EtOAc/Hexanes). Concentration of the appropriate fractions afforded 25.69 g (dried 5 h in vacuo, 80%, 100% based on **5**) of **11** as a thick yellowish oil, R_f (25% EtOAc/hexanes) = 0.64: IR (film) 2980, 2940, 1740–1705 (broad band; ester and carbamate) 1595, 1480, 1460, 1395, and 1370 (*tert*-butyl), 1360 (SO_2), 1260, 1160 (SO_2), 1090, 850, 835, 820, and 740 cm^{-1}; NMR ($CDCl_3$) δ 7.25–7.95 (4 H, q, aromatic), 5.5–6.0 (2 H, m, olefinic), 5.2 (1 H, m, allylic R_2CHN), 2.45 (3 H, s, aromatic $-CH_3$), 2.0–2.5 (4 H, m, overlapping $-CH_2-$), 1.55 (9 H, distorted t, *tert*-butyl) and 1.45 (9 H, s, *tert*-butyl); mass spectrum (70 eV) *m/e* 451 (M^+), 395 (M − 56, loss of isobutylene), 339 (M − 112, loss of two isobutylene + CO_2), 216, 183, 139, 84, and 82 (base peak). The NMR signal at δ 1.55 is assigned to the *tert*-butoxycarbonyl group; the splitting is possibly caused by hindered rotation because of the *N*-tosyl group. The trans stereochemistry is assumed on the basis of the starting material.

Anal. Calcd for $C_{23}H_{33}NO_6S$: C, 61.17; H, 7.36; N, 3.10. Found: C, 60.90; H, 7.36; N, 3.11.

Further elution of the column and concentration of the appropriate fractions gave 5.57 g of crude **4** [R_f (25% EtOAc/hexanes) = 0.45]. Recrystallization from $CHCl_3$/hexanes afforded a total (2 crops) of 4.37 g (17.5%, 90% recovery based on **4**) of **4** which was identical with the previously isolated material.

Controlled Potential Electrolysis of 11. In an electrolysis cell, 2.43 g (5.4 mmol) of **11** was added to 100 mL of preelectrolyzed 0.2 M TEAB/MeCN at −2.1 V (residual current = 1 mA). The current initially rose to 450 mA and then decayed to 10 mA after 3 h. TLC (25% EtOAc/hexanes) showed no starting material remaining, so water (100 mL) was added and the dark solution was extracted with ether. The organic phase was washed once with water and brine, and dried. Filtration and evaporation left a yellowish oil. Column chromatography (80 g of silica gel, eluted with EtOAc/hexanes) afforded 320 mg (17%) of **5**, R_f (25% EtOAc/hexanes) = 0.45 (identical with a previously isolated sample), and 1.22 g (after 2 h in vacuo, 76%) of **12** as a clear oil, which solidified upon standing, R_f (25% EtOAc/hexanes) = 0.71. Recrystallization from a minimum amount of petroleum ether (1 mL/1 g) gave fluffy white crystals, mp 65–68 °C: IR (KBr) 3390 and 3320 (NH), 2980, 2930, 1735 (ester), 1710 (carbamate), 1520, 1395 and 1370 (*tert*-butyl), 1320, 1250, 1160, 1055, 1045, 870 and 850 cm^{-1}; NMR ($CDCl_3$) δ 5.7 (2 H, m, olefinic), 4.55 (1 H, m, NH), 4.25 (1 H, m, allylic R_2CHN), 1.45 (9 H, s, *tert*-butyl) and 1.2–2.4 (5 H, m, ring H); mass spectrum (70 eV) *m/e* 297 (M^+), 262 (M − 15, loss of CH_3), 241 (M − 56, loss of isobutylene), 224 (M − 73, loss of *tert*-butoxy) and 185 (base peak, M − 112, loss of two isobutylenes).

Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.61; H, 9.15; N, 4.71. Found: C, 64.43; H, 9.14; N, 4.48.

When the reaction was repeated using 15.0 g (33.2 mmol) of **11** in 300 mL of 0.2 M TEAB/MeCN, 15 h was needed for completion. Isolation in the same manner (300 g of silica gel) afforded 6.29 g (64%) of **12** and 3.23 g (28%) of **5**.

Controlled Potential Electrolysis of 11 in the Presence of Phenol. The *N*-tosylcarbamate **11** (4.82 g, 10.7 mmol) was added to a preelectrolyzed solution of 5.0 g of phenol (53 mmol) in 100 mL of 0.2 M TEAB/MeCN at −2.1 V (residual current = 8 mA). After 6 h (the electrolysis was slightly exothermic), the current had decayed to 17 mA. Isolation as previously described gave 2.66 g (84%) of crude product. Trituration with 2 mL of petroleum ether afforded 2.45 g (total of 2 crops, 80%) of **12**.

Using 590 mg (1.3 mmol) of **11** and 650 mg (6.8 mmol) of phenol (under exactly the same conditions), 380 mg (98%) of crude product was obtained. Recrystallization from petroleum ether gave a total (2 crops) of 357 mg (92%) of **12**.

***tert*-Butyl 3-(*tert*-Butoxycarbonylamino)-2,3-dihydrobenzoate (13). Dehydroiodination.** A solution of cooled (−78 °C) lithium isopropylcyclohexylamide was prepared using 10.75 mL (24.6 mmol) of 2.4 M *n*-BuLi and 4.5 mL (24.7 mmol) of isopropylcyclohexylamine in 40 mL of THF in a 100-mL three-necked round-bottomed flask. The allylic carbamate **12** (2.0 g, 6.7 mmol) was added and after 10 min the cooling bath was changed to one maintained at −65 to −60 °C for 1 h. The resulting clear yellow solution of dianion was added using a cannula and positive N_2 pressure to a cooled (−78 °C) and stirred solution of 6.26 g (24.7 mmol) of I_2 in 30 mL of THF in a 250-mL round-bottomed flask under anhydrous conditions. After 2 h, the cooling bath was replaced by an ice bath for another 1.5 h. After an additional ½ h at room temperature, the reaction was quenched with water (20 mL) and extracted with ether which was washed once with cold 1 N HCl, with aqueous sodium bisulfite until colorless, then once with bicarbonate, and brine, and finally dried.

Filtration and evaporation gave a light yellowish oil which was immediately dissolved in 80 mL of benzene and 2.0 g (17.8 mmol) of diazabicyclo[2.2.2]octane (Dabco) was added in one portion. After stirring overnight, the reaction was taken up in ether which was washed once with cold 1 N HCl, bicarbonate, and brine, and dried. Concentration afforded 2.6 g of yellowish oil which was purified by column chromatography (200 g of silica gel, eluted with EtOAc/hexanes) to give two compounds, A and B.

Compound A (180 mg of a white semisolid, 9%) was tentatively identified as *tert*-butyl 5-(*tert*-butoxycarbonylamino)-2,5-dihydrobenzoate (**14**), R_f (25% EtOAc/hexanes) = 0.64: NMR ($CDCl_3$) δ 6.8 (1 H, m, α-hydrogen of α,β-unsaturated ester), 5.6–6.0 (2 H, m, olefinic), 4.9 (1 H, m, NH), 4.7 (1 H, m, allylic R_2CHN), 2.9 (H, d, allylic $-CH_2-$), 1.5 (9 H, s, *tert*-butyl) and 1.45 (9 H, s, *tert*-butyl).

This compound was unstable in the presence of air, decomposing completely to *tert*-butyl *N*-(*tert*-butoxycarbonyl)-*m*-anthranilate (**15**), R_f (25% EtOAc/hexanes) = 0.76, mp 112–115 °C (recrystallized from $CHCl_3$/hexanes): IR (KBr pellet) 3340 (NH), 2980, 2930, 1715–1680 (broad band, ester and carbamate), 1510, 1390, and 1370 (*tert*-butyl), 1305, 1245, 1170, 1110, 870, and 855 cm^{-1}; NMR ($CDCl_3$) δ 7.1–7.9 (4 H, m, aromatic), 7.0 (1 H, broad s, NH), 1.55 (9 H, s, *tert*-butyl) and 1.5 (9 H, s, *tert*-butyl).

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90; N, 4.77. Found: C, 65.39; H, 8.11; N, 4.79.

Compound B (1.80 g of a clear oil) was triturated with approximately 1 mL of petroleum ether to afford 1.78 g (90%) of *tert*-butyl 3-(*tert*-butoxycarbonylamino)-2,3-dihydrobenzoate (**13**) as a fluffy white solid, R_f (25% EtOAc/hexanes) = 0.57: mp 99–101 °C; IR (KBr) 3350 (NH), 2980, 2930, 1720–1680 (broad band, ester, and carbamate), 1510, 1395, and 1370 (*tert*-butyl), 1280, 1255, 1165, 1095, 1050, 850, 760, and 720 cm^{-1}; NMR ($CHCl_3$/hexanes) δ 7.0 (1 H, m, α-hydrogen, 6.1 (2 H, m, olefinic), 4.9 (1 H, m, allylic R_2CHN), 2.6 (2 H, d, of d, methylene), 1.5 (9 H, s, *tert*-butyl), and 1.45 (9 H, s, *tert*-butyl); mass spectrum (70 eV) *m/e* 295 (M^+), 260, 239 (M − 56, loss of isobutylene), 183 and 139 (base peak); UV_{max}(MeOH) 284 nm (ϵ 6240); GLPC analysis (2 m × 2 mm, 5% OV-17 on 80/100 mesh Gas Chrom Q, 195 °C) of **13** (t_r = 3.4 min) showed it to be contaminated with less than ½% of **12** (t_r = 2.9 min).

Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.05; H, 8.53; N, 4.74. Found: C, 64.94; H, 8.32; N, 4.55.

***dl*-Gabaculine (1).** The diene **13** (511.2 mg, 1.7 mmol) was dissolved in 1.5 mL of purified trifluoroacetic acid (distilled at 72 °C under N_2 and stored in a no-air container) under oxygen-free condi-

tions (exothermic reaction). After 2 min, all of the volatile material was removed under high vacuum leaving, after 2 h, a dark semisolid residue. Addition of a little distilled H_2O caused a white crystalline solid to precipitate (presumably the trifluoroacetate salt of 1). After warming gently to redissolve the solid, the solution was applied to a 1 × 20 cm column of Bio-Rad AG11A8 ion-retardation resin[36] and eluted with distilled H_2O. Lyophilization of the appropriate fractions (generally the first 3–10 mL of eluent, visualized by UV and ninhydrin test after spotting on a TLC plate) gave 169 mg (70%) of crude *dl*-gabaculine (1), mp 180–185 °C dec (lit.[4] mp 196–197 °C dec). Recrystallization from MeOH containing a minimum amount of H_2O gave 2 crops of an off-white solid: first crop (83 mg), mp 184–186 °C dec; second crop (32 mg), mp 194–196 °C dec. A third crop (49 mg, mp 182–186 °C dec) was recovered by addition of ether to the mother liquors for a total of 164 mg (68%) of 1: $UV_{max}(H_2O)$ 275 nm (ϵ 8500) (lit.[4] 275 nm (ϵ 8600)). NMR and IR data were consistent with the published values.[4] TLC analysis (7.5 EtOH, 2.5 H_2O, trace NH_4OH) showed a single spot, R_f = 0.64, which cospotted with an authentic sample derived from *dl*-gabaculine hydrochloride.

***dl*-Gabaculine Hydrochloride Salt.** *dl*-Gabaculine (mp 194–196 °C from above, 5 mg, 36 μmol) was dissolved in 0.5 mL of cooled (ice bath) absolute MeOH which had been saturated with dry HCl gas. The solvent was immediately removed by high vacuum to afford a white solid. Recrystallization from acetone containing a little methanol gave 4 mg (63%) of *dl*-gabaculine hydrochloride, mp 195–199 °C dec (lit.[4] mp 198–200 °C dec). Admixture with an authentic sample of racemic gabaculine hydrochloride had no effect on the melting point.

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Registry No.–1, 59556-18-2; 1·HCl, 59556-17-1; **4**, 65120-95-8; **6**, 65120-96-9; **7**, 65120-97-0; **11**, 65120-98-1; **12**, 65120-99-2; **13**, 65121-00-8; **14**, 65121-01-9; **15**, 65121-02-0; TsN=S=NTs, 851-06-9; TsN=Se=NTs, 60123-29-7; isobutylene, 115-11-7; 3-cyclohexene-1-carboxylic acid, 4771-80-6; *N*-sulfinyl-*p*-toluenesulfonamide, 4104-47-6; selenium, 7782-49-2; chloramine-T, 127-65-1; trifluoroacetic acid, 76-05-1; lithium cyclohexylisopropylamine, 32400-20-7; diphenyl diselenide, 1666-13-3; *tert*-butoxycarbonyl azide, 1070-19-5.

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