Palladium Mediated Approaches Towards Pyranose-Derived Dienes and spiroacetals

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Contents

Chapter 2

Abstract

A method for the generation of the spiroacetal nucleus of milbemycin β_3 was developed using modified Heck-Stille palladium coupling reactions.

Initial studies, in which 2,3-dihydro-2(H)-pyran was used as a simple model to obtain the spiroacetal nucleus, involved the coupling of the vinyl tri-n-butyl tin or zinc chloride derivative of 2,3-dihydro-2(H)-pyran with (*Z*,*E*)-4-hydroxy-3-methyl-1-iodopentene. Treatment of the resultant 1,3-diene with camphorsulphonic acid resulted in the formation of the spiroacetal.

Various conditions were examined to optimise the conversion of 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tri-n-butylstannyl-D-arabino-hex-1-enitol into glycosyl 1,3-dienes *via* palladium(0)-catalysed cross-coupling reactions. Diels-Alder reactions of the glycosyl 1,3-dienes prepared were examined using 4-phenyl-1,2,4-triazoline-3,5-dione as the dienophile.

The palladium(0)-catalysed cross-coupling reactions between 1,5-anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tri-n-butylstannyl-D-arabino-hex-1-enitol (and its zinc derivative) and (*Z*,*E*)-4-(t-butyldimethylsilyl)-1-iodopentene and (*Z*,*E*)-4-hydroxyl-1-iodopentene were investigated to optimise the formation of the glycosyl 1,3-diene precursor requisite for spiroacetal formation. Treatment of the precursor with camphorsulphonic acid resulted in the formation of spiroacetal analogue of milbemycin β_3. Cyclisation of the precursor with phenyl selenium chloride afforded the 11-phenylselenyl-spiroacetal analogue.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other University or Institute of learning.

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Mark and Ali for proof-reading this thesis.

Biography

The author graduated in Chemistry from Manchester University in 1991 and has since been engaged in research in the same department under the supervision of Dr. P. Quayle and received his M.Sc. in 1992.

Abbreviations

Ac	acetyl
Ar	aryl
Bn	benzyl
Bu	butyl
cat.	catalytic
CSA	camphorsulphonic acid
CI	chemical ionization
dba	dibenzylideneacetone
DBU	1,8-diazobicyclo[5,4,0]undec-7-ene
DIBAL-H	diisobutylaluminium hydride
DMF	dimethylformamide
DMSO	dimethyl sulphoxide
Et	ethyl
FG	functional group
h	hour
HCOSY	homoonuclear shift correlation
ir	infra red
M	molar
Me	methyl
min	minute
NMP	N-methyl-2-pyrrolidinone
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Ph	phenyl
PNB	*p*-nitrobenzyl
R	general functional group
r.t.	room temperature

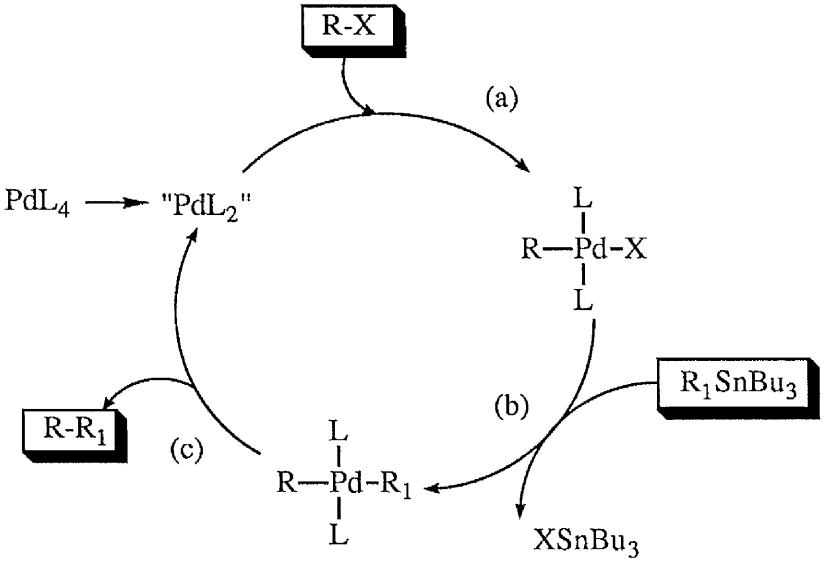
TBAF	tetrabutyl ammonium fluoride
TBDMS (=TBS)	*tertiary* butyldimethyl silyl
TBDPS	*tertiary* butyldiphenyl silyl
Tf	triflate
THF	tetrahydrofuran
DCM	DICHLOROMETHANE
AIBN	AZOISOBUTYRONITRILE
~	APPARENT

CHAPTER 1

1.1 INTRODUCTION

This thesis is concerned with the synthesis of the spiroacetal nucleus of milbemycin β_3 *via* Stille-type palladium(0)-catalysed cross-coupling reactions. These reactions generated the 1,3-diene precursors requisite for spiroacetal formation.

The proposed mechanism[1] involves oxidative addition of the vinylic halide to palladium(0) catalyst followed by vinylation of the vinylic palladium halide formed with the organometallic species. The final step is reductive elimination of the 1,3-diene (scheme 1, L=ligand e.g. triphenylphosphine, X=halide e.g. iodine).

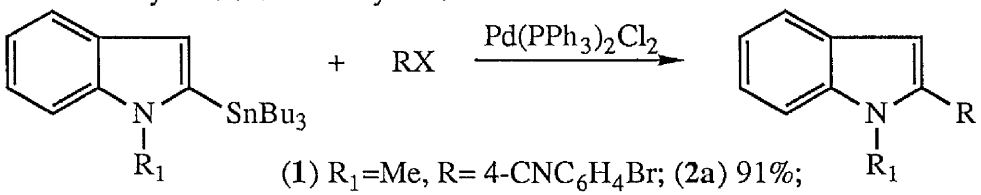


(a) Oxidative addition (b) Transmetallation (c) Reductive elimination

Scheme 1. Generalised mechanism for Stille coupling.

1.2 Palladium-Catalysed Cross-Coupling Reactions in Indole Systems

A general method for the synthesis of 2-substituted indoles *via* the palladium-catalysed coupling of indol-2-ylstannanes has been described by Labadie.[2] (N-Methylindo-2-yl)tributylstannane (**1**) reacts with a variety of electrophiles under very mild conditions (50-90% yield). ((N-*tert*-Butoxycarbonyl)indo-2-yl)tri-n-butylstannane (**3**) is much less reactive in the coupling reactions and reacts only with certain activated electrophiles (50-72% yield). [N-[[(Trimethylsilyl)ethoxy]methylindol-2-yl]tri-n-butylstannane (**4**) behaves similarly to (**1**) (50-90% yield).

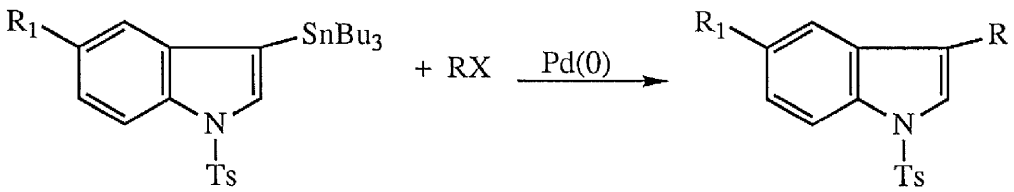


(**1**,**3**,**4**)

(**1**) R_1=Me, R= 4-CNC_6H_4Br; (**2a**) 91%;
R= 4-MeC_6H_4OTf; (**2b**) 90%; (**2a-e**)
(**3**) R_1=BOC, R= 4-CNC_6H_4Br; (**2c**) 66%;
R= 4-MeC_6H_4OTf; no reaction;
(**4**) R_1=SEM, R= 4-CNC_6H_4Br; (**2d**) 94%;
R= 4-MeC_6H_4OTf; (**2e**) 66%;

Scheme 2

The synthesis of 3-substituted indoles has been studied by Ortar.[3] This was achieved by the palladium-catalysed reaction of 1-tosyl-3-tri-n-butylstannyl-indoles (**5**) with a variety of vinyl, aryl and heteroaryl triflates and halides. The catalyst used for the triflates was $Pd_2(dba)_3$, $AsPh_3$ in DMF. This generated the 3-substituted indoles (**6**) in 84-94% yield. The reactivity of the various halides was investigated by adding copper(1) iodide as cocatalyst (see later). An improvement in the rate of cross-coupling was observed with yields 54-92%.

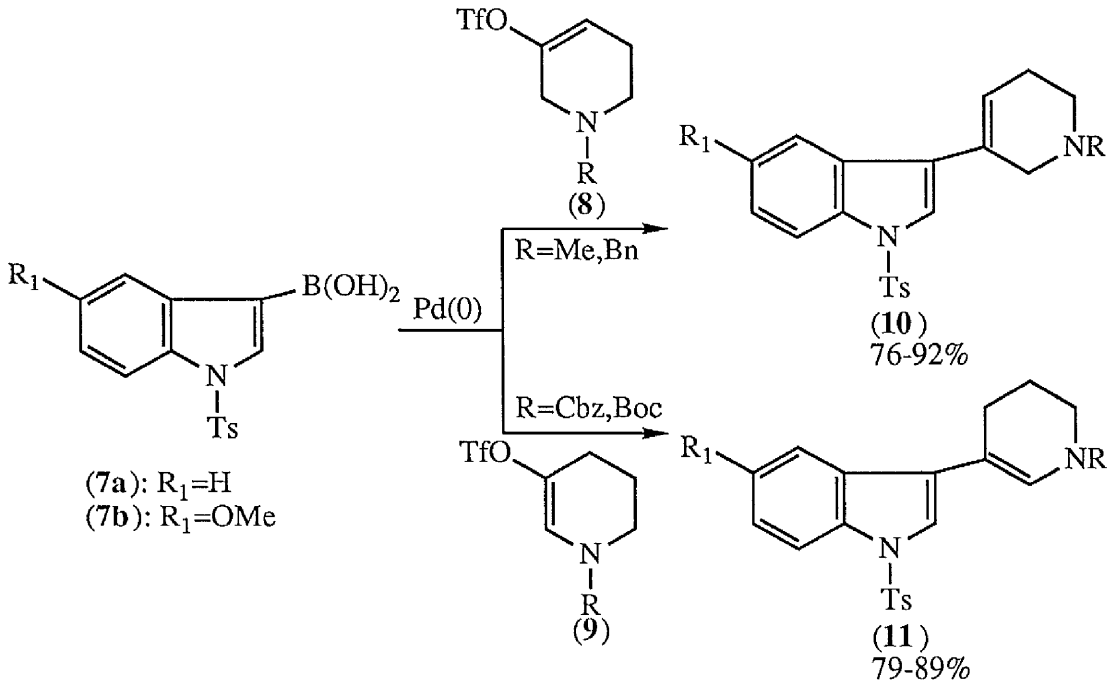


(**5a**): R_1=H
(**5b**): R_1=OMe

(**6**)

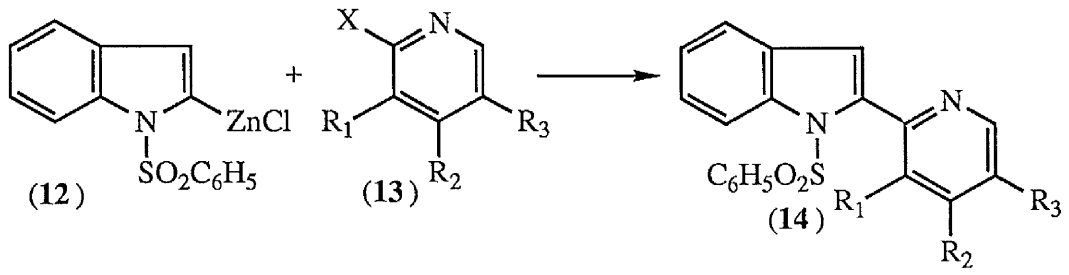
SCHEME 3

Martin[4] has investigated the palladium catalysed cross-coupling reaction between 3-indole boronic acids and vinyl triflates to introduce vinyl groups into indole 3-position. N-Tosyl-3-indolylboronic acids (**7**) were coupled with the triflates (**8**) or (**9**) in the presence of sodium bicarbonate, lithium chloride and tetrakis(triphenylphosphine)palladium(0) to give the desired products with good yields and high regioselectivity (scheme 4).



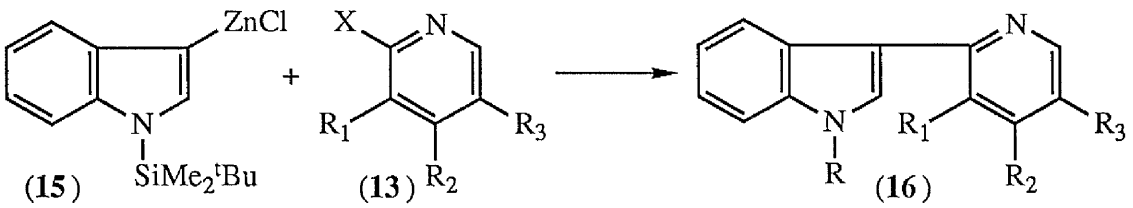
Scheme 4

Bosch[5] has reported an efficient and facile method for the preparation of 2-(2-pyridyl)indoles (**14**) based on the palladium(0)-catalysed coupling of a N-protected 2-indolylzinc derivative (**12**) with 2-halopyridines (**13**). 2-Chloro- and 2-bromopyridines, having alkyl or methoxy substituents, and 2-chloropyridines having electron-withdrawing nitro and groups, in general gave yields ranging from 70-90% (scheme 5).



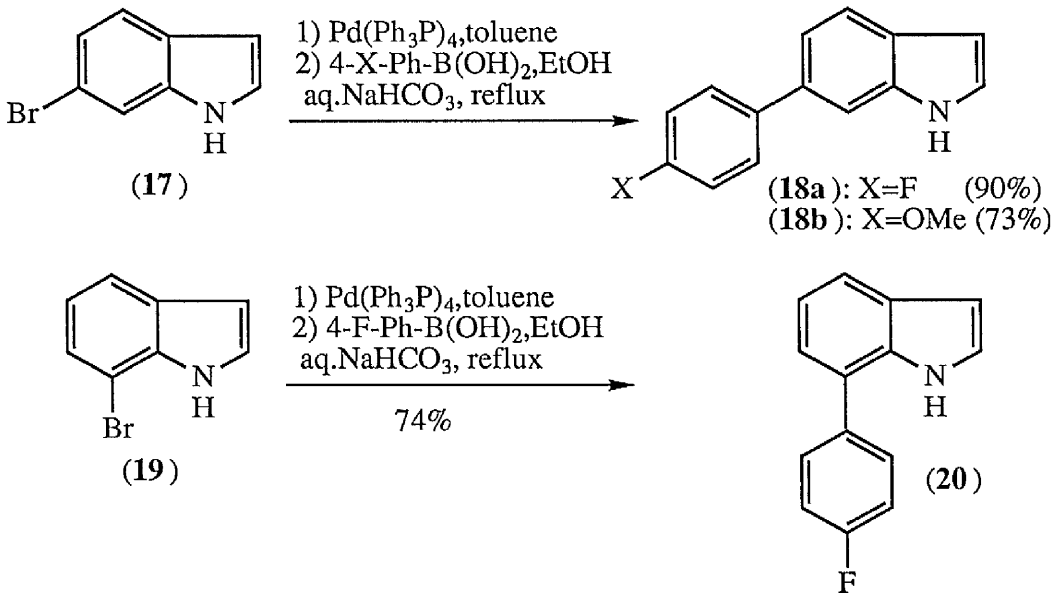
Scheme 5

Bosch[6] has developed this work further towards the synthesis of 3-(2-pyridyl)indoles (**16**). Using *tert*-butyldimethylsilyl group as the indole protecting group, the palladium-catalysed coupling of 1-(*tert*-butyldimethylsilyl)-3-indolylzinc chloride (**15**) with π-deficient or π-excedent heteroaryl halides were investigated. 2-Bromopyridines having electron-releasing alkyl or methoxy substituents, and 2-chloropyridines having strongly electron-withdrawing nitro or ester groups, were subjected to the cross-coupling conditions affording 3-arylindoles in excellent yield (77-97%) after removal of the protecting group (scheme 6). The catalyst system used in both these papers was "$Pd(PPh_3)_2$" generated *in situ* from $Pd(PPh_3)_2Cl_2$ and DIBAL-H in refluxing THF.



Scheme 6

Carrera[7] has investigated the palladium-catalysed cross-coupling of bromoindoles with various arylboronic acids using Suzuki methodology. Suzuki cross-coupling methodology[8] (scheme 7) was applied to the synthesis of 6-(4-fluorophenyl)indole (**18a**) and 6-(4-methoxyphenyl)indole (**18b**). 6-Bromoindole (**17**) was coupled directly with the appropriate boronic acid to give (**18a**) and (**18b**) in 90 and 73% yield respectively, no indole protection or functionalisation was required. The same method was employed for the preparation of 7-(4-fluorophenyl)indole (**20**) in 74% yield, using 7-bromoindole (**19**).



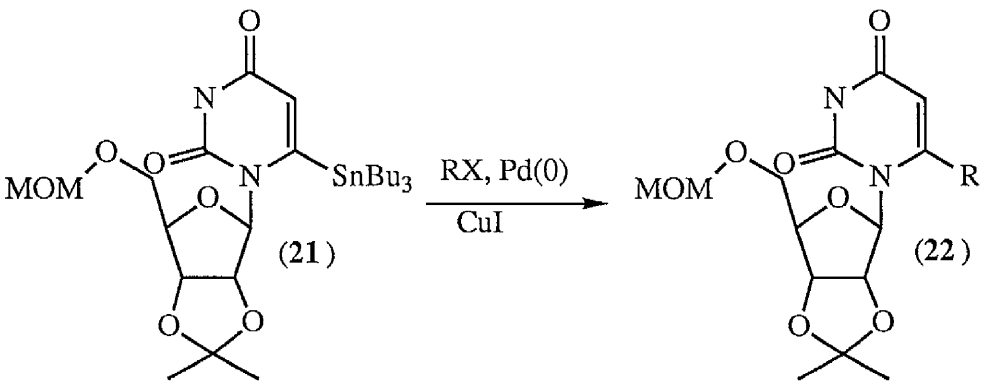
Scheme 7

1.3 The "Copper Effect" in the Stille Cross-Coupling Reaction

Farina[9] has studied the effect of adding copper(1) iodide on the kinetics of a typical Stille coupling. The "copper effect" is a complex phenomenon which is intimately dependent on the solvent and the palladium ligands used in a particular cross-coupling. With triphenylphosphine as palladium ligand, cocatalytic Cu(1) salts can yield a >100-fold rate increase over the traditional Stille conditions, but little effect was displayed when CuI was used in conjunction with a "soft" ligand, such as triphenylarsine. NMR studies suggest that CuI is an excellent scavenger for free ligand and since strong ligands in solution are known to inhibit the rate-limiting transmetallation, one effect of the copper salts is readily explained. In addition, however, when working in highly dipolar solvents like NMP and in the absence of strong ligands, unsaturated stannanes react with CuI to yield presumably an organocopper species, which then transmetallates to Pd(11).

Palmisano[10] investigated the palladium-catalysed reactions of 6-tri-n-butylstannyluridine derivative (**21**) with a variety of aryl, vinyl, alkynyl, and allyl halides for the synthesis of the corresponding cross-coupled products.

Iodobenzene was employed as a model partner and its coupling was attempted using various palladium complexes, such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(MeCN)_2Cl_2$, $Pd_2(dba)_3 \bullet CHCl_3$, and $Pd(OAc)_2$ as catalysts, in the presence of a ligand, such as triphenylphosphine (TFP) or tris(2-furyl) phosphine, in various solvents, such as THF, $CHCl_3$, DMF, N-methyl-2-pyrrolidinone (NMP). Although the results were condition dependent, low yields (≤35%) in the coupled product (**22**), messy reactions and long reaction times were uniformly observed. However, a spectacular improvement on the rate of the cross-coupling could be achieved by adding purified copper(1) iodide as cocatalyst. For instance, in the presence of the palladium catalyst alone and modelling the conditions on those of Farina[11] [$Pd_2(dba)_3$, TFP, NMP], the reaction proceeded very slowly giving 35% of (**22**) after 6 h (at 120°C), whereas in the presence of 5 mol% $Pd_2(dba)_3$ and 20 mol% CuI (Pd:ligand:CuI = 1:2:2), a good yield (72%) was obtained and the reaction took only 15 min (in THF at 60°C) to reach completion. Furthermore, $Pd(PPh_3)_4$ (10 mol%) in weakly co-ordinating solvent DMF (at 80°C) in the presence of CuI (20 mol%) also produced (**22**) in excellent yield (88%) (scheme 8).

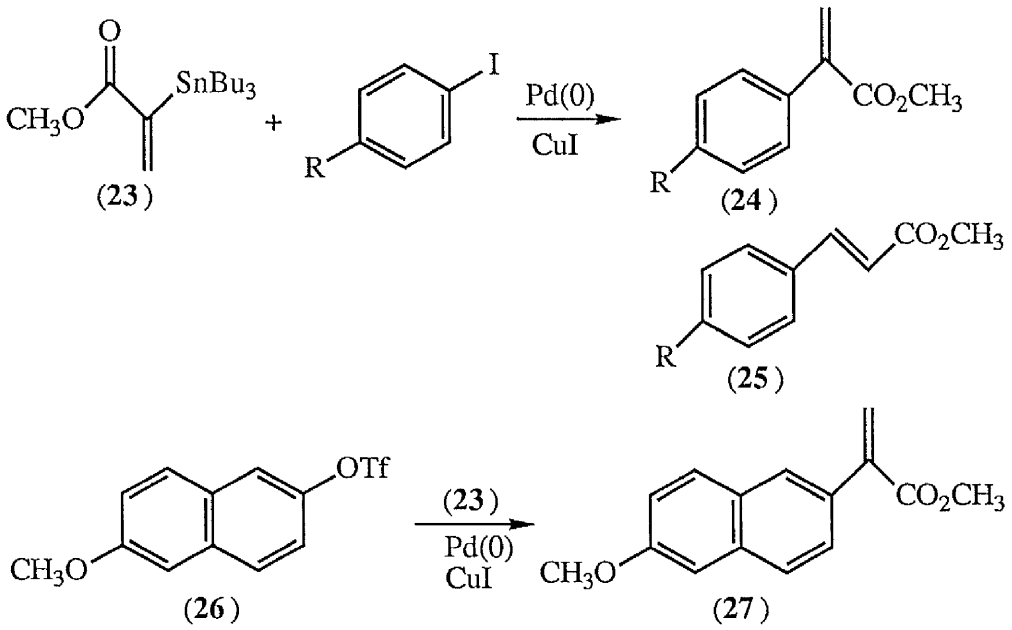


Scheme 8

The palladium-catalysed coupling of α-stannyl acrylate (**23**) to aryl iodides and triflates has been developed by Levin.[12] The coupling of (**23**) to substituted aryl iodides under Stille conditions[13] (Pd(0), toluene, 110°C) resulted in the formation of the undesired cinnamate ester (**25**), exclusively, presumably *via* a Heck reaction followed by protodestannylation. Using the copper(1) iodide

observation and the conditions described by Liebskind[14] (Pd(11), CuI, DMF), the coupling reaction proceeded at room temperature affording only the acrylate ester (24), in moderate yield. Optimising the conditions (10 mol% $Pd(PPh_3)_4$, stannane (23) 2.5 equivalents, CuI 0.75 equivalents in DMF at room temperature) generated the acrylate esters (24) in 42-92% yield.

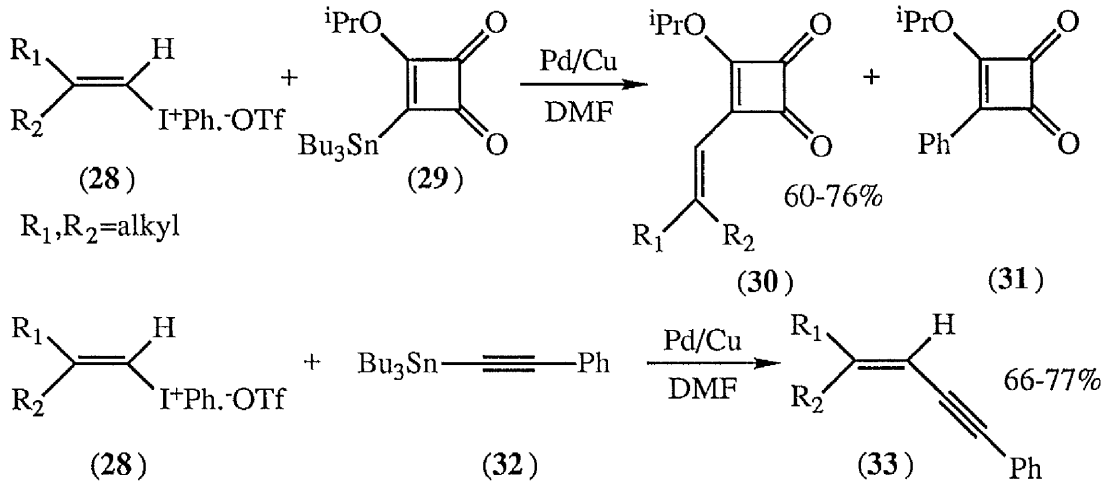
The palladium-catalysed coupling of stannyl acrylate (23) with aryl triflate (26) was achieved by modification of Stille's work on the palladium-catalysed coupling of vinyl triflates with organostannanes.[15] Lithium chloride was added to the usual reaction conditions ($Pd(PPh_3)_4$, CuI, DMF, room temp.) the coupling on triflate (26) proceeded to completion in 48 h providing a 71% yield of olefin (27) (scheme 9).



Scheme 9

Stang[16] has reported the palladium/copper catalysed coupling of trisubstituted alkenyl(phenyl)iodonium triflates with alkynl- and alkenylstannanes proceeded under mild conditions with retention of geometry of the alkenyl ligand of the iodonium salt. Coupling of the iodonium salts (scheme 10) occurs instantaneously at room temperature with 1.0 equivalent of alkenyl(phenyl)iodonium triflates (28), 1.0-1.5 equivalents of (alkenyl)- or

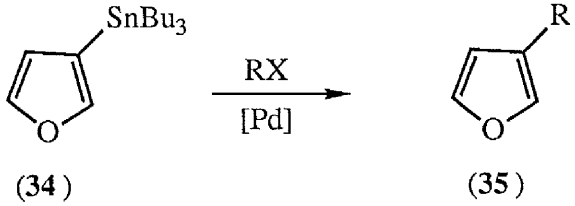
(alkynyl)stannane (**29, 32**), 5 mol% *trans*-benzyl(chloro)bis(triphenylphosphine)-palladium(11), and 8 mol% copper(1) iodide in DMF. Both copper and palladium were necessary for the desired reaction to occur.



Scheme 10

1.4 Palladium-Catalysed Cross-Coupling Reactions in Furans, Furanoid Glycals, Glucals and Pyranose Systems

The palladium-catalysed coupling reactions of 3-(tri-n-butylstannyl)furan (34) have been examined by Wong.[17] Stannane (34) coupled with aryl halides (e.g. PhI, PhBr, *p*-MeC_6H_4I), vinyl halides (e.g. (Z)- & (*E*)-MeCOCH=C(Me)Br, *trans*-PhCH=CHBr and *trans*-PhCH=CHI) and an allyl bromide (*trans*-$EtO_2CCH=CHCH_2Br$), catalysed by either $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$ or $Pd(MeCN)_2Cl_2$ in 60-80% yield (scheme 11).

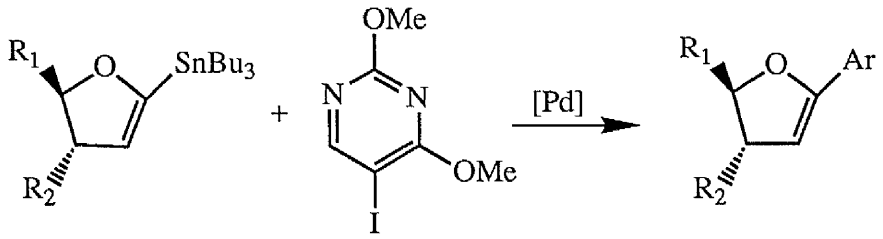


(34) (35)

Scheme 11

The palladium-mediated coupling of stannylated furanoid glycals with iodo aryl and heterocyclic derivatives has been developed by Daves[18] as a route to furanosyl C-glycosides. Stannylated furanoid glycals (**36a-d**) were coupled

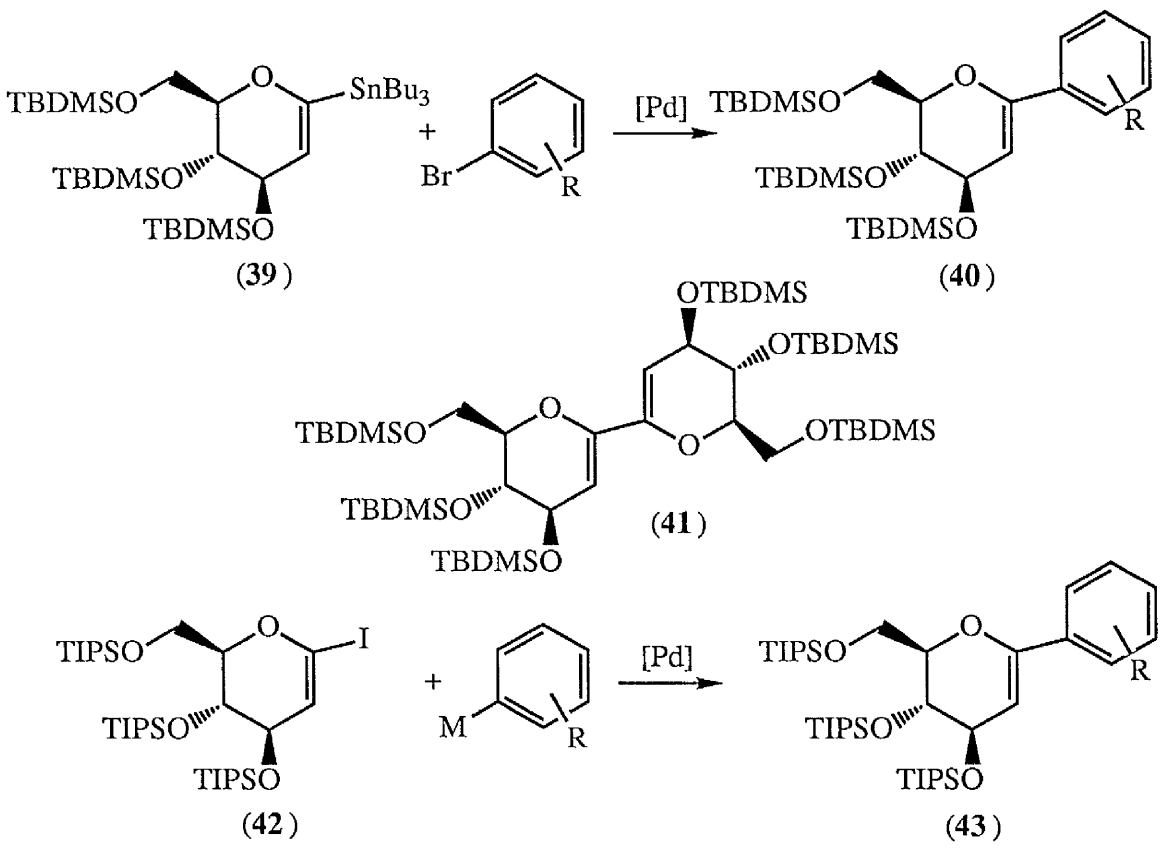
with iodoglycon derivatives (37) using triethylamine (2.0 eq.), triphenylarsine (0.2 eq.), palladium(11) acetate (0.1 eq.) in dry acetonitrile at 40-60°C (scheme 12).



(**36a**): R_1, R_2=H (**37**) (**38a**) 65%
(**36b**): R_1=CH_2OCPh_3, R_2=H (**38b**) 66%
(**36c**): R_1=CH_2OH, R_2=OH (**38c**) 54%
(**36d**): R_1=CH_2OBn, R_2=OBn (**38d**) 88%

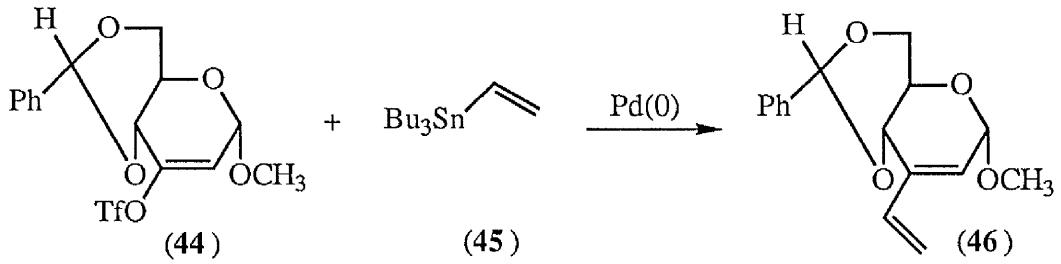
Scheme 12

Friesen[19] has prepared C-aryl glucals *via* palladium-catalysed cross-coupling methods. The C-aryl glucals have been prepared by the palladium-catalysed cross coupling of 1-tri-n-butylstannyl-3,4,6-tri-O-(*tert*-butyldimethyl-silyl)-D-glucal (**39**) and aryl bromides. The major by-product in all these reaction was the dimer (**41**), the product of the homocoupling of (**39**). Alternatively, the C-aryl glucals were obtained from the palladium-catalysed coupling of 1-iodo-3,4,6-tri-O-(triisopropylsilyl)-D-glucal (**42**) and a variety of metallated aromatics, including ArZnCl, $ArB(OH)_2$, and $ArB(OMe)_2$. The latter procedure afforded superior coupling yields (68-90%) under milder reaction conditions (scheme 13).



Scheme 13

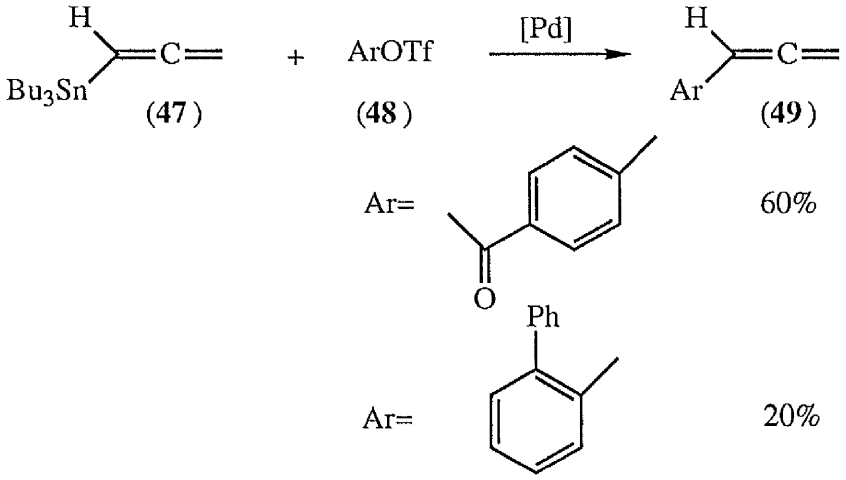
Enol triflate pyranose (44) have been shown by Voelter[20] to be versatile intermediates for the synthesis of semicyclic pyranoside conjugated dienes for carbocyclic systems. Reaction of (44) with tri-n-butylvinylstannane (45), tetrakis(triphenylphosphine)palladium(0) and lithium chloride according to Stille,[15] gave compound (46) in almost quantitative yield (scheme 14). With the same method, various conjugated compounds were obtained from triflate (44) in 80-100% yield with unsaturated tri-n-butylstannyl derivatives.



Scheme 14

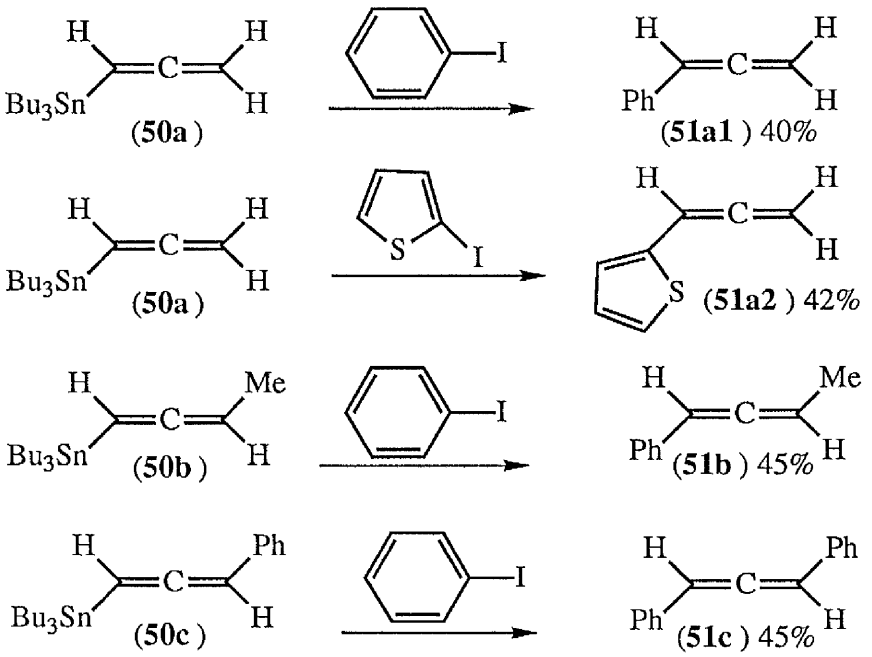
1.5 Palladium-Catalysed Cross-Coupling Reactions in Allenes, Enynes, Enediynes and Diarylalkynes Systems

Badone[21] has reported the application of the Stille reaction to the synthesis of aryl allenes (**49**) from the corresponding aryl triflates (**48**) and allenyltributyltin (**47**). The coupling protocol used was 2 mol% $Pd_2(dba)_3$, 8 mol% triphenylphosphine, 3 equivalents lithium chloride and 10 mol% purified CuI in DMF at 80°C. Tri-n-butylallenylstannane (**47**) was treated with a variety of aryl triflates. The coupling reaction was applicable to aryl triflates with various substituted functional groups. The yields were 60-71%, except for aryl triflates with electron-donating groups, which reacted only partially (20-31%) (scheme 15).



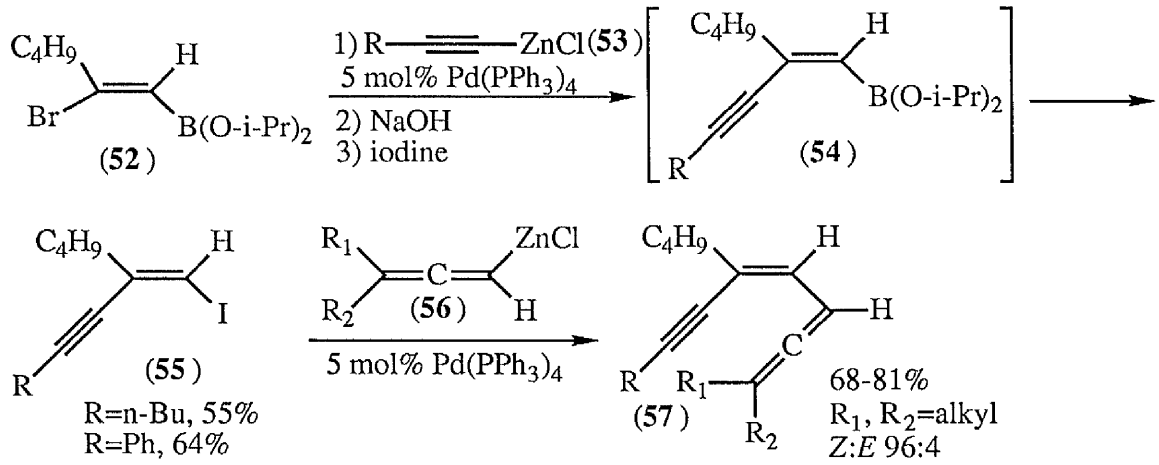
scheme 15

Braslau[22] has prepared substituted allenes by coupling stannyl allenes with aryl iodides under palladium(0) catalysis. The palladium(0)-catalysed coupling step was carried out using 3 mol% palladium dibenzylideneacetone chloroform complex and triphenylphosphine as ligand (Pd:ligand ratio of 1:4) in DMF at room temperature (scheme 16).



scheme 16

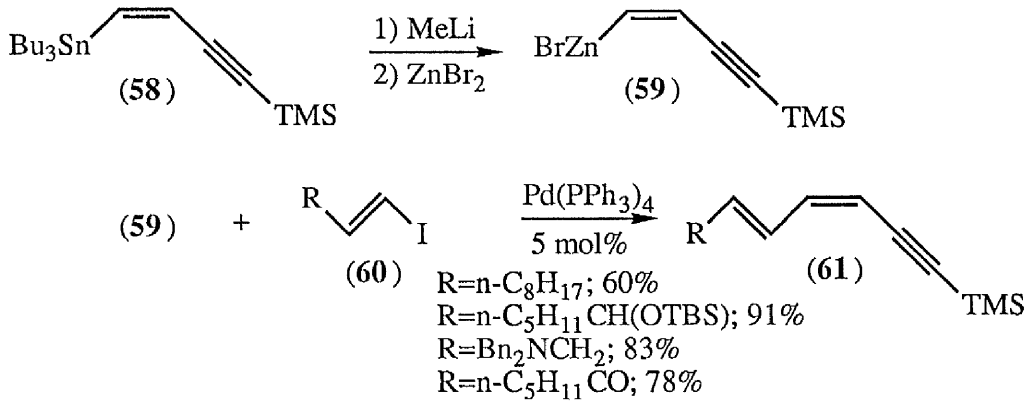
Wang[23] has developed a procedure for the synthesis of enyne-allenes. Alkenyl boronic ester (**52**) was palladium(0)-catalysed cross-coupled with acetylenic zinc chlorides and iodination furnished enyne iodides (**55**), which were then converted to enyne-allenes (**57**) by a second palladium(0)-catalysed reaction with allenic zinc chlorides (scheme 17).



scheme 17

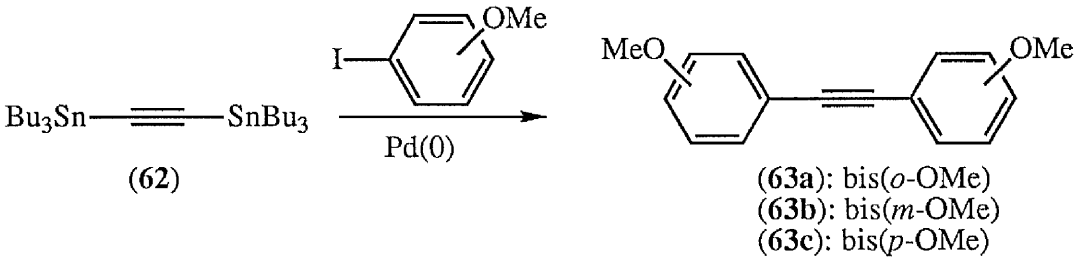
Lipshutz[24] used stannylated enynes as linchpins for palladium-catalysed couplings of unactivated vinyl iodides. Coupling reactions of unactivated vinyl

iodides (60) and zinc bromide derivative of 4-trimethylsilyl-1-buten-3-yne (59) afforded conjugated polyenynes in 78-91% yield (scheme 18).



Scheme 18

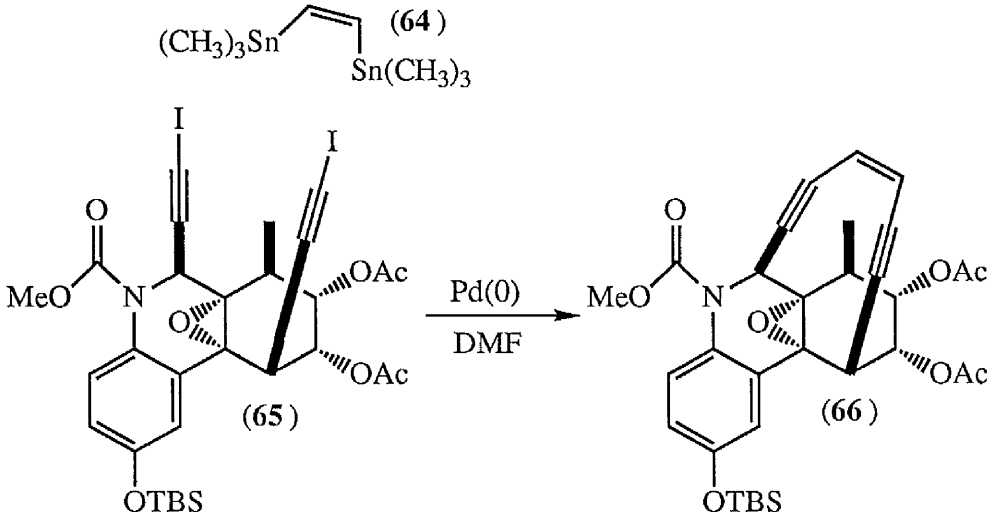
Cummins[25] has developed a synthesis of symmetrical diarylalkynes by double Stille coupling of bis(tri-n-butylstannyl)acetylene. The bis-stannane (62) and two equivalents of the iodoanisole were combined in dioxane with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and an excess of lithium chloride, and the reaction was refluxed for five hours (scheme 19). This provided the diarylacetylenes (**63a**, **63b**, and **63c**) in 85%, 70% and 71% yields respectively.



Scheme 19

Danishefsky[26] synthesised the deprotected phenol-acid ABC ring system of dynemicin A featuring a novel palladium-mediated double cross-coupling reaction to construct the cyclic enediyne. The bis-iodo acetylide (64) was treated with (Z)-bis(trimethylstannyl)ethylene (65) in the presence of tetrakis-

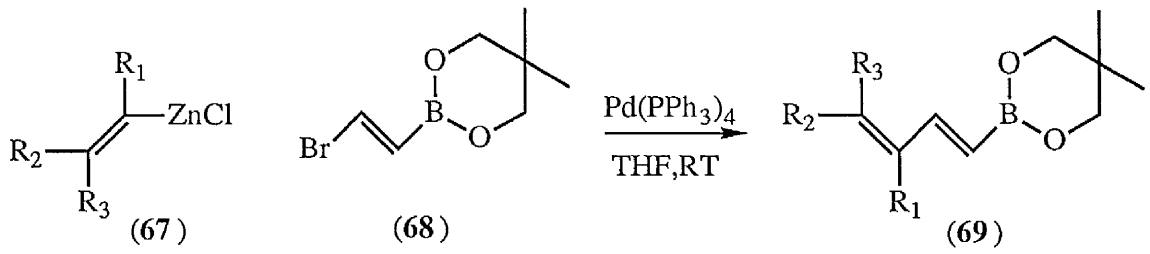
(triphenylphosphine)palladium(0) in DMF at 60°C. The enediyne (**66**) was obtained in 80% yield (scheme 20).



Scheme 20

1.6 Palladium-Catalysed Cross-Coupling Reactions of Various Organozinc Derivatives

Vaultier[27] has developed a general and highly stereoselective synthesis of 1-(dialkoxyboryl)-1,3-dienes that involves a palladium(0)-catalysed cross-coupling of boronic ester (**68**) with various alkenylzinc chlorides (scheme 21).

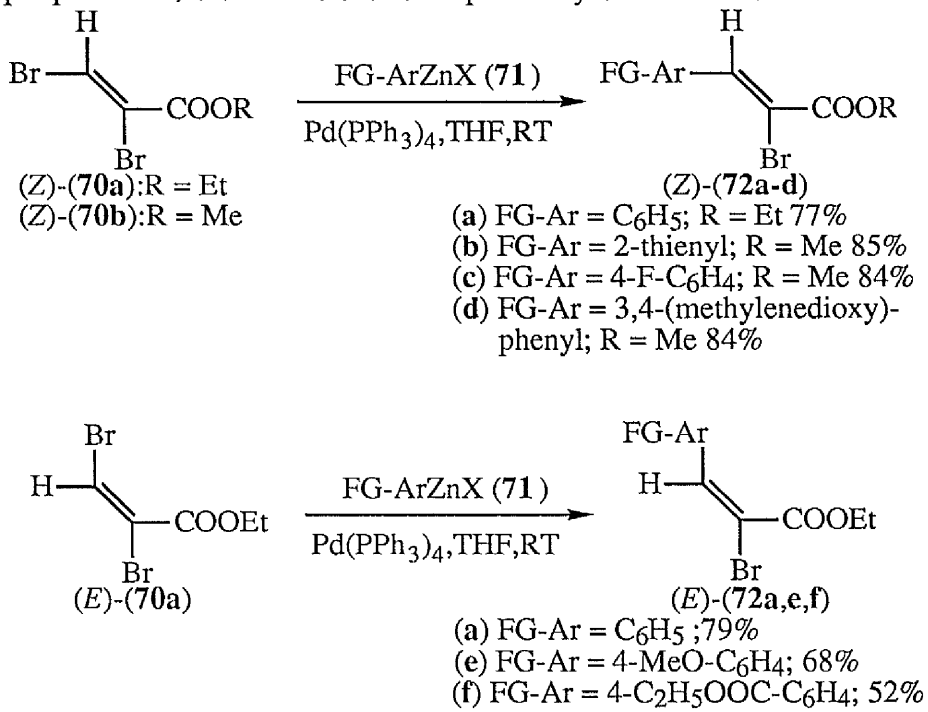


$R_1=R_2=R_3=H$	51%
R_1=Me, $R_2=R_3=H$	79%
$R_1=R_3=H$, R_2=TMS,	82%
R_1, R_2=2,3-dihydro-2(H)-pyran, $R_3=H$	66%

Scheme 21

Rossi[28] has prepared stereoisomerically pure (*Z*) and (*E*)-alkyl 2-bromo-3-(hetero)arylpropenoates, (*Z*)- and (*E*)-2 (**72**) by palladium(0)-mediated cross-

coupling reaction between (hetero)arylzinc halides (**71**) and (Z)- and (*E*)-alkyl 2,3-dibromopropenoates, (Z)- and (*E*)-(**70**) respectively (Scheme 22).



(Z)-(**70a**):R = Et
(Z)-(**70b**):R = Me

(Z)-(**72a-d**)

(**a**) FG-Ar = C_6H_5; R = Et 77%
(**b**) FG-Ar = 2-thienyl; R = Me 85%
(**c**) FG-Ar = 4-F-C_6H_4; R = Me 84%
(**d**) FG-Ar = 3,4-(methylenedioxy)-phenyl; R = Me 84%

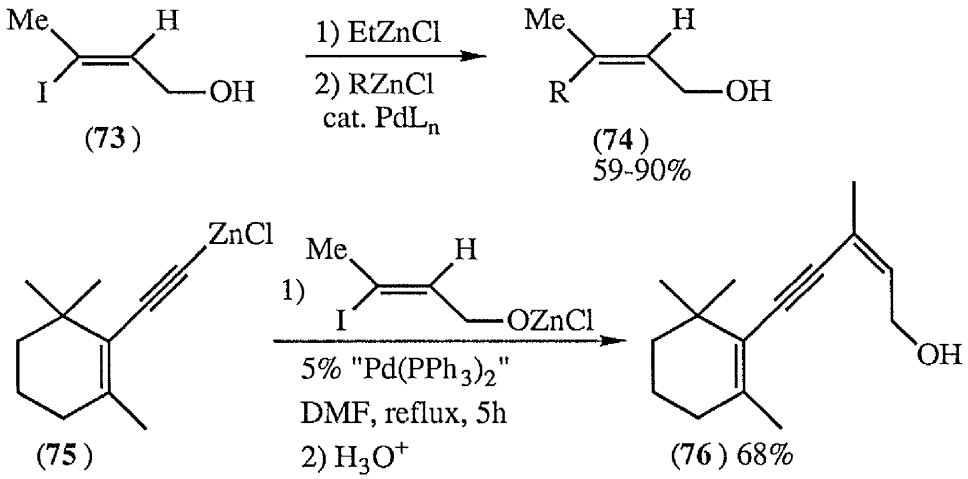
(*E*)-(**70a**)

(*E*)-(**72a,e,f**)

(**a**) FG-Ar = C_6H_5 ;79%
(**e**) FG-Ar = 4-MeO-C_6H_4; 68%
(**f**) FG-Ar = 4-C_2H_5OOC-C_6H_4; 52%

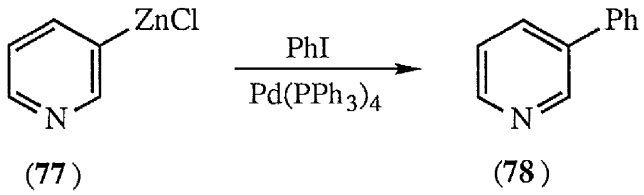
Scheme 22

Negishi[29] has reported the reaction of zinc protected (Z)-iodo-2-buten-1-ol with organozincs in the presence of 1-5 mol% of a Pd complex e.g. $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ and n-BuLi (2 equivalents), in DMF provides a highly stereoselective and high yielding procedure for preparing (Z)-3-methyl-2-alken-1-ols (scheme 23). The free hydroxyl group was protected by treating with ethylzinc halide generated *in situ* by the treatment of EtMgBr with dry $ZnCl_2$. In this manner, the sacrificial use of one equivalent of a more precious organozinc reagent could be avoided.



scheme 23

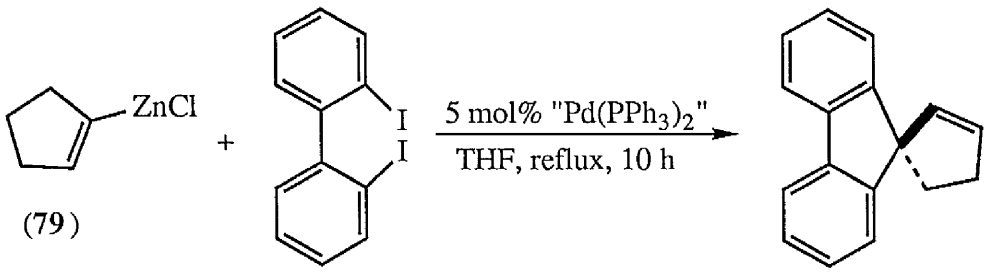
Sakamoto[30] has reported the first direct preparation of π-deficient heteroarylzinc halides from the corresponding heteroaryl halides (such as iodo- and bromo-substituted pyridine, pyrimidine and quinoline) with activated zinc, and the palladium-catalysed arylation and benzoylation of the zinc reagents. For example, 2-pyridinylzinc iodide (77) was reacted with iodobenzene in the presence of tetrakis(triphenylphosphine)palladium(0) at room temperature for 66 h to afford 2-phenylpyridine (78) in 77% yield (scheme 24). Unsymmetrical bi-heteroarenes such as bi-pyridines, pyridinyl-quinolines and pyridinyl-pyrimidine were synthesised in 60-84% yield.



Scheme 24

Katz[31] has developed the palladium-catalysed coupling of 2,2'-dihalobiaryls with metallated cyclopentenes for the synthesis of spiro[cyclopentene-1,9'-[9H]fluorene]s. In the presence of palladium catalysts, one of the two carbons attached to halogen in 2,2'-diiodobiphenyl (80) couples with unsaturated organometallics, after which the other adds to the newly

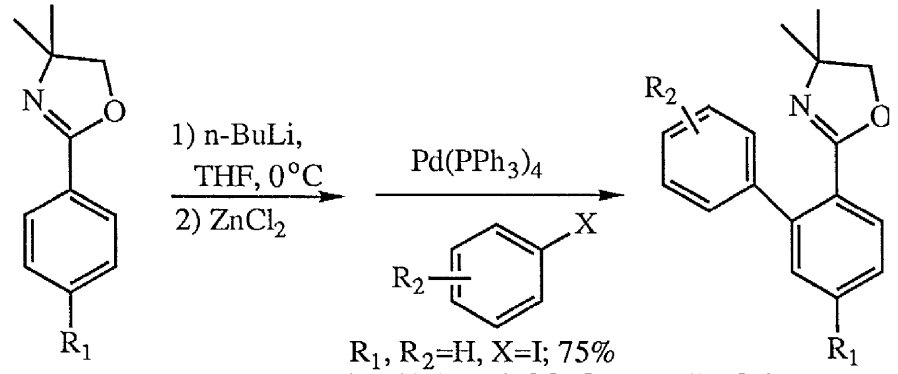
incorporated double bond (scheme 25). The same kind of product is formed by the analogous binaphthyl in 66% yield.



(79) (80) (81) 85%

Scheme 25

Koch[32] has reported a combined directed metallation-transmetallation-cross-coupling methodology for the regiospecific preparation of biologically active biaryls using aryl oxazolines or benzamides. The approach involved the directed metallation of an appropiate carboxy protecting group followed by transmetallation with zinc chloride then palladium-catalysed cross-coupling with either aryl triflates or aryl iodides (scheme 26). The reaction tends to work better for electron deficient aryl acceptors and is tolerant of many sensitive functional groups. Substitution is also acceptable on the aryl oxazoline.



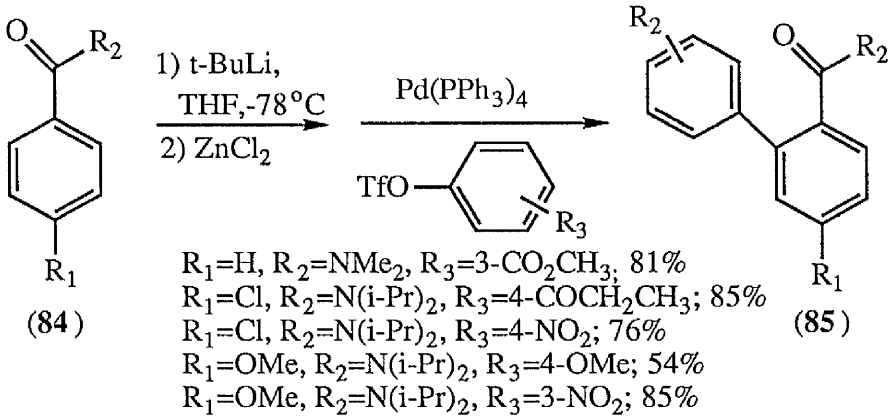
(82)

R_1, R_2=H, X=I; 75%
R_1=H, R_2=4-CO_2CH_3, X=I; 70%
R_1=H, R_2=4-OCH_3, X=I; 48%
R_1=H, R_2=3-NO_2, X=I; 54%
R_1=Cl, R_2=$COCH_2CH_3$, X=OTf; 72%

(83)

Scheme 26

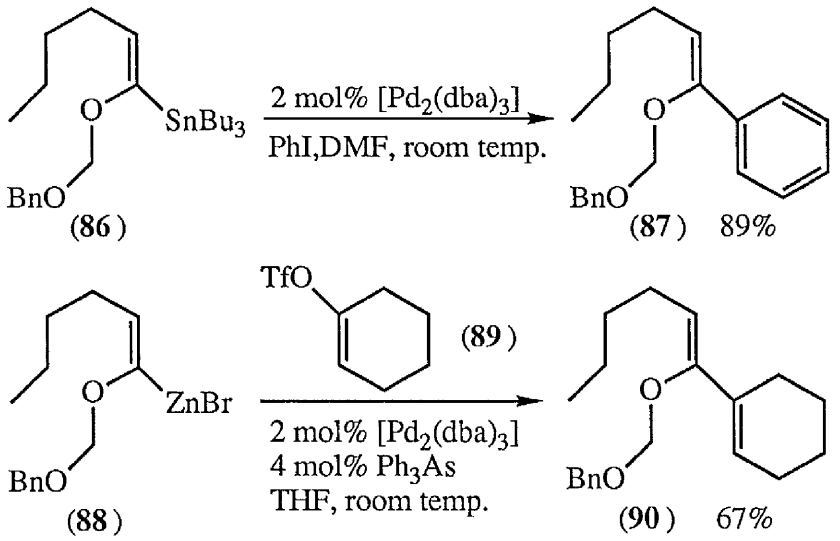
This methodology was applied to the cross-coupling reactions of dialkyl-benzamides with aryl triflates (scheme 27).



Scheme 27

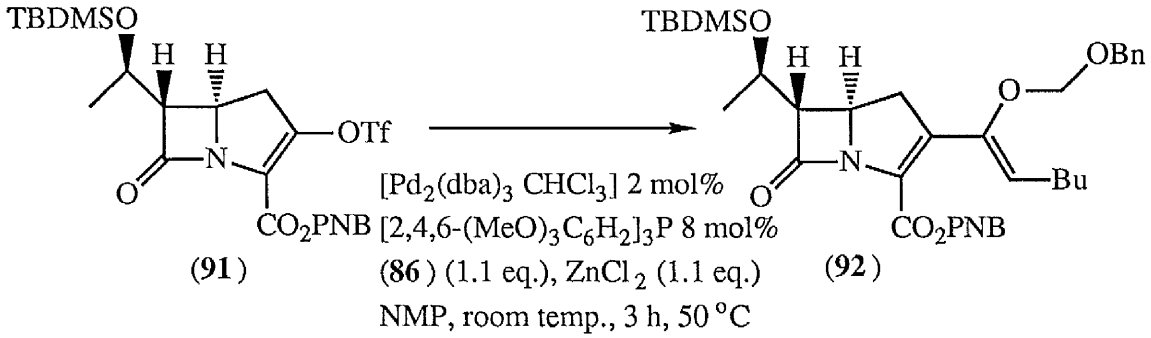
1.7 Palladium-Catalysed Coupling Reactions with Corresponding Organotin and Organozinc Reagents

Kocienski[33] has studied the palladium(0)-catalysed cross-coupling reactions of α-alkoxyalkenylstannanes and α-alkoxyalkenylzincs. The direct coupling of stannane (86) with iodobenzene using $[Pd_2(dba)_3]$ in DMF[34] afforded enol ether (87) in 89% yield. Application of this method to the coupling of stannane (86) and cyclohex-1-enyl trifluoromethanesulphonate (89) gave 30-40% of impure dienol ether (90). Both the yield (53%) and the quality of the product improved by adding 8 equivalents of lithium chloride. However, the best results were obtained using organozinc reagent (88) with 2 mol% $[Pd_2(dba)_3]$, 4 mol% $AsPh_3$, in THF at room temperature (scheme 28).[35,36]



Scheme 28

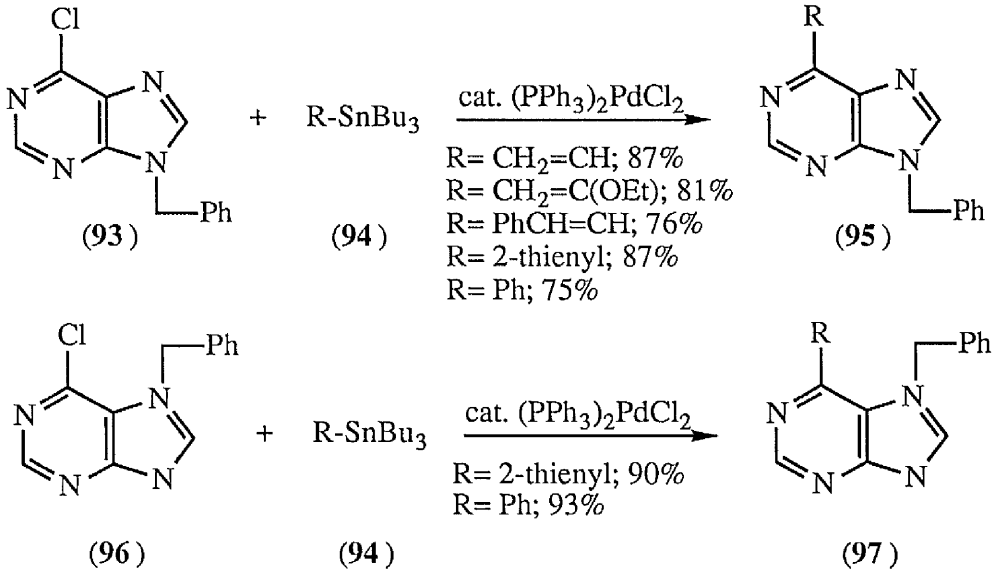
Neither method mentioned above could be applied to the coupling of stannane (86) (or its zinc derivative (88)) to the carbapenem trifluoromethane - sulphonate (**91**) (scheme 29); instead a third protocol was required whose success depended on the presence of the ligand tris(2,4,6-trimethoxyphenyl)-phosphine in conjunction with $[Pd_2(dba)_3]\bullet CHCl_3$ in N-methyl-2-pyrrolidinone as solvent.[37] The coupled carbapenem (**92**) was obtained in 50% yield.



Scheme 29

Gundersen[38] has reported N-9 and N-7 benzylated 6-halopurines participate in palladium-catalysed cross-coupling reactions with organotin and organozinc derivatives. Organostannanes are the reagents of choice for the introduction of alkenyl and aryl substituents, but organozinc compounds are the reagents of choice for the introduction of alkyl groups.

9-Benzyl-6-chloropurine (**93**) was coupled with a number of organostannanes (**94**) in the presence of bis(triphenylphosphine)palladium(11) chloride in DMF. Alkenyl- and arylpurines were obtained in 75-85% when the reaction mixtures were heated to 80-110°C. 7-Benzyl-6-chloropurine (**96**) was subjected to the set of reaction conditions as the N-9 alkylated isomer (**93**). The coupling with organostannanes (**94**) occurred more readily with the 7-substituted purine (**96**) than with the 9-substituted isomer (**93**), and the 6-substituted products (**97**) were isolated in higher yield (90-93%) compared to the couplings with purine (**93**) (scheme 30).

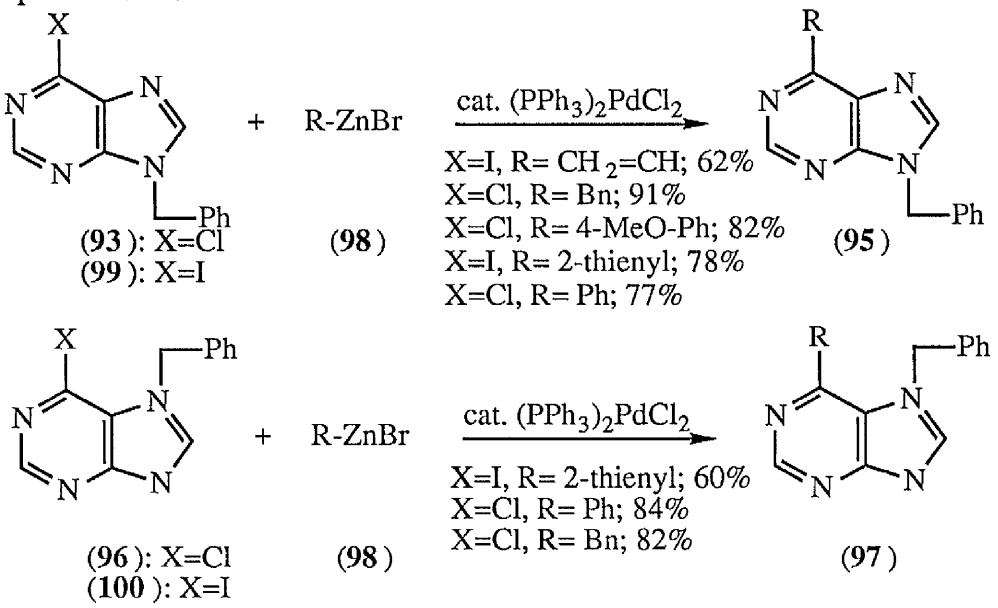


scheme 30

9-Benzyl-6-chloropurine (**93**) was reacted with a number of organozincs (**98**) in the presence of tetrakis(triphenylphosphine) palladium(0) at 50°C in THF (scheme 31). The chloropurine (**93**) reacted with phenyl-, benzyl- and alkylzinc reagents to afford coupling products (**95**) in 77-91% yield. Switching to 9-benzyl-6-iodopurine (**99**) as substrate, allowed coupling with vinyl- and thienylzinc reagents.

In the coupling reactions of organozinc reagents (**98**) with 7-benzyl-6-chloropurine (**96**), the phenyl-, benzyl-, and methylzinc bromides afforded the

coupled products (97) in 73-84% yield. Reaction of the thienyl reagent required 6-iodopurine (100).

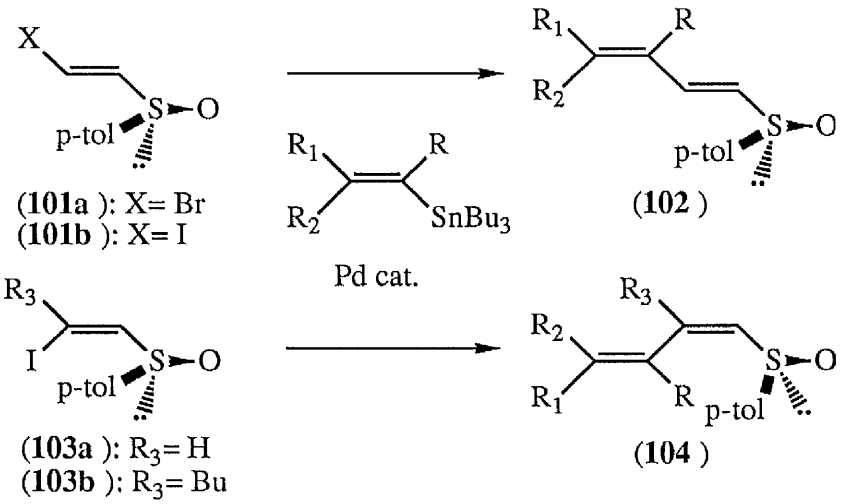


Scheme 31

1.8 Preparation of Dienyl and Enynyl Sulphoxides *via* Palladium-Catalysed Cross-Coupling Reactions

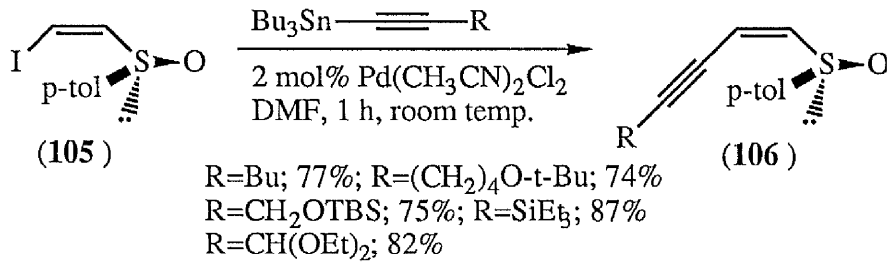
Paley[39] has reported the palladium-catalysed coupling of enantiopure 2-halovinylsulphoxides and (*E*)-vinyl stannanes proceeds in a stereospecific manner to afford enantiopure 1-sulphinyldienes. (*E, E*)-1-Sulphinyldienes (**102**) were obtained by the reaction of (*E*)-2-bromovinylsulphoxide (**101a**) with one equivalent of vinyltributylstannane by treating with $Pd_2(dba)_3 \bullet CHCl_3$ (2 mol%) and triphenylphosphine (8 mol%) in refluxing THF. These conditions applied to various vinyltri-n-butylstannanes generated (**102**) in 80-90% yield.

(*Z, E*)-Sulphinyldienes (**104**) were obtained *via* the (*Z*)-isomer (**103**) in the same way except the catalyst system used was $Pd(CH_3CN)_2Cl_2$ (2 mol%), in DMF at room temperature, in 76-93% yield (scheme 32).



Scheme 32

Paley[40] has also used Stille coupling procedures in the synthesis of (Z)-1-sulphinyl-1-en-3-ynes. Various stannylalkynes were coupled to (Z)-2-iodovinyl-sulphoxide (**105**) (scheme 33). Treatment of (**105**) with 1-tributylstannyl-1-hexyne (1.3 equivalents) in the presence of $Pd(CH_3CN)_2Cl_2$ (2 mol%), in DMF/THF (95:5) at room temperature afforded the desired enynyl sulphoxide (**106**) in 77% yield.

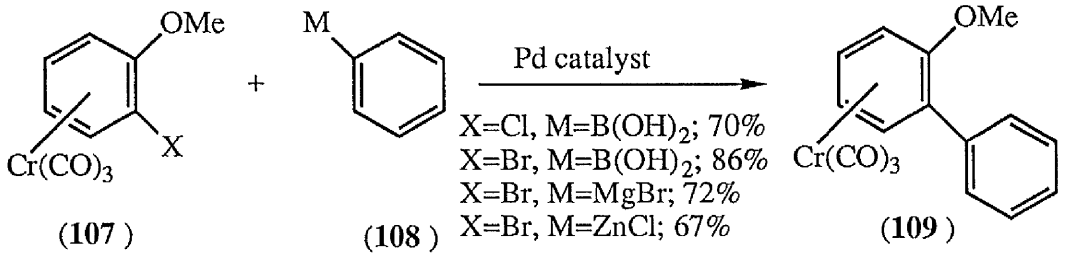


Scheme 33

1.9 Palladium-Catalysed Cross-Coupling Reactions with Arene-Chromium Tricarbonyl Complexes

Uemura[41] has reported that the cross-coupling of tricarbonyl(η^6-halobenzene) chromium complexes with aryl metals in the presence of palladium(0) catalyst produced mono-$Cr(CO)_3$ complexes of biphenyl compounds. (Arylhalide)$Cr(CO)_3$ complexes (**107**) were coupled with aryl metal (**108**) for the preparation of mono-$Cr(CO)_3$ complexes of *ortho* substituted bi-

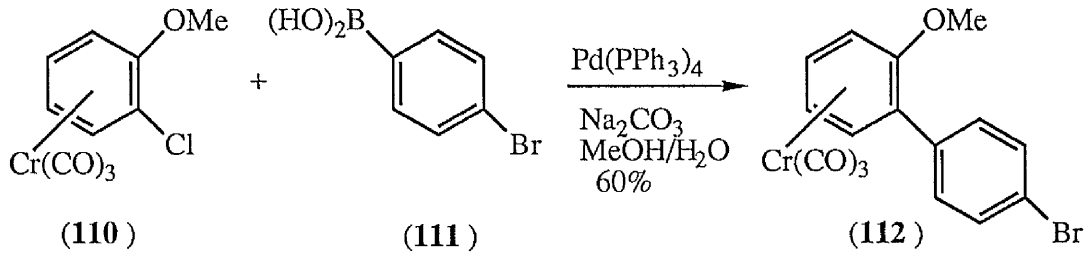
phenyl compounds (**109**) (scheme 34). The oxidative addition of the carbon-halogen bond of the arylhalide to the palladium(0) is accelerated by the coordination of an electron-withdrawing tricarbonylchromium group to the arene group.



(**107**) (**108**) (**109**)

Scheme 34

The cross-coupling reaction of (*o*-chloroanisole)$Cr(CO)_3$ (**110**) with *p*-bromophenylboric acid (**111**) proceeded to give the hetero-coupling product (**112**) in 60% yield without the formation of a homo-coupling product of *p*-bromophenylboric acid (scheme 35). In the oxidative addition step of the carbon-halogen bond of the arene to the palladium(0), C-Cl bond of the chromium complex (**110**) is preferred over the C-Br bond of (**111**), despite the presence of an electron donating methoxyl group at the *ortho* position of the chromium complex.

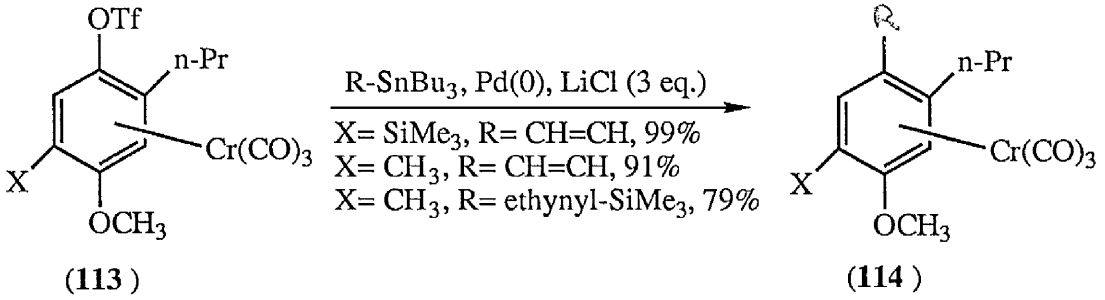


(**110**) (**111**) (**112**)

Scheme 35

Wulff[42] has reported the first Stille cross-couplings of arene-$Cr(CO)_3$ triflate complexes and organostannanes which occur with retention of the $Cr(CO)_3$ group under mild conditions even for highly hindered and electron rich aryl triflates. Arene-$Cr(CO)_3$ triflate complexes (**113, 115**) undergo Stille cross-coupling reactions with vinyl-, alkynyl-, and alkyl-stannanes under mild

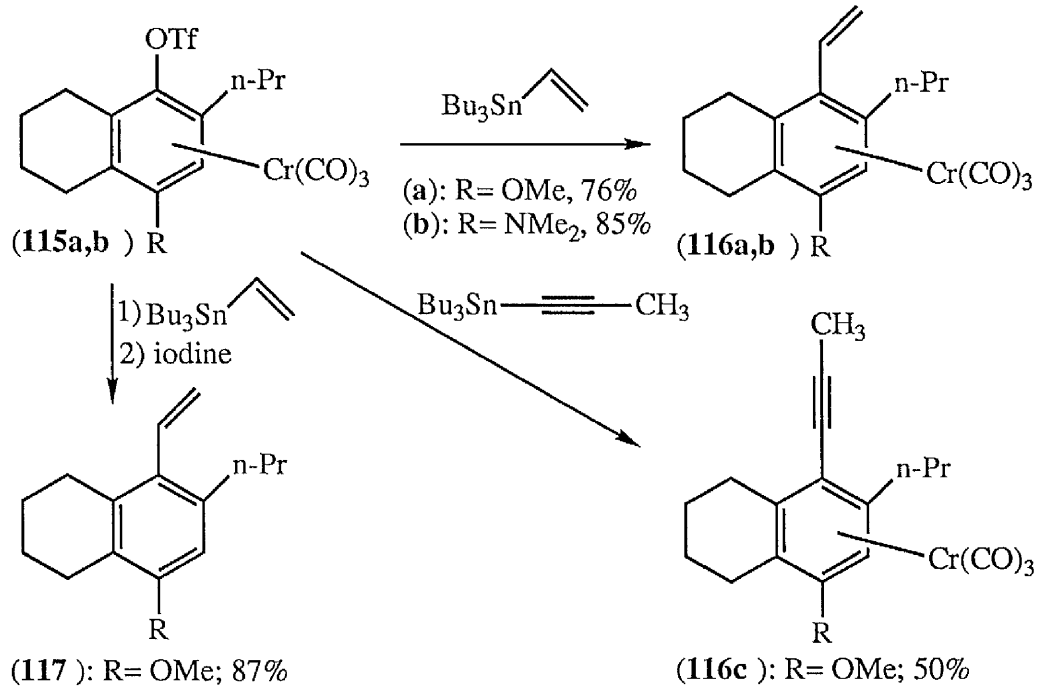
conditions (2 mol% $Pd(PPh_3)_4$, 1.05 equiv. of stannane, THF, reflux) to afford cross-coupled arene-$Cr(CO)_3$ complexes (**114, 116**) (schemes 36 and 37).



(**113**) (**114**)

scheme 36

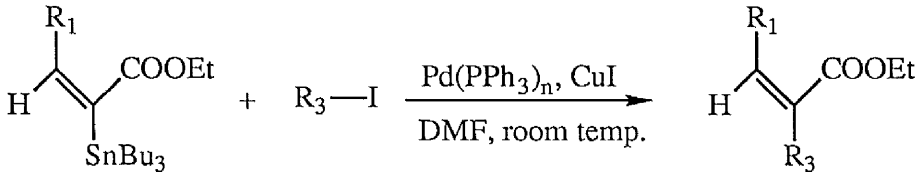
The efficacy of the chromium tricarbonyl group in promoting cross-coupling with electron rich aryl triflates was tested with *p*-(dimethylamino)-substituted triflate complex (**115b**). This complex underwent cross-coupling using the standard conditions with vinyltri-n-butyltin to give an 85% yield of arene-chromium tricarbonyl complex (**116b**). Metal-free cross-coupled products were obtained by oxidising the reaction mixture with excess iodine (scheme 37).



Scheme 37

1.10 Miscellaneous Palladium-Catalysed Cross-Coupling Reactions

Rossi[43] has developed the synthesis of stereoisomerically pure trisubstituted α,β-unsaturated esters using two different protocols. The first one involved the palladium(0)/copper(1)-mediated cross-coupling reaction for the synthesis of 2-(hetero)aryl and 2-(1-alkenyl) substituted ethyl 2-alkenoates, (**120**) (R_1 = alkyl, (hetero)aryl; R_2 = H; R_3 = aryl, alkenyl) from stannylesters (*E*)-(**118**) (R_1 = alkyl; R_2 = H) and aryl or alkenyl iodides (**119**) (scheme 38). The stannylesters (*E*)-(**118**) were reacted with 0.4 equivalents of iodide (**119**), in DMF at room temperature in the presence of 10 mol% of $Pd(PPh_3)_4$ and 0.75 equivalents of CuI.

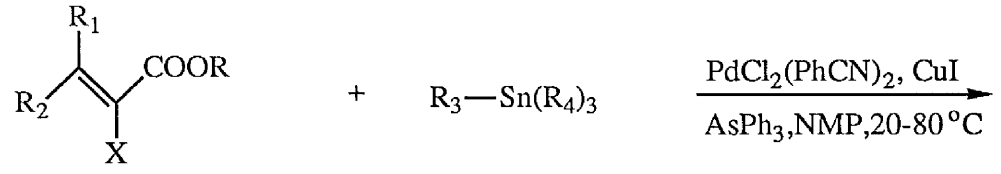


(*E*)-(**118**) (**119**) (**120**)

R_1=alkyl, aryl; R_3= aryl, alkenyl; 66-87%

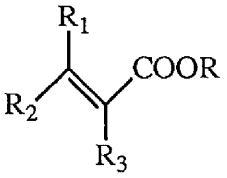
Scheme 38

The second protocol, which prepared stereodefined 2-aryl, 2-methyl, 2-(1-alkenyl) as well as 2-acyl substituted α,β-unsaturated esters, was based on the cross-coupling reaction between alkyl (Z)- or (*E*)-2-halo-2-alkenoates and organostannanes in NMP, in the presence of 5 mol% $PdCl_2(PhCN)_2$, 10 mol% $AsPh_3$ and 10 mol% CuI (scheme 39).



(*E*)-(**121**): R_1= alkyl, aryl; R_2=H
R= Et, Me; X=I
(*Z*)-(**122**): R_1= H; R_2= alkyl, aryl;
R= Et, Me; X= Br, I

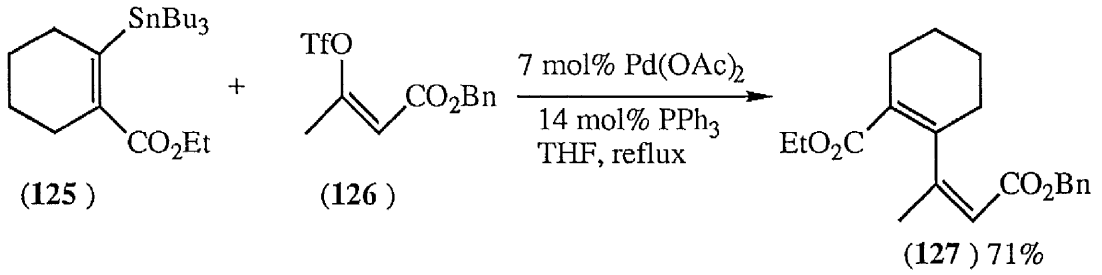
(**123**): R_3= alkenyl, aryl, Me;
R_4= Bu, Me



(*Z*)-(**124**): R_3= CH_2=CH; 69-84%
R_3= (Z)-EtOOC-C-CH=CH; 30%
R_3= Ph; 52%
(*E*)-(**124**): R_3= CH_2=CH; 80-85%
R_3= Ph, X=Br; 66%

Scheme 39

Houpis[44] has accomplished the synthesis of electron deficient dienes by palladium-catalysed coupling of β-stannyl-α,β-unsaturated esters with β-trifluoromethanesulphonyl-α,β-unsaturated esters and ketones. The optimum coupling conditions for the coupling of stannane (**125**) and enol triflate (**126**) were 7 mol% $Pd(OAc)_2$ and 14 mol% PPh_3 in THF at reflux (scheme 40).



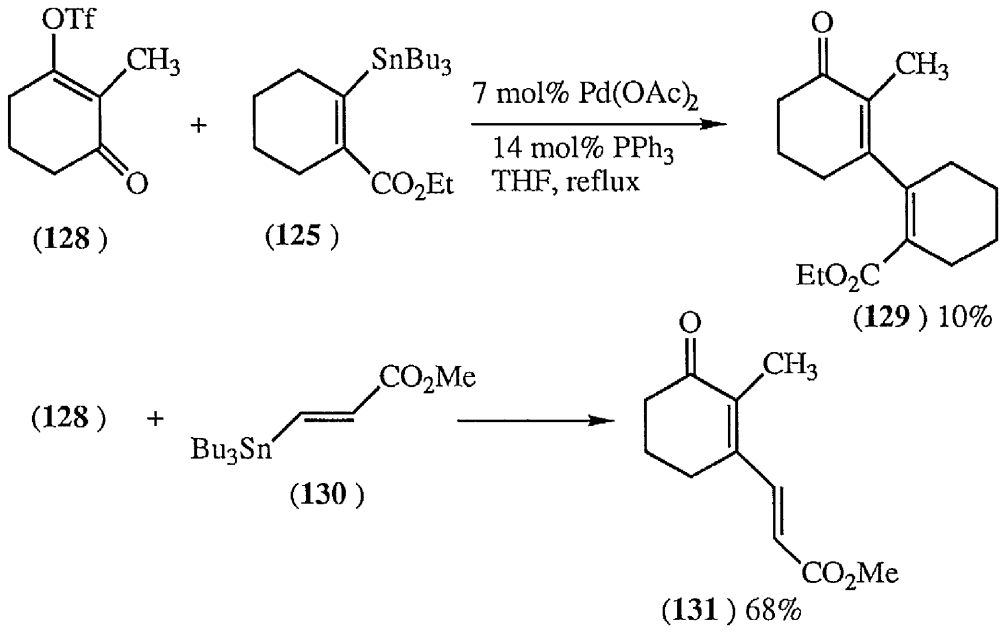
(**125**)

(**126**)

(**127**) 71%

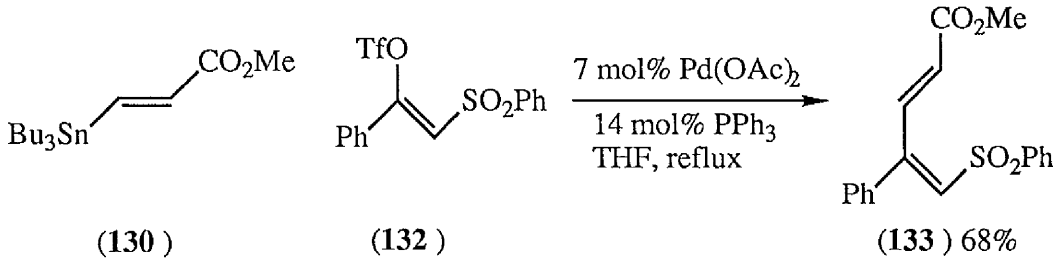
Scheme 40

The reaction of enone (**128**) with (**125**) gave only a small amount of the heterocoupled product (**129**) (10%) whereas stannane (**130**) gave the coupled product (**131**) in 68% yield. This shows the difference in reactivity between (*E*)- and (Z)-β-stannyl enoates (scheme 41).



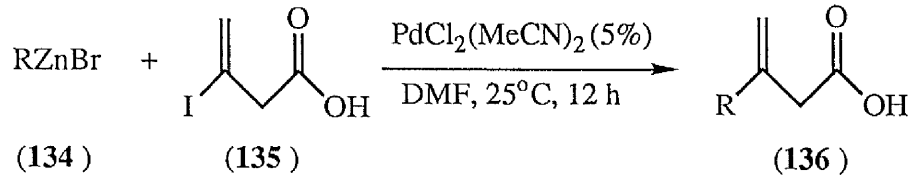
Scheme 41

The coupling of sulphone (**132**) with (**130**) gave the coupled product (**133**) in 68% yield under the standard reaction conditions (scheme 42).



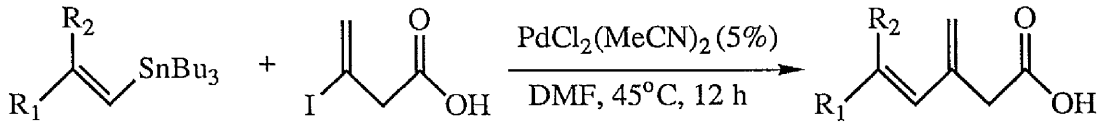
Scheme 42

Duchêne[45] has reported the synthesis of 3-substituted but-3-enoic acids *via* palladium-catalysed cross-coupling reaction of 3-iodobut-3-enoic acid (**135**) with organozinc and organotin compounds using $PdCl_2(MeCN)_2$ as catalyst and DMF as solvent. Alkyl, phenyl, benzyl, alkynyl and allyl organozinc reagents (**134**) were coupled with vinyl iodide (**135**) in 65-90% yield (scheme 43).



Scheme 43

However, the introduction of vinylic groups required the use of organozinc reagents in a solution of THF or HMPA, both of which are not appropriate in this reaction. So vinyltin compounds were used instead together with 5 mol% of dichlorobis(acetonitrile)palladium(11) using DMF as a solvent. The Stille cross-coupling reaction afforded dienes (**138**) in 50-82% yield (scheme 44).

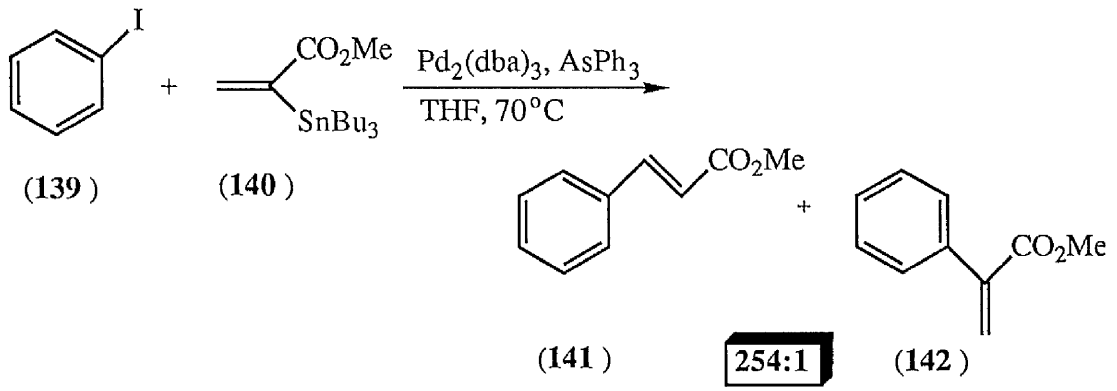


(**137**) (**135**) (**138**)

(**138a**): R_1=R_2= H, 60%; (**138b**): R_1= Ph, R_2= H, 82%;
(**138c**):R_1= $CH(OEt)_2$, R_2= H, 50%

Scheme 44

Busacca[46] has investigated the anomalous Stille reactions of methyl α-(tri-n-butylstannyl)acrylate and presented evidence of a palladium carbene intermediate. Contrary to expectations, the major product from the coupling reaction of vinylstannane (**140**) and iodobenzene (**139**) was found to be methyl cinnamate (**141**), while the Stille product (**142**) was only formed in trace amounts (scheme 45).

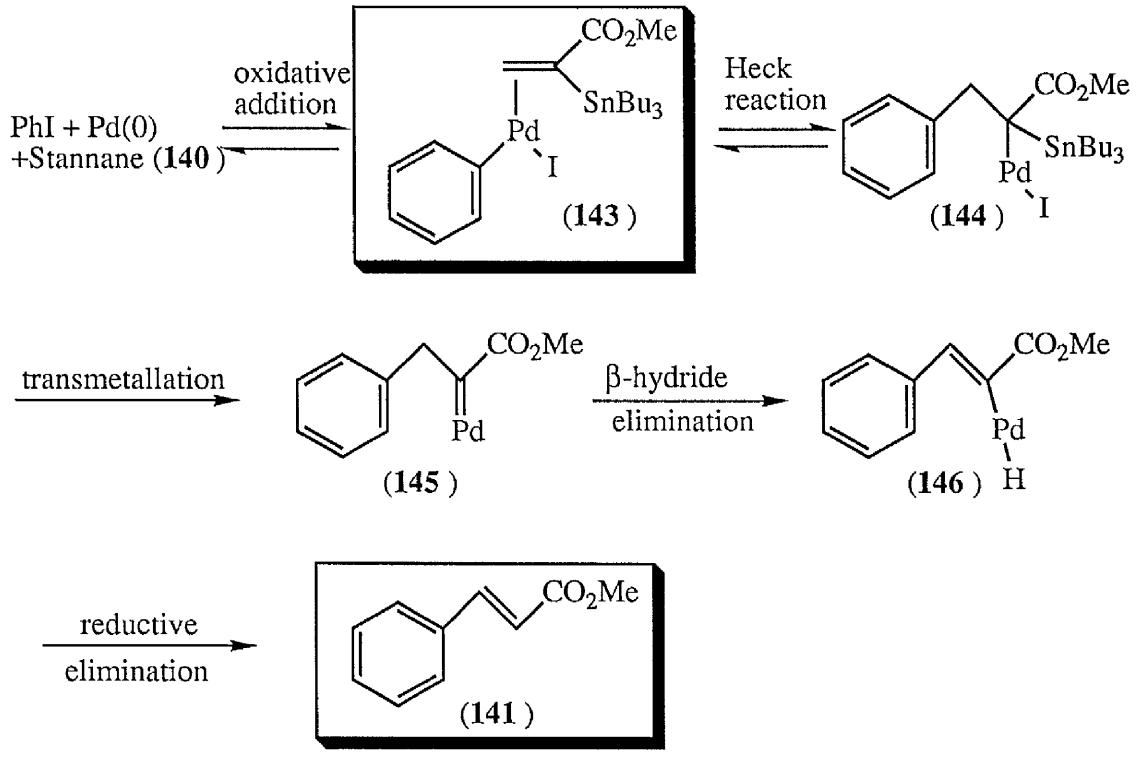


(**139**) (**140**) (**141**) (**142**)

Scheme 45

The proposal for this reaction mechanism is shown in scheme 46. Reversible oxidative addition of Pd(0) to iodobenzene (**139**) and subsequent

formation of a π-complex with stannane (**140**) would lead to species (**143**). Transmetallation of (**143**) within the normal Stille reaction mechanism would lead to a σ-vinyl species, which should rapidly eliminate methyl atropate (**142**) and regenerate Pd(0). However, the complex (**143**) may also be considered to be a precursor for the putative Heck adduct (**144**). Busacca proposed that the formation of methyl cinnamate may involve a 4-centre transmetallation of (**144**) to palladium(11) carbene intermediate (**145**), in which the cabomethoxy group acts as a stabilising moiety. The proposed carbene (**145**) would be expected to undergo a β-hydride elimination to palladium hydride (**146**), which could then reductively eliminate to the observed product (**141**) (scheme 46).

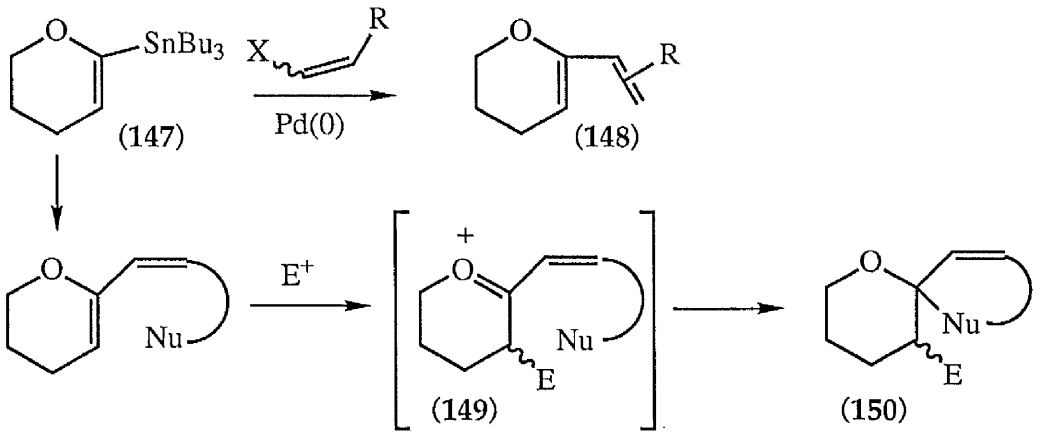


Scheme 46

CHAPTER 2

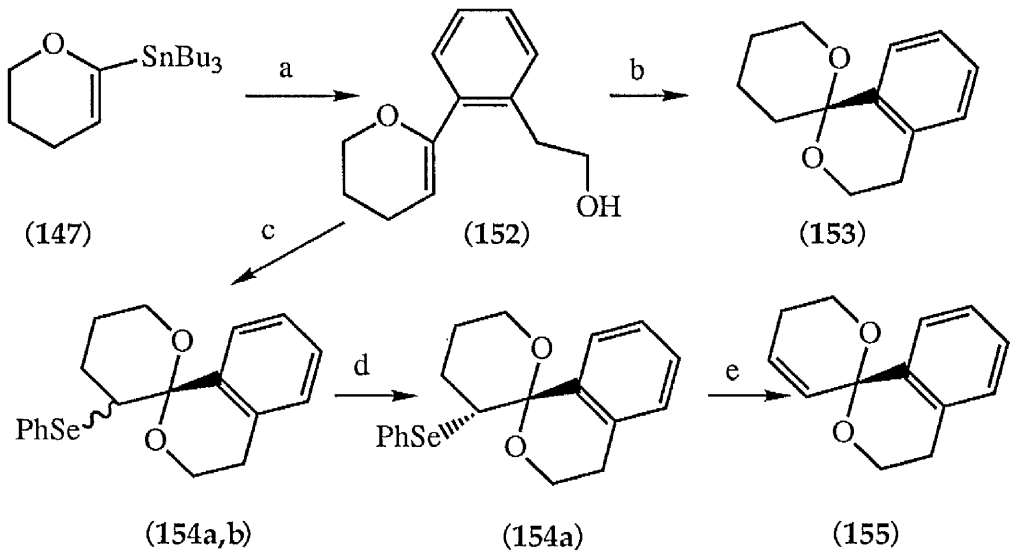
INTRODUCTION/PROPOSED APPROACH

Recently, our group reported that stannanes such as (147) undergo clean palladium-mediated cross-coupling reactions with a variety of vinyl (aryl) halides to afford the heterocyclic systems (148).[47] Subsequent addition of a suitable electrophilic trigger generates an oxonium cation (149) which undergoes intramolecular capture with a suitably positioned nucleophilic centre affording the functionalised spirocyclic species (150),[48] scheme 47.



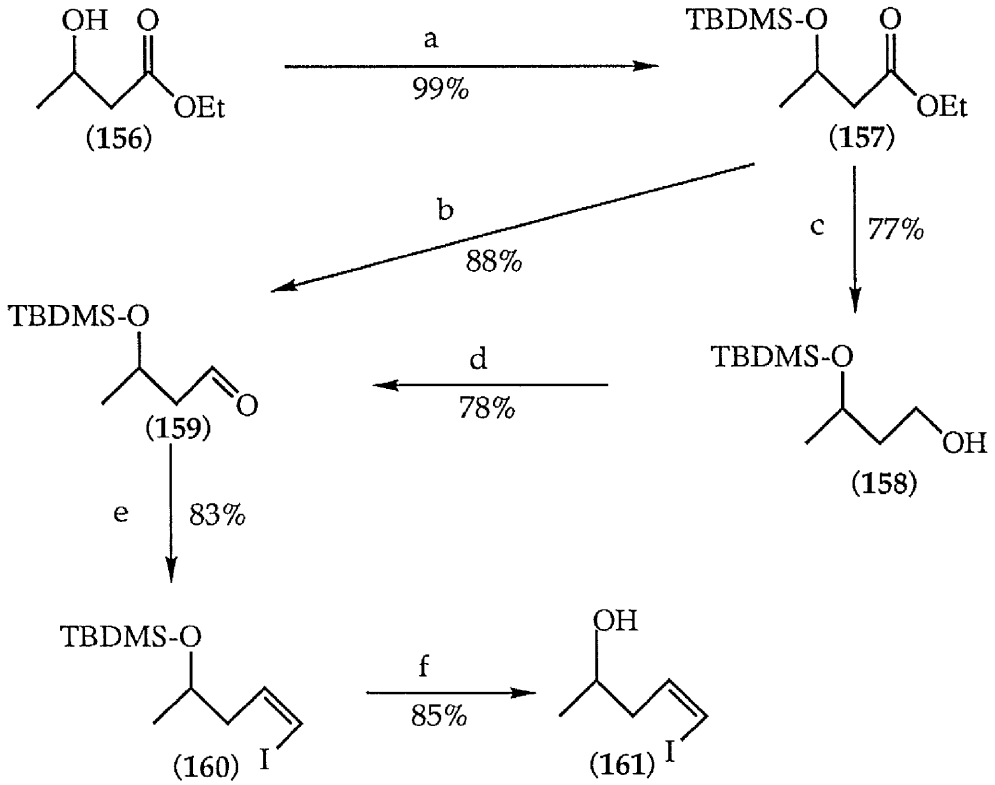
Scheme 47

Coupling of the stannane (147) with the bromide (151) afforded the enol ether (152) in 71% yield. Upon dissolution in "aged" $CDCl_3$ the alcohol (152) underwent spontaneous cyclisation to the spirocycle (153) in quantative yield. Alternatively, selenium induced cyclisation afforded a 1:1 mixture of the selenides (154a, b) (96%), which upon dissolution in "aged" $CDCl_3$ equilibrated to the diastereomerically pure spiroacetal (154a) in quantitative yield. Oxidation of the selenide (154a) using Davis's[49] oxaziridine afforded the unsaturated spirocycle (155) (99%) (scheme 48).

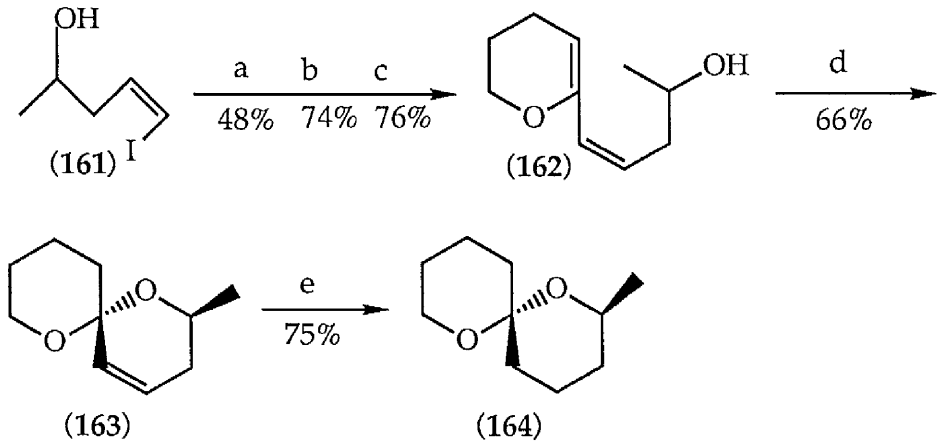


Scheme 48. *Reagents*: (a) (2-BrC_6H_4)CH_2CH_2OH, (**151**), $Pd(OAc)_2$, Et_3N, CH_3CN; (b) $CDCl_3$; (c) PhSeCl, pyridine, CH_2Cl_2; (d) $CDCl_3$; (e) Davis oxaziridine, pyridine, CH_2Cl_2, 40°C.

Our research group have demonstrated[50] that racemic ethyl-3-hydroxybutyrate (**156**), may be converted to its aldehyde (**159**) and Wittig olefination using Stork's[51] procedure afforded the iodo-olefin (**160**) (*Z*:*E* = 8.2:1). Deprotection yielded the iodo-olefin (**161**) which was subsequently coupled obtaining the diene (**162**) and spirocyclised to afford the unsaturated spirocycle (**163**).

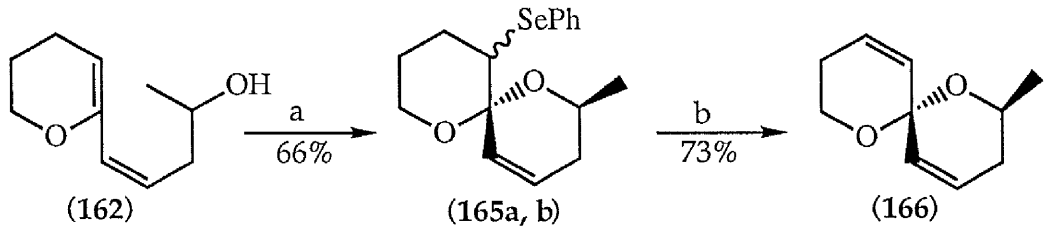


Scheme 49. *Reagents*: (a) DBU, TBDMS-Cl, CH_2Cl_2, 0°C, 3h; (b) DIBAL-H, THF, 0°C, 3h; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C; (d) DIBAL-H (1.6 eq.), toluene, -80°C, 1 h; (e) Ph_3P=CHI, THF, -78°C (generated from $[Ph_3PCH_2I]^+I^-$, $NaN(SiMe_3)_2$, rt); (f) CSA (cat.), MeOH.



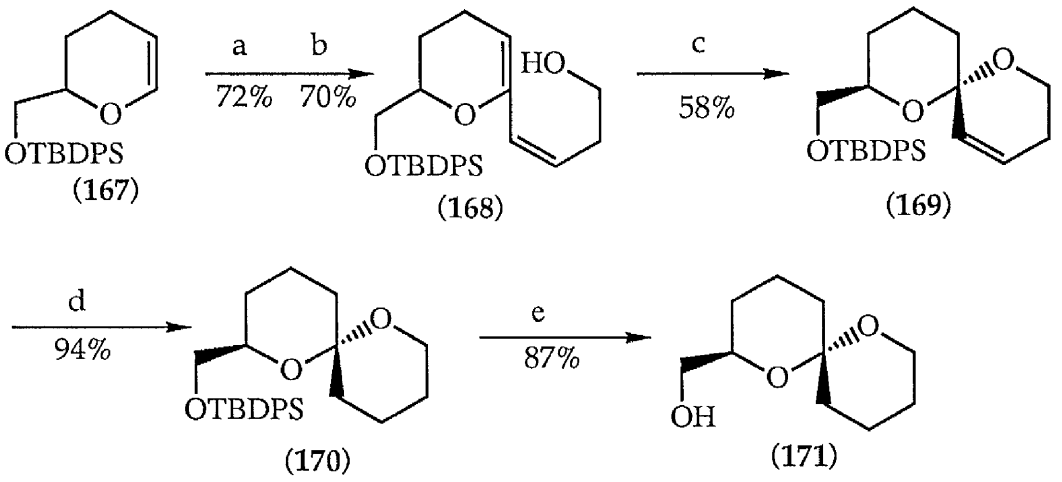
Scheme 50. *Reagents*: (a) **(181)**, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, CH_3CN, 80°C, 1.5 h; (b) **(182)**, Pd(0) (generated from $PdCl_2(PPh_3)_2$, DIBAL-H, 0°C); (c) **(182)**, $Pd(PPh_3)_4$; (d) CSA (cat.), CH_2Cl_2, 1 h; (e) H_2, Pd/C, EtOAc.

An alternative method of cyclisation of diene (**162**) was effected using phenylselenium chloride/pyridine.[52] This gave a mixture of diastereomeric selenides (**165a, b**) (11:7) in 66% yield. The diastereomeric mixture equilibrated in $CDCl_3$ after three days to afford selenide (**165a**) with the selenide moiety in the equatorial position. Oxidation of the selenide (**165a**) using an oxaziridine afforded the unsaturated spirocycle (**166**) (73%) (scheme 51).

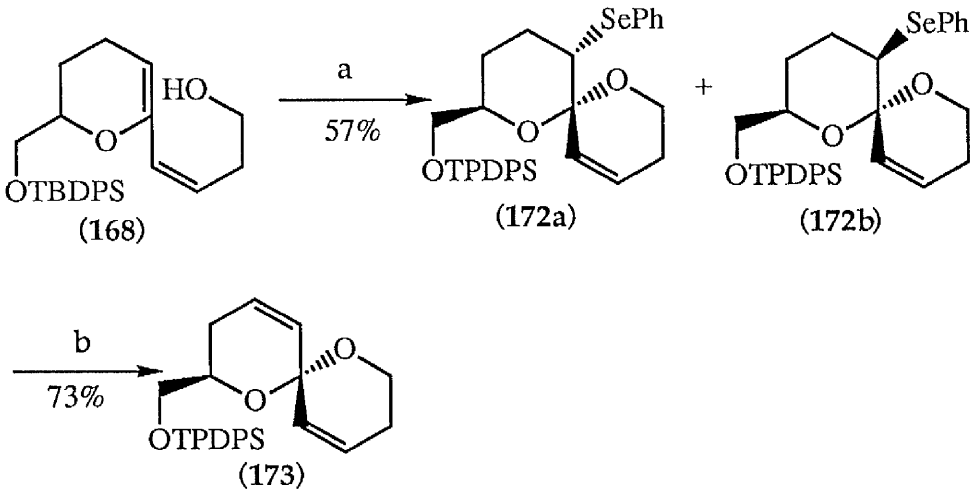


Scheme 51. *Reagents* (a) PhSeCl, pyridine, CH_2Cl_2, -78°C, 1h; (b) $PhSO_2N(O)CHPh$, pyridine, $CHCl_3$, reflux, 15 h.

We have extended this work to more functionalised systems. These results are consistent with previous model studies and are shown below.

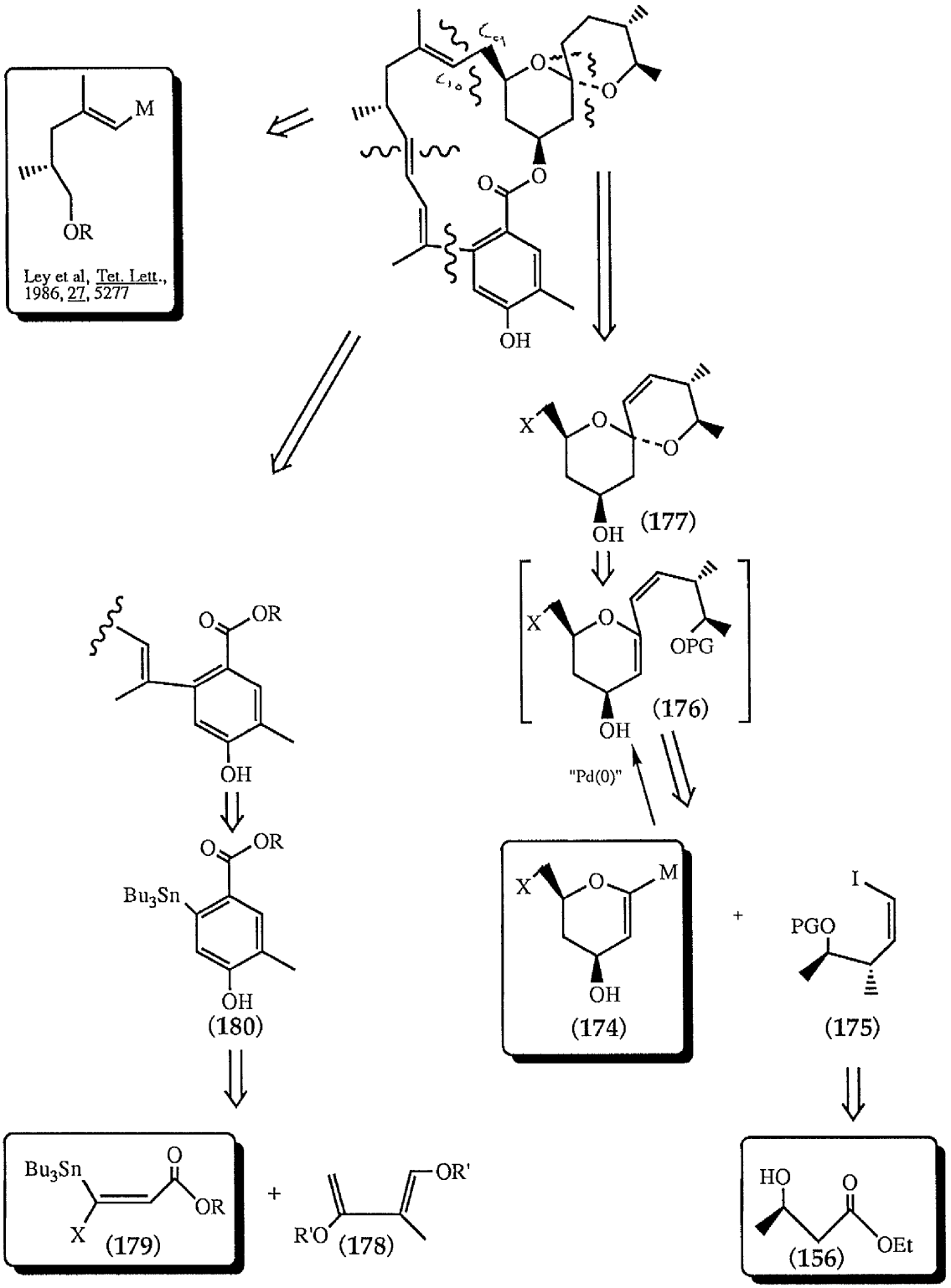


Scheme 52. *Reagents*: (a) (**182**) analogue, Pd(0) (generated from $PdCl_2(PPh_3)_2$, DIBAL-H, 0°C); (b) (**182**) analogue, $Pd(PPh_3)_4$; (c) CSA (cat.), CH_2Cl_2, 1 h; (d) H_2, Pd/C, EtOAc; (e) TBAF, THF, 12 h.



Scheme 53. *Reagents*: (a) PhSeCl, pyridine, CH_2Cl_2, -78°C, 1h; (b) $PhSO_2N(O)CHPh$, pyridine, $CHCl_3$, reflux, 15 h.

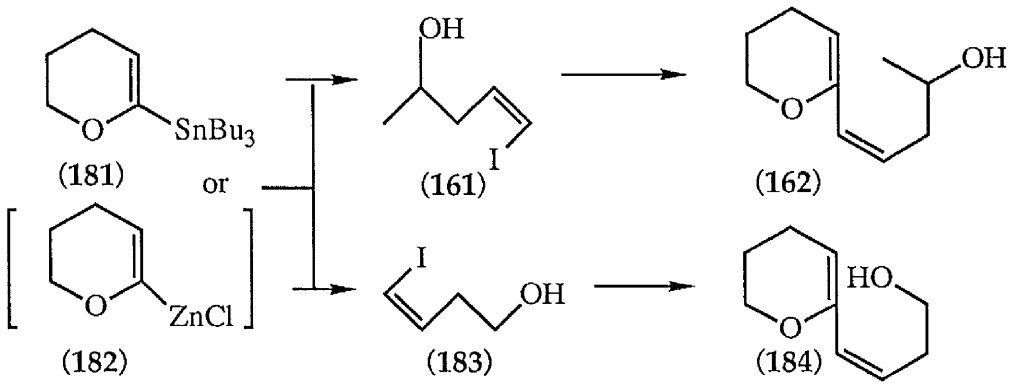
In this thesis this work is taken further towards the synthesis of an analogue of the northern hemisphere of milbemycin β_3. It is anticipated that Baker's[53] original approach to the introduction of the C_9-C_{10} bond could be realised using the methodology developed by Kotsuki[54] for the cuprate displacement of triflates possessing β-oxygen functionality.



Scheme 54

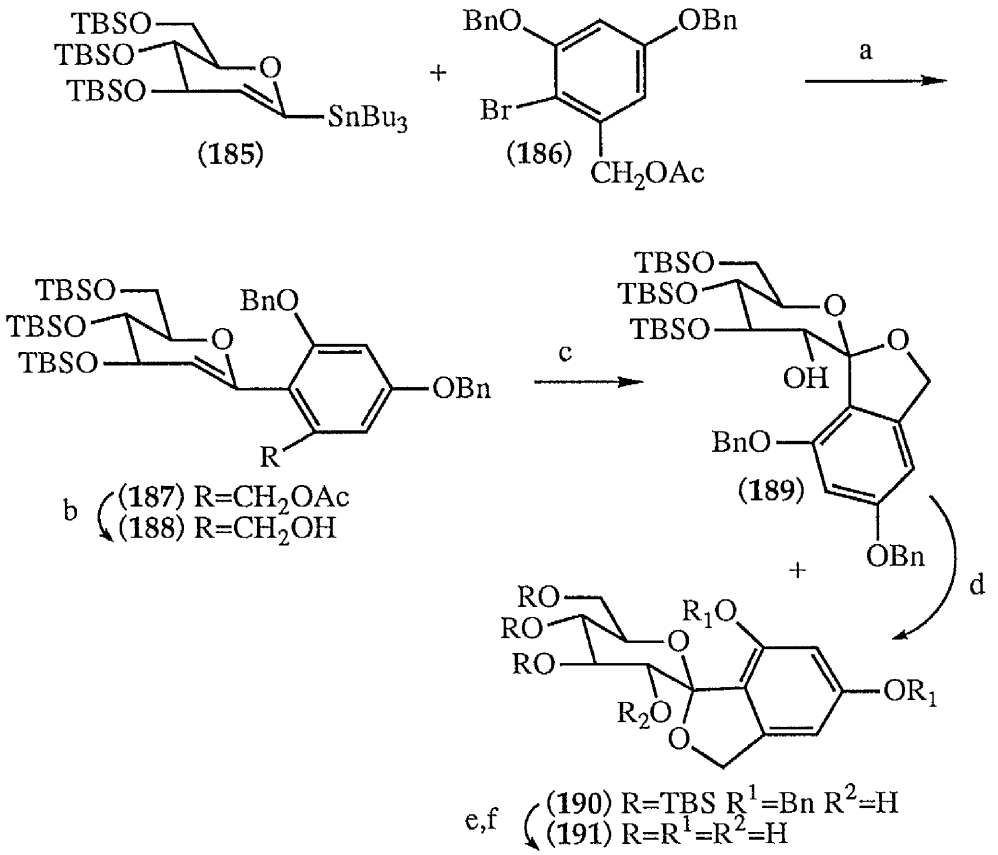
In this thesis the synthetic strategy proposed for palladium-mediated cross-coupling of vinyl organometallics with vinyl halides to afford 1,3-dienes is

investigated. The subsequent formation of spiroacetals is discussed and the synthetic utility of 1,3-dienes in Diels-Alder reactions is investigated. This strategy involved the coupling of stannane (**181**) or the organozinc (**182**) generated *in situ* with the vinyl iodide (**161**) or (**183**) to generate the 1,3-diene (**162**) or (**184**) and the subsequent cyclisation to form various spiroacetals (scheme 55).



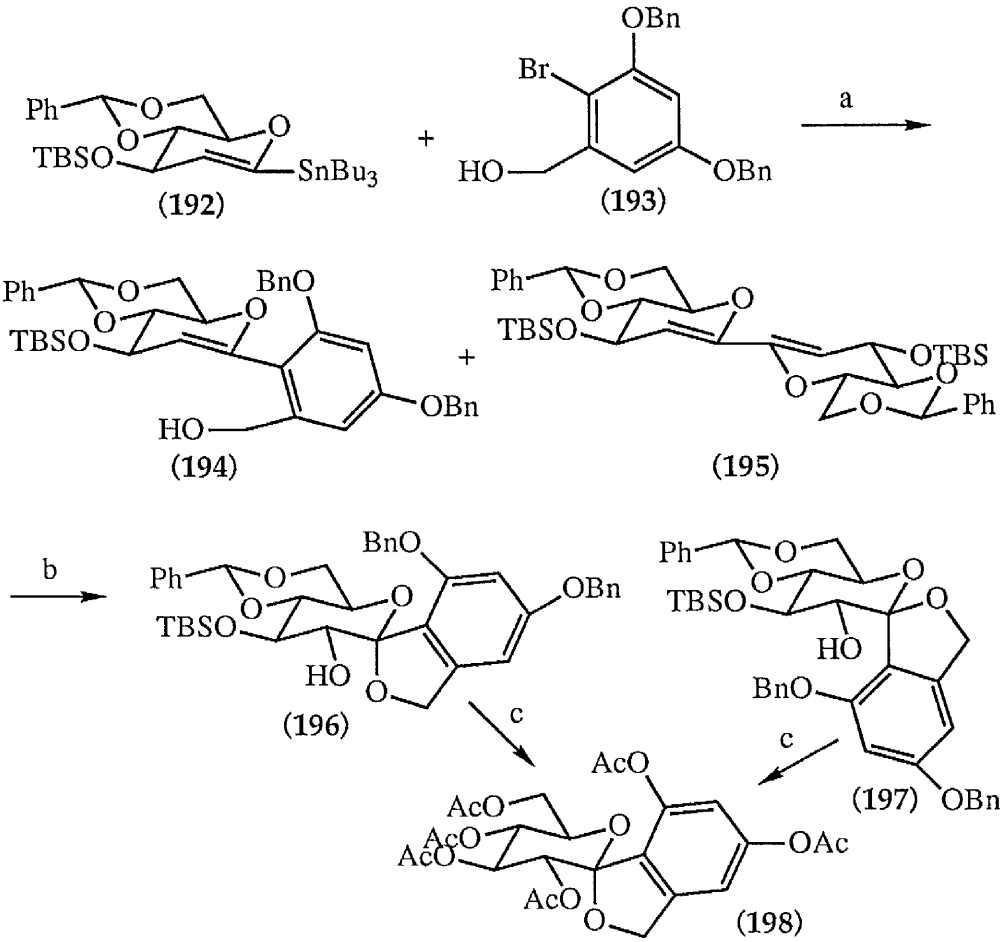
Scheme 55

Two independent reports of similar approaches to spirocyclic systems have appeared subsequent to our work in this area. Friesen[55] synthesised the C-arylglucoside spiroacetal nucleus of the papulacandins by coupling stannane (**185**) with the aryl bromide (**186**) affording the C-arylated product (**187**) in 85% yield (scheme 56). After reductive deprotection provided the benzyl alcohol (**188**) in 96% yield, spiroacetalisation was achieved by initial stereoselective α-epoxidation using dimethyl dioxirane. Rapid intramolecular trapping of the α-epoxide with the benzylic hydroxyl gave a mixture of spiroacetals (**189**) and (**190**) in a combined yield of 84% (**189**:**190** 1:5). Epimerisation of (**189**) to (**190**) was achieved using PPTS in $CHCl_3$ (overall yield 80%). Deprotection of (**190**) provided the synthetic papulacandin spiroacetal nucleus (**191**).



Scheme 56. *Reagents*: (a) $Pd(PPh_3)_2Cl_2$, C_7H_8, reflux; (b) LAH, Et_2O, 0°C; (c) dimethyldioxirane, CH_2Cl_2; (d) PPTS, $CHCl_3$, rt; (e) H_2, Pd/C, EtOAc, 40°C; (f) TBAF, THF, rt.

Dubois and Beau,[56] like Friesen, synthesised the spiroacetal nucleus papulacandin using a similar approach (scheme 57). These workers coupled 1-stannylglycal (**192**) with aryl bromide (**193**) using $Pd(PPh_3)_4$ catalyst in the presence of a sodium bicarbonate buffer and obtained the arylated glycal (**194**) in 78% yield, accompanied by dimer (**195**) (18%). Stereoselective epoxidation of (**194**) was accomplished with 3-chloroperbenzoic acid at -78°C, to provide exclusively the two isomers (**196**) (70%) and (**197**) (12%) with the D-gluco configuration. Both (**196**) and (**197**) gave after desilylation, hydrogenolysis and acetylation the same hexaacetate (**198**).



Scheme 57. *Reagents*: (a) $Pd(PPh_3)_4$, Na_2CO_3, CH_2Cl_2, C_7H_8, reflux, 3 h; (b) m-CPBA, $NaHCO_3$, CH_2Cl_2, 5 h, -78°C; (c) TBAF, THF, rt, 10 h; H_2, Pd/C, AcOEt:MeOH, 2:1, rt; Ac_2O, pyridine.

2.2 Coupling of 2,3-Dihydro-2(H)-pyran Derivative (182) and (Z,E) 4-Hydroxy-3-methyl-1-iodobutene (205) and Subsequent Spiroacetalisation.

Initially, racemic ethyl-3-hydroxybutyrate (**156**) was alkylated using Fráter's method[57] to generate the ester (**199**) (95% d.e.). The hydroxyl group of ethyl-3-hydroxy-2-methylbutyrate (**199**) was protected as the TBDMS derivative using standard conditions (DBU, TBDMS-Cl, dichloromethane) affording (**200**) in 87% yield. Reduction of the ester (**200**) to the aldehyde (**201**) using the method employed by Baker[58] was cleanly achieved. This unstable aldehyde was used immediately in the next step to prepare the vinyl iodide. This was achieved by a Wittig olefination sequence using Stork's[51] procedure. The ylid (**203**) was generated from iodomethyltriphenyl phosphonium iodide (**202**). This was effected by deprotonation of (**202**) using sodium hexamethyldisilazide at room temperature. After generation, the dark red coloured ylid (**203**) was cooled to -78°C and reacted with the aldehyde (**201**). The phosphonium salt (**202**) was prepared by the reaction of diiodomethane with triphenylphosphine in toluene at 45-50°C overnight in 92% yield.[59] The reduction/Wittig reactions combined proceeded in 41% overall yield resulting in a mixture of geometric isomers of the vinyl iodide (**204**), which were found to be light sensitive. The infra red spectrum showed a weak absorption characteristic of the alkene stretch (υ_{max} 1608 cm^{-1}). ^1H nmr analysis showed a characteristic distinction between the two isomers in the vinylic region. The Z-isomer showed a 1H doublet of doublets at δ 6.15 and 1H doublet δ 6.25 while the *E*-isomer showed a 1H doublet of doublets at δ 6.02 and a 1H doublet of doublets at δ 6.52 with a vicinal coupling constant *J* = 14.5 Hz.

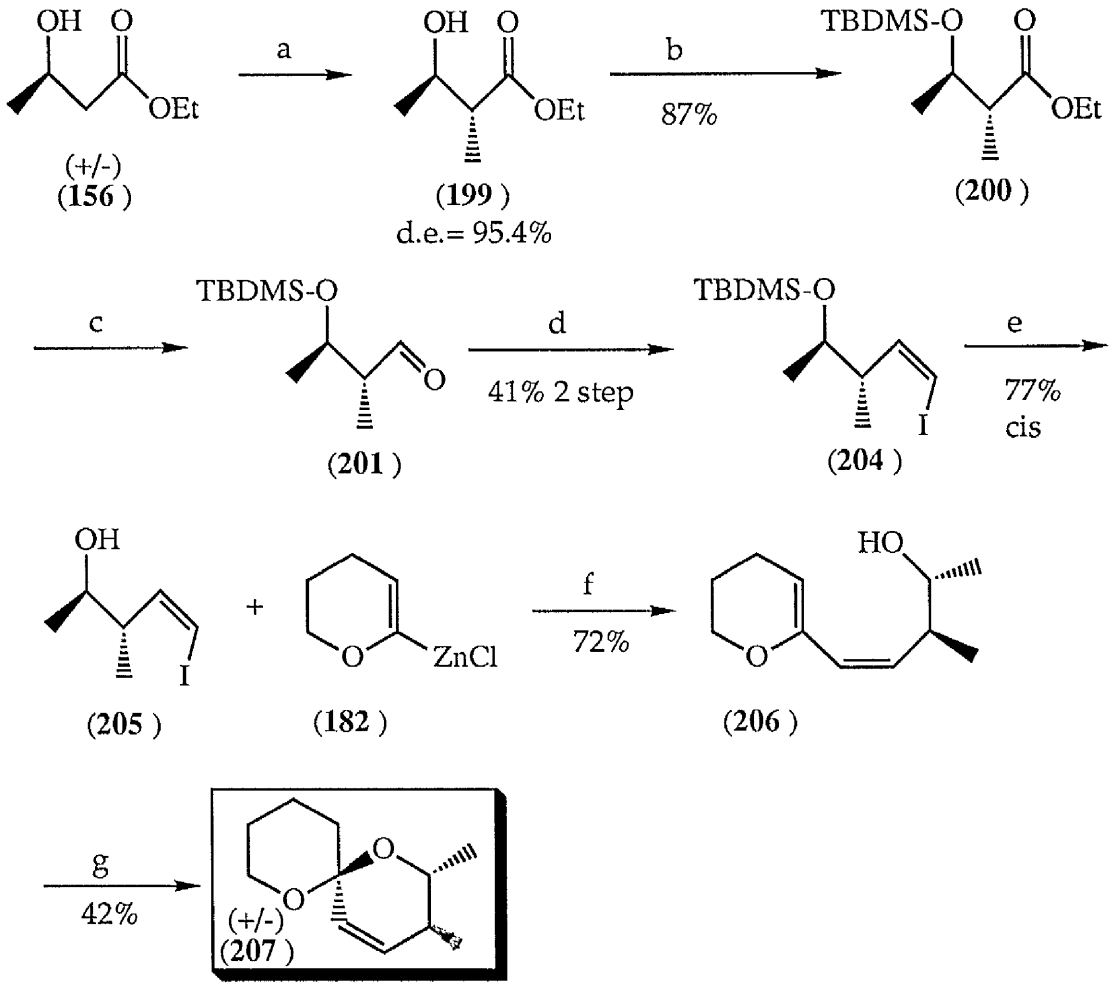
Deprotection of the alcohol was cleanly achieved using aqueous hydrogen fluoride in acetonitrile[60] to afford the Z-alcohol (**205**) in 77% yield (only Z isomer was isolated) (scheme 58). The infra red spectrum showed a weak absorption characteristic of the alkene stretch (υ_{max} 1609 cm^{-1}). ^1H nmr analysis showed a 1H doublet of doublets at δ 6.15 and 1H doublet δ 6.36. The Z-alcohol (**205**) was

coupled to 2,3-dihydro-2(H)-pyran by a palladium-catalysed cross-coupling reaction. 2,3-Dihydro-2(H)-pyran was transformed into the nucleophilic species, by: 1) generation of the carbanion in THF, with 1 eq. of t-butyl lithium and 2) transmetallation into zinc derivative by addition of 1 eq. of zinc chloride in ether, 4 eq. were used (one eq. just serves to deprotonate the free hydroxyl group of (**205**)) in the coupling step with 5% tetrakis(triphenylphosphine)palladium(0) as the catalyst. This generated the Z-1,3-diene (**206**) in 72% yield.

The isolation of the diene (**206**) is complicated by its acid instability with acid catalysed spiroacetalization taking place on chromotography or on standing in chloroform. The diene (**206**) was best purified on silica eluting with 15% ethyl acetate/petrol containing *ca*. 5% triethylamine. The infra red spectrum showed the appearance of a second weak absorption at 1656 cm^{-1}, corresponding to a second alkene stretching frequency. ^{1}H nmr analysis of the Z-isomer showed a 1H triplet at δ 4.66 (J = 4 Hz), 1H triplet at δ 5.21 (J = 12 Hz), and 1H doublet at δ 5.75 with a vicinal coupling constant J = 12 Hz.

The method employed for the cyclisation of the diene (**206**) was an acid catalysed spiroacetalization effected using camphorsulphonic acid (catalytic) in dichloromethane,[61] affording the spiroacetal (**207**) in 42% yield. In this thermodynamically controlled cyclisation step the most stable conformation of the spiroacetal was formed in which each ring oxygen is axial to the adjacent ring, thereby gaining stability from the anomeric effect in accordance with the well established principles governing these reactions elucidated by Deslongchamps.[62] The reaction should be quantitative but the yield is lower than expected due to the volatility of the spiroacetal (**207**).

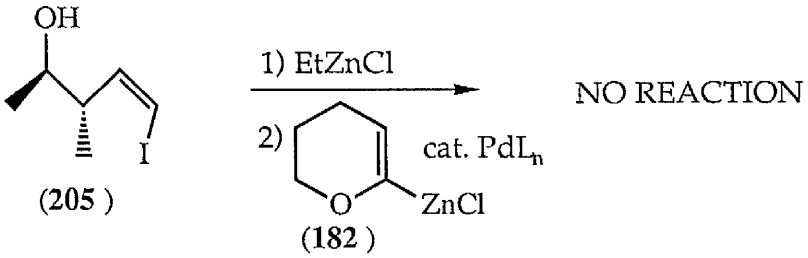
The infra red spectrum showed the disappearance of a weak absorption at 1610 cm^{-1}, corresponding to an alkene stretching frequency. ^{1}H nmr analysis showed the disappearance of a 1H triplet at δ 4.66 and the appearance of a 1H (5-H) double doublet (J 10, 2.5 Hz) at 5.54 and 1H dd (J = 10, 1.5 Hz) (4-H). ^{13}C analysis showed the appearance of the spiro carbon at δ 93.59.



Scheme 58.*Reagents*: (a) see ref. 57 (b) DBU, TBDMS-Cl, CH_2Cl_2, 0°C, 3h; (c) DIBAL-H (1.6eq.), toluene, -80°C, 1 h; (d) Ph_3P=CHI (**203**), THF, -78°C (generated from $[Ph_3PCH_2I]^+I^-$ (**202**) $NaN(SiMe_3)_2$, rt); (e) HF, CH_3CN; (f) $Pd(PPh_3)_4$; (g) CSA (cat.), CH_2Cl_2.

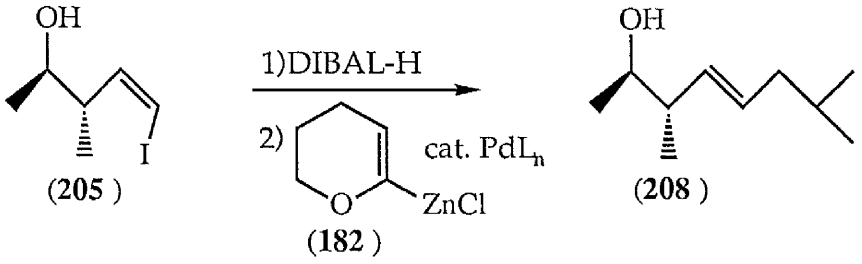
Attempts were made to increase the efficiency of the palladium cross-coupling reaction. Recently Negishi[29] has reported the reaction of zinc-protected (Z)-iodo-2-buten-1-ol with organozincs in the presence of 1-5 mol% of a Pd complex e.g. $Pd(PPh_3)_4$ or "Pd(0)" (generated *in situ* from $Pd(PPh)_2Cl_2$ and n-BuLi (2 eq.)), in DMF provides a highly stereoselective and yielding procedure for preparing (Z)-3-methyl-2-alken-1-ols. The free hydroxyl group was protected by treating with ethylzinc halide generated *in situ* by the treatment of EtMgBr with dry $ZnCl_2$. In this manner, the sacrificial use of one equivalent of a more

precious organozinc reagent could be avoided. Despite several attempts in our hands we could not repeat these results on our system.



Scheme 59

A second attempt was made to increase the efficiency of the palladium cross-coupling reaction. The free hydroxyl group was protected by treating with diisobutylaluminium hydride. The coupling reaction resulted in the transfer of an isobutyl group to the iodide position. ^{1}H nmr analysis showed a 1H triplet at δ 5.28 with vicinal coupling J = 11 Hz and 1H doublet of triplets at δ 5.59 (J = 11, 7 Hz).



Scheme 60

2.3 Synthesis of 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tri-n-butylstannyl-D-arabino-hex-1-enitol (218)

The synthesis began with methyl-α-D-glucopyranoside (**209**) and followed a procedure reported by Glaudeman and Fletcher.[63] The first step was to protect the hydroxyl groups on the starting material (**209**), which was carried out using potassium hydroxide and benzyl chloride in dioxane at reflux to afford methyl-2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside (**210a**). The next step was to selectively hydrolyse the methyl ether in the prescence of the benzyl ethers and the ring system. This was carried out using hot glacial acetic acid and boiling 2M sulphuric acid to give 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (**211**) in a low 30% overall yield.

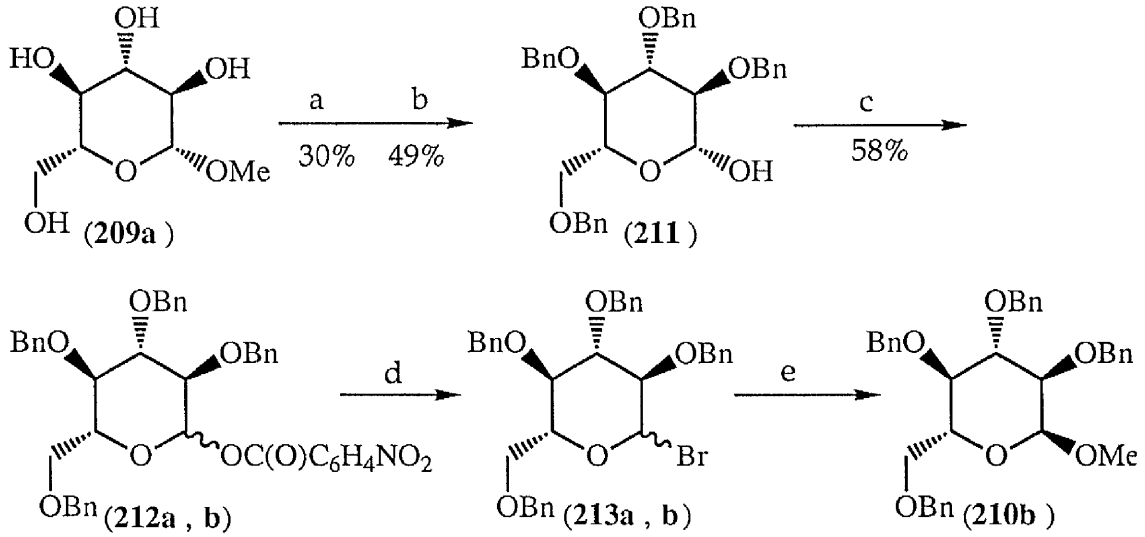
An alternative approach was sought in order to improve the low yield. This involved dissolving methyl-α-D-glucopyranoside (**209**) in DMF and adding it to sodium hydride, followed by the addition of tetrabutylammonium iodide and benzyl bromide. Hydrolysis using a weaker acid (0.5M sulphuric acid in acetic acid-water 8:2 v/v) as described by Anderson,[64] improved the combined yield to 49%. ^{1}H nmr analysis of alcohol (**211**) showed a single anomer exhibiting a 1H doublet (2-H) at δ 5.28 with a vicinal coupling J = 3.5 Hz.

The formation of a good leaving group at C-2 was achieved by reacting 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (**211a**) with *p*-nitrobenzoyl chloride to give 2,3,4,6-tetra-O-benzyl-1-O-*p*-nitrobenzoyl-α/β-D-glucopyranose (**212a, b**) in 58% yield as a mixture of two diastereoisomers (α:β 2:5). Analysis of the ^{1}H nmr spectrum showed a 1H doublet (2-H) at δ 5.28 with a vicinal coupling J = 8 Hz (**212b**) and a 1H doublet (2-H) at δ 6.65 with a vicinal coupling J = 3 Hz (**212a**).

A procedure for the stereoselective formation of a phenylsulphide moiety at C-1 has been shown by Anderson,[64] where an α-bromo at C-2 on the sugar was converted to a β-phenylsulphide as the exclusive stereoisomer. Employing Anderson's procedure the *p*-nitrobenzoyl group was replaced with a bromo group. This was achieved by bubbling anhydrous hydrogen bromide through a

solution of 2,3,4,6-tetra-O-benzyl-1-O-*p*-nitrobenzoyl-α-D-glucopyranose (**212a, b**) in dichloromethane to afford the required 2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside bromide (**213a, b**). Analysis of the crude ^{1}H nmr spectrum showed the loss of *p*-nitrobenzoyl proton signals at δ 8.18-8.36 and the hydrogen at C-2 shifting from δ 5.93 (**212b**) and δ 6.65 (**212a**) to δ 6.75 (J = 4.5 Hz).

Following Anderson's[64] procedure the bromide (**213a, b**) was dissolved in chloroform and added to a solution of thiophenol and 0.43M methanolic potassium hydroxide. The mixture was heated under reflux for 30 minutes and this resulted in the formation of methyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside (**210b**). ^{1}H nmr analysis showed a 1H doublet (2-H) at δ 4.32 with a vicinal coupling J = 8 Hz. The bromo group had been replaced by a methoxy group instead of the phenylsulphide group. Attempts to repeat Anderson's work failed to reproduce the sulphide (**215**).

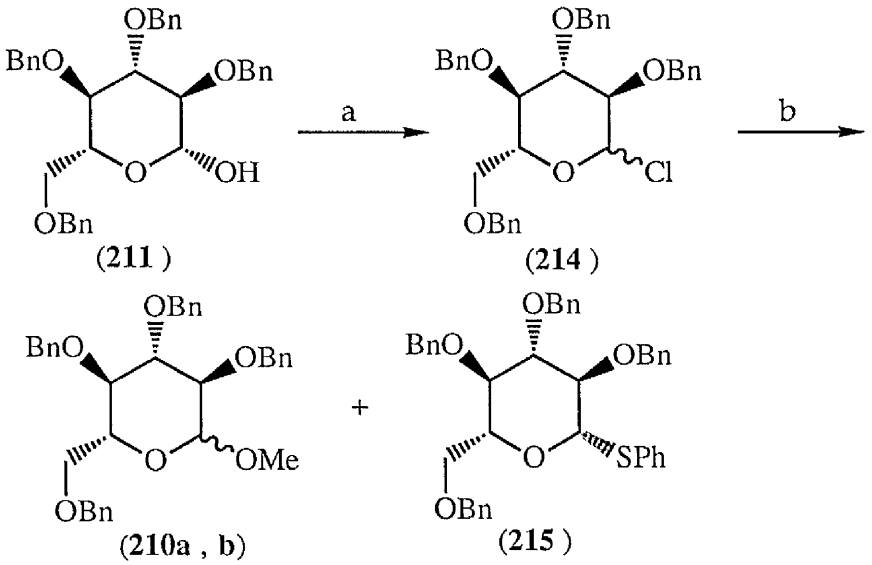


Scheme 61. *Reagents*: (a) KOH, BnCl, dioxane, reflux followed by acid hydrolysis; (b) NaH, BnBr, $(Bu)_4NI$, DMF followed by acid hydrolysis; (c) *p*-nitrobenzoyl chloride, pyridine, CH_2Cl_2; (d) HBr; (e) (PhSH/0.43M KOH).

Various approaches to synthesise phenyl-2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (**215**) were attempted. The use of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl chloride (**214**) was investigated instead of the bromide (**213**). The

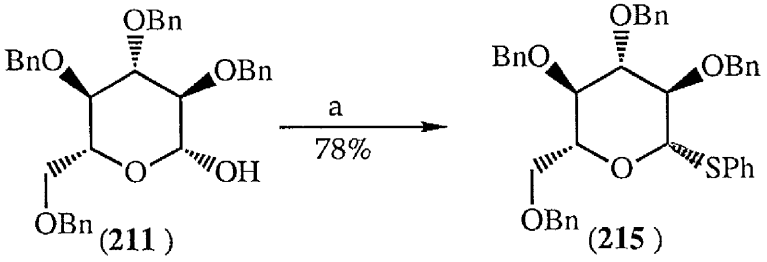
chloride[65] (**214**) was made by reacting 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (**211**) with thionyl chloride and a trace of DMF at 50°C for 20 minutes. The crude chloride (**214**) contained a mixture of diastereoisomers and was used immediately for all the reactions described.

Adapting Anderson's work by refluxing the solution of thiophenol and 0.43M methanolic potassium hydroxide before adding the chloride (**214**) resulted in a 1:1 mixture of methyl-2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranoside (**210a, b**) and phenyl-2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (**215**) in 7% yield.



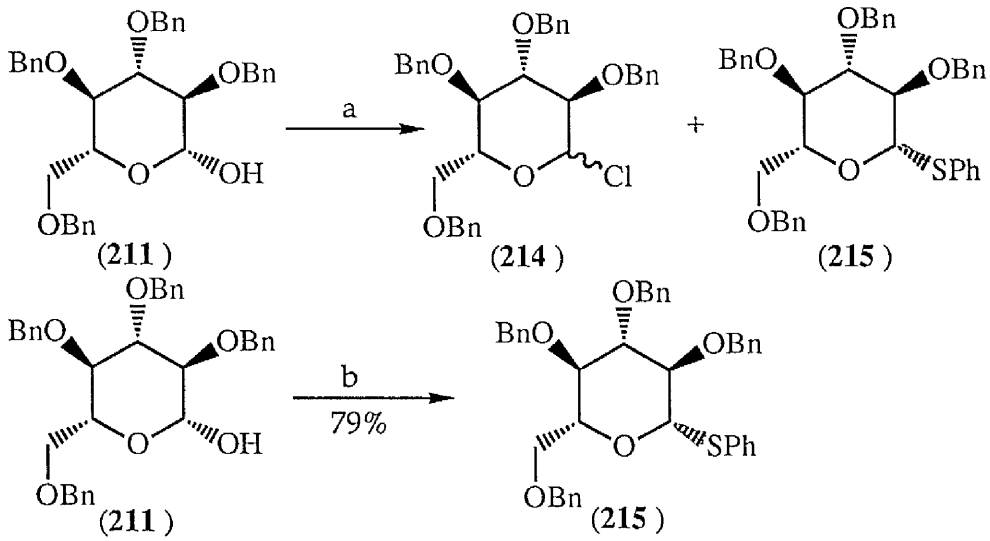
Scheme 62. *Reagents:* (a) $SOCl_2$, DMF, 50°C; (b) (PhSH/0.43M KOH, reflux).

Various bases were used in order to promote this displacement reaction. Triethylamine, Hunig's base and DBU all failed to yield product but n-butyl lithium worked. To a solution of thiophenol in THF at -78°C was added n-butyl lithium, the reaction was warmed to ambient temperature and stirred for 15 minutes. The chloride (**214**) was added at -78°C, allowed to warm up to room temperature and stirred overnight. This afforded after recrystallisation phenyl-2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (**215**) in 78% yield from the alcohol (**211**). ^{1}H nmr analysis showed a 1H doublet (2-H) at δ 4.65 with a vicinal coupling J = 10 Hz in accord with the assigned structure.



Scheme 63. *Reagents*: (a) $SOCl_2$, DMF, 50°C, 20 min; (b) (PhSH/nBuLi, -78°C-RT, 15 min), -78°C-RT.

An alternative approach used the procedure described by Williams,[66] this involved the direct conversion of an alcohol to a sulphide. 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (**211**) was dissolved in dichloromethane and a mixture of diphenyl disulphide and tri-n-butylphosphine was added. This resulted in a mixture of the chloride (**214a, b**) and sulphide (**215**). Tri-n-butylphosphine had reacted with the solvent to generate the chloride (**214a, b**). Switching the solvent to acetonitrile gave the sulphide (**215**) in 79% yield as the only product.

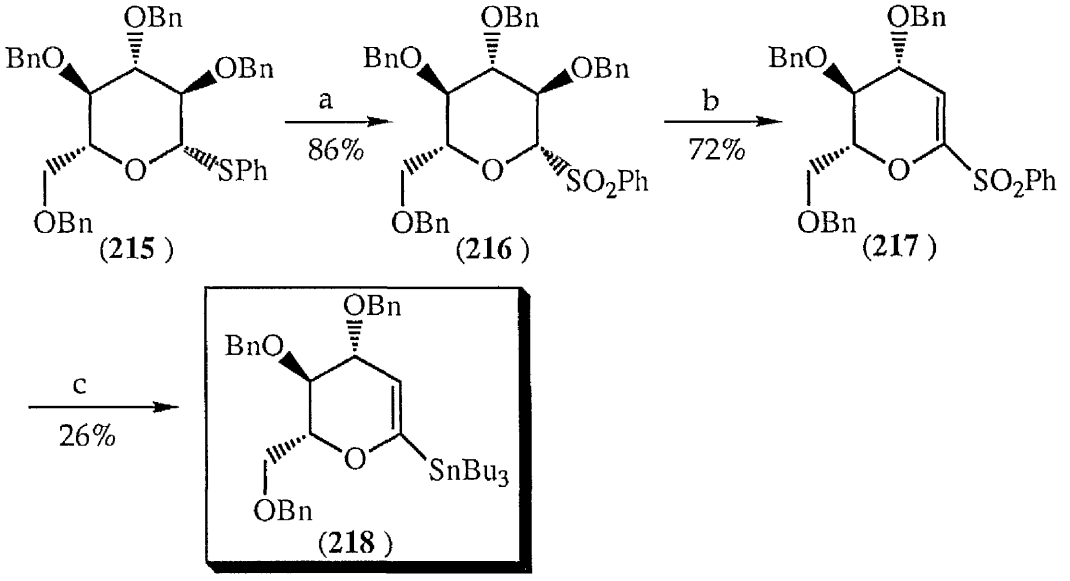


Scheme 64. *Reagents*: (a) n-Bu_3P, $(PhS)_2$, CH_2Cl_2; (b) n-Bu_3P, $(PhS)_2$, CH_3CN.

Oxidation (m-CPBA, $NaHCO_3$, CH_2Cl_2, 0-25°C) of phenyl-2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (**215**) furnished the corresponding phenylsulphone (**216**) in 84% yield. ^1H nmr analysis showed a 1H doublet (2-H) at δ 4.47 with a vicinal coupling J = 9 Hz. Base catalysed elimination (n-BuLi, THF, -78°C) of benzyl alcohol gave vinylic phenylsulphone (**217**) in 72% yield.

The infra red spectrum showed an absorption characteristic of an alkene stretch (υ_{max} 1649 cm^{-1}). ^1H nmr analysis showed a 1H doublet (3-H) at δ 6.28 with a vicinal coupling J = 3 Hz.

Treatment of phenylsulphone (217) with tri-n-butyltin hydride (n-Bu_3SnH, 2.5 eq., AIBN (cat.), toluene, reflux) afforded the vinylic tri-n-butyl stannane (218) in 26% together with starting sulphone (217) (51%). ^1H nmr analysis showed a 1H doublet (3-H) at δ 4.92 with a vicinal coupling J = 2.5 Hz and for $^{117,119}Sn$ satellites J = 26.5 Hz. Despite many attempts we could not improve the yield to the 77% yield published by Beau[67]

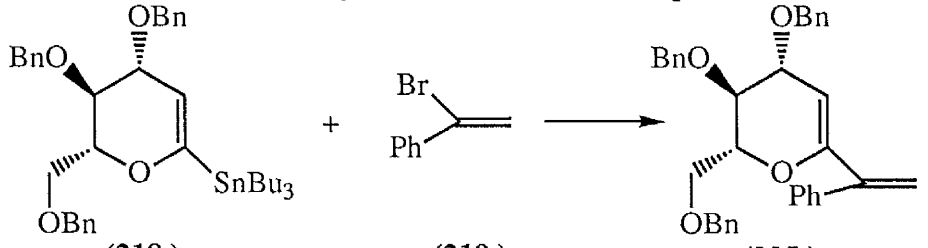


Scheme 65. *Reagents*: (a) m-CPBA, $NaHCO_3$, CH_2Cl_2, rt; (b) n-BuLi, THF, -78°C; (c) n-Bu_3SnH, 2.5 equiv., AIBN (cat.), toluene, reflux.

2.4 Palladium(0)-Catalysed Cross-Coupling Reactions Between 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tributylstannyl-D-arabino-hex-1-enitol (**218**) and Various Vinyl Halides (**219-224**)

Various conditions were examined to optimise the conversion of the stannylated glucal (**218**) into glycosyl 1,3-dienes. The model study used α-bromostyrene (**219**) as the vinyl halide. In total, seven palladium(0)-catalysed systems were employed, the best one was used to sythesise a variety of glycosyl 1,3-dienes (**225-230**).

In method A the catalyst used was palladium(11) acetate, which when refluxed in acetonitrile with tri-*o*-tolylphosphine and triethylamine generated active palladium (0).[68] Method B was exactly the same as method A except trifurylphosphine was used. Method C was exactly the same as method A except triphenylarsine was used. In method D bis(acetonitrile)dichloropalladium was used as catalyst in DMF at room temperature. Method E[3] involved tris(dibenzylideneacetone)dipalladium as the source of Pd(0) and triphenylarsine as the ligands in the presence of copper(1) iodide in DMF at 60°C. In method F bis(triphenylphosphine)dichloropalladium(11) was used as catalyst in THF at room temperature. Finally, in method G bis(triphenylphosphine)dichloro palladium(11) was used as catalyst in DMF at room temperature.



(**218**) (**219**) (**225**)

$Pd(OAc)_2$, $P(o\text{-}Tol)_3$, Et_3N, CH_3CN, reflux, 3h.	10%
$Pd(OAc)_2$, $P(TFP)_3$, Et_3N, CH_3CN, reflux, 3h.	12%
$Pd(OAc)_2$, $AsPh_3$, Et_3N, CH_3CN, reflux, 3h.	28%
$Pd(MeCN)_2Cl_2$, DMF, rt, 42h.	46%
$Pd(Ph_3P)_2Cl_2$, DMF, rt, 41h.	no reaction
$Pd(Ph_3P)_2Cl_2$, THF, rt, 26h.	no reaction
$Pd_2(dba)_3$, CuI, $AsPh_3$, 50°C, 48h.	<30%

Table 1

The best conditions were achieved using bis(acetonitrile)dichloro palladium as catalyst (method D). This afforded the glycosyl 1,3-diene (**225**) in 46% yield. The palladium(11) acetate methods furnished poor yields (A 10%, B 12%) despite a small improvement using triphenylarsine (C 28%). Method E produced an impure diene in <30% yield. Methods F&G failed to work.

The bis(acetonitrile)dichloropalladium was used as the catalyst to optimise the conversion of the stannylated glucal (**218**) into glycosyl 1,3-dienes (**225-230**). The results of this work are shown in the table below (table 2).

^{1}H nmr analysis of the glycosyl 1,3 dienes (**225-230**) were all characterised by a 1H doublet (3-H) at δ 4.91-5.24 with a vicinal coupling J = 3-4 Hz and vinylic proton(s). The infra red spectra showed the absorption characteristics of two alkene stretches (υ_{max}1604-1666 cm^{-1}).

^{1}H nmr analysis of the glycosyl 1,3 diene (**225**) was characterised by a 1H doublet (3-H) at δ 4.95 with a vicinal coupling J = 3 Hz and two vinylic proton singlets at δ 5.3 and δ 5.83. The infra red spectrum showed absorption characteristics of an alkene stretch (υ_{max}1645 cm^{-1}). ^{1}H nmr analysis of the *E*-glycosyl 1,3 diene (**226**) was characterised by a 1H doublet (3-H) at δ 5.11 with a vicinal coupling J = 3 Hz and two vinylic proton doublets at δ 6.52 and δ 7.06 with a vicinal coupling J = 15.5 Hz. The infra red spectrum showed absorption characteristics of two alkene stretches (υ_{max}1649 and 1615 cm^{-1}).

Coupling of stannane (**218**) with vinyl iodide (**221**) afforded Z-glycosyl 1,3 diene (**227**) with retention of stereochemistry, as judged by ^{1}H nmr. ^{1}H nmr analysis of the Z-glycosyl 1,3 diene (**227**) was characterised by a 1H doublet (3-H) at δ 5.24 with a vicinal coupling J = 3 Hz and two vinylic proton doublets at δ 5.89 and δ 6.08 with a vicinal coupling J = 12.5 Hz. The infra red spectrum showed absorption characteristics of two alkene stretches (υ_{max} 1657 and 1611 cm^{-1}). ^{1}H nmr analysis of the *E*-glycosyl 1,3 diene (**228**) was characterised by a 1H multiplet (3-H) at δ 5.1 and one vinylic proton singlet at δ 6.13. The infra red

spectrum showed absorption characteristics of two alkene stretches (υ_{max} 1643 and 1604 cm^{-1}).

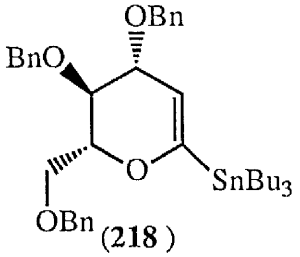
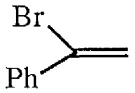
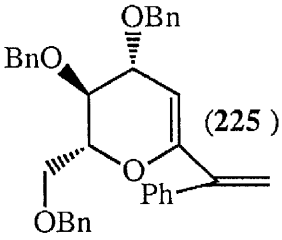
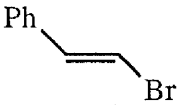
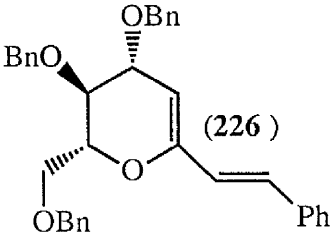
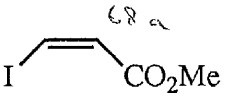
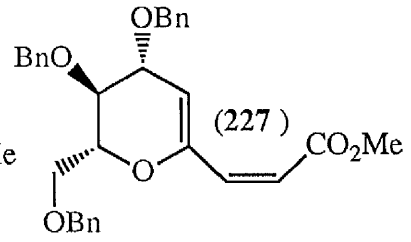
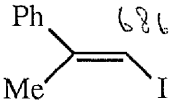
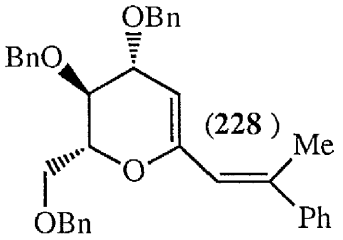
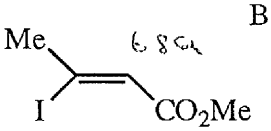
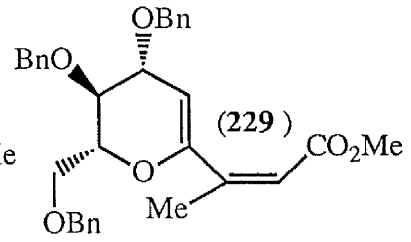
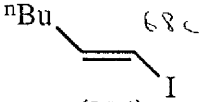
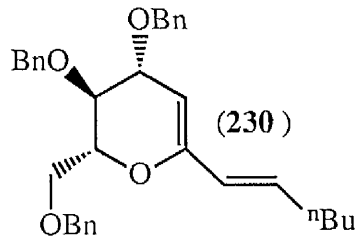
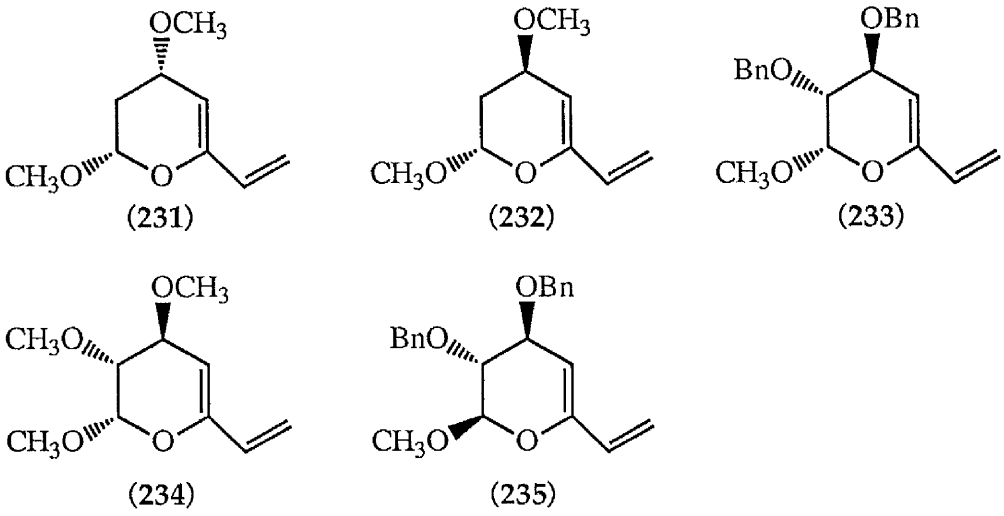
Stannane	Vinyl halide	Diene	Yield
 (218)	 (219)	 (225)	46%
	 (220) Z:*E* 1:5.7	 (226)	48% *E* only
	 (221)	 (227)	50%
	 (222)	 (228)	65%
	 (223)	 (229)	67%
	 (224) Z:*E* 1:9	 (230)	46% Z:*E* 1:9

Table 2

By analogy, coupling of vinyl iodide (**223**) afforded the Z-glycosyl 1,3 diene (**229**) in 67% yield as a single diastereoisomer. ^{1}H nmr analysis of the Z-glycosyl 1,3 diene (**229**) was characterised by a 1H doublet (3-H) at δ 5.11 with a vicinal coupling J = 4 Hz and one vinylic proton singlet at δ 5.82. The infra red spectrum showed absorption characteristics of one alkene stretch (υ_{max} 1622 cm^{-1}). ^{1}H nmr analysis of the *E*-glycosyl 1,3 diene (**230**) was characterised by a 1H doublet (3-H) at δ 4.91 with a vicinal coupling J = 3 Hz , 1H doublet at δ 6.52 and 1H doublet of triplets at δ 6.23 with a vicinal coupling J = 15.5 Hz. The infra red spectrum showed absorption characteristics of two alkene stretches (υ_{max} 1666 and 1622cm^{-1}).

2.5 Diels-Alder Reactions of Dieno-Pyranosides. Anomeric vs. Allylic Stereoselection.

Diels-Alder cycloadducts obtained from carbohydrate-derived dienes and dienophile substrates have been successfully used in approaches to carbocyclic-containing natural products.[69] A diene and a dienophile react to afford a carbocyclic compound with up to four stereogenic centres, in just one synthetic operation, and with a good control of regio- and stereochemistry. While most examples of carbohydrate substrates have used the sugar-derived partner as the dienophile, publications from the Fraser-Reid group[70] have detailed the use of diacetone glucose derived dienes in the synthesis of carbocyclic compounds. Giuliano and Buzby[71] extended this work to examine the effect of pyranoside substituents on the face of selectivity of the Diels-Alder reactions of hepta-4,6-dienopyranosides[72] with maleimide and N-phenylmaleimide.



Scheme 63

Productive [4 + 2] cycloaddition of (**231-235**) occurred only with excess maleimide and N-phenylmaleimide in refluxing benzene.[73] Dienopyranosides **231-235** underwent highly *endo*-selective cycloaddition with maleimide and N-phenylmaleimide preferentially from the face opposite the anomeric methoxyl to afford cycloadducts (**236-243**) (table 3) in modest to good yields (31 to 75% for diastereomeric mixtures). The effect of an allylic substituent at C-3 of the dienopyranoside exerted only modest effect on stereochemical outcome of the Diels-Alder reactions (compare entries 1 and 2), whereas changing the stereochemistry of the anomeric methoxyl group from α to β completely reversed the face selectivity of the cycloaddition reaction (compare entries 4 and 5).

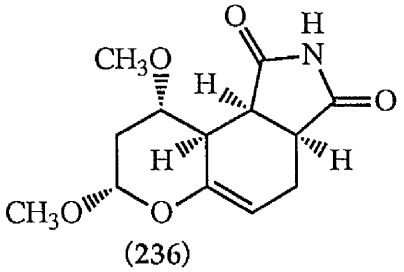
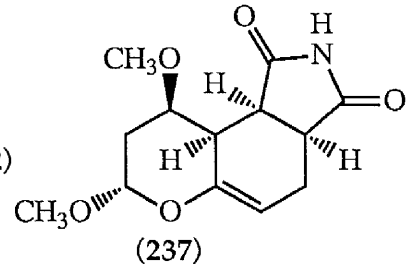
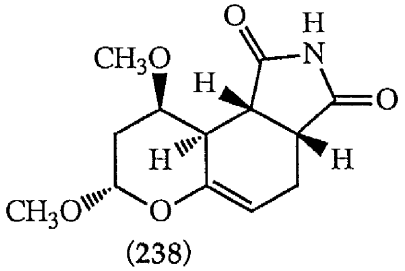
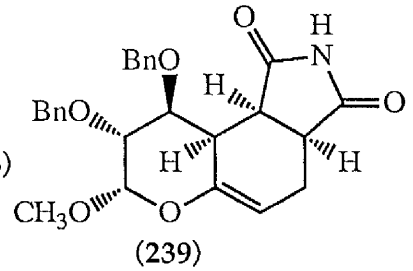
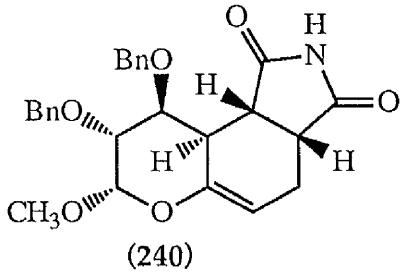
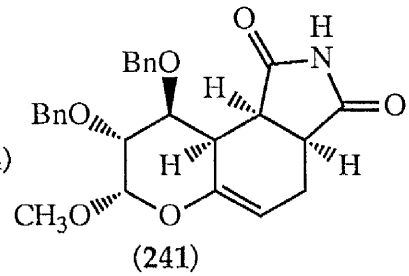
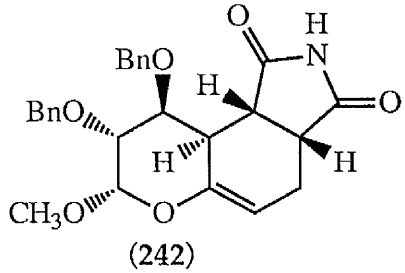
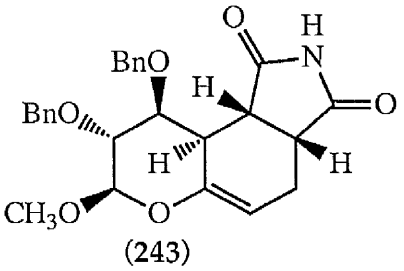
Entry	Diene	β-Face product	α-Face product	Ratio
1	(231)	 (236)		
2	(232)	 (237)	 (238)	4.1:1
3	(233)	 (239)	 (240)	4.7:1
4	(234)	 (241)	 (242)	6.4:1
5	(235)		 (243)	

Table 3

The face selectivity of the Diels-Alder reactions was explained by ground state conformational analysis (Fig. 1). Thus, the $^1H_2$ conformer of (**231**) was postulated to be more stable than the $^2H_1$ conformer by virtue of the anomeric

effect, even though the C-1 and C-3 substituents are in a 1,3-diaxial relationship to each other. ^1H nmr analysis and molecular mechanics calculations supported this hypothesis. Reaction of (**231**) was proposed to occur *via* the $^1H_2$ conformer from the less hindered α-face.

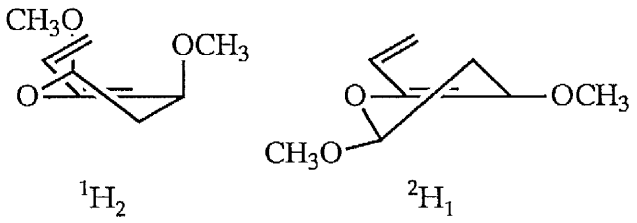


Figure 1 Half-chair conformations of (**231**).

2.6 Diels-Alder Reactions of Glycosyl 1,3-dienes (225-230) with 4-phenyl-1,2,4-triazoline-3,5-dione (244)

Glycosyl 1,3-diene (**225**) underwent a Diels-Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) to yield cycloadduct (**245**) in 89% yield as a single diastereoisomer. Glycosyl 1,3-diene (**226**) underwent a Diels-Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) to yield cycloadduct (**246**) in 45% yield as a single diastereoisomer. Glycosyl 1,3-diene (**227**) underwent a Diels-Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) to yield cycloadduct (**247**) in 86% yield as a two diastereoisomers (**a**:**b** 8.5:1). Glycosyl 1,3-diene (**228**) underwent a Diels-Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) to yield cycloadduct (**248**) in 10% yield as a single diastereoisomer. Glycosyl 1,3-diene (**229**) underwent a Diels-Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) to yield cycloadduct (**249**) in 93% yield as a two diastereoisomers (**a**:**b** 15.6:1). Glycosyl 1,3-diene (**230**) underwent a Diels-Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) to yield cycloadduct (**250**) in 76% yield as a single diastereoisomer.

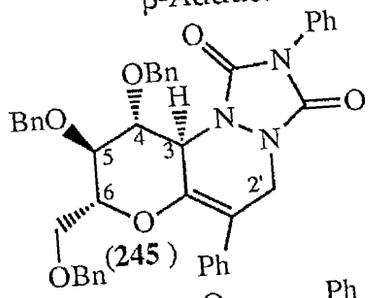
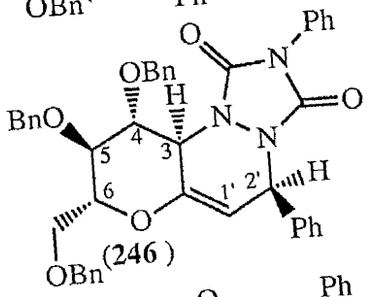
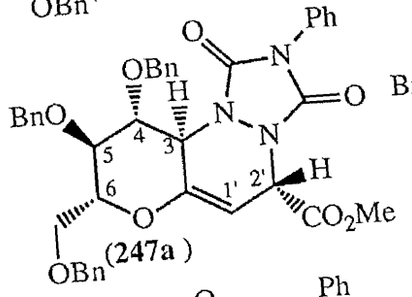
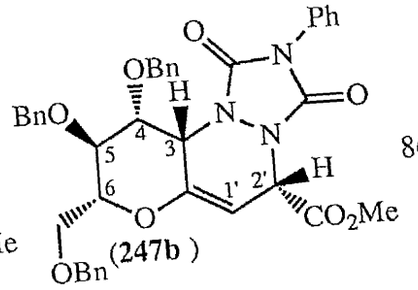
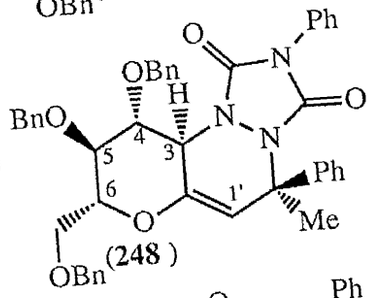
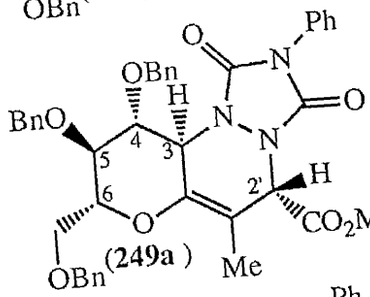
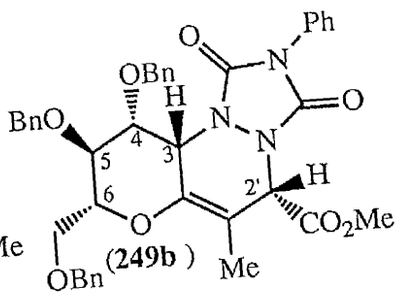
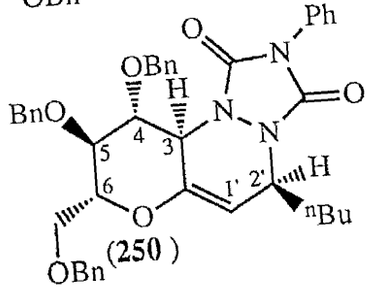
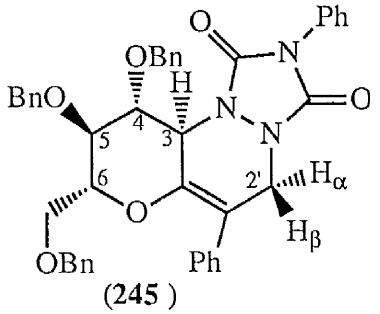
Diene	β-Adduct	α-Adduct	yield	ratio
(225)	 (245)		89%	
(226)	 (246)		45%	
(227)	 (247a)	 (247b)	86%	8.5:1
(228)	 (248)		10%	
(229)	 (249a)	 (249b)	93%	15.6:1
(230)	 (250)		76%	

Table 4

2.7 Stereochemical Assignments of the Cycloadducts (245-250)

Stereochemical assignments of the adducts (245-250) were initially based upon extensive ^1H nmr analysis which involved assignment of 3-H and determination of the vicinal coupling constant with 4-H. 2D HCOSY and ^1H decoupling experiments, determined that the sugar moiety existed in a chair conformation with the $J_{3,4}$ value determining the relative stereochemistry.

^1H nmr analysis of cycloadduct (245) showed a 1H doublet at δ 4.81 (J = 7.5 Hz, 3-H), 1H doublet of doublets at δ 4.2 (J = 15.5, 2 Hz, 2′-H_α), and 1H doublet at δ 4.72 with a geminal J = 15.5 Hz (2′-H_β). The infra red spectrum showed the appearance of a two strong absorptions at 1777 and 1720 cm^{-1}, corresponding to the two different imide carbonyl stretching frequencies. A decoupling experiment confirmed the assignment of 3-H by virtue of the long range coupling between 2′-H_α and 3-H (J = 2 Hz) (figure 2). Irradiation of 3-H at δ 4.81 resulted in 2′-H_α changing from a double doublet (J = 15.5, 2 Hz) to a doublet (J = 15.5 Hz). ^{13}C nmr showed the cycloadduct was homogeneous by virtue of one set of carbon signals.



(245)

Figure 2

^1H nmr analysis of cycloadduct (246) showed a 1H multiplet at δ 4.7 (3-H), 1H triplet at δ 5.41 (J = 2.5 Hz, 2′-H), and 1H doublet of doublets at δ 5.47 (J = 2.5, 1.5 Hz, 1′-H). The infra red spectrum showed the appearance of a two strong absorptions at 1779 and 1721 cm^{-1}, corresponding to the two different imide carbonyl stretching frequencies. ^{13}C nmr showed the cycloadduct was homogeneous by virtue of one set of carbon signals.

The results of nOe studies are shown on the diagram (figure 3). Irradiation of 6-H at δ 3.91 caused enhancements of 1′-H (0.3%), 4-H (2.8%) and 5-H (3.0%). Irradiation of 3-H at δ 4.70 caused enhancements of 1′-H (0.7%) and 2′-H (0.6%). Decoupling 3-H at δ 4.7 shows that 3-H couples to 4-H (changes from ~ triplet (J = 8 Hz) to double doublet (J = 8, 2 Hz)), 1′-H (double doublet (J = 2.5, 1.5 Hz) to doublet (J = 2.5 Hz) and 2′-H (triplet (J = 2.5 Hz) to doublet (J = 2.5 Hz)). These observations show 3-H is on the same face of the molecule as 4-H, proving the stereochemistry of 3-H and confirming that ring A is in a chair conformation (Figure 3).

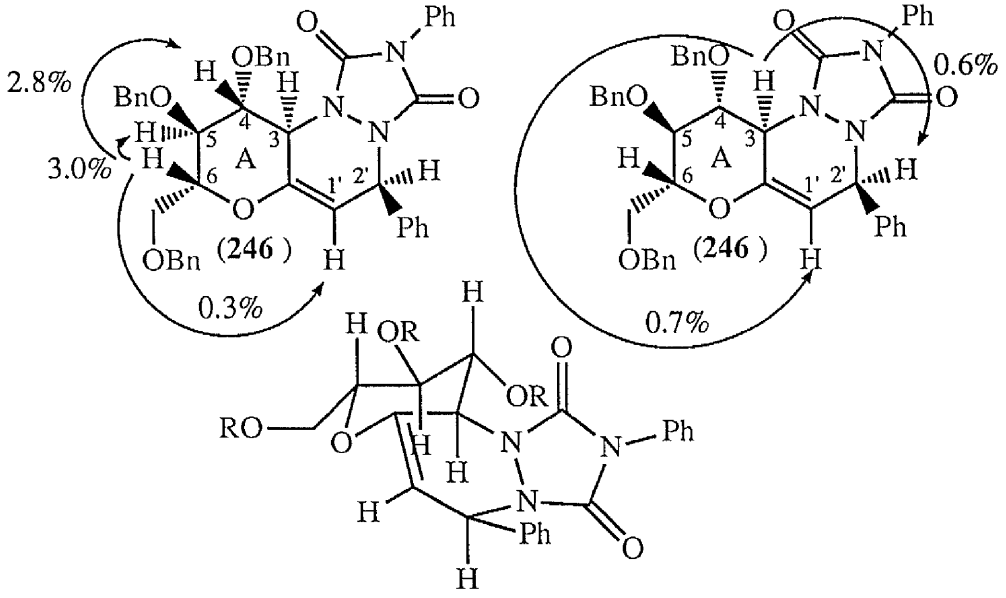


Figure 3

^{1}H nmr analysis of cycloadduct (**247a**) showed a 1H doublet at δ 4.71 (J = 10 Hz, 3-H), 1H doublet at δ 5.15 (J = 6.5 Hz, 2′-H), and doublet of doublets δ 5.79 (J = 6.5, 1 Hz, 1′-H). The infra red spectrum showed the appearance of a two strong absorptions at 1782 and 1731 cm^{-1}, corresponding to the two different imide carbonyl stretching frequencies. ^{13}C nmr showed the cycloadduct was homogeneous by virtue of one set of carbon signals.

Irradiation of 4-H at δ 3.96 resulted in 5-H changing from a triplet (J = 9 Hz) to a multiplet and 3-H changing from a doublet (J = 10 Hz) to a singlet.

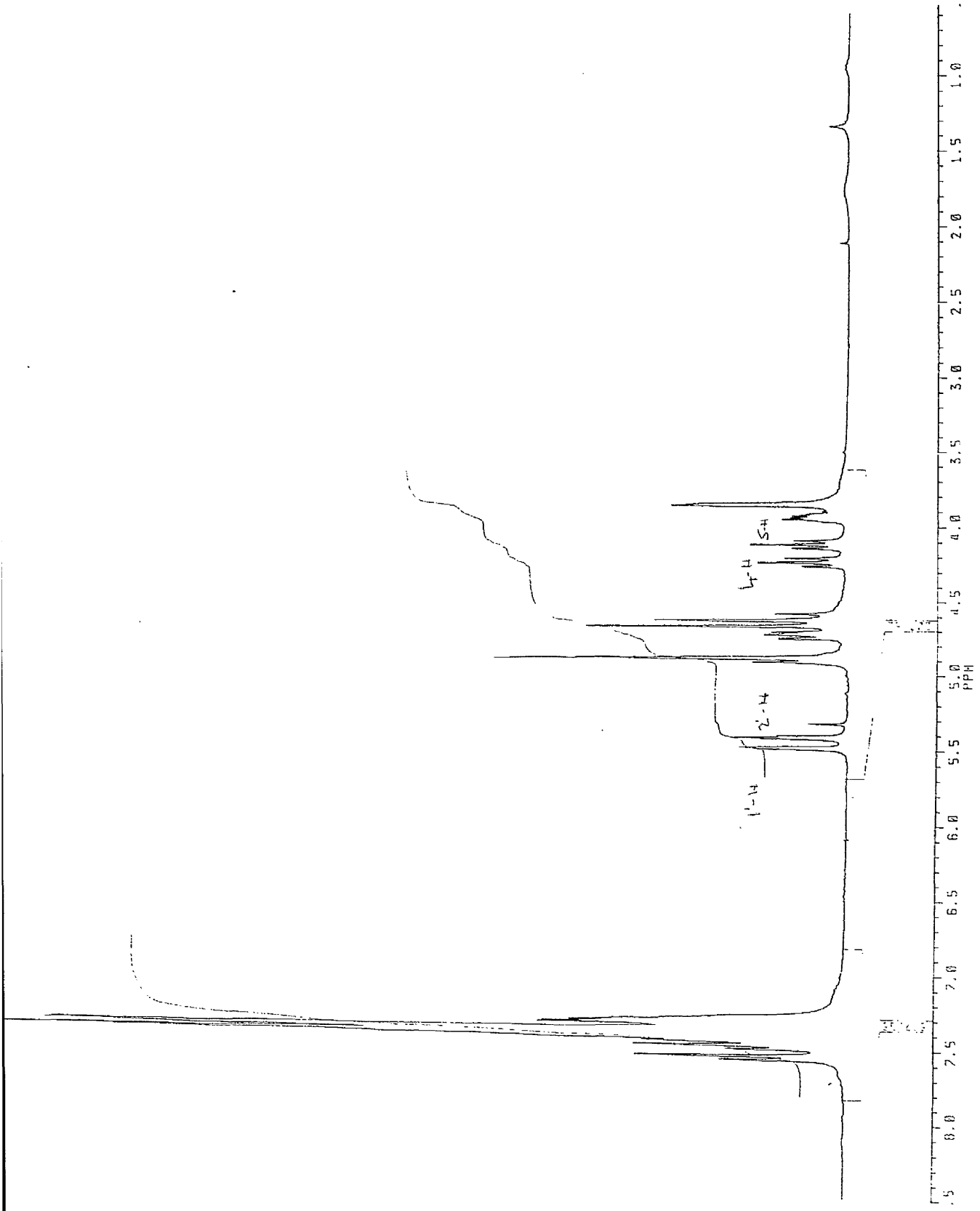


Figure 3a ^{1}H nmr of cycloadduct (246)

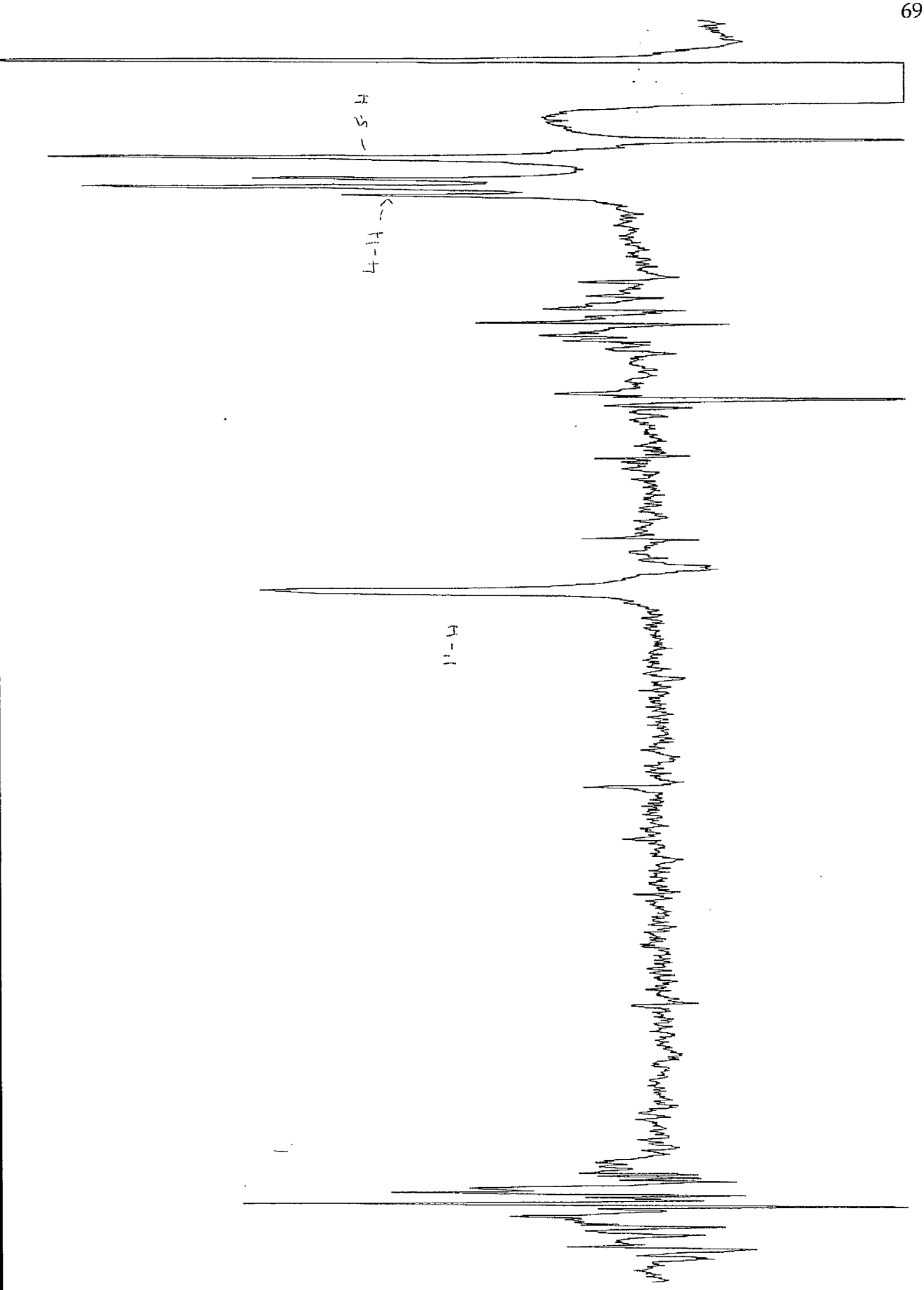


Figure 3b. nOe spectrum of cycloadduct (246): Irradiation of 6-H.

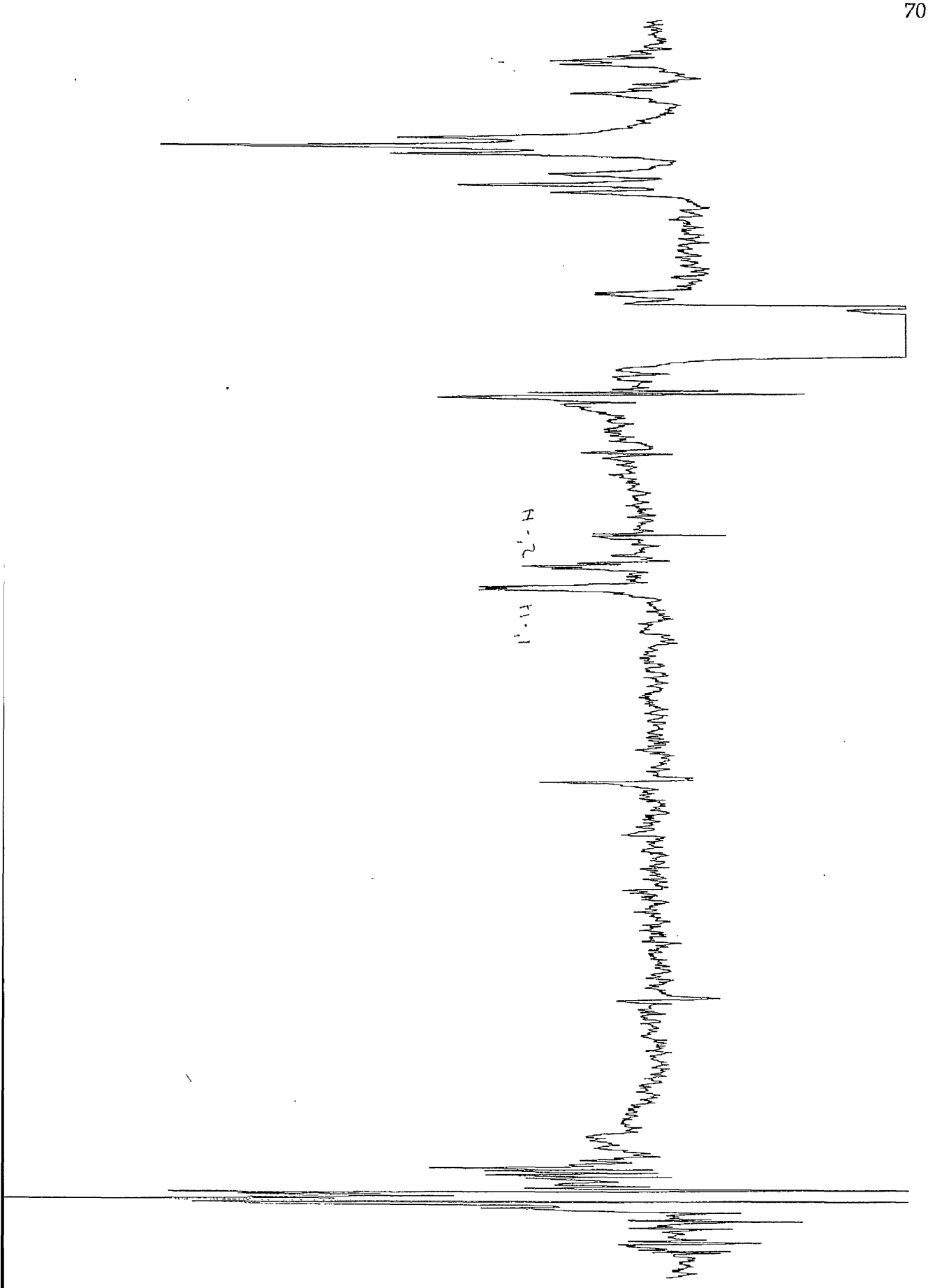


Figure 3c. nOe spectrum of cycloadduct (246): Irradiation of 3-H.

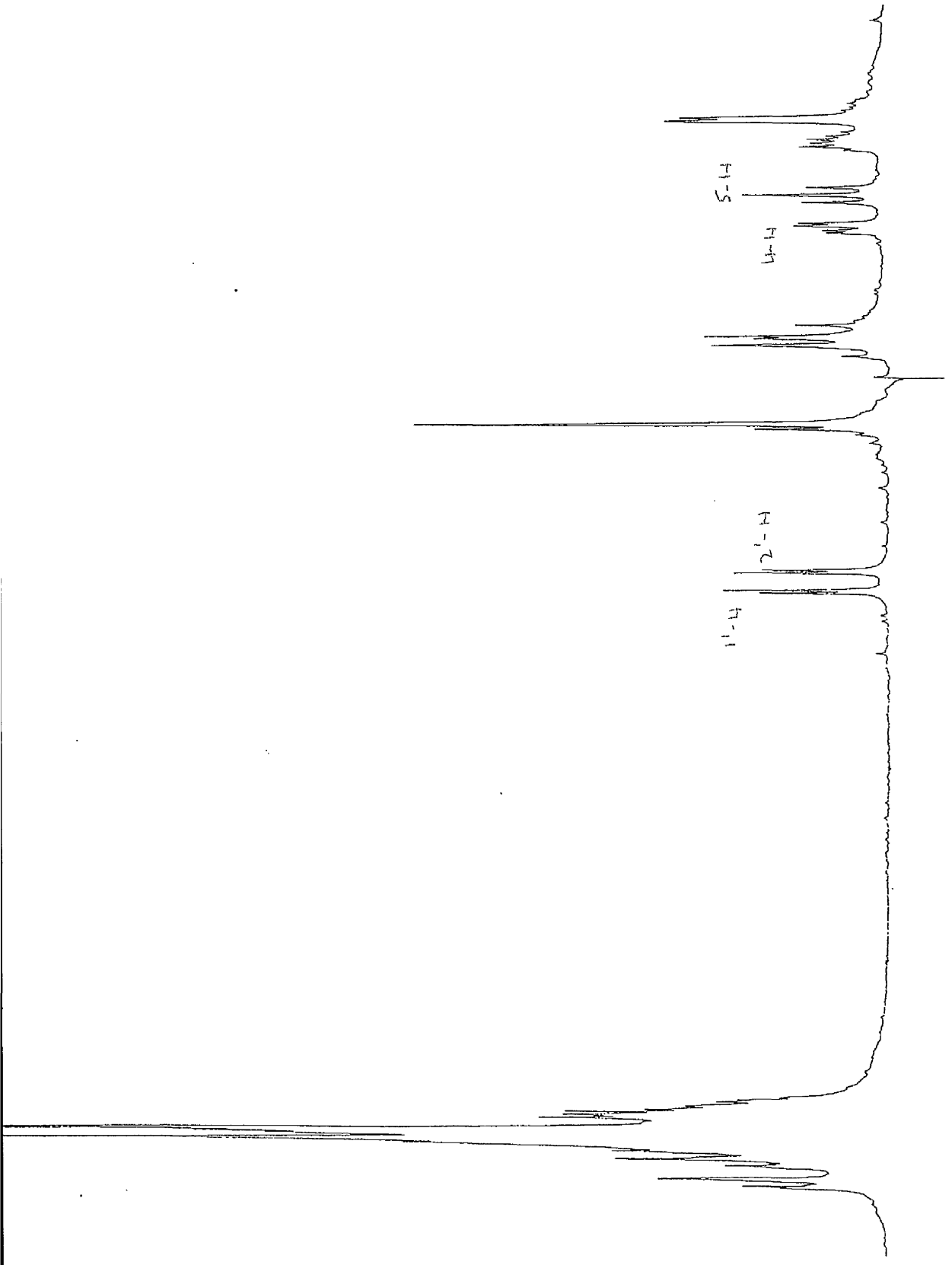
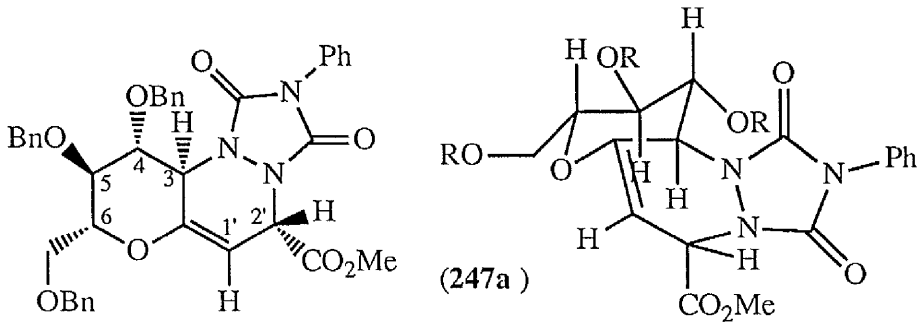


Figure 3d. ^{1}H decoupling spectrum of cycloadduct (246): Irradiation of 3-H.

Decoupling 5-H changed 6-H (multiplet to singlet) and 4-H (triplet (J = 9 Hz) to multiplet). Decoupling 3-H resulted in 4-H changing from triplet (J = 9 Hz) to doublet (J = 9 Hz). Decoupling 1′-H changed 2′-H (doublet (J = 6.5 Hz) to a singlet). These observations confirm the stereochemistry of 3-H (figure 4).



(247a)

Figure 4

^{1}H nmr analysis of cycloadduct (247b) showed a 1H broad singlet at δ 5.03 (3-H), 1H broadened doublets at δ 5.19 (J = 6.5 Hz, 2′-H) and δ 5.65 (J = 6.5 Hz, 1′-H). The infra red spectrum showed the appearance of a two strong absorptions at 1776 and 1716 cm^{-1}, corresponding to the two different imide carbonyl stretching frequencies. ^{13}C nmr showed the cycloadduct was homogeneous by virtue of one set of carbon signals.

The results of nOe studies are indicated on the diagram (figure 5). Irradiation of 3-H at δ 5.03 caused an enhancement of 6-H (4.9%) and 4-H (5.2%). This observations suggests that 3-H is on the same face of the molecule as 4-H and 6-H, proving the stereochemistry of 3-H. In addition, 5-H and 2′-H are essentially unchanged upon irradiation of 3-H, suggesting that the sugar moiety adopts a boat-type conformation. When diene (227) reacts with the dienophile (244), the sugar ring flips from a chair to a boat conformation, thereby minimising non-bonding interactions between the carbonyl and the phenyl group C-H (4-H position). 4-H moves down field by 0.65 ppm to δ 4.61 due to its proximity to carbonyl group in the imide ring system.

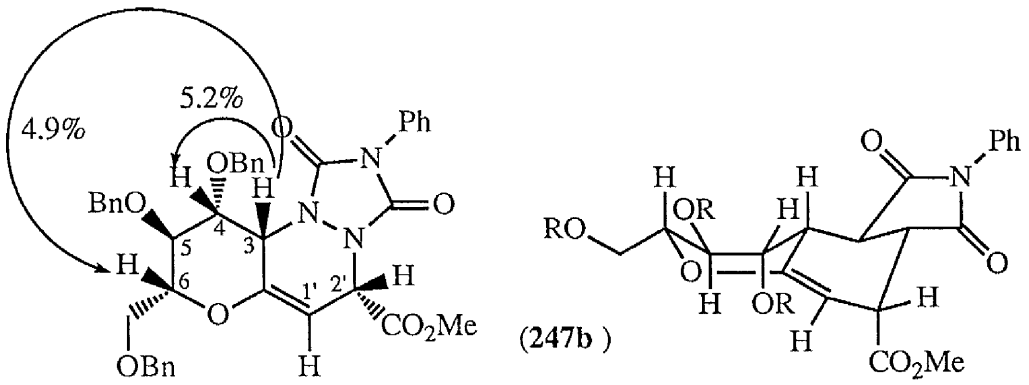


Figure 5

^{1}H nmr analysis of cycloadduct (**248**) showed a 1H doublet at δ 4.79 (J = 8.5 Hz, 3-H) and a 1H singlet at δ 5.36 (1′-H). The infra red spectrum showed the appearance of a two strong absorptions at 1779 and 1723 cm^{-1}, again corresponding to the two different imide carbonyl stretching frequencies. ^{13}C nmr showed the cycloadduct was homogeneous by virtue of one set of carbon signals.

Irradiation of the two-hydrogen multiplet centred at δ 4.14 ppm (4-H, 5-H) resulted in the doublet at δ 4.79 ppm (J = 8.5 Hz, 3-H) changing into a singlet, thereby supporting the stereochemical assignment as indicated in Figure 6.

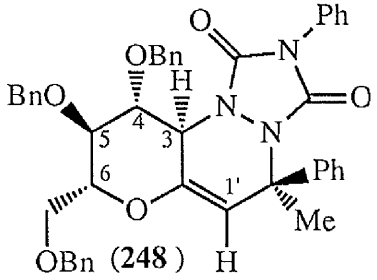


Figure 6

^{1}H nmr analysis of cycloadduct (**249a**) showed a 1H doublet at δ 4.68 (J = 8.5 Hz, 3-H), 1H broad singlet at δ 4.94 (2′-H). The infra red spectrum showed the appearance of a two strong absorptions at 1782 and 1724 cm^{-1}, corresponding to the two different imide carbonyl stretching frequencies. Irradiating 3-H resulted in 4-H changing from a triplet (J = 9.5 Hz) to a multiplet. ^{13}C nmr showed the cycloadduct was homogeneous by virtue of one set of carbon signals.

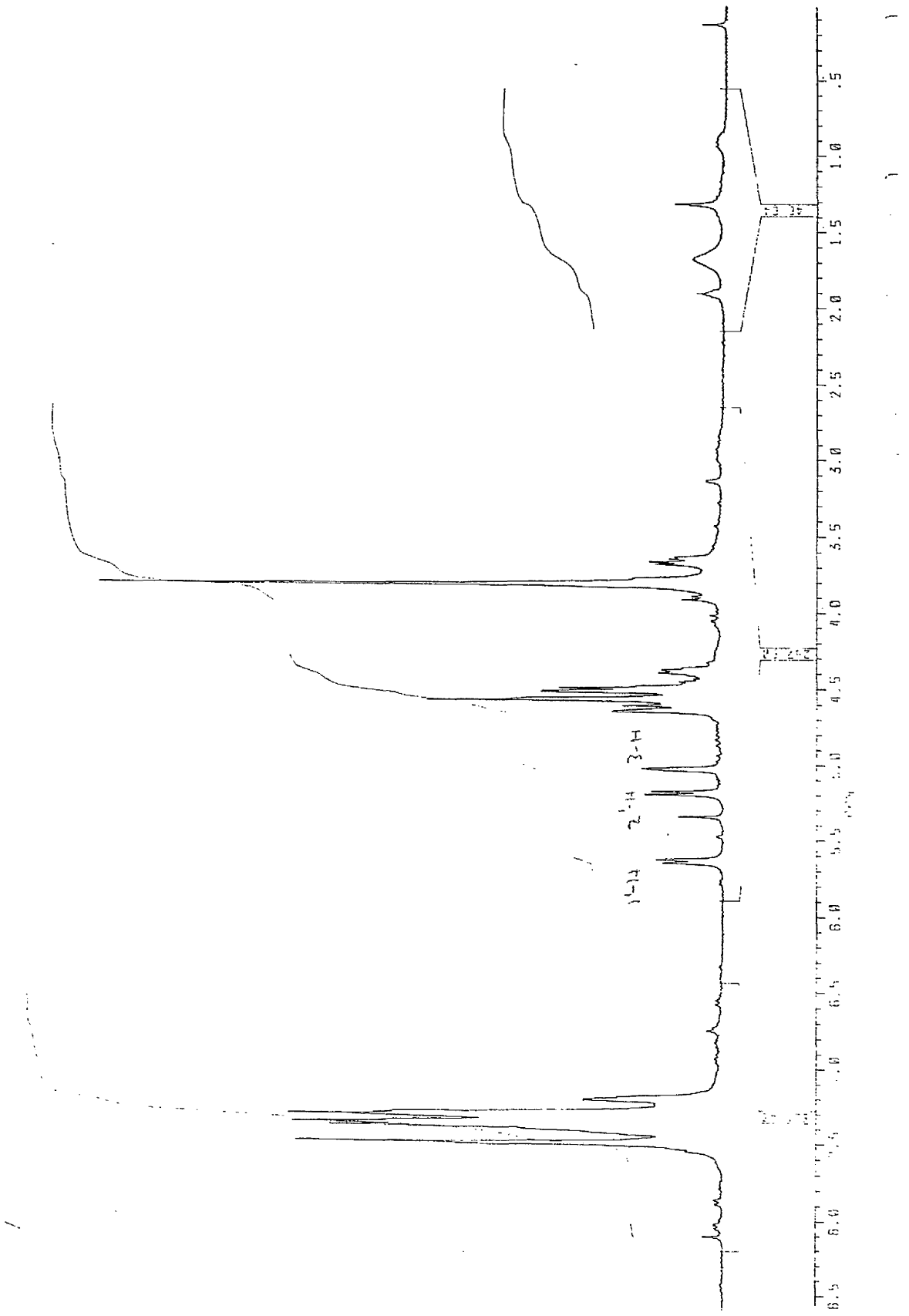


Figure 5a. ^{1}H nmr of cycloadduct (**247b**)

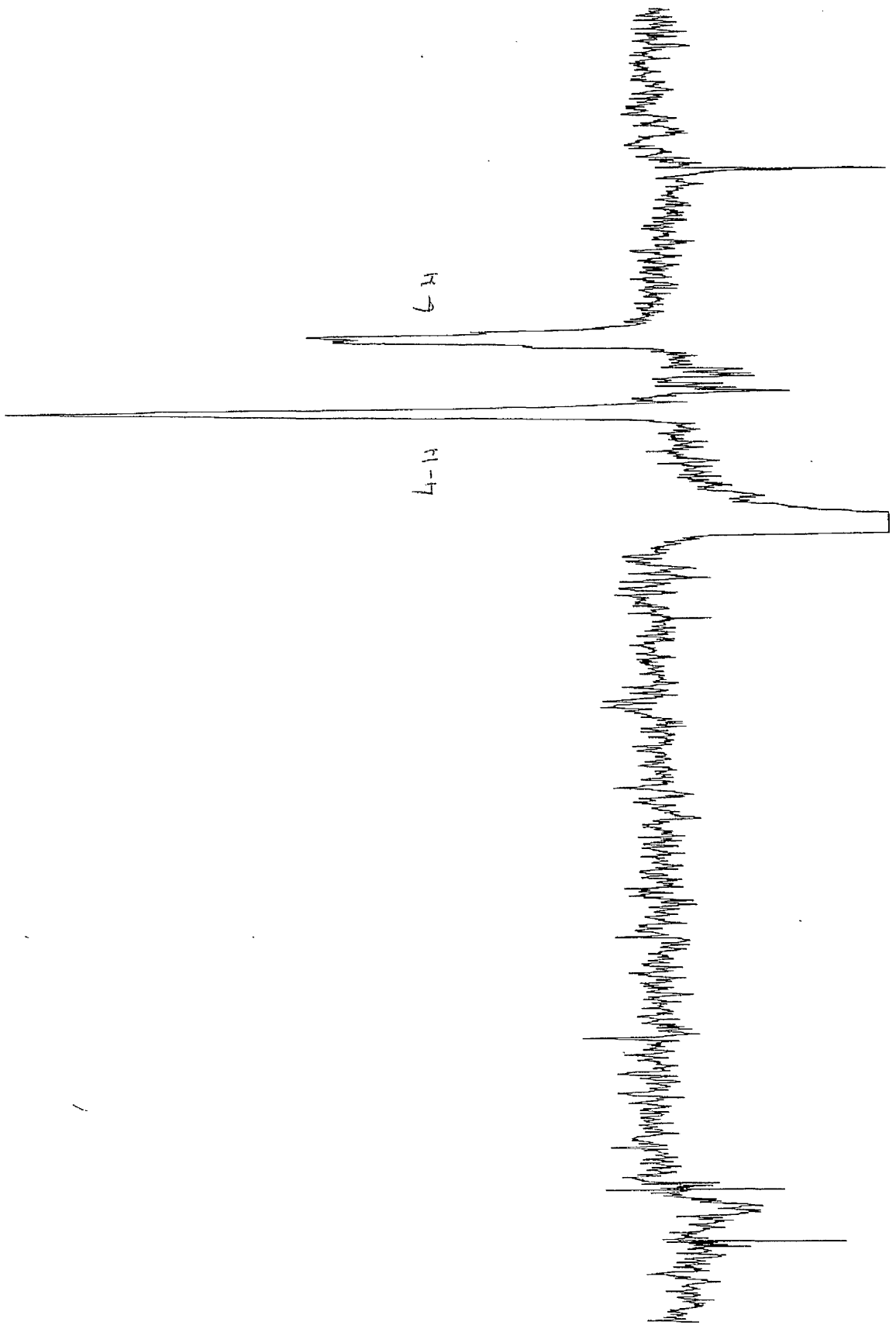
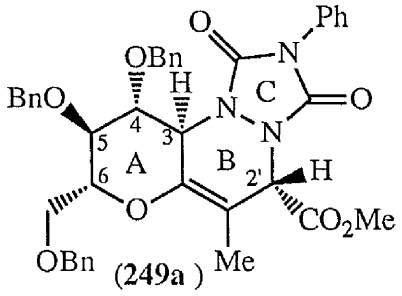


Figure 5b nOe spectrum of cycloadduct (247b): Irradiation of 3-H.

Conformation and assignment were confirmed by X-ray crystal structure. The X-ray confirmed the stereochemistry at C-2′, the sugar moiety (ring A) exists in a chair conformation and ring B approximates to a "half" chair.

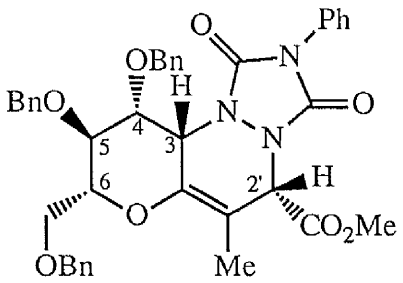


(249a)

Figure 7

^{1}H nmr analysis of cycloadduct (**249b**) showed a 1H broad singlet at δ 5.01 (3-H), 1H broad singlet at δ 5.03 (2′-H). The infra red spectrum showed the appearance of a two strong absorptions at 1774 and 1716 cm^{-1}, corresponding to the two different imide carbonyl stretching frequencies. ^{13}C nmr showed the cycloadduct was homogeneous by virtue of one set of carbon signals.

By analogy with (**247b**), when diene (**229**) reacts with the dienophile (**244**), the sugar ring flips from a chair to a boat conformation, thereby minimising non-bonding interactions between the carbonyl and the phenyl group C-H (4-H position). 4-H moves down field by 0.73 ppm to δ 4.62 due to its proximity to carbonyl group in the imide ring system.



(249b)

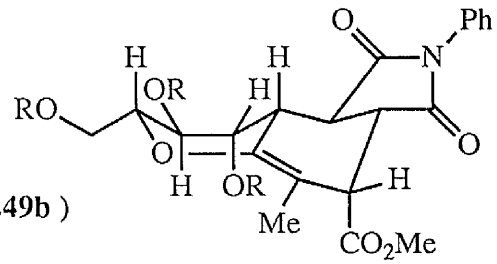


Figure 8

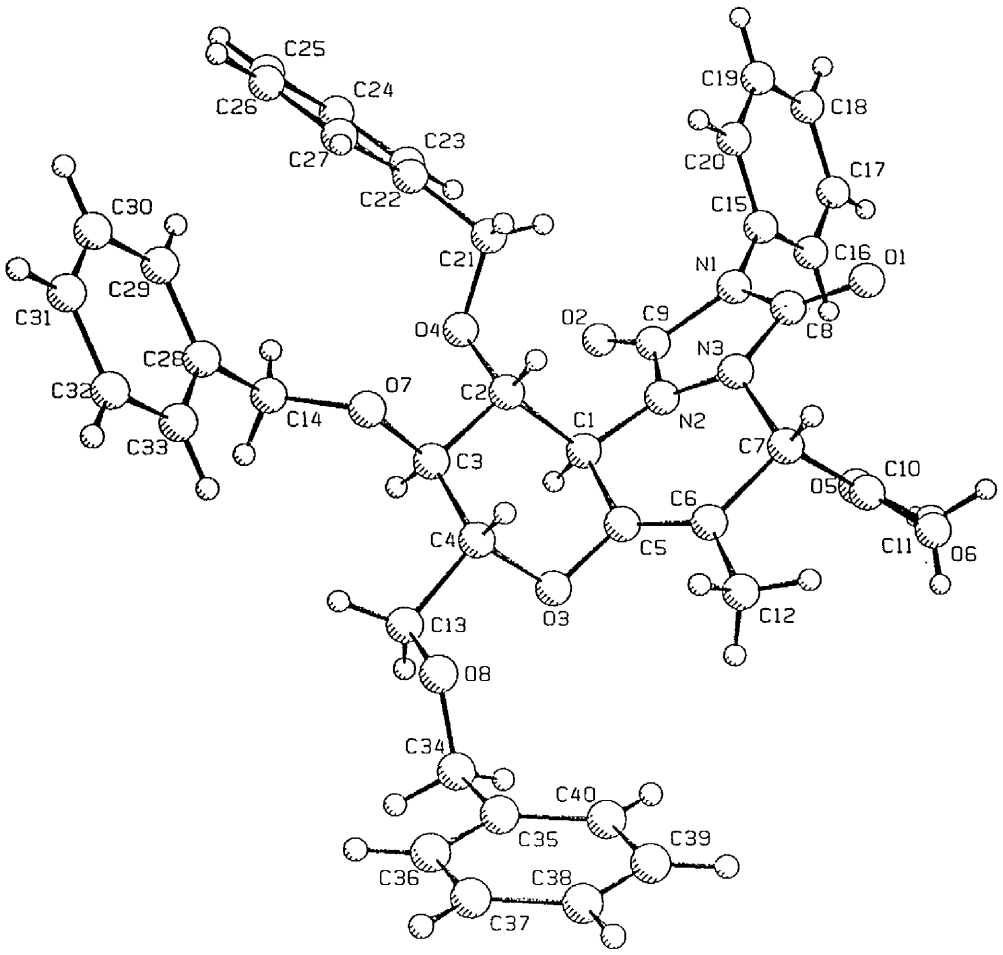


Figure 7a. X-ray crystal structure of cycloadduct (**249a**)

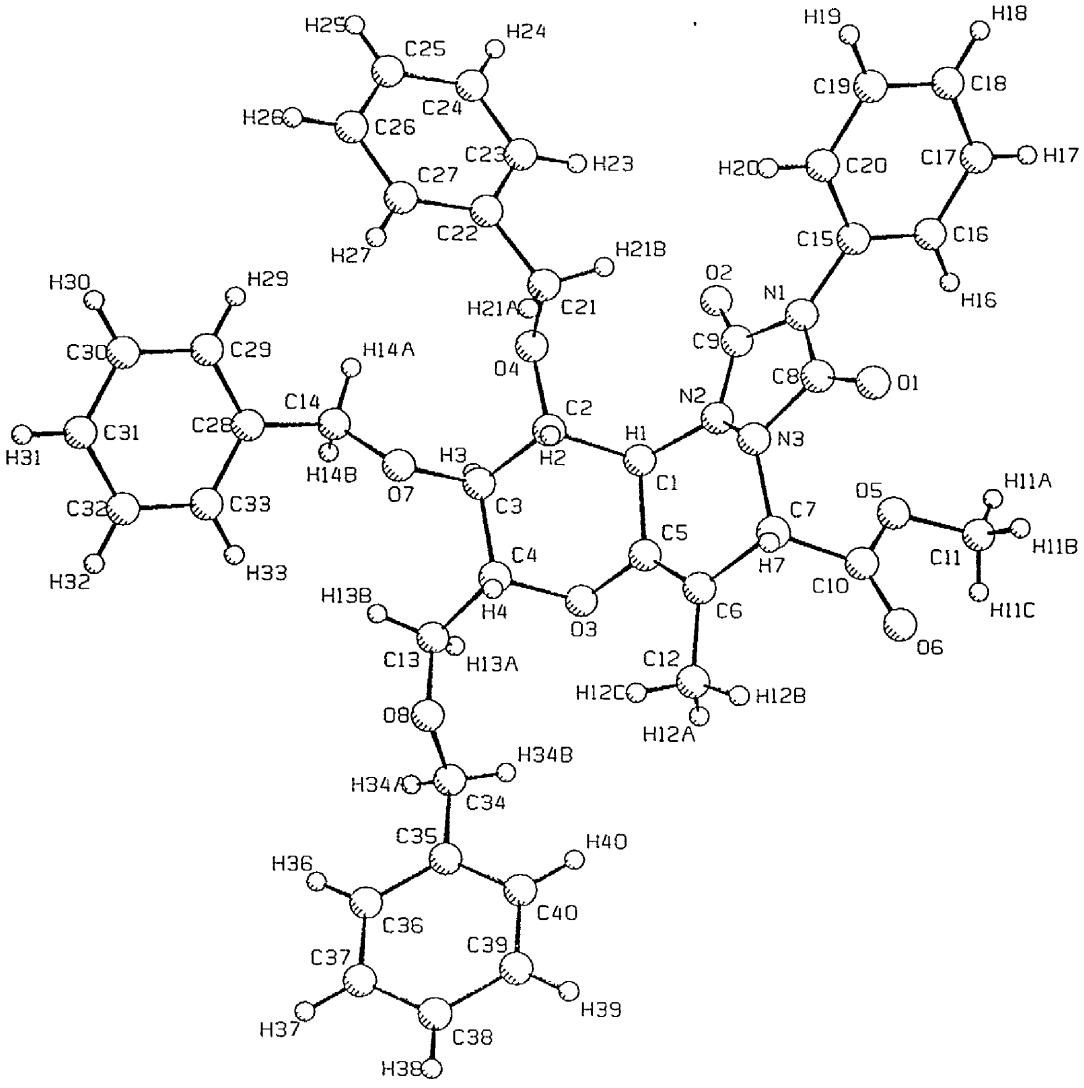


Figure 7b. X-ray crystal structure of cycloadduct (**249a**)

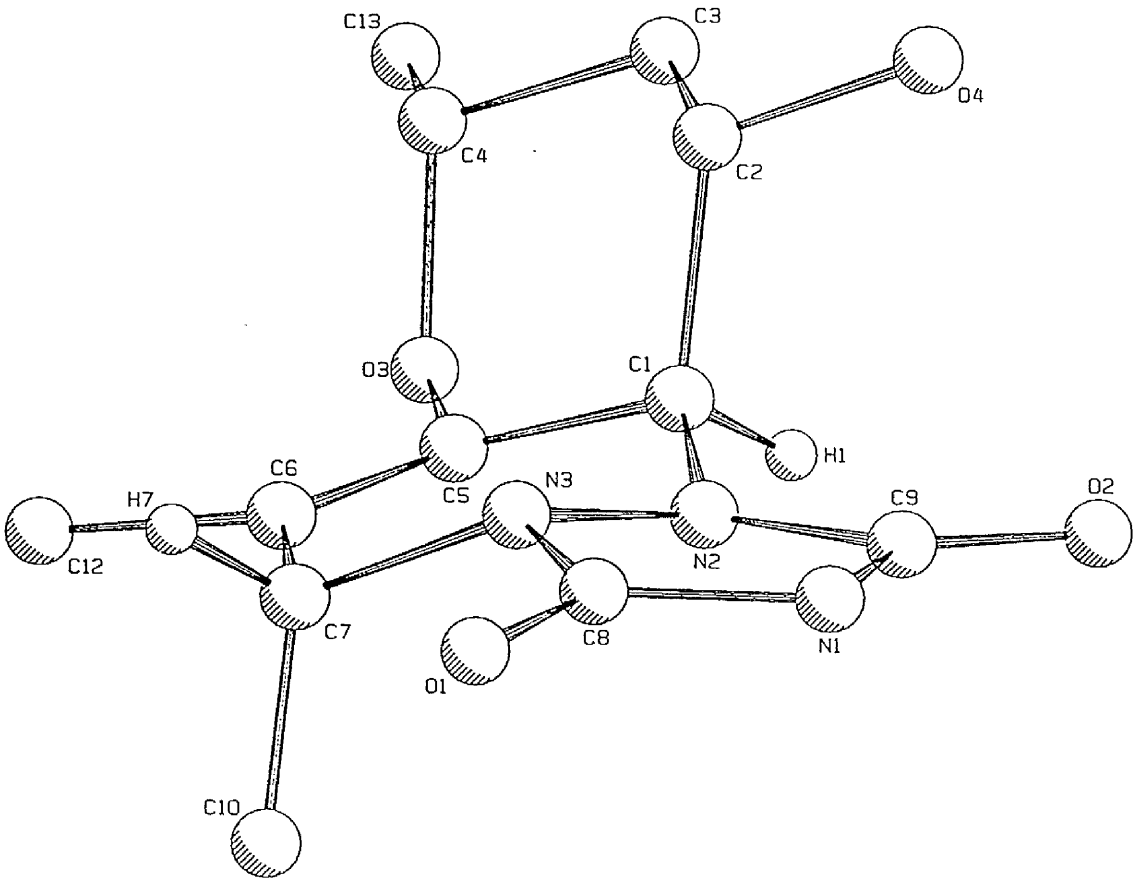


Figure 7c. X-ray crystal structure of cycloadduct (249a): view of ring A

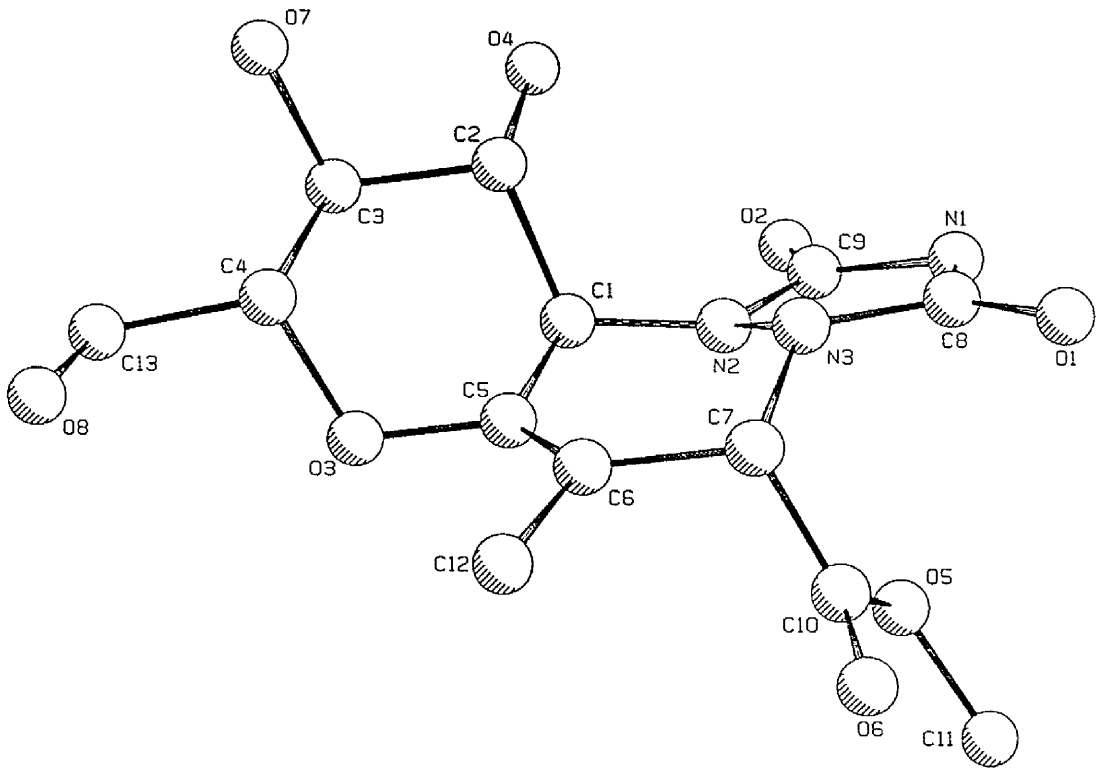


Figure 7d. X-ray crystal structure of cycloadduct (**249a**): view of ring B

^{1}H nmr analysis of cycloadduct (**250**) showed a 1H doublet at δ 4.58 (J = 8.5 Hz, 3-H), 1H multiplet at δ 4.44 (2′-H) and 1H doublet of doublets at d 5.45 (J = 2.5, 1 Hz, 1′-H). The infra red spectrum showed the appearance of a two strong absorptions at 1776 and 1720 cm^{-1}, corresponding to the two different imide carbonyl stretching frequencies. ^{13}C nmr showed the cycloadduct was homogeneous by virtue of one set of carbon signals.

Irradiation at 3-H resulted in 4-H changing from a triplet (J = 9 Hz) to doublet (J = 9 Hz) and 1′-H changing from a double doublet (J = 2.5, 1 Hz) to a doublet (J = 2.5 Hz). These observations confirm the stereochemistry of 3-H (figure 9).

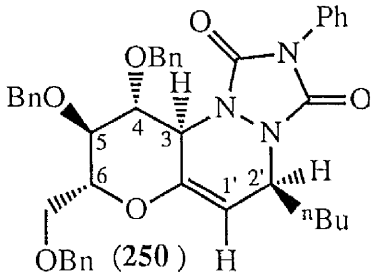
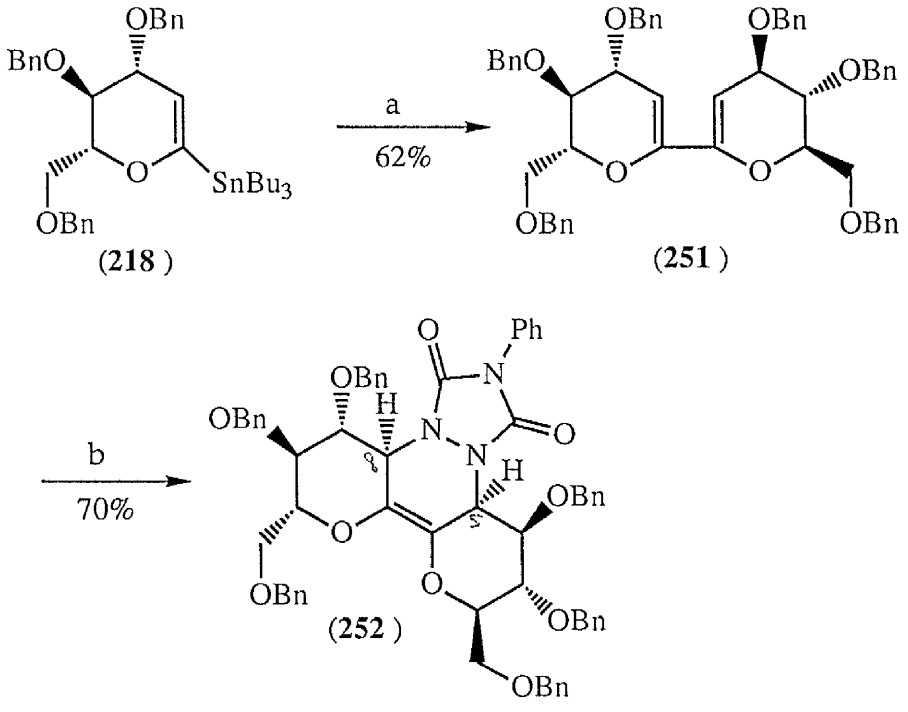


Figure 9

2.8 Homocoupling of Vinyl Stannane (218) and Subsequent Diels-Alder Reaction of Homocoupled Dimer (251)

Recently, our group has reported[74] a general method for the preparation of highly substituted, symmetrical buta-1,3-dienes based upon a copper(11)-promoted homocoupling[75] reaction of a variety of vinyl stannanes. To the vinyl stannane (**218**) in THF was added copper(11) nitrate (1 equivalent) in a single portion. This afforded the symmetrical homocoupled diene (**251**) in 62% yield. ^{1}H nmr analysis of the dimer (**251**) was characterised by a 2H doublet (J = 3 Hz, 5-H, 8-H) at δ 5.58. The infra red spectrum showed absorption characteristics of an alkene stretch (υ_{max} 1630 cm^{-1}).

The symmetrical homocoupled diene (**251**) underwent a Diels-Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) to yield cycloadduct (**252**) in 70% yield as a single diastereoisomer. ^{13}C nmr showed the loss of the symmetry.

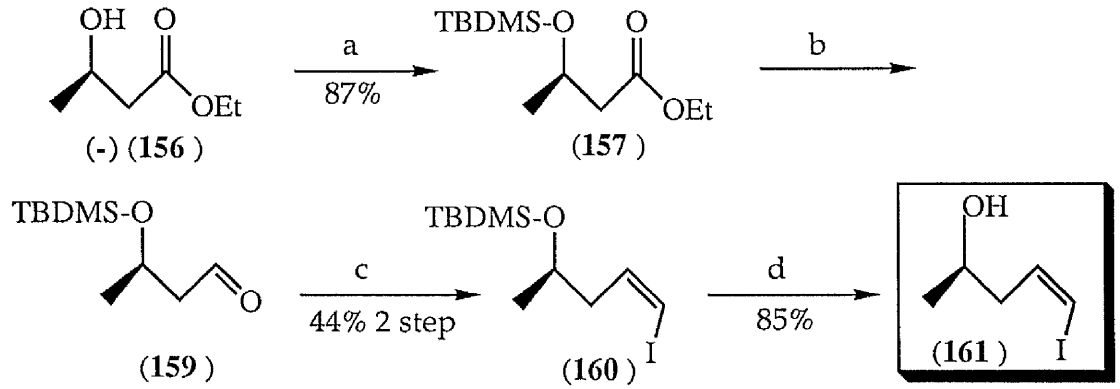


Scheme 67. *Reagents*: (a) $Cu(NO_3)_2$, THF; (b) 4-phenyl-1,2,4-triazoline-3,5-dione (**244**), CH_2Cl_2.

2.9 Synthesis of an Analogue of Northern Hemisphere of Milbemycin β_3

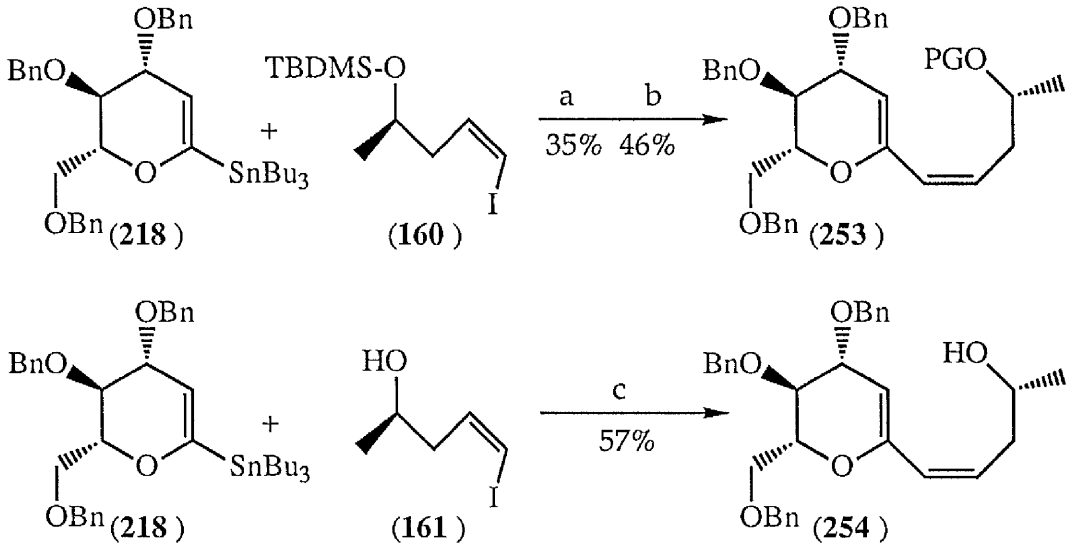
Initially, the hydroxyl group of ethyl-3-hydroxy-2-methylbutyrate (**156**) was protected as the TBDMS derivative using standard conditions (DBU, TBDMS-Cl, dichloromethane) affording (**157**) in 87% yield. Reduction of the ester (**157**) to the aldehyde (**159**). using the method employed by Baker[58] was achieved cleanly. This unstable aldehyde was used immediately in the next step to prepare the vinyl iodide. This was achieved by a Wittig olefination sequence using Stork's[51] procedure. The ylid (**203**) was generated from iodomethyl-triphenyl phosphonium iodide (**202**). This was effected by deprotonation of (**202**) using sodium hexamethyldisilazide at room temperature. After generation, the dark red coloured ylid (**203**) was cooled to -78°C and reacted with the aldehyde (**159**). The reduction/Wittig reactions combined proceeded in 41% overall yield resulting in a mixture of geometric isomers of the vinyl iodide (*Z*:*E* 19.8:1) (**160**), which were found to be light sensitive. The infra red spectrum showed a weak absorption characteristic of the alkene stretch (υ_{max} 1611 cm^{-1}). ^1H nmr analysis showed a characteristic distinction between the two isomers in the vinylic region. The Z-isomer showed a 2H multiplet at δ 6.30 while the *E*-isomer showed a 1H doublet at δ 6.06 and a 1H doublet of triplets at δ 6.55 with a vicinal coupling constant J = 14.5 Hz.

Deprotection of the alcohol was cleanly achieved using aqueous hydrogen fluoride in acetonitrile[60] to afford the alcohol (**161**) (*Z*:*E* 15.7:1) in 85% yield. The infra red spectrum showed a weak absorption characteristic of the alkene stretch (υ_{max} 1610 cm^{-1}). ^1H nmr analysis showed a characteristic distinction between the two isomers in the vinylic region. The Z-isomer showed a 1H quartet at δ 6.33 and 1H doublet δ 6.41 while the *E*-isomer showed a 1H doublet at δ 6.18 and a 1H doublet of triplets at δ 6.59 with a vicinal coupling constant J = 14.5 Hz.



Scheme 68. *Reagents*: (a) DBU, TBDMS-Cl, CH_2Cl_2, 0°C, 3h; (b) DIBAL-H (1.6eq.), toluene, -80°C, 1 h; (c) Ph_3P=CHI (**203**), THF, -78°C (generated from $[Ph_3PCH_2I]^+I^-$ (**202**) $NaN(SiMe_3)_2$, rt); (d) HF, CH_3CN;

Two methods were employed for the palladium(0) cross-coupling between the stannylated glucal (**218**) and vinyl iodide (**160**). The first used $[Pd_2(dba)_3]$ in DMF at room temperature.[33] This generated the glycosyl 1,3-diene (**253**) in 35% with some erosion of stereoselectivity (*Z*:*E* 9:1 to 3.2:1). In the second bis(acetonitrile)dichloropalladium was used as catalyst in DMF at room temperature. This generated the glycosyl 1,3-diene (**253**) in 46% again with some erosion of stereoselectivity (*Z*:*E* 19.8:1 to 8.6:1). The optimum yielding cross-coupling reaction was achieved between the stannylated glucal (**218**) and alcohol (**161**) using bis(acetonitrile)dichloropalladium as catalyst in DMF at room temperature. This generated the glycosyl 1,3-diene (**254**) in 57%, again with some erosion of stereoselectivity (*Z*:*E* 15.7:1 to 2.7:1).



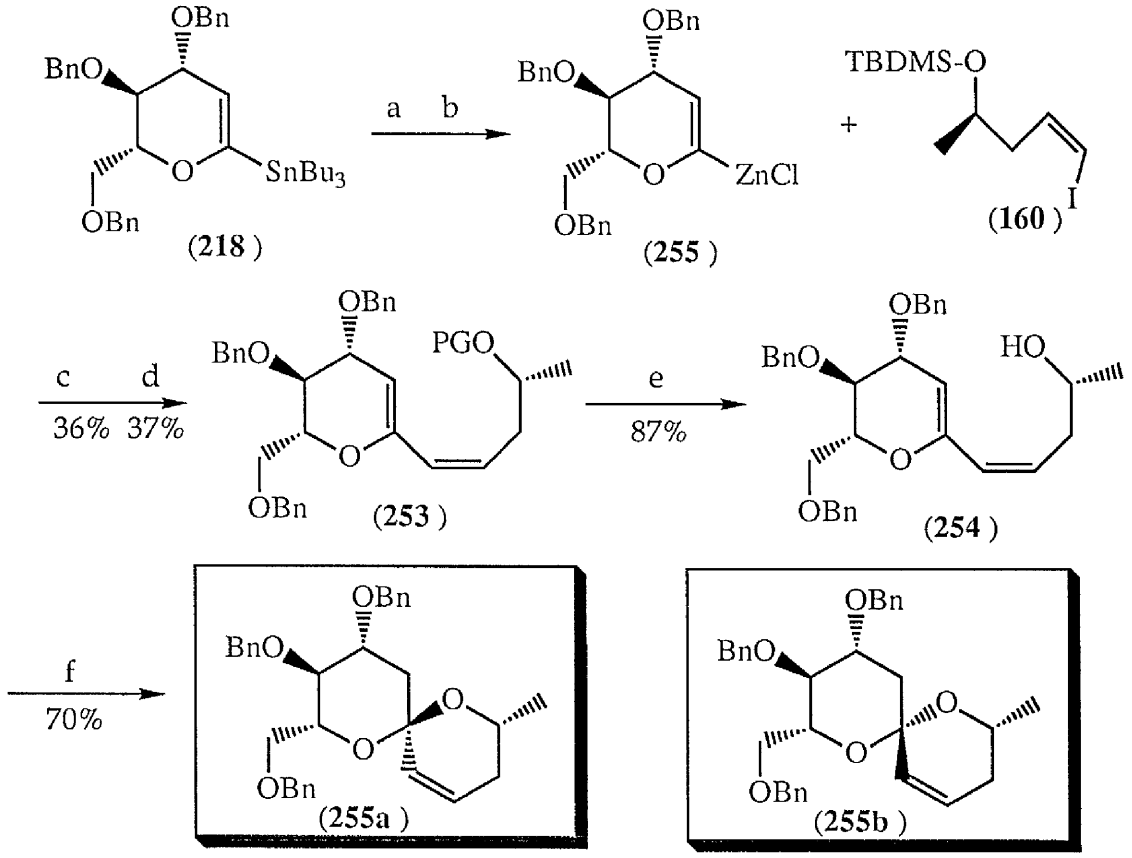
Scheme 69. *Reagents* : (a) $[Pd_2(dba)_3]$, DMF, rt, 42 h; (b) $Pd(CH_3CN)_2Cl_2$, DMF, rt, 41h; (c) $Pd(CH_3CN)_2Cl_2$, DMF, rt, 41h.

An alternative approach was sought to resolve the erosion of stereoselectivity. This was achieved by transmetallating the vinyl stannane (**218**) to corresponding vinyl zinc intermediate (**255**). The vinyl stannane (**218**) was treated with n-butyllithium in THF at -78°C for 15 minutes. The vinyl lithium intermediate was transmetallated with zinc chloride at this temperature generating the vinyl zinc intermediate (**255**) at ambient temperature. This reagent was used for in two palladium(0) cross-coupling reactions with vinyl iodide (**160**). The first used tetrakis(triphenylphosphine) palladium(0) as catalyst and afforded glycosyl 1,3-diene (**253**) in 36% yield with retention of stereoselectivity. The second used by Kocienski,[33] $[Pd_2(dba)_3]$ (2 mol%) and triphenylarsine (4 mol%) in THF at room temperature. This afforded glycosyl 1,3-diene (**253**) in 37% yield again with retention of stereoselectivity.

^1H nmr analysis of (Z)-glycosyl 1,3-diene (**253**) showed a 1H doublet at δ 4.95 (J = 3 Hz, 3-H), 1H doublet of triplets at δ 5.65 and 1H doublet at δ 5.76 with vicinal J = 12 Hz. The infra red spectrum showed the appearance of a second weak absorption at 1658 cm^{-1}, corresponding to a second alkene stretching frequency.

Deprotection of the hydroxyl group of glycosyl 1,3-diene (**253**) under standard conditions (TBAF, THF, 15 h) afforded the spiroacetal precursor (**254**) in 87% yield. Attempted acid deprotection (HF, CSA) decomposed the glycosyl 1,3-diene (**253**). ^{1}H nmr analysis of (Z)-glycosyl 1,3-diene (**254**) showed a 1H doublet at δ 4.96 (J = 3 Hz, 3-H), 1H doublet of triplets at δ 5.61 and 1H doublet at δ 5.84 with vicinal J = 12 Hz. The infra red spectrum showed two weak absorptions at 1657 and 1609 cm^{-1}, corresponding to the two alkene stretching frequencies.

The first method employed for the cyclisation of the diene (**254**) was the acid-catalysed spiroacetalisation effected using camphorsulphonic acid (catalytic) in dichloromethane[61] to give spiroacetal (**255a**) in 70% yield. A minor component, tentatively assigned as the anomer (**225b**) was seen from ^{1}H and ^{13}C nmr (spiro centre at δ 93.38).



Scheme 70. *Reagents* (a) ^{n}BuLi, THF, -78°C, 15 min; (b) $ZnCl_2$, -78°C, 2 h; (c) $Pd(PPh_3)_4$; (d) $[Pd_2(dba)_3]$, Ph_3As; (e) TBAF, THF, 12h; (f) CSA (cat.) CH_2Cl_2, 1 h.

The infra red spectrum showed the disappearance of a weak absorption at 1609 cm^{-1}, corresponding to an alkene stretching frequency. ^{1}H nmr analysis showed the disappearance of a 1H doublet at δ 4.96, which was replaced by the diastereotopic methylene protons 11_{ax}-H and 11_{eq}-H at δ 1.77 and δ 2.41 respectively and the appearance of a 2H multiplet at δ 5.7 (4-H, 5-H). ^{13}C analysis showed the appearance of the spiro carbon at δ 96.19.

The results of nOe studies are indicated on the diagram (figure 10). These observations confirm ring A exists in a chair conformation and that the oxygen substituents are axial with respect to each ring i.e the anomeric effect applies.

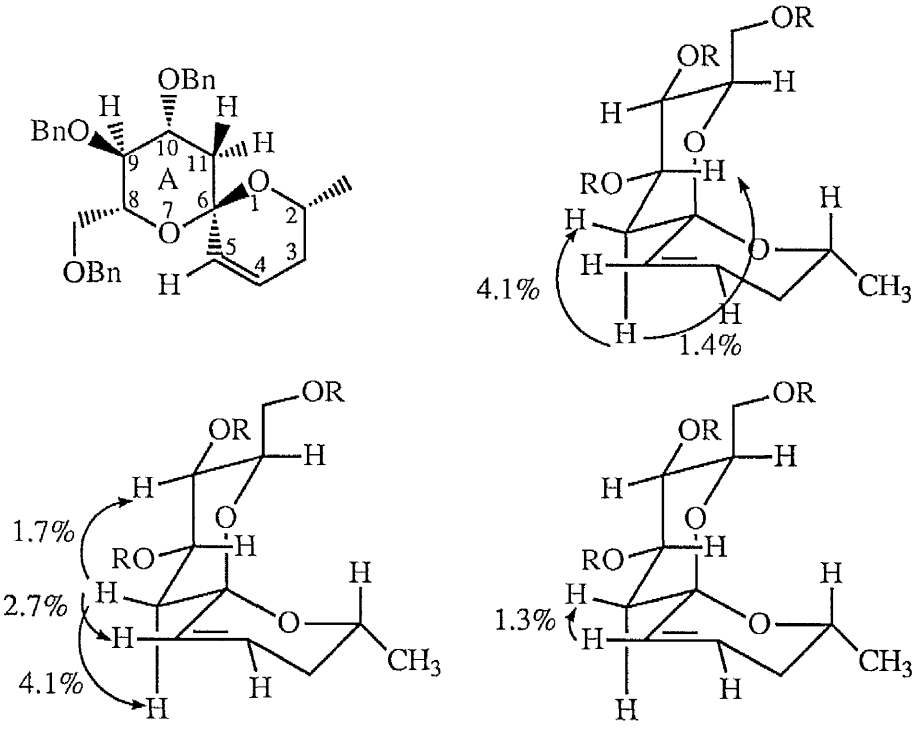


Figure 10

The second method of cyclisation of diene (**254**) was effected using phenylselenium chloride/pyridine[52] affording a mixture of diastereomeric selenides (**256a, b, c**) (1.5:1:3.2) in 43% yield which could be partially separated by column chromatography.

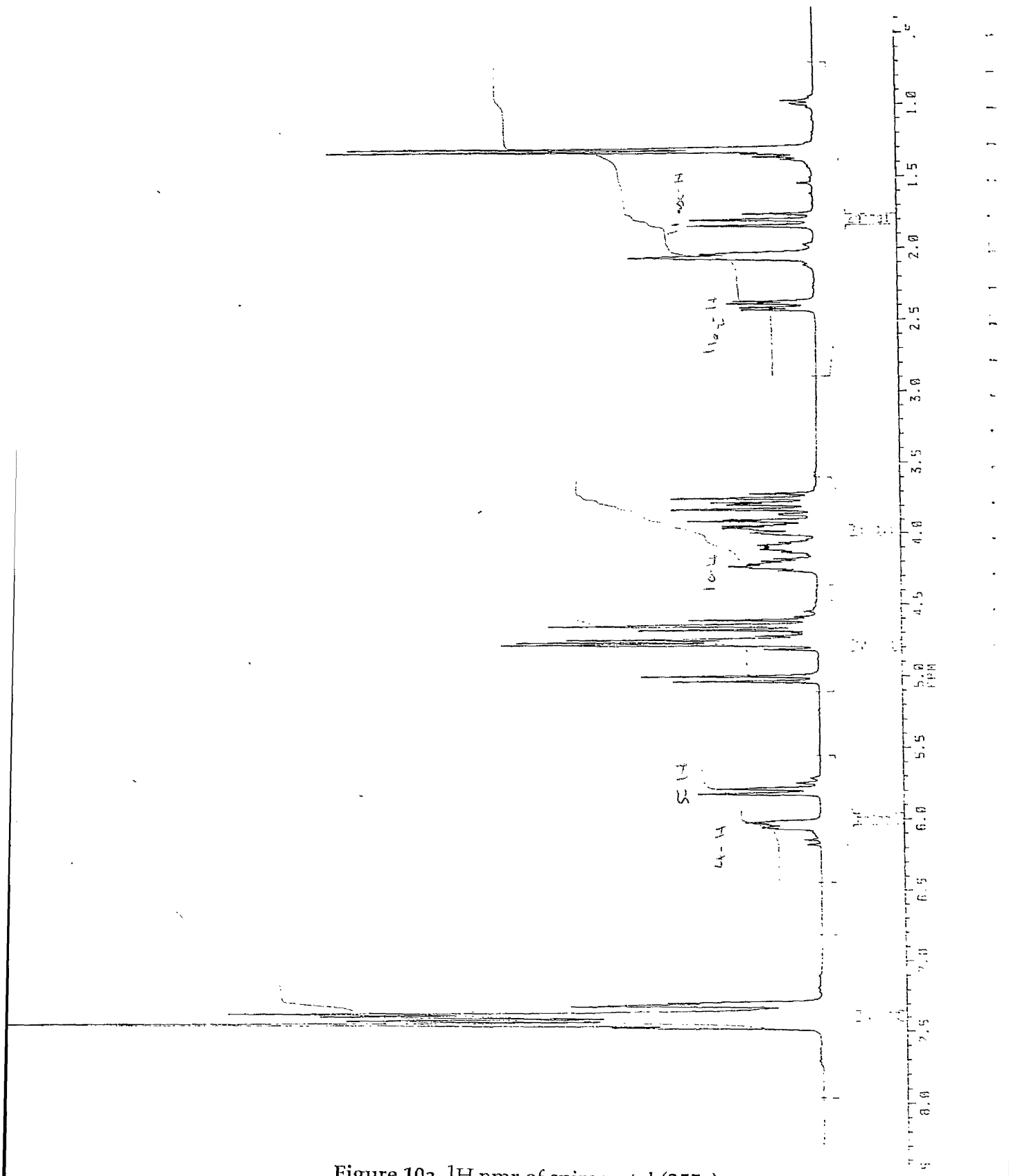


Figure 10a. ^{1}H nmr of spiroacetal (255a)

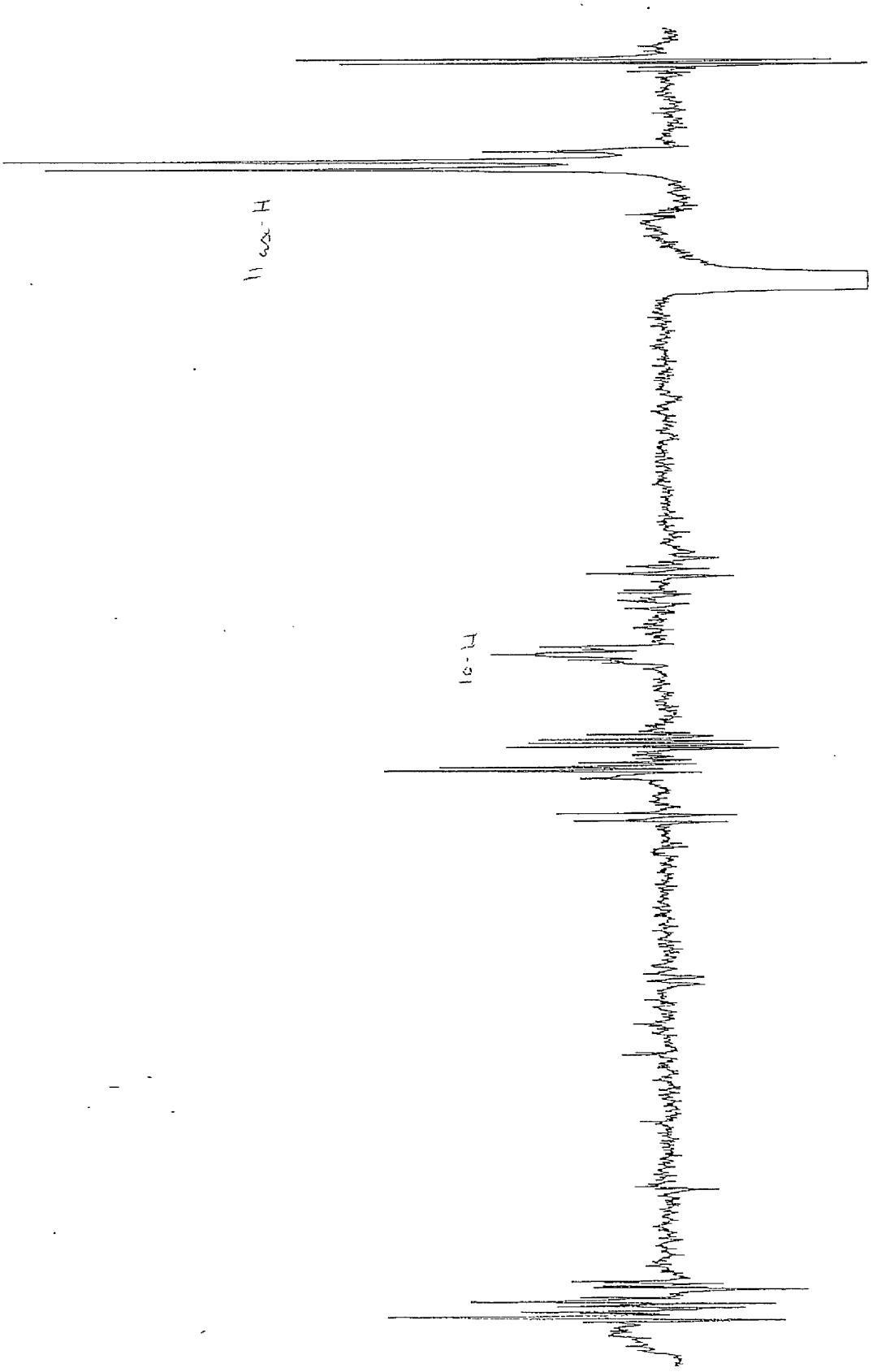


Figure 10b. nOe spectrum of spiroacetal (**255a**): Irradiation of 11_{eq}-H.

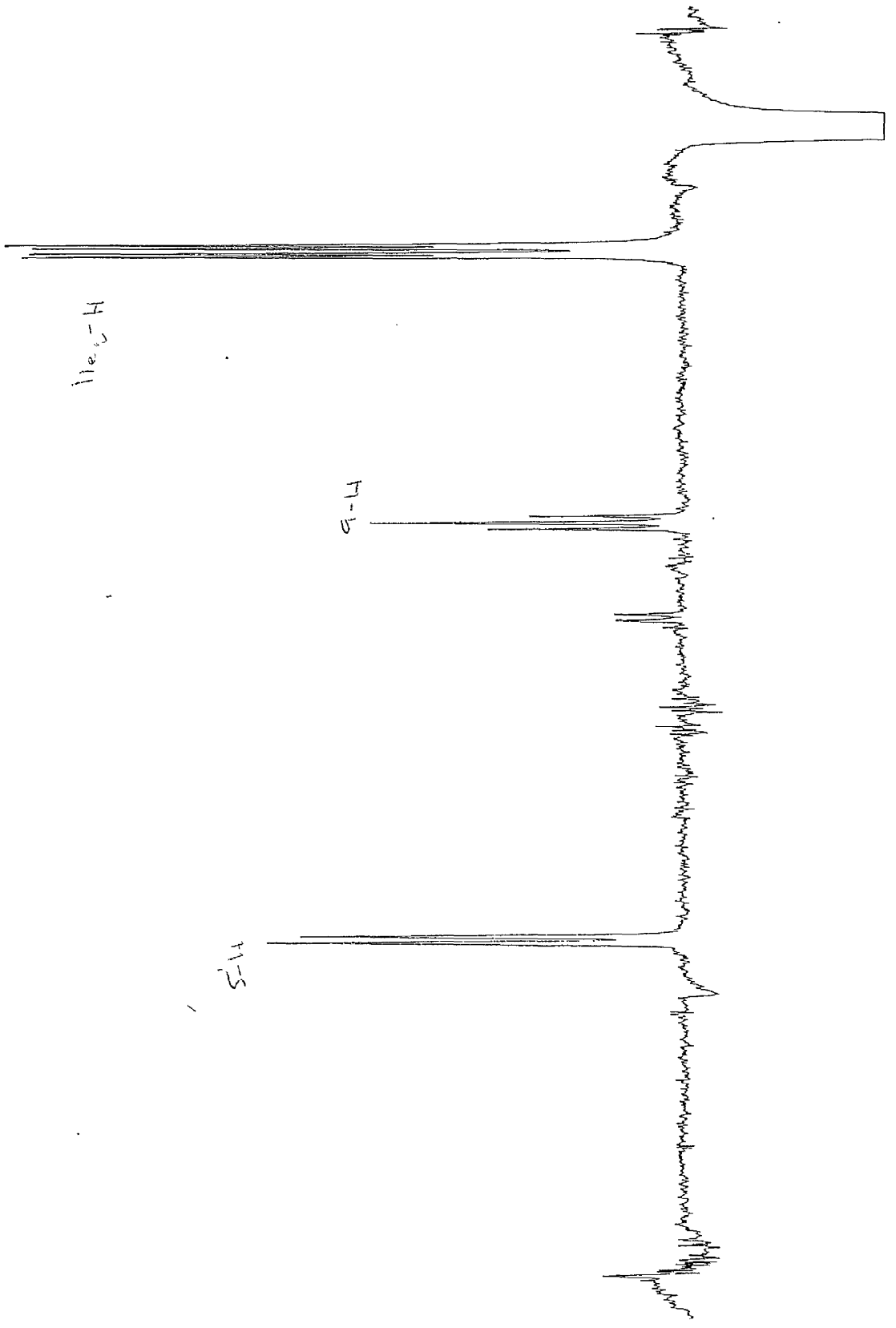


Figure 10c. nOe spectrum of spiroacetal (**255a**): Irradiation of 11_{ax}-H.

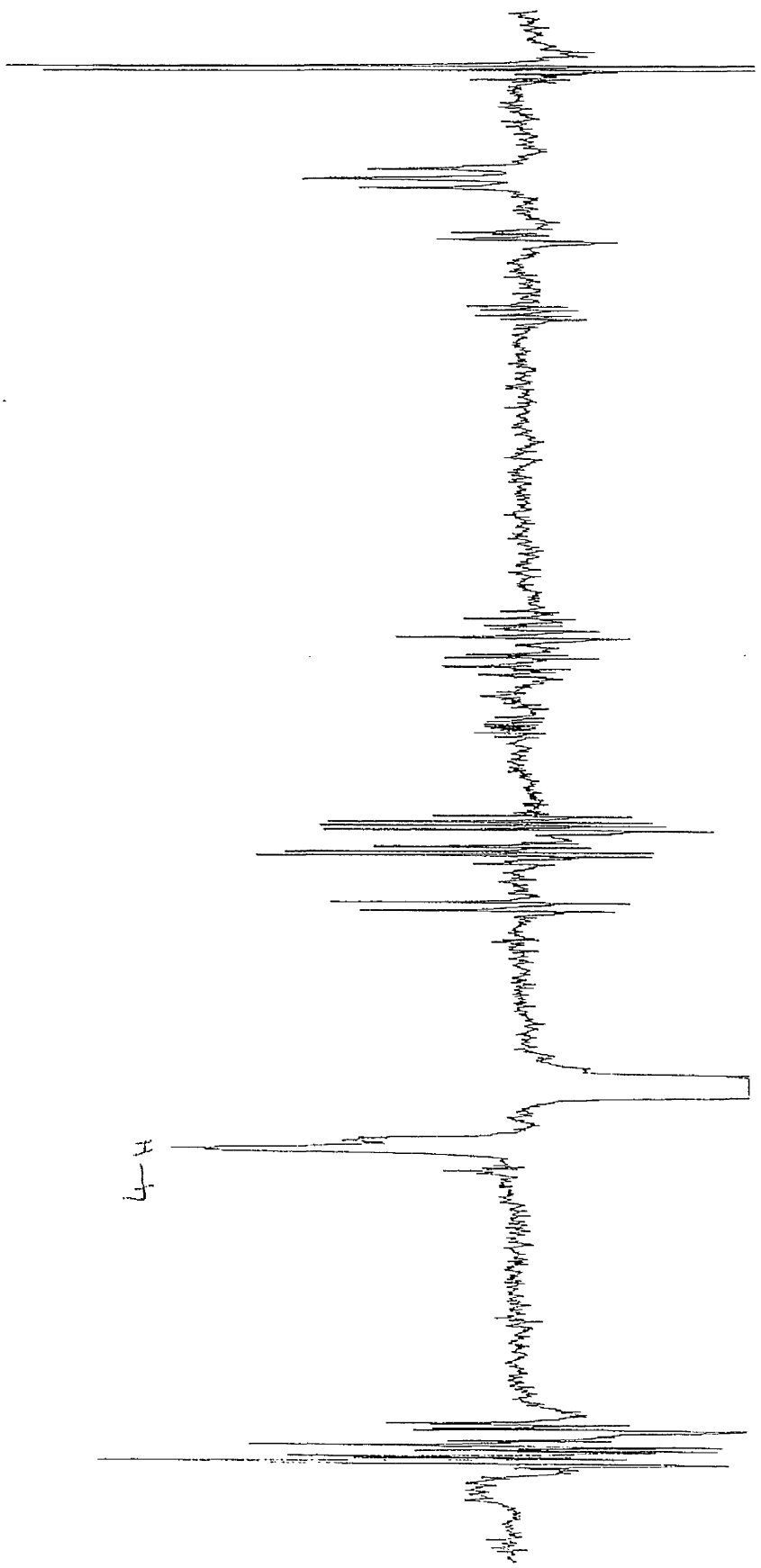
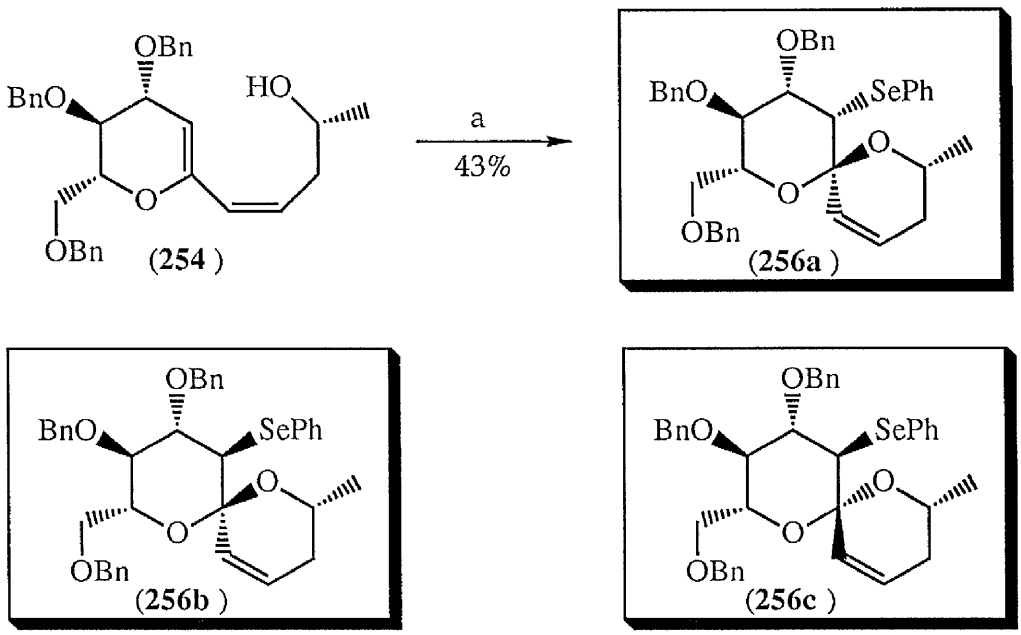


Figure 10d. nOe spectrum of spiroacetal (**255a**): Irradiation of 5-H.



Scheme 71. *Reagents*: (a) PhSeCl, pyridine, CH_2Cl_2, -78°C, 1 h.

The results of nOe studies are indicated on the diagram (figure 11). Irradiation of 5-H on selenide (**256a**) caused an enhancement of 11_{eq}-H (1.5%). Irradiation of 5-H on selenide (**256b**) caused an enhancement of 11_{ax}-H (3.4%). Irradiation of 11_{ax}-H on selenide (**256b**) caused enhancements of 5-H (1.7%), 9-H (0.4%), and 10-H (1.4%). These observations confirm ring A exists in a chair conformation and that the oxygen substituents are axial with respect to each ring.

Irradiation of 5-H on selenide (**256c**) caused an enhancement of 4-H (2.6%), 8-H (0.7%) and 10-H (0.7%). Irradiation of 11_{ax}-H on selenide (**256c**) caused an enhancement of 2-H (0.7%). These observations confirm ring A exists in a chair conformation with an equatorial C-O bond at the spiro centre.

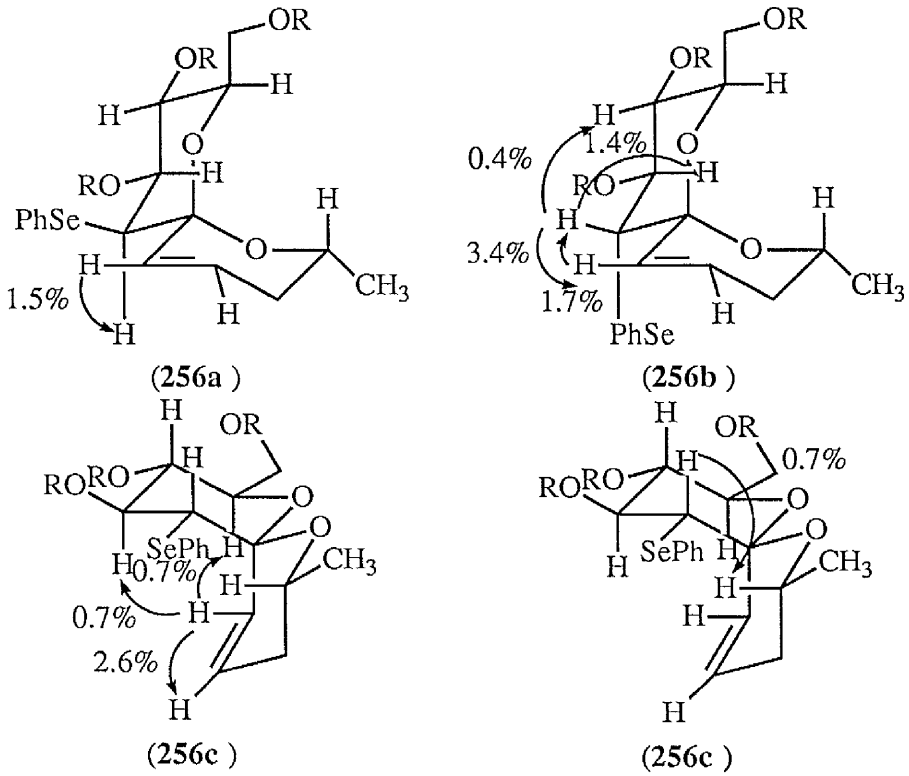

OR
OR
H
H
O
RO
H
PhSe
H
O
CH3
H
1.5%
H
H
(256a)
OR
OR
H
H
0.4%
1.4%
O
RO
H
H
H
3.4%
O
CH3
H
1.7%
H
PhSe
(256b)
H
OR
H
RO
RO
O
O
SePh
H
H
0.7%
CH3
H
0.7%
H
2.6%
H
(256c)
H
OR
H
0.7%
RO
RO
O
O
H
SePh
H
CH3
H
H
H
(256c)

Figure 11

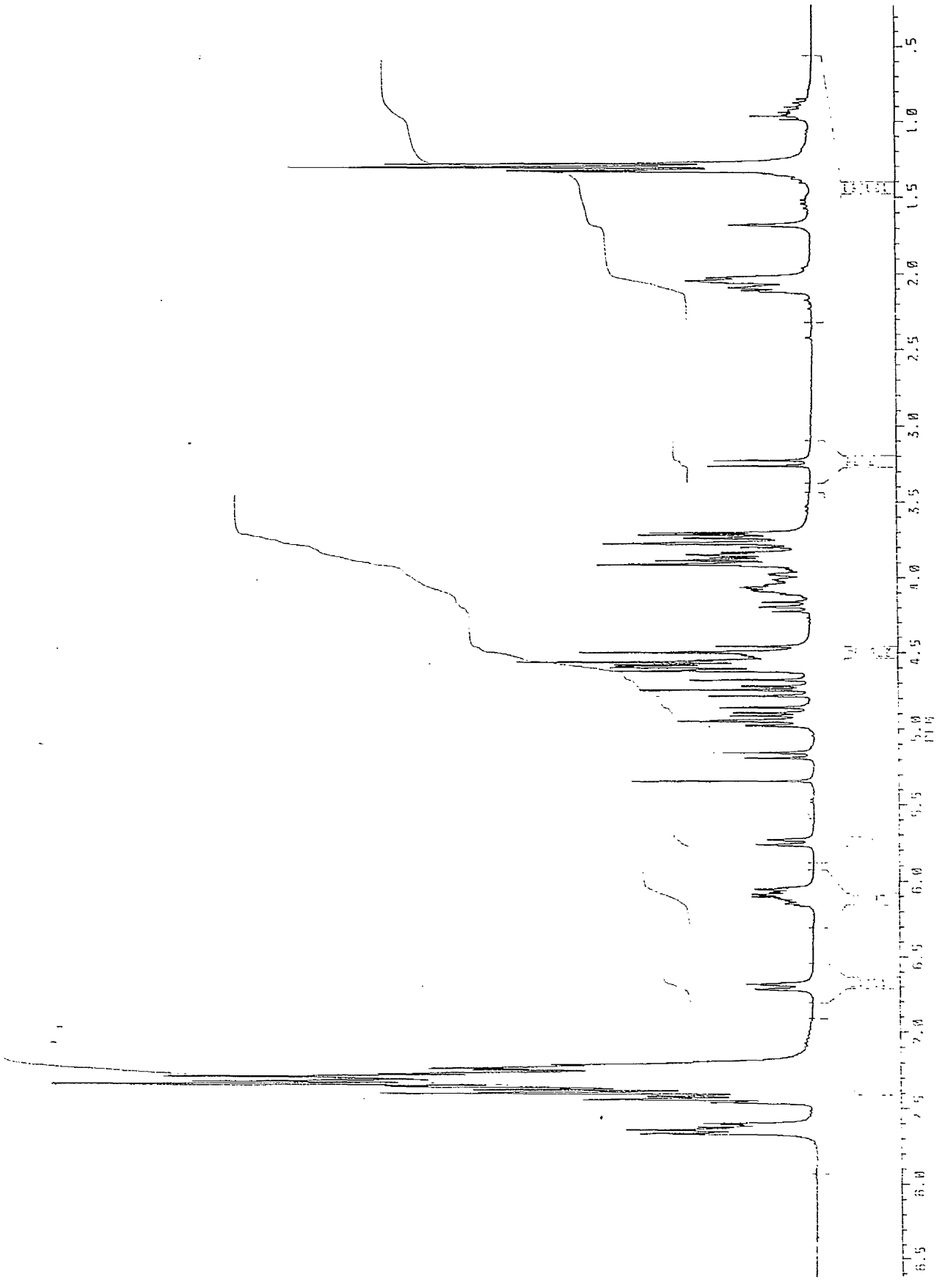


Figure 11a. ^{1}H nmr of spiroacetal (256a, b)

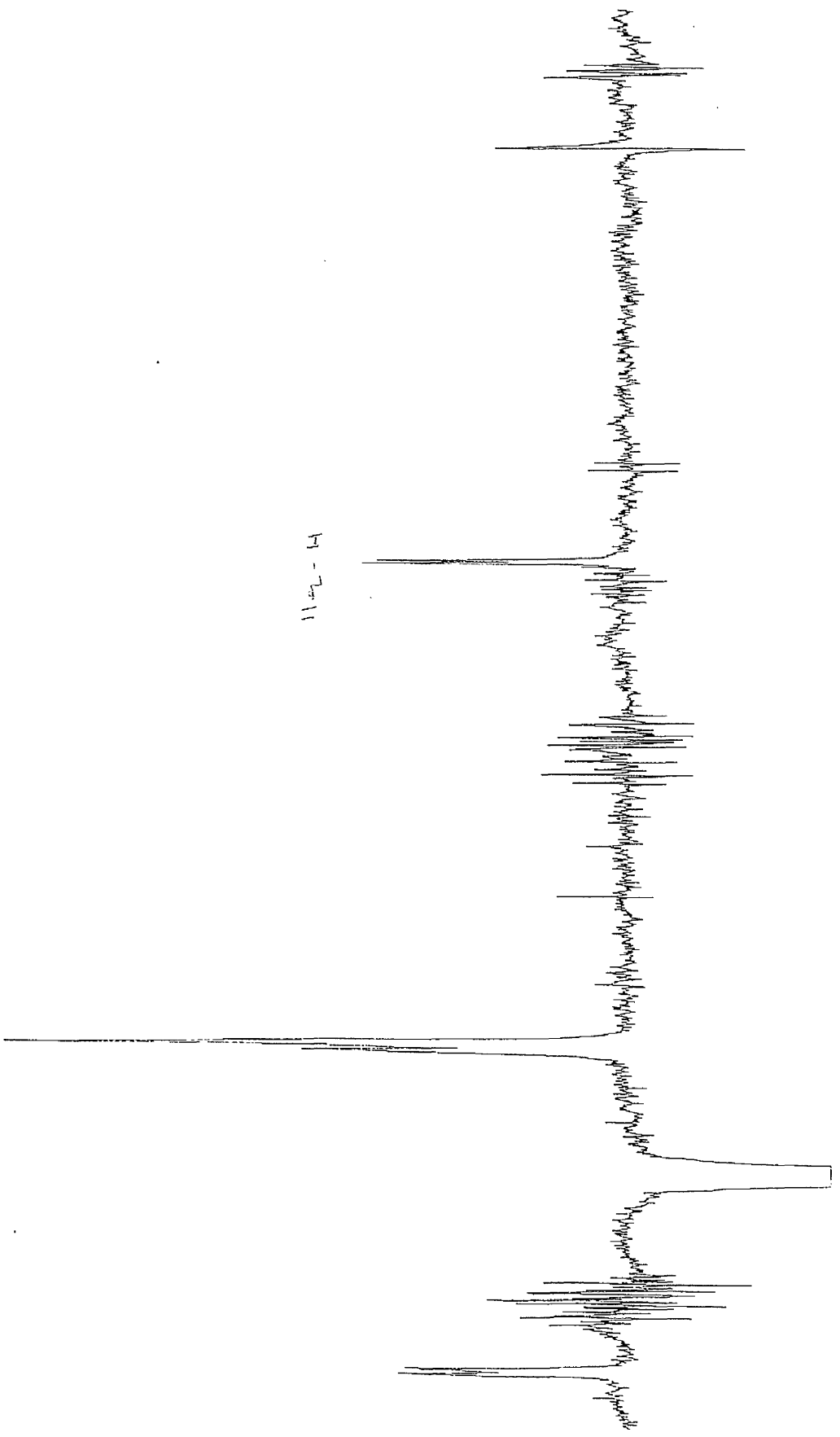


Figure 11b. nOe spectrum of spiroacetal (256a): Irradiation of 5-H

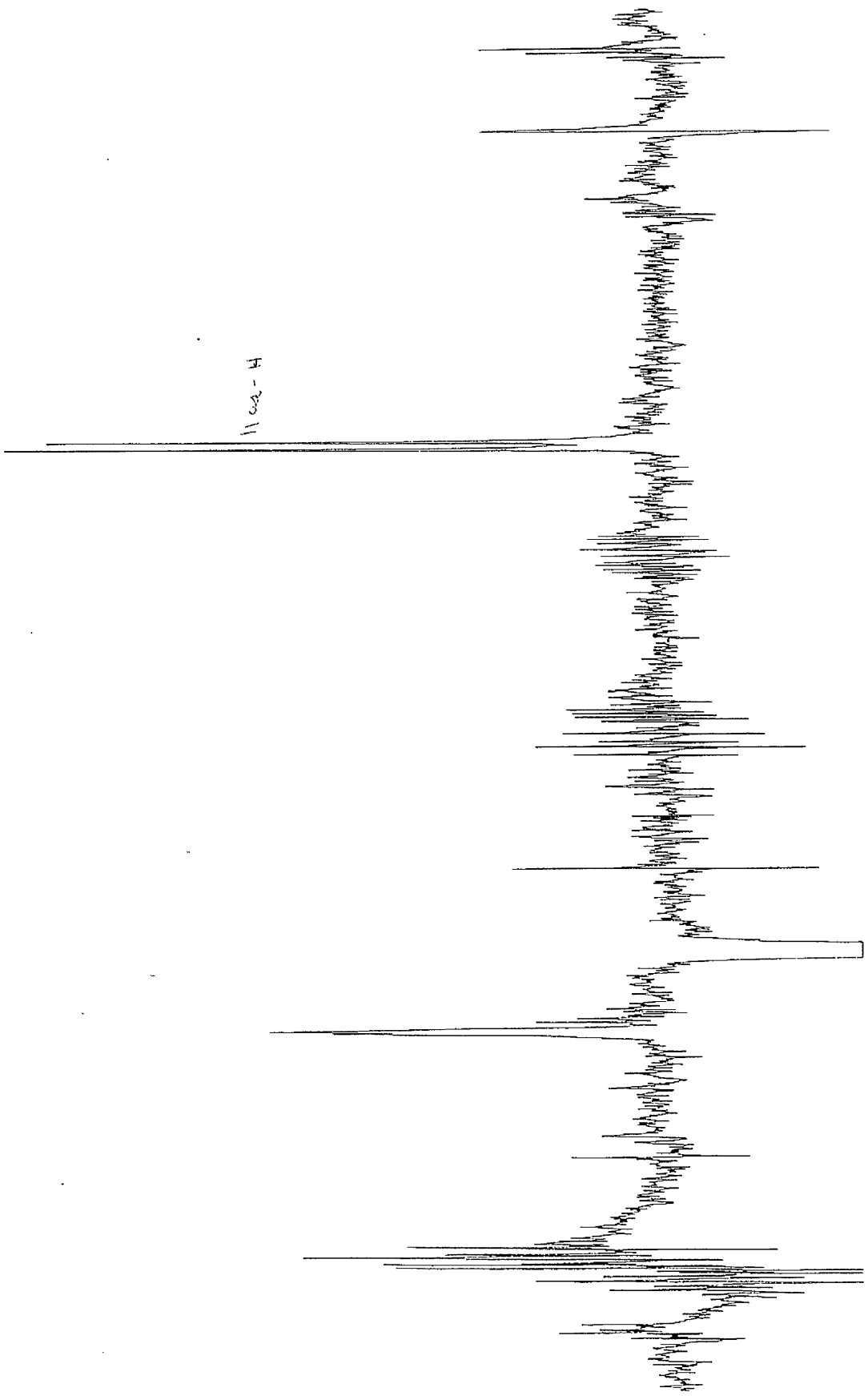


Figure 11c. nOe spectrum of spiroacetal (**256b**): Irradiation of 5-H

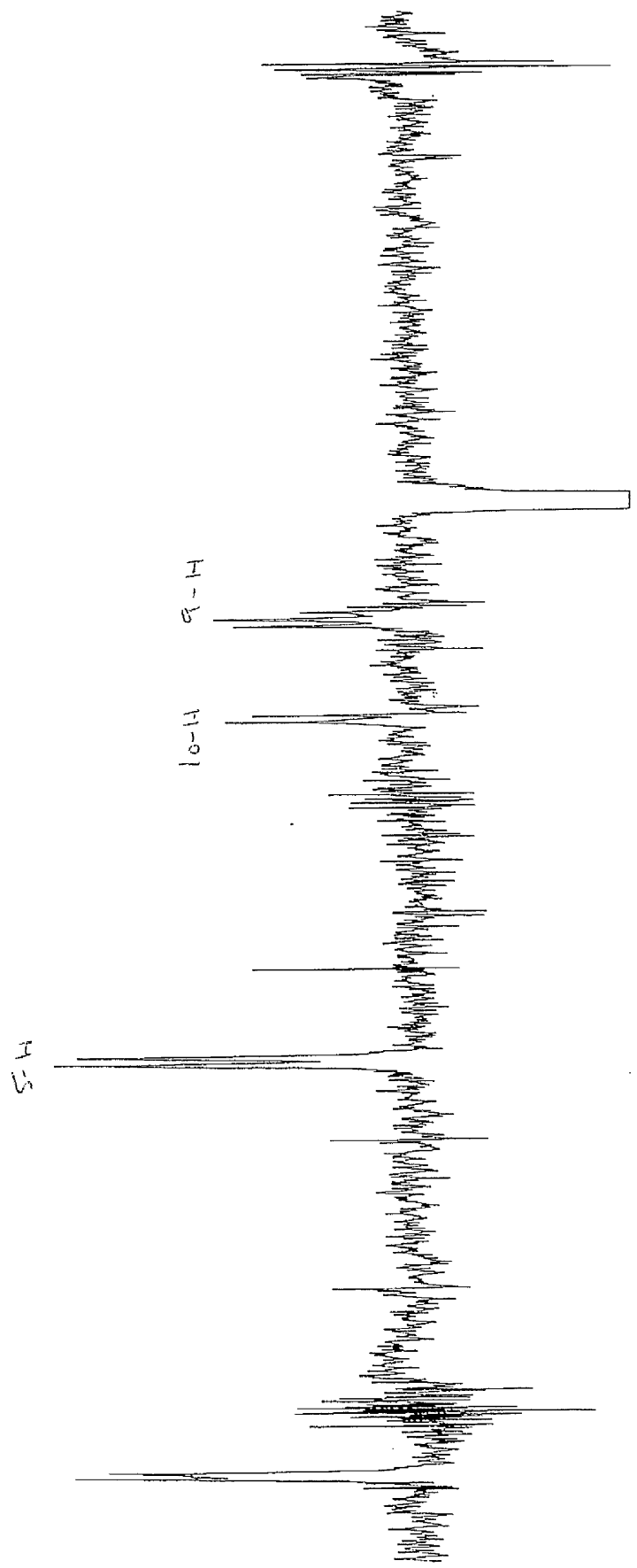


Figure 11d. nOe spectrum of spiroacetal (256b): Irradiation of 11_{ax}-H

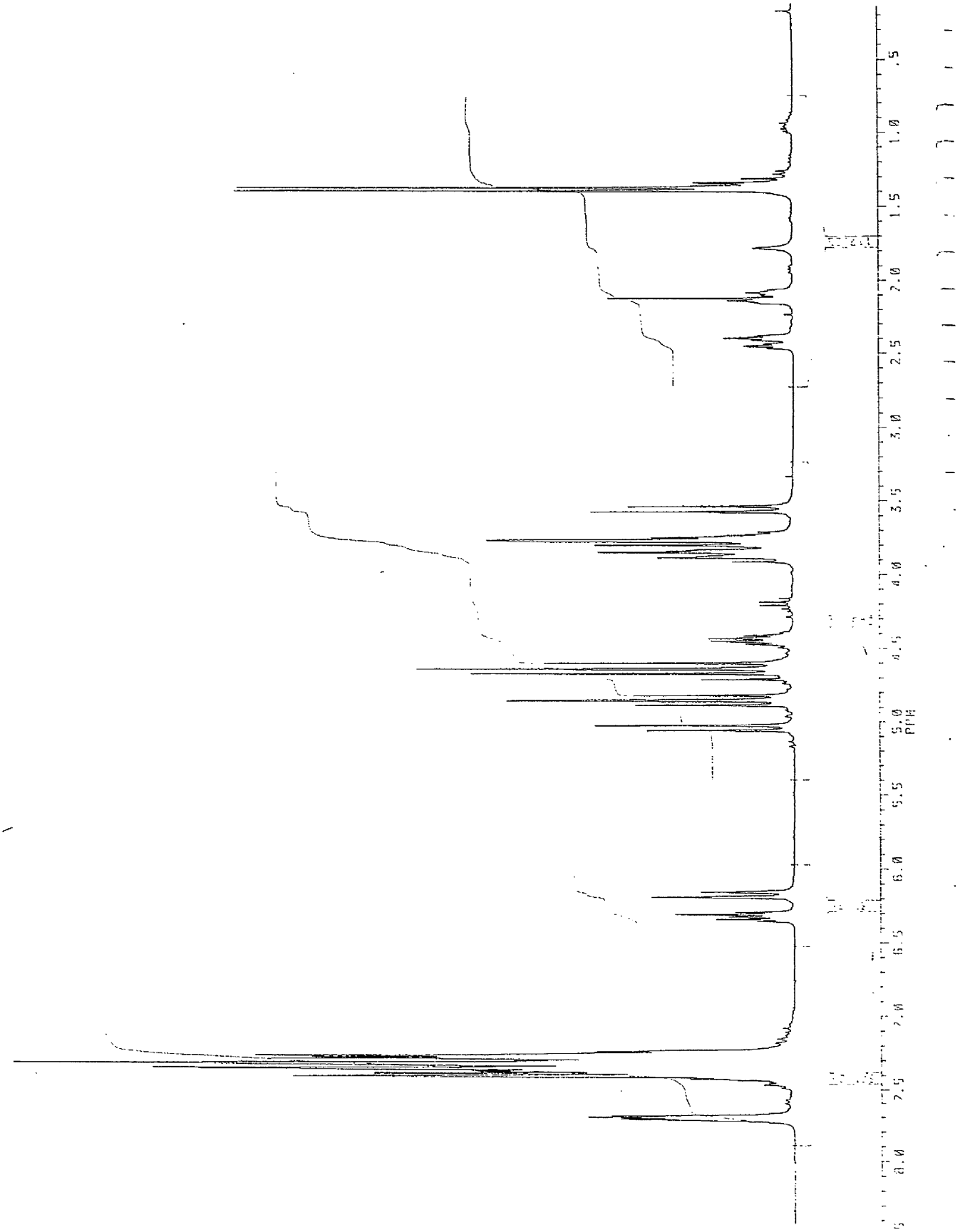


Figure 11e. ^{1}H nmr spectrum of spiroacetal (**256c**).

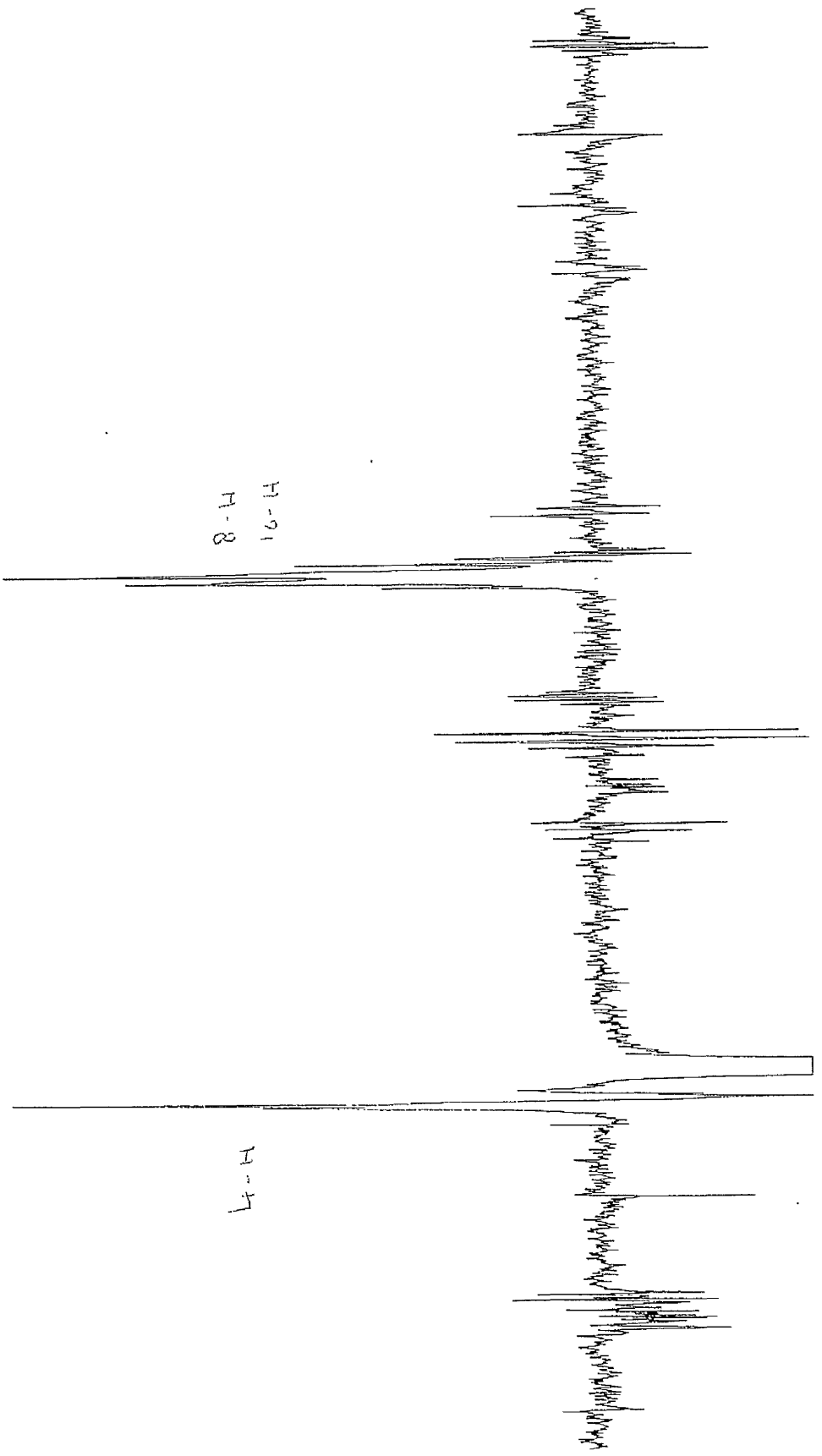


Figure 11f. nOe spectrum of spiroacetal (256c): Irradiation of 5-H

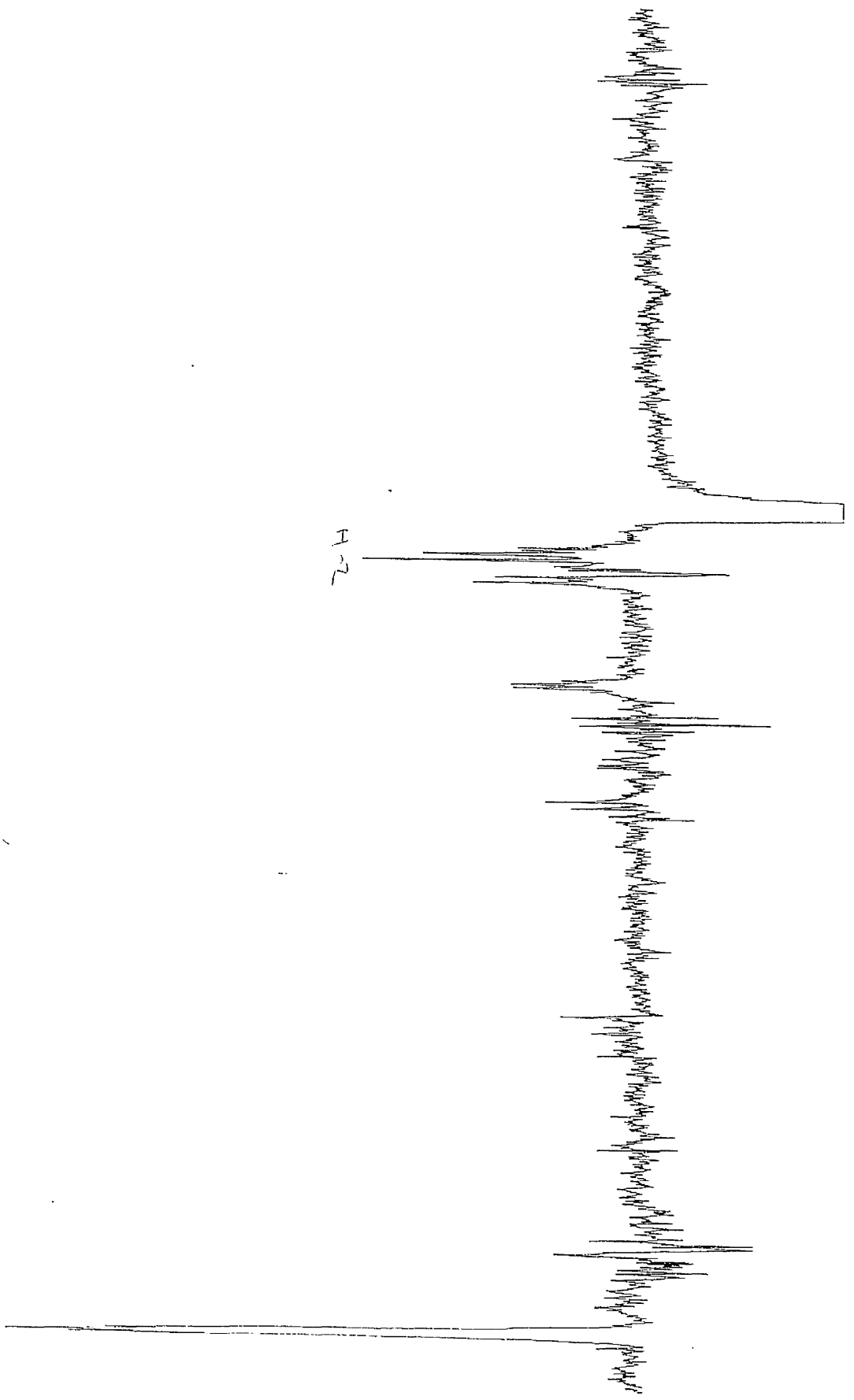
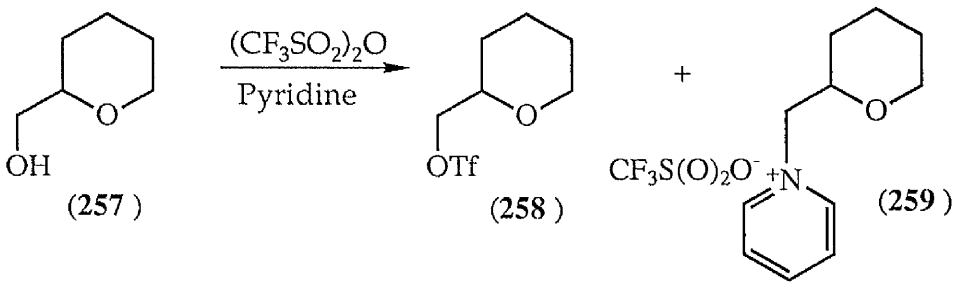


Figure 11g. nOe spectrum of spiroacetal (256c): Irradiation of 11_{ax}-H

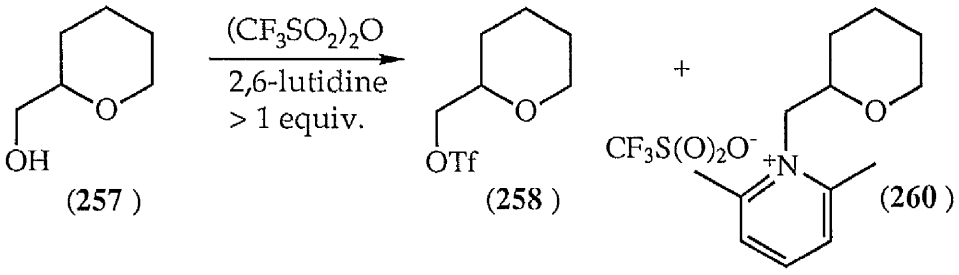
2.10 Model Study for the Introduction of the C_9-C_{10} Bond in Milbemycin β_3

It was anticipated that Baker's[53] original approach to the introduction of the C_9-C_{10} bond in Milbemycin β_3 could be realised using the methodology developed by Kotsuki[54] for the cuprate displacement of triflates possessing β-oxygen functionality. Tetrahydropyran-2-methanol (**257**) was used for the model study, using exactly the same procedure as Kotsuki. Following Kotsuki's procedure for the same starting alcohol (**257**), the alcohol (**257**) was treated with trifluoromethanesulphonic anhydride (1.5 eq.) in pyridine. Despite many attempts to repeat his work, the reaction generated an appreciable amount of pyridinium salt (**259**). The pyridine had displaced the triflate (**258**).



Scheme 72

Switching the base to 2,6-lutidine solved the problem although if more than one equivalent of base was used the lutidinium salt (**260**) was observed.



Scheme 73

Various cuprates were synthesised for the displacement of triflate (**258**) possessing β-oxygen functionality. The first was dimethyl cuprate, this generated ethyltetrahydropran (**261**) in 20% yield although the yield was

probably higher due to the volatile nature of the product. Diphenylcuprate afforded phenyltetrahydropyran (**262**) in 32% yield.

The use of higher order cyanocuprates "R_T(2-thienyl)Cu(CN)Li_2" were investigated. Lipshutz[76] developed these efficient reagents which promote selective ligand transfer. The reagent where R_T = phenyl was prepared and used as follows: to a solution of phenyllithium in THF, was added lithium 2-thienylcyanocuprate at -78°C, followed by an THF solution of the triflate (**258**). This generated phenyltetrahydropyran (**262**) in 37% yield but in the three reactions mentioned so far the triflate was made using pyridine as the base. When 2,6-lutidine was used as the base in the triflate reaction, the previously mentioned cuprate reaction proceeded in 55% yield.

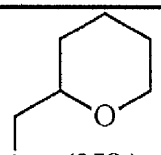
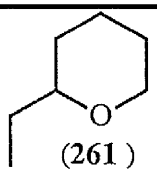
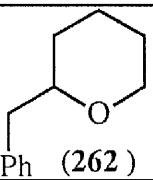
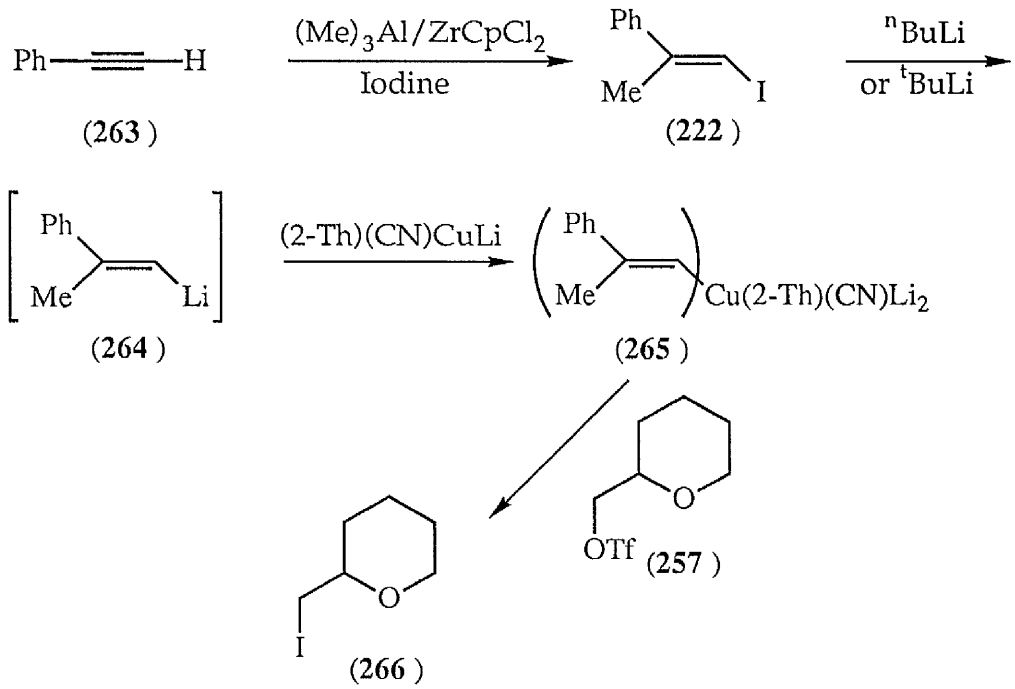
Entry	Substrate	Cuprate	Reaction time, h	Product	Overall yield, %
1[a]	 OTf (**258**)	Me_2CuLi (3 eq)	3	 (**261**)	20
2[a]	(258)	Ph_2CuLi (3 eq)	3	 Ph (**262**)	32
3[a]	(258)	(Ph)(2-Th)(CN) $CuLi_2$ (1.2 eq)	2	(262)	37
4[b]	(258)	(Ph)(2-Th)(CN) $CuLi_2$ (1.2 eq)	15	(262)	55

Table 5 [a] used pyridine as base. [b] used 2,6-lutidine as base.

In the milbemycin system we needed to insert a trisubstituted double bond. This was attempted starting from phenyl acetylene (**263**). The acetylene was converted to vinyl iodide (**222**) using trimethylaluminium/zirconocene chloride and quenching with iodine. The vinyl iodide was transmetallated to

vinyl lithium intermediate (**264**) using n-butyllithium (1 eq.) or t-butyllithium (2 eq.). To this was added lithium 2-thienylcyanocuprate at -78°C, followed by a THF solution of the triflate (**258**). This generated iodomethyltetrahydropyran (**266**). Liberated iodide displaced the triflate (**258**) before the cuprate reaction could occur.



Scheme 74

Conclusion

A method for the generation of the spiroacetal nucleus of milbemycin β_3 was developed using modified Heck-Stille palladium coupling reactions.

Initial studies, in which 2,3-dihydro-2(H)-pyran was used as a simple model to obtain the spiroacetal nucleus, involved the coupling of the vinyl tri-n-butyl tin or zinc chloride derivative of 2,3-dihydro-2(H)-pyran with (*Z*,*E*)-4-hydroxy-3-methyl-1-iodopentene. Treatment of the resultant 1,3-diene with camphorsulphonic acid resulted in the formation of the spiroacetal.

Various conditions were examined to optimise the conversion of 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tri-n-butylstannyl-D-arabino-hex-1-enitol into glycosyl 1,3-dienes *via* palladium(0)-catalysed cross-coupling reactions. Diels-Alder reactions of the glycosyl 1,3-dienes prepared were examined using 4-phenyl-1,2,4-triazoline-3,5-dione as the dienophile.

The palladium(0)-catalysed cross-coupling reactions between 1,5-anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tri-n-butylstannyl-D-arabino-hex-1-enitol (and its zinc derivative) and (*Z*,*E*)-4-(t-butyldimethylsilyl)-1-iodopentene and (*Z*,*E*)-4-hydroxy-1-iodopentene were investigated to optimise the formation of the glycosyl 1,3-diene precursor requisite for spiroacetal formation. Treatment of the precursor with camphorsulphonic acid resulted in the formation of spiroacetal analogue of milbemycin β_3. Cyclisation of the precursor with phenyl selenium chloride afforded the 11-phenylselenyl-spiroacetal analogue.

CHAPTER 3

3.1 GENERAL EXPERIMENTAL

All non-aqueous reactions were performed under an atmosphere of dry nitrogen at temperatures which were those of the external bath.

Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C nmr) spectra were recorded on Bruker AC 300 (300 MHz), Varian XL 300 (300 MHz), Varian Gemini 200 (200 MHz), and Bruker AC 80 (80 MHz) spectrometers, with residual non-deuterated solvent as internal standard. All chemical shifts are quoted in parts per million downfield from tetramethylsilane. *J* values are given in Hz. Splitting patterns were abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br).

Infra red spectra were recorded on a Perkin-Elmer 1710 FT spectometer as evaporated films unless otherwise stated. Absorption maxima (υ_{max}) were reported in wavenumber (cm^{-1}).

Mass spectra were recorded on Kratos MS20 and MS25 spectrometers. The modes of ionisation used were electron impact (EI) and chemical ionisation (CI). NH_3

Microanalysis was performed at the University of Manchester under supervision of Mr M.Hart.

Melting points were recorded on a Kofler heated stage microscope, and are uncorrected.

Petrol refers to that fraction of light petroleum ether which distils between 40°C and 60°C, and was redistilled prior to use. Tetrahydrofuran (THF) was dried over sodium/benzophenone and distilled under an atmosphere of dry nitrogen. Dichloromethane was dried over phosphorus pentoxide and distilled. Methanol was dried over magnesium methoxide and distilled. Triethylamine was dried over potassium hydroxide pellets and

Ethyl-3-hydroxy-2-methyl-butanoate (199)

To a solution of diisopropylamine (11.7 ml, 83.3 mmol) in THF (10 ml) was added n-butyllithium (2.5 M, 33.3 ml) dropwise at 0-10°C. The solution of lithium diisopropylamide was cooled to -50°C and ethyl-3-hydroxy-butanoate (4.9g, 37.1 mmol) was added keeping the temperature below -50°C. The mixture was stirred at -50°C for 1h. To the dianion was added a solution of methyl iodide (3.45 ml, 55.7 mmol) in DMPU (15 ml) keeping the temperature between -70°C and -45°C. The reaction mixture was allowed to warm up to ambient temperature. After stirring for 20 minutes the mixture was poured onto ice water and extracted with ether (3 x 50 ml). The organic extracts were washed with brine (5 x 30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* (**199**) (1.32 g, 24%). GLC showed 95.4 d.e.. υ_{max} (film) 3443, 2979, 2938, 1734, 1460, 1378, 1263, 1189, 1113, 926, 896 and 863 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.19 (3H, d, *J* 7 Hz, Me), 1.22 (3H, d, *J* 6 Hz, Me), 1.28 (3H, t, *J* 7 Hz, $\mathbf{CH_3}$-CH_2), 2.45 (1H, m, C(2)-H), 2.88 (1H, d, *J* 5.5 Hz, OH), 3.88 (1H, sextet, *J* 6.5 Hz, C(3)-H), 4.17 (2H, q, *J* 6.5 Hz, OCH_2); δ_C (50 MHz, $CDCl_3$) 14.3, 14.6, 21.0, 47.4, 61.0, 69.7, 176.3; m/z (CI) 147 [$[M+H]^+$, 93%], 164 [$[M+NH_4]^+$, 100%].

distilled. Pyridine was dried over potassium hydroxide pellets and distilled. Toluene was dried over sodium and distilled. Where ether is mentioned it refers to diethyl ether. n-Butyl lithium was supplied as solution in hexanes and t-butyl lithium as a solution in pentane.

Chromatography refers to flash column chromatography[77] and was carried out using Merck silica gel 60H (40-63 m, 230-400 mesh) as stationary phase. Thin layer chromatography was carried out on plates precoated with Kieselgel 60 F_{254} silica. Visualisation was achieved by ultraviolet absorption or treatment with an ethanolic solution of dodecamolybdophosphoric acid followed by heating.

3.2 Experimental Concerning Chapter Two

Ethyl-3-(t-butyldimethylsilyloxy)-2-methylbutanoate (156)

To a solution of racemic ethyl-3-hydroxy-2-methylbutanoate (**156**) (9.95 g, 68.1 mmol) in dichloromethane (10 ml) was added 1,8-diazobicyclo-[5,4,0]undec-7-ene (10.2 ml, 65.6 mmol) at 0°C followed by t-butyldimethylsilyl chloride (9.89 g, 65.6 mmol) in dichloromethane (10 ml). After 3 h at room temperature, the mixture was poured into water (100 ml), extracted into ether (100 ml) and washed with water (50 ml), hydrochloric acid (0.1 M, 50 ml), water (50 ml), saturated sodium bicarbonate (50 ml) and water (50 ml). The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by flash column chromatography (1:19 ethyl acetate petrol) to afford the *title compound* (156) (14.02 g, 87%) as a colourless oil; υ_{max}(film) 2958, 2931, 2858, 1737, 1474, 1376, 1320, 1256, 1185, 1113, 1068, 1039, 982, 953, 839, 811 and 776 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.06 (3H, s), 0.09 (3H, s), 0.9 (9H, s), 1.11 (3H, d, *J* 7Hz), 1.16 (3H, d, *J* 6Hz), 2.51 (1H, m), 4.04 (1H, m), 4.13 (2H, m); δ_C (75 MHz) -5.12, -4.32, 12.68, 14.19, 17.92, 20.24, 25.72, 48.15, 60.12, 70.15, 175.15; m/z (CI) 247 $[M+H]^+$, 100%].

(Z,E)-4-(t-Butyldimethylsilyloxy)-1-iodo-3-methylpentene (204)

DIBAL-H (1 M in toluene, 15.7 ml, 15.7 mmol) was added dropwise to a cooled (-80°C) and stirred solution of ethyl-3-(t-butyldimethylsilyloxy) butanoate (**200**) (2.42 g, 9.83 mmol) in anhydrous toluene (100 ml). After being stirred at -80°C for 1 h the reaction was quenched by dropwise addition of methanol (10 ml) keeping the temperature below -78°C. Citric acid (10% aqueous solution, 80 ml) was then added, the mixture was allowed to warm to room temperature, the organic phase was decanted off and the aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic phases were dried ($MgSO_4$), the solvent was removed under vacuum. The crude aldehyde (**201**) was used immediately in the next reaction.

To a suspension of iodomethyltriphenylphosphonium iodide (**202**) (6.51 g, 12.3 mmol) in THF (27 ml) at room temperature was slowly added sodium hexamethyldisilazide (1 M solution in THF, 11.3 ml). After stirring for 10 min, the dark red ylid (**203**) solution was cooled to -78°C and 3-(t-butyldimethylsilyloxy)-3-methylbutanal (**201**) (crude) was added slowly. The mixture was allowed to warm to room temperature and after 30 min, the solvent was removed *in vacuo*. The residue was washed with 3 x (50 ml 50:1 petrol:diethyl ether) and the supernatant filtered through celite to remove triphenylphosphine oxide. The combined eluents were concentrated *in vacuo* and the residue purified by flash column chromatography (dichloromethane /hexane 1:19) to afford the *title compound* (**204**) (1.38 g, 41%) as a colourless oil. Z-isomer; υ_{max}(film) 2957, 2927, 2885, 2857, 1608, 1472, 1462, 1375, 1259, 1152, 1086,1064, 1027, 1007, 956, 850, 837, 802, 775, 745, 699 and 665 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.095 (3H, s), 0.105 (3H, s), 0.93 (9H, s), 1.05 (3H, d, *J* 7 Hz), 1.12 (3H, d, *J* 6.5 Hz), 2.56 (1H, m), 3.85 (1H, m), 6.15 (1H, dd, *J* 9, 7.5 Hz), 6.25 (1H, d, *J* 7 Hz). δ_C (75 MHz): -4.75, -4.23, 15.76, 18.07, 21.45, 25.87, 49.65, 70.87, 81.90, 143.41. m/z (CI) 341 [[M+H]$^+$, 34%] (Found: m/z (CI) 341.0804. $C_{12}H_{25}SiOI$ requires m/z 341.0798). *E*-isomer υ_{max}(film) 2957, 2929, 2885, 2857,

1603, 1552, 1472, 1462, 1374, 1361, 1253, 1188, 1157, 1128, 1102, 1064, 1029, 1007, 988, 956, 837, 806, 775 and 663 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.1 (6H, s), 0.95 (9H, s), 1.02 (3H, d, *J* 6.5 Hz), 1.11 (3H, d, *J* 6 Hz), 2.2 (1H, m), 3.69 (1H, m), 6.02 (1H, dd, *J* 14.5, 0.5 Hz), 6.52 (1H, dd, *J* 14.5, 8.5 Hz). δ_C (75 MHz): -4.78, -4.35, 15.69, 18.07, 21.24, 25.86, 48.37, 71.23, 74.73, 149.04. m/z (CI) 341 [[M+H]$^+$, 36%] (Found: m/z (CI) 341.0807. $C_{12}H_{25}SiOI$ requires m/z 341.0798).

(Z)-4-Hydroxy-1-iodo-3-methylpentene (205)

To a solution of (*Z*,*E*)-4-(t-butyldimethylsilyloxy)-1-iodopentene (**204**) (1.29 g, 3.79 mmol) in acetonitrile (67 ml) was added 60% aqueous hydrogen fluoride (2.25 ml). The mixture was stirred for 10 minutes after which the solution was diluted with water and extracted with chloroform (2 x 50 ml). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by flash column chromatography (1:4 ethyl acetate petrol) to afford the *title compound* (**205**) (0.66 g, 77%) as a colourless oil; υ_{max}(film) 3376, 3064, 2969, 2929, 1609, 1452, 1376, 1352, 1262, 1200, 1152, 1112, 1085, 1045, 1015, 995, 929, 886, 797 and 702 cm^{-1}; δ_H (300 MHz, $CDCl_3$) : 1.08 (3H, d, *J* 7 Hz), 1.24 (3H, d, *J* 6.5 Hz), 2.58 (1H, m), 3.81 (1H, quintet, *J* 6 Hz), 6.15 (1H, dd, *J* 9,7 Hz), 6.36 (1H, d, *J* 7.5 Hz); δ_C (75 MHz): 15.65, 20.85, 46.70, 70.90, 83.35, 142.86. m/z (CI) 244 [[M+NH_4]$^+$, 100%] (Found: m/z (CI) 244.0204. $C_6H_{11}OI$ requires m/z 244.0198).

(Z)-2-(4-Hydroxy-3-methyl-1-pentenyl)-5,6-dihydro-2(H)-pyran (206)

A solution of t-butyl lithium (5.8 ml, 1.7 M solution in pentane) was added dropwise to a stirred solution of 2,3-dihydro-2(H)-pyran (0.8 ml, 9.36 mmol) in THF (5 ml) at -78°C. The mixture was allowed to warm to 0°C and was stirred at this temperature for 30 min, then recooled to -78°C. Zinc chloride (1 M solution in ether, 9.8 ml) was added dropwise and the resulting mixture was allowed to warm up to room temperature and to stir for 2 h. A

solution of (Z)-4-hydroxy-3-methyl-1-iodopentene (**205**) (500 mg, 1.17 mmol) and $Pd(PPh_3)_4$ (127 mg, 5 mol%) in THF (5 ml) was added to the vinyl zinc (**182**) at 5-10°C, and resulting mixture was stirred for 1 h. After quenching with sodium hydroxide (10 ml), the product was extracted with ether (3 x 30 ml), the ethereal extracts dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by flash column chromatography (3:1:16 ethyl acetate/ triethylamine/petrol) to afford the *title compound* (**206**) (290 mg, 72%); υ_{max}(film) 3412, 2969, 2930, 2874, 1723, 1656, 1610, 1450, 1394, 1375, 1353, 1311, 1274, 1234, 1153, 1086, 1060, 999, 972, 936, 893, 862 and 787 cm^{-1}; δ_H (200 MHz, C_6D_6) 1.03 (3H, d, *J* 6 Hz), 1.18 (3H, d, *J* 6 Hz), 1.35 (2H, quintet, *J* 6 Hz), 1.76 (2H, m), 3.39 (1H, m), 3.55 (1H, m), 3.68 (2H, t, *J* 6 Hz), 4.66 (1H, t, *J* 4 Hz), 5.21 (1H, t, *J* 12 Hz), 5.75 (1H, d, *J* 12 Hz); m/z (CI) 183 [[M+H]$^+$, 100%] (Found m/z (CI) 182.1301. $C_{11}H_{18}O_2$ requires m/z 182.1307).

(±) *E,E*-2,3-Dimethyl-1,7-dioxaspiro[5.5] undec-4-ene (207)

To a solution of 2-(4-hydroxyl-3-methyl-1-pentenyl)-5,6-dihydro-2(H)-pyran (**206**) (247 mg, 1.35 mmol) in dichloromethane (5 ml) was added camphorsulphonic acid (30 mg) and the mixture stirred at room temperature for 1 h. After quenching with saturated sodium bicarbonate, the product was extracted with ether (2 x 20ml), the ethereal extracts dried ($MgSO_4$), and evaporated and the residue purified by flash column chromatography (ethyl acetate/petrol 1:19) to afford the *title compound* (**207**) (105 mg, 42%) as a colourless oil; υ_{max}(film) 3034, 2939, 2872, 1657, 1450, 1398, 1378, 1269, 1225, 1204, 1186, 1169, 1106, 1091, 1074, 1055, 1002, 954, 923, 896, 813 and 723 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.92 (3H, d, *J* 6 Hz) 1.23 (3H, d, *J* 6.5 Hz), 1.45-1.65 (5H, m), 1.8-2.0 (2H, m), 3.55 (2H, m), 5.54 (1H, d, *J* 2.5 Hz), 5.64 (1H, d, *J* 10 Hz, 4-H) δ_C (75 MHz) 16.73, 18.52, 19.14, 25.13, 34.88, 36.22, 60.75, 69.46, 93.59, 129.39, 134.42; m/z (CI) 182 [M+H]$^+$,100%] (Found: m/z (CI) 183.1386. $C_{11}H_{19}O_2$ requires m/z 183.1386).

2,3,4,6-Tetra-O-benzyl-α-D-glucopyranose (211)

Method A: Methyl-α-D-glucopyranoside (**209**) (10.05 g, 51.7 mmol) was suspended in dry dioxane (30 ml) with powdered potassium hydroxide (50 g), and the mixture was boiled while benzyl bromide (63.5 ml, 55.1 mmol) was added dropwise. The mixture was refluxed for 30 minutes whereupon the dioxane was removed by fractional distillation. The residue was cooled and suffient water was added to dissolve the crystalline mass. The mixture was extracted with ether, washed with water, dried ($MgSO_4$), filtered through decolourising carbon and concentrated *in vacuo* to a syrup (**210a**).

The syrup was dissolved in hot glacial acetic acid (500 ml) and the solution diluted with boiling sulphuric acid (2M, 108 ml). After heating for 2 hours, the reaction was further diluted with boiling sulphuric acid (108 ml) and heating was continued for 24 h. The mixture was cooled and poured into water (4 L) and left at room temperature for 2 days. The crystals were collected and recrystallised from methanol to afford the *title compound* (8.4 g, 30%).

Method B: Sodium hydride (60% suspension in oil) (18.12 g, 0.454 mol) was suspended in DMF (50 ml) after being washed with hexane. α-Methylglucoside (20 g, 103 mmol) was dissolved in DMF (300 ml) and added to the mixture at 0°C. When the evolution of hydrogen had ceased, tetrabutylammonium iodide (380 mg, 1.03 mmol) was added followed by benzyl bromide (51.2 ml, 0.216 mol) dropwise. The mixture was stirred overnight and then poured into brine and extracted into ether (5 x 200ml). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under vacuum. The crude product was dissolved in 0.5M sulphuric acid in acetic acid-water 8:2 v/v (10.6 ml sulphuric acid, 400ml acetic acid, 100ml water) and refluxed for 15 minutes. After cooling, water (200 ml) was added and the solution was left to crystallise. After collection by filtration, the product was recrystallized from ethanol to afford the *title compound* (**211**) (26.97 g, 48.5%). m.p. 144-5 °C [lit.[63] m.p. 151-2 °C]; $[\alpha]_D$ +20.1 (c 0.029, $CHCl_3$)

2-Hydroxy-3,7-dimethyl-oct-4-ene (208)

The *title compound* was prepared as above except diisobutylaluminium hydride (1M in toluene, 2.5 ml) was added to vinyl iodide (**205**) (570 mg, 2.5 mmol) at -78°C and then allowed to warm up to room temperature before adding to vinyl zinc species (182). This afforded the *title compound* (**208**) (75 mg, 19%). υ_{max} (film) 3363, 2958, 2871, 1465, 1368, 1164, 1091, 1044, 1014, 924, 877, 831 and 792 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.95 (9H, m, 3 x Me), 1.22 (3H, d, *J* 7 Hz, Me), 1.65 (1H, septet, *J* 6.5 Hz, 7-H), 1.82 (1H, br s, OH), 2.0 (2H, m, 6-H), 2.45 (1H, m, 2-H), 3.52 (1H, quintet, *J* 6.5 Hz, 3-H), 5.28 (1H, t, *J* 11 Hz, 4-H), 5.59 (1H, dt, *J* 11, 7 Hz, 5-H); δ_C (50 MHz, $CDCl_3$) 16.9, 20.0, 22.1, 22.5, 28.6, 36.8, 39.9, 71.6, 131.3, 132.4; m/z (CI) 156 [[M^+, 38%], 174 [[$M+NH_4]^+$, 100%]. (Found: m/z (CI) 174.1855. $C_{10}H_{24}NO$ requires m/z 174.1858.

[lit. $[\alpha]_D$ +20.7 (c 2.19, $CHCl_3$)] υ_{max}(KBr disc) 3418, 3030, 2861, 1638, 1497, 1453, 1400, 1359, 1260, 1214, 1148, 1089, 859, 745 and 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.4-4.2 (7H, m), 4.5-5.1 (9H, m), 7.1-7.5 (20H, m, Ar); δ_C (75 MHz) 68.58, 68.91, 70.28, 73.29, 73.52, 74.69, 74.81, 75.09, 75.88, 77.72, 77.85, 79.97, 81.79, 83.13, 84.61, 91.34, 97.51, 127.71, 127.78, 127.88, 127.94, 128.01, 128.04, 128.12, 128.22, 128.47, 128.57, 137.78, 137.85, 137.90, 138.20, 138.54, 138.70; m/z (CI) 558 $[M+NH_4]^+$, 65%].

2,3,4,6-Tetra-O-benzyl-1-O-*p*-nitrobenzoyl-α/β-D-glucopyranose (212a, b)

A solution of pyranose (**211**) (8.14g, 15.07 mmol) in DCM (40 ml) was treated with with a solution of *p*-nitrobenzoyl chloride (3.35 g, 18.1 mmol) in a mixture of DCM (7 ml) and pyridine (2 ml) at room temp. overnight. The mixture was quenched with ice and stirred at room temp. for 2 h, then washed with water (15 ml), sulphuric acid (3M, 10 ml) and saturated aqueous sodium bicarbonate (10 ml). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* to a syrup. The residue was dissolved in hot ethanol (250 ml) and the solution allowed to crystallise. Recrystallisation from ethanol gave the *title compound* (**212a, b**) (a:b 2:5) (6.03 g, 58%); υ_{max} (KBr disc) 3031, 2868, 1741, 1607, 1529, 1497, 1454, 1350, 1268, 1074, 1028, 1014, 872, 839, 737, 719 and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.7-4.15 (8H, m), 4.5-5.1 (11H, m), 5.93 ($^5/_7$H, d, *J* 8 Hz), 6.65 ($^2/_7$H, d, *J* 3 Hz), 7.2-7.4 (20H, m, Ar), 8.18 ($^5/_7$H, d, *J* 8.5 Hz), 8.26 ($^2/_7$H, d, *J* 8.5 Hz), 8.32 ($^5/_7$H, d, *J* 8.5 Hz), 8.36 ($^2/_7$H, d, *J* 8.5 Hz); δ_C (75 MHz) 68.02, 73.41, 73.51, 73.60, 75.07, 75.57, 75.74, 76.80, 78.99, 80.62, 81.68, 84.99, 95.06, 123.58, 123.69, 127.82, 127.92, 127.99, 128.12, 128.19, 128.43, 128.48, 128.53, 128.57, 131.09, 131.17, 134.66, 135.16, 137,47, 137.76, 137.94, 138.25, 138.46, 150.82, 163.16; m/z (CI) 707 $[M+NH_4]^+$, 23%]. ١٥٥ (٣٥٪) ١٥٦ (١٠٠٪) ١٥٦ (٨٢٪) ٩١ (٦٥٪) ٣٢ (٢٦٪)

Methyl-2,3,4,6-tetra-O-benzyl-β–D-glucopyranoside (210b)

Method A: Crude bromide (**213a, b**) (2.9 mmol) was dissolved in chloroform (10 ml) and added to a solution of thiophenol (0.32 ml, 3.2 mmol) and methanolic potasssium hydroxide (0.43 M, 6.7 ml). The reaction mixture was refluxed for 30 minutes, cooled, diluted with water (5 ml) and extracted with chloroform (2 x 30 ml). The combined organic layers were washed with 10% sodium bicarbonate solution (3 x 20 ml), water (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:9 ethyl acetate/petrol) to afford the *title compound* (**210b**) as a white solid.

Method B: Crude chloride (**214**) (1.85 mmol) was dissolved in chloroform (10 ml) and added to a solution of thiophenol (0.2 ml, 2.0 mmol) and methanolic potasssium hydroxide (0.43 M, 4.5 ml) which had been refluxed for 10 minutes. The reaction mixture was refluxed for 30 minutes, cooled, diluted with water (5 ml) and extracted with chloroform (2 x 30 ml). The combined organic layers were washed with 10% sodium bicarbonate solution (3 x 20 ml), water (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. This afforded (**210a, b**) and sulphide (**215**) (81 mg, 7%).

(**210b**): δ_H (300 MHz, $CDCl_3$): 3.4-3.8 (9H, m), 4.28-4.97 (9H, m) 7.1-7.4 (20H, m); δ_C (75 MHz, $CDCl_3$) 57.8 69.7, 74.2, 75.5, 75.6, 75.7, 76.4, 78.6, 83.1, 85.4, 105.4, 128.3, 128.5, 128.6, 128.7, 128.8, 129.1, 138.8, 138.9, 139.3, 139.3; m/z (CI) 572 [$[M+NH_4]^+$, 100%], 573 (38%), 108 (45%), 91(47%).

2,3,4,6-Tetra-O-benzyl-α/β-D-glucopyranosyl bromide (213a, b)

Through a solution of pyranose (**212a, b**) (2.0g, 2.9 mmol) in DCM (10 ml) was bubbled anhydrous hydrogen bromide (made from the addition of bromine to tetralin) for 10-15 minutes at room temp. The precipitated *p*-nitrobenzoic acid was removed by filtration, and the filtrate was evaporated to dryness to afford the crude *title compound* (**213a, b**) as a syrup. δ_H (200 MHz, $CDCl_3$) 3.7 (2H, m), 3.95 (2H, m), 4.5-5.0 (10H, m), 6.75 (1H, d, *J* 4.5 Hz), 7.4 (20H, m, Ar).

Phenyl-2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranose (215)

Method A: To a solution of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (**211**) (1.0 g, 1.85 mmol) in acetonitrile (20 ml) was added a mixture of tri-n-butyl phosphine (0.75 ml, 3.7 mmol) and diphenyl disulphide (1.0 g, 4.62 mmol) in acetonitrile (3 ml). The solution was stirred for 3 h whereupon the mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (ethyl acetate/petrol 1:9) to give the *title compound* (**215**) (928 mg, 79%) as a white solid.

Method B: Thionyl chloride (167.5 ml) was added to 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (**211**) (49.27 g, 91.24 mmol) in the presence of DMF (2.5 ml). The solution was stirred for 10 minutes at 50°C whereupon it was cooled to room temperature and concentrated *in vacuo* to give crude 2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl chloride (**214**).

A solution of n-butyl lithium (71.3 ml, 1.6 M solution in hexanes) was added dropwise to a stirred solution of thiophenol (11.2 ml, 109.4 mmol) in THF (40 ml) at -78°C. The mixture was allowed to warm to 0°C and was stirred at this temperature for 15 min, then recooled to -78°C. The crude 2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl chloride (**214a, b**) was dissolved in THF (100 ml) and added dropwise. The resulting mixture was allowed to warm up to room temperature and to stir overnight. After quenching with

sodium hydroxide (10 ml), the product was extracted with ether (3 x 100 ml), the ethereal extracts dried ($MgSO_4$), concentrated *in vacuo*, and the residue crystallised from ethanol to afford the *title compound* (**215**) (44.86 g, 78%) as a white solid. m.p. 85-86°C [lit.[64] m.p. 93.5-94.5°C]; $[\alpha]_D$ +0.53 (c 0.032, $CHCl_3$) [lit.[64] $[\alpha]_D$ +0.65 ($CHCl_3$)]; υ_{max}(KBr disc) 3031, 2863, 1584, 1497, 1454, 1360, 1067, 1028, 726 and 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.5-3.9 (5H, m), 4.55-5.0 (10H, m), 4.65 (1H, d, *J* 10 Hz, 2-H), 7.25-7.7 (25H, m, Ar); δ_C (75 MHz) 69.06, 73.45, 75.10, 75.46, 75.88, 77.84, 79.12, 80.87, 86.79, 87.48, 127.47, 127.59, 127.70, 127.75, 127.85, 127.90, 127.98, 128.27, 128.38, 128.47, 128.49, 128.93, 131.97, 133.85, 138.07, 138.33, 138.43, 138.48; m/z (CI) 650 $[M+NH_4]^+$, 15%]; (Found: m/z (CI) 650.2927. $C_{40}H_{44}O_5NS$ requires m/z 650.2940).

2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl phenyl sulphone (216)

A solution of phenyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranose (**215**) (20.17 g, 31.86 mmol) in DCM (150 ml) was treated at 0°C with sodium bicarbonate (20 g, 0.25 mol) and 70% 3-chloroperoxybenzoic acid (19.63 g, 79.65 mmol), and kept for 4 h at room temperature. The mixture was diluted with DCM and the organic layer was washed with sodium bisulphate, 0.5M sodium hydroxide, and water, dried ($MgSO_4$) and the solvent was evaporated. The residue crystallised from ethanol to give the *title compound* (**216**) (21.15 g, 84%) as a white solid. m.p. 128-129°C [lit.[67] m.p. 136-137°C]; $[\alpha]_D$ +16.0 (c 0.030, $CHCl_3$) [lit.[67] $[\alpha]_D$ +19.0, $CHCl_3$)]; υ_{max}(KBr disc) 3031, 2922, 1497, 1452, 1331, 1309, 1156, 1083, 1028, 751 and 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.4 (1H, m, 6-H), 3.5-3.7 (3H, m, 5-H, CH_2OBn), 3.82 (1H, t, *J* 9 Hz, 4-H), 4.15 (1H, t, *J* 9 Hz, 3-H), 4.47 (1H, d, *J* 9 Hz, 2-H), 4.3-5.2 (8H, m, 4 x CH_2Ph), 7.2-7.7 (23H, m, Ar), 8.0 (2H, d, *J* 7.5 Hz); δ_C (75 MHz) 68.62, 73.50, 75.13, 75.51, 75.97, 76.97, 77.63, 79.70, 86.29, 91.14, 127.61, 127.69, 127.82, 127.96, 128.01, 128.40, 128.45, 128.54, 128.73, 129.71, 133.93, 137.18, 137.57, 137.75, 138.06, 138.19; m/z (CI) 682 $[M+NH_4]^+$, 38%]; (Found: m/z (CI) 682.2818. $C_{40}H_{44}O_7NS$ requires m/z 682.2838).

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-phenylsulphonyl-D-arabino-hex-1-enitol (217)

A solution of n-butyl lithium (16.2 ml, 1.6 M solution in hexanes) was added dropwise to a stirred solution of 2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl phenyl sulphone (**216**) (13.83 g, 20.8 mmol) in THF (30 ml) at -78°C and stirred for 30 minutes. The resulting mixture was treated at -78°C with solid ammonium chloride and concentrated to dryness. Dichloromethane (200 ml) was added and the organic layer was washed with saturated aqueous ammonium chloride (50 ml) and water (50 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was crystallised from methanol to give the *title compound* (**217**) (8.32 g, 72%) as white solid. m.p. 79-80°C [lit.[67] m.p. 85-86°C]; $[\alpha]_D$ -58.3 (c 0.032, $CHCl_3$) [lit.[67] $[\alpha]_D$ -58 (c 1.10, $CHCl_3$)]; υ_{max}(KBr disc) 3063, 3031, 2867, 1649, 1497, 1452, 1365, 1327, 1209, 1163, 1074, 1027, 819, 740 and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.76 (2H, m, CH_2OBn), 3.91 (1H, dd, *J* 8.5, 6 Hz, 5-H), 4.24 (1H, m, 6-H), 4.33 (1H, dd, *J* 6, 3 Hz, 4-H), 4.34-4.85 (6H, m, 3 x CH_2Ph), 6.28 (1H, d, *J* 3 Hz, 2-H), 7.25-8.05 (15H, m, Ar); δ_C (75 MHz) 67.55, 71.41, 73.34, 73.86, 74.83, 79.84, 105.77, 127.51, 127.66, 127.95, 128.04, 128.10, 128.37, 128.49, 128.63, 128.71, 129.09, 129.72, 133.95, 137.44, 137.75, 137.98, 152.54; m/z (CI) 574 $[M+NH_4]^+$, 95%]; (Found: m/z (CI) 574.2275. $C_{33}H_{36}O_6NS$ requires m/z 574.2263).

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tri-n-butylstannyl-D-arabino-hex-1-enitol (218)

A solution of sulphone (**217**) (3.65 g, 6.56 mmol) in toluene (73 ml) was stirred for 3 h at reflux in the presence of tri-n-butyltin hydride (5.4 ml, 19.7 mmol) and 2,2'-azobis(2-methylpropionitrile) (54 mg, 0.33 mmol). Evaporation of the solvent and flash column chromatography (triethylamine/petrol 2:98) of the residue gave the *title compound* (**218**) (1.2 g, 26%) as a colourless syrup; υ_{max}(film) 3030, 2955, 2925, 2870, 1605, 1496, 1454,

1361, 1263, 1098, 1045, 866, 734 and 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.94 (9H, t, *J* 7 Hz), 1.03 (6H, t, *J* 8 Hz), 1.38 (6H, sextet, *J* 7.5 Hz), 1.6 (6H, m), 3.8-4.0 (4H, m, 5-H, 6-H, CH_2OBn), 4.3 (1H, m, 4-H), 4.6-4.91 (6H, m, 3 x CH_2Ph), 4.92 (1H, d, *J* 3 Hz, 3-H, $^{117,119}Sn$ satellites *J* 26.5 Hz), 7.4 (15H, m, Ar); δ_C (75 MHz) 9.79, 13.75, 27.24, 28.97, 69.10, 70.38, 73.46, 73.83, 74.96, 77.42, 77.58, 111.01, 127.43, 127.49, 127.55, 127.61, 127.79, 127.95, 128.32, 128.37, 128.40, 138.65, 138.80, 164.94; m/z (CI) 599 [M-CH_2OBn], 6.1%]; (Found: m/z (CI) 649.2343. $C_{35}H_{45}O_4{}^{120}Sn$ requires m/z 649.2340).

Coupling of 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tri-n-butylstannyl-D-arabino-hex-1-enitol (218) with α-bromostyrene (219)

Method A: To a stirred mixture of palladium (II) acetate (11 mg, 5 mol%), tri-(*o*-tolyl)phosphine (30 mg, 10 mol%) and triethylamine (0.3 ml) in acetonitrile (5 ml) was added stannane (**218**) (704 mg, 1.0 mmol) followed by α-bromostyrene (**219**) (0.25 ml, 2.0 mmol). The reaction mixture was refluxed for 3 h and then a saturated solution potassium fluoride in 10% ammonium hydroxide was added. The resulting mixture was filtered and extracted with ether (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by flash column chromatography (1:9 ethyl acetate/petrol) to afford diene (**225**) (52 mg, 10%) as a colourless oil.

Method B: The coupled compound (**225**) was prepared according to method A except tri-n-furylphosphine (23 mg, 10 mol%) was used. Stannane (**218**) (699 mg, 0.99 mmol) afforded (59 mg, 12%).

Method C: The coupled compound (**225**) was prepared according to method A except triphenylarsine (30 mg, 10 mol%) was used. Stannane (**218**) (703 mg, 1.0 mmol) afforded (145 mg, 28%).

Method D: To a solution of bis(acetonitrile)dichloropalladium(11) (16 mg, 5 mol%) in DMF (10 ml) was added α-bromostyrene (**219**) (0.32 ml, 2.48

mmol) and stannane (**218**) (876 mg, 1.24 mmol). The orange solution immediately turned black upon addition of the stannane. The reaction mixture was stirred for 41 h at room temperature whereupon it was quenched with saturated solution potassium fluoride in 10% ammonium hydroxide was added. The resulting mixture was filtered and extracted with ether (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by flash column chromatography (1:19 ethyl acetate/petrol) to afford diene (**225**) (298 mg, 46%) as a colourless oil.

Method E: A mixture of α-bromostyrene (**219**) (0.25 ml, 1.98 mmol), stannane (**218**) (1.07g, 1.52 mmol), $Pd_2(dba)_3$ (70 mg, 0.05 equiv of Pd), $AsPh_3$ (93 mg, 0.3 mmol), CuI (57 mg, 0.3 mmol) in DMF (10 ml) was purged with nitrogen for 5 minutes and stirred at 60°C for 40h. The reaction mixture was then diluted with water, extracted with ether, washed with saturated potassium fluoride solution and then with water, dried ($MgSO_4$), and evaporated under vacuum. The residue was chromatographed (1:19 ethyl acetate/petrol) to afford diene (**225**) (298 mg, <30%) as a impure oil.

Diene (**225**) $[\alpha]_D$ -9.6 (c 0.015, $CHCl_3$); υ_{max}(film): 3030, 2865, 1645, 1597, 1495, 1454, 1363, 1287, 1208, 1097, 1028, 910, 777, 736 and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.92 (2H, m, $\mathbf{CH_2}$OBn), 4.01 (1H, dd, *J* 9, 5.5 Hz, 5-H), 4.23 (1H, m, 6-H), 4.34 (1H, dd, *J* 5.5, 3 Hz, 4-H), 4.5-4.94 (6H, m, 3 x $\mathbf{CH_2}$Ph), 4.95 (1H, d, *J* 3 Hz, 2-H), 5.3 (1H, s, 2'-H) 5.83 (1H, s, 2'-H), 7.35 (20H, m, Ar); δ_C (75 MHz) 68.63, 70.42, 73.48, 73.64, 74.35, 101.46, 116.02, 127.61, 127.70, 127.98, 128.40, 128.86, 129.03, 129.78, 138.34, 139.66, 143.84, 155.09); m/z (CI) 518 $[M+H]^+$, 62%]; (Found: m/z (CI) 519.2537. $C_{35}H_{35}O_4$ requires m/z 519.2535).

<u>Coupling of tin compound (218) with β-bromostyrene (220) (*Z*:*E*=5.7:1)</u>

The coupled compound (**226**) was prepared according to method D. Stannane (**218**) (957 mg, 1.36 mmol) afforded the *trans* diene (341 mg, 48%); $[\alpha]_D$ -6.6 (c 0.028); υ_{max}(film): 3062, 3029, 2866, 1649, 1615, 1496, 1453, 1368, 1297,

1206, 1100, 964, 911, 736 and 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.95 (2H, m, CH_2OBn), 4.01 (1H, dd, *J* 8.5, 5.5 Hz, 5-H), 4.25 (1H, m, 6-H), 4.4 (1H, dd, *J* 5.5, 3 Hz, 4-H), 4.6-4.97 (6H, m, 3 x CH_2Ph), 5.11 (1H, d, *J* 3 Hz, 2-H), 6.52 (1H, d, *J* 15.5 Hz, 1'-H), 7.06 (1H, d, *J* 15.5 Hz, 2'-H), 7.45 (20H, m, Ar); δ_C (75 MHz) 68.62, 70.53, 73.48, 73.60, 74.41, 76.54, 77.16, 101.49, 122.74, 126.81, 127.50, 127.65, 127.71, 127.73, 127.80, 127.91, 128.00, 128.43, 128.47, 128.69, 130.00, 136.75, 138.30, 138.35, 138.48, 151.85); m/z (CI) 519 $[M+H]^+$, 20%]; (Found: m/z (CI) 519.2521. $C_{35}H_{35}O_4$ requires m/z 519.2535).

Coupling of tin compound (218) with methyl(Z)-3-iodopropenoate (221)

The coupled compound (**227**) was prepared according to method D. Stannane (**218**) (777 mg, 1.10 mmol) afforded the *cis* diene (277 mg, 50%); $[\alpha]_D$ -35 (c 0.032, $CHCl_3$); υ_{max}(film): 3063, 3031, 2866, 1731, 1657, 1611, 1496, 1454, 1371, 1203, 1168, 1100, 907, 828, 738 and 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.7 (3H, s, Me), 3.8 (1H, dd, *J* 10.5, 2.5, CH_2OBn), 3.91 (1H, dd, *J* 10.5, 4.5 Hz, CH_2OBn), 4.0 (1H, dd, *J* 9, 6.5 Hz, 5-H), 4.1 (1H, dt, *J* 10, 3 Hz, 6-H), 4.39 (1H, dd, *J* 6.5, 3 Hz, 4-H), 4.55-4.93 (6H, m, 3 x CH_2Ph), 5.24 (1H, d, *J* 3 Hz, 3-H), 5.89 (1H, d, *J* 12.5 Hz, 2'-H), 6.08 (1H, d, *J* 12.5 Hz, 1'-H), 7.3 (15H, m, Ar); δ_C (75 MHz) 51.70, 68.54, 70.72, 73.53, 73.97, 74.07, 104.86, 121.17, 127.64, 127.72, 127.77, 127.97, 128.41, 128.46, 130.20, 138.11, 138.25, 138.30, 150.22, 167.79); m/z (CI) 518 $[M+NH_4]^+$, 10%]; (Found: m/z (CI) 518.2547. $C_{31}H_{32}O_6$ requires m/z 518.2543).

Coupling of tin compound (218) with (*E*)-iodophenylpropene (222)

The coupled compound (**228**) was prepared according to method D. Stannane (**218**) (733 mg, 1.04 mmol) afforded the *trans* diene (360 mg, 65%); $[\alpha]_D$ +0.9 (c 0.048, $CHCl_3$); υ_{max}(film): 3086, 3062, 3030, 2914, 2865, 1643, 1604, 1495, 1453, 1368, 1329, 1295, 1205, 1156, 1098, 1028, 911, 878, 821, 736 and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.5 (3H, s, Me), 3.9-4.1 (3H, m, CH_2OBn, 5-H), 4.29 (1H, m, 6-H), 4.45 (1H, m, 4-H), 4.65-5.02 (6H, m, 3 x CH_2Ph), 5.1 (1H, m, 3-H), 6.13

(1H, s, 1'-H), 7.45 (20H, m, Ar); δ_C (75 MHz) 18.15, 68.89, 70.46, 73.57, 73.70, 74.35, 76.98, 77.07, 101.89, 121.88, 126.15, 127.40, 127.70, 127.78, 127.83, 128.06, 128.33, 128.46, 128.50, 138.30, 138.38, 138.60, 140.07, 141.36, 153.30); m/z (CI) 533 $[M+H]^+$, 75%]; (Found: m/z (CI) 532.2610. $C_{36}H_{36}O_4$ requires m/z 532.2614).

Coupling of tin compound (218) with methyl(Z)-3-iodo-2-butenoate (223)

The coupled compound (**229**) was prepared accordind to method D. Stannane (**218**) (791 mg, 1.12 mmol) afforded the *cis* diene (408 mg, 71%) with the glucal dimer (**251**) (19:1); $[\alpha]_D$ +3.7 (c 0.015, $CHCl_3$); υ_{max}(film): 3030, 2865, 1739, 1622, 1496, 1454, 1365, 1289, 1231, 1162, 1103, 1042, 908, 738 and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.03 (3H, s, Me), 3.69 (3H, s, Me), 3.81 (1H, dd, *J* 10.5, 2, CH_2OBn), 3.92 (1H, dd, *J* 10.5, 4 Hz, CH_2OBn), 4.04 (1H, dd, *J* 10, 7 Hz, 5-H), 4.14 (1H, dt, *J* 8.5, 3 Hz, 6-H), 4.42 (1H, dd, *J* 6.5, 3 Hz, 4-H), 4.57-4.96 (6H, m, 3 x CH_2Ph), 5.11 (1H, d, *J* 4 Hz, 3-H), 5.82 (1H, s, 2'-H), 7.4 (15H, m, Ar); δ_C (75 MHz) 22.16, 51.52, 68.49, 70.68, 73.50, 73.89, 74.21, 74.30, 77.34, 77.83, 100.43, 120.22, 127.62, 127.72, 127.77, 127.80, 127.93, 128.01, 128.16, 128.23, 128.41, 128.47, 138.22, 138.27, 138.40, 138.48, 141.74, 152.58, 167.29); m/z (CI) 532 $[M+NH_4]^+$, 5%]; (Found: m/z (CI) 532.2678. $C_{32}H_{34}O_6$ requires m/z 532.2699).

Coupling of tin compound (218) with 1-iodo-1-hexene (224) (Z:*E*=1:9)

The coupled compound (**230**) was prepared according to method D. Stannane (**218**) (507 mg, 0.72 mmol) afforded the diene (166 mg, 46%), (Z:*E*=1:9); *E*-isomer: $[\alpha]_D$ -29.25 (c 0.016, $CHCl_3$); υ_{max}(film): 3088, 3063, 3031, 2955, 2926, 2870, 1666, 1622, 1587, 1497, 1455, 1369, 1294, 1191, 1100, 1045, 1028, 966, 908, 821, 735 and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.99 (3H, t, *J* 7 Hz), 1.45 (4H, m,), 2.20 (2H, q, *J* 7 Hz), 3.92 (2H, m, CH_2OBn), 3.975 (1H, dd, *J* 8.5, 5.5 Hz, 5-H), 4.2 (1H, m, 6-H), 4.36 (1H, dd, *J* 5.5, 3 Hz, 4-H), 4.6-4.96 (6H, m, 3 x CH_2Ph), 4.91 (1H, d, *J* 3 Hz, 3-H), 5.85 (1H, d, *J* 15.5 Hz, 1'-H), 6.13 (1H, dt, *J* 15.5, 7.5 Hz, 2'-H), 7.4 (15H, m, Ar); δ_C (75 MHz) 14.01, 22.34, 31.24, 32.16, 60.71, 70.38, 73.48,

73.58, 74.49, 77.05, 98.45, 124.27, 127.61, 127.71, 127.78, 128.01, 128.40, 128.45, 133.03, 138.37, 138.43, 138.59, 151.86); m/z (CI) 499 $[M+H]^+$, 11%]; (Found: m/z (CI) 499.2842. $C_{33}H_{39}O_4$ requires m/z 499.2848).

2,6:7,11-Dianhydro-1,3,4,9,10,12-hexa-O-benzyl-5,8-dideoxy-D-erythro-L-gulo-dodeca-5,7-dienitol (251)

To the vinyl stannane (**218**) (0.98 g, 1.39 mmol) in THF (20 ml) was added copper(11) nitrate (336 mg, 1.39 mmol) in a single portion. The mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate (60 ml) and washed with aqueous ammonia (45 ml, 5% soln.), water and then brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation of the residue from ethyl acetate/petrol (1:19) afforded the homocoupled diene (**251**) (360 mg, 62%) as a white solid; m.p. 108.8-109.2°C [lit.[67] m.p. 109°C]; $[\alpha]_D$-34 (c 0.032, $CHCl_3$) [lit.[67] $[\alpha]_D$-35 (c 0.6, $CHCl_3$)]; υ_{max}(KBr disc) 3031, 2865, 1630, 1496, 1454, 1364, 1279, 1209, 1063, 1078, 736 and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.88 (4H, m, 1-H, 12-H), 3.95 (2H, dd, *J* 8.5, 6 Hz, 3-H, 10-H), 4.19 (2H, m, 2-H, 11-H), 4.35 (2H, dd, *J* 5.5, 3.5 Hz, 4-H, 9-H), 4.58-4.92 (12H, m, 6 x $\mathbf{CH_2}$Ph), 5.58 (2H, d, *J* 3 Hz, 5-H, 8-H), 7.4 (30H, m, Ar); δ_C (75 MHz) 68.55, 70.35, 73.44, 73.64, 74.28, 76.03, 77.49, 97.89, 127.64, 127.76, 128.00, 128.18, 128,42, 138.24, 138.31, 138.41, 147.16; m/z (CI) 848 $[M+NH_4]^+$, 36%]; (Found: m/z (CI) 848.4169. $C_{54}H_{58}O_8N$ requires m/z 848.4162); (Found: C, 78.00; H 6.67. $C_{54}H_{54}O_8$ requires C, 78.05, H 6.55).

Diels-Alder Cycladdition Reactions

Cycloadduct (245)

Diene: (**225**) (124 mg, 0.24 mmol) (From coupling of 1,5-anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tri-n-butylstannyl-D-arabino-hex-1-enitol (**218**) with α-bromostyrene (**219**).

Dienophile: 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) (42 mg, .0.26 mmol).

A solution of the dienophile was added to stirred solution of the diene in dichloromethane at -78°C. After warming to room temperature, the reaction was stirred overnight. The solvent was removed and the residue was recrystallized from methanol affording the cycloadduct (**245**) (147 mg, 89%) as a white solid; m.p. 188-189°C ; $[\alpha]_D$ -14.9 (c 0.015, $CHCl_3$); υ_{max}(KBr disc) 2868, 1777, 1720, 1500, 1410, 1124, 1073, 739 and 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.6-3.8 (3H, m, CH_2OBn, 6-H), 4.1 (2H, m, 4-H, 5-H), 4.2 (1H, dd, *J* 15.5, 2 Hz, 2'-H), 4.45-4.9 (6H, m, 3 x CH_2Ph), 4.72 (1H, d, *J* 15.5 Hz, 2'-H), 4.81 (1H, d, *J* 7.5 Hz, 3-H), 7.1-7.6 (25H, m); δ_C (75 MHz) 47.96, 55.58, 68.4, 73.44, 73.73, 74.96, 75.24, 78.06, 82.20, 82.93, 116.24, 125.47, 125.47, 127.74, 127.76, 127.88, 127.98, 128.14, 128.19, 128.42, 128.45, 128.48, 129.14, 131.28, 133.35, 133.47, 137.30, 137.74, 137.83, 143.70, 149.93, 155.16; m/z (CI) 694 [M+H]$^+$, 6%]; (Found: m/z (CI) 694.2927. $C_{43}H_{40}O_6N_3$ requires m/z 694.2917); (Found: C, 74.0; H 5.4; N, 6.1. $C_{54}H_{54}O_8$ requires C, 74.4, H 5.6; N, 6.06).

Cycloadduct (246)

Diene: (**226**) (304 mg, 0.59 mmol) (From coupling of vinyl stannane (**218**) with β-bromostyrene (**220**).

Dienophile: 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) (103 mg, .0.64 mmol).

A solution of the dienophile was added to stirred solution of the diene in dichloromethane at -78°C. After warming to room temperature, the reaction was stirred overnight. The solvent was removed and the residue was purified by flash column chromatography (20% ethyl acetate/petrol) to

give the cycloadduct (**246**) (181 mg, 45%) as a syrup; $[\alpha]_D$ 62.9 [c 0.029]; υ_{max}(film) 3031, 2868, 1779, 1721, 1501, 1458, 1415, 1073, 737 and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.82 (2H, m, CH_2OBn), 3.91 (1H, m, 6-H), 4.12 (1H, t, *J* 8 Hz, 5-H), 4.24 (1H, t, *J* 8 Hz, 4-H), 4.55-4.9 (6H, m, 3 x CH_2Ph), 4.7 (1H, m, 3-H), 5.41 (1H, t, *J* 2.5 Hz, 2'-H), 5.47 (1H, dd, *J* 2.5, 1.5 Hz, 1'-H), 7.2-7.6 (25H, m, Ar); δ_C (75 MHz) 55.90, 59.03, 68.65, 73.58, 74.52, 74.67, 77.21, 77.27, 81.37, 82.09, 108.75, 125.21, 127.66, 127.86, 127.98, 128.11, 128.27, 128.50, 128.60, 128.97, 131.31, 137.30, 137.43, 137.70, 137.96, 146.92, 150.41, 153.24; m/z (CI) 694 $[M+H]^+$, 96%]; (Found: m/z (CI) 694.2917. $C_{43}H_{40}O_6N_3$ requires m/z 694.2917);

Cycloadducts (247)

Diene: (**227**) (222 mg, 0.44 mmol) (From coupling of vinyl stannane (**218**) with ester (**221**).

Dienophile: 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) (77 mg, .0.48 mmol).

A solution of the dienophile was added to stirred solution of the diene in dichloromethane at -78°C. After warming to room temperature, the reaction was stirred overnight. The solvent was removed and the residue was purified by flash column chromatography (30% ethyl acetate/petrol) to give the cycloadducts (**247a, b**) (255 mg, 86%) as white solids. (**a:b** 8.5:1). The diastereoisomers were recrystallised from methanol. Major diastereoisomer: m.p. 127.9-128.2°C ; $[\alpha]_D$ -118.4 (c 0.035, $CHCl_3$); υ_{max}(KBr disc) 3065, 3032, 2952, 2910, 2870, 1782, 1731, 1600, 1502, 1454, 1416, 1362, 1310, 1269, 1221, 1205, 1170, 1140, 1073, 1029, 1000, 994, 856, 803, 788, 733 and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.7-3.87 (6H, m, CH_2OBn, 6-H, CO_2Me), 3.96 (1H, t, *J* 9 Hz, 4-H), 4.1 (1H, t, *J* 9 Hz, 5-H), 4.54-4.92 (6H, m, 3 x CH_2Ph), 4.71 (1H, d, *J* 10 Hz, 3-H), 5,15 (1H, d, *J* 6.5 Hz, 2'-H), 5.79 (1H, dd, *J* 6.5, 1 Hz, 1'-H), 7.2-7.6 (20H, m, Ar); δ_C (75 MHz) 53.16, 55.00, 56.50, 68.19, 73.60, 75.22, 75.36, 77.87, 82.46, 83.00, 120.91, 126.05, 127.83, 127.90, 127.96, 128.02, 128.10, 128,26, 128.53, 128.56, 129.17, 131.41, 137.20, 137.62, 137.76, 150.16, 150.85, 155.61, 167.61; m/z (CI) 676 $[M+H]^+$, 95%]; (Found:

m/z (CI) 676.2645. $C_{39}H_{38}O_8N_3$ requires m/z 676.2659); (Found: C, 69.45; H 5.4; N, 6.3. $C_{39}H_{37}O_8N_3$ requires C, 69.3, H 5.5; N, 6.2). Minor diastereoisomer: $[\alpha]_D$ +162 (c 0.013, $CHCl_3$); υ_{max}(film) 2924, 1776, 1716, 1502, 1423, 1210, 1099, 737 and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.6-3.92 (6H, m, **CH_2**OBn, 5-H, CO_2**Me**), 4.39 (1H, m, 6-H), 4.45-4.6 (6H, m, 3 x **CH_2**Ph), 4.61 (1H, m, 4-H), 5.03 (1H, br s, 3-H), 5.19 (1H, d, *J* 6.5 Hz, 2'-H), 5.65 (1H, d, *J* 6.5 Hz, 1'-H), 7.2-7.6 (20H, m, Ar); δ_C (75 MHz) 51.46, 53.02, 54.12, 68.19, 71.89, 72.74, 73.24, 73.38, 73.62, 77.87, 98.30, 125.57, 127.67, 127.88, 128.02, 128.16, 128.20, 128.48, 128.59, 128.64, 129.11, 131.26, 137.00, 137.78, 148.77, 149.67, 152.45, 168.01; m/z (CI) 676 $[M+H]^+$, 90%]; (Found: m/z (CI) 676.2642. $C_{39}H_{38}O_8N_3$ requires m/z 676.2659).

Cycloadduct (248)

Diene: (**228**) (306 mg, 0.575 mmol) (From coupling of vinyl stannane (**218**) with (*E*)-iodophenylpropene (**222**)).

Dienophile: 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) (104 mg, .0.64 mmol).

A solution of the dienophile was added to stirred solution of the diene in dichloromethane at -78°C. After warming to room temperature, the reaction was stirred overnight. The solvent was removed and the residue was purified by flash column chromatography (20% ethyl acetate/petrol) to give the cycloadduct (248) (39 mg, 10%) as a syrup; $[\alpha]_D$ +35 (c 0.038, $CHCl_3$); υ_{max}(film) 3062, 3031, 2918, 2870, 1779, 1723, 1600, 1497, 1454, 1414, 1363, 1312, 1266, 1236, 1211, 1185, 1135, 1072, 1028, 912, 734 and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.88 (3H, s, Me), 3.65-3.9 (3H, m, **CH_2**OBn, 6-H), 4.14 (2H, m, 4-H, 5-H), 4.54-4.98 (6H, m, 3 x **CH_2**Ph), 4.79 (1H, d, *J* 8.5 Hz, 3-H), 5.36 (1H, s, 1'-H), 7.1-7.6 (25H, m, Ar); δ_C (75 MHz) 19.88, 54.66, 64.09, 68.28, 73.63, 74.97, 75.34, 78.24, 82.12, 82.79, 116.92, 125.18, 126.14, 127.88, 127.95, 128.14, 128.22, 128.43, 128.52, 128.58, 128.61, 128.92, 128.98, 131.38, 137.09, 137.72, 141.41, 145.63, 150.78, 153.71; m/z (CI) 707 $[M+H]^+$, 25%]; (Found: m/z (CI) 708.3061. $C_{44}H_{42}O_6N_3$ requires m/z 708.3074);

Cycloadducts (249)

Diene: (229) (346 mg, 0.65 mmol) (From coupling of vinyl stannane (218) with ester (223).

Dienophile: 4-phenyl-1,2,4-triazoline-3,5-dione (244) (114 mg, .0.71 mmol).

A solution of the dienophile was added to stirred solution of the diene in dichloromethane at -78°C. After warming to room temperature, the reaction was stirred overnight. The solvent was removed and the residue was purified by flash column chromatography (30% ethyl acetate/petrol) to give the cycloadducts (249a, b) (416 mg, 93%) as white solids. (a:b 15.5:1). The diastereoisomers were recrystallised from methanol; Major diastereoisomer: m.p. 144.9-145.3°C ; $[\alpha]_D$-93 (c 0.024, $CHCl_3$); υ_{max}(KBr disc) 3031, 2867, 1782, 1724, 1600, 1504, 1455, 1423, 1262, 1206, 1137, 1071, 1028, 912, 807, 737 and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.04 (3H, s, Me), 3.61 (1H, ddd, *J* 10, 3, 1.5 Hz, 6-H), 3.82 (1H, s, CO_2**Me**), 3.82 (2H, m, CH_2OBn), 3.89 (1H, t, *J* 9.5 Hz, 4-H), 4.08 (1H, t, *J* 9.5 Hz, 5-H), 4.35-4.95 (6H, m, 3 x **CH_2**Ph), 4.68 (1H, d, *J* 8.5 Hz, 3-H), 4.94 (1H, br s, 2'-H), 7.1-7.6 (20H, m, Ar); δ_C (75 MHz) 13.78, 53.04, 54.77, 60.61, 68.31, 73.55, 75.10, 75.36, 77.93, 81.78, 82.95, 111.43, 125.97, 127.74, 127.82, 127.92, 128.01, 128.27, 128.37, 128.47, 128.51, 129.16, 131.42, 137.24, 137.72, 137.83, 144.55, 150.12, 155.77, 167.70; m/z (CI) 690 $[M+H]^+$, 13%]; (Found: m/z (CI) 690.2798. $C_{40}H_{40}O_8N_3$ requires m/z 690.2815); (Found: C, 69.82; H 5.72; N, 6.22. $C_{39}H_{37}O_8N_3$ requires C, 69.67, H 5.67; N, 6.1). Minor diastereoisomer: m.p. 108.6-109.1°C ; $[\alpha]_D$ +133 (c 0.036, $CHCl_3$); υ_{max}(KBr disc) 3031, 2923, 1774, 1716, 1502, 1454, 1426, 1207, 1096, 1028, 912, 736, and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.04 (3H, s, Me), 3.62 (1H, dd, *J* 10.5, 5, Hz, **CH_2**OBn), 3.75-3.87 (2H, m, **CH_2**OBn, 5-H), 3.81 (3H, s, CO_2**Me**), 4.47 (1H, m, 6-H), 4.5-5.06 (6H, m, 3 x **CH_2**Ph), 4.62 (1H, m, 4-H), 5.01 (1H, br s, 3-H), 5.03 (1H, br s, 2'-H) 7.1-7.6 (20H, m, Ar); δ_C (75 MHz) 13.90, 51.27, 52.96, 58.27, 68.50, 71.83, 72.90, 73.05, 73.41, 78.15, 108.33, 125.56, 127.76, 127.85, 127.97, 128.17, 128.27, 128.49, 128.58, 128.61, 129.13, 131.33, 137.17, 137.81, 140.06, 149.63, 152.55, 168.02; m/z (CI) 690 $[M+H]^+$, 82%]; (Found:

m/z (CI) 690.2816. $C_{39}H_{38}O_8N_3$ requires m/z 690.2815); (Found: C, 69.79; H 5.87; N, 6.10. $C_{40}H_{40}O_8N_3$ requires C, 69.67, H 5.67; N, 6.10).

Cycloadduct (250)

Diene: (**230**) (77 mg, 0.155 mmol) (From coupling of vinyl stannane (**218**) with 1-iodo-1-hexene (**224**) (*Z*:*E*=1:9)

Dienophile: 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) (27 mg, .0.17 mmol).

A solution of the dienophile was added to stirred solution of the diene in dichloromethane at -78°C. After warming to room temperature, the reaction was stirred overnight. The solvent was removed and the residue was purified by flash column chromatography (20% ethyl acetate/petrol) to give the cycloadduct (**250**) (79 mg, 76%) as a syrup; $[\alpha]_D$ -4.2 (c 0.076, $CHCl_3$); υ_{max}(film) 2928, 1776, 1720, 1502, 1454, 1411, 1074, 736 and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.97 (3H, t, *J* 7 Hz), 1.25-1.45 (4H, m), 1.91 (1H, m), 2.16 (1H, m), 3.72 (1H, dt, *J* 9, 3 Hz, CH_2OBn), 3.82 (2H, m, 6-H, CH_2OBn), 3.87 (1H, t, *J* 9 Hz, 4-H), 4.04 (1H, t, *J* 9 Hz, 5-H), 4.44 (1H, m, 2'-H), 4.53-4.9 (6H, m, 3 x CH_2Ph), 4.58 (1H, d, *J* 8.5 Hz, 3-H), 5.45 (1H, dd, *J* 2.5, 1 Hz, 1'-H), 7.1-7.6 (20H, m, Ar); δ_C (75 MHz) 13.98, 22.58, 25.58, 33.39, 54.74, 56.00, 68.84, 73.61, 74.81, 75.21, 77.92, 82.28, 82.83, 109.07, 125.37, 127.88, 127.99, 128.08, 128.14, 128,48, 128.51, 128.55, 128.58, 129.03, 131.47, 137.30, 137.50, 137.73, 147.70, 149.78, 153.77; m/z (CI) 674 [M+H]$^+$, 75%]; (Found: m/z (CI) 674.3229. $C_{41}H_{44}O_6N_3$ requires m/z 674.3230).

Cycloadduct (252)

Diene: 2,6:7,11-Dianhydro-1,3,4,9,10,12-hexa-O-benzyl-5,8-dideoxy-D-erythro-L-gulo-dodeca-5,7-dienitol (**251**) (277 mg, 0.33 mmol).

Dienophile: 4-phenyl-1,2,4-triazoline-3,5-dione (**244**) (58 mg, .0.33 mmol).

A solution of the dienophile was added to stirred solution of the diene in dichloromethane at -78°C. After warming to room temperature, the reaction was stirred overnight. The solvent was removed and the residue

was purified by flash column chromatography (25% ethyl acetate/petrol) to give the cycloadduct (**252**) (236 mg, 70%) as a syrup; $[\alpha]_D$ +19 (c 0.029, $CHCl_3$); υ_{max}(film) 3062, 3030, 2867, 1775, 1718, 1600, 1496, 1454, 1410, 1364, 1294, 1208, 1130, 1070, 1028, 911, 805, 738 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 3.6-3.8 (5H, m), 3.89 (1H, t, *J* 8 Hz), 4.03 (1H, t, *J* 8 Hz), 4.26 (2H, m), 4.35-4.8 (13H, m), 4.845 (1H, t, *J* 3.5 Hz) 7.13-7.48 (35H, m, Ar); δ_C (75 MHz) 53.45, 55.98, 68.27, 69.13, 71.48, 73.21, 73.61, 73.78, 74.69, 75.15, 82.84, 83.24, 125.39, 127.90, 127.98, 128.08, 128.14, 128.17, 128.45, 128.59, 129.13, 130.42, 130.63, 131.24, 137.15, 137.71, 137.86, 138.01, 138.06, 148.84, 154.85; m/z FAB 1004 $[M-H]^+$, 75%]; (Found: m/z FAB 1005.4160. $C_{62}H_{59}O_{10}N_3$ requires m/z 1005.4200).

898 (50%) 790 (50%) 181 (100%)

Ethyl-(R)-(-)-3-(t-butyldimethylsilyloxy)-butanoate (157)

To a solution of ethyl-(R)-(-)-3-hydroxybutyrate (**156**) (4.95 g, 37.5 mmol) in dichloromethane (10 ml) was added 1,8-diazobicyclo[5,4,0]undec-7-ene (6.15 ml, 39.4 mmol) at 0°C followed by t-butyldimethylsilyl chloride (5.84 g, 39.4 mmol) in dichloromethane (10 ml). After 3 h at room temperature, the mixture was poured into water (100 ml), extracted with ether (100 ml) and washed with water (50 ml), hydrochloric acid (0.1M, 50 ml), water (50 ml), saturated sodium bicarbonate (50 ml) and water (50 ml). The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by flash column chromatography (1:19 ethyl acetate petrol) to afford the *title compound* (**157**) (7.9 g, 87%) as a colourless oil; $[\alpha]_D$ -23.9 (c 0.034, $CHCl_3$); υ_{max}(film) 2958, 2931, 2858, 1739, 1473, 1377, 1301, 1256, 1184, 1140, 1084, 1035, 1004, 940, 837, 811, 777 and 659 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.07 (3H, s, MeSi), 0.1 (3H, s, MeSi), 0.9 (9H, s, ^{t}BuSi), 1.23 (3H, d, *J* 6Hz, 4-H), 1.3 (3H, t, *J* 7Hz, OCH_2CH_3), 2.43 (1H, dd, *J* 14, 5.5 Hz, 2-H), 2.43 (1H, dd, *J* 14, 7.5Hz, 2-H), 4.15 (2H, m, OCH_2), 4.31 (1H, m, 3-H); δ_C (75 MHz) -5.03, -4.49 (Me_2Si), 14.21 (OCH_2CH_3), 17.97 (Me_3C), 23.94 (C-4), 25.75 (Me_3C), 44.99 (C-2), 60.27 (C-3), 65.88

(OCH_2), 171.72 (C-1); m/z (CI) 247 [[M+H]$^+$, 98%]; (Found: m/z (CI) 247.1722. $C_{12}H_{27}SiO_3$ requires 247.1722).

(Z,E)-(R)-(-)-4-(t-Butyldimethylsilyloxy)-1-iodopentene (160)

DIBAL-H (1 M in toluene, 50.3 ml, 50.3 mmol) was added dropwise to a cooled (-80°C) and stirred solution of ethyl-3-(t-butyldimethylsilyloxy) butanoate (**157**) (7.72 g, 31.4 mmol) in anhydrous toluene (225 ml). After being stirred at -80°C for 1 h the reaction was quenched by dropwise addition of methanol (32 ml) keeping the temperature below -78°C. Citric acid (10% aqueous solution, 320 ml) was then added, the mixture was allowed to warm to room temperature, the organic phase was decanted off and the aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic phases were dried ($MgSO_4$), the solvent was removed under vacuum. The crude aldehyde (**159**) was used immediately in the next reaction.

To a suspension of iodomethyltriphenylphosphonium iodide (**202**) (20.7 g, 39.0 mmol) in THF (90 ml) at room temperature was slowly added sodium hexamethyldisilazide (1 M solution in THF, 41 ml). After stirring for 10 min, the dark red ylid (**203**) solution was cooled to -78°C and 3-(t-butyldimethylsilyloxy) butanal (**159**) (crude) was added slowly. The mixture was allowed to warm to room temperature and after 30 min, the solvent was removed *in vacuo*. The residue was washed with 3 x (50 ml 50:1 petrol:diethyl ether) and the supernatant filtered through celite to remove triphenylphosphine oxide. The combined eluents were concentrated *in vacuo* and the residue purified by flash column chromatography (dichloromethane /hexane 1:19) to afford the *title compound* (**160**) (4.55 g, 44%) as a colourless oil, (Z:*E* = 19.8 :1); υ_{max}(film) 2956, 2928, 2887, 2857, 1611, 1471, 1377, 1361, 1308, 1256, 1131, 1089, 1022, 836, 808 and 776 cm^{-1}; δ_H (300 MHz, $CDCl_3$): Z-isomer; 0.07 (6H, s, Me_2Si), 0.9 (9H, s, ^{t}BuSi), 1.20 (1H, d, *J* 6 Hz, 5-H), 2.31 (2H, distorted triplet, 3-H), 4.0 (1H, sextet, *J* 6 Hz, 4-H), 6.30 (2H,

m, 2-H). *E*-isomer 0.07 (6H, s), 0.9 (9H, s), 1.18 (1H, d, *J* 6 Hz), 2.20 (2H, distorted triplet), 3.88 (1H, sextet, *J* 6 Hz), 6.06 (1H, d, *J* 14.5 Hz, 1-H), 6.55 (1H, dt, *J* 14.5, 7.5 Hz, 2-H). δ_C (75 MHz): -4.69, -4.46 (Me_2Si), 18.12 (Me_3C), 23.60 (C-5), 25.88 ($\mathbf{Me_3C}$), 44.55 (C-3), 67.30 (C-4), 83.71 (C-1), 138.33 (C-2). m/z (CI) 327 [[M+H]$^+$, 52%] (Found: m/z (CI) 327.0643. $C_{11}H_{24}SiOI$ requires m/z 327.0630).

(Z,E)-(R)-(-)-4-Hydroxy-1-iodopentene (161)

To a solution of (*Z*,*E*)-4-(t-butyldimethylsilyloxy)-1-iodopentene (**160**) (2.55 g, 7.82 mmol) in acetonitrile (140 ml) was added 60% aqueous hydrogen fluoride (4.6 ml). The mixture was stirred for 10 minutes after which the solution was diluted with water and extracted with chloroform (2 x 50 ml). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by flash column chromatography (1:4 ethyl acetate petrol) to afford the *title compound* (**161**) (1.41 g, 85%) as a colourless oil; (*Z*:*E* = 15.7:1); υ_{max}(film) 3346, 2968, 2927, 1610, 1455, 1375, 1307, 1262, 1122, 1082, 999, 973, 943 and 843 cm^{-1}; δ_H (300 MHz, $CDCl_3$) : *Z*-isomer 1.29 (3H, d, *J* 6.5 Hz, 5-H), 2.37 (2H, t, *J* 6.5 Hz, 3-H), 4.02 (1H, sextet, *J* 6.5 Hz, 4-H), 6.33 (1H, q, *J* 7 Hz, 2-H), 6.41 (1H, distorted d, *J* 8 Hz, 1-H);*E* -isomer 1.25 (3H, d,*J* 6.5 Hz), 2.13 (2H, t, *J* 6.5 Hz), 3.91 (1H, sextet, *J* 6.5 Hz), 6.18 (1H, d, *J* 15 Hz, 1-H), 6.59 (1H, dt, *J* 15, 7.5Hz, 2-H); δ_C (75 MHz): *Z*-isomer 23.21 (C-5), 44.09 (C-3), 66.90 (C-4), 84.88 (C-1), 137.56 (C-2); *E*-isomer 22.88 (C-5), 45.52 (C-3), 66.58 (C-4), 84.88 (C-1), 142.60 (C-2). m/z (EI) 212 [M$^+$, 5%] (CI) 230 [M$^+$, 1.9%] (Found: m/z (CI) 211.9702. C_5H_9OI requires m/z 211.9700).

Coupling of 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tri-n-butylstannyl-D-arabino-hex-1-enitol (218) with (Z,E)-4-(t-Butyldimethylsilyloxy)-1-iodopentene (160)

Method A: To a solution of bis(acetonitrile)dichloropalladium(11) (13 mg, 5 mol%) in DMF (10 ml) was added (*Z*,*E*)-4-(t-butyldimethylsilyloxy)-1-

iodopentene (**160**) (*Z*:*E* 19.8 :1) (0.43 g, 1.33 mmol) and stannane (**218**) (721 mg, 1.02 mmol). The orange solution immediately turned black upon addition of the stannane. The reaction mixture was stirred for 41 h at room temperature whereupon it was quenched with saturated solution potassium fluoride in 10% ammonium hydroxide was added. The resulting mixture was filtered and extracted with ether (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by flash column chromatography (1:19 ethyl acetate/petrol) to afford diene (**253**) (*Z*:*E* 8.6:1) (279 mg, 44.5%) as a colourless oil.

Method B: A mixture of tris(dibenzylideneacetone)dipalladium (11.5 mg, 2 mol%) and (*Z*,*E*)-4-(t-butyldimethylsilyloxy)-1-iodopentene (**160**) (*Z*:*E* 9;1) (0.41 g, 1.26 mmol) in DMF (10 ml) was stirred at ambient temperature for 10 minutes and then added to a solution of stannane (**218**) (443 mg, 0.63 mmol) in DMF (10 ml). The reaction was stirred for 42 h at ambient temperature whereupon it was quenched with saturated solution potassium fluoride in 10% ammonium hydroxide. The resulting mixture was filtered and extracted with ether (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by flash column chromatography (1:19 ethyl acetate/petrol) to afford diene (**253**) (*Z*:*E* 3.2:1) (137 mg, 35%) as a colourless oil.

Method C: A solution of n-butyl lithium (0.63 ml, 1.6 M solution in hexane) was added to a stirred solution of stannane (**218**) (672 mg, 0.95 mmol) in THF (5 ml) at -78°C. The mixture was stirred at this temperature for 15 min. Zinc chloride (1M solution in ether, 1.0 ml) was added dropwise and the resulting mixture was allowed to warm up to room temperature and to stir for 2 h. A solution of (*Z*,*E*)-4-(t-butyldimethylsilyloxy)-1-iodopentene (**160**) (*Z*:*E* 9:1) (0.62 g, 1.9 mmol) and tetrakis(triphenylphosphine)palladium(0) (52 mg, 5 mol%) in THF (3 ml) was then added to the organozinc intermediate (**255**). After 2 h, the solvent was evaporated under reduced pressure.

Purification of the residue by flash column chromatography (5% ethyl acetate in petrol) gave diene (**253**) (*Z*:*E* 9:1) (210 mg, 36%) as a colourless oil;

Method D: A solution of n-butyl lithium (0.65 ml, 1.6 M solution in hexane) was added to a stirred solution of stannane (**218**) (681 mg, 0.97 mmol) in THF (5 ml) at -78°C. The mixture was stirred at this temperature for 15 min. Zinc chloride (1 M solution in ether, 1.0 ml) was added dropwise and the resulting mixture was allowed to warm up to room temperature and to stir for 2 h. A solution of (*Z*,*E*)-4-(t-butyldimethylsilyloxy)-1-iodopentene (**160**) (*Z*:*E* 9:1) (0.63 g, 1.9 mmol), triphenylarsine (12 mg, 4mol%) and tris(dibenzylideneacetone)dipalladium (18 mg, 2 mol%) in THF (10 ml) was stirred in a separate flask for 10 minutes and then added to the organozinc intermediate (**255**). After 2 h, the solvent was evaporated under reduced pressure. Purification of the residue by flash column chromatography (5% ethyl acetate in petrol) gave diene (**253**) (*Z*:*E* 9:1) (222 mg, 37%) as a colourless oil; Z-isomer: $[\alpha]_D$ -24.4 (c 0.032, $CHCl_3$); υ_{max}(film): 3064, 3031, 2928, 2857, 1658, 1610, 1497, 1454, 1374, 1254, 1211, 1181, 1091, 1028, 909, 835, 809, 776, 735 and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.2(6H, s), 0.95 (9H, s), 1.17 (3H, d, *J* 6 Hz, 5'-H), 2.64 (1H, ddd, *J* 14, 7, 7 Hz, 3'-H), 2.71 (1H, ddd, *J* 12, 7, 7 Hz, 3'-H), 3.8-4.0 (4H, m, CH_2OBn, 5-H, 4'-H), 4.16 (1H, m, 6-H), 4.35 (1H, dd, *J* 6, 3 Hz, 4-H), 4.59-4.93 (6H, m, 3 x CH_2Ph), 4.95 (1H, d, *J* 3 Hz, 3-H), 5.65 (1H, dt, *J* 12, 7 Hz, 2'-H), 5.76 (1H, d, *J* 12 Hz, 1'-H), 7.35 (15H, m, Ar); δ_C (75 MHz) -4.62, -4.40, 18.18, 23.35, 25.95, 38.89, 68.70, 68.94, 70.35, 73.55, 73.63, 74.30, 76.84, 100.79, 124.03, 127.57, 127.61, 127.64, 127.67, 127.71, 127.78, 127.99, 128.37, 128.43, 129.51, 131.62, 138.27, 138.35, 138.54, 153.18); m/z (CI) 615 $[M+H]^+$, 5%]; (Found: m/z (CI) 615.3492. $C_{38}H_{51}O_5Si$ requires m/z 615.3492).

Coupling of 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-1-tri-n-butylstannyl-D-arabino-hex-1-enitol (218) with (*Z*,*E*)-4-Hydroxy-1-iodopentene (161)

To a solution of bis(acetonitrile)dichloropalladium(11) (16 mg, 5 mol. %) in DMF (10 ml) was added (*Z*,*E*)-4-Hydroxy-1-iodopentene (**161**) (*Z*:*E* 15.7:1) (0.34 g, 1.59 mmol) and stannane (**218**) (860 mg, 1.22 mmol). The orange solution immediately turned black upon addition of the stannane. The reaction mixture was stirred for 41 h at room temperature whereupon it was quenched with saturated solution potassium fluoride in 10% ammonium hydroxide was added. The resulting mixture was filtered and extracted with ether (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by flash column chromatography (1:5:14 triethylamine/ethyl acetate/petrol) to afford diene (**254**) (*Z*:*E* 2.7:1) (346 mg, 57%) as a colourless oil. *Z*-isomer: $[\alpha]_D$-34 (c 0.016, CH_2Cl_2); υ_{max}(film): 3063, 3029, 2964, 2904, 2866, 1657, 1609, 1496, 1454, 1371, 1326, 1299, 1285, 1258, 1207, 1179, 1098, 1027, 946, 736 and 698 cm^{-1}; δ_H (300 MHz, C_6D_6): 1.21 (3H, d, *J* 6 Hz, 5'-H), 2.64 (1H, ddd, *J* 14, 5 Hz, 3'-H), 2.9 (1H, ddd, *J* 14, 8 Hz, 3'-H), 3.75 (1H, dd, *J* 10.5, 3 Hz, CH_2OBn), 3.83 (1H, dd, *J* 10.5, 6 Hz, CH_2OBn), 3.85 (1H, m, 4'-H), 3.94 (1H dd, *J* 9, 6 Hz, 5-H), 4.18 (1H, m, 6-H), 4.31 (1H, dd, *J* 6, 3 Hz, 4-H), 4.37-4.87 (6H, m, 3 x CH_2Ph), 4.96 (1H, d, *J* 3 Hz, 3-H), 5.61 (1H, dt, *J* 12, 8 Hz, 2'-H), 5.84 (1H, d, *J* 12 Hz, 1'-H), 7.2-7.4 (15H, m); δ_C (75 MHz) 23.53, 39.37, 67.98, 69.23, 70.30, 73.55, 74.75, 77.06, 77.14, 101.95, 125.40, 127.69, 127.80, 127.87, 127.95, 128.01, 128.33, 128.48, 128.57, 131.00, 138.57, 139.09, 139.26, 153.34); m/z (CI) 393 [M^+-OBn], 25%]; (Found: m/z (CI) 393.2070. $C_{25}H_{29}O_4$ requires m/z 393.2066). *E*-isomer: υ_{max}(film): 3030, 2965, 2906, 2867, 1665, 1622, 1496, 1453, 1368, 1293, 1258, 1204, 1100, 1027, 992, 967, 940, 836, 821, 736 and 698 cm^{-1}; δ_H (300 MHz, C_6D_6): 1.06 (3H, d, *J* 6 Hz, 5'-H), 2.14 (2H, m, 3'-H), 3.64 (1H, sextet, *J* 6 Hz, 4'-H), 3.87 (2H, m, CH_2OBn), 4.12 (1H dd, *J* 8.5, 6 Hz, 5-H), 4.25 (1H, m, 6-H), 4.37 (1H, dd, *J* 6, 3 Hz, 4-H), 4.39-4.91 (6H, m, 3 x CH_2Ph), 4.93 (1H, d, *J* 3 Hz, 3-H), 5.87 (1H, d, *J* 15.5 Hz, 1'-H), 6.43 (1H, dt, *J* 15.5,

7.5 Hz, 2'-H), 7.1-7.4 (15H, m, Ar); δ_C (75 MHz) 23.12, 42.79, 67.16, 69.00, 70.33, 73.43, 73.59, 75.02, 77.17, 77.49, 99.99, 127.52, 127.70, 127.80, 127.84, 127.93, 128.02, 128.34, 128.46, 128.56, 128.93, 138.98, 139.20, 139.35, 151.80); m/z (CI) 393 [M^+-OBn], 12%]; (Found: m/z (CI) 393.2063. $C_{25}H_{29}O_4$ requires m/z 393.2066).

(Z)-Diene alcohol (254)

To a solution of the TBDMS-protected (Z)-alcohol (**253**) (213 mg, 0.35 mmol) in THF (10 ml) was added TBAF (1M in THF, 0.7 ml) and the resulting solution was stirred at room temperature for 16 h under nitrogen. Ether (30 ml) was added and the organic solution was washed with saturated aqueous ammonium chloride (2 x 15 ml) and brine (1 x 15 ml), then dried ($MgSO_4$), and concentrated *in vacuo*. Flash column chromatography (1:5:14 triethylamine/ethyl acetate/petrol) of the residue afforded the *title compound* (**254**) (171 mg, 87%) as a colourless viscous oil.

Spiroacetal (255)

To a solution of Z-diene alcohol (**254**) (182 mg, 0.36 mmol) in dichloromethane (5 ml) was added camphorsulphonic acid (30 mg) and the mixture stirred at room temperature for 1 h. After quenching with saturated sodium bicarbonate, the product was extracted into ether (2 x 20ml), the ethereal extracts dried ($MgSO_4$), and evaporated and the residue was purified by flash column chromatography (ethyl acetate/petrol 3:17) to afford the *title compound* (**255**) (127 mg, 70%); υ_{max}(film) 3031, 2968, 2927, 1661, 1496, 1454, 1399, 1365, 1309, 1245, 1215, 1177, 1097, 1028, 989, 911, 851, 735 and 698 cm^{-1}; δ_H (300 MHz, C_6D_6): 1.16 (3H, d, *J* 7.5 Hz, Me), 1.64 (1H, t, *J* 13 Hz, 3_{eq}-H), 1.77 (1H, t, *J* 12 Hz, 11_{ax}-H), 1.8 (1H, m, 3_{ax}-H), 2.41 (1H, dd, *J* 12.5, 5 Hz, 11_{eq}-H), 3.84 (1H, dd, *J* 11, 2 Hz, CH_2OBn), 3.9 (1H, t, *J* 9 Hz, 9-H), 3.95 (1H, dd, *J* 11, 5 Hz, CH_2OBn), 4.14 (1H, m, 2-H), 4.23 (1H, ddd, *J* 10, 5, 2 Hz, 8-H), 4.39 (1H, m, 10-H), 4.45-5.2 (6H, m, 3 x CH_2Ph), 5.7 (2H, m 4-H, 5-H), 7.1-7.5 (15H, m, Ar); δ_C (75

MHz) 21.13, 32.34, 40.62, 63.71, 70.12, 71.50, 72.56, 73.53, 75.08, 78.68, 78.97, 96.19, 127.44, 127.49, 127.54, 127.69, 127.89, 128.01, 128.33, 128.49, 129.94, 129.94, 139.28, 139.64, 139.73; m/z (CI) 501 $[M+H]^+$, 20%] (Found: m/z (CI) 501.2640. $C_{32}H_{37}O_5$ requires m/z 501.2641).

11-Phenylselenyl-spiroacetal (256)

To a solution of Z-diene alcohol (**254**) (394 mg, 0.79 mmol) in dichloromethane (10 ml) was added pyridine (0.1 ml, 6.4 mmol). The mixture was cooled to -78°C, phenyl selenium chloride (168 mg, 0.87 mmol) was added and the reaction was allowed to warm to room temperatue and stir for 1 h. After quenching with ice cold aqueous sodium bicabonate, the product was extracted into dichloromethane (3 x 30 ml), the combined extracts dried ($MgSO_4$), and evaporated and residue was purified by flash column chromatography (ethyl acetate/petrol 1:19) to afford the *title compound* (**256**) (221 mg, 43%) as a mixture of its diastereoisomers (**a**:**b**:**c** 1.5:1:3.2).

(**256a**: **256b** 1.5:1): υ_{max}(film) 3030, 2918, 1657, 1606, 1579, 1496, 1477, 1454, 1395, 1365, 1259, 1209, 1098, 1001, 910, 736 and 696 cm^{-1}; δ_H (300 MHz, $CHCl_3$): 1.28 ($^9/_5$H, d, *J* 7 Hz, Me), 1.32 ($^6/_5$H, d, *J* 3 Hz, Me), 2.07 (2H, m, 3-H), 3.42 ($^2/_5$H, d, *J* 11 Hz, 11_{ax}-H), 3.70 ($^3/_5$H, d, *J* 11 Hz, 11_{eq}-H), 3.72-4.13 ($^{18}/_5$H, m, 9-H), 4.19 ($^2/_5$H, dd, *J* 11, 9 Hz, 10-H), 4.44-5.21 (6H, m, 3 x CH_2Ph), 5.74 ($^2/_5$H, d, *J* 10 Hz, 5-H), 6.1 (1H,m, 4-H), 6.68 ($^3/_5$H, d, *J* 10Hz, 5-H), 7.1-7.6 (20H, m, Ar); δ_C (75 MHz) 20.98, 21.01, 31.68, 32.03, 55.33, 64.23, 64.74, 68.95, 69.43, 71.33, 71.82, 72.27, 73.38, 73.48, 74.96, 75.07, 75.94, 76.45, 79.40, 79.92, 83.28, 97.75, 98.56, 126.59, 127.03, 127.38, 127.43, 127.49, 127.62, 127.69, 127.75, 127.90, 127.96, 128.19, 128.25, 128.32, 128.38, 128.45, 128.84, 129.00, 129.27, 129.61, 131.55, 131.75, 132.88, 133.54, 138.30, 138.41, 138.46, 138.62; m/z (CI) 657 $[M+H]^+$, 57%] (Found: m/z (CI) 656.2050. $C_{38}H_{40}O_5{}^{80}Se$ requires m/z 656.2041).

(**256c**): υ_{max}(film) 3062, 3031, 2928, 1656, 1579, 1496, 1477, 1454, 1398, 1360, 1321, 1264, 1209, 1112, 1025, 910, 838, 785, 736 and 697 cm^{-1}; δ_H (300 MHz, $CHCl_3$):

1.37 (3H, d, *J* 7.5 Hz, Me), 2.10 (1H, m, 3-H), 2.43 (1H, dt, *J* 18, 5 Hz, 3-H), 3.55 (1H, d, *J* 12 Hz, 11_{ax}-H), 3.81 (5H, m, 8-H, 9-H, 10-H, CH_2OBn), 4.44 (1H, m, 2-H), 4.56-5.07 (6H, m, 3 x CH_2Ph), 6.13 (1H,d, *J* 11 Hz, 4-H), 6.32 (1H, dt, *J* 11, 5 Hz, 5-H), 7.2-7.25 (20H, m, Ar); δ_C (75 MHz) 21.71, 30.82, 57.39, 69.43, 69.87, 73.35, 73.42, 74.91, 75.44, 80.12, 83.58, 97.67, 123.47, 126.88, 127.52, 127.60, 127.82, 127.99, 128.15, 128,26, 128.34, 128.48, 128.72, 128.94, 131.13, 131.66, 133.13, 138.16, 138.30, 138.49; m/z (CI) 657 $[M+H]^+$, 32%] (Found: m/z (CI) 656.2042. $C_{38}H_{40}O_5{}^{80}Se$ requires m/z 656.2041).

2-Ethyltetrahydropyran (261)

To a mixture of tetrahydropyran-2-methanol (**257**) (0.51 g, 4.42 mmol) and pyridine (1.06 ml) in DCM (10 ml) at -15°C was added dropwise trifluoromethanesulphonic anhydride (1.1 ml, 6.6 mmol) in DCM (3 ml), and the reaction mixture was stirred for 0.5 h. After dilution with hexane, the organic layer was washed successively with water and saturated sodium bicarbonate solution, then dried ($MgSO_4$) and concentrated *in vacuo* (below 25°C). The crude product was used immediately for the next reaction.

To a solution of dimethylcuprate, (prepared from CuI (2.53 g) and methyllithium (1.4M solution in ether, 19 ml, 26.6 mmol) in ether (10 ml) at -30°C was added an ether (3 ml) solution of triflate (**258**), and the reaction mixture was warmed to 0°C. After 3 h of stirring, the mixture was quenched with saturated ammonium chloride-aqueous ammonia (9:1) and extracted with ether (3 x 50 ml). The combined organic phases were dried ($MgSO_4$), the solvent was removed under vacuum and the residue purified by flash chromatography (ethyl acetate/petrol 1:19) to afford the *title compound* (**261**) (101 mg, 20%); δ_H (200 MHz, $CDCl_3$) 0.9 (3H, t, *J* 7.5 Hz, Me), 1.1-1.9 (8H, m), 3.15 (1H, m, 6_{ax}-H), 3.4 (1H, m, 2-H), 3.96 (1H, m, 6_{eq}-H).

2-Benzyltetrahydropyan (262)

Method A: To a solution of diphenylcuprate, prepared from CuI (5.34 g, 28.1 mmol) and phenyllithium (1.8 M in cyclohexane/ether, 31.2 ml, 56.3 mmol) in ether (10 ml) at -30°C was added an ether (3 ml) solution of the triflate (**258**) (prepared using the method above from tetrahydropyran-2-methanol (**257**) (1.09g, 9.38 mmol)) and the reaction mixture was warmed to 0°C. After 3 h of stirring, the mixture was quenched with saturated ammonium chloride-aqueous ammonia (9:1) and extracted with ether (3 x 50 ml). The combined organic phases were washed with brine, dried ($MgSO_4$), the solvent was removed under vacuum and the residue purified by short-path distillation followed by flash column chromatography (dichloromethane/petrol 1:1) to afford the *title compound* (**262**) (0.52 g, 31.5%).

Method B: To a solution of phenyllithium (1.8M in cyclohexane/ether, 6.5 ml, 11.6 mmol) in THF (10 ml), was added lithium 2-thienylcyanocuprate (0.25M in THF, 46.4 ml, 11.6 mmol) at -78°C, followed by an THF solution of the triflate (**258**) (prepared using the method above from tetrahydropyran-2-methanol (**257**) (1.13 g, 9.73 mmol)). The reaction mixture was slowly warmed to 0°C and after 2 h stirring, the mixture was quenched with saturated ammonium chloride-aqueous ammonia (9:1) and extracted with ether (3 x 50 ml). The combined organic phases were dried ($MgSO_4$), the solvent was removed under vacuum and the residue purified by flash column chromatography (ethyl acetate/petrol 1:19) to afford the *title compound* (**262**) (0.64 g, 37%).

Method C: A solution of tetrahydropyran-2-methanol (**257**) (1.12 g, 9.64 mmol) in dichloromethane (15 ml) was cooled to -78°C and 2,6-lutidine (1.2 ml, 10.3 mmol) was added, followed by the slow addition of trifluoromethanesulfonic anhydride (1.85 ml, 11 mmol). After 30 min, the mixture was warmed to room temperature and poured into water. The

organic phase was separated and the aqueous phase was further extracted with dichloromethane (2 x 10 ml) and the combined extracts were dried ($MgSO_4$). The solvent was removed under vacuum leaving a residue which was immediately used in next reaction.

To a solution of phenyllithium (1.8M in cyclohexane/ether, 8 ml, 14.4 mmol) in THF (10 ml), was added lithium 2-thienylcyanocuprate (0.25 M in THF, 57.5 ml, 14.4 mmol) at -78°C, followed by an THF (3 ml) solution of the triflate (**258**). The reaction mixture was slowly warmed to 0°C and after 2 h stirring the mixture was quenched with saturated ammonium chloride-aqueous ammonia (9:1) and extracted with ether (3 x 50 ml). The combined organic phases were dried ($MgSO_4$), the solvent was removed under vacuum and the residue purified by flash column chromatography (ethyl acetate/ petrol 1:19) to afford the *title compound* (**262**) (0.94 g, 55%); υ_{max}(film) 3027, 2936, 2843, 1605, 1497, 1454, 1352, 1263, 1263, 1197, 1173, 1089, 1042, 901, 747 and 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.3-1.9 (6H, m, 3-H, 4-H, 5-H), 2.7 (1H, dd, *J* 11.5, 6.5 Hz, CH_2Ph), 2.94 (1H, dd, *J* 13.5, 6.5 Hz, CH_2Ph), 3.47 (1H, dt, *J* 11.5, 2.5 Hz, 6_{ax}-H), 3.5-3.6 (1H, m, 2-H), 4.04 (1H, td, *J* 11.5, 2 Hz, 6_{eq}-H), 7.2-7.4 (5H, m, Ar); δ_C (75 MHz) 23.53, 26.08, 31.47, 43.24, 68.67, 78.82, 126.12, 128.24, 129.42, 138.85; m/z (CI) 177 [[M+H]$^+$, 100%]. 159 (21%) 177 (47%) 117 (23.5%) 85 (100%)

<u>(*E*)-1-iodophenylpropene (222)</u>

To a suspension of zirconocene dichloride (5.84 g, 20 mmol) in dichloromethane (50 ml) was added trimethylaluminium (2 M in hexanes, 20 ml, 40 mmol) at room temperature. All the zirconocene dichloride dissolved within 10-15 min to give a lemon-yellow solution, to this was added (2.2 ml, 10 mmol) of phenylacetalene at room temperature. After being stirred for 24 h, to the reaction mixture was added (6.08 g, 24 mmol) of iodine dissolved in THF (30 ml) at 0°C. After the iodine colour faded, the reaction mixture was quenched with water-ether. The organic layer was separated, washed with

aqueous sodium thiosulphate, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol) to afford the *title compound* (**222**) (2.38 g, 49%); υ_{max} (film) 3061, 1596, 1568, 1463, 1442, 1376, 1294, 1201, 1061, 1027, 971, 795, 749 and 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.34 (3H, d, *J* 1 Hz, Me), 6.57 (1H, d, *J* 1 Hz) 7.3-7.4 (5H, m, Ar); δ_C (75 MHz), 24.45, 79.21, 126.07, 127.88, 128.49, 141.50, 147.27; m/z (CI) 244 [M^+, 91%]. 244 (44%) 138 (40%) 134 (29%) 132 (22%) 121 (28%) 119 (93%) 118 (36%) 91 (44%)

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Detector Aperture	6.0 mm horizontal 6.0 mm vertical
Crystal to Detector Distance	40 cm
Scan Type	$\omega/2\theta$
Scan Rate	8.0°/min (in omega) (2 rescans)
Scan Width	$(0.84 + 0.30 \tan\theta)°$
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 3148
Ranges of h,k,l	0 to 28, 0 to 33, 0 to 5
Corrections	Lorentz-polarization Absorption (trans. factors: 0.58 - 1.11) Decay (2.53% decline)

3. Structure Solution and Refinement

Structure Solution	Direct Methods
Hydrogen Atom Treatment	Included in calculated positions (d_{C-H} = 0.95Å)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ w\ (\|Fo\| - \|Fc\|)^2$
Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
p-factor	0.03
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>6.00\sigma(I)$)	991
No. Variables	161
Reflection/Parameter Ratio	6.16
Residuals: R; R_w	0.098; 0.123
Goodness of Fit Indicator	3.59
Max Shift/Error in Final Cycle	0.01
Maximum Peak in Final Diff. Map	0.39 $e^-/Å^3$
Minimum Peak in Final Diff. Map	-0.35 $e^-/Å^3$

EXPERIMENTAL DETAILS

1. Crystal Data

Empirical Formula	$C_{40}H_{39}N_3O_8$
Formula Weight	689.76
Crystal Colour, Habit	colourless, acicular
Crystal Dimensions (mm)	0.06 X 0.08 X 0.30
Crystal System	orthorhombic
No. Reflections Used for Unit Cell Determination (2θ range)	20 (19.9 - 30.0°)
Omega Scan Peak Width at Half-height	0.33
Lattice Parameters:	a = 24.988 (4)Å b = 29.859 (5)Å c = 4.7360 (9)Å V = 3534 (1)Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.296 g/cm^3
F_{000}	1456
$\mu_{(CuK\alpha)}$	7.06 cm^{-1}

2. Intensity Measurements

Diffractometer	Rigaku AFC5R
Radiation	CuKα (λ = 1.54178 Å)
Temperature	22°C
Attenuators	Zr foil (factors: 3.2, 9.5, 28.9)
Take-off Angle	6.0°

Intramolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	atom	atom	distance
O1	C8	1.22(3)	C5	C6	1.28(3)
O2	C9	1.21(3)	C6	C7	1.49(3)
O3	C4	1.49(3)	C6	C12	1.53(3)
O3	C5	1.38(3)	C7	C10	1.47(3)
O4	C2	1.41(2)	C14	C28	1.49(3)
O4	C21	1.42(3)	C21	C22	1.47(3)
O5	C10	1.27(3)	C34	C35	1.50(5)
O5	C11	1.44(3)	C15	C16	1.40(2)
O6	C10	1.25(3)	C15	C20	1.40(2)
O7	C3	1.47(3)	C16	C17	1.40(2)
O7	C14	1.44(3)	C17	C18	1.40(3)
O8	C13	1.45(3)	C18	C19	1.40(3)
O8	C34	1.29(5)	C19	C20	1.40(3)
N1	C8	1.38(3)	C22	C23	1.40(3)
N1	C9	1.42(3)	C22	C27	1.40(3)
N1	C15	1.39(2)	C23	C24	1.40(3)
N2	N3	1.41(3)	C24	C25	1.40(3)
N2	C1	1.43(2)	C25	C26	1.40(3)
N2	C9	1.36(3)	C26	C27	1.40(3)
N3	C7	1.49(3)	C28	C29	1.40(3)
N3	C8	1.36(3)	C28	C33	1.40(3)
C1	C2	1.57(3)	C29	C30	1.40(3)
C1	C5	1.46(3)	C30	C31	1.40(3)
C2	C3	1.53(3)	C31	C32	1.40(3)
C3	C4	1.54(3)	C32	C33	1.40(3)
C4	C13	1.55(4)	C35	C36	1.40(3)

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Distances Involving the Nonhydrogen Atoms (cont)

atom	atom	distance	atom	atom	distance
C35	C40	1.40(3)			
C36	C37	1.40(3)			
C37	C38	1.40(3)			
C38	C39	1.40(3)			
C39	C40	1.40(3)			

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Nonhydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
C4	O3	C5	112(2)	O3	C5	C1	113(2)
C2	O4	C21	113(2)	O3	C5	C6	121(2)
C10	O5	C11	118(2)	C1	C5	C6	124(2)
C3	O7	C14	114(2)	C5	C6	C7	125(2)
C13	O8	C34	117(3)	C5	C6	C12	122(2)
C8	N1	C9	109(2)	C7	C6	C12	113(2)
C8	N1	C15	128(2)	N3	C7	C6	107(2)
C9	N1	C15	123(2)	N3	C7	C10	114(2)
N3	N2	C1	118(2)	C6	C7	C10	112(2)
N3	N2	C9	109(2)	O1	C8	N1	126(2)
C1	N2	C9	127(2)	O1	C8	N3	126(2)
N2	N3	C7	116(2)	N1	C8	N3	108(2)
N2	N3	C8	107(2)	O2	C9	N1	126(2)
C7	N3	C8	121(2)	O2	C9	N2	129(2)
N2	C1	C2	114(2)	N1	C9	N2	106(2)
N2	C1	C5	108(2)	O5	C10	O6	124(2)
C2	C1	C5	108(2)	O5	C10	C7	118(2)
O4	C2	C1	115(2)	O6	C10	C7	118(2)
O4	C2	C3	106(2)	O8	C13	C4	102(2)
C1	C2	C3	105(2)	O7	C14	C28	110(2)
O7	C3	C2	107(2)	O4	C21	C22	109(2)
O7	C3	C4	101(2)	O8	C34	C35	112(4)
C2	C3	C4	114(2)	N1	C15	C16	122(2)
O3	C4	C3	106(2)	N1	C15	C20	118(2)
O3	C4	C13	107(2)	C16	C15	C20	120(1)
C3	C4	C13	113(2)	C15	C16	C17	120(1)

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Nonhydrogen Atoms (cont)

atom	atom	atom	angle	atom	atom	atom	angle
C16	C17	C18	120(1)	C38	C39	C40	120(2)
C17	C18	C19	120(1)	C35	C40	C39	120(2)
C18	C19	C20	120(2)				
C15	C20	C19	120(2)				
C21	C22	C23	114(2)				
C21	C22	C27	126(2)				
C23	C22	C27	120(1)				
C22	C23	C24	120(2)				
C23	C24	C25	120(2)				
C24	C25	C26	120(2)				
C25	C26	C27	120(2)				
C22	C27	C26	120(2)				
C14	C28	C29	122(2)				
C14	C28	C33	118(2)				
C29	C28	C33	120(2)				
C28	C29	C30	120(1)				
C29	C30	C31	120(2)				
C30	C31	C32	120(2)				
C31	C32	C33	120(1)				
C28	C33	C32	120(2)				
C34	C35	C36	116(2)				
C34	C35	C40	124(2)				
C36	C35	C40	120(2)				
C35	C36	C37	120(2)				
C36	C37	C38	120(2)				
C37	C38	C39	120(2)				

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Hydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
N2	C1	H1	108.35	H12B	C12	H12C	109.39
C2	C1	H1	108.56	O8	C13	H13A	111.44
C5	C1	H1	108.61	O8	C13	H13B	111.59
O4	C2	H2	110.06	C4	C13	H13A	110.89
C1	C2	H2	109.69	C4	C13	H13B	111.05
C3	C2	H2	109.84	H13A	C13	H13B	109.35
O7	C3	H3	111.39	O7	C14	H14A	109.32
C2	C3	H3	111.53	O7	C14	H14B	109.33
C4	C3	H3	111.74	H14A	C14	H14B	109.43
O3	C4	H4	110.28	H14A	C14	C28	109.17
C3	C4	H4	110.15	H14B	C14	C28	109.16
C13	C4	H4	110.25	O4	C21	H21A	109.91
N3	C7	H7	107.88	O4	C21	H21B	109.80
C6	C7	H7	108.00	H21A	C21	H21B	109.36
C10	C7	H7	107.69	H21A	C21	C22	109.46
O5	C11	H11A	109.98	H21B	C21	C22	109.43
O5	C11	H11B	109.54	O8	C34	H34A	109.24
O5	C11	H11C	109.53	O8	C34	H34B	109.75
H11A	C11	H11B	109.45	H34A	C34	H34B	109.26
H11A	C11	H11C	109.45	H34A	C34	C35	108.25
H11B	C11	H11C	108.87	H34B	C34	C35	108.74
C6	C12	H12A	109.52	C15	C16	H16	120.00
C6	C12	H12B	109.52	C17	C16	H16	120.00
C6	C12	H12C	109.57	C16	C17	H17	120.00
H12A	C12	H12B	109.35	C18	C17	H17	120.00
H12A	C12	H12C	109.47	C17	C18	H18	120.00

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Hydrogen Atoms (cont)

atom	atom	atom	angle	atom	atom	atom	angle
C19	C18	H18	120.00	C37	C36	H36	120.00
C18	C19	H19	120.00	C36	C37	H37	120.00
C20	C19	H19	120.00	C38	C37	H37	120.00
C15	C20	H20	120.00	C37	C38	H38	120.00
C19	C20	H20	120.00	C39	C38	H38	120.00
C22	C23	H23	120.00	C38	C39	H39	120.00
C24	C23	H23	120.00	C40	C39	H39	120.00
C23	C24	H24	120.00	C35	C40	H40	120.00
C25	C24	H24	120.00	C39	C40	H40	120.00
C24	C25	H25	120.00				
C26	C25	H25	120.00				
C25	C26	H26	120.00				
C27	C26	H26	120.00				
C22	C27	H27	120.00				
C26	C27	H27	120.00				
C28	C29	H29	120.00				
C30	C29	H29	120.00				
C29	C30	H30	120.00				
C31	C30	H30	120.00				
C30	C31	H31	120.00				
C32	C31	H31	120.00				
C31	C32	H32	120.00				
C33	C32	H32	120.00				
C28	C33	H33	120.00				
C32	C33	H33	120.00				
C35	C36	H36	120.00				

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Torsion or Conformation Angles

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
O1	C8	N1	C9	172(2)	O7	C3	C2	C1	167(2)
O1	C8	N1	C15	-6(4)	O7	C3	C4	C13	73(2)
O1	C8	N3	N2	-167(2)	O7	C14	C28	C29	114(2)
O1	C8	N3	C7	-31(3)	O7	C14	C28	C33	-63(2)
O2	C9	N1	C8	179(2)	O8	C13	C4	C3	-160(2)
O2	C9	N1	C15	-3(3)	O8	C34	C35	C36	90(3)
O2	C9	N2	N3	-173(2)	O8	C34	C35	C40	-86(4)
O2	C9	N2	C1	-20(4)	N1	C8	N3	N2	11(2)
O3	C4	C3	O7	-170(2)	N1	C8	N3	C7	146(2)
O3	C4	C3	C2	-56(3)	N1	C9	N2	N3	9(2)
O3	C4	C13	O8	84(2)	N1	C9	N2	C1	161(2)
O3	C5	C1	N2	-172(2)	N1	C15	C16	C17	-176(2)
O3	C5	C1	C2	63(2)	N1	C15	C20	C19	176(2)
O3	C5	C6	C7	-178(2)	N2	N3	C7	C6	-38(2)
O3	C5	C6	C12	6(3)	N2	N3	C7	C10	87(2)
O4	C2	C1	N2	66(2)	N2	C1	C2	C3	-178(2)
O4	C2	C1	C5	-173(2)	N2	C1	C5	C6	22(3)
O4	C2	C3	O7	-70(2)	N2	C9	N1	C8	-3(2)
O4	C2	C3	C4	179(2)	N2	C9	N1	C15	175(2)
O4	C21	C22	C23	-84(2)	N3	N2	C1	C2	79(2)
O4	C21	C22	C27	94(3)	N3	N2	C1	C5	-42(2)
O5	C10	C7	N3	-21(3)	N3	C7	C6	C5	19(3)
O5	C10	C7	C6	101(2)	N3	C7	C6	C12	-164(2)
O6	C10	O5	C11	6(4)	N3	C8	N1	C9	-5(2)
O6	C10	C7	N3	150(2)	N3	C8	N1	C15	177(2)
O6	C10	C7	C6	-88(3)	C1	N2	N3	C7	54(2)

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Torsion or Conformation Angles (cont)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
C1	N2	N3	C8	-168(2)	C8	N3	N2	C9	-12(2)
C1	C2	O4	C21	-105(2)	C8	N3	C7	C10	-45(3)
C1	C2	C3	C4	57(3)	C9	N1	C15	C16	-89(2)
C1	C5	O3	C4	-65(2)	C9	N1	C15	C20	95(2)
C1	C5	C6	C7	-13(4)	C10	C7	C6	C12	70(2)
C1	C5	C6	C12	171(2)	C13	O8	C34	C35	-180(2)
C2	O4	C21	C22	-154(2)	C14	C28	C29	C30	-177(2)
C2	C1	N2	C9	-71(3)	C14	C28	C33	C32	177(2)
C2	C1	C5	C6	-103(2)	C21	C22	C23	C24	177(2)
C2	C3	O7	C14	110(2)	C21	C22	C27	C26	-177(2)
C2	C3	C4	C13	-173(2)	C34	C35	C36	C37	-177(3)
C3	O7	C14	C28	168(2)	C34	C35	C40	C39	176(3)
C3	C2	O4	C21	139(2)	C15	C16	C17	C18	0(3)
C3	C2	C1	C5	-57(2)	C15	C20	C19	C18	0(3)
C3	C4	O3	C5	58(2)	C16	C15	C20	C19	0(3)
C4	O3	C5	C6	102(2)	C16	C17	C18	C19	0(3)
C4	C3	O7	C14	-131(2)	C17	C16	C15	C20	0(3)
C4	C13	O8	C34	-125(3)	C17	C18	C19	C20	0(3)
C5	O3	C4	C13	178(2)	C22	C23	C24	C25	0(3)
C5	C1	N2	C9	168(2)	C22	C27	C26	C25	0(3)
C5	C6	C7	C10	-106(3)	C23	C22	C27	C26	0(3)
C6	C7	N3	C8	-170(2)	C23	C24	C25	C26	0(3)
C7	N3	N2	C9	-151(2)	C24	C23	C22	C27	0(3)
C7	C10	O5	C11	176(2)	C24	C25	C26	C27	0(3)
C8	N1	C15	C16	89(3)	C28	C29	C30	C31	0(3)
C8	N1	C15	C20	-87(2)	C28	C33	C32	C31	0(3)

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Torsion or Conformation Angles (cont)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
C29	C28	C33	C32	0(3)					
C29	C30	C31	C32	0(3)					
C30	C29	C28	C33	0(3)					
C30	C31	C32	C33	0(3)					
C35	C36	C37	C38	0(3)					
C35	C40	C39	C38	0(4)					
C36	C35	C40	C39	0(4)					
C36	C37	C38	C39	0(3)					
C37	C36	C35	C40	0(3)					
C37	C38	C39	C40	0(4)					

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.