Tetrahedron Vol 44, No 13, pp 4243 to 4258, 1988
Printed in Great Britain

0040-4020/88 $3.00+.00

DIRECT REGIOSPECIFIC ALLYLIC AMINATION VIA SILICON INDUCED PERICYCLIC REACTIONS. A NOVEL SYNTHESIS OF GAMMA VINYL GABA.

G. DELBRIS[1] , J. DUNOGUES[2] and A. GADRAS[3]

1 Unité de Recherches de Cardiologie INSERM Avenue du Haut-Levêque
33600 PESSAC FRANCE
2 Laboratoire de Chimie Organique et Organométallique UA n°35 CNRS
Université de BORDEAUX I 33405 TALENCE FRANCE
3 Rhône-Poulenc Agrochimie Centre de Recherches de la Dargoire
14 Rue P. Baizet 69263 LYON FRANCE

(*Received in UK* 1 *December* 1987)

Summary -- Silylation of the product of the ene reaction of N-sulphinylbenzene sulphonamide and an alkene induces a [2,3]sigmatropic rearrangement, leading to an allylamine derivative. The reaction is used in a synthesis of γ-vinyl GABA.

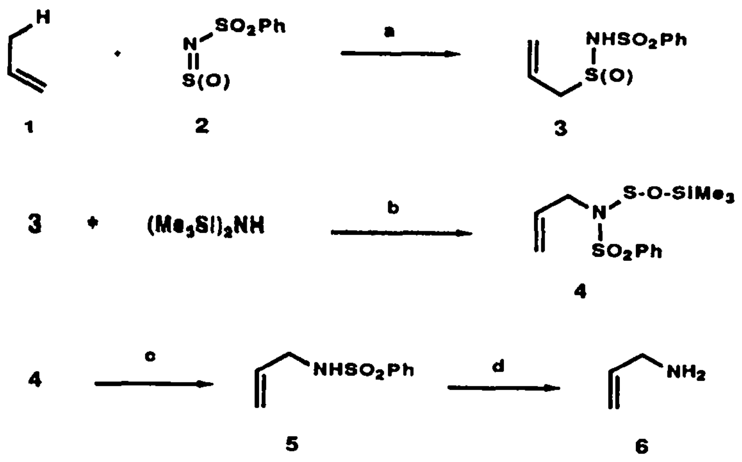
The allylic amine moiety, mainly in primary allylic amines, has been shown to be biologically important. Thus, compounds embodying this function have been found to be inhibitors of several enzymatic systems: (i) Gamma Aminobutyro Transaminase, where natural (1) and synthetic substances (2,3) affect the neurotransmittor GABA; (ii) MonoAmine Oxidase, where 2-phenyl-2-propenyl amines exhibit physiological activity (4, 5); (iii) Squalene Epoxidase, where a series of allylamines have antifungal properties (6); and (iv) Angiotensin Converting Enzyme, where terpenic amines are incorporated in active inhibitors (7). However there are few synthetic methods for the preparation of primary alylic amines that do not start from preexisting allylic functions, and they are often neither regio- nor stereoselective (8). The methods leading to the direct introduction of an amino group on an allylic carbon without ramification of the carbon chain are:

-Diels Alder reactions with N-sulphinyl derivatives or sulpho- or selenodiimides and subsequent Grignard reaction of the N-S bond (9), and amination methods which require reactions of sulpho- or selenodiimides with an olefin(10,11,12)

As a part of our ongoing interest in regioselective cheap and mild synthetic methods, we have investigated the possibility of an ene reaction with N-sulphinyl sulphonamides. Two examples of these reactions had been described previous to our first results, by Kataev and Plemenkov(13) and by Kresze et al.(14). We had previously shown that N-sulphinyl benzenesulphonamide behaves as one of the most potent enophiles ever described (15) and that this ene reaction may be the key step towards numerous synthetic goals; in the terpene series we proposed synthetic ways to allylic ketones(16) and nitriles(17) via allylsilanes, optically active terpenyl thiols(18),and alkylated terpene derivatives(19).

We now describe with this work a new, easy to run method for direct olefin allylic amination. We actually performed our reaction in the terpene series and we then applied this scheme to a new synthesis of gamma vinyl GABA. The reaction scheme is described in Chart I.

When 1 and 2 were mixed in an organic solvent such as Et$_2$O, complete dissolution of 2 occured readily accompanied by a bright yellow coloration of the medium; after a variable duration (mentioned in Table 1 but most often 2-3 hrs.) an abundant white precipitate of ene adduct 3 appeared, which was separated by filtration in a good state of purity without further crystallisation. A stoichiometric mixture of 3 and hexamethyldisilazane (HMDZ) was heated at 80° for 12 to 24 hours in 1,2-dichlorethane. The resulting brown solution containing 4 was then treated with aqueous sodium hydroxide (0.2 N,0°C,24h); the usual work up then afforded the allylic



a: Et$_2$O, 5min-48 h, 0°C

b: $(ClCH_2)_2$, 80°C, 4 h

c: NaOH, 0.2N, 0°, 2 h

d: Na, NH_3(liq)

CHART 1

amine protected as the sulphonamide 5. In order to obtain directly the free primary allylic amine, 4 was submitted to a more drastic alkaline hydrolysis (NaOH 2N,12h or Phase Transfer Catalyst TEBAC ,solid NaOH) which yielded mixtures of 5 and 6. As we verified that under these conditions 5 does not lead to 6 and as tertiary sulphonamides are known to be sensitive to alkaline cleavage(20) one may imagine that the hydroxide attack may occur on either sulphur-nitrogen bond (Chart 2).

If reaction takes place at sulphenamide S-N bond the secondary sulphonamide generated does not undergo a further hydrolysis yielding the primary amine. As the alkaline hydrolysis was not able to yield free primary amines we turned ourselves towards classical deprotection methods for amines(21). We found reduction by sodium in liquid ammonia to be an efficient method with regard to our substrates. Our results have been assembled in Table 1.

Direct allylic amination of olefines has been shown by Sharpless(11,12) and by Kresze(10,22) to proceed via a two step mechanism involving first an ene reaction with the Z double bond of sulphodiimides followed by a [2,3]

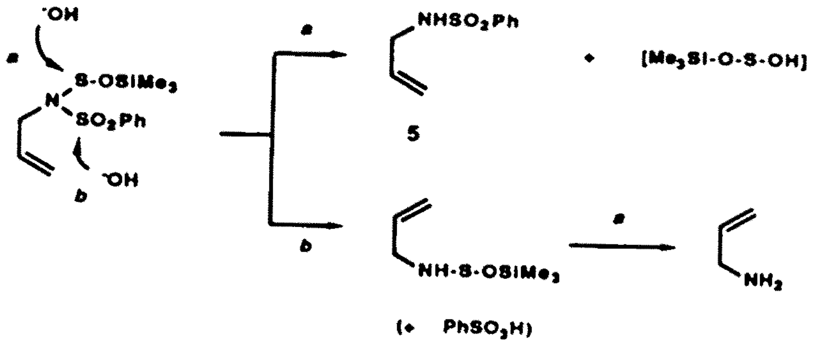


CHART 2

sigmatropic rearrangement with the second (E) S=N double bond(Chart 3).

In the absence of any Me_3Si-moiety, ene adducts of N-sulphinyl sulphonamides, as do allylic sulphinic acids, undergo retroene reaction(23) rather than Mislow Evans rearrangements. Only two examples leading to [2,3] sigmatropic rearrangements via prototropy have been described by Kresze(24,25) on sterically highly crowded or electronically disfavoured structures. A fairly consistent explanation of our results might lie in a [N→O] silatropy subsequent to the -NH substitution by a trimethylsilyl moiety. similar [N->O] silatropies had already been described with N-substituted amides(26) or sulphonamides(27). This silicon migration generates a S=N double bond which then enables [2,3] rearrangement. We could observe

some stages of this scheme, for example when performing our reaction with α-pinene, as shown in CHART 4.When treated with HMDZ at room temperature over

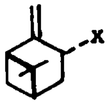
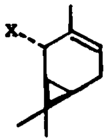
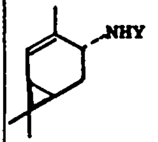
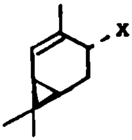
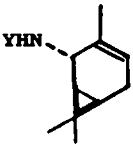
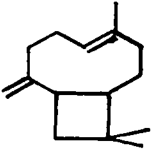
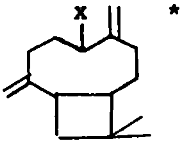
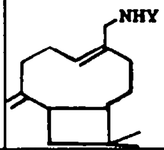
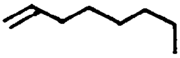
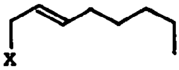
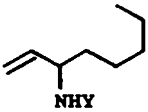
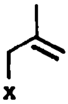
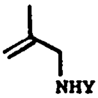
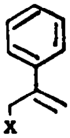
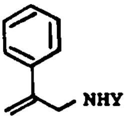
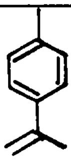
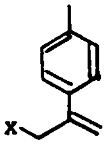
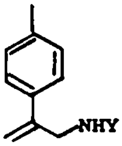
	ALKENE	ENE ADDUCT X = S(O)NHSO$_2$Ph	YIELD% time h	SULPHONAMIDE	GLOBAL YIELD
a			95 (16)	Y1=SO$_2$Ph Y2=H 	87 65
b			84 (0.5)	 Y1 Y2	76 60
c			92 (3)	 Y1 Y2	60 47
d			92 (8)	 Y1 Y2	68 48
e			50 (24)	 Y1 Y2	30 18
f			89 (2)	 Y1 Y2	80 48
g			88 (7)	 Y1 Y2	75 21**
h			80 (6)	 Y1 Y2	66 20**

Table 1

*performed with O=S=N-C$_6$H$_4$-SO$_2$-N=S=O (ref).**obtained as a 7/3 mixture of free primary amine and of sulphonamide under NaOH.TEBAC treatment.Under Na/NH$_3$ treatment. the C=C double bond is reduced(amine yield 50%).

a 3 hours period, the α-pinene adduct quantitatively led to the replacement of the N-H proton by a trimethylsilyl moiety. However ^1H chemical shift of Me_3Si (0.2ppm) does not allow us to determine the position of the tautomeric equilibrium. ^{29}Si NMR allowed us to uncover this ambiguity; only one signal was observed at δ= 34.7 ppm in good agreement with an oxygen bonded silicon atom rather than a nitrogen bonded one.

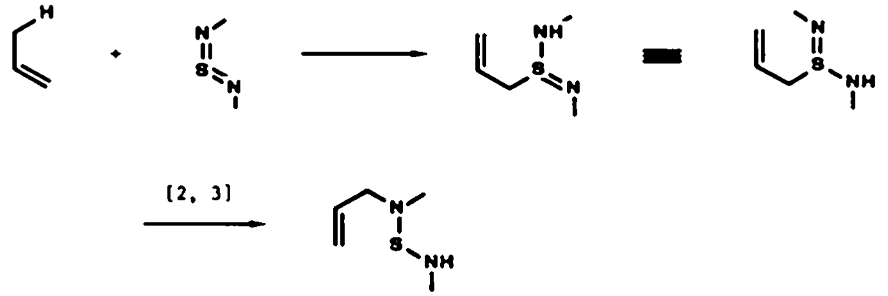


CHART 3

Thus, the chemical shift of the latter has been determined to lie between 5 and 10 ppm(26,27) while the chemical shifts of their tautomeric form have been shown to be higher than 25 ppm. After the reaction was complete the only ^{29}Si signal present was the one belonging to the transposed derivative 5 at δ= 29.3 ppm, once again in good agreement with the S-O-Si moiety. Thus it seems likely that the tautomeric equilibrium is shifted towards the form $PhSO_2$-N=S($OSiMe_3$) before transposition occurs.

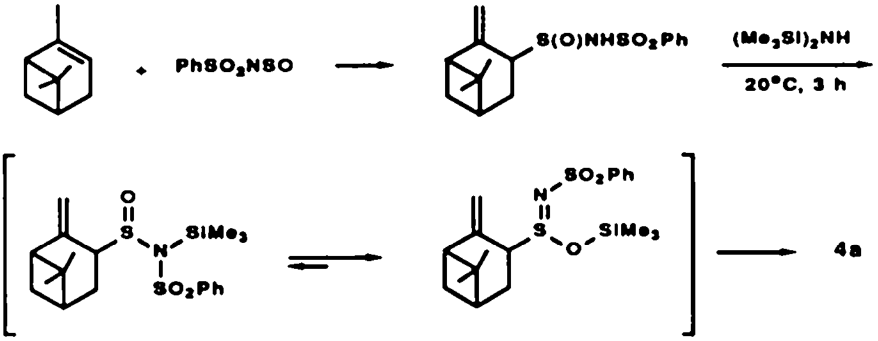


CHART 4

So we have in hand a regioselective method for the direct amination of olefins. Compared with previous methods described by Sharpless and Kresze, ours presents some advantages:

-i: the intermediate ene adduct may be isolated, and if necessary purified by recrystallization or chromatography.

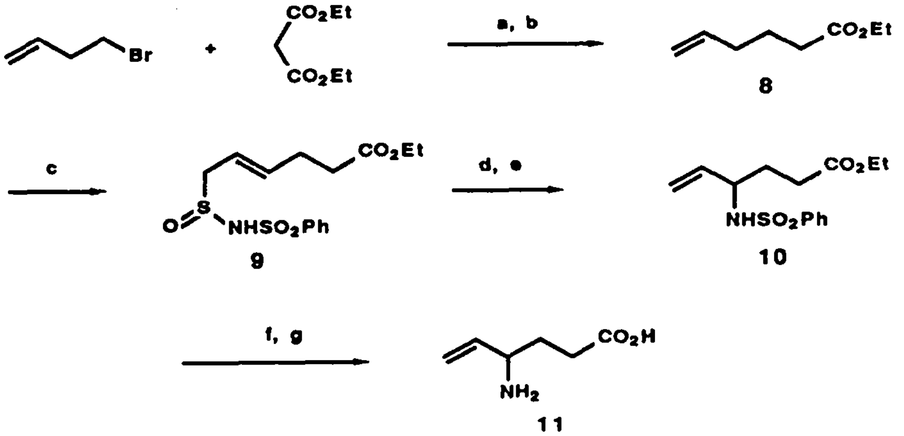
-ii:The ene reaction is always regioselective.

-iii: N-sulphinyl arene sulphonamides may be synthesized by large scale one-step procedure requiring only thionyl chloride and arene sulphonamides.

-iv: in our process, 4 is the only polar product arising from the reaction; one has not to separe equimolecular equivalents of both starting sulphonamide and allylated sulphonamide as in the sulphodiimide method.

We then chose to apply our method to a new synthesis of 4-amino 5-hexenoic acid (Gamma vinyl GABA). This compound is one of the most potent "suicide" inhibitors of GABA transaminase. GABA-T is a target enzyme involved in the metabolic degradation of the inhibitory neurotransmittor Gamma Amino Butyric Acid. Thus Gamma vinyl GABA shows important clinical properties in the treatment of several diseases such as Hundington disease or epilepsy (3,28).

During this work, when 2 was allowed to react with ethyl 5 hexenoate, synthesised by a malonic ester synthesis as shown on Chart 5, an insoluble white adduct could be isolated (75% yield) after 48 hours at room temperature. This adduct 9 was treated with one equivalent of HMDZ (80°,6h) and 10 was isolated as the only product after hydrolysis (NaOH 0.2N 20°4h). The protective groups were then removed by previously described procedures, the first ester group by alkaline saponification, then the benzenesulphonyl group by sodium/liquid ammonia reduction. 11 was purified by column chromatography (overall yield 26.5% from ethyl hexenoate).



a: EtONa, EtOH b: LiCl, DMSO c: 2, Et$_2$O, 0°C, 48 h d: HMDZ, (ClCH$_2$)$_2$, 80°C

e: NaOH 0.2N, 0°C f: NaOH, 80°C g: Na, NH$_3$ (liq)

CHART 5

AKNOWLEDGEMENTS

We kindly thank Dr. F.GOBERT Head oh the Analytical Departement of Rhône-Poulenc Centre de Recherches de Saint-Fons (Lyon) for performing most of the high field NMR spectra.

We are indebted to Société Rhône-Poulenc for generous financial support.

EXPERIMENTAL SECTION

General comments

Elemental microanalyses were performed by Service Central de Microanalyse du CNRS (Bp 22 69390 Vernaison) and gave satisfactory results when stability allowed i.e. for compounds 5 and 6.

Gaz chromatography was carried out on an Intersmat IGC 120 DFB equipped with 3m columns packed with Silicones SE30 (10%), OV225 (5%) or Carbowax 20M (15%) on Chromosorb P.

Infrared spectra were obtained on a Perkin Elmer 457 spectrometer.

Mass spectra have been performed on a Micromass 16F spectrograph equipped with a Data System 2040 data treatment unit.

^{1}H NMR spectra have been performed on the following spectometers: Perkin Elmer Hitachi R24B (60 MHz),Bruker WH360 and Bruker WH90.

^{13}C NMR spectra have been performed either on a Bruker WP60 spectrometer(15.08 MHz) using broad band decoupling and off resonance techniques or on a Bruker WP250 (62.9 MHz).In these spectra multiplicity has been determined by GASPE (Gated Spin Echo) and DEPT (Distortionless Enhancement by Polarization Transfer) techniques. Chemical shifts are reported downfield from TMS.

In general, reagent grade solvents were used without further purification. Chlorinated solvents (1,2-dichloroethane, chloroform, methylen chloride and carbon tetrachloride) were used after passage through alumina and storage over molecular sieves.

All glassware was dried at 100°c, assembled hot, and cooled under a stream of argon before use. All reactions were carried out undir stirring in argon atmosphere in a vacuum line. Organic extracts of reaction mixtures were dried over anhydrous sodium sulfate. Evaporation refers to removal of solvent under water aspirator pressure (bath temperature near 30°).

The following abbreviation will be used: Rf = TLC mobility relative to the specified solvent front (= 1).

ENE REACTION ADDUCTS SYNTHESIS.

Commercial benzene sulphonamide was dried by azeotropic distillation with benzene.

N-sulphinyl benzenesulphonamide 2.

2 has been prepared by Kresze's procedure slightly modified.

A mixture of benzene (250 mL), benzenesulphonamide (157g, 1mole), thionyl chloride (75 mL) and trimethylchlorosilane (5 mL) was heated to reflux until there is no more recrystallization on cooling (5 to 7 days). The resulting brown solution was evaporated and 2 was distilled under reduced pressure: Bp/5.10^{-3}torr = 110-120°C. CAUTION: decomposition occurs as soon as the bath temperature rises above 170°C.

The yellow stony solid which is obtained on cooling is recrystallized in toluene to yield 2 120g (60%) as pale yellow needles: mp = 73°c (Litt. 70°C).

Ene reaction: synthesis of adducts 3.

Alkene 1 (42.5 mmol.) was added at 0° to a solution of 2 (8.1g 40mmol.) in 40 mL ether. After a reaction time which is shown in table 1, hexane (80 mL) was added to complete precipitation of the white adduct 3 formed. 3 was filtered, washed twice with hexane (50 mL) and dried under vacuum. Adducts syntesized according to this procedure show a purity higher than 95% before any recrystallization.

3a Mp = 115°C

IR:3100 (NH) 1550 (C=C) 1380 and 1175(SO_2)cm^{-1}

^1H NMR($CDCl_3$)δ 0.67(s,3H,Me) 1.18 (s,3H,Me) 1.5-2.5 (very br.m, ring H) 3.3-3.8 (very broad m.,1H) 4.8-5.1 (m,2H,C=CH_2) 7.5 and 7.8 (two m., 5H, $PhSO_2$) (m, 1H, NH).

3b Obtained as a mixture of two diastereoisomers (9/1)

major diastereoisomer:

^1H NMR ($CDCl_3$) 0.50-0.67 (m,1H,C6-H) 0.87 (s,3H, Me) 0.97 (s,3H,Me) 1.39 (br d,1H,C1-H, J=5Hz) 1.87 (br s,3H,CH3) 2.07-2.47 (m,2H,C5-H_2) 3.6-3.83 (m,1H,C2-H) 5.83 (m,1H,C=C-H) 7.20-8.17 (2m,6H,Ph and NH).minor diastereoisomer:

^1H NMR ($CDCl_3$) 0.8-0.97 (m,4H,C6-H and s,3H,Me) 1.07 (s,3H,Me) 1.43 (d,1H,C1-H,J = 8Hz) 1.63 (br s,3H,Me) 2.07-2.57 (m,2H,C5-H_2) 3.47 (m,1H,C2-H) 5.33 (m,1H,C=C-H) 7.40 and 8.07 (2m,6H,Ph and NH).

3c

IR:3100 (NH) 1650 (C=CH_2) 1380 and 1175 (SO_2)cm^{-1}

^{1}H NMR($CDCl_3$):0.66-1.23 (m,8H,C1-H C6-H s,CH_3,0.8, s,CH_3,1.0) 1.6 (br s,1CH_3) 1.77-2.77 (m,2H,C5-H_2) 7.43-7.66 (m,3H,Ar) 7.80-8.07 (m,2H,Ar) 8.34 (m,1H,NH).

3d

IR:3150 (NH) 1650 (C=C) 1380 1170 and 1050 (SO_2 SO)

^{1}H NMR: 1.73 (s,3H,CH_3) 3.7 (s,2H,CH_2) 5 (s,2H,C=CH_2) 7.9 (m,4H,Ar) 9.6 (br s,1H,NH).

3e

IR:1670 (C=C) 1380 and 1175 (SO_2)cm^{-1}

^{1}H NMR:0.83 (m,3H,CH_3) 0.9-1.3 (m,6H,-(CH_2)-$_3$) 1.87(m,2H,-$\underline{CH}_2$-CH=CH_2) 3.53 (d,2H,-HC=CH-$\underline{CH}_2$-S(O)-,J2=6.5Hz) 5.83 (m,1H,C_4H_9-CH_2-$\underline{CH}$=CH-, J1=16Hz) 7.47 (m,3H,Ph) 7.80 (m,2H,Ph) 8.6 (br s,1H,NH).

3f

IR:3100 (NH) 1650 (C=C) 1380 and 1170 (SO_2)cm^{-1}

^{1}H NMR($CDCl_3$): 1.85 (s,3H,CH_3) 3.66 (s,2H) 4.96 (m,2H,C=CH_2) 7.53 (m,3H,Ph) 7.87 (m,2H,Ph) 9.4 (br s,1H,NH).

3g

IR:3100 (NH) 1660 (C=C) 1380 and 1170 (SO_2)cm^{-1}

^{1}H NMR($CDCl_3$): 4.1 (m,2H,-CH_2-) 5.17 and 5.33 (2br s,C=CH_2) 7.25 and 7.62 (2m,3H and 2H,C_6H_5) 9.2 (br s,1H,NH).

3h

IR:3100 (NH) 1660 (C=C) 1380 and 1170 (SO_2)cm^{-1}

^{1}H NMR($CDCl_3$+DMSO D_6):2.33 (s,3H,CH_3) 4.17 (m,2H,CH_2) 5.33 and 5.50 (2 br s,2H,C=CH_2) 7.1-8.2 (m,10H,C_6H_5-SO_2,-C_6H_4-,NH).

Amination reactions:synthesis of N-allylsulphonamides 5.

Ene reaction adducts 3 (30 mMol) were dissolved in 1,2-dichlorethane (25 mL). HMDZ (25 mL) was added and the medium was refluxed overnight. Dichlorethane and excess HMDZ were then evaporated to yield transposition compound 4 which often looks like a slightly brown waxy oil. This , dissolved in diethyl ether (20 mL), was hydrolysed overnight by a sodium hydroxide solution (0.2N,30mL). After neutralization and workup 5 was isolated, purified by column chromatography (CH_2Cl_2 0.5<Rf<0.7). 5 is then recrystallized in CCl_4 if necessary. 5g was recrystallized in hexane.

5a Mp(CCl_4/C_6H_6)= 93°C

IR:3280 (NH) 3040,3000(CH Ar) 1320,1160 (SO_2) cm^{-1}

^1H NMR ($CDCl_3$) δ 0.77(s,3H,Me) 0.93(d,1H,J7a-7e= -9Hz,C7-Ha) 1.16(s,3H,Me) 1.94(m,1H,C1-H) 1.97(m,1H,C5-H) 2.06(m,1H,C4-He) 2.14(m,1H,C4-Ha) 2.25(m,1H,C7-He) 3.36 and3.42(2m,2H,Jgem = -14 Hz, JNH = 6.5Hz,C10-H_2) 4.38(d,1H,J = 6.5Hz,NH) 5.28(m,1H,C3-H) 7.45(m,2H, meta HAr) 7.42(m,1H,para HAr) 7.80(m,2H,ortho HAr).

^{13}C NMR ($CDCl_3$) δ C1:43.9 C2:143.0 C3:120.2 C4:31.1 C5:40.6 C6:37.9 C8:26 C9:20.9 C10:48.1 Ar quat.C:140.1 Ar orthoC:127.0 Ar metaC:129.0 Ar paraC:132.5

MS:m/e (M^+)291(1.3) 170(44.6) 150(19.3) 141(43.3) 121(10.3) 119(53.1) 91(100) 77(77.7).

5b Mp (C_6H_6/(CCl_4)= 98°C.

IR: 3270 (NH), 1325 and 1160 (SO_2) cm^{-1}

^1H NMR ($CDCl_3$): 0.70 (m, 1H, C6H, J6-5a = 5.5 Hz, J6-5e = 9Hz) 0.72 (s, 3H, C9H_3) 0.88 (m,1H, C1-H) 0.97 (s,3H,C8-H_3) 1.36 (br s,3H, CH_3) 1.37 (m,1H,C5-Ha,J5a-5e = -15 Hz,J5a-4 = 5Hz) 1.88 (m, 1H,C5-He,J5e-4 = 2.5Hz) 3.30 (m,1H,C4-H,J4-NH =8.5Hz) 4.6 (d,1H,NH) 7.45 (m,2H,meta ArH) 7.50 (m,1H,para ArH) 7.85 (m,2H,ortho ArH).

^{13}C NMR ($CDCl_3$) δ: C1 23.1,C2 124.6,C3 136.1,C4 50.9,C5 26.8,C6 16.5,C7 23.0,C8 27.6,C9 14.8,C10 20.8,quat-ArC 141.5,orthoArC 126.9,metaArC 128.9,paraArC 132.3.

MS:m/e 150(5) 141(8) 134(70.4) 119(100) 117(93) 91(14.6) 77(38.1).

5c Mp(CCl_4) = 77°C

IR: 3260 (NH) 1330 and 1165 (SO_2)cm^{-1}

^1H NMR ($CDCl_3$)δ: 0.65 (s,3H,$CH_3$6) 0.76 (m,1H,C6-H) 0.83 (s,3H,CH_3) 1.4 (m,1H,C1-H) 1.60 (br s,3H,CH_3) 1.93-2.43 (m,2H,C5=H_2) 3.2 (m,1H,C2-H) 5.63 (m,1H,C4-H) 6.2 (NH) 7.5 and 7.85 (2m,3H and 2H,Ph).

MS:m/e 157(6) 134(27.5) 141(5) 119(100) 91(19) 77(24).

5d Wax

IR: 3300(NH) 3080(C=CH_2) 1630(C=C) 1325 and 1165 (SO_2)cm^{-1}

^1H NMR ($CDCl_3$)δ:0.83 (s,3H,CH_3) 0.87 (s,3H,CH_3) 1.1-1.77 and 1.9-2.67 (m,5H and m,7H, ring protons) 3.38 (d,2H,C15-H_2,J=6Hz) 4.63 and 4.73 (2m,2H,C=CH_2) 4.9 (t,1H,NH,J=6Hz) 5.3 (m,1H,C=C-H) 7.43 and 7.83 (2m,3H and 2H,Ph).

MS:m/e 359(1,M^+) 218(22.7) 189(28.2) 170(24.3) 141(38.7) 77(100).

5e Wax

IR: 3280(NH) 3060(C=CH_2) 1650(C=C) 1330 and 1165(SO_2)cm^{-1}.

^1H NMR (CCl_4)δ: 0.75 (t,3H,CH_3) 1.0-1.5 (m,8H,-$(CH_2)_4$-) 3.6

(m,1H,CH-N) 4.65-5.0 (m,2H,C=CH$_2$) 5.16-5.8 (m,1H,C=C-H) 5.93 (d,1H,NH,J=8Hz) 7.36 and 7.73 (2m,3H and 2H,Ph).

MS:m/e 267(04,M$^+$) 196(100) 141(39.5) 77(62.5).

5f Wax

IR: 3280(NH) 3060(C=CH$_2$) 1660(C=C) 1330 and 1160(SO$_2$)cm^{-1}

^{1}H NMR (CCl$_4$)δ: 1.47 (s,3H,CH$_3$) 3.28 (d,2H,CH$_2$,JCH$_2$-NH=6Hz) 4.57 and 4.67 (2 br s,C=CH$_2$) 5.73 (t,1H,NH,J=6Hz) 7.3 and 7.7 (2m,3H and 2H,Ph).

MS:m/e 211(4.8,M$^+$) 141(11.6) 77(63.6) 70(100).

5g Wax

IR: 3275(NH) 3060(C=CH$_2$) 1640(C=C) 1325 and 1165(SO$_2$)cm^{-1}

^{1}H NMR (CDCl$_3$)δ: 3.95 (d,2H,CH$_2$,JCH$_2$-NH=6Hz) 4.56 (t,1H,NH,J=6Hz) 5.12 (br s,1H,H\C=C/Ph) 5.28 (br s,1H,H\C=C\Ph) 7.42 (m,2H,meta ArH) 7.51 (m,1H,para ArH) 7.76 (m,2H,ortho ArH).

MS:m/e 273(17.9,M$^+$) 170(23.8) 141(54.6) 132(100) 130(40.7) 103(34.6) 77(92.4).

5h Mp(CCl$_4$) =120°C

IR: 3250(NH) 3080 3060 3020(C=CH$_2$ and C-H Ar)` 1630(C=C) 1325 and 1170(SO$_2$)cm^{-1}

^{1}H NMR (CDCl$_3$)δ: 2.2 (s,3H,CH$_3$) 3.87 (m,2H,CH$_2$) 4.83 (1N,NH) 5 and 5.17 (2br s,C=CH$_2$) 7.0(m,4H,-C$_6$H$_4$-) 7.37 and 7.67 (2 m,3H and 2H,Ph).

MS:m/e 287(19.8,M$^+$) 196(5.2) 170(16.6) 146(100) 144(50.7) 141(46.6) 117(66.5) 91(27.8) 77(78.8).

Free primary allylic amines synthesis.

-Sodium reduction

Sulphonamide 5 (25 mMol) was added in 250 mL of condensed ammonia. Complete dissolution occured. Then small pieces of sodium were added under stirring till persistence of the deep blue colour. At least four stoichiometric equivalents were necessary for this purpose (duration: 1h). After 15mn supplementary stirring excess sodium was neutralyzed with ammonium chloride. Medium was then left to room temperature to allow ammonia evolution (90 mn.).After hydrolysis and workup, amines were isolated by distillation.

-Phase transfer hydrolysis.

To a solution of 4 (30 mMol) in 1,2-dichlorethane were added, under vigorous stirring 4.8g (120 mMol) of pulverised sodium hydroxide along with 5% triethyl benzyl ammonium chloride (TEBAC).

After overnight reaction and adding ice water ,the medium was acidified to pH=3. Sulphonamide 5 was extracted with ether, then the aquous layer was treated with an alkaline NaOH solution to regenerate amine, which was extracted with ether.

This method was applied to some substrates and yielded the following mixtures of free amines and sulphonamides.

4	5/6 RATIO	OVERALL YIELD %
4a	72/28	68
4b	69/31	71
4d	86/14	63
4g	63/37	63
4h	65/35	60

Primary allylic amines 6.

6a Bp/27torr = 120°C.$[\alpha]_D^{22}$=+55.6 °(c=0.1 Mol/L $CHCl_3$)

^1H NMR ($CDCl_3$)δ: 0.82 (s,3H,$C8H_3$) 1.15 (d,1H,C7-Ha,J7a-7e=-9Hz) 1.28 (s,3H,$C9H_3$) 1.34 (s,2H,NH_2) 2.09 and 2.30 (2m,4H,C1-H,C5-H,$C4H_2$) 2.50 (m,1H,C7-He) 3.24 (m,2H,CH_2-N) 5.57 (m,1H,C3-H).

^{13}C NMR ($CDCl_3$)δ: C1:43.3 C2:148.6 C3:114.2 C4:30 C5:40 C6:36.8 C7:30.6 C8:25.2 C9:20.1 C10:46.1

MS *m/e*: 151(6.6,M^+) 119(23.4) 91(73.5) 30(100)

6b Bp/30torr = 135°C.$[\alpha]_D^{22}$=+212 °(c=0.1 Mol/L $CHCl_3$)

^1H NMR ($CDCl_3$)δ: 0.85 (s,3H,$C9H_3$) 0.93 (m, 2H, C1-H,C6-H) 1.09 (s,3H,$C8H_3$) 1.48 (br s,2H,NH_2) 1.73 (s,3H, CH_3) 1.62-1.87 (m,2H,$C5H_2$) 2.87 (m,1H,C4-H, J4-5a=5Hz, J4-5e=2.5Hz) 5.4 (m,1H,C2-H).

^{13}C NMR ($CDCl_3$)δ: C1:21.8 C2:119.7 C3:139.1 C4:48.0 C5:28.5 C6:16.3 C7:21.9 C9:14.2 C10:20.7.

MS *m/e*: 151(3.9,M^+) 136(33.7) 134(25.8) 119(67.8) 108(100) 93(38.8) 91(34.8) 77(21.3).

6c Bp/27torr = 110°C.$[\alpha]_D^{22}$=-69.2 °(c=0.1 Mol/L $CHCl_3$)

IR: 3360 3300(NH) 1590(C=C)cm^{-1}

^1H NMR ($CDCl_3$)δ: 0.71 (m,2H,C1-H,C6-H) 0.84 (s,3H,$C9H_3$) 1.02

(s,3H,C8H_3) 1.69 (br s,3H,CH_3) 2 (br s,2H,NH_2) 2.07 (m,1H,C5-Hβ) 2.31 (m,1H,C5-Hα) 3.04 (m,1H,C2-H) 5.27 (m,1H,C4-H)

^{13}C NMR ($CDCl_3$)δ: C1:27.9 C2:45.7 C3:133.8 C4:120.9 C5:20.6 C6:16.45 C7:14.70 C8:27.8 C9:12.6 C10:20.6

MS m/e: 151(15.3,M^+) 136(48) 119(77.3) 108(47.8) 93(100) 91(59.3) 77(36.9)

<u>6d</u> Bp/0.3torr = 75°C.$[\alpha]_D^{22}$=-12.9 °(c=0.1 Mol/L $CHCl_3$)

IR: 3380 3280(NH) 3080(C=CH_2) 1640(C=C) cm^{-1}

^{1}H NMR ($CDCl_3$)δ: 0.97 (m,6H,2 CH_3) 1.3-1.93 (m,5H,C1-H,C2H_2,C10H_2) 2-2.6 (m,7H,C3H_2,C6H_2,C7H_2,CH) 3.17 (br s,2H,NH_2) 4.67 and 4.73 (2 br s,2H,C=CH_2) 5.43 (m,1H,C5-H).

^{13}C NMR ($CDCl_3$)δ: C1:51.3 C2:25.9 C3:25.2 C4:139.3 C5:124.6 C6:26.9 C7:34.6 C8:154.8 C9:39.9 C10:39.5 C11:32.6 C12:29.45 C13:22.4 C14:110.0 C15:46.3

MS m/e: 219(6.6,M^+) 189(3.8) 30(100).

<u>6e</u> Bp/17torr = 100°C.

IR: 3330 3265(NH_2) 3080(C=CH_2) 1640(C=C) cm^{-1}

^{1}H NMR ($CDCl_3$)δ: 0.8 (m,3H,CH_3) 1.03-1.46 m,8H,-$(CH_2)_4$-) 2.47 (br s,2H,NH_2) (m,1H q-like,J_1=6Hz) 4.98 5.1 5.21 (3m,2H,C=CH_2) 5.83 (m,8 lines,1H,C=CH-, JC2H-C3H = 6Hz).

^{13}C NMR ($CDCl_3$)δ: C1:113.6 C2:142.9 C3:54.5 C4:37.2 C5:31.7 C6:25.6 C7:31.7 C8:18.9.

MS m/e: 127(0.8,M^+) 56(100).

<u>7f</u> Bp/27torr = 120°C.

IR: 3360 3300(NH) 1650 1500(C=C,Ph)cm^{-1}.

^{1}H NMR ($CDCl_3$)δ: 1.2 (m,6H,CH_3,CH,NH_2) 2.8 (m,2H,CH_2) 7.27 (s,5H,Ph).

^{13}C NMR ($CDCl_3$)δ: 18.8(CH_3) 43(CH) 49(CH_2) 125.8(para Ar C) 126.8(ortho Ar C) 128(meta Ar C) 144.6(quat Ar C).

MS m/e: 135(5.4,M^+) 105(6.1) 77(4.5) 30(100).

<u>Synthesis of Gamma Vinyl GABA (4-amino 5-hexenoic acid).</u>

Ethyl 5-hexenoate:

Small pieces of sodium (7.7g 0.34Mol) were added to absolute ethanol (170 mL) over a 2h. period (temp=50°C).After sodium complete comsumption, ethyl malonate (61g,0.38Mol) was added dropwise; the medium was then heated to 50°C for 30mn. 1-bromo 3-butene (45g,0.34Mole) was added and the solution was refluxed overnight. Ethanol was evaporated and substituted malonate was isolated by distillation after usual workup.

Bp/0.3torr = 60°C.

m=54.6g yield=75%

^{1}H NMR (CCl_4)δ: 1.1 (t,6H,CH_3-CH_2-O) 1.66 (m,4H,-$(CH_2)_2$-) 3.1 (m t-like, CH-$(CO_2Et)_2$) 4.1 (q,4H, CH_3-CH_2-O) 4.8 and 5 (2m,2H,C=CH_2) 5.4-6 (m,1H,C=CH-).

Desethoxycarbonylation reaction was performed using Krapcho's (30) method.

Result:

8: Bp/27torr = 73-75°C.

m= 30.2g yield=85%

IR:1735(C(=O)-O) 1645(C=C)cm^{-1}.

^{1}H NMR(CCl_4)δ: 1.13 (t,3H,CH_3) 1.3-2.3 (m,6H, -$(CH_2)_3$-) 4 (q,2H,-CH_2-O) 4.8 and 5 (2m,2H,C=CH_2) 5.3-6 (m,1H,C=CH-).

Synthesis of ene reaction adduct 9:

Ethyl 5-hexenoate (13.2g,93mMol) was added to 2 (19.3g, 93 mMol) in ethereal solution (70mL Et_2O). Reaction was complete after 40h. at room temperature. It yielded 9 (24g, 75%) as a waxy lightly coloured liquid.

^{1}H NMR($CDCl_3$)δ: 1.16 (dedoubled t,3H;CH_3) 2.1-2.5 (m,4H, -$(CH_2)_2$-) 3.6 (m,2H, CH_2-SO) 4.0 (dedoubled q,2H, O-CH_2) 5.1-6.1 (m,2H, tCH=CH,J=16Hz) 7.5 and 7.8 (2m,5H,Ph) 9.1 (br s,1H,NH).

Splitting of the signals at 1.16 and 4.0 ppm is presumed to occur because of the presence of the asymmetric sulphoxide group.

Synthesis of the amination derivative 10:

Adduct 9 was dissolved in dichloromethane (40mL); HMDZ (20mL) was added and the medium was refluxed over a 24h period. After evaporation of dichloromethane and the excess HMDZ, the resulting brown derivative was treated during 48h with a 0.2N sodium hydroxide solution. After neutralization 10 was extracted with ether.

10: 16.3g, yield= 78%.

^{1}H NMR(CCl_4)δ: 1.16 (dedoubled t,3H, CH_3) 1.76 (m,2H, C=C-C(N)-CH_2) 2.66 (m,2H, CH_2-CO_2) 3.65 (m,1H, CH-N) 4.1 (dedoubled q,2H, O-CH_2) 4.8 and 5 (2m,2H, C=CH_2) 5.1-5.7 (m,1H,C=CH-) 5.8 (m,1H,NH) 7.5 and 7.85 (2m,5H,Ph).

Synthesis of 4-amino 5-hexenoic acid 11:

10 was saponified by a potassium hydroxide solution (20g KOH in 25 mL water) at 100°c during 2h. After neutralization, acid was extracted with ether: 10.7g, 72% yield.

^{1}H NMR($CDCl_3$)δ: 1.8 (m,2H, C=C-C(N)-CH_2) 2.33 (m,2H,CH_2-CO_2H) 3.77 (m,1H,C=C-CH-N) 4.8 and 5 (2m,2H, C=CH_2) 5.27-5.73 (m,1H,C=CH-) 5.87 (d,J=8Hz, 1H,NH) 7.53 and 7.80 (2m,5H,Ph) 9.5 (1H,OH).

Amine deprotection is then performed as described for the preparation of 6 .

4-benzenesulphonamido 5-hexenoic acid (10.7g,39.5mMol) dissolved in 8 mL THF was added to liquid ammonia (180 mL). Small pieces of sodium (4.6g,0.2Mol) were added slowly. After workup ether extraction eliminated organic residues(0.4g).

The aquous layer was evaporated to yield a yellowish solid containing 11 along with NaCl. After acidification and water evaporation the major part of NaCl was precipitated by methanol.

Crude 11 (4.3g) was purified by column chromatography on Duolite ES 861 (eluant water).

11: 3.83g 63% yield Mp:209°C (litt:210).

^{1}H NMR(D_2O)δ:some signals are doubled because of the presence of the two enantiomers.

1.75-2.1 (m,2H, $\underline{CH_2}$-CH_2-CO_2H) 2.38 (m,triplet like, 2H, CH_2-CO_2H) 3.74 (m,1H, CH-N) 5.36 and 5.42 (2m,2H, C=CH_2) 5.66-5.84 (m,1H,C=CH-).

REFERENCES

-1- RANDO R.R.; Biochemistry 1977, 16, 4604.

KOBAYASHI K.; MIYASAWA S.; TERAHARA A.; MISHIMA H.; KURIHARA H.; Tetrahedron Lett. 1976, 537.

-2- METCALF B.W.; JUNG M.J.; Mol. Pharmacol. 1979, 16, 539.

-3- BURKHART J.P.; HOLBERT G.W.; METCALF B.W.; Tetrahedron Lett. 1984, 25, 5267.

LIPERT B.; METCALF B.W.; CASARA P.; Eur.J.Biochem. 1977, 74, 441.

-4- Mc DONALD I.A.; LACOSTE J.M.; BEY P.; WAGNER J.; ZREIKA M.; PALFREYMAN M.G.; J.Am.Chem.Soc. 1984, 106, 3354.

Mc DONALD I.A.; LACOSTE J.M.; BEY P.; PALFREYMAN M.G.; ZREIKA M.; J.Med.Chem. 1985, 28, 186.

-5- KRAUS J.L.; YAOUANC J.J.; Mol.Pharmacol. 1977, 13, 378.

-6- PETRANIY G.; RYDER N.S.; STUTZ A.; Science 1984, 224, 1239.

-7- SUH J.T.; J.Med.Chem. 1985, 28, 57.

-8- Review: CHEIKH R.B.; CHAABOUNI R.; LAURENT A.; MISON P.; NAFTI A.; Synthesis 1985, 28, 57.

-9- WEINREB S.M.; GARIGAPATI R.S.; GAINOR J.A.; Heterocycles 1984, 21, 309.

-10- BUSSAS R.; KRESZE G.; Liebigs Ann. Chem. 1980, 629.

-11- SHARPLESS K.B.; HORI T.; J. Org. Chem. 1976, 41, 176.

-12- SHARPLESS K.B.; HORI T.; TAUESDALE L.K.; DIETRICH C.O.; J.Am.Chem.Soc. 1976, 98, 269.

-13- KATAEV E.G.; PLEMENKOV V.V.; Zhur.Obshch. Khim. 1966, 2, 1119.

-14- SCHONBERGER N.; KRESZE G.; Liebigs Ann. Chem. 1975, 1725.

-15- DELERIS G.; KOWALSKI J.; DUNOGUES J.; CALAS R.; Tetrahedron Lett. 1977, 4211.

-16- PILLOT J.P.; DELERIS G.; DUNOGUES J.; CALAS R.; J. Org. Chem. 1979, 44, 3397.

-17- DELERIS G.; DUNOGUES J.; CALAS R.; J. Organometal. Chem. 1976, 116, C45.

-18- GADRAS A.; DUNOGUES J.; CALAS R.; DELERIS G.; J.Org.Chem. 1984, 49, 442.

-19- DELERIS G.; DUNOGUES J.; GADRAS A.; Tetrahedron Lett. 1984, 25, 2135.

-20- SEARLES S.Jr.; NUKINA S.; Chem. Rev. 1959, 59, 1077.

-21- du VIGNEAUD V.; BEHRENS O.K.; J. Biol. Chem. 1937, 59, 1077. BIRH A.J.; SMITH H.; Quat. Rev. 1958, 12. KOVACS J.; GATAK V.R.; J.Org.Chem. 1966, 31, 119.

-22- KRESZE G.; MUNSTERER H.; J. Org. Chem. 1983, 48, 3561.

-23- HORI T.; SHARPLESS K.B.; J. Org. Chem. 1979, 44, 3452.

-24- KRESZE G.; BUSSAS R.; Liebigs Ann. Chem. 1980, 843.

-25- BUSSAS R.; KRESZE G.; Liebigs Ann. Chem. 1982, 545.

-26- ILEY J.; BASSINDALE A.R.; PATEL J.; J. Chem. Soc. Perkin Trans.II 1984, 2, 77.

-27- BLASCHETTE A.; RINNE D.; HARSMANN H.C.; Z. Anorg. Allg. Chem. 1976, 420, 55.

-28- ROBERTS E.; Biochem. Pharmacol. 1974, 23, 2637.

BARBEAU E.; Lancet II 1973, 1499.

METCALF B.W.; JUNG M.; (Merrell), U.S.Pat. 4.039.549 (1975).

METCALF B.W.; CASARA P.; Tetrahedron Lett. 1973, 3337.

GITTOS M.W.; LETERTRE G.J.;(Merrell), Belg.Pat. 873.766, 1978.

-29- DELERIS G.; GADRAS A.; unpublished.

-30- KRAPCHO A.P.; Synthesis 1982, 805.