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Studies Directed Towards the Enantioselective Total Synthesis of *trans*-Dihydrolycorcidine

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ACKNOWLEDGEMENTS

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I would finally like to thank my family for their patience and support over the past four years.

ABSTRACT

CHAPTER 1

A brief overview on *ortho*-quinodimethane chemistry as well as the use of imine derivatives as dienophiles in Diels-Alder reactions is presented. Previous total syntheses of Narcissus alkaloids are also discussed.

CHAPTER 2

Our first *ortho*-quinodimethane approach to the title compound is described. This approach utilizes aryl anion methodology for construction of the *ortho*-quinodimethane precursor. The development of the alkylation of aryl anions with alkyl triflates with and without the use of cerium trichloride will be discused.

CHAPTER 3

Our second *ortho*-quinodimethane approach to the title compound is described. This approach utilizes the Wittig reaction for construction of the *ortho*-quinodimethane precursor.

CHAPTER 4

This chapter describes the lateral metalation approach. In this approach we attempted to use lateral metalation methodology to construct the required tricylic system. During this approach we discovered that *ortho*-metalation of a doubly activated aromatic position is favoured exclusively over lateral metalation. We also found that both the aromatic ring and the amide moiety must achieve planarity for lateral metalation to occur.

CHAPTER 5

This chapter describes the *ortho*-metalation approach to the title compound. This approach describes the use of *ortho*-metalation methodology to construct the tricyclic ring system.

CHAPTER 6

Our third *ortho*-qunodimethane approach to the title compound will be described. In this approach we construct the *ortho*-quinodimethane precursor via Wittig methodology.

CHAPTER 7

In our final *ortho*-quinodimethane approch to the title compound we synthesize 5,6-methylenedioxy 1,3-dihydrobenzo[c]thiophene 1,1-dioxide as the *ortho*-quinodimethane precursor. The dienophile is attached via sulfone anion chemistry.

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LIST of ABBREVIATIONS

Ac.....acetyl

AIBN.....azobisisobutyronitrile

Aq.....aqueous

Ar.....aryl

atm.....atmosphere(s)

Bn.....benzyl

br.....broad

Bz.....benzoyl

C.I.....chemical ionization

cm.....centimeter

d.....doublet

DA.....Diels-Alder

dd.....doublet of doublets

DEPT.....distortionless enhanced polarization transfer

DMAP.....4-*N*,*N*-dimethylamino pyridine

DME.....dimethoxyethane

DMF.....dimethylformamide

DMSO.....dimethyl sulfoxide

E.I. .....electron impact

eq.....equivalent(s)

Ether.....diethyl ether

Et.....ethyl

FAB.....fast atom bombardment

g.....gram(s)

h.....hour(s)

HMPA.....hexamethylphosphoric triamide

HOMCOR.....homonuclear correlation

HPLC.....high performance liquid chromatography

Hz.....hertz

i-Pr.....*i*-propyl

I.R.....infrared

L.....leaving group

LDA.....lithium diisopropylamide

LHMDS.....lithium hexamethyldisilazide

M^+.....parent molecular ion

m-CPBA.....*meta*-chloroperoxybenzoic acid

M.....molar

m.....multiplet

m.p. .....melting point

M.S.....mass spectrum

m/z.....mass to charge ratio

Me.....methyl

mesylate.....methanesulfonate

min.....minute(s)

mL.....milliliter

mmol.....millimole

Ms.....methanylsulfonyl

n-Bu.....*n*-butyl

n-BuLi.....*n*-butyllithium

N.R.....no reaction

NBS.....*N*-bromosuccinimide

NCS.....*N*-chlorosuccinimide

nmr.....nuclear magnetic resonance

o-QDM.....*ortho*-quinodimethane

Ox.....oxidation

p-TSA.....*p*-toluenesulfonic acid

PCC.....pyridinium chlorochromate

PDC.....pyridinium dichromate

Ph.....phenyl

PhS.....thiophenyl

PMP.....*p*-methoxyphenyl

pmr.....proton magnetic resonance

ppm.....parts per million

PPTS.....pyridinium *p*-toluenesulfonate

Py.....pyridine

q.....quartet

R.T.....room temperature

s-BuLi.....*s*-butyllithium

s.....singlet

t-BuLi.....*t*-butyllithium

t.....triplet

TBDMS.....*tert*-butyldimethylsilyl

TBS.....*tert*-butyldimethylsilyl

TEA.....triethylamine

Tf.....trifluoromethanesulfonate

TFA.....trifluoroacetic acid

THF.....tetrahydrofuran

THP.....tetrahydropyranyl

TLC.....thin layer chromatography

TMEDA.....*N,N,N',N'*-tetramethylethylenediamine

TMS.....trimethylsilyl

Tr.....triphenylmethyl

Triflate.....trifluoromethanesulfonate

Trityl.....triphenylmethyl

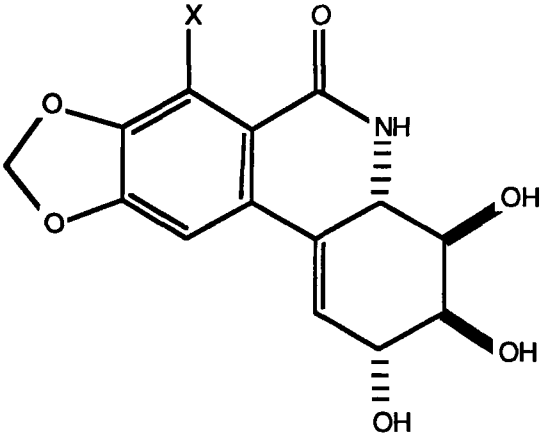
Ts.....*p*-tolylsulfonyl

°C.....degrees Celsius

CHAPTER 1

INTRODUCTION

Lycorcidine[1] **1** (margetine[2]) and narciclasine[3] **2** (lycoricidinol[1]) have been isolated from the non-basic constituents of *Amaryllidaceae* plants. These are known as narcissus alkaloids and have shown a number of interesting biological effects. These effects include potent antitumor activity against larynx carcinoma and cervix carcinoma.[4] It has also been shown that both *cis* and *trans*-dihydronarciclasines exhibit antitumor activity.[2,4]



1, X=H
2, X=OH

---

[1]) T, Okamoto, Y. Torii, and Y. Isogai, *Chem. Pharm. Bull. (Tokyo)*, **16**, 1860(1968).

[2]) a) A. Mondon, and K. Krohn, *Chem. Ber.*, **103**, 2729(1970). b) C. Fuganti, a. Selva, and F. Piozzi, *Chem. et Ind. (Milano)*, **49**, 1196(1967).

[3]) a) G. Ceriotti, *Nature*, **213**, 595(1967). b) F. Piozzi, C. Fuganti, R. Mondelli, and G. Ceriotti, *Tetrahedron*, **24**, 1119(1968). c) G. Savona, F. Piozzi, and M.L. Marino, *J. Chem. Soc. Chem. Commun.*, 1006(1970).

[4]) A. Mondon and K. Krohn, *Chem. Ber.*, **108**, 445(1975).

The compounds of this class have attracted considerable interest due to the range and potency of their biological effects. There have only been a few syntheses[5,6,7] and partial syntheses[8] reported. Of these, only the two most interesting will be discussed. Only one of these, Paulsens synthesis of (+)-lycorcidine **1** was enantioselective.[6] He achieved the desired chirality by elaborating D-glucose.

Paulsens synthesis involved removal of the primary acetonide of 3-O-benzyldiacetone-D-glucose **3** followed by oxidative cleavage of the resulting diol to give aldehyde **4.** This aldehyde was then condensed with nitromethane to give a nitroderivative, which was subsequently dehydrated to the nitroalkene **5**. The lithium derivative **6**, derived from lithium-halogen exchange of the isopropyl ester of bromopiperonylic acid, was then reacted with the nitroolefin **5** to give Michael adducts **7** and **8** in a 1:1 ratio, which were separated chromatographically.

The desired diastereomer **7** was treated with acetic acid to cleave the remaining acetonide. This induced opening of the furanoside and treatment with potassium carbonate initiated recyclization to the cyclohexane **9**, followed by formation of the γ-lactone **10**.

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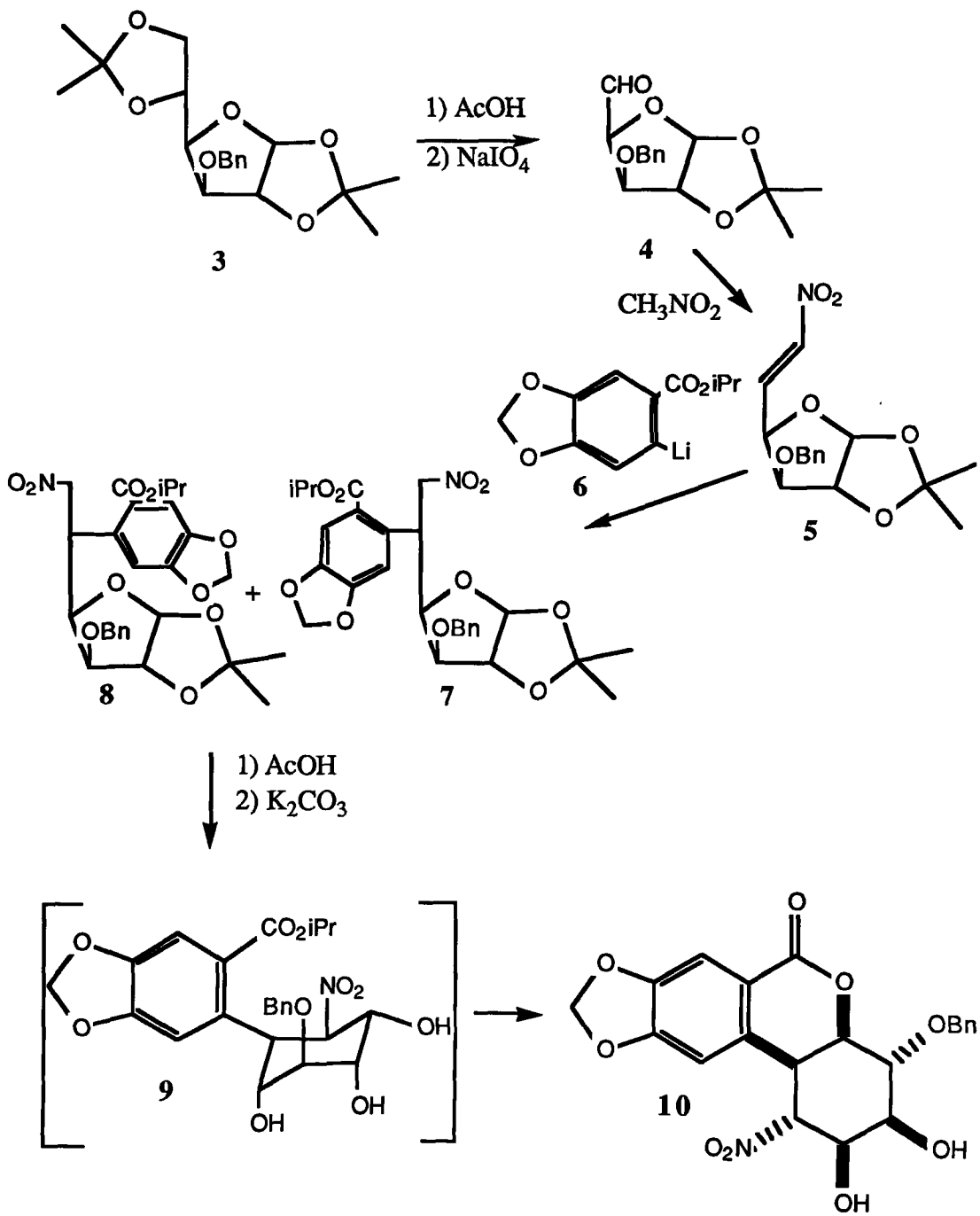
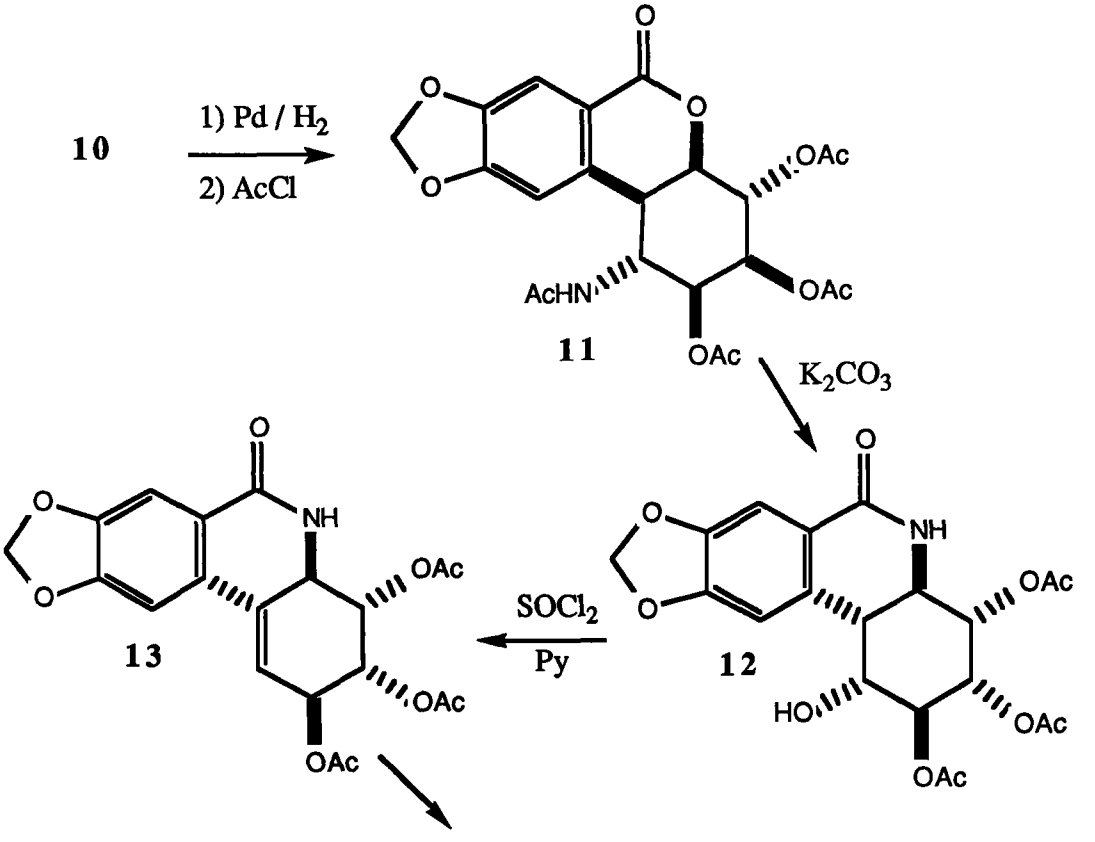
5) S. Ohta and S. Kimoto, *Tetrahedron Lett.*, 935(1982).
6) H. Paulsen and M. Stubbe, *Liebegs Ann. Chem.*, 535(1981).
7) G.E. Keck, E. Boden, and U. Sonnewald, *Tetrahedron Lett.*, 935(1981).
8) T. Weller and D. Seebach, *Tetrahedron Lett.*, 935(1982).

Reaction with hydrogen and palladium achieved both reduction of the nitro group and cleavage of the benzyl ether. The resulting hydroxy-amine was then acetylated to give **11**. The thus obtained *N*-acetate was cleaved with potassium carbonate, thereby converting the γ-lactone into a γ-lactam **12**. This lactam was then dehydrated with thionyl chloride in pyridine to give triacetate **13** which was subsequently deprotected to give (+)-lycorcidine **1**.


1) AcOH
2) NaIO4
CHO
OBn
3
4
CH3NO2
NO2
CO2iPr
Li
6
5
O2N
CO2iPr
iPrO2C
NO2
OBn
8
7
1) AcOH
2) K2CO3
CO2iPr
BnO
NO2
OH
9
10
OBn
O2N
OH



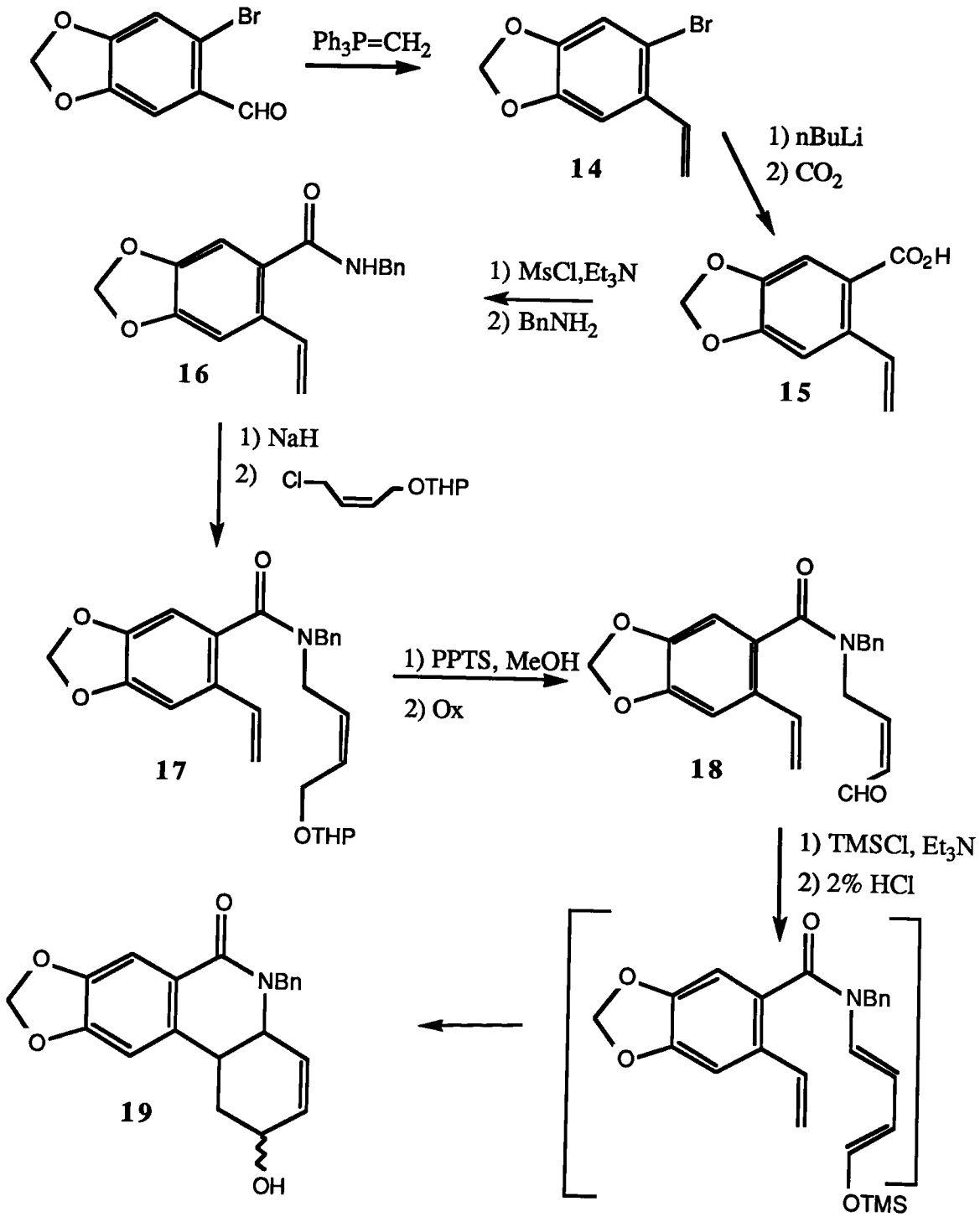
Paulsens synthesis involved a seventeen-step sequence resulting in an overall yield of less than 1.8%. His route also required a separation of a 1:1 mixture of diastereomers.

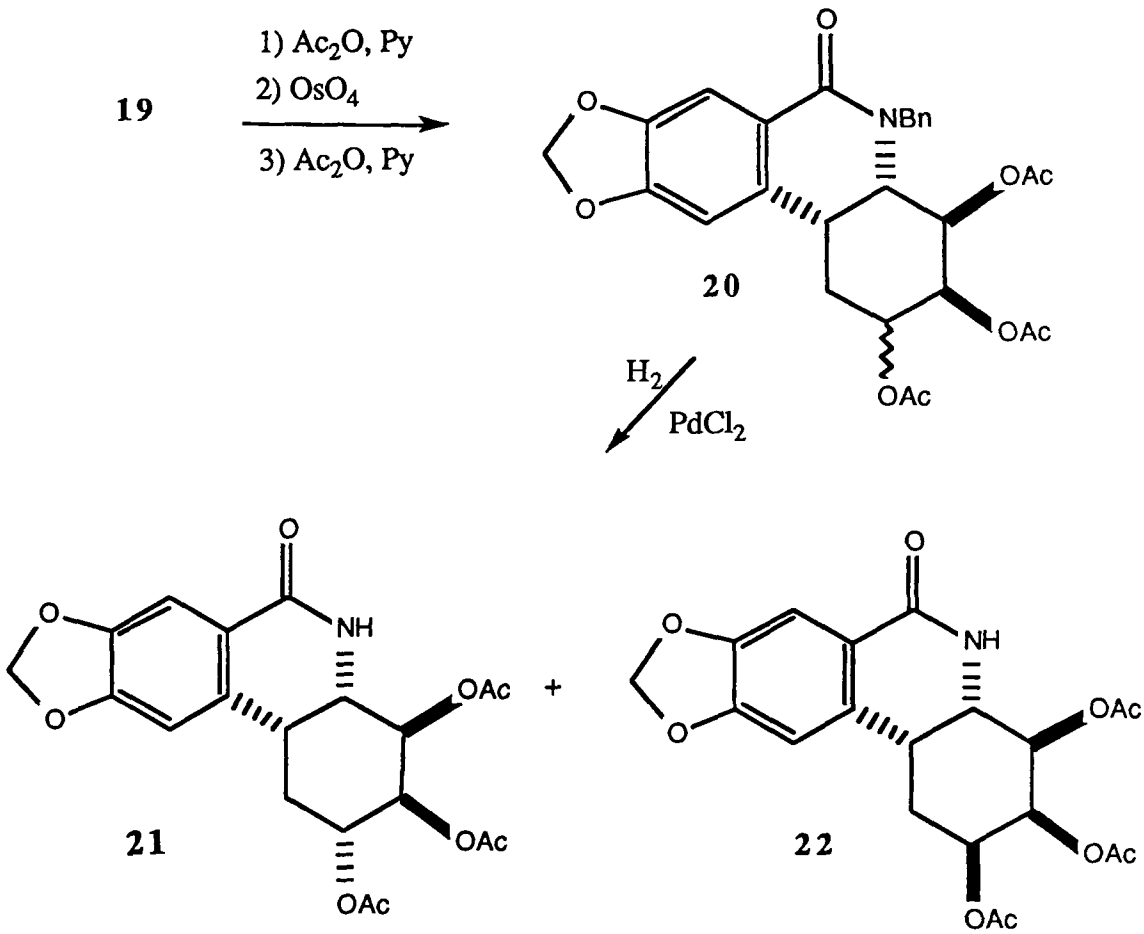
Kecks racemic synthesis of *cis*-dihydrolycorcidine involved an intramolecular Diels-Alder reaction as his key step.[7] He constructed the triene by initially converting bromopiperonal into bromostyrene **14** via Wittig methylenation. Conversion to acid **15** was

accomplished by metal-halogen exchange followed by quenching with carbon dioxide. The amide **16** was prepared from benzylamine and the mixed anhydride from acid **15** and methanesulfonyl chloride.

The sodium salt of **16** was alkylated with *cis*-1-chloro-2-butene-4-tetrahydropyranyl ether to give diene **17**. Aldehyde **18** was prepared by cleavage of the THP ether and Corey-Suggs oxidation. The triene was produced as an intermediate by reaction with TMSCl in DMF, which spontaneously underwent Diels-Alder reaction, the resulting adduct upon exposure to 2% HCl gave alcohol **19**. Acetylation of **19** followed by *cis*-hydroxylation with osmium tetraoxide and further acetylation gave triacetate **20** as an inseparable mixture of isomers. The benzyl group was removed by hydrogenolysis to give amides **21** and **22** in a 3:1 ratio which were separated chromatographically.

The Keck synthesis of racemic *cis*-lycorcidinol-triacetate involved eleven steps however the overall yield cannot be calculated from the available published data.


Br
CHO
$Ph_3P=CH_2$
Br
14
1) nBuLi
2) CO_2
CO_2H
15
1) MsCl,Et_3N
2) $BnNH_2$
NHBn
16
1) NaH
2)
Cl
OTHP
NBn
17
OTHP
1) PPTS, MeOH
2) Ox
NBn
18
CHO
1) TMSCl, Et_3N
2) 2% HCl
NBn
OTMS
NBn
19
OH

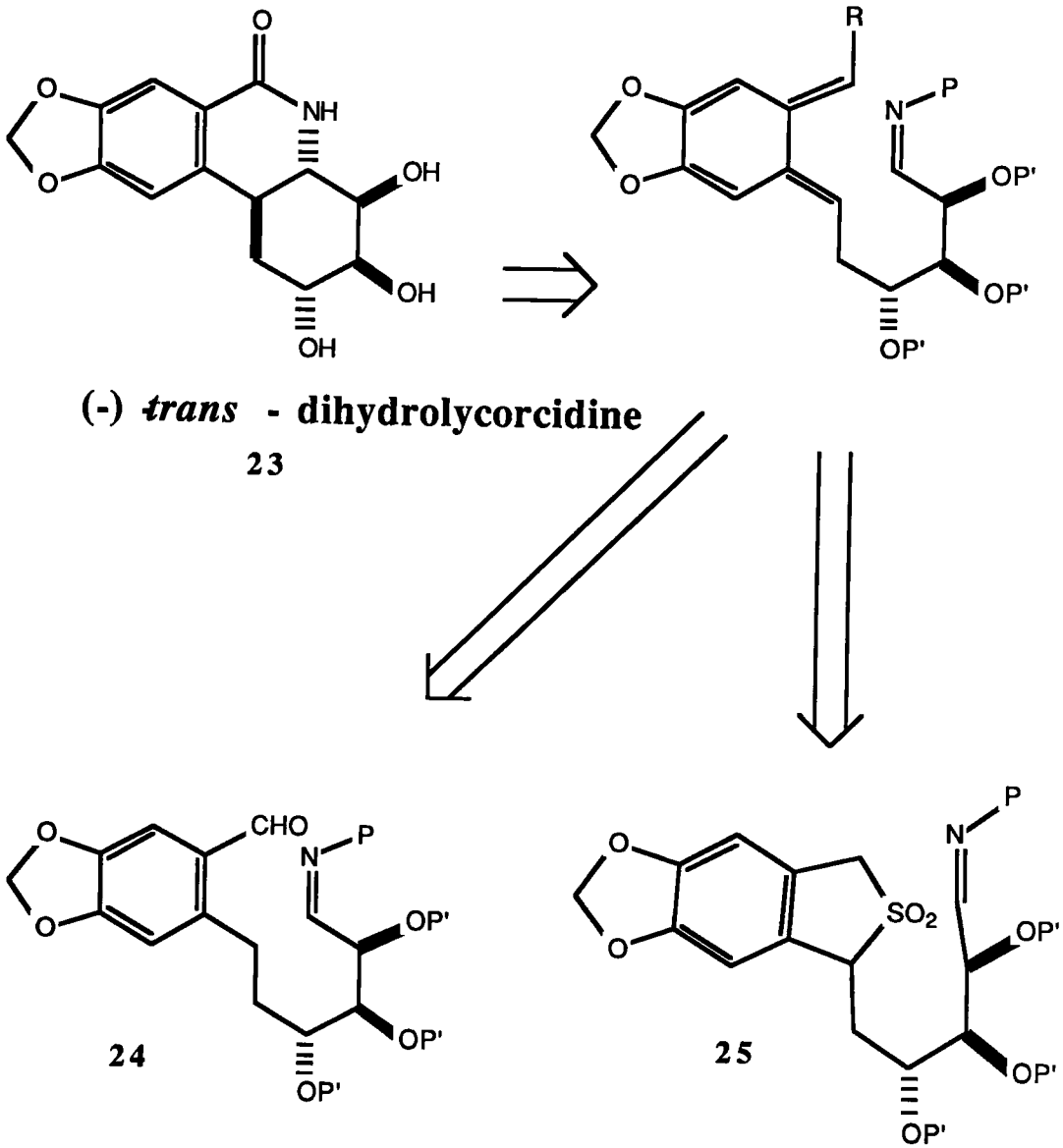


Since this class of compounds appeared to be of interest both biologically and synthetically, and since the known syntheses are lengthy and inefficient we decided that they would be worthy synthetic targets.

A key step in our proposed synthesis of (-)-*trans*-dihydrolycorcidine **23** involves generation of an *ortho*-quinodimethane as an intermediate which will be used as a diene in an intramolecular Diels-Alder reaction. It was anticipated that the *o*-quinodimethane necessary for our synthesis could be generated either photochemically via photoenolization of a piperonal derivative **24** or via chelotropic extrusion of sulfur dioxide from an appropriate sulfone **25**. The generated *ortho*-quinodimethane should be trapped intramolecularly by an imine to give a Diels-Alder adduct which upon further manipulation should yield **23** (this is outlined in Scheme 1).

Such an approach would have the following potential advantages, (**a**) the synthesis would yield the optically active natural product, because we intend to incorporate an appropriate carbohydrate derivative which should also impart some asymmetric induction on the Diels-Alder reaction, (**b**) the use of different carbohydrates would produce different natural products and derivatives, and (**c**) this approach may be efficient because of its relative shortness.

SCHEME 1



(-) *trans* - dihydrolycorcidine

23

24

25

Asymmetric induction in the intramolecular Diels-Alder reaction has been well documented.[9] The two most favoured transition states are shown below. It would appear that the most stable transition state involves the approach of the dienophile from the underneath involving only one axial alkoxy group, which would give the undesired stereoisomer. It has been shown in our laboratory that varying the solvent can effect which Diels-Alder adduct one obtains.[10] It is therefore hoped that one can favour the approach of the dienophile from the top, which leads to the desired stereoisomer by varying either the oxygen protecting groups or the solvent the Diels-Alder reaction is carried out in. The substituent on the nitrogen of the dienophile may also effect the stereochemical outcome of the reaction. All of these factors will have to be investigated.

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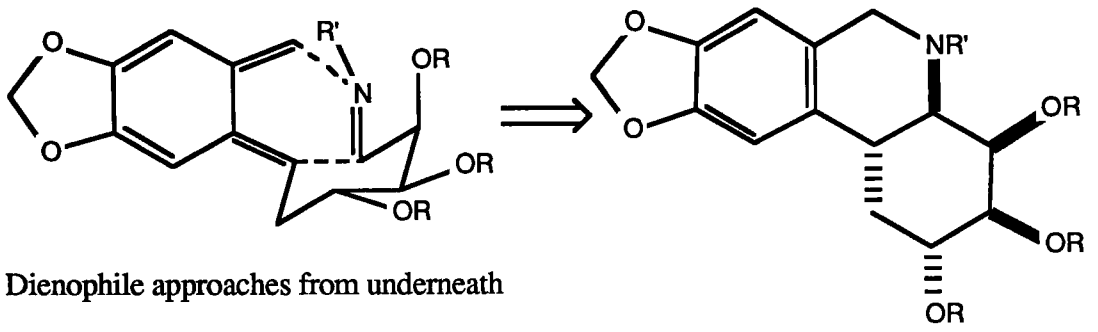
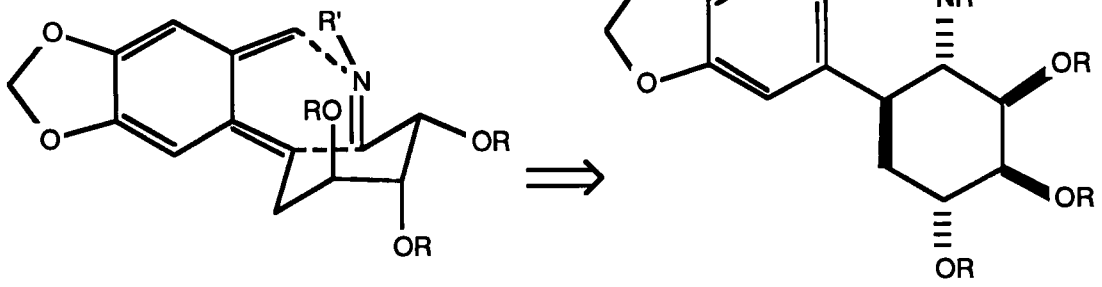
9) a) A.G. Fallis, *Can. J. Chem.*, **62**, 183(1984), b) T. Kametani, K. Suzuki and H. Nemoto, *J. Org. Chem.* **47**, 2331(1982).

10) D. MacDonald, Ph.D. Thesis, University of Ottawa, (1987).

Diels Alder Transition states



Dienophile approaches from underneath



Dienophile approaches from the top

o-Quinodimethanes have been utilized extensively as intermediates in the total synthesis of natural products. Their modes of generation and uses have been the subject of a recent review.[11a]

Kametani has reviewed the syntheses of various alkaloids, some of which utilize *o*-quinodimethanes in intermolecular Diels-Alder reactions with imines.[11b]

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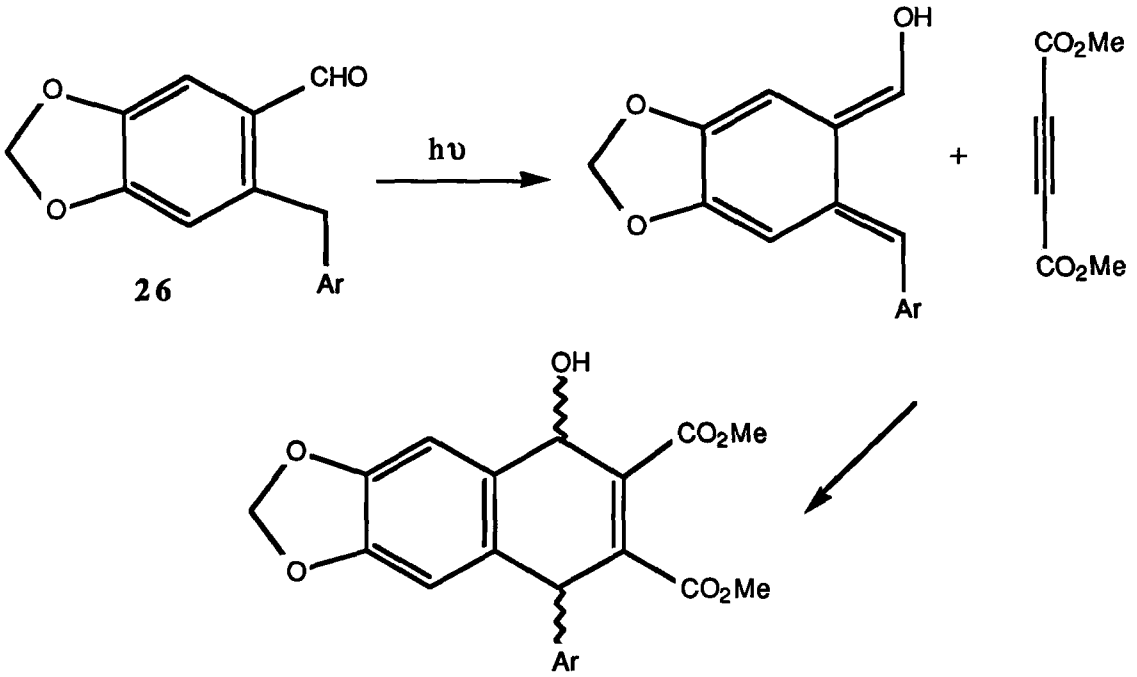
11) a) J.L. Charlton and M.M. Alauddin, *Tetrahedron*, **43**, 2873(1987), b) T. Kametani and K. Fukumoto, *Heterocycles*, **8**, 465(1977).

The proposed photoenolization is similar to earlier work done by Sammes *et al.*,[12] in which they photolyzed a piperonal derivative **26** and trapped the *o*-quinodimethane generated with dimethylacetylene dicarboxylate to afford an intermediate **27** in their synthesis of tetradehydropodophyllotoxin.



26 **27**

Glinski and Durst also produced via photolysis a similar *o*-quinodimethane, and trapped it with dimethyl fumarate to give an intermediate in their synthesis of racemic epiisopodophyllotoxin.[13]

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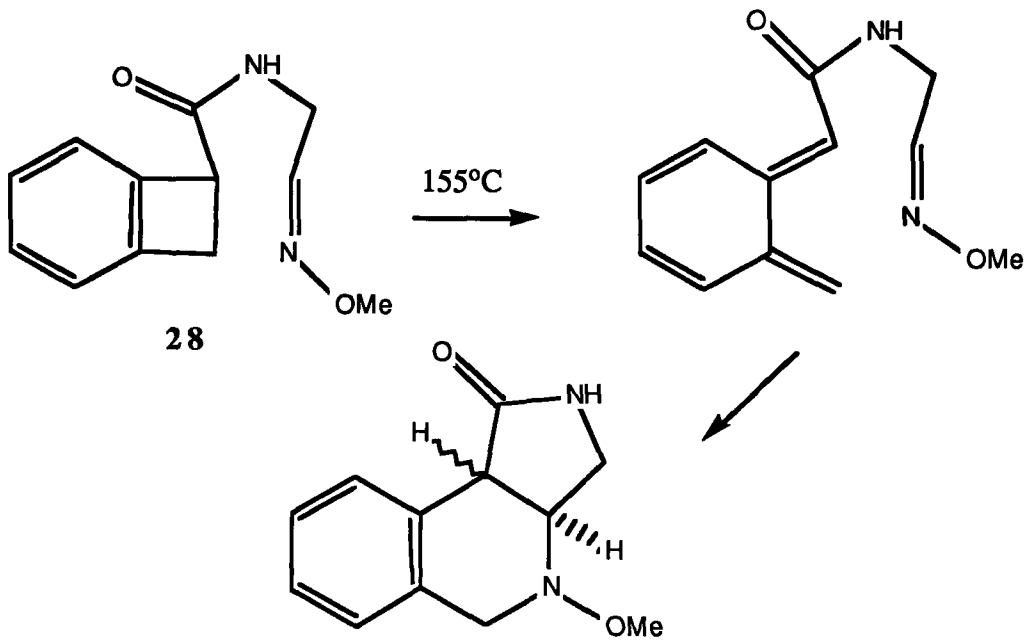
[12]) B.J. Arnold, S.M. Mellows, and P.G. Sammes, *J. Chem. Soc. Perkin Trans. I*, 1266(1973).

[13]) M.B. Glinski and T. Durst, *Can. J. Chem.*, **61**, 573(1982).

Oppolzer reported that an oxime methyl ether **28** could be trapped intramolecularly by an *o*-quinodimethane.[14] Also Weinreb has reviewed a series of intramolecular imino-Diels-Alder reactions used in the total syntheses of various alkaloids.[15] These examples should give precedence to the trapping of an *o*-quinodimethane with an imine derivative, such as is required in our proposed synthesis of **23**.



28

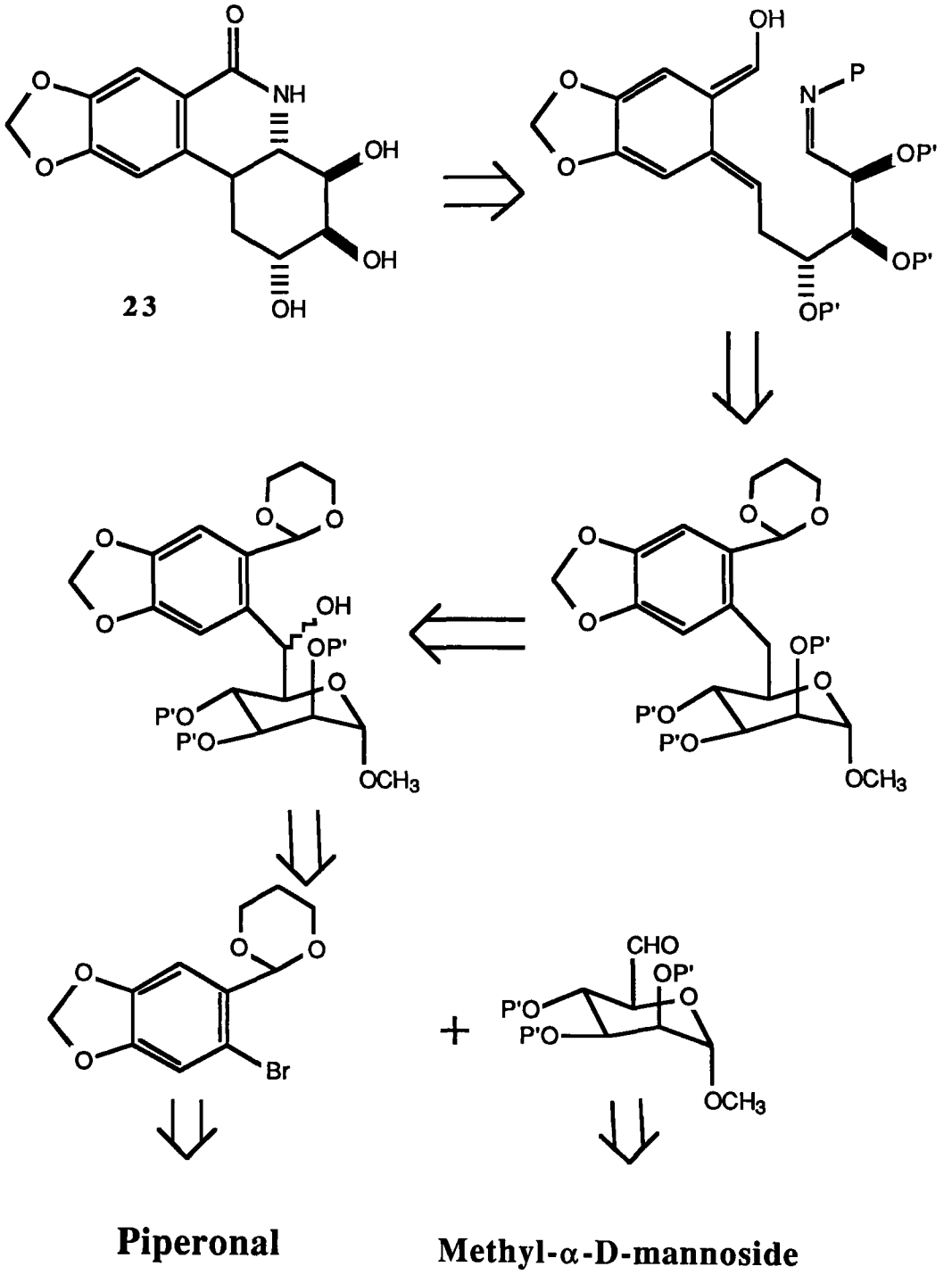
14) W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, *11*, 1031(1971).
15) S.M. Weinreb, *Acc. Chem. Res.*, **18**, 16(1985).

CHAPTER 2

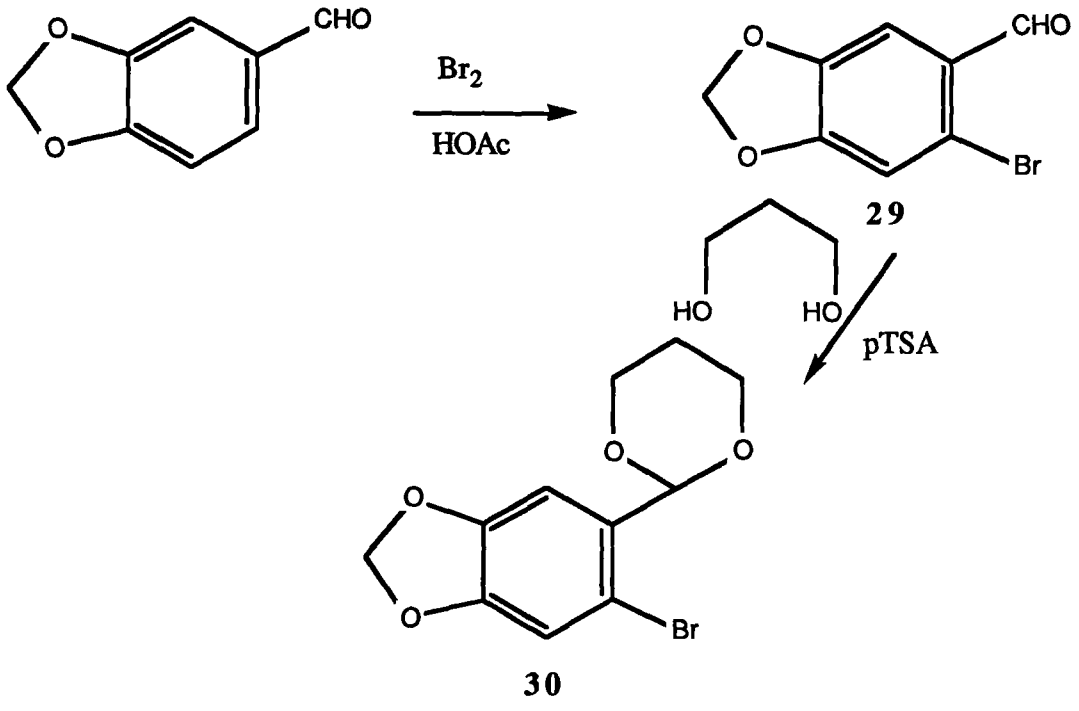
ORTHO-QUINODIMETHANE APPROACH 1

The original route investigated involved an intramolecular Diels-Alder reaction between an imine and an *o*-quinodimethane. As mentioned in the introduction, imines are known to react with *o*-quinodimethanes to give tetrahydroisoquinolines and thus this seemed to be a plausible approach. The required absolute stereochemistry for (-)-*trans*-dihydrolycorcidine **23** would be obtained from a suitable carbohydrate and the predicted geometry of the Diels-Alder reaction. The *o*-quinodimethane would be generated by photoenolization of a suitably substituted *o*-tolualdehyde derivative. The starting materials required for this approach are readily available piperonal and methyl-α-D-mannopyranoside; the retrosynthetic outline is shown in Scheme 2.

SCHEME 2


O
NH
OH
OH
OH
23
OH
P
N
OP'
OP'
OP'
O
O
O
O
OH
OP'
P'O
P'O
O
OCH3
O
O
O
O
OP'
P'O
P'O
O
OCH3
O
O
O
O
Br
+
CHO
OP'
P'O
P'O
O
OCH3
Piperonal
Methyl-α-D-mannoside

Piperonal was brominated with bromine in acetic acid to give cleanly bromide, **29**.[16] This was followed by acetalization with 1,3-propanediol in the presence of *p*-toluenesulfonic acid (*p*-TSA) to give the propylene acetal **30** {^{1}H nmr ($CDCl_3$) (300MHz) δ: 1.42 (dt, 1H, 13.5Hz, 1.2Hz), 2.22 (m, 1H), 3.98 (dt, 2H, 12Hz, 2.5Hz), 4.24 (ddd, 2H, 12Hz, 5Hz, 1.2Hz), 5.66 (s, 1H), 5.94 (s, 2H), 6.95 (s, 1H), 7.15 (s, 1H); exact mass calculated for $C_{11}H_{11}O_4Br$: 285.9840, found: 285.9859}. The ethylene acetal was not used since it was feared that, upon exposure to strong base, anion formation on the dioxolane ring resulting in eventual formation of ethylene could be possible.



16) F. Dallacker, *Liebigs Ann. Chem.*, **633**, 14(1960).

The carbohydrate portion required for coupling was prepared according to the following procedure, which is a slight modification of the known literature preparation of this compound. The primary hydroxyl group of methyl-α-D-mannoside was first protected as its triphenylmethyl ether, **31**,[17] by reaction with triphenylmethyl chloride in the presence of DMAP and TEA in DMF. This was followed by perbenzylation with sodium hydride and benzyl bromide. Subsequently the primary hydroxyl group was deprotected by exposure to 1N HCl in acetone, to give **32**.[18] The primary hydroxyl group was then oxidized to the aldehyde, **33**,[18] {ir (film) υ: 1710 (CHO) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 3.36 (s, 3H, OCH_3), 3.70-4.06 (m, 4H), 4.37-4.85 (m, 7H), 7.13-7.35 (m, 15H), 9.72 (s, 1H, C<u>H</u>O); M.S. (C.I. ether) (m/z) 480 ($M+H_2O$), 448 ($M-CH_3$), 327 ($M-(Bn+CHO+CH_3)$)} via Swern methodology.[19] The overall yield of **33** from methyl-α-D-mannoside was 72%.

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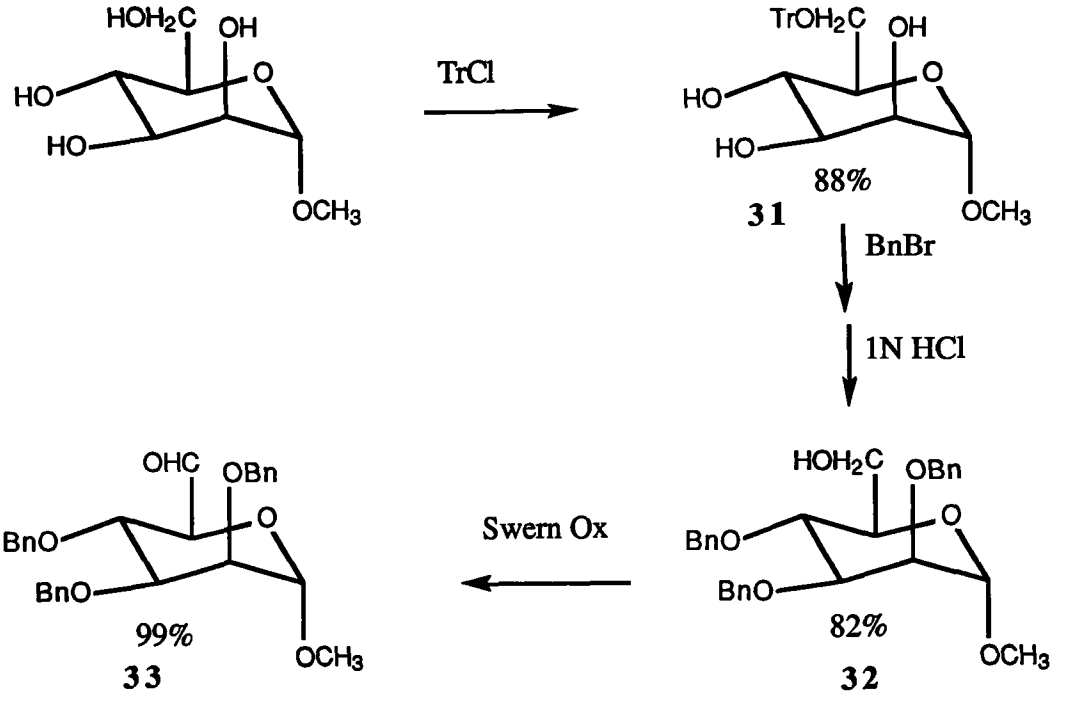
[17]) A.J. Watters, R.C. Hockett and C.S. Hudson, *J. Am. Chem. Soc.*, **61**, 1528(1939).

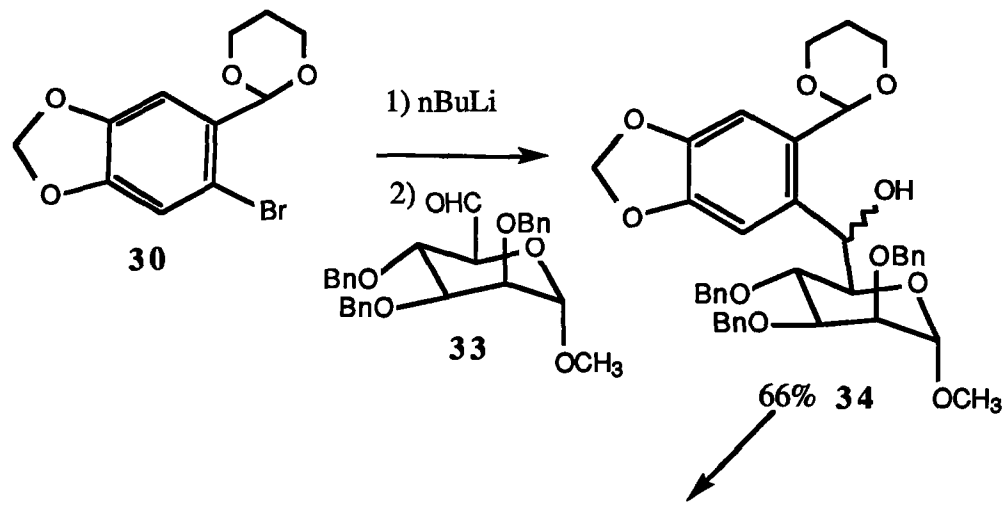
[18]) H.B. Boren, K. Elkind, P.J. Garegg, B. Lindberg and A. Pilotti, *Acta. ,Chem. Scand.*, **26**,4143(1972).

[19])a) R.E. Ireland and D.W. Norbeck, *J. Org. Chem.*, **50**, 2198(1985)., b) A,J. Mancuso, S.L. Huang and D. Swern, *J. Org. Chem.*, **43**, 2480(1978).



The bromide **30** was treated with *n*-BuLi to achieve lithium-halogen exchange, and the resulting lithio-derivative was added to aldehyde **33**, to give the alcohol, **34**, {ir (film) υ: 3610 (O-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.50 (m, 2H), 1.56 (br s, 1H, OH), 3.17 (s, 3H, OCH_3), 3.41-3.94 (m, 5H), 4.58-5.20 (m, 10H), 5.38 + 5.52 (s, 1H, ArC<u>H</u>(OH)R, diastereomers), 5.78 (s, 1H), 5.83 (dd, 2H, 1Hz), 7.02 (s, 1H), 7.16 (s, 1H), 7.20-7.34 (m, 15H); M.S. (m/z): 594 (M-$HO(CH_2)_3OH$); M.S. (C.I. ether) (m/z): 595 (M+1-$HO(CH_2)_3OH$)}. It was then necessary to cleave the undesired alcohol. This was attempted

by transfer hydrogenolysis[20] under a variety of conditions. These included the use of both 1,3-cyclohexadiene and cyclohexene as hydrogen sources, and solvents varying from ethanol to DMF, also both 5% and 10% palladium on carbon were used as catalysts. However, all attempts to reduce the alcohol failed.



Transfer hydrogenolysis failed

The alcohol, **34**, was then oxidized with PCC to the ketone **35**, {ir (film) υ: 1765 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.56 (m, 2H), 3.29 (s, 3H, OCH_3), 3.38-3.99 (m, 5H), 4.11-5.07 (m, 10H), 5.59 (s, 1H), 6.10 (s, 2H), 7.14 (s, 1H), 7.23 (s, 1H), 7.26-7.36 (m, 15H); M.S.

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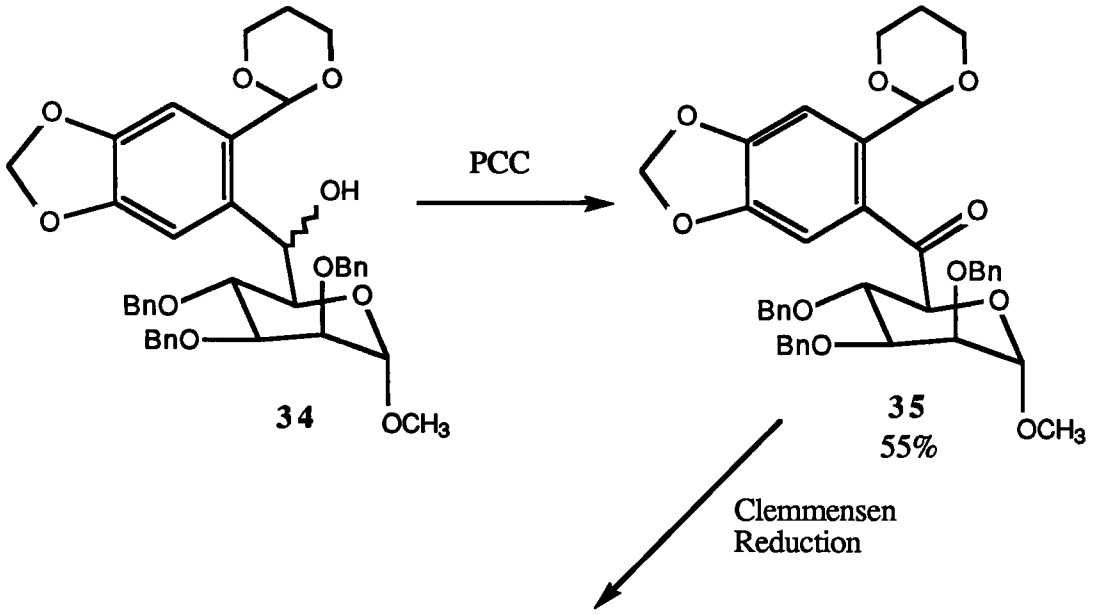
20) A.M. Felix, E.P. Heimer, T.J. Lambros, C. Tzougraki and J. Meienhofer, *J. Org. Chem.*, **43**, 4194(1978).

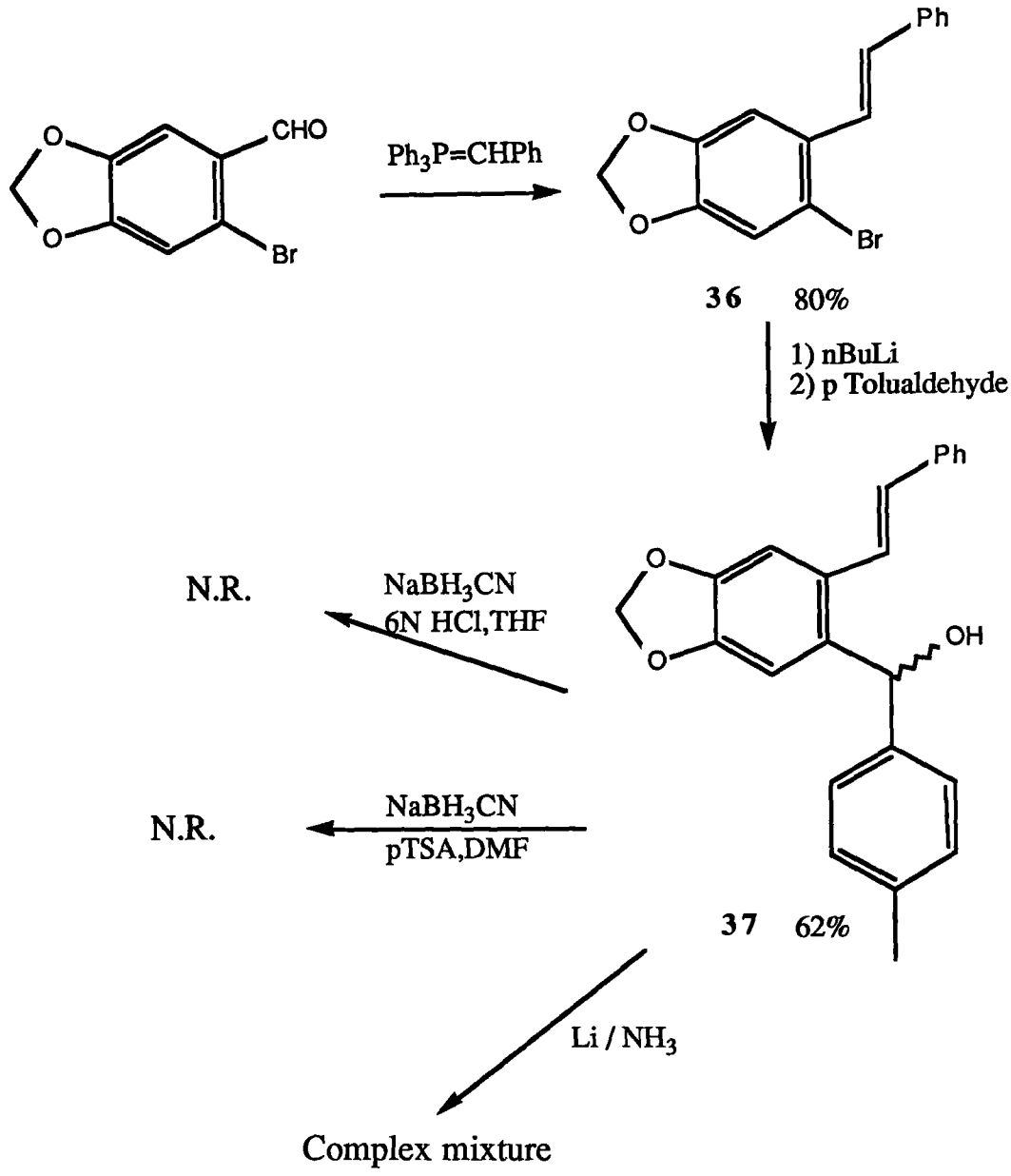
(C.I. ether) (m/z): 669 (M+1); M.S. (C.I. isobutane) (m/z): 669 (M+1)}. A Clemmensen reduction of the ketone was then attempted, but the acidic conditions required for the reduction resulted in cleavage of the propylene acetal. This was apparent by the disappearance of the signals at 1.56 and 3.50ppm due to the acetal and the appearance of an aldehydic signal at 9.50ppm in the ^1H nmr spectrum.



Since it appeared that protection of the aldehyde as the propylene acetal was incompatible with the conditions required to

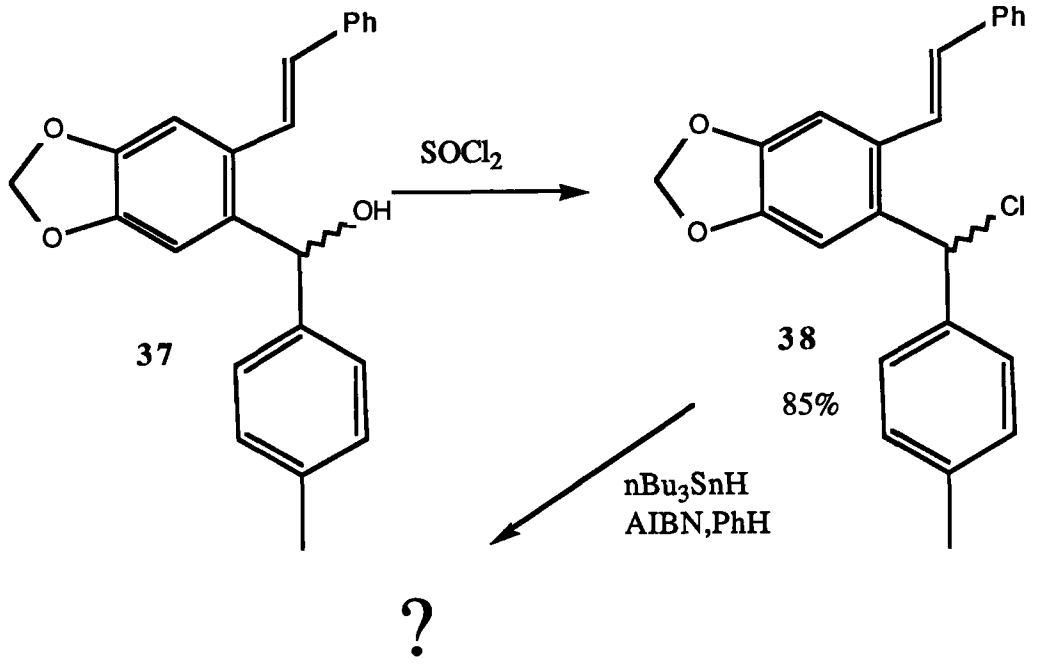
bring about desired changes in other parts of the molecule a radically different protecting group was sought. The β-phenylethylene group was expected to be ideal since such a group would be very stable to base and reasonably inert to acids. The aldehyde could later be revealed oxidatively.

A Wittig reaction between bromopiperonal, **29**, and triphenylphosphonyl-α-phenylmethylide smoothly gave the required olefin, **36** {^{1}H nmr ($CDCl_3$) (300MHz) δ: (*trans*-isomer) 5.98 (s, 2H), 6.50 (d, 1H, 12.4Hz), 6.60 (d, 1H, 12.4Hz), 7.14 (s, 1H), 7.19 (dd, 1H, 4Hz, 1Hz), 7.25 (s, 1H), 7.36 (dd, 2H, 6Hz, 1Hz), 7.50 (dd, 2H, 6Hz, 1Hz); M.S. (m/z): 302 (M^+), 304 (M+2), 224 (M+1-Br)}. The assignment of the *trans* geometry follows clearly from the 12.4Hz coupling constant between the styryl hydrogens. The *ortho*-lithio derivative of **36** was obtained via a lithium-halogen exchange reaction, utilizing *n*-BuLi in THF at -78°C. In a model study, the lithio derivative was trapped with *p*-tolualdehyde to give alcohol **37** {ir (film) υ: 3405 (O-H) cm^{-1}; ^{1}H nmr ($CDCl_3$) (300MHz) δ: 1.50 (br s, 1H, OH), 2.28 (s, 3H, CH_3), 5.86 (m, 1H), 5.92 (dd, 2H, 1.5Hz), 6.78 (m, 1H), 6.96 (s, 1H), 7.02-7.40 (m, 11H); M.S. (m/z): 344 (M^+), 326 (M-H_2O) (100%), 296 (M-CH_2O_2)} in 62% yield. Removal of the undesired hydroxyl group was attempted employing a variety of methods. Reduction with lithium/ammonia resulted in a complex mixture, whereas the use of sodium cyanoborohydride in THF with 6N HCl and sodium cyanoborohydride in DMF in the presence of *p*-TSA only gave recovered starting material.



Since direct reduction of the hydroxyl group failed, **37** was converted into the chloride, **38**, {ir (film) υ: 2905 (C-H), 1605 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$) (60MHz) δ: 2.25 (s, 3H), 5.70 (m, 1H), 5.85 (s, 2H), 6.50 (m, 1H), 6.60-7.35 (m, 12H)} with thionyl chloride. The

chloride, **38**, was subjected to free radical reduction conditions with tri-*n*-butyl tin hydride in the presence of aza-bis-*iso*-butyronitrile (AIBN). A complex mixture was obtained, from which the desired compound could not be isolated.



The failure to reduce the undesired alcohol prompted the attempt of direct alkylation of the aromatic anion. It has been shown that aryl copper salts can be alkylated with alkyl halides[21] and also that it is possible to generate alkyl copper reagents and couple them with aryl halides[22] (Figure 1). The aryl-copper derivative of **36** was prepared by lithium-halogen exchange with *n*-butyllithium in the presence of the cuprous iodide-tri-*n*-butylphosphine complex.[23]

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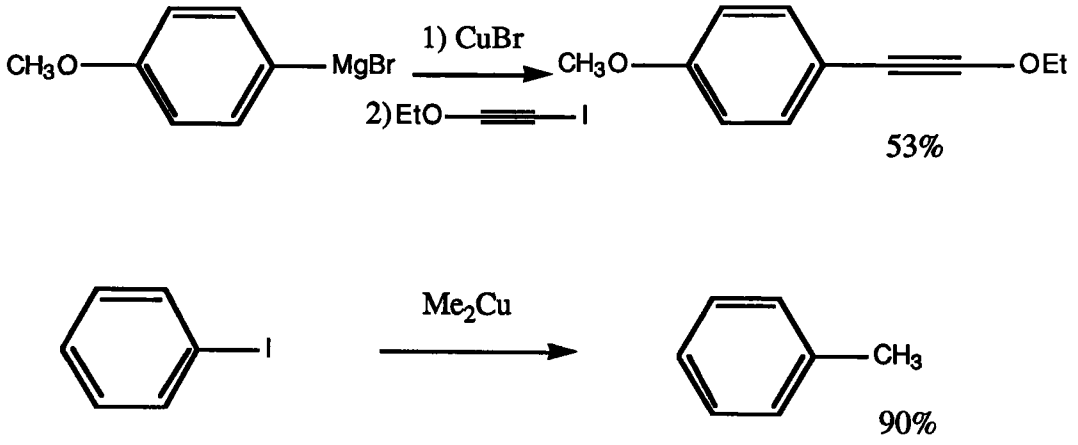
21) W. Verboom, H. Westmijze, H.J.T. Bos, and P. Vermeer, *Tetrahedron Lett*, 1441(1978).

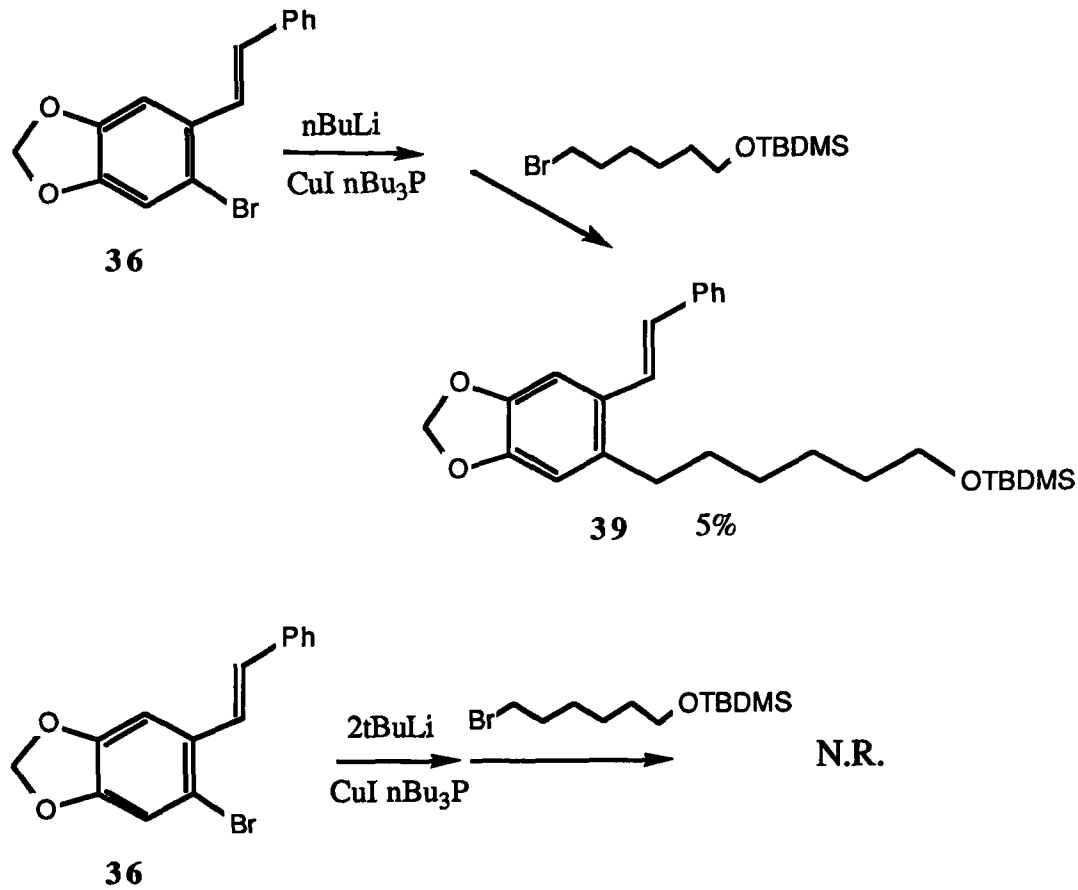
22) E.J. Corey and G.H. Posner, *J. Am. Chem. Soc.*, **89**, 3911(1967).

23) H.O. House, C.Y. Chu, J.M. Wilkins, and M.J. Umen, *J. Org. Chem.*, **40**, 1460(1975).

Reaction with 6-*t*-butyldimethylsilyloxy-1-bromohexane gave the desired alkylation product, **39**, albeit in a very poor yield, of 5%. Changing the alkyllithium base from *n*-butyllithium to *t*-butyllithium did not make any improvement. Generating the alkyl copper reagent derived from 6-*t*-butyldimethylsilyloxy-1-bromohexane and reacting it with aryl bromide, **36**, gave none of the desired product.

FIGURE 1





The low yields obtained in the direct alkylation of aryl anions via published methodology prompted us to search for a new method for achieving such an interconversion. The mechanism of the reaction of aryllithiums with alkyl halides is not clearly defined and may involve either radicals (single electron transfer) or S_N2 displacement. If the latter mechanism is operative, it was

rationalized that acceptable yields in the carbon-carbon bond forming reaction might be attained by utilizing the best readily available leaving group. Trifluoromethanesulfonates (triflates) have been known for the past 15-20 years and successfully used in difficult displacement reactions where the corresponding tosylates or mesylates failed.[24] Triflates of primary alcohols are readily prepared by reaction of the alcohol with trifluoromethanesulfonic anhydride in methylene chloride at -78°C to 0°C in the presence of triethylamine.

Aryl bromide, **36**, was subjected to lithium-halogen exchange conditions followed by reaction with *n*-propyl triflate. The desired alkylation product, **40**, was obtained in an acceptable 41% yield, thereby giving credence to the above rationalization. The product, **40**, {ir (film) υ: 2950 (ArC-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.91 (t, 3H, 8Hz), 1.54 (m, 2H), 2.51 (dd, 2H, 8Hz, 1Hz), 5.86 (s, 1H), 6.49-6.68 (m, 2H), 7.11-7.25 (m, 7H); M.S. (m/z): 266 (M^+), 237 (M-CH_2CH_3)} was easily identified by its molecular ion of 266 in the mass spectrum and the presence of propyl group signals in the ^1H nmr spectrum.

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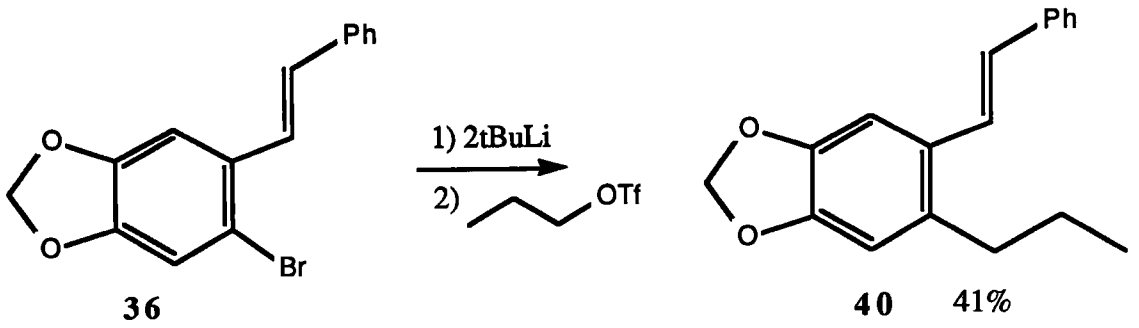
[24]) J.B. Hendrickson, D.D. Sternbach and K.W. Blair, *Acc. Chem. Res.*, **10**, 306(1977).



36 **40** 41%

Based on the favourable result in the simple model study it was decided to attempt the preparation of **42**, the coupling product between the lithio derivative of **36** and the primary triflate **41** derived from mannose according to the procedure of Ambrose and Binkley.[25] This triflate, **41**, obtained in 80% isolated yield, was added to a THF solution of the ortho-lithio derivative of **36** at -78°C and the solution was stirred for 10 min. Upon warming the reaction mixture to R.T. and usual work-up, chromatography of the crude product afforded on elution with 5% ethyl acetate/hexanes, the desired alkylation product **42** {^{1}H nmr ($CDCl_3$) (60MHz) δ: 3.28 (s, 3H, OCH_3), 3.50-4.20 (m, 6H), 4.35-4.90 (m, 7H), 5.79 (s, 2H), 5.85 (m, 1H), 6.40 (s, 1H), 6.65 (s, 1H), 6.95-7.35 (m, 19H); M.S. (C.I. ether) (m/z): 671 (M+1)} in a surprisingly good yield (65%). The C.I. mass spectrum ((m/z): 671 (M+1)) showed that carbon-carbon bond formation had indeed taken place.

With compound **42** safely in hand it was felt that a major hurdle in the synthesis of (-)-*trans*-dihydrolycorcidine had been

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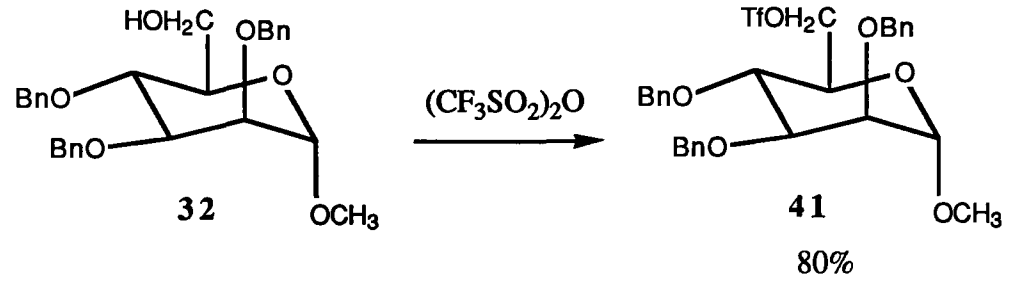
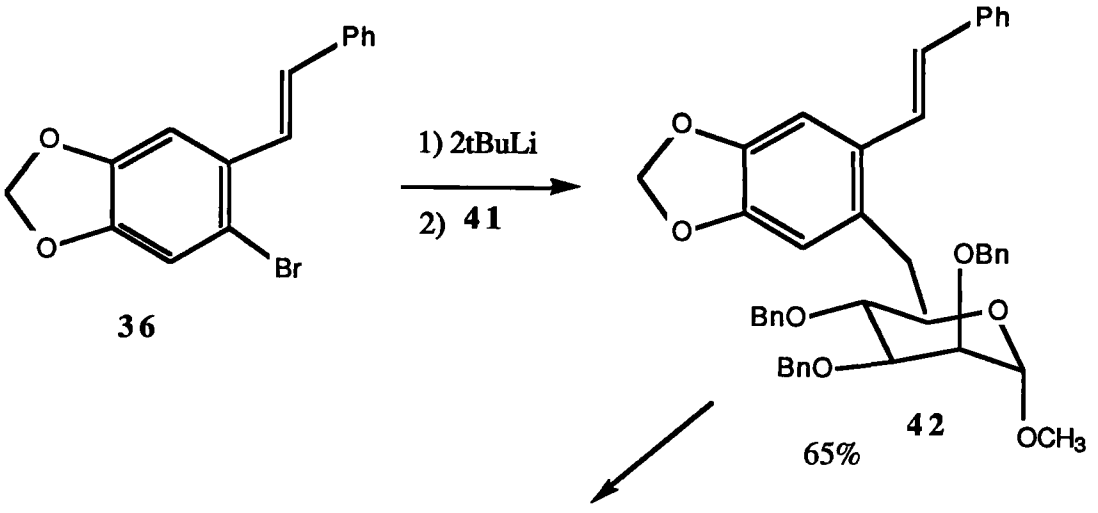
25) M.G. Ambrose and R.W. Binkley, *J. Org. Chem.*, **48**, 674(1983).

cleared. We were thus surprised and disappointed to discover the surprising (to us) resistance of the methyl glycoside of **42** to hydrolysis. Compound **42** was treated with 2N sulfuric acid in dioxane at 100°C for 2 days, but no cleavage was observed. Perhaps this is rather common knowledge amongst carbohydrate chemists but unfortunately we were not aware of it.



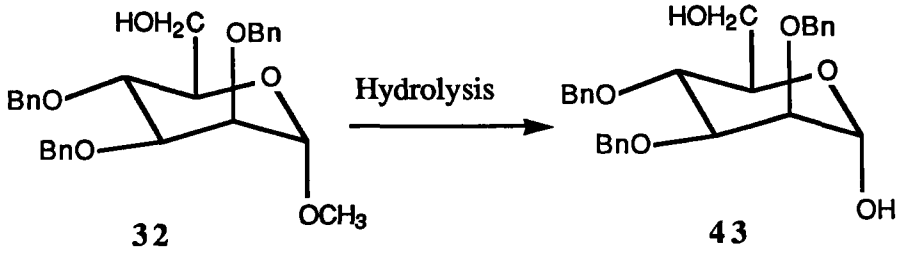


Could not cleave
methyl glycoside

Conditions required to cleave the methyl glycoside of mannose derivative, **32**, were probed; these results are tabulated in Table I. Due to the low yield and harsh conditions an alternative procedure was tried. It had been shown by Olah that trimethylsilyl iodide cleaved methyl ethers and acetals[26]. So, the 6-O-trityl methyl mannoside, **31**, was exposed to two equivalents of trimethylsilyl chloride/sodium iodide in acetonitrile. It was hoped that this would cleave both the triphenylmethyl ether and methyl glycoside. However, only the triphenymethyl ether was cleaved to give the alcohol, **32**.

Table 1

Attempts at Hydrolysis of Methyl Glycoside **32**

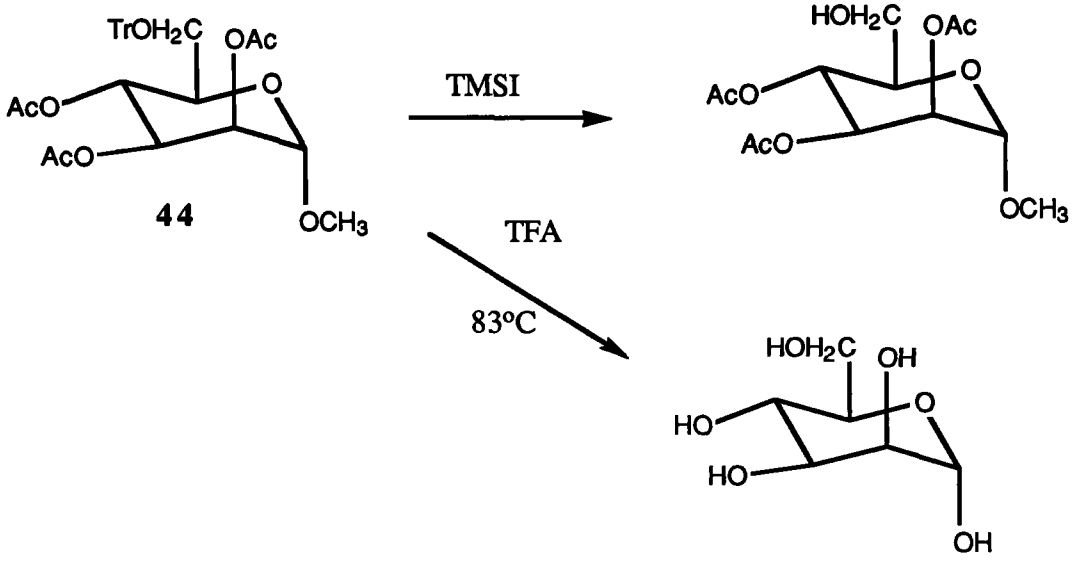


32 **43**

Acid	Solvent	Temperature	Time	Result
1N H_2SO_4	1,4-dioxane	100°C	8 h	N.R.
"	"	23°C	3 days	N.R.
4N H_2SO_4	"	100°C	2 days	20% **43**
"	"	"	3 days	30% **43**

26) G. Olah, S.C. Narang, B.G.B. Gupta, and R. Malhotra, *J. Org. Chem.*,**44**, 1247(1979).

It was thought that the benzyl protecting groups may have hindered the cleavage of the methyl glycoside so changing these to acetates may have allowed for its cleavage. The peracetylated analogue **44** was prepared via known methodology.[17] It was subjected to trimethylsilyl iodide treatment, which again only resulted in cleavage of the trityl group. When **44** was treated with trifluoroacetic acid in refluxing 1,2-dichloroethane cleavage of the acetates was observed, but, when lower temperatures were employed only cleavage of the trityl group resulted.

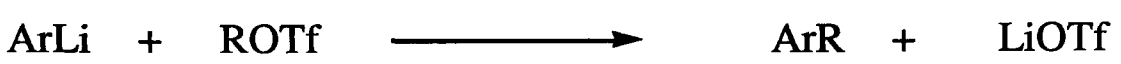


Since it was very difficult to cleave the methyl glycoside this approach was abandoned.

Since a new method of alkylating aryl anions with alkyltriflates had been discovered in this approach, the scope and generality of the reaction (Figure 2) was then studied. Along with the examples

already mentioned aryl anions generated via ortho-metalation and by direct lithiation of heterocycles were also studied.

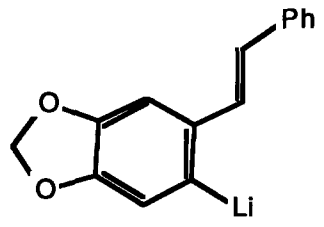
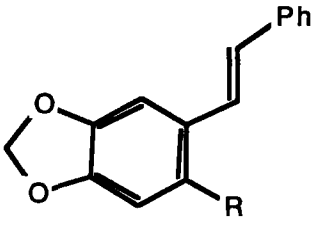
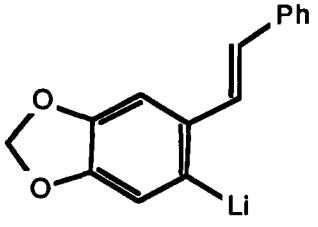
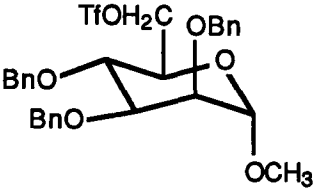
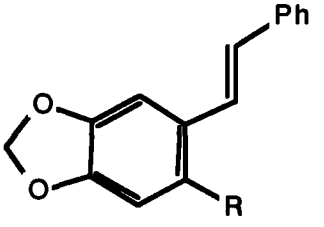
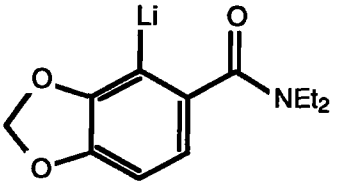
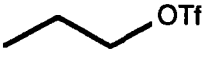
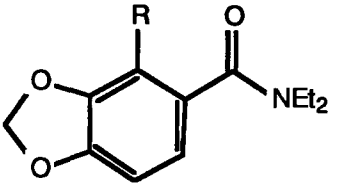
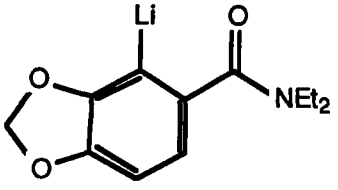
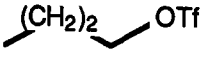
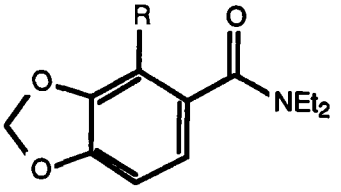
FIGURE 2

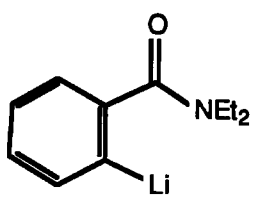


The yields in most instances were acceptable (approximately 50%) except in the cases of thiophene and furan where the yields were poor. It is presumed that the poor yields in the heterocyclic examples are due to competing alkylation on the heteroatom by the highly reactive alkyltriflate followed by rapid decomposition. In the thiophene example another monoalkylation and an unsymmetrical dialkylation product were observed possibly due to electrophilic aromatic substitution reactions of the heterocycle and the alkyltriflate. These results are shown in Table 2.

TABLE 2

ALKYLATION OF ARYL ANIONS WITH ALKYLTRIFLATES

Aryllithium	Alkyltriflate (ROTf)	Product	Yield
			41%
			65%
			47%
			35%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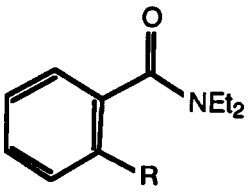
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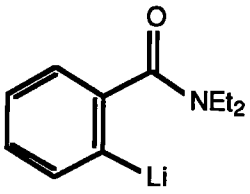
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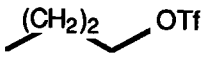
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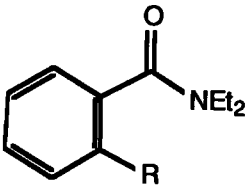
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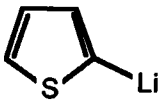
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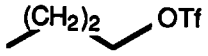
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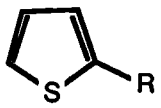
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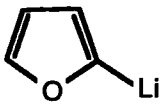
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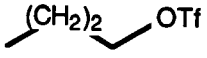
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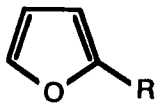
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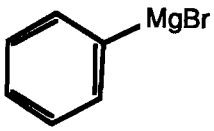
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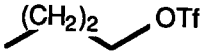
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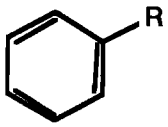
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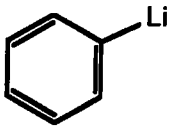
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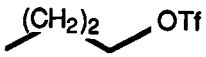
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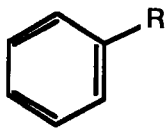

R

0%

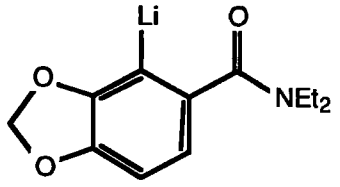
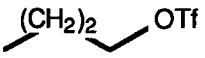
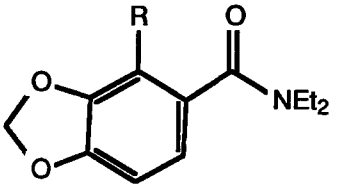
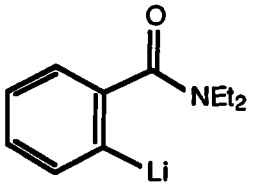
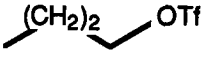
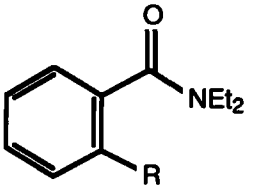
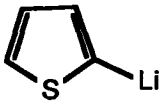
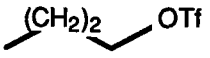
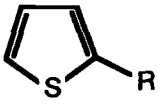
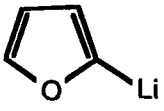
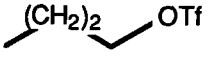
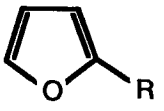
It appeared that a competing reaction with the alkylation was elimination of the triflate by the aryllithium to give an olefin, due to the isolation of a small amount of the elimination product in the case of triflate **41**. It was reasoned that if one could lower the basicity of the aryllithium species one might achieve higher yields in the alkylation reaction. It had been practice in aldol condensations to add cerium trichloride in order to lower the basicity of alkyllithium nucleophiles.[27] It was thought that adding an equivalent of anhydrous cerium trichloride to the aryllithium might reduce its basicity and therefore increase the yield of the displacement of the alkyl triflate. In some cases the improvement in the yield of the alkylation was as high as 50%. These results are shown in Table 3.

---

27) T. Imamoto, Y. Sugiura and N. Takiyama, *Tetrahedron Lett.*, 4233(1984).

TABLE 3

ALKYLATION OF ARYL ANIONS WITH ALKYLTRIFLATES IN THE PRESENCE OF ONE EQUIVALENT OF $CeCl_3$

Aryllithium	Alkyltriflate (ROTf)	Product	Yield
			50%
			28%
			20%
			5%

CHAPTER 3

ORTHO-QUINODIMETHANE APPROACH 2

Due to problems with the approach described in Chapter 2, an alternate pathway was investigated. It is very similar to the first in that the key step which generates the tricyclic ring system involves the same intramolecular Diels-Alder reaction. The difference is that the required intermediate imine would be obtained via a Wittig reaction as opposed to using aryl anion methodology. It had been shown by the Syntex[28] and Merck[29] groups that it was possible to perform a Wittig reaction with a carbohydrate hemiacetal (Figure 3). The carbohydrate portion required is now a pentose which would be obtained by degradation of a mannose derivative. The methyl mannoside still had to be cleaved, but, since the cleavage occurs early in the synthesis harsh conditions and possibly a low yield could be tolerated. The retrosynthetic outline is shown in Scheme 3.

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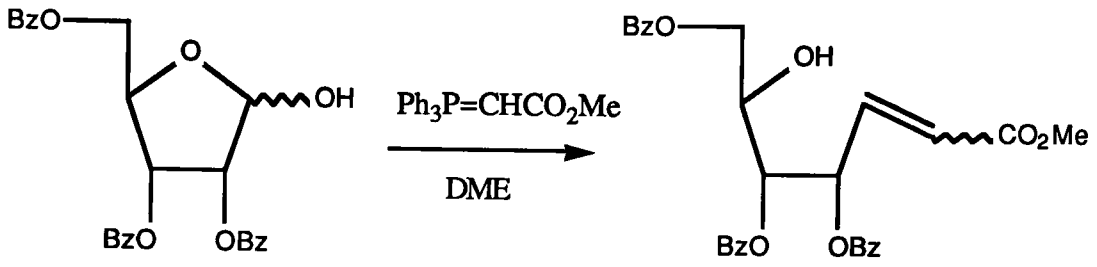
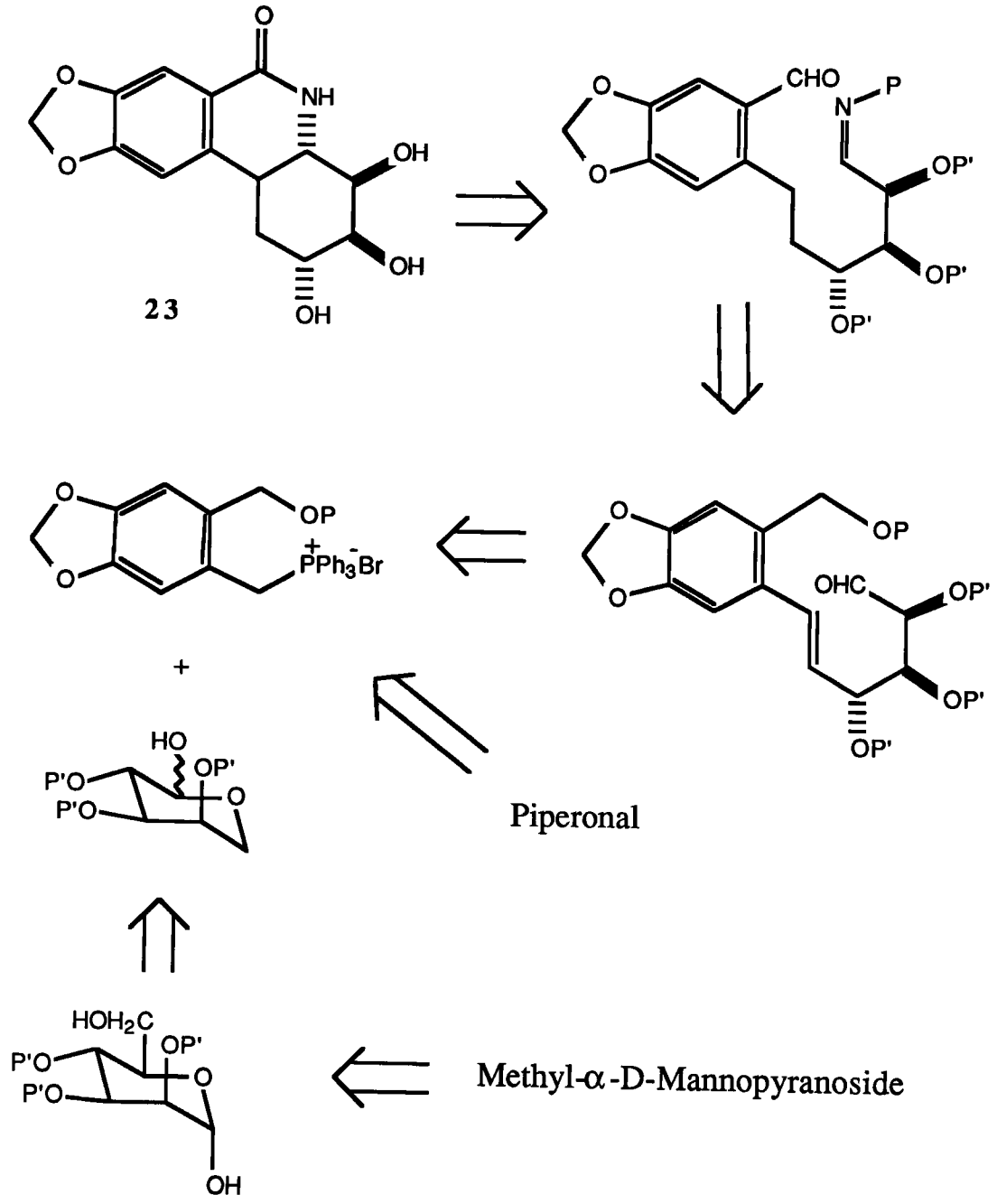
28) H. Ohrui, G.H. Jones, J.G. Moffatt, M.L. Maddox, A.T. Christensen, and S.K. Byram, *J. Am. Chem. Soc.*, **97**, 4602(1975).

29) a) J. Rokach, R. Zamboni, C. Lau, and Y. Guindon, *Tetrahedron Lett.*, 2759(1981), b) *ibid*, 2763(1981).

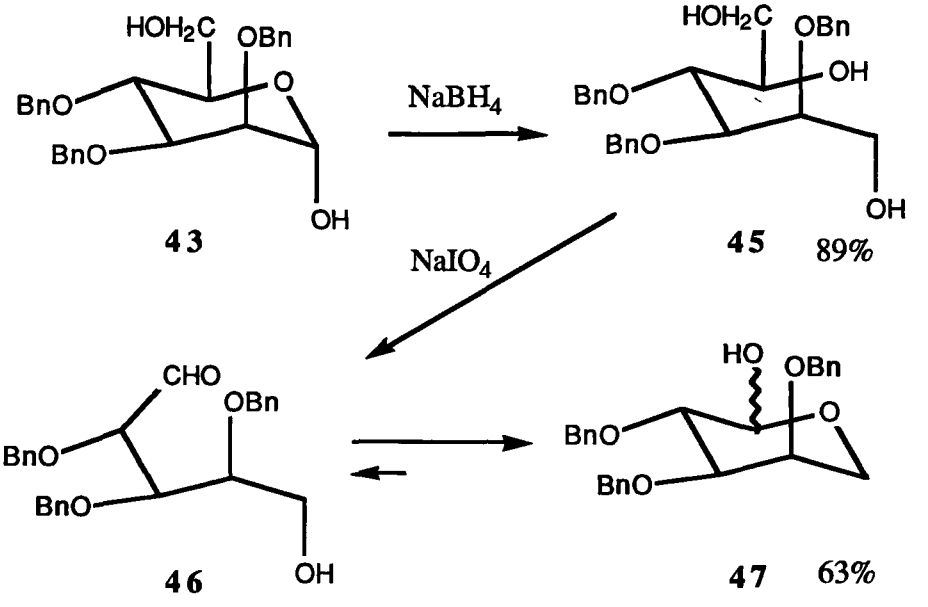
FIGURE 3



SCHEME 3


O
NH
OH
OH
OH
23
CHO
N
P
OP'
OP'
OP'
OP
PPh3Br
OP
OHC
OP'
OP'
OP'
+
HO
OP'
P'O
P'O
Piperonal
HOH2C
OP'
P'O
P'O
OH
Methyl-α-D-Mannopyranoside

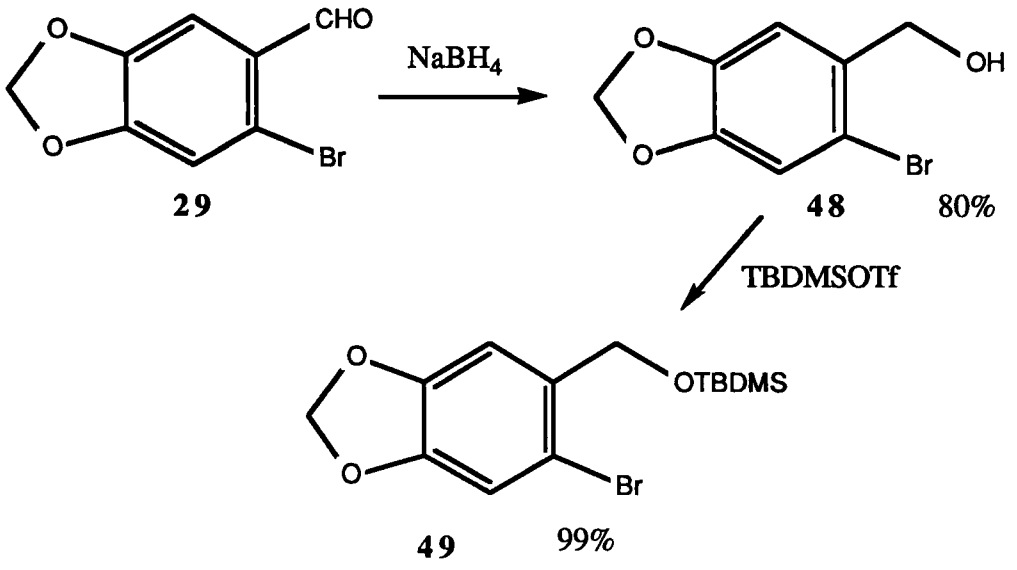
The reducing sugar **43**,[30] prepared by the cleavage of the methyl glycoside **32**, was reduced with sodium borohydride to give the triol **45** in very good yield. The 5,6-diol group was oxidatively cleaved with sodium periodate to give 2,3,4-tri-*O*-benzyl-D-arabinose **46**, known to exist as pyranose **47** {ir (KBr pellet) υ: 3425 (O-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.53 (br s, 1H, OH), 3.62 (dd, 1H, 2Hz, 1Hz), 3.77 (m, 2H), 3.80 (dd, 1H, 4Hz, 2Hz), 3.86 (t, 1H, 4Hz), 4.52-4.79 (m, 7H), 7.22-7.33 (m, 15H); M.S. (C.I. ether) (m/z): 420 (M^+), 403 (M+1-H_2O), 329 (M-Bn), 311 (M-(Bn+H_2O))}.



For this sequence it was anticipated that bromopiperonal, **29**, would best be protected by reduction and conversion to its *t*-butyldimethylsilyl ether. Thus bromopiperonal, **29**, was reduced with

30) E.S. Rachaman, R. Eby and C. Schuerch, *Carbohydrate Res.*, **67**, 147(1978).

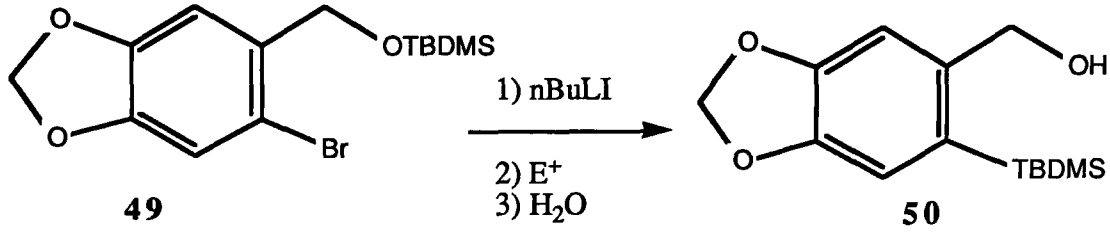
sodium borohydride to give bromopiperonol, **48**, which was quantitatively converted with TBDMS triflate[31] into its TBDMS ether, **49** {^{1}H nmr ($CDCl_3$) (60MHz) δ: 0.05 (s, 6H), 0.80 (s, 9H), 4.38 (s, 2H), 5.68 (s, 2H), 6.67 (s, 1H), 6.80 (s, 1H); M.S. (m/z): 344 (M^+), 346 (M+2), 329 (M-CH_3), 331 (M+2-CH_3), 287 (M-*t*-Bu), 289 (M+2-*t*-Bu), 213 (M-TBDMSO) (100%), 215 (M+2-TBDMSO) (100%)}. The aryl anion was then generated by lithium-halogen exchange. Attempts were then made to trap it with various one-carbon electrophiles, shown in Table 4.



31) E.J. Corey, H. Cho, C. Rucker, and D.H. Hua, *Tetrahedron Lett.*, 3455(1981).

Table 4

Reaction of Organolithium Derivative from **49** with Various Electrophiles

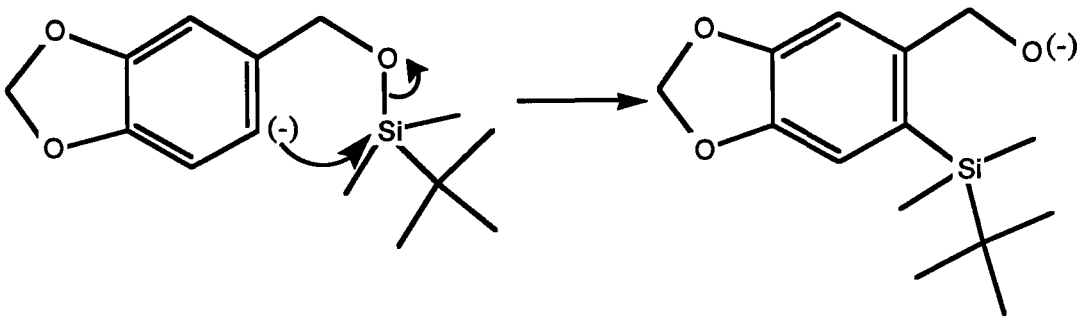


49 **50**

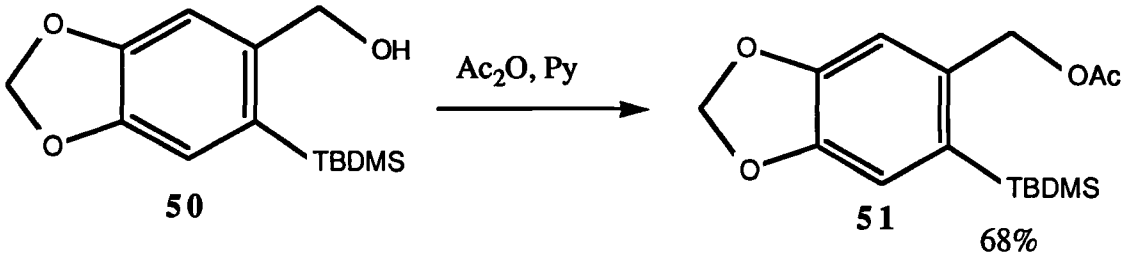
Electrophiles	Product
Formaldehyde	**5 0**
DMF	**5 0**
Methyl formate	**5 0**
N-Formylmorpholine	**5 0**
Ethyl chloroformate	**5 0**
Carbon dioxide	**5 0**

Instead of the hoped for attack of the carbanion on the incoming electrophile, another reaction was observed. It turned out to be silyl transfer from oxygen to carbon as shown in Figure 4.

FIGURE 4



There have been only three similar reports in the literature[32], all involving the less sterically hindered trimethylsilyl group. The product of silyl transfer, **50** {ir (film) υ: 3600 (O-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.32 (s, 6H), 0.86 (s, 9H), 4.63 (s, 2H), 5.93 (s, 2H), 6.92 (s, 1H), 7.02 (s, 1H); ^{13}C nmr ($CDCl_3$) (DEPT) δ: -3.03 (CH_3), 17.69 (quaternary), 26.81 (CH_3), 65.38 (CH_2), 100.82 (CH_2), 109.19 (CH), 114.82 (CH), 128.20 (quaternary), 141.35 (quaternary), 146.41 (quaternary), 148.66 (quaternary); M.S. (m/z): 266 (M^+), 209 (M-*t*-Bu), 191 (M-(*t*-Bu+H_2O); M.S. (C.I. ether) (m/z): 267 (M+1), 249 (M+1-H_2O), 209 (M-*t*-Bu)}, was converted into its acetate, **51**, for further characterization .



50 **51** 68%

32) a) R.J. Billedeau, M.P. Sibi, and V. Snieckus, *Tetrahedron Lett.*, 4515(1983)., b) J.R. Green M. Majewski, B.I. Alo, and V. Snieckus, *Tetrahedron Lett.*, 535(1986).

A different hydroxyl protecting group was tried in order to avoid the transfer reaction problem. A methylthiomethyl ether was utilized under the conditions described by Corey.[33] This reaction was not clean, and attempts to purify the compound seemed only to result in its decomposition.

It was then decided to take advantage of the symmetry element of the target hydroxy-bromide. The strategy now involved preparation of the Wittig salt of the dibromide, and addition of the other required carbon atom at a later point in the synthesis.

Bromopiperonol, **48** was smoothly converted via the dibromide **52** into the triphenylphosphonium salt, **53** {ir (KBr pellet) υ: 3000 (Ar-H), 1430,1110,1000 (Ar-P) cm^{-1}: ^1H nmr (DMSO-d_6) (300MHz) δ: (5.00 d, 2H, 14Hz), 6.06 (s, 2H), 6.60 (d, 1H, 2Hz), 7.15 (d, 1H,1Hz), 7.63 (m, 6H), 7.78 (m, 6H), 7.93 (m, 3H); M.S. (FAB) (m/z): 475 (cation), 477 (C+2), 395 (C-1-Br)}. The ylid was generated with sodium hydride, but was found not to react with the hemiacetal **47**. A variety of conditions were tried (varying the temperature and base) but, in all cases no reaction took place. Presumably, the ylid used was not stabilized enough to allow for reaction with the hemiacetal. As a result this approach was no longer pursued.

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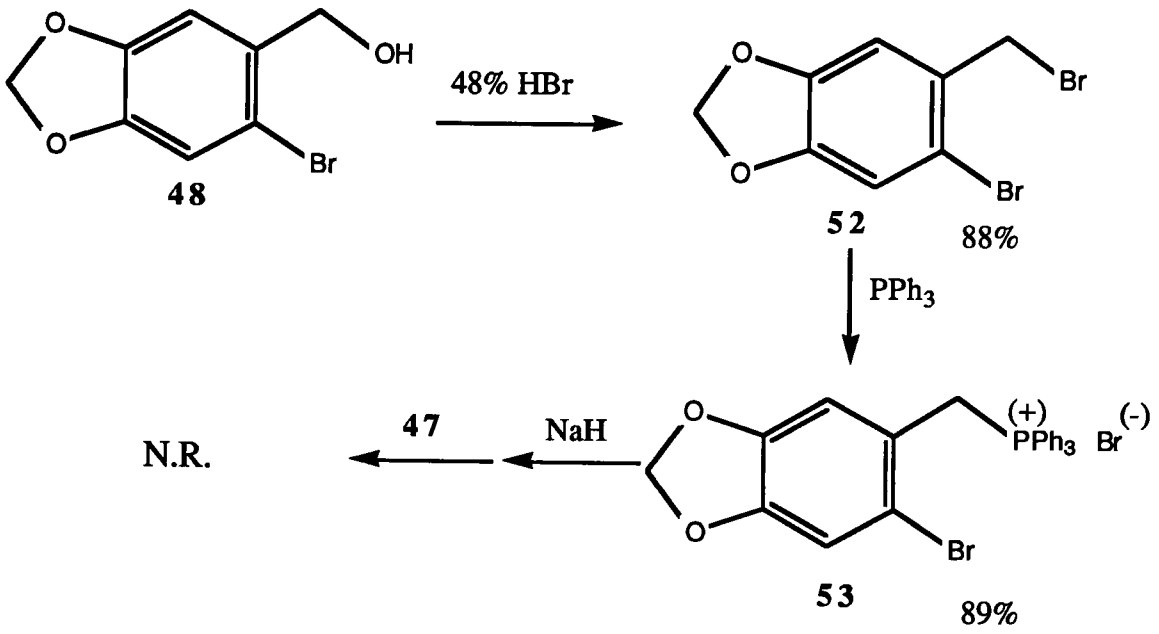
33) E.J. Corey and M.G. Bock, *Tetrahedron Lett.*, 3269(1975).


O
O
OH
Br
48
48% HBr
O
O
Br
Br
52
88%
PPh3
O
O
(+)
PPh3
Br
(-)
Br
53
89%
NaH
47
N.R.

CHAPTER 4

LATERAL METALATION APPROACH

This approach to *trans*-dihydrolycorcidine **23** involves lateral metalation of an *N,N*-dialkyl-*o*-toluamide, followed by trapping with a suitable imine. The nitrogen anion generated should then be able to displace intramolecularly the dialkylamino moiety of the amide leaving a δ-lactam. The lithium dialkylamide released as a result of the ring closure should be a suitable base to deprotonate the *o*-methylene group, giving an anion which can be subsequently trapped by a pendant epoxide or other suitable leaving group. The retrosynthetic outline of this approach is shown in Scheme 4.

Lateral metalation is the metalation of a benzylic position located ortho to a group which can stabilize the benzylic anion, such as a carboxylic acid, ester or amide function. Lateral metalation has been used extensively in organic synthesis.[34]

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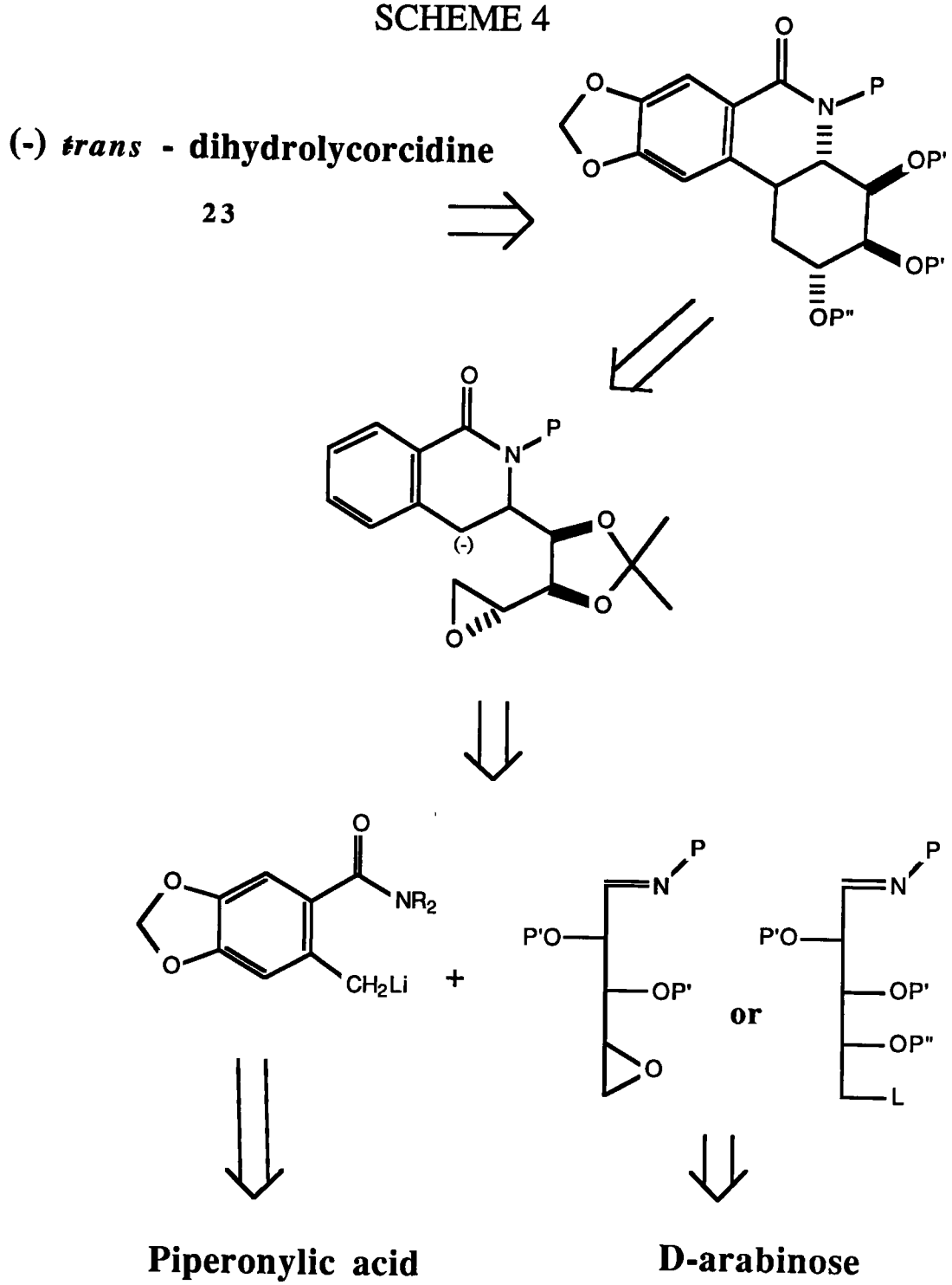
34) a) C. Mao, I.T. Barnish, and C.R. Hauser, J. Het. Chem., 83(1969), b) S.O. DeSilva, I. Ahmed, and V. Sneickus, Can. J. Chem., 57, 1598(1969), c) Y. Ito, Y. Kobashi, and T. Saegusa, Chem. Lett., 1563(1980), d) F.J. Leeper, and J. Staunton, J. Chem. Soc., Chem. Commun., 206(1980), e) F.M. Hauser R.P. Rhee, and S. Prasanna, Synthesis, 72(1980), f) G.A. Kraus, J. Org. Chem., 46, 201(1981), g) P. Beak, A. Tse, J. Hawkins, C. Chen, and S. Mills, Tetrahedron, 39, 1983(1983).

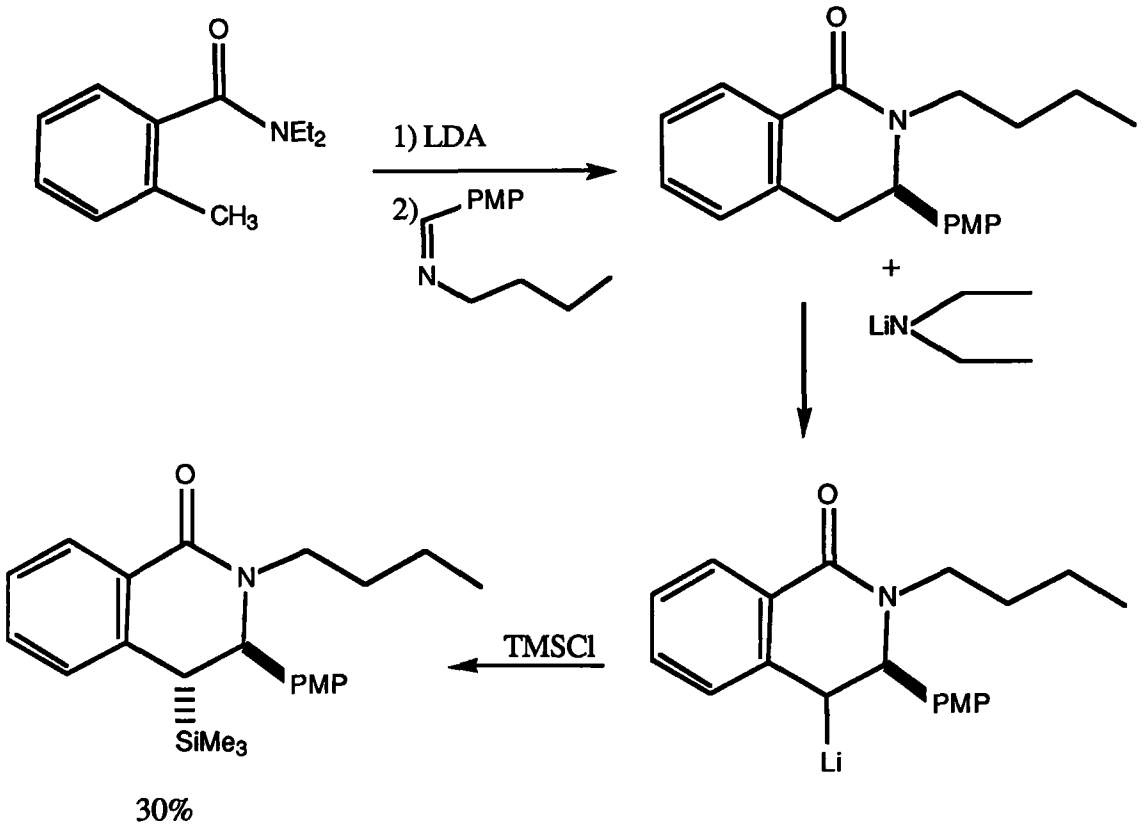
SCHEME 4


(-) trans - dihydrolycorcidine
23
O
O
O
N
P
OP'
OP'
OP"
(-)
O
O
O
NR2
CH2Li
+
P'O
OP'
O
or
P'O
OP'
OP"
L
Piperonylic acid
D-arabinose

This approach was based on work done by Clark,[35] in which lithiated *N*,*N*-diethyl-*o*-toluamides were trapped with aromatic imines to give cyclic amides and lithium diethylamide. It was further shown that the lithium diethylamide generated was indeed capable of deprotonating the *o*-methylene group by trapping experiments using TMSCl as shown in Figure 5.

35) R.D. Clark, *Heterocycles*, **23**, 825(1985).

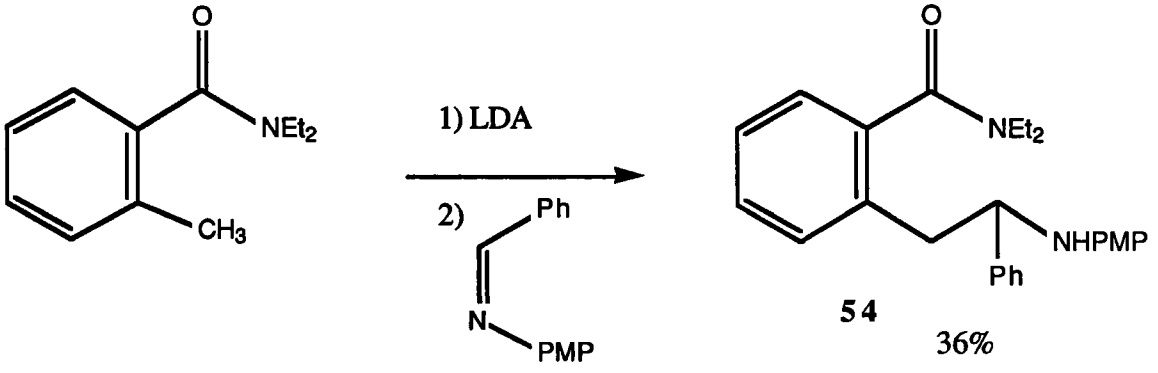
FIGURE 5



This new approach to *trans*-dihydrolycorcidine required an imine derived from a suitable carbohydrate. In addition the protecting group on nitrogen would have to be removed easily following the two cyclizations. Therefore, the *n*-butyl or any other simple alkyl group could not be employed. It was hoped that these requirements would not cause any major difficulty.

Initial model studies were to probe for a suitable imine nitrogen protecting group. In an initial experiment

benzylidine-*p*-methoxyaniline was reacted with lithiated *N,N*-diethyl-*o*-toluamide. A product, **54**, {ir (KBr pellet) υ: 1610 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.06 (t, 3H, 7Hz), 1.34 (t, 3H, 7Hz), 3.14 (m, 2H), 3.62 (m, 2H), 3.64 (s, 3H), 3.75 (m, 2H), 4.60 (br s, 1H, N<u>H</u>), 6.60 (dd, 1H, 6.4Hz, 2.3Hz), 7.13-7.43 (m, 13H); M.S. (m/z): 402 (M^+), 330 (M-NEt_2), 280 (M-NPMP), 212 (CH(Ph)NHPMP$^+$) (100%)} resulting from trapping of the imine was isolated, but no intramolecular *trans*-amidation took place.

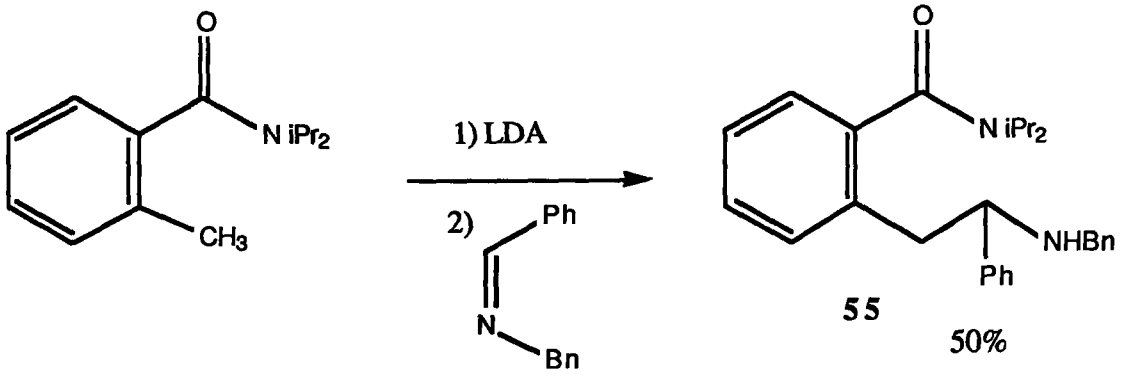


54

36%

An *N*-benzyl protected imine was then tried, with the hope that this group would facilitate both the intramolecular *trans*-amidation and possibly also increase the yield of the initial condensation reaction. Under the same standard conditions used above the reaction of the lithio derivative of *N,N*-diisopropyl-*o*-toluamide with benzylidine benzylamine, gave the initial condensation product, **55** in an improved yield of 50%, but again no intramolecular *trans*-amidation took place. The condensation product, **55**, {ir (film) υ: 1612 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.14 (m, 6H),

1.56 (m. 6H), 3.01 (m,1H), 3.25 (m, 1H), 3.49 (m, 2H), 4.25 (m, 2H), 4.78 (br s, 1H, NH), 6.48+6.75 (d, 1H, 6Hz, rotational isomers), 7.05-7.60(m, 13H), 7.62 (dd, 1H, 2Hz, 1Hz); M.S. (m/z): 414 (M^+), 415 (M+1), 323 (M-Bn), 309 (M-NBn)}.



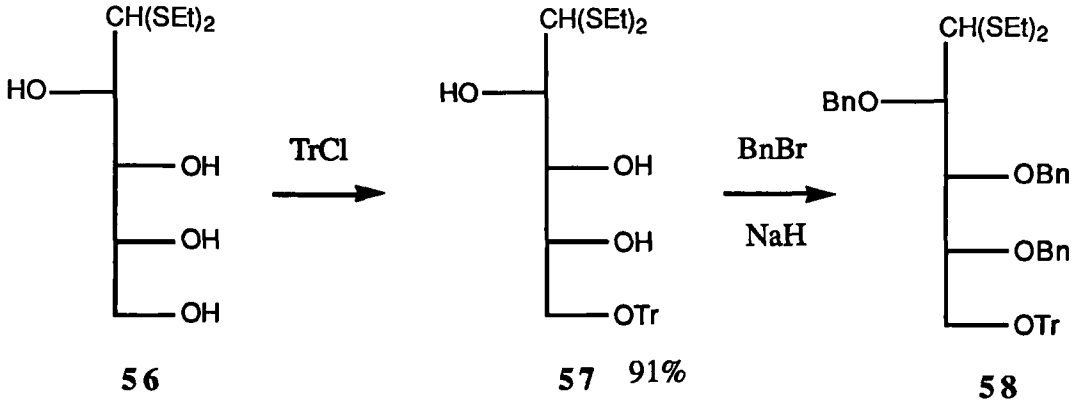
55

50%

Although cyclized products were not obtained in the one-pot sequence shown above, cyclization could be induced upon treatment with base under somewhat harsher conditions, *i.e.* with NaH in refluxing THF. Suitable carbohydrate imines were therefore prepared.

The carbohydrate necessary to give the required stereocenters is the readily available D-arabinose. From the earlier model studies, it appeared that protection of the nitrogen as an *N*-benzyl imine would be the one of choice. If the carbohydrate were perbenzylated, all of the protecting groups could be removed at once.

The diethyl mercaptal, **56**, prepared by the method of Zinner,[36] was smoothly converted into the 5-O-trityl derivative,[37] **57**, in 91% yield by standard methodology. Compound **57** was then perbenzylated using sodium hydride and benzyl bromide in DMF. Unfortunately the yield of the desired perbenzylated product, **58**, was poor and it was difficult to obtain pure; therefore another set of protecting groups was sought.



56 **57** 91% **58**

The new target, the known diisopropylidene compound[38] **59**, was prepared according to a described procedure.[39] The aldehyde functionality of **59** was revealed with mercuric chloride[40] and the aldehyde, **60**, {ir (film) υ: 1730 cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.24 (s, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 3.93-4.40 (m, 5H), 9.74 (d, 1H, 1Hz, C<u>H</u>O); M.S. (C.I. ether) (m/z): 231 (M+1) (100%), 230

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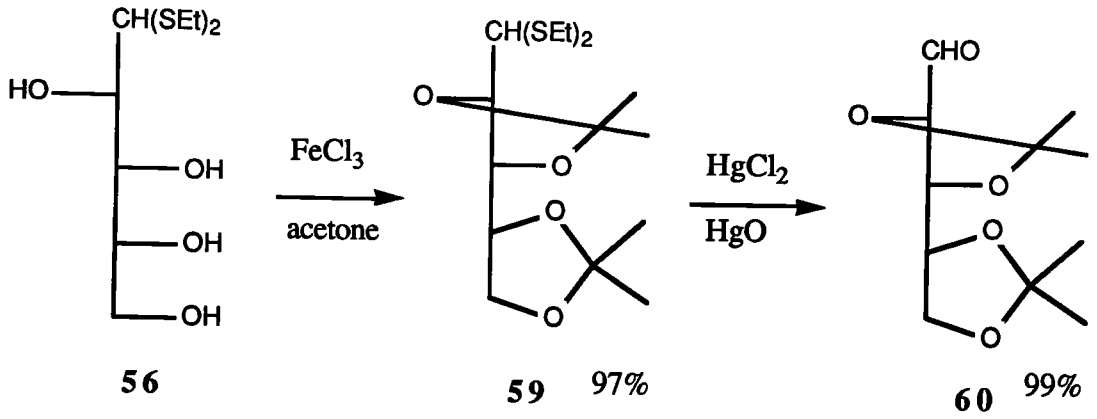
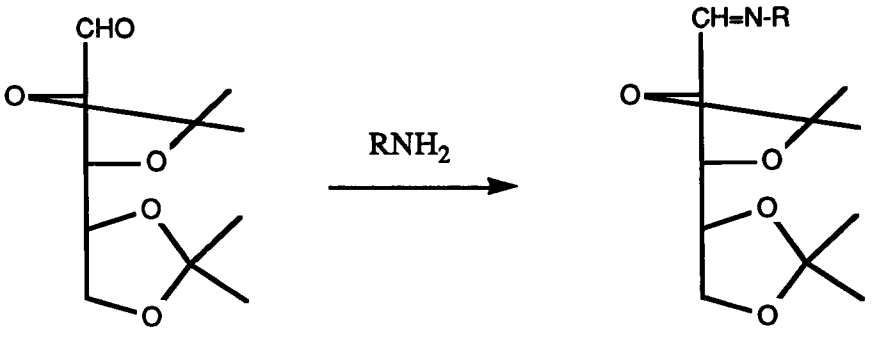
36) H. Zinner, H. Brandner, and G. Rembarz, *Chem. Ber.*, **89**, 800(1956).
37) N.W. Bristow and B. Lithgoe, *J. Chem. Soc.*, 2306(1949).
38) K. Gatzi and T. Reichstein, *Helv. Chim. Acta.*, **21**, 914(1938).
39) R.P. Singh, M.M. Gharia, F. Dasgupta, and H.C. Srivastava, *Tetrahedron Lett.*, 439(1977).
40) H. Zinner, G. Rembarz, And H.P. Klocking, *Chem. Ber.*, **90**, 2688(1957).

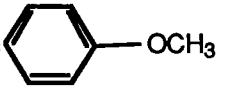
(M^+), 215 (m-CH_3), 173 (M+1-CH_3COCH_3)} thus obtained was reacted with various amines to give the corresponding imines in good yields. These imines were characterized by their ^1H nmr spectra which showed the (-C<u>H</u>=N-) signal at δ=7.72 for **61**, 7.25, for **62**, and 7.93ppm for **63**. Further purification was not feasible since the imines were somewhat unstable toward silica gel chromatography.



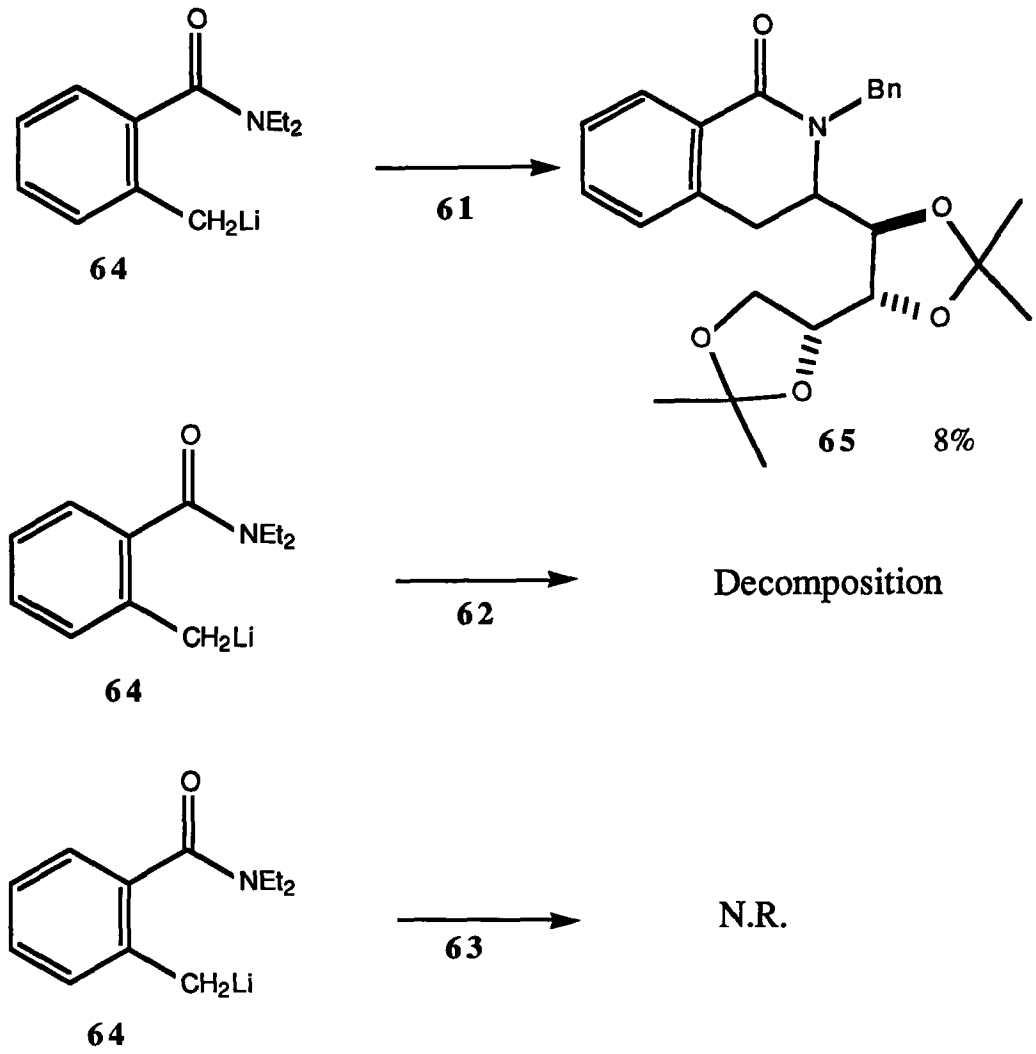
56 **59** 97% **60** 99%



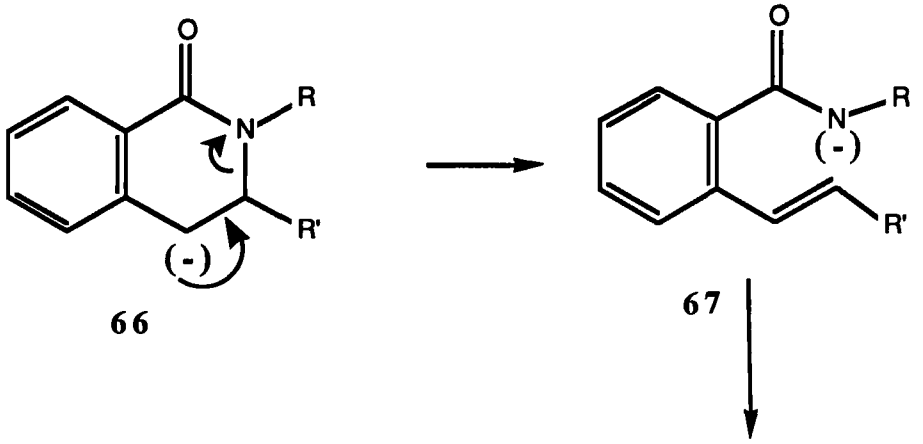
60

61	R=CH_2Ph	90%
62	R= 	80%
63	R=OCH_3	56%

The lithio derivative **64** derived from *N,N*-diethyl-*o*-toluamide by reaction with LDA at -78°C for 5 min.was allowed to react with the above imines. No reaction was observed with the methyl oxime **63** either at -78°C or at room temperature for 18h and only the starting materials were recovered, while exposure to *N*-*p*-methoxyphenylimine **62** gave a complex mixture of products. Reaction with the *N*-benzylimine **61** gave the desired product, **65**, {ir (film) υ: 1650 cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.25 (s, 3H), 1.33 (s, 3H), 1.46 (s, 6H), 3.16 (s, 3H), 3.65 (m, 2H), 3.80 (m, 1H), 4.07 (m, 2H), 4.22 (d, 1H, 7Hz), 5.86 (d, 1H, 7Hz), 7.06 (d, 1H, 3Hz), 7.13-7.40 (m, 7Hz), 8.08 (d, 1H, 3Hz); M.S. (E.I.) (m/z): 437 (M^+), 422 ($M-CH_3$)} but in a disappointing 8% yield.



It was thought that the complex mixture evolving from the reaction of **64** with *N*-*p*-methoxyphenylimine, **62**, and the low yield with the *N*-benzyl derivative **61** may have been due to the unstable nature of the cyclized product under the reaction conditions. For example, the diethylamide generated as a result of the cyclization could conceivably generate a new laterally metalated anion, **66**, which could fragment to **67** and then to further products.



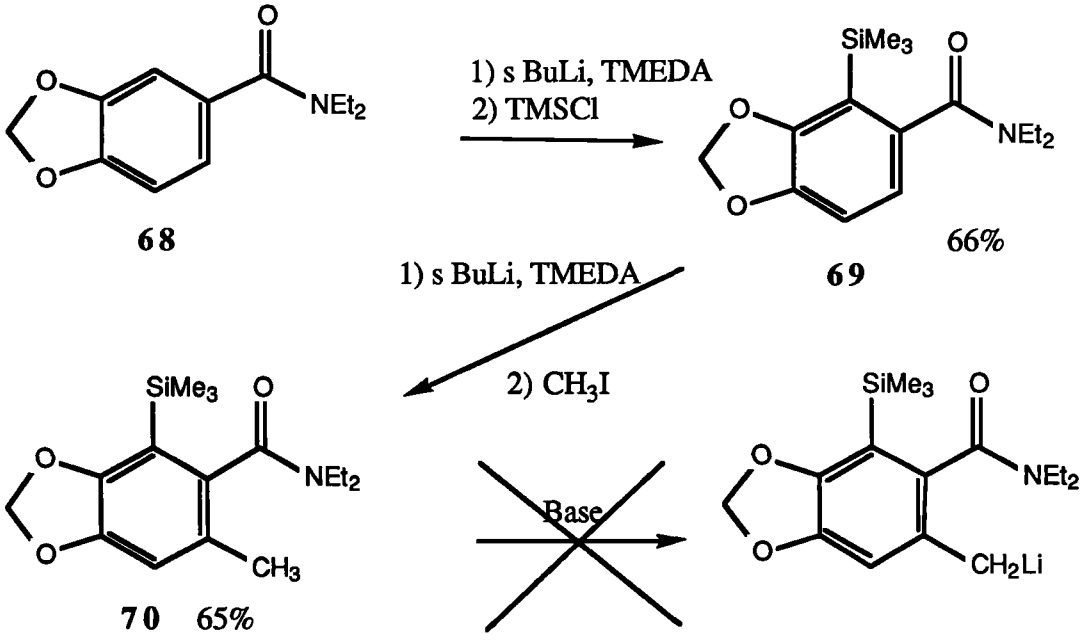
66 67

possible further reactions

To eleviate this potential problem it would be necessary to design an imine which contains an internal trap for the anion of type **66**. Confident that this sequence to *trans*-dihydrolycorcidine would be successful, preparation the *o*-toluamide **70** required for the synthesis of the natural product was initiated. This compound was derived from piperonylic acid. The diethylamide, **68**, was prepared from piperonylic acid via its acid chloride. Since the position most susceptible to ortho-metalation would be between the amide and methylenedioxy groups, that position was blocked with a trimethylsilyl group. This was accomplished by metalation[41] with *s*-BuLi at -78°C for 15 min. followed by quenching with TMSCl which afforded **69**. Subsequent metalation of **69** under the same conditions followed by quenching with methyl iodide afforded the desired *o*-toluamide, **70** {ir (film) υ: 1622 ($Ar(C=O)NR_2$) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.25 (s, 9H), 1.03 (t, 3H, 7Hz), 1.24 (t, 3H,

41) R.J. Mills and V. Snieckus, *J. Org. Chem.*, **48**, 1567(1983).

7Hz), 2.13 (s, 3H), 3.10 (m, 3H), 3.90 (dq, 1H, 7Hz, 6.5Hz), 5.86 (d, 1H, 1.5Hz), 5.89 (d, 1H, 1.5Hz), 6.62 (s, 1H); M.S. (m/z): 307 (M^+), 292 (M-CH_3) (100%), 278 (M-Et), 235 (M-NEt_2)}.

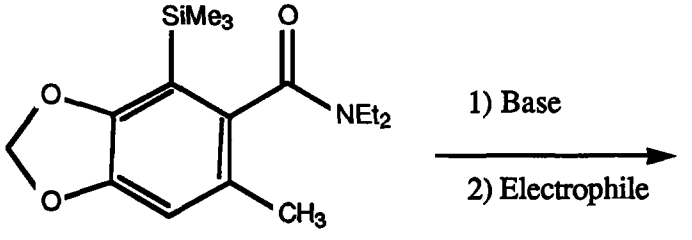


Surprisingly all attempts to laterally metalate *o*-toluamide, **70**, failed under a variety of reaction conditions and with a variety of bases (Table 5). No reaction occurred, only starting amide was recovered. On one occasion reaction of **70** with *t*-BuLi at 0°C in ether, followed by quenching with benzaldehyde, afforded a product in 10% yield which was identified as **71** on the basis of its ^1H nmr and mass spectral data {ir (film) υ: 3950 (O-H), 1630 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (60MHz) δ: 0.21 (s, 9H), 0.80 (t, 3H, 7Hz), 1.02

(t, 3H, 7Hz), 1.82 (s, 3H), 2.90 (m, 3H), 3.45 (m, 1H), 4.20 (s, 1H), 5.60 (s, 2H), 6.20 (s, 1H), 7.20 (m, 3H), 7.45 (m, 2H); M.S. (m/z): 306 (M-(H_2O+Ph), 292 M-(H_2O+NEt_3)}. This product resulted from metalation on the aromatic ring.

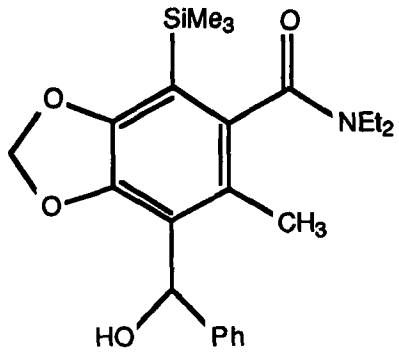
Table 5

Attempts at Lateral Metalation of **70**



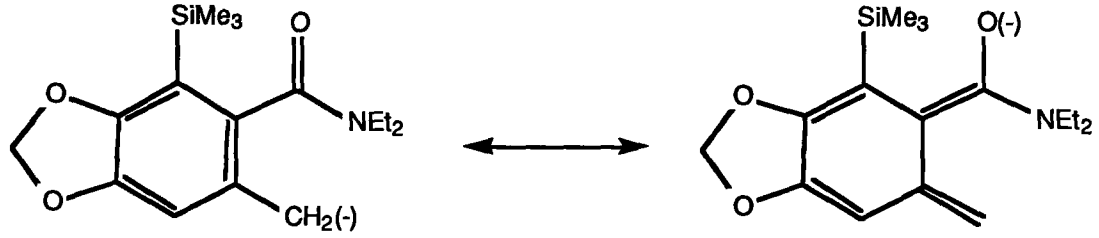
70

Base	Temp.	Solvent	Electrophile	Result
LDA	-78°C	THF	D_2O	N.R.
s-BuLi/TMEDA	"	"	"	"
LDA	-50°C	"	"	"
"	-40°C	"	"	"
"	0°C	"	CH_3I	"
"	"	ether	PhCHO	**71**



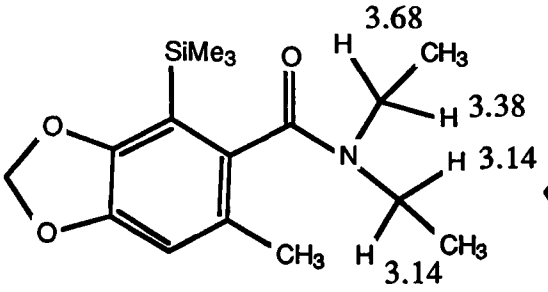
71

A possible explanation for the desired anion not being formed may be that the trimethylsilyl group causes the carbonyl in the amide to rotate out of the plane of the aromatic ring. The π-system of the amide, therefore, cannot overlap with the π-system of the aromatic ring. Such overlap is thought to stabilize an anion generated on the methyl group.[40]

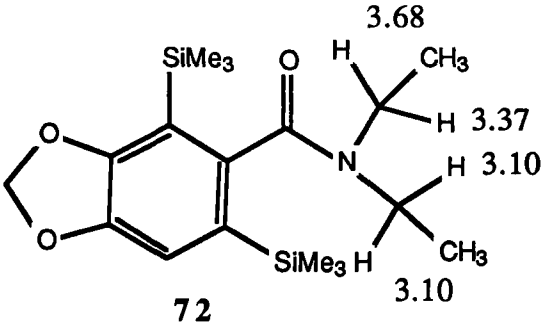


The fact that the silyl group does keep the amide out of the plane of the aromatic ring is in agreement with the 300MHz ^{1}H NMR spectrum of **70**. It appears that the molecule is chiral due to such restricted rotation, and this makes the methylene protons of the ethyl groups prochiral and thus renders them non-equivalent. This is similar to chirality of *o,o'*-disubstituted biphenyls and binaphthyls where steric hindrance prevents the rings from being coplanar. The

phenomenon is very distinct not only in the *o*-toluamide, **70**, but also in the doubly silylated compound **72** prepared by silylation of the corresponding dianion. This phenomenon is better illustrated by the inclusion of the 300MHz ^1H nmr spectra of **70** and **72** on the next two pages, these clearly show the separation between 2.5 and 4.0ppm of the methylene protons of the diethylamides.

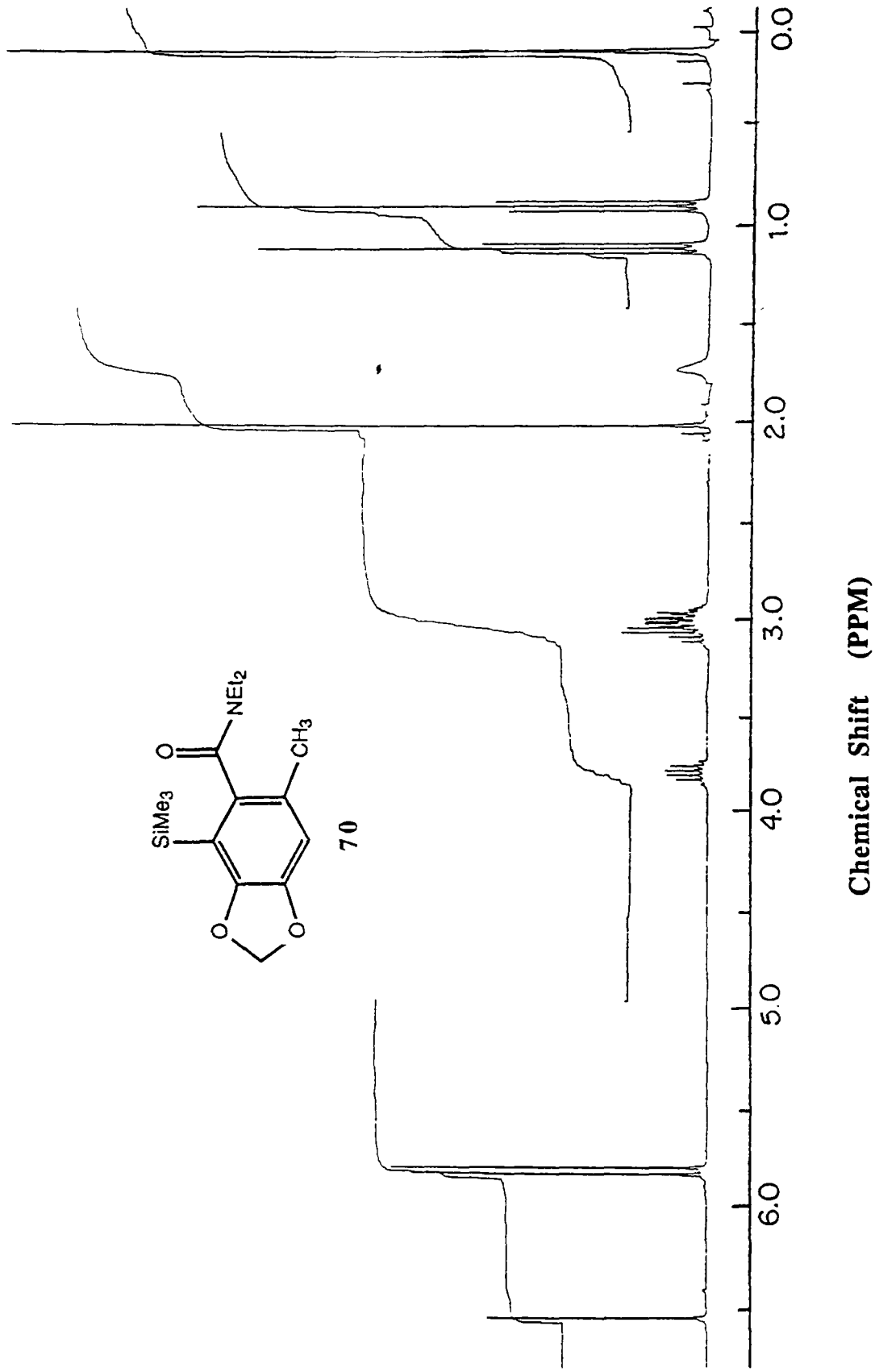


70

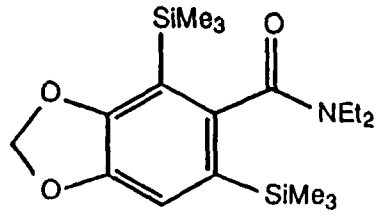


72

300MHz ^{1}H NMR SPECTRUM OF **70**

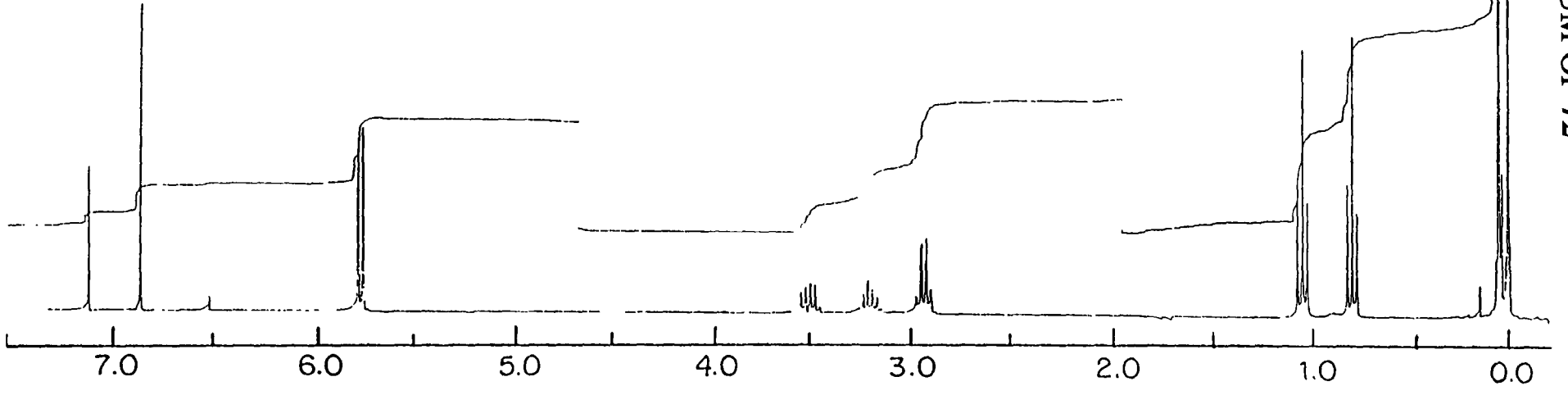


70



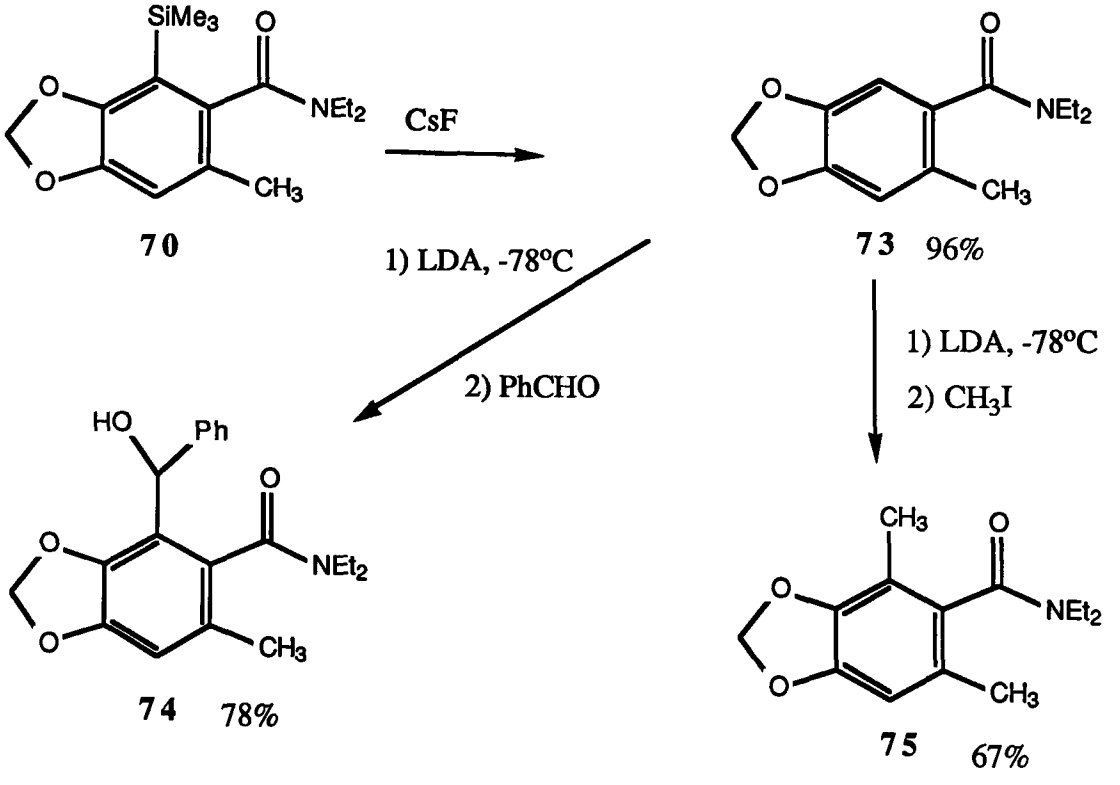
72

300MHz ^{1}H NMR SPECTRUM OF **72**



Chemical Shift (PPM)

The trimethylsilyl group appeared to prevent anion formation at the ortho-methyl group in **70**. Since it was not required in the final product it was removed. Furthermore it has been pointed out by Snieckus that, in general, lateral metalation is favoured over ortho-metalation.[42] The TMS group of **70** was removed cleanly by use of cesium fluoride in wet DMF to give the *o*-toluamide **73** in 96% yield. Unfortunately, reaction of, **73** with LDA at -78°C, followed by quenching with either methyl iodide or benzaldehyde, gave only the undesired products, **74** and **75**, resulting from ortho-metalation.

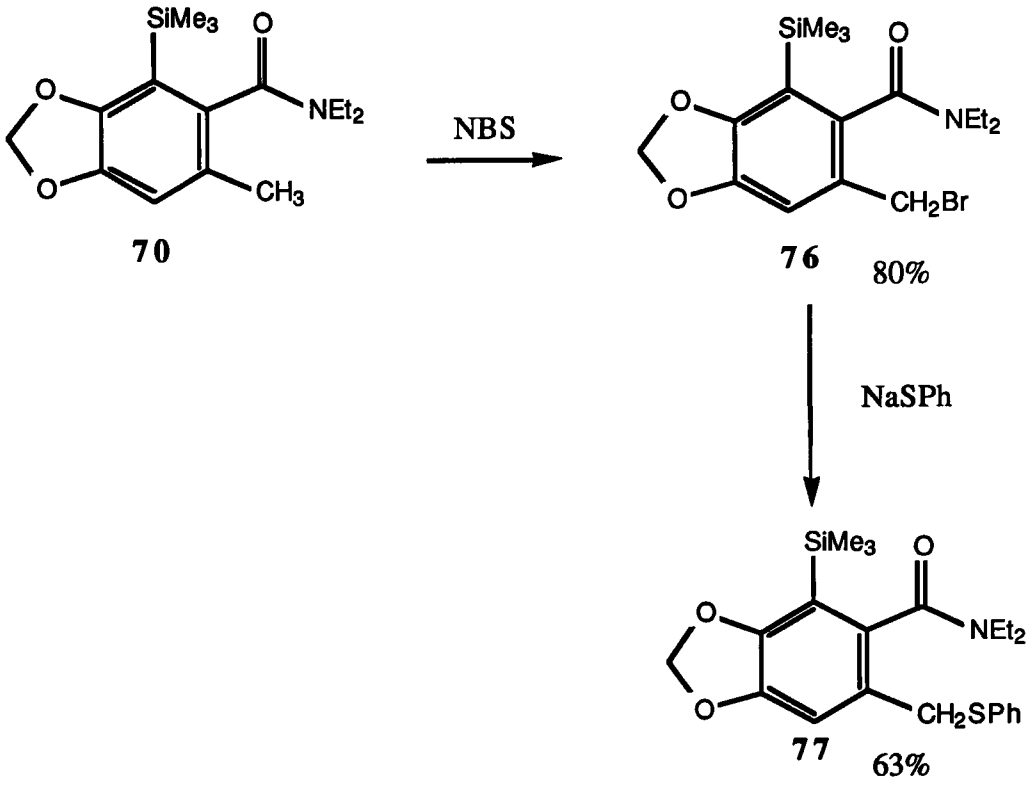


42) R.J. Mills and V. Snieckus, *Tetrahedron Lett.*, 479(1984).

Obviously for compound **73** the general comment concerning the preference of lateral vs ortho metalation does not hold since the ortho-position is doubly activated by both the amide and methylenedioxy functions. Generation of the dianion resulting from ortho-metalation followed by lateral-metalation of **73** was attempted under a variety of conditions, such as treatment with two equivalents of *s*-BuLi/TMEDA for various time periods (30 min. to 3h) at -78°C, but these attempts proved fruitless.

In a final approach the methyl group of toluamide **70** was brominated with NBS in refluxing carbon tetrachloride to give cleanly the bromomethyl derivative **76**. From this compound it was expected to generate the desired anion directly via metal-halogen exchange or to displace the bromide by thiophenolate in the hope that the PhS group would sufficiently increase the acidity of the benzylic hydrogens and thus lead to lateral metalation. All attempts to achieve lithium-halogen exchange in the bromide **76** failed, leaving only unreacted bromide.

Reaction of the bromide **76** with sodium thiophenolate in THF gave the expected sulfide, **77** {ir (film) υ: 1624 ($Ar(C=O)NR_2$) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.26 (s, 9H), 1.07 (t, 3H, 6.5Hz), 1.19 (t, 3H, 6.5Hz), 3.03 (q, 1H, 6.5Hz), 3.19 (m, 2H), 3.94 (q, 1H, 6.5Hz), 3.96 (d, 1H, 13Hz), 4.03 (d, 1H, 13Hz), 5.90 (d, 1H, 2.5Hz), 5.93 (d, 1H, 2.5Hz), 6.88 (s, 1H), 7.83 (m, 5H); M.S. (m/z): 415 (M^+), 400 M-CH_3), 342 (M-TMS), 306 (M-SPh), 292 (M-CH_2SPh)}.



Our expectations of the increased acidity of the CH_2SPh vs the methyl group was realized. The α-phenylthiomethyl compound, **77**, when treated with *s*-BuLi/TMEDA followed by quenching with benzaldehyde, gave the coupling product, **78**, in 70% yield. However, here, too, the approach was foiled since attempts to condense the sulfur-stabilized anion with a variety of imines including **61** and the *N*-aryl and *N*-sulfonyl-imines shown in Figure 6 failed and resulted in recovery of both starting materials, probably because of the lower reactivity of the imines relative to aldehydes. Thus the lateral metalation approach outlined in Scheme 4 was abandoned.

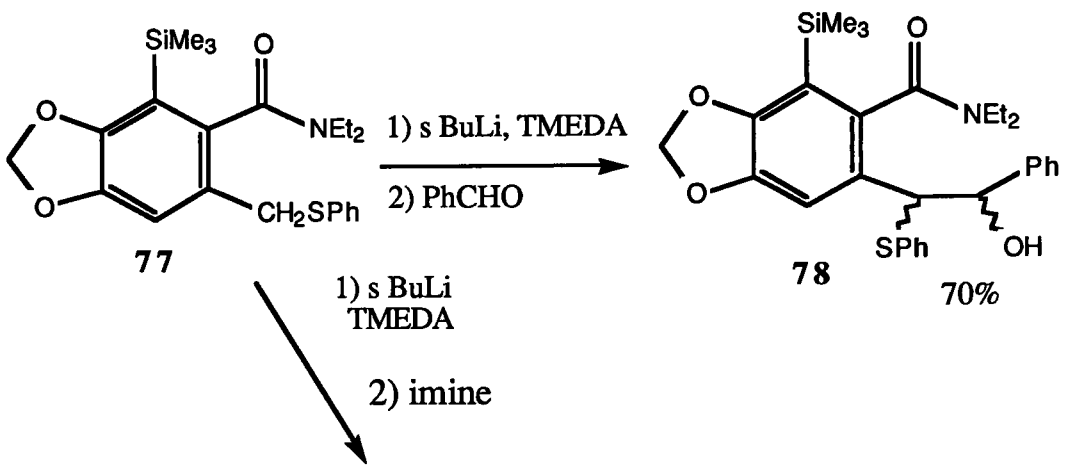
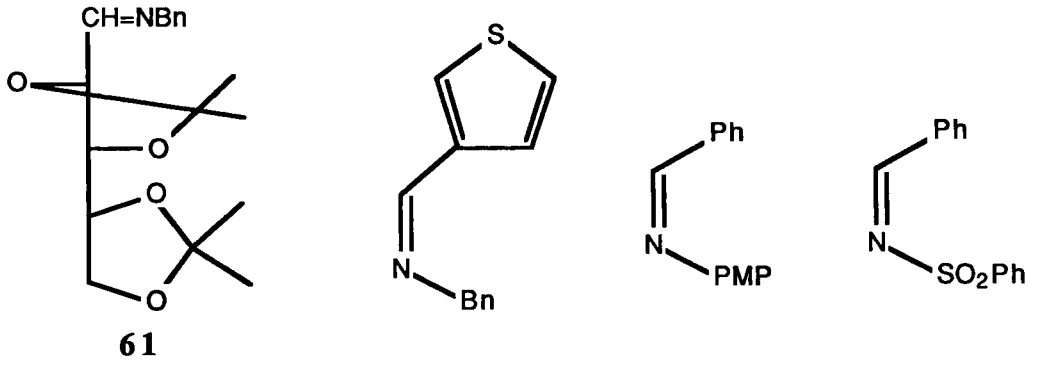


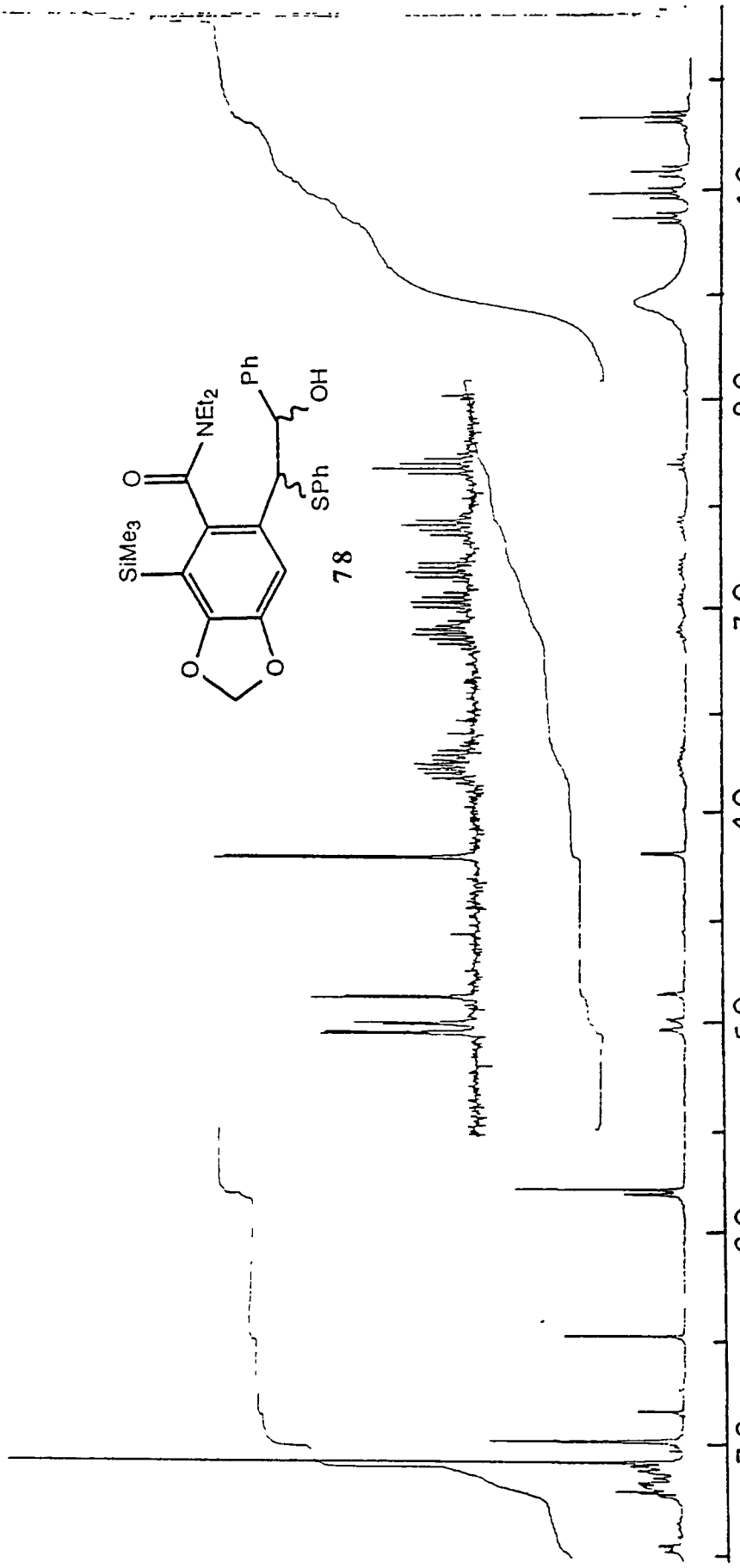
FIGURE 6



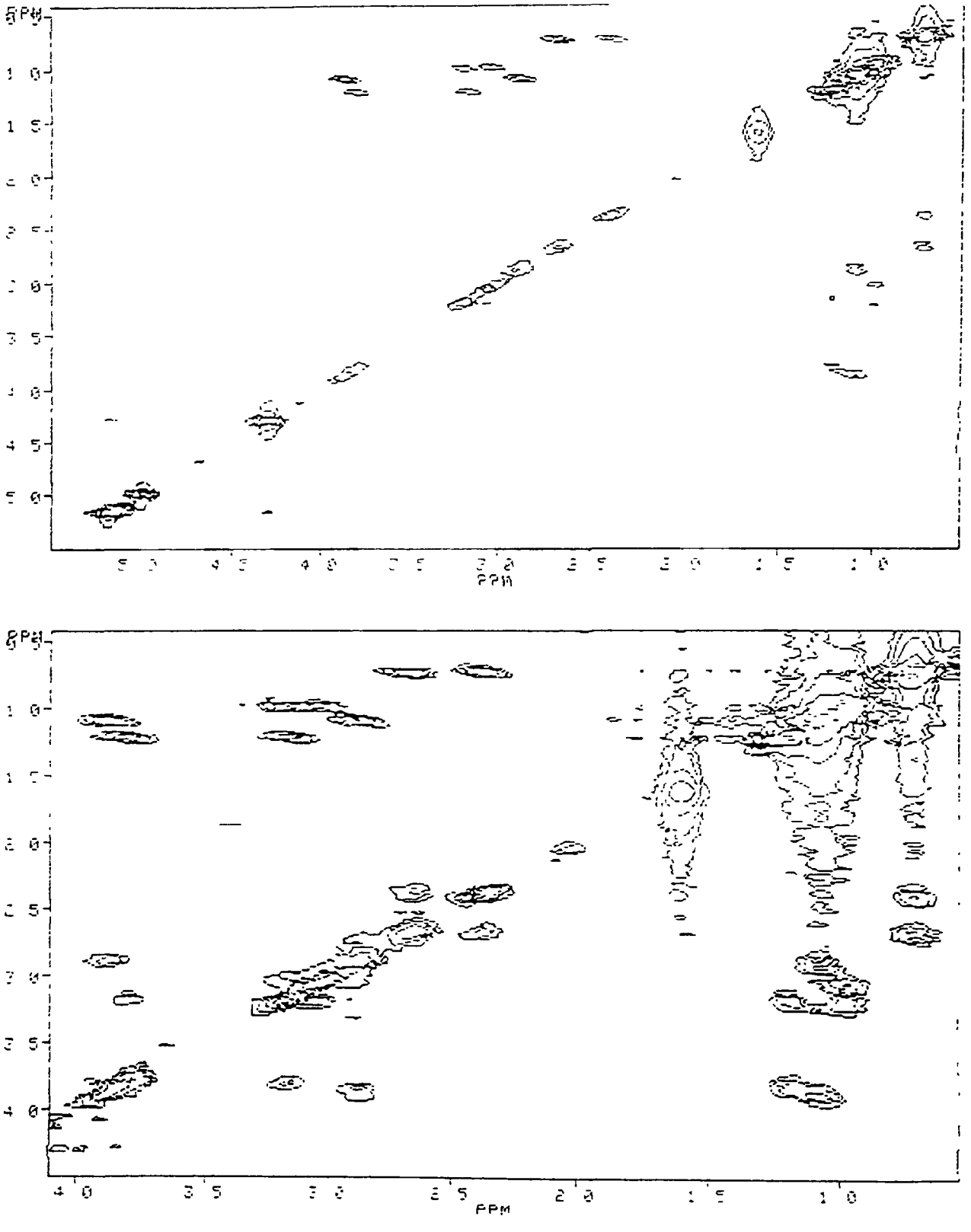
The next page shows the 300MHz ^{1}H nmr spectrum of compound **78** is included since it is a mixture of diastreomers and difficult to interpret and cannot be fully explained in the experimental section. The following page shows the 2D HOMCOR spectrum which was included to aid in the interpretation of the ^{1}H nmr spectrum. Using this it is possible to to assign which protons are

coupled to each other but, it is impossible to assign them to each diastereomer.

300MHz ^{1}H NMR SPECTRUM OF **78**



HOMCOR SPECTRUM OF 78



Chemical Shift (PPM)

CHAPTER 5

ORTHO-METALATION APPROACH

This approach involved the generation of a dianion from an *o*-bromobenzoic acid and subsequent quenching with an epoxide to ultimately give a γ-lactone. The ortho-metalated dianion necessary would be produced by halogen-lithium exchange. Halogen-lithium exchange is a common and widely used method for generating aryl-lithio species.[43] The γ-lactone could then be converted into the desired γ-lactam. This is outlined in Scheme 5 on the following page.

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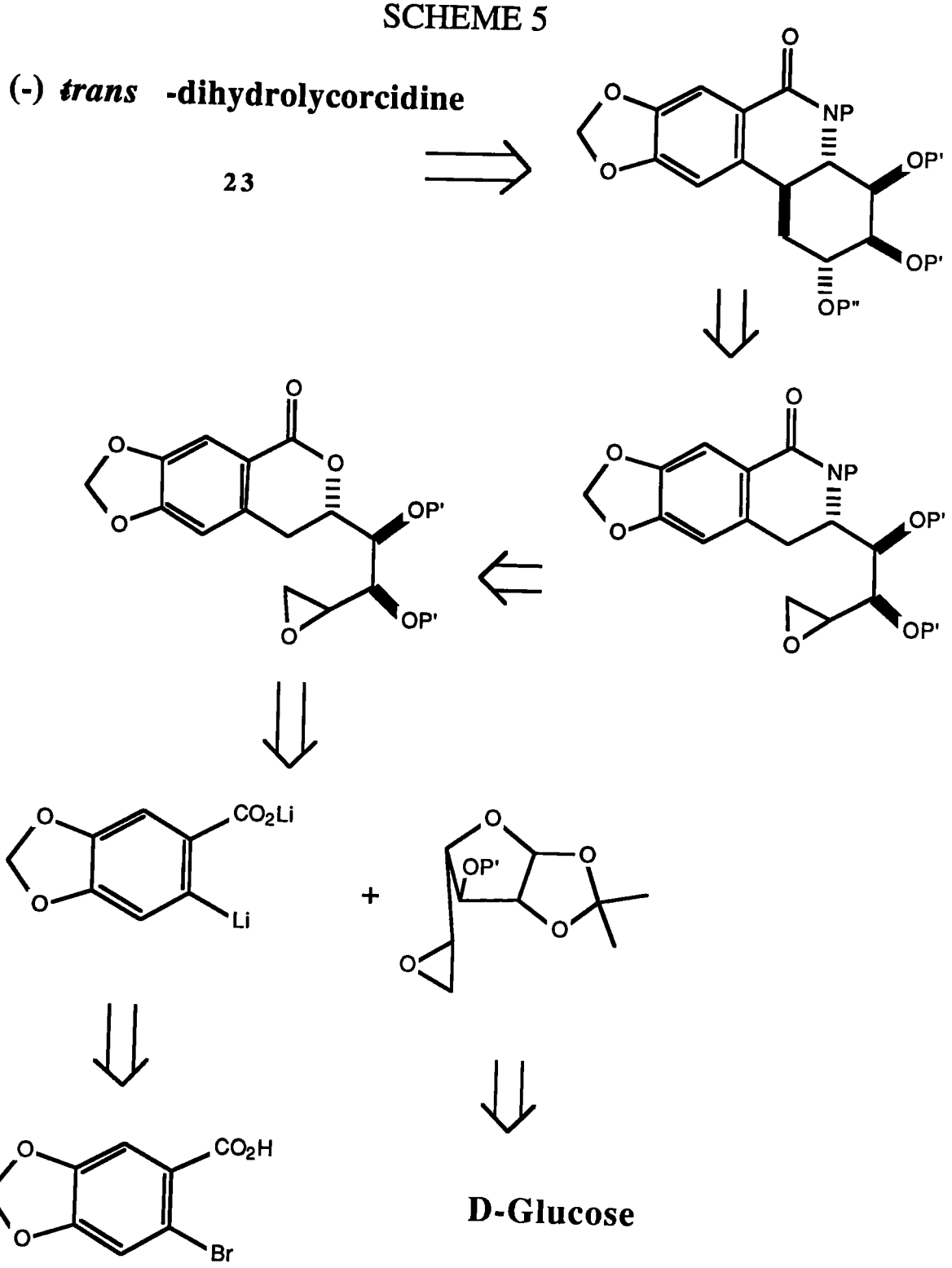
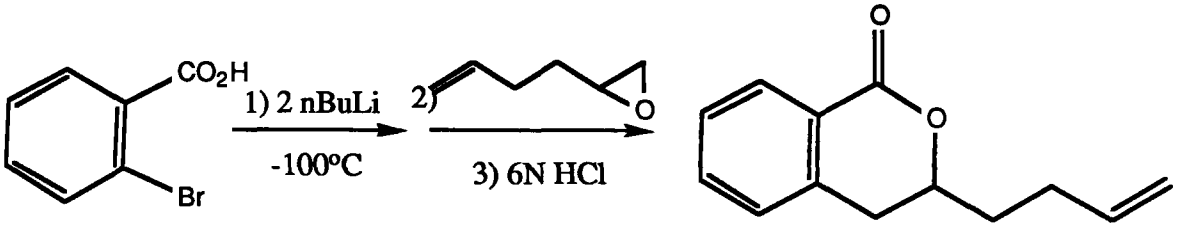
43) W.E. Parham and C.K. Bradsher, *Acc. Chem. Res.*, **15**, 300(1982).

SCHEME 5


(-) trans -dihydrolycorcidine
23
NP
OP'
OP'
OP"
NP
OP'
OP'
OP'
OP'
CO2Li
Li
OP'
+
CO2H
Br
D-Glucose

For a model study 5,6-epoxy-1-hexene was chosen and it was reacted with the dianion generated from *o*-bromobenzoic acid.[44] The desired lactone **79** {ir (film) υ: 3075 (Ar-H), 2930 (C-H), 1610 (ArC-C), 1642 ($RCH=CH_2$), 1725 ($ArCO_2R$) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.85 (m, 2H), 2.27 (m, 2H), 2.91 (m, 2H), 4.50 (m, 1H), 4.98 (m, 2H), 5.80 (m, 1H), 7.23 (dd, 1H, 7Hz, 1Hz), 7.37 (ddd, 1H, 8Hz, 7.5Hz, 1Hz), 7.51 (ddd, 1H, 7.5Hz, 7Hz, 1Hz), 8.07 (dd, 1H, 8Hz, 1Hz); ^{13}C nmr ($CDCl_3$) (DEPT) δ: 29.06 (CH_2), 33.24 (CH_2), 34.13 (CH_2), 77.87 (CH), 115.57 (CH_2), 125.08 (quaternary), 127.25 (CH), 127.52 (CH), 130.14 (CH), 133.55 (CH), 137.06 (CH), 138.94 (quaternary), 165.36 (quaternary); M.S. (m/z): 202 (M^+), 184 (M-H_2O), 147 (M-($(CH_2)_2CH=CH_2$))} was obtained, but in a disappointing yield.



79 27%

Due to the low yield obtained and the fact that it had been shown by Ellefson,[45] that very harsh conditions would be required to convert the lactone into the hydroxyamide required to prepare the

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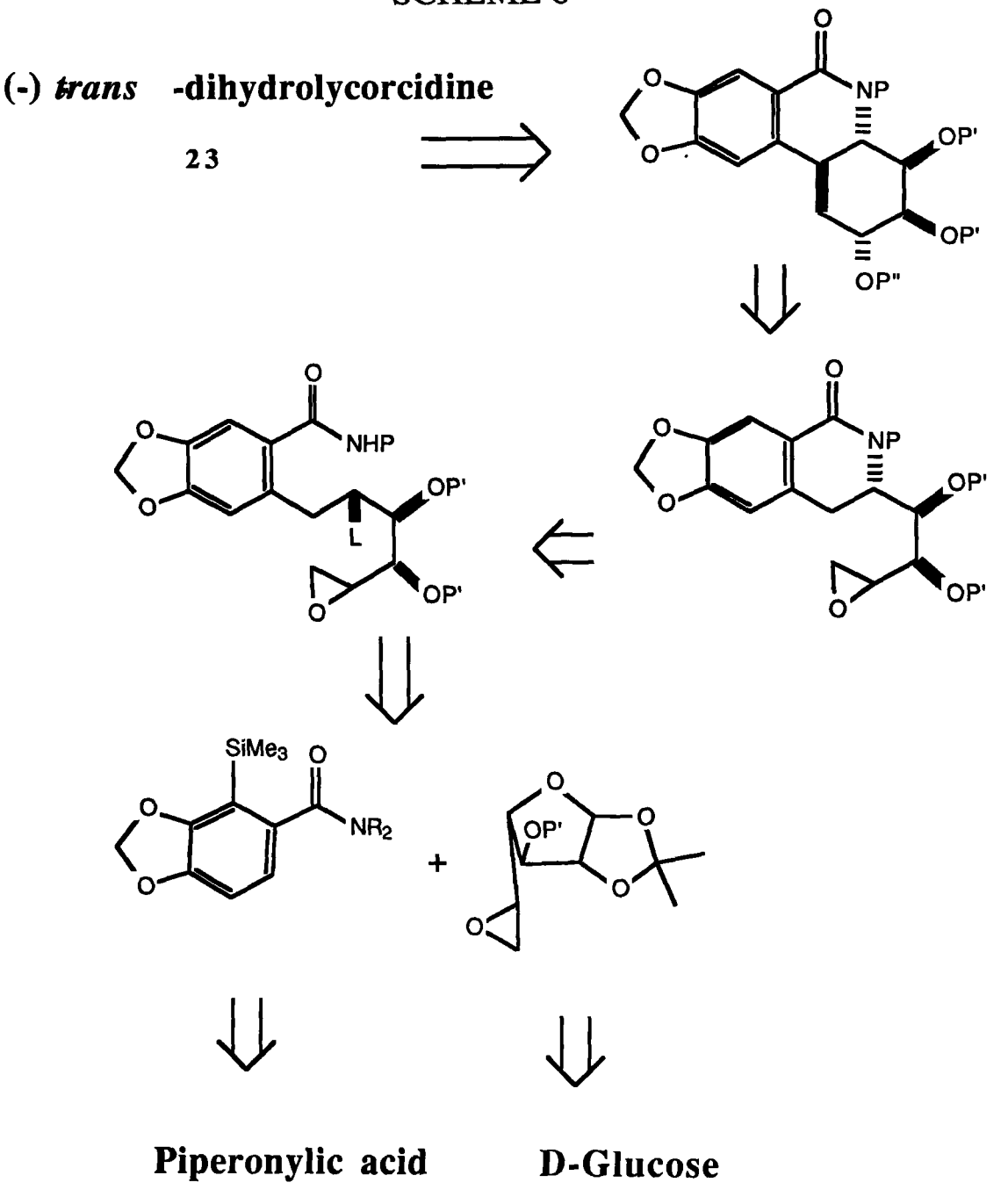
44) W.E. Parham and Y.A. Sayed, *J. Org. Chem.*, **39**, 2053(1974).
45) C.R. Ellefson, *J. Org. Chem.*, **44**, 1533(1979).

required lactam, it was decided to try to obtain the hydroxyamide directly. To obtain the desired hydroxy-amide directly, directed or ortho-metalation techniques had to be employed to generate the desired aryl-anion, which would be condensed with a suitable epoxide. This technique has been developed by Beak, Meyers and Snieckus and has been the subject of recent reviews.[46] This modified approach is outlined in Scheme 6.

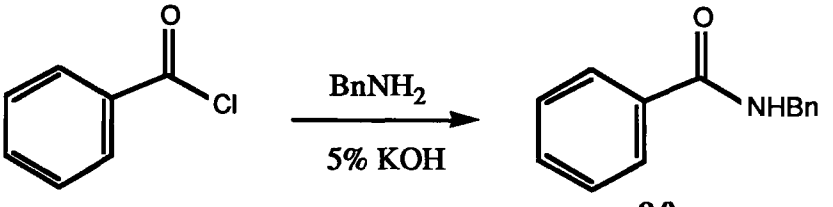
---

[46])a) P. Beak and V. Snieckus, *Acc. Chem. Res.*, **15**, 306(1982), b) p. Beak, A. Tse, J. Hawkins, C. Chen, and S. Mills, *Tetrahedron*, **39**, 1983(1983), N.S. Narasimhan and R.S. Mali, *Topics in Current Chem.*, **138**, 64(1987).

SCHEME 6


(-) trans -dihydrolycorcidine
23
O
NP
OP'
OP'
OP"
NHP
L
SiMe3
NR2
+
Piperonylic acid
D-Glucose

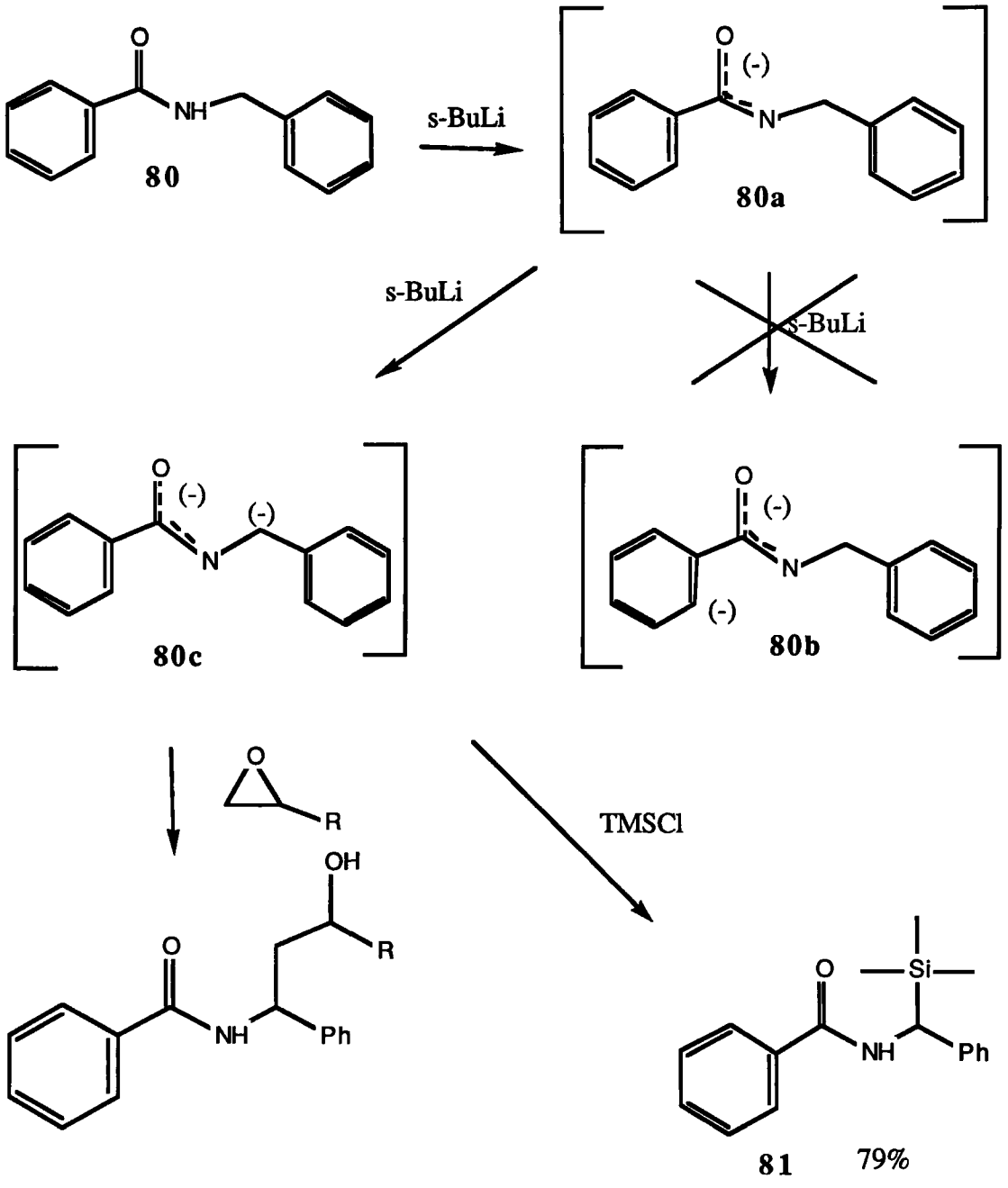
N-Benzylbenzamide,[46] **80**, was synthesized from benzoyl chloride and benzylamine via a Schotten-Baumann reaction. Reaction of **80** with 2 equivalents of *s*-butyllithium at -78°C followed by quenching with trimethylsilyl chloride or epoxides gave the products **81** and **82** or **83** respectively. Thus further metalation of the amide mono-anion derived from **80** occurred preferentially at the benzylic carbon rather than ortho to the amide function. This result was rather surprising since *N*-lithio amide groups such as found in benzamide **80a** are known to be rather potent ortho metalating groups.[47] Furthermore, anion formation α to a nitrogen especially a nitrogen, bearing a partial negative charge is typically an unfavorable process.[48]



80

47)a) W.H. Puterbaugh and C.R. Hauser, *J. Org. Chem.*, **29**, 853(1964)., b) N.S. Narasimhan and R.S. Mali, *Synthesis*, 957(1983).

48) R.E. Ludt and C.R. Hauser, J. Org. Chem., 36, 1607(1971).

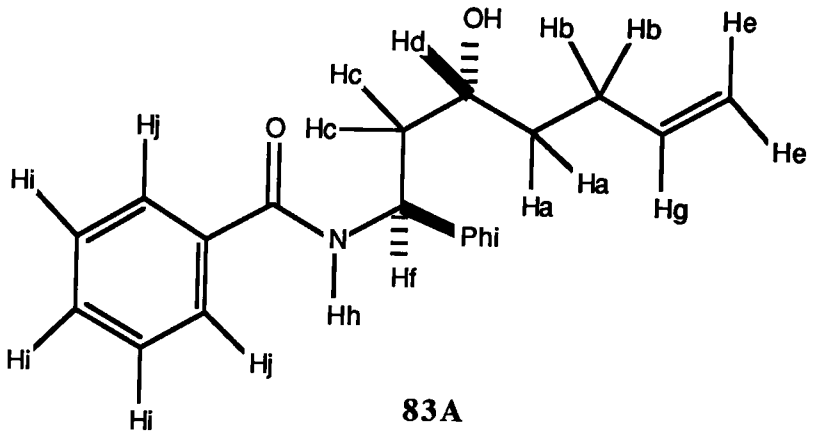


82 R= Ph 65%

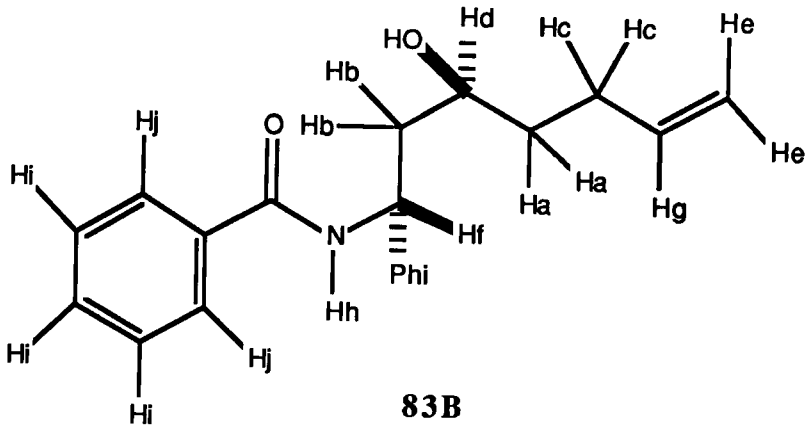
83 R= $(CH_2)_2CH=CH_2$ 59%

Alcohol **83** was obtained as a 1:1 mixture of diastereomers (**83A** and **83B**) which could be separated chromatographically. A 2D Homonuclear correlation proton NMR spectrum was obtained for each diastereomer to assign each proton signal unambiguously.

Structure **83A**				Structure **83B**			
1.62	m	2H	Ha	1.55	m	2H	Ha
1.97	m	2H	Hb	1.98	m	2H	Hb
2.13	m	2H	Hc	2.04	m	2H	Hc
3.70	m	1H	Hd	3.76	m	1H	Hd
4.93	m	2H	He	4.96	m	2H	He
5.47	m	1H	Hf	5.15	m	1H	Hf
5.80	m	1H	Hg	5.81	m	1H	Hg
6.86	d	1H	Hh	7.10	d	1H	Hh
7.40	m	8H	Hi	7.35	m	8H	Hi
7.78	dd	2H	Hj	7.78	dd	2H	Hj

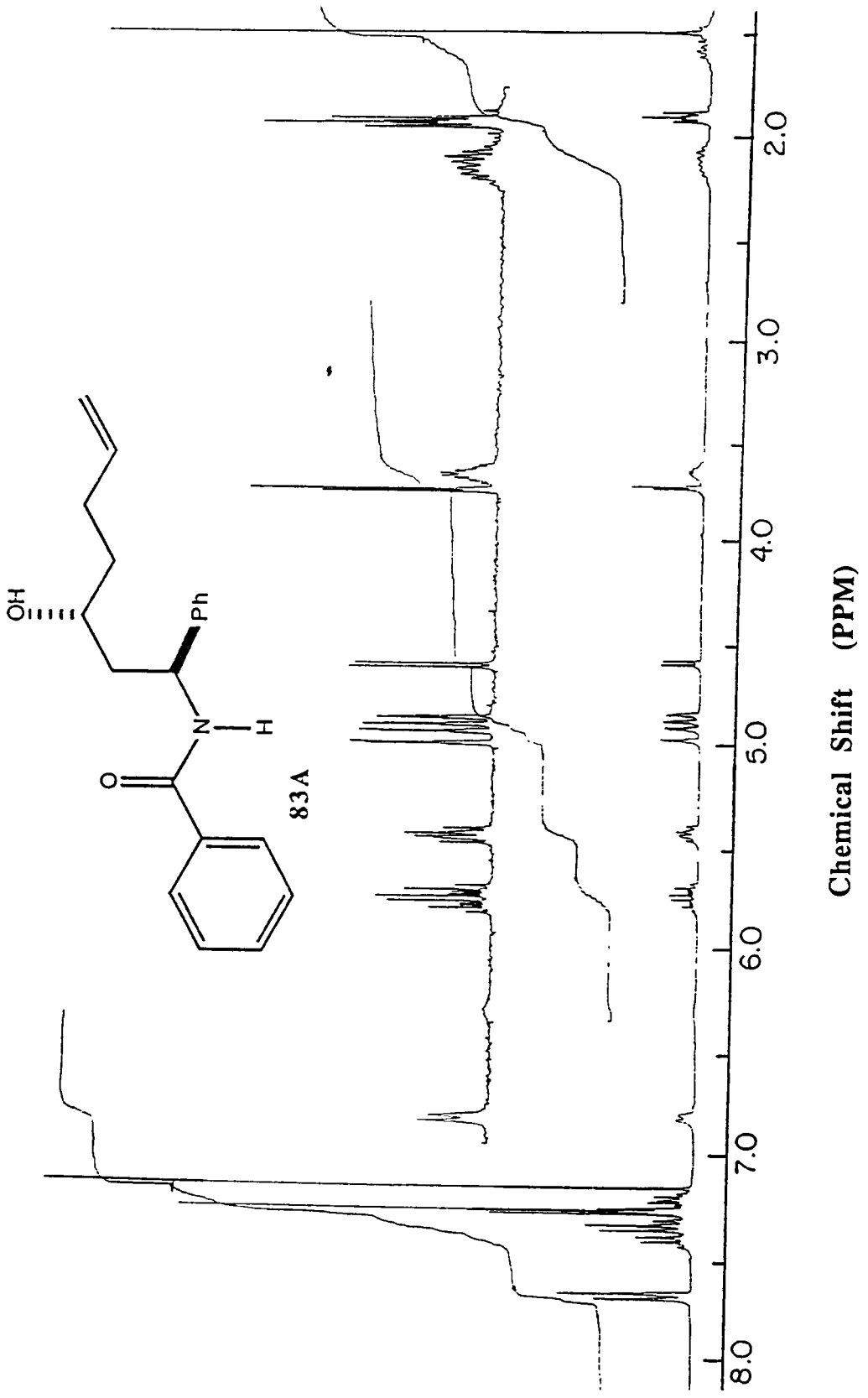

OH
Hd
Hb
Hb
He
Hc
Hj
O
Hc
He
Hi
Ha
Ha
Hg
N
Phi
Hf
Hh
Hi
Hj
Hi

83A

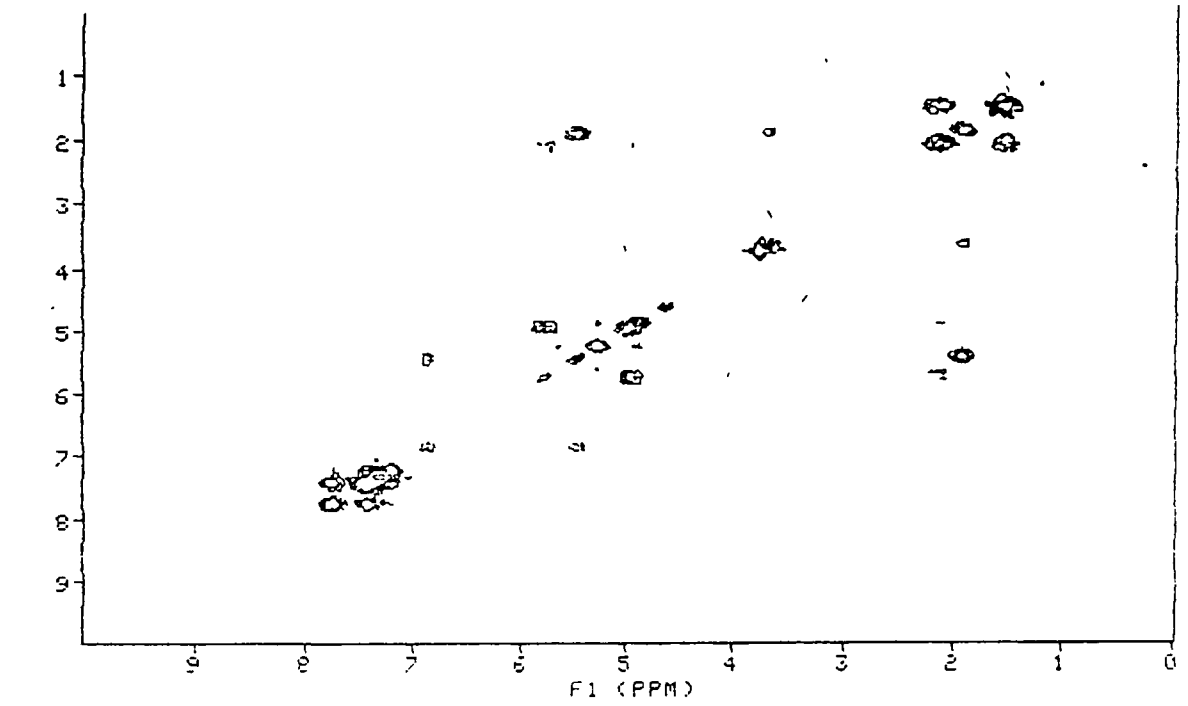

Hd
HO
Hc
Hc
He
Hb
Hj
O
Hb
He
Hi
Ha
Ha
Hg
N
Hf
Phi
Hh
Hi
Hj
Hi

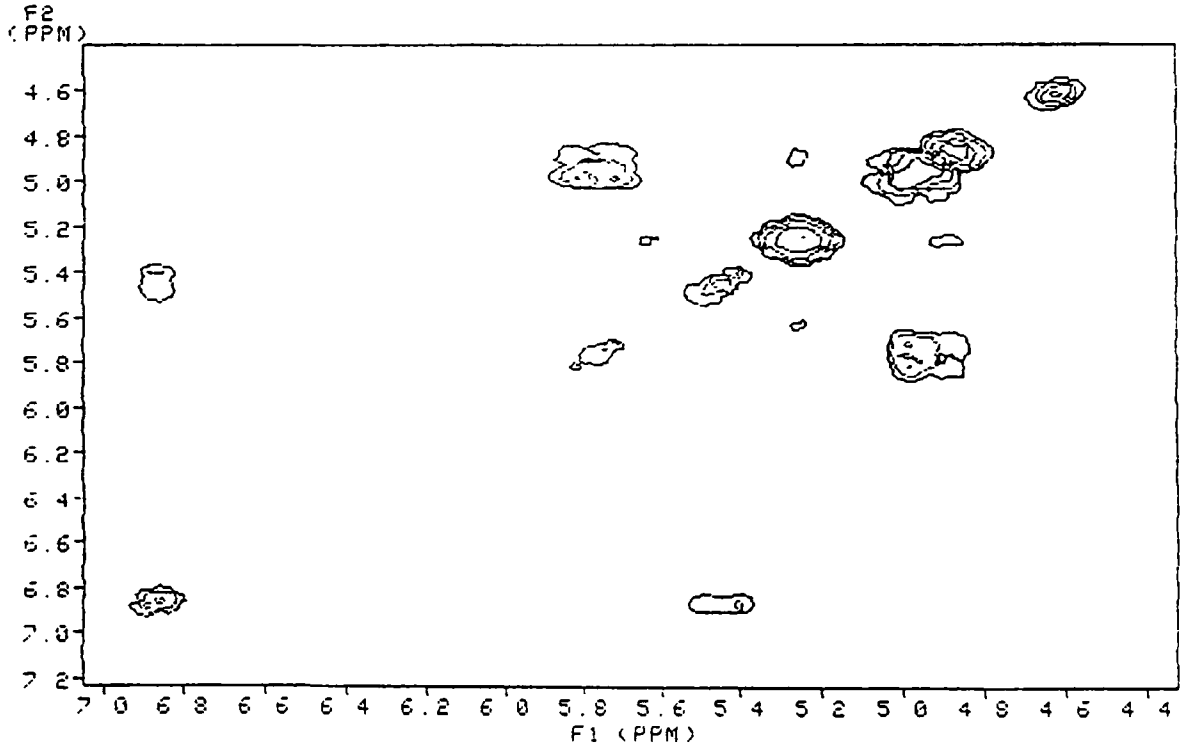
83B

300MHz ^{1}H NMR SPECTRUM OF **83A**



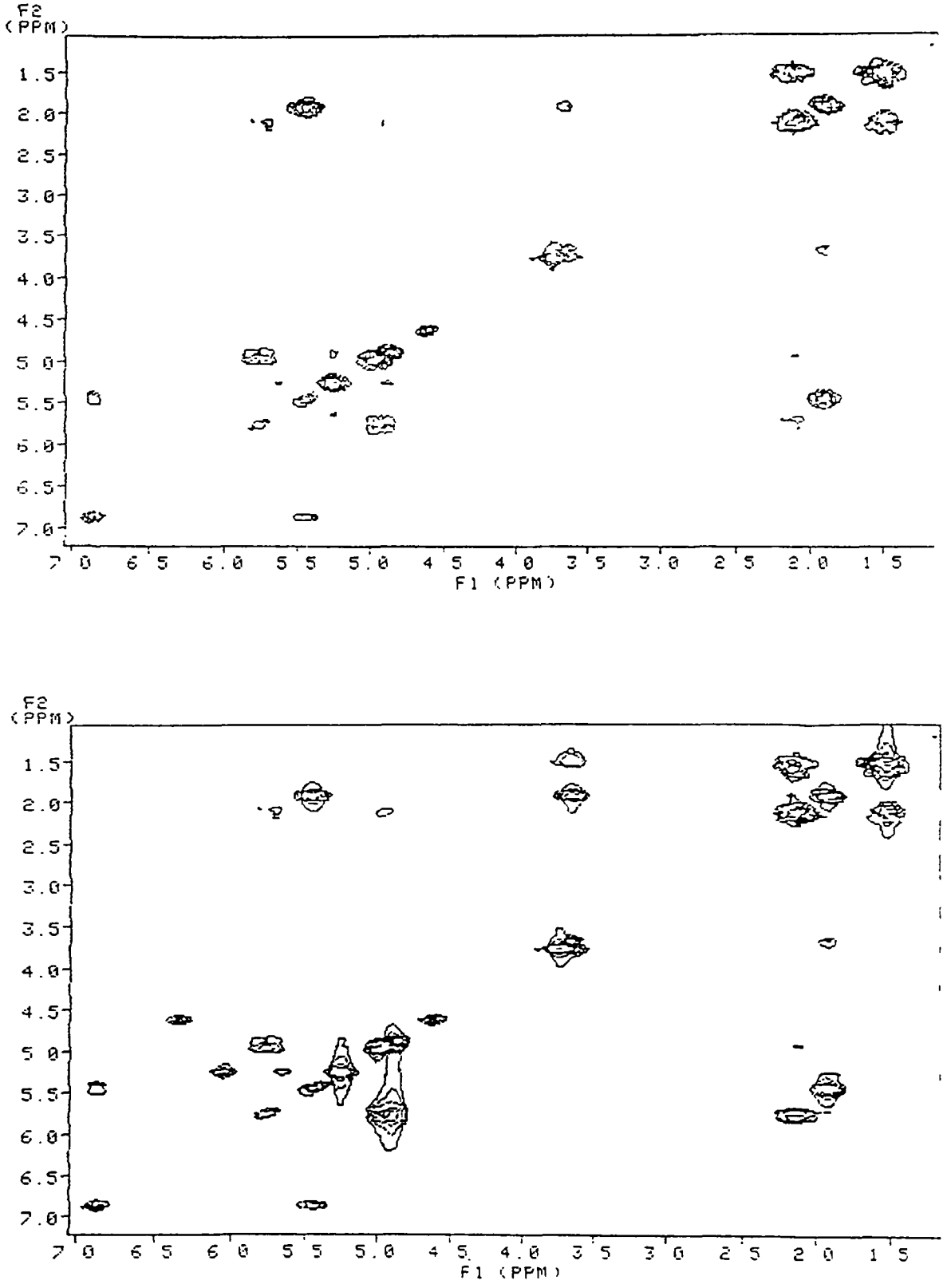
HOMCOR SPECTRUM OF **83A**





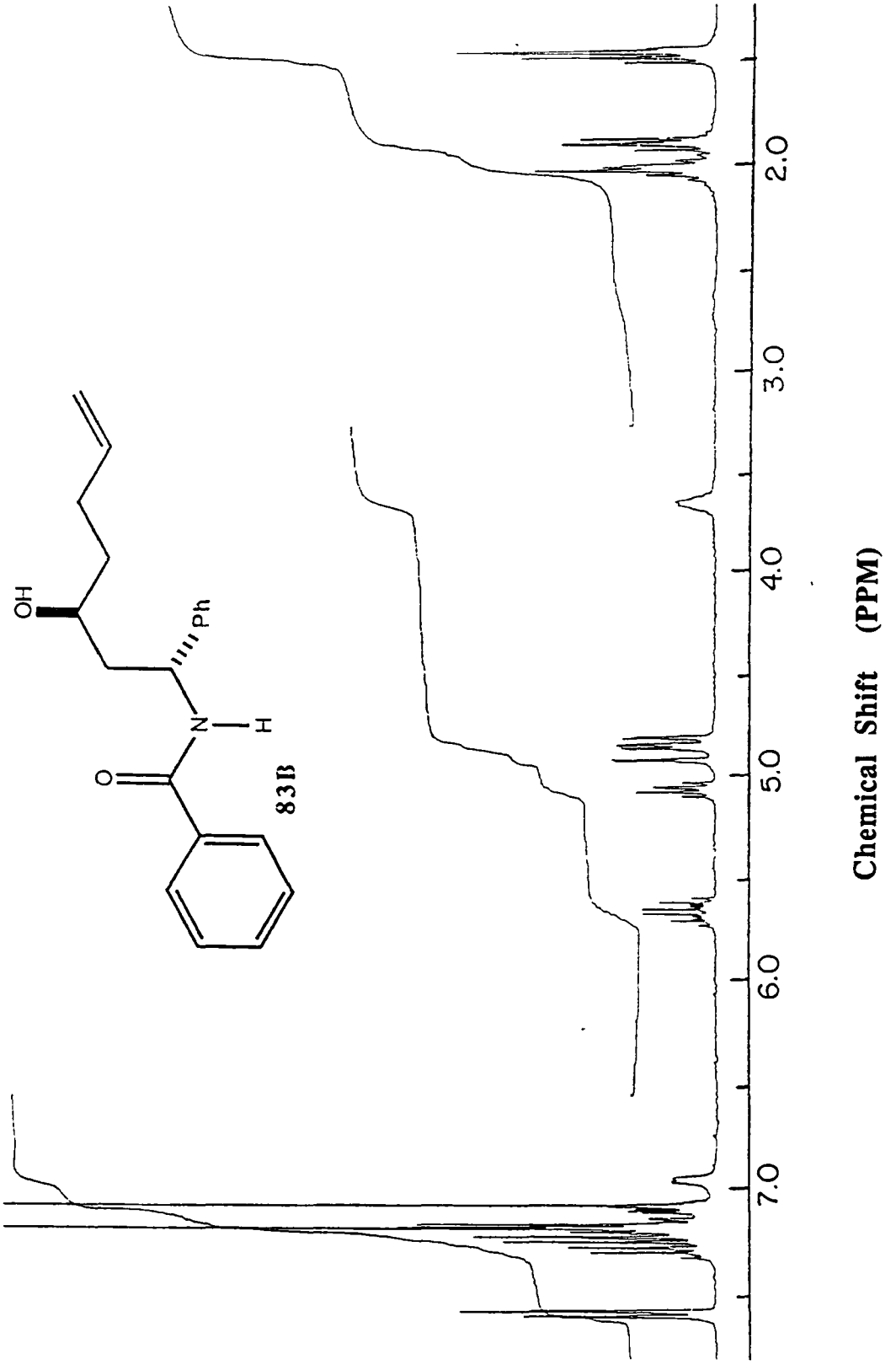
Chemical Shift (PPM)

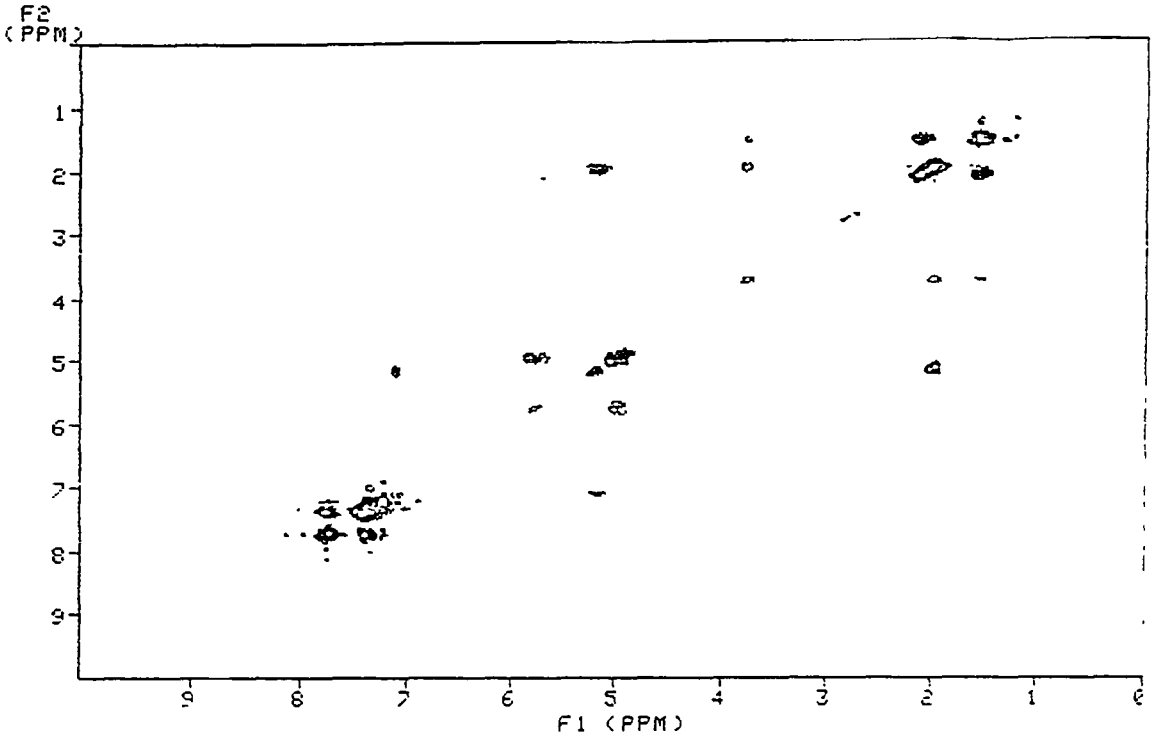
EXPANSION OF HOMCOR SPECTRUM OF **83A**

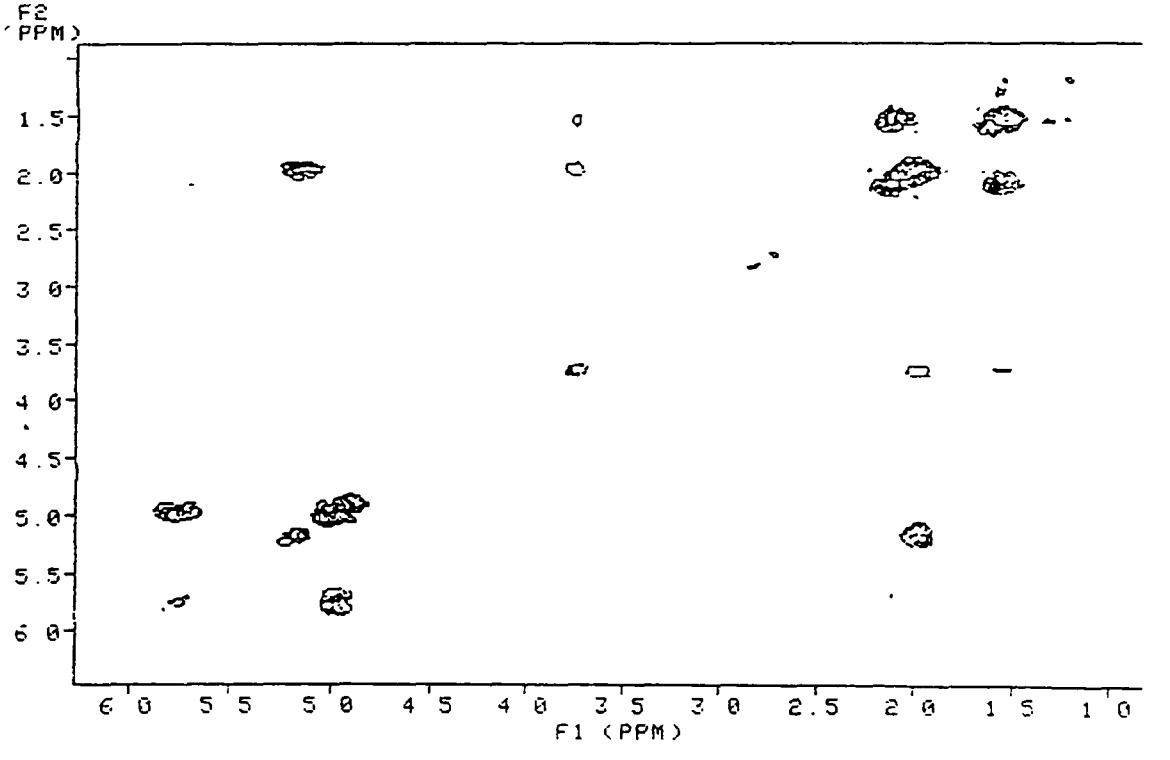


Chemical Shift (PPM)

300MHz ^{1}H NMR SPECTRUM OF **83B**







Chemical Shift (PPM)

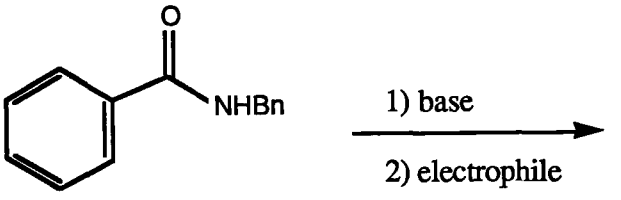
In order to favor the formation of dianion **80b**, changing the size of the alkyllithium base was first attempted, but only the benzylic dianion **80c** was obtained. Changing the counter-ion on the nitrogen from lithium to sodium was also attempted in an effort to enhance the formation ortho-metalated dianion **80b**, but this too failed. When benzamide **80** was treated with 2 equivalents of *s*-BuLi/TMEDA at either -78 or 25°C, the product resulting from silylation of the benzylic position, **81**, was obtained along with a product resulting from disilylation of the benzylic and ortho positions, **84**. The structure of **84** was verified by its ^{1}H, ^{13}C nmr and mass spectral data {^{1}H nmr ($CDCl_3$) (300MHz) δ: 0.06 (s, 9H), 0.21 (s, 9H), 4.86 (d, 1H, 9Hz), 6.30 (br d, 1H, 9Hz), 7.40 (m, 8H), 7.63 (dd, 1H, 6Hz, 1Hz); ^{13}C nmr ($CDCl_3$) (DEPT) δ: -3.26 (CH_3), 0.10 (CH_3), 46.47 (CH), 125.62 (CH), 125.74 (CH), 125.95 (CH), 128.21 (CH), 129.41 (CH), 135.39 (CH), 140.31 (quaternary), 141.12 (quaternary), 142.35 (quaternary), 170.50 (quaternary); M.S. (m/z): 355 (M^+), 354 (M-H), 340 M-CH_3), 282 (M-TMS) (100%), 178 (PhChTMSNH$^+$), 177 (TMSPhCO$^+$), 73 (TMS^+)}.

When alkyl iodides were used to quench the dianion **80c** a mixture of products was obtained resulting from *N*-alkylation (**85** and **87**) and dialkylation (**86** and **88**), since these products were inseparable they were not charecterized fully. These results are shown in Table 6. This alkylation of the benzylic position of *N*-benzylbenzamides had been mentioned in the literature by Tischler, who generated the benzylic dianion **80c** with two

equivalents of LDA.[49]

Table 6

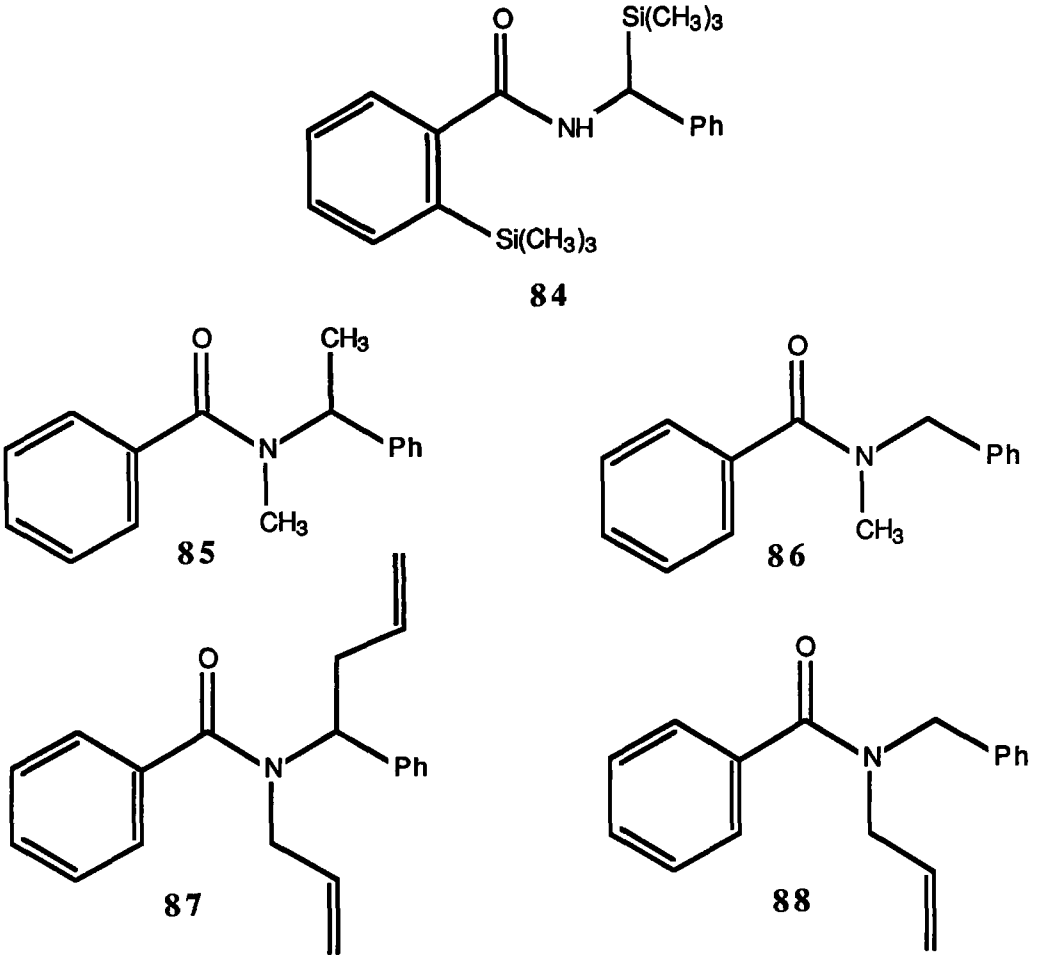
Preparation of the dianion of **80**



80

Base	Additive	Temp.	Electrophile	Temp.	Products
2 sBuLi	TMEDA	-78°C	5,6-epoxy-1-hexene	-78°C	decomp.
"	"	-78-0°C	"	0°C	"
"	"	0-25°C	"	25°C	"
"	"	-78-25°C	"	-78-25°C	**83**
2 nBuLi	none	"	"	"	**83**
NaH/nBuLi	"	"	"	"	?
2 sBuLi	TMEDA	-78-0°C	styrene oxide	0°C	decomp.
"	"	-78-25°C	"	25°C	**82**
2 nBuLi	none	-78-0°C	"	0°C	decomp.
"	"	"	TMSCl	"	N. R.
"	"	-78-25°C	"	25°C	**81**
2 sBuLi	TMEDA	"	"	"	**81 + 84**
"	"	"	"	-78°C	**81 + 84**
"	"	"	MeI	-78-25°C	**85 + 86**
2 nBuLi	"	"	"	"	**85 + 86**
"	"	"	allyl iodide	"	**87 + 88**
2 sBuLi	TMEDA	"	"	"	**87 + 88**

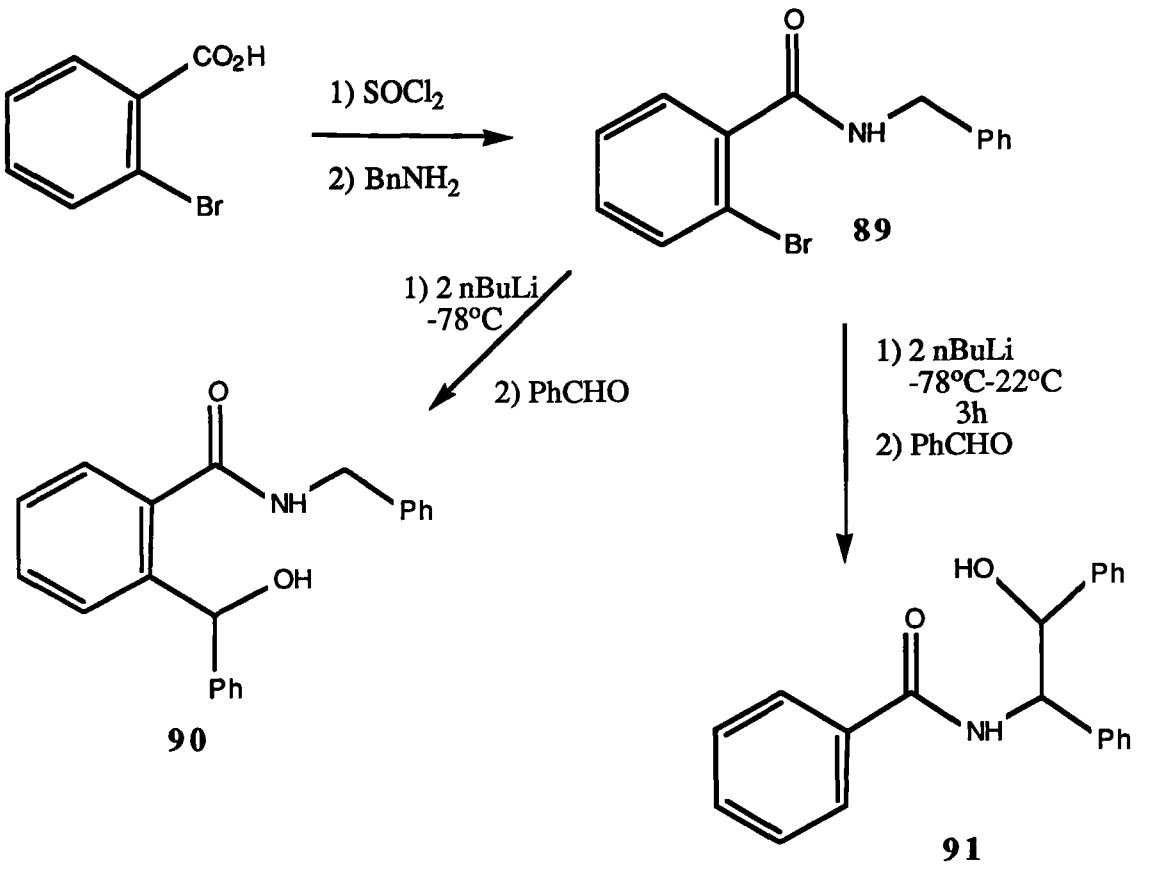
[49]) A.N. Tischler and M.H. Tischler, *Tetrahedron Lett.*, 3(1978).



At this stage it was surmised that the ortho-metalated dianion **80b** might best be generated by a halogen-metal exchange reaction involving the *N*-benzyl*o*-bromo-benzamide, **89**. This compound was prepared from *o*-bromobenzoic acid via the acid chloride. When the amide **89** was reacted with two equivalents of *n*-butyllithium at -78°C for 15 minutes, followed by quenching with benzaldehyde, the ortho-substituted product, **90**, {ir (film) υ: 3410 (O-H), 1635 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 4.37 (dd, 2H, 5Hz,

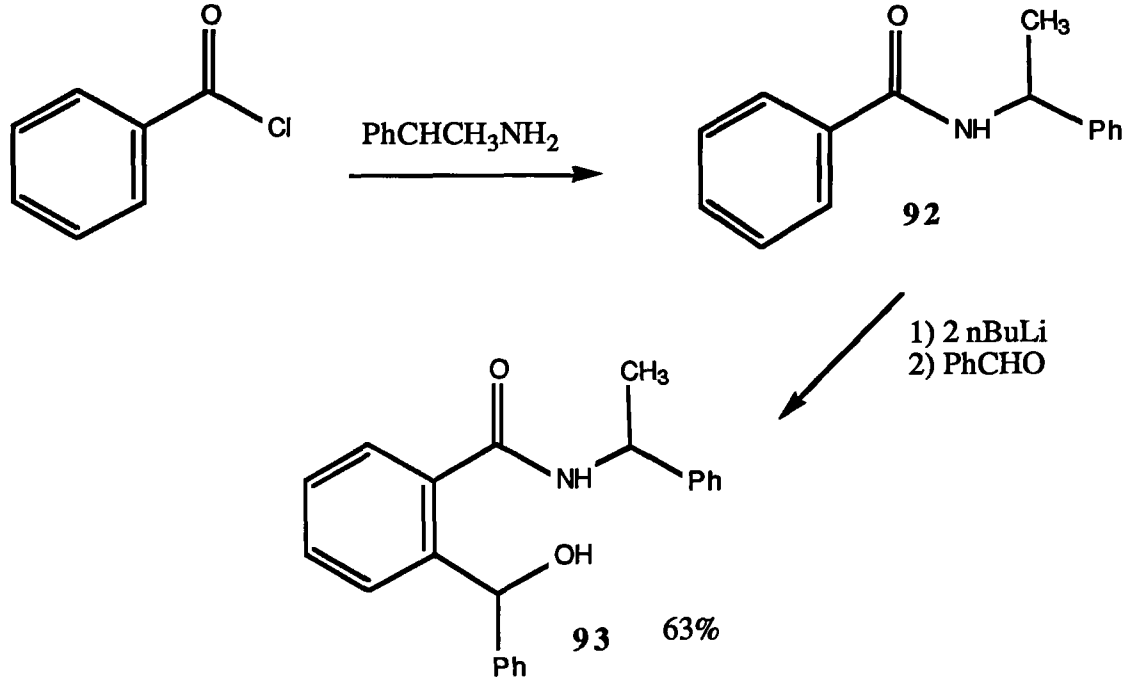
4.5Hz), 5.49 (d, 1H, 8Hz), 5.91 (d, 1H, 8Hz), 6.04 (br d, 5Hz), 7.24 m, 14H); M.S. (m/z): 317 (M^+), 211 (M-PhCHO), 105 ($PhCO^+$) (100%), 91 ($PhCH_2^+$), 77 (Ph^+)} was obtained in 40% yield, along with *N*-benzylbenzamide, **80** as a result of the bromine in **89** being replaced with hydrogen.

Since aryllithiums typically do not react with epoxides at -78°C it was necessary to investigate the stability of the dianion **80b**. A solution of **80b** was therefore allowed to warm slowly to R.T. prior to the addition of benzaldehyde. The product **91** {ir (film) υ: 3425 (O-H), 1630 ($Ar(C=O)NR_2$) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 2.67 (d, 1H, 4Hz), 5.13 (dd, 1H, 4Hz, 4Hz), 5.41 (dd, 1H, 4Hz, 3Hz), 6.99 (d, 1H, 3Hz), 7.35 (m, 10H), 7.74 (m, 2H); M.S. (m/z): 241 ($M-C_6H_4$), 211 (M-PhCHO), 105 ($PhCO^+$), 91 ($PhCH_2^+$), 77 (Ph^+); M.S. (C.I. ether) (m/z): 318 (M+1)} resulting from isomerization of **80b** to **80c** was obtained.



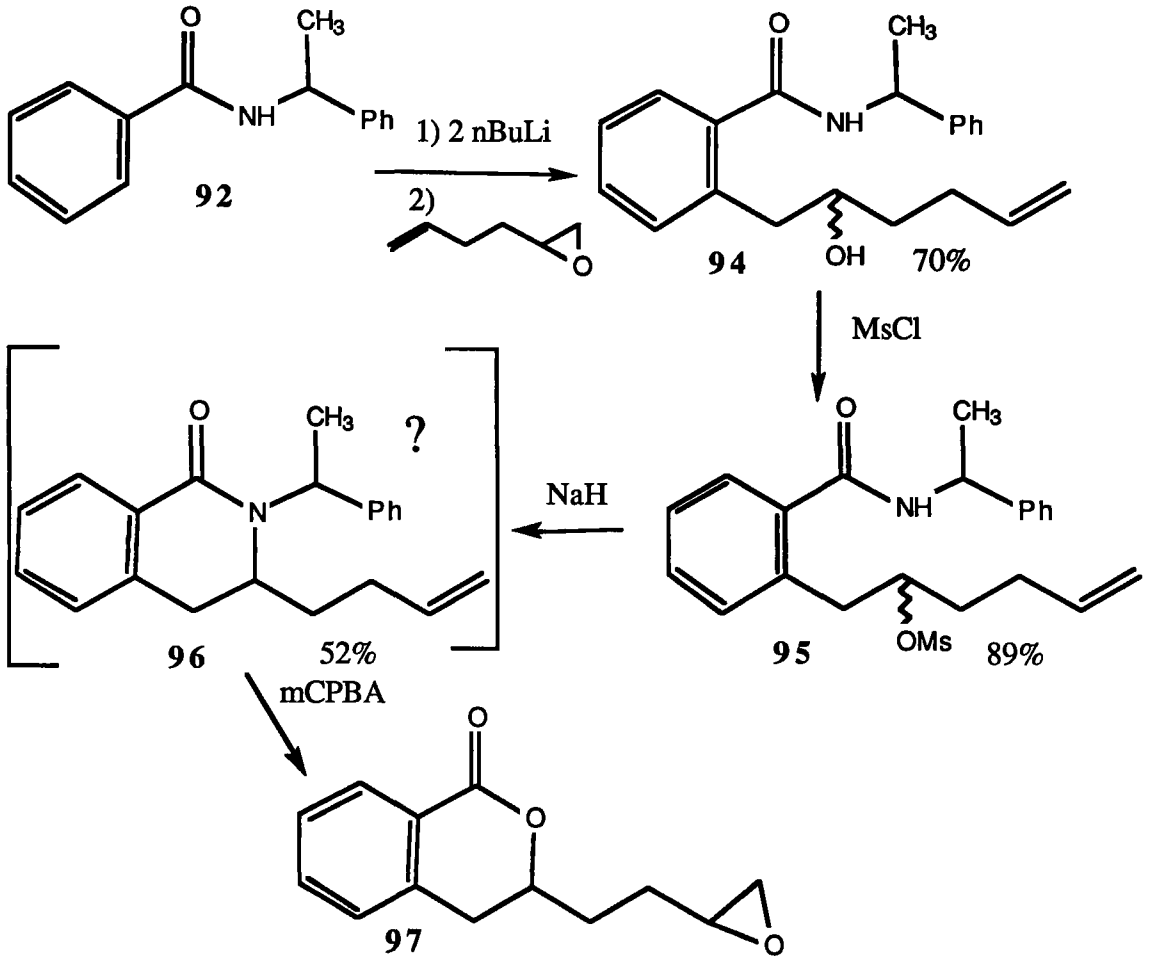
In order to disfavor deprotonation at the *N*-benzylic carbon by a combination of steric and electronic effects, the dianion formation of *N*-α-methylbenzylbenzamide, **92**, prepared from benzoyl chloride and α-methylbenzylamine, was investigated. A dianion was formed by the addition of two equivalents of *n*-butyllithium to a THF solution of **92** at -78°C followed by warming to 22°C. The solution containing the dianion was recooled to -78°C and benzaldehyde was added. The reaction mixture was then allowed to warm slowly to R.T. prior to quenching with water. Work-up followed by chromatography afforded **93** as a colourless oil in 63% yield. The ^{1}H nmr spectrum

showed the benzylic methyl group as a pair of doublets at 1.15 and 1.43ppm, J=7Hz, thereby demonstrating that the benzylic hydrogen in **92** had been retained.



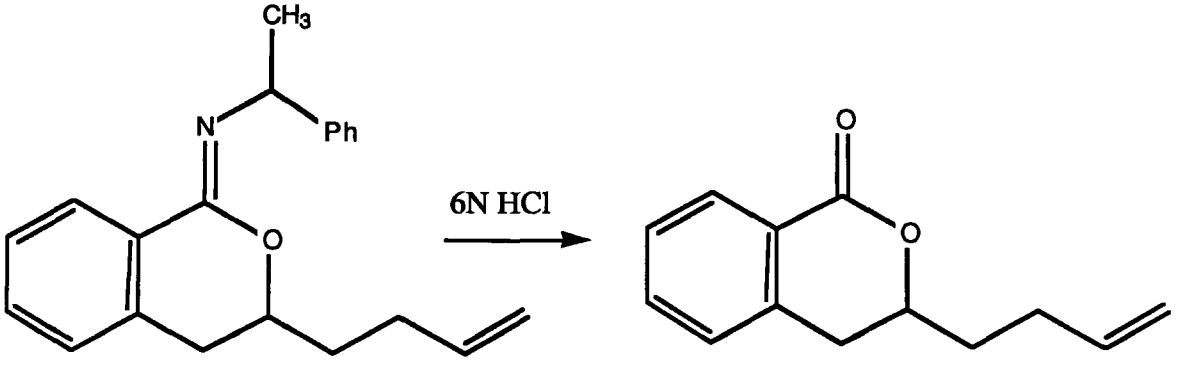
Treatment of the dianion derived from **92** with 5,6-epoxy-1-hexene also gave the ortho-substituted product **94**, {ir (film) υ: 3300 (N-H, O-H), 1640 ($R_2C=CH_2$), 1630 (Ar(C=O)NHR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.58 (m, 5H), 2.26 (m, 2H), 2.81 (m, 2H), 3.82 (m, 1H), 5.06 (m, 2H), 5.30+5.57 (q, 1H, 7Hz) (diastereomers), 5.83 (m, 1H), 6.50+6.66 (2br s, 1H) (diastereomers), 6.81 (br s, 1H), 7.16-7.49 (m, 8H), 7.75 (m, 1H); M.S. (m/z): 323 (M^+), 305 ($M-H_2O$), 290 ($M-(H_2O+CH_3)$), 239 ($M-CH_2=CHCH_2C=O$), 105 ($PhCHCH_3^+$), 84 ($CH_2=CHCH_2C=O^+$) (100%)} in 70% yield. This hydroxy-amide was

then converted into its mesylate, **95**; a singlet at 3.05ppm in the ^1H nmr spectrum was representative of the introduction of the methanesulfonyl group. Treatment of mesylate **95** with sodium hydride in THF gave what appeared to be the cyclic amide, **96** on the basis of an infrared spectrum (1655 cm^{-1}, indicative of an aromatic amide) and its ^1H nmr, ^{13}C nmr and mass spectral data .



Epoxidation of the terminal olefin in what appeared to be **96** was attempted with *m*- CPBA. The ^1H nmr spectrum of the product

isolated after chromatography showed that the α-methylbenzyl group had been lost, the mass spectrum showed a molecular ion of 218, and an infrared signal was present at 1725 cm^{-1}. Theses facts were consistent with the assignment of the δ-lactone structure **97** to this product. Such a product could not have been derived from the amide **96**, but was plausible as a hydrolysis product of the imidate **98**. To prove that the sodium hydride cyclization product was in fact the imidate, it was hydrolyzed with 6N HCl. The amide should be resistant to hydrolysis. Hydrolysis did occur giving the lactone, **79**, identical in every respect with the material described earlier on page 72. The preferential cyclization via the amide oxygen attack resulting in imidate formation is probably a result of the methyl group on the α-methylbenzamide hindering attack by nitrogen sufficiently and thereby favoring cyclization via the oxygen terminus of the amide anion.



98 **79**

Cyclization of hydroxyamide **94** was also attempted under the conditions described by Miller,[50] *i.e.*, with triphenylphosphine and diethylazodicarboxylate. This only resulted in the formation of a complex mixture of products.

Since it had been shown by Ellefson[42] that a simple *N*-benzylbenzamide did cyclize via nitrogen, a protecting group smaller than the α-methylbenzyl which would still ensure ortho-metalation was needed. *N*-Benzyloxybenzamide, **99**, was prepared from benzoyl chloride under standard conditions. The benzamide was treated with two equivalents of *n*-BuLi in THF at -78°C, and after allowing the THF solution of the dianion to warm to R.T. it was recooled to -78°C and treated with an epoxide. After 18h the reaction was quenched with water, but after the usual work-up and chromatography only benzamide and benzaldehyde were isolated. It appeared that after the amide monoanion was formed, the second equivalent of base removed a benzylic proton, resulting in β-elimination of benzaldehyde and thus leaving the parent benzamide.

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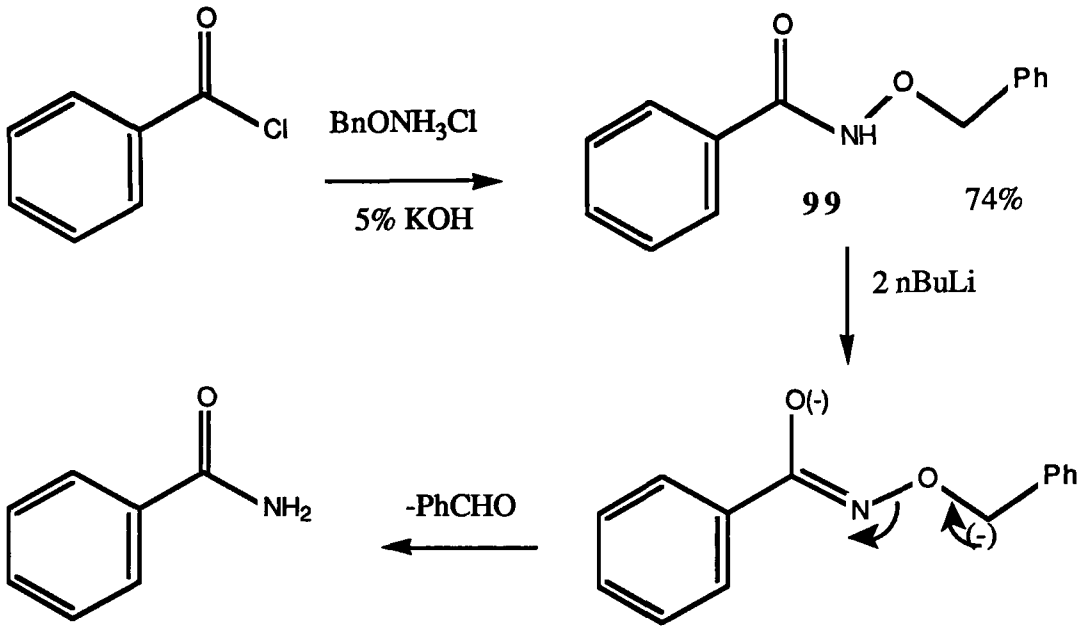
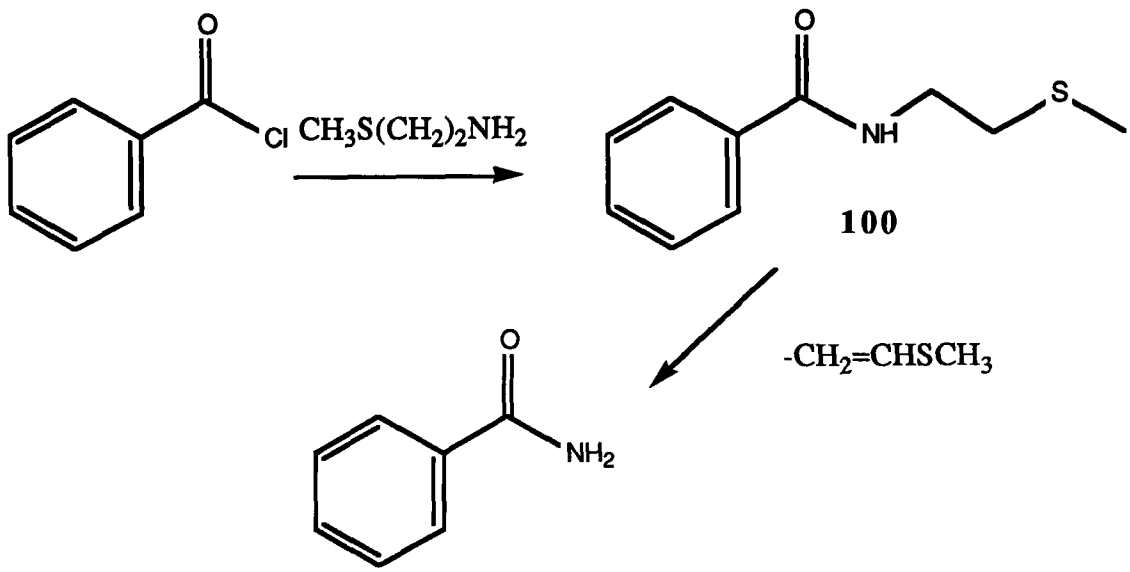
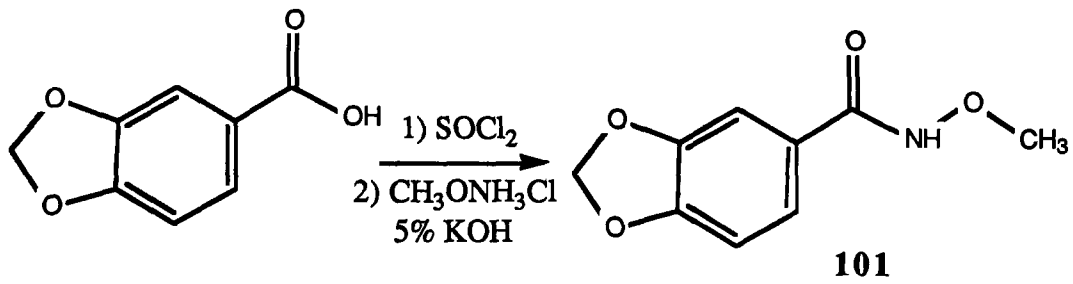
50) M.J. Miller, P.G. Mattingly, M.A. Morrison and J.F. Kerwin Jr., *J. Am. Chem. Soc.*,**102**, 7026(1980).



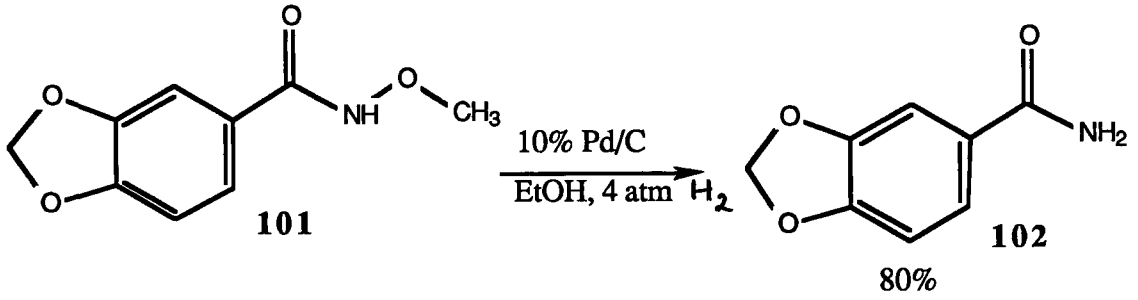
The next amide tried was the methylthioethyl amide, **100**, again prepared from benzoyl chloride. This protecting group was chosen because it should allow for ortho-metalation and can be readily removed with either mercuric chloride or silver nitrate.[32] This benzamide, **100**, was exposed to the same conditions described above for the *N*-benzyloxybenzamide, **99**, but again only the parent benzamide was isolated after work-up and chromatography. In this case, the second equivalent of base deprotonated α to the sulfur atom, which also resulted in β-elimination.



The *N*-methoxyl group was considered next. No method for cleaving this group could be found in the literature, but it was thought that cleavage of the nitrogen-oxygen bond could be achieved by hydrogenolysis. In this case the *N*-methoxyamide, **101**, prepared from piperonylic acid via the acid chloride, rather than an unsubstituted model benzamide.



Prior to studying the reaction of **101** with base the removal of the *N*-methoxy protecting group was investigated. This was accomplished by using hydrogen at four atmospheres of pressure and 10% palladium on charcoal as the catalyst. Under these conditions the parent piperonylamide, **102**, was obtained in 80% yield.

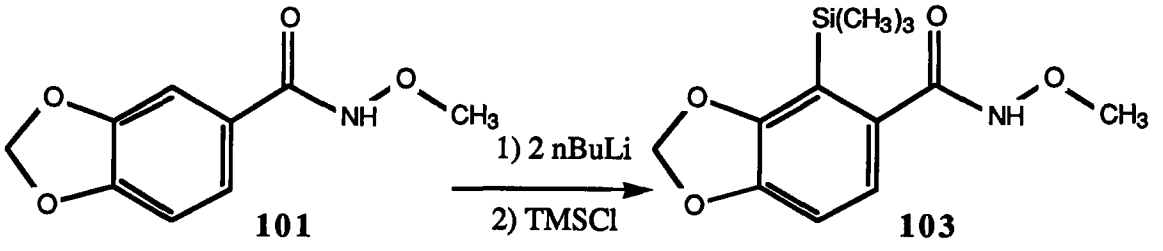


101 **102**

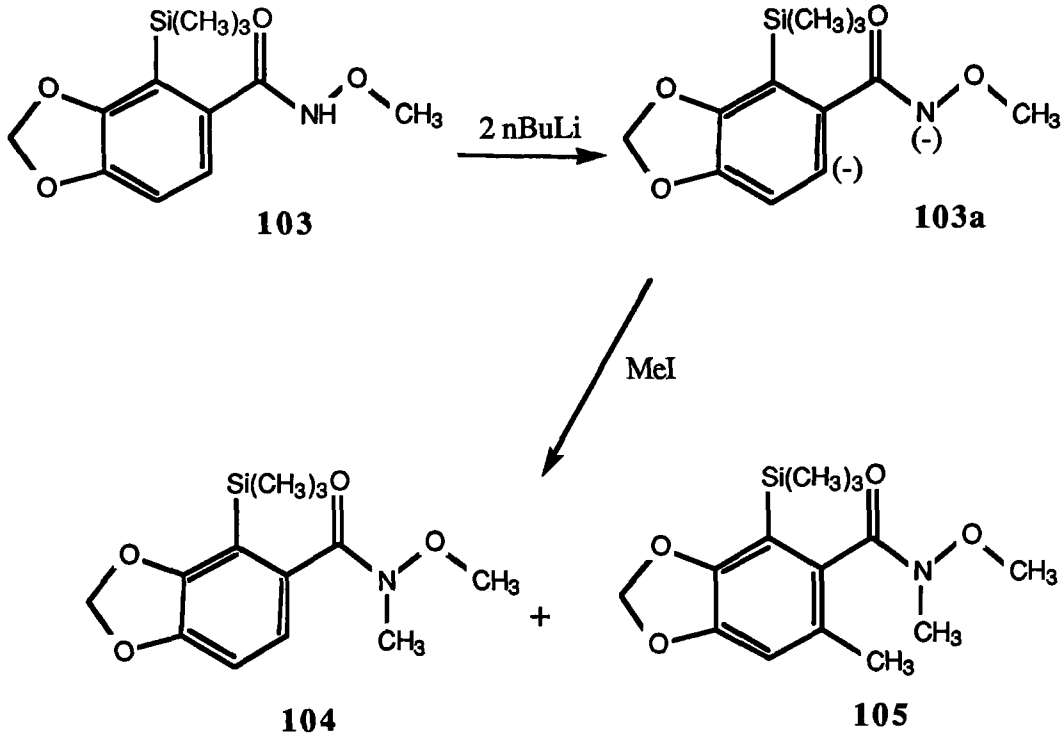
80%

Since the position most susceptible to metalation would be between the amide and the methylendioxy groups, it had to be protected via its trimethylsilyl derivative. A THF solution of amide **101** was treated with two equivalents of *n*-BuLi at -78°C, allowed to reach R.T., recooled to -78°C, and quenched with TMSCl. Upon usual work-up and chromatography the desired silylated derivative, **103**, {m.p. 112-114°C; ir (KBr pellet) υ: 1655 (Ar(C=O)NHR) cm^{-1}: ^1H nmr (300MHz) ($CDCl_3$) δ: 0.34 (s, 9H), 3.85 (s, 3H), 5.93 (s, 2H), 6.72 (d, 1H, 8Hz), 6.90 (d, 1H, 8Hz), 8.29 (m, 1H, N<u>H</u>); M.S. (m/z): 267 (M^+), 252 ($M-CH_3$), 235 ($M-CH_3OH$), 221 ($M-NHOCH_3$) (100%)} was obtained in 65% yield. A THF solution of amide **103** and TMEDA was treated with two equivalents of *s*-BuLi at -78°C, and the reaction mixture was allowed to warm to R.T for 1h, then recooled to -78°C, and the

resulting dianion **103a** treated with methyl iodide. After the usual work-up and chromatography an inseparable mixture (9:1) of *N*-methylated **104** and *N,C*-dimethylated **105** products were obtained, since the mixture was inseparable these compounds could not be fully characterized. Unfortunately, treatment of amide **103** under the conditions described above followed by quenching with either benzaldehyde or an epoxide did not give the desired product resulting from generation of the ortho-metalated dianion, **103a**.



101 **103**



103 **103a**

104 **105**

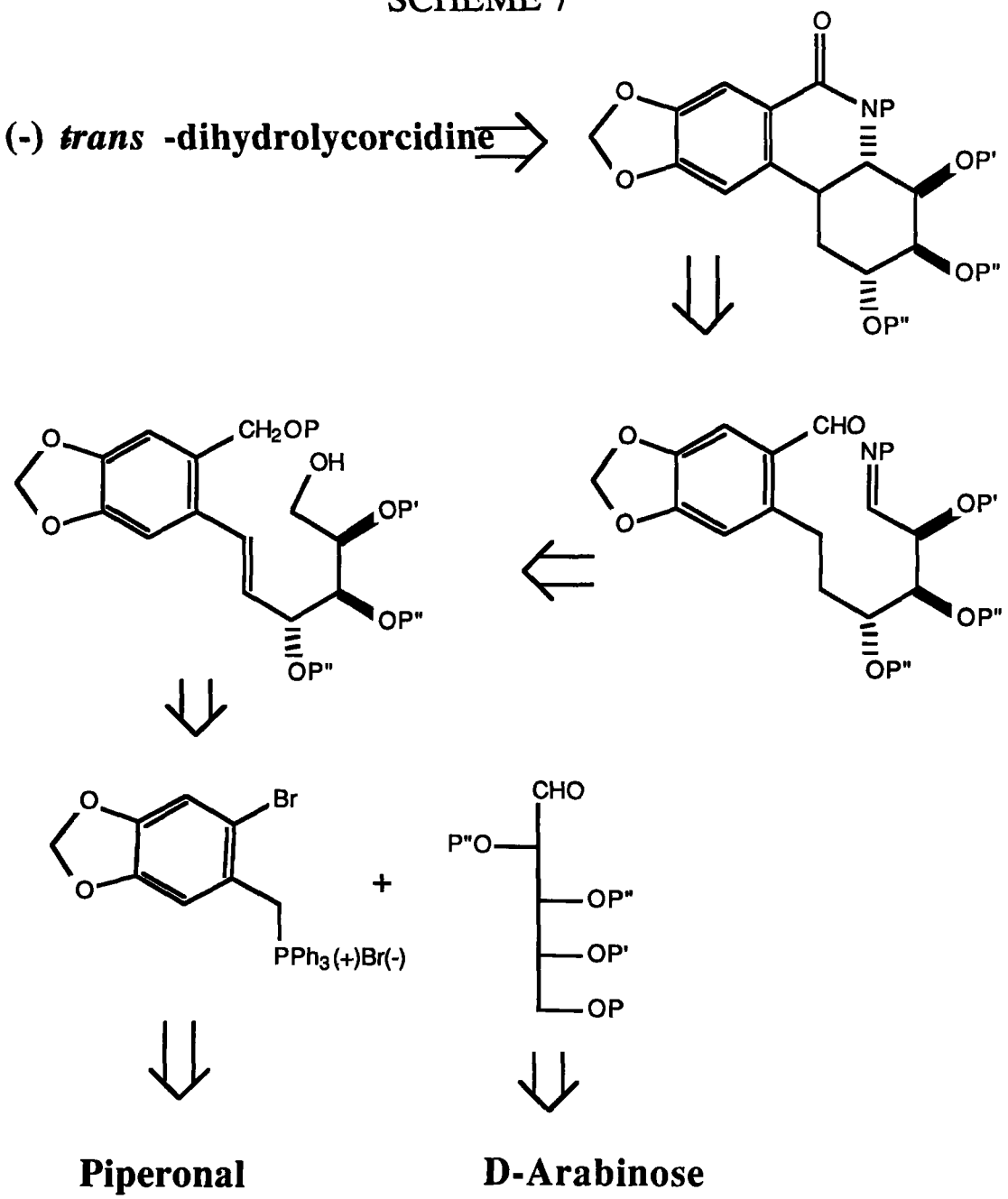
Since the ortho-metalated dianion, **103a**, could not be formed cleanly, this approach was terminated.

CHAPTER 6

ORTHO-QUINODIMETHANE APPROACH 3

As in our first two approaches this one involves the photochemical generation of an *o*-QDM and subsequent intramolecular trapping with an oxime methyl ether. This approach utilizes two intermediates from earlier approaches and joins them via a Wittig reaction. This Wittig reaction differs from the one attempted in chapter 3 in that it involves a free aldehyde rather than a hemiacetal. The retrosynthetic outline is shown in Scheme 7.

SCHEME 7


(-) trans -dihydrolycorcidine
O
NP
OP'
OP"
OP"
CH2OP
OH
OP'
OP"
OP"
CHO
NP
OP'
OP"
OP"
Br
PPh3(+)Br(-)
+
CHO
P"O
OP"
OP'
OP
Piperonal
D-Arabinose

Phosphonium salt **53** was reacted with sodium methoxide to generate an ylid which was reacted with diisopropylidene *al*-D-arabinose, **60**, to give olefin **106**, {ir (KBr pellet) υ: 2980 (ArC-H), 2790 (C-H), 1500 (C=C) cm^{-1}; ^1H nmr (*trans*-isomer) (200MHz) ($CDCl_3$) δ: 1.30 (s, 6H), 1.36 (s, H), 1.42 (s, 3H), 3.77 (m, 2H), 3.84 (m, 1H), 3.99 (m, 1H), 4.59 (dd, 1H, 9.5Hz, 7.5Hz), 5.70 (dd, 1H, 11.5Hz, 9.5Hz), 5.97 (s, 2H), 6.66 1(d, H, 11.5Hz), 7.02 (s, 1H), 7.15 (s, 1H); ^1H nmr (*cis*-isomer) (300MHz) ($CDCl_3$) δ: 1.31 (s, 6H), 1.38 (s, 3H), 1.44 (s, 3H), 3.77 (m, 2H), 3.84 (m, 1H), 4.05 (m, 1H), 4.73 (dd, 1H, 9Hz, 7.5Hz), 5.60 (dd, 1H, 11Hz, 7.5Hz), 5.95 (s, 2H), 6.79 (d, 1H, 11Hz), 7.02 (s, 1H), 7.15 (s, 1H); M.S. (m/z): 426 (M^+), 428 (M+2), 411 (M-CH_3), 413 (M+2-CH_3), 368 (M-CH_3COCH_3), 370 (M+2-CH_3COCH_3), 353 (M-(CH_3COCH_3+CH_3)), 355 (M+2-(CH_3COCH_3+CH_3)), 348 (M-Br); exact mass calculated for $C_{16}H_{23}O_6Br$: 426.0677, found: 426.0634} in 50% yield as a mixture (1:8) of *cis* and *trans*-isomers. In attempts to increase the yield other bases were tried. The use of LDA or LHMDS gave only the *trans*-isomer, as evidenced by the J=11.5Hz coupling constant for the olefinic protons, in poor yield, along with a product, **107**, which resulted from cleavage of the carbon-phosphorus bond. The formation of **107** was apparent by the appearance of a singlet at δ=2.28ppm in the ^1H nmr spectrum corresponding to the benzylic methyl group. The use of hydroxide resulted in **107**. This carbon-phosphorus bond cleavage reaction has been well documented,so the 50% yield had to be tolerated.[51]

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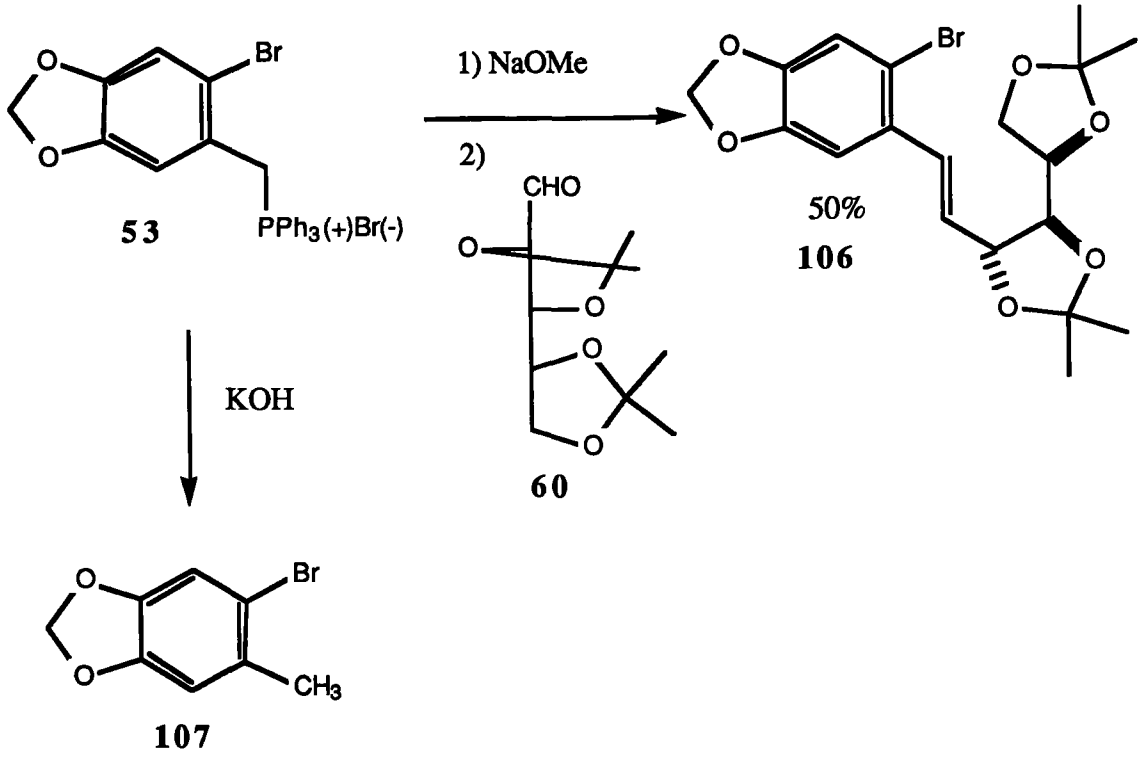
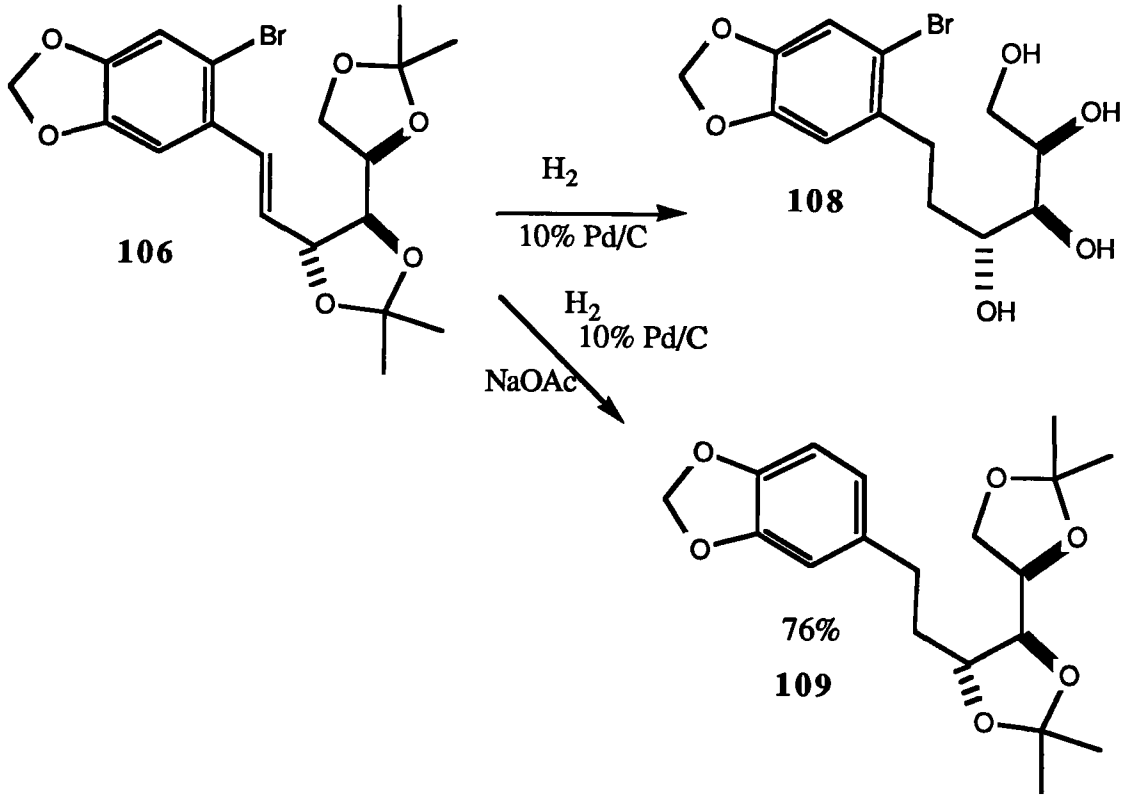
51) C.A. Vanderwerf, W.E. McEwen and M. Zange, *J. Am. Chem. Soc.*, **81**, 3806(1959).



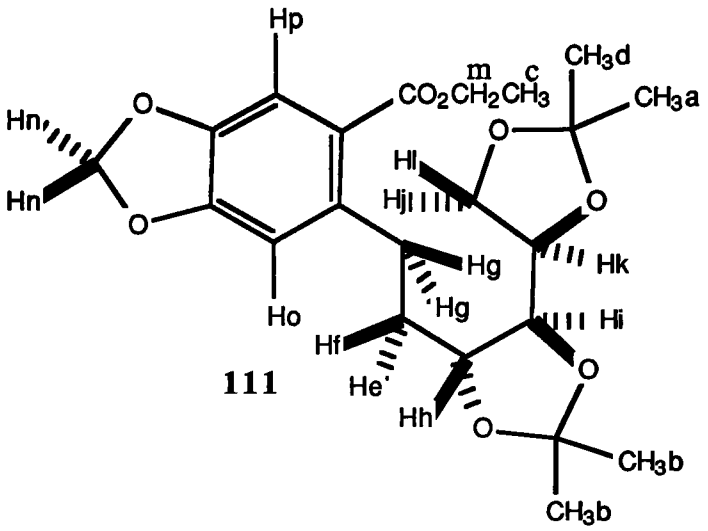
When olefin **106** was hydrogenated using 10% palladium on carbon in ethanol a product, **108**,{ir (KBr pellet) υ: 3610 (O-H) cm^{-1}; ^1H nmr (300MHz) (d_6 acetone) δ: 1.25 (m, 2H), 2.04 (m, 2H), 3.40 (m, 2H), 3.69 (m, 3H), 5.92 (s, 2H), 6.71 (s, 1H), 6.74 (s, 1H); M.S. (m/z): 349 (M+1), 351 (M+3), 348 (M^+), 350 (M+2), 330 (M-H_2O), 332 (M+2-H_2O), 295 (M-1-3H_2O), 297 (M+1-3H_2O), 271 (M+1-Br), 270 (M-Br)}

resulting from reduction of the double bond and cleavage of the acetonides was obtained. It is presumed that residual acid from the preparation of the catalyst resulted in the cleavage. This problem was soon remedied by the use of sodium acetate in the reaction medium, but, unfortunately along with the desired reduction of the olefin the aromatic bromide was also reduced to give compound **109** {ir (film) υ: 2950 (C-H) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.32 (s, 3H), 1.35 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.80 (m, 1H), 1.99 (m, 1H), 2.75 (m, 2H), 3.56 (dd, 1H, 8Hz, 7Hz), 3.88-4.12 (m, 4H), 5.90 (s, 2H), 6.70 (m, 3H); M.S. (C.I. ether) (m/z): 351 (M+1), 350 (M^+), 335 (M-CH_3), 293 (M+1-CH_3COCH_3) (100%)} in 76% yield.



Since the bromide was being reduced it was decided to introduce the necessary carbon atom first. This was accomplished by exposing the bromide, **106**, to lithium-halogen exchange conditions followed by quenching with ethyl chloroformate to give ester, **110** {m.p. 80-82°C; ir (KBr pellet) υ: 2980 (ArC-H), 2800 (C-H), 1720 ($ArCO_2Et$), 1600 (ArC=C) cm^{-1}; ^1H nmr (mixture of *cis* + *trans*) (300MHz) ($CDCl_3$) δ: 1.20-1.44 (m, 15H), 3.77-4.55 (m, 7H), 5.63+5.97 (dd's, 1H, (11Hz, 9Hz)(10Hz, 9Hz)), 5.99+6.02 (s's, 2H), 6.77+7.16 (d's, 1H, (10Hz)(11Hz)), 6.95+7.05 (s's, 1H), 7.34+7.45 (s's, 1H); M.S. (C.I. ether) (m/z): 421 (M+1), 363 (M+1-CH_3COCH_3) (100%), 305 (M+1-2(CH_3COCH_3)), 377 (M-OEt); Elemental Analysis calculated for $C_{22}H_{28}O_8$: C 62.83, H 6.71, found: C 62.68, H 6.57} in 55% yield. The olefin was then reduced to give ester, **111**, in 90% yield via catalytic hydrogenation with 10% palladium on carbon in the presence of sodium acetate.

The 2DJ ^1H nmr spectrum of **111** was recorded to unambiguously assign all of the protons in the ^1H nmr spectrum, and also to obtain the coupling constants. The 2DJ spectrum allows for the calculation of the coupling constants for each signal.

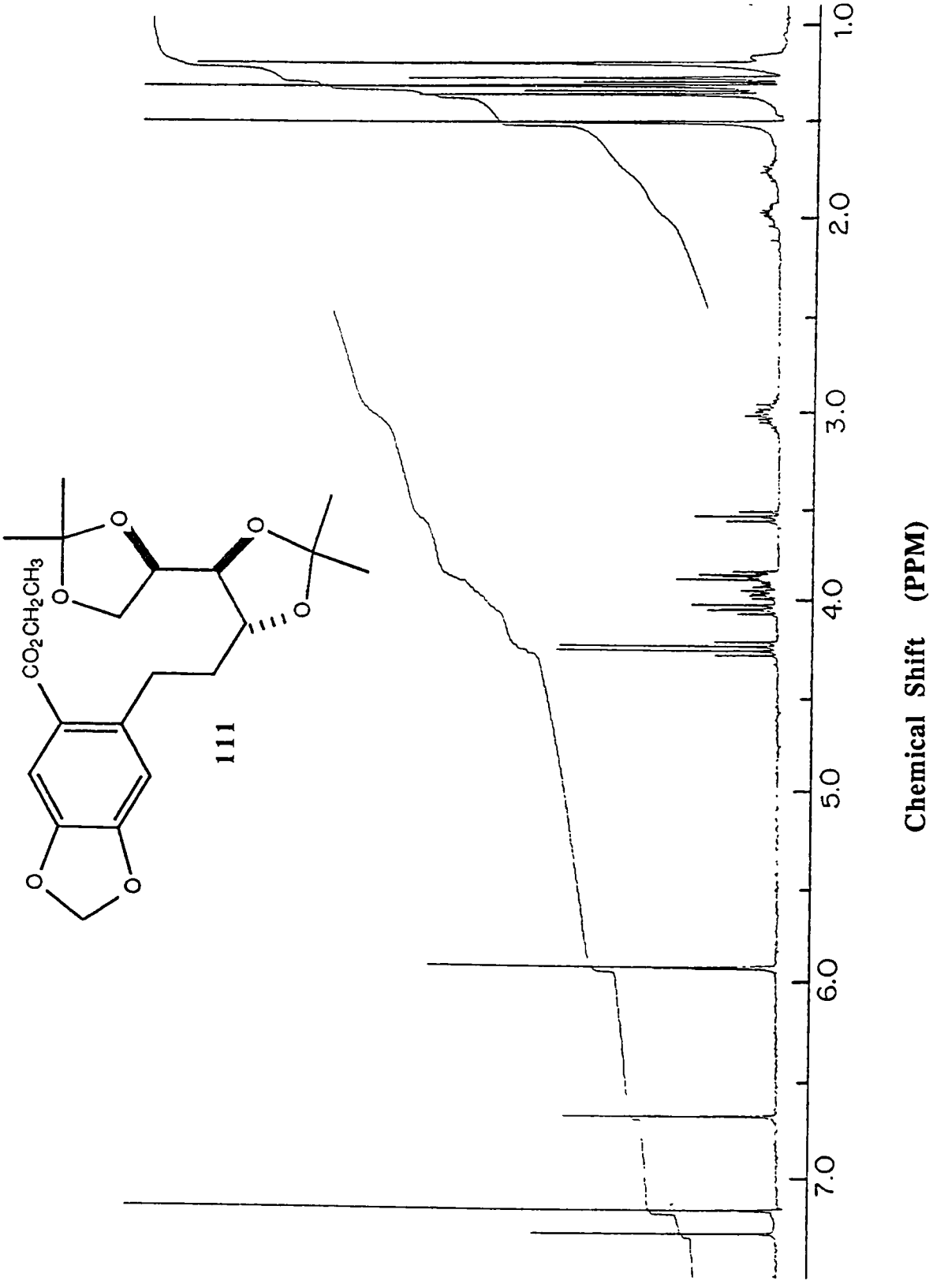


111

Structure **111**

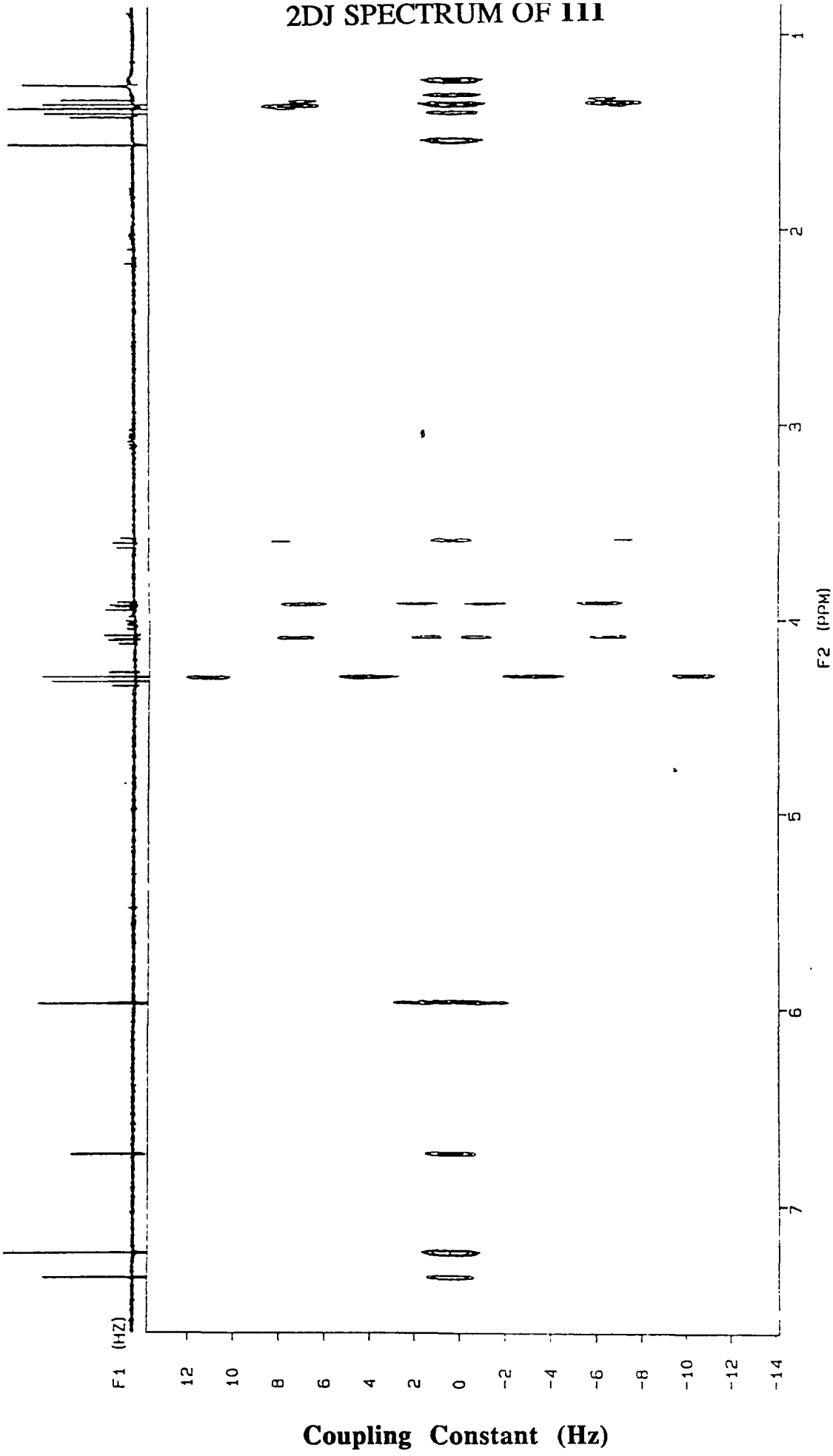
Chemical shift	Multiplicity	Integration	J Value	Assignment
1.31	s	3H		a
1.35	s	6H		b
1.36	t	3H	7Hz	c
1.40	s	3H		d
1.80	m	1H		e
2.01	m	1H		f
3.06	m	2H		g
3.59	t	1H	7.5Hz	h
3.91	dd	1H	8Hz,5Hz	i
3.93	m	1H		k
4.01	m	1H	6Hz	l
4.09	dd	1H	8Hz,6Hz	m
4.29	q	2H	7.5Hz	n
5.97	dd	2H	2Hz	o
6.74	s	1H		p
7.36	s	1H		q

300MHz ^{1}H NMR SPECTRUM OF **111**



111

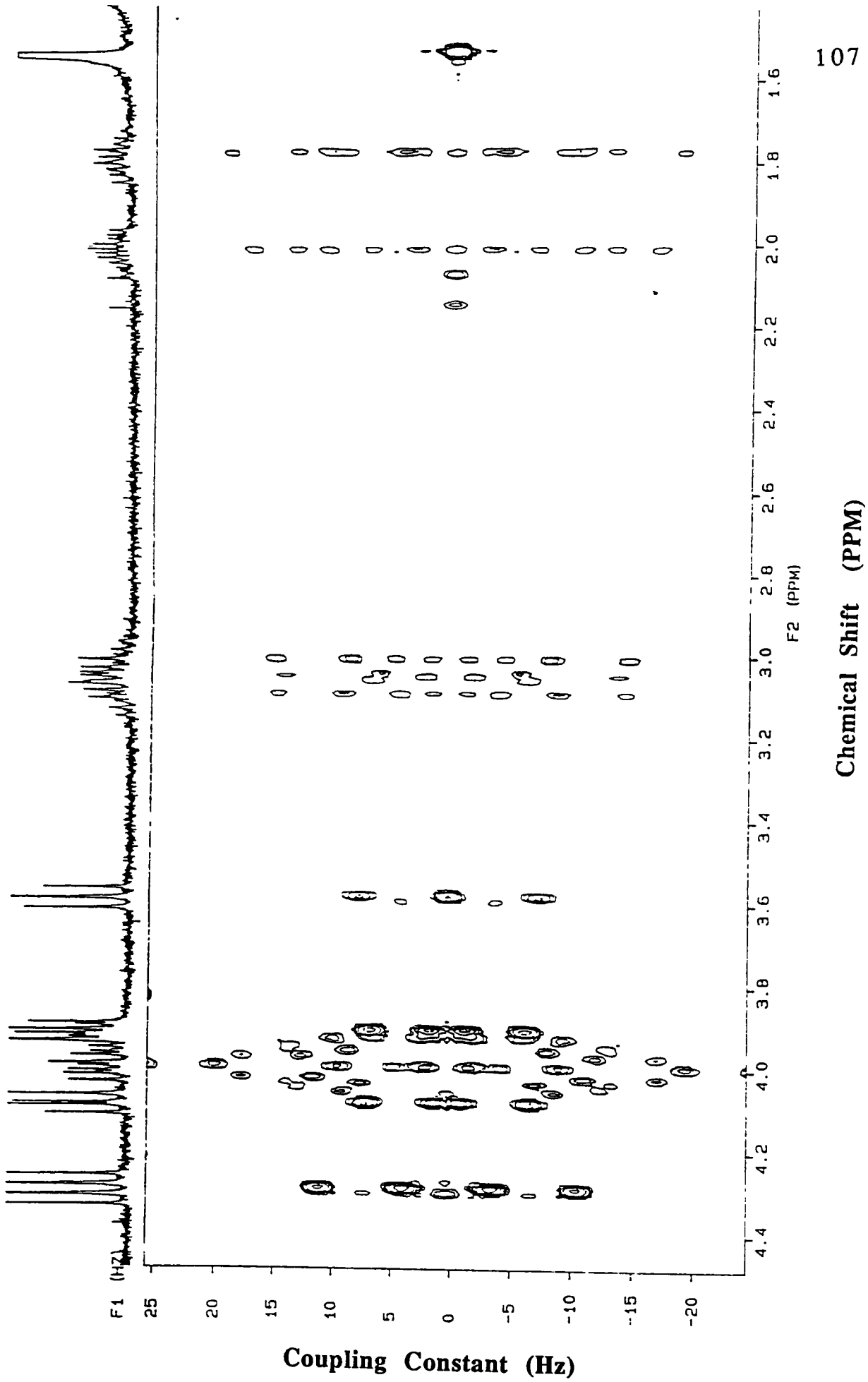
2DJ SPECTRUM OF 111



Coupling Constant (Hz)

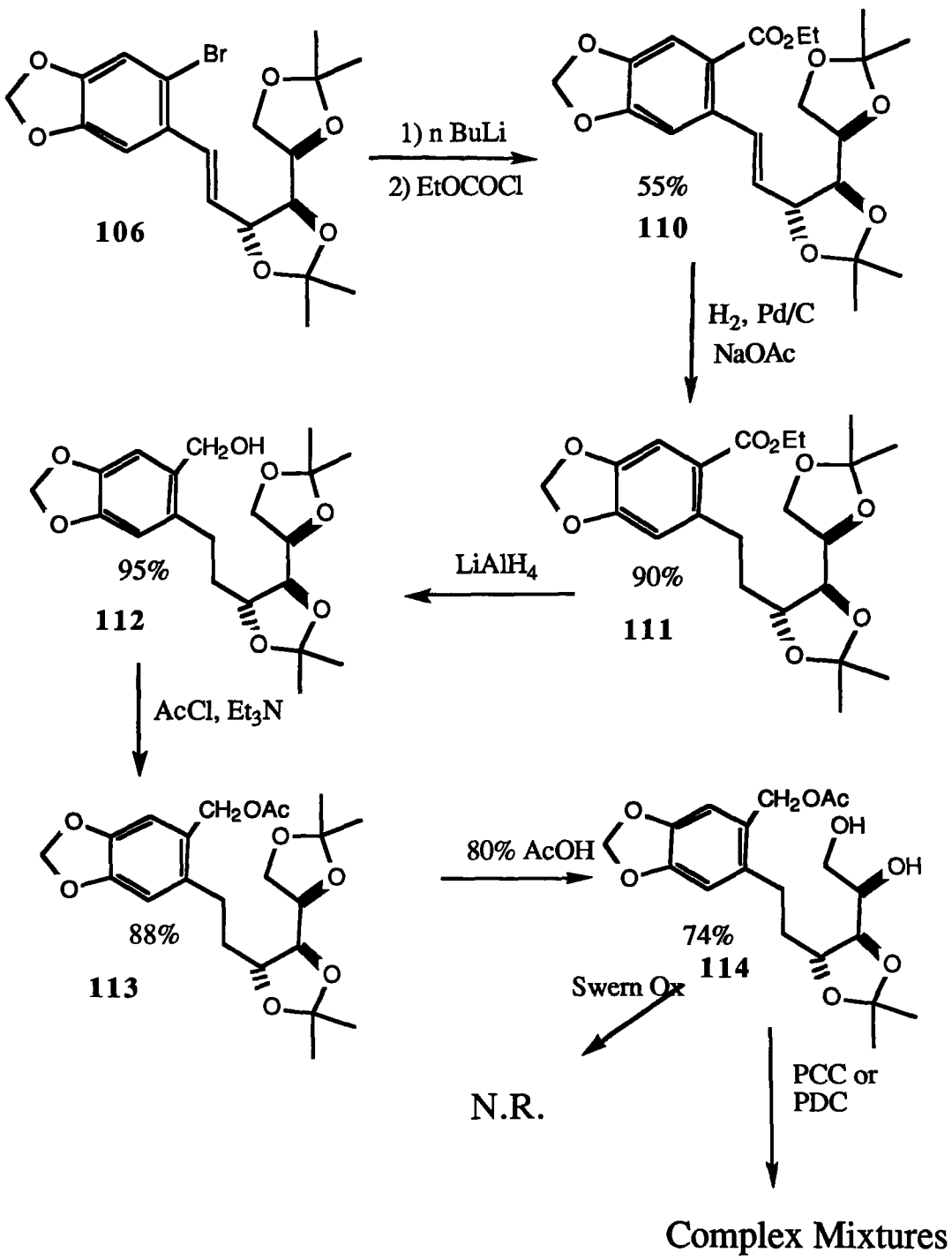
Chemical Shift (PPM)

EXPANSION OF 2DJ SPECTRUM OF **111**



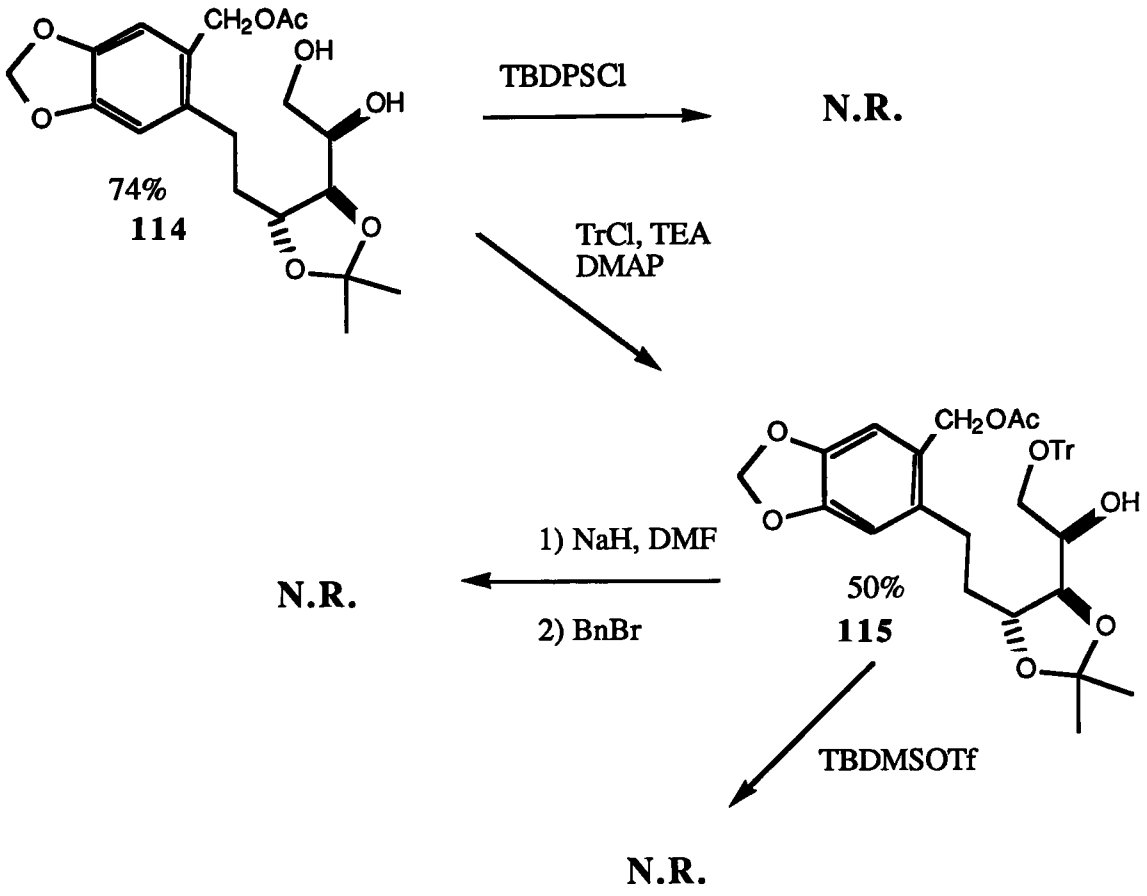
The ester function was then reduced with lithium aluminum hydride to give alcohol, **112**, in 95% yield, shown by the appearance of a signal at 3430 cm^{-1} corresponding to an O-H stretching vibration in the infrared spectrum. The primary alcohol was acetylated with acetyl chloride to give acetate **113** in 88% yield, as evidenced by the appearance of a singlet at δ=2.06ppm in the ^1H nmr spectrum. The primary acetonide was then cleaved selectively upon exposure to 80% acetic acid to give diol, **114** {ir (film) υ: 3440 (O-H), 2920 (C-H), 1735 ($CH_3(C=O)OR$) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.37 (s, 3H), 1.47 (s, 3H), 1.55 (br s, 2H, O<u>H</u>), 1.80 (m, 1H), 1.96 (m, 1H), 2.06 (s, 3H), 2.70 (m, 1H), 2.80 (m, 1H), 3.76 (m, 4H), 3.98 (m, 1H), 5.05 (s, 2H), 5.91 (s, 2H), 6.71 (s, 1H), 6.80 (s, 1H); M.S. (C.I. ether) (m/z): 383 (M+1), 382 (M^+), 367 ($M-CH_3$), 364 ($M-H_2O$), 339 ($M+1-CH_3CO$), 324 ($M+1-CH_3COCH_3$), 323 ($M-CH_3CO_2$)}, in 74% yield.

Selective oxidation of the primary hydroxyl group in **114** was first attempted by Swern methodology, but this resulted only in recovery of starting diol. Attempts at oxidation using either PCC or PDC both resulted in complex mixtures.



Selective protection of the primary alcohol was initially attempted with TBDPSCl, but, even under quite vigorous conditions

no reaction took place. It was possible to prepare the trityl ether, **115** {ir (film) υ: 3420 (O-H), 2920 (C-H) cm^{-1}; ^1H nmr (60MHz) ($CDCl_3$) δ: 1.29 (s, 3H), 1.45 (s, 3H), 1.60 (br s, 1H, O<u>H</u>), 1.75 (m, 1H), 1.95 (m, 1H), 2.04 (s, 3H), 2.40 (m, 1H), 2.70 (m, 1H), 3.30 (m, 2H), 3.85 (m, 3H), 5.00 (s, 2H), 5.85 (s, 2H), 6.60 (s, 1H), 6.80 (s, 1H), 7.33 (m, 15H)}, in 50% yield using trityl chloride in the presence of TEA and DMAP at 60°C in DMF for 2 days. It was then attempted to protect the secondary alcohol in **115** as a benzyl ether, but no reaction with benzyl bromide was observed even under forcing conditions. The alcohol, **115**, was then treated with TBDMSOTf but again no reaction occurred; apparently the secondary alcohol is very sterically hindered.

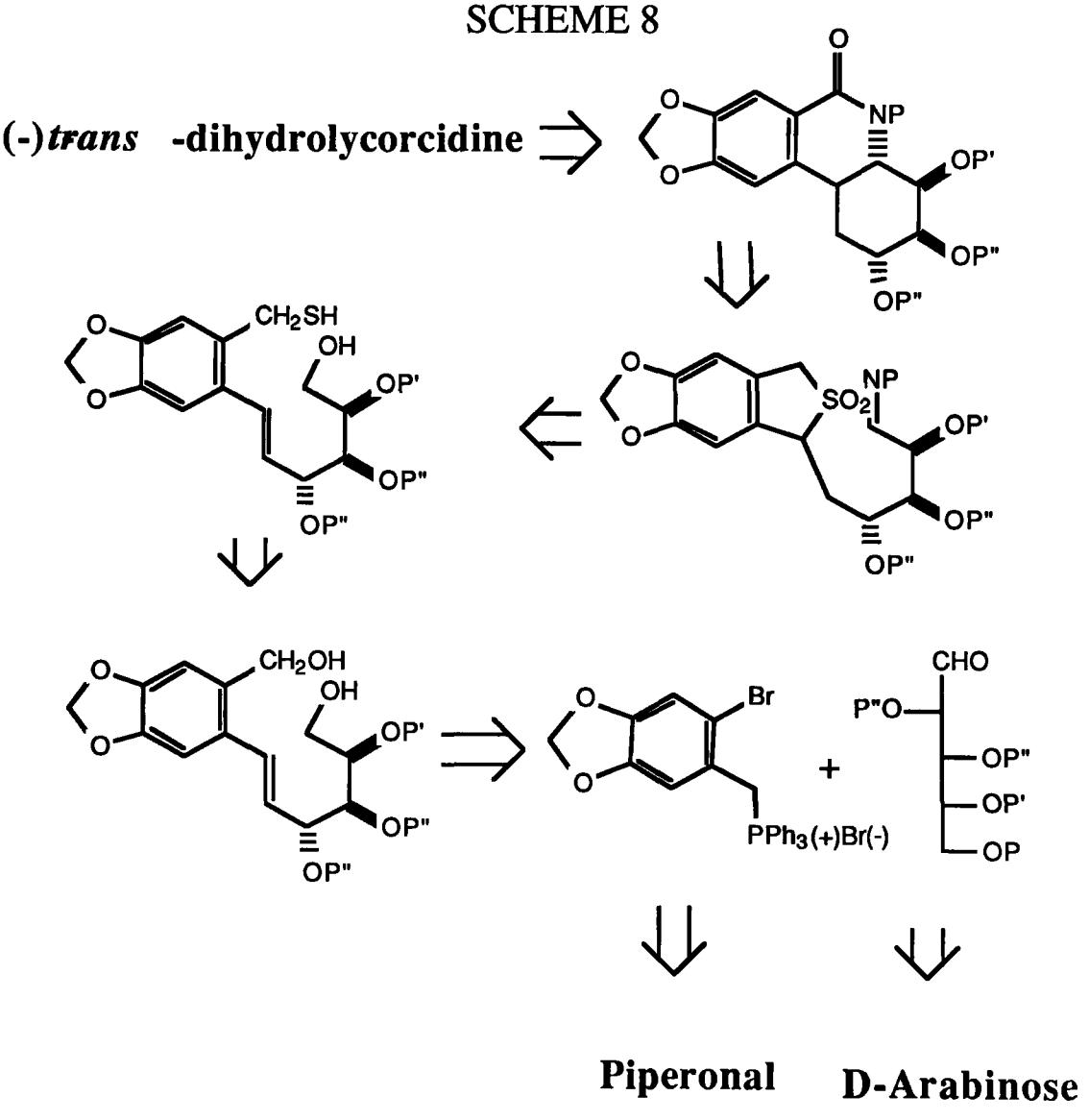


Since it was impossible to differentiate the primary and secondary hydroxyl groups this approach was no longer pursued.

It was then thought that it might be possible to prepare the cyclic sulfone necessary to generate the desired *ortho*-quinodimethane, by conversion of the bromo derivative **106** generated earlier, into a benzylic alcohol which in turn could be converted into the thiol. This thiol should cyclize under free radical conditions to give a cyclic sulfide which could be oxidized to the desired sulfone. After selective hydrolysis of the primary acetonide,

selective differentiation of the primary and secondary alcohols may then be accomplished. Since the cyclic structure should be more rigid the diol may experience less steric hindrance. This route is outlined in Scheme 8.

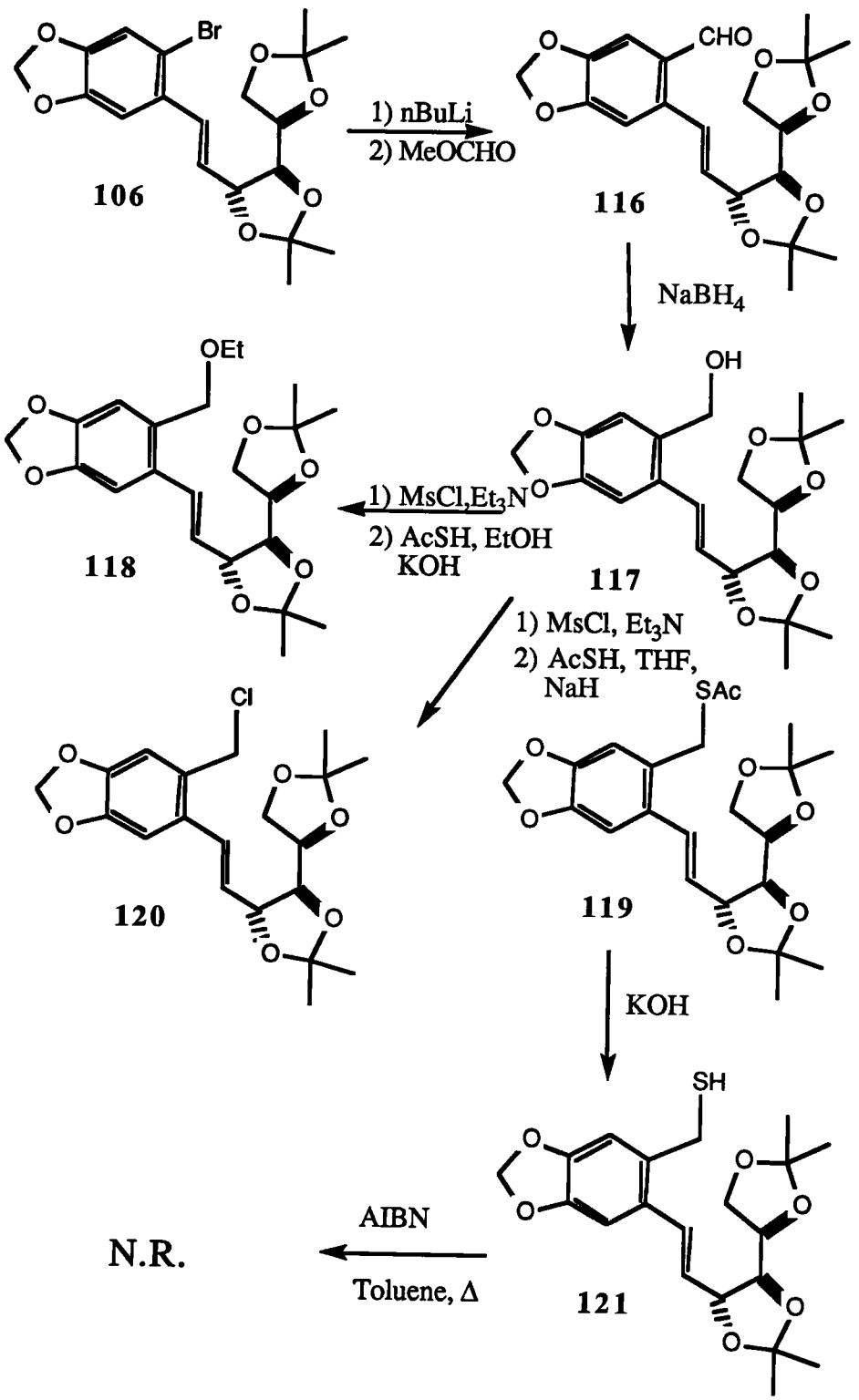
SCHEME 8



Aldehyde **116** was prepared in 52% yield, from bromide **106**, by generation of the anion via lithium-halogen exchange, followed by quenching with methyl formate. The aldehyde **116**, which showed the typical aldehydic proton signal at δ=9.95ppm in the ^1H nmr spectrum, was reduced cleanly to the alcohol **117** {ir (film) υ: 3420 (O-H) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) (*trans*-isomer) δ: 1.27 (s, 6H), 1.35 (s, 3H), 1.43 (s, 3H), 1.46 (br s, 1H, OH), 3.71 (dd, 1H, 8Hz, 7Hz), 3.89-4.05 (m, 3H), 4.36-4.59 (m, 3H), 5.75 (dd, 1H, 11Hz, 9Hz), 5.95 (dd, 2H, 2.5Hz, 2Hz), 6.82-6.93 (m, 3H); M.S. (m/z): 378 (M^+), 360 ($M-H_2O$), 320 ($M-CH_3COCH_3$)}, in 93% yield, by treatment with sodium borohydride in ethanol. Alcohol, **117**, was then converted into its mesylate, followed by the attempted in situ displacement of the mesylate with thiolacetic acid in ethanol. Unfortunately, under these conditions the only product isolated was the ethyl ether, **118**, which was of no use to us. The structure of the ethyl ether, **118**, was confirmed by the distinctive ethyl ether pattern of signals at δ=1.21, (t, J=7Hz) and δ=3.50, (q, J=7Hz) in the ^1H nmr spectrum and the appearance of the molecular ion in the mass spectrum.

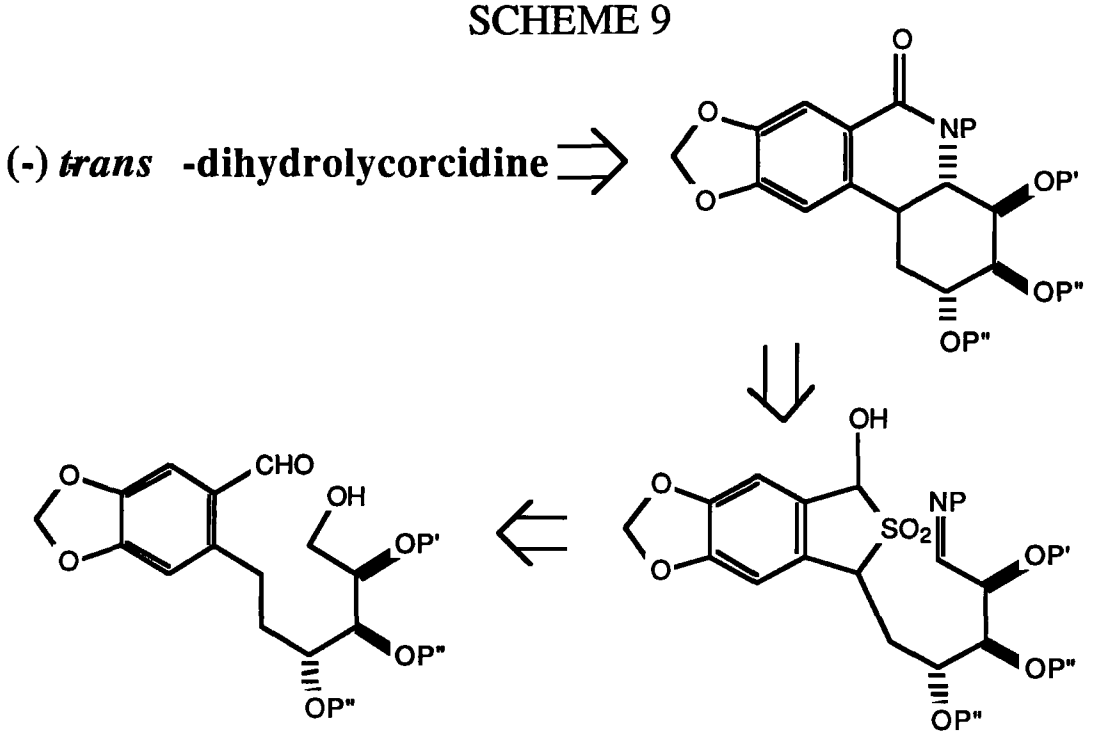
However, by use of sodium thiolacetate in THF was used to effect the displacement, the desired thiolacetate, **119** {ir (film) υ: 2990 (C-H), 1690 ($S(C=O)CH_3$), 1620 (C=C) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) (*trans*-isomer) δ: 1.31 (s, 3H), 1.32 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 2.31 (s, 3H), 3.76 (m, 1H), 3.85 (m, 1H), 3.96-4.10 (m, 2H), 4.02 (s, 2H), 4.50 (dd, 1H, 9Hz, 7.5Hz), 5.70 (dd, 1H, 11Hz, 9Hz), 5.93 (s, 2H), 6.70 (d, 1H, 11Hz), 6.81 (s, 1H), 6.99 (s, 1H); M.S. (C.I. ether) (m/z): 436 (M^+), 421 ($M-CH_3$), 393 ($M-COCH_3$), 379 ($M+1-CH_3COCH_3$),

360 (M-AcSH)}, was indeed obtained in 41% yield. As a byproduct a small amount of chloride **120** resulting from displacement of the mesylate with chloride ion from the triethyl ammonium chloride present in the mixture from the mesylation procedure was isolated. The structure of the chloride **120** was determined by the characteristic M^+ and M+2 pattern in the mass spectrum. The acetyl group in **119** was cleaved quantitatively by treatment with potassium hydroxide to give thiol, **121** {ir (KBr pellet) υ: 2990 (C-H), 2460 (S-H), 1640 (C=C), 1485 (ArC-C) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) (mixture of *cis* and *trans*) δ: 1.29 (s, 3H), 1.32 (s, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 1.86 (dd, 1H, 8Hz, 7Hz, SH), 3.47-3.61 (m, 4H), 3.67-4.09 (m, 2H), 4.52 (m, 1H), 5.73 (m, 1H), 5.94 (s, 2H), 6.62-6.96 (m, 3H); M.S. (C.I. ether) (m/z): 395 (M+1), 361 (M-SH), 337 (M+1-CH_3COCH_3)}, in 98% yield. The removal of the acetyl group was shown by the disappearance of the acetyl signal at δ=2.31ppm in the ^1H nmr spectrum. Thiol, **121**, was exposed to free radical conditions but none of the desired radical induced cyclization product was obtained.


Br
106
1) nBuLi
2) MeOCHO
CHO
116
NaBH4
OH
117
OEt
118
1) MsCl,Et3N
2) AcSH, EtOH
KOH
1) MsCl, Et3N
2) AcSH, THF,
NaH
SAc
119
Cl
120
KOH
SH
121
AIBN
Toluene, Δ
N.R.

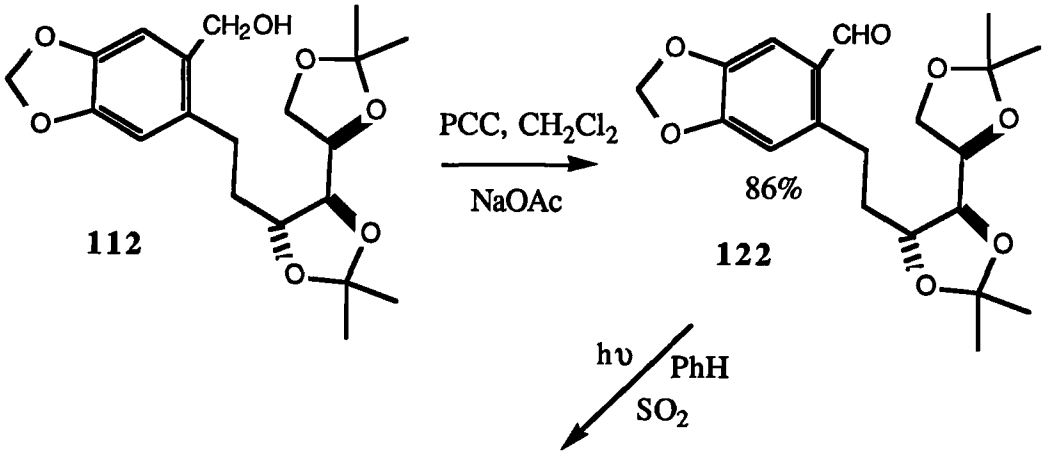
Since the desired cyclization could not be achieved, this approach was also no longer pursued. It was thought that it might be possible to prepare the hydroxy-sulfone directly via photolysis of the saturated aldehyde and trapping of the *ortho*-quinodimethane generated with sulfur dioxide. This is shown in Scheme 9.

SCHEME 9



Firstly alcohol **112** was oxidized with pyridinium chlorochromate to give saturated aldehyde **122** in 86% yield. Then irradiation of aldehyde **122** was performed using a medium-pressure lamp through a pyrex filter in the presence of sulfur dioxide in benzene for periods ranging from four to eight hours but

no reaction was observed. The fact that this photochemistry does not work is in agreement with a very recent paper published by Charlton.[52] In this paper he speculates that the alkoxy substituents affect the reactivity of the excited state of the aldehyde by lowering the $\pi\pi^*$ state below that of the more reactive $n\pi^*$ state thereby blocking the intramolecular hydrogen abstraction and *ortho*-quinodimethane formation.



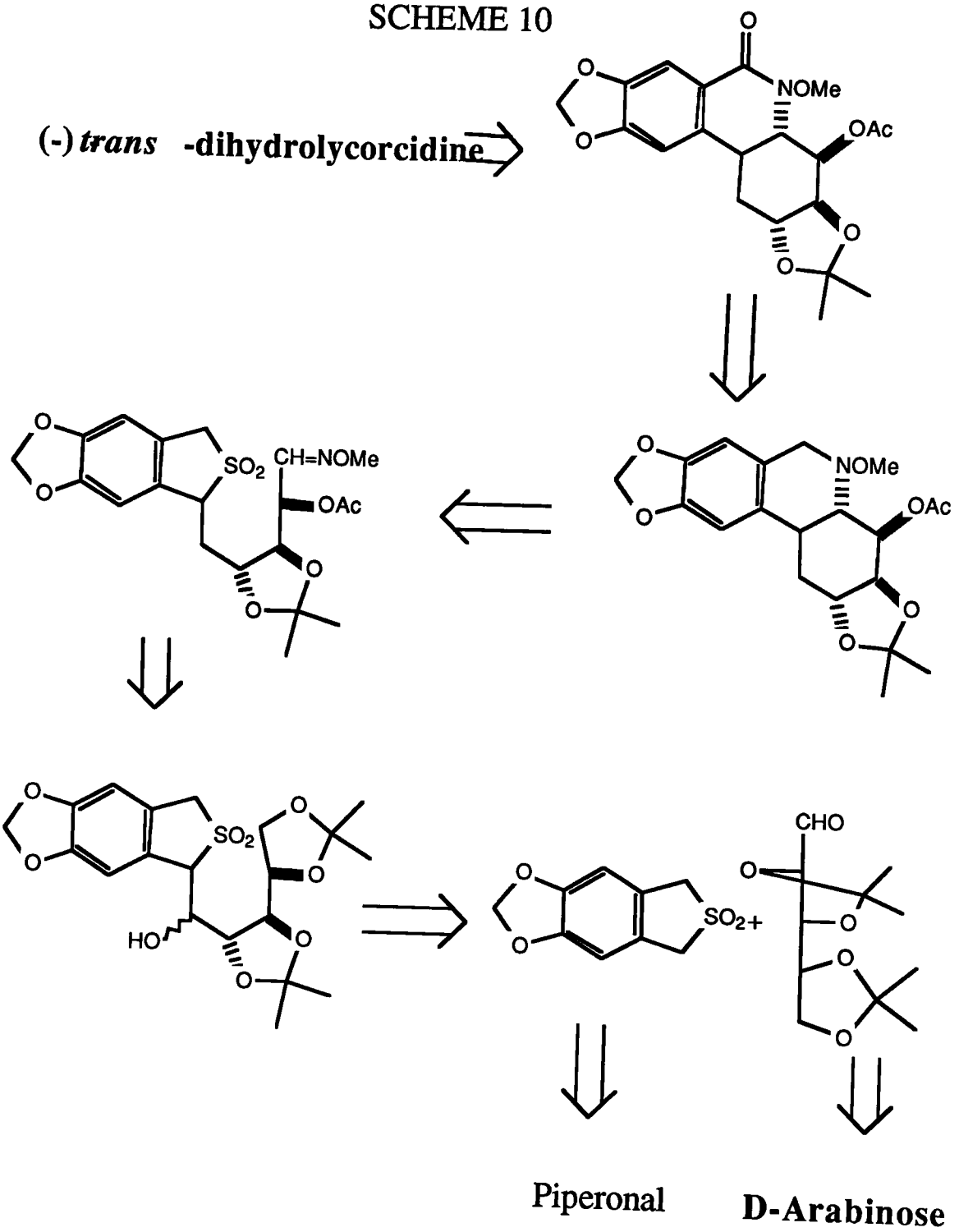
52) J.L. Charlton and K. Koh, Tetrahedron Lett., 5595(1988).

CHAPTER 7

ORTHO-QUINODIMETHANE APPROACH 4

This approach involves generation of an *o*-quinodimethane by chelotropic extrusion of sulfur dioxide from a 1,3-dihydrobenzothiophene 2,2-dioxide. The *o*-QDM generated should be trapped intramolecularly by an oxime methyl ether. This approach utilizes piperonal and D-arabinose as starting materials and is outlined in Scheme 10.

SCHEME 10


(-) trans -dihydrolycorcidine
NOMe
OAc
SO2
CH=NOMe
OAc
NOMe
OAc
SO2
HO
SO2+
CHO
Piperonal
D-Arabinose

Piperonal was converted to dichloride **122** via known methodology.[53] The dichloride, **122**, was converted into cyclic sulfide, **123** {m.p. 117-119°C; ir (KBr pellet) υ: 2910 (C-H), 1485 (Ar-C) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 4.14 (s, 4H), 5.94 (s, 2H), 6.65 (s, 2H); M.S. (m/z): 180 (M^+) (100%), 179 (M-1) (99%), 150 (M-CHO); exact mass calculated for $C_9H_8O_2S$: 180.0245, found: 180.0233}, with sodium sulfide in DMF in 68% yield. When metalation of sulfide **123** was attempted by stirring it with *s*-BuLi in THF at -78°C for 1h, followed by quenching with TMSCl, the only product obtained was the one resulting from ortho-metalation of the aromatic ring, giving the aromatic silane, **124**, in 63% yield. The fact that silylation occurred on the aromatic ring is shown by the appearance of only one aromatic proton at δ=6.38ppm in the ^1H nmr spectrum.

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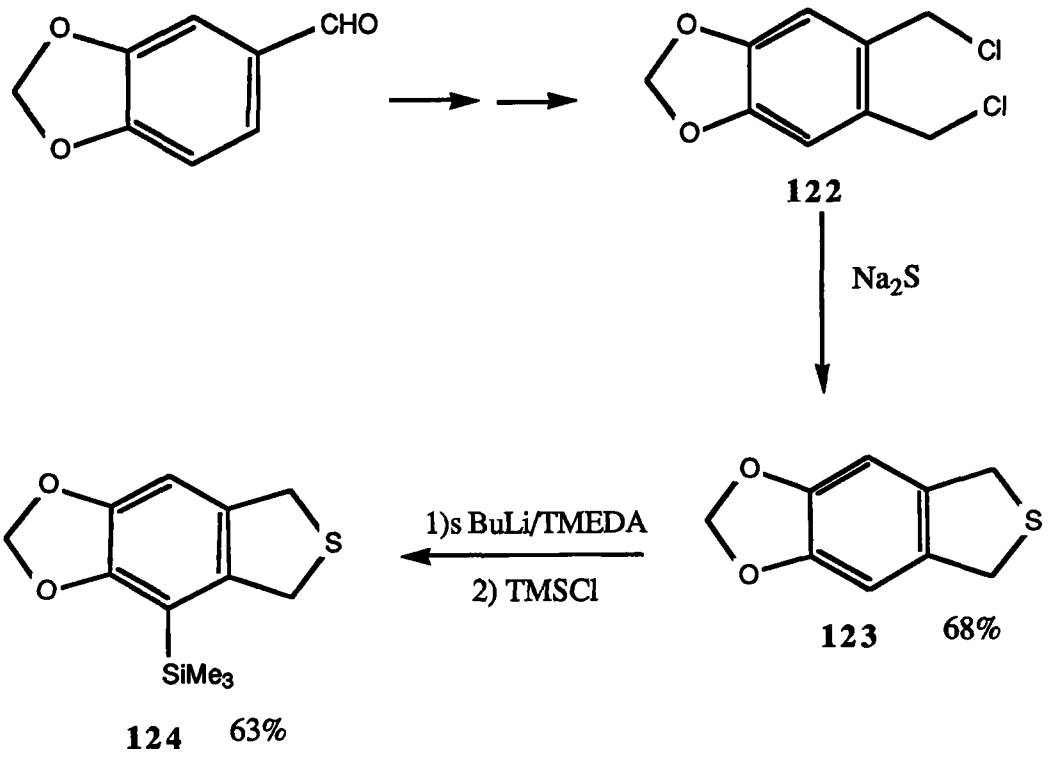
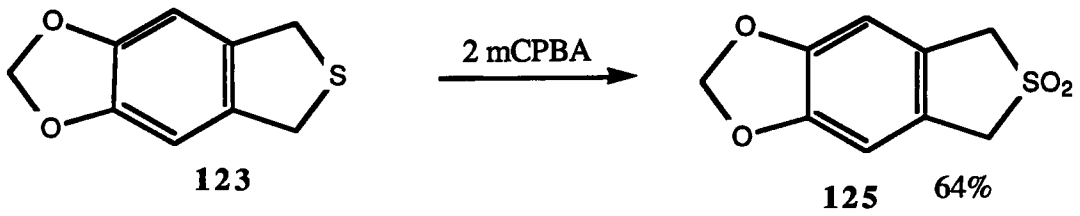
53) F. Dallacker, K. Glombitza and M. Lipp, *Liebigs Ann. Chem.*, **634**, 67(1961).



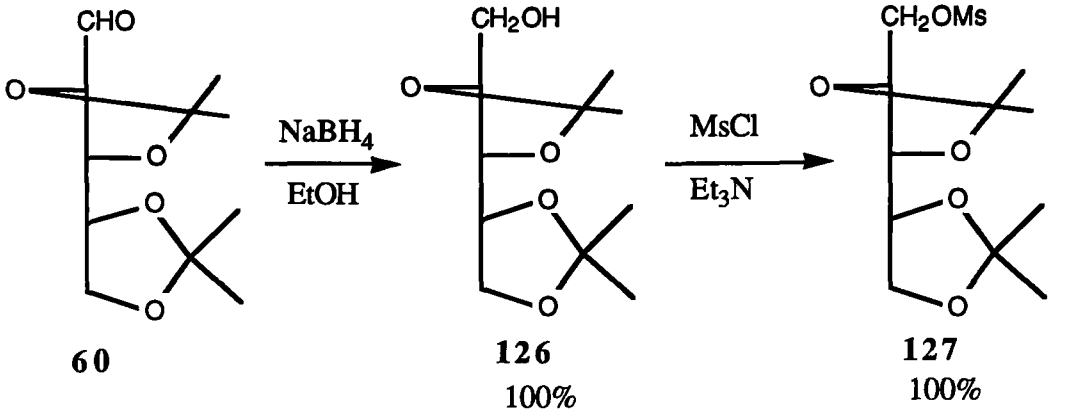
To enhance the acidity of the alpha-methylene protons the sulfide, **123**, was oxidized to its sulfone, **125** {m.p. 185°C decomposes; ir (KBr pellet) υ: 2995 (ArC-H), 2900 (C-H), 1480 (ArC-C), 1315, 1125 (RSO_2R) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 4.25 (s, 4H), 5.98 (s, 2H), 6.72 (s, 2H); M.S. (m/z): 212 (M^+), 148 ($M-SO_2$) (100%); exact mass calculated for $C_9H_8O_4S$: 212.0141, found: 212.0141}. This was done by treatment of the cyclic sulfide, **123**, with two equivalents of *m*-CPBA in ethyl acetate, in 64% yield.



123 **125** 64%

Di-O-isopropylidene aldehydo-D-arabinose, **60**, was reduced with sodium borohydride in ethanol to give the known arabinitol,[54] **126**, quantitatively. The reduction was verified by the appearance of an O-H stretching band at 3425 cm^{-1} in the infrared spectrum. The alcohol was converted into its mesylate, **127** {m.p. 41-42°C; ir (KBr pellet) υ: 2980 (C-H), 1380, 1180 (RSO_2OR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.32 (s, 3H), 1.38 (s, 3H), 1.40 (s, 6H), 3.05 (s, 3H), 3.71 (dd, 8Hz, 8.5Hz), 3.94 (dd, 1H, 4.5Hz, 8.5Hz), 4.04 (m, 1H), 4.15 (m, 2H), 4.29 (dd, 1H, 5.5Hz, 11Hz), 4.52 (dd, 1H, 2.5Hz, 11Hz); M.S. (C.I. ether) (m/z): 311 (M+1), 295 ($M-CH_3$), 253 ($M+1-CH_3COCH_3$)}, cleanly by treatment with methane-sulfonyl chloride.

54) H. Zinner and H. Kirsten, *Chem. Ber.*, **97**, 1654(1964).



60 **126** 100% **127** 100%

Cyclic sulfone, **125**, was metalated by treatment with LDA in THF at -78°C for 15 min., and mesylate **127** was added. No alkylation product was obtained, only the starting materials were recovered. Attempts were made to convert the mesylate to the iodide via standard methodology, but in all instances only the starting mesylate, **127**, was recovered. Prepare of the known triflate[55] from arabinitol, **126**, was also attempted by treatment with triflic anhydride in the presence of triethylamine at -78°C, but it appeared to be very unstable and decomposed under the reaction conditions.

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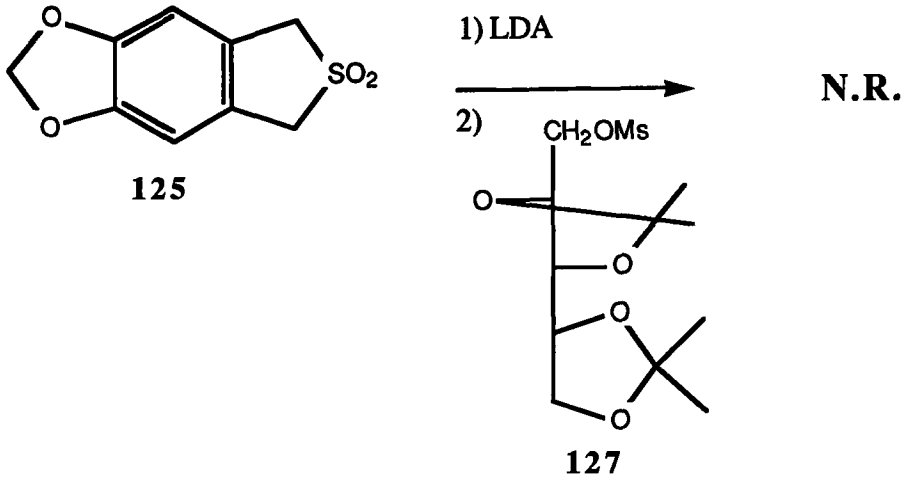
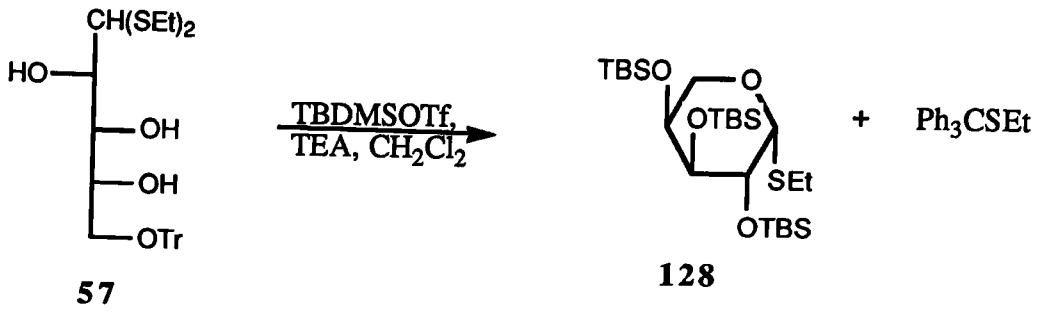
55) C.Y. Shiue, R.R. MacGregor, R.E. Lade, C.N. Wan andA.P. Wolf, *Carbohydrate Res.*, **74**, 323(1979).



125 **127**

It was thought that the mesylate, even though primary was sterically hindered by the neighbouring acetonide function. A different series of protecting groups for the arabinose portion was then studied. It had been shown in an earlier approach that the 2,3,4-tri-O-benzyl-5-O-trityl derivative of arabinose could not be prepared cleanly. When attempts were made to prepare the tri-(*t*-butyldimethylsilyl)-5-O-trityl derivative, by treatment of the diethyl mercaptal of 5-O-trityl-D-arabinose, **57**, with excess TBDMSOTf in methylene chloride in the presence of triethylamine at O °C, a somewhat surprising result was obtained. The products obtained were ethyl triphenylmethyl sulfide and the ethyl thioglycoside**128**. These products may result from initial persilylation of the triol to give the desired trisilylated product, **129**, which is then followed by further silylation of one of the sulfur atoms to give cation **130**. This cation can then eliminate tert-butyldimethylsilyl ethyl sulfide with the help of the other sulfur

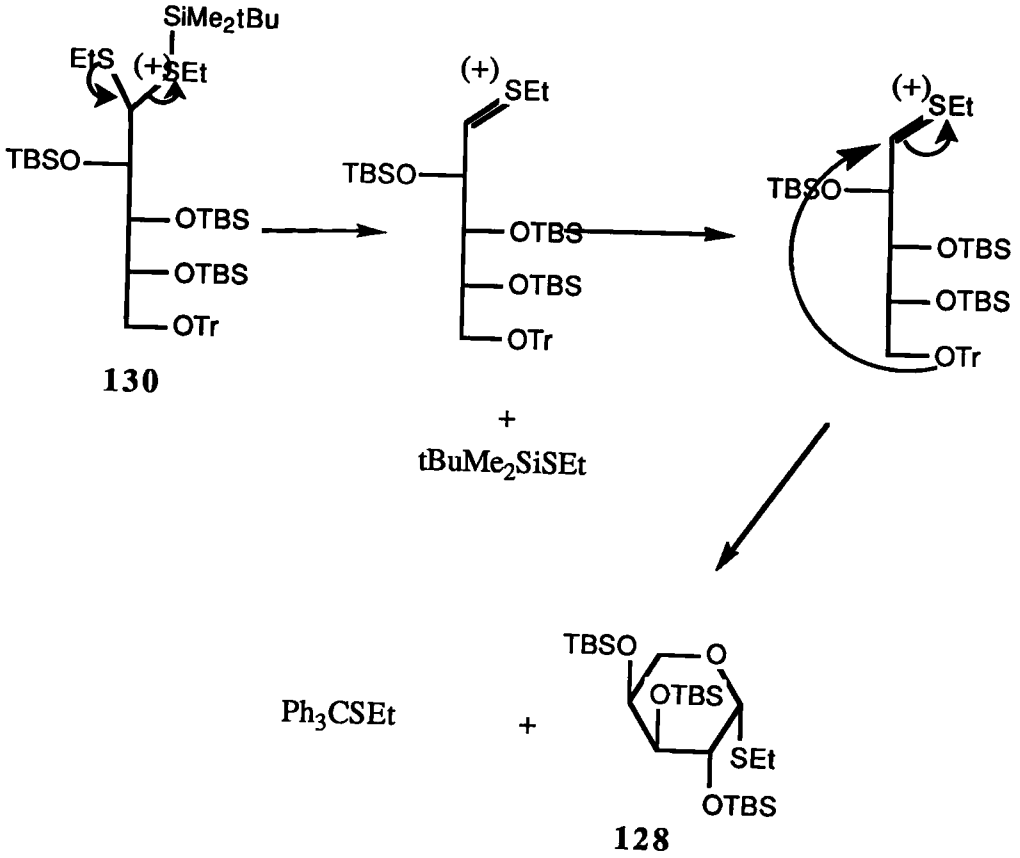
atom. This new vinylic sulfur cation can now be attacked internally by the oxygen of the primary trityl ether which would subsequently lose the trityl cation and give pyranose, **128**. The trityl cation could then react with the tert-butyldimethylsilyl ethyl sulfide to give trityl ethyl sulfide and thus regenerating TBDMSOTf. This is shown in Figure 7.



57

128

FIGURE 7



130

128

The peracetylated derivative,[56] **131**, was prepared cleanly in 95% yield by treating the D-arabinose diethyl thioacetal **57** with acetic anhydride in pyridine. The structure of **131** was consistent with the appearance of three signals at δ=1.78, 2.11, 2.12ppm, each integrating for three protons corresponding to the three acetates in the ^1H nmr spectrum.. The thioacetal was then cleaved in 90% yield with mercuric chloride to give tri-O-acetyl-D-arabinose, **132**, shown by the appearance of a singlet at δ=9.51ppm corresponding to an aldehydic proton in the ^1H nmr spectrum. The aldehyde was then reduced to the arabinitol, **133**, in 98% yield, with borane·THF complex because sodium borohydride in ethanol effected cleavage of the acetates. The reduction was verified by the appearance of an O-H band at 3420 cm^{-1} in the infrared spectrum. Arabinitol **133** was quantitatively converted into its mesylate, **134** { ir (KBr pellet) υ: 2980 (C-H), 1385, 1180 (RSO_2OR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 2.05 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 3.00 (m, 2H), 3.04 (s, 3H), 4.35 (m, 5H), 7.27 (m, 15H); M.S. (C.I. ether) (m/z): 503 ($M-SO_3CH_3$), 339 ($M-(2HOAc+CH_3SO_3H+Ac)$), 243 (Ph_3C^+) (100%)}.

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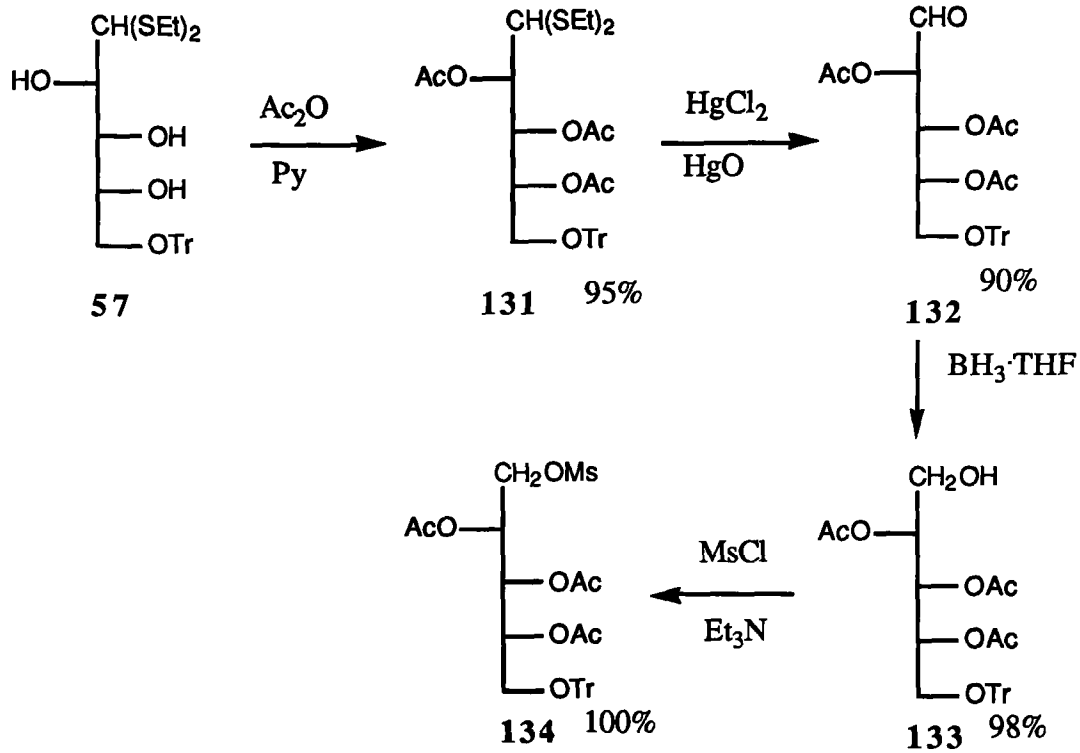
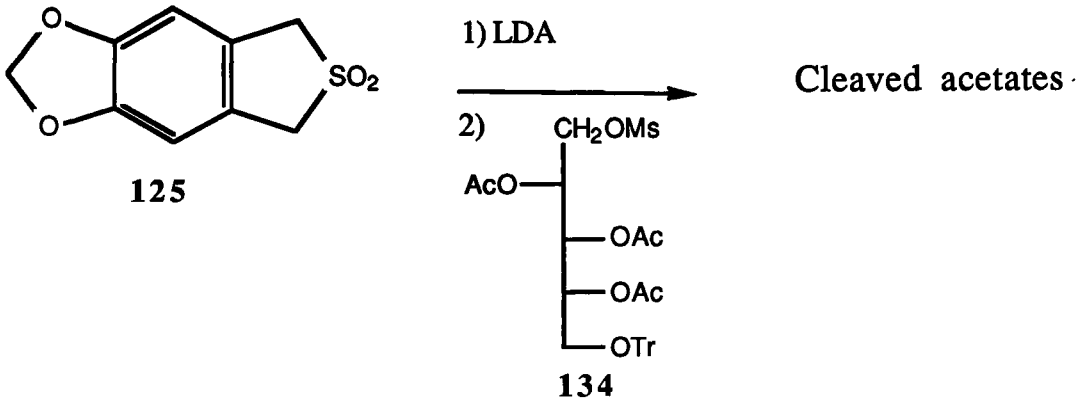
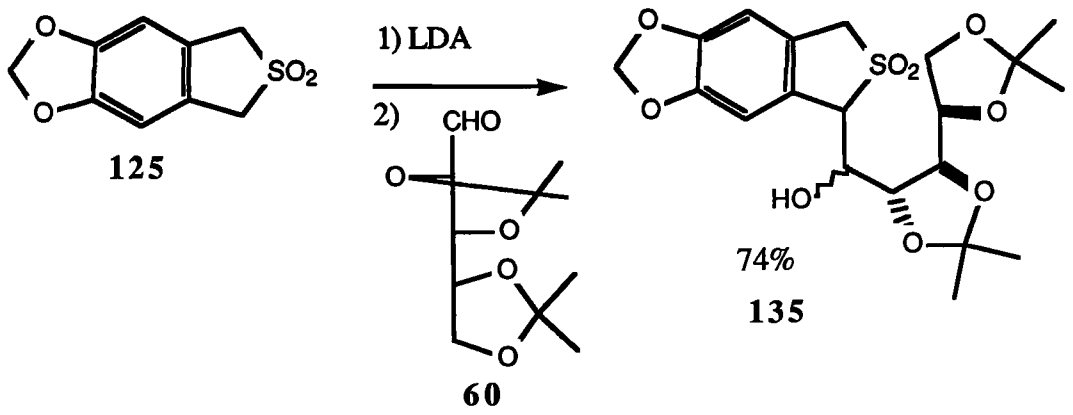
56) M.L. Wolfrom, J.L. Quinn and C.C. Christman, *J. Am. Chem. Soc.*, **57**, 713(1935).



This mesylate, **134,** was reacted with the anion generated from sulfone, **125,** under the conditions described earlier, but only cleavage of the acetates resulted, and none of the condensation product was observed.



The α-anion generated from sulfone, **125**, under the same conditions as described earlier, was reacted with the diisopropylidene arabinose, **60**, and the desired alcohol, **135** {m.p. 52-54°C; ir (KBr pellet) υ: 3420 (O-H), 2995 (ArC-H), 2910 (C-H), 1485 (ArC-C), 1315, 1220 (RSO_2R) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.30 (m, 12H), 1.70 (br s, 1H, O<u>H</u>), 3.98 (m, 2H), 4.15 (m, 3H), 4.25 (s, 2H), 5.98 (s, 2H), 6.72 (s, 1H), 6.77+6.86 (s's, 1H) (diastereomers); M.S. (C.I. ether) (m/z): 443 (M+1), 425 (M+1-H_2O), 385 (M+1-CH_3COCH_3), 379 (M+1-SO_2)}, was obtained in 74% yield.



125 60 135

Deoxygenation of the alcohol was now necessary. It had been shown in the literature that conversion of hydroxyl groups to xanthates followed by reduction with tri-*n*-butyltin hydride was an efficient method of deoxygenating sterically hindered hydroxyl groups.[57] The alcohol, **135**, was then converted into xanthate, **136** {ir (film) υ: 1320, 1225 (RSO_2R), 1215 (C=S) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.40 (m, 12H), 2.29+2.79 (s's, 3H), 4.00 (br m, 7H), 4.25 (s, 2H), 5.98+6.03 (s's, 2H), 6.72 (s, 1H), 6.91+6.96 (s's, 1H); M.S. (C.I. ether) (m/z): 533 (M+1), 517 ($M-CH_3$), 442 ($M+1-CS_2CH_3$), 425 ($M-OCS_2CH_3$)} in 25% yield. This xanthate, **136**, was then treated with tri-*n*-butyltin hydride in the presence of AIBN in refluxing toluene. The desired deoxygenation was achieved to give **137**, but, unfortunately the elimination product **138** was also obtained. The yield in the xanthate formation was low and the mixture of deoxygenation and elimination products was difficult to separate, so

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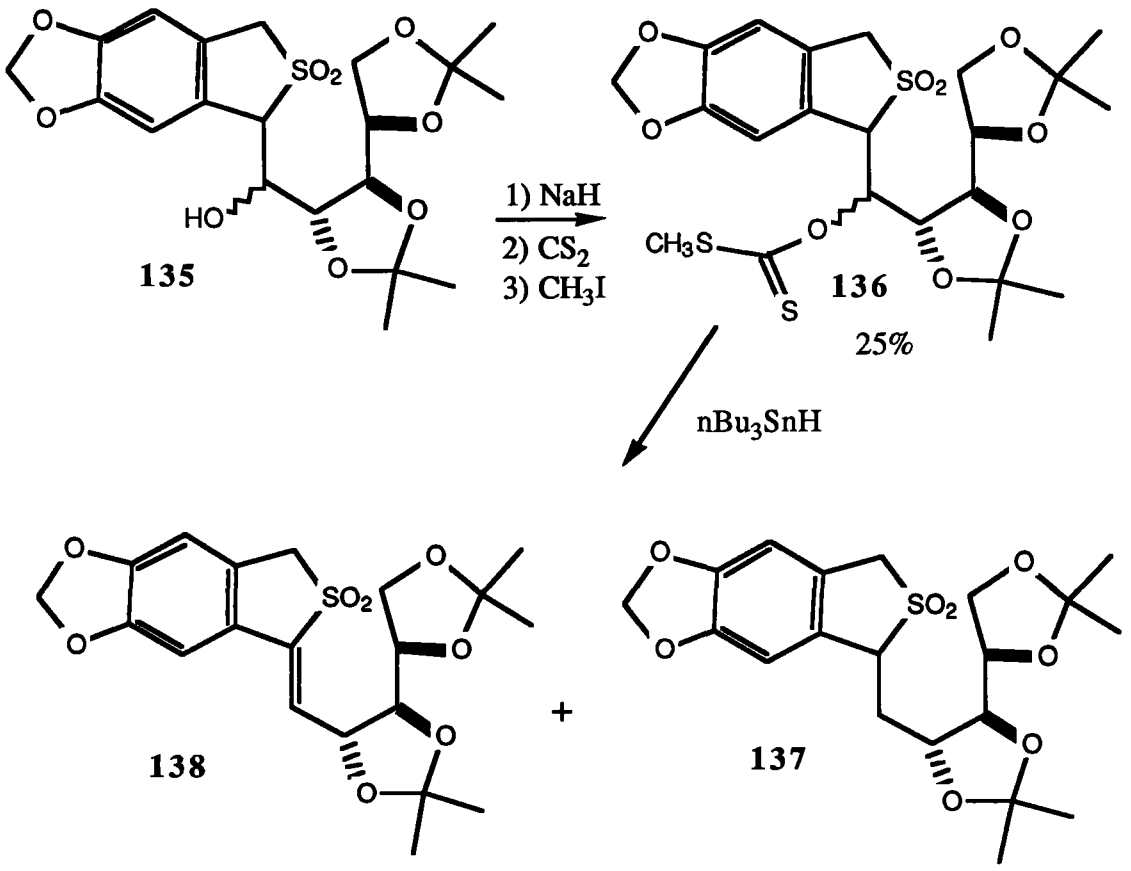
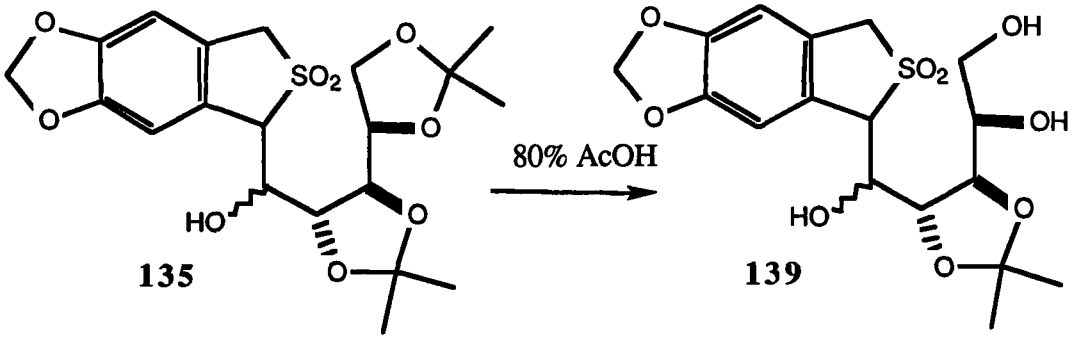
57) a)S. Iacono and J.R Rasmussen, *Organic synthesis*, **64**, 57(1985), b) D. Barton and s. McCombie, *J. Chem. Soc., Perkin 1*, 1796(1975).

attempts to eliminate the hydroxyl and reduce the resulting double bond were investigated.



Conversion of alcohol, **135**, into a derivative suitable for elimination, such as the mesylate, chloride or even the acetate, proved to be impossible. The xanthate, **136**, prepared earlier was exposed to sodium hydride in THF at R.T. for 18h to purposely effect elimination, but only very poor yields of the desired elimination product, **138**, were obtained.

In an attempt to eliminate the hydroxyl group directly, alcohol **135** was treated with thionyl chloride in pyridine, but, only starting material was recovered. Alcohol, **135**, was exposed to 80% acetic acid for two days in an effort to possibly cause elimination along with mono-deprotection. The only product isolated was a small amount of mono-deprotected material **139**; it was assumed that mostly the di-deprotected material was obtained and lost during the work-up.



Other methodology known to achieve difficult dehydrations was saught. The Burgess reagent ($MeO_2N^{(-)}SO_2N^{(+)}Et_3$), which is known to be an active dehydrating agent was first employed.[58] The alcohol, **135**, was treated with the reagent in refluxing acetonitrile for 24 hours and no reaction was observed, only the alcohol was recovered. Martins sulfurane which had been shown to effect dehydration where the Burgess reagent had failed was tried as a last

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58) E.M. Burgess, H.R. Penton Jr. and E.A. Taylor, *J. Org. Chem.*, **38**, 26(1973).

resort.[59] Treatment of alcohol, **135**, with Martins sulfurane initially at -50°C, but no reaction took place, and even warming to 25°C for 18h still effected no reaction. So at this point no possible remedy; for the deoxygenation could be found, again, the approach was abandoned.

59) R.J. Arhart and J.C. Martin, *J. Am. Chem. Soc.*, **94**, 5003(1972).

CONCLUSIONS

Even in retrospect, the various routes investigated for the synthesis of *trans*-dihydrolycorcidine seem rational and reasonable. However none was successfully completed. In each case problems were encountered which could not be overcome. One reason for this difficulty may have been philosophical in nature. For example the route described in chapter 2 was abandoned because we were not satisfied with a 10-20% yield in the hydrolysis of a methyl glycoside. Approximately 10-20 experimental variations were attempted. When does one stop and turn to a new route? Should one have been satisfied with a 20% yield in the hydrolysis and carried on to finish the synthesis or was it more reasonable to try an alternate route. Since similar molecules had already been synthesized it was felt that a better synthesis not just another synthesis was required.

The key difficulties encountered in each approach are briefly described below.

The problems with the first ortho-quinodimethane approach were firstly the inability to deoxygenate a benzylic hydroxyl function. Eventhough all of the conceivable methods for deoxygenation were not attempted, this problem was eventually avoided by the discovery of new methodology in the development of direct alkylation of aryl-anions with alkyl triflates.

The second problem was the resistance of the methyl glycoside to hydrolysis. There may have been alternate methods known to cleave the methyl glycoside known such as dimethylboron bromide, borontrichloride or borontribromide but, since these are Lewis acid

catalyzed methods there existed a possibility that either the methylene dioxy or benzyl protecting groups may have been cleaved. Also preparation of a different, and a possibly more easily removable glycoside could have been envisaged but, this would have involved adding several steps and possibly changing the other protecting groups to ones resistant to the conditions required to cleave the new glycoside. In any case it had been later shown that the photochemical generation of the ortho-quinodimethane was not possible.

The first problem encountered in the second ortho-quinodimethane approach was the transfer of a silyl group from oxygen to carbon. This is one of few examples known of this type of migration and is unusual in that all other documented examples occur with the smaller trimethylsilyl group, using the tertiarybutyldimethylsilyl group usually deters this migration but not in this case. This problem was overcome by the generation of this anion at a later stage in the synthesis.

The second problem was encountered when the Wittig reaction was attempted on a hemi-acetal. There have been several examples of such a reaction but only with stabilized ylids. The ylid necessary for this synthesis was not stabilized and therefore did not work and the approach was abandoned.

The problems with the lateral metalation approach were initially the inability to achieve lateral metalation of the desired toluamide derivative. This was overcome by the further activation of this position by the preparation of a phenyl sulfide. Even though the desired metalation could now be achieved it was impossible to

condense the resulting anion with any imine electrophile. During this approach it was proved that contrary to speculation in the literature, ortho-metalation of a doubly activated position is favoured over lateral metalation even when a base such as LDA is employed.

Also evidence supporting the theory that lateral metalation cannot be accomplished if the aromatic ring and the amide function cannot achieve planarity to allow for overlap of the π-orbitals was obtained. Spectral data supporting the fact that planarity could not be achieved also showed that the pentasubstituted aromatic system was so rigid that even though there is no chiral center in the molecule the molecule is chiral, similar to binaphthyl examples.

The initial setback in the ortho-metalation approach was the inability to cleanly generate the ortho-metalated dianion of *N*-benzylbenzamide. This was overcome by using α-methylbenzylbenzamide, but this created another problem in that after the desired alkylation had been achieved, cyclization through nitrogen could not be achieved. Only cyclization through the oxygen atom of the amide was observed. Attempts made to alleviate this problem by changing the amide protecting group were thwarted when both the *N*-benzyloxy and *N*-ethylthiomethyl groups were lost during anion formation via β-elimination processes. When the protecting group was *N*-methoxyl, a procedure for its removal via hydrogenolysis was developed, but unfortunately even though there was some evidence for the formation of the desired dianion, it could not be obtained cleanly.

During the third ortho-quinodimethane approach one major problem was encountered the selective differentiation of adjacent

primary and secondary hydroxyl groups. The protection of the primary hydroxyl group could be accomplished with difficulty but this hindered the secondary position to such a great extent that it could not be protected. In an attempt to alleviate this problem preparation of a cyclic sulfide was attempted, hoping that the formation of the five membered ring would relieve some of the steric hindrance. Unfortunately the radical induced cyclization of the thiol could not be achieved.

The final approach achieved the first synthesis of 5,6-methylenedioxy 1,3-dihydrobenzo[c]thiophene 1,1-dioxide **125**, and some of its anion chemistry was explored. Also the attempted preparation of the benzylic α-sulfenyl anion of 5,6-methylenedioxy 1,3-dihydrobenzo[c]thiophene **123**, led unexpectedly to the ortho-lithiation. The problem with this approach was similar to one encountered earlier, the deoxygenation of a hydroxyl group. Many attempts were made to deoxygenate or eliminate this alcohol, but, all attempts failed.

Given additional time it is felt that the final approach has the best chance for success, by possibly ignoring the free hydroxyl group which could not be eliminated cleanly. The primary acetonide could then be cleaved selectively, replaced by a benzylidene protecting group which may be cleaved with NBS under free radical conditions to give the primary bromide and secondary hydroxyl protected as its benzoyl ester, the bromide could then be elaborated into the aldehyde via known methodology. This aldehyde could then be transformed into the necessary methyl oxime. A variation on this would be to hydrogenolyze the benzylidene group which would give

a free hydroxyl at the primary position leaving the secondary position protected.

It is also conceivable that the compound could be assembled using an intermolecular Diels-Alder reaction between an *ortho*-quinodimethane generated from the benzocyclobutanol derived from piperonal and the diactone arabino methyloxime **63** mentioned earlier. This should give the required regiochemistry where the nitrogen is attached to the carbon bearing oxygen, the only question is how much influence the chiral centres on the oxime will have on the newly forming centres. The resulting hemi-aminal could be oxidized to an amide, the primary acetoanide could be cleaved selectively and the resulting diol converted into an epoxide. Now one would have to close the third ring by generating a benzylic anion which would be stabilized by the cyclic amide, and opening the epoxide with this anion. All that would then be required would be deprotection.

Even though this intermolecular Diels-Alder approach looks promising, one would have to give it much more thought before pursuing it. Selection of protecting groups and preparation of leaving groups is never as trivial as it looks.

EXPERIMENTAL

Melting points were determined by use of a Gallenkamp digital melting point apparatus and are uncorrected. Infrared (IR) spectra were taken from films on sodium chloride plates for oils, and from chloroform ($CHCl_3$) solutions or potassium bromide (KBr) pellets for solids, using a Perkin Élmer 783 spectrophotometer. Frequencies are reported in cm^{-1}. Mass spectra were recorded on an AEIMS 9025 instrument. The peak intensities are given as a % of the base peak (100%) intensity. Optical rotations were measured using a Perkin Elmer 241 polarimeter.

Proton NMR spectra were taken in deuterochloroform ($CDCl_3$), unless otherwise noted, using a Varian XL-300 300MHz spectrometer. The chemical shifts are reported in ppm downfield relative to the internal standard tetramethylsilane (delta scale). The coupling patterns are noted as singlets (s), doublets (d), triplets (t), quartets (q), doublets of doublets (dd), broad (br) or multiplets (m).

Column chromatography was accomplished using Baker or Terochem 60-200 mesh silica gel as the adsorbent. Thin layer chromatography (TLC) was performed on Merck 60 F-254 and Kieselgel 60 F-254 precoated silica gel plates of 0.25mm thickness. Purifications by Chromatotron were performed on a Harrison Research Chromatotron model 7924 using silica gel-coated rotors (1mm, 2mm, and 4mm thickness).

Tetrahydrofuran (THF) was distilled over sodium-benzophenone under a nitrogen atmosphere prior to use.

Diisopropylamine, dimethyl sulfoxide (DMSO), hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were distilled from calcium hydride under a nitrogen atmosphere. Methylene chloride was dried by distillation from phosphorus pentaoxide. All other solvents or reagents were distilled or were of reagent grade quality.

Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvent with a Buchi evaporator connected to a water aspirator. Unless otherwise indicated all reactions were conducted under an atmosphere of nitrogen.

6-Bromopiperonal *n*-propylene acetal 30

A solution of bromopiperonal **29** (10.00 g, 43.68 mmol), 1,3-propanediol (10.00 g, 131.58 mmol) and *p*-TSA (100 mg) in toluene (150 mL) was refluxed for 18 h using a Dean-Stark apparatus to remove water. After cooling the resulting solution was washed with saturated sodium bicarbonate (50 mL), water (2x50 mL), dried and concentrated to yield a yellow oil, which was purified by crystallization from ether to give **30** as a white solid, m.p. 89.3-90.2°C; 11.41 g (91%); ir (KBr pellet) υ: 2920 (C-H), 1500 (ArC-C) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.42 (dt, 1H, 13.5Hz, 1.2Hz), 2.22 (m, 1H), 3.98 (dt, 2H, 12.2Hz, 2.4Hz), 4.24 (ddd, 2H, 12.2Hz, 5Hz, 1.2Hz), 5.66 (s, 1H), 5.94 (s,2H), 6.95 (s, 1H), 7.15 (s, 1H); M.S. (m/z): 286 (M+) (47%), 288 (M+2) (47%), 285 (M-1) (22%), 287 (M+2-1) (25%), 228 (M-$(CH_2)_3O$) (81%), 230 (M+2-$(CH_2)_3O$) (78%), 207 (M-Br)

(61%), 199 (M-$(CH_2)_3O_2CH$) (18%), 201 (M+2-$(CH_2)_3O_2CH$)(15%); exact mass calculated for $C_{11}H_{11}O_4Br$: 285.9840, found: 285.9859.

Methyl 6-O-triphenylmethyl-α-D-mannopyranoside 31[17]

Triethylamine (0.78 g, 7.73 mmol) was added to a solution of methyl α-D-mannopyranoside (1.00 g, 5.15 mmol), triphenylmethyl chloride (1.58 g, 5.67 mmol) and N,N-dimethylaminopyridine(DMAP) (10 mg) in DMF (8 mL), which was stirred for 18 h. The reaction was then quenched with water and the mixture extracted with ethyl acetate (2x20 mL). The combined organic phases were washed with water (2x20 mL), brine, dried and concentrated to yield a pink solid. The crude solid was recrystallized from ethanol to give **31** as a white solid, 1.98 g (88%); (only literature data available has compound co-crystallized with pyridine[17]) m.p. 73.4-76.2°C; $[\alpha]^{22}$ (c 0.15, $CHCl_3$) +15.24°; ir (KBr pellet) υ: 3420 (O-H), 2925 (C-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.55 (br s, 3H, OH), 3.36 (s, 3H, OCH_3), 3.22-3.27 (m, 5H), 3.90 (q, 1H, 2.0Hz), 4.70 (d, 1H, 1.5Hz), 7.11-7.49 (m, 15H); M.S. (C.I. ether) (m/z): 436 (M^+) (15%), 400 (M-H_2O) (1%), 244 (TrO^+) (100%).

Methyl 2,3,4-Tri-O-benzyl-α-D-mannopyranoside 32[18]

A solution of **31** (1.90 g, 4.36 mmol) in DMF (10 mL) was added to sodium hydride (60% in mineral oil) (washed with hexanes) (1.74 g, 43.58 mmol), and after the addition was complete, benzyl bromide (7.45 g, 43.58 mmol) was added dropwise. The reaction temperature was raised to 60°C and maintained for 18h. The

reaction was quenched with methanol and the solution was stirred at 22°C for 1h. Water was then added and the resulting mixture was extracted with ether (3x20 mL). The combined ether extracts were washed with water (4x20 mL), brine, dried and concentrated to yield a yellow oil.

The crude oil was dissolved in acetone (100 mL), water (50 mL) and 10% HCl (10 mL) and refluxed for 3h. The reaction mixture was cooled, quenched with saturated sodium bicarbonate, and acetone was removed in vacuo. The residue was extracted with methylene chloride (3x20 mL), the combined organic phases were dried and concentrated to yield a yellow oil. The crude oil was purified by flash chromatography (30% ethyl acetate/hexanes). A thick oil resulted, **32**, 1.65 g (82%); $[\alpha]^{22}$ (c 0.21, $CHCl_3$) +28.5° (lit. value[18] $[\alpha]^{18}$ (c 0.49, $CHCl_3$) +30°))(ir (film) υ: 3570 (O-H), 3110 (Ar-H), 1610 (ArC-C) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.58 (br s, 1H, OH), 3.28 (s, 3H, OCH_3), 3.54-4.12 (m, 5H), 4.60-4.96 (m, 7H), 7.20-7.40 (m, 15H); M.S. (C.I. ether) (m/z): 465 (M+1) (1%), 447 (M+1-H_2O) (1%); M.S. (m/z): 373 (M-(H_2O+Bn)) (8%), 91 (Bn^+) (100%).

Methyl 2,3,4-tri-O-benzyl-α-D-manno-hexodialdo-1,5-pyranoside 33[18]

Oxalyl chloride (0.17 g, 1.36 mmol) was added to dimethyl sulfoxide (DMSO) (0.21 g, 2.71 mmol) in dry methylene chloride (10 mL) at -78°C. This was followed by the addition of alcohol, **32**, (0.52 g, 1.13 mmol) in dry methylene chloride (5 mL). After 10 min. triethylamine (TEA) (0.28 g, 2.72 mmol) was added, and the reaction

temperature was then raised to 22°C. The reaction was quenched with water, and the mixture extracted with methylene chloride (2x10 mL). The combined organic extracts were washed with water (3x15 mL), dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (30% ethyl acetate/hexanes) to yield aldehyde **33**, 0.52 g (100%); ir (film) υ: 1710 (CHO) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 3.36 (s, 3H, OCH_3), 3.70-4.06 (m, 4H), 4.37-4.85 (m, 7H), 7.13-7.35 (m, 15H), 9.72 (s, 1H, C<u>H</u>O);(lit.[18] ^1H nmr ($CDCl_3$) (60MHz) δ: (only signals reported) 3.45 (s, 3H, OCH3), 4.7-4.9 (m, 7H), 7.3-7.6 (m, 15H), 10.0 (s, 1H)); M.S. (C.I.ether) (m/z): 480 ($M+H_2O$) (1%), 448 ($M-CH_3$) (4%), 327 (M-(Bn+CHO+CH_3)) (65%).

Methyl-2,3,4-Tri-O-benzyl-6-C-(6-(1,3-dioxan-2-yl)-benzo-1,3-dioxolan-5-yl)-α-D-mannopyranoside 34

A solution of *n*-butyllithium (2.5M in hexanes) (0.27 mL, 0.68 mmol) was added to a solution of bromide **30** (0.19 g 0.68 mmol) in THF (10 mL) at -78°C. After 10 min. a solution of aldehyde **33** (0.32 g, 0.68 mmol) in THF (8 mL) was added. After 15 min. the reaction was quenched with saturated ammonium chloride, and the reaction mixture was extracted with ether (2x20 mL). The combined organic extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (40% ethyl acetate/hexanes) to yield **34**, 0.30 g (66%); ir (film) υ: 3610 (O-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.50 (m, 2H), 1.56 (br s, 1H, OH), 3.17 (s, 3H, OCH_3), 3.41-3.94 (m, 5H), 4.58-5.20 (m, 10H), 5.38 + 5.52 (s, 1H, ArC<u>H</u>(OH)R, diastereomers),

5.78 (s, 1H), 5.83 (dd, 2H, 1Hz), 7.02 (s, 1H), 7.16 (s, 1H), 7.20-7.34 (m, 15H); M.S. (m/z): 594 (M-HO$(CH_2)_3$OH) (16%); M.S. (C.I. ether) (m/z): 595 (M+1-HO$(CH_2)_3$OH) (8%).

Attempted transfer hydrogenolysis of 34 (typical procedure)

A mixture of alcohol **34** (0.25 g, 0.37 mmol), cyclohexene (0.05g, 0.61 mmol), and 5% palladium on charcoal (50 mg) in ethanol (10 mL) was stirred at 25°C for 42h. The catalyst was removed by filtration through a plug of Celite and the solvent was removed in vacuo. It appeared that the alcohol was still present from the ^1H nmr and ir spectra.

Methyl 2,3,4-Tri-O-benzyl-6-C-(6-(1,3-dioxan-2-yl)-benzo-1,3-dioxolan-5-yl)-6-oxo-α-D-mannopyranoside 35

A solution of alcohol **34** (0.08 g, 0.12 mmol) in methylene chloride (2 mL) was added to a slurry of pyridinium chlorochromate (0.04 g, 0.18 mmol) and sodium carbonate (0.05 g, 0.49 mmol) in methylene chloride (5 mL). The resulting brown slurry was stirred at ambient temperature for 18h. The reaction mixture was then poured into anhydrous ether (20 mL), precipitated solid was removed by filtration through a pad of silica, and solvent was removed in vacuo to yield a colourless oil. The oil was purified by preparative TLC (30% ethyl acetate/hexanes) to yield ketone, **35**, 0.05g (55%); ir (film) υ: 1765 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.56 (m, 2H), 3.29 (s, 3H, OCH_3), 3.38-3.99 (m, 5H), 4.11-5.07 (m,

10H), 5.59 (s, 1H), 6.10 (s, 2H), 7.14 (s, 1H), 7.23 (s, 1H), 7.26-7.36 (m, 15H); M.S. (C.I. ether) (m/z): 669 (M+1) (7%); M.S. (C.I. isobutane) (m/z): 669 (M+1) (4%).

Attempted Clemmensen reduction of ketone 35

A mixture of ketone **35** (0.14 g, 0.21 mmol) and zinc amalgam (100 mg) in 50% HCl (5 mL) was stirred for 20 min at 25°C. The reaction mixture was poured into water, and extracted with ether (2x10 mL). The combined ether extracts were washed with water (3x10 mL), saturated sodium bicarbonate (2x10 mL), water, brine, dried and concentrated to yield a yellow oil. It appeared that the acetal had been cleaved due to the disappearance of the signals at 1.56 and 3.50ppm due to the acetal and the appearance of a signal at 9.65ppm due to an aldehyde.

4,5-Methylenedioxy-2-(2-phenylvinyl) bromobenzene 36

Benzyltriphenylphosphonium bromide (5.70 g, 13.17 mmol) was added slowly to a slurry of sodium hydride (60% in mineral oil) (washed with hexanes) (0.58 g, 14.49 mmol) in THF (20 mL); a few drops of ethanol were added to catalyze the reaction. After the evolution of hydrogen had ceased a solution of 6-bromopiperonal, **29**, (3.00 g, 13.17 mmol) in THF (20 mL) was added dropwise, and stirring was continued for 18h. The reaction was quenched with water, the mixture extracted with ether (2x20 mL), and the extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a red oil. The oil was purified by flash chromatography

(hexanes) to yield **36**, as a yellow oil, ((1:2) mixture of *cis* and *trans*-isomers), 3.18 g (80%); ir (film) υ: 1600 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: (*trans*-isomer) 5.98 (s, 2H), 6.50 (d, 1H, 12.4Hz), 6.60 (d, 1H, 12.4Hz), 7.14 (s, 1H), 7.19 (dd, 1H, 4Hz, 1Hz), 7.25 (s, 1H), 7.36 (dd, 2H, 6Hz, 1Hz), 7.50 (dd, 2H, 6Hz, 1Hz); M.S. (m/z): 302 (M^+) (55%), 304 (M+2) (43%), 224 (M+1-Br) (28%).

1,2-Methylenedioxy-4-(2-phenylvinyl)-5-(α-hydroxy-*p*-xylyl) benzene 37

A solution of *n*-butyllithium (2.6M in hexanes) (0.40 mL, 1.03 mmol) was added to a solution of bromide, **36** (0.31 g, 1.03 mmol) in THF (10 mL) at -78°C. After 10 min. a solution of *p*-tolualdehyde (0.12 g 1.03 mmol) in THF (5 mL) was added, the reaction mixture was allowed to warm to 22°C over 3h. The reaction was quenched with saturated ammonium chloride, the mixture poured into ether-water, the aqueous phase was extracted with ether (2x20 mL), the combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes) to yield **37** as a colourless oil, 0.22 g (62%); ir (film) υ: 3405 (O-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.50 (br s, 1H, OH), 2.28 (s, 3H, CH_3), 5.86 (m, 1H), 5.92 (dd, 2H, 1.5Hz), 6.78 (m, 1H), 6.96 (s, 1H), 7.02-7.40 (m, 11H); M.S. (m/z): 344 (M^+) (12%), 326 (M-H_2O) (100%), 296 (M-CH_2O_2) (6%).

Attempted reduction of alcohol 37 with sodium cyanoborohydride

A mixture of alcohol, **37** (0.08 g, 0.23 mmol), sodium cyanoborohydride (0.02 g, 0.28 mmol) and *p* TSA (50 mg) in THF (5 mL) was stirred at 25°C for 1h. The reaction was quenched with water, and the mixture extracted with ether (2x10 mL). The combined ether extracts were washed with saturated sodium bicarbonate, water, brine, dried and concentrated to yield only starting alcohol, **37**, as determined by the ^1H nmr and mass spectra.

Attempted reduction of alcohol 37 with lithium in ammonia

A solution of alcohol **37** (0.20 g, 0.58 mmol) in THF (10 mL) was added to a mixture of ammonia (freshly distilled from sodium) (10 mL), lithium (0.01 g, 1.74 mmol) and THF (5 mL) at -78°C. The addition seemed to consume the blue colour as it was produced. After 15 min the blue colour persisted, the reaction was quenched with saturated ammonium chloride solution and the ammonia was allowed to evaporate. After the usual work-up a yellow oil resulted which appeared to be a complex mixture by TLC analysis.

1,2-Methylenedioxy-4-(2-phenylvinyl)-5-(α-chloro-*p*-xylyl) benzene 38

Thionyl chloride (0.07 g 0.58 mmol) was added to a solution of alcohol **37** (0.13 g, 0.39 mmol) in dry methylene chloride (8 mL) at 0°C. After stirring for 1.5h, solvent was removed in vacuo to yield a

yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes) to yield **38** as a yellow oil, 0.12 g(85%); ir (film) υ: 2905 (C-H), 1605 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$) (60MHz) δ: 2.25 (s, 3H), 5.70 (m, 1H), 5.85 (s, 2H), 6.50 (m, 1H), 6.60-7.35 (m, 12H).

Attempted reduction of chloride 38 with tri-*n*-butyltin hydride

A solution of chloride **38** (0.12 g, 0.33 mmol), tri-*n*-butyltin hydride (0.12 g, 0.398 mmol) and AIBN (20 mg) in benzene (25 mL) was refluxed for 24h. TLC analysis showed that starting chloride, **38**, was still present along with some decomposition product.

1,2-Methylenedioxy-4-(2-phenylvinyl)-5-(6-*t*-butyldimethylsilyloxyhexyl) benzene 39

A solution of *n*-butyllithium (2.6M in hexanes) (0.30 g, 0.79 mmol) was added to a solution of bromide **36** (0.24 g, 0.79 mmol) in THF (10 mL) at -78° C. After 5 min. a solution of tri-*n*-butylphosphine-cuprous iodide complex (0.31 g, 0.79 mmol) in THF (5 mL) was added. After 10 min. a solution 6-bromo-1-*t*-butyldimethylsilyloxyhexane (0.23 g, 0.79 mmol) in THF (5 mL) was added dropwise. The mixture was then allowed to warm slowly to 22°C, stirred for 18h, quenched with saturated ammonium chloride, and extracted with ether (2x15 mL). The combined ether extracts were washed with water (20 mL), brine, dried and concentrated to give a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes), to give mainly recovered silyl ether as well as desired product **39**, 0.07 g (5%);

ir (film) υ: 2950 (ArC-H) cm^{-1}; ^1H nmr ($CDCl_3$) (60MHz) δ: 0.05 (s, 6H), 0.85 (s, 9H), 1.30 (m, 8H), 2.55 (m, 2H), 3.50 (m, 2H), 5.90 (s, 2H), 6.50-6.70 (m, 2H), 7.11-7.25 (m, 7H); M.S. (C.I. ether) (m/z): 439 (M+1) (2%), 424 (M+1-CH3) (20%), 323 (M-TBDMS) (43%).

1,2-Methylenedioxy-4-(2-phenylvinyl)-5-*n*-propyl benzene 40

A solution of *t*-butyllithium (1.42M in pentanes) (1.11 mL, 1.58 mmol) was added to a solution of bromide **36** (0.20 g, 0.66 mmol) in hexanes (8 mL) at -78°C. After 10 min. a solution of *n*-propyl triflate (0.15 g, 0.79 mmol) in THF (5 mL) was added and the reaction mixture was allowed to warm slowly to 22°C. The reaction was quenched with saturated ammonium chloride, extracted with ether (2x20 mL), the combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to give a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes) to give **40** as a colourless oil, 0.07 g (41%); ir (film) υ: 2950 (ArC-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.91 (t, 3H, 8Hz), 1.54 (m, 2H), 2.51 (dd, 2H, 8Hz, 1Hz), 5.86 (s, 2H), 6.49-6.68 (m, 2H), 7.11-7.25 (m, 7H); M.S. (m/z): 266 (M^+) (20%), 237 (M-CH_2CH_3) (10%).

Methyl 2,3,4-tri-O-benzyl-6-O-trifluoromethylsulfonyl-α-D-mannopyranoside 41

Trifluoromethanesulfonic anhydride (0.43 g, 1.51 mmol) was added to a solution of alcohol **32**, (0.50 g, 1.08 mmol) and triethylamine (0.16 g, 1.54 mmol) in dry methylene chloride (10 mL)

at -78°C. The reaction mixture was allowed to warm to 22°C, stirred for a further 1h, poured into ice-cold saturated sodium bicarbonate, and extracted with methylene chloride (3x15 mL), the combined organic phases were dried and concentrated to yield **41** as a yellow oil, 0.82 g (80%). Due to the unstable nature of **41** it was used without purification. ^{1}H nmr ($CDCl_3$) (60MHz) δ: 3.30 (s,3H, OCH_3), 3.55-4.20 (m, 5H), 4.25-5.10 (m, 8H), 7.05-7.45 (br s, 15H); M.S. (C.I. ether) (m/z): 505 (M-Bn) (1%).

Methyl 2,3,4-Tri-O-benzyl-6-C-(6-(2-phenylvinyl)-benzo-1,3-dioxolan-5-yl)-α-D- mannopyranoside 42

A solution of *t*-butyllithium (1.42 M in pentanes) (2.93 mL, 4.16 mmol) was added to a solution of bromide **36** (0.60 g, 1.98 mmol) in THF (5 mL) at -78°C. After 5 min. a solution of triflate, **41**, (1.30 g, 2.18 mmol) in hexanes (10 mL) was added at once. After 10 min. the reaction mixture was allowed to warm to 22°C and stirred for 15h. The reaction was quenched with saturated ammonium chloride, and the mixture extracted with ether (2x20 mL), the combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a dark oil. The oil was purified by flash chromatography (5% ethyl acetate/hexanes) to give **42**, 0.87 g (65%); ir (film) υ: 2910 (C-H), 1605 (C=C) cm^{-1}; ^{1}H nmr ($CDCl_3$) (60MHz) δ: 3.28 (s, 3H, OCH_3), 3.50-4.20 (m, 6H), 4.35-4.90 (m, 7H), 5.79 (s, 2H), 5.85 (m, 1H), 6.40 (s, 1H), 6.65 (s, 1H), 6.95-7.35 (m, 19H); M.S. (C.I. ether) (m/z): 671 (M+1) (1%).

Generation of Aryl Anions

Method A (Lithium-Halogen Exchange)

A solution of *n*BuLi (1.2 eq) was added to a solution of aryl halide (1.0 eq) in THF at -78°C. After 10-20 min. it was used as described below.

Method B (Ortho-Metalation)

A solution of *s*BuLi (1.2 eq) was added to a solution of the benzamide (1.0 eq) and TMEDA (1.0 eq) in THF at -78°C. After 30 min. it was used as described below.

Method C (Direct Deprotonation)

A solution of *n*BuLi (1.2 eq) was added to the aromatic species (1.0 eq) in THF at -78°C. After 30 min. it was used as described below.

Reaction of Aryl Anions with alkyl triflates (Typical procedure)

A THF solution of the aryl anion was generated at -78°C. After 10 min. a solution of triflate (1.5 equivalents) in hexanes was added and the reaction mixture was allowed to warm slowly to 22°C. The reaction was quenched with saturated ammonium chloride, and the mixture extracted with ether (2x20 mL), the combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to give the crude alkylation product. The crude product was purified by either flash chromatography or chromatotron.

Reaction of Aryl Anions with alkyl triflates in the presence of Cerium Trichloride (Typical procedure)

A THF solution of the aryl anion was generated at -78°C. After 10 min. anhydrous cerium trichloride (1.5 equivalents) was added. After an additional 10 min. a solution of triflate (1.5 equivalents) in hexanes was added and the reaction mixture was allowed to warm slowly to 22°C. The reaction was quenched with saturated ammonium chloride, extracted with ether (2x20 mL), the combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to give the crude alkylation product. The crude product was purified by either flash chromatography or chromatotron.

Spectral Data for:

***N,N*-Diethyl-2-*n*-propylpiperonylamide:**

ir (film) υ: 1615 (Ar(C=O)NEt_2) cm^{-1}; ^1H nmr ($CDCl_3$)(300MHz) δ: 0.92 (t, 3H, 7Hz), 1.03 (t, 3H, 7Hz), 1.21 (t, 3H, 7Hz), 1.57 (m, 2H), 2.50 (m, 2H), 3.12 (m, 2H), 3.24 (m, 1H), 3.75 (m, 1H), 5.94 (s, 2H), 6.64 (s, 2H); M.S. (m/z): 263 (M^+) (26%), 248 (M-CH_3) (3%), 234 (M-Et) (2%), 220 (M-$(CH_2)_2CH_3$) (14%), 191 (M-NEt_2) (100%); exact mass calculated for $C_{15}H_{21}NO_3$: 263.1521, found: 263.1507.

***N,N*-Diethyl-2-*n*-pentylpiperonylamide:**

ir (film) υ: 1615 (Ar(C=O)NEt_2) cm^{-1}; ^1H nmr ($CDCl_3$)(300MHz) δ: 0.86 (t, 3H, 7Hz), 1.04 (t, 3H, 7Hz), 1.21 (t, 3H, 7Hz), 1.29 (m, 4H), 1.57 (m, 2H), 2.53 (m, 2H), 3.09 (m, 2H), 3.14 (m, 1H), 3.75 (m, 1H), 5.94 (s, 2H), 6.64 (s, 2H); M.S. (m/z): 291 (M^+) (40%), 262 (M-Et) (3%), 248 (M-$(CH_2)_2CH_3$) (18%), 234 (M-$(CH_2)_3CH_3$) (6%), 219 (M-

NEt_2)(100%); exact mass calculated for $C_{17}H_{25}NO_3$: 291.1887, found: 291.1860.

N,N-Diethyl-2-*n*-propylbenzamide:[60]

ir (film) υ: 1620 (Ar(C=O)NEt_2) cm^{-1} (lit. value[60] ir (KBr) υ: 1623 cm^{-1}); ^1H nmr ($CDCl_3$)(60MHz) δ: 1.15 (m, 9H), 1.65 (m, 2H), 2.45 (m, 2H), 2.90-3.70 (m, 4H), 7.10-7.40 (m, 4H); M.S. (m/z): 219 (M^+) (30%), 204 (M-CH_3) (12%), 190 (M-Et) (5%), 176 (M-$(CH_2)_2CH_3$) (14%), 147 (M-NEt_2)(100%)

N,N-Diethyl-2-*n*-pentylbenzamide:[60]

ir (film) υ: 1620 (Ar(C=O)NEt_2) cm^{-1} (lit. value[60] ir (KBr) υ: 1621 cm^{-1}); ^1H nmr ($CDCl_3$)(60MHz) δ: 0.70-1.50 (m, 14H), 1.65 (m, 2H), 2.35 (m, 2H), 2.90-3.85 (m, 4H), 7.20-7.70 (m, 4H); M.S. (m/z): 247 (M^+) (20%), 218 (M-Et) (5%), 204 (M-$(CH_2)_2CH_3$) (7%), 190 (M-$(CH_2)_3CH_3$) (12%), 175 (M-NEt_2) (100%)

2-*n*-Pentylthiophene:[61]

ir (film) υ: 2950 (Ar-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.88 (t, 3H, 7Hz), 1.32 (m, 4H), 1.65 (m, 2H), 2.72 (t, 2H. 8Hz), 6.77 (m, 1H), 6.91 (m, 1H), 7.09 (m, 1H); M.S. (m/z): 154 (M^+) (52%), 139 (M-CH_3) (1%), 125 (M-Et) (1%), 111 (M-$(CH_2)_2CH_3$) (12%), 97 (M-$(CH_2)_3CH_3$) (100%).

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60) R.E. Ludt, J.S. Griffith, K.N. McGrath, and C.R. Hauser, *J. Org. Chem.*, **38**, 1668(1973).

61) J.S. Danste, A.C. Kock-Van Dalen, J.W. DeLeeuw, and P.A. Schenck, *J. Chromatogr.*, **435**, 435(1988).

2-*n*-Pentylfuran:[62]

ir (film) υ: 2960 (Ar-H) cm^{-1}; ^1H nmr ($CDCl_3$) (60MHz) δ: 0.90 (t, 3H, 7Hz), 1.30-1.98 (m, 6H), 2.68 (m, 2H), 5.95 (m, 1H), 6.25 (m, 1H), 7.15 (m, 1H); M.S. (m/z): 138 (M^+) (30%), 123 (M-CH_3) (12%), 109 (M-Et) (5%), 95 (M-$(CH_2)_2CH_3$) (7%), 81 (M-$(CH_2)_3CH_3$) (100%).

Attempted hydrolysis of glycoside 42

A mixture of glycoside **42** (0.03 g, 0.05 mmol) in 1,4-dioxane (3 mL) and 1N sulfuric acid (5 mL) was refluxed for 18h. According to TLC analysis no reaction had taken place.

2,3,4-Tri-O-benzyl-D-mannopyranose 43[30]

A mixture of mannoside, **32**, (1.77 g, 3.81 mmol) in dioxane (5 mL) and 4N sulfuric acid (15 mL) was refluxed for 3 days, neutralized with saturated sodium bicarbonate, and extracted with ether (2x20 mL), and the combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (ethyl acetate) to yield **43** as a colourless oil, 0.51 g (30%); ir (film) υ: 3420 (O-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.79 (br s, 2H, OH), 3.75-3.86 (m, 4H), 3.96 (m, 2H), 4.61-4.94 (m, 6H), 5.19 (d, 1H, 2Hz, anomeric H), 7.26-7.35 (m, 15H) (lit.[30] ^1H nmr only stated 3 benzyl groups and 2 exchangable protons); M.S. (C.I. ether) (m/z): 451 (M+1) (1%), 433 (M+1-H_2O) (28%), 415 (M+1-$2H_2O$) (2%).

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62) A.J. Birch, *J. Chem. Soc.*, 809(1945).

2,3,4-Tri-O-benzyl-D-mannitol 45

A mixture of **43** (0.20 g, 0.44 mmol) and sodium borohydride (0.04 g, 0.89 mmol) in ethanol (20 mL) was stirred at 22°C for 18h. The reaction mixture was then acidified with 10% HCl and the solvents were then removed in vacuo. The residue was takenup in ethyl acetate/water, the aqueous phase extracted with ethyl acetate (3x20 mL). The combined organic phases were washed with water (2x20 mL), brine, dried and concentrated to yield a white solid, **45**, 0.18 g (89%); ir (KBr pellet) υ: 3430 (O-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.60 (br s, 3H, OH), 3.45 (t, 1H, 1.5Hz), 3.56 (dd, 1H, 5.5Hz, 1.5Hz), 3.72 (dt, 1H, 13Hz, 1.5Hz), 3.80 (dd, 1H, 3.5Hz, 1.5Hz), 4.22 (dd, 1H, 7Hz, 1Hz), 4.38-4.64 (m, 8H), 5.45 (br s, 1H), 7.21-7.36 (m, 15H); M.S. (C.I. ether) (m/z): 453 (M+1) (1%), 435 (M+1-H_2O) (21%), 434 (M-H_2O) (5%), 398 (M-2H_2O) (1%), 339 (M-(Bn+H_2O)) (5%).

2,3,4-Tri-O-benzyl-D-arabinose 47

A solution of sodium metaperiodate (0.09 g, 0.44 mmol) in water (5 mL) was added to a solution of **45** (0.18 g, 0.39 mmol) in acetone/water (10 mL) at 0°C. After 2h the reaction mixture was saturated with sodium chloride and extracted with methylene chloride (5x20 mL). The combined organic extracts were dried and concentrated to yield **47** as a white solid, 0.10 g (63%); ir (KBr pellet) υ: 3425 (O-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.53 (br s, 1H, OH), 3.62 (dd, 1H, 2Hz, 1Hz), 3.77 (m, 2H), 3.80 (dd, 1H, 4Hz, 2Hz), 3.86

(t, 1H, 4Hz), 4.52-4.79 (m, 7H), 7.22-7.33 (m, 15H); M.S. (C.I. ether) (m/z): 420 (M^+) (1%), 403 (M+1-H_2O) (21%), 329 (M-Bn) (5%), 311 (M-(Bn+H_2O)) (30%).

6-Bromopiperonol 48

Sodium borohydride (5.00 g, 13.58 mmol) was added to a solution of 6-bromopiperonal, **29**, (10.00 g, 43.86 mmol) in THF (200 mL) and ethanol (200 mL), which was stirred for 18 h. The reaction mixture was acidified with 10% HCl, the resulting acidic solution was extracted with ether (3x150 mL). The combined ether extracts were washed with water (100 mL), brine, dried and concentrated to yield a white solid. The solid was recrystallized from ether to give **48** as white needles, 8.17 g (81%); m.p. 159.8-161.7°C; ir (KBr pellet) υ: 3210 (O-H), 2900 (C-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 4.63 (s, 2H), 5.96 (s, 2H), 6.96 (s, 1H), 6.99 (s, 1H); M.S. (m/z): 230 (M^+) (47%), 232 (M+2) (48%), 213 (M-OH) (24%), 215 (M+1-OH) (24%), 199 (M-CH_2OH) (4%), 151 (M-Br) (82%); exact mass calculated for $C_8H_7O_3Br$: 229.9578, found: 229.9591.

6-Bromopiperonol *t*-butyldimethylsilyl ether 49

t-Butyldimethylsilyl triflate (0.86 g, 3.26 mmol) was added to a solution of 6-bromopiperonol, **48**, (0.50 g, 2.17 mmol) and 2,6-lutidine (0.46 g, 4.34 mmol) in dry methylene chloride (5 mL) at 0°C. After stirring for 2h the reaction mixture was quenched by pouring it into ice-cold 1% HCl. The organic phase was washed with 1% HCl (3x15 mL), dried and concentrated to yield a pink oil. The oil

was purified by flash chromatography (10% ethyl acetate/hexanes) to give **49** as a colourless oil, 0.74 g (99%); ir (film) υ: 2905 (C-H) cm^{-1}; ^1H nmr ($CDCl_3$) (60MHz) δ: 0.05 (s, 6H), 0.80 (s, 9H), 4.38 (s, 2H), 5.68 (s, 2H), 6.67 (s, 1H), 6.80 (s, 1H); M.S. (m/z): 344 (M^+) (1%), 346 (M+2) (1%), 329 (M-CH_3) (1%), 331 (M+2-CH_3) (1%), 287 (M-*t*-Bu) (70%), 289 (M+2-*t*-Bu) (70%), 213 (M-TBDMSO) (100%), 215 (M+2-TBDMSO) (100%).

6-*t*-Butyldimethylsilyl piperonol 50 (typical procedure)

A solution of *n*-butyllithium (2.6 M in hexanes) (0.95 mL, 2.48 mmol) was added to a solution of 6-bromopiperonol, **48**, (0.71 g, 2.06 mmol) in THF (8 mL) at -78°C. After 10 min. the electrophile (2.48 mmol) was added, the reaction mixture was allowed to warm to 22°C and after quenching with saturated ammonium chloride, extracted with ether (2x15 mL). The combined ether extracts were washed with water (2x15 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (20% ethyl acetate/hexanes) to yield **50** as a colourless oil, 0.23 g (46%); ir (film) υ: 3600 (O-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.32 (s, 6H), 0.86 (s, 9H), 4.63 (s, 2H), 5.93 (s, 2H), 6.92 (s, 1H), 7.02 (s, 1H); ^{13}C nmr ($CDCl_3$) (DEPT) δ: -3.03 (CH_3), 17.69 (quaternary), 26.81 (CH_3), 65.38 (CH_2), 100.82 (CH_2), 109.19 (CH), 114.82 (CH), 128.20 (quaternary), 141.35 (quaternary), 146.41 (quaternary), 148.66 (quaternary); M.S. (m/z): 266 (M^+) (2%) , 209 (M-*t*-Bu) (100%), 191 (M-(*t*-Bu+H_2O) (62%); M.S. (C.I. ether) (m/z): 267 (M+1) (25%), 249 (M+1-H_2O) (97%), 209 (M-*t*-Bu) (100%).

α-Acetoxy-3,4-methylenedioxy-6-*t*-butyldimethylsilyltoluene 51

Acetic anhydride (5 mL) was added at 0°C to a solution of alcohol, **50**, (0.18 g, 0.68 mmol) in pyridine (10 mL), which was then allowed to warm slowly to ambient temperature and stirred for 18h. It was then poured into ice-water, which was extracted with ether (3x20 mL). The combined ether extracts were washed with 10% HCl (4x20 mL), water, brine, dried and concentrated to yield a yellow solid **51**, 0.14 g (68%); m.p. 50-51°C; ir (KBr pellet) υ: 2940 (C-H), 1732 (Ar(C=O)CH_3) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.30 (s, 6H), 0.86 (s, 9H), 2.06 (s, 3H), 5.03 (s, 2H), 5.94 (s, 2H), 6.89 (s, 1H), 6.94 (s, 1H); M.S. (C.I. ether) (m/z): 293 (M-CH_3) (2%), 249 (M- OAc) (100%).

3,4-Methylenedioxy-6-bromobenzyl bromide 52

A slurry of 48% hydrobromic acid (10 mL) and 6-bromopiperonol, **48**, (2.00 g, 8.70 mmol) in acetic acid (10 mL) stirred for 18h. The reaction mixture was poured into ice-water, which was extracted with methylene chloride (3x20 mL). The combined organic extracts were dried and concentrated to yield a white solid. The solid was recrystallized from ether to yield **52** as a white solid, 2.23g (88%); m.p. 96.2-96.8°C; ir (KBr pellet) υ: 2990 (Ar-H), 1620 (ArC-C), 720 (C-Br) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 4.54 (s, 2H), 5.98 (s, 2H), 6.89 (s, 1H), 6.99 (s, 1H); M.S. (m/z): 292 (M^+) (6%), 294 (M+2) (13%), 296 (M+4) (6%), 213 (M-Br) (100%), 215

(M+2-Br) (99%); exact mass calculated for $C_8H_6O_2Br_2$: 291.8734, found: 291.8745.

α-Triphenylphosphonium-3,4-methylenedioxy-6-bromotoluene bromide 53

A solution of dibromide, **52**, (2.23 g, 7.64 mmol) and triphenyl phosphine (2.00 g, 7.64 mmol) in toluene (50 mL) was refluxed for 4h. The resulting white solid **53** was filtered, 3.77 g (89%); m.p. 227°C decomposes; ir (KBr pellet) υ: 3000 (Ar-H), 1430,1110,1000 (Ar-P) cm^{-1}: ^1H nmr (d_6 DMSO) (300MHz) δ: 5.00 (d, 2H, 14Hz), 6.06 (s, 2H), 6.60 (d, 1H, 2Hz), 7.15 (d, 1H,1Hz), 7.63 (m, 6H), 7.78 (m, 6H), 7.93 (m, 3H); M.S. (FAB) (m/z): 475 (cation) (2%), 477 (C+2) (2%), 395 (C-1-Br) (3%).

Attempted Wittig reaction between phosphonium salt 53 and hemiacetal 47

A mixture of phosphonium salt, **53** (0.26 g, 0.47 mmol), sodium hydride (60% in mineral oil) (washed with hexanes) (0.02 g, 0.47 mmol) and ethanol (3 drops) in THF (8 mL) was refluxed until an orange solution resulted. A solution of hemiacetal, **47** (0.10 g, 0.23 mmol) in THF (5 mL) was added dropwise. After 5h the reflux was stopped and the reaction was quenched with water and extracted with ether. The combined ether extracts were washed with water, brine, dried and concentrated to yield a yellow oil, which contained none of the desired product, as shown by the crude ^1H nmr spectrum.

N,N-Diethyl-2-(2-phenyl-2-*p*-methoxyphenylamino) ethylbenzamide 54

A solution of *n*-BuLi (2.4M in hexanes) (0.44 mL, 1.05 mmol) was added to a solution of diisopropylamine (0.15 ml, 1.05 mmol) in THF (4 mL) at -78°C. After 5 min a solution of *N,N*-diethyl-*o*-toluamide (0.20 g, 1.05 mmol) in THF (3 mL) was added, followed by benzylidene*p*-methoxyphenyl aniline (0.27 g, 1.26 mmol) in THF (3 mL). The temperature of -78°C was maintained for 10 min. The reaction was quenched with 10% HCl, and the mixture extracted with ether (2x20 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (20% ethyl acetate/hexanes). A white solid resulted which was recrystallized from ether to give white crystals, **54**, 0.16 g (36%); m.p. 142.7-143.2°C; ir (KBr pellet) υ: 3310 (N-H), 2920 (C-H), 1610 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) (60.4°C) δ: 0.99 (t, 3H, 7Hz), 1.28 (t, 3H, 7Hz), 2.85 (m, 1H), 3.05 (m, 3H), 3.58 (m, 2H), 3.61 (s, 3H), 4.50 (br s, 1H, N<u>H</u>), 6.37 (d, 2H, 9Hz), 6.60 (d, 2H, 9Hz), 7.24 (m, 8H), 7.41 (m, 2H); M.S. (m/z): 402 (M^+) (5%), 330 (M-NEt_2) (1%), 280 (M-NPMP) (1%), 212 (CH(Ph)$NHPMP^+$) (100%); exact mass calculated for $C_{26}H_{30}N_2O_4$: 402.2307, found: 402.2322.

N,N-Diisopropyl-2-(2-phenyl-2-benzylamino) ethylbenzamide 55

A solution of *n*-BuLi (2.4M in hexanes) (0.28 mL, 0.69 mmol) was added to a solution of diisopropylamine (0.10 mL, 0.69 mmol) in THF (4 mL) at -78°C. After 5 min a solution of *N,N*-diisopropyl-*o*-toluamide (0.15 g, 0.69 mmol) in THF (5 mL) was added, this was followed by *N*-benzyl benzylimine (0.16 g, 0.82 mmol) in THF (4 mL). The temperature of -78°C was maintained for a further 20 min. The reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (2x20 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (20% ethyl acetate/hexanes) to give a colourless oil, **55**, 0.14 g, (50%); ir (KBr pellet) υ: 3350 (N-H), 2925 (C-H), 1612 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.14 (m, 6H), 1.56 (m. 6H), 3.01 (m,1H), 3.25 (m, 1H), 3.49 (m, 2H), 4.25 (m, 2H), 4.78 (br s, 1H, NH), 6.48+6.75 (d, 1H, 6Hz, rotational isomers), 7.05-7.60(m, 13H), 7.62 (dd, 1H, 2Hz, 1Hz); M.S. (m/z): 414 (M^+) (2%), 415 (M+1) (8%), 323 (M-Bn) (100%), 309 (M-NBn) (67%).

5-O-Triphenylmethyl-D-arabinose diethyl dithioacetal 57[37]

Triethylamine (0.33 g, 3.25 mmol) was added to a solution of triphenylmethyl chloride (0.65 g, 2.32 mmol), D-arabinose diethyl dithioacetal **56** (0.52 g, 2.03 mmol) and DMAP (10 mg) in DMF (15 mL) the mixture was stirred at 22°C for 18h and after quenching with water, extracted with ethyl acetate (3x20 mL). The combined organic extracts were washed with water (2x20 mL), brine, dried and

concentrated to give a yellow solid. The solid was purified by flash chromatography (30% ethyl acetate/hexanes) and recrystallized from ether/hexanes to give **57** as a white solid, 0.92 g (91%); $[\alpha]^{24}$ (c 0.13, CHCl3): -34.5°; m.p. 110-112°C (lit.[37] [α]22 (c 3.1, CHCl3) -37.5, m.p. 107°C); ir (KBr pellet): 3450 (O-H) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.24 (t, 3H, 7.5Hz), 1.25 (t, 3H, 7.5Hz), 2.58 (m, 3H, OH), 2.63 (q, 2H, 7.5Hz), 2.66 (q, 2H, 7.5Hz), 3.32 (m, 2H), 3.71 (dd, 1H, 9Hz, 0.5Hz), 3.90 (t, 1H, 0.5Hz), 4.02 (d, 1H, 9Hz), 4.09 (t, 1H, 1Hz), 7.27 (m, 9H), 7.41 (m, 6H); M.S. (C.I. ether)(m/z): 255 (M-Ph_3CO) (1%), 243 (Ph_3C^+) (99%).

5-O-Triphenylmethyl-2,3,4-tri-O-benzyl-D-arabinose diethyl dithioacetal 58

A solution of **57** (0.92 g, 1.85 mmol) in DMF (10 mL) was added to sodium hydride (60% in mineral oil) (washed with hexanes) (0.74 g, 18.47 mmol) followed by benzyl bromide (3.16 g, 18.47 mmol) in DMF (3 mL) at 0°C. After the addition was complete the reaction temperature was raised to 60°C for 18h. Heating was stopped and the reaction was quenched with methanol and stirring was continued for an hour. Water was added and the mixture was extracted with ether (3x20 mL). The combined ether extracts were washed with water (3x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (20% ethyl acetate/hexanes) then again using hexanes, a slightly yellow oil resulted **58**, 0.78 g (55%), still a complex mixture of **58** and two other components; ir (film) υ: 3060 (ArC-H), 2920 (C-H), 1450 (ArC-

C); ^{1}H nmr ($CDCl_3$) (300MHz) δ: complex; M.S. (C.I. ether)(m/z): 678 (M-Bn) (1%); M.S. (FAB): 753 (M-CH_3) (1%), 707 (M-SEt) (1%).

2,3:4,5-Di-O-isopropylidene-D-arabinose 60[40]

A mixture of dithioacetal, **59**, (0.50 g, 1.48 mmol), mercuric chloride (0.44 g, 1.63 mmol) and mercuric oxide (0.71 g, 3.26 mmol) in 95% acetone/water (25 mL) was refluxed for 3h, filtered through Celite, and washed with 1:1 methylene chloride/hexanes (100 mL). The organic phase was washed with 5N ammonium acetate (2x50 mL), brine, dried and concentrated to give **60** as a colourless oil, 0.34 g (99%), pure by TLC; $[a]^{22}$ (c 0.26, acetone) +19.8° (lit.[40] $[a]^{20}$ (c 1.44, acetone) +20.9°) ir (film) υ: 1735 cm^{-1}; ^{1}H nmr ($CDCl_3$) (300MHz) δ: 1.24 (s, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 3.93-4.40 (m, 5H), 9.74 (d, 1H, 1Hz, C<u>H</u>O); M.S. (C.I. ether) (m/z): 231 (M+1) (100%), 230 (M^+) (80%), 215 (m-CH_3) (28%), 173 (M+1-CH_3COCH_3) (46%).

***N*-Benzyl-2,3:4,5-di-O-isopropylidene-D-arabinosylimine 61**

A mixture of aldehyde **60** (0.36 g, 1.57 mmol), freshly distilled benzylamine (0.17 g, 1.57 mmol) and anhydrous magnesium sulfate in methylene chloride (10 mL) was stirred at 22°C for 18 h. The mixture was then filtered through a plug of celite and solvent was removed in vacuo to yield a yellow oil **61**, 0.45 g (90%); ir (film) υ: 1650 (C=N) cm^{-1}; ^{1}H nmr ($CDCl_3$) (60 MHz) δ: 1.31 (s, 6H), 1.48 (s, 6H), 3.75-4.20 (m, 5H), 4.60 (br s , 2H), 7.25 (s, 5H), 7.72 (d, 1H,

10Hz); M.S. (C.I. ether) (m/z): 320 (M+1) (100%), 319 (M^+) (12%), 262 (M-CH_3COCH_3) (6%).

N-*p*-Methoxyphenyl-2,3:4,5-di-O-isopropylidene-D-arabinosylimine 62

A mixture of aldehyde, **60** (0.29 g, 1.27 mmol), *p*-anisidine (0.16 g, 1.27 mmol) and anhydrous magnesium sulfate in methylene chloride (8 mL) was stirred at 22°C for 18 h. The mixture was filtered through a pad of Celite and solvent removed in vacuo to yield **62** as a yellow oil, 0.34 g (80%); ir (film) υ: 1620 (C=N) cm^{-1}; ^1H nmr ($CDCl_3$) (60MHz) δ: 1.38 (s, 6H), 1.47 (s, 6H), 3.70 (s, 3H), 3.80-4.20 (m, 6H), 6.78 (d, 2H, 18Hz), 6.92 (d, 2H, 18Hz), 7.93 (d, 1H, 10Hz); M.S. (C.I. ether) (m/z): 336 (M+1) (60%).

N-Methoxy-2,3:4,5-di-O-isopropylidene-D-arabinosylimine 63

A solution of aldehyde, **60** (0.16 g, 0.71 mmol), methoxylamine hydrochloride (0.06 g, 0.71 mmol) and sodium acetate (0.58 g, 7.10 mmol) in water/THF (10 mL) was stirred for 18 h. The mixture was extracted with ether (2x15 mL), the combined ether extracts were dried and concentrated to yield **63** as a yellow oil, 0.12 g (56%); ir (film) υ: 1690 (C=N) cm^{-1}; ^1H nmr ($CDCl_3$) (60MHz) δ: 1.33 (s, 3H), 1.38 (s, 9H), 3.74 (s, 3H), 3.80-4.50 (m, 5H), 7.25 (d, 1H, 18Hz); M.S. (C.I. ether) (m/z): 260 (M+1) (45%).

N-Benzyl-1-oxo-3-[1,2:3,4-di-O-isopropylidene-(1R,2S,3R)-1,2,3,4-tetrahydoxybutyl]-tetrahydroisoquinoline 65

A solution of *n*-BuLi (2.4M in hexanes) (0.25 mL, 0.61 mmol) was added to a solution of diisopropylamine (0.06 g, 0.61 mmol) in THF (3 ml) at -78°C. After 5 min a solution of *N*,*N*-diethyl-*o*-toluamide (0.12 g, 0.61 mmol) in THF (3 mL) was added; a purple colour resulted. The imine, **61** (0.23 g, 0.73 mmol) in THF (5 mL), was added, and the brown mixture was stirred at -78°C for 0.5h, then quenched with 10% HCl, and extracted with ether (2x15 mL). The combined ether extracts were washed with water (3x15 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by thick layer chromatography (20% ethyl acetate/hexanes) to yield **65** as a colourless oil, 0.02 g (8%); ir (film) υ: 1650 cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.25 (s, 3H), 1.33 (s, 3H), 1.46 (s, 6H), 3.16 (s, 3H), 3.65 (m, 2H), 3.80 (m, 1H), 4.07 (m, 2H), 4.22 (d, 1H, 7Hz), 5.86 (d, 1H, 7Hz), 7.06 (d, 1H, 3Hz), 7.13-7.40 (m, 7Hz), 8.08 (d, 1H, 3Hz); M.S. (E.I.) (m/z): 437 (M^+) (1%), 422 (M-CH_3) (2%).

N,N-Diethylpiperonylamide 68

Thionyl chloride (89.71 g, 753083 mmol) was added to a mixture of piperonylic acid (25.00 g, 150.60 mmol) in benzene (200 mL), the mixture was then refluxed for 3h. The solvent was removed in vacuo and the resulting solid was added to a mixture of diethylamine (13.19 g, 180.72 mmol) in 5% KOH (200 mL) at 0°C. After stirring for 1h, the resulting solid was filtered by suction and recrystallized from ethanol to yield a yellow solid, **68**, 26.10 g (78%);

m.p. 69.3-70.1°C; ir (KBr pellet) υ: 2980 (C-H), 1618 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) (55°C) δ: 1.16 (t, 6H, 7Hz), 3.39 (q, 4H, 7Hz), 5.95 (s, 2H), 6.78 (dd, 1H, 7Hz, 1Hz), 6.84 (s, 1H), 6.86 (d, 7Hz); M.S. (m/z): 221 (M^+) (22%), 220 (M-1) (17%), 192 (M-Et) (2%), 149 (M-NEt_2) (100%), 121 (M-$CONEt_2$) (12%); exact mass calculated for $C_{12}H_{15}NO_3$: 221.1051, found: 221.1033.

2-Trimethylsilyl-*N*,*N*-diethylpiperonylamide 69

A solution of *s*-BuLi (1.3M in pentanes) (2.46 mL, 3.20 mmol) was added to a solution of amide, 65, (0.59 g, 2.67 mmol) and TMEDA (0.37 g, 3.20 mmol) in THF (10mL) at -78°C. After 15 min freshly distilled TMSCl (0.58 g, 5.24 mmol) was added and the reaction mixture was allowed to warm to 22°C over 2h. The reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (2x15 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes) to give **69** as a colourless oil, 0.51 g (66%); b.p. 150-153°C (0.05 mmHg); ir (film) υ: 2980 (C-H), 1620 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.27 (s, 9H), 1.08 (t, 3H, 7Hz), 1.23 (t, 3H, 7Hz), 3.24 (q, 2H, 7Hz), 3.46 (q, 2H, 7Hz), 5.92 (s, 2H), 6.64 (d, 1H, 8Hz), 6.75 (d, 1H, 8Hz); M.S. (m/z): 293 (M^+) (8%), 292 (M-1) (7%), 278 (M-CH_3) (100%), 264 (M-Et) (1%), 235 (M-2Et) (2%), 221 (M+1-TMS) (78%).

2-Trimethylsilyl-6-methyl-*N,N*-diethylpiperonylamide 70

A solution of *s*-BuLi (1.3M in pentanes) (6.96 mL, 8.66 mmol) was added to a solution of amide, **69**, (1.50 g, 5.12 mmol) and TMEDA (1.00 g, 8.66 mmol) in THF (15 mL) at -78°C. After 1h at -78°C methyl iodide (2.46 g, 17.32 mmol) was added and the reaction mixture was allowed to warm to 22°C over 3h. It was quenched with saturated ammonium chloride and extracted with ether (2x25 mL). The combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes) to give **70** as a colourless oil, 1.02 g (65%); ir (film) υ: 2950 (C-H), 1622 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.25 (s, 9H), 1.03 (t, 3H, 7Hz), 1.24 (t, 3H, 7Hz), 2.13 (s, 3H), 3.10 (m, 3H), 3.90 (dq, 1H, 7Hz, 6.5Hz), 5.86 (d, 1H, 1.5Hz), 5.89 (d, 1H, 1.5Hz), 6.62 (s, 1H); M.S. (m/z): 307 (M^+) (19%), 292 (M-CH_3) (100%), 278 (M-Et) (3%), 235 (M-NEt_2) (85%); exact mass calculated for $C_{16}H_{25}NO_3Si$: 307.1602, found: 307.1625.

2-Trimethylsilyl-5-(α-hydroxy-α-phenylmethyl)-6-methyl-*N,N*-diethylpiperonylamide 71

A solution of *t*-BuLi (1.25M in pentanes) (0.82 mL, 1.03 mmol) was added to a solution of amide **70**, (0.26 g, 0.87 mmol) and TMEDA (0.12 g, 1.03 mmol) in ether (10 mL) at 0°C. After 10 min benzaldehyde (0.22 g, 2.06 mmol) was added. After the reaction had reached 22°C, the reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (2x15 mL). The

combined extracts were washed with water (2x15 mL), brine, dried and concentrated to yield a yellow oil, The oil was purified by flash chromatography (20% ethyl acetate/hexanes) to give **71** as a colourless oil, 0.04 g (10%); ir (film) υ: 3950 (O-H), 1630 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (60MHz) δ: 0.21 (s, 9H), 0.80 (t, 3H, 7Hz), 1.02 (t, 3H, 7Hz), 1.82 (s, 3H), 2.90 (m, 3H), 3.45 (m, 1H), 4.20 (s, 1H), 5.60 (s, 2H), 6.20 (s, 1H), 7.20 (m, 3H), 7.45 (m, 2H); M.S. (m/z): 306 (M-(H_2O+Ph) (18%), 292 M-(H_2O+NEt_3) (7%).

2,6-Di-trimethylsilyl-*N,N*-diethylpiperonylamide 72

A solution of *s*-BuLi (1.3M in pentanes) (7.02 mL, 9.13 mmol) was added to a solution of amide **68**, (0.96 g, 4.37 mmol) and TMEDA (1.06 g, 9.13 mmol) in THF (20 mL) at -78°C. After 15 min freshly distilled TMSCl (1.48 g, 13.69 mmol) was added and the reaction temperature was allowed to rise to 22°C over 2h. The reaction was quenched with saturated ammonium chloride and extracted with ether (2x20 mL). The combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow solid. The solid was recrystallized from ether to give **72** as a yellow solid 0.64 g (41%); m.p. 66-68°C; ir (KBr pellet) υ: 2960 (C-H), 1625 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.21 (s, 9H), 0.26 (s, 9H), 0.99 (t 3H, 7.5Hz), 1.24 (t, 3H, 7.5Hz), 3.10 (q, 2H, 7.4Hz), 3.37 (q, 1H, 7.5Hz), 3.68 (q, 1H, 7.5Hz), 5.89 (d, 1H, 2.5Hz), 5.92 (d, 1H, 2.5Hz), 6.99 (s, 1H); M.S. (m/z): 365 (M^+) (7%), 350 (M-CH_3) (100%), 293 (M-NEt_2) (32%); exact mass calculated for $C_{18}H_{31}NO_3Si_2$: 365.1861; found: 365.1851.

6-Methyl-*N,N*-diethylpiperonylamide 73

A solution of amide **70** (1.02 g, 3.32 mmol) and cesium fluoride (25 mg) in DMF (20 mL) containing five drops of water was refluxed for 2.5h. The reaction mixture was cooled and extracted with ether (2x15 mL). The combined ether extracts were washed with water (3x15 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes) to give **73** as a colourless oil, 0.73 g (96%); ir (film) υ: 1618 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.03 (t, 3H, 7Hz), 1.22 (t, 3H, 7Hz), 2.17 (s, 3H), 3.14 (q, 2H, 7Hz), 3.39 (m, 1H), 3.68 (m, 1H), 5.92 (s, 2H), 6.62 (s, 1H), 6.64 (s, 1H); M.S. (m/z): 235 (M^+) (18%), 220 (M-CH_3) (10%), 163 (M-NEt_2) (100%).

2-(α-Hydroxy-α-phenylmethyl)-5-methyl-*N,N*-diethylpiperonylamide 74

A solution of *n*-BuLi (2.6M in hexanes) (0.34 mL, 0.89 mmol) was added to a solution of diisopropylamine (0.09 g, 0.89 mmol) in THF (5 mL) at -78°C. After 10 min a solution of amide **73** (0.21 g, 0.89 mmol) in THF (5 mL) was added and the temperature was maintained at -78°C. After 10 min freshly distilled benzaldehyde (0.09 g, 0.89 mmol) was added, whereby the colour changed from red to yellow. The mixture was then allowed to warm slowly to R.T. and after quenching with saturated ammonium chloride, extracted with ether (2x15 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a green oil.

The oil was purified by flash chromatography (20% ethyl acetate/hexanes) to give **74** as a colourless oil 0.24g (78%); ir (film) υ: 3420 (O-H), 1622 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr (60MHz) ($CDCl_3$) δ: 0.90 (t, 3H, 7Hz), 1.10 (t, 3H, 7Hz), 2.10 (s, 3H), 2.20 (m, 2H), 2.95 (m, 2H), 3.30 (m, 3H), 4.50 (m, 1H), 5.75 (s, 2H), 6.40 (s, 1H), 7.20 (m, 5H); M.S. (m/z): 235 (M-PhCHO) (47%), 220 (M-(PhCHO+CH_3) (22%), 163 (M-(PhCHO+NEt_2)) (100%).

2, 6-Dimethyl-*N,N*-diethylpiperonylamide 75

A solution of *n*-BuLi (2.6M in hexanes) (0.21 mL, 0.57 mmol) was added to a solution of diisopropylamine (0.06 g, 0.57 mmol) in THF (5 mL) at -78°C. After 10 min a solution of amide **73** (0.13 g, 0.57 mmol) in THF (5 mL) was added and a red colour resulted. After 10 min methyl iodide (0.20 g, 1.43 mmol) was added and the red colour disappeared. The reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (2x15 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a green oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes) to give **75** as a colourless oil, 0.10 (67%); ir (film) υ: 2950 (C-H), 1620 Ar(C=O)NR_2) cm^{-1}; ^1H nmr (60MHz) ($CDCl_3$) δ: 1.10 (t, 3H, 7Hz), 1.35 (t, 3H, 7Hz), 2.15 (s, 3H), 2.25 (s, 3H), 3.15 (q, 2H, 7Hz), 3.55 (q, 2H, 7Hz), 5.95 (s, 2H), 6.65 (s, 2H).

2-Trimethylsilyl-6-bromomethyl-*N,N*-diethylpiperonylamide 76

A solution of amide **70** (0.57 g, 1.86 mmol), NBS (0.33 g, 1.86 mmol) and AIBN (50 mg) in carbon tetrachloride (20 mL) was refluxed for 18 h. The solution was cooled, succinimide removed by filtration and solvent removed in vacuo to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes) to give **76** as a colourless oil, 0.57 g (80%); ir (film) υ: 2955 (C-H), 1625 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.26 (s, 1H), 1.10 (t, 3H, 7Hz), 1.27 (t, 3H, 7Hz), 3.10 (m, 3H), 3.97 (q, 1H, 7Hz), 4.38 (d, 1H, 0.5Hz), 4.39 (d, 1H, 0.5Hz), 5.93 (d, 1h, 1.5Hz), 5.95 (d, 1H, 1.5Hz), 6.90 (s, 1H); M.S. (m/z): 385 (M^+) (1%), 387 (M+2) (1%), 370 (M-CH_3) (4%), 372 (M+2-CH_3) (4%), 306 (M-Br) (11%).

2-Trimethylsilyl-6-phenylthiomethyl-*N,N*-diethylpiperonylamide 77

Thiophenol (0.08 g, 0.72 mmol) was added to a slurry of sodium hydride (50% in mineral oil) (washed with hexanes) (0.03 g, 0.72 mmol) in THF (5 mL) at R.T., whereby vigorous bubbling occurred. After 5 min a solution of bromide **76** (0.22 g, 0.56 mmol) in THF (5 mL) was added and stirring was continued for 2 h. The reaction was then quenched with saturated ammonium chloride and the mixture extracted with ether (2x15 mL). The combined ether extracts were washed with waster (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (20% ethyl acetate/hexanes) to give **77** as a colourless oil, 0.15 g (63%); ir (film) υ: 2955 (C-H), 1624 (Ar(C=O)NR_2)

cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.26 (s, 9H), 1.07 (t, 3H, 6.5Hz), 1.19 (t, 3H, 6.5Hz), 3.03 (q, 1H, 6.5Hz), 3.19 (m, 2H), 3.94 (q, 1H, 6.5Hz), 3.96 (d, 1H, 13Hz), 4.03 (d, 1H, 13Hz), 5.90 (d, 1H, 2.5Hz), 5.93 (d, 1H, 2.5Hz), 6.88 (s, 1H), 7.83 (m, 5H); M.S. (m/z): 415 (M^+) (7%), 400 (M-CH_3) (5%), 342 (M-TMS) (17%), 306 (M-SPh) (100%), 292 (M-CH_2SPh) (37%).

6-(2-Phenyl-2-hydroxy-1-phenylthioethyl)-2-trimethylsilyl-*N,N*-diethylpiperonylamide 78

A solution of *s*-BuLi (1.25M in pentanes) (0.11 mL, 0.13 mmol) was added to a solution of amide, **77**, (0.05 g, 0.11 mmol) and TMEDA (0.02 g, 0.13 mmol) in THF (5 mL) at -78°C. After 10 min freshly distilled benzaldehyde (0.01 g, 0.13 mmol) was added (red colour disappeared) and the reaction mixture was allowed to warm slowly to R.T. The reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (3x10 mL). The combined extracts were washed with water (2x15 mL), brine, dried and concentrated to yield a yellow solid. The solid was recrystallized from ether/hexanes to give **78** as a white solid, 0.04 g (70%); ir (KBr pellet) υ: 3450 (O-H), 1620 (Ar(C=O)NR_2) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) (HOMCOR) (1:1 mixture of diastereomers) δ: 0.25+0.26 (s's, 9H), 0.77+1.03 (t's, 3H, 7Hz), 1.14+1.25 (t's, 3H, 7Hz), 2.41+3.06 (dq's, 1H, 7Hz, 1Hz), 2.71+3.21 (dq's, 1H, 7Hz, 1Hz), 2.91+3.21 (dq's, 1H, 7Hz, 1Hz), 4.03 (dq, 1H, 7Hz, 1Hz), 1.72 (br s, 1H, O<u>H</u>), 4.31 (d, 3Hz)+5.11 (d, 3.5Hz) (1H), 4.99 (d, 3Hz)+5.17 (d, 3.5Hz)

(1H), 5.95+5.96 (s's, 2H), 6.63+6.99 (s's, 1H), 7.14-7.66 (m, 10H); (M.S. (m/z): 506 (M-CH_3) (2%), 415 (M-PhCHO) (27%).

Attempted reaction of the anion derived from 78 with an imine (typical procedure)

A solution of *s*-BuLi (1.25M in hexanes) (2.28 mL, 2.85 mmol) was added to a solution of sulfide **78** (0.70 g, 2.19 mmol) and TMEDA (0.33 g, 2.85 mmol) in THF (10 mL) at -78°C; a deep red colour resulted. After 10 min a solution of the imine (2.85 mmol) in THF (5 mL) was added and the reaction temperature was allowed to rise slowly to R.T. After 18h only the two starting materials were present; no reaction had occurred.

3-(3-butenyl)-isochroman-1-one 79

A solution of *n*-BuLi (2.63M in hexanes) (1.89 mL, 4.98 mmol) was added to a solution of 2-bromobenzoic acid (0.50 g, 2.49 mmol) in THF (10 mL) at -95°C (methanol/liq. N_2). After 10 min a solution of 5,6-epoxy-1-hexene (0.24 g, 2.49 mmol) in THF (8 mL) was added and the reaction mixture was allowed to warm slowly to R.T. and stirred for 18h. The reaction was quenched with 6N HCl (10 mL) and stirring was continued for 2 h. The reaction mixture was extracted with ether (2x15 mL), the combined extracts were washed with water (10 mL), saturated sodium bicarbonate (2x15 mL), water (2x15 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes) to give **79** as a colourless oil, 0.14 g (27%); ir (film)

υ: 3075 (Ar-H), 2930 (C-H), 1610 (ArC-C), 1642 ($RCH=CH_2$), 1725 ($ArCO_2R$) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.85 (m, 2H), 2.27 (m, 2H), 2.91 (m, 2H), 4.50 (m, 1H), 4.98 (m, 2H), 5.80 (m, 1H), 7.23 (dd, 1H, 7Hz, 1Hz), 7.37 (ddd, 1H, 8Hz, 7.5Hz, 1Hz), 7.51 (ddd, 1H, 7.5Hz, 7Hz, 1Hz), 8.07 (dd, 1H, 8Hz, 1Hz); ^{13}C nmr ($CDCl_3$) (DEPT) δ: 29.06 (CH_2), 33.24 (CH_2), 34.13 (CH_2), 77.87 (CH), 115.57 (CH_2), 125.08 (quaternary), 127.25 (CH), 127.52 (CH), 130.14 (CH), 133.55 (CH), 137.06 (CH), 138.94 (quaternary), 165.36 (quaternary); M.S. (m/z): 202 (M^+) (19%), 184 ($M-H_2O$) (19%), 147 ($M-((CH_2)_2CH=CH_2)$) (75%).

N-Benzylbenzamide 80[49]

Benzoyl chloride (20.00 g, 142.86 mmol) was added slowly to a vigorously stirred suspension of benzylamine (15.28 g, 142.86 mmol) in 5% KOH (250 mL). After 30 min the addition was complete. The white solid was filtered and recrystallized from ethanol to yield **80** as a white solid, 16.94 g (56%); m.p. 107-108°C; ir (KBr pellet) υ: 3290 (N-H), 3065 (C-H), 1639 (ArCONHR) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 4.67 (d, 2H, 6Hz), 6.45 (br s, 1H, N<u>H</u>), 7.27-7.54 (m, 8H), 7.80 (dd, 2H, 7Hz, 1.5Hz); M.S. (m/z): 211 (M^+) (81%), 134 (M-Ph) (4%), 105 ($PhCO^+$) (89%), 91 ($PhCH2^+$) (22%), 77 (Ph^+) ((100%); exact mass calculated for $C_{14}H_{13}NO$: 211.1024, found: 211.1010.

N-(α-Trimethylsilyl) benzylbenzamide 81

A solution of *n*-BuLi (1.25M in hexanes) (3.65 mL, 4.74 mmol) was added to a solution of amide **80** (0.50 g, 2.37 mmol) in THF

(10 mL) at -78°C. After warming to R.T., TMSCl (0.51 g, 4.74 mmol) was added, and the deep blue colour disappeared immediately. After stirring for 1h, the reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (2x20 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a white solid. The solid was recrystallized from ether to give **81** as a white solid, 0.53 g (79%); ir (KBr pellet) υ: 2950 (C-H), 1640 (Ar(C=O)NHR) cm^{-1}; ^{1}H nmr ($CDCl_3$) (300MHz) δ: 0.07 (s, 9H), 4.82 (d, 1H, 8.5Hz), 6.48 (br d, 1H, 8.5Hz), 7.30 (m, 8H), 7.57 (dd, 2H, 7Hz, 1.5Hz); ^{13}C nmr ($CDCl_3$) (DEPT) δ: -3.24 (CH_3), 46.83 (CH), 125.37 (CH), 125.89 (CH), 125.89 (CH), 126.80 (CH), 128.38 (CH), 128.59 (CH), 131.32 (CH), 135.03 (quaternary), 141.29 (quaternary), 167.24 (quaternary); M.S. (m/z): 283 (M^+) (42%), 282 (M-H) (54%), 268 ($M-CH_3$) (16%), 178 ($PhCHTMSNH^+$) (17%), 163 ($PhCHTMSNH-CH_3$) (6%), 105 ($PhCO^+$) (50%), 73 (TMS^+) (100%).

N-(α-2-Hydroxy-2-phenylethyl)benzylbenzamide 82

A solution of *s*-BuLi (1.25M in pentanes) (3.65 mL, 4.74 mmol) was added to a solution of amide **80** (0.50 g, 2.37 mmol) and TMEDA (0.55 g, 4.74 mmol) in THF (10 mL) at -78°C. After allowing the dianion solution to warm to R.T. a solution of styrene oxide (0.37 g, 3.08 mmol) in THF (5 mL) was added; after 5 min the colour turned from a deep blue to red. After 3h the reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (2x20 mL). The combined extracts were washed with water (2x20

mL), brine, dried and concentrated to yield a pink solid. The solid was recrystallized from ether/ethanol to give **82** as a white solid, 0.51 g (65%); ir (KBr pellet) υ: 3450 (O-H), 1635 Ar(C=O)NHR) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 3.09 (m, 1H, OH), 3.22 (dt, 1H, 9Hz, 4Hz), 3.98 (m, 1H), 4.09 (dd, 1H, 11.5Hz, 4Hz), 5.65 (dd, 1H, 9Hz, 8Hz), 7.35 (m, 9H), 7.80 (m, 2H); M.S. (m/z): 313 ($M-H_2O$) (3%), 211 ($M-PhCHOCH_2$) (27%), 105 ($PhCO^+$) (100%), 91 ($PhCH2^+$) (19%), 77 (Ph^+) (37%).

N-(α-2-Hydroxyhex-5-enyl) benzylbenzamide 83

A solution of *n*-BuLi (2.63M in hexanes) (1.80 mL, 4.74 mmol) was added to a solution of amide, **80**, (0.50 g, 2.37 mmol) in THF (8 mL) at -78°C. After the reaction temperature had been allowed to rise to R.T. it was again lowered to -78°C and a solution of 5,6-epoxy-1-hexene (0.23 g, 2.37 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm slowly to R.T., stirred for 18h, and after quenching with saturated ammonium chloride, extracted with ether (2x15 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (30% ethyl acetate/hexanes) to give two colourless oils (1:1 ratio of diastereomers), **83A**, 0.328 g and **83B**, 0.334, total yield 90%. ir (film) υ: 3935 (O-H), 3020 (C-H), 1660 (ArC=O(NHR)), 1520 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: (**83A**): 1.62 (m, 2H), 1.97 (m, 2H), 2.13 (m, 2H), 3.70 (m, 1H), 4.93 (m, 2H), 5.47 (m, 1H), 5.80 (m, 1H), 6.86 (d, 1H, 9Hz), 7.40 (m, 8H), 7.78 (dd, 2H, 8Hz, 1Hz); (**83B**): 1.55

(m, 2H), 1.98 (m, 2H), 2.04 (m, 2H), 3.76 (m, 1H), 4.96 (m, 2H), 5.15 (m, 1H), 5.81 (m, 1H), 7.10 (d, 1H, 7Hz), 7.35 (m, 8H), 7.78 (dd, 1H, 7Hz, 1.5Hz); M.S. (m/z): (**83A**): 309 (M^+) (1%), 291 (M-H_2O) (1%), 255 (M-((CH_2)$_2$CH=CH_2)) (1%), 204 (M-PhCO) (4%), 105 ($PhCHO^+$) (100%); (**83B**): 309 (M^+) (2%), 291 (M-H_2O) (4%), 255 (M-((CH_2)$_2$CH=CH_2)) (1%), 204 (M-PhCO) (13%), 119 ($PhC{=}ON^+$) (68%), 105 ($PhCO^+$) (100%).

Reaction of the dianion of 80 with TMSCl

A solution of *s*-BuLi (1.25M in pentanes) (3.65 mL, 4.74 mmol) was added to a solution of amide **80** (0.50 g, 2.37 mmol) and TMEDA (0.55 g, 4.74 mmol) in THF (10 mL) at -78°C. After warming to R.T. TMSCl (0.51 g, 4.74 mmol) was added; the deep blue colour disappeared immediately. After stirring for 1h, the reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (2x20 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/hexanes) to give a mixture of the mono- and disilylated compounds (**81** + **84**). Some of the disilylated compound **84** was isolated pure for spectral analysis; ir (film) υ: 2950 (C-H), 1640 (Ar(C=O)NHR) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 0.06 (s, 9H), 0.21 (s, 9H), 4.86 (d, 1H, 9Hz), 6.30 (br d, 1H, 9Hz), 7.40 (m, 8H), 7.63 (dd, 1H, 6Hz, 1Hz); ^{13}C nmr ($CDCl_3$) (DEPT) δ: -3.26 (CH_3), 0.10 (CH_3), 46.47 (CH), 125.62 (CH), 125.74 (CH), 125.95 (CH), 128.21 (CH), 129.41 (CH), 135.39 (CH), 140.31 (quaternary), 141.12 (quaternary), 142.35 (quaternary), 170.50 (quaternary); M.S. (m/z): 355 (M^+) (3%),

354 (M-H) (4%), 340 (M-CH_3) (12%), 282 (M-TMS) (100%), 178 (PhChTMSNH$^+$) (14%), 177 (TMSPhCO$^+$) (12%), 73 (TMS$^+$) (40%).

Reaction of the dianion of 80 with methyl iodide

A solution of *s*-BuLi (1.25M in pentanes) (3.65 mL, 4.74 mmol) was added to a solution of amide **80** (0.50 g, 2.37 mmol) and TMEDA (0.55 g, 4.74 mmol) in THF (10 mL) at -78°C. The mixture was allowed to warm to R.T., then cooled again to -78°C, and methyl iodide (0.40 g, 2.84 mmol) was added. The deep blue colour disappeared immediately. After again reaching R.T., saturated ammonium chloride was added and the mixture extracted with ether (2x20 mL). The combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (30% ethyl acetate/hexanes) to give a mixture of the mono- and di-methylated compounds (**85** + **86**, 0.44 g), which were inseparable; G.C.M.S. (m/z): (**85**): 239 (M$^+$) (63%), 224 (M-CH_3) (24%), 105 (PhCO$^+$ or PhCHCH$_3^+$) (100%); (**86**): 225 (M$^+$) (84%), 210 (M-CH_3) (4%), 120 (M-PhCO) (20%), 105 (PhCO$^+$) (100%), 91 (PhCH2$^+$) (26%), 77 (Ph$^+$) (87%).

Reaction of the dianion of 80 with allyl iodide

A solution of *s*-BuLi (1.25M in pentanes) (3.65 mL, 4.74 mmol) was added to a solution of amide **80** (0.50 g, 2.37 mmol) and TMEDA (0.55 g, 4.74 mmol) in THF (10 mL) at -78°C. The solution was allowed to warm to R.T., cooled again to -78°C, and allyl iodide (0.48 g, 2.84 mmol) was added. The deep blue colour disappeared

immediately. After again reaching R.T., the reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (2x20 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (30% ethyl acetate/hexanes) to give a mixture of the mono- and di-allylated compounds (**87** + **88**, 0.41 g), which were inseparable.

N-Benzyl-2-bromobenzamide **89**

A mixture of *o*-bromobenzoic acid (5.00 g, 24.90 mmol) and thionyl chloride (14.82 g, 124.50 mmol) in benzene (100 mL) was refluxed for 1h. The solvent was removed in vacuo and the crude chloride was stirred for 1h with a mixture of benzylamine (3.46 g, 32.37 mmol) and 5% KOH (40 mL). The resulting white solid was filtered and recrystallized from ethanol to yield **89** as a white solid, 5.50 g (76%); m.p. 120-121°C; ir (KBr pellet) υ: 3250 (N-H), 1649 (Ar(C=O)NHR) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 4.64 (d, 2H, 5.5Hz), 6.23 (br s, 1H), 7.40-7.22 (m, 7H), 7.55 (m, 2H); M.S. (m/z): 289 (M^+) (76%), 291 (M+2) (72%), 210 (M-Br) (60%), 185+183 ($BrPhCO^+$) (100%), 157+155 ($PhBr^+$) (29%), 132 ($PhCH_2NH{=}C{=}O^+$) (8%); exact mass calculated for $C_{14}H_{12}NOBr$: 289.0153, found: 289.0126.

2-(α-Hydroxybenzyl) *N*-benzyl benzamide **90**

A solution of *n*-BuLi (2.33M in hexanes) (1.55mL, 3.63 mmol) was added to a solution of bromoamide **89** (0.50 g, 1.73 mmol) in THF (8 mL) at -78°C. After 15 min a light orange colour resulted;

then freshly distilled benzaldehyde (0.22 g, 2.08 mmol) was added , the orange colour disappeared and a yellow colour persisted. The reaction mixture was allowed to warm slowly to R.T., then stirred for 18h, and after quenching with water, extracted with ether (2x15 mL). The combined extracts were washed with water (2x15 mL), brine, dried and concentrated to yield a colourless oil. The oil was purified by flash chromatography (30% ethyl acetate/hexanes) to give **90** as a colourless oil, 0.20 g (40%); ir (film) υ: 3410 (O-H), 1635 (Ar(C=O)NHR) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 4.37 (dd, 2H, 5Hz, 4.5Hz), 5.49 (d, 1H, 8Hz), 5.91 (d, 1H, 8Hz), 6.04 (br d, 5Hz), 7.24 (m, 14H); M.S. (m/z): 317 (M^+) (1%), 211 (M-PhCHO) (54%), 105 ($PhCO^+$) (100%), 91 ($PhCH_2^+$) (15%), 77 (Ph^+) (52%).

N-(α-Hydroxybenzyl) benzylbenzamide 91

A solution of *n*-BuLi (2.33M in hexanes) (1.55mL, 3.63 mmol) was added to a solution of bromoamide **89** (0.50 g, 1.73 mmol) in THF (8 mL) at -78°C. After 15 min a light orange colour resulted, the reaction was then allowed to warm to R.T, and freshly distilled benzaldehyde (0.22 g, 2.08 mmol) was added , the orange colour disappeared and a yellow colour persisted, then stirried for 18h, quenched with water and extracted with ether (2x15 mL). The combined extracts were washed with water (2x15 mL), brine, dried and concentrated to yield a colourless oil. The oil was purified by flash chromatography (30% ethyl acetate/hexanes) to give **91** as a colourless oil, 0.19 g (35%); ir (film) υ: 3425 (O-H), 1630 (Ar(C=O)NHR) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 2.67 (d, 1H, 4Hz),

5.13 (dd, 1H, 4Hz, 4Hz), 5.41 (dd, 1H, 4Hz, 3Hz), 6.99 (d, 1H, 3Hz), 7.35 (m, 10H), 7.74 (m, 2H); M.S. (m/z): 241 (M-C_6H_4) (2%), 211 (M-PhCHO) (51%), 105 ($PhCO^+$) (100%), 91 ($PhCH_2^+$) (10%), 77 (Ph^+) (58%); M.S. (C.I. ether) (m/z): 318 (M+1) (64%).

N-(α-Methylbenzyl)benzamide **92**

Benzoyl chloride (5.75 g, 41.32 mmol) was slowly added to dl-α-methylbenzylamine (5.00 g, 41.32 mmol) in 5% KOH (40 mL) and stirred for 1h. The white solid was then filtered and recrystallized from ethanol to yield **92** as a white solid, 7.64 g (82%); m.p. 108-111°C; ir (KBr pellet) υ: 2990 (C-H), 1638 (Ar(C=O)NHR) cm^{-1}; ^1H nmr ($CDCl_3$) (300MHz) δ: 1.60 (d, 3H, 7Hz), 5.33 (q, 1H, 7Hz), 6.24 (br s, 1H), 7.50-7.24 (m, 8H), 7.75 (dd, 2H, 5Hz, 1.5Hz); M.S. (m/z): 225 (M^+) (4%), 210 (M-CH_3) (1%), 120 (M- $PhCHCH_3$) (2%), 105 ($PhCO^+$ or $PhCHCH_3^+$) (100%), 77 (Ph^+) (69%).

2-(α-Hydroxy-α-phenyl)-methyl-*N*-(α-methylbenzyl)benzamide **93**

A solution of n-BuLi (2.33M in hexanes) (2.00 mL, 4.67 mmol) was added to a solution of amide **92** (0.50 g, 2.22 mmol) in THF (10 mL) at -78°C. After allowing the anion solution to warm to R.T. a deep purple colour resulted. The reaction temperature was again lowered to -78°C, and freshly distilled benzaldehyde (0.28 g, 2.66 mmol) was added. The purple colour disappeared and a light yellow colour persisted. After warming to R.T. and addition of water the mixture was extracted with ether (2x15 mL). The combined extracts

were washed with water (2x15 mL), brine, dried and concentrated to yield a yellow solid. The solid was purified by flash chromatography (30% ethyl acetate/ hexanes) to yield **93** as a colourless oil, 0.39g (63%); ir (film) υ: 3425 (N-H, O-H), 1635 (Ar(C=O)NHR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.15+1.42 (d's, 3H, 7Hz), 4.90 (m, 1H), 5.65 (m, 3H), 7.15 (m, 14H).

2-(2-Hydroxyhex-5-enyl)-*N*-(α-methylbenzyl)benzamide 94

A solution of *n*-BuLi (2.33M in hexanes) (2.00 mL, 4.67 mmol) was added to a solution of amide **92** (0.50 g, 2.22 mmol) in THF (10 mL) at -78°C. After allowing the anion solution to warm to R.T. a deep purple colour resulted. The reaction temperature was again lowered to -78°C, and a solution of 5,6-epoxy-1-hexene (0.26 g, 2.66 mmol) in THF (5 ml) was added. The purple colour disappeared and a light yellow colour persisted. After warming to R.T. the reaction was quenched by the addition of water, and the mixture extracted with ether (2x 15 mL). The combined extracts were washed with water (2x15 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (30% ethyl acetate/ hexanes) to yield **94** as a colourless oil, 0.50g (70%); ir (film) υ: 3300 (N-H, O-H), 1640 ($R_2C=CH_2$), 1630 (Ar(C=O)NHR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.58 (m, 5H), 2.26 (m, 2H), 2.81 (m, 2H), 3.82 (m, 1H), 5.06 (m, 2H), 5.30+5.57 (q, 1H, 7Hz) (diastereomers), 5.83 (m, 1H), 6.50+6.66 (2br s, 1H) (diastereomers), 6.81 (br s, 1H), 7.16-7.49 (m, 8H), 7.75 (m, 1H); M.S. (m/z): 323 (M^+) (1%), 305 ($M-H_2O$) (2%),

290 (M-(H_2O+CH_3)) (2%), 239 (M-CH_2=$CHCH_2C$=O) (43%), 105 ($PhCHCH_3^+$) (98%), 84 (CH_2=$CHCH_2C$=O^+) (100%).

2-(2-Methylsulfonylhex-5-enyl)-*N*-(α-methylbenzyl) benzamide 95

A solution of alcohol **94** (0.34 g, 1.06 mmol), and methanesulfonyl chloride (0.24 g, 2.12 mmol) in pyridine (10 mL) was left at 5°C for 18h. The reaction mixture was poured into ice-water (50 mL), and extracted with methylene chloride (3x25 mL). The combined organic extracts were washed with water (4x25 mL), dried and concentrated to yield a red oil. The oil was purified by flash chromatography (20% ethyl acetate/ hexanes) to yield **95** as a yellow oil, 0.38 g (89%); ir (film) υ: 3415 (N-H), 1650 (Ar(C=O)NHR), 1642 (RCH=CH_2), 1350, 1172 (ROSO_2CH_3) cm^{-1}; ^1H nmr (60MHz) ($CDCl_3$) δ: 1.50+1.65 (d's, 3H, 7Hz), 2.25 (m, 2H), 2.75 (s, 3H), 2.80 (m, 2H), 5.06 (m, 2H), 5.60 (m, 2H), 7.30 (m, 8H), 7.70 (m, 1H), 8.40 (m, 2H); M.S. (m/z): 403 (M+2) (1%), 388 (M+2-CH_3) (1%), 305 (M-CH_3SO_3H) (14%), 290 (M-(CH_3SO_3H+CH_3) (55%).

3-(3,4-Epoxy-butyl)-isochroman-1-one 97

A solution of olefin **98** (0.12g, 0.39 mmol) and *m*-CPBA (80%) (0.10 g, 0.47 mmol) in 1,2-dichloroethane (6 mL) was refluxed for 6h. The mixture was then cooled to R.T., washed with 10% sodium bisulfite (3x10 mL), saturated sodium bicarbonate (3x10 mL), dried and concentrated to give a yellow oil. The oil was purified by flash chromatography to yield **97** as a colourless oil, 0.06 g (50%); ir (film)

υ: 3050 (Ar-H), 2925 (C-H), 1725 (Ar(C=O)OR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 2.95 (m, 4H), 2.52 (m, 1H), 2.78 (m, 1H), 2.95 (m, 3H), 4.55 (m, 1H), 7.23 (dd, 1H, 7Hz, 1Hz), 7.37 (ddd, 1H, 7Hz, 7Hz, 1Hz), 7.52 (ddd, 1H, 7.5Hz, 7Hz, 1Hz), 8.07 (d, 1H, 7.5Hz); M.S. (m/z): 218 (M^+) (2%), 200 ($M-H_2O$) (7%), 182 ($M-2H_2O$) (17%).

3-(3-butenyl)-1-α-methylbenzylimino-isochroman 98

A solution of mesylate **95** (0.36 g, 0.90 mmol) in THF (20 mL) was added to sodium hydride (60% in mineral oil) (washed with hexanes) (0.07 g, 2.25 mmol) at R.T. After the addition was complete the reaction mixture was refluxed for 18h. The mixture, was cooled and, after addition of water, extracted with ether (3x20 mL). The combined extracts were washed with water (3x20 mL), brine, dried and concentrated to yield a dark oil. The oil was purified by flash chromatography (10% ethyl acetate/ hexanes) to give **98** as a colourless oil, 0.14 g (52%); ir (film) υ: 2910 (C-H), 1655 (Ar(C=N)OR), 1645 ($RCH=CH_2$) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.46+1.47 (d, 3H, 7Hz) (diastereomers), 1.80 (m, 2H), 2.22 (m, 2H), 2.81 (m, 2H), 4.10+4.26 (m, 1H) (diastereomers), 4.96 (m, 2H), 5.15 (q, 1H, 7Hz), 5.81 (m, 1H), 7.08-7.35 (m, 6H), 7.48 (t, 2H, 7Hz), 8.21 (m, 1H); ^{13}C nmr (DEPT) ($CDCl_3$) δ: 24.86 (CH_3), 29.42 (CH_2), 34.28 (CH_2), 34.47 (CH_2), 54.11 (CH), 75.57 (CH), 115.62 (CH_2), 126.06 (CH), 126.48 (CH), 126.62 (CH), 126.94 (CH), 127.20 (CH), 127.24 (CH), 127.29 (CH), 127.82 (quaternary), 128.02 (quaternary), 128.06 (quaternary), 130.20 (CH), 137.54 (quaternary); M.S. (m/z): 305 (M^+) (27%), 290

(M-CH_3) (100%), 248 (M-Me_3C) (20%); Exact mass calculated for $C_{21}H_{23}NO$: 305.1781, found: 305.1779.

Hydrolysis of imidate 98 to give lactone 79

A solution of imidate **98** (0.07 g, 0.21 mmol) in THF (5 mL) and 6N HCl (3 mL) was stirred for 2h and then extracted with ether (2x10 mL). The combined ether extracts were washed with water (2x10 mL), brine dried and concentrated to give a slightly yellow oil. This oil was identical in all respects with lactone **79**, obtained earlier.

Attempted cyclization of hydroxyamide 94 with triphenylphosphine and diethyl azodicarboxylate

Diethyl azodicarboxylate (0.21 g, 1.23 mmol) was added to a solution of hydroxyamide **94** (0.33 g, 1.02 mmol), and triphenylphosophine (0.27 g, 1.02 mmol) in THF (15 mL). After stirring for 18h it appeared by TLC analysis that no reaction had taken place.

N-Benzyloxybenzamide 99

Benzoyl chloride (2.10 g, 15.00 mmol) was added to *O*-benzylhydroxylamine hydrochloride (2.40 g, 15.00 mmol) in 5% KOH (30 mL) and stirred for 1 h. The white precipitate was collected by suction filtration and recrystallized from 95% ethanol to yield **99** as a white solid, 2.52 g (74%); m.p. 106-107°C; ir (KBr pellet) υ: 2340 (N-H), 1648 (Ar(C=O)NHOR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 5.02 (s, 2H), 7.46 (m, 8H), 7.63 (dd, 2H, 6.5Hz, 1.5Hz), 8.53 (m, 1H); M.S.

(m/z): 227 (M^+) (2%), 121 (M-OBn) (17%), 91 ($PhCH_2^+$) (100%), 105 ($PhCO^+$) (74%).

Attempted generation of the dianion of benzamide 99 and quenching with 5,6-epoxy-1-hexene

A solution of *n*-BuLi (2.53M) (1.92 mL, 4.85 mmol) was added to a solution of benzamide **99** (0.50 g, 2.20 mmol) in THF (8 mL), at -78°C. After allowing the reaction temperature to rise to R.T. it was again lowered to -78°C, and a solution of 5,6-epoxy-1-hexene (0.26 g, 2.64 mmol) in THF (8 mL) was added and the mixture was allowed to slowly warm to R.T. After 18 h, the reaction was quenched with water and the mixture extracted with ether (3x20 mL). The combined ether extracts were washed with water (3x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/ hexanes) to give the parent benzamide and benzaldehyde.

N-(2-Methylthioethyl)benzamide 100

Benzoyl chloride (5.23 g, 37.36 mmol) was added to 2-aminoethyl methylsulfide (3.40 g, 37.36 mmol) in 5% KOH (30 mL) and stirred for 3h. The reaction mixture was extracted with ether (3x25 mL), the combined ether extracts were washed with brine, dried and concentrated to yield a yellow solid. The solid was recrystallized from ether/ hexanes to give **100** as white solid, 5.30 g (73%); m.p. 60-62°C; ir (KBr pellet) υ: 3410 (N-H), 2920 (C-H), 1635 (Ar(C=O)NHR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 2.13 (s, 3H), 2.74

(dd, 2H, 7Hz, 6Hz), 3.65 (dd, 2H, 7Hz, 5Hz), 6.58 (m, 1H), 7.46 (m, 3H), 7.77 (dd, 2H, 7Hz, 1.5Hz); M.S. (m/z): 195 (M^+) (8%), 149 (M+1-SCH_3) (3%), 148 (M-SCH_3) (2%), 105 ($PhCO^+$) (100%), 77 (Ph^+) (58%); exact mass calculated for $C_{10}H_{13}NOS$: 195.0685, found: 195.0701.

Attempted generation of the dianion of benzamide 100 and quenching with 5,6-epoxy-1-hexene

A solution of *n*-BuLi (2.53M) (1.34 mL, 3.38 mmol) was added to a solution of benzamide, **100**, (0.30 g, 1.54 mmol) in THF (8 mL), at -78°C. After allowing the reaction temperature to rise to R.T. it was again lowered to -78°C and a solution of 5,6-epoxy-1-hexene (0.18 g, 1.85 mmol) in THF (5 mL) was added. The reaction was allowed to proceed at R.T. 18h and then, quenched with water. The mixture extracted with ether (3x20 mL). The combined extracts were washed with water (3x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/ hexanes) to give the parent benzamide and benzaldehyde.

N-Methoxypiperonylamide 101

A mixture of thionyl chloride (17.92 g, 150.62 mmol) and piperonylic acid (5.00 g, 30.12 mmol) in benzene (100 mL) was refluxed for 2h. Removal of the solvent in vacuo resulted in the acid chloride as a yellow solid. The crude piperonoyl chloride was added to a solution of methoxylamine hydrochloride (2.50 g, 30.12 mmol) in 10% KOH (30 mL), at 0°C; THF (10 mL) was added to aid in dissolving

the acid chloride. After 18h, the white precipitate was collected by suction filtration and recrystallized from 95% ethanol to give **101** as a white solid, 3.23 g (55%); m.p. 83-84°C; ir (KBr pellet) υ: 3450 (N-H), 3200 (C-H), 1650 (Ar(C=O)NHOR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 3.85 (s, 3H), 6.01 (s, 2H), 6.80 (d, 1H, 8Hz), 7.22 (m, 2H), 8.62 (m, 1H); M.S. (m/z): 195 (M^+) (31%), 165 (M+1-OCH_3) (10%), 149 ($CH_2O_2PhCO^+$) (100%), 121 ($CH_2O_2Ph^+$) (25%); exact mass calculated for $C_9H_9NO_4$: 195.0538, found: 195.0534.

Hydrogenolysis of amide 101 to give piperonylamide 102

A mixture of amide **101** (0.10 g, 0.51 mmol) and 10% palladium on carbon (25 mg) in ethanol (20 mL) was shaken under a hydrogen atmosphere (4 atm) for 19h. The catalyst was removed by filtration and the solvent evaporated to yield **102** as a white solid, 0.07 g (80%); ir (KBr pellet) υ: 1662 (Ar(C=O)NH_2) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 5.75 (br s, 2H, NH), 6.02 (s, 2H), 6.82 (d, 1H, 8Hz), 7.24-7.34 (m, 2H); M.S. (m/z): 165 (M^+) (83%), 149 (M-NH_2) (100%), 121 (M-$CONH_2$) (25%); M.S. (C.I. ether) (m/z): 166 (M+1) (100%), 149 (M-NH2) (11%).

N-Methoxy-2-trimethylsilylpiperonylamide 103

A solution of *n*-BuLi (1.91M) (6.42 mL, 12.27 mmol) was added to a solution of piperonylamide **101** (1.04 g, 5.33 mmol) in THF (20 mL), at -78°C. After allowing the reaction temperature to rise to R.T. it was again lowered to -78°C and freshly distilled trimethylsilyl chloride (1.33 g, 12.27 mmol) in THF (5 mL) was added and the

mixture was allowed to slowly warm to R.T. After 18 h, the reaction was quenched with water and the mixture extracted with ether (3x20 mL). The combined extracts were washed with water (3x20 mL), brine, dried and concentrated to yield a yellow solid. The solid was purified by flash chromatography (10% ethyl acetate/ hexanes) to give **103** as a white solid, 0.92 g (65%); m.p. 112-114°C; ir (KBr pellet) υ: 1655 (Ar(C=O)NHR) cm^{-1}: ^1H nmr (300MHz) ($CDCl_3$) δ: 0.34 (s, 9H), 3.85 (s, 3H), 5.93 (s, 2H), 6.72 (d, 1H, 8Hz), 6.90 (d, 1H, 8Hz), 8.29 (m, 1H, NH); M.S. (m/z): 267 (M^+) (3%), 252 (M-CH_3) (42%), 235 (M-CH_3OH) (8%), 221 (M-$NHOCH_3$) (100%).

Reaction of amide 103 with 2 equivalents of *s*-butyllithium and quenching with methyl iodide

A solution of *s*-BuLi (1.30M) (0.37 mL, 0.95 mmol) was added to a solution of piperonylamide**101** (0.12 g, 0.45 mmol) and TMEDA (0.11 g, 0.95 mmol) in THF (8 mL), at -78°C. After allowing the reaction temperature to rise to R.T. and stirring for 1h, it was again lowered to -78°C and methyl iodide (0.27 g, 1.90 mmol) was added and the mixture was allowed to slowly warm to R.T. After 18h, the reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (3x20 mL). The combined extracts were washed with water (3x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/ hexanes) to give a mixture (9:1) of *N*-methylated **104** and *N,C*-dimethylated **105** , 0.12 g, which were difficult to separate, (only compound **104** could be isolated) ^1H nmr (60MHz)

($CDCl_3$) δ: 0.20 (s, 9H), 3.20 (s, 3H), 3.55 (s, 3H), 5.98 (s, 2H), 6.80 (s, 2H) .

3,4-Methylenedioxy-6-(1,2-dideoxy-3,4:5,6-di-O-isopropylidene-D-arabino-hex-1-enit-1yl) bromobenzene 106

A solution of sodium methoxide (0.09 g, 1.62 mmol) in methanol (6 mL) was added to a mixture of the phosphonium salt **53** (0.75 g, 1.35 mmol) and diisopropylidene arabinose **60** (0.31 g, 1.35 mmol) in methanol (15 mL) and stirred at R.T. for 18h. The methanol was removed in vacuo, the resulting solid was washed with ether (3x20 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/ hexanes) to give **106** as a colourless oil (8:1 mixture *trans:cis*), 0.29 g (50%); ir (KBr pellet) υ: 2980 (ArC-H), 2790 (C-H), 1500 (C=C) cm^{-1}; ^1H nmr (*trans*-isomer) (200MHz) ($CDCl_3$) δ: 1.30 (s, 6H), 1.36 (s, H), 1.42 (s, 3H), 3.77 (m, 2H), 3.84 (m, 1H), 3.99 (m, 1H), 4.59 (dd, 1H, 9.5Hz, 7.5Hz), 5.70 (dd, 1H, 11.5Hz, 9.5Hz), 5.97 (s, 2H), 6.66 1(d, H, 11.5Hz), 7.02 (s, 1H), 7.15 (s, 1H); ^1H nmr (*cis*-isomer) (300MHz) ($CDCl_3$) δ: 1.31 (s, 6H), 1.38 (s, 3H), 1.44 (s, 3H), 3.77 (m, 2H), 3.84 (m, 1H), 4.05 (m, 1H), 4.73 (dd, 1H, 9Hz, 7.5Hz), 5.60 (dd, 1H, 11Hz, 7.5Hz), 5.95 (s, 2H), 6.79 (d, 1H, 11Hz), 7.02 (s, 1H), 7.15 (s, 1H); M.S. (m/z): 426 (M^+) (6%), 428 (M+2) (6%), 411 (M-CH_3) (3%), 413 (M+2-CH_3) (3%), 368 (M-CH_3COCH_3) (1%), 370 (M+2-CH_3COCH_3) (1%), 353 (M-(CH_3COCH_3+CH_3)) (2%), 355 (M+2-(CH_3COCH_3+CH_3)) (2%), 348

(M-Br) (6%); exact mass calculated for $C_{16}H_{23}O_6Br$: 426.0677, found: 426.0634.

Reaction of phosphonium salt 53 with LDA followed by quenching with diisopropylidene arabinose 60

A solution of LDA (4.02 mmol) in THF (6 mL) was added to the phosphonium salt **53** (1.78 g, 3.22 mmol) in THF (10 mL) at -78°C, a thick red solution resulted. After 5 min. a solution of diisopropylidene arabinose **60** (0.62 g, 2.68mmol) in THF (8 mL) was added and slowly warmed to R.T. and stirred for 18h. The reaction was quenched with water and the mixture extracted with ether (3x20 mL). The combined extracts were washed with 10% HCl, water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate/ hexanes) to give **106** (exclusively trans) as a colourless oil 0.14 g (12%); and mainly **107** resulting from reduction of the carbon-phosphorous bond, 0.35 g (61%); ir (film) υ: 2910 (ArC-H) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 2.28 (s, 3H), 5.92 (s, 2H), 6.69 (s, 1H), 6.97 (s, 1H); M.S. (m/z): 214 (M^+) (73%), 216 (M+2) (71%), 213 (M-1) (34%), 215 (M+2-1) (37%), 135 (M-Br) (45%).

Reduction of olefin 106 to give tetraol 108

Hydrogen gas was bubbled through a mixture of olefin **106** (0.16 g, 0.36 mmol) and 10% palladium on carbon (10 mg) in ethanol (10 mL) for 1h. The catalyst was removed by filtration and the solvent was removed in vacuo to yield a yellow solid. The solid was

recrystallized from ethanol to give **108** as a white solid, 0.12 g (95%); ir (KBr pellet) υ: 3610 (O-H) cm^{-1}; ^1H nmr (300MHz) (d_6 acetone) δ: 1.25 (m, 2H), 2.04 (m, 2H), 3.40 (m, 2H), 3.69 (m, 3H), 5.92 (s, 2H), 6.71 (s, 1H), 6.74 (s, 1H); M.S. (m/z): 349 (M+1) (2%), 351 (M+3) (2%), 348 (M^+) (1%), 350 (M+2) (1%), 330 (M-H_2O) (5%), 332 (M+2-H_2O) (5%), 295 (M-1-3H_2O) (6%), 297 (M+1-3H_2O) (6%), 271 (M+1-Br) (37%), 270 (M-Br) (33%).

Reduction of olefin 106 to give debrominated product 109

Hydrogen gas was bubbled through a mixture of olefin **106** (0.36 g, 0.84 mmol) and 10% palladium on carbon (50 mg) and sodium acetate (0.20 g) in ethanol (30 mL) for 1h. The catalyst was removed by filtration and the solvent was removed in vacuo to yield a yellow solid. The solid residue was taken-up in methylene chloride, the organic phase was washed with water (2x25 mL), dried and concentrated to yield **109** as a colourless oil, 0.25 g (87%); ir (film) υ: 2950 (C-H) cm^{-1}; ^1H nmr (300MHz) (CDCl3) δ: 1.32 (s, 3H), 1.35 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.80 (m, 1H), 1.99 (m, 1H), 2.75 (m, 2H), 3.56 (dd, 1H, 8Hz, 7Hz), 3.88-4.12 (m, 4H), 5.90 (s, 2H), 6.70 (m, 3H); M.S. (C.I. ether) (m/z): 351 (M+1) (14%), 350 (M^+) (42%), 335 (M-CH_3) (13%), 293 (M+1-CH_3COCH_3) (100%).

Ethyl 3,4-methylenedioxy-6-(1,2-dideoxy-3,4:5,6-di-O-isopropylidene-D-arabino-hex-1enit-1-yl) benzoate 110

A solution of *s*-BuLi (0.90M) (0.55 mL, 0.49 mmol) was added to a solution of bromide **106** (0.18 g, 0.41 mmol) in THF (8 mL) at

-78°C. After 15 min. freshly distilled ethyl chloroformate (0.72 g, 2.05 mmol) was added and the reaction mixture was allowed to warm to R.T. over 2 h. The mixture was quenched with saturated ammonium chloride and the mixture extracted with ether (2x20 mL). The combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by chromatotron (10% ethyl acetate/ hexanes) to give **110** as white solid, 0.11 g (55%); m.p. 80-82°C; ir (KBr pellet) υ: 2980 (ArC-H), 2800 (C-H), 1720 ($ArCO_2Et$), 1600 (ArC=C) cm^{-1}; ^1H nmr (mixture of *cis* + *trans*) (300MHz) ($CDCl_3$) δ: 1.20-1.44 (m, 15H), 3.77-4.55 (m, 7H), 5.63+5.97 (dd's, 1H, (11Hz, 9Hz)(10Hz, 9Hz)), 5.99+6.02 (s's, 2H), 6.77+7.16 (d's, 1H, (10Hz)(11Hz)), 6.95+7.05 (s's, 1H), 7.34+7.45 (s's, 1H); M.S. (C.I. ether) (m/z): 421 (M+1)(5%), 363 (M+1-CH_3COCH_3) (100%), 305 (M+1-2(CH_3COCH_3)) (7%), 377 (M-OEt) (1%); Elemental Analysis calculated for $C_{22}H_{28}O_8$: C 62.83, H 6.71, found: C 62.68, H 6.57.

Ethyl 3,4-methylenedioxy-6-(1,2-dideoxy-3,4:5,6-di-O-isopropylidene-D-arabino-hexity-1-yl) benzoate 111

Hydrogen gas was bubbled through a mixture of olefin **110** (0.40 g, 0.96 mmol), 10% palladium on carbon (25 mg) and sodium acetate (0.50 g) in a mixture of ethanol (20 mL) and THF (15 mL) for 2h. The catalyst was removed by filtration and solvents removed in vacuo. The solid residue was taken-up in methylene chloride, the organic phase was washed with water (2x25 mL), dried and concentrated to yield **111** as a colourless oil, 0.37 g (90%); ir (film) υ:

2920 (ArC-H), 2820 (C-H), 1715 ($ArCO_2Et$) cm^{-1}; ^1H nmr (300MHz) (2DJ) ($CDCl_3$) δ: 1.31 (s, 3H), 1.35 (s, 6H), 1.36 (t, 3H, 7Hz), 1.40 (s, 3H), 1.80 (m, 1H), 2.01 (m, 1H), 3.06 (m, 2H), 3.59 (t, 1H, 7.5Hz), 3.93 (m, 1H), 3.91 (dd, 1H, (ABX), J_{AB} 8Hz, J_{BX} 5Hz), 4.01 (m, 1H, J_{AX} 6Hz), 4.09 (dd, 1H, (ABX), J_{AB} 8Hz, J_{AX} 6Hz), 4.29 (q, 2H, 7Hz), 5.97 (dd, 2H, J_{BX} 5Hz), 6.74 (s, 1H), 7.36 (s, 1H); M.S. (m/z): 422 (M^+) (7%), 407 (M-CH_3) (14%), 364 (M-CH_3COCH_3) (11%); M.S. (C.I. ether): 423 (M+1) (17%), 365 (M+1-CH_3COCH_3) (80%), 347 (M+1-2(CH_3COCH_3)) (17%); exact mass calculated for $C_{22}H_{30}O_8$: 422.1940, found: 422.1997.

3,4-Methylenedioxy-6-(1,2-dideoxy-3,4:5,6-di-O-isopropylidene-D-arabino-hexit-1-yl) benzyl alcohol 112

Lithium aluminum hydride (0.03 g, 0.87 mmol), was added to a solution of ester **111** (0.37 g, 0.87 mmol) in THF (20 mL) and the mixture was then refluxed for 1.5h. The reaction was quenched with 10% NaOH (3 mL), water (5 mL), the water was then removed by the addition of anhydrous magnesium sulfate. The white solid was removed by filtration through a celite pad, washed with ether and the solvents were removed in vacuo, a colourless oil resulted. The oil was purified by flash chromatography (25% ethyl acetate/ hexanes) to yield **112** as a colourless oil 0.38 g (95%); ir (film) υ: 3430 (O-H), 2815 (C-H), 1735 (ArC-C) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.31 (s, 3H), 1.33 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.82 (m, 1H), 2.01 (m, 1H), 2.31 (dd, (ABX), 1H, J_{AX} 4Hz, J_{BX} 5Hz), 2.80 (m, 2H), 3.54 (t, 1H, 7.5Hz), 3.96 (m, 3H), 4.08 (m, 1H), 4.55 (dd, 1H, (ABX), J_{AB}

1Hz, J_{BX} 5Hz), 4.61 (dd, 1H, (ABX), J_{AB} 1Hz, J_{AX} 4Hz), 5.91 (s, 2H), 6.70 (s, 1H), 6.84 (s, 1H); M.S. (C.I. ether) (m/z): 381 (M+1) (10%), 380 (M^+) (40%), 362 (M-H_2O) (99%), 322 (M-CH_3COCH_3) (2%), 305 (M+1-(CH_3COCH_3+H_2O)) (65%).

3,4-Methylenedioxy-6-(1,2-dideoxy-3,4:5,6-di-O-isopropylidene-D-arabino-hexit-1-yl) benzyl acetate 113

Freshly distilled acetyl chloride (0.01 g, 0.12 mmol) was added to a solution of alcohol **112** (0.03 g, 0.09 mmol) and triethylamine (0.01 g, 0.12 mmol) in dry methylene chloride (3 mL) at 0°C. After 3h the reaction was quenched with cold 5% HCl, the organic phase was separated and washed with cold saturated sodium bicarbonate, dried and concentrated to yield a colourless oil. The oil was purified by chromatotron (15% ethyl acetate/ hexanes) to give **113** as a colourless oil, 0.04 g (88%); ir (film) υ: 2990 (C-H), 1740 ($CH_3(C=O)OR$) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.31 (s, 3H), 1.35 (s, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.82 (m, 1H), 2.05 (m, 1H), 2.06 (2, 3H), 2.74 (m, 1H), 2.80 (m, 1H), 3.54 (dd, 1H, 8Hz, 7Hz), 3.98 (m, 3H), 4.10 (dd, 1H, 8Hz, 6Hz), 5.04 (s, 2H), 5.91 (s, 2H), 6.72 (s, 1H), 6.81 (s, 1H); M.S. (C.I. ether) (m/z): 423 (M+1) (2%), 422 (M^+) (6%), 407 (M-CH_3) (3%), 364 (M-CH_3COCH_3) (4%), 306 (M-2(CH_3COCH_3)) (18%), 305 (M-(CH_3COCH_3+CH_3CO_2)) (84%).

3,4-Methylenedioxy-6-(1,2-dideoxy-3,4-O-isopropylidene-D-arabino-hexit-1-yl) benzyl acetate 114

A solution of acetate **113** (0.31, 0.73 mmol) in 80% acetic acid (7 mL) was stirred at R.T. for 8h. The acetic acid was removed in vacuo and the residue was taken-up in chloroform (15 mL). The chloroform phase was washed with water (3x20 mL), saturated sodium bicarbonate (2x20mL), again with water (20 mL), dried and concentrated to yield a yellow oil. The oil was purified by chromatotron (40% ethyl acetate/ hexanes) to yield **114** as a colourless oil, 0.22 g (74%); ir (film) υ: 3440 (O-H), 2920 (C-H), 1735 ($CH_3(C=O)OR$) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.37 (s, 3H), 1.47 (s, 3H), 1.55 (br s, 2H, O<u>H</u>), 1.80 (m, 1H), 1.96 (m, 1H), 2.06 (s, 3H), 2.70 (m, 1H), 2.80 (m, 1H), 3.76 (m, 4H), 3.98 (m, 1H), 5.05 (s, 2H), 5.91 (s, 2H), 6.71 (s, 1H), 6.80 (s, 1H); M.S. (C.I. ether) (m/z): 383 (M+1) (2%), 382 (M^+) (10%), 367 ($M-CH_3$) (1%), 364 ($M-H_2O$) (1%), 339 ($M+1-CH_3CO$) (2%), 324 ($M+1-CH_3COCH_3$) (2%), 323 ($M-CH_3CO_2$) (6%).

Attempted Swern oxidation of diol 114

DMSO (0.01 g, 0.18 mmol), was added to a solution of oxalyl chloride (0.01 g, 0.09 mmol), in dry methylene chloride (4 mL), at -60°C. After 10 min. a solution of diol **114** (0.03 g, 0.08 mmol) in dry methylene chloride (3 mL) was added and this temperature maintained for 10 min. The temperature was then allowed to warm slowly to 0°C. The reaction was then quenched by the addition of triethylamine (0.04 g, 0.41 mmol) and the reaction temperature

raised slowly to R.T. After the usual work-up only starting diol, **114** was recovered.

Attempted oxidation of diol 114 with PCC or PDC

A solution of diol **114** (0.12 mmol) in methylene chloride (2 mL) was added to a slurry of PCC or PDC (0.18 mmol) and sodium carbonate (0.05 g, 0.49 mmol) in methylene chloride (5 mL). The resulting brown slurry was stirred at ambient temperature for 18h. The reaction mixture was then poured into anhydrous ether (20 mL) and precipitated solid was removed by filtration through a pad of silica, solvent was removed in vacuo to yield a dark oil. The oil appeared to be a complex mixture of products.

3,4-Methylenedioxy-6-(6-O-triphenylmethyl-1,2-dideoxy-3,4-O-isopropylidene-D-arabino-hexit-1-yl) benzyl acetate 115

Triethylamine (0.08 g, 0.83 mmol), was added to a solution of diol **114** (0.13 g, 0.33 mmol), triphenylmethyl chloride (0.11 g, 0.40 mmol) and DMAP (10 mg) in DMF (3 mL). After stirring at 60°C for 2 days the reaction was quenched by the addition of water and the mixture extracted with ethyl acetate (2x15 mL). The combined organic extracts were washed with water (3x15 mL), brine, dried and concentrated to yield a slightly yellow oil. The oil was purified by chromatotron (20% ethyl acetate/ hexanes) to give **115** as a colourless oil, 0.10 g (50%); ir (film) υ: 3420 (O-H), 2920 (C-H) cm^{-1}; ^1H nmr (60MHz) ($CDCl_3$) δ: 1.29 (s, 3H), 1.45 (s, 3H), 1.60 (br s, 1H, O<u>H</u>), 1.75 (m, 1H), 1.95 (m, 1H), 2.04 (s, 3H), 2.40 (m, 1H), 2.70

(m, 1H), 3.30 (m, 2H), 3.85 (m, 3H), 5.00 (s, 2H), 5.85 (s, 2H), 6.60 (s, 1H), 6.80 (s, 1H), 7.33 (m, 15H).

Attempted benzylation of trityl ether 115

A solution of trityl ether **115** (0.34 g, 0.55 mmol) in DMF (4 mL) was added to a slurry of sodium hydride (60% in mineral oil) (washed with hexanes) (0.03 g, 0.82 mmol). After the evolution of hydrogen had ceased benzyl bromide (0.14 g, 0.82 mmol) was added to the mixture which was then warmed to 60°C. After 2 days the reaction was quenched with saturated ammonium chloride, and worked-up in the usual manner. Only the starting trityl ether **115** was recovered as shown by the ^{1}H nmr spectrum..

Attempted reaction of trityl ether 115 with TBDMSOTf

t -Butyldimethylsilyl triflate (0.22 g, 0.82 mmol) was added to a solution of trityl ether **115** (0.34 g, 0.55 mmol) and 2,6-lutidine (0.12 g, 1.10 mmol) in dry methylene chloride (5 mL) at 0°C. After stirring for 2 days the reaction mixture was quenched by pouring into ice-cold 1% HCl. The organic phase was washed with 1% HCl (3x15 mL), dried and concentrated to yield a pink oil. The oil consisted mainly of starting trityl ether **115** as indicated by the ^{1}H nmr spectrum.

3,4-Methylenedioxy-6-(1,2-dideoxy-3,4:5,6-di-O-isopropylidene-D-arabino-hex-1-enit-1-yl) benzaldehyde 116

A solution of *s*-BuLi (0.90M) (3.72 mL, 3.36 mmol) was added to a solution of bromide **106** (0.96 g, 2.24 mmol) in THF (8 mL) at -78°C. After 15 min. this solution was added to freshly distilled methylformate (0.60 g, 10.00 mmol) and the reaction mixture was allowed to warm to R.T. over 2 h. The reaction was quenched with water and the mixture extracted with ether (2x20 mL). The combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by chromatotron (20% ethyl acetate/ hexanes) to give **116** as colourless oil, 0.44 g (52%); ir (film) υ: 1625 (C=C), 1700 (CHO) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.40 (m, 12H), 3.90 (m, 4H), 4.45 (m, 1H), 5.80 (m, 1H), 6.00 (s, 2H), 6.90 (s, 1H), 7.10 (m, 1H), 7.30 (m, 1H), 10.15+10.30 (s's, 1H); M.S. (m/z): 361 ($M-CH_3$) (20%), 301 ($M-(H_2O+CH_3COCH_3)$) (3%); M.S. (C.I. ether) (m/z): 375 (M-1) (34%), 348 (M-CHO) (58%).

3,4-Methylenedioxy-6-(1,2-didehydro-1,2-dideoxy-3,4:5,6-di-O-isopropylidene-D-arabino-hex-1-enit-1-yl) benzyl alcohol 117

Sodium borohydride (0.44 g, 1.16 mmol) was added to a solution of aldehyde **116** (0.13 g, 3.49 mmol) in THF/ethanol (20 mL). After 18h the reaction was quenched with 10% NaOH and the ethanol was removed in vacuo. The resulting slurry was extracted with ether (3x20 mL), the combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a

colourless foam. The foam was purified by chromatotron (20% ethyl acetate/ hexanes) to give **117** as a white foam, 0.41 g (93%); ir (film) υ: 3420 (O-H) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) (*trans*-isomer) δ: 1.27 (s, 6H), 1.35 (s, 3H), 1.43 (s, 3H), 1.46 (br s, 1H, O<u>H</u>), 3.71 (dd, 1H, 8Hz, 7Hz), 3.89-4.05 (m, 3H), 4.36-4.59 (m, 3H), 5.75 (dd, 1H, 11Hz, 9Hz), 5.95 (dd, 2H, 2.5Hz, 2Hz), 6.82-6.93 (m, 3H); M.S. (m/z): 378 (M^+) (4%), 360 (M-H_2O) (19%), 320 (M-CH_3COCH_3) (2%).

Reaction of alcohol 117 with MsCl followed by treatment with thiolacetic acid in ethanol

Methanesulfonyl chloride (0.15 g, 1.29 mmol) was added to a solution of alcohol **117** (0.41 g, 1.08 mmol) and triethylamine (0.13 g, 1.29 mmol) in dry methylene chloride (15 mL) at 0°C. Simultaneously thiolacetic acid (0.12 g, 1.62 mmol) was added to a solution of KOH (0.09 g, 1.62 mmol) in ethanol (15 mL) at R.T. After 1h the solution of crude mesylate was added to the solution of potassium thiolacetate. After stirring for 2.5h at R.T. the solvents were removed in vacuo and the residue was taken-up in ether-water. The aqueous phase was extracted with ether (3x20 mL), the combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by chromatotron (20% ethyl acetate/ hexanes) to give ethyl ether, **118**, 0.24 g (55%); ir (film) υ: 1620 (C=C) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) (*trans*-isomer) δ: 1.21 (t, 3H, 7Hz), 1.29 (s, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 1.42 (s, 3H), 3.50 (q, 2H, 7Hz), 3.76 (dd, 1H, 7Hz, 6.5Hz), 3.84 (m, 1H), 3.95-4.10 (m, 2H), 4.36 (s, 2H), 4.55 (dd, 1H, 10Hz, 8Hz), 5.66

(dd, 1H, 11Hz, 10Hz), 5.93 (s, 2H), 6.77 (d, 1H, 11Hz), 6.89 (s, 1H), 7.01 (s, 1H); M.S. (m/z): 406 (M^+) (12%) , 391 (M-CH_3) (6%), 360 (M-EtOH) (4%).

3,4-Methylenedioxy-6-(1,2-dideoxy-3,4:5,6-di-O-isopropylidene-D-arabino-hex-1-enit-1-yl) benzylthiolacetate 119

Methanesulfonyl chloride (0.27 g, 2.34 mmol) was added to a solution of alcohol **117** (0.74 g, 1.96 mmol) and triethylamine (0.23 g, 2.34 mmol) in dry methylene chloride (25 mL) at 0°C. After 1h, thiolacetic acid (0.22 g, 2.94 mmol) was added, followed by the addition of triethylamine (0.30 g, 2.94 mmol) and the reaction temperature was allowed to warm slowly to R.T.

After 1h the reaction mixture was washed with water (2x20 mL), dried and concentrated to yield a yellow oil. The oil was purified by chromatotron (10% ethyl acetate/ hexanes) to give **119** as a colourless oil, 0.42 g (50%), along with chloride, **120**, 0.21 g (27%); spectral data for **119**; ir (film) υ: 2990 (C-H), 1690 (S(C=O)CH_3), 1620 (C=C) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) (*trans*-isomer) δ: 1.31 (s, 3H), 1.32 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 2.31 (s, 3H), 3.76 (m, 1H), 3.85 (m, 1H), 3.96-4.10 (m, 2H), 4.02 (s, 2H), 4.50 (dd, 1H, 9Hz, 7.5Hz), 5.70 (dd, 1H, 11Hz, 9Hz), 5.93 (s, 2H), 6.70 (d, 1H, 11Hz), 6.81 (s, 1H), 6.99 (s, 1H); M.S. (C.I. ether) (m/z): 436 (M^+) (16%), 421 (M-CH_3) (4%), 393 (M-$COCH_3$) (7%), 379 (M+1-CH_3COCH_3) (18%), 360 (M-AcSH) (15%). Spectral data for **120**; ir (film) υ: 2990 (C-H), 1485 (ArC-C), 1620 (C=C) cm^{-1}; ^1H nmr

(300MHz) ($CDCl_3$) (*trans*-isomer) δ: 1.29 (s, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 1.42 (s, 3H), 3.76 (dd, 1H, 7.5Hz, 7Hz), 3.88 (m, 1H), 3.98-4.10 (m, 2H), 4.50 (d, 2H, 4Hz), 4.56 (dd, 1H, 7Hz, 2Hz), 5.76 (dd, 1H, 11Hz, 10Hz), 5.96 (s, 2H), 6.83 (d, 1H, 11Hz), 6.84 (s, 1H), 7.01 (s, 1H); M.S. (C.I. ether) (m/z): 396 (M^+) (7%), 398 (M+2) (3%), 361 (M-Cl) (6%), 339 (M+1-CH_3COCH_3) (15%).

3,4-Methylenedioxy-6-(1,2-dideoxy-3,4:5,6-di-O-isopropylidene-D-arabino-hex-1-enit-1-yl) benzylthiol 121

A solution of 10% NaOH (10 mL) was added to a solution of thiolacetate **119** (0.42 g, 0.96 mmol) in ethanol (20 mL). After 0.5h the solvents were removed in vacuo and the residue taken-up in ether-water. The aqueous phase was extracted with ether (2x20 mL), the combined extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a white solid. The solid was recrystallized from ether/ hexanes to give **121** as a white solid, 0.37 g (98%); ir (KBr pellet) υ: 2990 (C-H), 2460 (S-H), 1640 (C=C), 1485 (ArC-C) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) (mixture of cis and trans) δ: 1.29 (s, 3H), 1.32 (s, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 1.86 (dd, 1H, 8Hz, 7Hz, S<u>H</u>), 3.47-3.61 (m, 4H), 3.67-4.09 (m, 2H), 4.52 (m, 1H), 5.73 (m, 1H), 5.94 (s, 2H), 6.62-6.96 (m, 3H); M.S. (C.I. ether) (m/z): 395 (M+1) (11%), 361 (M-SH) (7%), 337 (M+1-CH_3COCH_3) (55%).

Attempted free radical cyclization of thiol 121

A solution of thiol **121** (0.29 g, 0.75 mmol) and AIBN (50 mg) in benzene (80 mL) was refluxed for 30h. By TLC and ^1H nmr it appeared that no reaction was taking place.

3,4-Methylenedioxy-6-(3,4:5,6-di-O-isopropylidene-D-arabino-hexit-1-yl) benzaldehyde 122

A solution of alcohol **112** (0.15 g, 0.40 mmol) in methylene chloride (5 mL) was added to a slurry of PCC (0.17 g, 0.79 mmol) and sodium acetate (0.26 g, 3.16 mmol) in methylene chloride (10 mL). The resulting brown slurry was stirred at ambient temperature for 18h. The reaction mixture was then poured into anhydrous ether (20 mL) and precipitated solid was removed by filtration through a pad of silica, solvent was removed in vacuo to yield a slightly yellow oil. The oil was purified by chromatotron (20% ethyl acetate/ hexanes) to give **122** as a colourless oil, 0.13 g (86%); ir (film) υ: 1710 (CHO) cm-1; 1H nmr (60MHz) ($CDCl_3$) δ: 1.10 (m, 2H), 1.35 (m, 12H), 1.95 (m, 2H), 3.05 (m, 2H), 3.95 (m, 3H), 5.95 (s, 2H), 6.70 (s, 1H), 7.25 (s, 1H), 10.15 (s, 1H).

Photolysis of aldehyde 122 in the presence of sulfur dioxide

A solution of aldehyde **122** (0.12 g, 0.33 mmol) and sulfur dioxide (0.17 g, 2.67 mmol) in degassed benzene (20 mL) was irradiated for 1-5h with a medium pressure lamp, using a pyrex filter. Both TLC and ^1H nmr analysis showed that no reaction was occurring.

5,6-Methylenedioxy 1,3-dihydrobenzo[c]thiophene 123

Sodium sulfide nonahydrate (7.16 g, 29.82 mmol), was dissolved in DMF (300 mL), some heating was required to help in dissolving of the sodium sulfide, a blue solution resulted. 4,5 Methylenedioxy α,α' *o*-xylene dichloride (5.00 g, 22.94 mmol) was then added and the blue colour disappeared immediately. After stirring at R.T. for 1.5h the reaction mixture was poured into water and extracted with ethyl acetate (5x100 mL). The combined organic phases were washed with water (5x100 mL), brine (3x100 mL), dried and concentrated to yield an off white solid. The solid was purified by flash chromatography (10% ethyl acetate/ hexanes) to give **123** as a white solid, 2.81 g (68%); m.p. 117-119°C ; ir (KBr pellet) υ: 2910 (C-H), 1485 (Ar-C) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 4.14 (s, 4H), 5.94 (s, 2H), 6.65 (s, 2H); M.S. (m/z): 180 (M^+) (100%), 179 (M-1) (99%), 150 (M-CHO) (14%); exact mass calculated for $C_9H_8O_2S$: 180.0245, found: 180.0233.

4-Trimethylsilyl-5,6-methylenedioxy-1,3 - dihydrobenzo[c]thiophene 124

A solution of *s*-BuLi (1.2M in hexanes) (1.53 mL, 1.83 mmol) was added to a solution of sulfide **123** (0.28 g, 1.53 mmol) and TMEDA (0.21 g, 1.83 mmol) in THF (10 mL) at -78°C. The temperature was maintained at -78°C for 1h, and freshly distilled TMSCl (1.98 g, 18.30 mmol) was added and the temperature was raised to -10°C. The reaction was quenched with saturated

ammonium chloride and the mixture extracted with ether (2x20 mL). The combined ether extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by chromatotron (10% ethyl acetate/ hexanes) to give **124** as a colourless oil, 0.35 g (63%); ir (film) υ: 2920 (C-H), 1480 (ArC-C) cm^{-1}; ^1H nmr (60MHz) ($CDCl_3$) δ: 0.21 (s, 9H), 3.87 (s, 4H), 5.62 (s, 2H), 6.38 (s, 1H); M.S. (m/z): 252 (M^+) (100%), 237 (M-CH_3) (46%), 207 (M-3CH_3) (22%), 179 (M-TMS) (60%); exact mass calculated for $C_{12}H_{16}O_2SSi$: 252.0460, found: 252.0650.

5,6-Methylenedioxy-1,3-dihydrobenzo[c]thiophene 2,2-dioxide 125

m-CPBA (80%) (5.84 g, 27.17 mmol) was added portion-wise to a cooled solution of sulfide **123** (1.63 g, 9.06 mmol) in ethyl acetate (80 mL). After allowing to warm to R.T. the reaction mixture was stirred for 18h. The precipitated *m*-chlorobenzoic acid was removed by filtration and the filtrate was washed with 10% sodium bisulfite (3x25 mL), saturated bicarbonate (3x25 mL), brine, dried and concentrated to yield a yellow solid. The solid was recrystallized from ethyl acetate to give **125** as a white solid, 1.22 g (64%); m.p. 185°C decomposes; ir (KBr pellet) υ: 2995 (ArC-H), 2900 (C-H), 1480 (ArC-C), 1315, 1125 (RSO_2R) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 4.25 (s, 4H), 5.98 (s, 2H), 6.72 (s, 2H); M.S. (m/z): 212 (M^+) (21%), 148 (M-SO_2) (100%); exact mass calculated for $C_9H_8O_4S$: 212.0141, found: 212.0141.

2,3:4,5-Di-O-isopropylidene-D-arabinitol 126[54]

Sodium borohydride (0.22 g, 5.92 mmol) was added to a solution of aldehyde **60** (1.36 g, 5.92 mmol) in ethanol (40 mL), the reaction mixture was then allowed to stir at R.T. for 18h. The ethanol was removed in vacuo and the residue was taken-up in ethyl acetate and 10% NaOH. The aqueous phase was extracted with ethyl acetate (2x20 mL) and the combined organic extracts were washed with water (2x20 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by flash chromatography (20% ethyl acetate/ hexanes) to give **126** as a colourless oil, 1.37 g (100%); $[\alpha]^{22}$ (c 0.28, $CHCl_3$) +1.00°; (lit.[54] $[\alpha]^{27}$ (c 4.55, $CHCl_3$) +0.97°); ir (film) υ: 3425 (O-H), 2920 (C-H) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.33 (s, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 2.28 (br s, 1H, O<u>H</u>), 3.70 (dd, 1H, 5Hz, 8Hz), 3.77 (dd, 1H, 7.5Hz, 8Hz), 3.96 (br m, 4H), 4.16 (dd, 1H, 6Hz, 8Hz); M.S. (C.I. ether) (m/z): 233 (M+1) (68%), 217 (M-CH_3) (22%), 201 (M-CH_2OH) (12%), 175 (M+1-CH_3COCH_3) (100%).

2,3:4,5-Di-O-isopropylidene-1-methylsulfonyl-D-arabinitol 127

Methanesulfonyl chloride (0.32 g, 2.84 mmol) was added to a solution of alcohol **126** (0.55 g, 2.37 mmol) and TEA (0.36 g, 3.56 mmol) in dry methylene chloride (25 mL) at 0°C. After 2h the reaction mixture was poured into water and the aqueous phase was extracted with methylene chloride (2x20 mL). The combined organic phases were washed with cold 2% HCl (3x15 mL), water (2x15 mL), dried and concentrated to yield a yellow solid. The solid was purified by chromatotron (20% ethyl acetate/ hexanes) to give **127**

as a white solid, 0.73 g (100%); m.p. 41-42°C; ir (KBr pellet) υ: 2980 (C-H), 1380, 1180 (RSO_2OR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.32 (s, 3H), 1.38 (s, 3H), 1.40 (s, 6H), 3.05 (s, 3H), 3.71 (dd, 8Hz, 8.5Hz), 3.94 (dd, 1H, 4.5Hz, 8.5Hz), 4.04 (m, 1H), 4.15 (m, 2H), 4.29 (dd, 1H, 5.5Hz, 11Hz), 4.52 (dd, 1H, 2.5Hz, 11Hz); M.S. (C.I. ether) (m/z): 311 (M+1) (85%), 295 (M-CH_3) (32%), 253 (M+1-CH_3COCH_3) (100%).

Attempted reaction of the lithium anion of 125 with mesylate 127

A solution of *n*-BuLi (2.26M in hexanes) (0.39 mL, 0.89 mmol) was added to a solution of diisopropylamine (0.09 g, 0.89 mmol) in THF (4 mL) at -78°C. After 10 min. a solution of sulfone **125** (0.16 g, 0.74 mmol) in THF (8 mL) was added dropwise, the solution became deep green. After 15 min. a solution of mesylate **127** (0.23 g, 0.74 mmol) in THF (8 mL) was added and the reaction mixture was allowed to warm slowly to R.T., the green colour persisted. The reaction was quenched with saturated ammonium chloride and worked-up in the usual manner, only the starting materials were recovered, no reaction had taken place.

Reaction of triol 57 with TBDMSOTf

TBDMSOTf (5.91 g, 23.32 mmol) was added to a solution of triol **57** (2.70 g, 5.42 mmol) in dry methylene chloride (80 mL) at 0°C. This was followed by the addition of 2,6-lutidine (4.99 g, 46.62 mmol), the reaction mixture was then allowed to warm slowly to R.T. and stir for 18h. The reaction mixture was poured into ice-water

and the aqueous phase was extracted with methylene chloride (3x25 mL). The combined organic phases were washed with water (3x25 mL), cold 2% HCl; (3x25 mL), water (2x25 mL), dried and concentrated to yield a brown oil. The oil was purified by flash chromatography to give triphenylmethyl ethyl sulfide, 1.40 g (85%); m.p. 118-119°C; ir (KBr pellet) υ: 3010 (C-H) cm^{-1}: ^1H nmr (200MHz) ($CDCl_3$) δ: 1.07 (t, 3H, 7.5Hz), 2.14 (q, 2H, 7.5Hz), 7.28 (m, 9H), 7.40 (m, 6H); M.S. (m/z): 275 (M-Et) (1%), 243 (M-SEt) (100%), 61 ($M-Ph_3C$) (1%), and arabinosyl ethyl sulfide, **128**, 3.21 g, 80%;

2,3,4-Tri-O-acetyl-5-O-triphenylmethyl-D-arabinose diethyl dithioacetal 131[56]

Acetic anhydride (3.14 g, 30.78 mmol) was added to a solution of triol **57** (2.19 g, 4.40 mmol) in pyridine (15 mL) at 0°C. After the addition was complete the ice-bath was removed and the reaction mixture was stirred at R.T. for 18h. The reaction mixture was poured into ice-water and extracted with ether (3x25 mL). The combined extracts were washed with water (4x25 mL), dried and concentrated to yield a white foam. The foam was purified by flash chromatography (20% ethyl acetate/ hexanes) to give **131** as a white foam, 2.61 g (95%); m.p. 103-105°C (lit.[56] m.p. 101-102°C); ir (film) υ: 3060 (Ar-H), 2980 (C-H), 1745 (broad) (C=O), 710 (C-SR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.20 (m, 6H) 1.84 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 2.63 (m, 4H), 3.14 (m, 2H), 3.83 (d, 1H, 8Hz), 5.15 (m, 1H), 5.25 (dd, 1H, 2.5Hz, 8Hz), 5.80 (dd, 1H, 2.5Hz, 8.5Hz), 7.22 (m, 9H),

7.38 (m, 6H); M.S. (C.I. ether) (m/z): 563 (M-SEt) (1%), 243 (Ph_3C^+) (100%).

2,3,4-Tri-O-acetyl-5-O-triphenylmethyl-D-arabinose 132

A mixture of dithioacetal **131** (0.66 g, 1.05 mmol), mercuric chloride (0.31 g, 1.16 mmol) and mercuric oxide (0.51 g, 2.32 mmol) in 95% acetone/water (25 mL) was refluxed for 4h. The reaction mixture was filtered through Celite, washed with 1:1 methylene chloride/hexanes (100 mL). The organic phase was washed with 5N ammonium acetate (2x50 mL), brine, dried and concentrated to give **132** as a colourless oil, 0.49 g (90%); ir (film) υ: 1730 (CH=O), 1745 (broad) (C=O) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.78 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 3.09 (dd, 1H, 4Hz, 11Hz), 3.35 (dd, 1H, 2.5Hz, 11Hz), 5.22 (m, 1H), 5.40 (d, 1H, 2Hz), 5.90 (dd, 1H, 2Hz, 9Hz), 7.22 (m, 9H), 7.38 (m, 6H), 9.51 (s, 1H); M.S. (C.I. ether) (m/z): 357 (M-(2(OAc)+Ac)) (1%), 243 (Ph_3C^+) (88%).

2,3,4-Tri-O-acetyl-5-O-triphenylmethyl-D-arabinitol 133

A solution of borane·THF (1.0M in THF) (1.39 mL, 1.39 mmol) was added to a solution of aldehyde**132** (0.48 g, 0.93 mmol) in THF (20 mL) at 0°C. After 1h the reaction was quenched with methanol and the solvents were removed in vacuo to yield a white foam. The foam was purified by chromatotron (20% ethyl acetate/ hexanes) to give **133** as a white foam, 0.47 g (98%); ir (film) υ: 3420 (O-H), 1745 (broad) (C=O) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.83 (s, 3H), 2.01 (s, 3H), 2.12 (s, 3H), 3.02 (dd, 1H, 4Hz, 11Hz), 3.35 (dd, 1H, 2Hz,

11Hz), 3.45 (m, 1H), 3.63 (m, 2H), 5.15 (m, 2H), 5.65 (dd, 1H, 2Hz, 9.5Hz), 7.24 (m, 9H), 7.36 (m, 6H); M.S. (C.I. ether) (m/z): 259 (M-(Ph_3C+H_2O) (1%), 243 (Ph_3C^+) (56%).

2,3,4-Tri-O-acetyl-1-methylsulfonyl-5-O-triphenylmethyl-D-arabinitol 134

Methane sulfonyl chloride (0.12 g, 1.08 mmol) was added to a solution of alcohol **133** (0.47 g, 0.90 mmol) and TEA (0.11 g, 1.08 mmol) in dry methylene chloride (15 mL) at 0°C. After 2h the reaction mixture was poured into water and the aqueous phase was extracted with methylene chloride (2x20 mL). The combined organic phases were washed with cold 2% HCl (3x15 mL), water (2x15 mL), dried and concentrated to yield a yellow oil. The oil was purified by chromatotron (30% ethyl acetate/ hexanes) to give **134** as a colourless oil, 0.54 g (100%); ir (KBr pellet) υ: 2980 (C-H), 1385, 1180 (RSO_2OR) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 2.05 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 3.00 (m, 2H), 3.04 (s, 3H), 4.35 (m, 5H), 7.27 (m, 15H); M.S. (C.I. ether) (m/z): 503 ($M-SO_3CH_3$) (5%), 339 (M-(2HOAc+CH_3SO_3H+Ac) (9%), 243 (Ph_3C^+) (100%).

Attempted reaction of the lithium anion of 125 with mesylate 134

A solution of *n*-BuLi (2.4M in hexanes) (0.10 mL, 0.23 mmol) was added to a solution of diisopropylamine (0.02 g, 0.25 mmol) in THF (4 mL) at -78°C. After 10 min. a solution of sulfone **125** (0.04 g, 0.19 mmol) in THF (4 mL) was added dropwise, the solution

became deep green. After 15 min. a solution of mesylate **134** (0.12 g, 0.19 mmol) in THF (4 mL) was added and the reaction mixture was allowed to warm slowly to R.T., the green colour disappeared. The reaction was quenched with saturated ammonium chloride and worked-up in the usual manner, it appeared that the acetates had been cleaved, as shown by the disappearance of the singlets corresponding to the acetates in the crude ^1H nmr spectrum.

1-(2,3:4,5-Di-O-isopropylidene-D-arabinit-1-[R,S]-yl)-5,6-methylenedioxy-1,3-dihydrobenzo[c]thiophene 2,2-dioxide 135

A solution of *n*-BuLi (2.20M in hexanes) (2.44 mL, 5.38 mmol) was added to a solution of diisopropylamine (0.65 g, 6.45 mmol) in THF (15 mL) at -78°C. After 10 min. a solution of sulfon **125** (0.95 g, 4.48 mmol) in THF (8 mL) was added dropwise, the solution became deep green. After 15 min. a solution of aldehyde **60** (1.03 g, 4.48 mmol) in THF (8 mL) was added and the reaction mixture was allowed to warm slowly to R.T., the green colour disappeared. The reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (2x15 mL). The combined extracts were washed with water (3x15 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by chromatotron (20% ethyl acetate/hexanes) to yield **135** as a yellow solid, 1.47 g (74%); m.p. 52-54°C; ir (KBr pellet) υ: 3420 (O-H), 2995 (ArC-H), 2910 (C-H), 1485 (ArC-C), 1315, 1220 (RSO_2R) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.30 (m, 12H), 1.70 (br s, 1H, O<u>H</u>), 3.98 (m, 2H), 4.15 (m, 3H), 4.25 (s, 2H), 5.98 (s, 2H), 6.72 (s, 1H), 6.77+6.86 (s's, 1H) (diastereomers);

M.S. (C.I. ether) (m/z): 443 (M+1) (23%), 425 (M+1-H_2O) (1%), 385 (M+1-CH_3COCH_3) (44%), 379 (M+1-SO_2) (1%).

1-([1R,S]-O-[(methylthio)thiocarbonyl]-2,3:4,5-di-O-isopropylidene-D-arabinityl)-5,6-methylenedioxy 1,3-dihydrobenzo[c]thiophene 2,2-dioxide 136

A solution of alcohol **135** (0.50 g, 1.13 mmol) in THF (8 mL) was added to a slurry of sodium hydride (50% in mineral oil) (washed with hexanes) (0.08 g, 1.70 mmol) and imidizole (10 mg) in THF (10 mL). After 15 min. carbon disulfide (0.26 g, 3.40 mmol) was added at once and stirring at R.T. was continued. After 35 min. methyl iodide (0.29 g, 2.00 mmol) was added and the reaction mixture stirred for a further 15 min. The reaction was quenched with saturated ammonium chloride and the mixture extracted with ether (3x15 mL). The combined extracts were washed with water (2x15 mL), brine, dried and concentrated to yield a yellow oil. The oil was purified by chromatotron (15% ethyl acetate/ hexanes) to give **136** as a colourless oil, 0.15 g (25%); ir (film) υ: 1320, 1225 (RSO_2R), 1215 (C=S) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.40 (m, 12H), 2.29+2.79 (s's, 3H), 4.00 (br m, 7H), 4.25 (s, 2H), 5.98+6.03 (s's, 2H), 6.72 (s, 1H), 6.91+6.96 (s's, 1H); M.S. (C.I. ether) (m/z): 533 (M+1) (6%), 517 (M-CH_3) (13%), 442 (M+1-CS_2CH_3) (17%), 425 (M-OCS_2CH_3) (2%).

Treatment of xanthate 136 with tri-*n*-butyltinhydride

A solution of xanthate **136** (0.29 g, 0.55 mmol) and tri-*n*-butyltinhydride (0.25 g, 0.85 mmol) in toluene (50 mL) was refluxed for 18h. The toluene was then removed in vacuo, the residue was partitioned between acetonitrile and hexanes. The acetonitrile layer was washed with hexanes (3x20 mL) and acetonitrile removed in vacuo. The residue is taken-up in (10:1) hexanes/ ethyl acetate and filtered through a pad of silica gel, and the solvents removed in vacuo to yield a yellow oil. The oil was purified by chromatotron to give a mixture of deoxygenated material, **137** and elimination product, **138,** only the olefin could be isolated, ir (film) υ: 1610 (C=C), 1330, 1220 (RSO_2R) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) (*cis*-isomer) δ: 1.32 (s, 3H), 1.40 (s, 3H), 1.46 (s, 3H), 1.47 (s, 3H), 4.00 (m, 2H), 4.14 (dd, 1H, 8Hz, 6.5Hz), 4.25 (s, 2H), 4.28 (m, 1H), 5.11 (dd, 1H, 9.5Hz, 8Hz), 6.03 (s, 2H), 6.17 (d, 1H, 9.5Hz), 6.67 (s, 1H), 6.91 (s, 1H); M.S. (m/z): 409 ($M-CH_3$) (4%), 366 ($M-CH_3COCH_3$) (11%), 360 ($M-SO_2$) (1%), 308 ($M-2CH_3COCH_3$) (17%).

Attempted reaction of alcohol 135 with methane sulfonyl chloride

Methane sulfonyl chloride (0.16 g, 1.42 mmol) was added to a solution of alcohol **135** (0.50 g, 1.18 mmol) and TEA (0.14 g, 1.42 mmol) in dry methylene chloride (15 mL) at 0°C. After 2h the reaction mixture was poured into water and the aqueous phase was extracted with methylene chloride (2x20 mL). The combined organic

phases were washed with cold 2% HCl (3x15 mL), water (2x15 mL), dried and concentrated to yield a yellow foam. Only starting alcohol was recovered as confirmed by ^{1}H nmr analysis..

Attempted reaction of alcohol 135 with acetyl chloride

Acetyl chloride (0.06 g, 0.71 mmol) was added to a solution of alcohol **135** (0.25 g, 0.59 mmol) and TEA (0.07 g, 0.71 mmol) in methylene chloride (10 mL) at 0°C. After warming to R.T. the reaction mixture was stirred for 18h. The reaction mixture was poured into water and the aqueous phase was extracted with methylene chloride (2x20 mL). The combined organic phases were washed with cold 2% HCl (3x15 mL), water (2x15 mL), dried and concentrated to yield a yellow foam. Only starting alcohol was recovered, as shown by ^{1}H nmr.

Attempted elimination of alcohol 135 with thionyl chloride in pyridine

Thionyl chloride (0.12 g, 1.00 mmol) was added to a solution of alcohol **135** (0.22 g, 0.50 mmol) in pyridine (5 mL). After stirring for 18h at R.T. the reaction mixture was poured into water and the aqueous phase was extracted with methylene chloride (2x10 mL). The combined organic phases were washed with cold 2% HCl (3x10 mL), water (2x10 mL), dried and concentrated to yield a yellow foam. Only starting alcohol was recovered, as shown by ^{1}H nmr..

Treatment of alcohol 135 with 80% acetic acid

A solution of alcohol **135** (0.52 g, 1.18 mmol) in 80% acetic acid (10 mL) was stirred at R.T. for 72h. The acetic acid was then removed in vacuo and the residue taken-up in chloroform, the chloroform was then washed with water (3x10 mL), saturated sodium bicarbonate (3x10 mL), water (2x10 mL), dried and concentrated to yield **139** as a colourless oil, 94 mg (20%); ir (film) υ: 3420 (O-H) cm^{-1}; ^1H nmr (300MHz) ($CDCl_3$) δ: 1.42 (s, 3H), 1.45 (s, 3H), 1.66 (br s, 3H, OH), 3.47-3.91 (m, 4H), 4.06 (d, 1H, 15Hz), 4.38 (m, 3H), 5.99 (s, 2H), 6.75 (s, 1H), 6.87 (s, 1H); M.S. (C.I. ether) (m/z): 403 (M+1) (50%), 385 (M+1-H_2O) (2%), 345 (M+1-CH_3COCH_3) (100%).

Attempted elimination of alcohol 135 with Burgess reagent ($MeO_2N(-)SO_2N(+)Et_3$)

A solution of alcohol **135** (0.21 g, 0.47 mmol) in acetonitrile (4 mL) was added dropwise to a solution of Burgess reagent (0.14 g, 0.59 mmol) in acetonitrile (10 mL). The solution was warmed to 50°C for 1.5h, TLC showed only starting alcohol. The reaction mixture was then heated to reflux for 24h, TLC still showed only starting alcohol.

Attempted elimination of alcohol 135 with Martins sulfurane ($(PhC(CF_3)_2O)_2SPh_2$)

A solution of Martins sulfurane (0.49 g, 0.73 mmol) in dry methylene chloride (8 mL) was added dropwise to a solution of alcohol **135** (0.27 g, 0.61 mmol) in dry methylene chloride at -78°C.

After warming to R.T. the reaction was allowed to stir for 18h. The solvent was removed in vacuo and the resulting brown oil was chromatographed (20% ethyl acetate/ hexanes), none of the desired elimination product was obtained only starting alcohol was recovered, as shown by ^{1}H nmr.

CLAIMS to ORIGINAL RESEARCH

1. The alkylation of numerous aromatic anions with various alkyltriflates was performed. It was also found that the use of one equivalent of cerium trichloride seems to enhance the alkylation reaction presumably by lowering the basicity of the aryl anion. This method was developed and found to be general and superior to existing methodology.

2. It was found that ortho-metalation on a doubly activated aromatic position was favoured exclusively over lateral metalation.

3. It was shown that lateral metalation cannot be achieved if the aromatic ring and the amide function cannot achieve planarity to allow for overlap of the π-orbitals.

4. Generation of the dianion of α-methylbenzylbenzamide and trapping with an epoxide proceeded to give compound **94** in good yield. Conversion of this alcohol to mesylate **95** followed by treatment with base did not give the expected cyclic amide **96** but the cyclic imidate **98**.

5. When attempts were made to generate the dianion of either *N*-benzyloxy- or *N*-ethylthiomethylbenzamides (**99, 100**) the protecting groups in both cases were lost via β-elimination processes to give the parent benzamide.

6. The previously unknown cleavage of an *N*-methoxyl protecting group of an amide via hydrogenolysis was performed cleanly.

7. Attempted generation of a benzylic sulfenyl anion of 5,6-methylenedioxy 1,3-dihydrobenzo[c]thiophene **123** led unexpectedly to exclusive formation of the ortho-lithioanion.

8. The first synthesis of 5,6-methylenedioxy 1,3-dihydrobenzo[c]thiophene 1,1-dioxide **125** was accomplished.

9. The anion chemistry of **125** was explored.