THE UTILITY OF SULFUR (IV) AND SELENIUM (IV) IMIDO COMPOUNDS IN ORGANIC SYNTHESIS

by

Stephen Paul Singer
B.S., Clarkson College of Technology
1973

Submitted in Partial Fulfillment of
the Requirements for the Degree of
Doctor of Philosophy
at the
Massachusetts Institute of Technology
January 1977

Signature of Author Signature redacted
Department of Chemistry, January 15, 1977

Certified by Signature redacted
Thesis Supervisor

Accepted by Signature redacted
Chairman, Departmental Committee on Graduate Students

This Doctoral Thesis has been examined by a committee of the Department of Chemistry as follows:

Professor F. D. Greene Signature redacted
Chairman

Professor K. B. Sharpless Signature redacted
Thesis Supervisor

Professor J. Baldwin Signature redacted

THE UTILITY OF SULFUR (IV) AND SELENIUM (IV) IMIDO COMPOUNDS IN ORGANIC SYNTHESIS

by

Stephen P. Singer

Submitted to the Department of Chemistry at the Massachusetts Institute of Technology on January 15, 1977, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

ABSTRACT

PART I: ENE AND DIELS-ALDER REACTIONS OF SULFUR (IV) AND SELENIUM (IV) IMIDO COMPOUNDS

Some reactions of the mono- and diimido sulfur and selenium compounds derived from SO_2 and SeO_2 with alkenes and dienes were explored. N-Sulfinylsulfonamides (i.e. O=S=N-Ts) undergo a reversible ene reaction with olefins and can be used to introduce deuterium (or tritium) in the allylic position. The corresponding selenium compound (O=Se=N-Ts) gives directly either allylic sulfonamides or alcohols with olefins, but with 1,3-dienes yields allylic azridines as the major product. Selenium diimide (Ts-N=Se=N-Ts) was found to react with 1,3-dienes to give 1,2-diaminated products which can be rationalized by decomposition of an initially formed (2+4) cycloaddition product. The analogous bis-alkoxycarbonyl sulfur and selenium diimides were prepared, but their reactivity in an ene fashion was low.

PART II: TOTAL SYNTHESIS OF d,l-GABACULINE

d,l-Gabaculine, specific inhibitor of γ-aminobutyrate aminotransferase, was synthesized in 6 steps in 23% overall yield starting from 3-cyclohexene-1-carboxylic acid. The key reactions were an allylic amination using TsN=S=N-Ts and the selective removal of the N-p-toluenesulfonyl protecting group by electrolysis.

Thesis Supervisor: K.B. Sharpless

Title: Professor of Chemistry

ACKNOWLEDGEMENTS

The author thanks the Chemistry Department of M.I.T. for financial support in the form of a Teaching Assistantship (1973-4) and to the Union Carbide Company for a Fellowship (summer, 1974) and especially to his Research Advisor, Professor K.B. Sharpless for guidance, encouragement and enthusiasm.

The author also owes thanks to the other members of the laboratory for help, patience and extra glassware, not to mention an occasional beer.

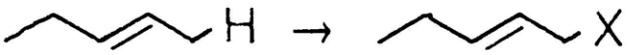
Finally, my wife, Sue, deserves a special mention for continuing moral support and a gold star for typing this thesis.

TO MY PARENTS
AND
SUSAN

TABLE OF CONTENTS

INTRODUCTION

One long standing problem in organic synthesis has been the selective replacement of an allylic C-H bond by some other functionality (Eq. 1). In view of the extensive methodology which

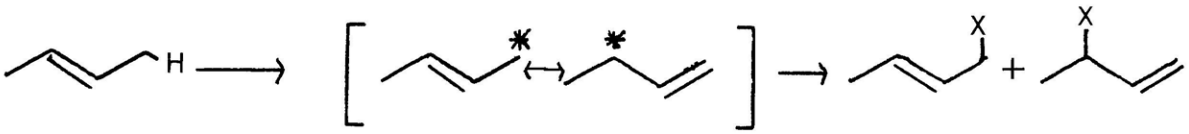


(Eq. 1)

has been developed for the introduction, transformation and reduction of C-C double (and triple) bonds, direct methods for the introduction of a functional group at a specific position relative to the unsaturation would constitute a powerful procedure in total synthesis. Ideally, an allylic oxidation of this type should be accomplished with the following characteristics: 1) in high yield under mild, neutral conditions 2) without shift in position or loss of stereochemistry of the double bond 3) high positional regioselectively in unsymmetrical alkenes and 4) high stereoselectively. However, since the reaction requires cleavage of a relatively strong C-H sigma bond in the presence of a weaker, more accessible pi bond, no reagent can fulfill all of these requirements.

There are many reagents that do perform allylic oxidations within certain limitations and they can be classified into two general categories. The first involves a direct abstraction of an allylic hydrogen to produce some type of resonance stabilized intermediate which upon trapping gives the observed products

(Eq. 2). Some reagents included in this category are: 1) Chromium (VI)



(Eq. 2)

* = radical, cation, anion

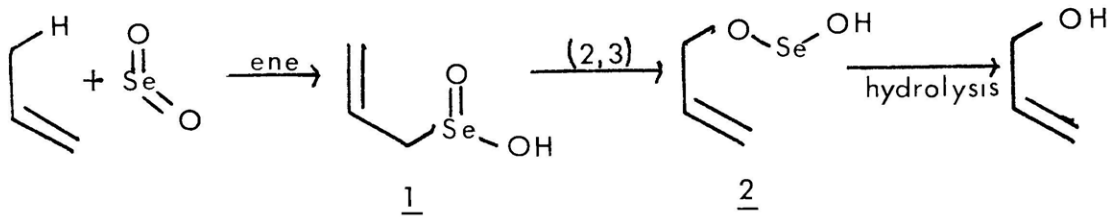
compounds[1a,b] 2) Lead Tetraacetate[2a-e] 3) Mercuric Acetate[2c;3a-e] 4) Peroxyesters[4a,b] and 5) N-Haloamides.[5a-c] As a particular example, the reaction of N-bromosuccinimide, a typical N-haloamide, with an olefin yields an allylic bromide. The key intermediate is a resonance stabilized allyl radical which no longer has the particular stereochemistry or regiochemistry associated with the starting material. The result is a product mixture whose composition depends solely on the constraints of the exact system. Neverless, the reaction has found great use in synthesis because the conditions are mild and the yields high. The second category of reagents used for allylic oxidation is based on selenium and sulfur compounds of which selenium dioxide is the classic example.

The use of selenium dioxide for the oxidation of an allylic position in an alkene was first demonstrated in 1932 by Schenk and Borgwandt,[6] just after Riley and coworkers[7] found that SeO_2 oxidizes carbonyl compounds to alpha -dicarbonyls. Since then, the utility and limitations of selenium dioxide as a reagent has been reviewed by several authors.[8a-e]

Although the mechanism of allylic oxidation of olefins by SeO_2 was a subject of controversy for many years, it has been shown that the reaction proceeds initially by an ene or ene-type reaction[9a,b;10c,d] between the olefin and SeO_2 (Scheme I). The

resulting allylic seleninic acid (1) then undergoes a (2,3) sigmatropic rearrangement[10a,b; 11] to a Se (II) ester (2) which upon hydrolysis affords the observed products. It is this sequence of ene reaction followed by (2,3) rearrangement which accounts for the known stereochemical and positional selectivity of this reaction. However, this reaction suffers from low yields because of over-oxidation and the formation of selenium containing by-products.

Scheme I



1 2

Recently, it was found[12] that analogs of selenium dioxide in which the oxygens were replaced by nitrogens (3) would also perform allylic oxidations in the same manner (Scheme II). In this case, allylic N-(p-toluenesulfonyl)amines are the isolated products. Besides the obvious synthetic utility, the advantage of substituting imido groups for oxo groups lies in the fact that nitrogen is trivalent. The extra group (-R) allows for control over the reactivity of the reagent in two ways; sterically and electronically (things that are not possible with oxygen).

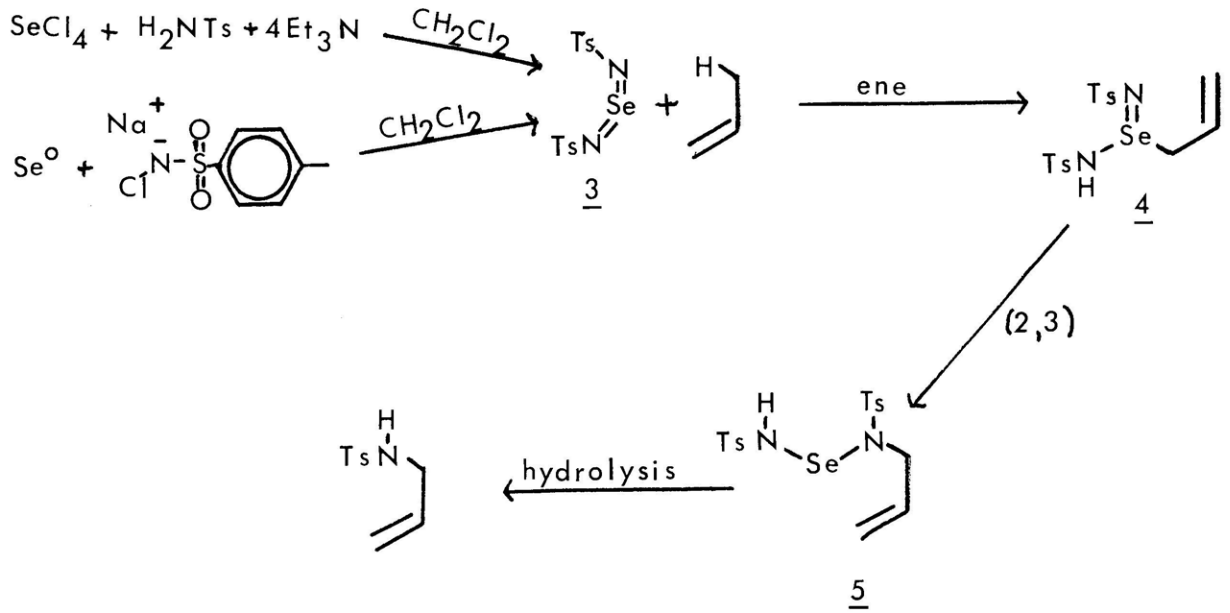
The steric bulk of the -R should offer control over both the positional selectivity in unsymmetrical olefins and the stability of the reagent itself. Variations in electronegativity can also be used to increase or decrease reactivity, since the ene reaction is facilitated by electron deficiency in the enophile.[9a] In practice, N-benzenesulfonyl derivatives were found to give superior results in terms of both stability and reactivity of the selenium diimide reagents. Generally speaking, a N-benzenesulfonylimido group can be considered not only inherently more bulky than an oxo group, but also its equal (or better) in terms of electron-withdrawing properties. For example, compare the pKa's for the following compounds:[13a,b]

H_2O	15.7	NH_3	36	$H_2N\text{-}SO_2\phi$	10.1	$H_2N\text{-}Ts$	10.35
CH_3OH	16.0					CH_3NHTs	11.35

The sulfonamide derivatives are all more acidic than the corresponding oxygen compound. In N-tosylsulfilimines, the α-hydrogens are approximately 4 times more acidic than the corresponding protons in sulfoxides (pK_a -1.96 vs pK_a -.488)[14] and Oae and coworkers have shown by various physical methods that the S=N bond in N-tosylsulfilimines is longer and more polar than the S=O bond in sulfoxides.[15a-d] The same conclusions were reached for the

mono-N-tosylimido analogs of sulfones, the N-tosylsulfoximines.[16]

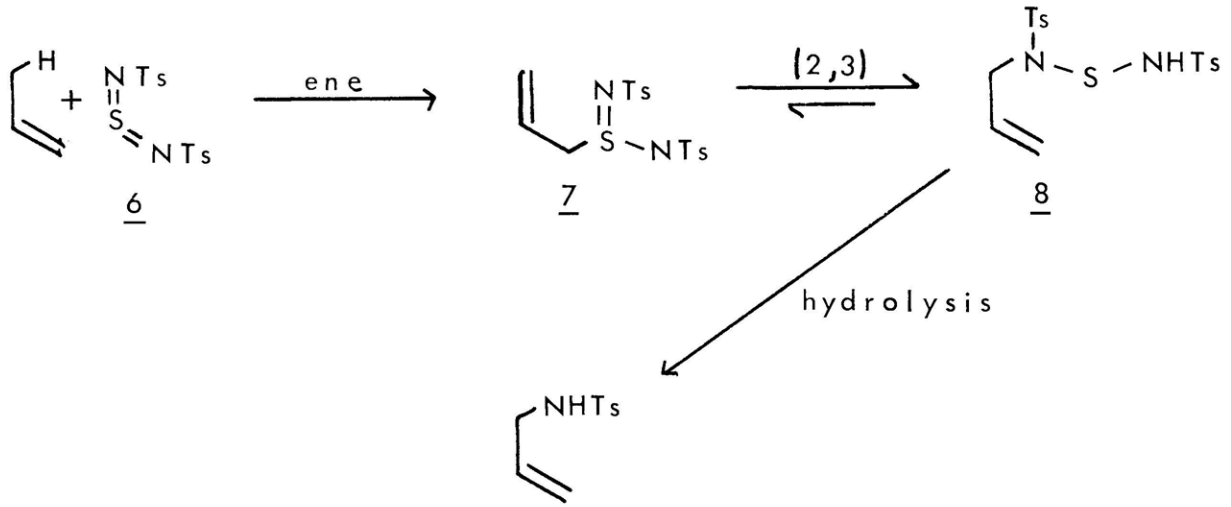
Scheme II



Unlike the bis-N-tosylseleniumdiimide reagent[12] (3,R=Ts) the sulfur analog (bis-N-(p-toluenesulfonyl)sulfurdiimide 6) is a well known, stable, monomeric compound whose chemistry has been explored primarily by Kresze.[17] But like the selenium reagent, it is a powerful enophile in its reactions with olefins (Scheme III) and in some cases, it is superior for the synthesis of allylic sulfonamides.[18a,b] There are two major differences between the sulfur- and selenium-derived reagents; the position of equilibrium for the (2,3) rearrangement and the rate of hydrolysis of the

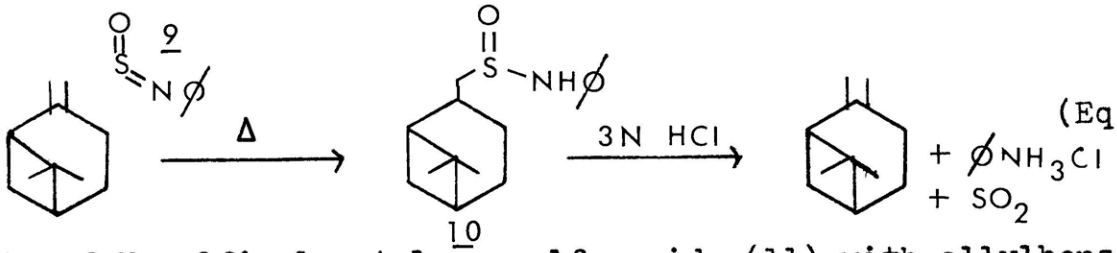
S(II) vs Se(II) amides. As shown in Scheme II (for the selenium diimide), the equilibrium is thought to lie completely on the side of the Se(II) amide 5 which can either hydrolize directly in the reaction mixture or when the reaction is quenched with H_2O. In addition, the Se(II) amide 5 can disproportionate to selenium metal and more Se(IV) imido reagent. This accounts for the fact that in some cases, less than 1 equivalent of 3 is required for the best yields of allylic sulfonamides from alkenes.[12] In any case, the Se(II) amide 5 cannot be isolated although similar selenium(II) amides such as $\emptyset SeNEt_2$ are known.[19] In Scheme III (for the sulfur diimide), the product is a mixture (as determined by nmr) of the initial ene product 7 and the (2,3) shifted disulfenamide 8. This mixture can be isolated and is only slowly hydrolized by water to an allylic sulfonamide.

Scheme III



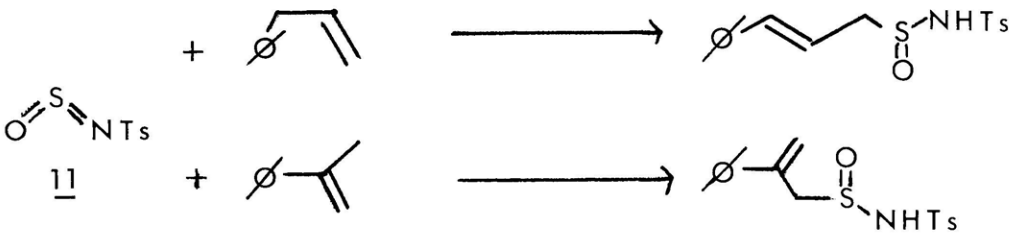
6 7 8

There are a few examples of ene reactions involving N-sulfinylamines,[20] the mono-imido derivative of sulfur dioxide. In 1966, Kataev and Plemenkev[21] found that N-sulfinylaniline 9 and β-pinene react to give a crystalline adduct 10 from which β-pinene could be liberated upon hydrolysis. (Eq. 3). More recently, the



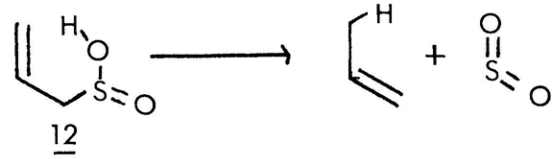
(Eq. 3)

ene adducts of N-sulfinyl-p-toluenesulfonamide (11) with allylbenzene or α-methylstyrene were isolated (Eq. 4).[18b] The parent compound of



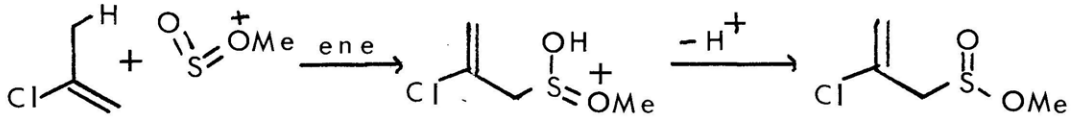
(Eq. 4)

this series, sulfur dioxide, does not react with olefins to give stable adducts. In fact, if the expected adduct, an allylic sulfinic acid (12), is independently synthesized, it immediately decomposes to olefin and sulfur dioxide by a retroene reaction (Eq. 5).[17] However, an ene reaction does occur between methylated



(Eq. 5)

sulfur dioxide (generated from SbF_5-CH_3F in liquid SO_2 at -65°C) and certain olefins (Eq. 6).[22] The resulting product is an allylic

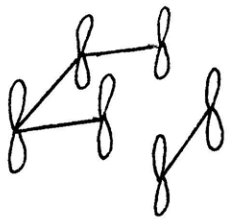


(Eq. 6)

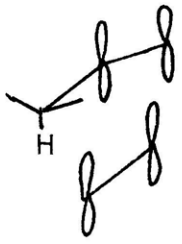
methyl sulfinate. Unfortunately, the reaction is not useful due to the strongly acidic nature of the medium.

In summary so far, allylic oxidation of olefins are generally based on either a hydrogen abstraction from an allylic position or by an ene reaction followed by rearrangement. The abstraction methods generally require "hit it with a hammer" type conditions and so suffer the consequences, whereas the ene/rearrangement methods represent a mild, indirect way to avoid the sigma vs pi bond problem mentioned at the beginning. The sulfur and selenium reagents which fall into this latter category, and upon which this thesis is based, are listed in Table 1.

Conjugated dienes represent a special class of olefins. In the presence of activated double bonds, they undergo (4+2) cycloaddition, the well-known Diels-Alder reaction.[23] The Diels-Alder addition and ene reaction are structurally related cyclic six electron processes. One of the main differences between them is the way in which the bonding is maximized in the transition state (Eq. 7).[9a] As a general rule, the same electronic and steric factors



Diels—Alder Transition State

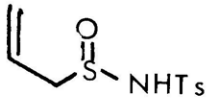
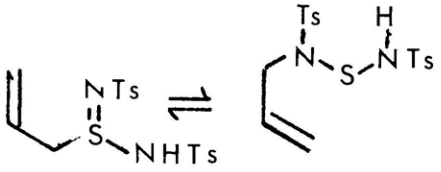


Ene Transition State

(Eq. 7)

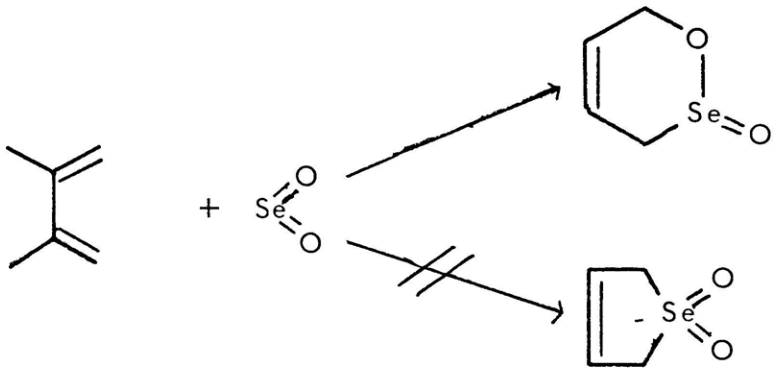
which makes good enophiles in the ene reaction also makes them good dienophiles in the Diels-Alder. Therefore, it is not surprising that the sulfur and selenium reagents previously discussed form

Table 1 (Ene Reactions of S(IV) and Se(IV) Compounds)

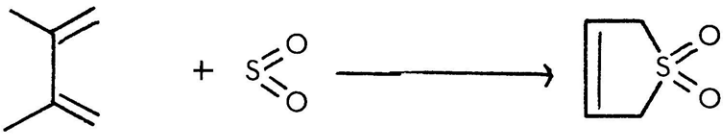
Compound	Ene Reaction?	Eventual Product
O=S=O	No	-
O=Se=O	Yes	Allylic Alcohols
O=S=N-Ts	Yes	
O=Se=N-Ts	?	?
TsN=S=N-Ts	Yes	
TsN=Se=N-Ts	Yes	Allylic Sulfonamides

Diels-Alder cycloaddition products with 1,3 dienes.

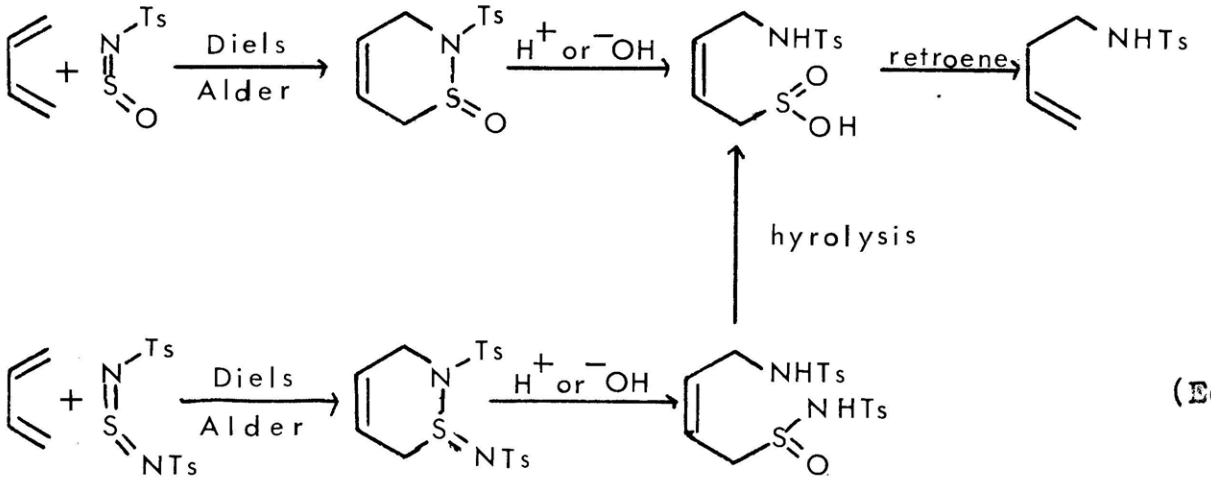
In 1968, Mock and McCausland[24a] showed that reaction of selenium dioxide with 2,3-dimethylbutadiene gave a (4+2) cycloaddition product (Eq. 8), rather than the previously proposed cyclic selenone.[24a] This is in contrast to the sulfur dioxide addition to dienes where 5-membered cyclic sulfones are known to be formed (Eq. 8).[25a-d] Diels-Alder adducts of both



(Eq. 8)



N-sulfinylsulfonamides[20, 26a,b] and bis-N-sulfonylsulfurdiimides[17, 26a] are known (Eq. 9). As expected, hydrolysis of the adducts yields N-alk-3-enylsulfonamides through the mechanisms shown. A summary

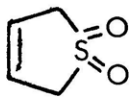
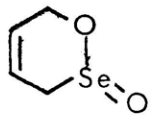
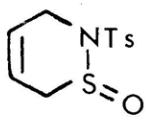
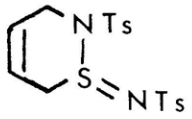


(Eq. 9)

of the Diels-Alder reactions of the above compounds is shown in Table 2.

Examination of Tables 1 and 2 show that ene and Diels-Alder reactions are not known for all compounds that can be derived from sulfur and selenium dioxides by successive replacement of the oxo groups by N-Ts imido groups. It was the purpose of this work to explore the unknown chemistry of these species and apply the findings toward the development of useful synthetic procedures. In addition, imido groups substituted with groups other than sulfonyl were investigated.

Table 2(Cycloadditions of S(IV) and Se(IV) Compounds)

Compounds	(4+2) Cycloaddition?	Eventual Product
O=S=O	No	
O=Se=O	Yes	
O=S=NTs	Yes	
O=Se=NTs	?	?
TsN=S=NTs	Yes	
TsN=Se=NTs	?	?

RESULTS AND DISCUSSION

Reactions of N-Sulfinylsulfonamides

The work in this section was done in conjunction with Dr. Tetsuo Hori. For the sake of completeness, all results and experimental details will be reported in this thesis, with appropriate references to the particular experiments performed by Dr. Hori.

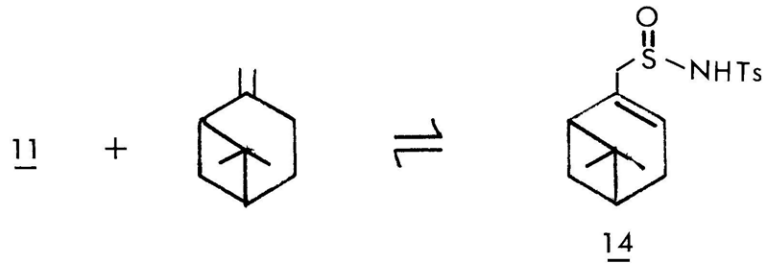
N-Sulfinylsulfonamides such as 11 or 13 are thermally stable

11 13

yellow solids, and are prepared by the reaction of a small excess of thionyl chloride with dry sulfonamide in benzene at reflux.[20] When the reaction is complete,[27] the solvent is removed under reduced pressure and the resulting yellow oil distilled. Yields are usually between 60-70% on a 100g-250g scale. Although N-sulfinylsulfonamides are moisture sensitive and should be stored in a dessicator, the reaction with atmospheric moisture is sufficiently slow that they can be weighed out quickly in air without special precautions.

When 1.1 equivalent of 11 was stirred with 1 equivalent of

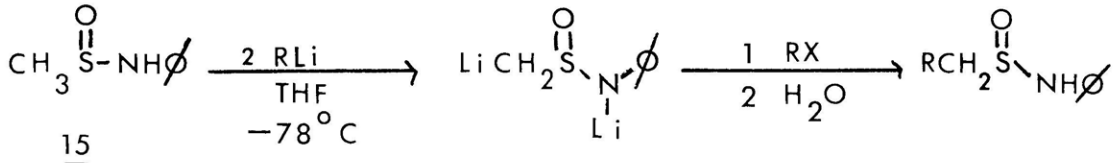
β-pinene in benzene under anhydrous conditions and cooled slightly for 10 minutes, the N-tosylsulfinamide 14 was isolated in 89% yield by filtration (Eq. 10). The reaction was found to be revers-



(Eq. 10)

ible since glpc injection (>200°C) of 14 gave β-pinene. β-Pinene was also recovered when a solution of 14 was refluxed in benzene in the presence of excess water; the other product under these conditions was p-toluenesulfonamide formed by hydrolysis of 11.

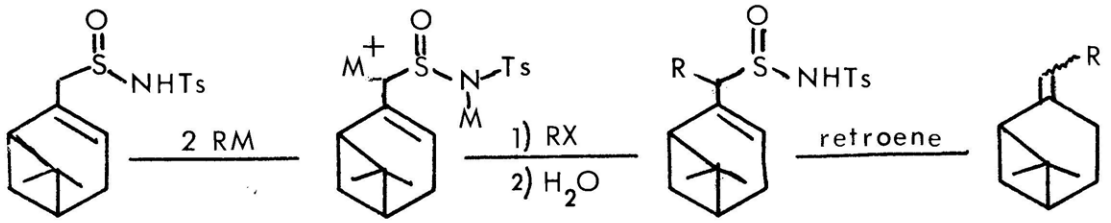
Allylic sulfinamides such as 14 can be envisioned as valuable synthetic intermediates. One possiblity involves the hydrogens alpha to the sulfur which should be acidic and therefore removable by strong base. Corey and Durst have shown that sulfinamides such as 15 can be dilithiated by alkyllithium reagents at -78°C and react cleanly at the more reactive carbon with various electrophiles (Eq. 11).[28a-c]



(Eq. 11)

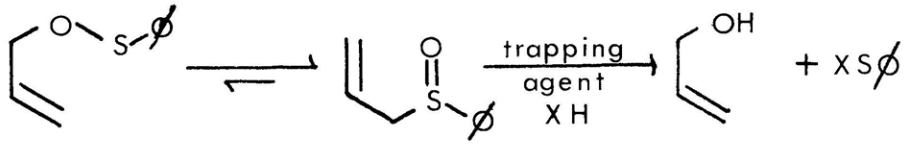
As shown in (Eq. 12), alkylation of the dianion of 14, followed by

a retroene reaction would yield the synthetic equivalent of a vinyl anion. In practice, this approach failed.[29]



(Eq. 12)

Allylic S(IV) species exist in equilibrium with the corresponding (2,3) shifted isomers.[30a-c] In the cases of both allylic N-sulfonylsulfinamides and allylic phenyl sulfoxides, the equilibrium lies almost entirely to the right (Eq. 13). Since it has been



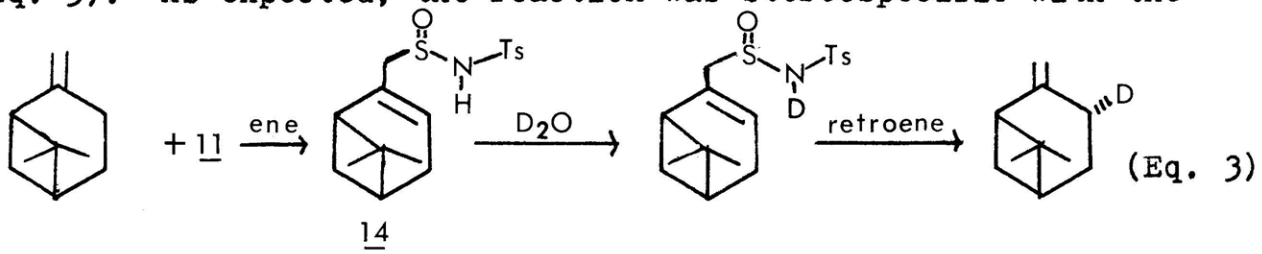
(Eq. 13)

shown that rearranged allylic alcohols are formed from allylic phenyl sulfoxides in the presence of trapping agents,[30c] similar methods were examined for 14. Among the reagents tried were Et_2NH, Et_2NH-HCl, Ad_2O, various trivalent phosphorus compounds, thiols, thioacetic acid and $HgCl_2$. In all cases, β-pinene but no allylic alcohol (or sulfonamide) was found.

The N-H hydrogen in the ene adducts (i.e. 14) is exchangeable. If this proton is replaced by deuterium with excess D_2O, the retroene reaction should introduce a deuterium only in the allylic position. This would constitute a method for direct allylic

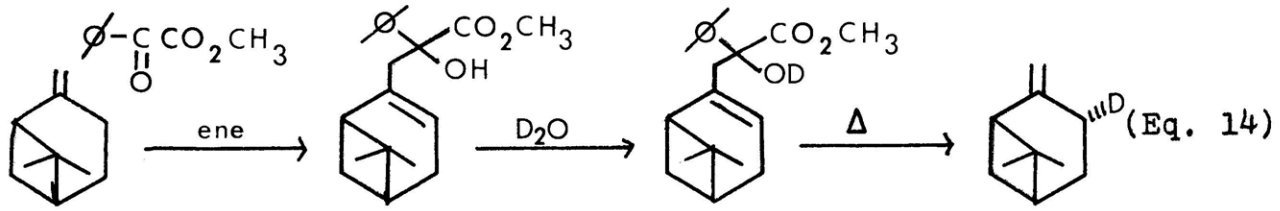
monodeuteration of an alkene, The introduction of deuterium into an organic molecule is an area of interest since labelled compounds are very useful as mechanistic probes.[31]

When a solution of 14 was refluxed in benzene containing excess D_2O, the β-pinene that was recovered was 86%d_1 and 14%d_0 (isolated 14 under the same conditions gave 2%d_0, 95%d_1 and 3%d_2). (Eq. 3). As expected, the reaction was stereospecific with the



14 (Eq. 3)

deuterium being introduced exclusively trans to the gem-dimethyl bridge.[32] These results and yields are similar to the stereospecific retroene reaction of the deuterated adduct of β-pinene and methyl phenyl glyoxylate[33a] as shown in (Eq. 14).



(Eq. 14)

Table 3 shows the results for the allylic deuteration of a variety of alkenes. Generally, the olefins were recovered in yields >50% and> 75% monodeuterated in the allylic position depending on the structure and reactivity of the starting material. Except for case (3), the initial ene adducts were not isolated before addition of D_2O. It should be pointed out that the reaction is not general for all cases because N-sulfinylsulfonamides

Table 3 (Allylic Deuteration of Alkenes)

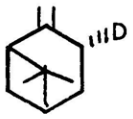
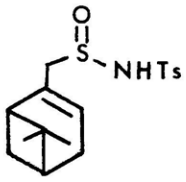
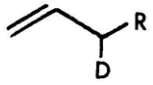
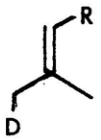
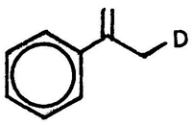
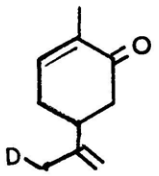
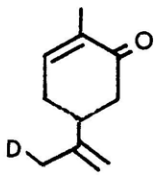
Case[4]	Olefin	Reagent[2]	Product[1]	Deuterium Incorporation[1]	Recovery[3]
1	β-Pinene	1.2 TsNSO		14% d_0 86% d_1	59%
2	β-Pinene	2 MsNSO	"	3% d_0 94% d_1 4% d_2	51%
3		-	"	4% d_0 95% d_1 3% d_2	78%
4	1-Dodecene	3 TsNSO		4% d_0 93% d_1 2% d_2	46%
5	Citronellol Methyl Ether	2 TsNSO		11% d_0 87% d_1 2% d_2	68%
6	α-Methyl-styrene	1.2 TsNSO		15% d_0 84% d_1 1% d_2	79%
7	l-Carvone	2 TsNSO		(Crude) 13% d_0, 46% d_1, 35% d_2, 6% d_3 (Exchanged) 16% d_0, 82% d_1, 2% d_2	39% (After Exchange)

Table 3 (Continued)

Case[4]	Olefin	Reagent[2]	Product[1]	Deuterium Incorporation[1] (Crude)	(Exchanged)	Recovery[3]
8	l-Carvone	2 MsNSO		16% d_0 20% d_1 37% d_2 25% d_3 2% d_4	16% d_0 75% d_1 9% d_2	39% (After Exchange)

Footnotes for Table 3

1) See the experimental section for all details concerning the reactions, the recovery and identification of products and the calculations of deuterium content.

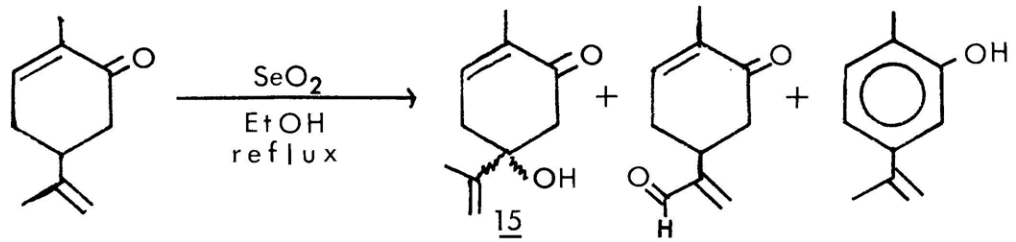
2) TsNSO = N-sulfinyl-p-toluenesulfonamide. MsNSO = N-sulfinyl-methylsulfonamide. The numbers refer to the number of equivalents used.

3) Based on starting olefin

4) Cases 1-6 were performed by Dr. T. Hori

are only moderately powerful enophiles. Cyclic olefins as well as those that are electron poor or hindered are poor substrates for this system. Among the compounds which were not reactive are cyclohexene, 4-t-butylcyclohexene, Δ^2-cholestene, α-pinene and cholesterol. Under forcing conditions (refluxing benzene), 4-t-butylcyclohexene gave t-butylbenzene in good yield.[29] Kresze has also noticed aromatization in the reaction of the related bis-N-p-toluenesulfonylsulfurdiimide with certain olefins.[34a]

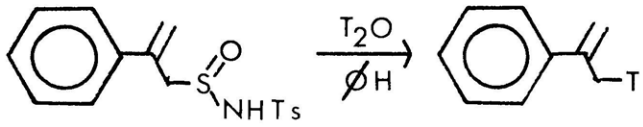
l-Carvone deserves special mention since it is the only example in Table 3 of an olefin with exchangeable protons. Exchange of the crude deuterated product with ethanolic NaOH at 60°C for 3 hours gave l-carvone that was >75% d_1 (90% recovery). Nmr integration indicated that the deuterium was located in the vinyl methyl group, although Büchi and Wüest[34b] have shown that the major product of SeO_2 oxidation of carvone was the optically inactive hydroxy ketone 15.



Since there was no loss in the optical activity of the re-isolated l-carvone, the deuterium cannot be located in the ring. Recovery was high even though there was some aromatization (between 5-10%) to dehydrocarvacrol (2-methyl-5-isopropenylphenol).

In the same manner, alkenes can be tritiated by use of T_2O in place of D_2O. For example, α-methylstyrene with an activity

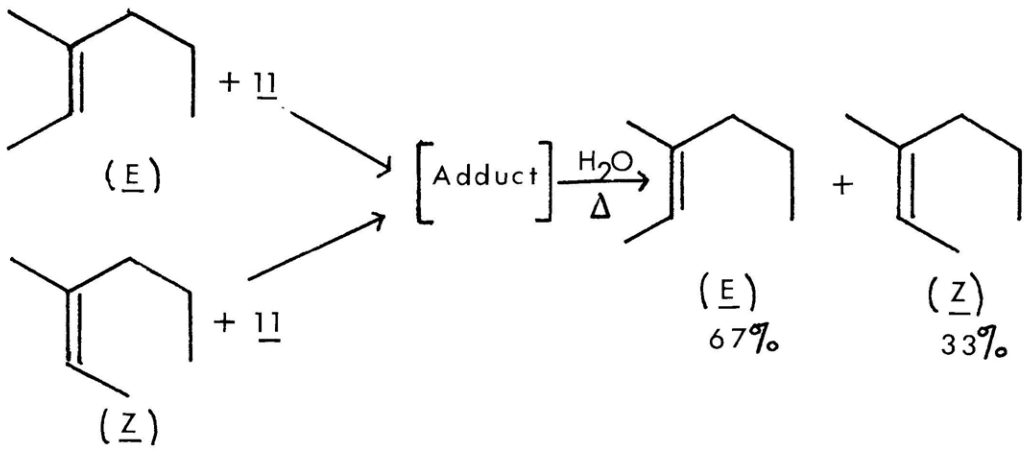
of .8 uCi/umole was isolated (47%) when 2 mmoles of its crystalline adduct 16 was refluxed for 20 hours in 5 ml benzene containing .1 ml T_2O (10^3 m Ci/ml for a total activity of 7.7 uCi per mole of available protons) (Eq. 15). This represents an incorporation of approximately 10% of the total activity into the olefin. Use of



16 (Eq. 15)

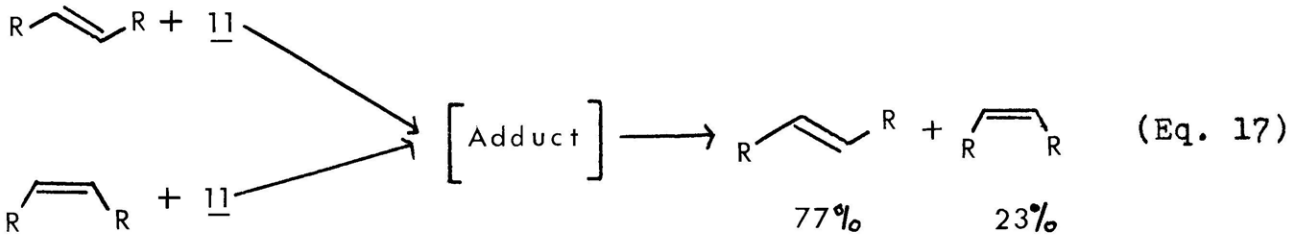
.1 ml D_2O under identical conditions gave α-methylstyrene which was 22%d_0, 40%d_1, 22%d_2 and 10%d_3. These results indicate that under these conditions the ene and retroene reactions are occurring many times over before the N-sulfinylsulfonamide is hydrolized.

One complicating factor in the utility of this reaction is the loss in stereochemistry for di- and tri-substituted olefins. This is the outcome of the shift in double bond as well as the steric requirements in the transition states during the ene/retroene reactions. When the adduct of 11 with either (E)- or (Z)- 3-methyl-2-hexene is refluxed for 24 hours in benzene/water, the same 33% (Z)/67% (E) mixture is observed (Eq. 16). Similar treatment of



(Eq. 16)

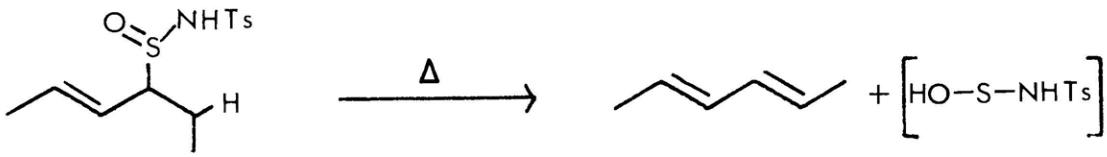
either cis- or trans-5-decene gave the same 23% cis/77% trans mixture. (Eq. 17). Control experiments in both cases showed



(Eq. 17)

$R = C_4H_9$

the olefins to be stable under the reaction conditions. Recovery yields are generally less than 80%. One reason for this is that when a suitable β-hydrogen is available, elimination to a diene (Eq. 18) competes with the retroene reaction. The yield of diene products usually are less than 15%. Whether the elimination is

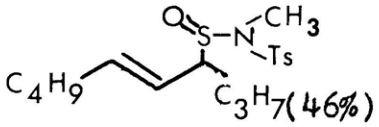
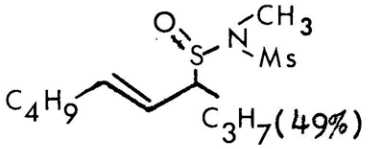
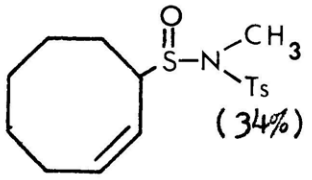
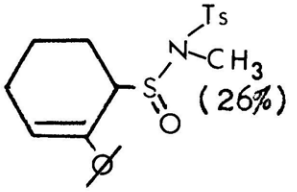


(Eq. 18)

a syn elimination as is the case for the phenylsulfoxides[35a] and phenylselenoxides[35b] or a ElcB type elimination is uncertain. Preliminary results indicate that mixtures of geometrical isomers occur where possible.[35] It is interesting to note that allylic phenylsulfoxides[30c] and phenylselenoxides[10b, 35c] only undergo (2,3) rearrangement when possible, not elimination as in this case.

The retroene pathway can be removed from N-tosylsulfinamides by alkylation of the nitrogen, thereby causing the elimination to diene to predominate (Table 4). Aklylation of the nitrogen in

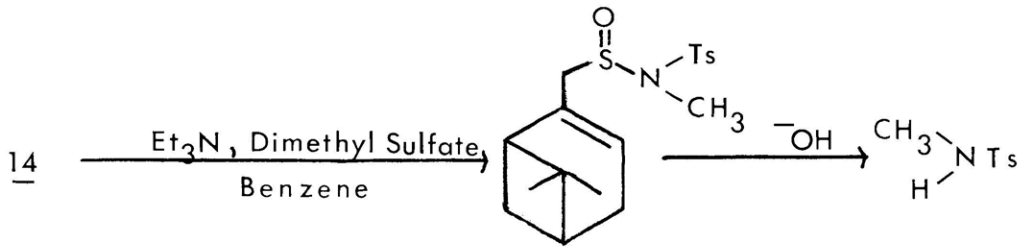
Table 4 (Pyrolysis of N-Methyl-N-Tosyl Allylic Sulfinamides[1])

Case	Olefin	Product (Yield[2])	Method of Pyrolysis	Yield Diene	Yield Olefin
1	t-5-decene		A	67%	14%
			B	72%	3%
2	t-5-decene		A	42%	5%
			B	46%	16%
3	Cyclooctene		A	11%	15%
			B	75%	15%
4	1-phenyl-1-cyclohexene		B[3]	6%	5%
			C[4]	90%	6%

Footnotes for Table 4

1) See experimental section for all details concerning the preparation of starting materials, the pyrolysis and isolation and identification of the products.
2) Yields are isolated material based on starting olefin. They are not maximized nor corrected for recovered olefin.
3) 61% Biphenyl was also recovered.
4) 4% Biphenyl was also recovered.

N-tosylsulfinamides can be accomplished either by Et_3N and dimethylsulfate in benzene or by tetramethylammonium hydroxide and methyl iodide in DMF. Diazomethane is unsuitable since in some cases, O-methylated products are formed. The location of the methyl group on nitrogen was determined by hydrolysis of the methylated derivative of 14 to give N-methyl-p-toluenesulfonamide (Eq. 19). Three methods of pyrolysis were used for the methylated derivatives (see Table 4); sealed tube in benzene at 150°C (method A),



(Eq. 19)

destructive kugelrohr distillation at 150-175°C under N_2 (method B) glpc injection (method C). In all cases examined, some starting olefin was produced along with the diene. The origin of the olefin is not known.

This method is the synthetic equivalent of dehydrogenating an olefin to a symmetrically expanded diene (Eq. 20). Experimental

(Eq. 20)

proof of this was found by pyrolysis (by either method B or C) of the N-methyl adduct derived from 1-phenyl-1-cyclohexene (case 4 in Table 4). purification by preparative glpc and UV analysis showed the diene to be the expected 2-phenyl-1,3-cyclohexadiene.[37]

None of the alternative 1-phenyl isomer[37] was detected (mimimum detection limit 14%). Unfortunately, because of low overall yields, the formation of product mixtures and the low reactivity of some olefins with N-sulfinylsulfonamides, this is not a practical synthetic method.

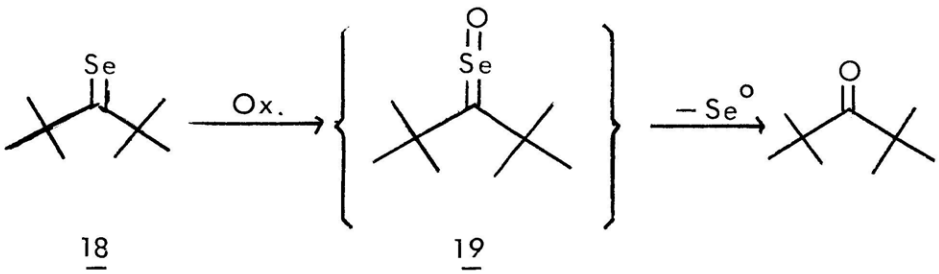
Reactions of O=Se=N-Ts with Alkenes and Dienes

Although N-sulfonylsulfonamides are well-known and stable compounds, the isolation or properties of the analogous selenium compounds such as N-seleninyl-p-toluenesulfonamide 17 have never been reported. In fact, only two examples of seleninyl type

O=Se=N-Ts

17

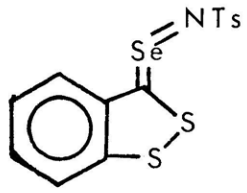
are known. Oxidation of the selenoketone 18 gave di-t-butylketone and selenium metal as the only products. The likely intermediate in this reaction is di-t-butylselenine 19 (Eq. 21).[38] Under the same



18 19 (Eq. 21)

reaction conditions, the corresponding thiocarbonyl gave di-t-butylsulfine, which is stable and can be fully characterized.

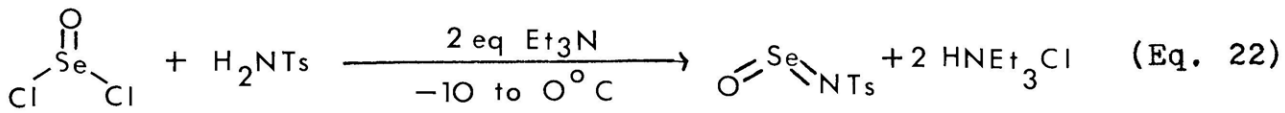
Oae[39] has synthesized the selenium (IV) imido compound 20 and found it to be a fairly stable, crystalline compound. In addition, alpha-



20

carbonylselenines have been postulated as transient intermediates in the oxidation of ketones by SeO_2.[40]

Conceptually, the most direct route for the preparation of 17 is the reaction of selenium oxychloride with p-toluenesulfonamide in the presence of 2 equivalents of base (Eq. 22). When this was



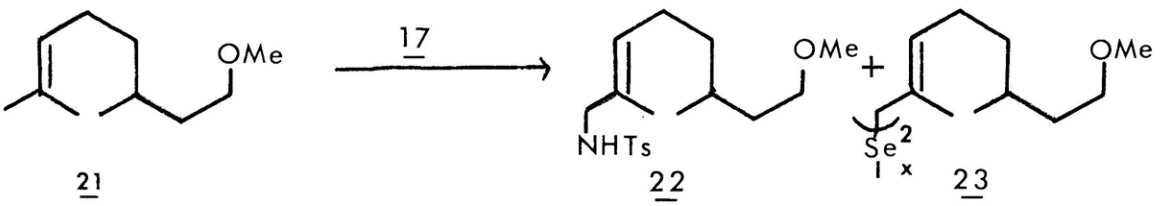
(Eq. 22)

17

done at temperatures greater than -10°C in either methylene chloride or THF under strictly anhydrous conditions, a yellow-orange solution or suspension (depending on exact reaction conditions) resulted. The solution was not stable indefinitely since prolonged standing caused the precipitation of red selenium metal. No attempts were made at the full characterization of the above solution and it was generally used as formed.

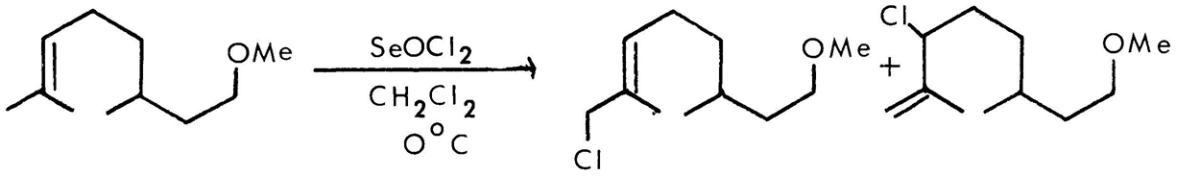
Addition of citronellol methyl ether (21) to a solution of "17" at -10°C caused an immediate, slight by exothermic reaction and after a few hours, the formation of red selenium metal. Basic aqueous workup and purification by chromatography gave an allylic sulfonamide 22 as the major product (53%) along with approximately

14% of a selenium-containing product 23 as well as a trace of α,β-unsaturated imine (Eq. 23). No allylic alcohol was formed.



21 22 23 (Eq. 23)

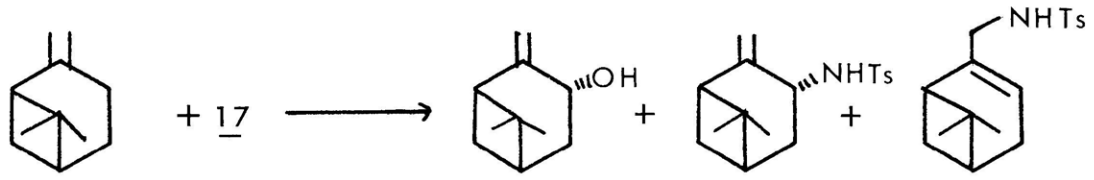
This can be compared with the selenium diimide reagent which yielded 58% 22 and 7% 23 from 21.[12] Reaction of 21 and selenium oxychloride along under the same conditions gives a mixture of isomeric allylic chlorides and some 23 as the main products (Eq. 24).[29] It is very unlikely that 22 arises from the reaction of allylic chloride mixture



(Eq. 24)

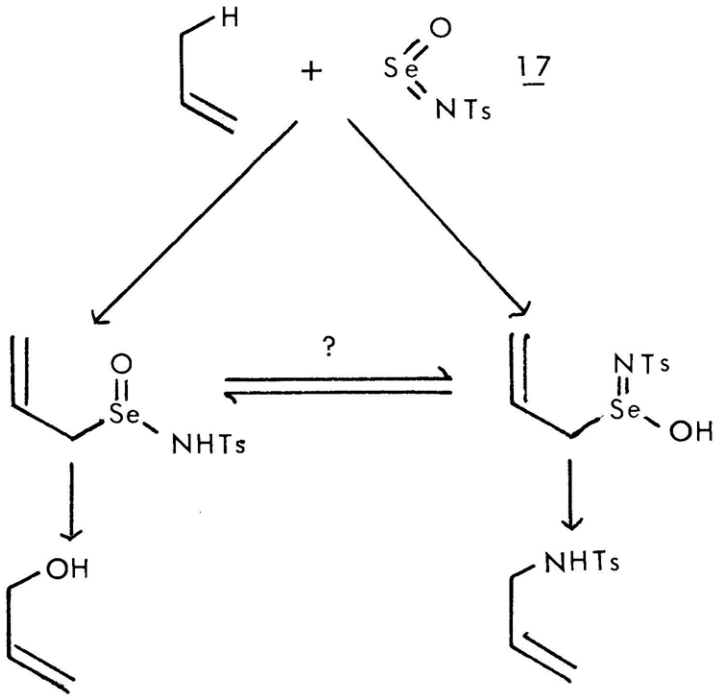
with p-toluenesulfonamide. The selenium-containing compound 23, which can also be isolated from SeO_2 oxidation of 21, could not be characterized. It seemed to be (by nmr) a mixture of mono- and diselenides containing some of the 1,3-shifted isomers.

Addition of β-pinene to "17" prepared in the same manner gave trans-pineneol (24) as the major product (Eq. 25). Only small amounts of allylic sulfonamides 25 and 26 were formed.



24 25 26 (Eq. 25)

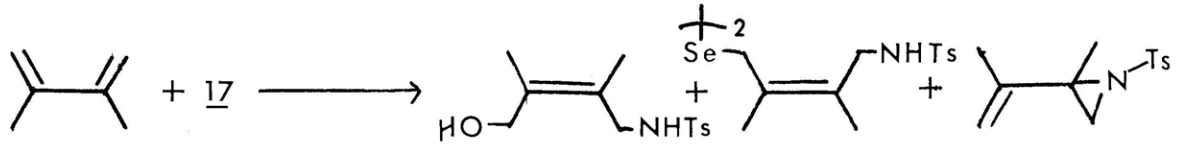
Although none of these experiments demonstrate definite proof for the existence of 17 as such, the observed products can be explained by an initial ene reaction of 17 with the olefin. The intermediate allylic Se(IV) species could exist in either of two forms which are interconvertible by proton transfer. If the ratio can be influenced by steric factors, then it is reasonable that different olefins give different products as in the case observed.



Since the reaction of "17" with alkenes did not seem to offer any significant advantages over the existing methods for allylic oxidation, this aspect was not pursued further.

In an effort to determine if monomeric species such as 17 were actually present in solution, trapping experiments with dienes were performed. By analogy with N-sulfinylsulfonamides, a normal Diels-Alder (2+4) cycloaddition adduct between the diene and the more more polar Se=N bond (such as 27) was expected.

When 2,3-dimethylbutadiene was added to a solution of "17" in methylene chloride at -10° C, an immediate reaction took place. Aqueous workup gave a complex mixture from which three major products were isolated by chromatography (Eq. 26). The yields shown are for

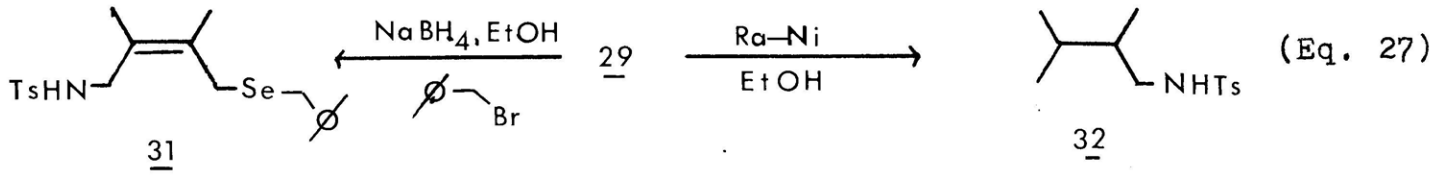


(Eq. 26)

28 (4%) 29 (10%) 30 (15%)

isolated material. While the structure of 28 and its acetate derivative were evident from the spectral data, (compounds 28 and 29 are thought to possess the stereochemistry shown, but the lack of the other possible isomers prevent definite assignment at this time), the structures of compounds 29 and particularly 30 were not certain from the spectra above.

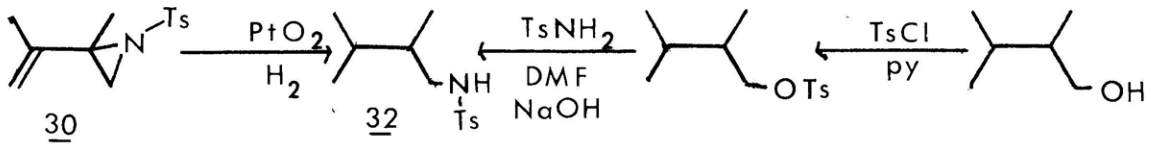
Reduction of 29 with $NaBH_4$ in EtOH (typical conditions for the reduction of a diselenide to its sodium salt) and addition of benzyl bromide gave the benzylated selenide 31, while Raney-Nickel reduction in refluxing EtOH gave N-tosyl-2,3-dimethylbutylamine (32). These reactions are shown in (Eq. 27). The azirdine ring of 30 was strongly



31 32 (Eq. 27)

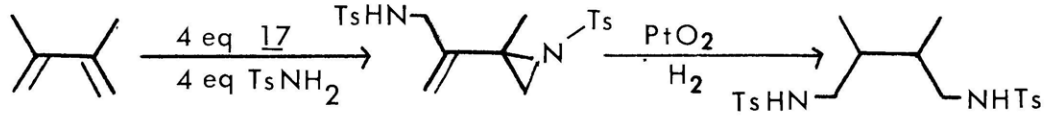
indicated by ir and nmr which showed an isopropenyl group but no N-H or O-H. (The ms of 30 had a strong molecular ion peak at M^+ 251 (2,3-dimethylbutadiene + N-Ts) and peaks at 236 (M-15), 155 (Ts) and

96 (base peak)). Hydrogenation of 30 with Adam's catalyst and 5 p.s.i. hydrogen in EtOAc gave a quantitative yield of 32 identical in all respects with an authentic sample (Eq. 28).



30 32 (Eq. 28)

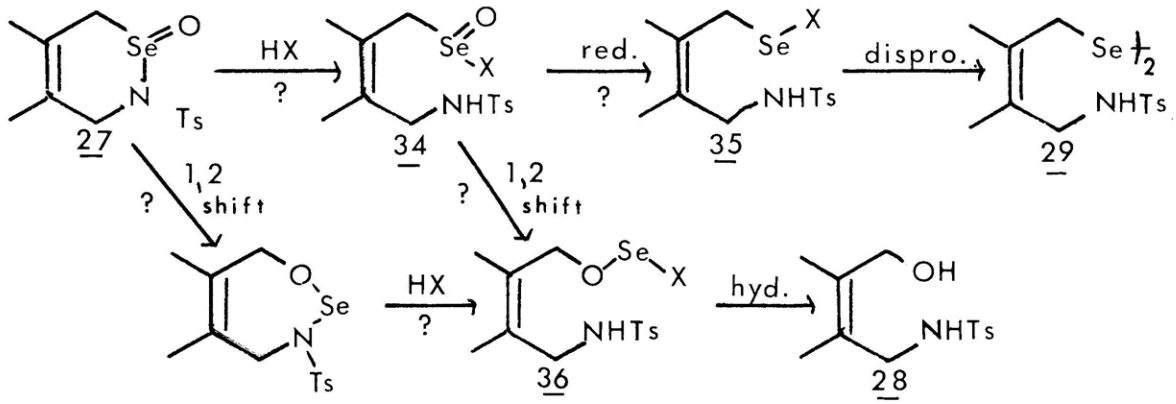
Reaction of 2,3-dimethylbutadiene with 4 equivalents of 17 containing 4 equivalents (excess) p-toluenesulfonamide under the same reaction conditions resulted in a cleaner reaction giving only one major product, the allylic sulfonamide-azirdine 33 in 42% isolated yield (Eq. 29). Compound 33 was characterized by spectral



33 (Eq. 29)

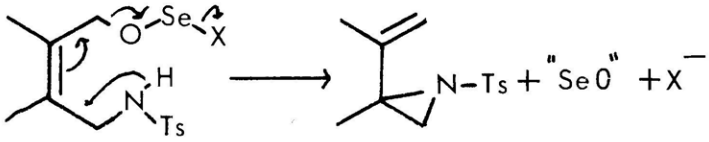
data as well as by hydrogenation to N,N'-ditosyl-1,4-diamino-2,3-dimethylbutane.

Obviously, any proposed mechanism for the formation of 28, 29, 30 and 33 must be speculative, but it seems likely that the precursor for all of these products is the Diels-Alder adduct 27. One mode of decomposition for 27 is the addition of some adventitious acidic species (HX) across the Se-N bond (Eq. 30). This is not unreasonable since some seleninamides are readily



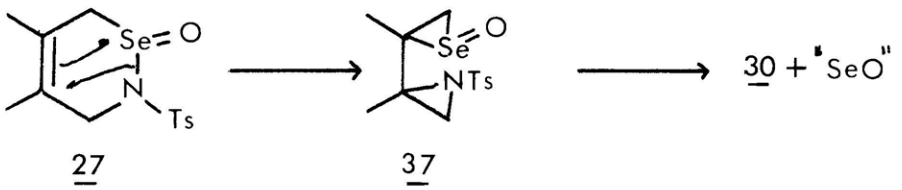
(Eq. 30)

hydrolyzed.[19] The reduction[41] of the ring-opened Se(IV) ester 34 to the Se(II) ester 35 followed by disproportionation[42] leads to the diselenide 29. A competing 1,2 shift[35b] of 27 would result in, after hydrolysis of the initially formed 36, the formation of 28. The ester 36 might also be the source of 30 by an intramolecular Sn2' type reaction (Eq. 31).



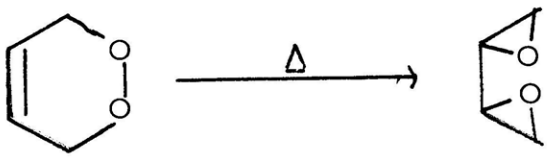
(Eq. 31)

An alternative mechanism for the formation of 30 is a rearrangement of 27 to the azirdine-episelenoxide 37 (Eq. 32) in the same



(Eq. 32)

manner that the Diel-Alder adducts of dienes and singlet oxygen rearrange to diepoxides when heated (Eq. 33).[43] The episelenoxide



(Eq. 33)

might be expected to decompose to olefin and "SeO" in analogy to the known thermal elimination of an episulfoxide to olefin and sulfur monoxide.[44] The "SeO" can either disproportionate as does sulfur monoxide[45] or act as the reducing agent in (Eq. 30).

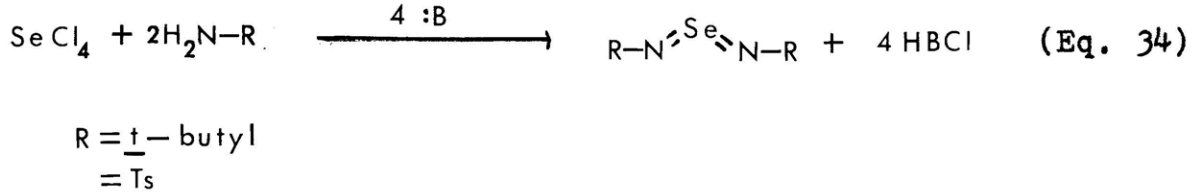
In the case of 33, the excess sulfonamide most likely exerts its influence on the reaction by facilitating the cleavage of the initial adduct 27 (see next section). Although there is no experimental proof, the allylic sulfonamide 33 probably results from the action of excess 17 on the primary product 30.

The reaction could not be extended to other dienes. Reaction of 1,3-cyclohexadiene with 17 only gave a complex mixture of selenium-containing compounds.

Reactions of Selenium Diimide with Dienes

As previously mentioned, the addition of alkenes to a solution of selenium (IV) diimide results in the eventual formation of N-substituted allylic amines.[12] The required diimides can be generated in two ways. If 2 equivalents of an primary amine are added to one equivalent of $SeCl_4$ in the presence of 4 equivalents of base, a yellowish suspension thought to contain the selenium (IV)

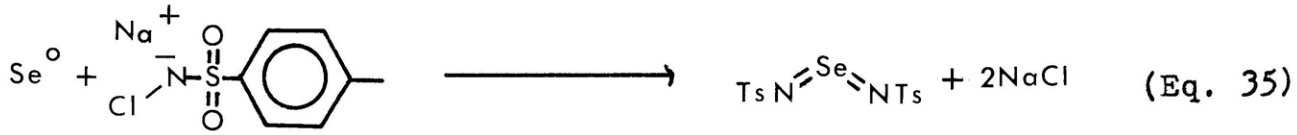
diimide results (Eq. 34). For R=Ts, an alternative method is the



(Eq. 34)

R = t-butyl
= Ts

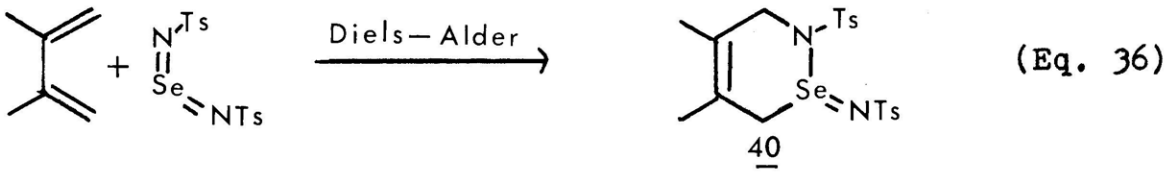
oxidation of grey selenium metal with chloramine-T (38) in methylene chloride (Eq. 35). The resulting white suspension is more stable



(Eq. 35)

38 39

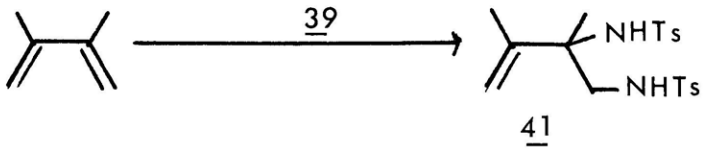
than the reagent derived from $SeCl_4$ and is superior in terms of ease of preparation and overall yield. However, in neither case is the actual reactive species known. In an attempt to trap the proposed monomeric intermediate 39, dienes were added in the hope of forming (4+2) adducts such as 40 (Eq. 36). When 2,3-dimethylbutadiene was



(Eq. 36)

40

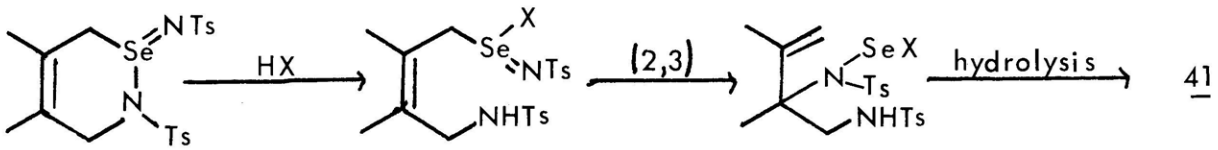
added to solution prepared as in (Eq. 35) or (Eq. 36), no 40 was found, but instead small amounts of the vicinal disulfonamide 41 were isolated (Eq. 37). The mechanism of formation of 41 is thought to proceed by the pathway shown in Scheme IV.



41

2% from Eq.34
4% from Eq.35 (Eq. 37)

Scheme IV



40 42 43

As in the case of O=Se=NTs, the products are almost certainly derived from the initially formed (4+2) cycloadduct, the selenolactam 40, by cleavage of the weak Se-N bond by some acidic species (HX). (2,3)-Rearrangement to the selenium (II) amide 43, followed by hydrolysis, yields 41. In the absence of a cleaving reagent, 40 seems to decompose to various selenium containing products. Under these conditions, p-toluenesulfonamide, which is present either as unreacted material in (Eq. 35) or as an impurity in the chloramine-T in (Eq. 36), probably acts as the acidic species HX. Examination of Table 5 shows that this 1,2-diamination occurs with many 1,3-dienes. The best conditions found were 1.1 equivalent reagent (since the

Table 5 (1,2-Diamination of 1,3-Dienes)[1]

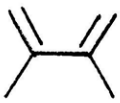
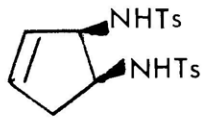
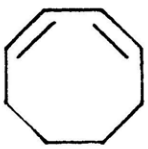
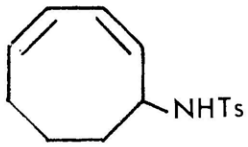
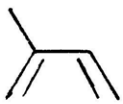
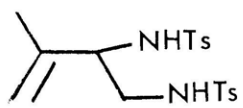
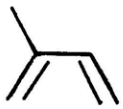
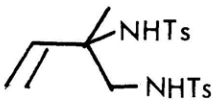
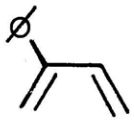
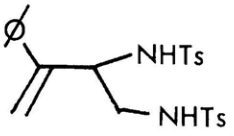
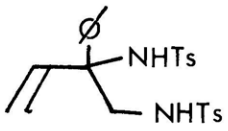
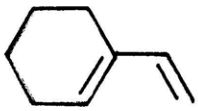
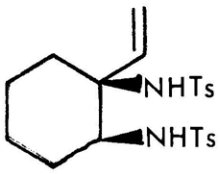
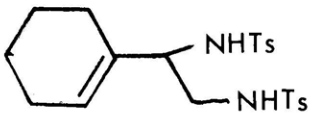
Case	Diene	Equivalents of 17	Equivalents of $TsNH_2$	Products	% Yield[2]
1		1.1	1.1	41	68%
2	"	1.1	0	41	4%
3	"	2.5	0	41	61%
4		3.75	3.75	44	37%
5	"	1.25	1.25	44	29%
6	"	2.5	0	44	15%
7	"	1.1	0	44	0%
8		1.1	1.1		40%
9		1.1	1.1		52%
10		1.1	1.1		26%

Table 5 (1,2-Diamination of 1,3-Dienes)[1]

Case	Diene	Equivalents of 17	Equivalents of $TsNH_2$	Products	% Yield
10					8%
11		1.1	1.1		45%
					8%
12		1.1	1.1		37%
					4%

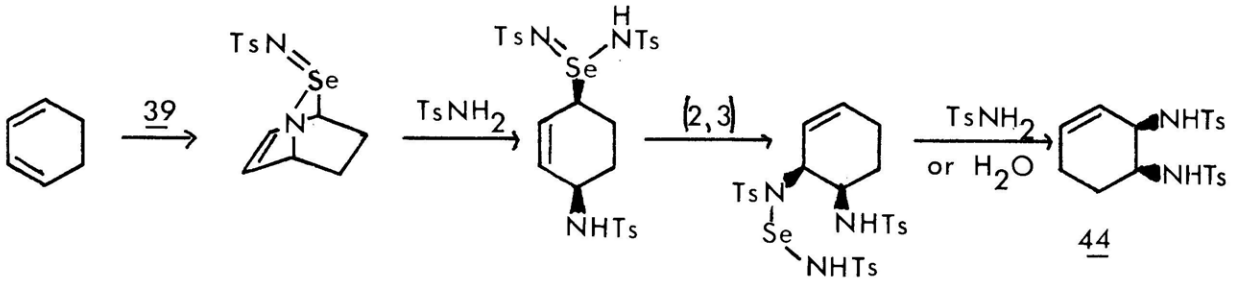
Footnotes for Table 5

1) See Experiment section for details.

2) Yields refer to isolated, recrystallized (where possible) material.

derived from chloramine-T and selenium metal was generally a better source of 39, it was used for all of the subsequent work) containing 1.1 equivalent p-toluenesulfonamide in methylene chloride at room temperature. The purpose of the added $TsNH_2$ is presumed to facilitate cleavage of the (4+2) adduct 40. The reagent generated in this fashion appears to be different from that without added p-toluenesulfonamide. It forms more rapidly and the suspension has a silver-grey luster as opposed to the plain white suspension normally formed. As shown in Table 6, the new reagent also reacts with olefins to give allylic sulfonamides in yields equal or slightly better than the reagent without added sulfonamide. However, the presence of large amounts of $TsNH_2$ sometimes complicates the isolation of the desired product.

Application of the mechanism in Scheme IV to cyclic 1,3-dienes predicts that the sulfonamide groups should be cis to each other since all steps must occur on the same face of the molecule as shown for 1,3-cyclohexadiene (Eq. 38). In nmr decoupling experiments on the product 44, the coupling constant between the ring protons



(Eq. 38)

was found to be 4Hz. According to the Karplus rule,[46] this is consistent only with a cis relationship between the sulfonamides (pseudoaxial-pseudoeqoaturial as in 44a) or with a trans relation-

Table 6 (Effect of $TsNH_2$ on Allylic Amination of Cyclohexene)[1]

Case	Equivalents of 39	Equivalents of $TsNH_2$	-NHTs[2]
1	.63	0	37%
2	.63	.63[3]	40%
3	.63	.63[4]	35%
4	1.25	0	54%
5	1.25	1.25[3]	64%
6	1.25	1.25[4]	56%

Footnotes for Table 6

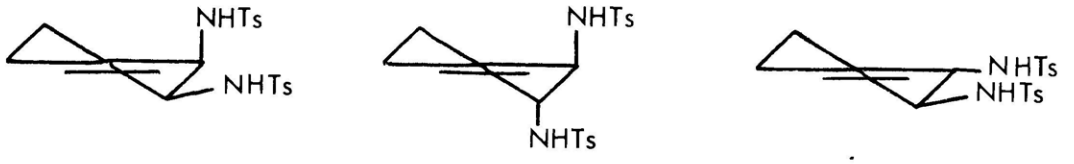
1) See experimental section for details.

2) Yields were determined by glpc using an internal standard.

3) $TsNH_2$ added before the reagent was generated.

4) $TsNH_2$ added to previously formed reagent.

ship in which the sulfonamides are both pseudoaxial (44b). The presumably more stable dipseudoequatorial trans conformer (44c) would be expected to have a coupling constant of least 10 Hz. Hydrogenation of 44 over Adam's catalyst in EtOAc gave only cis-1,2-di(p-toluenesulfonamido)cyclohexane, identical in all respects with an authentic sample and different from the trans-isomer[47] (Eq. 39).



(Eq. 39)

44a
cis

44b
less stable trans

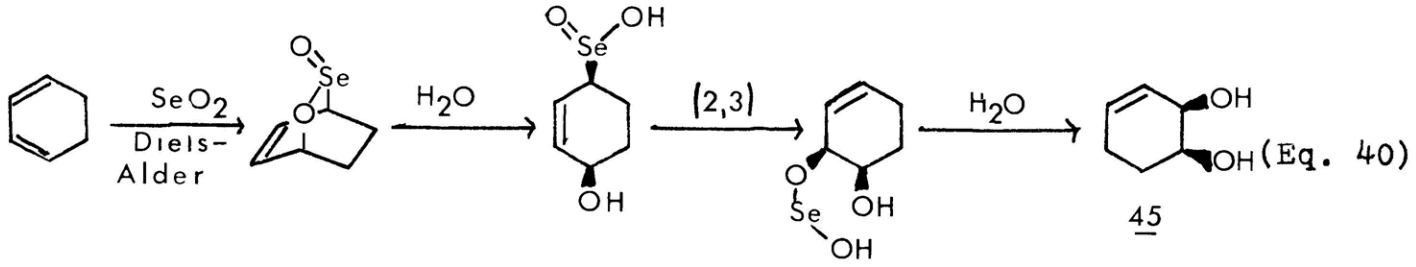
44c
more stable trans

Not all 1,3-dienes give products resulting from (4+2) cycloaddition (see case 9 in Table 4). 1,3-Cyclooctadiene gave an allylic sulfonamide resulting from ene reaction and no disulfonamide. For this particular diene, this is not unusual behavior since Chapman and Dominiani have shown that its reactivity (in a (4+2) cycloaddition or ene sense) depends on the dienophile.[48]

Even though no diene remains after a few hours; the yields of disulfonamide generally are only poor to fair. Polar, solid by-products are formed in most cases and were separated from the desired disulfonamides by chromatography on alumina. Although these amorphous solids are soluble in polar solvents, repeated attempts at recrystallization were fruitless. Nmr showed only broad, badly resolved bands corresponding roughly to a mixture of p-toluenesulfonamide and diene. The origin and exact nature of this material is unclear,

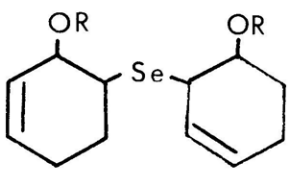
but one possibility is that it arises from polymerization of the diene during the course of the reaction.[49] Some dienes, such as mycrene and 1-acetoxy-1,3-butadiene which are normally reactive in (4+2) cycloadditions but are sensitive to cationic or radical polymerization, gave only polar material and no disulfonamides at all.

Seleninolactones analogous to the lactam intermediate 40 have been isolated from the reaction of selenium dioxide with dienes.[24a,b] It seemed likely that under aqueous conditions such lactones should undergo hydrolysis and (2,3) rearrangement to 1,2-diols in the same manner shown in Scheme IV (Eq. 40). In support of this reasoning,

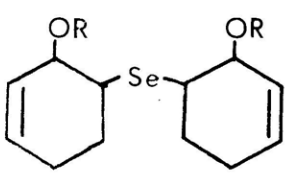


45

reaction of 1,2-cyclohexadiene with 1 equivalent of selenium dioxide in aqueous t-butanol gave cis-3,4-dihydroxycyclohexene (45) in 22% isolated yield (Eq. 40).[50] The only other product of this reaction appeared to be the dihydroxy selenide 46a (52%) perhaps resulting from the electrophile addition of HO-Se-OH across one double bond of the diene. The nmr of 46a and its diacetate derivative (46b) clearly indicated the gross structure to be the non-symmetrical



46
a: R=OH
b: R=Ac



47

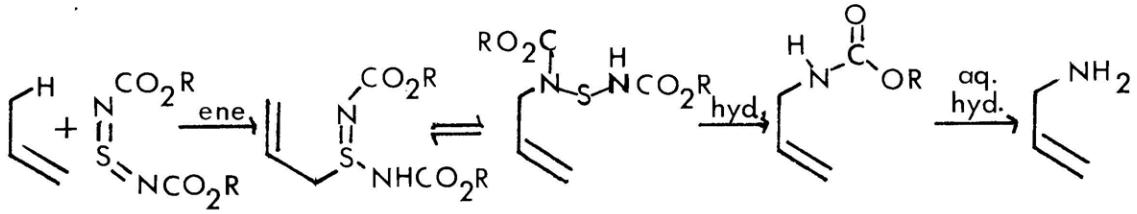
46 as opposed to the other possible (and expected!) isomer 47. Unfortunately, the thermal sensitivity of 46a or b prevented complete characterization.

Parts of this work have been published.[51]

Reactions of N-Alkoxycarbonyl Imido Compounds

Allylic sulfonamides are the major products derived from the reaction of either TsN=S=NTs or TsN=Se=NTs with alkenes. In some circumstances, the removal of the tosyl group is not compatible with other functionality in the molecule (see Part II of this thesis) so the utility of reagents substituted with other types of imino groups was briefly investigated.

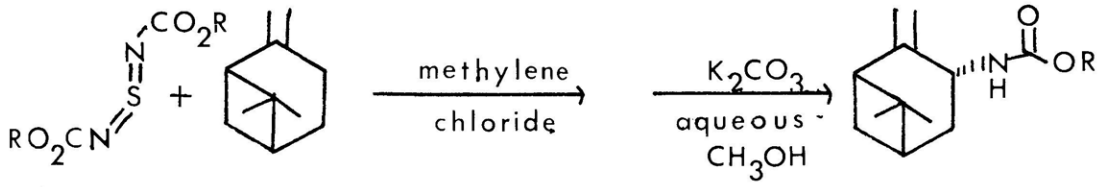
One promising class of reagents was the bis-alkoxylcarbonyl-diimides. For these compounds, the ultimate products should be allylic carbamates. This would be useful since carbamates can be hydrolized under mild conditions[52] whereas sulfonamides generally cannot (Eq. 41). Both bis-methoxy-[53a] and bis-ethoxy-[53b] carbonyl-



(Eq. 41)

sulfurdiimines are known as well as the related benzoyl derivative.[53c]

Reaction of either 49 or the previously unknown t-butoxy compound 50 (prepared in the same way as 49 according to Ref. 53b) with β-pinene gave low yields (less than 30%) of the appropriate allylic carbamate (Eq. 42). These results were not encouraging

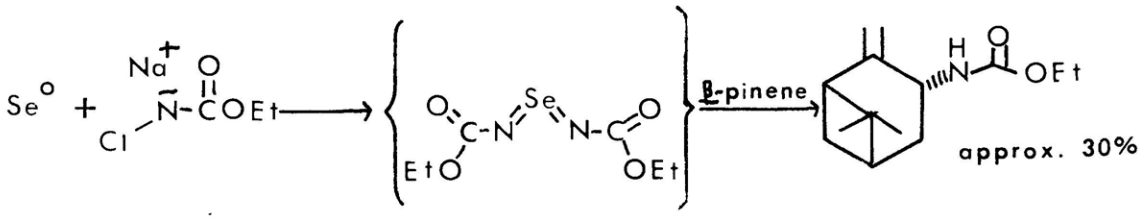


(Eq. 42)

49 : R=Et

50 : R=t-butyl

since the reaction with β-pinene, a particularly reactive olefin, could not be forced to completion even with excess diimide. The selenium analogs, prepared in situ as shown in Eq. 43, showed a similar lack of reactivity.[29]



(Eq. 43)

EXPERIMENTAL

General Comments

Nuclear magnetic resonance spectra were recorded either using a 60 MHz Varian Associates T-60 or a 90 MHz Hitachi-Perkin Elmer R22 spectrometer (used for all decoupling experiments). Chemical shifts are reported in δ using TMS as an internal standard unless otherwise noted. Infrared spectra were recorded on a Perkin Elmer 567 grating spectrophotometer. Ultra-violet measurements were made on a Cary 14 UV-Visible spectrophotometer using 1 cm quartz cells. Mass spectra were recorded with a Hitachi-Perkin Elmer RMU-6E mass spectrometer.

Elemental microanalyses were performed by Midwest Microblab, Ltd. (Indianapolis, Indiana) 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.

Analytical thin layer chromatography (tlc) was carried out using either silica gel (or alumina) F-254 coated glass or aluminum plates (EM Laboratories, Inc, 20 cm x 20 cm x 200-250 microns) cut into appropriately sized strips. Visualization was generally accomplished by UV light or by a spray of saturated ceric sulfate in 20% H_2SO_4 followed by heating or by iodine vapors. For preparative tlc, 20 cm x 20 cm x 1000 or 2000 microns commercially prepared plates of silica gel were used ("Uniplate," Analtech, Inc.) and visualized by UV light and/or charring with a red hot wire or by warming the edge of the plate after spraying with ceric sulfate.

Column chromatography was carried out in appropriate glass columns using silica gel (70-230 mesh, EM or Quantum Industries) or alumina (EM or ICN Life Sciences, Inc.) and freshly distilled solvents.

Analytical gas-liquid phase chromatography (glpc) was performed on Perkin Elmer flame ionization models 990, 3920, and 3920B and a Hewlett-Packard Model 402 gas chromatographs. The columns used were all glass, 2 mm i.d. and will be referred to by length and % loading of the liquid phase. Preparative glpc work was done on a Varian Aerograph Model 920 (thermal conductivity).

The internal standard method was used for quantitative analyses, with response factors determined separately under the analysis conditions by means of a standard solution. Response factors (RF) are defined as:

$$RF = \frac{\text{moles product}}{\text{moles standard}} \times \frac{\text{area standard}}{\text{area product}}$$

Peak areas were measured by electronic integration with either Hewlett-Packard Models 3373B or 3380A electronic integrators.

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 thru 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 $< 30^{\circ}C$).

The following abbreviations will be used: brine = saturated aqueous NaCl, bicarbonate = saturated aqueous $NaHCO_3$, ether = diethyl ether, DMF = dimethylformamide, THF = tetrahydrofuran, EtOAc = ethyl acetate, ir = infrared, nmr = nuclear magnetic resonance (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = unresolved multiplet), mp = melting point, bp = boiling point, t_r = glpc retention time under the specified conditions, Rf = tlc mobility relative to the solvent front (=1), and r.t. = room temperature.

Nmr coupling constants will not be included unless they are of particular importance. Ir assignments will be noted when possible.

Kugelrohr distillation refers to bulb-to-bulb distillation on a Buchi kugelrohr using a hot air oven. The temperatures reported indicate the oven temperature at the time of distillation and not the actual boiling point of the material.

All olefins and dienes were passed through a short plug of neutral alumina, activity I, just before use. All experiments with a reference to [29] were performed by Dr. Hori.

O=S=N-Ts Reactions-Allylic Deuteration and Tritiation

N-Sulfinyl-p-toluenesulfonamide (11)

This procedure is a slightly modified version of Kresze's.[17] In a 2.0l round-bottomed flask fitted with a reflux condenser and

$CaCl_2$ trap, a mixture of 250g p-toluenesulfonamide (1.46 mole, Eastman Organic Chemicals), and 200g thionyl chloride (1.68 mole) in 1.0 l dry benzene was heated for 5 days at reflux. After cooling to r.t., the solvent and excess $SOCl_2$ were evaporated, first at H_2O aspirator pressure, then under high vacuum, to leave approximately 300g of dark orange oil. Kugelrohr distillation in three 100g portions gave a total of 196g 11 (bp 130-140°C, 0.06 torr, 62%) which crystallized upon standing to a bright yellow solid, mp 47-51°C (lit.[17] mp 53°C).

Addition of 1% N,N-dichloro-p-toluenesulfonamide (prepared from the addition of $TsNH_2$ in acetic acid to a NaOCl solution ("Chlorox") at 0°C, also commercially available) decreased the time needed for completion. For example, the reaction of 125g $TsNH_2$ (0.73 mole) and 173g thionyl chloride (1.46 mole) in 100 ml benzene under the same conditions was complete in only 16 hours. Evaporation followed by distillation in the same manner gave 11 in 69% yield.

N-Sulfinylmethylsulfonamide (13)

N-Sulfinylmethylsulfonamide was prepared by Mr. John Taylor according to the procedure described for 11 using 15.1g methylsulfonamide (16 mmol) and 14 ml $SOCl_2$ (19 mmol) in 30 ml benzene. Kugelrohr distillation (165°C, 0.02 torr, lit.[17] bp 80°, 10^{-4} torr) gave 13.9g of bright yellow oil (62%).

Reaction of 11 with β-Pinene

To a 100 ml round-bottomed flask under anhydrous conditions containing a solution of 5.4g TsNSO (24.9 mmol) in 50 ml THF (benzene or CH_3CN gave equivalent results) was added, with stirring and cooling (ice bath), 3.6 ml β-pinene (22.7 mmol). After stirring overnight at r.t., the solution was concentrated to about 1/2 volume and cooled. The resulting white precipitate was collected and washed with a small amount of hexanes. After drying in vacuo, 7.13g of 6,6-dimethylbicyclo(3.1.1)hept-2-en-2-yl-N-(p-toluenesulfonyl)methylsulfinamide (14) was obtained (89%), 137-139°C; ir (KBr pellet) 3050 (NH), 2920 (CH), 1595, 1375 (SO_2), 1320, 1185, 1165 (SO_2), 1080, 1065, 860 and 815 cm^{-1}; nmr ($CHCl_3$) δ 9.0 (1H, broad s, exchangeable with D_2O, N-H), 7.9 -7.2 (4H, q, aromatic), 5.60 (1H, broad s, olefinic), 3.55 (2H, broad s, $-CH_2-S$), 2.4 (3H, s, aromatic $-CH_3$), 2.2 (5H, m, ring -H), 1.2 (3H, s, $-CH_3$), 1.0 (1H, m, bridgehead) and 0.7 (3H, d, $-CH_3$). Upon standing at r.t. in the solid state, 14 slowly decomposed to β-pinene and a solid residue consisting mostly of $TsNH_2$.

Anal. Calcd for $C_{17}H_{23}NO_3S_2$: C, 57.76; H, 6.56; N, 3.96. Found: C, 57.00; H, 6.90; N, 3.80.

trans-3-Phenyl-2-propenyl-N-(p-toluenesulfonyl)sulfinamide

In the same manner 1.18g allylbenzene (10 mmol) and 2.2g TsNSO (10.14 mmol) were mixed in 20 ml benzene. After 3 hours at r.t.,

10 ml pentane was added and the reaction mixture cooled. After filtering and drying *in vacuo*, 1.99g of white crystals were obtained (59%), mp 154 -155°C; ir (KBr pellet) 3250, 3060 (NH), 2940 (CH), 1595, 1490, 1450, 1360 (SO_2), 1105, 1165 (SO_2), 1100 and 965 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (4H, q, aromatic), 7.3 (5H, s, aromatic), 6.7(1H, d(J = 8 Hz), Ø-CH=), 6.90 (1H, m, =CH-R), 3.9 (2H, d,-CH_2-S) and 2.3 (3H, s, aromatic -CH_3).

Anal. Calcd for $C_{16}H_{17}NO_3S_2$: C, 57.28; H, 5.11; N, 4.18. Found: C, 57.33; H, 4.98; N, 3.96.

10-N-(p-Toluenesulfonyl)sulfinamido)-l-carvone

l-Carvone (300 mg, 2 mmol, Aldrich Chemical Co., distilled 98 -100°C at 7 torr) was added to a stirred solution of 520 mg TsNSO (2.40 mmol) in 3 ml benzene in a 25 ml round-bottomed flask under anhydrous conditions. After 24 hours at r.t., a small amount of $TsNH_2$ was filtered off and the filtrate eluted through silica gel (10g) with hexanes (100 ml) followed by 50% EtOAc/hexanes (50 ml) and finally with EtOAc (50 ml). The EtOAc fractions were concentrated to give a yellow oil (600 mg) which were rechromatographed on 20g silica gel, eluted first with 35% EtOAc/hexane to separate $TsNH_2$, then with EtOAc. Concentration of the appropriate fractions gave, after drying *in vacuo*, 375 mg of 10-(N-(p-toluenesulfonyl) sulfinamido)-l-carvone (37%) as a deep yellow oil; ir (film) 3500-3000 (broad band), 2980, 1670 (C=O), 1595, 1370 (SO_2), 1330, 1240, 1160 (SO_2), 1090, 1040 and 900 cm^{-1}; nmr ($CHCl_3$) δ 9.0 (1H, s,

N-H) 7.2-7.9 (4H, q, aromatic), 6.75 (1H, R-CH = R), 5.1 (2H, d, $=CH_2$), 3.75 (2H, s, $-CH_2-S$), 2.5 (5H, m, ring H), 2.4 (3H, s, aromatic $-CH_3$) and 1.75 (3H, broad s, $-CH_3$).

Hydrolysis of 14 with H_2O

To a 25 ml round-bottomed flask with a magnetic stirrer (anhydrous conditions) was added 176 mg 14 (0.5 mmol) in 10 ml benzene. After 6 hours of refluxing, practically no change had occurred. Five ml H_2O was added and refluxing continued. After 14 hours, no 14 remained the tlc showed the presence of $TsNH_2$. β-Pinene was detected by glpc (6' 3% UCW-98 on 80/100 mesh Gas Chrom Q, 90°C, co-injection with an authentic sample).

Allylic Deuteration of β-Pinene with TsNSO (11)[29]

A solution of 520 mg TsNSO (2.4 mmol) in 20 ml benzene was prepared in a 50 ml round-bottomed flask under anhydrous conditions. β-Pinene (0.32 ml, 2 mmol) was added with stirring. The reaction could be conveniently monitored by glpc for the disappearance of olefin (after the removal of the adduct by passing an aliquot through a plug of neutral alumina with hexanes). When the reaction was completed (6 hours), 10 ml D_2O (> 99.7% isotopic purity, obtained from Merck, Sharp and Dohme, Ltd.) was added to the flask and, after fitting a reflux condenser, the mixture was heated at 90°C for 12 hours (after which time no adduct remained by tlc). The benzene layer was separated and passed through a short column of silica gel

(30g) with hexanes (50 ml) The resulting solution was concentrated to leave 190 mg of crude product which was kugelrohr distilled (90 -100°C, water aspirator pressure) to give 162 mg of trans-(3-d)-β-pinene (59%); nmr ($CHCl_3$)δ 4.5 (2H, m, $=CH_2$), 2.35 (3H, m, ring H), 1.9 (3H, m, ring H), 1.4 (1H, d, bridgehead H), 1.25 (3H, s, $-CH_3$) and 0.7 (3H, s, $-CH_3$). Deuterium analysis by standard ms techniques [54] (including corrections for natural abundance) showed the deuterated β-pinene to be 14% d_0 and 86% d_1.

Allylic Deuteration of β-Pinene with MsNSO (13)[29]

Using the exact procedure described for TsNSO, β-pinene (0.32 ml, 2 mmol) was deuterated using 0.57g 13 (4 mmol). The trans-(d-d)-β-pinene recovered (51%) was 3% d_0, 94% d_1, and 4% d_2.

Hydrolysis of 14 with D_2O[29]

Two mmol of 14 (0.71g), the 1:1 adduct between β-pinene and TsNSO, was refluxed for 12 hours in a mixture of 10 ml benzene and 5 ml D_2O in a 25 ml round-bottomed flask under anhydrous conditions. Isolation by passage of the benzene phase through silica gel (30g) with hexanes (30 ml), evaporation and kugelrohr distillation gave trans-(3-d)-β-pinene (215 mg, 78%) which was 2% d_0, 95% d_1 and 3% d_2.

Allylic Deuteration of 1-Dodecene[29]

Using the same procedure and scale described for _-pinene, except that 3 equivalents of TsNSO were used, 1-dodecene gave 3-(d)-1-dodecene (46%); nmr ($CHCl_3$) δ 5.5 (1H, m, =CH-R), 4.7 (2H, m, $=CH_2$), 1.9 (1H, m, allylic H) and 1.0 -0.8 (13H); 4% d_o, 93% d, and 2% d_2.

Allylic Deuteration of Citronellol Methyl Ether[29]

Using the same procedure and scale for β-pinene except that 2 equivalents of TsNSO were used, citronellol methyl ether (46% recovery) was deuterated (11% d_o, 37% d_1, 2% d_3). The deuterium was apparently located in one of the vinyl methyl groups (the location is not certain due to overlapping peaks in the nmr). A diene was also isolated (7%) as a minor by-product.

Allylic Deuteration of α-Methylstyrene[29]

Using the same procedure and scale for β-pinene, 3-(d)-2-phenyl-1-propene was isolated (79%) from α-methylstyrene. Because of a large (M-1) peak in the ms of α-methylstyrene, the deuterium content was analyzed after reduction to cumene with Na metal in abs. EtOH[55a] and was found to be 15% d_o, 84% d_1 and 1% d_2.

Allylic Deuteration of l-Carvone using TsNSO

A mixture of 1.0g l-carvone (Aldrich, 6.66 mmol, α_d=-55.6° (C = 8.65 in abs EtOH)) and 2.89g TsNSO (13.3 mmol) was stirred in 20 ml benzene in a 50 ml round-bottomed flask (anhydrous conditions) for 24 hours. Glpc showed no olefin remaining, so 12 ml D_2O (> 99.7%d) was added and the mixture refluxed for 7 1/2 hours. The reaction was cooled, taken up in ether which was washed once with H_2O, once with brine and dried. Filtration and evaporation left 700 mg of crude oil which was kugelrohr distilled (50 -70°C, 0.5 torr) to give 450 mg of deuterated l-carvone contaminated with approximately 5% of dehydrocarvacrol. Pure l-carvone, isolated by preparative glpc (8' x 1/4" 20% SE-30 on 45/60 mesh Chromsorb W, 150°C) was 13% d_0, 46% d_1, 35% d_2 and 6% d_3, and showed little change in optical rotation (α_d= -54.7°(C = 8.45 in abs. EtOH)).

The excess deuterium was exchanged by heating the crude deuterated l-carvone (250 mg) in 5 ml 60% EtOH containing 3 drops 50% NaOH solution at 50 -60°C for 3 hours in a 25 ml round-bottomed flask under N_2. Extraction with hexane (washed once with H_2O, once with brine and dried) followed by evaporation gave 240 mg of yellowish oil which was kugelrohr distilled to give 230 mg of 10-(d)-l-carvone (90%, 39% overall): nmr ($CHCl_3$) δ 6.75 (1H, m, olefinic), 4.7 (2H, broad s, $=CH_2$), 2.5 (5H, m, ring H) and 1.75 (5H, two overlapping s, $-CH_3$ and $-CH_2D$). A pure sample of 10-(d)-l-carvone was collected by preparative glpc: 16% d_0, 82%

d_1 and 2% d_2, α_d= -55.0°(C = 9.45 in abs. EtOH).

Allylic Deuteration of l-Carvone using MsNSO

Using the same procedure and scale as the deuteration of l-carvone with TsNSO except with 1.88g MsNSO (13.3 mmol), crude deuterated l-carvone was re-isolated in 45% yield, again contaminated with 5% dehydrocarvacrol. The l-carvone, isolated by preparative glpc, was 17% d_0, 20% d_1, 37% d_2, 25% d_3, and 2% d_4. Exchange under the same conditions gave 10-(d)-l-carvone 90%, 39%, overall) which was 16% d_0, 75% d_2 and 9% d_3.

Allylic Tritiation of α-Methylstyrene

In a dry 25 round-bottomed flask fitted with a reflux condenser and $CaCl_2$ trap, a mixture of 670 mg N-(p-toluenesulfonyl)-2-phenyl-2-propenyl-sulfinamide (2 mmol, recrystallized from $CHCl_3$ and dried *in vacuo*) and 0.1 ml T_2O (1 Ci/ml for a total of 100 uCi) in 5 ml benzene was refluxed for 14 hours. After cooling, 5 ml pentane was added and the organic phase eluted through a 7.0 cm x 0.5 cm silica gel column with an additional 5 ml pentane. The resulting solution was concentrated to afford 120 mg of an oil which was kugelrohr distilled (80-90°C, H_2O aspirator pressure) to give 110 mg of tritiated α-methylstyrene (49%). Glpc analysis (6' 3% OV-17 on 80/100 mesh Gas Chrom Q, 70°C) showed only one

peak which co-injected with an authentic sample. A 9.1 mg sample (77 umol) was found to have 5.5×10^5 cpm (7.1×10^5 cpm/umol); since 1 uCi = 8.8×10^5 cpm (1 uCi = 2×10^6 dpm x counter efficiency = 0.4 cpm/dpm), the activity of the α-methylstyrene was 0.8 uCi/umol. Further distillation of the product caused no significant change in activity. Since a total of 77 uCi/umol of available H^+ (10^3 uCi distributed over 110 umol H^+ from T_2O and 20 umol H^+ from adduct) was present, this represents only about 10% incorporation. Replacement of the T_2O by 0.1 ml D_2O under identical conditions and workup gave α-methylstyrene which was 25% d_0, 40% d_1, 22% d_2 and 10% d_3.

Reaction of (E)- or (Z)-3-Methyl-2-Hexene with TsNSO

In a 25 ml round-bottomed flask a solution of either 0.49g (E)- or (Z)-3-methyl-2-hexene (5 mmol, Chemical Samples Co.) and 1.1g TsNSO (5.07 mmol) in 10 ml benzene was stirred at r.t. for 14 hours (under anhydrous conditions). Ten ml of H_2O was added and after 12 hours at r.t., it was refluxed for another 14 hours. Glpc analysis (6' 10% UCW-98 on 80/100 mesh Gas Chrom Q, 10°C, t_r((Z)- olefin)=8.5 min, t_r((E)- olefin)=9.3 min) of both reaction mixtures showed the same ratio (E)/(Z) = 2 (33% (Z), 67% (E)). The products were identified by glpc co-injection. Under the same conditions using 0.87g (5.08 mmol) $TsNH_2$ in place of TsNSO, both isomers were recovered unchanged.

Reaction of cis- or trans-5-Decene with TsNSO

In a 25 ml round-bottomed flask equipped with a magnetic stirrer under anhydrous conditions, a mixture of 0.7g of either cis- or trans-5-decene (5 mmol, Chemical Samples Co.) and 1.62g TsNSO (7.46 mmol) in 5 ml benzene were stirred at r.t. for 20 hours. Two ml of H_2O and 50 mg of $HgCl_2$ (0.18 mmol) was added and after refluxing for 14 hours, the mixture was taken up in hexanes, washed once with H_2O and passed through neutral alumina (5g) with 15 ml hexanes. Evaporation and kugelrohr distillation of the residue (80°, 35 torr) gave 0.30g of cis-5-decene (43%) and 0.31g of trans-5-decene (44%), respectively. Glpc analysis (6' 10% UCW-98 on 80/100 mesh Gas Chrom Q, $140^\circ C$) showed both isomers to be contaminated with approximately 8% of a diene (assumed to be 4,6-decadiene)(t_r(5-decene, cis and trans isomers are not separated) = 2.6 min, t_r(diene, all isomers) = 3.3 min).

The recovered olefins (0.30g cis; 0.30g trans (2.1 mmol) were in 10 ml CH_2Cl_2 in separate 25 ml round-bottomed flasks and 0.47g of MCPBA (2.7 mmol) was added at $0^\circ C$. After standing overnight at r.t., the reactions were taken up in ether and washed once with 1:1 4% NaOH/brine, H_2O, brine and dried. Glpc analysis (6' 3% OV-17 on Gas Chrom Q, $90^\circ C$) of both reaction mixtures showed the same mixture of cis- and trans-5-decene epoxides t_r(trans-5-decene epoxide) =4.4 min, t_r(cis-5-decene epoxide) =5.0 min) consisting of 23% cis/77% trans. No 5-decene remained

in either of the reaction mixtures. Authentic samples of the epoxides were prepared by MCPBA oxidation of the pure isomers. When a sample of cis-5-decene was subjected to the exact same series of reactions with the exception that 1.27g $TsNH_2$ (7.42 mmol) was used in place of TsNSO, the resulting cis-5-decene epoxide (isolated in nearly quantitive yield) was found to be 98% cis and 2% trans (commercial cis-5-decene is contaminated with approximately 2% trans isomer).

N-Methylation of 14 with Triethylamine/Dimethylsulfate

Et_3N (2.6 ml, 18.6 mmol) was added to a stirred suspension of 5.98g 6,6-dimethylbicyclo(3.1.1)hep-2-en-2-yl-N-(p-toluenesulfonyl)methylsulfinamide (14, 17.4 mmol) in 40 ml benzene in a 100 ml round-bottomed flask. After all of the adduct had dissolved, dimethylsulfate (0.90 ml, 9.5 mmol) was added and stirring continued overnight at r.t. The reaction mixture was taken up in EtOAc, washed with H_2O, brine and dried. Filtration and evaporation gave 7.83g of clear oil which upon trituration with hexanes gave a white solid. Recrystallization ($CHCl_3$/hexanes) gave a total (2 crops) of 4.98g (80%) of 6,6-dimethylbicyclo-(3.1.1)hep-2-ene-2-yl-N-methyl-N-(p-toluenesulfonyl)sulfinamide as white needles, mp 113 -114°C; ir(10% in $CHCl_3$) 2920 (CH), 1595, 1355 (SO_2), 1305, 1165 (SO_2) and 1089 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (4H, q, aromatic), 5.75 (1H, broad, s, olefinic), 3.6 (2H, s, CH_2-S), 2.85 (3H, s, CH_3-N), 2.4 (3H, s, aromatic -CH_3), 2.4 -2.0

(5H, m, ring H), 1.3 (3H, s, $-CH_3$), 1.25 (1H, m, bridgehead) and 0.9 (3H, s, $-CH_3$).

Anal. Calcd for $C_{18}H_{25}NO_3S_2$: C, 58.82; H, 6.86; N, 3.81. Found: C, 58.70; H, 6.94; N, 3.59.

N-Methylation of 14 with Tetramethylammonium Hydroxide/CH_3I

The adduct 14 was prepared *in situ* using 1.0g β-pinene (7.3 mmol) and 2.4g TsNSO (11 mmol) in 20 ml benzene as previously described. The benzene was removed as completely as possible by roto-vac and the residue immediately redissolved in a ice cold mixture of 6.7g tetramethylammonium hydroxide solution (7.3 mmol, 10% in H_2O, Eastman Organic Chemicals) in 20 ml DMF followed immediately by 1.25 ml (20 mmol) of iodomethane. After stirring at r.t. for 3/4 hours, water was added followed by extraction with two portions of 1:1 ether/EtOAc which was washed three times with H_2O, once with brine and dried. Filtration and evaporation gave 2.3g of a white semi-solid which was recrystallized ($CHCl_3$/hexanes) to give 1.65g (61%) of the N-methyl adduct.

Hydrolysis of N-Methyl 14 to N-Methyl-p-toluenesulfonamide

6,6-Dimethylbicyclo(3.1.1.)hept-2-en-2yl-N-methyl-N-(p-toluene-sulfonyl)sulfinamide (500 mg, 1.36 mmol) was dissolved in a mixture of 5 ml Claisen's Alkali (35g KOH/25 ml H_2O/100 ml CH_3OH) and 5 ml

60% CH_3OH. After standing at r.t. for 5 hours and heating on a steam bath for an additional 1 1/2 hours, the residual oil was dissolved in 2% NaOH, washed twice with ether (discarded), neutralized with 10% HCl to pH 5 and extracted twice with 1:1 EtOAc/ether which was washed with brine and dried. Filtration and evaporation gave 370 mg of a yellow oil which was purified by preparative tlc (2000 micron silica gel eluted with 30% EtOAc/hexanes, Rf =0.29) to give N-methyl-p-toluenesulfonamide (230 mg crude, 217 mg recrystallized ($CHCl_3$/hexanes), 91%), mp 76 -77°C (lit. mp 78°C); nmr ($CHCl_3$) δ 7.2- 7.9 (4H, q, aromatic), 5.25 (1H, q, N-H), 2.6 (3H, d, CH_3-N) and 2.4 (3H, s, aromatic -CH_3).

6-(Dec-4-enyl)-N-methyl-N-(p-toluenesulfonyl)sulfinamide

In a 100 ml round-bottomed flask with a magnetic stirrer under anhydrous conditions, 3.15g TsNSO (14.5 mmol) was added to a solution of 2.0g t-5-decene (14.3 mmol) in 30 ml benzene. After 15 hours at r.t., 2.1 ml Et_3N (15 mmol) and 0.87 ml dimethylsulfate (9.2 mmol) were added and stirring continued overnight. EtOAc was added and the organic phase washed with H_2O, brine and dried. Filtration and evaporation left a light yellow oil which was purified by column chromatography (50g silica gel; packed with hexanes and eluted with 5% EtOAc/hexanes; 50 ml fractions). Concentration of appropriate fractions (identified by tlc) gave, after 2 hours in vacuo, 2.45g (46%) of the N-methyl adduct as a yellowish oil, Rf = 0.47 (25% EtOAc/hexanes); ir (film) 2960, 2930, 2870, 1595, 1490, 1460, 1355 (SO_2), 1240, 1165 (SO_2), 1090 and 970 cm^{-1}; nmr

($CHCl_3$) δ 7.2-7.9 (4H, q, aromatic), 5.0-6.0 (2H, m, olefinic), 3.3 (1H, d of t, R_2CH-S), 275 (3H, s, N-CH_3), 2.4 (3H, s, aromatic -CH_3) and 2.1-0.9 (16H, m).

6-(Dec-4-enyl)-N-methyl-N-methylsulfonylsulfinamide

In a 50 ml round-bottomed flask with a magnetic stirrer, under anhydrous conditions, 2.0g MsNSO (14.2 mmol) was added to a solution of 1.0g t-5-decene (7.1 mmol) in 20 ml benzene. After 20 hours at r.t., the solvent was removed and the oily residue redissolved in a solution of ice cold tetramethylammonium hydroxide (6.6g, 10% in H_2O, 7.25 mmol) and 20 ml DMF. CH_3I (1.25 ml, 20 mmol) was then immediately added. After 40 minutes at r.t., the reaction was taken up in EtOAc, washed three times with H_2O, once with brine and dried. Filtration and evaporation gave a light yellow oil (2.03g) which was purified by column chromatography (30g silica gel; packed with hexanes and eluted with 100 ml 5% EtOAc/hexanes, 300 ml 10%, 200 ml 15%; 50 ml fractions). Concentration of appropriate fractions (identified by tlc) gave after 2 hours in vacuo, 1.03g (49%) of the N-methyl adduct, Rf = 0.22 (25% EtOAc/hexanes); ir (film) 2960, 2930, 2870, 1460, 1355 (SO_2), 1160 (SO_2), 1095 and 965 cm^{-1}; nmr ($CHCl_3$) δ 5.0-6.0 (2H, m, olefinic), 2.3 (1H, d of t, R_2CH -S), 3.05 (3H, d(J = 1Hz), SO_2-CH_3), 3.0 (3H, s, N-CH_3), 2.15 (2H, d of t, allylic H) and 1.6-0.9 (14H, m).

Cyclooct-2-enyl-N-methyl-N-(p-toluenesulfonyl)sulfinamide

In a 100 ml round-bottomed flask with a magnetic stirrer, under anhydrous conditions, 8.0g TsNSO (36.9 mmol) was added to a solution of 2.0g cyclooctene (18.1 mmol, Aldrich Chemical Co.) in 40 ml benzene. After 36 hours at r.t., the solvent was removed and the oily residue redissolved in a solution of ice cold tetramethylammonium hydroxide (16.6g, 10% in H_2O, 18.2 mmol) and 40 ml DMF. After 45 minutes at r.t., EtOAc was added and the organic phase washed three times with H_2O, once with brine and dried. Filtration and evaporation left 3.96g of a clear oil which was purified by column chromatography (65g silica gel; packed with hexanes and eluted with 200 ml: hexanes, 5% EtOAc/hexanes, 10%, 15%, 20%; 50 ml fractions). Concentration of appropriate fractions gave, after 2 hours *in vacuo*, 2.13g of a clear oil (34%), Rf = 0.33 (25% EtOAc/hexanes), which crystallized upon standing. Recrystallization ($CHCl_3$/hexanes) gave 1.29g (total of 2 crops) of the N-methyl adduct, mp 109 -111°C; ir (10% in $CHCl_3$) 2930, 2860, 1595, 1445, 1355 (SO_2), 1160 (SO_2) and 1090 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (4H, q, aromatic), 5.3 -6.0 (2H, m, olefinic), 3.75 (1H, d of t, R_2 CH-S), 2.83 (3H, s, N-CH_3), 2.4 (3H, s, aromatic -CH_3), 2.15 (2H, m, allylic H) and 1.65 (8H, m, ring H).

Anal. Calcd for $C_{16}H_{23}NO_3S_2$: C, 56.27; H, 6.79; N, 4.10. Found: C, 56.18; H, 6.91; N, 4.10.

2-Phenylcyclohex-2-enyl-N-methyl-N-(p-toluenesulfonyl)sulfinamide

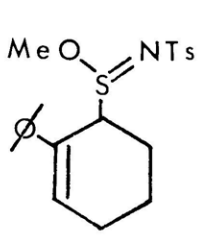
In a 50 ml round-bottomed flask with a magnetic stirrer, under

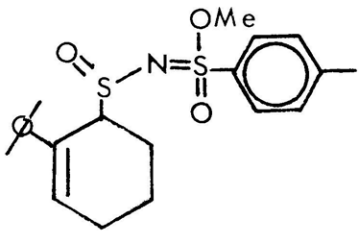
anhydrous conditions, 3.25g TsNSO (15 mmol) was added to a solution of 1.0g 1-phenyl-1-cyclohexene (6.3 mmol, Aldrich Chemical Co.) in 20 ml benzene. After 36 hours, the reaction mixture was cooled in a refrigerator for approximately 1 hour. The resulting precipitate was collected by suction filtration (washed with 25 ml dry pentane) and dried (1.90g, 80% yield of 2-phenylcyclohex-2-enyl-N-(p-toluene-sulfonyl)sulfinamide). This solid (5 mmol) was suspended in 40 ml benzene and 0.80 ml Et_3N (5.7 mmol) added followed by 0.6 ml dimethylsulfate (6.3 mmol). After 2 hours at r.t., the reaction was taken up in ether which was washed twice with H_2O, once with brine and dried. Filtration and evaporation left 0.96g of a white solid which was purified by column chromatography (25g silica gel; packed with hexane and eluted with 100 ml: hexanes, 5% EtOAc/hexanes, 10% 15%; 10 ml fractions). Concentration of the appropriate fractions gave 0.52g (26%) of the N-methyl adduct (recrystallized from EtOAc/hexanes), mp 160 -161°C (decomposition with evolution of gas), Rf = 0.47 (35% EtOAc/hexanes), not very soluble in ether, benzene or EtOAc; ir (10% in $CHCl_3$) 2940, 1595, 1490, 1445, 1360 (SO_2), 1305, 1165 (SO_2), 1090, 900 and 890 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (4H, q, aromatic), 735 (5H, broad s, aromatic), 625 (1H, broad t, olefinic), 4.15 (1H, broad s, R_2CH-S) 2.4 (6H, s, aromatic $-CH_3$ and N-CH_3, addition of shift reagent causes splitting into 2 singlets in ratio of 1:1) and 2.4 -1.8 (6H, m, ring H).

Anal. Calcd for $C_{20}H_{23}NO_3S_2$: C, 61.67; H, 5.95; N, 3.60. Found: C, 61.56; H, 5.98; N, 3.64.

An additional minor product (160 mg) was isolated from the early fractions of the column and, on the basis of spectral data,

tentatively identified as either of the two O-methylated products shown below:





mp 96 -98°C (transparent blocks from $CHCl_3$/hexanes), Rf = 0.85 (35% EtOAc/hexanes); ir (KBr pellet) 3030, 2940, 1595, 1495, 1445, 1425, 1395, 1360, 1340, 1325, 1305, 1290, 1220, 1185, 1180, 1165, 1090, 1060, 975, 950, 925, 910, 900, 865, 820, 700 and 690 cm^{-1}; nmr ($CHCl_3$) δ 6.95 -7.5 (4H, q, aromatic), 7.0 (5H, broad s, aromatic), 6.1 (1H, broad t, olefinic), 5.3 (1H, broad s, R_2 CH-S), 3.9 (3H, s, $-OCH_3$), 2.35 (3H, s, aromatic $-CH_3$) and 2.4 -1.5 (6H, m, ring H).

Anal. Calcd for $C_{20}H_{22}NO_3S_2$: C, 61.67; H, 5.95; N, 3.60. Found: C, 61.42; H, 5.90; N, 3.55.

Pyrolysis of 6-(Dec-4-enyl)-N-methyl-N-(p-toluenesulfonyl)sulfinamide-Method A

In a screw-top combustion tube (obtained from the Lab Crest Scientific Division of the Fischer and Porter Company, consisting of a thick-walled glass tube fitted with a teflon lined, screw-on metal cap), a mixture of 750 mg (2 mmol) of N-methyl adduct in approximately 1 ml benzene was heated at 150°C (oil bath) for 2 1/4 hours. After cooling to r.t., the resulting dark brown solution was

taken up in hexanes, washed with H_2O and dried. Filtration and evaporation gave 0.67g of a yellowish semisolid which was passed through a short column of neutral alumina (2g) with hexanes (5 ml). Concentration of the filtrate afforded 210 mg of a clear oil. Glpc analysis (6' UCW-98 on 80/100 mesh Gas Chrom Q, 140°C) showed only two peaks corresponding to 5-decene (19% by area, t_r = 2.4 minutes) and 4,6-decadiene (81% by area, t_r = 3 minutes). Both peaks were separated by preparative glpc (12' x 3/8" stainless steel, 20% OV-17 on 45/60 mesh Chromsorb W, 175°C). The peak corresponding to 5-decene was identical to t-5-decene and showed no absorbance in the UV. 4,6-Decadiene, a colorless oil, showed λ_{max} (isooctane) = 232 nm (log ϵ = 4.4).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 87.04; H, 13.29. The spectral data does not allow for the assignment of or the exact location of the double bonds. The diene is assumed to be the 4,6-isomer by analogy with the case of 1-phenyl-1-cyclohexene. The calculated yield of 5-decene was 14%; 4,6-decadiene 67%.

Pyrolysis of 6-(Dec-4-enyl)-N-methyl-N-(p-toluenesulfonyl)sulfinamide-Method B

In a Buchi kugelrohr distillation apparatus using a flamed-dried flask and receiver under a N_2 atm., 1.0g of the N-methyl adduct (2.7 mmol) was heated at 180°C (air bath). After 45 minutes, a total of 280 mg of a slightly yellow oil was recovered from the receiver. Glpc analysis (by area %) showed it to consist of 96%

diene and 4% 5-decene along with traces of impurities. (< 1% total) The diene, purified by preparative glpc, was identical to the previously isolated material. The calculated yield of 5-decene is 3%; 4,6-decadiene 72%.

Pyrolysis of 6-(Dec-4-enyl)-N-methyl-N-methylsulfonylsulfinamide-Method A

Using the same procedure described for the tosyl case, 250 mg (0.85 mmol) of the N-methyl adduct derived from MsNSO was heated at 150° for 2 hours in benzene in a combustion tube. Sixty mg of a clear oil was recovered. Glpc analysis (6' 10% UCW-98 on 80/100 mesh Gas Chrom Q, 135°C) showed this to be 82% diene and 18% 5-decene. The calculated yield for 5-decene is 9%; 4,6-decadiene 42%.

Pyrolysis of 6-(Dec-4-enyl)-N-methyl-N-methylsulfonylsulfinamide-Method B

Using the same procedure as described for the tosyl case, 450 mg (1.52 mmol) of the N-methyl adduct was destructively kugelrohr distilled at 150°C under N_2 to give 130 mg of a clear oil. Glpc showed this to be 74% diene and 26% 5-decene. The calculated yield for 5-decene is 16%; 4,6-decadiene 46%.

Pyrolysis of Cyclooct-2-enyl-N-methyl-N-(p-toluenesulfonyl)sulfinamide-Method A

A mixture of 54.2 mg (0.16 mmol) of the N-methyl adduct from

cyclooctene and 64.9 mg n-$C_{11}H_{23}$ (0.415 mmol, internal standard) was heated in benzene at 150°C for 1 1/2 hours. Glpc analysis (8' x 1/4" aluminum tubing, 10% β,β-dioxyopropionitrile on 80/100 mesh Gas Chrom Q, 90°C) of the crude reaction mixture showed a 10% yield of 1,3-cyclooctadiene(identified by co-injection with an authentic sample, Aldrich Chemical Co.), t_r = 6.6 minutes (t_r (C_{11}) = 3 minutes). Cyclooctene (t_r = 4.7 minutes) was not observed under these conditions because of interference from benzene (t_r = 4.9 minutes). However, on 6' UCW-98 on 80/100 mesh Gas Chrom Q at 100°, the total yield of 1,3-cyclooctadiene/cyclooctene (not separated), t_r = 2.0 minutes (t_r (C_{11}) = 6.6 minutes), was calculated at 26%. The calculated yield of cyclooctene is 15%, 1,3-cycloctadiene 11%.

Pyrolysis of Cyclooct-2-enyl-N-methyl-N-(p-toluenesulfonyl)sulfinamide-Method B

As previously described, 350 mg (1.03 mmol) of the N-methyl adduct was destructively kugelrohr distilled under N_2 at 175°C. After 45 minutes, 100 mg of a yellowish oil was collected. This was passed through a short plug of neutral alumina with 3 ml pentane. Evaporation gave 80 mg of a clear oil, λ_{max} (isooctane) = 228 nm (log ϵ =3.70, corrected for presence of olefin). Authentic 1,3-cyclooctadiene has λ_{max} (cyclohexane) 228 nm (log ϵ =3.75).[55b] Glpc analysis (8' x 1/4" aluminum tubing, 10% β,β-dioxyopropionitrile on 80/100 mesh Gas Chrom Q, 90°C) showed this to consist of 83% 1,3-cyclooctadiene and 17% cyclooctene. The calculated yield of

cyclooctene is 12%; 1,3-cyclooctadiene 60%.

Pyrolysis of 2-Phenylcyclohex-2-enyl-N-methyl-N-(p-toluenesulfonyl) sulfinamide-Methods B and C

As previously described, 280 mg (.72 mmol) of the N-methyl adduct was destructively kugelrohr distilled under N_2 at 175°C. After 20 minutes, 80 mg of a white semisolid was collected. Glpc analysis (6' 10% Carbowax 20M on 80.100 mesh Gas Chrom Q, 150°C) showed a mixture (by area %) of 6.5% 1-phenylcyclohexene (t_r = 10.6 minutes), 85% biphenyl (t_r = 17.4 minutes) and 7.7% diene (t_r = 13.0 minutes). After 20 minutes at r.t. in open air, these values had changed to 6.6% 1-phenylcyclohexene, 93% biphenyl and 0.4% diene.

Injection of a 25% solution of the N-methyl adduct in CH_3OH directly into the gas chromatograph (injection port temperature 250°C) gave (by area %) 6.4% 1-phenylcyclohexene, 3.6% biphenyl and 90% diene,

The diene produced from both methods B and C was separately purified by preparative glpc (20' x 3/8" stainless steel, 20% Carbowax 20M on 45/60 mesh Chromsorb W at 200°C, t_r = 22 minutes (t_r (biphenyl) = 26.5 minutes, t_r (1-phenylcyclohexene) = 19 minutes, collected at liquid N_2 temperatures). The resulting oils were weighed and dissolved up in cyclohexane (10 ml volumetric flasks). UV analysis showed both samples to be identical; λ_{max} = 276 nm (ϵ = 7500). Some biphenyl (λ_{max} = 230) was present in each sample. Both 2-phenyl-1,3-cyclohexadiene (λ_{max} = 276 nm(ϵ = 8140)) and 1-phenyl-1,3-cyclohexadiene(λ_{max} = 303 nm,

ϵ = 13800) are known.[37] Not more than 14% of the 1-phenyl isomer can be present in the isolated samples.

Both 1-phenylcyclohexene and biphenyl were identified by co-injection which authentic samples. Biphenyl was isolated from the distillate (Method B) and was identical (tlc, mp and mixed mp) with an authentic sample.

O=Se=N-Ts Reactions

Reaction of 17 with Citronellol Methyl Ether (21).

Under anhydrous conditions, a slurry of 0.55 ml Et_3N (4 mmol, distilled from CaH_2 and stored over 4 Å sieves under N_2) and 0.34g p-toluenesulfonamide (1.98 mmol, Eastman Organic Chemicals, dried in vacuo) was prepared in 4 ml CH_2Cl_2 at 0°C (ice bath) in a 25 ml round-bottomed flask equipped with a dropping funnel and magnetic stirrer. A solution of 0.14 ml selenium oxychloride (2.04 mmol, distilled 64 -65°C at 3.25 torr and stored in a no-air container under N_2) in 2 ml CH_2Cl_2 was added through the dropping funnel over a period of approximately 5 minutes. After the addition was complete (the resulting homogeneous solution had a yellow-orange color), a solution of 0.34g citronellol methyl ether (3 mmol) in 2 ml CH_2Cl_2 was added slowly. After 1 hour at 0°C, the ice bath was removed and stirring continued for 1 1/2 hours at r.t. The reaction was quenched with H_2O and filtered through Celite to remove red Se^o (washed with ether). The organic phase was washed once with 1:1 4% NaOH/brine, once with 5% HCl, once with brine and

dried. Filtration and evaporation gave 0.65g of a thick yellow oil which was purified by preparative tlc (2000 microns silica gel eluted with 30% EtOAc/hexanes). The major fraction (22), a yellowish oil with Rf = 0.5 (35% EtOAc/hexanes), was identical with authentic allylic sulfonamide[12] and weighed 0.36g (53%); ir (film) 3280 (N-H); 2920, 2870 (O-H), 1600, 1450, 1330 (SO_2), 1160 (SO_2), 1115, 1095 and 6665 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.8 (4H, q, aromatic), 5.2 (1H broad T, olefinic), 4.9 (d, N-H), 3.3 (4H, m, CH_2-N and CH_2O), 3.25, (3H, s, $-OCH_3$), 2.4 (3H, s, aromatic $-CH_3$) and 2.0 -0.9 (8H, m). The minor product 23 (Rf = 0.72 (35% EtOAc/hexanes)), a yellow oil which slowly deposited red Se^o, weighed 90 mg (14%); nmr δ ($CHCl_3$) 5.35 (3/4 H, broad t, olefinic), 5.00 (1/4 H, d, olefinic), 3.9 (2H, d of t, $-Se-CH_2-$), 3.25 (3H, s, $-OCH_3$) and 2.1 -0.9 (8H, m).

Reaction of 17 with β-Pinene

To a solution of 17 in CH_2Cl_2 at 0°C prepared under the same conditions described above was added a solution of 0.2720g β-pinene (2 mmol) and 0.1990 squalane (0.4706 mmol internal standard) in 2 ml CH_2Cl_2. The resulting solution was allowed to warm to r.t. over a period of 6 hours. The reaction was quenched with 5% NaOH, filtered through Celite (washed with ether). The organic phase was washed with brine and dried.

Glpc analysis of the product showed the presence of the allylic sulfonamide of β-pinene (25), t_r = 6.4 minutes (6' 3% OV-17 on 80/100

mesh Gas Chrom Q at 230°C, calculated yield 4%), a trace of the rearranged sulfonamide 26 (t_r = 7.7 minutes) and trans-pinenol 24 (t_r = 1.4 minutes, 6' 3% OV-17 on 80/100 mesh Gas Chrom Q at 160°C, 45% yield). The product identities were confirmed by co-injection as well as tlc comparison with authentic samples.

Reaction of 17 with 2,3-Dimethylbutadiene

Under anhydrous conditions in 50 ml round-bottomed flask equipped with a dropping funnel, a solution of 1.4 ml $SeOCl_2$ (20.4 mmol) in 8 ml CH_2Cl_2 was added, slowly (total time 10 minutes) and with stirring at 0°C (ice bath), to a slurry of 3.4g p-toluenesulfonamide (19.8 mmol) and 5.5 ml Et_3N (39.5 mmol) in 10 ml CH_2Cl_2. The resulting solution was heterogeneous and red-orange in color. After an additional 5 minutes, a solution of 2,3-dimethylbutadiene (0.8g, 10 mmol, Aldrich Chemical Co.) in 3 ml CH_2Cl_2 was added slowly. After 2.5 hours, the reaction was quenched with 10 ml H_2O followed by 25 ml 2% NaOH; after 10 minutes of stirring at r.t., it was filtered through Celite (ether-EtOAc wash) and taken up in 1:1 ether/EtOAc, which was washed twice with 2% NaOH, once with 10% HCl, brine and dried. Filtration and evaporation afforded 3.18g of a red-orange oil. This crude product was chromatographed (175g alumina activity III, packed using 10% EtOAc/hexanes; eluted with 25% EtOAc/hexanes; 100 ml fractions) combination according to tlc gave 3 major products: N-(p-toluene-sulfonyl)-4-amino-2,3-dimethylbut-2-enol (28), 110 mg of an oil, Rf (40% EtOAc/hexanes) = 0.54; ir (film) 3500, 3285 (OH and NH), 2920, 1595, 1430, 1320 (SO_2) 1160 (SO_2), 1090, 1050 and 910 cm^{-1};

nmr ($CHCl_3$)δ7.2 -7.8 (4H, q, aromatic), 5.1 (1H, t, exchangeable with 0.1N NaOD/D_2O, N-H), 3.9 (2H, s, CH_2-O), 3.55 (2H, d, CH_2-N), 2.4 (3H, s, aromatic -CH_3), 1.9 -1.75 (1H, broad s, exchangeable, -OH), 1.7 (3H, s, vinyl -CH_3) and 1.6 (3H, s, vinyl -CH_3). N-(p-toluenesulfonyl)-4-amino-2,3-dimethylbut-2-enyldiselenide (29), 350 mg of a bright yellow oil, Rf = 0.31; ir (film) 3280 (NH), 2920, 1595, 1420, 1335 (SO_2), 1160 (SO_2), 1095, 1045, 910 and 815 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.8 (4H, q, aromatic), 5.4 -5.2 (1H, broad t, exchangeable, N-H), 3.45 (4H, broad m, CH_2-N and CH_2-Se) 2.4 (3H, s, aromatic -CH_3) and 1.8 (6H, broad s, vinyl -CH_3). N-(p-Toluenesulfonyl)-2-methyl-2-methyl-2-isopropenylazirdine (30), 370 mg of a yellowish oil, Rf = 0.5; ir (film) 2980 (C-H), 1595, 1495, 1450, 1385, 1325 (SO_2), 1160 (SO_2), 1120, 1105, 1090, 1020, 955, 875, 820 and 715 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (4H, q, aromatic), 4.9 (2H, d, isopropenyl = CH_2), 2.75 (1H, s, diastereomeric CH_2-N), 2.4 (4H, s, aromatic -CH_3 and diastereomeric H_2C  , addition of shift reagent caused shift 2 distinct singlets in the ratio of 1:3), 1.9 (3H, s, vinyl CH_3) and 1.85 (3H, d, vinyl CH_3); (70ev) 251 (M^+), 236 (M-15, loss of methyl), 155 ($SO_2C_7H_7$), 96 (base peak, $C_6H_{10}N$) and 91 (C_7H_7).

Acetylation of 28

Crude 28 (60 mg, 0.22 mmol) was dissolved in 2 ml dry pyridine and 0.5 ml Ac_2O added. After 2 hours at r.t., the reaction was poured onto ice, extracted with 1:1 EtOAc/ether, which was washed once with 1:1 4% NaOH/brine, sat'd $CuSO_4$, H_2O and dried. Filtration

and evaporation gave 62 mg of N-(p-toluenesulfonyl)-4-amino-2,3-dimethyl-but-2-enyl acetate as a yellowish oil (89%); ir (film) 3280 (N-H), 2920, 1735 (C=O), 1595, 1420, 1320 (O_2), 1245 and 1160 (SO_2) cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (4H, q, aromatic), 4.95 (2H, d, CH_2-OAc) 4.6 (1H, broad, N-H), 3.55 (2H, t, CH_2-N), 2.4 (3H, s, aromatic $-CH_3$) 2.1 (3H, s, acetate), 1.75 (3H, s, vinyl-CH_3) and 1.65 (3H, s, vinyl-CH_3).

N-(p-Toluenesulfonyl)-4-amino-2,3-dimethylbut-2-enylbenzylselenide (31)

To a 25 ml round-bottomed flask with a magnetic stirrer under nitrogen containing a solution of 29 (210 mg, 0.32 mmol) dissolved in 5 ml absolute EtOH was added just enough $NaBH_4$ to completely decolorize the solution, followed by 0.12 ml benzyl bromide (1 mmol). After 1 hour at r.t., the reaction was taken up in ether and washed with H_2O, brine and dried. Filtration and evaporation gave a light yellow oil which was extracted with small portions of pentane (to remove excess benzyl bromide) leaving 180 mg of an oil. Purification by preparative tlc (2000 micron silica gel eluted with 35% EtOAc/hexanes) gave 70 mg of 31 (26%) as a thick oil; ir (film) 3280 (N-H), 2920, 1600, 1495, 1450, 1330 (SO_2), 1160 (SO_2), 1095 and 1050 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (4H, q, aromatic), 7.15 (5H, broad s, aromatic), 4.8 (1H, broad s, N-H), 3.7 (2H, d, CH_2-N), 3.2 (2H, s, $-CH_2$-Se-), 2.4 (3H, s, aromatic $-CH_3$) and 1.6 (6H, broad s, vinyl $-CH_3$).

Raney-Nickel Reduction of 29

To a 25 ml round-bottomed flask equipped with a magnetic stirrer and a reflux condenser charged with 29 (100 mg, 0.15 mmol) in 5 ml absolute EtOH was added 1.0g activated Raney-Nickel (ROC/RIC, washed with EtOH). After 1 1/4 hour at reflux, the reaction was cooled, filtered and extracted twice with 1:1 ether/EtOAc which was washed with H_2O, brine and dried. Filtration and evaporation gave 32 (20 mg, 26%) which was identical by nmr, ir and tlc comparison with an authentic sample.

Hydrogenation of 30

To a 25 ml round-bottomed flask containing 150 mg of crude 30 (0.6 mmol) in 4 ml EtOAc was added approximately 5 mg of Adam's catalyst (PtO_2). After flushing 3 minutes with N_2 and 3 minutes with H_2, a constant pressure of 5 p.s.i. H_2 was maintained for 5 hours. The reaction was then filtered through Celite and concentrated to give 84 mg of 32 (55%), which was identical with an authentic sample.

N-(p-Toluenesulfonyl)-2,3-dimethylbutylamine (32)

A flask containing 0.36g 50% NaOH solution (4.5 mmol), 0.73g $TsNH_2$ (4.4 mmol) and 1.0g 2,3-dimethyl-1-butyltosylate (3.9 mmol, prepared by reaction of 2,3-dimethyl-1-butanol (Aldrich Chemical Co.) and TsCl in pyridine) dissolved in 8 ml DMF was heated at

60°C for 6 hours. Water was added and the reaction mixture extracted twice with $CHCl_3$ which was washed once with H_2O and dried. Filtration and evaporation gave a clear oil still containing some DMF. A portion of this crude product was purified by preparative tlc (2000 microns silica gel eluted with 30% EtOHc/hexanes) to give 32 as a clear oil, Rf (50% EtOAc/hexanes) = 0.6; ir (film) 3290 (NH), 2960, 1595, 1400, 1320 (SO_2), 1160 (SO_2) and 1090 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (4H, q, aromatic), 5.1 (1H, broad s, N-H), 2.8 (2H, m, CH_2-N) 2.4 (3H, s, aromatic $-CH_3$), 1.8 -1.2 (2H, m, R_2CH $-CHR_2$) and 0.8 (6H, m, $-CH_3$).

Anal. Calcd for $C_{13}H_{21}NO_2S$: C, 61.14; H, 8.29; N, 5.49. Found: C, 61.18; H, 8.49; N, 5.28.

Reaction of 17 with 2,3-Dimethylbutadiene in the Presence of $TsNH_2$

2,3-Dimethylbutadiene (0.41g, 5 mmol) was added to a solution of 17 at -10°C (ice/EtOH) prepared as previously described using the following amounts of reagents: 1.37 ml $SeOCl_2$ (20 mmol), 5.14g $TsNH_2$(30 mmol) and 5.7 ml Et_3N (40 mmol) in a total of 50 ml CH_2Cl_2. After stirring overnight while allowing to warm to r.t., the reaction was quenched with H_2O and stirred for 1/2 hour, then poured into a mixture of 50 ml 1:1 ether/EtOAc and 50 ml 2% NaOH. After filtering through Celite, the organic phase was washed once with 2% NaOH, brine and dried. Filtration and evaporation gave a dirty yellow-orange solid which was chromatographed on

300g of alumina (activity III) packed using 30% EtOAc/hexanes. Elution with 1.0 l 30%, 500 ml 35%, 500 ml 40%, 500 ml 45% and finally with 60% EtOAc/hexanes (approximately 200 ml collected per fraction) gave, after identification and combination of fractions by tlc, 200 mg 29 (14%, identical to the previously isolated sample), 150 mg 30 (12%, identical to the previously isolated sample) and 920 mg 33, which was recrystallized from acetone/cyclohexane in 2 crops to afford a total of 880 mg of white crystals (42%), mp 113°C; ir (KBr pellet) 3330 (NH), 2995, 1595, 1450, 1420, 1335, 1315 (SO_2), 1305, 1290, 1120 (SO_2), 1115, 1090, 1050, 835 and 825 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.8 (8H, two overlapping q, aromatic), 5.5 (1H, t, N-H), 5.15 (2H, s, $=CH_2$), 3.55 (2H, d, CH_2-N), 2.6 (1H, s, diastereomeric H_2C-N), 2.4 (4H, s, aromatic $-CH_3$ and diastereomeric H_2C-N, can be separated by shift reagent into 2 singlets in the ratio 1:3) and 1.7 (3H, s, methyl).

Anal. Calcd for $C_{20}H_{24}N_2O_4S_2$: C, 57.12; H, 5.75; N, 6.66. Found: C, 57.06; H, 5.75; N, 6.44.

Hydrogenation of 33

To a 25 ml round-bottomed flask containing 200 mg 33 (0.48 mmol) in 10 ml EtOAc was added approximately 5 mg Adam's catalyst. After flushing with N_2 for a few minutes followed by a H_2 flush, a constant H_2 pressure of approximately 5 p.s.i. was maintained for 10 hours. The reaction was then filtered and concentrated to give 210 mg of a white solid which was recrystallized from acetone/

cyclohexane to give 194 mg of N, N'-di-(p-toluenesulfonyl)-1,4-diamino-2,3-dimethylbutane (96%), mp 124 -125°C, identical in all respects to an authentic sample (including mixed mp).

N, N'-Di-(p-toluenesulfonyl)-1,4-diamino-2,3-dimethylbutane.

A mixture of 1.0g (2.3 mmol) of the ditosylate prepared from 2,3-dimethyl-1,4-butandiol[55c] and 0.5g sodium azide (7.7 mmol) was heated in 15 ml DMF at 60°C for 6 hours. Thre reaction was quenched with water and extracted once with 1:1 EtOAc/ether which was washed three times with H_2O, once with brine and dried. Filtration and evaporation gave 280 mg of a yellowish oil which was immediately redissolved in dry ether under N_2 and reduced with excess $LiAlH_4$ at 0° (ice bath). After 1 hour, the reaction was quenched with 1.0g TsCl (5.26 mmol). After stirring overnight, water was added and extracted once with 1:1 EtOAc/ether which was washed twice with H_2O, once with brine and dried. Filtration and evaporation gave a yellowish solid which was recrystallized from acetone/cyclohexane to give 81 mg of white crystals (8%), mp 124 -125°C; ir (KBr pellet) 3270 (NH), 2900, 1595, 1420, 1325 (SO_2), 1155 (SO_2), 1090, 1050 and 820 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (8H, q, aromatic), 5.0 (2H, broad s, NH), 2.85 (4H, m, CH_2-N), 2.4 (6H, s, aromatic $-CH_3$), 1.85 (2H, m, R_2CH $-CHR_2$), 1.7 (6H, t, $-CH_3$).

Anal. Calcd for $C_{20}H_{28}N_2O_4S_2$: C, 56.57; H, 6.65; N, 6.60. Found: C, 56.37; H, 6.71; N, 6.48.

Reaction of TsN=Se=NTs with Dienes-1,2-Diamination of 1,3-Dienes

Selenium Tetrachloride/p-Toluenesulfonamide Reagent-Reaction with 2,3-Dimethylbutadiene

A suspension of 0.56g $SeCl_4$ (2.5 mmol, ROC/RIC) and 0.87g $TsNH_2$ (5.1 mmol) in 5 ml CH_2Cl_2 was prepared in a 25 ml three-necked round-bottomed flask equipped with a dropping funnel and a magnetic stirrer under anhydrous conditions. A solution of 1.42 ml Et_3N (10.2 mmol) in 5 ml CH_2Cl_2 was added, slowly (total time 10 minutes) with stirring and cooling (ice bath). Ten minutes after the addition was complete, 2,3-dimethylbutadiene (210 mg, 2.5 mmol) in 1 ml CH_2Cl_2 was added to the resulting yellowish-brown solution. After 5 hours (with gradual warming to r.t.), the reaction was quenched with H_2O and filtered through Celite (wahsed with ether). The organic phase was washed with H_2O, brine and dried. Filtration and evaporation left 1.24g of a yellowish solid consisting mostly of $TsNH_2$. After preliminary column chromatography (25g silica gel; eluted with 20% EtOAc/hexanes), the residual yellow oil (650 mg) was purified by preparative tlc (2000 micron silica gel eluted with 30% EtOAc/hexanes). The major product isolated (150 mg crude), Rf (30% EtOAc/hexanes) = 0.39, upon recrystallization from $CHCl_3$/hexanes, was identified as N,N'-di-(p-toluenesulfonyl)-3,4-diamino-2,3-dimethylbut-1-ene 41 (21 mg, 2%), mp 136°C; ir (10% in $CHCl_3$) 3280 (NH), 2920 (CH), 1595, 1410, 1330 (SO_2), 1160 (SO_2), 1090 and 910 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (8H, two overlapping q, aromatic),

5.65 (1H, s, exchanged with 0.1N NaOD/D_2O, N-H), 5.4 (1H, t, exchanged with 0.1N NaOD/D_2O, N-H), 4.9 (2H, d, isopropenyl CH_2), 3.1 (2H, d of d, collapses to d with base, diastereomeric R-CH_2-N), 2.4 (6H, s, aromatic -CH_3), 1.5 (3H, s, -CH_3) and 1.3 (3H, s, -CH_3).

Anal. Calcd for $C_{20}H_{26}N_2O_4S_2$: C, 56.85; H, 6.20; N, 6.63; O, 15.14. Found: C, 56.76; H, 6.28; N, 6.40; O, 15.31.

Selenium Metal/Chloramine-T Reagent-Reaction with 2,3-Dimethylbutadiene

The reagent was prepared in a 25 ml round-bottomed flask under anhydrous conditions by stirring a mixture of 0.47g selenium metal (6 mmol, dried in vacuo 80°C, ROC/RIC) and 2.6g anhydrous chloramine-T (11.4 mmol, dried in vacuo at 80°C, Aldrich Chemical Co. (sold as the trihydrate)) in 16 ml CH_2Cl_2 at r.t. for 22 hours. The resulting white slurry was cooled to 0°C (ice bath) and 0.41g of 2,3-dimethylbutadiene (5 mmol) addes. After 6 hours (with gradual warming to r.t.), the dark grey-brown suspension was quenched with H_2O and filtered through Celite (washed with ether). The organic phase was washed once with H_2O, brine and dried. Filtration and evaporation gave a yellowish solid which was purified by column chromatography (60g silica gel; packed with hexanes, eluted with 100 ml: 5% EtOAc/hexanes, 10%, 20%, 20%, 50%, 100% EtOAc; 50 ml fractions). Concentration of appropriate fractions (identified by tlc) gave 0.45g of the disulfonamide contaminated with $TsNH_2$. This crude product was dissolved in EtOAc, washed twice with 5%

NaOH and dried. Filtration and evaporation gave a white solid which was recrystallized ($CHCl_3$/hexanes) to give 85 mg (4%) N,N'-di-(p-toluenesulfonyl)-3,4-diamino-2,3-dimethylbut-1-ene (41).

1,2-Diamination of 2,3-Dimethylbutadiene (Se^o/Chloramine-T/$TsNH_2$ Reagent

Under anhydrous conditions, a 100 ml round-bottomed flask with a magnetic stirrer was charged with 1.08g Se^o (13.6 mmol), 5.69g anhydrous chloramine-T (25 mmol) and 2.14g p-toluenesulfonamide (12.5 mmol, dried in vacuo at 80°C) in 50 ml CH_2Cl_2 (for a total of 12.5 mmol of reagent). After stirring at r.t. for 20 hours, the resulting suspension had a distinct silver-grey luster which was different from the reagent generated without $TsNH_2$. 2,3-Dimethylbutadiene (0.82g, 10 mmol) was added and the stirring continued overnight. Water (20 ml) was added and, after 15 additional minutes, the dark reaction mixture was poured into a mixture of 100 ml 1:1 EtOAc/ether and 100 ml 1:1 4% NaOH/brine. After filtering through Celite, the organic phase was washed twice with 1:1 4% NaOH/brine, once with brine and dried. Filtration and evaporation gave 4.88g of crude product. Column chromatography (300g alumina, activity III (6% H_2O by weight added to activity I) packed with 20% EtOAc/hexanes; eluted with 500 ml: 30%, 40%, 50%, 60%, 70%; 200 ml fractions) and concentration of appropriate fractions (identified by tlc) gave 2.95g of N,N'-di-(p-toluenesulfonyl)-3,4-diamino-2,3-dimethylbut-1-ene 41. Recrystallization ($CHCl_3$/hexanes) gave

2.88g (total of 2 crops) of pure product (68%).

1,2-Diamination of 1,3-Cyclohexadiene

In the exact manner previously described, 10 mmol of 1,3-cyclohexadiene (0.80g, Aldrich) was added to 12.5 mmol of previously generated Se^{o}/chloramine-T/$TsNH_2$ reagent in 50 ml CH_2Cl_2. After column chromatography (same conditions), 1.23g of crude product was obtained. Recrystallization ($CHCl_3$) gave 1.20g (total of two crops, 29%) of N,N'-di-(p-toluenesulfonyl)-1,2-diaminocyclohex-3-ene 44, Rf (60% EtOAc/hexanes) = 0.43, mp 158 -159°C; ir (10% in $CHCl_3$) 3360 (NH), 3020, 2920, 1595, 1420, 1335 (SO_2), 1290, 1160 (SO_2), 1090, 1000, 960 and 895 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -8.0 (8H, two overlapping q, aromatic), 5.75 (2H, two overlapping d, exchanged with 0.1N NaOD/D_2O, N-H), 5.6 and 5.0 (2H, m, olefinic), 3.45 (1H, m, allylic R_2CH-N) 3.25 (1H, m, R_2CH-N), 2.35 (6H, s, aromatic -CH_3) and 2.2 -1.2 (4H, m, ring H).

Anal. Calcd for $C_{20}H_{24}N_2O_4S_2$: C, 57.12; H, 5.75; N, 6.66; O, 15.22. Found: C, 57.13; H, 5.86; N, 6.76; O, 15.25.

Nmr decoupling results ($CHCl_3$ containing 0.1N NaOD/D_2O): irradiation of the multiplet at 5.55 caused collapse of the multiplet at 3.45 to a doublet, J = 4 Hz (measured at a sweep width of 400 Hz). Little change in the multiplet at 3.25 was observed.

cis-N,N'-Di-(p-toluenesulfonyl)-1,2-diaminocyclohexane 44a (Hydrogenation of 44)

To a 25 ml round-bottomed flask containing 44 (250 mg, 0.59 mmol) dissolved in 8 ml EtOAc was added 3 mg PtO_2 (Adam's catalyst). After flushing 3 minutes with N_2 and 3 minutes with H_2, a constant H_2 pressure of 5 p.s.i. was mantained for 6 hours. After filtering through Celite and concentration, 264 mg of a white solid was obtained. Recrystallization from $CHCl_3$/hexanes gave 243 mg 44a (97%), mp 168-169°C, identical in every respect to an authentic sample (including mixed mp).

cis-N,N'-Di-(p-toluenesulfonyl)-1,2-diaminocyclohexane (44a)

In a 50 ml Erlenmeyer flask, 250 mg of cis-1,2-diaminocyclohexane·2HCl[47] (1.3 mmol) was dissolved in a cooled mixture of 2 ml ethyldiisopropylamine and 20 ml pyridine (stored over KOH). p-Toluenesulfonyl chloride (1.5g, 7.9 mmol) was added and the reaction left at r.t. overnight. After pouring onto ice, the resulting white precipitate was collected, washed with H_2O and dried. Two recrystallizations from $CHCl_3$/hexane gave 430 mg (76%) of 44a, Rf (50% EtOAc/hexanes) = 0.46, mp 168-169°C; ir (10% in $CHCl_3$) 3280, 3020, 2940, 2860, 1595, 1450, 1415, 1330 (SO_2), 1155 (SO_2), 1090, 1000 and 985 cm^{-1}; nmr ($CHCl_3$) δ 7.2-7.9 (8H, two overlapping q, aromatic), 5.65 (2H, d, N-H), 3.15 (2H, m, R_2CH-N), 2.4 (6H, s, aromatic $-CH_3$) and 1.35 (8H, m, ring H).

Anal. Calcd for $C_{20}H_{26}N_2O_4S_2$: C, 56.85; H, 6.20; N, 6.63; O, 15.14. Found: C, 56.57; H, 6.36; N, 6.42; O, 14.95.

trans-N,N'-Di-(p-toluenesulfonyl)-1,2-diaminocyclohexane 44b or 44c

In the same manner, 250 mg (1.3 mmol) of trans-1,2-diaminocyclohexane ·2HCl was ditosylated with 1.5g TsCl (7.9 mmol) in 2 ml ethyldiisopropylamine and 20 ml pyridine. Recrystallization ($CHCl_3$/hexanes) of the crude product gave 512 mg (91%) of the trans isomer, Rf (50% EtOAc/hexanes), = 0.60 mp 181 -185°C; ir (10% in $CHCl_3$) 3250 (NH), 2930, 1595, 1385, 1330 (SO_2), 1160 (SO_2), 1080 and 900 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (8H, two overlapping q, aromatic), 5.1 (2H, d, N-H), 2.9 (2H, broad s, R_2CH-N), 2.4 (6H, s, aromatic $-CH_3$) and 2.0 -1.0 (8H, m, ring H).

1,2-Diamination of Cyclopentadiene

In the same manner and scale described for 2,3-dimethylbutadiene, cyclopentadiene (0.66g, 10 mmol, bp 40°C, freshly prepared from the thermal cracking of the commercial dimer (Eastman Organic Chemicals) at 170°C and stored at -78°C until used) was added to 12.5 mmol of the Se^0/chloramine-T/$TsNH_2$ reagent. Column chromatography (300g alumina activity III, packed with 25% EtOAc; eluted with 500 ml: 30% EtOAc/hexanes, 40%, 5 x 50%, 55%; 200 ml fractions) gave 1.79g of crude disulfonamide. Recrystallization ($CHCl_3$/hexanes) gave 1.62g (total of 2 crops, 40%) of cis-N,N'-di(p-toluenesulfonyl)-3,4-diaminocyclopentene, Rf (60% EtOAc/hexanes) = 0.5, mp 142.5°C; ir (10% in $CHCl_3$) 3300, 2920, 1595, 1490, 1410,

1340 (SO_2), 1160 (SO_2), 1120, 1090, 1040, 965, 940 and 905 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (8H, two overlapping q, aromatic), 5.9 (2H, overlapping d, exchanged with 0.1N NaOD/D_2O, N-H), 5.7 and 5.3 (2H, m, olefinic), 41 (1H, m, allylic R_2CH-N), 3.9 (1H, m, R_2CH-N) 2.4 (6H, s, aromatic $-CH_3$) and 2.4 -2.2 (2H, m, ring H). The cis stereochemistry is assumed by analogy with the case of 1,3-cyclohexadiene.

Anal. Calcd for $C_{19}H_{24}N_2O_4S_2$: C, 55.86; H, 5.92; N, 6.86; O, 15.66. Found: C, 56.56; H, 5.56; N, 6.61; O, 15.69.

Attempted 1,2-Diamination of 1,3-Cyclooctadiene

In the same manner and scale described for 2,3-dimethylbutadiene, 1,3-cyclooctadiene (1.08g, 10 mmol, Aldrich Chemical Co., freshly distilled (80°C at 100 torr) before use) was added to 12.5 mmol of the Se^o/chloramine-T/$TsNH_2$ reagent. Column chromatography (300g alumina activity III, packed with 15% EtOAc/hexanes; eluted with 500 ml: 20%, 30%, 35%, 40%, 45%, 60%, 75%; 200 ml fractions) gave 1.55g of crude product. Recrystallization ($CHCl_3$/hexanes) gave 1.43g (total of 2 crops, 52%) of 5-(p-toluenesulfonylamido)-1,3-cyclooctadiene, Rf (50% EtOAc/hexanes) = 0.41, mp 113 -114°C; ir (10% in $CHCl_3$) 3370, 3260, 2930, 1595, 1445, 1405, 1330 (SO_2), 1305, 1290, 1160 (SO_2), 1095, 1070, 1050 and 900 cm^{-1}; nmr ($CHCl_3$) δ 7.8 -7.2 (4H, q, aromatic), 5.65 (3H, m, olefinic), 5.15 (1H, m, olefinic), 4.1 (1H, d of t, allylic R_2CH-N), 2.4 (3H, s, aromatic $-CH_3$), 2.15 (2H, m, allylic $-CH_2-$) and 1.8 -1.2 (4H, m, ring H).

Anal. Calcd for $C_{15}H_{19}NSO_2$: C, 64,95, H, 6.90; N, 5.05. Found: C, 64.67; H, 7.08; N, 4.77.

1,2-Diamination of Isoprene

In the same manner and scale described for 2,3-dimethylbutadiene, isoprene (0.68g, 10 mmol, Aldrich Chemical Co., freshly distilled (bp 30°C) before use) was added to 12.5 mmol of the Se°/chloramine-T/$TsNH_2$ reagent. Column chromatography (300g alumina activity III, packed 25% EtOAc/hexanes; eluted with 500 ml: 30%, 35%, 40%, 2 x 50%, 60%, 2 x 75%; 200 ml fractions) gave two major products, A (350 mg of yellowish semisolid, Rf (60% EtOAc/hexanes) = 0.72) and B (1.60g of yellowish solid, Rf (60% EtOAc/hexanes) = 0.63).

A was purified by preparative tlc (2000 microns silica gel eluted with 50% EtOAc/hexanes) to give 160 mg (8%) of N,N'-di-(p-toluene-sulfonyl)-3,4-diaminobut-1-ene; ir (film) 3370, 3000, 2950, 1595, 1500, 1420, 1390, 1340 (SO_2), 1160 (SO_2), 1105, 1060 and 830 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.8 (8H, two overlapping q), 5.7 (1H, s, exchanged with 0.1N NaOD/D_2O, N-H), 5.7 -4.9 (3H, m, $-CH=CH_2$), 5.1 (1H, t, exchanged with 0.1N NaOD/D_2O, N-H), 3.1 and 3.0 (2H, both broad s, diastereomeric $-CH_2-N$), 2.4 (3H, s, aromatic CH_3) and 1.25 (3H, s, CH_3).

Recrystallization (acetone/CCl_4) of B gave 1.06g (total of 2 crops, 26%) of N,N'-di-(p-toluenesulfonyl)-2-methyl-3,4-diaminobut-1-ene, mp 144 -145°C; ir (10% in $CHCl_3$) 3300, 2920, 1595, 1405, 1330 (SO_2), 1305, 1160 (SO_2), 1090 and 910 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.8 (8H, q, aromatic), 5.65 (1H, d, exchanged with 0.1N NaOD/D_2O, N-H), 5.3 (1H, t, exchanged with 0.1N NaOD/D_2O, N-H),

4.75 (2H, broad s, isopropenyl $=CH_2$), 3.7 (1H, d of t, allylic R_2CH-N), 3.05 and 2.95 2H, m (collapses to d of d in base), diastereomeric $-CH_2-N$), 2.4 (6H, s, aromatic $-CH_3$) and 1.45 (3H, s, isopropenyl $-CH_3$).

Anal. Calcd for $C_{19}H_{24}N_2O_4S_2$: C, 55.86; H, 5.92; N, 6.86; O, 15.66. Found: C, 55.79; H, 5.83; N, 6.66; O, 15.92.

1,2-Diamination of 2-Phenyl-1,3-butadiene

In the same manner and scale described for 2,3-dimethyl-butadiene, 2-phenyl-1,3-butadiene (1.30g, 10 mmol, prepared by literature methods,[56] bp 60°C at 17 torr) was added to 12.5 mmol of the Se^0/chloramine-T/$TsNH_2$ reagent. Column chromatography (300g alumina activity III, packed with 20% EtOAc/hexanes; eluted with 500 ml: 30%, 35%, 40%, 2 x 50%; 200 ml fractions) gave two major products, A (390 mg of yellowish semisolid, Rf (50% EtOAc/hexanes) = 0.54 and B (2.13g of white solid, Rf (50% EtOAc/hexanes) = 0.44.

A was purified by preparative tlc (2000 microns silica gel eluted with 50% EtOAc/hexanes) to give 300 mg (8%) of N,N'-di-(p-toluenesulfonyl)-3-phenyl-3,4-diaminobut-1-ene; ir (film) 3280 (NH), 3040, 2950, 1595, 1500, 1450, 1340 (SO_2), 1225, 1160 (SO_2), 1100, 905 and 830 cm^{-1}; nmr ($CHCl_3$) δ 7.2 -7.9 (8H, two overlapping q, aromatic), 5.9 (1H, s, exchanged with 0.1N NaOD/D_2O, N-H), 5.4 (1H, t, exchanged with 0.1N NaOD/D_2O, N-H), 4.9 -5.9 (3H, m, R-CH=CH_2), 3.4 and 3.3 (2H, overlapping d, diastereomeric

$-CH_2-N$) and 2.4 (6H, s, aromatic $-CH_3$).

B was recrystallized ($CHCl_3$/hexanes) to give 2.05g (45%) of N,N'-di-(p-toluenesulfonyl)-2-phenyl-3,4-diaminobut-1-ene, mp 157°C; ir (10% in $CHCl_3$) 3350 (N-H), 2980, 2920, 1595, 1490, 1400, 1335 (SO_2), 1305, 1160 (SO_2) 1090 and 815 cm^{-1}; nmr ($CHCl_3$) δ 7.0 -7.8 (8H, two overlapping q, aromatic), 6.9 (1H, t, exchanged with 0.1N NaOD/D_2O, N-H), 5.7 (1H, d, exchanged with 0.1N NaOD/D_2O, N-H), 5.2 (2H, broad s, $=CH_2$), 4.3 (1H, m, collapses in base to t, allylic R_2CH-N), 3.05 (2H, m, dollapses in base to two overlapping d at 3.1 and 3.0, diastereomeric $-CH_2-N$) and 2.4 (6H, s, aromatic $-CH_3$).

Anal. Calcd for $C_{24}H_{26}N_2O_4S_2$: C, 61.25; H, 5.57; N, 5.95. Found: C, 60.97; H, 5.74; N, 5.65.

1,2-Diamination of 1-Vinyl-1-cyclohexene

In the same manner and scale described for 2,3-dimethyl-butadiene, 1-vinyl-1-cyclohexene (1.08g, 10 mmol, prepared by literature methods[57], bp 86 -91°C at 130 torr) was added to 12.5 mmol of the Se^0/chloramine-T/$TsNH_2$ reagent. Column chromatography (300 g alumina activity III, packed with 25% EtOAc/hexanes; eluted with 500 ml: 30%, 35%, 40%, 45%, 3 x 50%; 200 ml fractions) gave two major products, A (275 mg of yellowish oil, Rf (60% EtOAc/hexanes) = 0.67) and B (1.83g of white solid, Rf (60% EtOAc/hexanes) = 0.6).

A was recrystallized ($CHCl_3$/hexanes) to give 175 mg (4%) of yellowish crystals of N,N'-di(p-toluenesulfonyl)-1,2-diamino-(1-cyclohexenyl)ethane, mp 99 -106°C; ir (10% in $CHCl_3$) 3300 (NH)

2930, 1395, 1330 (SO_2),1305, 1195, 1160 (SO_2), 1090 and 945 cm^{-1}; nmr ($CHCl_3$) δ 7.1 -7.9 (8H, two overlapping q, aromatic), 5.75 (1H, s, exchanged with 0.1N NaOD/D_2O, N-H), 5.4 (1H, t, exchanged with 0.1N NaOD/D_2O, N-H), 5.1 (1H, t, olefinic), 3.6 (1H, m, allylic R_2CH-N), 3.0 (2H, m, diastereomeric $-CH_2$-N), 2.4 (6H, s, aromatic $-CH_3$) and 1.9 -1.1 (8H, m, ring H).

B was recrystallized ($CHCl_3$/hexanes) to give 1.73 (total of 2 crops, 37%) of N,N'-di-(p-toluenesulfonyl)-1,2-diamino-1-vinylcyclohexane, mp 151 -154°C; ir (10% in $CHCl_3$) 3300, 2930, 2860, 1595, 1450, 1400, 1330 (SO_2), 1305 1160 (SO_2), 1090, 995 and 930 cm^{-1}; nmr ($CHCl_3$) δ 7.1 -7.9 (8H, two overlapping q, aromatic), 5.7 (2H, m, exchanged with 0.1N NaOD/D_2O, overlapping N-H), 4.75 -5.8 (3H, m, $-CH=CH_2$), 3.0 (1H, d of t, collapses in base to t, R_2CH-N) 2.4 (6H, s, aromatic $-CH_3$) and 1.7 -1.0 (8H, m, ring H),

Anal. Calcd for $C_{22}H_{28}N_2O_4S_2$: C, 58.90; H, 6.29; N, 6.24. Found: C, 58.61; H, 6.36; N, 5.82.

Allylic Amination of Cyclohexene with Se^o/Chloramine-T/$TsNH_2$

The following stock solutions of TsN=Se=NTs were prepared in the usual manner; I 1.08g Se^o (13.7 mmol), 5.69g (25 mmol) anhydrous chloramine-T and 2.14g (12.5 mmol) $TsNH_2$ in 50ml CH_2Cl_2 (12.5 mmol) reagent, 2.5M in TsN=Se=NTs and $TsNH_2$), II 1.08g Se^o (13.7 mmol) and 5.69g (25 mmol) chloramine-T in 50 ml CH_2Cl_2 (12.5 mmol reagent, 2.5M in TsN=Se=NTs). In six separate 25 ml round-bottomed flasks with magnetic stirring under anhydrous conditions, the following was added:

Experiment A (reagent: olefin = 0.63) 10 ml I 0.593g cyclohexene (7.22 mmol), 0.067g n-$C_{24}H_{50}$ (0.196 mmol); Experiment B (reagent: olefin = 1.25): 10 ml I, 0.342g cyclohexene (4.16 mmol), 0.038g n-$C_{24}H_{50}$ 0.113 mmol); Experiment C (reagent: olefin = 0.63): 10 ml II, 0.629g cyclohexene (7.66 mmol), 0.071g n-$C_{24}H_{50}$ (0.108 mmol); Experiment D(reagent: olefin = 1.25): 10 ml II, 0.324g cyclohexene (3.94 mmol), 0.036g n-$C_{24}H_{50}$ (0.107 mmol); Experiment E (reagent: olefin = 0.63): 10 ml II, 0.86g $TsNH_2$ (50 mmol), 0.611g cyclohexene (7.44 mmol), 0.069 n-$C_{24}H_{50}$ (0.202 mmol); Experiment F (reagent: olefin = 1.25): 10 ml II, 0.86g $TsNH_2$ (5.0 mmol), 0.324g cyclohexene (3.94 mmol), 0.036g n-$C_{24}H_{50}$ (0.107 mmol), After 24 hours at r.t., approximately 10 drops were removed from each of the reaction mixtures and dissolved in a mixture of 1 ml EtOAc, 1 ml H_2O and 1 ml brine. Glpc analysis of the organic phase, 6' 3% OV-17 on 80/100 mesh Gas Chrom Q, 240°C, t_r (3-p-toluene-sulfonamidocyclohexene) = 5.1 minutes, t_r(n-$C_{24}H_{50}$)= 3.1 minutes) gave the following yields of allylic sulfonamide: Experiment A = 40%, Experiment B = 64%, Experiment C = 37%, Experiment D = 54%, Experiment E = 35% and Experiment F = 56%. The presence of allylic sulfonamide in Experiment A was confirmed by glpc co-injection and tlc comparison with an authentic sample.

Reaction of 1,3-Cyclohexadiene with SeO_2 in Aqueous tert-BuOH

In a 50 ml Erlenmeyer flask, a mixture of 0.56g SeO_2 (5.04 mmol, 99.5% purity, ROC/RIC) and 0.40g 1,3-cyclohexadiene (5 mmol) in 15 ml 90% tert-BuOH/10% H_2O was stirred at r.t. for 24 hours.

Five ml H_2O was added and the reaction mixture extracted overnight with 75 ml CH_2Cl_2 in a continuous liquid - liquid extractor (Lab Glass, Inc.). The CH_2Cl_2 was separated, dried, filtered and evaporated to yield a yellow oil (1.14g) containing some red Se^o. Column chromatography (50g silica gel, packed with 50% EtOAc/hexanes; eluted with 60% EtOAc/hexanes; 40 ml fractions) gave only two compounds.

The major product (0.35g, Rf (EtOAc) = 0.47), a yellow oil, was tentatively identified as 3-(cyclohexen-4-ol)-4-cyclohexen-3-ol) selenide 46a (52%, 63% based on SeO_2); ir (film) 3350 (broad band, OH), 3330, 2920 (CH), 1430, 1380, 1335, 1265, 1230, 1155, 1060, 1010, 960, 900 and 735 cm^{-1}; nmr ($CHCl_3$+ D_2O) δ 5.75 (4H, m, olefinic), 4.25 (1H, m, allylic R_2CH-O), 3.9 (2H, m, overlapping allylic R_2CH -Se, R_2CH-O), 3.1 (1H, m, R_2CH-Se) and 2.4 -1.6 (8H, ring H). The minor product (0.12g, Rf (EtOAc) = 0.34), a clear oil, was identified on the basis of special comparison with the published data[50] as cis-3,4-dihydroxycyclohexene 44 (21%, 66% based on SeO_2); ir (film) 3400 (broad band, OH), 3030, 2920, 1450, 1435, 1395, 1230, 1210, 1155, 1080, 980, 880 and 735 cm^{-1}; nmr ($CHCl_3$ + D_2O) δ 5.8 (2H, m, olefinic), 4.1 (1H, m, allylic R_2H-O), 3.85 (1H, m, R_2CH-O), 2.15 (2H, m, allylic $-CH_2-$) and 1.8 (2H, m, ring H).

The dihydroxy selenide 46a (220 mg, 0.8 mmol) was dissolved in 5 ml pyridine and 2 ml Ac_2O added with cooling. After standing overnight at 0^oC, it was poured onto ice. The resulting mixture was extracted once with ether, which was washed once with 1:1 ice/ concentrated HCl, H_2O and dried. Filtration and evaporation gave 214 mg of 46b (74%) as a yellow oil; ir (film) 3030, 2930, 1740

(acetate), 1430, 1370, 1240, 1040, 945, 900 and 735 cm^{-1}: nmr ($CHCl_3$) δ 5.45 -6.1 (2H, m, olefinic), 5.35 (1H, m, allylic R_2CH-OAc), 5.1 (1H, m, R_2CH-OAc), 4.0 (1H, m, allylic R_2CH-Se), 3.35 (1H, m, R_2CH-Se), 2.4 -1.8 (8H, m, ring H), 2.15 (3H, s, -OAc) and 2.10 (3H, s, -OAc): ms (70 ev) showed no molecular ion, base peak at m/e 80 (Se^{80}), no major peaks (> 20% base peak) between 100-357 mass units.

The diol 44 (340 mg, 2.98 mmol) was hydrogenated overnight using PtO_2 (Adam's catalyst) in 10 ml EtOAc at 5 p.s.i. H_2. After filtering through Celite, the solvent was evaporated leaving a yellowish oil (340 mg, 98% crude). Tlc of this crude product showed only the cis isomer (Rf = 0.40 (EtOAc)) and none of the trans (Rf = 0.31 (EtOAc)). Two recrystallizations from ether gave pure cis-1,2-cyclohexane diol, mp 93 -95°C, identical in all respects to an authentic sample (including mixed mp).

Reactions of N-Alkoxycarbonyl Imido Compounds

Bis-tert-butoxycarbonylsulfurdiimide (50)

To a 50 ml Erlenmeyer flask containing 5.0g (42.7 mmol) tert-butylcarbamate[58] dissolved in 15 ml tert-BuOH was added 11 ml (92.2 mmol) tert-butyl hypochlorite (Frinton Labs). After 2 hours, brine was added and the mixture extracted with ether which was washed with H_2O and dried. Filtration and evaporation afforded a yellowish oil. Distillation (31 -32°C at 0.5 torr) gave 5.44g (68%) of N,N-dichloro-t-butylcarbamate; ir (film) 2980, 2930, 1755

(carbamate), 1475, 1455, 1380, 1270, 1240, 1145 and 875 cm^{-1}; nmr ($CHCl_3$) δ 1.45 (singlet).

A mixture of 0.5g (2.7 mmol) N,N-dichloro-t-butylcarbamate and 0.047g (1.5 mmol) of sulfur in 10 ml benzene was refluxed for 8 hours in a 25 ml round-bottomed flask under anhydrous conditions. After cooling to r.t., the solvent was removed under high-vacuum and the dark residue kugelrohr distilled (120 -130°C at 0.5 torr) to give 0.25g (70%) of a very H_2O sensitive yellow oil thought to contain 50; ir (film) 2980, 2930, 1710 (carbamate), 1475, 1455, 1395, 1370, 1295, 1240 (N=S=N), 1050 (N=S=N), 845 and 775 cm^{-1}.

Reaction of 50 with β-Pinene

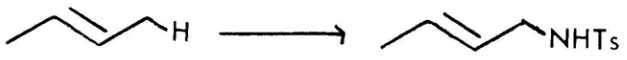
β-Pinene (0.05 ml, 0.32 mmol) was added to a stirred solution of 0.25g (0.95 mmol) of 50 in 10 ml benzene in a 25 ml round-bottomed flask under anhydrous conditions. After stirring overnight, the solvent was removed and the dark residue redissolved in 10 ml 60% CH_3OH made basic with 0.5g K_2CO_3. After stirring overnight, it was taken up in ether, which was washed once with H_2O and dried. Filtration and evaporation gave a yellowish semi-solid. After removal of some tert-butylcarbamate, kugelrohr distillation (130°C at 0.5 torr) gave 16 mg (some decomposition occurred during distillation, approximately 20% yield) of tert-butoxycarbonyl-3-amino-β-pinene as a light yellow oil; ir (film) 3360 (NH), 2980, 2930, 1700 (tert-butoxycarbamate), 1480, 1390, 1370, 1250, 1060 and 895 cm^{-1}; nmr ($CHCl_3$) δ 4.9 (2H, d, $=CH_2$), 4.6

(1H, t, allylic R_2CH-N), 3.5 (1H, d, N-H), 2.6 -1.9 (5H, m, ring H), 1.5 (1H, d, bridgehead H), 1.45 (9H, s, tert-butyl), 1.3 (3H, s, $-CH_3$) and 0.85 (3H, s, $-CH_3$).

Part II: Total Synthesis of d,l-Gabaculine

Introduction

The first part of this thesis discussed the chemistry and synthetic applications of sulfur (IV) and selenium (IV) imido compounds. Without doubt, the most important aspect of this area is the allylic amination of alkenes by TsN=S=NTs[18a,b] or TsN=Se=NTs.[12] This new synthetic method directly introduces a nitrogen, protected as the N-p-toluenesulfonyl derivative, in an allylic position (Eq. 1). In the past, the synthetic strageties needed

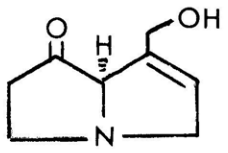


(Eq. 1)

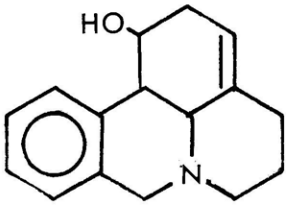
to create this type of functionality have relied on indirect, multistep operations. In view of the potential scope of this reaction, it was decided to apply the allylic amination sequence to a total synthesis in order to demonstrate its overall utility.

Because we were not interested in the synthesis of any particular natural product, it was important to choose a synthetic target that would best demonstrate the advantages and limitations of the method. Since there is no natural product which contains a p-toluenesulfonamide group (allylic or otherwise), it was particularly

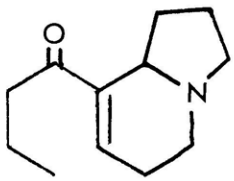
important that the target serve as a suitable test for the removal of the N-p-toluenesulfonyl group in the presence of other functionality. It was also desirable that the target would: 1) demonstrate that the reagent is compatible with commonly found functional groups 2) show the positional and stereo-selectivity inherent in the reaction 3) be a molecule of some interest and/or usefulness 4) be relatively simple in structure. Below are shown a small sample of typical natural products containing an allylic nitrogen and so might be considered as possible candidates:



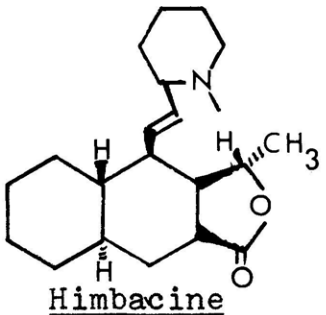
Retronecine



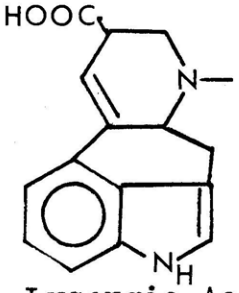
Pluviine



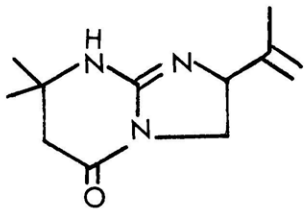
Elaeokanine A



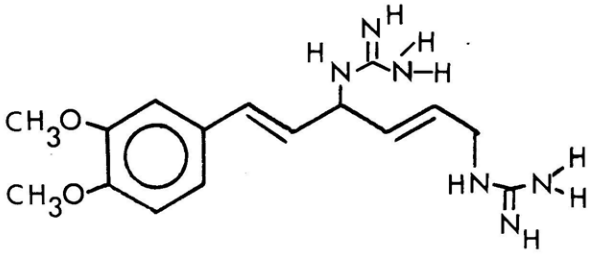
Himbacine



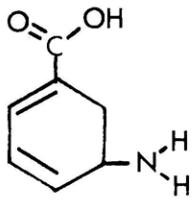
Lysergic Acid



Alchornine



Acanthoine



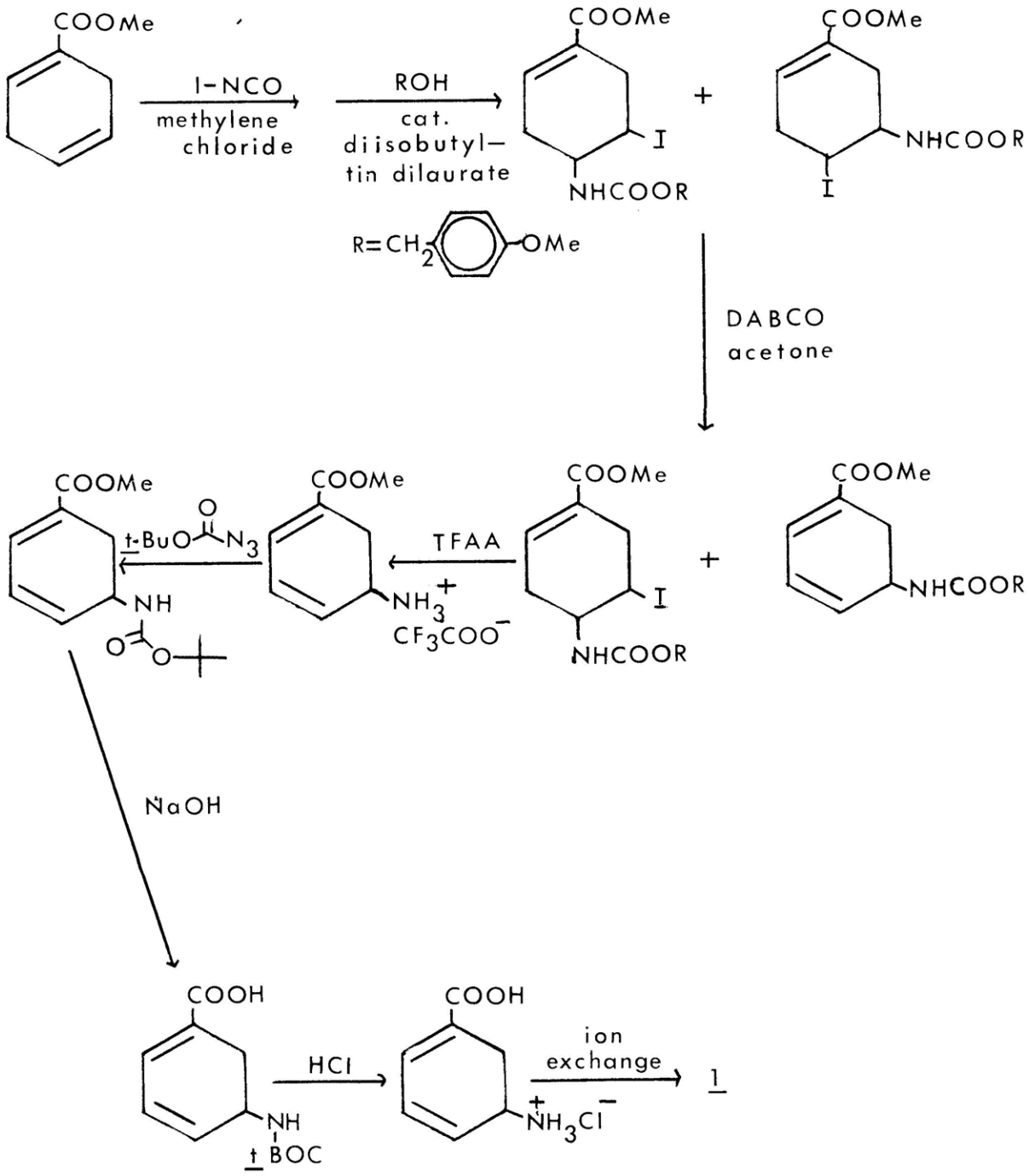
Gabaculine

Of these compounds, the two which best fit the needs described above were acanthoine[59] and gabaculine.[60] The latter would seem

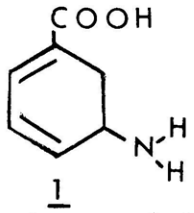
to be an excellent choice since it will be sensitive to both oxidation (being a dihydrobenzene derivative) and reduction (being a conjugated dienoic carboxylic acid). Although it has no stereochemistry *per se*, the allylic amination reaction on some suitable unsymmetric cyclohexenyl precursor will involve both positional and stereo-selectivity. It has practical advantages in that the synthesis should be only a few steps, and that, as will be discussed later, gabaculine is a subject of current biochemical interest. It is with the total synthesis of d,l-gabaculine that this part of the thesis is concerned.

Gabaculine was first isolated (in an unspecified manner) from a culture filtrate of *Streptomyces toyocaensis* subspecies 1039 by Mishima and coworkers in 1976.[60] It was an optically active ($\alpha_d = -454^\circ$ (C = 1, H_2O)) amorphous powder, and was assigned the structure 1 on the basis of the following physical and chemical data; ms: M^+ 139.0642 ($C_7H_9NO_2$), ir: 1650 cm^{-1} (conjugated carbonyl group), uv: λ_{max} 275 nm (ϵ=8600) (carbonyl conjugated with a dienyl group) and nmr (D_2O): δ 6.82 (1H, ABX multiplet, α-proton in a α,β-unsaturated carbonyl), 6.47 and 6.06 (2H, multiplet (J = 9.5 H_z), vicinal olefinic protons), 4.11 (1H, m, allylic ring proton next to nitrogen) and 2.77 (2H, doublet of doublet, allylic-CH_2-). Gabaculine also reacted with diazomethane to give an ester (indicating the presence of a carboxylic acid group) and gave a positive ninhydrin test (primary amino group). The structure 1 was confirmed by the total synthesis of racemic material (Scheme 1). The overall yield of d,l-gabaculine by Mishima's

Scheme I

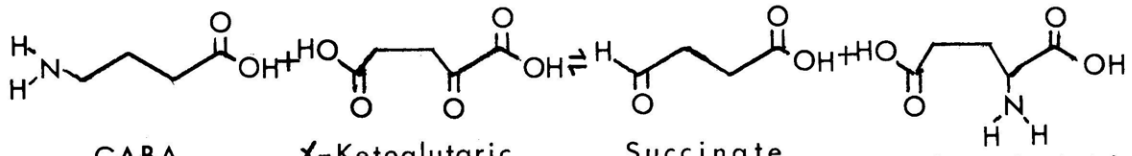

COOMe
I-NCO
methylene chloride
ROH
cat. diisobutyl–tin dilaurate
I
NHCOOR
R=CH2
OMe
DABCO
acetone
t-BuO
N3
NH
TFAA
NH3+
CF3COO−
NaOH
COOH
HCl
ion exchange
NH3Cl−
t BOC
1

method was approximately 20% (total of 7 steps).



1

Gabaculine was found to be an inhibitor of γ-aminobutyrate aminotransferase.[60] This enzyme (m.w. 109,000, composed of two nonidentical subunits) is directly involved in the metabolism of γ -aminobutyric acid (generally abreviated as GABA, from which the name gabaculine is derived), an important inhibitory transmitter substance in the nervous system.[61a,b] In the presence of the enzyme, GABA (derived from glutamic acid by glutamic acid decarboxylase) and γ-ketoglutaric acid are reversibly transformed to succinate semialdehyde and l-glutamic acid (Eq. 1). The equilibrium value (succinic semialdehyde) (l-glutamic acid)/



GABA γ-Ketoglutaric Acid Succinate Semialdehyde l-Glutamic Acid

(GABA) (γ -ketuglutaric acid) = 0.1 at pH 7.4-8.8 (20-38°C).[62] Although the exact mechanism by which GABA inhibits neural transmission is still a subject of controversy,[61b] it is known that excess GABA in the C.N.S. has anticonvulsant properties, whereas a defiency leads to seizures.

γ-Aminobutyrate aminotransferase, isolated either from mouse brain[63a] or Pseudomonas fluorescens[63b] can be considered as a

member of the general class of aminotransferases.[64] This class of enzymes all share a common mechanism (Scheme II) based on condensation of covalently bound pyridoxal phosphate with an amino group of the substrate. Enzyme - assisted rearrangement to an imine (step 2) followed by proton transfer (step 3) gives an intermediate which affords a carbonyl compound and a pyridoxamine upon hydroysis. Recondensation (step 5) following the same sequence of events in reverse finally results in a net exchange of an amino group for a carbonyl group. In the case of γ-aminobutyrate amino-transferase, these reactions are all stereospecific (synthetic d,l-gabaculine has 1/2 the activity of natural l-gabaculine).

In view of the mechanism, it is not surprising that amino-transferases are sensitive to inhibition by any reagent capable of reacting with carbonyl or imino groups. Table 1 lists a few of some nonspecific inhibitors of γ-aminobutyrate aminotransferase. However, three compounds (ethanolamino-O-sulfate,[65] 4-aminohex-5-ynoic acid[66] and gabaculine,[67a]) have been shown to be specific irreversible γ-aminobutyrate aminotransferase inhibitors. The mechanism of inhibition by these three compounds share a common feature in that, in the process of catalytic turnover, some inter-mediate produced from the initial compound by the enzyme is irreversibly intercepted and thus "kills" the active site (these types of compounds are also known as "sucide substrates"[67b,c]). Table 2 compares the effectiveness of these three compounds.

Scheme II

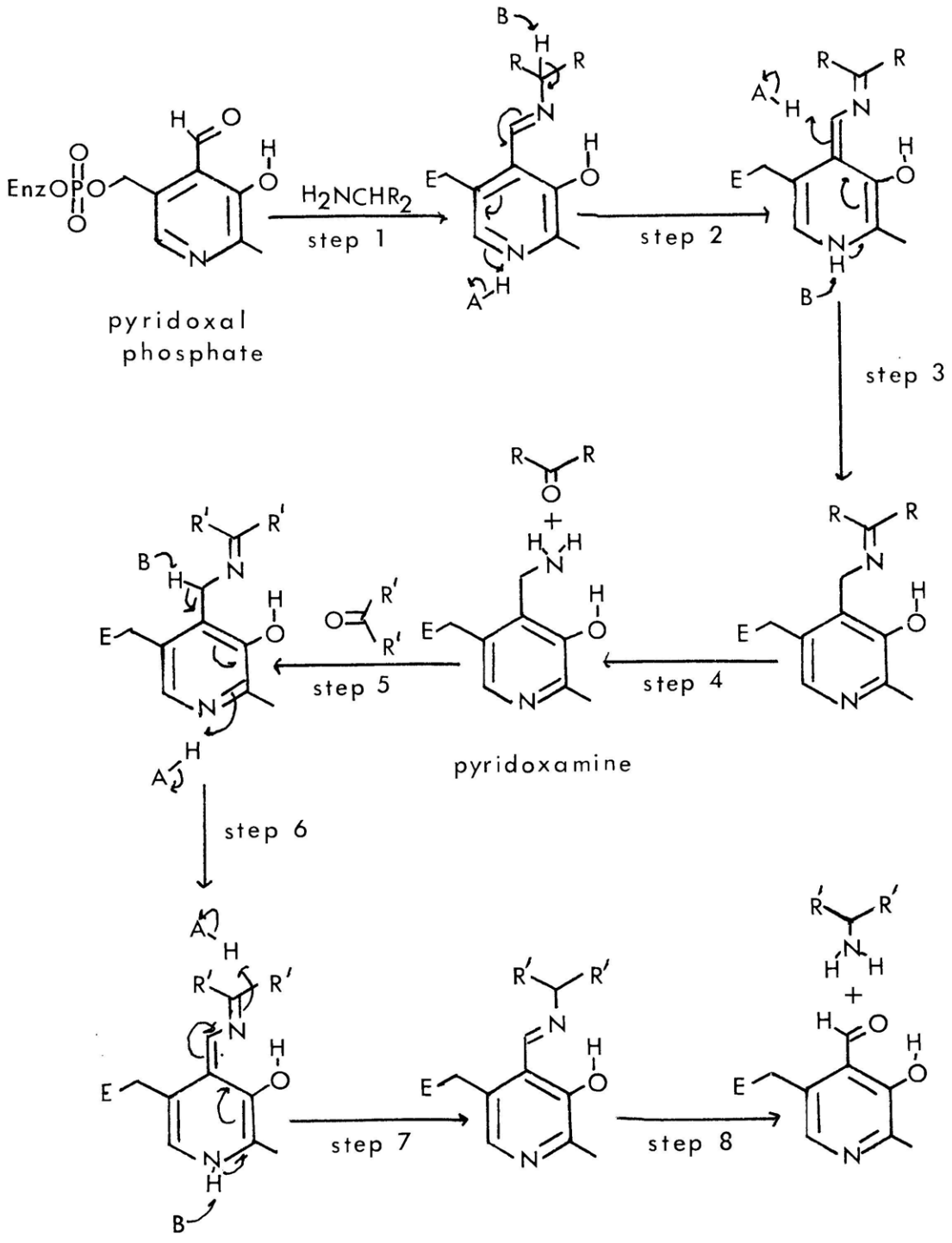

pyridoxal phosphate
step 1
step 2
step 3
step 4
step 5
step 6
step 7
step 8
pyridoxamine

Table 1

(Inhibiters of γ-Aminobutyrate Aminotransferase)
(Taken in Part From Ref. 63a)

Compound	Concentration (M)	% Inhibition
$Hg(OAc)_2$	10^{-6}	85
$Cd(OAc)_2$	10^{-6}	26
$Zn(OAc)_2$	10^{-6}	0
KCN	10^{-5}	50
NH_2OH	2×10^{-5}	50
NH_2OH	10^{-6}	80
NH_2NH_2	10^{-5}	30
$HSCH_2CH_2CO_2H$	1.3×10^{-6}	50

Table 2

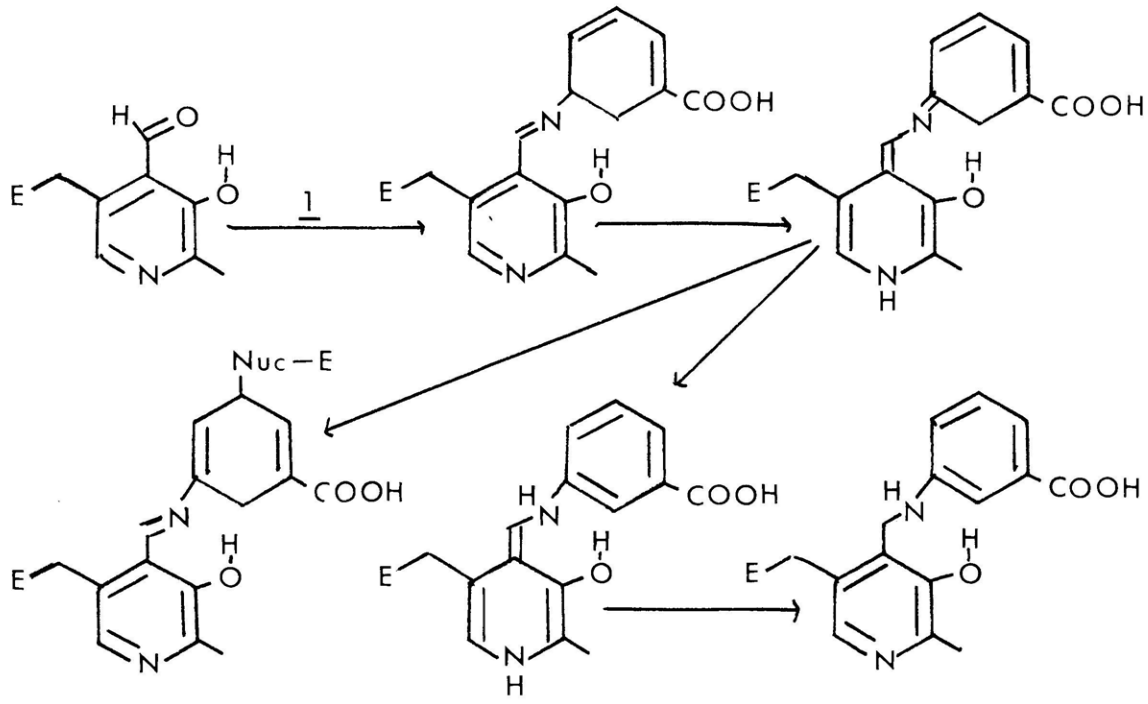
(Specific Irreversible Inhibiters of
γ-Aminobutyrate Aminotransferase)

Compound	K_I
Ethanolamine-O-Sulfate	4.4×10^{-4} M
4-Aminohex-5-ynoic Acid	3.4×10^{-4} M
Gabaculine	5.8×10^{-7} M

If the mechanism shown in Scheme II is applied to the case of gabaculine (Scheme III), there are two possible mechanisms by which the active site could be destroyed.[67a] First,

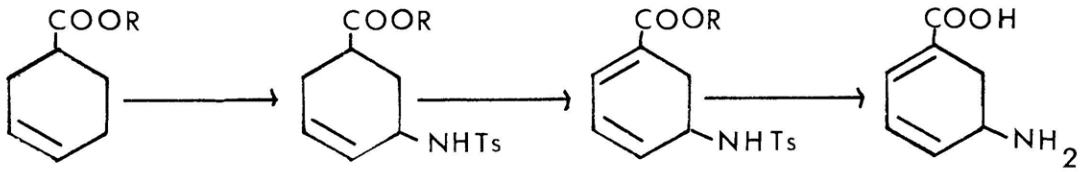
aromatization of the rearranged imine by proton transfer would leave a m-anthranilic acid derivative which could not be returned to the catalytic cycle. Secondly, interception by an enzyme nucleophile by Michael addition should also lead to a permanently bound adduct. It should be noted that m-anthranilic acid does not inhibit this enzyme.

Scheme III



Our synthetic strategy for the synthesis of d,l-gabaculine is simple. The first step is selective allylic amination at the 5 position of a suitably protected 3-cyclohexene-1-carboxylic acid. Introduction of α,β-unsaturation (preferably by use of a phenylselenoxide elimination) and removal of protecting

groups (ester and p-toluenesulfonyl) would lead to the desired product.

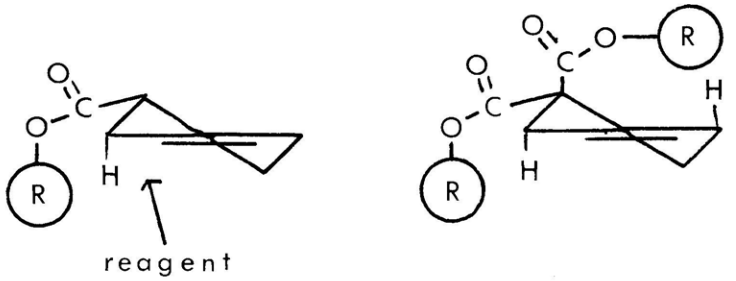


(Eq. 2)

1

RESULTS AND DISCUSSION

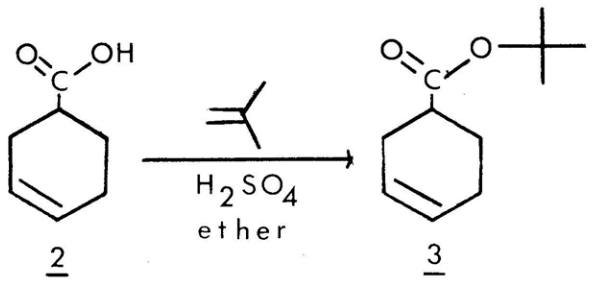
The starting material for the synthesis of gabaculine (1) was 3-cyclohexene-1-carboxylic acid (2) which is commercially available and contains the complete carbon skeleton needed. It contains two different allylic positions (carbons 2 and 5), but only allylic amination at the 5 position will lead to 1. It was felt that the positional selectivity could be controlled by esterification of the carboxylic acid with a large, bulky group. Hopefully, this would disfavor the approach of the reagent towards the 2 position (Eq. 3). However, the alternative method of further increasing the bulk in the area by using a 1,1-dicarboxylic ester might be expected to disfavor the 5 position as well because of 1,3-diaxial interactions (Eq. 3).



(Eq. 3)

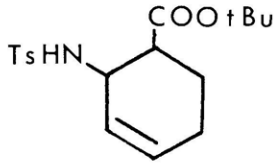
Preliminary experiments involving the allylic amination reaction were carried out using tert-butyl-3-cyclohexene-1-carboxylate(3)[68] The use of tert-butyl esters in organic synthesis has been extensive[69] and it is well known that while extremely resistant to basic hydrolysis, they can be easily

revolved under mildly acidic conditions.[69,70] The tert-butyl ester 3 was synthesized in 79% yield from reaction of 2 with isobutylene under acid catalysis (Eq. 4).

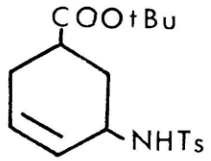


2 3 (Eq. 4)

When 3 was added to a solution of TsN=S=NTs in CH_2Cl_2 at r.t.,[18a] a slow reaction took place (5 days). Workup using K_2CO_3 in aqueous MeOH followed by column chromatography afforded a white solid (yield ranged from 50% to 70%). Although homogeneous by tlc, nmr 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 alpha to a tosyl group are observed, as well as absorptions 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 0.1N 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[12] also gave a mixture of 4 and 5 (45% yield) in the ratio of 1:1 (by nmr).

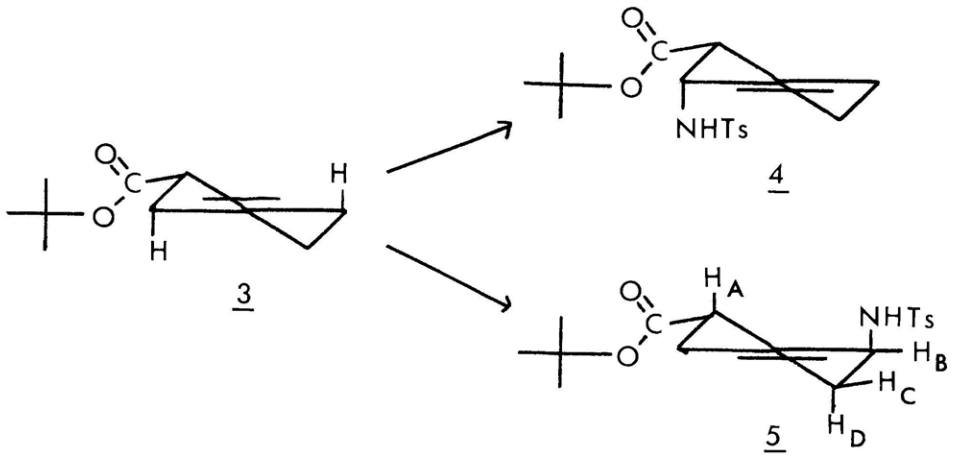


4



5

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 (see Part 1 of this thesis) preferentially involves the replacement of a pseudoaxial hydrogen by a pseudoaxial substituent. For example, reaction of either SeO_2[71] or TsN=Se=NTs[72] 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 during the transition state of the ene reaction.[9a] Using this reasoning, the allylic sulfonamide 4 is predicted to be the cis- and 5 the trans-isomer (Eq. 5).

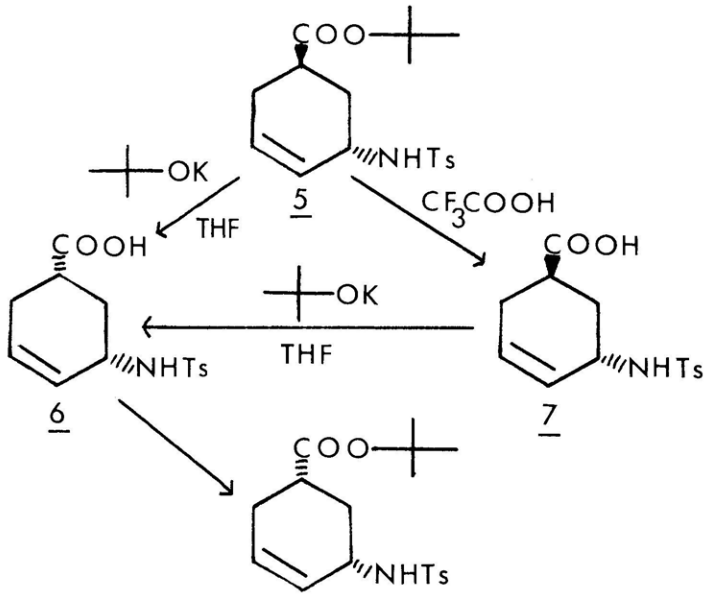


3 → 4 + 5 (Eq. 5)

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.[46] 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 anti-periplanar elimination of an axial sulfonamide anion. The trans relationship in 5 was demonstrated by both nmr and chemical correlations. High field nmr (270 MHz)[72] showed a symmetrical 8-line AB portion of an ABXX' pattern (centered at approximately δ 2.1 in d_6-benzene) for the H_C/H_D methylene group in 5. Irradiation of δ 4.05 (the allylic proton alpha to the sulfonamide group) caused a collapse of the multiplet to an "AB quartet" (J_{AB} = 11.77 Hz) and allowed J_{BC} and J_{BD} to be calculated as 6.6 Hz and 8.1 Hz, respectively. These values indicated that H_B is pseudoequatoral and therefore, the sulfonamide group is pseudoaxial. Unfortunately, the coupling constants involving H_A could not be determined because of interference from overlapping signals. Similar values for the coupling constants were found in the assignment of stereochemistry for the products of Pd-catalyzed allylic alkylation of cis- and trans-3-acetoxy-5-carbomethoxycyclohexene.[73] In an attempt to epimerize 5 to the diequatorial (cis) isomer, it was treated with excess potassium tert- butoxide in THF.

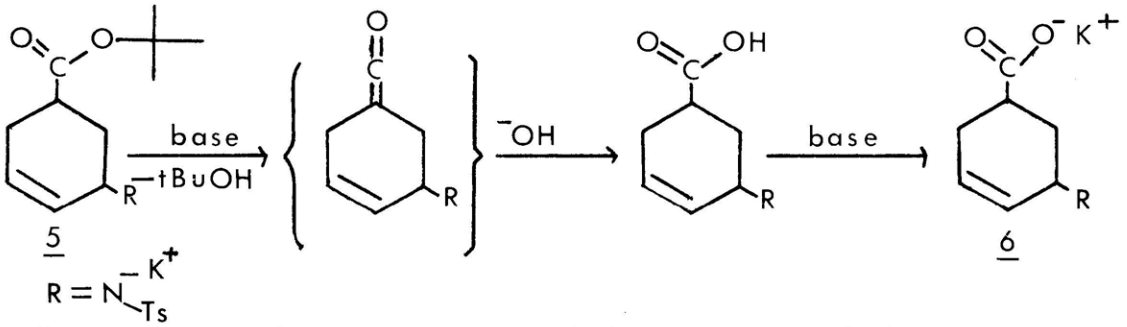
However, the only product isolated (74% yield, mp 162-165°C) was not the expected tert-butyl ester, but rather a carboxylic acid (6). This acid (6) was completely different from the carboxylic acid (7) formed from 5 by treatment with trifluoroacetic acid (76%, mp 174-175°C). However, treatment of 7 with excess potassium tert-butoxide in THF gave 6 in 61% isolated yield. When 6 was heated in tert-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. These reactions are outlined in Scheme IV.

Scheme IV



The hydrolysis of 5 to the carboxylic acid 6 under these conditions is not without precedent. Hydrolysis of hindered

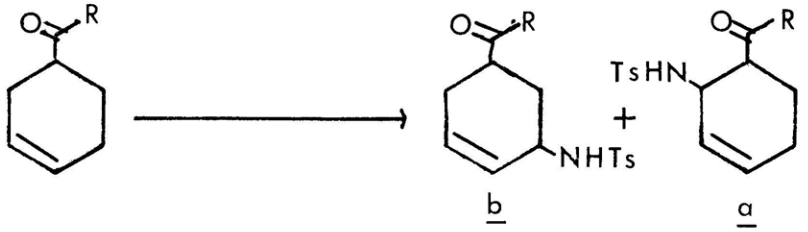
esters by potassium tert-butoxide has been known for many years, although the conditions needed are usually quite vigorous.[74] One alternative mechanism is a base-catalzed elimination of tert-BuOH to form a ketene which is then trapped by KOH (normally found as an impurity in commercial potassium tert-butoxide) (Eq. 6).[75]



(Eq. 6)

In order to improve the positional selectivity of the allylic amination reaction, a survey of different ester derivatives was undertaken (Table 3). The compounds listed in Table 3 were all (except for the methyl ester) prepared from the reaction of 3-cyclohexene-1-acid chloride with the appropriate alcohol. 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-toluenesulfonyl amido isomer (a) and the upper field signal to the 5-isomer (b). Two trends can be observed in Table 3; first, the sulfur based reagent is more sensitive to steric factors than the selenium reagent, and secondly, the isolated yield of product is reduced when the steric bulk is increased. In the case of the N,N-dicyclohexylamide derivative, the allylic amination

Table 3



b a

R	Reagent	Equivalents	Total Yield	Ratio (a:b)
-OCH_3	S	1.2	80%	2:3[1]
	Se	1.25	49%	1:1[1]
-O-tert-butyl	S	1.25	70%	1:3
	Se	1.25	45%	1:1
-$OCH\phi_2$	S	5	50%[2]	1:4
	Se	5	-	-
-2,4,6-trimethylphenol	S	5	40%[2]	1:6
	Se	5	-	-
-N,N-dicyclohexylamine	S	5	32%	1:20

Footnotes for Table 3

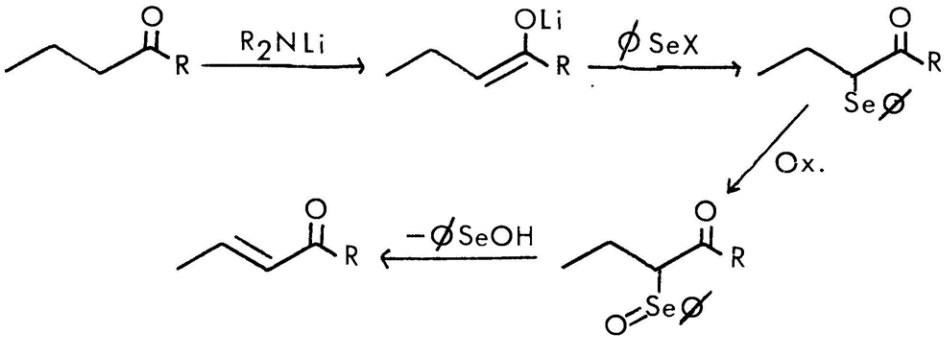
1) ratio confirmed by glpc.

2) no allylic sulfonamide could be isolated.

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.

It should be pointed out that although pure 5 could be isolated by fractional recrystallization of chromatographically purified crude product, there was a great loss of material (usually only 15-30% of the total amount of 5 present was recovered as pure product). A much better method was the direct recrystallization (from cyclohexane) of the crude product (no chromatography was necessary) to afford a mixture of approximately 80% 5 and 20% 4. Usually, less than 5% of 5 remained in the mother liquor. This mixture was not changed upon further recrystallization from cyclohexane and was used for most of the following exploratory work.

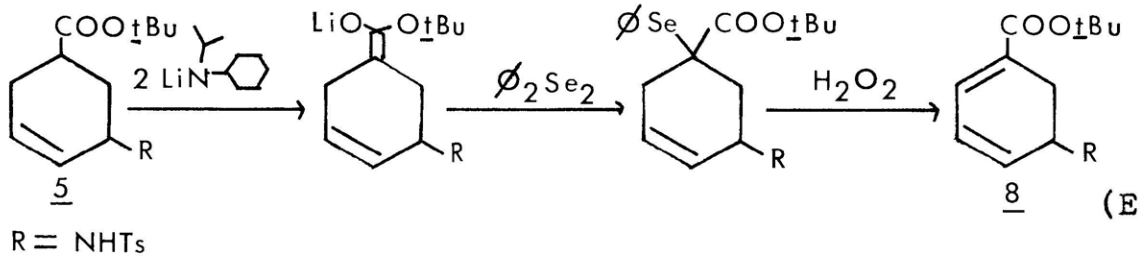
Having 5 in hand, the next step was the introduction of α,β-unsaturation in order to form the dienoic ester system. The classical and still widely used procedure for this type of transformation is halogenation-dehydrohalogenation. However, in recent years, equivalent methods utilizing a phenylselenoxide elimination have been developed independently by Reich[76] and Sharpless[35b] and on the related phenylsulfoxide and methylsulfoxide eliminations by Trost.[77] In the selenium case, (Eq. 7) a phenylselenide moiety is generally introduced alpha to the



(Eq. 7)

ester by quenching of the enolate with ∅-Se-X (X = Cl, Br, Se∅). Oxidation (by various methods) gives a phenylselenoxide which decomposes at r.t. by syn elimination to give the α,β-unsaturated ester and phenylselenenic acid, which in the presence of excess oxidizing agent, is transformed to phenylseleninic acid. This reaction is mild and simple.

The dianion of 5 was generated with a slight excess of lithium cyclohexylisopropylamide in THF at -78°C by the method of Rathke and Lindert.[78] After quenching the enolate with 2 equivalents of dry diphenyldiselenide, the resulting crude phenylselenide (not isolated) was directly oxidized in THF at 0°C with H_2O_2. From the reaction, the tert-butyl ester of N-p-toluenesulfonyl-gabaculine (8) was isolated in 82% yield as a white crystalline solid (mp 90-92°C). (Eq. 8). Only traces

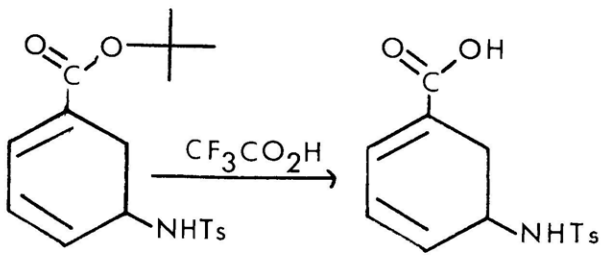


R = NHTs

(Eq. 8)

of aromatic compounds were found.

Removal of the tert-butyl ester from 8 was accomplished by treatment with trifluoroacetic acid for 5 minutes at r.t. (Eq. 9).[70] Removal of volatile material by high vacuum gave



8 9 (Eq. 9)

N-p-toluenesulfonyl-gabaculine (9) as a gummy semisolid in quantative 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 r.t. It was generally prepared as needed and used in crude form.

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 4 lists some of the methods. Because of the sensitive nature of the desired product, only the first two methods, electrochemical and sodium napthalene (and possibly sodium in liquid NH_3) were considered mild enough.

Table 4

(Methods for Cleavage of Sulfonamide Groups)

Method	Ref.
Electrochemical	79
a) Tetramethylammonoum amalgam/MeOH	80
b) Pb cathode/NaOH in aqueous methanol	81
c) DMF/R_4N^+ X^- (controlled potential)	79
d) CH_3CH/R_4N^+ X^- (controlled potential)	82
Sodium Napthalene	83,84
Sodium bis(2-methoxyethoxy)Aluminum Hydride	85
Sodium-Ammonia	86
HBr-Phenol	87
Pyridine Hydrochloride	87
50% Sodium Amylate	87
Concentrated HCl	87

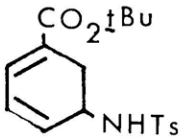
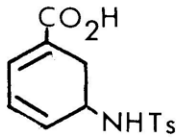
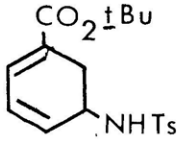
When 9 was subjected to deprotection by either of these two methods under various conditions, no gabaculine was found. The only products which were isolated (in low yields) seemed by nmr to have one or both or the double bonds reduced. Similar treatment of 8 gave approximately the same results. The tert-butyl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

In order to clarify the situation, the reduction potentials of 8 and 9, was well as the saturated derivative 5, were measured by polarography (Table 5). 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 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, reprotection of the resulting amino group and continue or 2) lower the reduction potential of the sulfonamide group below that of the double bond.

Table 5

(Comparison of Reduction Potentials)

Compounds	$E_{1/2}$(Measured in 0.2M TEAB[a]/MeCN)[b]
 8	-2.12 V, -2.5 V
 9	-1.73 V, -2.5 V
 5	-2.34 V

Footnotes for Table 5

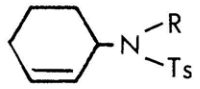
a) TEAB = Tetraethylammonium Bromide.

b) vs. calomel reference electrode.

It is known[82,88] that electron-withdrawing substituents on aromatic sulfonamide groups lower the reduction potential. For the case in hand, this approach would not be practical since the necessary substituted sulfur or selenium diimides for the allylic amination reaction are not easy to prepare. Alternatively, almost nothing is known about the effects of substitutions on the nitrogen of a primary sulfonamide. Using N-p-toluenesulfonyl-cyclohex-3-enamine as a model substrate, the reduction potentials of a number of N-substituted derivatives were measured (Table 6). 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.

Table 6

(Effect of R- on Reduction Potentials)



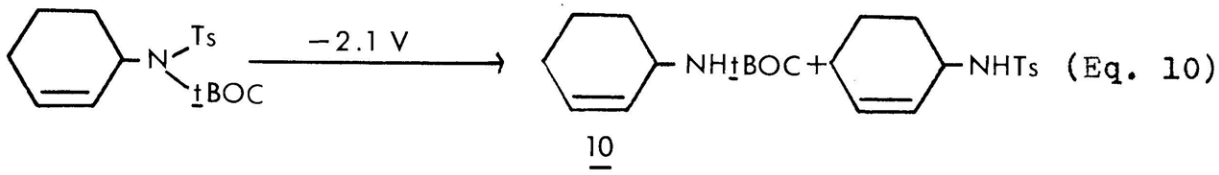
R-	$E_{1/2}$(0.2M TEAB[a] in MeCN)[b]
-H	-2.31 V
$-CH_3$	-2.30 V
$-CH_2\phi$	-2.29 V
$-\overset{O}{\overset{\|}{C}}CH_3$(Ac)	-1.91 V
$-\overset{O}{\overset{\|}{C}}OC(CH)_3$ (t-BOC)	-2.06 V

Footnotes for Table 6

a) TEAB = Tetraethylammonium Bromide.

b) vs. calomel reference electrodes.

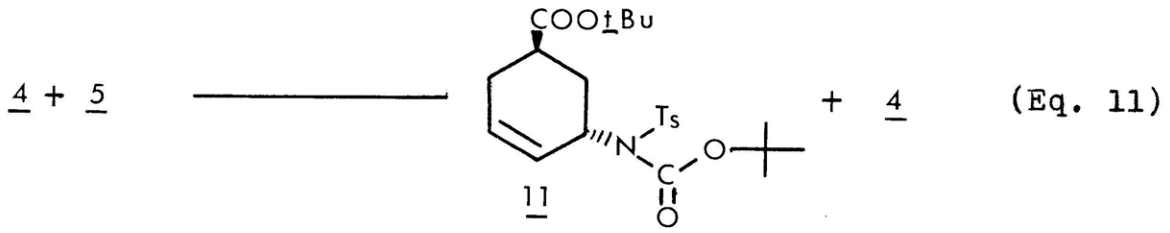
The use of an electron-withdrawing acyl group clearly reduces the reduction potential of the sulfonamide. The fact that the reduction wave is due to the Ts- group was demonstrated by a preparative scale electrolysis of the N-tosyl-tert-butoxycarbonyl derivative at -2.1 V (0.2M TEAB in MeCN) (Eq. 10).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



10 (Eq. 10)

necessary to remove it before the unsaturation was introduced.

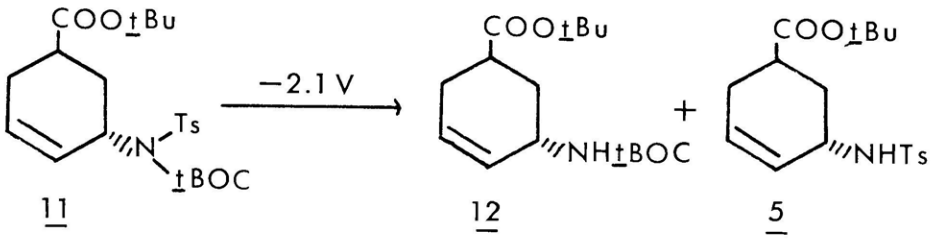
In an attempt to prepare the tert-BOC derivative of 5, the 20% 4/80% 5 mixture was subjected to 1.2 equivalents of NaH in DMF, followed by 1.5 equivalents of tert-butoxycarbonylazide (Eq. 11).[89]



11 (Eq. 11)

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). 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 materal).

The N-tosyl carbamate 11, a yellow oil, had a $E_{1/2}$ = -2.06 V. Preparative scale controlled potential electrolysis at -2.1 V (0.2M TEAB/MeCN) gave, in analogy to the model compound, two products: the desired allylic carbamate 12 and the starting allylic sulfonamide 5. (Eq. 12). The isolated yields depended on concentration and time of reaction, ranging from 76% 12 and 12%



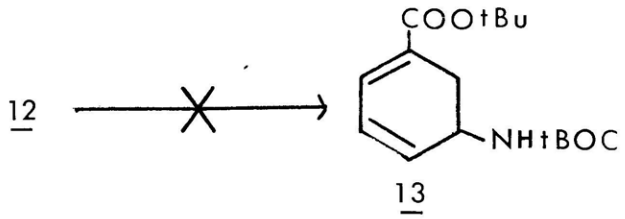
11 12 5 (Eq. 12)

5 (2.4g 11 in 100 ml electrolyte, 3 hours) to 64% 12 and 28% 5 (15.0g 11 in 300 ml electrolyte, 15 hours). 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 equivalents) to act as a proton source[82] 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 8g 11 in 100 ml electrolyte, 6 hours) to 92% (0.6g 11 100 ml electrolyte, 1.5 hours). The carbamate 12 was a white, crystalline solid, mp 65-68°C, which was very soluble in organic solvents and was best recrystallized from a very small amount of petroleum ether.

The advantage of using a tert-butoxycarbonyl (abbreviated as

tert-BOC) in the previous reactions lies in its facile hydrolysis under very mild acidic conditions,[69] which allows it to be removed at the same time as the tert-butyl ester. Because of their acid sensitivity, tert-BOC protecting groups have found much use in amino acid chemistry.[90]

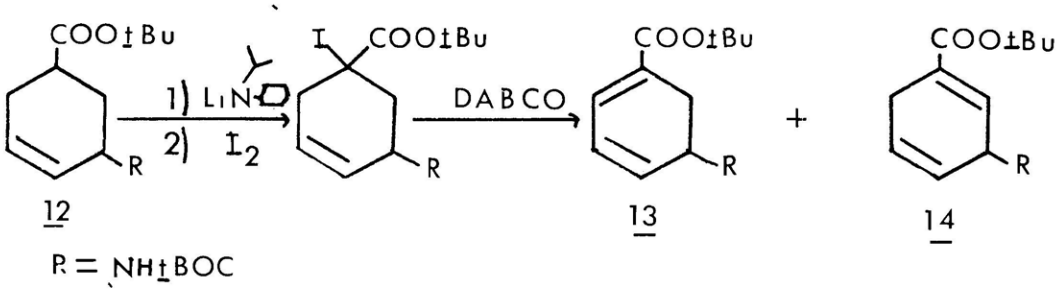
When 12 was subjected to the same reaction sequence using the phenylselenoxide elimination to dehydrogenate 5 to 8 (as previously shown in Eq. 8), none of the corresponding diene 13 was found (Eq. 13). The problem did not lie in the formation of the dianion (formed at -60° to -65°C) nor in the quenching with



12 13 (Eq. 13)

diphenyldiselenide since the crude selenylated product did not contain any starting material. Oxidation 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 mixture of products.

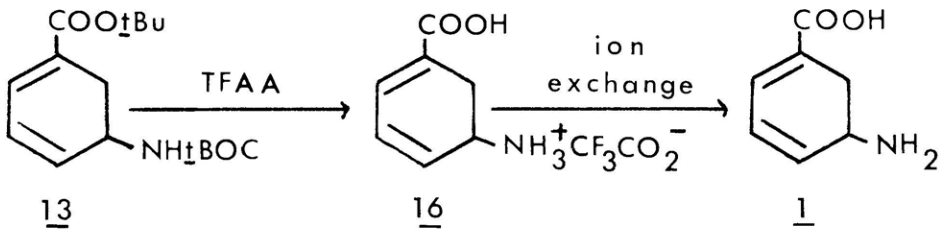
Since the phenylselenoxide route did not seem to be viable for the formation of 13, the dianion was alternatively quenched with iodine by the method of Rathke and Lindert.[91] The resulting crude α-iodo ester was then treated with base in benzene at r.t. to give 13 in 90% isolated yield (Eq. 14). The only other product isolated (9%) was the 2,5-dihydrobenzene derivative 14,



(Eq. 14)

which was unstable in the presence of air and quickly (< 10 minutes at r.t.) aromatized to the corresponding 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 1/2% 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 minutes followed by removal of the volatile material under high vacuum (Eq. 15). The residue 16 (the trifluoracetate salt of 1) was generally not isolated, but dissolved in H_2O and directly



(Eq. 15)

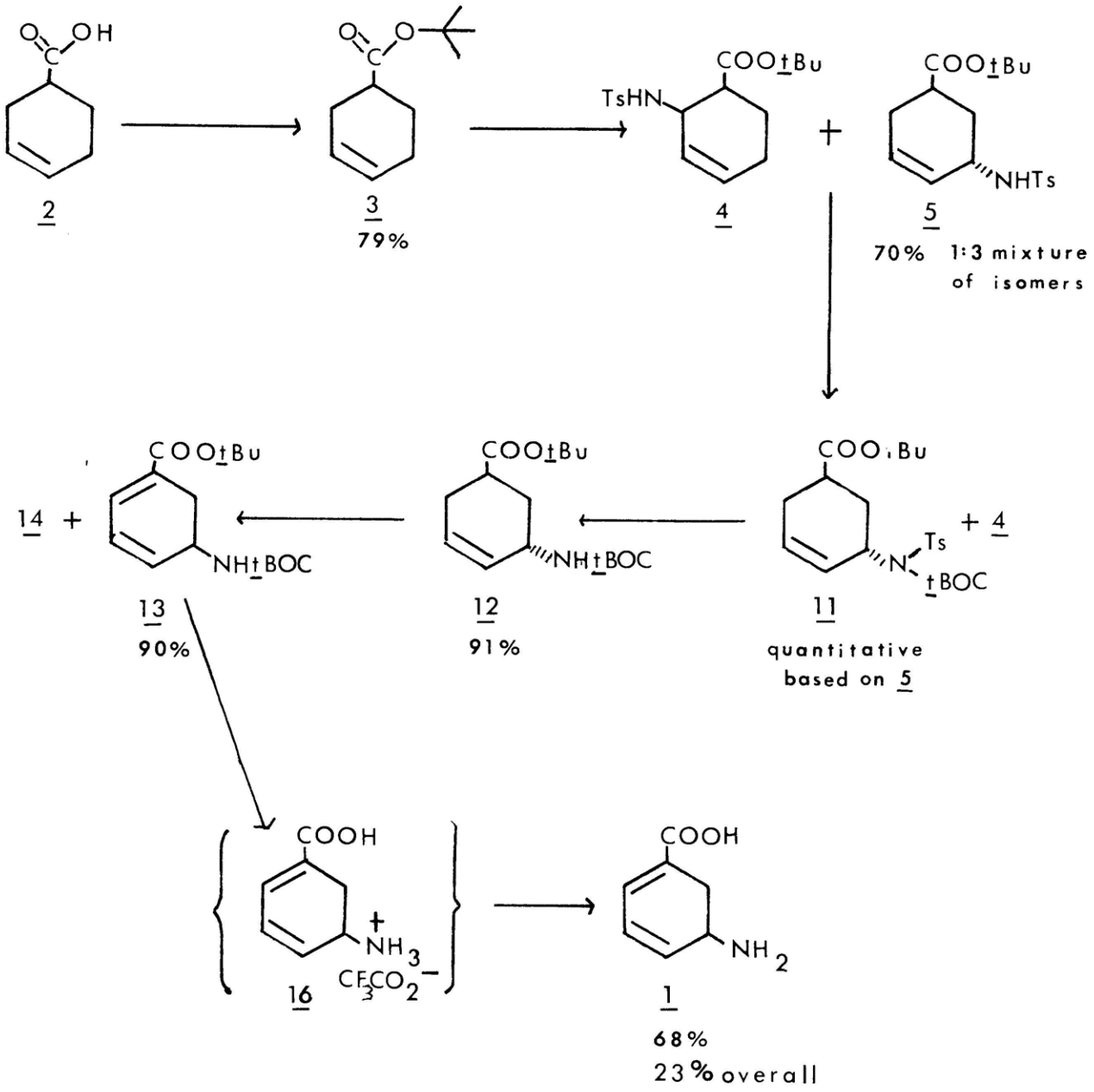
eluted through an ion-exchange resin. Use of undistilled CF_3CO_2H under the same conditions caused some aromatization to m-anthranilic acid (however, this by-product was easily removed since it was insoluble in H_2O).

Use of the cation-exchange resin SP Sephadex C-25 (Pharmacia Fine Chemicals, Inc., used by Mishima to isolate 1 from gabaculine·HCl[60]) 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. The use of a AG11A8 ion-retardation resin (Bio-Rad Laboratories)[92] gave much better results. On this particular resin, neutral species (such as 1) are not retained, salts are slowly eluted and acids are strongly bound. Lypophilization of the appropriate fractions (identified by tlc with visualization by UV and ninhydrin test) gave d,l-gabaculine (1) as an amorphous off-white powder in 68% yield. This material, mp 194-196°C (after recrystallization from aqueous MeOH, lit.[60] mp 196-197°C) gave nmr, ir and UV data consistent with the published values. The tlc behavior (7.5 parts EtOH, 2.5 parts H_2O, trace NH_4OH) was identical with an authentic sample. A small sample of 1 was treated with HCl gas in MeOH at 0°C (Eq. 16) to give d,l-gabaculine·HCl salt, mp 195-9°C (lit.[60] mp 198-200°C) which gave an undepressed mp upon admixture with an authentic sample of the racemic hydrochloride obtained from Mishima.

A summary of the exact route used to synthesize d,l-gabaculine (1) is shown in Scheme V. This synthesis is comparable to Mishima's[60] 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.[94] Although this has not been done, use of optically active material should lead to optically active gabaculine. Since only l-gabaculine is active towards γ-aminobutyrate aminotransferase,[60] this will have the effect of increasing the overall yield of the active agent.

Scheme V


COOH
2
COOtBu
3
79%
TsHN
COOtBu
4
COOtBu
NHTs
5
70% 1:3 mixture of isomers
+ 4
Ts
N
tBOC
11
quantitative based on 5
COOtBu
NHtBOC
12
91%
14 +
COOtBu
NHtBOC
13
90%
COOH
NH3
CF3CO2−
16
COOH
NH2
1
68%
23% overall

EXPERIMENTAL

General Comments

The instrumentation, materials and methods are described at the beginning of the experimental section of Part I.

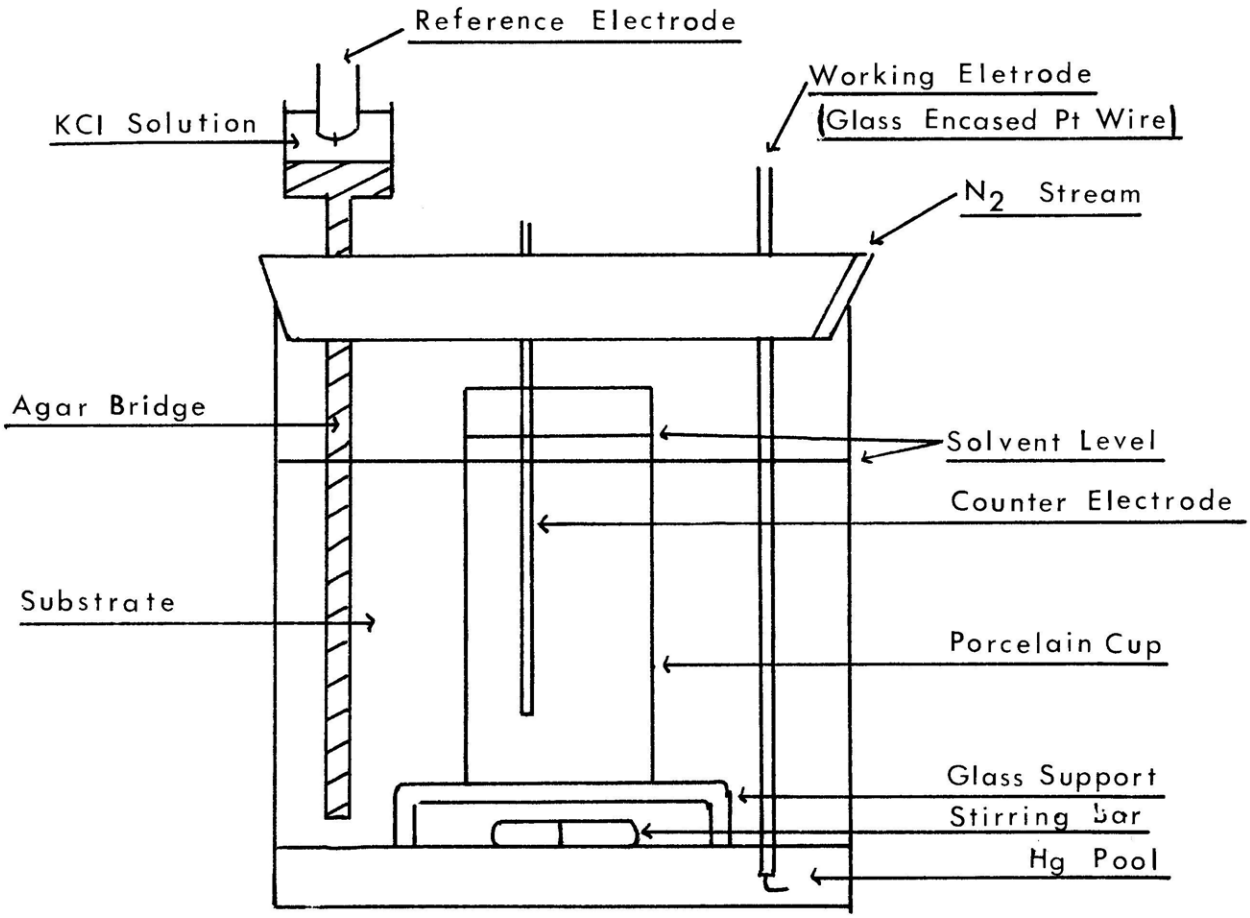
Tetraethylammonium bromide (Eastman Organic Chemicals) was recrystallized from $CHCl_3/CCl_4$ and dried at 110°C under vacuum for 12 hours. Spectro grade acetonitrile (stored over 4 Å sieves) was used for the electrochemical experiments (approximately the same results were found using acetronitrile which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

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

Polarographic measurements were made using a Princeton Applied Research Model 174A Polarographic Analyzer with a Houston Instrument Ommgraphic 2000 recorder and a standard divided polargraphic cell. An automatic drop timer set at 0.5 second and a Hg column of approximately 100 cm were used. 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 minutes. 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 in the apparatus shown below. 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 counter electrode (anode). The cell was divided by means of a unglazed, porous porcelain cup (Coors #70004) which was continuously extracted with refluxing acetone and then dried at 110°C under vacuum before use. The electrolysis cell was flushed with slow stream of N_2 and, before the addition of substrate, preelectrolyzed at a potential 100 mv more negative than the desired potential.



Electrolysis Cell

tert-Butyl 3-Cyclohexene-1-carboxylate(3)

Isobutylene (The Matheson Co.) was condensed at -78°C (dry ice/isopropanol 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 pre-cooled Fischer-Porter pressure bottle containing 10.0g (79.4 mmol) 3-cyclohexene-1-carboxylic acid (Frinton Labs.) and 1 ml concentrated H_2SO_4 in 20 ml ether. The reaction vessel was sealed and allowed to warm to r.t. After 14 hours of stirring (magnetic), the pressure bottle was opened slightly (caution!) and the excess isobutylene 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, once with brine and dried. Filtration and evaporation afforded 13.94g of a yellowish oil which was distilled (bp 44-46°C at 0.6 torr) to give 11.38g (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 ($CHCl_3$) δ 5.65 (2H, broad s, olefinic), 2.4-1.8 (7H, m, ring H) and 1.45 (9H, s, tert-butyl). This reaction has been run on scales up to 35g (0.28 mole) 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 TsN=S=NTs[17]

N-Sulfinyl-p-toluenesulfonamide (196g, 0.9 mole prepared as described in the experimental section of Part I) was divided in two portions and each was dissolved in 100 ml benzene under a N_2 atomsphere in a glove bag (Instruments for Research and Industry Co.). Pyridine (0.75 ml, stored over KOH) was added. After standing overnight, the resulting yellow precipitate was filtered off using an oven-dried sintered-glass funnel and dried under high vacuum to afford bis-N-(p-toluenesulfonyl)sulfodiimide (150g, 90%), mp 40-45°C (lit.[17] mp 48-50°C). This material is very water sensitive and is best stored in a desicator under N_2 and handled under an inert atomsphere either in a glove bag or dry box.

Reaction of TsN=S=NTs with 3-Preliminary Experiment

tert-Butyl 3-cyclohexene-1-carboxylate (0.91g, 5 mmol) was added to a stirred solution of 3.45g (9.3 mmol) TsN=S=NTs in 15 ml CH_2Cl_2 in a 50 ml round-bottomed flask under anhydrous conditions. After 3 days at r.t., the dark reaction mixture was concentrated to a thick oil which was redissolved in 25 ml 60% CH_3OH containing 3.0g 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, brine and dried. Filtration and evaporation left 2.02g of yellowish oil which was purified by column chromatography (75g silica gel, packed with hexanes; eluted with 200 ml hexanes,

100 ml 5%, 10%, 15%, 20%, then 25% EtOAc/hexanes; 40 ml fractions). After concentration of the appropriate fractions, 1.1g (63%) of a slightly yellow oil (Rf (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 pellet) 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 ($CHCl_3$) δ 7.2-7.9 (4H, q, aromatic), 5.4 and 5.75 (2H, m, olefinic), 4.95 (1H, d, N-H), 4.1 (1H, m, allylic R_2CH-N), 2.45 (3H, s, aromatic $-CH_3$), 1.8-2.4 (5H, m, ring H) and 1.45 (9H, s, tert-butyl). When the olefinic proton at δ 5.4 was irradiated ($CHCl_3$ containing 0.1N 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 pellet) 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 ($CHCl_3$) δ 7.2-7.9

(4H, q, aromatic), 5.35 and 5.75 (2H, m, olefinic), 5.0 (1H, d, N-H), 3.9 (1H, m, allylic R_2CH-N), 2.45 (3H, s, aromatic $-CH_3$), 1.8-2.4 (4H, m, ring H) and 1.45 (9H, 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)[12] was prepared by stirring a mixture of 0.69g selenium metal (8.7 mmol) and 3.42g anhydrous chloramine-T (15 mmol) in 20 ml CH_2Cl_2 at r.t. for 20 hours. tert-Butyl 3-cyclohexene-1-carboxylate (0.91g, 5 mmol) was added to the resulting white slurry. After 2 days, the dark reaction mixture was quenched with 1:1 5% NaOH/brine. EtOAc/ether (1:1) was added and both phases filtered through Celite. The organic phase was separated, washed once with 1:1 4% NaOH/brine, brine and dried. Filtration and evaporation afforded about 3g of crude product which was purified by column chromatography (as previously described) to give 790 mg (after 2 hours in vacuo, 45%) of a slightly yellow oil. Nmr integration of the multiplets at δ 4.1 and δ 3.9 showed an approximate ($\pm$ 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) (27.5g, 0.151 mole)

was added to a stirred solution of 80.0g of TsN=S=NTs (0.216 mole) in 300 ml CH_2Cl_2 (dried by passage thru neutral alumina and stored over 4 Å sieves) in a 500 ml round-bottomed flask under anhydrous conditions. After 8 days at r.t., the reaction mixture was concentrated and the residue redissolved in 300 ml CH_3OH. Water (200 ml) was added followed by 70g K_2CO_3 in three portions. After 16 hours, the reddish solution was taken up in 350 ml 1:1 EtOAc/ether which was washed twice with 1:1 4% NaOH/brine, once with brine and dried. Filtration and evaporation gave a dark red-yellow oil which was passed through a short plug of silica gel (80g) with 15% EtOAc/hexanes. Concentration of the filtrate gave 49.6g of crude product. Trituration with 200 ml of cyclohexane while cooling (crystallization was usually induced by scratching or with seed crystals) afforded 33.33g (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 200g silica gel (packed with hexanes; eluted with 500 ml hexanes, 5% EtOAc/hexanes, then 2 l 10%; 100 ml fractions). Combination of appropriate fractions and evaporation afforded 5.9g of a red-yellow oil. Recrystallization from cold cyclohexane as above gave an additional 4.03g 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) 5 in

10 ml THF in a two-necked, round-bottomed flask under anhydrous conditions. After 36 hours at r.t., water was added, the reaction mixture acidified with 1 N HCl (to pH~1) and extracted with 1:1 EtOAc/hexanes. 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 (12.4 mg, 74%), Rf (10% EtOH/EtOAc) = 0.1, mp 162-165°C; ir (KBr pellet) 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 ($CHCl_3$ + d_6-DMSO) δ 11.5 (1H, broad s, exchangeable with D_2O, CO_2H), 7.2-7.9 (4H, q, aromatic), 6.9 (1H, d, N-H), 5.2-5.8 (2H, broad m, olefinic), 3.95 (1H, m, allylic R_2CH-N), 2.45 (3H, s, aromatic $-CH_3$) and 1.8-2.5 (5H, m, ring H). Equivalent results were obtained if the reaction mixture was refluxed for 1 hour instead of stirring 36 hours at r.t.

Reaction of 5 with Trifluoroacetic Acid

One gram of 5 (2.85 mmol) was dissolved in 4.0 ml of trifluoroacetic acid. After 15 minutes, the volatile material was removed by high vacuum and the residue recrystallized ($CHCl_3$/hexanes). trans-5-(p-Toluenesulfonamido)-3-cyclohexene-1-carboxylic acid (0.64g, 76%) 7, Rf (10% EtOAc/hexanes) = 0.65, was obtained, mp 174-175°C; ir (KBr pellet) 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 ($CHCl_3$ + d_6-DMSO) δ 11.0 (1H, broad s, CO_2H), 7.2-7.9 (4H, q, aromatic), 7.05 (1H, d, N-H), 5.6 and 5.35 (2H, m, olefinic), 3.95 (1H, m, allylic R_2CH-N), 2.45 (3H, s, aromatic $-CH_3$) and 1.8-2.5 (5H, 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 7 (0.25 mmol) and 200 mg (1.8 mmol) potassium tert-butoxide in 5 ml THF was refluxed for 3 hours 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) to 6.

Attempted Esterification of 6 with tert-BuOH/Acid

The carboxylic acid 6 (50 mg, 0.17 mmol) and 2 drops of concentrated H_2SO_4 were dissolved in approximately 1.5 ml of tert-BuOH in a combustion tube. After heating 2.5 hours at 130°C, the tube was cooled, opened and the solution quenched with 1:1 4% NaOH/brine. This was extracted with 1:1 EtOAc/ether which was washed once with brine and dried. Filtration and evaporation

afforded a small amount (less than 10 mg) of a yellowish oil. Tlc (25% EtOAc/hexanes) showed one main UV active product, Rf = 0.33 (authentic 5 had Rf = 0.24). Nmr ($CHCl_3$) of this crude product showed the presence of a tosyl group (δ 7.2-7.9 and δ 2.4), an olefin (δ 5.2 and 5.6), an allylic sulfonamide (multiplet, δ 3.9) and a tert-butyl ester (δ 1.45) as well as other unidentified peaks (mostly in the region of δ 0.2-1.4).

Preparation of N,N-Dicyclohexyl-3-cyclohexene-1-carboxylic Acid Amide

3-Cyclohexene-1-acid chloride (1.5g, 10.4 mmol, prepared from the acid by reaction with thionyl chloride[94]) was added slowly to a stirred solution of 5.17 ml (26 mmol) dicyclohexylamine in 20 ml benzene/20 ml DMF (exothermic reaction). After 5 hours, EtOAc was added and the organic phase washed twice with H_2O, once with 1 N HCl, bicarbonate and brine and then dried. Filtration and evaporation gave an oil which solidified upon standing. Recrystallization (petroleum ether) afford 2.55g (85%) of N,N-dicyclohexyl-3-cyclohexene-1-carboxylic acid amide, mp 92-93°C; ir (KBr pellet) 2930 (CH), 1620 (Amide), 1460, 1455, 1440, 1315, 1240, 1180, 1145, 1125, 1045, 895 and 735 cm^{-1}; nmr ($CHCl_3$) δ 5.55 (2H, broad s, olefinic), and 0.8-3.6 (29H, broad m, ring H).

Other hindered esters were prepared in a similar manner using the appropriate alcohol and Et_3N as a base, and had the expected spectral properties. The benzhyrol ester was white crystalline solid, mp 54-56°C ($EtOH/H_2O$); the 2,4,6-trimethylphenol

ester was a clear oil, kugelrohr distilled at 130-135°C (0.4 torr). Attempts to prepared the trityl, tricyclohexylmethanol and trinorbornylmethanol esters were unsuccessful because of the apparent instability of the desired products.

Allylic Amination of N,N-Dicyclohexyl-3-cyclohexene-1-carboxylic Acid Amide

In the manner previously described, 0.71g (2.46 mmol) of the amide and 4.57g (12.4 mmole) TsN=S=NTs were allowed to react in 40 ml CH_2Cl_2. After 3 days at r.t., the dark reaction mixture was concentrated and the residue redissolved in 30 ml 60% CH_3OH containing 3g K_2CO_3. After 8 hours, the reddish mixture was extracted twice with EtOAc which was washed twice with H_2O, once with brine and dried. After filtration and evaporation, the resulting oil was purified by column chromatography (75g silica gel, packed with hexanes; eluted with 500 ml: hexanes, 10%, 20%, 4 x 25% EtOAc/hexanes; 125 ml fractions). Concentration of the appropriate fractions gave 570 mg of a white solid. Nmr indicated this to consist of a mixture of $TsNH_2$ and allylic aminated product (δ 3.9 and 4.1 were in the ratio of at least 20:1). After removal of $TsNH_2$ (precipitation from $CHCl_3$/hexane) and recrystallization from hexanes, N,N-dicyclohexyl-5-(p-toluenesulfonamido)-3-cyclohexene-1-carboxylic acid amide (212 mg, 32%) was obtained, Rf (35% EtOAc/hexanes) = 0.5, mp 189-193°C; ir (KBr pellet) 3160 (NH), 2940 (CH), 1610 (amide), 1455, 1440, 1330 (SO_2), 1165 (SO_2),

1155, 1055, 945 and 815 cm^{-1}; nmr ($CHCl_3$) δ 7.2-7.9 (4H, q, aromatic), 5.9 and 5.35 (2H, m, olefinic), 5.0 (1H, d, aromatic), 3.9 (1H, m, allylic R_2CH-N), 2.45 (3H, s, aromatic $-CH_3$) and 1.2-3.8 (broad m, ring H). None of the 2-isomer was present in the recrystallized product as judged by nmr.

tert-Butyl 3-(p-Toluenesulfonamido)-2,3-dihydrobenzoate (8)

trans-tert-Butyl 5-(p-toluenesulfonamido)-3-cyclohexene-1-carboxylate 5 (1.05g, 2.99 mmol) was added to a stirred and cooled (-78°C, dry ice/isopropanol) solution of lithium cyclohexylisopropylamide (prepared at -78°C by the addition of 3.0 ml 2.4 M (7.2 mmol) n-BuLi in hexanes (Ventron) to 1.38 ml (7.6 mmol) cyclohexylisopropylamine in a 100 ml three-necked, round-bottomed flask under anhydrous conditions). After 1/2 hour, a precooled (-78°C) solution of 2.34g (7.5 mmol) diphenyldiselenide (recrystallized from hexanes and dried in vacuo) in 10 ml THF was added quickly by cannula using positive N_2 pressure. After 2.5 hours with gradual warming to r.t., 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, brine and then dried. Filtration and evaporation afforded a yellow oil, which was redissolved in 50 ml THF, cooled to 0°C (ice bath) and 3.4g 30% H_2O_2 (30 mmol) added in three portions over 1 1/2 hours. After another 1 1/2 hours at r.t., the colorless reaction mixture was taken up in 1:1 ether/EtOAc which was washed once with bicarbonate, brine and dried. Filtration and evaporation gave 1.45g of a light yellowish oil. This material, although fairly

pure by tlc, was best purified by column chromatography (60g alumina activity III, packed with hexanes; eluted with 100 ml 100% hexanes, 10%, 20% and 300 ml 25% EtOAc/hexanes; 40 ml fractions). 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, Rf (35% EtOAc/hexanes) = 0.63, mp 90-92°C; ir (KBr pellet) 3250 (NH), 2980, 1725 and 1705 (ester), 1595, 1580, 1440, 1370, 1330 (SO_2), 1160 (SO_2), 1095 and 810 cm^{-1}; nmr ($CHCl_3$) δ 7.25-7.9 (4H, q, aromatic), 6.95 (1H, d, α-hydrogen), 5.8-6.2 (2H, m, olefinic), 5.0 (1H, d, exchangeable with 0.1N NaOD/D_2O, N-H), 4.1 (1H, m, collapses to d of d in base, allylic R_2CH-N), 2.6 (2H, d of d, $-CH_2-$), 2.45 (3H, s, aromatic $-CH_3$) and 1.5 (9H, s, tert-butyl); UV (absolute MeOH) λ_{max} 239 ($\log \epsilon = 4.07$) and $\lambda_{max} = 283$ ($\epsilon = 4225$).

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 CF_3CO_2H under N_2. After 5 minutes, 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 (1H, d, α-hydrogen), 7.2-7.8 (6H, m, aromatic and olefinic), 5.15 (1H, m, allylic R_2CH-N),

5.00 (1H, d, N-H), 2.8 (2H, m, $-CH_2-$) and 2.45 (3H, s, aromatic $-CH_3$). Cleavage of the tert-butyl ester with HCl gas in CH_2Cl_2 at -10°C (1 hour), followed by concentration by high vacuum, gave the same material. Because of its gummy nature and instability, 9 was generally not isolated.

Reduction of 9 with Sodium-Napthalene

Freshly prepared 9 (from 100 mg (0.285 mmol) 8 and 1 ml CF_3CO_2H as above) was dissolved in 1 ml degassed DME (dried over Na metal). This solution was added by syringe to a dark green solution of sodium-napthalene (prepared by stirring a mixture of 59 mg (2.46 mmol) Na° and 330 mg (2.57 mmol) napthalene in 4 ml DME for 1 1/2 hours at r.t.). After 5 minutes, the mixture was quenched with H_2O (1 ml) followed by a mixture of 10 ml 3 N HCl and 10 ml ether. After stirring 1/2 hour, the aqueous phase was passed through an ion-exchange resin (Dowex AG50W-X8, 10 cm x 1 cm column) with distilled water until the pH of the elutant was the same as the added water. Elution with 2% NH_4OH and lypophilization of the fractions which gave a positive ninhydrin test afforded 9 mg (22%) of a white solid identified as 5-amino-3-cyclohexene-1-carboxylic acid, mp 241-245°C (from ether/MeOH); ir (KBr pellet) 3500-2200 (broad band, amino acid OH and NH), 1640 and 1550 (amino acid CO_2H), 1400, 1350, 1050, 910 and 615 cm^{-1}; nmr (D_2O) δ 5.75 and 6.2 (2H, m, olefinic), 4.05 (1H, m, allylic R_2CH-N), 2.6 (2H, m, allylic $-CH_2-$) and 1.5-2.1 (3H, m, ring H); no UV absorbance.

The same compound was isolated in better yield (approximately 50%) when 5 was subjected to the same reaction conditions or when 13 was deprotected with CF_3CO_2H followed by passage through an ion-exchange resin (Bio-Rad AG11A8, 43% isolated yield).

Reduction of 8 with Tetramethylammonium Amalgam[80]

tert-Butyl 3-(p-toluenesulfonylamido)-2,3-dihydrobenzoate (100 mg, 0.28 mmol) and tetramethylammonium chloride (1.0g, 9.1 mmol) were dissolved in 50 ml 80% CH_3OH/H_2O in the electrolysis apparatus described in the beginning of the experimental section. Approximately 40g of liquid Hg was used. At a potential of -3.3 V, the current was approximately 750 ma and did not decay over a period of 1 hour (it was necessary to cool the electrolysis cell with ice). The current was stopped, the solvent filtered and then partitioned between ether and 3N HCl. After 15 minutes, the aqueous phase was passed through an ion-exchange column (Dowex AG50W-X8). Approximately 10 mg of an amorphous white solid was recovered upon elution with 2% NH_4OH; the nmr of this crude material showed no olefinic protons although a tert-butyl ester (singlet at δ 1.5) was evident.

N-(tert-Butoxylcarbonyl)-N-(p-toluenesulfonyl)cyclohex-3-enamine

Sodium hydride (50% suspension in oil, 130 mg, 2.7 mmol) was added in small portions to a stirred solution of 400 mg (1.63 mmol)

of 3-(p-toluenesulfonamido)cyclohexene[12] in 10 ml DMF in a 25 ml round-bottomed flask under anhydrous conditions. After ten minutes the evolution of H_2 had ceased, so 500 mg (3.5 mmol) of tert-butoxycarbonyl azide[89] was added and the reaction heated at 55°C for 12 hours. The reaction was cautiously quenched with H_2O and extracted with ether which was washed three times with H_2O and dried. Filtration and evaporation gave a yellowish oil which was purified by column chromatography (25g silica gel, packed with 100% hexanes, eluted with 5% EtOAc/hexanes) to give 540 mg (94%) of N-(tert-butoxycarbonyl)-N-(p-toluenesulfonyl)cyclohex-3-enamine as a clear oil: ir (film) 2980, 2930, 1725 (carbamate), 1595, 1450, 1395 and 1370 (tert-butyl), 1360 (SO_2), 1250, 1160 (SO_2), 1090, 1005 and 665 cm^{-1}: nmr ($CHCl_3$) δ 7.25-7.95 (4H, q, aromatic, 5.7 (H, m, olefinic), 5.2 (1H, m, allylic R_2CH-N), 2.45 (3H, s, aromatic $-CH_3$), 2.1 (2H, m, allylic $-CH_2-$), 1.4 -1.7 (4H, m, ring H) and 1.45 (9H, s, tert-butyl). Kugelrohr distillation (170-175°C at 0.5 torr) caused extensive decomposition.

Controlled Potential Electrolysis of N-(tert-Butoxycarbonyl)-N-(p-toluenesulfonyl)cyclohex-3-enamine.

In the apparatus described at the beginning of the experimental section, 500 mg (1.42 mmol) of the N-tosylcarbamate was added to 60 ml of pre-electrolyzed (at -2.2 V, residual current = 0.7 ma at -2.1 V) 0.2 M TEAB/MeCN at a set potential of -2.1 V. The current immediately rose to approximately 300 ma but the temperature of the

electrolysis solution never rose above r.t. After 1 1/2 hours, the current had decayed to 3 ma, so the current was stopped, water (40 ml) was added and the yellowish solution taken up in ether which was washed once with brine and dried. Column chromatography (30g silica gel, packed with hexanes; eluted with 300 ml hexanes, 5% and 10% EtOAc/hexanes, 50 ml fractions) of the crude product gave 80 mg (22%) of 3-(p-toluenesulfonamido)cyclohexene, Rf (25% EtOAc/hexanes) = 0.4 and 220 mg (78%) of 3-(N-tert-butoxycarbonylamino) cyclohexene (10) as a clear oil which solidified upon standing 2 weeks at 0°C, mp 55-57°C; ir (film) 3340 (NH), 2980, 2930, 1695 (carbamate, shoulder at 1740), 1500, 1390 and 1365 (tert-butyl), 1240, 1170, 1065, 1020 and 860 cm^{-1}; nmr ($CHCl_3$) δ 5.4-6.0 (2H, m, olefinic), 4.7 (1H, d, NH), 4.2 (1H, m, allylic R_2CH-N), 1.45 (9H, s, tert-butyl) and 0.8-2.1 (6H, m, ring H).

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, 25g, 71.2 mmol) was added in small portions with stirring and cooling (ice bath) to a suspension of 4.3g NaH (50% in oil, 89.6 mmol) in 250 ml DMF in a 500 ml round-bottomed flask under anhydrous conditions. After warming to r.t (1 hour), tert-butoxycarbonyl azide[89] (15.3g, 106.9 mmol) was added. After heating at 60-70°C for 13 hours, 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, once with brine and dried. Filtration and evaporation afforded 43.4g of yellowish oil.

Column chromatography (400g silica gel, packed with hexanes; eluted with 2l of hexanes, 1 l 5%; 2 l 10% EtOAc/hexanes; 250 ml fractions). After concentration of the appropriate fractions afforded 25.69g (dried 5 hours *in vacuo*, 80%, 100% based on *5*) of *11* as a thick yellowish oil, Rf (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 ($CHCl_3$) δ 7.25-7.95 (4H, q, aromatic), 5.5-6.0 (2H, m, olefinic), 5.2 (1H, m, allylic R_2CH-N), 2.45 (3H, s, aromatic $-CH_3$), 2.0-2.5 (4H, m, overlapping $-CH_2-$), 1.55 (9H, distorted t, *tert*-butyl) and 1.45 (9H, s, *tert*-butyl); ms (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 with 20% EtOAc/hexanes and concentration of the appropriate fractions gave 5.57g of crude *4* (Rf (25% EtOAc/hexanes) = 0.45). Recrystallization from $CHCl_3$/hexanes afforded a total (2 crops) of 4.37g (17.5%, 90% recovery based on *4*) of 4 which was identical to the previously isolated

material.

Controlled Potential Electrolysis of 11

In the electrolysis cell previously described, 2.43g (5.4 mmol) of 11 was added to 100 ml of pre-electrolyzed (-2.2 V, residual current = 1 ma at -2.1 V) 0.2 M TEAB/ MeCN at -2.1 V. The current initially rose to 450 ma and then decayed to 10 ma after 3 hours. Tlc (25% EtOAc/hexanes) showed no starting material remaining, so water (100 ml) was added and the dark solution extracted with ether. The organic phase was washed once with water, brine and dried. Filtration and evaporation left a yellowish oil. Column chromatography (80g silica gel, packed with hexanes; eluted 200 ml 100% hexanes, 400 ml (0% EtOAc/hexanes, 200 ml 15%, 20%; 50 ml fractions) afforded 320 mg (17%) of 5, Rf (25% EtOAc/ hexanes) = 0.45 (identical to a previously isolated sample) and 1.22g (after 2 hours in vacuo, 76%) of 12 as a clear oil, which solidified upon standing, Rf (25% EtOAc/hexanes) = 0.71. Recrystallization from a minimum amount of petroleum ether (1 ml/1g) gave fluffy white crystals, mp 65-68°C: ir (KBr pellet) 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 ($CHCl_3$) δ 5.7 (2H, m, olefinic), 4.55 (1H, m, NH), 4.25 (1H, m, allylic R_2CH-N), 145 (9H, s, tert-butyl) and 1.2-2.4 (5H, m, ring H); ms (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 15.0g (33.2 mmol) of 11 in 300 ml of 0.2 M TEAB/MeCN (using a 600 ml beaker and a 75 mm long ceramic cup for the electrolysis cell), it took 15 hours for completion. Isolation in the same manner (300g silica gel) afforded 6.29g (64%) of 12 and 3.23g (28%) of 5.

Controlled Potential Electrolysis of 11 in the Presence of Phenol

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

Using 590 mg (1.3 mmol) of 11 and 650 mg (6.8 mmol) 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.

Attempted Dehydrogenation of 12 to 13-Phenylselenoxide Elimination

In a 50 ml three-necked round-bottomed flask under anhydrous

conditions, 2.1 ml of 2.4 M (5.2 mmol) n-Buli was added by syringe to a cooled (-78°C) and stirred solution of 0.95 ml (5.2 mmol) of isopropylcyclohexylamine in 20 ml THF. After 10 minutes, a solution of 670 mg (2.37 mmol) 12 in 1.5 ml THF was added by cannula using positive N_2 pressure. The temperature was maintained at -65° to -60°C with a dry ice/isopropanol bath. After 30 minutes, a solution of 1.62g (5.2 mmol) diphenyldiselenide (recrystallized hexanes, dried *in vacuo*) in 3 ml THF was added in the same manner. After 6 hours with gradual warming to r.t., the reaction was quenched with water (20 ml) and extracted with ether. The organic phase was washed twice with ice-cold 0.5N HCl, once with brine and concentrated to a yellow oil. Tlc and glpc indicated only traces of 12 in the crude product.

This material was redissolved in 30 ml THF containing a few drops of HOAc, cooled in an ice bath and 8g 30% H_2O_2 (71 mmol) added slowly in small portions over a period of 1 hour. After stirring overnight with gradual warming to r.t., the colorless reaction mixture was extracted with ether, which was washed once with H_2O, bicarbonate brine and dried. Filtration and evaporation afforded 670 mg of a yellowish oil, consisting of at least five products by tlc (15% EtOAc/hexanes). Column chromatography (40g silica gel, packed with hexanes; eluted with 200 ml hexanes, 800 ml 5%, 200 ml 5%, 10% EtOAc/hexanes; 40 ml fractions) did not yield any compounds with the spectral properties expected for 13.

Other methods for oxidation[35b,76] gave similar complex mixtures from which no 13 could be isolated.

tert-Butyl 3-(tert-Butoxycarbonylamino)-2,3-dihydrobenzoate (13)-Dehydroiodination

A solution of cooled (-78°C) lithium isopropylcyclohexylamide was prepared according to Rathke and Lindert[78,91] using 10.75 ml (24.6 mmol) 2.4 M n-BuLi and 4.5 ml (24.7 mmol) isopropylcyclohexylamine in 40 ml THF in a 100 ml three-necked round-bottomed flask. The allylic carbamate 12 (2.0g, 6.7 mmol) was added and after 10 minutes, the cooling bath was changed to one maintained at -65° to -60°C for 1 hour. 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 6.26g (24.7 mmol) I_2 in 30 ml THF in a 250 ml round-bottomed flask under anhydrous conditions. After 2 hours, the cooling bath was replaced by an ice bath for another 1.5 hours. After an additional 1/2 hour at r.t., the reaction was quenched with water (20 ml) and extracted with ether which was washed once with cold 1N HCl, with aqueous sodium bisulfite until colorless, then once with bicarbonate, brine and finally dried.

Filtration and evaporation gave a light yellowish oil which was immediately dissolved in 80 ml benzene and 2.0g (17.8 mmol) diazabicyclo(2.2.2)octane (DABCO) was added in one portion. After stirring overnight, the reaction was taken up in ether which was washed 1 x cold 1N HCl, bicarbonate, brine and dried. Concentration afforded 2.6g of yellowish oil which was purified by column chromatography (200g silica gel, packed with hexanes; eluted with 1 l hexanes, 1.5 l 5%, 10% EtOAc/hexanes; 200 ml fractions) to

give two compounds, A and B.

A (180 mg of a white semisolid, 9%) was tentatively identified as tert-butyl 5-(tert-butoxycarbonylamino)-2,5-dihydrobenzoate 14, Rf (25% EtOAc/hexanes) = 0.64: nmr ($CHCl_3$) δ 6.8 (1H, m, α-hydrogen of α,β-unsaturated ester), 5.6-6.0 (2H, m, olefinic), 4.9 (1H, m, N-H), 4.7 (1H, m, allylic R_2CH-N), 2.9 (2H, d, allylic $-CH_2-$), 1.5 (9H, s, tert-butyl) and 1.45 (9H, s, tert-butyl).

This compound was unstable in the presence of air, decomposing completely within 10 minutes of isolation to tert-butyl N-(tert-butoxycarbonyl)-m-anthranilate (15), Rf (25% EtOAc/hexanes) = 0.76, mp 112-115°C (recrystallized from $CHCl_3$/hexanes): ir (KBr pellet) 3340 (NH), 2980, 2930, 1715-1680 (broad bond, ester and carbamate), 1510, 1390 and 1370 (tert-butyl), 1305, 1245, 1170, 1110, 870 and 855 cm^{-1}: nmr ($CHCl_3$) δ 7.1-7.9 (4H, m, aromatic), 7.0 (1H, broad s, NH), 1.55 (9H, s, tert-butyl) and 1.5 (9H, 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.

B(1.80g of a clear oil) was triturated with approximately 1 ml of petroleum ether to afford 1.78g (90%) of tert-butyl 3-(tert-butoxycarbonylamino)-2,3-dihydrobenzoate 13 as a fluffy white solid, Rf (25% EtOAc/hexanes) = 0.57, mp 99-101°C; ir (KBr pellet) 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 (1H, m, α-hydrogen, 6.1 (2H, m, olefinic), 4.9 (1H, m, allylic R_2CH-N) 2.6 (2H, d, of

d, methylene), 1.5 (9H, s, tert-butyl) and 1.45 (9H, s, tert-butyl): ms (70 ev) m/e 295 (M^+), 260, 239 (M-15, loss of tert-butoxy), 183 and 139 (base peak): UV (absolute MeOH) λ_{max} 284 nm (ϵ=6240). Glpc analysis (6' 5% OV-17 on 80/100 mesh Gas Chrom Q, 195°C) of 13 t_r = 3.36 minutes) showed it to be contaminated with less than 1/2% of 12 (t_r = 2.86 minutes).

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.

d,l-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 conditions (exothermic reaction). After 2 minutes, all of the volatile material was removed under a high vacuum leaving, after 2 hours, a dark semi-solid 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 cm x 20 cm column of Bio-Rad AG11A8 ion-retardation resin[92] and eluted with distilled H_2O. Lypophilization of the appropriate fractions (generally the first 3-10 ml of elutant, visualized by UV and ninhydrin test after spotting on a tlc plate) gave 169 mg (70%) of crude d,l-gabaculine (1), mp 180-185°C (lit.[60] mp 196-197°C). 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; second crop (32 mg), mp 194-196°C. A third crop (49 mg, mp 182-186°C) was recovered by addition of ether to the mother liquors for a total of 164 mg (68%) of l: UV (H_2O) λ_{max} 275 nm (ϵ=8500) (lit.[60] λ_{max} 275 (ϵ=8600)). Nmr[93] and ir data were consistent with the published values.[60] Tlc analysis (7.5 EtOH, 2.5 H_2O, trace NH_4OH) showed a single spot, Rf = 0.64, which co-spotted with an authentic sample derived from d,l-gabaculine·HCl.[93]

d,l-Gabaculine Hydrochloride Salt

d,l-Gabaculine (mp 194-196°C from above, 5 mg, 36 umol) 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 d,l-gabaculine·HCl, mp 195-199°C (lit.[60] 198-200°C). The melting point was not depressed when mixed with an authentic sample of racemic gabaculine hydrochoride salt.[93]

REFERENCES AND NOTES

1. a) W.G. Dauben et al, J. Org. Chem., 34, 3587 (1969).
   b) K.B. Wiberg, "Oxidation in Organic Chemistry," Academic Press, N.Y., 1965. pp 105-109.

2. a) K.B. Wiberg, ibid., pp 377-340.
   b) M. Stefanovic et al, Helv. Chem. Acta., 53, 1895 (1970).
   c) K.B. Wiberg and S.D. Nielsen, J. Org. Chem., 29, 3353 (1964).
   d) E. Zbiral, Synthesis, 285 (1975). (LTA/azide)
   e) D.H.R. et al, J. Chem. Soc. (D), 1031 (1968). (LTA/NBS)

3. a) W. Treibs and H. Bast, Ann., 561, 105 (1949).
   b) W. Treibs et al, Ann., 581, 59 (1958).
   c) W. Treibs and M. Weissenfels, Ber., 93 1374 (1960).
   d) I. Alkonyi, Ber., 95, 279 (1962).
   e) Z. Rappoport et al, J. Am. Chem. Soc., 94, 2320 (1972).

4. a) G. Sosnovsky, and S. Lawesson, Angew. Chem. Int. Ed., 3 (4), 269 (1964).
   b) D.J. Rawlinson and G. Sosnovsky, Synthesis, 1-28 (1972).

5. a) C.Djerassi, Chem, Rev., 43, 271 (1948).
   b) R. Filler, Chem. Rev., 63, 21 (1963).
   c) L. Horner and E. Winkelmann, "Newer Methods of Preparative Organic Chemistry," 3, 151 (1964).

6. E. Schwenk and E. Borgwangt, Ber., 65, 1601 (1932).

7. H.L. Riley et al, J. Chem. Soc., 1875 (1932).

8. a) T.W. Campbell et al, Chem. Rev., 50, 279 (1952).
   b) G.R. Waitkins and C.W. Clark, Chem. Rev., 36, 235 (1945).
   c) N. Rabjohn, "Organic Reactions," 5, 331 (1959).
   d) E.N. Trachtenberg, in Oxidation, Vol. 1, R. Augustine, Ed., Marcel Dekker, N.Y., 1969, pp 119-187.
   e) R.A. Jerussi, in Selective Organic Transformations, Vol. 1, B. Thyagarajan, Ed., Wiley-Interscience, N.Y. 1970, pp 301-326.

9. a) H.M.R. Hoffmann, Angew. Chem. Int. Ed., 8, 556 (1969).
   b) E. Keung and H. Alper, J. Chem. Ed., 49, 97 (1972).

10. For an overall view of SeO_2 oxidations, see the Ph.D. theses (M.I.T.) of R. Lauer (1974), H. Jensen (1974), M. Young (1975) and K. Gordon (1975).

    a) K.B. Sharpless and R. Lauer, J. Amer. Chem. Soc., 94, 7154 (1972).

10. b) K.B. Sharpless et al, Tet. Let., 22, 1979 (1973).
c) D. Arigoni et al, J. Amer. Chem. Soc., 95, 7917 (1973).
d) K.B. Sharpless and H. Jensen, J. Org. Chem., 40, 264 (1975).

11. R.B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag-Chemie, Academic Press, Germany, 1971. Chapter 7, pp 114-132.

12. K.B. Sharpless et al, J. Amer. Chem. Soc., 98, 269 (1976).

13. a) A.J. Gordon and R.A. Ford "The Chemist's Companion." J. Wiley and Sons, New York, N,Y., 1972 pp 60-62.
b) I. Pitman et al, J. Chem. Soc. (B), 1230 (1969).

14. K. Anderson et al, J. Org. Chem., 31, 2859 (1966).

15. a) S. Oae et al, Tetrahedron, 27, 4921 (1971).
b) S. Oae et al, Tetrahedron Lett., 649 (1975).
c) S. Oae et al, ibid., 1059 (1974).
d) S. Oae et al, Bull. Chem. Soc. Jap., 46, 3482 (1973).

16. S. Oae et al, Int. J. Sulfur Chem., Part A, 2, 49 (1972).

17. G. Kresze and W. Wucherpfenning, Angew. Chem. Internat. Ed., 6, 149 (1967).

18. a) K.B. Sharpless and T. Hori, J. Org. Chem., 41, 176 (1976).
b) N. Schonberger and G. Kresze, Justus Liebigs Ann. Chem., 1725 (1975).

19. H.J. Reich and J.M. Renga, J. Org. Chem., 40, 3313 (1975).

20. G. Kresze et al, Angew, Chem. Internat. Ed., 1, 89 (1962).

21. E. Kataev and V. Plemenkov, J. Org. Chem. USSR, 2, 1119 (1966), translated from Zhurnal Organicheskoi Khimii, 2, 1124 (1966).

22. P. Peterson et al, J. Amer. Chem. Soc., 97, 3517 (1975).

23. A. Wasserman, "Diels-Alder Reactions", Elsevier Publishing Co., New York, N.Y. 1965.

24. a) W. Mock and J. McCausland, Tet. Let., 391 (1968).
b) H.J. Backer and J. Strating, Rec. Trav. Chim., 53, 1113 (1934).

25. a) W. Mock, J. Amer. Chem. Soc., 88, 2857 (1966).
b) S. MacGregor and D. Lemal, ibid., 88, 2850 (1966).
c) W. Mock, J. Amer. Chem. Soc. 97, 3666 (1975).
d) W. Mock, ibid., 97, 3673 (1975).

26. a) W. Mock and R. Nugent, ibid., 97, 6521 (1975).
b) W. Mock and R. Nugent, ibid., 97, 6526 (1975).

27. The reaction is complete when the sulfonamide is completely dissolved and does not reprecipitate upon cooling. In benzene, this usually takes approximately 1 week. In pure thionyl chloride, it only takes overnight, but the reaction product is not as clean and the distilled yield is lower. Addition of 1% N,N-dichlorosulfonamide to the reaction mixture in benzene speeds up the reaction and gives a clean product and comparable yields. See the experimental section.

28. a) E.J. Corey and T. Durst, J. Amer. Chem. Soc., 88, 5656 (1966).
b) E.J. Corey and T. Durst, ibid., 90, 5548 (1965).
c) E.J. Corey and T. Durst, ibid., 90, 5553 (1968).

29. T. Hori, personal communication.

30. a) P. Bickart et al, J. Amer. Chem. Soc., 90, 4869 (1968).
b) R. Tang and K. Mislow, ibid., 92, 2100 (1970).
c) D. Evans and G. Andrews, Acct. of Chem. Res., 7, 142 (1974).

31. "Weygand/Hilgetag, Preparative Organic Chemistry," G. Hilgetag and A. Martini, Eds., John Wiley and Sons, New York, N.Y., 1972, Chapter 2 and references cited within.

32. T. Hori, personal communication. The stereochemistry and location of the deuterium was determined by comparison of deuterium nmr with the literature date (Refs. 33a,b). In addition, oxidation of the mono-deutero-β-pinene with SeO_2 gave trans-pineneol containing no deuterium by ms.

33. a) V. Garsky et al, J. Amer. Chem. Soc., 96, 4207 (1974).
b) R. Hill et al, ibid, 96, 4201 (1974).

34. a) G. Kresze and N. Schöenberger, Justus Liebigs Ann. Chem., (6), 847 (1974).
b) G. Büchi and H. Wüest, J. Org. Chem., 34, 857 (1969).

35. a) D. Emerson et al, J. Org. Chem., 32, 102 (1967).
b) K.B. Sharpless et al, Chem. Scripta, 8A, 9 (1975).
c) There is one example of an allylic selenoxide eliminating to give a diene (W. Salmond, Ger. Offen., 2,547, 199, May 13, 1976: CA 85: 46964a). In this steroidal case, the phenylselenoxide substituent was fixed in an equatorial position which favored elimination rather than rearrangement.

36. Pyrolysis of the N-methylated adduct from 3-hexene, as well as the unmethylated material, gave a mixture of all three possible isomers (cis, cis; cis, trans; trans, trans) as shown by co-injection on glpc with authentic samples. However, due to the volatility of the dienes, no conclusions could be reached over the yields or ratios of the various products.

37. P.J. Grinsdale et al, J. Org. Chem., 33, 1116 (1968).

38. T. Back et al, Chem. Comm., 539 (1975).

39. S. Oae et al, Tet, Let., 1059 (1974).

40. K.B. Sharpless and K. Gordon, J. Amer. Chem. Soc., 98, 300 (1976).

41. The exact nature of the required reducing agent in this case is unknown. However, selenoxides are easily reduced to the selenide under mild conditions; for a discussion see "Organic Selenium Compounds: Their Chemistry and Biology, "D. Klayman and W. Gunther, Eds., Wiley-Interscience, N.Y., 1973 pp 206-209.

42. Selenenic acids and some of their derivatives disproportionate readily. For a discussion, see ibid, pp 103-105.

43. a) C.S. Foote et al, J. Amer. Chem. Soc., 95, 586 (1973).
b) M. Matic and D. Sutton, J. Chem. Soc., 349 (1953).
c) E. Agnello et al, J. Amer. Chem. Soc., 78, 4756 (1956).

44. S. Saito, Tet. Let., 4961 (1968).

45. P. Schenk and R. Steudel, Angew, Chem. Int. Ed., 4, 402 (1965).

46. L. Jackman, S. Sternhell, "Applications of nmr in Organic Chemistry, 2nd Ed.," Pergamon Press, Oxford, Eng., 1969. pp 280-300.

47. Authentic cis and trans -1,2-diaminocyclohexane·HCl salts were prepared by literature methods (A.I. Smith, U.S. Patent 3-167-586 (1965) and were kindly supplied by D.S. Kemp and R.V. Punzar of M.I.T.

48. O.L. Chapman and S.J. Dominianni, J. Org. Chem., 31, 3862 (1966).

49. In general, dienes are sensitive to polymerization. For leading discussions, see R.W. Lenz, "Organic Chemistry of Synthetic High Polymers," Interscience Publishers, N.Y., 1967, Chapter: 9.12 and 14. Also "The Chemistry of Cationic Polymerizations," P. Plesch, Ed., Pergamon Press, N.Y., 1963, Chapter 8. In this case, polymerization might be caused by the presence of Se(II) compounds acting as Lewis acids.

50. H.Z. Sable et al, Tetrahedron, 26, 1509 (1970).

51. K.B. Sharpless and S.P. Singer, J. Org. Chem., 41, 2504 (1976).

53. a) J. Hancock and A. Markert, Tet. Let., 6157 (1966).

53. b) E. Levchenko et al, Z. Org. Khim., 3, 2068 (1967).
c) E. Levchenko and E. Dorokhova, ibid., 5, 1516 (1969).

54. K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Company, Inc., New York, N.Y., 1962. Chapter 5.

55. a) A. Klages, Ber., 35, 2640 (1902).
b) A. Cope and L. Estes, Jr., Amer. Chem. Soc., 72, 1128 (1950).
c) G. Zweifel et al, J. Amer. Chem. Soc., 84, 183 (1962).

56. A.Z. Shikmamedbekova and S.I. Sadykh-Zade, Azerb. Khim., No. 1, 73-7 (1962). (CA 58:4444f).

57. S.F. Birch et al, J. Org. Chem., 20, 1178-90 (1955).

58. B. Loev et al, Organic Syntheses, Collective Volume V, pp 162-165.

59. B. Frydeman and V. Deulofeu, Tetrahedron, 1063 (1962).

60. K. Kobayashi, S. Miyazawa, A. Terahara, H. Mishima, H. Kurihara, Tet. Let., 537 (1976).

61. a) C.F. Baxter, "The Nature of γ-Aminobutyric Acid," Chapter 9 in Handbook of Neurochemistry, Vol. 3, A. Lajtha, Ed., Plenum Press, N.Y., 1970, and reference cited within.
b) B. Meldrum, "Epilepsy and γ-Aminobutyric Acid-Mediated Inhibition," Chapter I in International Review of Neurobiology, Vol. 17, C. Pfeiffer and J. Smythies, Eds., Academic Press, N.Y., 1975, and references cited within.

62. The E. Barman Enzyme Handbook, Vol 1, Springer-Verlag, N.Y., 1969, p. 370.

63. a) A. Schousboe et al, J. Neurochem., 23, 1189 (1974).
b) E. Scott and W. Jacoby, J. Biol. Chem., 234, 932 (1958).

64. A.E. Braunstein, "Amino Group Transfer," Chapter 10 in The Enzymes, Vol. 9, P.D. Boyer, Ed., 1973.

65. L. Fowler and R. John, Biochem. J., 130, 569 (1972), and L. Fowler, J. Neurochem., 21, 437 (1973).

66. M.J. Jung and B. Metcalf, Biochem. Biophys. Res. Commum., 67, 301 (1975).

67. a) R.R Rando and F. Bangerter, J. Amer. Chem. Soc., 98, 6762 (1976).

67. b) R.R Rando, Acc. Chem. Res., 8, 281 (1975).
c) R.R. Rando, Science, 185, 320 (1974).

68. T. Valega et al, J. Econ. Entomol., 60 (3), 835 (1967). (CA 67:20999u)

69. J. McOmie, Ed., Protective Groups in Organic Chemistry, Plenum Press, London, Eng., 1973, Chapter 5.

70. D.A. Cornforth, J. Chem. Soc. (C), 2799 (1969).

71. O. Rosenheim and W. Starling, J. Chem. Soc., 377 (1937).

72. The 270 MHz nmr spectra was taken at the Southern New England High Field NMR facility at Yale University.

73. B. Trost and T. Verhoeven, J. Org. Chem., 41, 2315 (1976).

74. D. Pearson and C. Buehler, Chem. Rev., 27, 45 (1974).

75. This elimination is similar to the dehydrochlorination of acid chlorides to ketenes with base. In this case, only an equilibrium amount of ketene is needed; since the trapping with KOH followed by proton transfer is almost certainly irreversible.

76. H. Reich and S. Shah, J. Amer. Chem. Soc., 97, 3250 (1975).

77. B.M. Trost et al, J. Amer. Chem. Soc., 98, 4887 (1976).

78. M. Rathke and A. Lindert, J. Amer. Chem. Soc., 93, 2318 (1971).

79. V. Mairanovsky, Angew. Chem. Int. Ed. Eng., 15 (5), 281 (1976).

80. K. Okumura et al, Chem. Ind., 929 (1971).

81. L. Horner and H. Neumann, Chem. Ber., 98, 3462 (1965).

82. P. Cottrell and C. Mann, J. Amer. Chem. Soc., 93, 3579 (1971)

83. S. Ji et al, J. Amer. Chem. Soc., 89, 5311 (1967).

84. W. Closson et al, J. Amer. Chem. Soc., 92, 650 (1970).

85. E. Gold and E. Babad, J. Org. Chem., 37, 2208 (1972).

86. V. du Vigneaud and O. Behrens, J. Biol. Chem., 117, 27 (1937).

87. S. Searles and S. Nokima, Chem. Revs., 59, 1077 (1959).

88. L. Horner and R. Singer, Tet. Let., 1545 (1969).

89. Caution: tert-Butoxycarbonyl azide (Aldrich Chemical Co.) has been recently found to be extremely shock sensitive and

89. thermally unstable at temperatures above 80°C, decomposing with apparent detonation (W. Fenton, Chem. Eng. News, 54 (22) 3 (1976). and H. Koppel, ibid, 54 (39), 5(1976).). It is no longer commercially available. In these experiments, no trouble was experienced.

90. L. Carpino, Accts. Chem. Res., 6, 191 (1973).

91. M. Rathke and A. Lindert, Tet. Let., 3995 (1971).

92. Bio-Rad Laboratories Chemical Division, Technical Bulletin 1005, April, 1973.

93. We kindly thank Dr. Mishima for copies of the original nmr spectra of 1 and its HCl salt, the experimental details of his synthesis, and for the authentic sample of d,l-gabauline. HCl.

94. W. von E. Doering et al, J. Amer. Chem. Soc., 94, 3833 (1972).