THE SYNTHESIS OF

β-LACTAMS

FROM SULPHONYL ISOCYANATES

THESIS
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To Wendy, My Wife

PREFACE

The work described in this thesis was carried out between October 1979 and July 1982 at Imperial College, University of London.

I would like to thank Dr. A.G.M. Barrett for his help and guidance over the last three years and all my friends, especially Dr. H. Sheth and Mr. S.B. Kalindjian, for their support and encouragement.

I should also like to express my gratitude to all those involved in running the mass spectral and microanalytical service at Imperial College. Special thanks also go to Mr. J. Pepercorn and Dorothy for invaluable technical support.

I am most grateful to Miss A. Hopkins for typing this thesis and to everyone who corrected my spelling.

Finally, I should like to acknowledge the support of I.C.I. Pharmaceuticals and the S.R.C. through the C.A.S.E. scheme and thank Dr. M.J. Betts for taking care of me during my period with I.C.I.

A. Fenwick

ABSTRACT

β-lactams are readily formed in the reaction of chlorosulphonyl isocyanate (CSI) with olefins. CSI does not, however, give β-lactams on reaction with vinyl ethers, including glucals. The cycloaddition of an isocyanate with a glucal would lead to a highly functional β-lactam, which would be a useful intermediate, particularly in the preparation of oxacephems. We, therefore, set out to prepare a range of isocyanates in order to define structural features, that would not only give β-lactams on reaction with an enol ether, but which could be subsequently N-deprotected under mild conditions.

In all but one case, arene- and alkane-oxysulphonyl isocyanates gave α,β-unsaturated amides with 3,4-dihydro--2H-pyran. 2,2,2-Trichloroethyloxysulphonyl isocyanate formed a β-lactam, but this was only stable at low temperatures. Analogous arene- and alkane-sulphonyl isocyanates also gave α,β-unsaturated amides with 3,4-dihydro-2H-pyran, except for toluene-4-sulphonyl isocyanate. This gave 8-(toluene-4-sulphonyl)-8-aza-2-oxabicyclo [4.2.0.]octan-7-one, however, the nitrogen substituent could not be removed under conditions in which the β-lactam survived. α,β-unsaturated amides were also obtained from the reaction of 3,4-dihydro-2H-pyran with acyl isocyanates. Reaction of 5-methyl-3,4-dihydro-pyran with trifluoroacetyl isocyanate gave 8-(trifluoroacetyl)-8-aza-6-methyl-2-oxa bicyclo[4.2.0.]octan-7-one. This could

readily be N-deprotected to give the corresponding azetidinone. CSI and 2,2,2-trichloroethyloxysulphonyl isocyanate also gave analogous β-lactams with 5-methyl-3,4-dihydropyran, but these could not be N-deprotected without loss of the β-lactam moiety.

The isocyanates were all reacted with methylene-cyclohexane to give N-substituted 1-azaspiro-[3,5]-non-2-ones. The 2,2,2-trichloroethylsulphonyl, 2,2,2-trichloroethyloxysulphonyl and trifluoroacetyl groups were all successfully removed to give free NH β-lactams.

An attempt was also made to reduce 1-(2,2,2-trichloroethyloxysulphonyl)-1-aza-7-phenylspiro-[3,5]-non-2-one to the corresponding sulphamic acid. This group having been recently identified in sulfazecin and isosulfazecin.

The reaction of 3,4,6-tri-O-(trimethylsilyl)-D-glucal with trifluoroacetyl isocyanate yielded a β-lactam, which could be N-deprotected. These β-lactams could not, however, be isolated.

Arene- and alkane-oxysulphonyl isocyanates, and arene- and alkane-sulphonyl isocyanates were shown to give α,β-unsaturated amides with 3,4-dihydro-2H-pyran. By using 5 substituted-3,4-dihydro-pyrans, however, it was possible to form a β-lactam with trifluoroacetyl-isocyanate which could be N-deprotected. In this, it

was found to be superior to chlorosulphonyl isocyanate, as β-lactams, so formed from CSI, could not be N-deprotected without loss of the β-lactam moiety.

CONTENTS

Recent Developments in the Use of D-Glucose in the Synthesis of Natural Products

The growing importance of stereospecific syntheses has led to carbohydrates being used as chiral synthons in ever increasing numbers. Carbohydrates are ideally suited to this purpose as they are a cheap and abundant source of chiral material, available in various chain lengths and highly functionalised. Furthermore, sugars are available as enantiomericly pure material from nature and undergo reaction with a high degree of stereoselection. The assignment of the relative stereochemistry, in most sugars at least, is relatively easy using NMR and usually leads directly to the absolute configuration.

Although, on the surface, the use of a sugar might seem to be disadvantageous because of the large number of hydroxyl groups involved, this is not so. The hydroxyl groups all possess subtle differences which can be used to distinguish between them and selectively introduce a wide range of functional groups. Furthermore, the conformational bias of the carbohydrate structure can itself be used to generate fresh chiral centres following the loss of existing chirality.

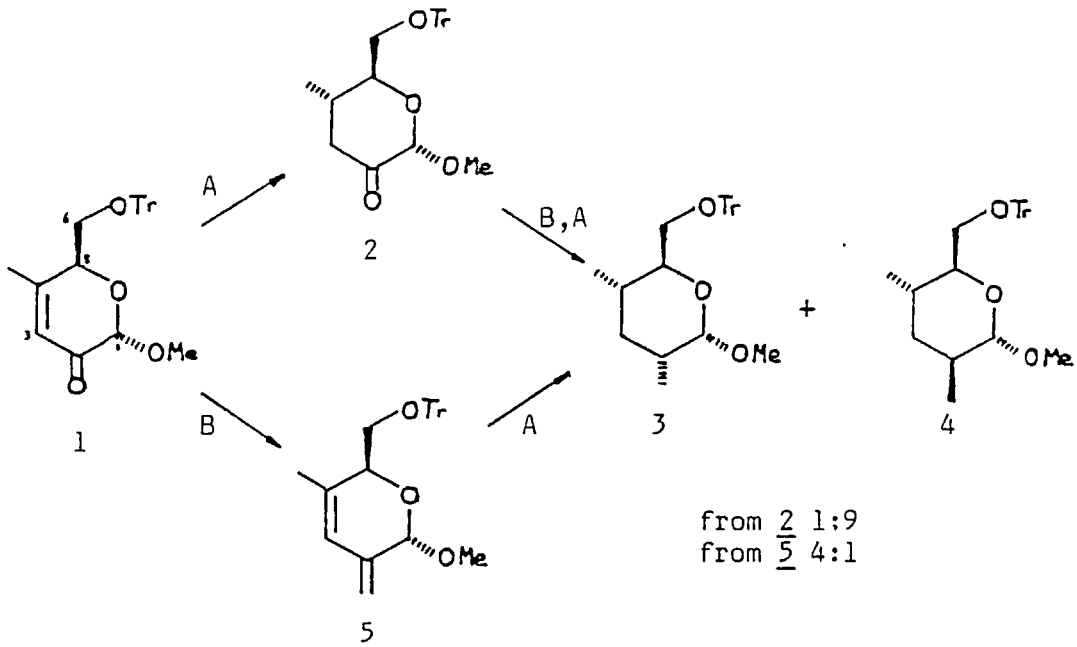
Several good reviews exist on the topic, the most recent being in 1980[1,2,3,4,5]. Since this time a great number of syntheses have been published using various sugars as their starting point. It is intended to concentrate on those syntheses which have used glucose, or a derivative of glucose, as their starting point.

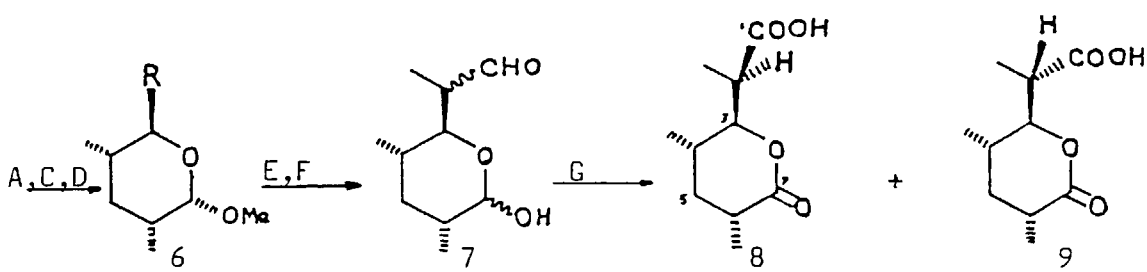
Prelog-Djerassi lactone (8)

The Prelog-Djerassi lactone (8) is a degradation product of both narbomycin and methimycin and has been shown to be important for macrolide construction.[6,7,8] Several syntheses of it, in a racemic form, exist as well as a few stereoselective syntheses including one based on carbohydrates.[9,10] Two syntheses have recently been published which start from glucose derivatives, one giving a mixture of the C_2 epimers (8) and (9), Scheme I, and the other giving the prelog-Djerassi lactone (8) stereospecifically, Scheme II.[11,12]

Starting from methyl α,D-glucopyranoside Fraser-Reid prepared the enone (1), which was then taken through to the dimethyl species (3).[11] Hydrogenation of the enone (1) followed by a Wittig reaction with methylenetriphenylphosphorane gave the exocyclic methylene group. On subjecting this to further hydrogenation, the dimethyl compound (4) was obtained as the predominant isomer.[12] This contains the C_2 methyl group with the wrong stereochemistry for (8). It was reasoned that by performing the Wittig reaction first, the diene (5) so formed should adopt the same conformation as the enone (1). Subsequent hydrogenation should then lead to the dimethyl species with the desired stereochemistry (3). This was found to be the case, giving the correct isomer (3) as the major product. Further hydrogenation lead to the loss of the trityl group, the resulting alcohols being separated on silica to give the alcohol (6a). This was then elaborated using standard procedures to give a mixture of the Prelog-Djerassi.

lactone (8) and its C-2 epimer (9) in 47% overall yield from (6c).





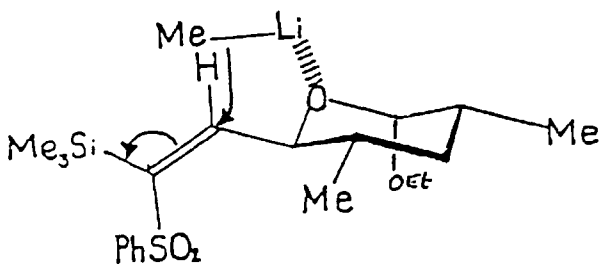
R = A CH_2OH
B CHO
C $COCH_3$

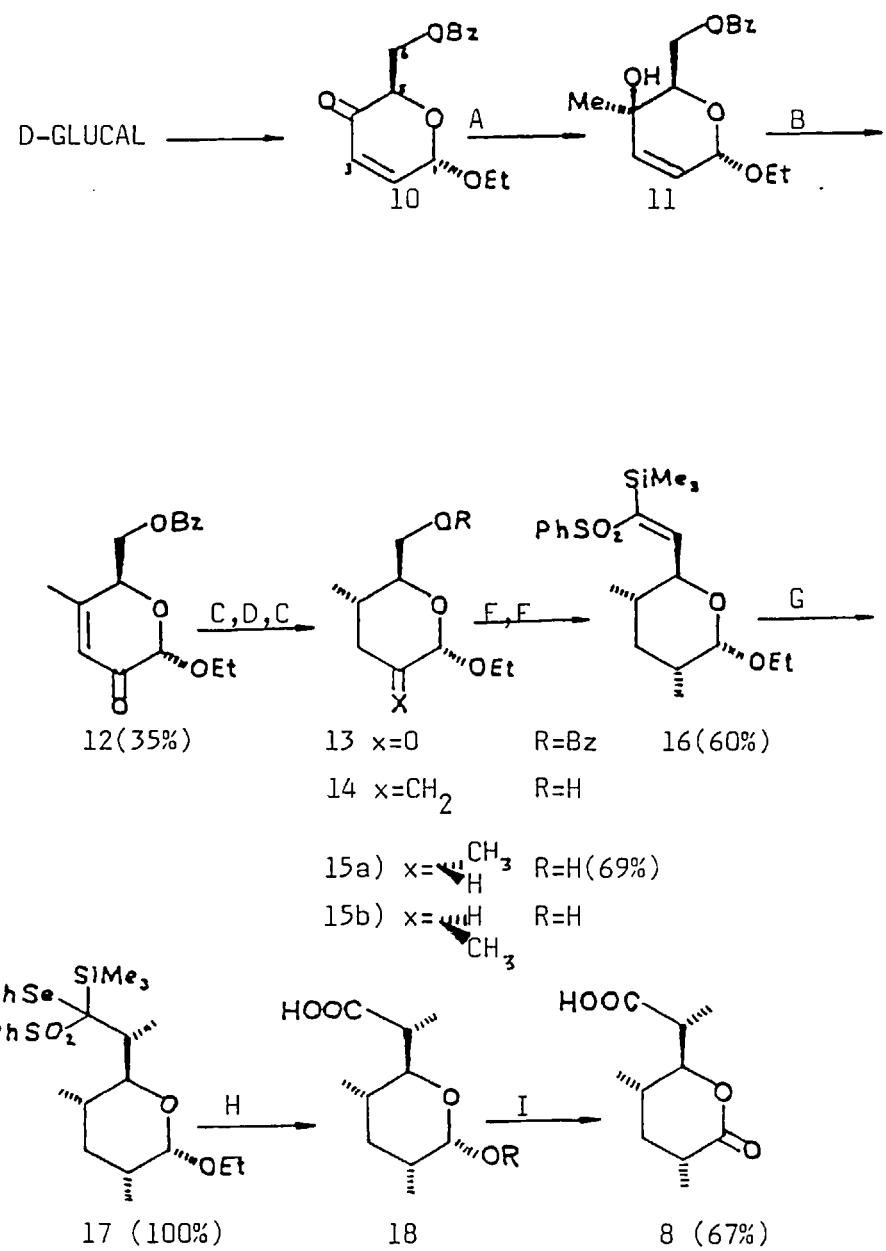
A) H_2/Pd, B) $Ph_3P{=}CH_2$, C) PCC, D) 1) MeLi, 2) PCC, E) $Ph_3P{=}CH_2OMe$, F) 1% HCl, G) 'Jones'

SCHEME 1

The second synthesis of the prelog-Djerassi lactone, although much longer, did produce the desired compound without the presence of the other epimer.[13] D-glucal was converted in five steps to the enone (10).[14] This was converted using standard methodology to give the dimethyl species (15) as a mixture of C_2 epimers (15a) and (15b) in the ratio 3:1. After separation, (15a) was converted to the vinylsulphone (16) in 60% yield by Swern oxidation followed by condensation with bis(trimethylsilyl)-thiophenylmethyllithium and treatment with m-chloroperbenzoic acid.[15] This key intermediate was treated with methyllithium and phenylselenium chloride to give the adduct (17) which was successively treated with 30% hydrogen peroxide and acid to give the acid (18). Oxidation of the hemiacetal (18) then gave the prelog-Djerassi lactone (8) in 10% overall yield from (10).

The key steps in this syntheses were firstly, the conversion of the hetero-olefin (16) to the intermediate (17) via heteroconjugate addition of methyl-lithium, fig 19, followed by trapping of the carbanion intermediate with phenylselenium chloride. Secondly, the conversion of (17) to the acid (18) via sila-pummerer rearrangement should be noted.





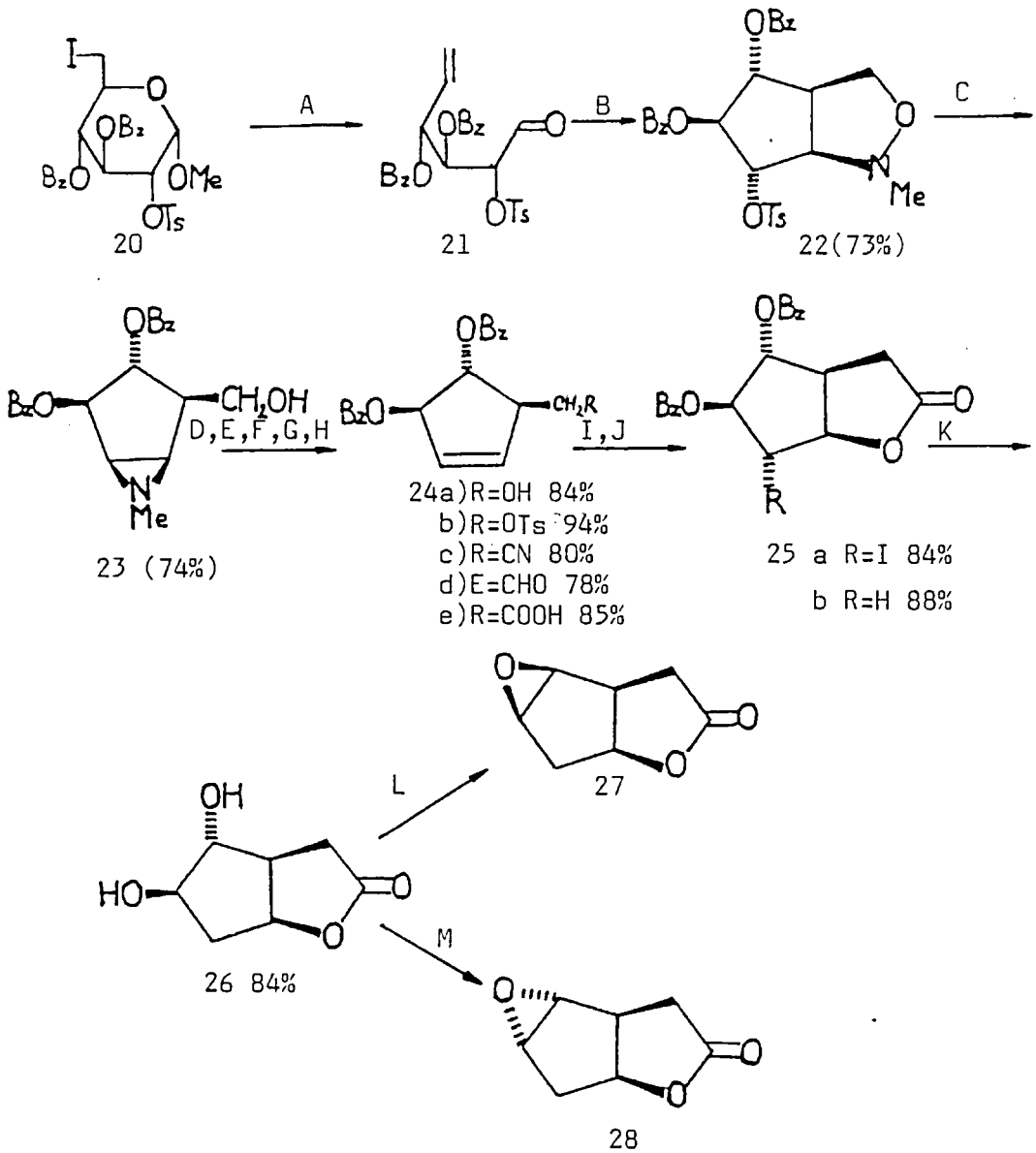
A) MeLi/iPr_2O, B) CrO_3, C) H_2/Pd, D) $Ph_3P{=}CH_2$, E) $(COCl)_2$/DMSO/Et_3N,
F) PhS $(Me_3Si)_2CLi$: mCPBA, G) MeLi/PhSeCl, H) $H_2O_2/H^+{}_3O$,
I) Br_2/ArONa

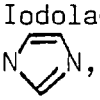
SCHEME II

The strategy of both these syntheses is similar up to the introduction of the acid function. Although Isobe starts from a more simple sugar, once he has introduced the first methyl group, and oxidised his compound, the enone (12) produced by his route is very similar to Fraser-Reid's starting enone (1). Another important point of comparison between the two papers is that whereas Fraser-Reid claimed that hydrogenation of the enone (1) followed by a Wittig reaction and further hydrogenation, led to the dimethyl species (4) with the incorrect stereochemistry, Isobe used precisely this route to obtain the correct isomer (15) from (14), the difference in the alkoxy substituent on C_6 being the most likely reason for this anomaly. Both of these syntheses can be classified as cyclic transfer of stereochemistry as defined by Fraser-Reid in his review.[4]

Prostaglandins

Considerable work has been done on the use of sugars in the preparation of prostaglandins, the most notable being Stork's synthesis of $F_{2\alpha}$.[16] Stork's route suffered from being not readily adaptable to other prostaglandins; a recent synthesis of an intermediate (27) claims, however, to offer a general synthesis of prostaglandins from sugar synthon, Scheme III.[17] Using a modification of the method of Bernet and Vasella, the iodo sugar (20) was taken through to the cyclopentane system (22).[18] Reduction of this with hydrogen over Raney nickel resulted not only in the expected reduction of the heterocycle, but, a

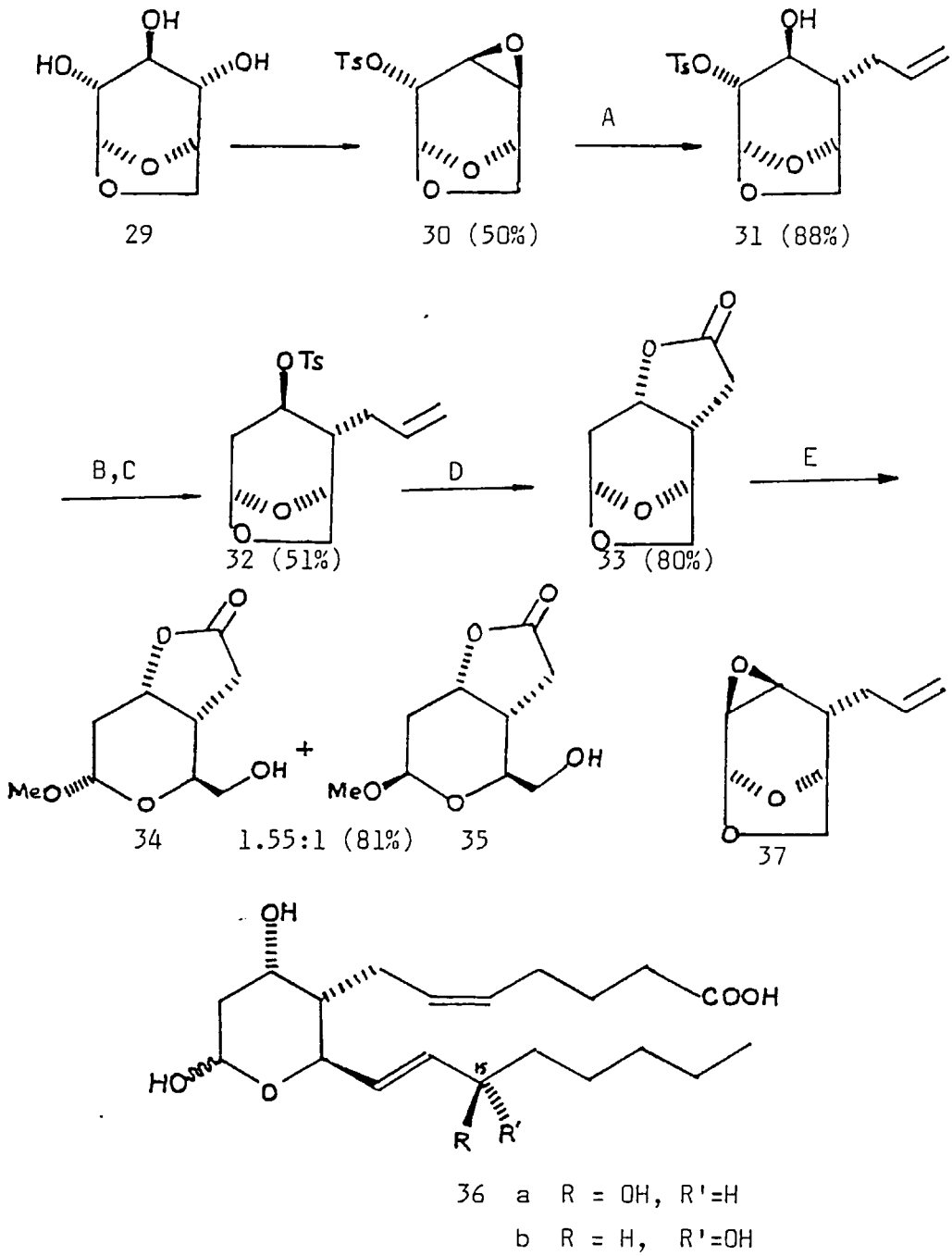


A) Zn, △, B) $MeNH_2OHCl$, Py/EtOH, C) Ni/H_2 IATM, D) mCPBA,
E) TsCl/Py, F) NaCN, DMSO, G) Raney Ni, NaH_2PO_2, $PhNH(CH_2)_2NHPh$,
H) PCC, I) Iodolactonisation, J) Bu_3SnH, K) K_2CO_3, MeOH,
L) NaH,  , M) $Et_2CN{=}NCO_2Et$, Ph_3P.

SCHEME III

concomitant intra-molecular displacement of the toluene-4-sulphonyloxy group to give the aziridine (23). Treatment of this with m-chloroperbenzoic acid produced an alkene (24a) which was converted, using standard techniques, into the hydroxy lactone (26). The epoxide required (27) was obtained exclusively by treating the diol (26) with toluene—4-sulphonylimidazole and sodium hydride. Diethyl azodicarboxylate-triphenylphosphine, which is supposed to activate sterically accessible hydroxy groups, gave, exclusively, the wrong epoxide. This can be attributed to the triphenylphosphine adduct from the endohydroxy being stabilised by co-ordination with the lactone ring.

As with the previous example, much work has been carried out in synthesising thromboxanes (36). Another carbohydrate-based synthesis of a key intermediate (34) used in the synthesis of thromboxane B_2 (35) has emerged, Scheme IV.[19] This intermediate (34) has been used several times and has been prepared from both carbohydrates and non-carbohydrate sources.[20,21] The synthesis started with levoglucosan (29) which was converted to the known epoxy-tosylate (30).[22] The opening of the epoxide, to give the allyl derivative (31), went stereo- and regio-specifically; this could be predicted in the light of work carried out on these systems.[25] The regiospecific reduction of the tosylate (31), could again be predicted. Work carried out previously by the authors had demonstrated the intermediacy of epoxide (37) in the reduction.[25] The presence of the 4α-allyl substituent then ensures that only the 3β-alcohol is obtained. Tosylate (32) was



29 30 (50%) 31 (88%)

32 (51%) 33 (80%)

34 1.55:1 (81%) 35 37

36 a R = OH, R'=H

b R = H, R'=OH

A) $CH_2CHMgCl$, CuI, B) $LiEt_3BH$ 3 eq.; C) TsCl/Py, D) RhO_2,$NaIO_4$, acetone/H_2O, E) H^+, MeOH.

SCHEME IV

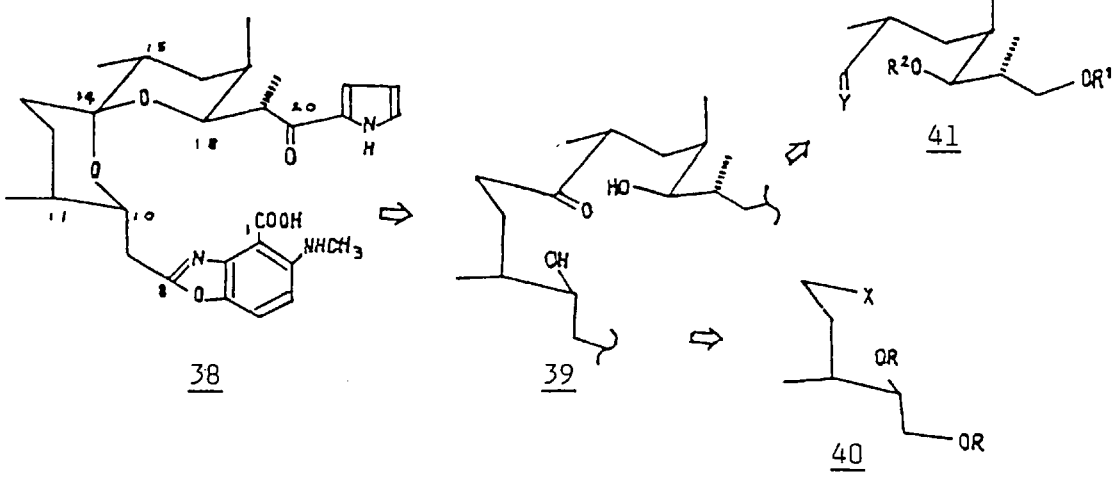
converted by known techniques to the intermediate (34) and its β-isomer (35). Using standard prostaglandin chemistry, the intermediate (34) was converted to thromboxane B_2 (36a) and its C_{15} epimer (36b).

The synthesis compares favourably with previous syntheses of the intermediate, (34).[20] Two of the steps, (29) to (30) and (31) to (32) are not very high yielding, resulting in an overall yield of 9% for the intermediate (34). Although reports of other syntheses of this intermediate do not give the yields of every step, they appear, in general, to produce a higher overall yield.[20] The main failure of Robert's synthesis, Scheme IV, must be the formation of the intermediate as a pair of epimers (34) and (35). This is wasteful in synthetic terms and requires a separation on silica which is avoided in the other syntheses.

Polyether antibiotic A 23187

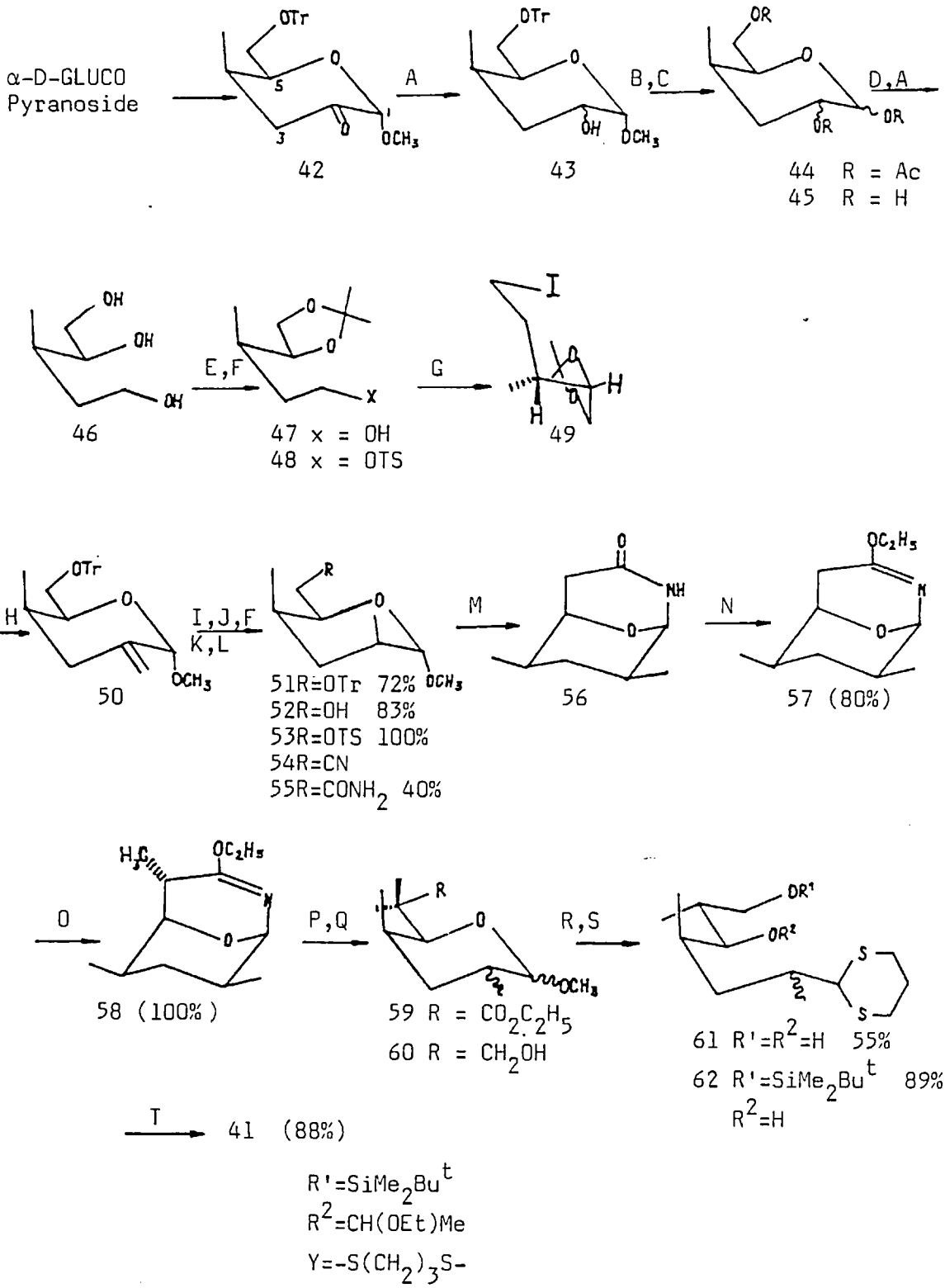
The polyether antibiotic A 23187 (38), is a divalent cation ionophore with high biological activity which has been synthesised on two previous occasions.[23] A preliminary report of a new synthesis by Ogawa of the chiral portion of (38), from α-D-glucopyranoside, has now appeared, Scheme V.[24] All the chiral centres of (38) are located around the spiro ketal which Ogawa envisaged could be formed from a keto diol (39). Further reterosynthesis reveals two target synthons (40) and (41) which can both be prepared from the ketone (42).

The ketone (42) was converted by standard methodology to the synthon (49) in 20% overall yield. Treatment of ketone (42) with methylenetriphenylphosphorane gave the exocyclic methylene compound (50) which on hydrogenation gave the dimethyl species (51) as the major isomer (3.5:1). This ketone is the C_4 epimer of the ketone, (2), used by Fraser-Reid in his prelog-Djerassi lactone synthesis, Scheme I, where he obtained the equivalent product, (4), on hydrogenation, with a ratio of 9:1. Standard techniques were employed to take the trityl compound (51) through to the imidate (57) which was alkylated exclusively from the less hindered side to give (58). Again using standard procedures this was taken



38 39 41 40

SCHEME V



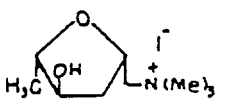
A) $NaBH_4$, B) Ac_2O, $BF_3.OEt_2$, C) 1) 1% NaOMe/MeOH, 2) HCl,
D) $NaIO_4$, EtOH, E) $Me_2C(OMe)_2H^+$, F) TsCl/Py, G) NaI, acetone, Δ,
H) $Ph_3P{=}CH_2$, I) Pd/C, J) Na/NH_3, K) NaCN,DMF, $^nBu_4NBr$
L) 30% H_2O_2, acetone, Na_2CO_3(aq), M) pTsOH, Δ, N) $Et_3O.BF_4$, O) LDA,MeI,
P) 5%H_2SO_4MeOH, Q) $LiAlH_4$, R) $SH(CH_2)_3SH$, MeI, S) $^tBuMe_2SiCl$, imidazole,
T) CH_2CHOEt, Py, TsOH

through to the sython (41). During the reduction of ester (59) with lithium aluminium hydride, the C_2 methyl group was found to epimerize. Examination of the bis-trimethylsilyl derivative of (61) revealed as much as 25% contamination. Coupling of these two portions, using the Corey-Sedack method, should give the C_9 to C_{20} portion of the antibiotic A 23187.[26]

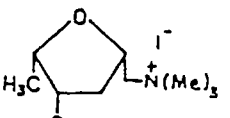
The presence of the C_2 epimer in synthon (41) should not lead to difficulties. This eventually becomes the C_{15} of (38) which has been shown to equilibrate to give the desired equational methyl diastereoisomer under acidic conditions.[23a] Both the previous syntheses of synthon (38) constructed the C_{10}-C_{18} portion as the chiral synthon from non-carbohydrate material.[23a, b] Of the three, the Evans, synthesis is clearly the best, being shorter and higher yielding.[23a] Ogawa's synthesis compares favourably with that by Grieco, although it does have the advantage of being convergent synthesis.[23b]

Muscarine

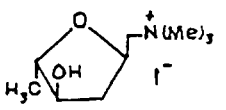
Muscarine (63) is an alkaloid, isolated from fly agaric, which is present as one of four racemates. A number of syntheses of both optically pure muscarines and d l mixtures have been carried out, however, there is still a need for a simple, stereo-specific synthesis of these compounds.[27] A recent synthesis, starting from D-glucose, has attempted to provide such a route to epiallomuscarine (63d), isoepiallomuscarine (69) and



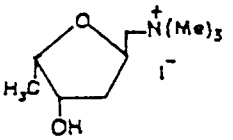
muscarine (a)



epimuscarine (b)



allomuscarine (c)

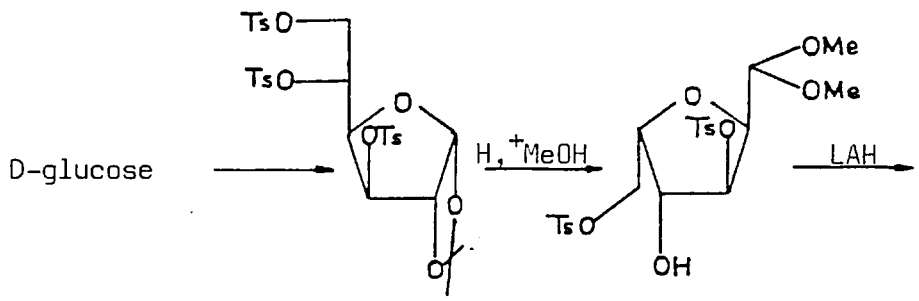


epiallomuscarine (d)

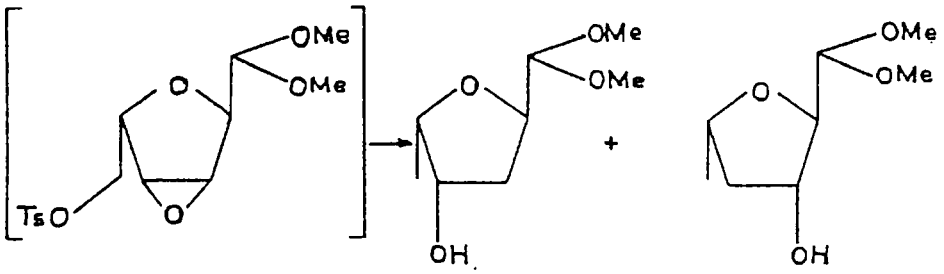
63

hydroxyepiallomuscarine (70), Scheme VI.[28] Only the first of these constitutes one of the natural racemates, the other two being unnatural analogues.

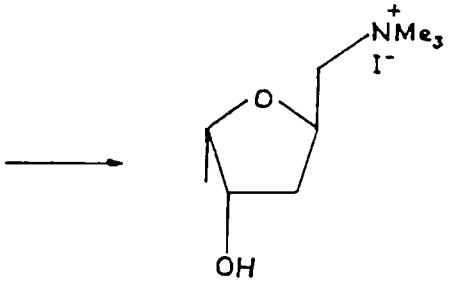
The synthesis fails to achieve its intended role as a simple, stereo-specific synthesis of the muscarines. Although, it is an improvement on most of the previous syntheses, it is still too long and low yielding, especially when compared to Mabarak's synthesis.[27a] As with all the previous syntheses, including the much more elegant synthesis by Whiting, this synthesis requires the separation of the C-3 alcohols (67) and (68).[27c] The initial rearrangement of the tosylate (64) to the acetal (65), first used by Defaye, was a good first step.[29] This, however, is out-weighed by the inability to open up the epoxide (66) regio-specifically to alcohol (67), and the long, low yielding conversion of the dimethyl acetal group to the quaternary ammonium group.



64 65

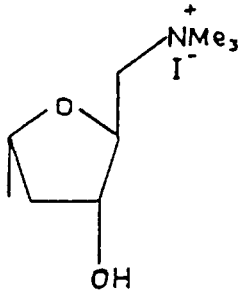


66 67 3:2 68

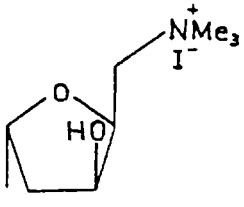


63(d)

SCHEME VI



69



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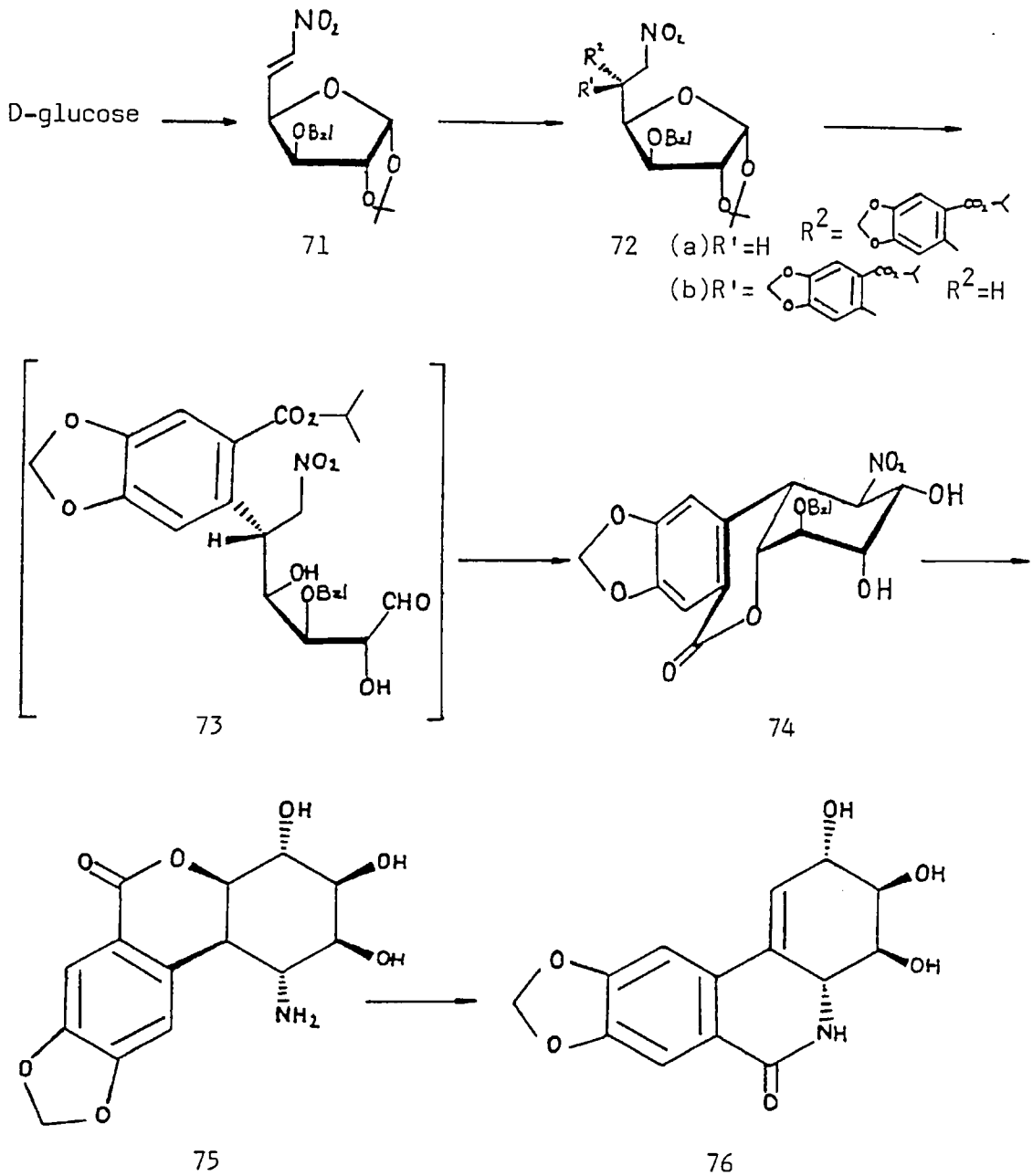


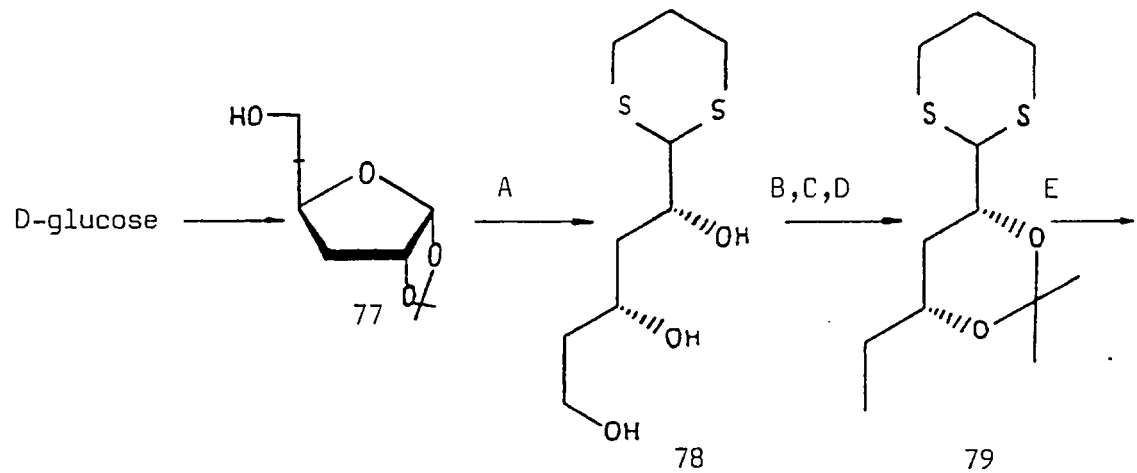
SCHEME VII

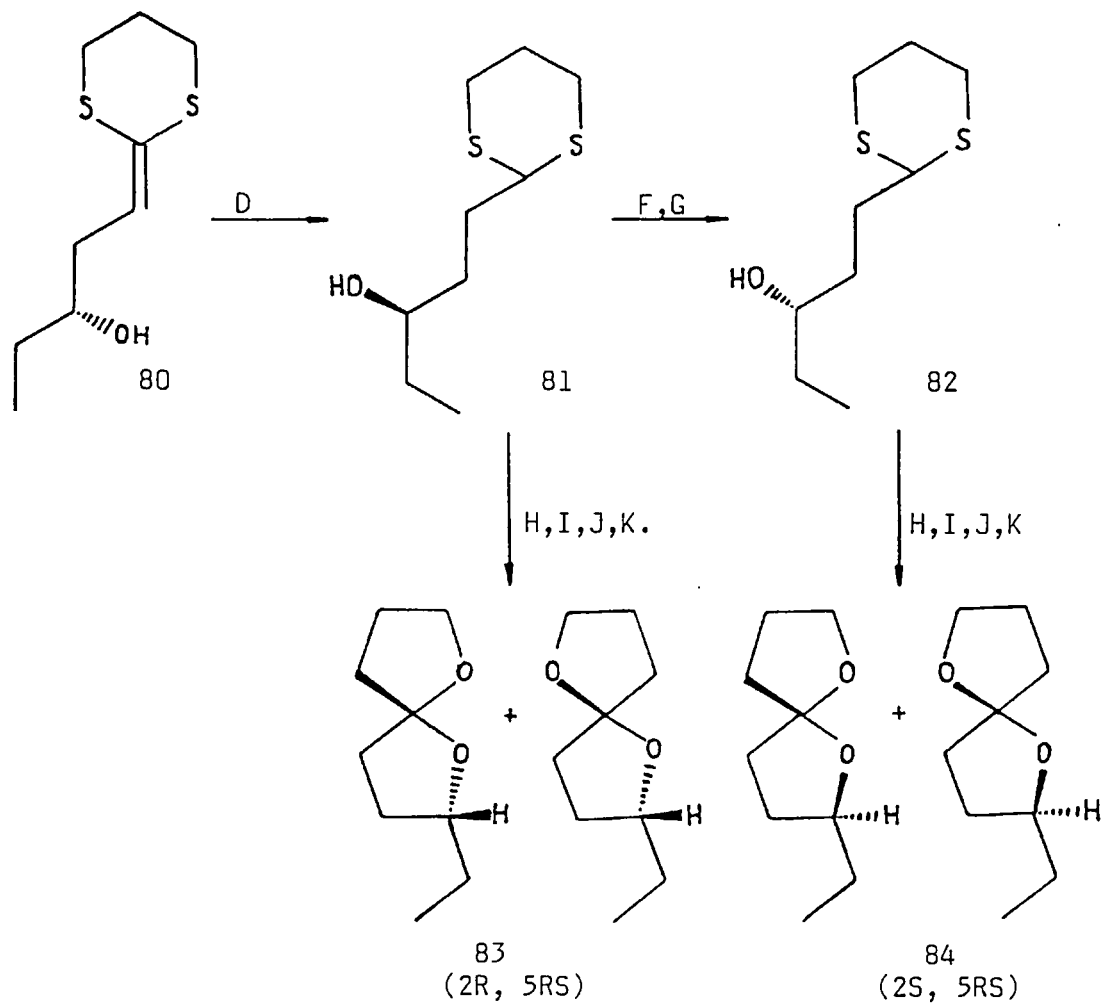
Lycoricidin

Another alkaloid, (+)-Lycoricidin (76), has also recently been synthesised from D-glucose, Scheme VII.[30] The synthesis makes good use of the stereochemistry of D-glucose, although it requires the separation of 2 isomers (72a) and (72b) in order to establish one important chiral position. The synthesis contains no novel steps and is straight-forward and efficient.

Chalcogran

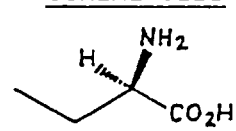
Chalcogran, the aggregation pheremone of a bark beetle, is a spiro-ketal which occurs as the mixture of diastereomers (83) and (84). Two related beetles both produce pheremones which appear identical by gas chromatography, but which are species specific. It is suggested that the specificity of the pheremone arises from differing chirality of the principle pheremone and, with this in mind, a synthesis of (2R, 5RS) chalcogran (83) and (2S, 5RS) chalcogran (84) from D-glucose has been undertaken, Scheme VIII.[31] Although the synthesis achieves its objective of synthesising chalcogran as optically active pairs of diastereomers in good yield, as an example of synthesis from a carbohydrate synthon it is not good. The amount of synthetic effort required to remove unwanted oxygen functions, in arriving at the key synthon (81), is out of all proportion to the complexity of the product. Other syntheses of optically active chalcogran have started from other, more simple, optically active material and have proved far more elegant





A) $SH(CH_2)_3SH,BF_3.OEt_2$, B) $C_3H_6O,CuSO_4,H_2SO_4$, C) TsCl/Py, D) LAH,
E) n-BuLi, F) PPh_3, Benzoic acid $Et_2CN{=}NCO_2Et$, G) MeO^-,MeOH, H) THP,TsOH,
I) 1) n-BuLi, 2) $Bc(CH_2)_3OTHP$, J) Collidine, HCl,HgO, MeOH, H_2O, K) H^+.

SCHEME VIII

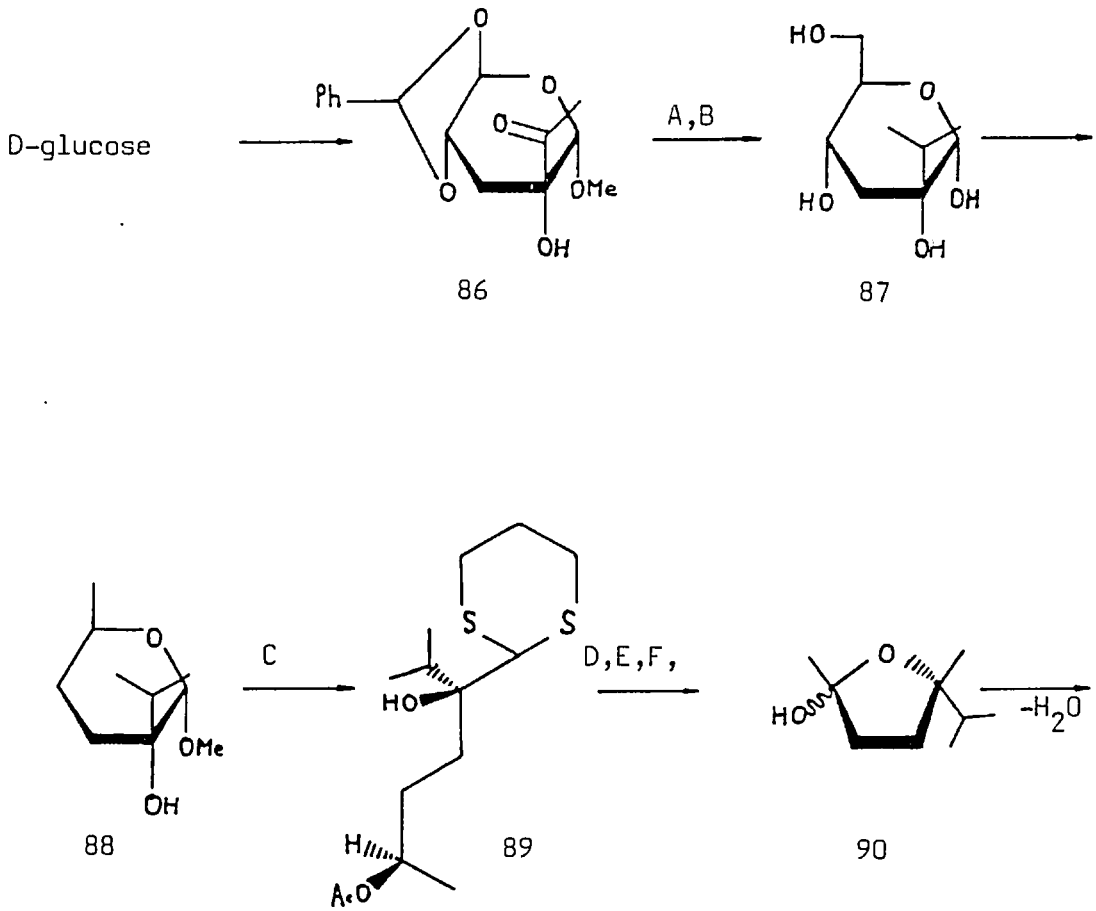


85

and shorter.[32] In particular Mori's synthesis of both pairs of diastereomers (83) and (84) started from D-(-)-α-amino-n-butyric acid, a far more suitable chiral precursor for a compound containing so few chiral centres.[32a] Indeed a synthesis employing modern assymetric synthetic methods would be more appropriate for chalcogran than the synthesis outlined by Franke.[31]

(S)-2,5-di-methyl-2-isopropyl-2,3-dihydrofuran

A new type of insect pheromone (S)-2,5-di-methyl-2-isopropyl-2,3-dihydrofuran (91) has been synthesised from D-glucose in an optically pure form, Scheme IX.[33] As with the preceeding synthesis, scheme VIII, the synthesis has been badly designed. Only one chiral centre is present in the product and by starting with a sugar, a great deal of effort is spent in reducing the number of chiral centres to this one. Once more the use of recent assymetric synthetic methods, or a simple optically active starting material would lead to a much more efficient and elegant synthesis of the pheremone (91).



A) $Ph_3P{:}CH_2$, B) Pd/H_2, C) $SH(CH_2)_3SH$, HOAc, D) RANEY Ni, E) MeO^-, F) Py/CrO_3

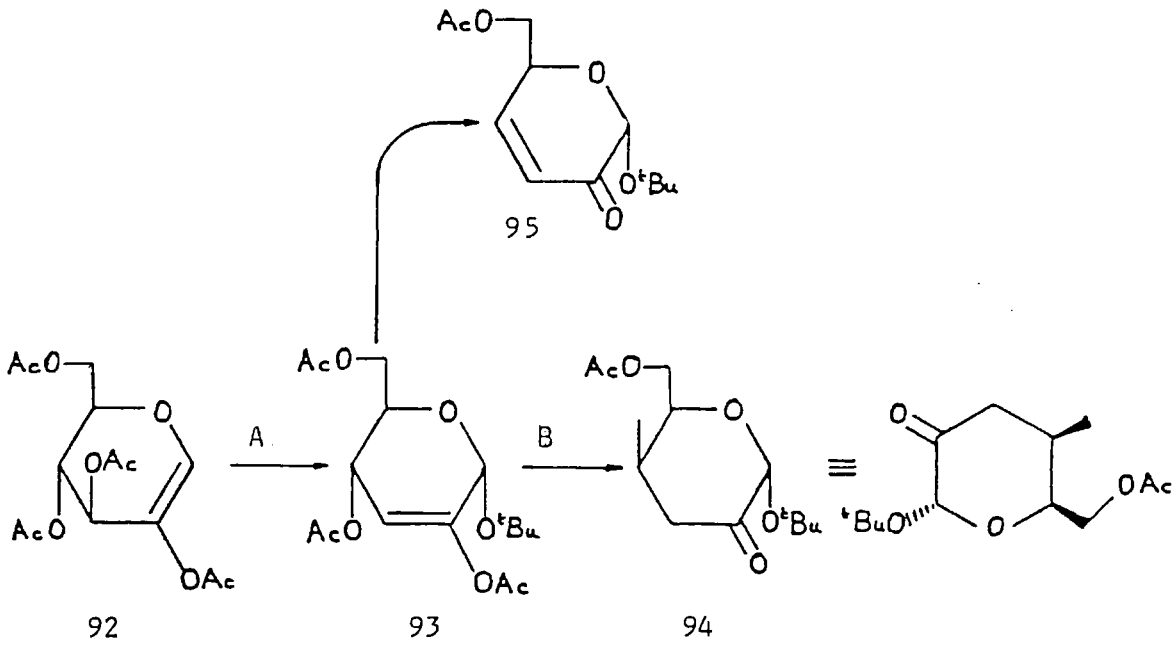
SCHEME IX

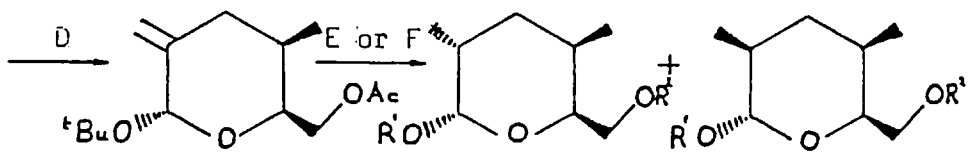
The Synthesis of key synthons

Hanessian took tri-O-acetyl-2-acetoxy-D-glucal (92) and converted it to a series of compounds which could be used as synthons for a number of natural products, Scheme X. Synthons (97a) and (94) were proposed as precursors for use in the synthesis of ionophore antibiotic A 23187, (38), whereas lactone (100) was put forward as a possible precursor for multistriatin and several other polyether antibiotics.

The most important feature of this work is the reaction of lithium dimethylcuprate with glucal (93) to give the 4R isomer stereospecifically The mechanism involves the intermediate formation of the enone (95) which then undergoes 1,4-conjugate addition. The stereospecific formation of the 4R isomer is due to a more favoured axial attack on the conformationally biased system. Comparison of the precursors for ionophore A 23187 suggested by Hanessian, used by Ogawa in his carbohydrate based synthesis, scheme V, reveals a remarkable similarity between synthons (94) and (42) and between synthons (97a) and (51).[24] The difference in stereochemistry between the C_2 methyl of (97a) and (51) is unimportant as in the final product this methyl group can be readily equilibriated.[23a]

Two papers concerning the synthesis of segments of 14-membered ring macrolide antibiotics have recently appeared from Kochekov, Scheme XI.[34] The routes proposed to the synthons (102), (106), (112) and (114) are all



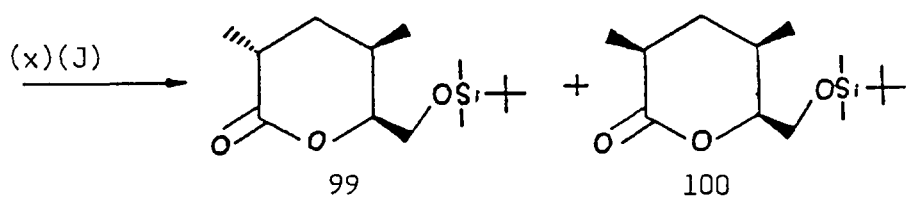


SCHEME XI

96

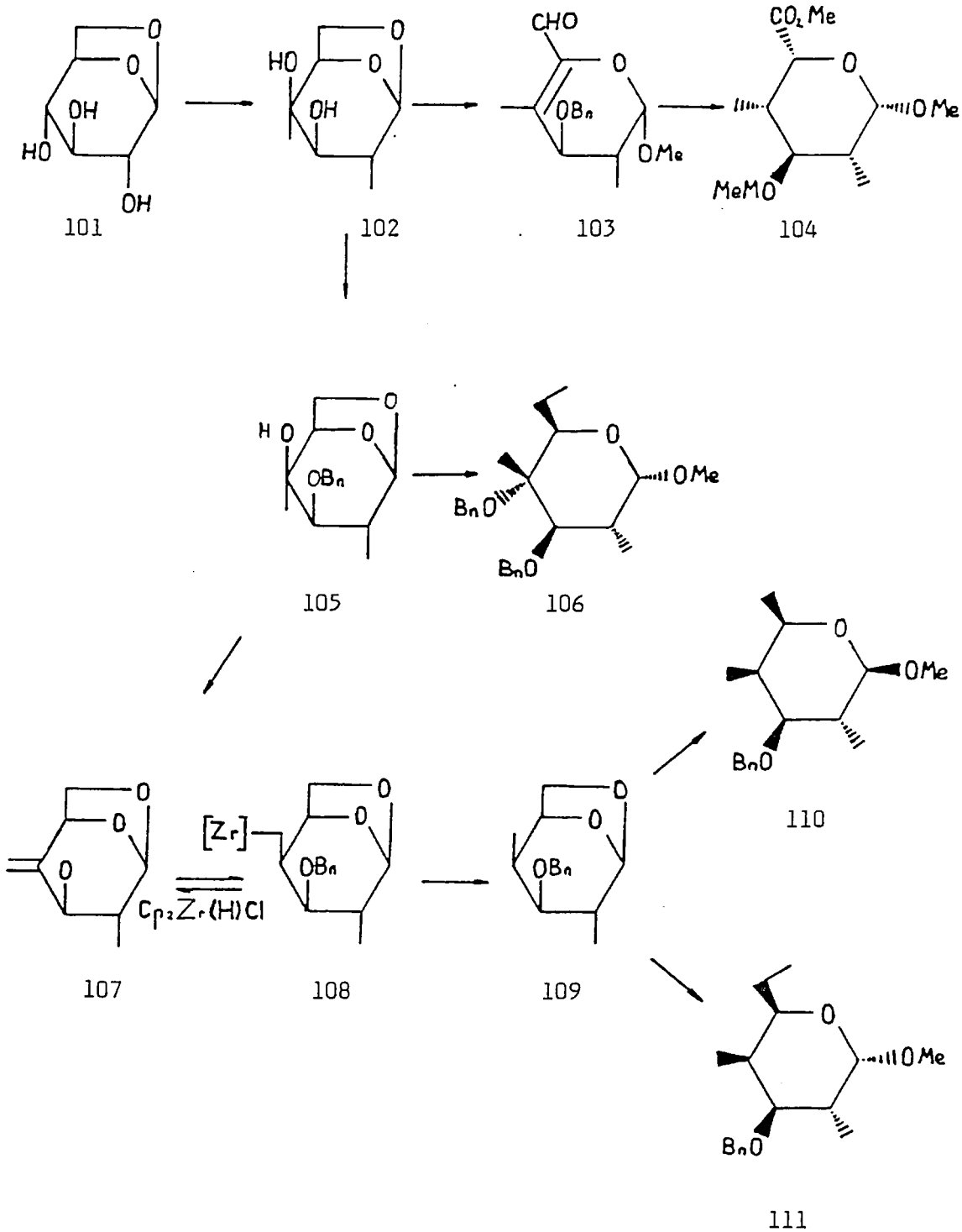
97 A R=AcR'=tBu
B R=H R'=tBu
C R=tBDPSi R'=tBu

98 A R=Ac R'=tBu
B R=H R'=tBu
C R=TBDPSi R'=tBu



SCHEME X

A) $BF_3.OEt_2$, tBuOH, B) $LiCuMe_2$, 2 eq. C) a) $(MeO)_2PO(CH_2)Li$ b) $LiCuMe_2Li$ 1 eq., D) $Ph_3P=CH_2$ E) $(Ph_3P)_3RHCl/H_2$, F) Pd/C, G) Na, MeOH, H) tBDPSi Cl, I) AcOH, THF, J) collins.



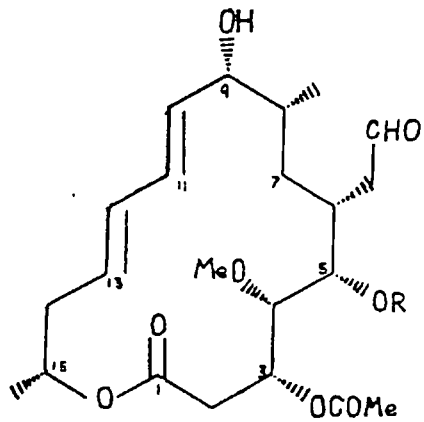
SCHEME XI

fairly long however, the overall yields are reasonable; (102) is formed in 41% yield and (106) is formed in 26% yield. The yields claimed are open to some speculation though, as in places there are discrepancies between the yields claimed in the text and reaction schemes. Most of the steps are standard, the only real point of interest being the hydrozirconation of olefin (107) which gave predominantly the α-methyl compound (109).

16-membered ring macrolides

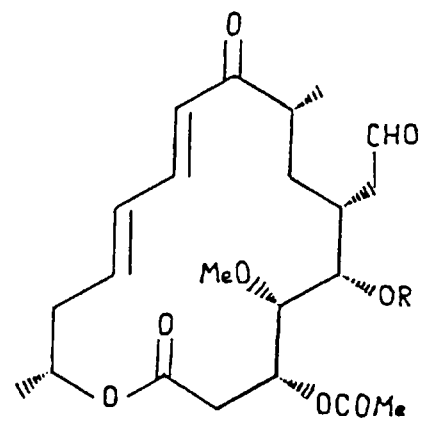
The 16-membered ring macrolide antibiotics are an important group of medicinally active compounds. Their complex structures and large size has made them a challenge which has only recently been met. Two syntheses of carbomycin B (magnamycin B) (112) and leucomycin A_3 (113) (josamycin) have recently appeared, both making use of carbohydrate precursors.[35,43] Both authors have also made use of the similarity of tylosin (114) to the previously mentioned macrolides, to synthesise a tylosin aglycone, tylonolide (143), by the same route.[42,44]

Tatsuta has put forward a highly stereospecific synthesis of the natural optically active form of these macrolides, Scheme XII.[35] The synthesis is convergent, involving the formation of the C_1-C_{10} (123) and C_{11}-C_{16} (155) units from D-glucose; the synthesis of the latter unit has already been described.[36]



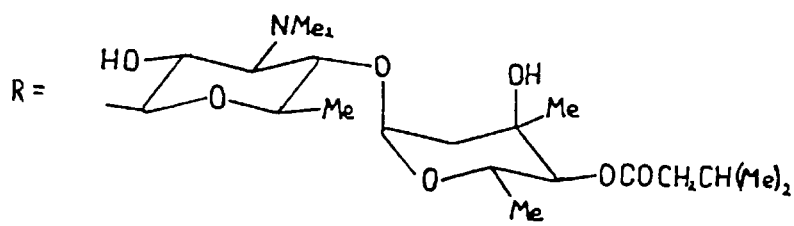
113

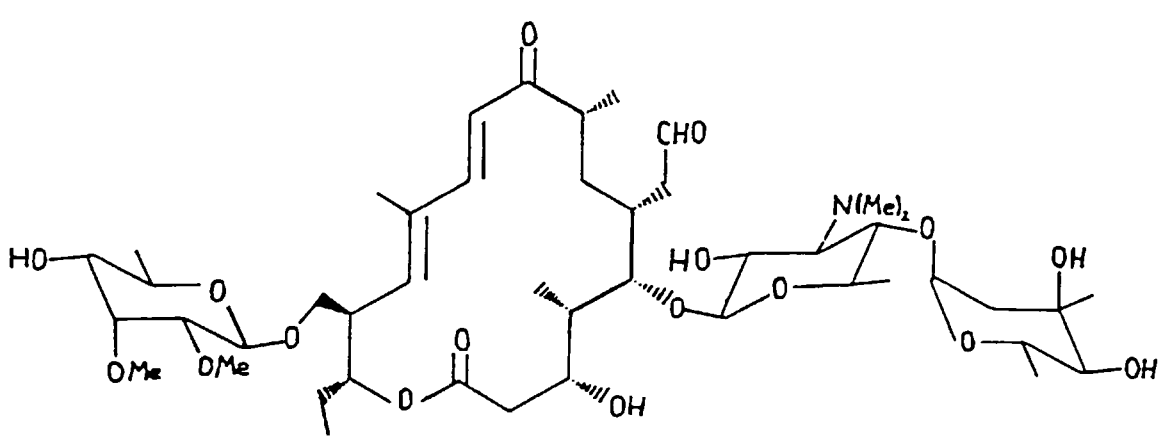
Leucomycin A_3



112

Carbomycin B



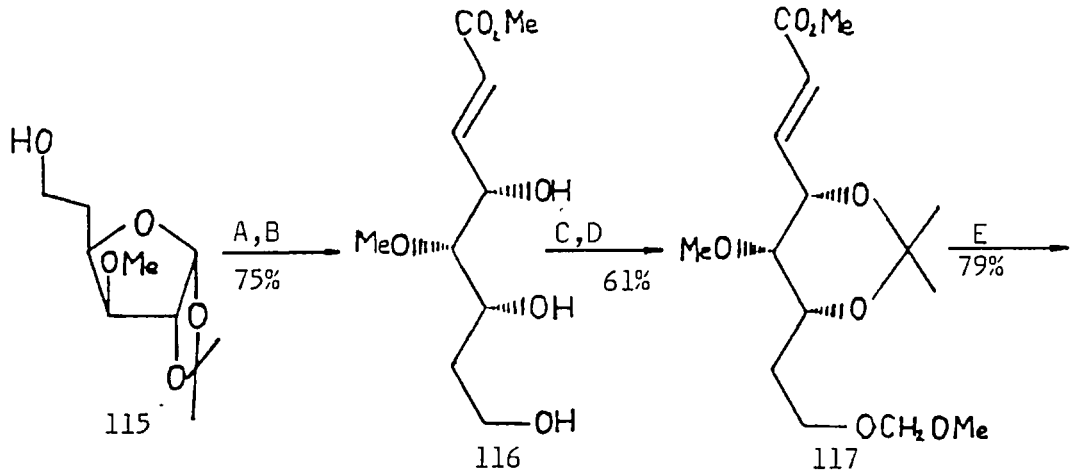


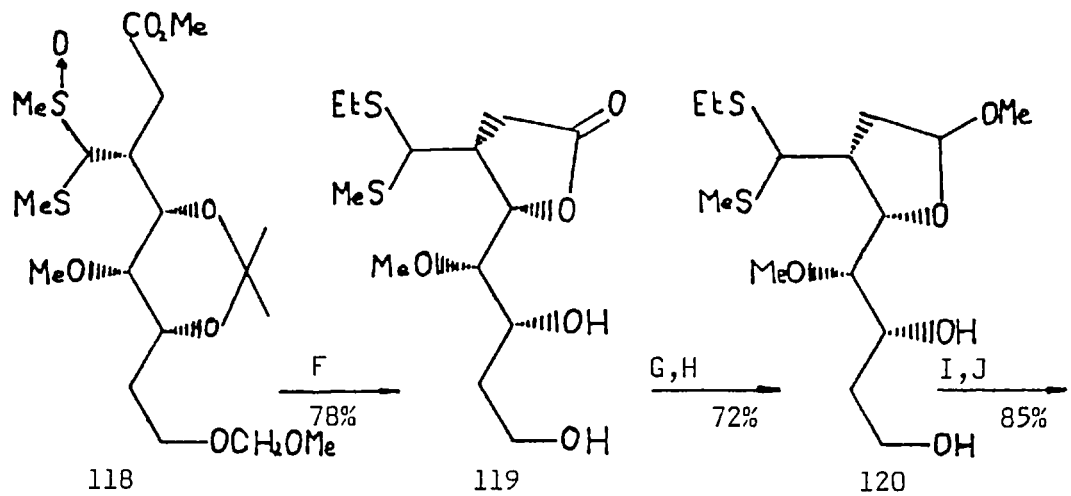
Tylosin

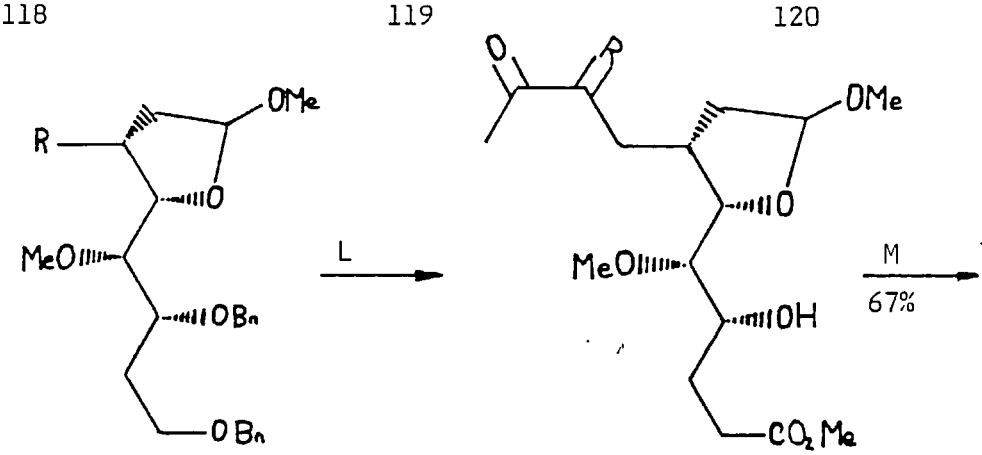
114

The known acetonide (115) was prepared from 1,2,: 5,6-di-o-isopropylidene-α-D-glucose and was taken on by standard procedures to the open-chain ester (117).[37] This is very similar to the compound prepared by Nicolaou in his earlier synthesis of the right hand side of these macrolides.[38] The addition of a masked aldehyde function to this resulted in the formation of the ester (118) stereospecifically with the correct stereochemistry at C_6.[41] It is to be expected that the approach of the anion to the unsaturated ester (117) would be from the least hindered side. Moreover, the C_5 oxygen function is in a position to direct the delivery to give the desired 6R configuration.

Conversion of sulphoxide (118) to the $C_{1-}C_{10}$ synthon (123) was straightforward; reduction of the immediate precursor to (123), however, resulted in the formation of C_8 epimers. Aldol condensation of the previously prepared aldehyde (155) with ketone (123) gave the acyclic precursor to the macrolide (125). At this point the synthesis appeared to run into difficulties; the hydrolysis of the ester (125) to an acid went in poor yield, also forming quantities of the 2,3-unsaturated acid. Even worse was to follow when the macrolactonisation of the system, using Masamune's method, gave a poor yield.[39] At this point in a synthesis, an overall yield of 7% for the conversion of hydroxy ester (125) to lactone (127), must be considered disasterous. The macrolactone (127) was taken through to the aglycone (130), which had previously been converted to the macrolides, carbomycin B (112) and

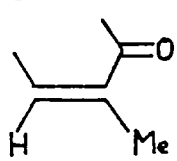






121 R = CHO

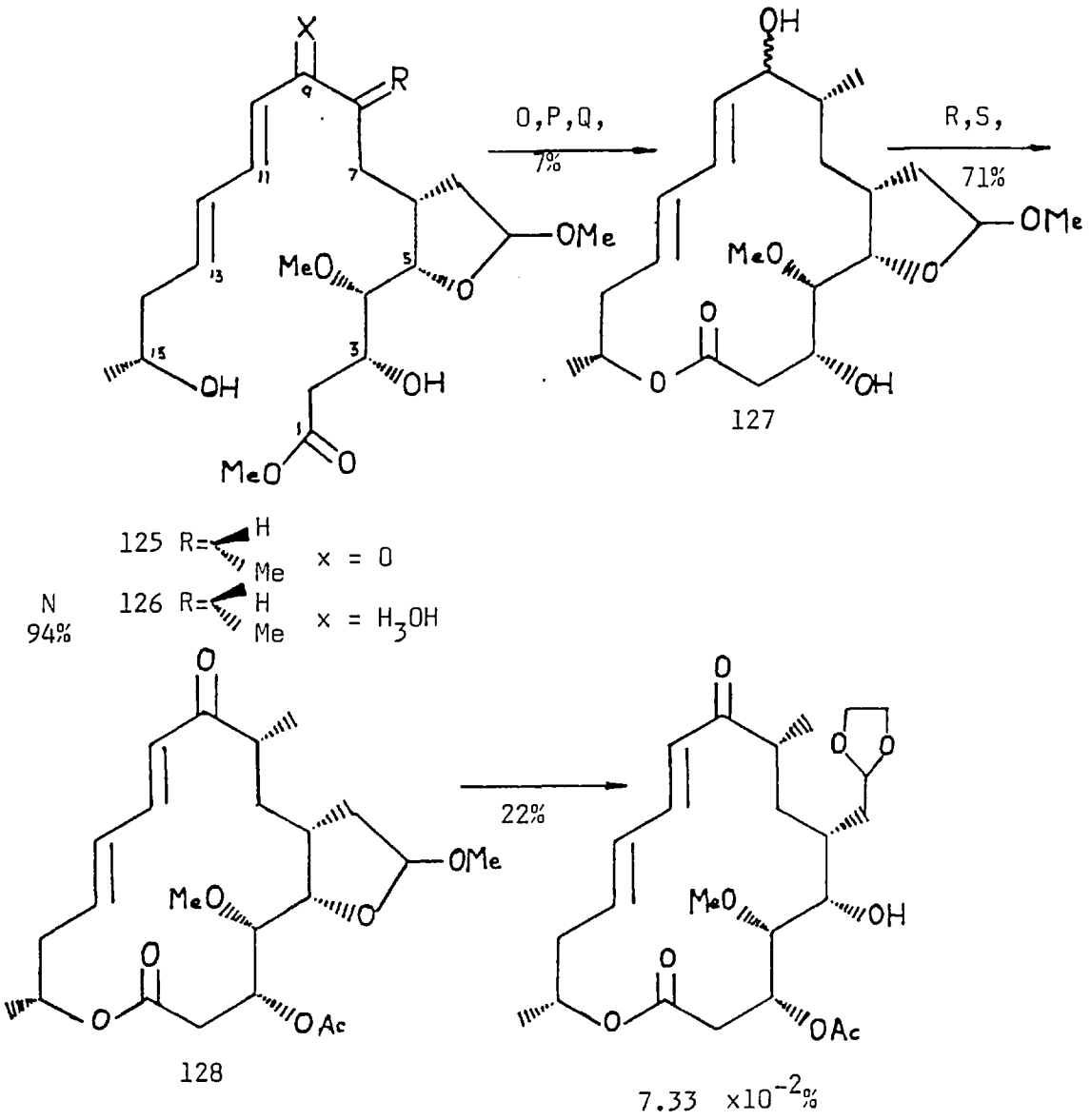
122 R =



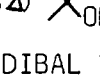
R= H
123 Me 3 44%

R= Me
124 H 1 14%

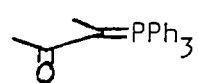
122

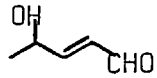


SCHEME XII

A) 6N H_2SO_4, B) Ph_3P=CHCOOMe, C) $MeOCH_2Cl$, $(Et)_2N$—/,Δ)  , TsOH

E) 1.1 eq BuLi, 1.1 eq  F) EtSH, BF_3OEt_2, G) DIBAL H,

H) Amberlyst 15 H^+ I) BnBr,NaH, J) $CdCO_3$,$HgCl_2$, K) 

L) Pd black $NaHCO_3$, M) LDA,  N) $NaBH_4$, O) 0.2N KOH

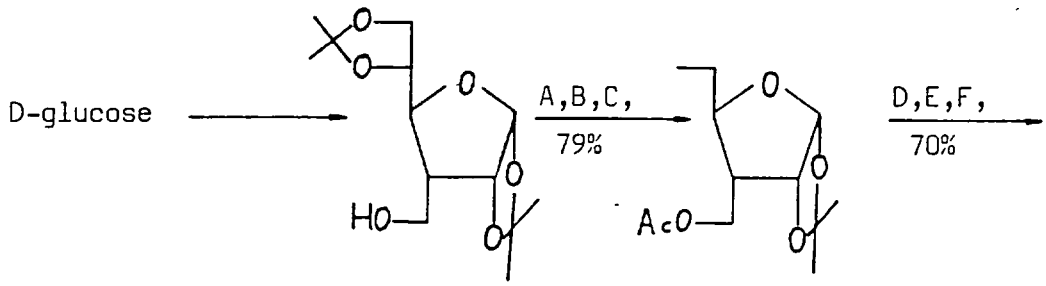
P) 1) Et_2PCl,Et_3N 2) C_5H_5STh, Q) Na_2HPO_4, CF_3COOAg, Drierite,

R) CrO_3 HMPTA, S) Ac_2O.Py, T) 4% H_3PO_4 aq THF, U)  TSOH

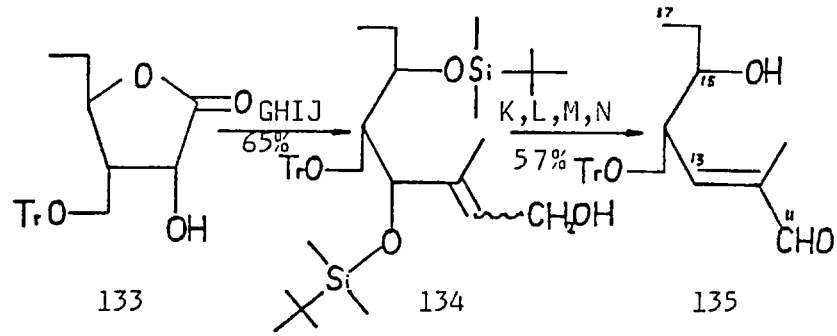
leucomycin A_3 (113).[40] Once more though, a very low yield was recorded at a very late stage of the synthesis.

In the related synthesis of tylonolide (143), Tatsuta appears to have learned from the mistakes of the previous synthesis, Scheme XIII.[42] Tylonolide (143) is an aglycone of tylosin (114) and is structurally very similar to carbomycin B (112) and leucomycin A_3(113). The overall strategy employed is the same as in the previous syntheses as, indeed are a great many of the steps.

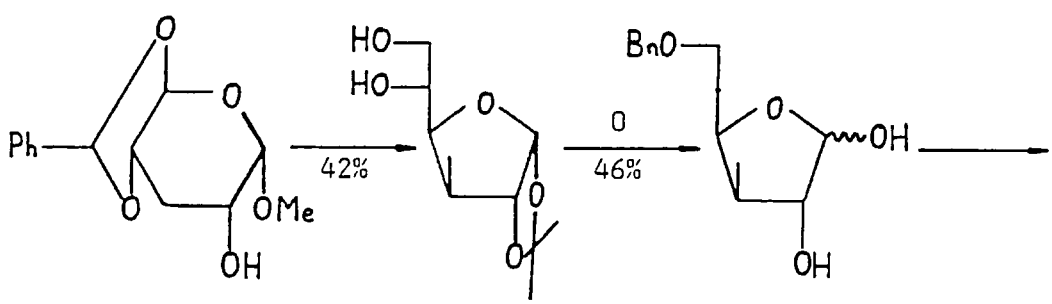
The formation of the C_{11}-C_{17} segment (135) from D-glucose was by standard techniques, and gave the synthon in a stereohemically unambigous manner in good yield. The C_1-C_{10} fragment (140) was prepared by a broadly similar route to the synthesis of the corresponding synthon in Tatsuta's previously outlined macrolide synthesis, Scheme VII. A different sequence of steps was necessary to prepare the lactol (138), in order to accomodate the C_4 methyl group, however, the subsequent steps to give hydroxyketone (140) were virtually identical to those used in the previous synthesis. One slight difference was that Michael's addition of the aldehyde equivalent to give sulphoxide (139), resulted in the formation of an isomeric pair. In the previous synthesis, scheme XII, Tatsuta found only a single isomer resulted from Michael addition of the aldehyde equivalent to olefin (117). The isomers were, however, shown to arise about the C_7 position rather than the C_6 position. The effect of steric hinderance at the C_5 oxygen again



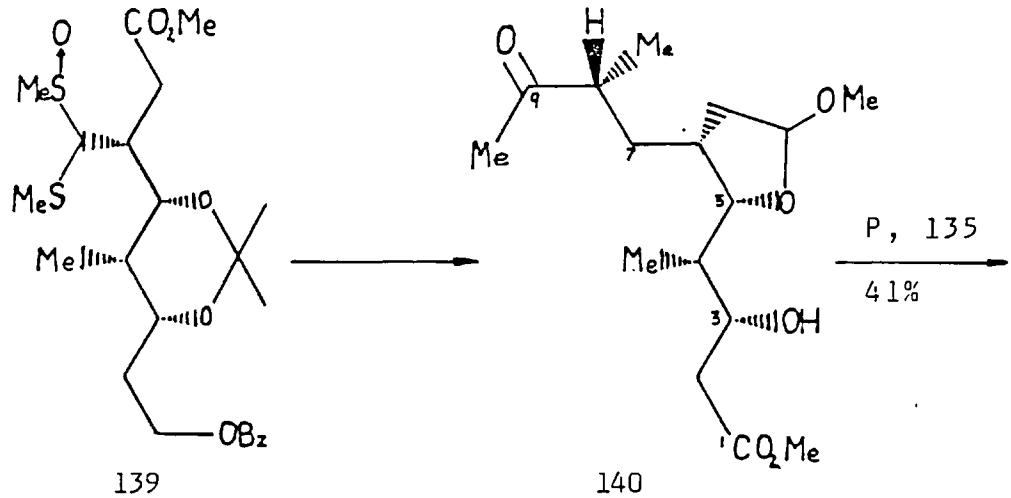
131 132



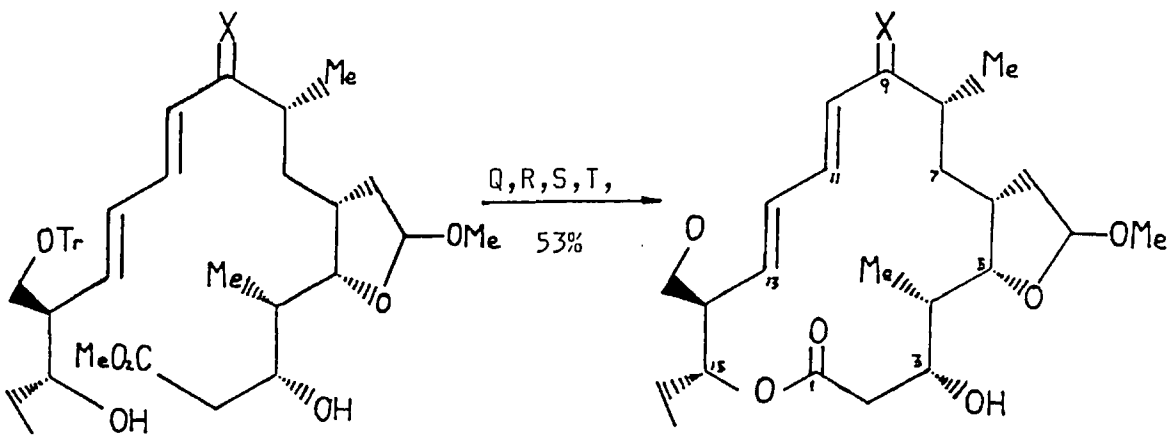
133 134 135



136 137 138



139 140



x = H, OH epimers 142

x = O 141 —U, 85%→ x = O 143

SCHEME XIII

A) $Ac_2O.Py$, B) 1) AcOH, 2) $NaIO_4$, 90% MeOH, 3) $Zn(BH_4)_2$, 4) TsCl/Py, C) $MeMgBr(LiCuCl_4)$, D) H_2SO_2/tBuOH, E) Br_2 (70% Dioxione), F) TrCl, G) MeLi, H) $Ph_3PCHCOOMe$/PhMe, J) $tBuMe_2S.Cl$/imidazole, J) LAH, K) BH_3-Me_2S/CH_2Cl_2; EtOH/NaOH/H_2O_2, L) $NaIO_4$, M) MeONa, N) Bu_4NF, O) 1) $NaIO_4$, 2) $Ph_3P{=}OH_2OCH_3Cl$, 3) 90% AcOH, 4) $NaBH_4$, 5) BnBr/NaH, 6) H_2SO_4tBuOH, P) LDA, Q) $NaBH_4$, R) 0.2N KOH/aq, S) 2,2 dipyridyldisulphide (Ph_3P), T) PhMe 110°C, U) CrO_3/HMPT.

produced the required C_6 isomer.

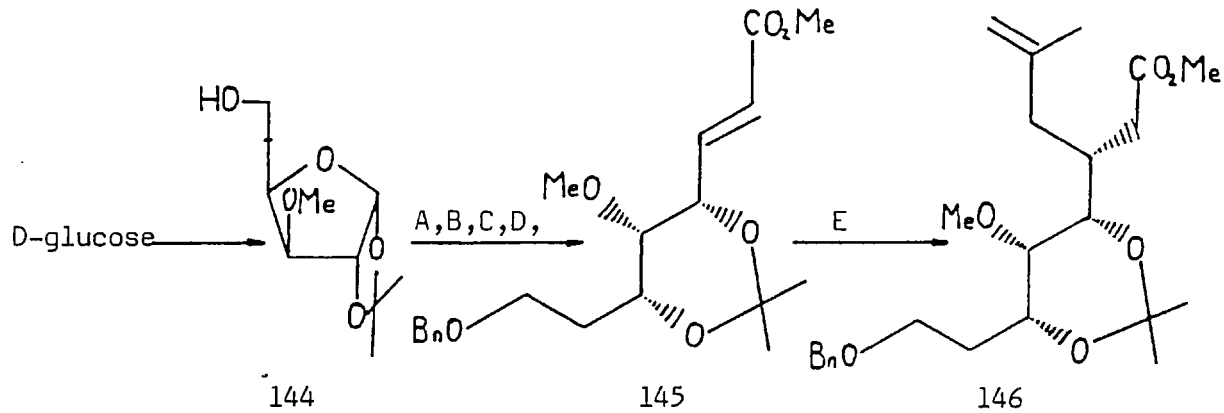
The aldol condensation of the two synthons to give the linear precursor (141) went in similar yield to the formation of the corresponding adduct (125) in Tatsuta's previously outlined macrolide synthesis, Scheme XII. Tatsuta, however, altered the subsequent steps with great success. Hydrolysis of the ester was achieved in 85% yield, as opposed to the 42% obtained for the hydrolysis of the equivalent ester in Tatsuta's previous synthesis. Furthermore, hydrolysis proceeded without formation of the 2,3-unsaturated acid. The lactonisation step was accomplished using a 2-pyridine thiol ester as the activating group instead of using Masamune's method with the benzene thiol ester. Lactonisation was achieved in an overall yield of 69%, instead of the 17% obtained previously, and helped to give the product with a ten-fold increase in the overall yield. Although, the overall strategy is the same, the improvements incorporated in the latter stages of this synthesis make it far better than Tatsuta's previous macrolide synthesis.

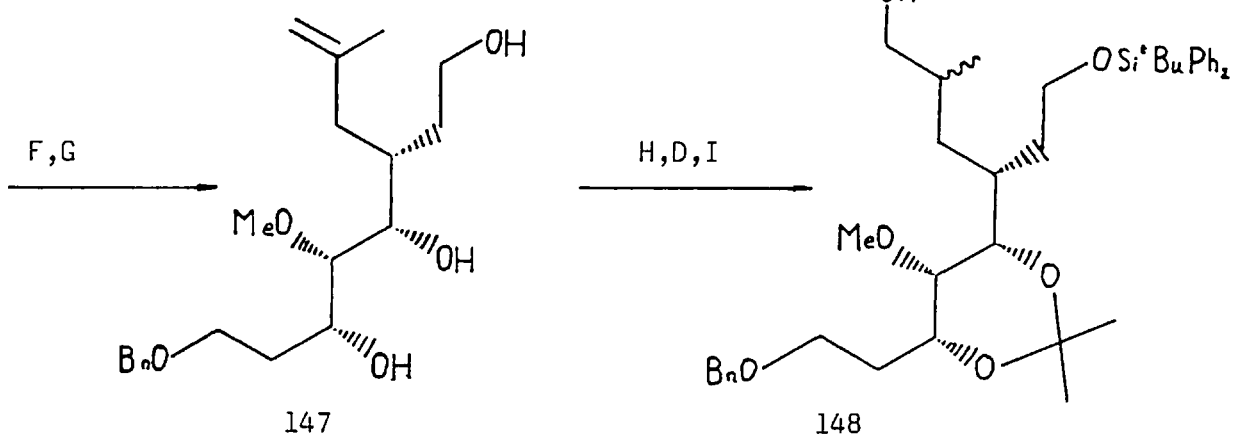
Several papers have recently been published by Nicolaou concerning the total synthesis of carbomycin B (112), leucomycin A_3 (113) and o-mycinosyltylonolide (177) from glucose, Scheme XIV.[43,44] An early communication of the synthesis of the right hand C_1-C_9 segment of the first two, was largely incorporated in the eventual synthesis.[38]

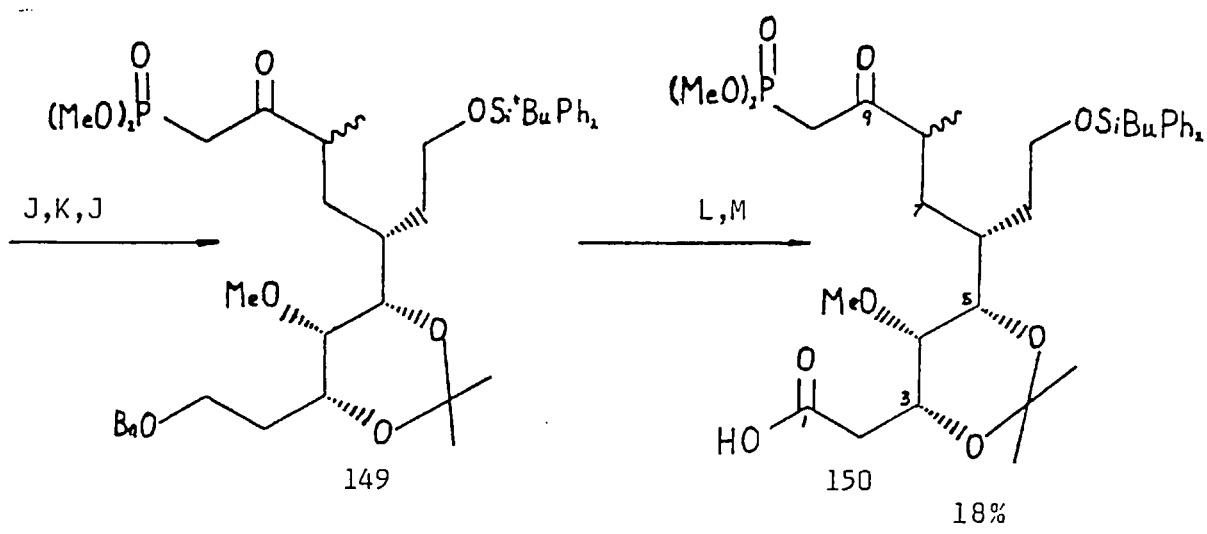
The strategy employed in synthesising carbomycin B (112) and leucomycin A_3(113) was largely the same as that employed by Tatsuta in his synthesis. Formation of the C_{11}-C_{15} segment (155), as the identical synthon, was not in fact from a carbohydrate, but was achieved in excellent yield. The C_1-C_{10} synthon (150) was similar to Tatsuta's synthon (123), but contained a dimethylphosphonate residue at C_{10}, as well as a few other more superficial differences. A mixture of diastereoisomers was again obtained at C_8 and chromatography was required to separate them. The main differences between the two syntheses arise from the different approach to cyclizing the macrocycle. Nicolaou used a ketophosphonate-based cyclization, which he had previously developed, to form the macrolide, whereas Tatsuta used a more traditional macrolactonisation.[45]

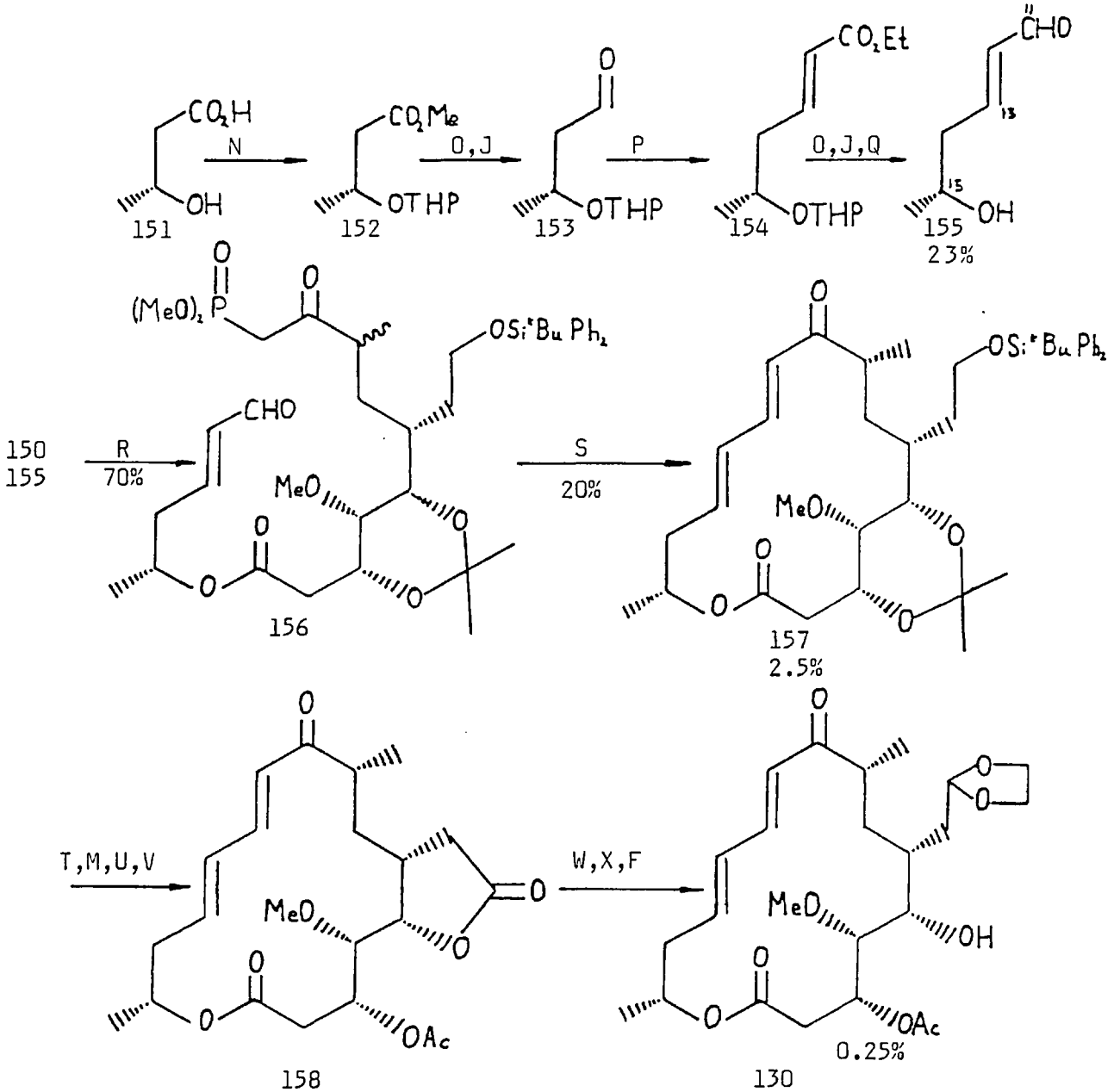
The C_1-C_{10} synthon (150) was prepared from D-glucal in 18% yield using a stereoselective Michael reaction. The Michael acceptor (145) was synthesised using standard techniques, and was reacted with a lithium cuprate to give the ester (146) almost exclusively. Conversion of this to the triol (147) enabled the structure to be proved by X-ray crystallography. The triol was then taken through to the synthon (150) by standard techniques; hydroboration of the double bond in the triol (147) giving rise to a diastereomeric mixture at C_8.

Coupling of the synthons (155) and (150) followed by ketophosphonate—based cyclization under high dilution

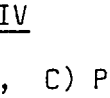
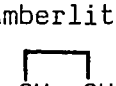

D-glucose
A,B,C,D,
E
144
145
146


F,G
H,D,I
147
148


J,K,J
L,M
149
150
18%



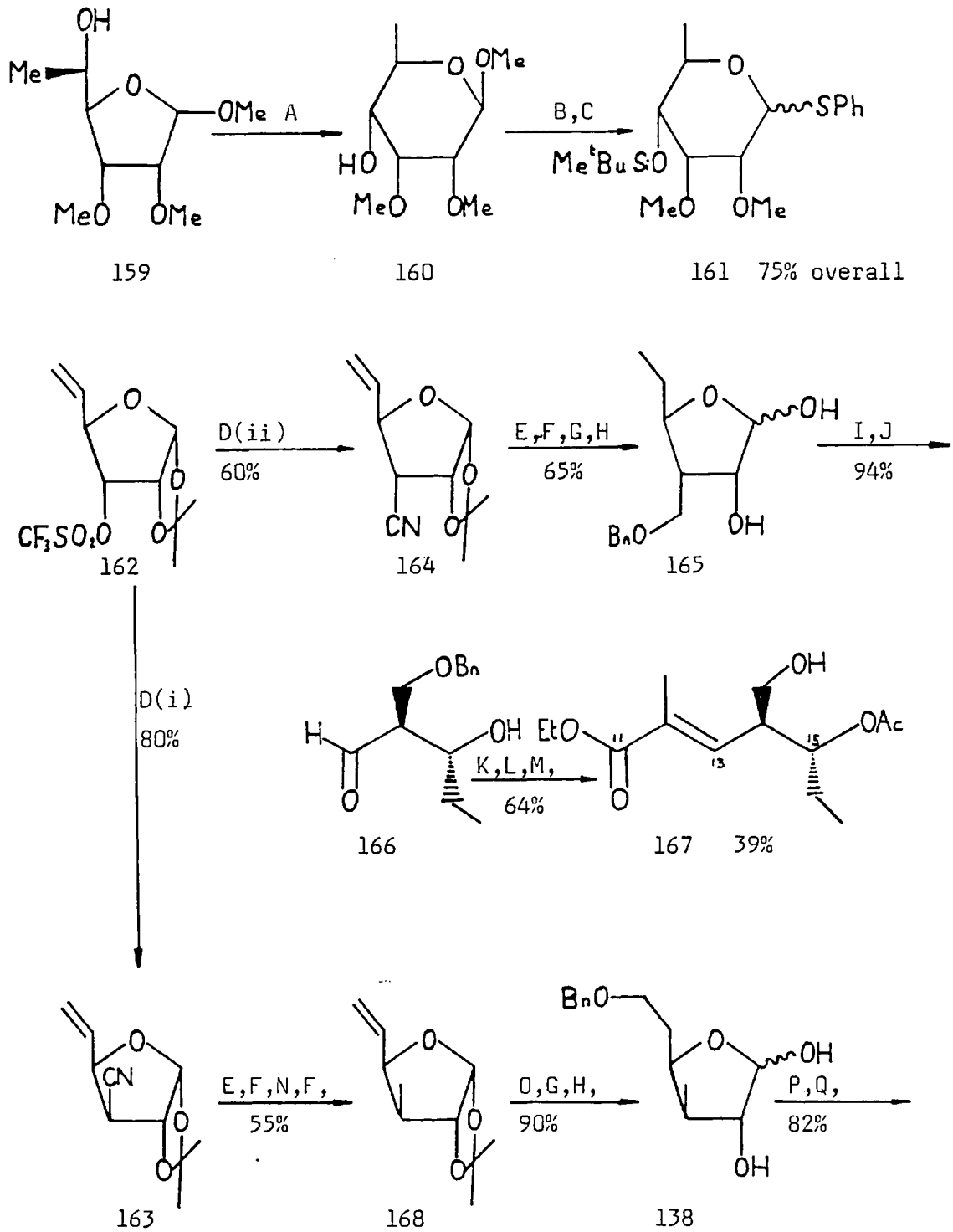
SCHEME XIV

A) BnBr, NaH, B) Amberlite IR-I20H, C) Ph_3P=CHCOOMe D)  , H^+ E) CuI_2,  F)  , H^+, G) LAH, H) $Ph_2tBuSiCl$,imidazole, I) BH_3; $NaOHH_2O_2$, J) PCC, K) BuLi,$CH_3(MeO)_2PO$, L) Pd/C,H_2 M) 'JONES', N) (a) CH_2N_2 (b) THP,TsOH, O) DIBALH, P) Ph_3P=CHCOOEt, Q) AcOH,THF,H_2O, R) DCC, 4-(dimethylamino)pyridine, S) Na, Toluene, high dilution, T) HF.Py, U) HCl/THF, V) Ac_2O,Py, 4-(dimethylamino)-pyridine, W) $LiA(OtBu)_3H$, X) DDQ.

conditions gave the basic skeleton of the macrolide (157). This was elaborated to the key intermediate (130) in 0.25% overall yield. This intermediate is the same moiety that Tatsuta produced and has been transformed to carbomycin B (112) and leucomycin A_3(113).

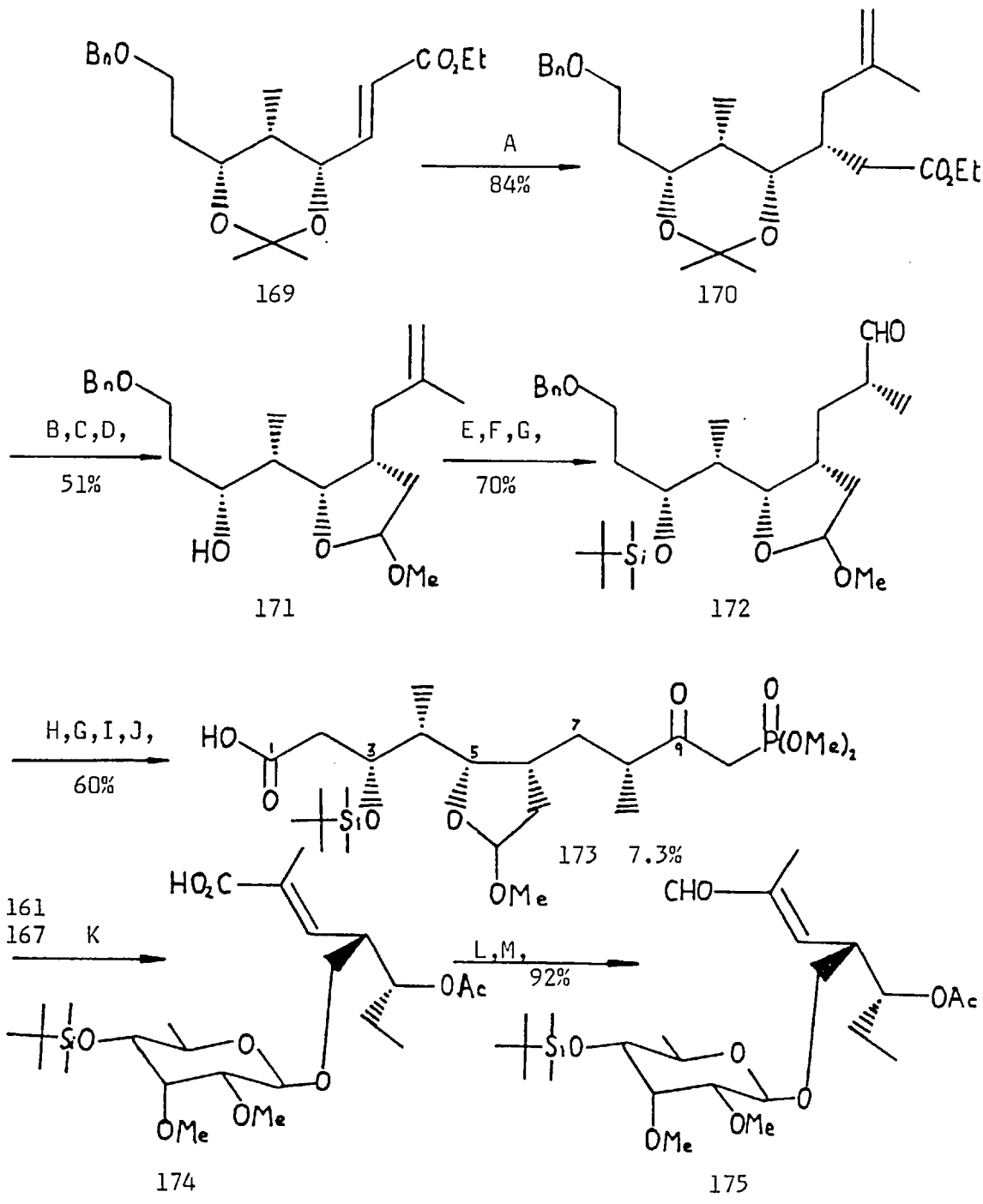
In his related synthesis of a tylosin (114) degradation product, o-mycinosyltylonolide (176), Nicolaou has used the same strategy, Scheme XV. In preparing the macrolide (176), Nicolaou has given himself three synthons to aim for, two of which are similar to those prepared in his previous synthesis. The sugar unit (161) was prepared efficiently from L(+)rhamnose whilst the C_1-C_{10} (173) and C_{11}-C_{15} (167) synthons were both synthesised from the glucose derivative (162).

Treatment of the sugar (162) with potassium cyanide gave either the kinetic product (163), or thermodynamic product (164) depending on the reaction time. The thermodynamic nitrile (164) was readily converted to the C_{11}-C_{15} synthon by standard procedures in good yield. The kinetic product (163) was taken through to the lactol (138) and then to the Michael acceptor (169) without any difficulties. Again Michael addition of a cuprate reagent was found to proceed stereoselectively giving the adduct (170) with the desired isomer as the major product; the ratio of diastereomers was found to be 5:1. X-ray crystallographic studies on (171) showed this to possess the correct stereo-chemistry. Hydroboration of this system was found to go regio- and stereo-



A) HCl/MeOH, B) $tBuMe_2SiCl$, imidazole, C) $PhSSiMe_3$, $Me_3SiOSO_2CF_3$, D) KCN (anhydrous) i) 6hr, ii) 48hr, E) DIBAL, dil H_2SO_4, F) LAH, G) BnBr, KH, H) Amberlite IR 120 H, I) $NaBH_4$, J) $NaIO_4$, K) $Ph_3P{=}CMeCOOEt$, L) Ac_2O,Py, DMAP, M) $PhSSiMe_3$, $n\text{-}Bu_4NI$, ZnI_2, CH_2ClCH_2Cl, N) MsCl, Et_3N, O) Disiamylborase; NaOH, H_2O_2, P) $Ph_3P{=}CHCOOEt$, Q)  , H^+

SCHEME XV



50% β

33% α

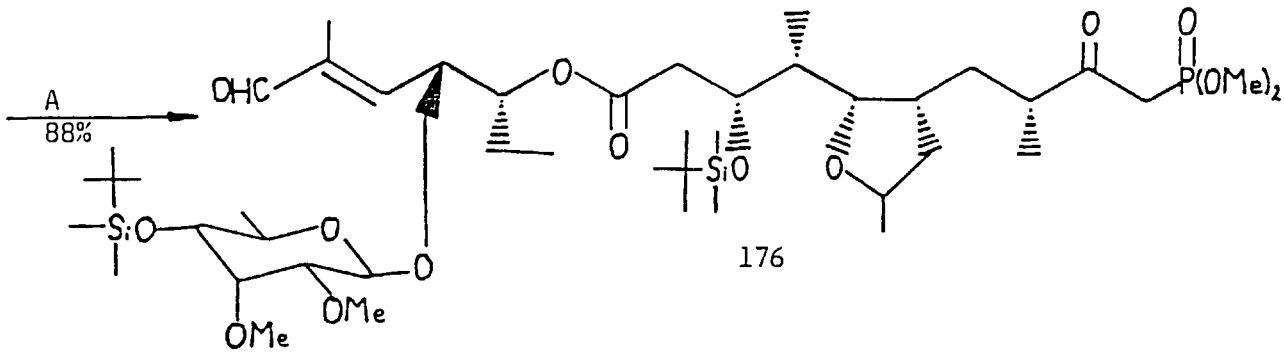
A) CuI,  , B) CH_2OHCH_2OH, H^+, C) DIBAL, Dil H_2SO_4,

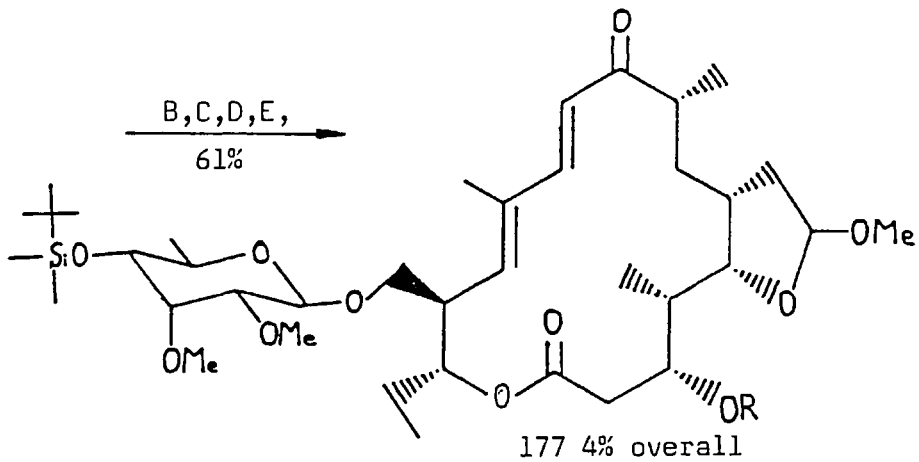
D) HCl/MeOH, E) $tBuMe_2SiCl$ imidazole, F) BH_3; NaOH, H_2O_2,

G) CrO_3.Py, HCl, NaOAc, H) $PO(OMe)CH_2Li$, I) Pd/C, H_2, J) JONES,

K) CH_2CN,NBS, L) DIBAL, M) MnO_2

SCHEME XV Contd.





A) DCC, DMAP, 173, B) K_2CO_3 (anhydrous powder), 18 Crown 6, Dil Toluene, C) HF.Py, D) Dibal, 4 eq, E) DDQ.

SCHEME XV CONTD.

selectively giving, after oxidation, the aldehyde (172) as the major isomer. This was then carried through to the C_1-C_{10} synthon (173) in an overall yield of 7.3%.

Coupling of the sugar moiety (161) with the C_{11}-C_{15} synthon (167) gave mainly the desired α-anomer (174). Minor alterations of (174) gave the aldehyde (175) which was coupled with the remaining synthon (173) to give the acyclic precursor (176). This precursor was designed so as to have its substituents as similar as possible to those found in the natural product (114). Nicolaou anticipated that this would favour cyclization by lowering the entropy factors involved. Internal ketophosphonate

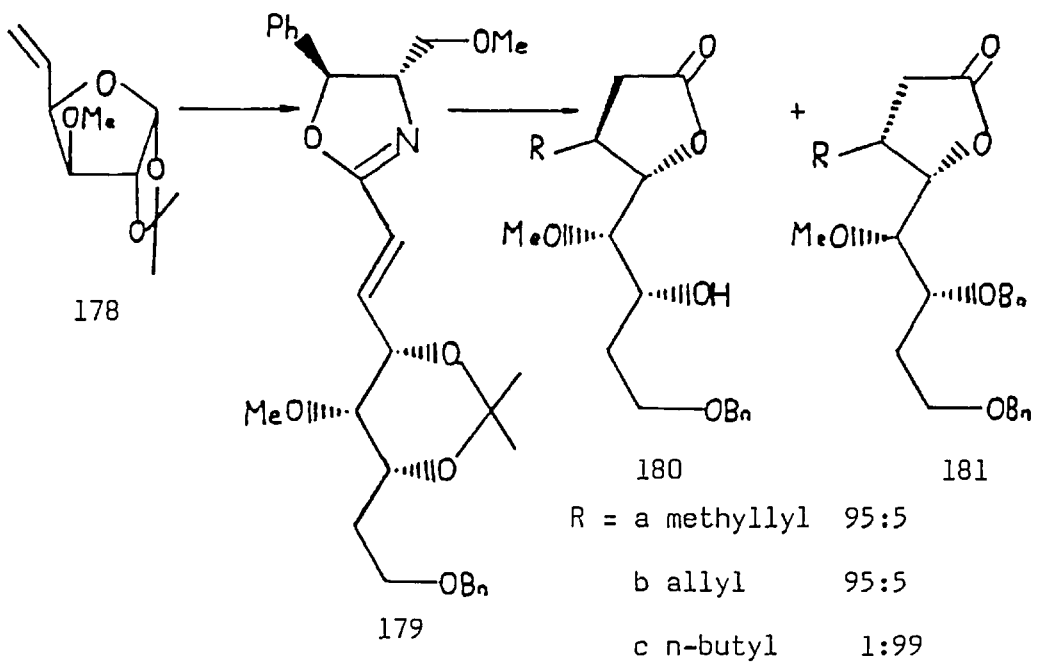
condensation of the aldehyde (175) lead to the cyclic product in an 80% yield. This was then readily converted to the final product in an excellent overall yield of 4%.

It is interesting that hydroboration of olefin (171) gave the product stereoselectively, whereas, in the previous synthesis, Nicolaou found hydroboration of olefin (147) gave a mixture of isomers at C_8, Scheme XIV. The most crucial difference between the two cases is the absence of the acetylide at C_3-C_5 in olefin (171), which contains a protected lactol at C_5-C_6. The result of this difference would be to alter the conformation in the region of the double bond and hinder the approach of the borane from the far side, as drawn.

The approach to the synthesis of 16-membered ring macrolides adopted by Nicolaou and Tatsuta is very similar. It is especially interesting that they both adopt the use of a stereospecific Michael reaction to control stereochemistry at C_6. Tatsuta's first synthesis unfortunately, appears to be rushed towards the end, possibly in an attempt to publish his work first. The problems encountered in the latter stages are, however, overcome in his tylonolide (143) synthesis where his cyclization gives far better yields. Nicolaou's ring closure certainly appears to be superior, giving excellent yields of the macrocycles. Undoubtedly, Nicolaou's second synthesis, of O-mycisosyltylonolide (177), is superior to the other 16-membered ring macrolide syntheses described here. It is highly stereo-

specific and has a high overall yield. The problem with the formation of the C_8 diastereoisomers is overcome, and it is at the same time both divergent and convergent.

A final paper concerning these compounds was published by Ziegler in which he discusses approaches towards developing an alternative to the stereospecific Michael used by the previous two authors, Scheme XVI.[46] Conjugate addition of alkyllithium reagents to α,β-unsaturated oxazolines, in a similar fashion to that used by Meyers, was put forward as his alternative.[47] The olefin (178), derived from D-glucose, was converted to the E oxazoline (179) using standard procedures. The conjugate addition of organolithium reagents containing the $C_{7,8}$ and $_9$ centres and the C_8 methyl gave mixed results. The initial use of methylallyllithium gave the product (180), with the incorrect trans stereochemistry. The use of 2-methylpropyllithium, however, gave predominantly the correct isomer.



R = a methyllyl 95:5
b allyl 95:5
c n-butyl 1:99
d 2methylpropyl 7:93

SCHEME XVI

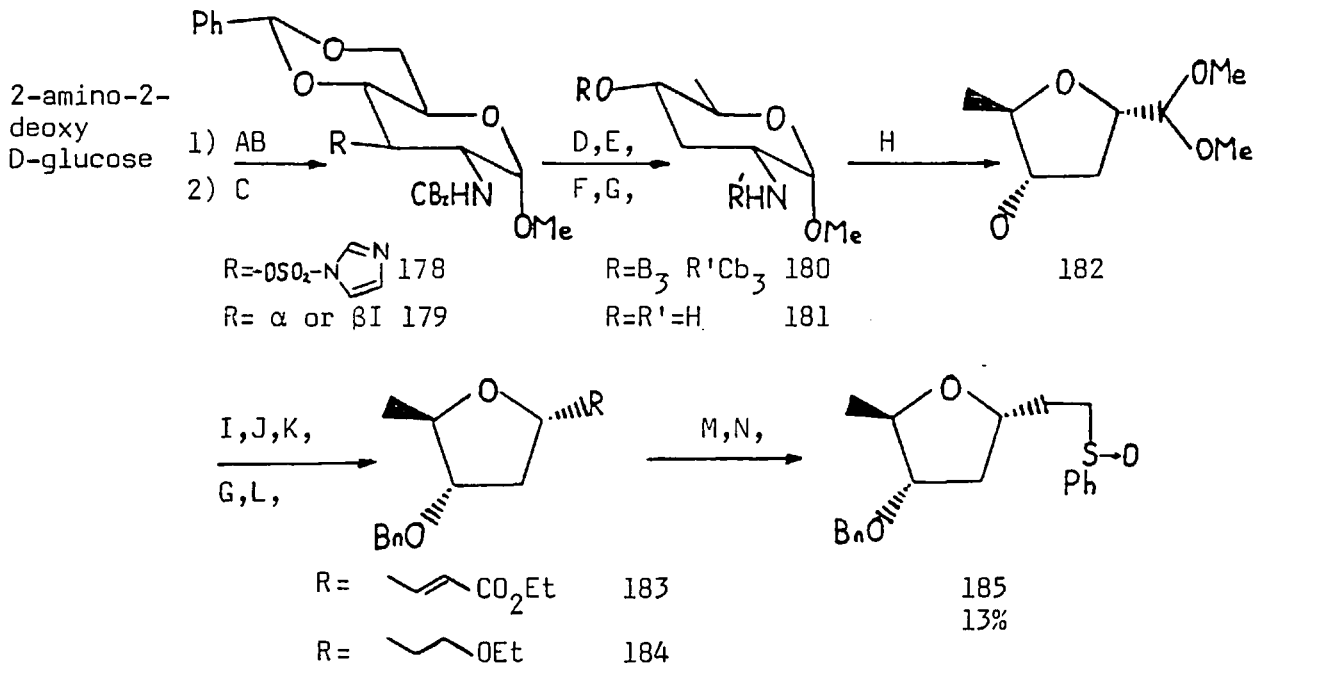
Boromycin

Boromycin (198) is a novel boron containing antibiotic, the degradation of which has yielded a $C_{13}H_{24}O_4$ and a $C_{18}H_{32}O_5$ portion.[48] Hanessian has recently published a synthesis of the latter portion (197) from the synthons (193) and (185), both of which were constructed from D-glucose, scheme XVII.[49]

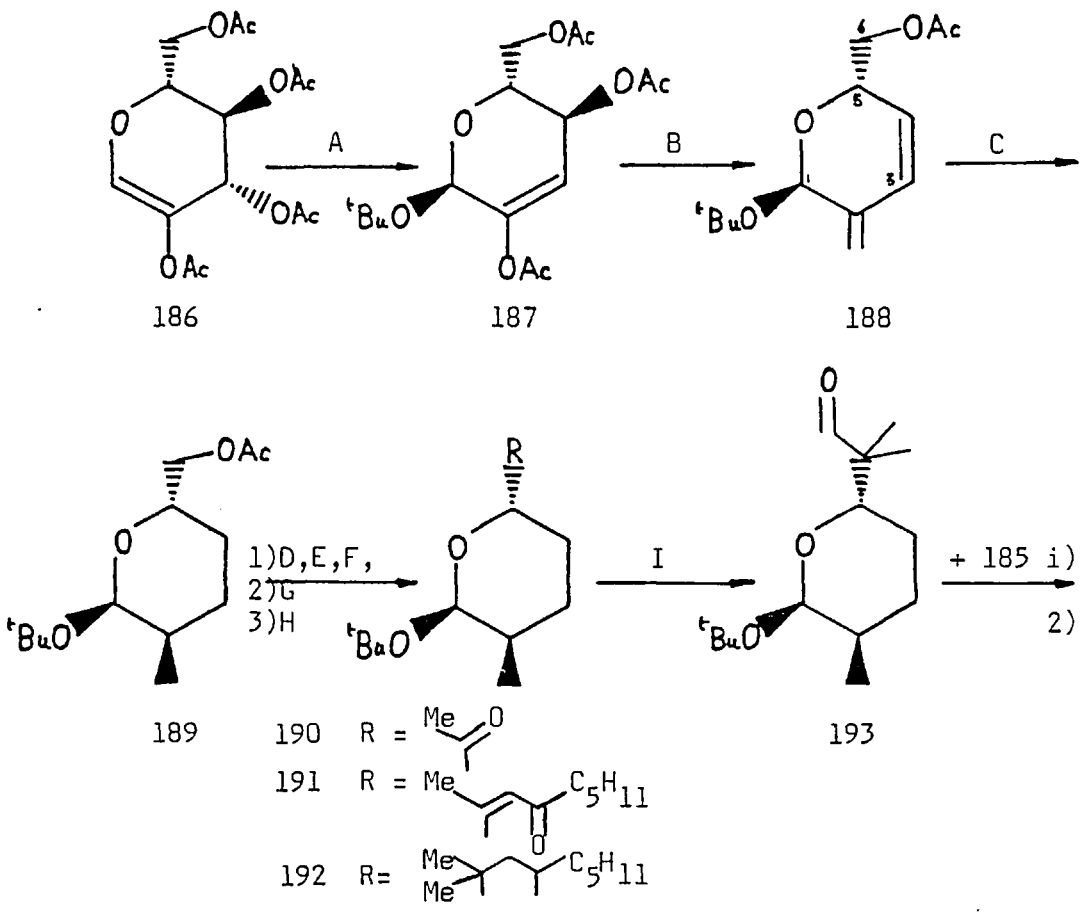
The readily available D-glucosamine was converted to the iodide (179) via the novel imidazole sulphonate (178), the use of which is claimed to reduce complications arising from neighbouring group participating and oxazolidone formation. Conversion to the sulphoxide (185) was straightforward giving an overall yield of 13%.

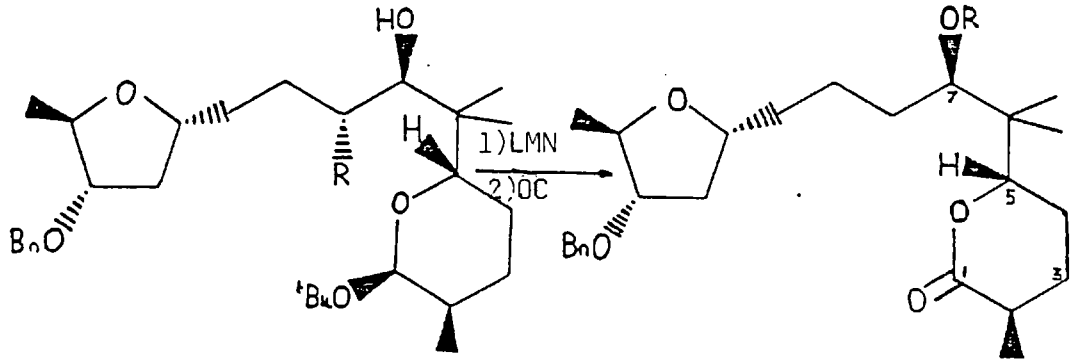
The second synthon (192) was prepared from 2-acetoxy-D-glucal (186) which was initially converted to the tertiary butyl glycoside (187). Reaction of this with 2.5 eq. of a Wittig reagent gave the diene (188) in a remarkable reaction. It is proposed that initial attack of the Wittig reagent on the enol acetate group gave an enone which then underwent the standard Wittig reaction. That this initial acetate attack occurs is shown by the formation of a small amount of the C_6 alcohol. As anticipated hydrogenation of (188) gave mainly the desired methyl isomer (9:1); the bulky ^{t}butyl group hindering the upper face.

The coupling of these synthons, by attack of the anion of (185) into (193), gave the desired skeleton (194).



A) Ref (49(7)) then $PhCHO_3$,HCO_2H B) $SOCl_2$, 2 eq imidazole, C) Bu_4NI, D) NMS, $BaCO_3$, E) Bu_3SnH, AIBN, F) NaOMe, MeOH, G) Pd/C, H_2, H) N_2O_3, H_2O; HCl, MeOH, I) BnBr, NaH, J) AcOH, THFaq, K) $Ph_3P{=}CHCO_2Et$, L) LAH, M) PhSSPh, Bu_3P, N) mCPBA.



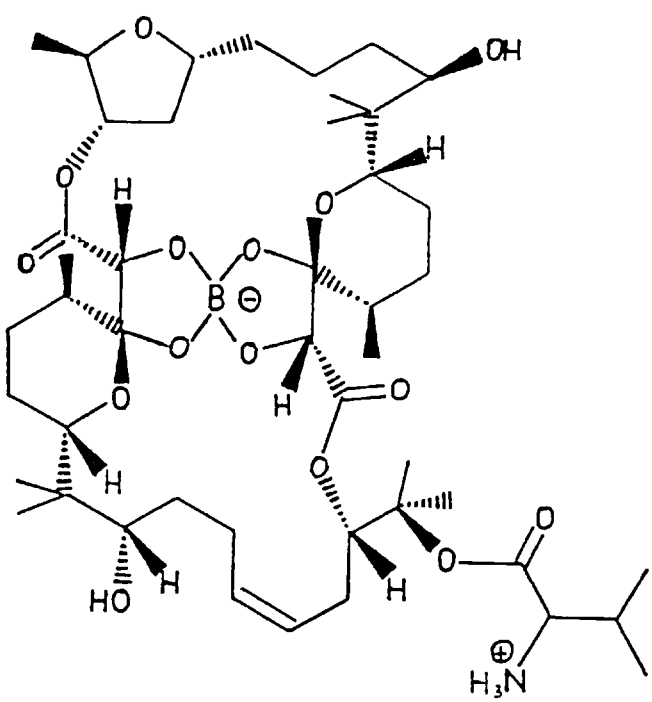


R=SOPh 194 R=$OCO_2CH_2CCl_3$ 196

R=H 195 =H 197

A) tBuOH, $BF_3.OEt_2$, B) $Ph_3P=CH_2$, acetylation, C) Pd/C, H_2, D) NaOMe, MeOH, E) 'Collins', F) MeMgBr;'Collins', G) NaH, $(MeO_2)P(O)CH_2COC_5H_{11}$, H) Me_2CuLi; Me_3SiCl, Et_2N, I) O_3, 1% py, J) LDA, K) Raney Ni; Pd/C, H_2, L) Cl_3CCH_2OCOCl, M) HCl,THF aq, N) PCC, NaOAc, O) Zn.THF.eq KH_2PO_4.

SCHEME XVII



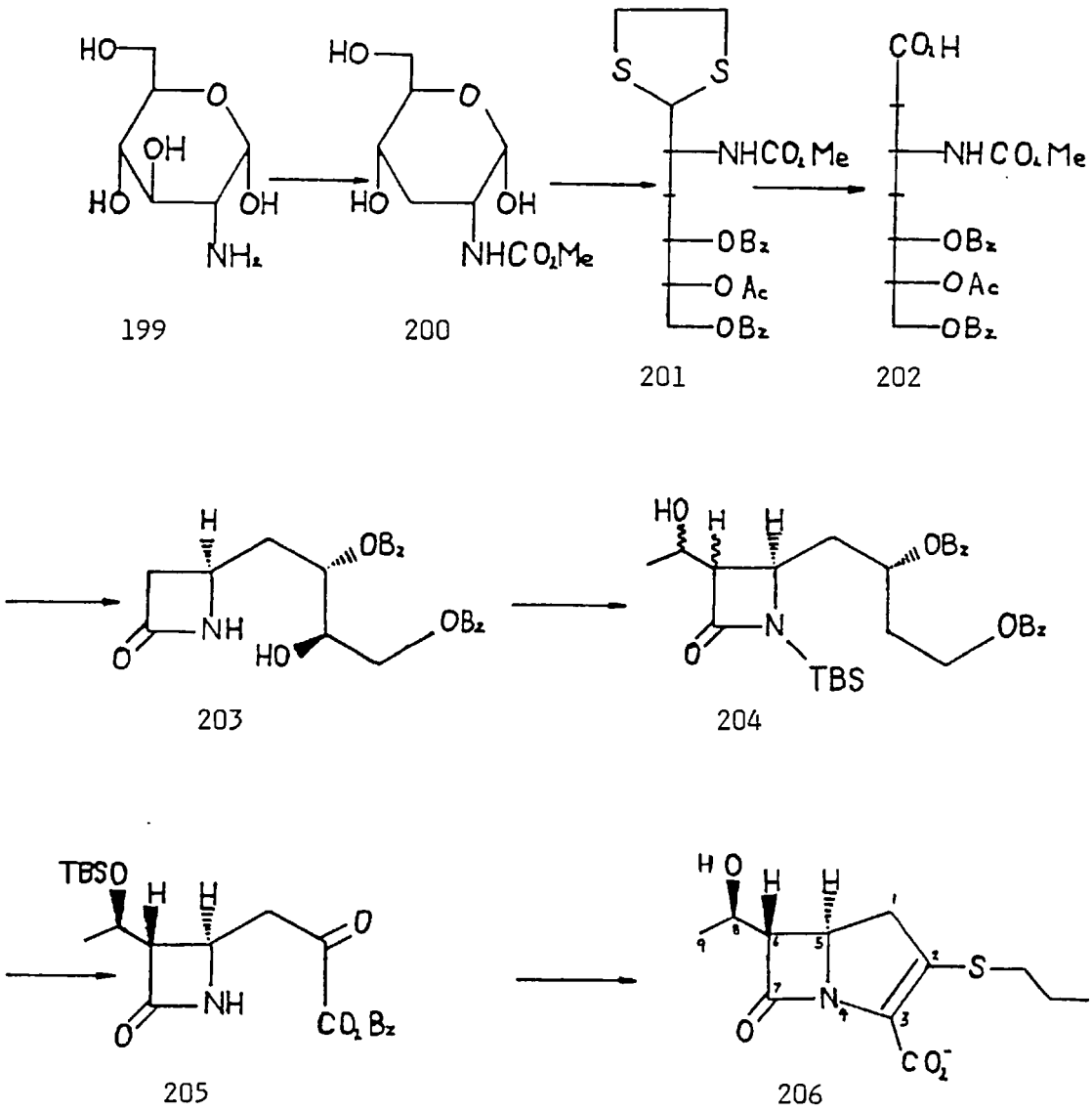
198

The C_7 alcohol was obtained as predominantly the desired isomer (1.5:1); after removal of the sulphoxide group and separation, the unwanted isomer could be converted to a mixture rich in the desired C_7 epimer. The formation of the trichloroethoxycarbonyl protected lactone (196) gave a compound which could be used in the eventual synthesis of boromycin (198), removal of this group then gave the target compound (197).

At a recent IUPAC conference, Hanasian outlined his strategy for the construction of the lower portion of the molecule starting from D-arabinose.

(+)-Thienamycin

Thienamycin (206) is an important β-lactam exhibiting broad antibiotic activity. Several stereocontrolled total syntheses of (+)-thienamycin (206) exist.[51] Of these syntheses only one managed to control all three chiral centres;[51c] the others generally giving a mixture of C8 isomers which require further manipulation to give the desired 8S configuration.[51a,b,d] A recent synthesis of a precursor to (+)-thienamycin (206) has appeared from D-glucosamine (199), scheme XVIII.[52] The synthesis has two main failings, firstly it exhibits very little stereocontrol and secondly, by using such a highly functionalised chiral starting material, it spends a lot of time in destroying unwanted chirality. The synthesis makes use of only one of the chiral centres of the starting material; the other two centres are

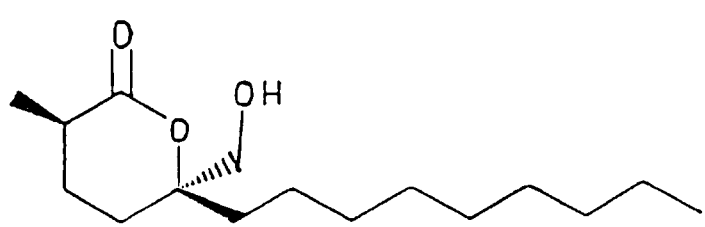


SCHEME XVIII

introduced by isolating the intermediate (204), with the correct 6S,8S- stereochemistry, from a mixture of all four possible diastereomers. Even though this isomer is formed as the major isomer, (39%), and with recycling of the unwanted isomers, it is obtained in an overall yield of 63%, this is not really stereocontrol. Previous stereocontrolled syntheses of (+)-thienamycin (206) have been either from much more simple chiral material, such as L-aspartic acid,[51a,d] D-allo or L-threonine,[51c] or from 6-aminopenicillanic acid.[51b] All of these syntheses are superior to Shiozaki's synthesis.

(-)-Malyngolide

(-)-Malyngolide (207) is an antibiotic isolated from blue-green algae. A synthesis of Malyngolide (207) from D-glucose has been published giving the antibiotic in 30% yield.[53] Apart from giving a good yield of the final product the synthesis makes very poor use of the starting material. The target molecule contains only two chiral centres which, in itself requires the destruction of most of the inherent chirality of the starting sugar. Only one of the available chiral centres is transfered to the product in this synthesis though, the C2 methyl group being formed as a mixture of isomers requiring separation.



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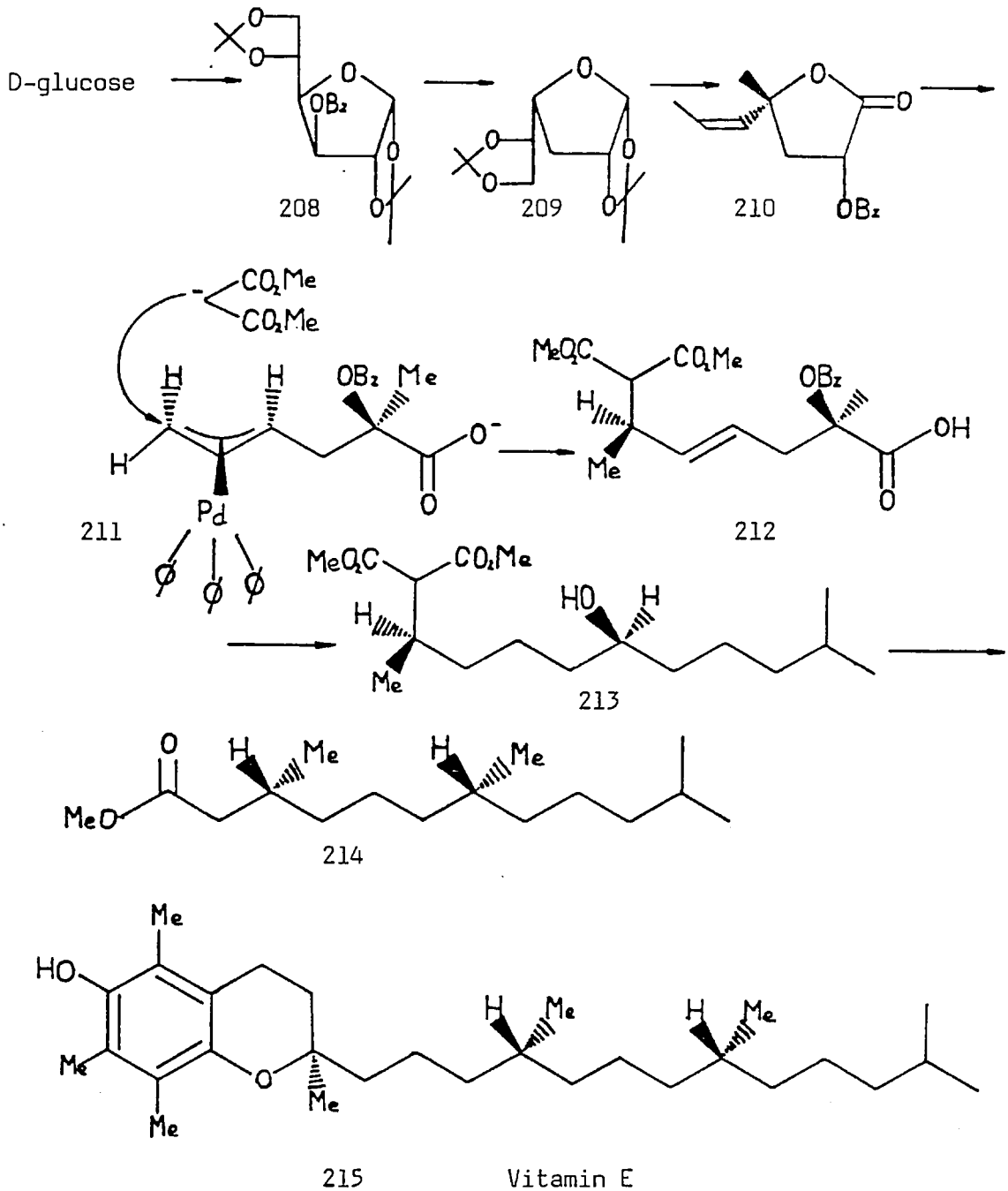


SCHEME XIX

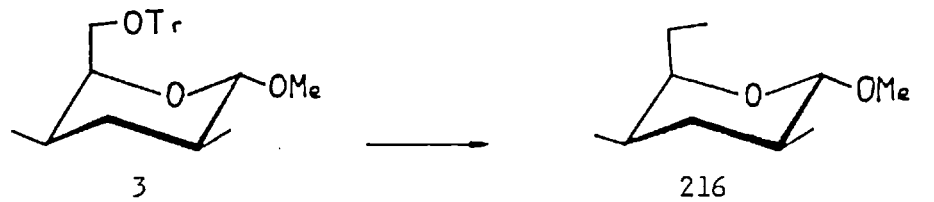
Vitamin E side chain

As an extension of his recently developed transfer of chirality via organopalladium chemistry,[54] Trost has undertaken the synthesis of optically active Vitamin E side chain (214) from D-glucose, Scheme XIV.[55] Whilst the chirality transfer in order to establish the stereochemistry at C-3 is impressive, as an example of a synthesis from a carbohydrate precursor it is poor. Most of the inherent stereochemistry of D-glucose is destroyed in reaching the key intermediate (210). Either a more direct stereospecific synthesis of the intermediate (210) or an alternative strategy to synthesising (214), from a more simple chiral starting material, is called for. Previously the side chain (214) has been prepared via a stereoselective Claisen rearrangement on chiral allylic alcohols.[56] The technique for generating chiral centres with a 1,5 relationship from a sugar could well prove more suited to a target with a large number of chiral centres, such as the macrocyclic rings.

Serricornin

A stereospecific syntheis of the (4S, 6R, 7R) isomer (219) from synthon (3), derived from glucose[11] has appeared, scheme XX.[57] The synthon (3) is identical to that used by Fraser-Reid in his Prelog-Djerassi lactone synthesis, scheme 1.[11] The synthesis of Serricornin (219) was straightforward, making good use of the stereochemistry of the sugar and proceeding with good yield. Together with the previous synthesis of the (4RS, 6R, 7S)

and (4RS, 6R, 7R) isomers this synthesis established (4S, 6S, 7S) Serricornin as the naturally occurring isomer.[58]



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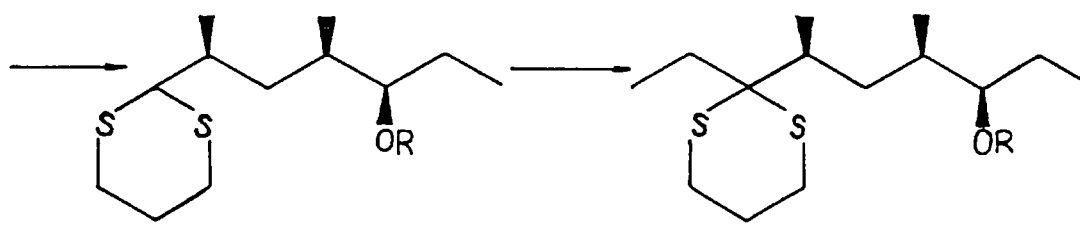
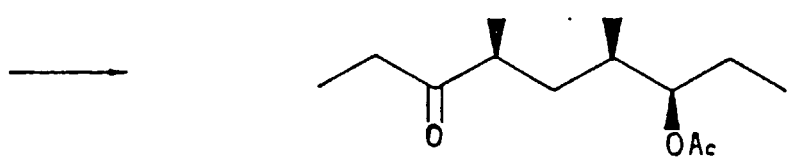


217 218

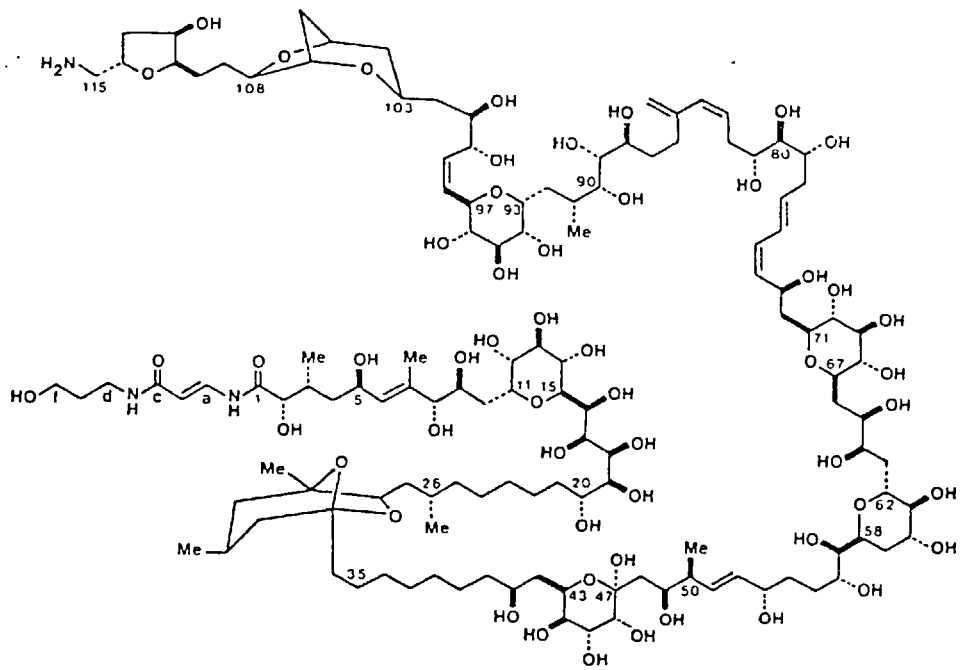


219

Palyotoxin

Glucose was also used to establish the absolute stereochemistry of palyotoxin (220).[59] Kishi synthesised a number of degradation products of palyotoxin (220) in order to compliment the existing knowledge about its

stereochemistry and proposed structure (220) as its absolute stereochemistry Seven degradation products were synthesised from glucose, all of these being straightforward leading to highly chiral poly oxygenated fragments.[59]



220

A growing number of syntheses are making use of the chirality of carbohydrates in order to establish, unambiguously the stereochemistry of the product. As the most widely available sugar, D-glucose in particular has been used in a large number of syntheses. However, with the recent advent of techniques for the introduction of new chiral centres, for instance the Sharpless epoxidation, the area to which carbohydrate based synthesis are applicable is becoming restricted.[60] A large number of syntheses covered in the review are of small molecules with very few chiral centres. These syntheses would have been much better if a simple chiral starting material or an asymmetric synthesis had been employed. In these cases, the use of a glucose based synthon only served to lengthen the synthesis unnecessarily. In the case of larger molecules with more chiral centres, such as the macrolide compounds, carbohydrate synthons still offer the best starting material. The syntheses of carbomycin B, leucomycin A_3 and tylonolide by Tatsuta and Nicolaou illustrate the advantages of carbohydrate synthons for such products. The trend towards the synthesis of larger and more complex natural products, such as palyotoxin, means that despite the increasing number of asymmetric techniques there is still a future role for carbohydrate derived synthons.

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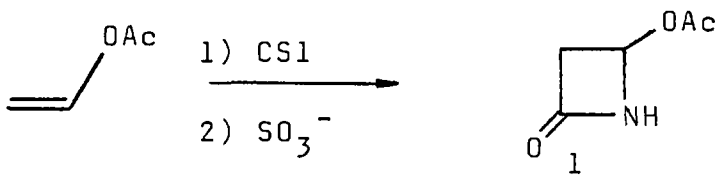
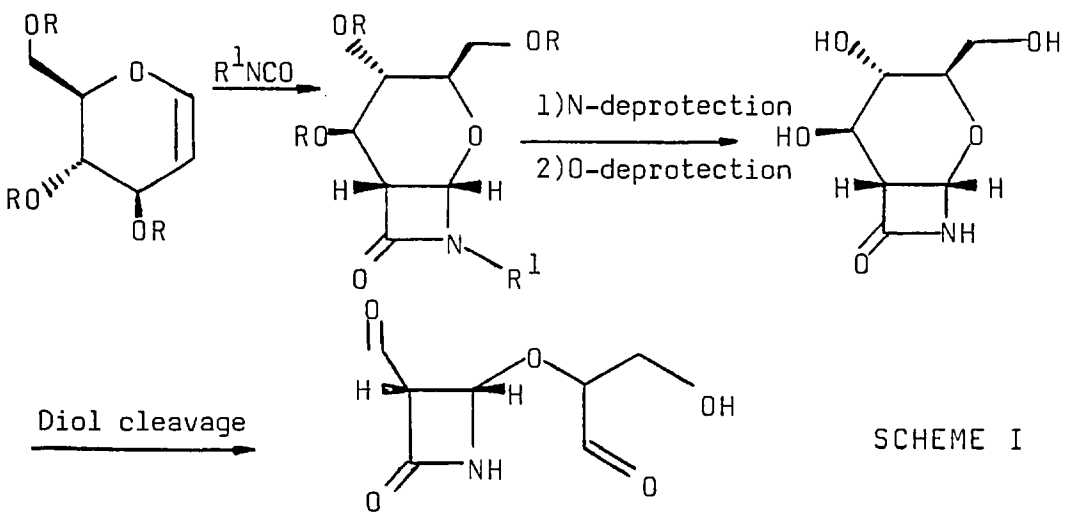
DISCUSSION

INTRODUCTION

β-lactams are readily formed in the reaction of isocyanates, especially chlorosulphonyl isocyanate (CSI), with olefins.[1] Of the numerous examples of this type of reaction in the literature, the reaction of chlorosulphonyl isocyanate with vinyl acetate is particularly noteworthy. The resulting β-lactam, 4-acetoxyazetidin-2-one (1) serves as an intermediate in a large number of syntheses of more complex β-lactams.[2] The cycloaddition of an isocyanate



with a glucal would lead to a highly functional β-lactam which could be a useful intermediate, particularly in the preparation of oxacephems (Scheme 1). Chlorosulphonyl oxcyanate, however, does not give β-lactams on reaction with glucals but acts as a lewis acid causing their dimerisation.[3]



SCHEME I

We, therefore, set out to prepare a range of isocyanates in order to define structural features which would not only give β-lactams on reaction with enol ethers,

including glucals, but which could be subsequently N-deprotected under mild conditions. The work described herein can be divided into three main categories:-

1) The preparation of a range of isocyanates and their subsequent reaction with various olefins and enol ethers. These may be conveniently subdivided into:-

a) Sulphonyl and oxysulphonyl isocyanates and

b) acyl isocyanates

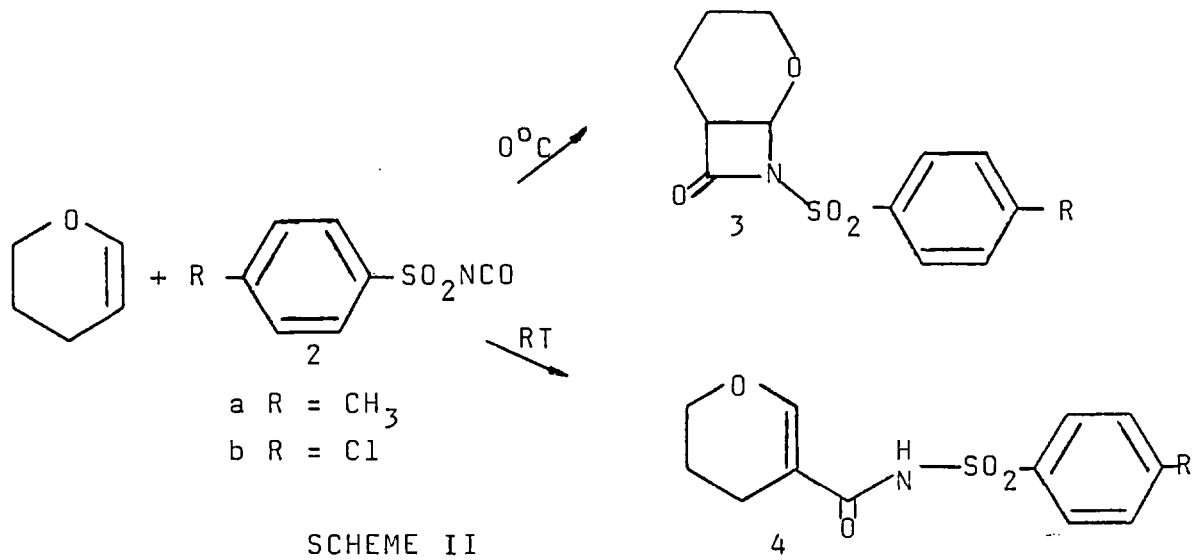
2) Studies on the deprotection of N-sulphonyl, N—oxysulphonyl and N-acyl β-lactams.

3) Studies directed towards the formation of β-lactams containing the N-sulphonic acid function via the cycloaddition of an oxysulphonyl isocyanate and an olefin.

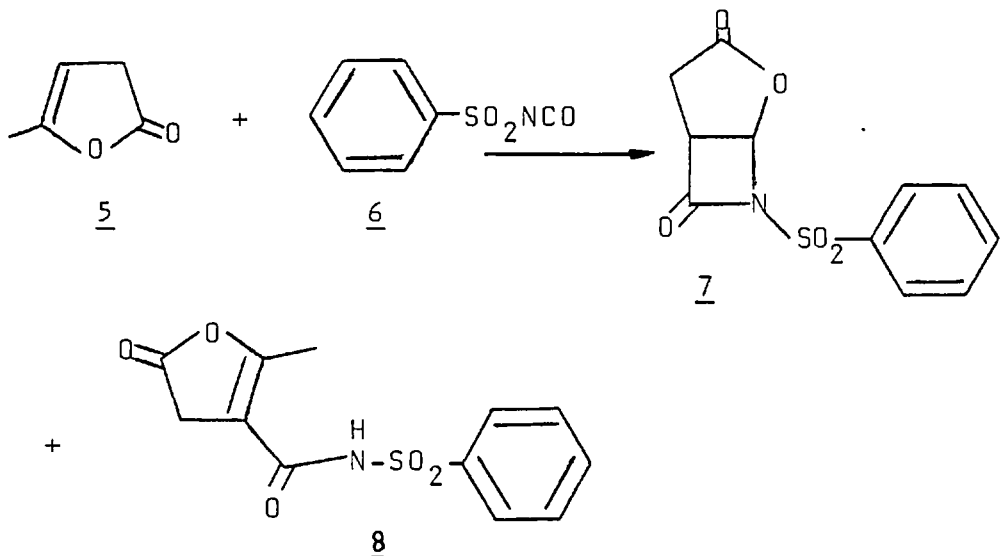
Toluene-4-sulphonyl Isocyanate (2a)

In order to meet both our requirements, an isocyanate must possess a substituent which is electron withdrawing. Aliphatic and aromatic isocyanates, which are not sufficiently electron deficient, do not in general react with enol ethers, although phenyl isocyanate has been shown to react with ketene acetals to give β-lactams.[1] Sulphonyl isocyanates, on the other hand, have been shown to give β-lactams on reaction with enol ethers.

Both toluene-4-sulphonyl isocyanate (2a) and 4-chlorobenzenesulphonyl isocyanates (2b) have been shown to give β-lactams with enol ethers such as n-butylvinyl ether and dihydropyran (Scheme II).[4] The most interesting of these reactions is the reaction of toluene-4-sulphonyl isocyanate (2a) with 3,4 -dihydro-2H-pyran, this being superficially a good model for the reaction with a glucal. Benzenesulphonyl isocyanate (6) has also been claimed to give a mixture of a cyclic (7) and linear (8) product with α-angelicalactone (5) (Scheme III).[4]



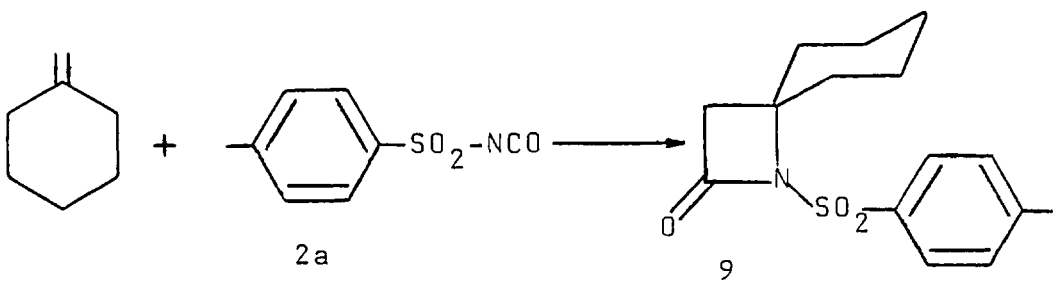
SCHEME II



SCHEME III

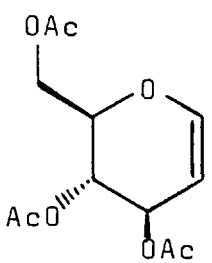
Toluene-4-sulphonyl isocyanate (2b) has also been shown to give a β-lactam on reaction with highly nucleophilic olefins such as 1,2-dimethoxyethene (12a).[6]

Repeating the work of Effenberger, toluene-4-sulphonyl isocyanate (2a), was found to give the linear adduct (4a) on reaction with 3,4 -dihydro-2H-pyran at room temperature.[4,7] On lowering the temperature to 0°C the β-lactam (3a) was obtained in good yield (70%). Effenberger had reported that the β-lactam (3a) was the major product at room temperature, this discrepancy is most likely due to our using carbon tetrachloride in place of benzene as the solvent. Toluene-4-sulphonyl isocyanate (2a) was also found to give a spiro β-lactam (9) on reaction with methylenecyclohexane (Scheme IV), although it failed to react with 3,4,6-tri-O-acetyl-D-glucal (10).



2a 9

SCHEME IV



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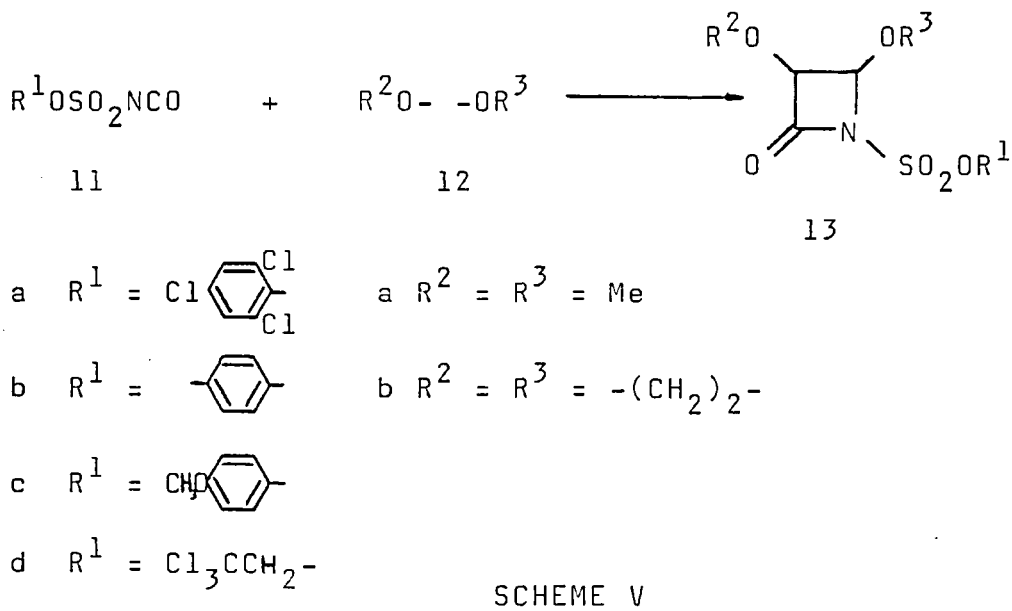
Toluene-4-oxysulphonyl Isocyanate (11b)

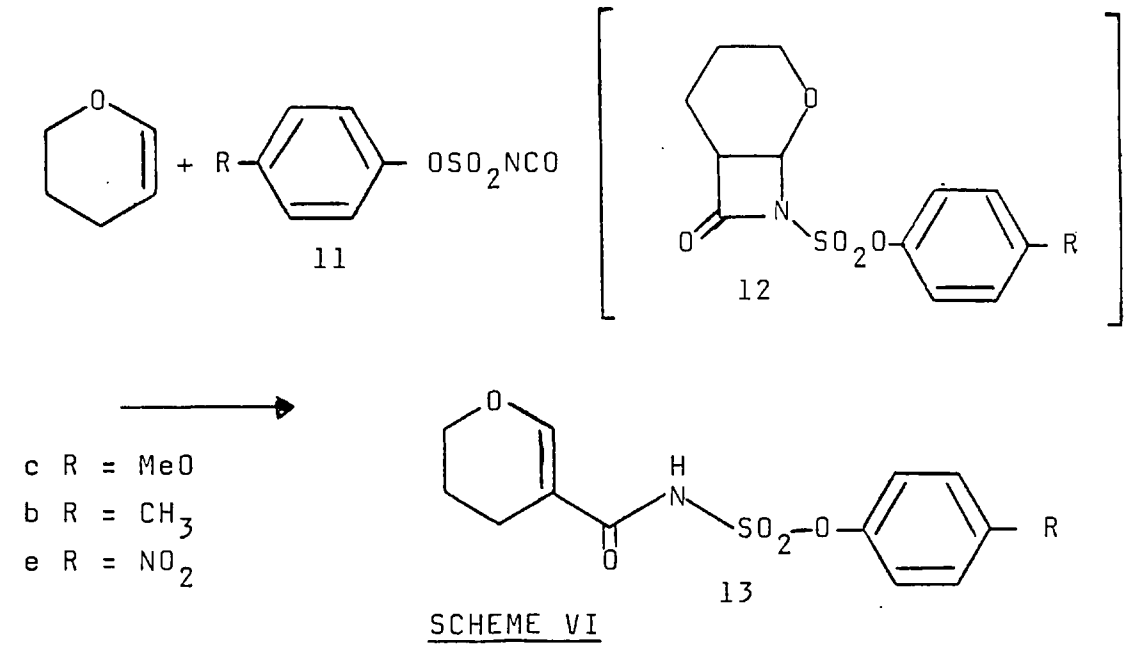
By preparing the oxysulphonyl analogue of toluene-4-sulphonyl isocyanate (2a) we hoped to overcome the deficiencies of this isocyanate; its sluggish reactivity and failure to react with 3,4,6 -tri-O-acetyl-D-glucal (10), and the difficulty in deprotecting the resulting β-lactams under mild conditions. The oxysulphonyl group is much more electron withdrawing than the sulphonyl group and so renders toluene-4-oxysulphonyl isocyanate (11b) much more reactive as well as making the toluene-4-oxysulphonyl moiety a better leaving group. 4-Methoxybenzeneoxysulphonyl isocyanate (11c), 2,4,6 -trichlorobenzeneoxysulphonyl isocyanate (11a) and 2,2,2 -trichloroethoxysulphonyl isocyanate (11d) have all been shown to give β-lactams with dialkoxyolefins such as 1,2-dimethoxyethene (12a) and 2,3-dihydro-p-dioxin (12b) (Scheme V).[6]



SCHEME V

Toluene-4-oxysulphonyl isocyanate (11b) was readily prepared by reaction of p-cresol with chlorosulphonyl isocyanate at elevated temperatures.[8] Reaction of this

isocyanate (11b) with 3,4,-dihydro-2H-pyran gave a linear adduct (13b) as the only isolated product, although infra red spectroscopy clearly showed a β-lactam, probably (12b), as an intermediate (Scheme VI).

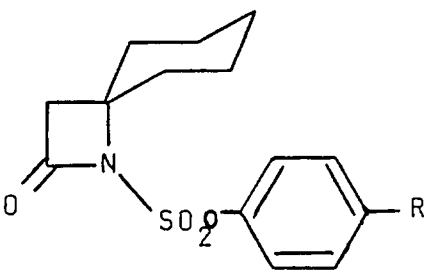


SCHEME VI

The reaction was easily followed by solution infra red spectroscopy as the β-lactam carbonyl at 1800cm^{-1}, and the amide carbonyl at 1705cm^{-1} were easily identified. This reaction was typical of the reaction of arene-oxy-sulphonyl isocyanates with 3,4 -dihydro-2H-pyran. The initial product formed was the β-lactam (12b), the concentration of which slowly increased for a period of time, dependent on the temperature. After one hour, at 0°C, the amide (13b) started to appear; over the next two hours the amount of amide steadily increased whilst the amount of β-lactam remained constant. Finally after three hours, at 0°C, the β-lactam disappeared to leave only the α,β - unsaturated amide (13b). The rate of reaction was affected by temperature, varying between one hour at room

temperature and eighteen hours at -78°C, the final product, however, was always the same.

As with the previous isocyanate (2a) reaction with methylenecyclohexane gave a spiro-β-lactam (14a). Similarly, no reaction was observed between 3,4,6 -tri-O-acetyl-D-glucal (10) and toluene-4-oxysulphonyl isocyanate (11b).



14

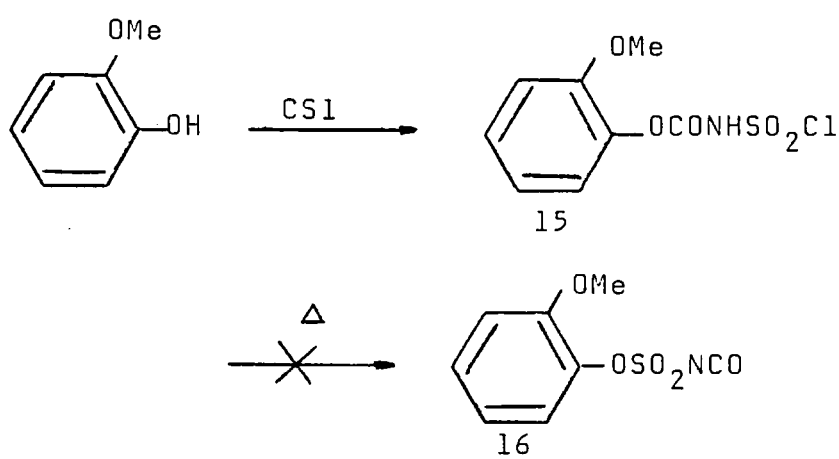
a R = CH_3-
b R = CH_3O-
c R = NO_2-

4-Methoxybenzeneoxysulphonyl Isocyanate (11c)

Slightly disappointed, but not discouraged by the failure of toluene-4-oxysulphonyl isocyanate (11b) to give a stable β-lactam, we set about modifying the isocyanate. Two closely related isocyanates were prepared which would slightly alter the electron withdrawing power of the oxysulphonyl group. 4-Methoxybenzeneoxysulphonyl isocyanate (11c) had been prepared previously and had been shown to give β-lactams with dialkoxyolefins such as 1,2-dimethoxy ethene (12a).[6,8] The effect of the methoxy group is to release electron density into the aromatic ring and thereby lessen the electron withdrawing nature of the oxysulphonyl group. Reaction of this isocyanate (11c) with 3,4 -dihydro-2H-pyran resulted in formation of the linear, 1:1 adduct (13c). The rate of the reaction was significantly slower than in the case of

(11b), which is as one would expect given the reduced electron withdrawing power of the group attached to the isocyanate. Reaction of the isocyanate (11c) with methylenecyclohexane resulted in the formation of the spiro-β-lactam (14b). Again the reaction rate was significantly slower than in the case of isocyanate (11b). No reaction was observed with 3,4,6 -tri-O-acetyl-D-glucal (10).

An attempt to prepare the isomeric isocyanate, 2-methoxybenzeneoxysulphonyl isocyanate (16) by the same method as was used to prepare isocyanate (11c), failed. Although it was possible to form the urethane (15), resulting from attack of the phenol on the isocyanate moiety of chlorosulphonyl isocyanate, on heating the mixture gave an intractable gum.[8] (Scheme VII).

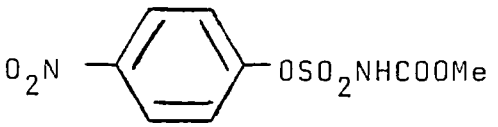


SCHEME VII

4-Nitrobenzeneoxysulphonyl Isocyanate (11e)

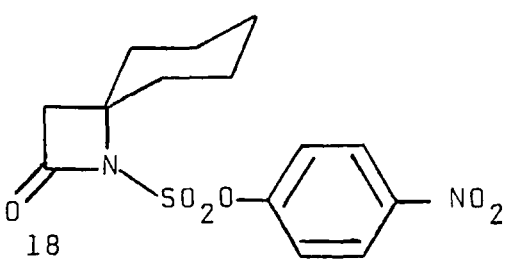
A third isocyanate of this type, 4-nitrobenzeneoxy-sulphonyl isocyanate (11e) was prepared in an identical manner to isocyanates (11b) and (11c).[8] This isocyanate had not previously been prepared, and was characterised

by reaction with methanol to produce the urethane derivative (17a). The 4-nitro group has the opposite effect of the



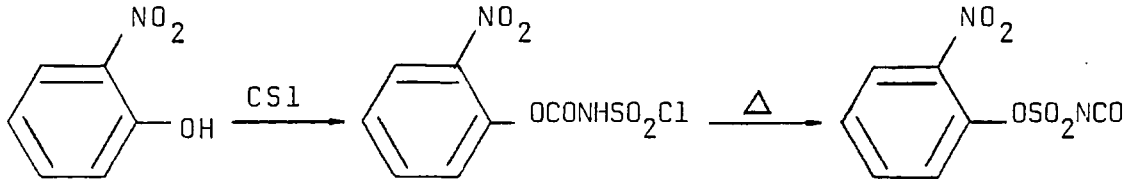
17a

4-methoxy group and increases the electron withdrawing nature of the group on the isocyanate. Reaction of this isocyanate (11e) with 3,4 -dihydro-2H-pyran resulted in the formation of a black, polymeric gum. This is the same result as when chlorosulphonyl isocyanate reacts with 3,4 -dihydro-2H-pyran, although the reaction is not as exothermic or rapid. Lower temperatures did not alter the course of the reaction. Reaction of isocyanate (11e) with methylenecyclohexane resulted in rapid formation of 1-(nitrobenzene-4-oxysulphonyl)-1-azaspiro[3,5]non-2-one (18).



18

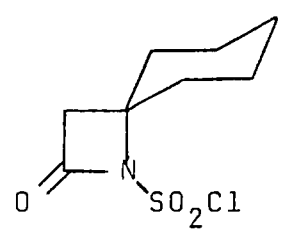
The isomeric isocyanate, 2-nitrobenzeneoxysulphonyl isocyanate (20), could not be prepared by this route (Scheme VIII). Although the intermediate urethane (19) could be prepared in good yield, it was not stable and, if left, rapidly decomposed. On heating the urethane (19), in order to perform the rearrangement, none of the pure isocyanate (20) could be isolated, although a strong isocyanate absorption was observed in the solution infra



19 20

SCHEME VIII

red spectra of the mixture. The addition of methylene-cyclohexane to the mixture gave a spiro β-lactam (21) which was shown to be identical to that formed on reaction with chlorosulphonyl isocyanate. It is conceivable that the urethane (19) underwent equilibration on heating to produce 2-nitrophenol and chlorosulphonyl isocyanate.

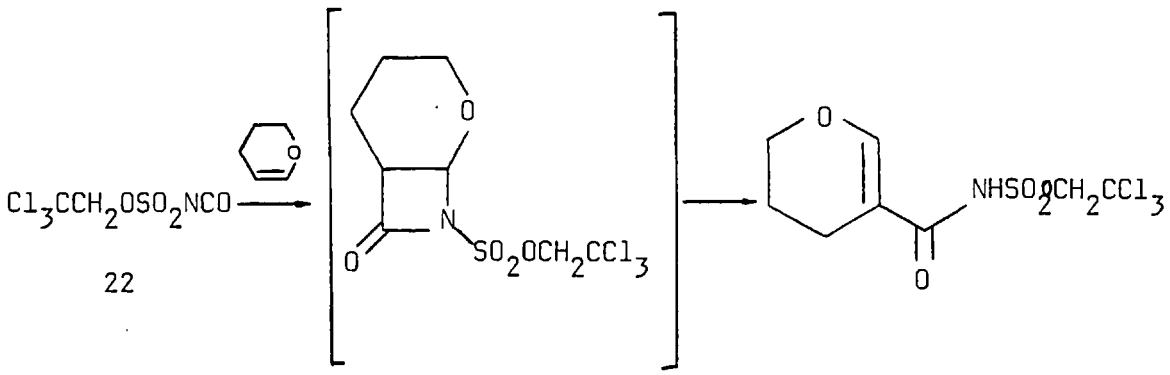


21

2,2,2 -Trichloroethoxysulphonyl Isocyanate (22)

The final oxysulphonyl isocyanate prepared was very different from the first three. 2,2,2 -Trichloroethoxy-sulphonyl isocyanate (22) had been shown to give β-lactams with dialkoxyolefins such as 1,2 -dimethoxyethene (12a) and the 2,2,2 -trichloroethyloxysulphonyl should be easily removed by dissolving metal reduction.[6,8,9] Reaction of this isocyanate (22) with 3,4 -dihydro-2H-pyran was a welcome restorative. At room temperature, reaction gave the linear 1:1 adduct (24) in good yield

(78%). The reaction followed a similar path to the reaction of the other oxysulphonyl isocyanates (11b), (11c) and (11e) with 3,4 -dihydro-2H-pyran, the β-lactam (23) being observed as an intermediate (Scheme IX). At -20°C,

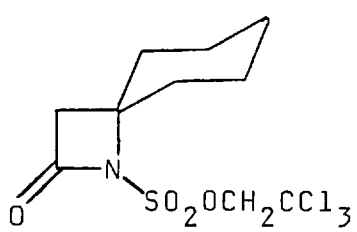


22 23 24

SCHEME IX

however, it was possible to form the β-lactam (23) as the major product; moreover it appeared to be stable at this temperature for several hours. Unfortunately, it was not possible to isolate the pure β-lactam; on attempting to do so it decomposed to the N-sulphonyl amide (24).

Reaction of the isocyanate (22) with methylenecyclohexane gave the spiro-β-lactam (25) in good yield (99%).

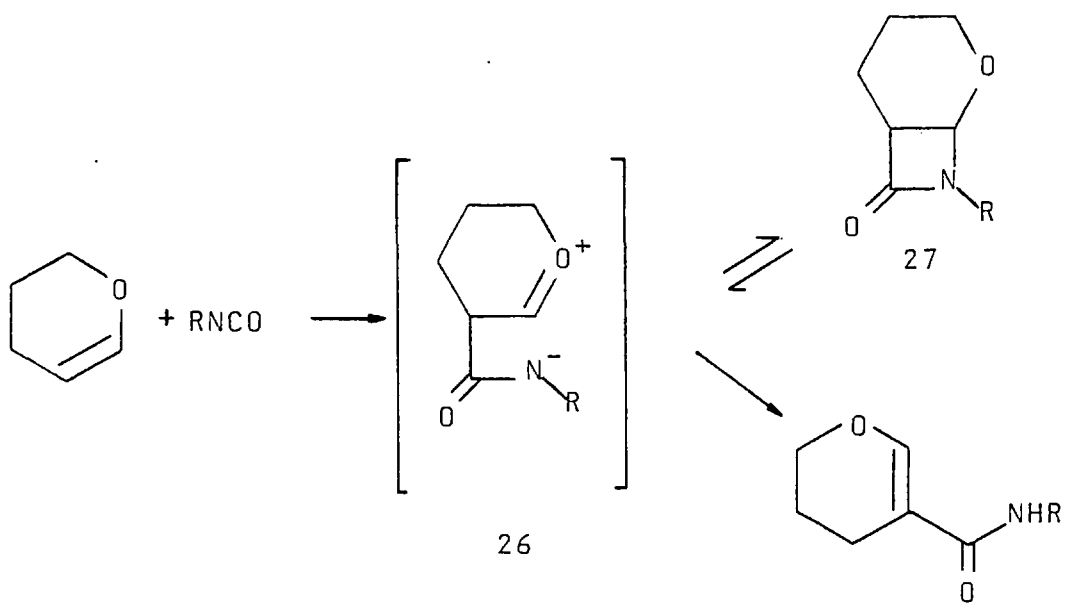


25

The isocyanate (22) also reacted with 3,4,6 -tri-O-acetyl-D-glucal (10) to give a mixture of products. There was no β-lactam in the mixture and it would seem unlikely that

it contained a linear adduct analogous to the adduct obtained with 3,4 -dihydro-2H-pyran (24) as the mixture did not contain the necessary vinyl protons in its NMR spectrum at δ6.2.

None of the oxysulphonyl isocyanates, which we examined appeared to be consonant with the ideal isocyanate for which we are searching. This could well be as a result of their being too electron withdrawing; the effect of this being to destabilise the initial β-lactam formed from them. This would be in accordance with both the proposed mechanism (Scheme X) and our observations.[4] Initial reaction leads to the intermediate zwitterion (26), which under these conditions gives the kinetic product, the β-lactam (27). The β-lactam is in equilibrium with the zwitterion, and so the effect of the electron withdrawing group destabilising the β-lactam, is to push the reaction over towards the formation of the thermodynamically favoured amide (28).



26 27 28

SCHEME X

Comparison of the pKa's of methanesulphonic acid (29) and sulphuric acid, monomethyl ester (30) reveal that, on addition of the extra oxygen to the system, the group becomes much more electron withdrawing.[10,11] This tends to support the argument that the oxysulphonyl isocyanates are more electron withdrawing than the sulphonyl isocyanates and hence destabilise the β-lactams formed from them.

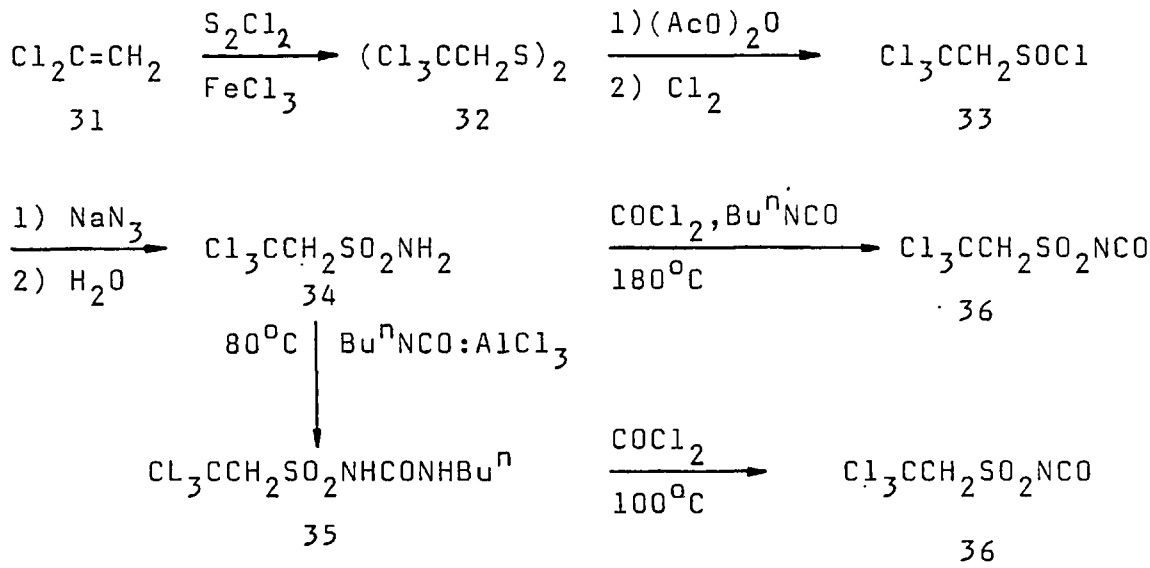
$Me\text{-}SO_3H$ pKa (H_2O, 25°C) -1.92
29

$Me\text{-}O\text{-}SO_3H$ pKa (H_2O, 25°C) -3.4
30

2,2,2-Trichloroethylsulphonyl Isocyanate (36)

2,2,2-Trichloroethoxysulphonyl isocyanate (36) proved the best of the oxysulphonyl isocyanates, and so in order to reduce its electron withdrawing nature, we decided to prepare the corresponding sulphonyl isocyanate. Given that toluene-4-sulphonyl isocyanate (2a) formed a stable β-lactam with 3,4 -dihydro-2H-pyran whereas toluene-4-oxysulphonyl isocyanate (11b) had not, we felt that 2,2,2 -trichloroethylsulphonyl isocyanate (36) would be a propitious choice of isocyanate.

2,2,2 -Trichloroethylsulphonamide (34) was readily formed from 1,1 -dichloroethane (31) via the disulphide (32) and sulphinyl chloride (33).[12,13,14] It had been anticipated that the sulphonamide (34) would be transformed to the isocyanate by treatment with phosgene at



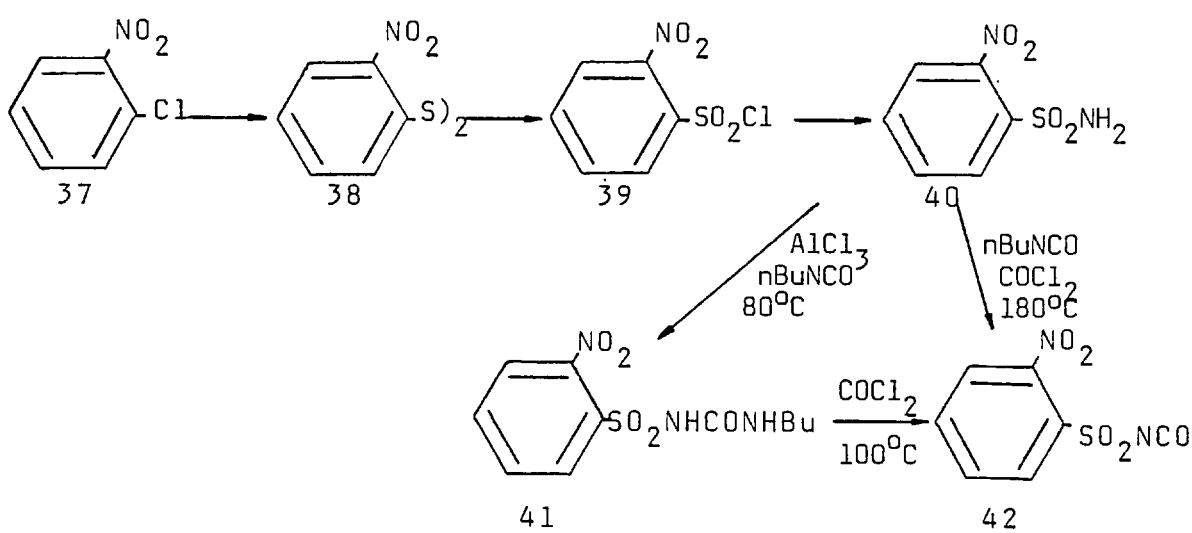
SCHEME XI

high temperature. This has analogy with the preparation of toluene-4-sulphonyl isocyanate (2a).[7] No sign of any isocyanate was noted under these conditions, and several methods of activating the sulphonamide (34) towards attack by phosgene were examined. The use of ethyl di-isopropyl-amine or sodium hydride as base as well as the substitution of oxalyl chloride for phosgene all resulted in no production of the isocyanate (36). However, the sulphon-amide (34) was converted into 2,2,2 -trichloroethyl-sulphonyl isocyanate (36) by treating a refluxing solution of the sulphonamide (34) and butyl isocyanate in 3,4,6 -tri-chlorobenzene with phosgene.[15] Although the isocyanate (36) appeared to be formed in good yield, it proved very difficult to isolate as the solvent, 3,4,6 -trichlorobenzene, tended to co-distil. This solvent was necessary in order to reach a high enough temperature to effect the trans-formation of the sulphonamide (34) to the n-butyl urea (35). By pre-forming a complex between aluminium chloride

and n-butyl isocyanate, the sulphonamide (34) was converted, in reasonable yield, into the urea (35).[39] Once formed, the urea (35) could be converted to 2,2,2 -trichloroethylsulphonyl isocyanate (36) by treatment with phosgene at 100°C.[16] This removed the need for the high boiling 3,4,6 -trichlorobenzene and gave the pure isocyanate (36) readily.

2-Nitrobenzenesulphonyl Isocyanate (42)

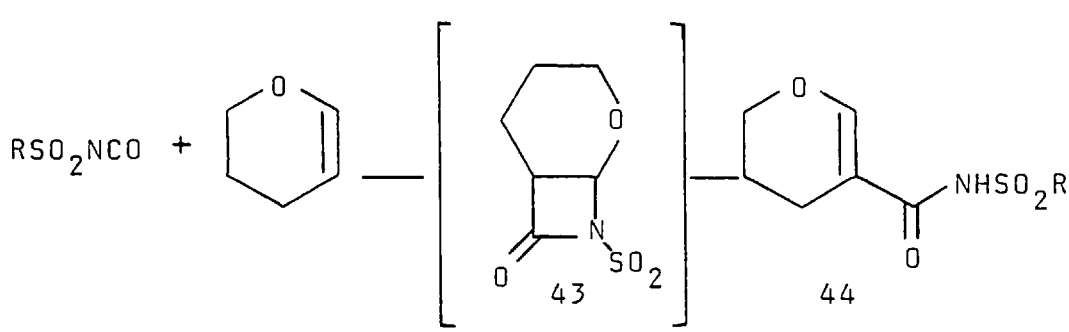
A second isocyanate, 2-nitrobenzenesulphonyl isocyanate (42) was also prepared alongside 2,2,2-trichloroethylsulphonyl isocyanate (36) by a similar route Scheme XII.[17,18] It was again found that direct treatment of the sulphonamide (40) with phosgene did not give the isocyanate (42). Attempts to activate the sulphonamide (40) towards attack by phosgene by forming the sodium, tetra n-butyl ammonium or triton B salts all failed.



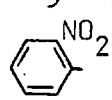
SCHEME XII

However, by using n-butyl isocyanate as catalyst, the reaction between the sulphonamide (40) and phosgene gave the isocyanate (42). This route was not however satisfactory, since, at the high temperatures required, considerable decomposition occurred and thus the isocyanate (42) was prepared via the urea derivative (41).[39]

Reaction of these isocyanates (36) and (42) with 3,4 -dihydro-2H-pyran proved a major blow to morale. The course of the reaction was essentially that which had been observed with the oxysulphonyl isocyanates. As had been expected the reactivity of the sulphonyl isocyanates (36) and (42) was considerably lower than the oxysulphonyl isocyanates previously prepared. The stability of the intermediate β-lactams (43a) and (43b) however, had not increased, and the isolated products were still the α,β-unsaturated amides (44a) and (44b).



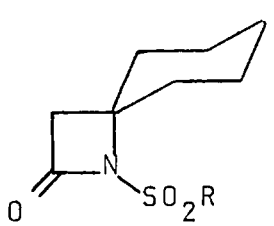
a R = Cl_3CCH_2-

b R = 

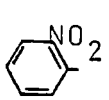
It is clear in the case of the isocyanate (36), that the presence of the nitro group makes the nitrobenzene-4-sulphonyl group more electron withdrawing than the toluene-4-sulphonyl group in isocyanate (2a). The

increased electron withdrawing power must be sufficient to destabilise the β-lactam (43b) in favour of the amide (44b). In the case of isocyanate (36), it is not so easy to compare the electron withdrawing capacities of the 2,2,2 -trichloroethylsulphonyl group, with the toluene-4-sulphonyl group of isocyanate (2a). Comparison of the rates of reaction of isocyanates (36) and (42) with 3,4 -dihydro-2H-pyran, however, shows that 2,2,2 -trichloroethylsulphonyl isocyanate (36) is the more reactive. This can be taken as an indication that the 2,2,2 -trichloroethylsulphonyl group is more electron withdrawing than the 4-nitrobenzenesulphonyl group, and hence more electron withdrawing than the toluene-4-sulphonyl group. In the reaction with methylenecyclohexane, however, direct comparison is possible, and whereas 2,2,2 -trichloroethylsulphonyl isocyanate (36) took 2 days to go to completion, toluene-4-sulphonyl isocyanate (2a) took four weeks.

Reaction of isocyanates (36) and (42) with methylenecyclohexane gave the spiro-β-lactams (45a) and (45b) in good yields after 48hr at room temperature.



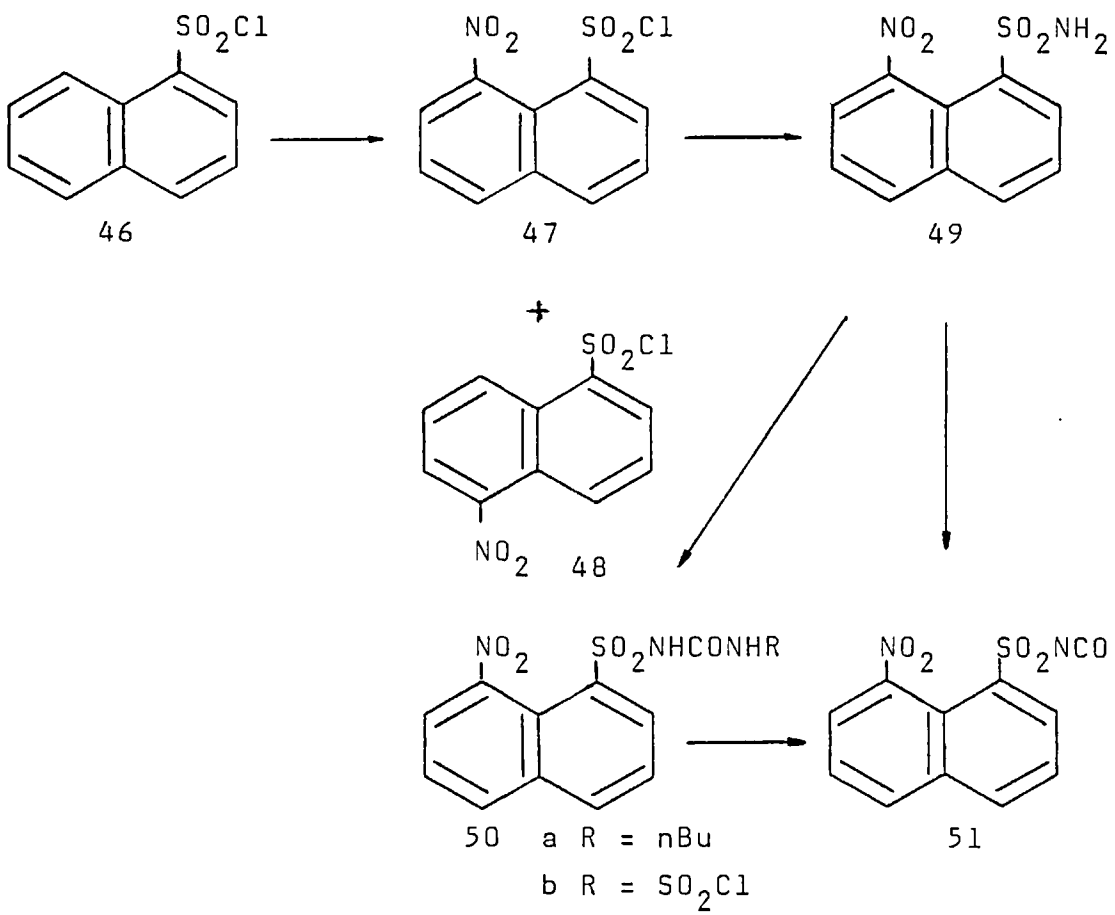
a R = Cl_3CCH_2-

b R = 

45

8-Nitronaphthalene-1-sulphonyl Isocyanate (51)

With the failure of isocyanates (36) and (42) to give stable β-lactams, we decided to look at two other, slightly different sulphonyl isocyanates. The first of these, 8-nitronaphthalene-1-sulphonyl isocyanate (51) has two advantages over the previously examined 4-nitrobenzene-sulphonyl isocyanate (42). The 1,8 disposition of the nitro group and sulphonyl isocyanate group on the naphthalene nucleus means that there is no significant increase in the electron withdrawing properties of the sulphonyl group. Secondly, the proximity of the nitro group to the sulphonyl means that on reduction of the nitro by hydrogenation, rapid attack of the intermediate hydroxylamine onto the sulphonyl group should occur thereby mediating β-lactam liberation.



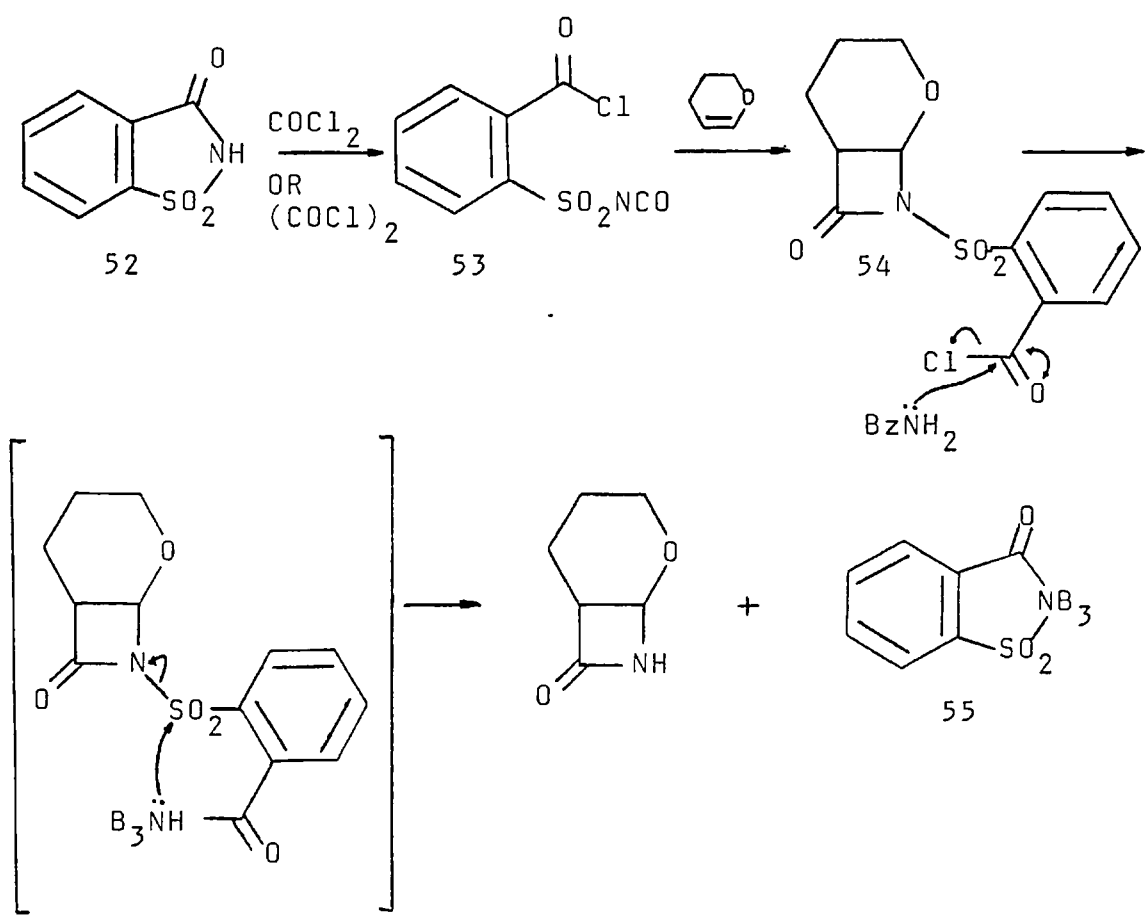
SCHEME XIII

The preparation of sulphonamide (49) from naphthalene-1-sulphonyl chloride (46) by nitration and conversion to the sulphonamide was fairly straight forward (Scheme XIII). The separation of the 8-nitro (47) and 5-nitro (48) isomers, after nitration of the sulphonyl chloride (46), did give some difficulties but, by using preparative HPLC these were overcome. Conversion of sulphonamide (49) to isocyanate (51) had been expected to be simple but could not be achieved. The sulphonamide (49) had been reported as being thermally unstable and, on attempted phosgenation at high temperature, it decomposed.[19] An attempt to prepare the substituted urea (50a), by the same route as used to prepare 1-(nitrobenzene-4-sulphonyl)-3-butyl urea (41) failed.[39] Even when the system was activated by the formation of the sodium or potassium salts none of the substituted urea (50a) was formed. A derivative, probably the substituted urea (50b), was formed on reaction of sulphonamide (49) with chlorosulphonyl isocyanate, as attested by tlc behaviour and infra red spectroscopy, but on heating with phosgene it decomposed to give the starting sulphonamide (49). Reaction of 8-nitronaphthalenesulphonyl chloride (47) with silver cyanate also failed to give the isocyanate (51). This method had previously been employed in the synthesis of benzenesulphonyl isocyanate, although in low yield.[20] The failure to convert the sulphonamide (49) to the isocyanate (51) must be due to the close proximity of the nitro group to the sulphonamide, resulting in the sulphonamide being too sterically congested for reaction

or by decomposition via a peri-reaction.

2-(Chlorocarbonyl)benzenesulphonyl Isocyanate (53)

The final sulphonyl isocyanate we attempted to prepare was 2-(chlorocarbonyl)benzenesulphonyl isocyanate (53). It was proposed that on treating saccharin (52) with oxalyl chloride or phosgene the isocyanate (53) would be generated (Scheme XIV). This isocyanate (53) would provide an excellent leaving group, as treatment of a β-lactam (54) derived from it with a nucleophile, for example benzylamine, would result in the generation of N-benzyl saccharin (55) and the N-unsubstituted β-lactam (Scheme XIV).

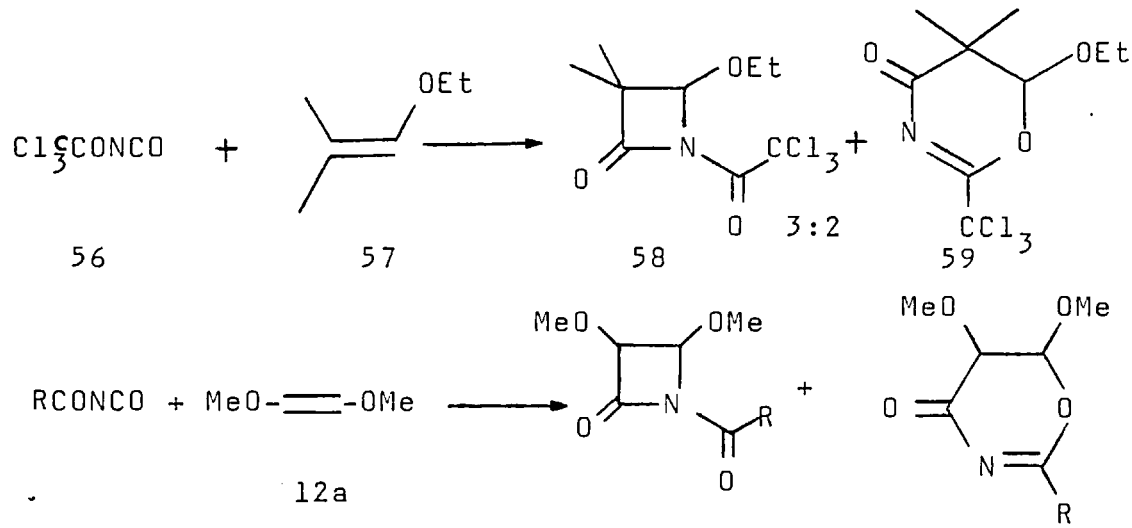


SCHEME XIV

Treatment of saccharin (52) with both phosgene or oxalyl chloride resulted in the formation of an intermediate. The infra red spectrum of this revealed the total loss of the saccharin carbonyl at 1640cm^{-1}, and the appearance of new absorptions at 1750cm^{-1} and 1720cm^{-1} in the case of phosgene treatment, and 1770cm^{-1}, 1750cm^{-1} and 1720cm^{-1} in the case of treatment with oxalyl chloride. On heating these intermediates up to 180^{o}C, a small absorption was noted at 2240cm^{-1} in the infra red spectrum; prolonged heating however, resulted in the disappearance of this absorption. Whilst it would seem likely that a small amount of isocyanate (53) was produced by the treatment of saccharin (52) with phosgene or oxalyl chloride, a lot of decomposition occurred during the reaction and only the starting saccharin was isolated in the end.

Acyl Isocyanates

With the failure of both the oxysulphonyl isocyanates and the sulphonyl isocyanates to give stable β-lactams with enol ethers, we examined several acyl isocyanates. Trichloroacetyl isocyanate (56) has been shown to give β-lactams with enol ethers such as 2-methyl-propenyl ethyl ether (57) and with dialkoxy olefins such as 1,2 -dimethoxyethene (12a) (Scheme XV).[21,22]



56 R = CCl_3 62 R = CCl_3 65 R = CCl_3

79 R = CF_3 63 R = CF_3 66 R = CF_3

61 R = Ph 64 R = Ph 67 R = Ph

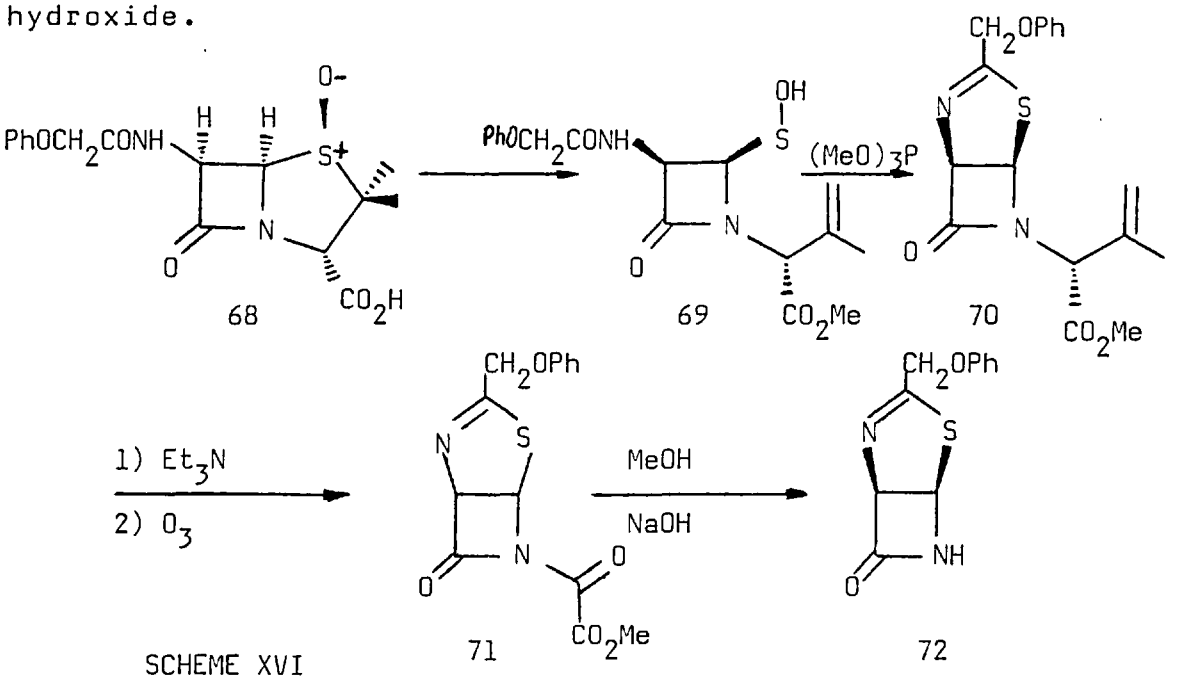
SCHEME XV

Dialkoxyolefins such as (12a) have also been shown to give β-lactams with trifluoroacetyl isocyanate (60) and benzoyl isocyanate (61).[22] In all of these reactions, the formation of the β-lactam is accompanied by the formation of a six membered ring derivative.[21,22] We prepared both trifluoroacetyl (79) and methoxalyl (73) isocyanate to examine their suitability for the formation of β-lactams from enol ethers.

Methoxalyl Isocyanate (73)

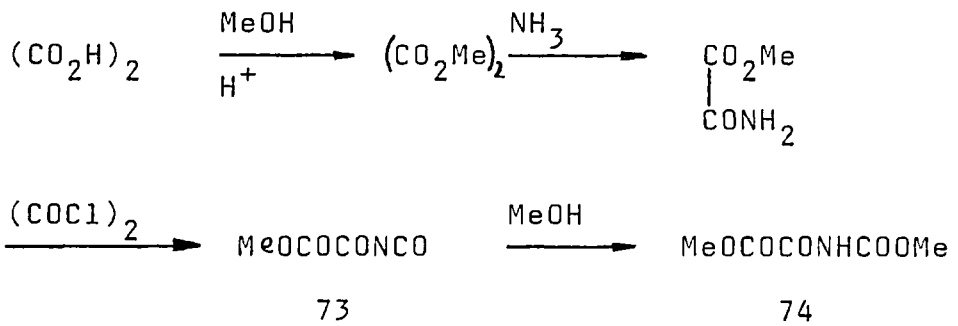
The rearrangement reaction of penicillin sulphoxides are of profound importance in the partial synthesis of cephalosporin antibiotics (Scheme XVI).[23,24] On heating, penicillin β-sulphoxides, including (68), produce the corresponding sulphenic acid (69) as a reactive intermediate. This has been intercepted with diverse

nucleophiles and electrophiles. For example with trimethyl phosphite as trapping agent, the β-lactam (70) was produced. Cooper found that β-lactam (70) could readily be degraded via reaction with triethylamine, followed by ozonolysis to produce the N-methoxalyl β-lactam (71).[24] Significantly for our work the methoxalyl group could be readily, and selectively removed using methanolic sodium hydroxide.



SCHEME XVI

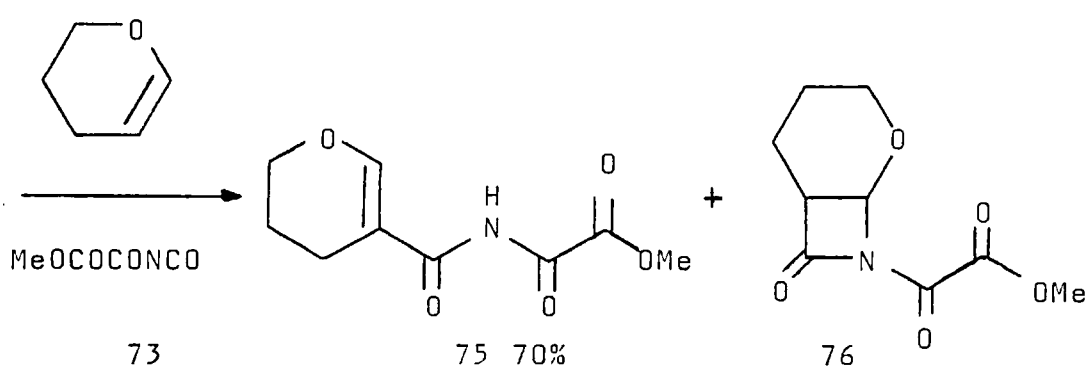
In view of this mild method for the removal of the methoxalyl group from a β-lactam nitrogen we considered that methoxalyl isocyanate (73) would be a useful reagent to synthesise. The synthesis of isocyanate (73) was



SCHEME XVII

achieved without any problems from oxalic acid by the route shown in Scheme XVII. The isocyanate (73) was fully characterised by reaction with methanol to give the urethane derivative (74).

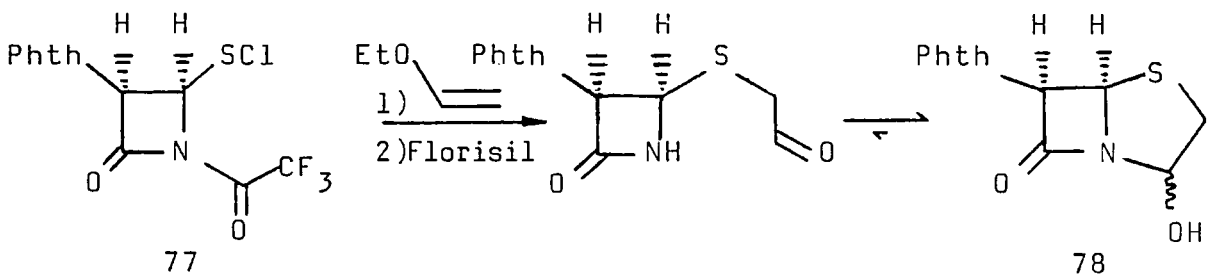
Reaction of isocyanate (73) with 3,4 -dihydro-2H-pyran was disappointing and frustrating. The reaction appeared to be variable in its rate and products. At times, on mixing the isocyanate (73) and dihydropyran a rapid reaction would ensue, whereas at other times no reaction was noted. The only isolated product was the linear α,β-unsaturated amide (75); although a β-lactam, most probably (76), was observed by solution infra red spectroscopy it could not be isolated. No reaction was noted with methylenecyclohexane and further work on the isocyanate was abandoned.



SCHEME XVIII

Trifluoroacetyl Isocyanate (79)

The second acyl isocyanate we prepared was trifluoroacetyl isocyanate (79). As with the previous acyl isocyanate (73), a mild method for detrifluoroacetylating the N-trifluoroacetyl-β-lactams already exists.[25] As part of a program involving the reconstruction of the penam ring system, Sheehan prepared the sulphenyl chloride (77) as a reactive intermediate. Reaction of this with ethyl vinyl ether, followed by chromatography on florisil gave the thiazolidine (78) (Scheme XIX). It is the chromatography on florisil which effects the removal of the trifluoroacetyl residue as well as the hydrolysis of the α-chloro ether.



SCHEME XIX

Several methods were found to prepare trifluoroacetyl isocyanate (79) in the literature, however, we were only able to prepare the isocyanate by one of these routes.[26,27,28] The reaction of trifluoroacetamide with oxalyl chloride gave very small amounts of the isocyanate (79); even when the sodium or tetra n-butylammonium salts were used, equation 1.[26] The volatile nature of trifluoroacetamide appeared to be the problem in this reaction as

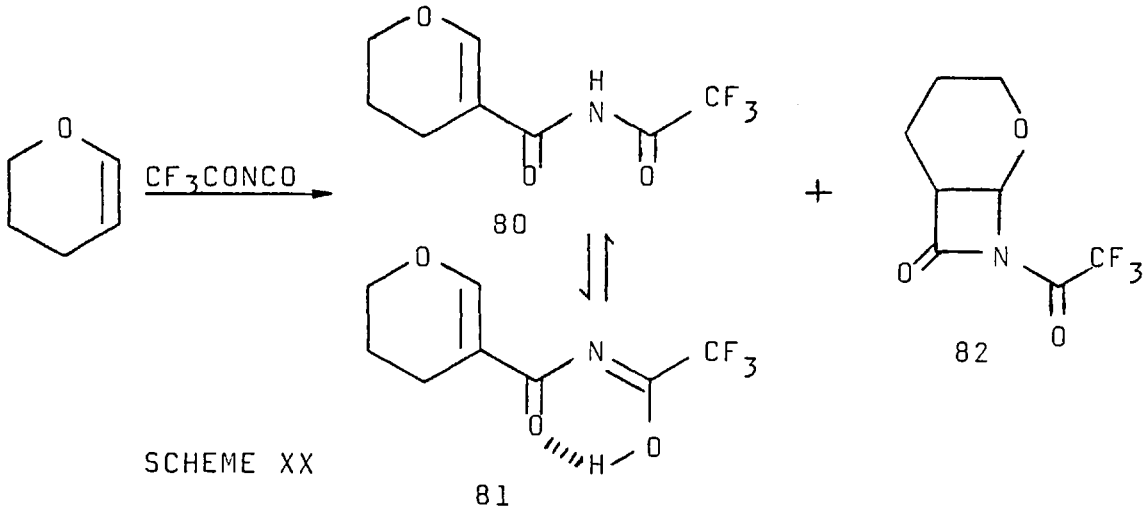
it was readily lost from the reaction mixture. The preparation of trifluoroacetyl isocyanate by the reaction of cyanuric acid and trifluoroacetic anhydride also failed to work, equation 2.[27] The report on this reaction was on a very small scale and it is likely the authors employed a vacuum line technique. Finally, the reaction of trifluoroacetyl chloride with potassium cyanate in a lithium chloride - potassium chloride eutectic at 450°C gave the isocyanate (79) in 40% yield, equation 3.[28]

$$CF_3CONH_2 \xrightarrow[CH_2Cl_2,\ \Delta]{(COCl)_2} CF_3CONCO \quad (79) \qquad 1$$

$$(CF_3CO)_2O \xrightarrow[-78^oC]{HNCO} CF_3CONCO \quad (79) \qquad 2$$

$$CF_3COCl \xrightarrow[LiCl/KCl,\ 450^oC]{KNCO} CF_3CONCO \quad (79,\ 40\%) \qquad 3$$

The reaction of trifluoroacetyl isocyanate (79) with 3,4 -dihydropyran as with the previous acyl isocyanate (73), proved variable and disappointing. The only isolated product was the α,β-unsaturated amide (81). Although an intermediate which was probably the β-lactam (82) was observed by solution infra red spectroscopy, and on occasions appeared to be the major product, it could never be isolated and the result was not reproducible (Scheme XX). The stable adduct isolated appears to be mainly in the enolic form (81) and not as the imide (80). The infra red spectrum shows a strong absorption at 3370cm^{-1} and, in the carbonyl region, at 1680cm^{-1} and 1630cm^{-1}. Both the H^1 NMR and C^{13}NMR spectrum appeared to be correct

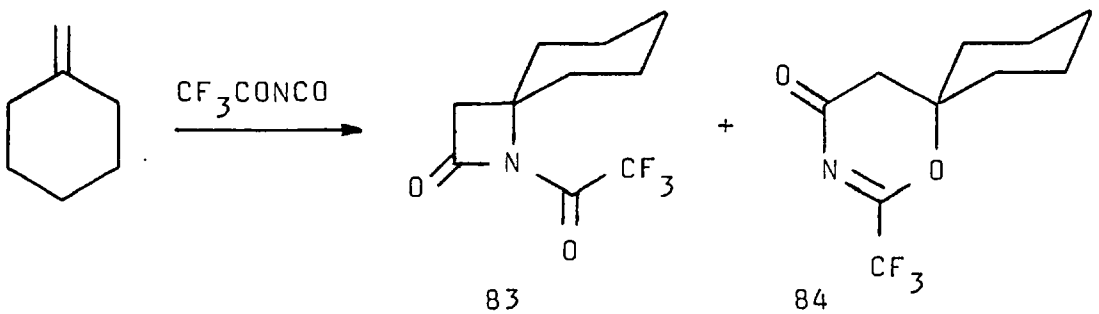


SCHEME XX

for either form of the linear adducts (80) or (81), however, the infra red spectrum can only fit the structure (81). The absorption at 3370cm^{-1} is too intense to be due to an NH stretch, as would be necessary for the imide (80). Moreover the trifluoroacetyl carbonyl stretch, which is characteristically at 1740cm^{-1}, is absent. The absorption at 1630cm^{-1} is due to the enol ether stretch, and occupies its normal position. However, the 1680cm^{-1} absorption, due to the unsaturated amide carbonyl stre tch, is at a slightly lower frequency than expected. All of these unexpected changes in the infra red spectrum are explained by the proposed structure (81).

Reaction of trifluoroacetyl isocyanate (79) with methylenecyclohexane resulted in the formation of a mixture of the β-lactam (83) and the dihydrooxazinone (84) (Scheme XXI). With 3,4,6-tri-O-acetyl-D-glucal (10), trifluoroacetyl isocyanate (79) reacted to give a mixture, which showed a small absorption at 1800cm^{-1} in the infra red spectrum. When the reaction was carried out in acetonitrile, it was possible to observe the total

disappearance of the enol ether stretch in the infra red spectrum. The absorption at 1800cm^{-1} was not strong, however, and the reaction resulted in a complex mixture of products. Originally, trifluoroacetyl isocyanate (79) gave unreproducible results in its reaction with 3,4 -dihydro-2H-pyran, methylenecyclohexane and 3,4,6 -tri-O-acetyl-D-glucal (10). In all three cases the rate of reaction and the product varied. It was thought that this could be as the result of catalysis by an impurity carried over from the preparation of the isocyanate.



83 84

SCHEME XXI

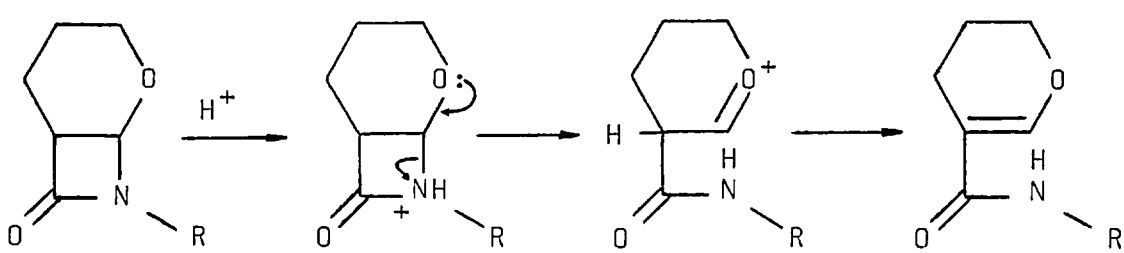
Several possible impurities from the preparation were examined in the reaction of trifluoroacetyl isocyanate (79) with 3,4,6-tri-O-acetyl-D-glucal (10); this had shown the greatest variation in its reactivity. None of the possible contaminants (Table 1) were responsible for any possible catalysis, and the reason for the problem remains a mystery. On examining the reaction of the isocyanate (79) at a later date, the same problem did not occur, and reproducible results were obtained.

Investigation into possible catalysts for the reaction of trifluoroacetyl isocyanate (79) with 3,4,6-tri-O-acetyl-D-glucal			
Additive	Solvent	Temperature	Product
CF_3COOH	$CHCl_3$	RT	All reeactions
CF_3CONH_2	$CHCl_3$	RT	were very slow
Pyridine	$CHCl_3$	RT	and showed no
$(CF_3CO)_2O$	$CHCl_3$	RT	formation of
-	$CHCl_3$	45°C	β-lactam.

TABLE 1

The N-Desulphonylation and Deacylation of N-Sulphonyl and N-Acyl-β-lactams

Our twin objectives were to find an isocyanate which would, on reaction with an enol ether, give a β-lactam which could be deprotected under mild conditions. As well as examining the reaction of various isocyanates with enol ethers, we also carried out a concurrent program of deprotection reactions on β-lactams formed from these isocyanates. Such deprotections were best carried out under neutral conditions, as certainly under acid conditions an easy pathway for the loss of the β-lactam existed (Scheme XXII).

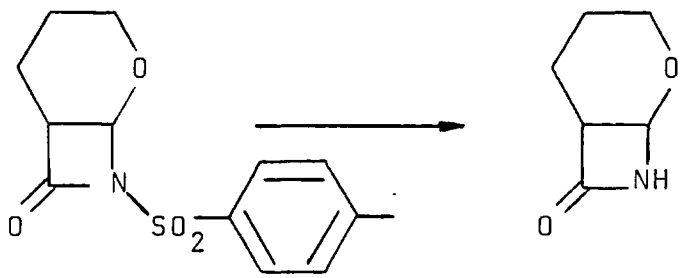


SCHEME XXII

Aryl sulphonamides cannot be converted to amines by alkaline hydrolysis or catalylic reduction but are susceptible to reduction by electron transfer.[29]

Removal of the Toluene-4-sulphonyl Group

The first deprotection we attempted was of the bicyclic β-lactam (3a) by reductive cleavage of the N-toluene-4-sulphonyl group (Scheme XXIII). Reaction of chromous acetate resulted in rapid loss of the starting β-lactam (3a), a complex mixture of products being obtained.[30] This mixture showed an absorption at 1760cm^{-1} in the infra red spectrum which may have been due to the deprotected β-lactam (85), but the compound decomposed on attempted isolation.



3a 85

SCHEME XXIII

Treatment of the amide (4a), the ring opened form of β-lactam (3a), resulted in slow loss of starting material to give an intractable mixture of products. The fact that the amide was reduced slowly means that the loss of the β-lactam moiety is subsequent to any reduction which might be occurring. Carrying out the reaction on β-lactam (3a) at a lower temperature made no difference.

Using aluminium amalgam to deprotect the β-lactam (3a) produced the same result only much slower.[31] Again the mixture showed an absorption at 1760cm^{-1} in the infra red spectrum but no β-lactam was present in the product after work up. It had been hoped that by reducing the system faster, less subsequent decomposition would occur.

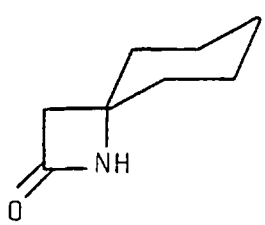
The final reductant used to effect the transformation of the N-toluene-4-sulphonyl β-lactam (3a) into the N-unsubstituted β-lactam (85) was titanium (III) chloride. This was used in neutral aqueous solution containing the chelating ligand, EDTA, to maintain the solubility of the titanium (III). Reaction of this with β-lactam (3a) resulted in the instantaneous loss of starting material giving a complex mixture of products. Once more the mixture showed an absorption at 1760cm^{-1} in the infra red spectrum although no β-lactam could be isolated. It was noted that the purple colour of the titanium (III) ion persisted for several days, even though only one equivalent was used. Moreover, the reaction was found to have gone to completion after the addition of only 0.2 equivalents of titanium (III) chloride. It was subsequently found that the addition of a small amount of water resulted in instantaneous loss of starting material and the formation of a complex mixture of products. The mixture of products obtained here appeared to be similar to the mixture obtained using titanium (III) chloride. With these discouraging results we left this sytem.

Removal of the 2,2,2 -trichloroethoxysulphonyl group

The 2,2,2 -trichloroethoxysulphonyl group presents a much easier target to remove and should be readily cleaved by an electron transfer reaction.[32] The deprotection of 1-(2,2,2 -trichloroethoxysulphonyl)-1-aza-spiro[3,5]non-2-one (25) was initially attempted using the iodide ion. Sodium iodide and tetra n-butylammonium iodide both resulted in slow loss of the β-lactam (25)

giving a complex mixture of products. Control reactions without iodide present showed that β-lactam (25) was stable under the reaction conditions. Thus, the destruction of β-lactam (25) can be put down to the effects of the iodide ion.

The β-lactam (25) was successfully converted to the azetidinone (86) using zinc under neutral conditions.[33] It was decided not to carry out the reaction in the more usual acid medium, although there was no reason to suppose this would not be successful.[34] The β-lactam (25) was a model for β-lactams derived from enol ethers, and as stated earlier these are not stable under acid conditions. The β-lactam (86) was found to be identical with an authentic sample prepared by reaction of chlorosulphonyl isocyanate with methylenecyclohexane followed by dechlorosulphonylation.[35] Treatment of the protected



86

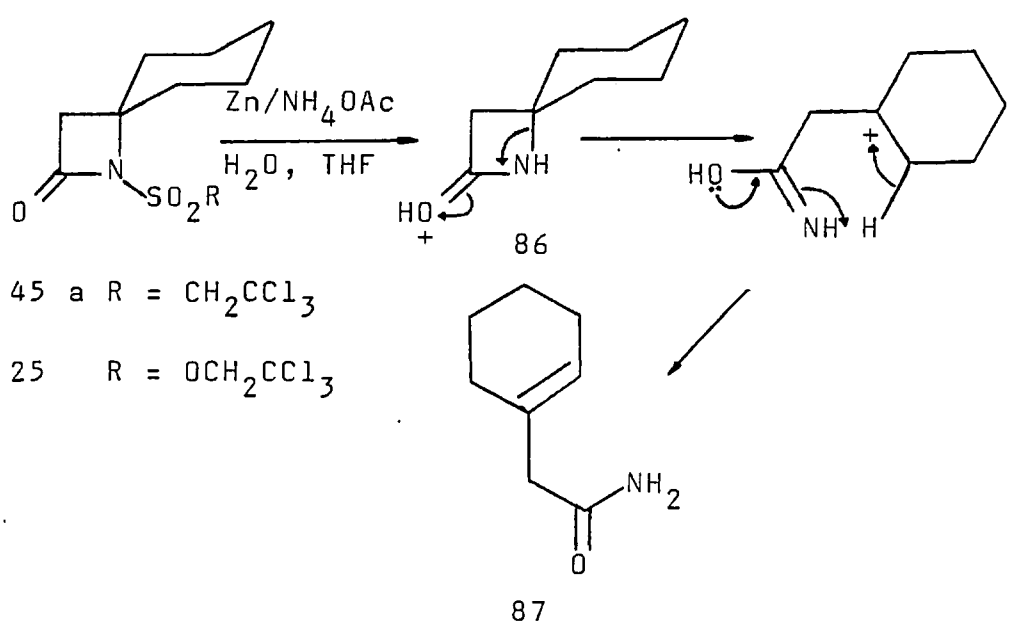
spiro β-lactam (25) with activated zinc in an organic solvent failed to cleave the 2,2,2-trichloroethylsulphonyl group, even when the zinc had been freshly precipitated from solution. Deprotection of β-lactam (25) to the azetidinone (86) was accompanied by the formation of a small amount of an amide (87), (11%).

The N-deprotection of 1-(2,2,2-trichloroethoxysulphonyl)-1-azaspiro[3,5]non-2-one (25)		
Reductant	Solvent	Product
Na I	Acetone	β-lactam destroyed, complex mixture of products
-	Acetone	starting β-lactam recovered
$n\text{-}Bu_4N^+I^-$	THF	β-lactam destroyed, complex mixture of products
-	THF	starting β-lactam recovered
Zn (activated)	THF	Starting β-lactam recovered
Zn/NH_4OAc	THF/H_2O	reduced to give β-lactam 86 (30%) and 87 (11%)

TABLE II

Removal of the 2,2,2-trichloroethylsulphonyl group

The reduction of the closely related N-2,2,2-trichloroethylsulphonyl β-lactam (45a) with zinc in neutral conditions was also attempted. Reduction was very slow and resulted in the amide (87) being produced as the major product (68%), the azetidinone (86) being a minor product (19%). There is little evidence on which to base a mechanism for the formation of the amide (87), however, it is possible to speculate. The cleavage of the C_1-C_4 bond of β-lactam (86) would relieve strain and with the spiro centre at C_4 would result in the formation of a



45 a R = CH_2CCl_3

25 R = OCH_2CCl_3

SCHEME XXIV

relatively stable tertiary cation. Abstraction of a proton from a position on the cyclohexyl ring, adjacent to the cation would result in the quenching of the cation

in a six membered ring transition state to give the amide (87) (Scheme XXIV).

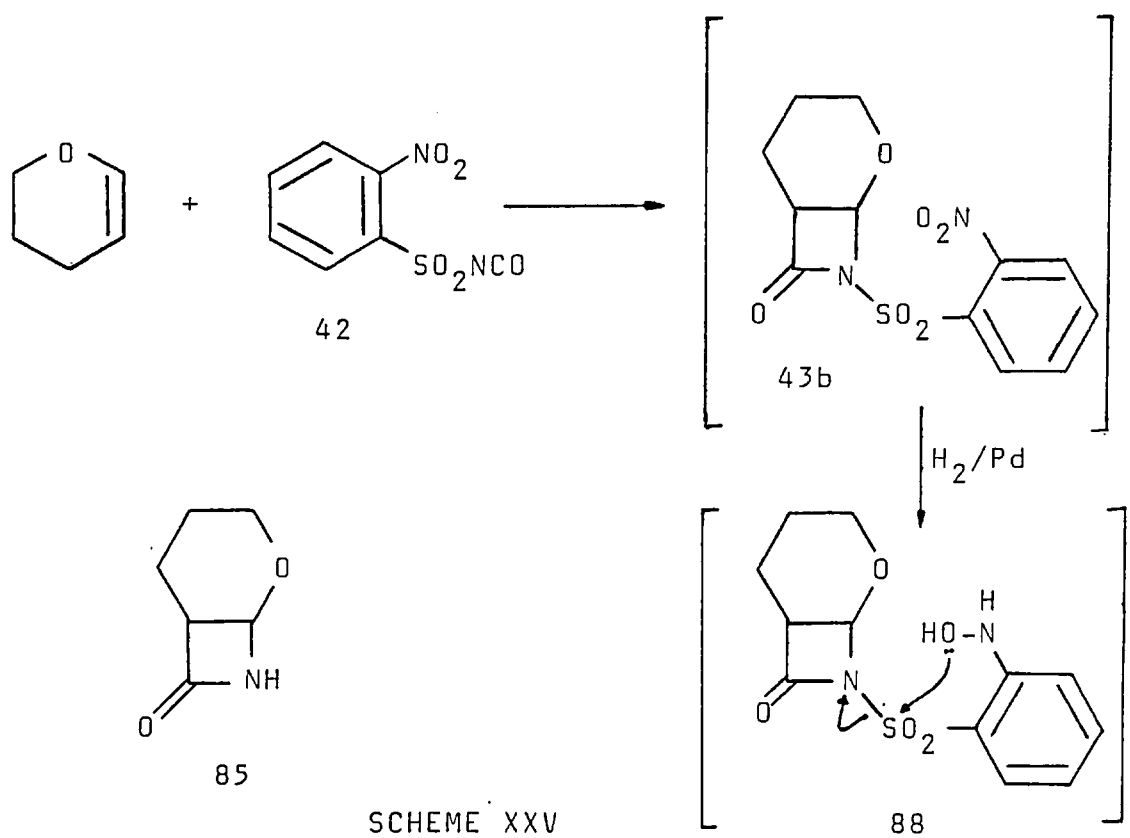
With the problems encountered in N-deprotecting the 2,2,2-trichloroethylsulphonyl β-lactam (45a) we decided to find a homogenecus reducing system which could be used in an organic solvent, in the expectation that this would lead to rapid, clean reduction of the β-lactam (45a). With this in mind, we attempted to prepare tetra ^{n}butyl-ammonium dithionite from sodium dithionite and either tetra n-butylammonium iodide or tetra n-butylammonium sulphate without any success. As an alternative we carried out the deprotection of β-lactam (45a) using sodium dithionite and a phase transfer catalyst. This system proved most satisfactory, though the reaction was again fairly slow and did not go to completion. In the presence of 15-Crown-5, a reasonable degree of N-deprotection was achieved in a clean reaction.

The N-deprotection of 1-(2,2,2-trichloroethylsulphonyl)-1-azaspiro[3,5]non-2-one (45a)		
Reductant	Reaction Time	Product
Zn/NH_4OAc THF/H_2O	5 weeks	86 (19%), 87 (68%)
$Na_2S_2O_4$, DMF tetra n-butylammonium iodide	2 weeks	starting material (17%), 86 (24%)
$Na_2S_2O_4$, DMF 15-Crown-5	2 weeks	starting material (21%), 86 (72%)

TABLE III

Removal of the 2-Nitrobenzenesulphonyl group

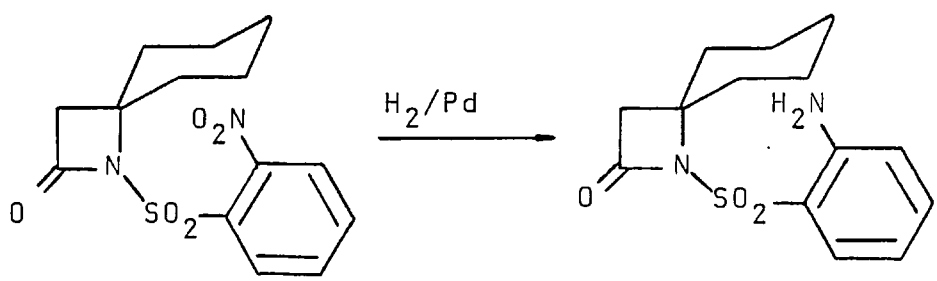
Despite the fact we had been unable to isolate a β-lactam from the reaction of 3,4-dihydro-2H-pyran and 2-nitrobenzenesulphonyl isocyanate (42), we decided to attempt to deprotect the intermediate β-lactam (43b) when its concentration in the reaction mixture reached a maximum. Accordingly, we reacted 3,4-dihydro-2H-pyran with the isocyanate (42) in chloroform at 0°C and after 3h



SCHEME XXV

removed the solvent keeping the mixture cold. The resulting oil, which still contained an absorbtion of 1800cm^{-1} in its infra red spectra, was then hydrogenated. No β-lactam was evident in the intractable mixture of products.

In order to investigate further the removal of the 2-nitrobenzenesulphonyl group, the analogous spiro β-lactam (45b) was also hydrogenated. The sole product from this, however, was the amine (89) (78%). We had anticipated that in hydrogenating the nitro group, the intermediate hydroxylamine could attack the sulphonyl group, (Scheme XXV), liberating the β-lactam nitrogen. It is reasonable to suppose that reduction of the nitro function is rapid compared to attack of the intermediate hydroxyl amine (88) on the sulphonyl group.

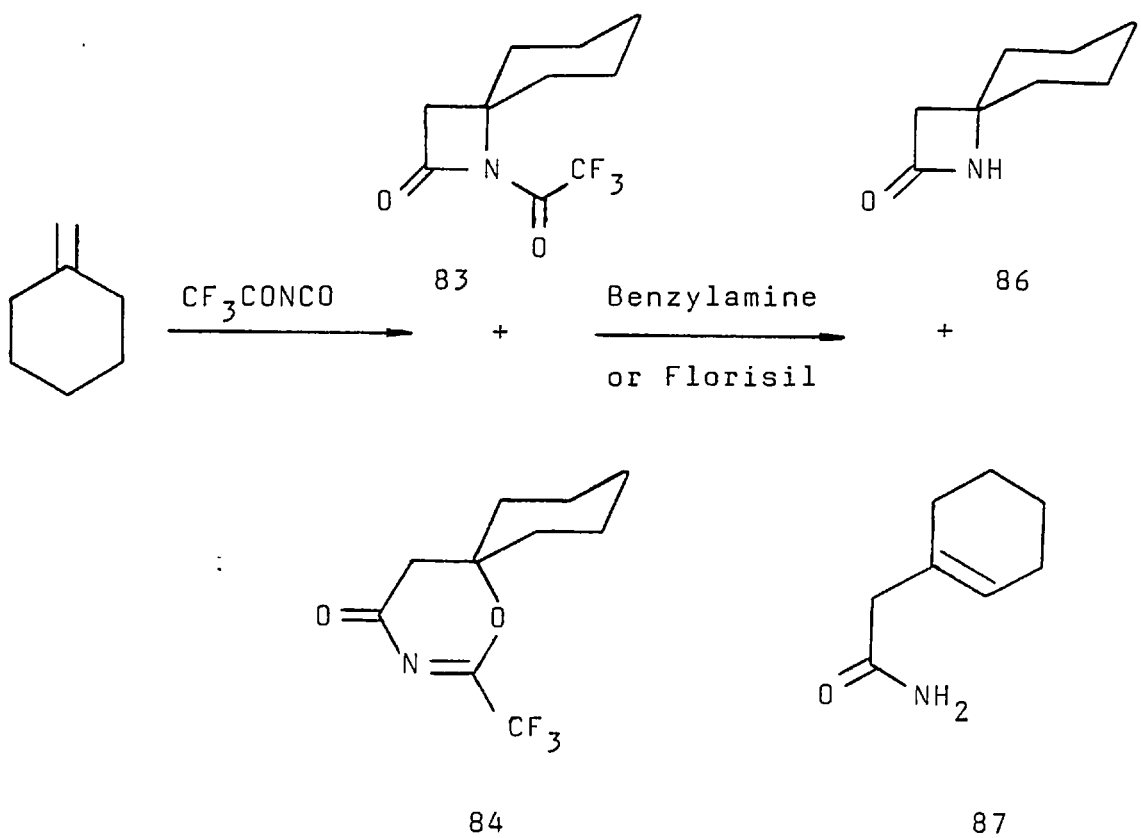


45b 89

Removal of the Trifluoroacetyl group

The reaction of trifluoroacetyl isocyanate (79) and methylenecyclohexane produced a mixture of the spiro β-lactam (83) and the oxazinone (84). This mixture was successfully N-deprotected by two procedures. Treatment of the mixture, at low temperature, with benzylamine in

THF solution, or chromatography of the mixture on Florisil, both yielded a mixture of the free β-lactam (86) and the amide (87). The yields were not high,

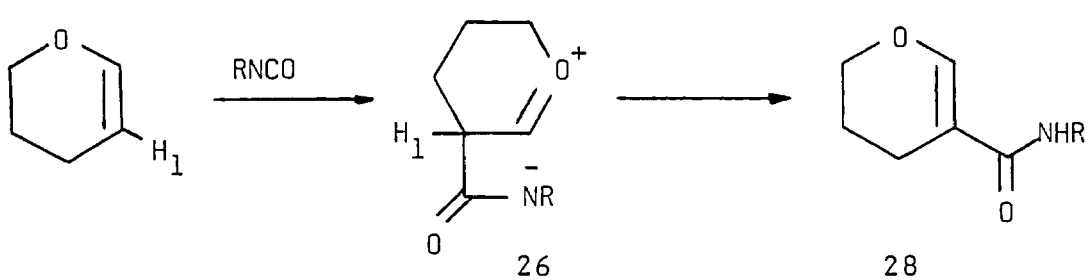


however it is clear from a comparison of the ratio of the two N-trifluoroacetyl compounds (83) and (84) with the isolated yields of β-lactam (86) and amide (87), that some of the azetidinone (86) was lost during isolation.

N-deprotection of β-lactam (83) and oxazalone (84)		
Ratio 83:84	Deprotection conditions	Product
7:3	Benzylamine -78°C	β-lactam (86) 34%, amide (87) 11%
7:3	Florisil	β-lactam (86) 37%, amide (87) 31%

TABLE IV

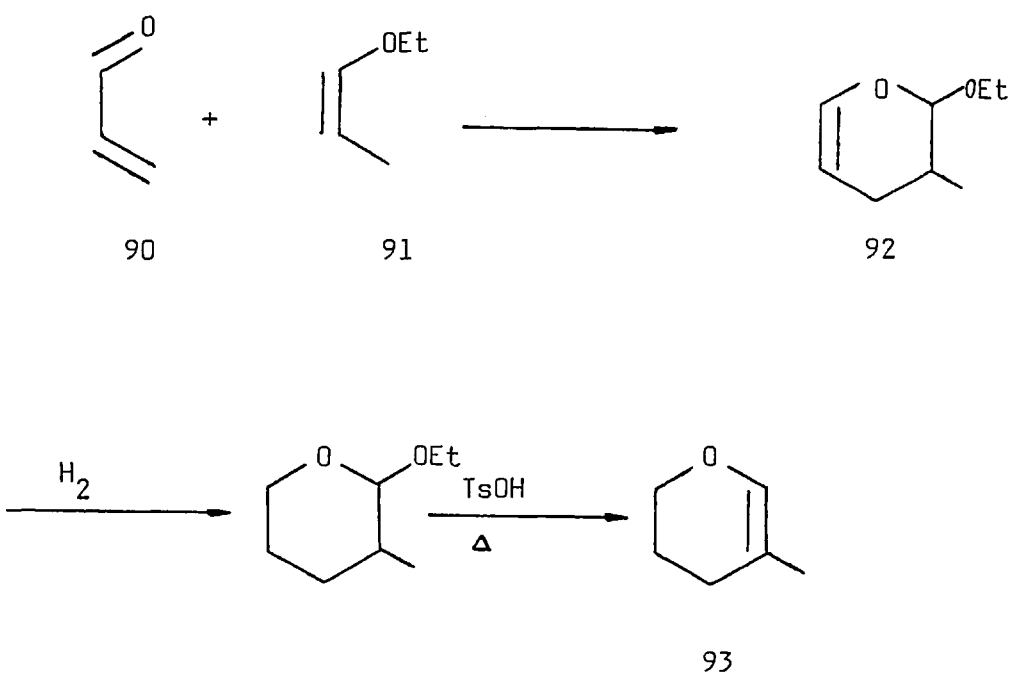
The failure to form a stable β-lactam, on reaction of 3,4-dihydro-2H-pyran with any of our isocyanates, can not be totally ascribed to the electron withdrawing power of the nitrogen substituent. The presence of a proton (H_1), β to the pyran oxygen results in a ready pathway from the intermediate zwitterion (26) to produce the α,β-unsaturated amide (28) (Scheme XXVI). In order to overcome this, 5-substituted 3,4-dihydro-2H-pyran (93) and (102) were prepared and reacted with 2,2,2-trichloroethoxysulphonyl (22), methoxalyl (73), trifluoroacetyl (79) and chlorosulphonyl isocyanates.



26 28

SCHEME XXVI

5-Methyl-3,4-dihydro-2H-pyran (93) has been described in the literature and was prepared with ease[36,37] (Scheme XXVII). Cycloaddition of acrolein (90) with ethyl propenyl ether (91) resulted in the formation of 3-ethoxy-2-methyl-3,4-dihydro-2H-pyran (92) which, after hydrogenation and elimination of ethanol gave the required dihydropyran (93). Reaction of dihydropyran (93) with chlorosulphonyl isocyanate and isocyanates (22), (73) and (79) resulted in the formation of β-lactams (94a), (94b) and (94c). The β-lactams could not be isolated without decomposing but the reaction appeared to proceed cleanly



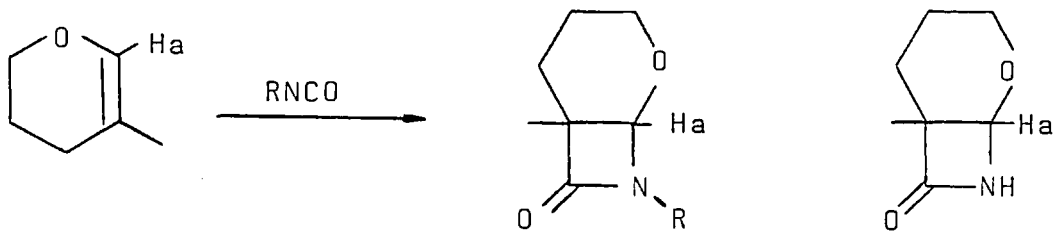
SCHEME XXVII

and in good yield as judged by both NMR and infra red spectroscopy (Scheme XXVIII). β-Lactams (94a), (94b) and (94c) were stable enough to have the solvent removed without decomposing, and survived for several weeks at -20°C, although at room temperature they totally decomposed in 1 week. Of the isocyanates used only methoxalyl isocyanate (73) showed no sign of reaction with 5-methyl-3,4-dihydro-2H-pyran (93).

Reaction of 5-Methyl-3,4-dihydro-2H-pyran with various isocyanates

Isocyanates	Solvent	Temp.	Reaction Time	Product
$ClSO_2NCO$	$CHCl_3$	-18°C	10 min	β-lactam (94a)
$Cl_3CCH_2OSO_2NCO$ (22)	$CHCl_3$	RT	2 days	β-lactam (94b)
CF_3CONCO (79)	$CHCl_3$	RT	12 hr	β-lactam (94c)
MeOCOCONCO (73)	$CHCl_3$	RT	5 weeks	No reaction
MeOCOCONCO (73)	$CHCl_3$	45°C	5 weeks	No reaction

TABLE V



93 R = a SO_2Cl 94 95

b $SO_2OCH_2CCl_3$

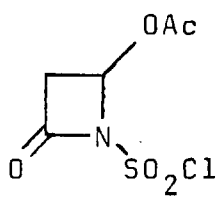
c $COCF_3$

d COCOOMe

SCHEME XXVIII

The N-substituents of the bicyclic β-lactams (94b) and (94c) had both been previously removed from β-lactams by ourselves and several methods exist in the literature for the removal of an N-sulphonyl chloride from a β-lactam.[38,35] We were, therefore, full of hope as we examined the N-deprotection of β-lactams (94a), (94b) and (94c). Removal of the N-chlorosulphonyl group from β-lactam (94a) was attempted, without success, using sodium sulphite and sodium bicarbonate in both aqueous THF, and the two phase water/chloroform system at low temperature.[38] A similar lack of success resulted when attempting to bring about this transformation using either thiophenol and pyridine or propan-1,3-dithiol and ethyldiisopropylamine.[35] In each case complete loss of the β-lactam moiety was noted. Given that, on attempting to

deprotect the analogous N-toluene-4-sulphonyl β-lactam (3a) it had been shown to be water sensitive; it is not surprising that the sodium sulphite method of removing the N-sulphonyl chloride group from β-lactam (94a) failed. The reason for the failure of the remaining deprotections is not known. This result was particularly disappointing as these same methods had been successful in N-deprotecting N-chlorosulphonyl-4-acetoxyazetidin-2-one (96).



96

Treatment of the N-2,2,2-trichloroethoxysulphonyl β-lactam (94b) with zinc/copper couple resulted in the slow loss of the starting β-lactam at room temperature.[40] At 50°C, however, the reaction was complete overnight. Both reactions resulted in the formation of an oil and a white solid. The oil contained a complex mixture of products, but did show a carbonyl absorbtion at 1750cm^{-1}, which corresponds to the deprotected β-lactam (95). On attempted isolation, however, this material decomposed. In view of the zinc/copper couple reductions of the spiro β-lactam (111), it was thought that the white solid could be the zinc salt of β-lactam (95). Atomic analysis

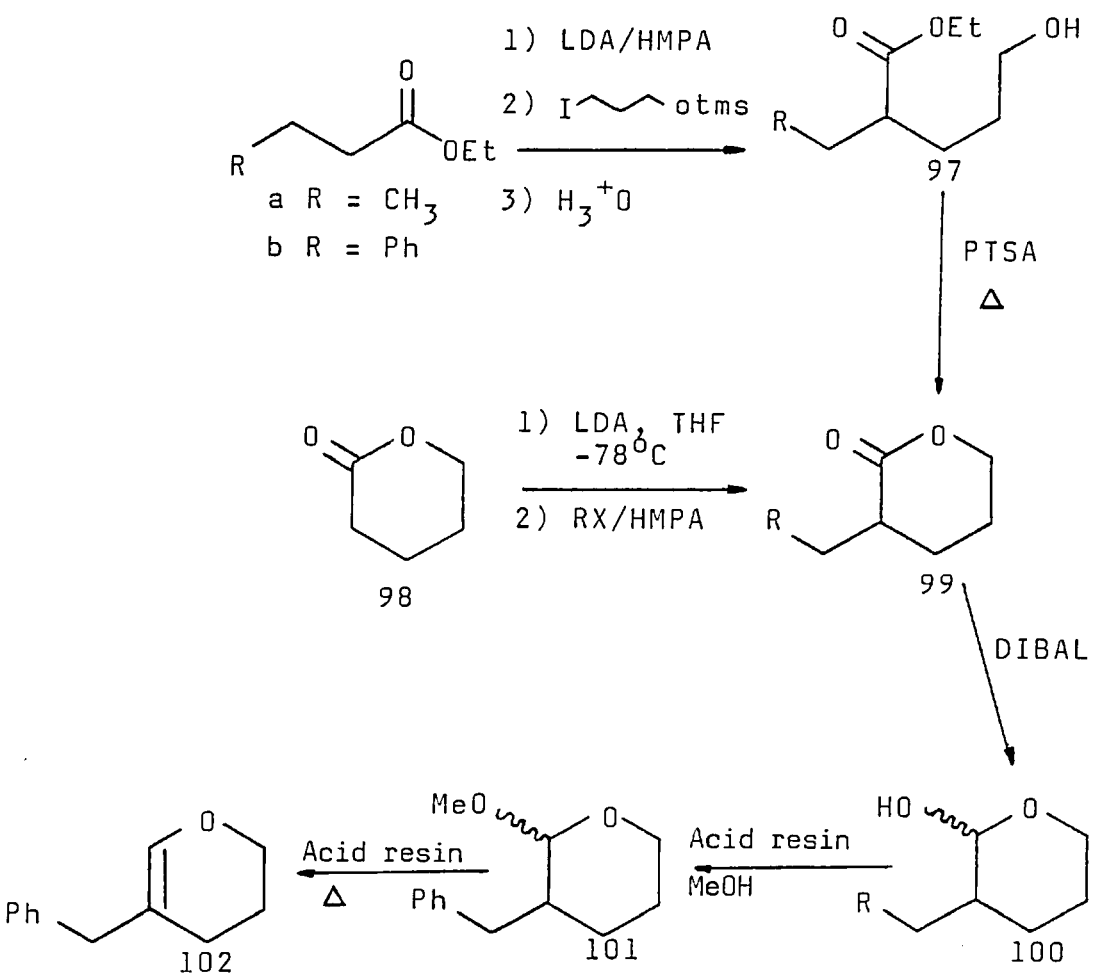
confirmed the presence of zinc, however, treatment with hydrogen sulphide or acid failed to liberate any of the NH β-lactam (95). The deprotection of β-lactam (94b) was also attempted using freshly prepared aluminium amalgam.[41] This resulted in the slow loss of the starting β-lactam (94b) and gave a complex mixture of products. Again a weak absorbtion was visible at 1760cm^{-1} in the infra red spectrum, but it was not possible to isolate the component with this absorption.

The deprotection of the last of these bicyclic β-lactams (94c) finally *ful*filled our twin objectives, of both forming a β-lactam from an enol ether, and deprotecting it under mild conditions. Treatment of β-lactam (94c) with benzylamine at low temperature gave, after purifying, a 41% yield of the NH β-lactam (95). This β-lactam was also obtained, in a much better yield of 62%, by eluting β-lactam (94c) down a florisil column with diethylether.[25] The latter method of deprotection was more easily performed, gave a better yield and resulted in virtually a single component material (tlc).

The N-deprotection of the N-trifluoroacetyl β-lactam (94c)	
Deprotecting System	Product
Benzylamine -78°C	NH β-lactam (95), 41%
Florisil	NH β-lactam (95), 62%

TABLE VI

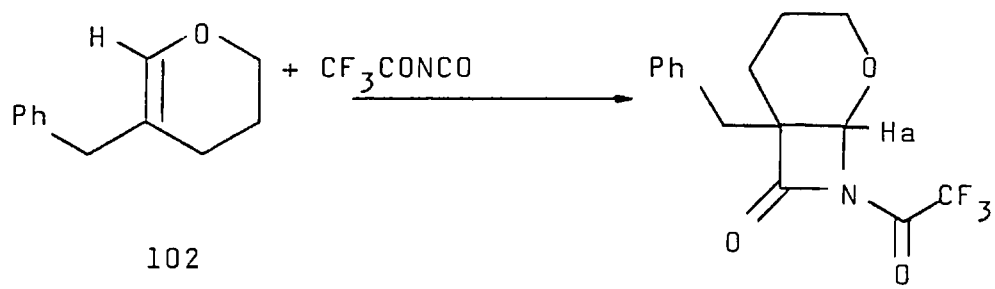
With the successful formation of β-lactam (94c) and its deprotection to β-lactam (95) we decided to prepare a second 5-substituted dihydropyran. 5-Benzyl-3,4-dihydro-2H-pyran (102) was prepared by the route shown (Scheme XXIX). According to Schlessinger it is possible to form the ethyl lactone (99a) from S-valeralactone (98) via metalation with lithium di-isopropylamide followed by treatment with ethyliodide.[42] Repeating this reaction



SCHEME XXIX

using benzyl bromide did not yield any of the benzyl lactone (99b). On repeating Schlessinger's preparation of the ethyl lactone (99a) only a 25% yield was obtained compared to a claimed yield of over 90%.[42] A similar result to ours was obtained by a colleague who devised the route shown to prepare the ethyl lactone (99a).[43] Using this route, the benzyl lactone (99b) was prepared in good yield (87%). Reduction of this with di-isobutylaluminium hydride gave the lactol (100) which was not isolated but taken straight through to the methyl ether (101) in a reasonable yield (53%). After some difficulty the methyl ether was converted to the dihydropyran (102) by heating with Amberlyst IR 120 H resin, the yield for this step was a little lower, however, (40%). A lot of the losses in this step arose during purification and it is likely that this yield could be improved.

Reaction of trifluoroacetyl isocyanate (79) with 5-benzyl-3,4-dihydro-2H-pyran (102) gave the bicyclic β-lactam (103) (Scheme XXX). The reaction was a lot slower than the corresponding reaction with 5-methyl-3,4-dihydro-2H-pyran (102) had been; taking three weeks for the complete consumption of the isocyanate (79) although not consuming all of the dihydro pyran (102). Attempting to increase the rate of reaction, by increasing the temperature, resulted in the formation of a mixture of the bicyclic β-lactam and several unidentified compounds. On chromatography of the N-trifluoroacetyl-β-lactam (103) on florisil using diethylether as eluent, the free NH β-lactam



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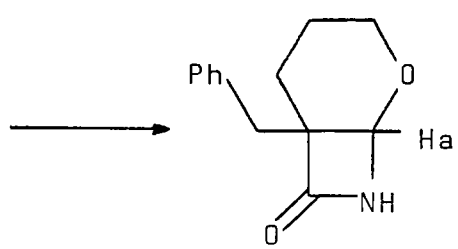
103

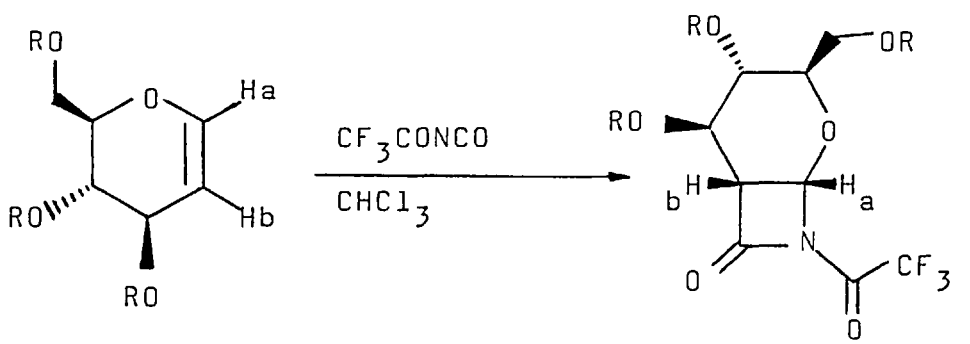


104

SCHEME XXX

(104) was obtained in modest yield (40%) together with some starting dihydropyran (102) (25%).

Our spirits boosted by our success with the 5-substituted dihydropyrans (93) and (102) we again turned our attention to the reaction of trifluoroacetyl isocyanate (79) with glucals. 3,4,6-Tri-O-benzyl-D-glucal (105a) reacted slowly with trifluoroacetyl isocycanate (79) to give a single product, although reaction did not go to completion (Scheme XXXI). This product appeared to be the β-lactam (105a), although this could not be isolated. Analysis of the reaction mixture clearly showed an absorption at 1800cm^{-1} in the infra red spectrum. The position of the doublet due to the proton, Ha, in the NMR spectra was also seen to move from 6.3 to 5.85. This is the same shift as was observed for the



105

a R = Bz

b R = TMS

c R = H

106

a R = Bz

b R = TMS

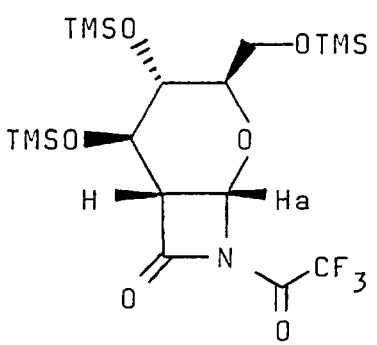
SCHEME XXXI

corresponding proton, Ha, in the reaction of trifluoroacetyl isocyanate (79) with both 5-substituted dihydropyrans (93), and (102). The coupling constant associated with proton Ha is 5.5Hz and indicates the expected cis stereochemistry across the ring junction.

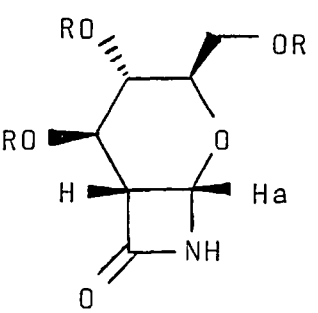
Treatment of glucal (105c) with trimethylsilyl chloride and pyridine resulted in the formation of 3,4,6-tri-O-(trimethylsilyl)-D-glucal (105b) in high yield.[44] This was reacted, without purification, with trifluoroacetyl isocyanate (79). The reaction was complete after 2 weeks, as judged by both infra red and NMR spectroscopy, to give the β-lactam (106b) as the major product. The β-lactam carbonyl was clearly visible in the infra red spectrum at 1820cm^{-1}, with a second absorption at 1740cm^{-1} due to the trifluoroacetyl carbonyl. NMR spectroscopy again showed a shift in the absorption of proton (Ha) of the bicyclic β-lactam (106b), from 6.05 to 5.6. This compares favourably with the shift in the absorption of the corresponding proton, Ha, in the reaction of trifluoroacetyl isocyanate (79) with both 5-substituted dihydropyrans (93) and (102). A coupling constant of J=5.5Hz was observed for the ring junction proton (Ha), in the NMR spectrum of bicyclic β-lactam (106b) indicating cis stereochemistry across the ring junction. The reaction was not very clean, several doublets appearing in the region of 6.0- 5.5 in the NMR spectrum, as well as an absorption at 1775cm^{-1} in the infra red spectrum. In the reaction of trifluoroacetyl isocyanate (79) with both sugars (105a) and (105b), the

use of acetonitrile resulted in complex mixture of products. The highest yields of the β-lactams (106a) and (106b) appeared to result from reaction of the isocyanates (79) and glucals (105a) and (105b) in concentrated chloroform solution.

The β-lactam (106a) derived from the benzyl sugar (105a) was chromatographed on florisil with diethyl ether as eluent, however, the resulting oil contained no β-lactam. The presence of the starting sugar (105a) could be detected in the product by NMR spectroscopy, though none of the other products could be identified. On eluting the β-lactam (106b) down a florisil column a mixture of products was obtained (Scheme XXXII). Infra red and NMR spectra revealed that the trimethylsilyl protected β-lactam (107a) was a major component of this mixture. The β-lactam carbonyl was clearly visible at 1755cm^{-1} in the infra red spectrum, and the NMR spectrum revealed not only the presence of the trimethylsilyl group, but a doublet at 5.25, J=5Hz, due to the ring junction proton Ha. Again the shift in this proton mirrored the shift of the corresponding proton in the deprotections of the bicyclic β-lactams (94) and (103).



106b

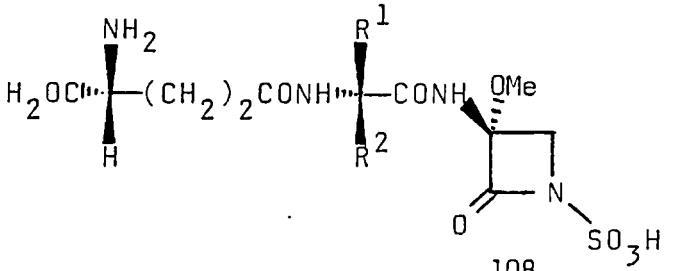


107 a R = TMS
b R = H

It had been expected that, on chromatography of florisil, the β-lactam (106b) would be O-deprotected to give the triol (107b). With the trimethylsilyl groups still in position the problem arose of how to isolate the deprotected β-lactam (107a). Chromatography on silica would not be feasible with the TMS groups present and so their removal was effected by treatment with acid. This resulted in the formation of an intractable gum, the infra red spectrum of which revealed a mixture of products, possibly containing a β-lactam. The presence of hydroxyl groups, as indicated by infra red spectroscopy, showed that the trimethylsilyl groups had been removed, however, separation of the products was not possible. A second sample of protected β-lactam (106b) was treated with florisil yielding a mixture of the NH β-lactam (107a) and several unidentified products. Judging by NMR spectroscopy the mixture contained 25-30% of the β-lactam (107a) however, tlc on alumina revealed numerous, close running compounds. With the realisation that β-lactam (107a) could not be isolated by chromatography on alumina, the mixture was not investigated further.

Studies directed towards the formation of β-lactams containing the N-sulphonic acid function via the cycloaddition of an oxysulphonyl isocyanate and an olefin

At this stage, we decided to explore the possibility of reducing the N-trichloroethoxysulphonyl group to the N-sulphonic acid. This would be of great interest as this residue is found in the naturally occurring monolactams, sulfazecin (108a) and isosulfazecin (108b).[45]



108

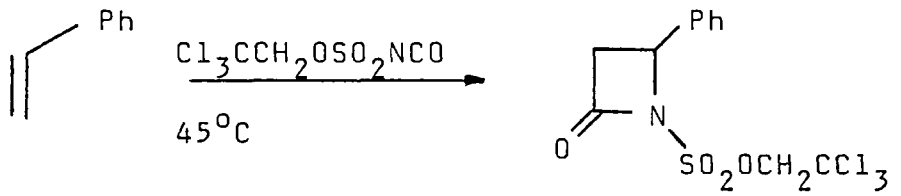
a $R^1 = CH_3$ $R^2 = H$

b $R^1 = H$ $R^2 = CH_3$

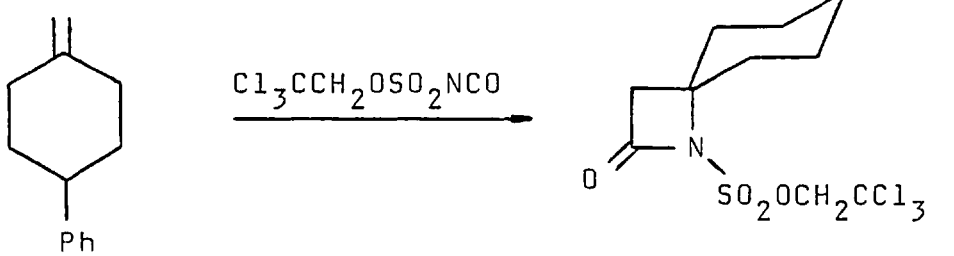
The presence of the N-sulphonic acid is likely to make this compound water soluble. Since the reducing systems envisaged involve partitioning between water and an organic solvent, this could present a problem in isolating any N-sulphonic acid β-lactams formed. For this reason, it was proposed to use HPLC to both monitor the reactions and isolate the products, however, in order to do this it was necessary to include a UV tag on the molecules.

Reaction of 2,2,2 -trichloroethoxysulphonyl isocyanate (22) with styrene lead to the azetidinone (109) in 55% yield. Initially the reaction was conducted at room temperature and lead to a complex mixture of products.

On increasing the temperature of the reaction mixture and concentration of the reagents, the β-lactam (109) was obtained cleanly (Scheme XXXIII). 1-Methylene-4-phenylcyclohexane (110) was prepared in 37% yield from the Wittig condensation reaction of 4-phenylcyclohexane with methylenetriphenylphosphorane.[46] Reaction of this with isocyanate (22) gave, in 69% yield, the spiro β-lactam (111) (Scheme XXXIV).

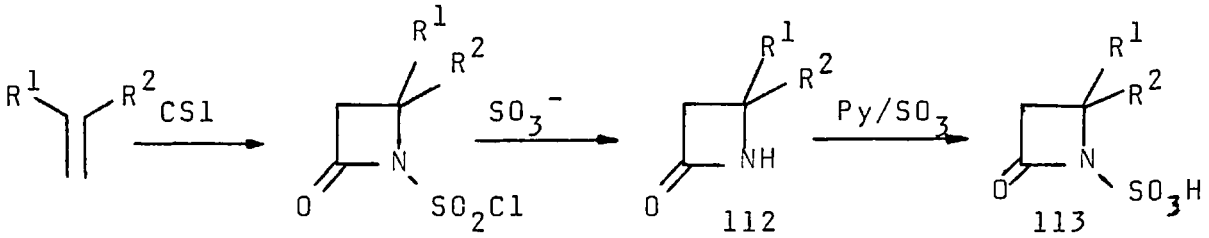


SCHEME XXXIII 109



110 SCHEME XXXIV 111

With both of these systems, authentic samples of the N-sulphonic acid β-lactams (113a) and 113b) were prepared. Reaction of methylene-4-phenylcyclohexane (110) or styrene with chlorosulphonyl isocyanate, followed by de-sulphonylation with sodium sulphite, afforded the azetidinones (112a) and (112b). Treatment of these with the pyridine/sulphur trioxide complex then gave the β-lactams (113a) and (113b) (Scheme XXXV).[47] The original



a R_1 = H R_2 = Ø

b R_1, R_2 = (C_5H_{10})Ø

SCHEME XXXV

work up for the reaction involved acidifying a solution of the pyridinium sulphonate and extracting with dichloromethane.[47] This proved unsatisfactory as it was very difficult to obtain the correct pH and so the sulphonic acids (113a) and (113b) were liberated by ion exchange chromatography.

The β-lactams (113a) and (113b) were found to have too long a retention time on silica HPLC, and to come through virtually with the front on reverse phase HPLC. Increasing the chain length of the reverse phase packing material did not increase their retention time sufficiently and so an ion pairing agent, Waters pic A reagent, was added to the eluant. The N-sulphonic acid, long chain amine ion pair which was formed with the pic A reagent, increased the retention times of the β-lactams (113a) and (113b) on a reversed phase column and so made their detection possible.[48]

Reduction of the β-lactam (109) with triethylenediaminechromium II perchlorate in DMF resulted in its conversion into the azetidinone (112a) in good yield.[49]

The N-deprotection of N-(2,2,2-trichloroethoxysulphonyl) β-lactams with chromous complexes		
β-lactam	Reductant	Product
109	$Cr^{II}(en)x$	instantaneous reduction to 112a 87%
109	$Cr^{II}(ClO_4)_2$	instantaneous reduction to 112a 94%
111	$Cr^{II}(en)x$	instantaneous reduction to 112a 38%

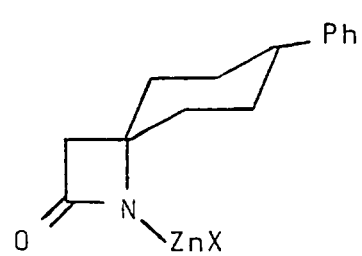
2-Oxo-4-phenylazetidine-1-sulphonic acid (113a) was detected by HPLC during the reaction or on work up. The reduction was rapid, the purple colour of the complex being discharged within 2 minutes. Chromium II perchlorate effected the same transformation in even better yield. With the spiro β-lactam (111) triethylenediamine-chromium II perchlorate again resulted in very rapid reduction to the azetidinone (112b), although in lower yield. The chromous complexes are homogeneous reducing systems and afford a high degree of control over the amount of reductant used. We had hoped in this way to prevent any possible over reduction of the 2,2,2 -trichloroethoxysulphonyl group and thus obtain the N-sulphonic acid β-lactams (113a) and (113b). It had been anticipated that the reduction of the 2,2,2 -trichloroethoxysulphonyl group would require 2 electrons per molecule and accordingly 2 equivalents of the chromous complex had been used. When just one equivalent of the chromous complex was employed, work up resulted in a mixture of starting material (109), azetidinone (112a) and several minor, unidentified compounds. HPLC of the mixture revealed no 2-oxoazetidine sulphonic acid derivatives before or after work up.

Our previous attempts to deprotect N-2,2,2 -trichloroethoxysulphonyl β-lactams (25) and (45a) using zinc in an organic solvent had failed. Using a zinc/copper couple, however, we were able to effect this trans formation.[48] In the case of the β-lactam (109) a very good yield of the azetidinone (112a) was obtained on treatment

The N-deprotection of β-lactams (109) and (111) using zinc/copper couple					
β-lactam	Amount Zn/Cu	Temp.	Reaction Time	Solvent	Products
109	1.3eq	45°C	24hr	THF	112a (97%)
109	0.6eq	45°C	3d	THF	112a (54%) 109 (25%)
109	4.7eq Zn	45°C	3d	THF	112a (76%) 109 (14%) (activated zinc used)
109	0.6eq	45°C	7d	Et_2O	no reaction, even when extra Zn/Cu (3eq) added
111	1.7eq	RT	24hr	THF	solid intermediate columned on silica, 112b (26%) 111 (4%)
111	1.7eq	55°C	48hr	THF	solid intermediate columned on silica, 112b (42%)
111	1.5eq	45°C	24hr	THF	solid intermediate treated with HCl 112b (37%)
111	7.7eq	45°C	24hr	THF	solid intermediate treated with HCl 112b (41%)

TABLE VII

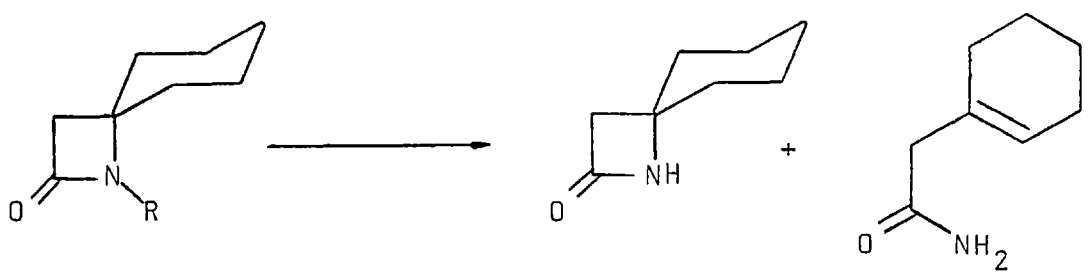
with a slight excess of the couple in THF. As with the previous reducing system it had been anticipated that, by not having a large excess of reductant, the reduction could be stopped at the N-sulphonic acid stage. Again it was found that the use of one electron equivalent resulted in incomplete reaction and gave none of the N-sulphonic acid (113a). β-lactam (109) was also found to be reduced to the azetidinone (112a) by activated zinc in THF. The reaction did not go to completion, even though a larger excess of zinc was used, indicating that zinc alone is not as effective a reductant as the couple. In the reduction of the spiro β-lactam (111) the process again yielded the azetidinone (112b), although in much lower yield. The two β-lactams, (109) and (111), behaved very differently in this reaction. The first β-lactam (109), remained in solution at all times, whereas in the case of the spiro β-lactam (111), a white precipitate formed. This solid was sparingly soluble in hot THF and contained a carbonyl absorption at 1720cm^{-1} in the infra red spectrum. On treatment of the precipitate with acid, either by dissolving it in hydrochloric acid or eluting it through a column of silica, the azetidinone (112b) was obtained. Atomic analysis of the white solid revealed the presence of zinc, although only as one quarter of the theoretical quantity corresponding to the salt (114), and it was proposed that the solid was the



114 x = ?

zinc salt of the azetidinone (114). An attempt to liberate the azetidinone (112b) from the zinc salt (114) by treatment with hydrogen sulphide did not succeed, though this could be as a result of the insoluble nature of the zinc salt (114). It is likely that in the reduction of the mono cyclic N-2,2,2 -trichloroethoxy-sulphonyl β-lactam (109) with the zinc/copper couple, the zinc salt was also obtained initially, however, as this was soluble it was more easily dealt with and was never isolated.

In both the triethylenediamine chromium II perchlorate and zinc/copper couple reductions, the yields of azetidinone (112b) from the spiro β-lactam (111) were lower than the yields of the azetidinone (112a) from the monocyclic β-lactam (109). This is not due to the 2,2,2 - trichloroethoxysulphonyl group being less easily reduced, as this would only result in slower reduction. The problem appears to lie in the stability of the spiro system. It is to be remembered that in the N-deprotection, with zinc under neutral conditions, of the spiro β-lactam (25), and to a greater degree the β-lactam (45a), a second process leading to the amide (87) occurred, Scheme XXXVI.



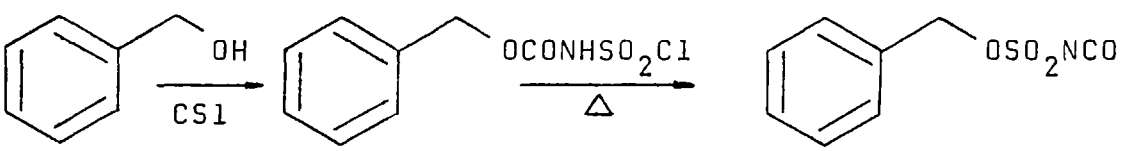
25 R = $Cl_3CCH_2OSO_2$ 86 87

45a R = $Cl_3CCH_2SO_2$

SCHEME XXXVI

Although a comparable compound was not identified in the reduction of β-lactam (111), it is likely that a similar process is resulting in the loss of β-lactam in the reactions of β-lactam (111). That this process is occurring is supported by the observation that the yield of the intermediate solid is much greater than the eventual yield of the azetidinone. The acid treatment necessary to convert one to the other being responsible for the loss of β-lactam.

Having failed to reduce the N-2,2,2 -trichloro-ethoxysulphonyl β-lactams (109) and (111) to the N-sulphonic acid β-lactams (113a) and (113b), we attempted to prepare benzyloxysulphonyl isocyanate (116). It was anticipated that this isocyanate would give β-lactams with olefins which, upon hydrogenation, would yield 2-oxoazetidine-1-sulphonic acid derivatives.



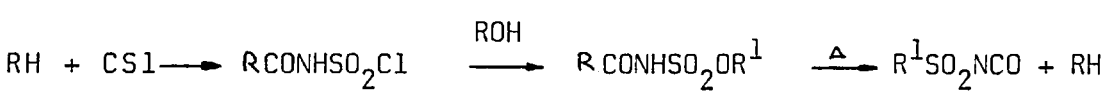
115 116

SCHEME XXXVII

The isocyanate (116) was apparently formed by reacting chlorosulphonyl isocyanate with benzyl alcohol initially at room temperature and subsequently at 100°C.[8] Even after several fractional distillations, however, it

was not possible to separate the isocyanate (116) from an unknown impurity. It was thought, from the NMR spectrum of the mixture, that the impurity was derived from the solvent, toluene. On attempting to perform the rearrangement of the intermediate urethane (115) in a different solvent, however, only polymer was obtained.

Similar isocyanates, including methoxysulphonyl isocyanate (120a) and allyloxysulphonyl isocyanate (120c) had previously been prepared by the thermolysis of N-substituted sulphonamides (119b) and (119d), scheme XXXVIII. Attempts to prepare benzyloxysulphonyl isocyanate (116) by this route via (119b) or (119d) failed, even when using temperatures in excess of those reported in the literature and attempts to prepare this isocyanate were abandoned.



117 118 119 120

a R = 2,4,6-$Cl_3C_6H_2O$, R^1 = CH_3-

b R = 2,4,6-$Cl_3C_6H_2O$, R^1 = $PhCH_2$-

c R = succinimido R^1 = CH_2CHCH_2-

d R = succinimido R^1 = $PhCH_2$-

SCHEME XXXVIII

CONCLUDING REMARKS

Despite the claim that sulphonyl isocyanates react with enol ethers to give β-lactams, our research has shown that this reaction is not general. Only where the electron withdrawing power of the sulphonyl substituent is sufficiently low, as in toluene-4-sulphonyl isocyanate (2a), is the resulting β-lactam stable. Unfortunately, it is not possible to remove the toluene-4-sulphonyl group from a β-lactam without the loss of a β-lactam moiety.

We have been able to show, however, that trifluoro-acetyl isocyanate (79) does give β-lactams on reaction with enol ethers or glucals. Furthermore, it is possible to N-deprotect these β-lactams under very mild conditions.

Although we were unable to prepare any N-sulphonic acid β-lactams using the isocyanates at our disposal, this approach is attractive and might still prove successful.

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EXPERIMENTAL

GENERAL EXPERIMENTAL DETAILS

Melting points were determined using a Koffler hot stage melting point apparatus.

Infra-red spectra were recorded using a Perkin Elmer 298 or 257 grating infra-red spectrophotometer.

^{1}H Nuclear magnetic resonance spectra were recorded on either a Varian T60 60MHz spectrometer, a Varian E.M. 360 60MHz spectrometer or a Brucker W.M. 250MHz spectrometer.

Mass spectra have been recorded as the ten strongest peaks in descending order.

Thin layer chromatography was performed on Merck pre-coated GF 254 silica-gel plates.

Medium pressure column chromatography was performed on Merck Kieselgel 60M.

The following abbreviations were used:

THF = Tetrahydrofuran

DMF = Dimethylformamide

Experiment 1

The Preparation of 1-(Toluene-4-sulphonyl)-1-azaspiro-[3,5]-nonan-2-one (9).

Toluene-4-sulphonyl isocyanate (2a) (0.21g, 1mmol) was added to a solution of methylenecyclohexane (0.1g, 1mmol) in chloroform (4ml). After four weeks the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title compound (0.27g, 89%), m.p. 144-145°C. ν_{max} (nujol mull) 1785 (s), 1595 (w), 1150 (s), and 690 (m) cm^{-1}, δH ($CDCl_3$) 7.83 and 7.23 (4H, ABq, J = 8Hz), 2.7 (2H, s), 2.4 (3H, s), and 2.4-0.9 (10H, m), m/e 96, 83, 81, 85, 91, 67, 47, 68, 155 and 55 (Found: C, 61.49; H, 6.54; N, 4.80. $C_{15}H_{19}NO_3S$ requires C, 61.41; H, 6.53; N, 4.77%).

Experiment 2

The Attempted Reaction of Toluene-2-sulphonyl Isocyanate (2a) with 3,4,6 -Tri-O-acetyl-D-glucal (10)

Toluene-4-sulphonyl isocyanate (2a) (0.21g, 1mmol) was added to a solution of 3,4,6 -tri-O-acetyl-D-glucal (0.27g, 1mmol) is chloroform (4ml). After four weeks at room temperature no reaction was evident.

Experiment 3

The Preparation of N-(Toluene-4-oxysulphonyl)-5,6-dihydro-4H-pyran-3-carboxamide (13b)

1) Toluene-4-oxysulphonyl isocyanate (11b) (0.43g, 2mmol) was added to a solution of 3,4-dihydro-2H-pyran (0.17g, 2mM) in chloroform (4ml). After leaving overnight

at room temperature the solvent was removed under reduced pressure and the residue was recrystallised from dichloromethane to give the title compound (13b) (0.36g, 61%) as white needles, m.p. 117°C, ν_{max} (nujol) 1705 (s), 1630 (s), 1500 (s), 1180 (s), 1145 (s), 1030(s), 875(s) and 830(s)cm^{-1}, δH ($CDCl_3$) 7.65 (1H, s), 7.25 (4H, s), 4.15 (2H, t, J = 5.5Hz), 2.38 (3H, s), 2.25 (2H, t, J = 5.5Hz), and 1.95 (2H, m), m/e 108, 107, 77, 111, 79, 187, 55, 85, 109 and 91 (Found: C, 52.29; H, 5.05; N, 4.69. $C_{13}H_{15}NO_5S$ requires C, 52.52; H, 5.09; N, 4.71%).

2) The above experiment was repeated except that it was conducted at 0°C. After leaving overnight the solvent was removed under reduced pressure to give the title compound (13b) (0.41g, 69%).

3) The above experiment was repeated except that it was conducted at -78°C. After leaving overnight, the solvent was removed under reduced pressure to give the title compound (13b) (0.38g, 64%).

Experiment 4

The Preparation of 1-(Toluene-4-oxysulphonyl)-1-azaspiro [3,5]-non-2-one (14a)

Toluene-4-oxysulphonyl isocyanate (11b) (0.21g, 1mmol) was added to methylenecyclohexane (0.1g, 1mmol) in carbon tetrachloride (2ml). After 1 week at room temperature the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title compound (14a) (0.30g, 97%), m.p. 89-90°C, ν_{max} ($CHCl_3$) 3440 (s), 2940 (m), 1795 (s), 1660 (m), 1390 (s), 1180 (s) and 1050 (m) cm^{-1}, δH ($CDCl_3$)

7.13 (4H, s), 2.76 (2H, s), 2.33 (3H, s) and 2.15-0.8 (10H, m), m/e 96, 81, 244, 67, 93, 95, 18, 55, 106 and 108 (Found: C, 58.28; H, 6.20; N, 4.56. $C_{15}H_{19}NO_4S$ requires C, 58.23; H, 6.19; N, 4.53%).

Experiment 5

The Attempted Reaction of Toluene-4-oxysulphonyl Isocyanate (11b) with 3,4,6-Tri-O-acetyl-D-glucal (10)

Toluene-4-oxysulphonyl isocyanate (11b) (0.21g, 1mmol) was added to 3,4,6 -tri-O-acetyl-D-glucal (10) (0.27g, 1mmol) in THF (3ml). After 3 weeks no reaction had occurred.

Experiment 6

The Preparation of N-(4-Methoxybenzeneoxysulphonyl)-5,6-dihydro-4H-pyran-3-carboxamide (13c)

4-Methoxybenzeneoxysulphonyl isocyanate (11c)(0.46g, 2mmol) was added to 3,4-dihydropyran (0.17g, 2mmol) in chloroform (4ml). After leaving overnight at room temperature the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title compound (13c) (0.44, 70%), m.p. 106-107°C, ν_{max} ($CHCl_3$) 3390 (w), 3010 (w), 1725 (s), 1595, (m), 1500 (s), 1430 (s) and 1170 (s) cm^{-1}, δH ($CDCl_3$) 7.55 (1H, s), 7.23, 6.86 (4H, ABq, J = 9Hz), 4.05 (2H, t, J = 6Hz), 3.8 (3H, s) and 2.2-1.4 (4H, m), m/e 124, 111, 123, 109, 55, 95, 210, 83, 81 and 91 (Found: C, 49.80; H, 4.79; N, 4.48. $C_{13}H_{15}NO_6S$ requires, C, 49.83; H, 4.83; N, 4.47%).

Experiment 7

The Preparation of 1-(4-Methoxybenzeneoxysulphonyl)-1-azaspiro-[3,5]-nonan-2-one (14b).

4-Methoxybenzeneoxysulphonyl isocyanate (11c) (0.46g, 2mmol) was added to methylene cyclohexane (0.2g, 2mmol) in chloroform (4ml). After 3 days at room temperature the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title compound (14b) (0.57g, 88%), m.p. 89-90°C ν_{max} (nujol mull) 1790 (s), 1590 (w), 1255 (m), 1180 (s), 1150 (s), 1050 (m), 1025 (m), 875 (m) and 835 (m) cm^{-1}, δH ($CDCl_3$) 7.14 and 6.76 (4H, ABq, J = 9Hz), 3.80 (3H, s), 2.76 (2H, s), and 2.3-0.8 (10H, m), m/e 122, 123, 229, 325 ($M^{+\cdot}$), 41, 108, 95, 67 and 81 (Found: C, 55.30; H, 5.84; N, 4.33. $C_{15}H_{19}NO_5S$ requires, C, 55.37; H, 5.89; N, 4.31%).

Experiment 8

The Attempted Reaction of 4-Methoxybenzeneoxysulphonyl Isocyanate (11c) with 3,4,6 -Tri-O-acetyl-D-glucal (10)

4-Methoxybenzeneoxysulphonyl isocyanate (11c) (0.23g, 1mmol) was added to 3,4,6 -tri-O-acetyl-D-glucal (10) (0.27g, 1mmol) in carbon tetrachloride (2ml). After leaving at room temperature for three weeks no reaction could be observed.

Experiment 9

The Attempted Preparation of 2-Methoxybenzeneoxysulphonyl Isocyanate (16)

Chlorosulphonyl isocyanate (4.5g, 0.032mmol) in dry

xylene (5ml) was added over 30 min. to a solution of 2-methoxyphenol (3.72g, 0.03mmol) in dry xylene (5ml) under nitrogen. On complete addition the mixture was refluxed overnight. A glass-like solid was obtained which contained neither isocyanate nor carbonyl functional groups as shown by the infra red spectrum.

Experiment 10

The Preparation of N-(2,2,2-Trichloroethoxysulphonyl)-5,6-dihydro-4H-pyran-3-carboxamide (24)

2,2,2-Trichloroethoxysulphonyl isocyanate (22) (0.25g, 1mmol) was added to 3,4-dihydro-2H-pyran (0.09g, 1.1mmol) in carbon tetrachloride ($2cm^3$). After leaving overnight at room temperature the solvent was removed under vacuum and the residue recrystallised from dichloromethane to give the title compound (24) (0.26g, 78%), m.p. 134°C, ν_{max} ($CHCl_3$) 3395 (w), 1690 (s), 1610 (s), 1440 (s), 1175 (s), 1090 (s) and 1005 (s) cm^{-1}, δH ($CDCl_3$) 7.67 (1H, s), 5.06 (2H, s), 4.14 (2H, t, J = 6Hz), 2.3 (2H, t, J = 6Hz), and 1.98 (2H, m), m/e 126, 111, 110, 82, 189, 83, 127, 336 ($M^{+\cdot}$), 338 ($M^{+\cdot}$) and 188, (Found: C, 28.08; H, 2.89; N, 4.07. $C_8H_{18}Cl_3NO_5S$ requires C, 28.38; H, 2.98; N, 4.14%.

Experiment 11

The Attempted Preparation of 8-(2,2,2-Trichloroethoxysulphonyl)-8-aza-2-oxabicyclo[4.2.0]octan-7-one (23).

The above experiment was repeated except the reaction was carried out at -20°C. After 20 min. the reaction was complete. Examination of the reaction mixture by infra

red spectroscopy revealed a carbonyl stretch at 1800cm^{-1} which was still present after 1hr. On attempted isolation the product decomposed to give a white solid (0.24g, 71%) which was identical with compound (24) prepared in the previous experiment.

Experiment 12

The Preparation of 1-(2,2,2-Trichloroethoxysulphonyl)-1-azaspiro[3,5]nonan-2-one (25)

2,2,2-Trichloroethoxysulphonyl isocyanate (22) (0.25g, 1mmol) was added to methylenecyclohexane (0.1g, 1mmol) in carbon tetrachloride (2ml). After 2 days the solvent was removed under reduced pressure and the residue was recrystallised from dichloromethane to give the title compound (25) (0.34g, 99%), m.p. 137°C, ν_{max} ($CHCl_3$), 3440 (m), 3360 (m), 1810 (s), 1405 (s), 1170 (m), 1125 (s), and 640 (m) cm^{-1}. δH ($CDCl_3$) 4.8 (2H, s), 2.85 (2H, s) and 2.15-0.90 (10H, m), m/e 96, 81, 67, 54, 68, 55, 41, 97, 95 and 177 (Found: C, 34.36; H, 4.01; N, 3.96. $C_{10}H_{14}Cl_3NO_4S$ requires C, 34.23; H, 4.03; H, 3.99%).

Experiment 13

The Preparation of 1-(2,2,2-Trichloroethoxysulphonyl)-1-aza-7-phenylspiro[3,5]nonan-2-one (111)

2,2,2-Trichloroethoxysulphonyl isocyanate (22) (2.53g, 10mmol) was added to a solution of methylene-4-phenylcyclohexane (1.6g, 9.4mmol) in diethyl ether (3ml) at room temperature. After leaving overnight the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give

the title β-lactam (111) (2.75g, 69%), m.p. 119-120°C, ν_{max} ($CHCl_3$) 1800 (s) (β lactam CO), 1775 (s), 1150 (m), and 980 (m) cm^{-1}, δH ($CDCl_3$) 7.5 (5H, s), 4.9 (2H, s), 3.1 (sH, s) and 3.0-1.8 (9H, m), m/e 104, 91, 79, 117, 156, 214, 77, 76, 80 and 114 (Found: C, 44.90; H, 4.10; N, 3.10. $C_{16}H_{18}Cl_3NO_3S$ requires C, 45.03; H, 4.25; N, 3.28%).

Experiment 14

The Preparation of N-(2,2,2-Trichloroethoxysulphonyl)-4-phenylazetidin-2-one (109)

2,2,2 -Trichloroethoxysulphonyl isocyanate (22) (2.5g, 10mmol) was added to styrene (1.04g, 10mmol) in diethyl ether (1ml). The solution was warmed to 35°C for 2 days. After cooling a white precipitate was filtered off and recrystallised to give the title β-lactam (109) (1.93g, 55%), m.p. 102-104°C, ν_{max} (CH_2Cl_2) 1810 (s), 1380 (m), 1185 (s), 1130 (m), 995 (s) and 850 (m) cm^{-1}, δH ($CDCl_3$, 100 MHz), 7.86 (5H, s), 4.13 (1H, dd, $\underline{J}$ = 7, 4.5Hz), 3.96 (2H, s) and 3.06, 2.60 (2H, ABX system, $\underline{J}_{AB}$ = 18Hz, $\underline{J}_{AX}$ = 7 Hz, $\underline{J}_{BX}$ = 4.5 Hz) m/e 104, 135, 103, 106, 359 ($M^{+\cdot}$), 357 ($M^{+\cdot}$), 78, 77, 168 and 105. (Found: C, 37.0; H, 2.6; N, 3.7. $C_{10}H_{10}Cl_3NO_4S$ requires C, 36.8; H, 2.8; N, 3.9%).

Experiment 15

The Preparation of 1-(2,2,2 -Trichloroethoxysulphonyl)-8-aza-6-methyl-2-oxa bicyclo[4.2.0]octan-7-one (94b)

2,2,2 -Trichloroethoxysulphonyl isocyanate (22) (0.25g, 1mmol) was added to 5-methyl-3,4-dihydro-2H-

pyran (93) (0.1g, 1mmol) and dry chloroform (4ml). After 2 days at room temperature the solvent was removed under reduced pressure to give an oil which probably contained the title compound (94b) (0.34g). ν_{max} ($CHCl_3$)cm^{-1}. 2940 (m), 1800 (s), 1400 (s), 1130 (s), 980 (m) and 850 (m)cm^{-1}, δH ($CDCl_3$) 5.35 (1H,s), 4.8 (2H, s), 3.9 (2H, t, J = 8Hz), 2.4-1.5 (4H, m), and 1.4 (3H, s). This material was subsequently used crude.

Experiment 16

The Reaction of 2,2,2 -Trichloroethoxysulphonyl isocyanate (22) with 3,4,6 -tri-O-acetyl-D-glucal (10).

The isocyanate (22) (0.25g, 1mmol) was added to a solution of 3,4,6 -tri-O-acetyl-D-glucal (10) (0.27g, 1mmol) in chloroform (4ml). After 18h the solvent was removed under reduced pressure to give a complex mixture of products containing no β-lactam.

Experiment 17

The Preparation of N-(4-Nitrobenzeneoxycarbonyl)sulphonyl chloride (19a)

A solution of chlorosulphonyl isocyanate (4.5g, 0.32mmol) in diethyl ether (10ml) was added over 30 minutes to a stirred solution of 4-nitrophenol (4.17g, 0.03mmol) in diethyl ether (30ml). After a further 2h the solvent was removed under reduced pressure and the residue was recrystallised from diethyl ether to give the title compound (19a) (8.4g, 100%), m.p. 85°C, ν_{max} ($CHCl_3$) 1775 (s), 1620 (m), 1595 (s), 1345 (s), 1285 (s), 1150 (s) and 860 (s)cm^{-1}, δH ($CDCl_3$) 8.16 and

6.91 (4H, ABq, J = 9Hz), and 5.3-4.6 (1H, br), m/e 244, 109, 65, 63, 81, 64, 62, 106 and 139 (Found: C, 30.05; H, 1.83; N, 9.96. $C_7H_5ClN_2O_6S$ requires C, 29.96; H, 1.80; N, 9.98%).

Experiment 18

The Preparation of 4-Nitrobenzeneoxysulphonyl Isocyanate (11e)

The above urethane (19a) (8.4g, 0.03mmol) was dissolved in toluene (30ml) and refluxed overnight. The solvent was removed under reduced pressure to give a black solid from which the title compound (11e) was distilled (5.5g, 66%) as a yellow solid, b.p. 120°C at 0.04mmHg, ν_{max} (CH_2Cl_2) 2260 (s), 1615 (m), 1590 (m), 1525 (s), 1345 (s), 1170 (s) and 860 (s)cm^{-1}, δH ($CDCl_3$) 8.40 and 7.53 (4H, ABq, J = 9Hz), m/e 244 ($M^{+\cdot}$), 91, 106, 63, 155, 64, 92, 65, 62 and 190.

Experiment 19

The Preparation of O-Methyl N-(4-Nitrobenzeneoxysulphonyl) Carbamate (17)

The above isocyanate (11e) (0.25g, 1mmol) was added to methanol (5ml) at 0°C. After 30min. the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title compound (17) (0.27g, 97%), m.p. 122°C, ν_{max} (nujol mull) 3190 (s), 1770 (s), 1620 (m), 1590 (m), 1520 (s), 1485 (s), 1255 (m), 1195 (s), 1180 (s), 1115 (m), 895 (s) and 760 (s)cm^{-1}, δH ($CDCl_3$/d^6acetone) 8.33 and 7.56 (4H, ABq, J = 9Hz), 8.2-7.2 (1H, br.) and 3.85

(3H, s), m/e 138, 90, 243, 65, 144, 105, 64, 63, 91 and 92 (Found: C, 34.98; H, 2.92; N, 10.10. $C_8H_8N_2O_7S$ requires C, 34.79; H, 2.92; N, 10.14%).

Experiment 20

The Attempted Preparation of 2-Nitrobenzeneoxysulphonyl Isocyanate (20).

A solution of chlorosulphonyl isocyanate (4.5g, 0.032mmol) in diethyl ether (10ml) was added over 30 mins. to a stirred solution of 2-nitrophenol (4.17g, 0.03mmol) in diethyl ether (30ml). After 2h the solvent was removed under reduced pressure and was replaced with toluene (30ml). After refluxing overnight the solvent was removed under reduced pressure to leave recovered 2-nitrophenol (4.0g).

Experiment 21

The Preparation of 1-(4-Nitrobenzeneoxysulphonyl)-1-aza-spiro[3,5]nonan-2-one (18)

Methylenecyclohexane (0.27g, 2.8mmol) was added to a solution of 4-nitrobenzeneoxysulphonyl isocyanate (11e) (0.7g, 2.8mmol) in carbon tetrachloride (2ml) at 0°C. After 0.5h the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title β-lactam (18) (0.90g, 95%), m.p. 99-100°C, ν_{max} (nujol) 3530 (w), 1795 (s), 1615 (w), 1590 (w), 1395 (m), 1350 (s), 1145 (s) and 865 (s) cm^{-1}, δH ($CDCl_3$) 8.32 and 7.55 (4H, ABq, J = 9Hz), 3.1 (2H, s) and 2.3-1.55 (10H, m), m/e 244, 81, 96, 106, 63, 64, 92, 95, 54 and 67 (Found: C, 49.59;

H, 4.69; N, 8.20. $C_{14}H_{16}N_2O_6S$ requires C, 49.41; H, 4.74; N, 8.23%).

Experiment 22

The Reaction of 4-Nitrobenzeneoxysulphonyl Isocyanate (11e) with 3,4-Dihydro-2H-pyran

1) 4-Nitrobenzeneoxysulphonyl isocyanate (11e) (0.49g, 2mmol) was added to a solution of 3,4-dihydro-2H-pyran (0.32g, 2mmol) in chloroform (4ml). After 18h at room temperature the solvent was removed from the dark brown solution to give a polymeric gum.

2) The above reaction was repeated at -20°C. Reaction was complete after 18h to give polymeric material.

Experiment 23

The Preparation of N-(2-Nitrobenzenesulphonyl)-N'-butyl-urea (41)

1) 2-Nitrobenzenesulphonamide (40) (4.6g, 0.02mmol) was added to a clear solution of n-butyl isocyanate (2g, 0.02mmol) and anhydrous aluminium chloride (3g, 0.023mmol) in nitrobenzene (75ml). After heating for 4h at 80°C followed by stirring at room temperature overnight the mixture was added to an ice water mixture (300ml) containing concentrated hydrochloric acid (10ml). After separating from the aqueous layer, petroleum was added to the nitrobenzene to give a precipitate. The solid was collected by filtration and was recrystallised from toluene to give the title compound (41) (3.2g, 52%), m.p. 132-140°C, ν_{max} (nujol) 3320 (s), 3100 (m), 1665 (s), 1535 (s), 1165 (s) and 730 (m) cm^{-1}, δH ($CDCl_3$/d^6acetone)

8.4 - 7.7 (4H, m), 6.7 - 6.1 (1H, br), 3.0 - 3.4 (2H, m), and 1.7 - 0.6 (7H, m), m/e 186, 202 (M^{+}), 50, 64, 65, 76, 92, 258, 51 and 115 (Found: C, 43.61; H, 4.86; N, 13.88. $C_{11}H_{15}N_3O_5S$ requires C, 43.88; H, 5.02; N, 13.94%).

Experiment 24

The Preparation of 2-Nitrobenzenesulphonyl Isocyanate (42)

1) N-(2-Nitrobenzenesulphonyl)-N-butylurea (41) (3g, 0.01mmol) was heated in chlorobenzene (50ml) to 120°C and a solution of phosgene (4g) in chlorobenzene (20ml) was added over 46 min. After heating for a further 2h, the solution was cooled and the solvent removed under reduced pressure. The residue was recrystallised from carbon tetrachloride and chloroform to give the title compound (42) (1.2g, 49%), m.p. 73-74°C, ν_{max} ($CHCl_3$) 2240 (s) and 1360 (s)cm^{-1}, δH ($CDCl_3$) 8.5-7.6 (4H, m), m/e 228(M^{+}), 186, 50, 90, 76, 64, 92, 187 and 51.

2) n-Butyl isocyanate (4.6g, 0.047mmol) was added to a suspension of nitrobenzenesulphonamide (40) (9.5g, 0.047mmol) in 1,2-dichlorobenzene (40ml). The mixture was heated to 180°C and phosgene (10g) in 1,2-dichlorobenzene was added over 45min. After heating for a further 2h, the solution was cooled and excess phosgene was removed by blowing dry nitrogen through the solution. The solvent was removed under reduced pressure and the residue recrystallised from chloroform and carbon tetrachloride to give isocyanate (42) (6.9g, 49%), m.p. 73-74°C.

3) 2,2,2 -Trichloroethoxysulphonyl isocyanate (22) (2.53g, 10mmol) was added to 2-nitrobenzenesulphonamide (40)) (5.05g, 25mmol) in 1,3,5-trichlorobenzene. After heating at 170°C for 2h a solution of phosgene (11.5g) in 1,3,5,-trichlorobenzene (50ml) was added over 30min. After heating overnight the solution was cooled and the solvent removed under reduced pressure. Distillation of the residue yielded the isocyanate (42) (0.9g, 16%), b.p. 137°C at 0.35 mmHg.

Experiment 25

The Preparation of O-Methyl N-(2-Nitrobenzenesulphonyl) Carbamate (17b)

2-Nitrobenzenesulphonyl isocyanate (42) (0.23g, 1mmol) was added to methanol (5ml) at 0°C. After 30 min. the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title compound (17b) (0.24g, 92%), m.p. 195°C, ν_{max} (nujol) 3260 (s), 1770 (s), 1540 (s), 1425 (s), 1240 (s), 1065 (s) and 880 (s)cm^{-1}, δH ($CDCl_3$/d^6acetone) 8.2-7.5 (4H, m) and 3.7 (3H, s), m/e 185, 64, 50, 76, 92, 48, 63, 65, 89 and 201. (Found: C, 36.93; H, 3.09; N, 10.60. $C_8H_8N_2O_6S$ requires C, 36.93; H, 3.10; N, 10.77%).

Experiment 26

Attempted Preparations of 2-Nitrobenzenesulphonyl Isocyanate (42)

1) 2-Nitrobenzenesulphonamide (40) (18g, 0.09mmol) was heated to 170°C in 1,3,5 -trichlorobenzene (60ml).

Phosgene was passed through the solution of 5h after which heating was continued overnight. No isocyanate was formed as evidenced by infra red spectroscopy.

2) A solution of sodium (0.24g) in methanol (2ml) was added to nitrobenzenesulphonamide (2.02g, 0.01mmol) in methanol (20ml). After stirring for 2h at room temperature the solvent was removed under reduced pressure and the residue redissolved in toluene (50ml). The solution was heated to reflux and phosgene was bubbled through it overnight. No isocyanate was detected.

3) The experiment above was repeated except a methanolic solution of benzyltrimethylammonium hydroxide was employed. No isocyanate was produced.

4) The experiment above was repeated except an aqueous solution of tetrabutylammonium hydroxide was used. Water was removed by azeotroping with toluene before treatment with phosgene. No isocyanate was produced.

Experiment 27

The Preparation of N-(2-Nitrobenzenesulphonyl)-5,6-dihydro-4H-pyran-3-carboxamide (44b)

2-Nitrobenzenesulphonyl isocyanate (42) (0.23g, 1mmol) was added to 3,4-dihydro-2H-pyran (0.09g, 1.1mmol) in chloroform (4ml) at 0°C. After leaving overnight the solvent was removed under reduced pressure and the residue recrystallised from ethyl acetate and petroleum to give the title compound (44b) (0.18g, 58%), m.p. 198-200°C, ν_{max} (nujol) 3280 (s), 1690 (s), 1640 (s), 1550 (s), 1450 (s), 1180 (s), 1170 (s), 790 (s) and 750 (s)cm^{-1},

δH ($CDCl_3$), 8.4-7.55 (4H, m), 7.15-6.4 (1H, br), 4.25-3.85 (2H, m) and 2.5-1.6 (4H, m), m/e 110, 115, 108, 128, 80, 64, 109, 82, 83 and 65 (Found: C, 46.28; H, 3.85; N, 8.98. $C_{12}H_{12}N_2O_6S$ requires C, 46.17; H, 3.87; N, 8.97%).

Experiment 28

The Preparation of 1-(2-Nitrobenzenesulphonyl)-1-azaspiro-[3,5]nonan-2-one (45b)

Nitrobenzenesulphonyl isocyanate (42) (0.23g, 1mmol) was added to methylenecyclohexane (0.1g, 1mmol) in chloroform (4ml). After three days at room temperature the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title compound (45b), (0.32g, 98%), m.p. 115-116°C, ν_{max} ($CHCl_3$) 2460 (m), 2380 (m), 1800 (s), 1550 (s), 1375 (s), 1150 (s), 1130 (s), 1050 (m) and 915 (m)cm^{-1}, δH ($CDCl_3$) 8.5-7.5 (4H, m), 2.96 (2H, s) and 2.5-0.9 (10H, m), m/e 80, 96, 138, 244, 95, 67, 55, 106, 93 and 65 (Found: C, 51.80; H, 4.70; N, 8.50. $C_{14}H_{16}N_2O_5S$ requires C, 51.84; H, 4.97; N, 8.64%).

Experiment 29

The Attempted Preparation of 2,2,2 -Trichloroethylsulphonyl Isocyanate (36)

1) 2,2,2 -Trichloroethylsulphonamide (34) (1.2g, 5.5mmol) was treated with oxalyl chloride (0.9g, 1.5eq.) in 1,2-dichloroethane (10ml) at reflux. After 24h no isocyanate had been formed.

2) Di-isopropylethylamine (0.13g, 1eq.) was added to

a solution of 2,2,2 -trichloroethylsulphonamide (34) (0.21g, 1mmol) in 1,2,-dichloroethane (30ml) at 40°C. After stirring for 3h oxalyl chloride (0.9g, 1.5 eq.) was added. Stirring at 40°C for 24h produced no detectable isocyanate.

3) Chlorosulphonyl isocyanate (0.14g, 1mmol) was added to 2,2,2 -trichloroethylsulphonamide (0.21g, 1mmol) in chloroform (20ml). When the infra red spectrum showed complete loss of starting material, oxalyl chloride (0.9g, 1.5 eq.) was added and the mixture was heated to 60°C. After 24h no isocyanate had formed.

4) The experiment above was repated except that on complete loss of the starting material the chloroform was removed under reduced pressure and was replaced with 1,3,5-trichlorobenzene (20ml). Phosgene was bubbled through this mixture at 180°C overnight. No isocyanate could be observed.

5) 2,2,2 -Trichloroethylsulphonamide (34) (0.21g, 1mmol) was heated to 180°C in 1,3,5-trichlorobenzene (20ml) and phosgene was bubbled through the solution for 12h. No isocyanate (36) was formed.

6) 2,2,2 -Trichloroethylsulphonylchloride (0.2g, 0.9mmol) was treated with benzyl carbamate (0.15g, 1mmol) in both refluxing toluene and refluxing chloroform. No reaction occurred in either case.

Experiment 30

The Preparation of N-(2,2,2 -trichloroethylsulphonyl)-N'-butylurea (35)

1) 2,2,2 -Trichloroethylsulphonamide (34) (4.3g,

0.02mmol), anhydrous aluminium chloride (3g, 0.023mmol) and n-butyl isocyanate (1.9g, 0.02mmol) were mixed together and heated to 80°C for 1h. After cooling the mixture was triturated with 10% hydrochloric acid (30ml) and extracted with diethyl ether (2 x 30ml). The ethereal layer was dried and evaporated to give a solid which was recrystallised from toluene to give the title compound (35) (2.5g, 40%), m.p. 120°C, ν_{max} (nujol) 3350 (s), 1670 (s), 1355 (s), 1160 (s), 930 (m) and 810 (m)cm^{-1}, δH ($CDCl_3$/d^6acetone) 6.5-6.0 (1H, br), 4.8 (2H, s), 3.5-3.05 (2H, m) and 1.8-0.7 (7H, m), m/e 30, 36, 57, 73, 41, 61, 94, 95, 72 and 56 (Found: C, 27.15; H, 4.02; N, 9.20. $C_7H_{13}Cl_3N_2O_3S$ requires C, 26.98; H, 4.21; N, 8.99%).

2) A solution of n-butyl isocyanate (1.9g, 0.02mmol) in nitrobenzene (75ml) was added to anhydrous aluminium chloride (3g, 0.023mmol). When the solution became clear 2,2,2 -trichloroethylsulphonamide (34) (4.3g, 0.02mmol) was added. The mixture was heated for 5h at 80°C, followed by stirring at room temperature overnight. The solution was then added to a stirred mixture of concentrated hydrochloric acid (20ml) and iced water (600ml). After separating the organic layer, petroleum was added giving a precipitate. The precipitate was collected by suction filtration and was recrystallised from toluene to give the title compound (35) (4.9g, 76%), m.p. 120°C.

Experiment 31

The Preparation of 2,2,2 -Trichloroethylsulphonyl Isocyanate (36)

1) N-(2,2,2 -Trichloroethylsulphonyl)-N'-butylurea (35) (18g, 58mmol) was heated to 120°C in chlorobenzene (300ml) and phosgene (12g) in chlorobenzene was added over 1h. After heating for a further 2h the solvent was removed under reduced pressure. Distillation of the residue afforded the title isocyanate (36) , (9.38g, 68%), b.p. 75°C at 0.25mmHg, m.p. 41-41.5°C, ν_{max} ($CHCl_3$) 2240 (s), 1375 (s), 1155 (m), 1055 (w) and 910 (w)cm^{-1}, δH ($CDCl_3$) 4.6 (2H, s), m/e 131, 133, 80, 95, 96, 61, 140, 95, 176 and 98.

2) n-Butyl isocyanate (0.99g, 0.01mmol) was added to a suspension of 2,2,2 -trichloroethylsulphonamide (34) (3.4g, 0.016mmol) in 1,2-dichlorobenzene (40ml). The mixture was heated to 180°C and phosgene (10g) in 1,2-dichlorobenzene was added over 1h. After heating for a further 1h, the mixture was cooled and the solvent removed under reduced pressure. Fractional distillation gave the title isocyanate (36)) (1.57g, 66%), b.p. 87°C at 0.45mmHg.

Experiment 32

The Preparation of O-Methyl N-(2,2,2 -Trichloroethylsulphonyl) Carbamate (74)

2,2,2 -Trichloroethylsulphonyl isocyanate (36) (0.24g, 1mmol) was added to methanol (5ml) at 0°C. After 30 min. the solvent was removed under reduced pressure and the residue recrystallised from ethyl acetate and

petroleum to give the title compound (17c) (0.24g, 88%), m.p. 108°C, ν_{max} (nujol) 3260 (s), 1770 (s), 1540 (s), 1425 (s), 1240 (s), 1065 (s) and 880 (s) cm^{-1}, δH ($CDCl_3$/ d^6acetone) 4.8 (2H, s) and 3.85 (3H, s), m/e 158, 160, 58, 94, 96, 60, 30, 79, 31 and 161 (Found: C, 17.91; H, 2.19; N, 5.07, $C_4H_6Cl_3NO_4S$ requires C, 17.76; H, 2.24; N, 5.18%).

Experiment 33

The Preparation of N-(2,2,2 -Trichloroethylsulphonyl)-5,6-dihydro-4H-pyran-3-carboxamide (44a)

1) 2,2,2 -Trichloroethylsulphonyl isocyanate (36) (0.24g, 1mmol) was added to 3,4 -dihydropyran (0.09g, 1.1mmol) in chloroform (4ml) at room temperature. After 3h the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title compound (44a) (0.30g, 93%), m.p. 123-125°C, ν_{max} (nujol mull) 3100 (m), 2930 (s), 1670 (s), 1600 (s), 1240 (s), 1160 (s), 1040 (s), 925 (s), 870 (s), 800 (m) and 705 (m)cm^{-1}, δH ($CDCl_3$), 8.66 (1H, s), 7.63 (1H, s), 4.80 (2H, s), 4.03 (2H, t, J = 5Hz) and 2.4-1.6 (4H, m), m/e 110, 109, 36, 126, 83, 82, 56, 38, 27 and 43. (Found: C, 30.09; H, 3.07; N, 4.34. $C_8H_{10}Cl_3NO_4S$ requires C, 29.79; H, 3.13; N, 4.34%).

2) The above experiment was repeated except that it was carried out at -20°C. After 6h the solvent was removed under reduced pressure to give the same derivative (44a) (0.27g, 84%).

3) The above experiment was repeated except that diethyl ether was used and the reaction was carried out

at -20°C. After 5h the solvent was removed under reduced pressure to give the same derivative (44a) (0.25g, 78%).

Experiment 34

The Preparation of 1-(2,2,2 -Trichloroethylsulphonyl)-1-azaspiro[3,5]nonan-2-one (45a)

2,2,2 -Trichloroethylsulphonyl isocyanate (36) (1g, 4.2mmol) was added to methylenecyclohexane (0.41g, 4.2mmol) in chloroform (15ml). After 1 week the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title compound (45a) (1.17g, 83%), m.p. 135°C, ν_{max} (nujol mull) 1820 (s), 1190 (m), 1180 (m), 1005 (m), 870 (s), 770 (m) and 725 (m), δH ($CDCl_3$) 4.46 (2H, s), 2.46 (2H, s) and 2.24-0.7 (10H, m), m/e 96, 81, 91, 67, 68, 63, 39, 41, 55 and 155, (Found: C, 35.85; H, 4.18; N, 4.14 $C_{10}H_{14}Cl_3NO_3S$ requires, C, 35.89; H, 4.22; N, 4.19%).

Experiment 35

The Attempted Preparation of Trifluoroacetyl isocyanate (79) from Trifluoroacetamide

1) Oxalyl chloride (13.9g, 0.1mmol) was added to trifluoroacetamide (10g, 0.09mmol) and carbon tetrachloride (50ml) in a pressure bottle. After leaving at 70°C overnight the bottle was cooled to 0°C and opened. A considerable pressure of hydrogen chloride had formed but very little isocyanate (79) was present.

2) Oxalyl chloride (13.9g, 0.11mmol) was added to trifluoroacetamide (10g, 0.09mmol) in carbon tetrachloride (30ml) and the mixture was refluxed using a strobmeier

apparatus. After 3 days no significant amount of isocyanate (79) had formed.

3) Trifluoroacetamide (1.13g, 10mmol) was dissolved in THF (10ml) and added to a stirred mixture of sodium hydride (0.24g, 1 eq.) in THF (20ml). After hydrogen evolution had ceased, the solvent was removed under reduced pressure to give a hygroscopic white solid (1.3g). This was treated with either i; excess oxalyl chloride in refluxing chloroform, ii; excess oxalyl chloride in refluxing toluene or iii; phosgen in refluxing 1,3,5-trichlorobenzene. In all cases no isocyanate (79) was formed after 24hr reflux.

4) Trifluoroacetamide (1.4g, 10mmol) was added to an aqueous solution of tetra n-butyl ammonium hydroxide (1.5molar, 6.7ml). After stirring for 2h the mixture was dried by azeotroping with toluene to give the quaternary ammonium salt (3.8g, 10mmol). This was then treated in the same way as the sodium salt. In neither case was isocyanate (79) formed.

5) 2,2,2 -Trichloroethoxysulphonyl isocyanate (22) (2.23g, 1 eq) was added to trifluoroacetamide (1g) in diethyl ether (30ml). After 2h the solvent was removed under reduced pressure and 1,2,4-trichlorobenzene (30ml) and oxalylchloride (1.3g, 1 eq) were added. No isocyanate (79) had formed after heating at 70°C for 24h.

Experiment 36

The Attempted Preparation of Trifluoroacetyl Isocyanate (79) from Cyanuric Acid or Potassium Cyanate

1) Cyanuric Acid (0.13g, 1mmol) was added to tri-

fluoroacetic anhydride (0.5g) in dichloromethane (20ml). After stirring for 1 week at 60°C there was no sign of reaction.

2) The above experiment was repeated except that trifluoroacetic anhydride (20ml) was used in place of the dichloromethane. No reaction occurred.

3) Part 1 of the experiment was repeated, except that a sealed tube at 130°C for 48h was used. A weak carbonyl stretch (1690cm^{-1}) was evident in the product but no isocyanate was formed.

4) Potassium isocyanate (0.08g, 1mmol) was used in place of cyanuric acid in part 1 of the experiment. No isocyanate was formed.

5) Part 2 of the experiment was repeated using potassium isocyanate (0.08g, 1mmol) in place of cyanuric acid. No reaction occurred.

6) Cyanuric acid was replaced by potassium isocyanate (0.08g, 1mmol) in part 3 of the experiment. A weak carbonyl stretch was observed in the product but none of the desired isocyanate (79) was found.

Experiment 37

The Preparation of Trifluoroacetyl Isocyanate (79)

A three necked flask, equiped with a gas inlet tube and an outlet leading to a cardice trap, was charged with lithium chloride (58.5g) and potassium chloride (69.9g). The mixture was heated to 480°C where upon it melted. The melt was dried by passing silicon tetrachloride through, with a stream of dry nitrogen gas, and potassium cyanate (6.7g, 0.08M) was added. When all the potassium cyanate

had dissolved trifluoroacetylchloride (7g, 0.05mmol) was slowly passed through the melt, the product being collected in the cardice trap. Distillation of the colourless liquid in the trap gave trifluoroacetyl isocyanate (2.9g, 40%) b.p. 38°C, ν_{max} ($CHCl_3$), 2210 (s), 2230 (s), 1765 (s), 1175 (s) and 1015 (s), ^{13}C NMR ($CDCl_3$) δ 114.6 (q, $\underline{J}$ = 4.5) and 155.9 (q, $\underline{J}$ = 0.72).

Experiment 38

The Preparation of N-(Trifluoroacetyl)-5,6-dihydro-4H-pyran-3-carboxamide (81)

Trifluoroacetyl isocyanate (79) (0.14g, 1mmol) was added to 3,4 -dihydropyran (0.09g, 1.1mmol) in chloroform (0.5ml). After 24h at room temperature the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate and petroleum to give the title compound (81) (0.17g, 76%) m.p. 95°C, ν_{max} (nujol mull) 3370 (s), 1680 (s), 1630 (s), 1600 (m), 1185 (s), and 1070 (m) cm^{-1}, δ H($CDCl_3$) 7.65 (1H, s), 8.1 - 6.5 (1H, br), 4.06 (2H, t, $\underline{J}$ = 5Hz) and 2.35 - 1.6 (4H, m),[^{13}C NMR, δ 173 (s), 161.7 (q), 156 (s), 115.4 (q), 105 (s), 67 (s), 21 (s) and 19 (s)]. m/e 127, 82, 83, 55, 56, 27, 99, 111, 53 and 39 (Found: C, 42.97; H, 3.63; N, 6.27. $C_8H_8F_3NO_3$ requires C, 43.06; H, 3.61; N, 6.23%).

Experiment 39

The Preparation of 1-(Trifluoroacetyl)-1-azaspiro[3,5]-nonan-2-one (83)

Trifluoroacetyl isocyanate (79) (0.14g, 1mmol) was

added to methylenecyclohexane (0.1g, 1mmol) in chloroform (4ml). After 3 weeks the solvent was removed under reduced pressure to give an oil containing a mixture of two products. Further purification was not possible and the mixture was used as isolated, (0.24g) ν_{max} ($CDCl_3$) 2920 (s), 1820 (s), 1780 (m), 1750 (s), 1360 (m) and 1170 (s), δH ($CDCl_3$) 3.2 (s), ($\underline{CH_2}$ of β-lactam), 2.8 (s) ($\underline{CH_2}$ of six membered ring compound) and 2.3 - 1.0 (m) (cyclohexyl ring).

Experiment 40

The Preparation of 6-Methyl-8-trifluoroacetyl-8-aza-2-oxa-bicyclo[4,2,0]-octan-7-one (94c).

Trifluoroacetyl isocyanate (79) (0.14g, 1mmol) was added to 5-methyl-3,4 -dihydropyran (93) (0.1g, 1mmol) in chloroform (4ml). After 24h at room temperature the solvent was removed under reduced pressure to give (94c) crude as a pale yellow oil which was used without further purification (0.23g). ν_{max} ($CHCl_3$) 1810 (s), 1720 (s) and 1360 (m) cm^{-1}, δH ($CDCl_3$) 5.45 (1H, s), 3.85 (2H, t, $\underline{J}$ = 5Hz), 2.3 - 1.5 (4H, m), and 1.35 (3H, s).

Experiment 41

The Preparation of 3-Benzyltetrahydropyran-2-one (99)

Butyllithium (65mmol, 43.3ml) was concentrated to half its volume by blowing a stream of argon gas over it. This was added dropwise to di-isopropylamine (9ml) in THF (6ml) at -76°C. After warming to room temperature THF (86ml) was added and the mixture was cooled to -76°C. HMPA (23ml) was added slowly over 1h followed by a further

0.5h stirring. Ethyl dihydrocinnamate (11.4ml, 65mmol) in THF (35ml) was added over 1h, the solution immediately darkened and on complete addition had gone black. After stirring for a further hour 1-iodo-3-trimethylsilyloxypropane (13.7g, 8.7ml, 50mmol) was added rapidly and the colour was discharged. After stirring for 1h the solution was warmed up to room temperature over 0.5h, the mixture was cooled to -76°C again and was poured into 10% hydrochloric acid (100ml). The mixture was extracted with diethyl ether (500ml) and the extract washed with saturated sodium metabisulphite solution and with water. Drying over magnesium sulphate and evaporation under reduced pressure gave a yellow oil (17.1g). This was dissolved in toluene (800ml) and refluxed with 4-toluenesulphonic acid monohydrate (0.12g) for 2h. The toluene was distilled off slowly and the residue purified by column chromatography on silica (diethyl ether:dichloromethane:petroleum, 1:4:4) to give the title compound (99) (8.3g, 87%), ν_{max} (neat) 2960 (s), 1730 (s), 1600 (w), 1350 (m), 1395 (m), 1245 (s), 1150 (s), 1070 (s), 965 (m), 740 (m) and 700 (s) cm^{-1}, δH ($CDCl_3$) 7.2 (5H, s), 4.2 (2H, t, J = 6Hz), 3.23 (1H, Quintet, J = 9Hz), 2.78 and 2.5 (2H, ABq, J_{AB} = 8Hz), and 2.05-1.3 (4H, m), m/e 190, 91, 147, 148, 118, 119, 65, 78, 92 and 31. This was identical to an authentic sample.

Experiment 42

The Preparation of 3-Benzyl-2-methoxytetrahydro-2H-pyran (101)

The lactone (99) (8.3g, 44mmol) was dissolved in

toluene (100ml) and was cooled to -78°C. A solution of di-isobutylaluminium hydride in toluene (27ml, 34% w/w, 1.23 eq) was added over 1h followed by a further 1h stirring. To this solution was added a mixture of hydrochloric acid (100ml, 10%) and ice (100g). Extraction with diethyl ether followed by washing with saturated sodium hydrogen carbonate and water, drying (magnesium sulphate) and evaporating under reduced pressure gave a colourless oil (6.5g). This oil was added to methanol (200ml) and amberlyst IR120H resin (5g). After stirring overnight the resin was removed by filtration and the methanol evaporated under reduced pressure. Traces of water were removed from the residue by azeotroping with toluene and the compound was then purified further by column chromatography on silica to give the title compound (101)(4.77g, 53%), ν_{max} (neat) 2970 (s), 1605 (w), 1450 (m), 1120 (s), 1050 (s), 960 (s), 750 (m) and 700 (s) cm^{-1}, δH ($CDCl_3$) 7.16 (5H, s), 4.26 (1H, d, J = 3Hz), 3.5 (2H, t, J = 5Hz), 3.3 (3H, s), 3.28 (1H, Quintet, J = 9Hz), 2.6 and 2.3 (2H, ABq, J = 10Hz) and 1.7-1.3 (4H, m), m/e 91, 118, 117, 174, 114, 104, 128, 115, 175, and 206M^+, (Found: C, 75.90; H, 8.93. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%).

Experiment 43

The Attempted Formation of 5-Benzyl-3,4 -dihydro-2H-pyran (102)

1) The intermediate lactol (100) (0.19g) from the previous experiment was added to 4-toluenesulphonic acid (4mg) in toluene (20ml). After refluxing for 1h, toluene (15ml) was distilled off slowly and the resulting solution

was partitioned between water and diethyl ether. The ether extract was dried (magnesium sulphate) and evaporated under reduced pressure to give an oil (0.1g) which contained none of the desired product as judged by NMR and infra red spectroscopy.

2) The methyl ether (101) (0.18g) was added to toluene (20ml) and 4-toluenesulphonic acid (15mg). After refluxing for 2h half of the solvent was distilled off slowly. TLC and a solution infra red spectrum indicated complete reaction to give a less polar hydroxyl free compound. The remaining solvent was removed without heating under high vacuum to give an intractable oil.

3) The methyl ether (101) (0.1g) was added to a solution of trifluoroacetic acid (0.1ml) in deuterio-chloroform (1ml) at 60°C. A small amount of the desired product (102) was seen to have been formed immediately. After leaving overnight all the starting material had been consumed to give a complex mixture of products including a small amount of the desired enol ether (102).

Experiment 44

The Preparation of 5-Benzyl-3,4-dihydro-2H-pyran (102).

The methyl ether (101) (4.77g) was dissolved in toluene (300ml) and amberlyst IR 120 H (10g) was added to this. After refluxing for 4h the solvent was slowly distilled off over 3h. The resin was removed by filtration and the toluene was removed under reduced pressure to give an oil (4.2g) which was purified by column chromatography on silica to give the title compound (102) (1.6g, 40%) m.p. 120-121°C, ν_{max} ($CDCl_3$), 2920 (s),

1665 (s), 1610 (m), 1430 (m), 1260 (m), 1230 (m) and 1130 (s), δH ($CDCl_3$) 7.15 (5H, s), 6.23 (1H, s), 3.8 (2H, t, J = 3Hz), 3.1 (2H, s), and 1.76 (4H, s), M/e 174 ($M^{+\cdot}$), 83, 91, 115, 173, 117, 131, 104, 65 and 129,

Experiment 45

The Preparation of 6-Benzyl-8-(trifluoroacetyl)-8-aza-2-oxabicyclo[4.2.0]octan-7-one (103)

1) Trifluoroacetyl isocyanate (79) (0.16g, 1.1mmol) was added to 5-benzyl-3,4-dihydropyran (102) (0.18g, 1mmol) in chloroform (2ml). After three weeks the solvent was removed under reduced pressure to give crude (103) as a pale yellow oil which was used without further purification (0.31g), ν_{max} ($CDCl_3$), 1820 (s), 1740 (s), 1380 (m), 1230 (s), 1170 (s) and 1080 cm^{-1}, δH ($CDCl_3$) 7.23 (5H, s), 5.53 (1H, s), 3.76 (2H, t, J = 6Hz), 3.08, 2.78 (2H, ABq, J_{AB} = 14Hz), and 2.1 - 1.2 (4H, m).

2) The above experiment was repeated except that it was conducted in deuteriochloroform (0.5ml). After three weeks reaction was complete, giving the β-lactam (103) which was used crude.

3) The above reaction was repeated on a 0.25mmol scale at 50°C. Reaction was complete after 1 week and was shown to contain the β-lactam (103) albeit in grossly impure form.

4) The above experiment was repeated on a 0.25mmol scale at 50°C and using diethyl ether (0.5ml) as solvent. After 1 week reaction was complete and was shown to contain the β-lactam (103) as well as a considerable amount of

other products.

Experiment 46

The Attempted Reaction of Trifluoroacetyl Isocyanate (79) with 3,4,6 -Tri-O-acetyl-D-glucal (10).

1) Trifluoroacetyl isocyanate (79) (0.14g, 1mmol) was added to a solution of 3,4,6 -tri-O-acetyl-D-glucal (10) (0.27g, 1mmol) in diethyl ether (2ml) at room temperature. After 2 months very little reaction was evident.

2) The above reaction was repeated using chloroform as the solvent. Very little reaction was evident after 2 months.

3) The above reaction was repeated using chloroform as the solvent. After 3 weeks at 50°C no reaction had occurred.

4) The above reaction was repeated, on half the scale, using acetonitrile as the solvent. After 2 weeks nearly all of the enol ether stretch in the infra red spectra had disappeared and an absorbtion at 1800cm^{-1} was present. On evaporation the 1800cm^{-1} absorbtion disappeared from the residue which contained a complex mixture of compounds.

5) The above reaction was repeated using acetonitrile (0.5ml) as the solvent. After 3 weeks the reaction was complete and the solution was chromatographed on florisil (10g), eluting with diethyl ether (500ml). The solvent was removed under reduced pressure to give an oil which contained no β-lactam and consisted of a complex mixture of products.

Experiment 47

The Attempted Reaction of Trifluoroacetyl isocyanate (79) with 3,4,6 -Tri-O-benzyl-D-glucal (105a).

1) Trifluoroacetyl isocyanate (79) (0.07g, 0.5mmol) was added to a solution of 3,4,6 -tri-O-benzyl-D-glucal (105a) (0.21g, 0.5mmol) in chloroform (0.5ml). After 3 weeks at room temperature no further change was occurring in the infra red spectrum, which showed an absorbtion at 1800cm^{-1}. The solution was chromatographed on florisil (10g) using diethyl ether (500ml) as eluent. Examination of the oil, resutling from removing the diethyl ether under reduced pressure, by both proton NMR and infra red spectroscopy, revealed no β-lactam was present in a complex mixture of products.

2) The above experiment was repeated using deutreriochloroform (0.5ml) the benzyl sugar (105a) (0.38g, 0.9mmol) and trifluoroacetyl isocyanate (79) (0.14g, 1.1 eq). After 3 weeks a considerable amount of the desired product (106a) was visible by spectral data. ν_{max} ($CDCl_3$) 2840 (s), 1810 (s), 1740 (s), 1630 (s) and 1340 (m), δH ($CDCl_3$) 7.3 (m), 6.1 (d, J = 5Hz), 4.7 (s) and 4.7-3.5 (m). The mixture was chromatographed on florisil (10g), eluting with diethyl ether (500ml). No β-lactam was present in the product on removing the solvent under reduced pressure.

3) The above reaction was repeated using acetonitrile (1ml) as the solvent but after 3 weeks there was no sign of any β-lactam in the dark brown solution. Removal of the solvent under reduced pressure revealed some starting material (105a) in a complex mixture of products.

Experiment 48

The Reaction of Trifluoroacetyl Isocyanate (79) with 3,4,6 -Tri-O-(trimethylsilyl)-D-glucal (105b).

1) Trifluoroacetyl isocyanate (79) (0.14g, 1mmol) was added to a solution of the sugar (105b) (0.180g, 0.5mmol) in chloroform (0.5ml). After 10 days at room temperature no further change was visible and the mixture was used crude in the next step, ν_{max} ($CDCl_3$), 1820 (s), 1750 (s), 1620 (w), 1500 (s), 1150 (s) and 840 (m)cm^{-1}, δH ($CDCl_3$) 6.05 (d, $\underline{J}$ = 6Hz), 4.8 - 3.5 (m), 0.5 - 0 (m).

2) The above experiment was repeated using acetonitrile (0.5ml) as the solvent. After 2 weeks no further change was visible, and an absorbtion at 1820cm^{-1} was visible in the infra red spectrum. Removal of the solvent under reduced pressure gave an oil which was used crude in the next stage.

3) The above experiment was repeated with the trimethylsilyl sugar (105b) (0.24g, 0.7mmol), trifluoroacetyl isocyanate (79) (0.2g, 2 eq) and deutreriochloroform (0.5ml). After 3 weeks, no further change was evident and the mixture was used in the next stage crude.

Experiment 49

Attempted Catalysis of the Reaction between Trifluoroacetyl Isocyanate (79) and 3,4,6 -Tri-O-acetyl-D-glucal (10).

1) Trifluoroacetyl isocyanate (79) (0.08g, 1.1 eq) was added to a solution of 3,4,6 -tri-O-acetyl-D-glucal (10) (0.14g, 0.5mmol) in deuteriochloroform (0.5ml) containing trifluoroacetic acid (0.006g). The mixture was sealed and left at room temperature. After 1 month NMR spectroscopy revealed that very little reaction had occurred and no β-lactam had been formed.

2) The above experiment was repeated except trifluoroacetamide (0.05g) was used in place of trifluoroacetic acid. No reaction was evident after 1 month.

3) The above experiment was repeated except pyridine (1 drop) was used in place of trifluoroacetic acid. No reaction was evident after 1 month.

4) The above experiment was repeated except trifluoroacetic anhydride (1 drop) was used in place of trifluoroacetic acid. No reaction was evident after 1 month.

5) The above experiment was repeated except no additive was used and the reaction was conducted at 45°C. No reaction was evident after 1 month.

Experiment 50

The Preparation of Methoxalyl Isocyanate (73)

Oxalyl chloride (15g, 1.2 eq) was added slowly to methyl oxamate (10.3g, 0.1mmol) in chloroform (150ml). After stirring vigorously overnight at room temperature

the solvent was removed at reduced pressure. Fractional distillation of the residue gave the title compound (73) (7.1g, 55%), b.p. 45°C at 2mm Hg, ν_{max} (CH_2Cl_2) 2215 (s), 1740 (s), 1720 (s) and 1075 (s) cm^{-1}, δH ($CDCl_3$) 4.03 (s), m/e 117, 96, 59, 129 $M^{+\cdot}$, 81, 90, 116, 95 and 73.

Experiment 51

The Preparation of N-Methoxalyl-O-Methyl Carbamate (74).

Methoxalyl isocyanate (73) (0.13g, 1mmol) was added to methanol (5ml) at 0°C. After 0.5h the solvent was removed under reduced pressure and the residue was recrystallised from methanol to give the title compound (74) (0.16g, 99%), m.p. 141-142°C, ν_{max} (nujol) 3350 (s), 1800 (s), 1735 (s), 1530 (s), 1120 (s), 1045 (s), 880 (m), and 730 (m) cm^{-1}, δH ($CDCl_3$) 9.9-9.3 (1H, br), 3.95 (3H, s), and 3.85 (3H, s), m/e 44, 31, 29, 32, 64, 59, 43, 45, 36 and 41 (Found: C, 37.16; H, 4.33; N, 8.60. $C_5H_7NO_4$ requires C, 37.28; H, 4.38; N, 8.69%).

Experiment 52

The Preparation of N-Methoxalyl-5,6-dihydro-4H-pyran-3-carboxamide (75)

1) Methoxalyl isocyanate (73) (0.13g, 1mmol) was added to 3,4 -dihydropyran (0.09g, 1.1mmol) in diethyl ether (4ml). After 40 min at room temperature the solvent was removed under reduced pressure and the residue recrystallised from ethyl acetate and petroleum to give the title compound (75), (0.15g, 70%), m.p. 66-68°C, ν_{max} ($CHCl_3$), 3380 (m), 1760 (s), 1740 (s), 1170 (s) and 990 (s), δH ($CDCl_3$) 7.8 (1H, s), 4.15 (2H,

t, J =6Hz), 3.9 (3H, s) and 2.5-1.7 (4H, m), m/e 111, 109, 71, 126, 83, 82, 110, 55, 59 and 31 (Found: C, 50.76; H, 5.17; N, 6.60. $C_9H_{11}NO_5$ requires C, 50.71; H, 5.20; N, 6.57%).

2) The above experiment was repeated in carbon tetrachloride (4ml) at room temperature. No reaction was observed after 1 month.

3) The above experiment was repeated in chloroform (4ml), no reaction was observed after 1 month.

4) The above experiment was repeated using 1,2-dimethoxy ethane (4ml) as solvent. No reaction was observed after three weeks.

5) The above experiment was repeated in acetonitrile (4ml). After 24h the solvent was removed under reduced pressure to give the title compound (75) (0.13g, 61%).

Experiment 53

The Attempted Reaction of Methoxalyl isocyanate (73) with Methylenecyclohexane

Methoxalyl isocyanate (73) (1.3g, 10mmol) was added to methylenecyclohexane (0.96g, 10mmol) in chloroform (4ml). After five weeks no reaction had occurred.

Experiment 54

The Reaction of Methoxalyl isocyanate (73) with 5-Methyl-3,4-dihydro-2H-pyran (93)

1) Methoxalyl isocyanate (73) (0.13g, 1mmol) was added to a solution of 5-methyl-3,4 -dihydro-2H-pyran (93) (0.1g, 1mmol) in chloroform (4ml). After five weeks at room temperature, no reaction had occurred.

2) The above experiment was repeated except that it was conducted at 55°C. After 3 weeks, no reaction had occurred except that the solution had become yellow.

3) The above experiment was repeated using diethyl ether (4ml) as the solvent. After 10 weeks at room temperature no reaction had occurred.

Experiment 55

The Reaction of Chlorosulphonyl Isocyanate with 5-Methyl-3,4 -dihydro-2H-pyran (93)

1) Chlorosulphonyl isocyanate (0.14g, 1mmol) was added to 5-methyl-3,4-dihydro-2H-pyran (93) (0.1g, 1mmol) in chloroform (4ml) at -18°C. The solvent was removed under reduced pressure after 10 min to give an oil (0.24g) which was used crude, ν_{max} ($CHCl_3$), 1815cm^{-1}, δH ($CDCl_3$) 5.5 (1H, s), 3.95 (2H, t, $\underline{J}$ = 5Hz), 2.3-1.5 (4H, m), and 1.4 (3H, s).

2) The above experiment was repeated at room temperature and gave a mixture of products which could not be separated.

Experiment 56

The Attempted Preparation of 8-Nitro-naphthalene-1-sulphonyl Isocyanate (51)

1) 8-Nitronaphthalenesulphonamide (49) (0.25g, 1mmol) was heated to 180°C in 1,3,5 -trichlorobenzene (25ml) together with n-butyl isocyanate (0.025g, 0.25eq). After 15 min complete decomposition of the sulphonamide to an intractable mixture of products had occurred.

2) To a suspension of silver cyanate (0.2g, 1.4 eq)

in THF (2ml) was added, with stirring, a solution of 8-nitronaphthalenesulphonyl chloride (47) (0.24g, 1mmol) in THF (2ml). The mixture was stirred in the dark at 45°C for two weeks. No reaction occurred.

3) The above experiment was repeated using toluene as solvent and heating at 100°C overnight. No reaction occurred but considerable discolouration was evident.

4) Chlorosulphonyl isocyanate (0.93g, 1.1 eq) was added to the sulphonamide (49) (1.52g, 6mmol) in THF (50ml). After 0.5h the solvent was removed and the residue (2.3g) was heated to 100°C in chlorobenzene. Phosgene (16g) dissolved in chlorobenzene (30ml) was added over 30 mins and then heating was continued for a further 2h. On cooling a solid precipitated and was collected by suction filtration. The solid (1.1g) was shown to be the starting sulphonamide (49).

Experiment 57

The Attempted Preparation of N-Butyl-N'-(8-Nitronaphthalenesulphonyl)Urea (50)

1) A solution of n-butyl isocyanate (1.6g, 16mmol) in nitrobenzene (75ml) was added to anhydrous aluminium chloride (2.4g, 18mmol) with stirring. To the resulting solution 8-nitronaphthalenesulphonamide (49) (3.8g, 16mmol) in nitrobenzene (20ml) was added and the mixture was heated for 4h at 80°C. A small amount of nitrobenzene (20ml) was removed under reduced pressure and the residue was poured into ice/water (300ml) containing concentrated hydrochloric acid (10ml). The organic phase was separated and petroleum was added to give a solid

precipitate which was identified as starting material (49).

2) 8-Nitronaphthalenesulphonamide (49) (0.25g, 1mmol) was added to sodium hydride (0.03g, 1.3mmol) in THF (10ml) with rapid stirring. After 1h effervence had ceased and a precipitate had formed. n-Butyl isocyanate (0.125ml, 1.1eq) was added and the precipitate redissolved. After stirring overnight at room temperature a fresh precipitate had formed and this was collected by suction filtration. The brown solid (0.3g) was shown to be starting material (49).

3) A solution of sodium (0.024g, 1mmol) in methanol (2ml) was added to the sulphonamide (49) (0.25g, 1mmol) in methanol (20ml). After 0.5h all the sulphonamide (49) had dissolved and the solvent was removed under reduced pressure to give initially a yellow/brown oil which rapidly turned olive green. THF (20ml) and n-butyl isocyanate (0.16g, 1.6eq) were added to the oil. After stirring for three days a small amount of the sulphonamide (49) was present; the remainder of the material was in the form of an intractable green gum.

4) Potassium t-butoxide (0.11g, 1 eq) was added to the sulphonamide (49) (0.25g, 1mmol) in THF (20ml) with stirring. A precipitate formed rapidly and the solution became pink. n-Butyl isocyanate (0.16g, 1.6eq) was added and the precipitate immediately dissolved, the colour changing to a muddy brown. After stirring overnight the solution was concentrated under reduced pressure to give a precipitate which was collected by suction filtration. The solid (0.3g) was shown to be the sulphonamide (49).

5) The sulphonamide (49) (0.47g, 2mmol) was added to

a stirred suspension of sodium hydride (0.08g, 3mmol) in THF (25ml). After stirring overnight the solvent was removed under vacuum to give a solid residue. This was suspended in nitrobenzene (20ml) and was added to a solution of n-butyl isocyanate (0.25g, 2.5mmol) and anhydrous aluminium chloride (0.33g, 2.5mmol) in nitrobenzene (20ml). The mixture was heated at 80°C for 4h and left at room temperature overnight. The mixture was poured into ice/water (200ml) containing concentrated hydrochloric acid (5ml) with rapid stirring. After separating the organic phase, petroleum was added to give a precipitate which was collected by suction filtration. The solid (0.42g) was shown to be starting material (49).

Experiment 58

The Attempted Preparation of 2-(Chlorocarbonyl)benzenesulphonyl Isocyanate (53)

1) Oxalyl chloride (1.4g, 1.1eq) was added to saccharin (52) (2.5g, 10mmol) in THF (20ml). After stirring at room temperature overnight the mixture was refluxed for 6 days. No isocyanate was formed.

2) The above experiment was repeated except that the THF was removed after stirring overnight and was replaced with 1,3,5 -trichlorobenzene. After 48h reflux, no isocyanate (53) was formed.

3) A solution of phosgene (1g) in chlorobenzene (20ml) was added over 1h to a solution of saccharin (52) (2.15g, 10mmol) in chlorobenzene (20ml) at 120°C. Hydrochloric acid was evolved and infra ref spectroscopy indicated that the saccharin was all consumed. After 36h at 120°C

no isocyanate was formed.

4) Phosgene was bubbled through a solution of saccharin (52) (2.15g, 10mmol) in 1,3,5 -trichlorobenzene (20ml) at reflux for 4h. After refluxing for a further 4 days no isocyanate (53) was formed.

Experiment 59

The Attempted Preparation of Benzyloxysulphonyl isocyanate (116)

1) A solution of chlorosulphonyl isocyanate (1.41g, 10mmol) in toluene (10ml) was added over 30 min to benzyl-alcohol (1.08g, 10mmol) in toluene (10ml). A precipitate formed and the mixture was refluxed overnight. Hydrochloric acid was liberated and a strong isocyanate absorbtion in the infra red spectrum (2220cm^{-1}) was noted. After removing the solvent under reduced pressure the residue was fractionally distilled to give the impure isocyanate (116) (1.45g), 88^{o}C at 0.35mm Hg, ν_{max} (neat) 3015 (m), 2915 (m), 2220 (s), 1595 (m), 1515 (m), 1495 (m), 1455 (m), 1380 (s), 1175 (s), 725 (s), 700 (m) and 655 (m) cm^{-1}, δH ($CDCl_3$) 7.1 (m), 3.93 (d, J = 2Hz), 2.43 (1H, s) and 2.23 (3H, d, J = 4Hz).

2) The above experiment was repeated using chloro-benzene as the solvent. On warming to 100^{o}C a violent release of hydrochloric acid occurred with the formation of a large amount of polymeric material.

3) Chlorosulphonyl isocyanate was added slowly to a solution of succinimide (1g, 10mmol) in acetonitrile (5ml). After stirring for 1h the solution was cooled to -10^{o}C and the solid filtered off and washed with cold

acetonitrile (1.85g, 77%). This was taken without further purification and was added to benzyl alcohol (8.3g, 10eq) at 0°C with stirring. After warming to room temperature and stirring for 2h a precipitate was observed. The mixture was added to ice/water and the solid was collected by suction filtration (2.25g, 92%). The solid was identified as probably being N(-benzyl-oxysulphonyl)carbamoyl-succinimide from the spectral data below and was taken without further purification. On heating under high vacuum, a small amount of benzyl alcohol was collected at 97°C, 0.3mm Hg. However, the solid failed to decompose to the isocyanate on heating to 200°C at 0.3mm Hg. ν_{max} (jujol mull) 3370 (m), 1750 (s), 1710 (s), 1580 (m), 1325 (m), 1170 (s), 800 (w), 745 (m) and 695 (s) cm^{-1}, δH ($CDCl_3/d^6$acetone) 7.3 (5H, s), 5.05 (2H, s) and 2.7 (4H, d, J = 4Hz), m/e 99, 43, 56, 55, 142, 70, 42, 41, 60 and 98.

Experiment 60

The Preparation of N-(Benzyloxysulphonyl)-O-(2,4,5 -Trichlorophenyl) carbamate (119a)

1) Chlorosulphonyl isocyanate (1.41g, 10mmol) was added over 30 min to a solution of 2,4,6,-trichlorophenol (1.97g, 10mmol) in toluene (5ml). After stirring overnight the mixture was cooled to -10°C and the precipitate which had formed, was collected by suction filtration (2.33g). The solid was then added over 30 min to benzyl alcohol (8g) at -10°C with stirring. After 2h at room temperature a very fine precipitate had appeared and the mixture was added to ice/water (200ml). The oily organic

layer produced was extracted into warm carbon tetrachloride. After removing the solvent under reduced pressure a solid was collected by suction filtration (0.56g). This was shown to be N-(chlorosulphonyl)-O-(2,4,6 -trichlorophenyl)-carbamate (118b) formed in the initial reaction.

2) The foregoing carbamate (118b) (4.3g, 10mmol) was added to a mixture of sodium phenylmethoxide (1.3g) in THF (20ml). An immediate exothermic reaction occurred to give, after removing the solvent under reduced pressure, a gummy solid containing a mixture of products.

3) The foregoing carbamate (118b) (4.3g, 10mmol) was added to a mixture of sodium phenylmethoxide (1.3g) in dichloromethane (20ml) at -18°C. After stirring at room temperature overnight a white precipitate formed which was collected by suction filtration (3.8g) and which was probably N-(benzyloxysulphonyl)-O-(2,4,6 -trichlorophenyl)-carbamate (119b) ν_{max} (nujol mull)3400 (m), 1710 (s), 1600 (m), 1550 (w) and 1230 (m) cm^{-1}, δH (d^6DMSO) 7.2 (2H, s), 7.03 (5H, s) and 4.8 (2H, s), m/e 90, 105, 108, 196, 198, 77, 91, 107, 79 and 151.

Experiment 61

The Attempted Preparation of Benzyloxysulphonyl isocyanate (116)

The solid phase from the above reaction was heated under vacuum (210°C at 0.03mm Hg). No benzyloxysulphonyl isocyanate (116) was formed and the residue was found to have decomposed to an unidentifiable solid.

Experiment 62

The Attempted N-Deblocking of N-(Toluene-4-sulphonyl)-5,6-dihydro-4H-pyran-3-carboxamide (4a)

Chromium II acetate (0.7g, 5mmol) was added to a stirred solution of the title compound (4a) (0.28g, 1mmol) in dry THF (10ml) under nitrogen. After stirring at room temperature for 1 week the starting material had all been consumed and a new absorbtion appeared at 1640cm^{-1} in the infra red spectrum. Attempts to isolate the non β-lactam product by column chromatography on silica resulted in decomposition.

Experiment 63

Attempted N-Deblocking of 8-(Toluene-4-sulphonyl)-8-aza-2-oxabicyclo[4.2.0]octan-7-one (3a).

1) Chromium II acetate (0.7g, 5mmol) was added to a stirred solution of the title compound (3a) (0.28g, 1mmol) in dry THF (10ml) under nitrogen. After 3 min at room temperature the mixture was added to a dilute solution of sodium hydrogen carbonate, extracted with diethyl ether (50ml), dried and evaporated to give an oil (0.1g). An attempt to separate the mixture by column chromatography on silica gave an intractible mixture of compounds.

2) The experiment above was repeated except that it was carried out at 0^{o}C. Reaction was complete after 4h, however, on attempted product isolation and purification the material decomposed.

3) Freshly prepared aluminium amalgam[1](0.2g, excess) was added to a stirred solution of the β-lactam (3a) (0.28g, 1mmol) in THF (10ml). After 48h at room

temperature the mixture was worked up as above, however, no β-lactam products could be isolated from the mixture.

4) The previous reaction was repeated except that it was carried out at -20°C. After 72h the reaction was worked up as above. No β-lactam products could be isolated from the mixture.

5) The previous reaction was repeated except a larger excess of aluminium amalgam (1.6g) was used. After 3h reaction was complete but work up as previous yielded no β-lactam containing products.

6) A solution of the β-lactam (3a) (0.28g, 1mmol) in THF (15ml) at 0°C was deoxygenated with a stream of nitrogen. To this was added a deoxygenated solution of ammonium acetate (0.65g) in a mixture of water (2ml) and a solution of titanium III chloride in 30% hydrochloride acid (0.62ml, 1.1mmol). Reaction was instantaneous but the β-lactam ring did not survive the reaction conditions.

7) The reaction was carried out as above except that it was performed at -20°C. No β-lactam was present in the crude product.

8) The reaction was carried out as above except ethylenediaminetetraacetic acid tetra-sodium salt (0.38g, 1.3eq) was added to the titanium III chloride solution followed by sufficient 0.880 ammonia to raise the pH to a value of 7.0. No β-lactam could be isolated.

9) The β-lactam (3a) (0.28g, 1mmol) was dissolved in THF (15ml) and was left at 0°C. After 48h no β-lactam containing material remained in the solution and a complex mixture of products had been formed.

10) The β-lactam (3a) (0.28g, 1mmol) was dissolved in

THF (16ml) and water (0.5ml) was added to the solution at $0^{o}C$. The β-lactam disappeared instantaneously to give a complex mixture of products similar to those obtained in the preceeding reactions.

Experiment 64

The Attempted N-Deblocking of 1-(2,2,2 -Trichloroethoxy-sulphonyl)-1-azaspiro-[3,5]-nonan-2-one (25)

1) The β-lactam (25) (0.35g, 1mmol) was added to sodium iodide (0.16g, 1.1eq) in acetone (20ml) with stirring at room temperature. After 1 week the solvent was removed under reduced pressure to give a complex mixture containing no β-lactams.

2) The above experiment was repeated without using sodium iodide. No reaction was observed and the starting material was recovered.

3) The β-lactam (25) (0.35g, 1mmol) was added to tri-n-butyl-N-methyl ammonium iodide (0.36g, 1.1eq) in THF (8ml) with stirring at room temperature. After 1 week the solvent was removed under reduced pressure to give a complex mixture containing no β-lactam.

4) The above experiment was conducted in the absence of the quaternary ammonium salt. No reaction was observed and the starting material was recovered.

5) Activated zinc dust (0.1g) was added to a solution of the β-lactam (25) (0.35g, 1mmol) in THF (20ml) with stirring. After 1 week no reaction was observed and starting material was recovered.

Experiment 65

The Reduction of 1-(2,2,2 -Trichloroethoxysulphonyl)-1-azaspiro-[3,5]-nonan-2-one (25)

1) Activated zinc dust (0.1g) was added to a mixture of the β-lactam (25) (0.35g, 1mmol) and ammonium chloride (0.11g, 2mmol) in aqueous THF (20ml). After 72 h the mixture was filtered through a celite pad and the filtrate extracted with diethyl ether (100ml). The ethereal layer was washed with water (20ml), dried (magnesium sulphate) and evaporated under reduced pressure to give a yellow oil. Chromatography on silica gel afforded two main products: a colourless oil 1-azaspiro[3,5]-2-one (86) (41mg, 30%), ν_{max} ($CHCl_3$) 3410 (w), 2940 (m), 2860 (w), 1745 (s), 1375 (m), 1120 (m) and 1050 (m) cm^{-1}, δH ($CDCl_3$) 7.6-7.0 (1H, br), 2.7 (2H, s), and 2.1-1.4 (10H, br), m/e 96, 81, 54, 67, 68, 55, 82, 97, 69 and 95, and cyclohex-1-ene-acetamide (87) (15mg, 11%), m.p. 146-148°C, ν_{max} ($CHCl_3$), 3520 (w), 3410 (w), 2915 (m), 1675 (s), 1575 (m), 1360 (m) and 1125 (m) cm^{-1}, δH ($CDCl_3$) 6.9-5.5 (2H, br), 5.9-5.5 (1H, s), 2.85 (2H, s), 2.01 (4H, br) and 1.63 (4H, br), ^{13}C NMR 173.7 (s), 133.1 (s), 126.8 (s), 46.0 (s), 28.4 (s), 25.4 (s), 22.8 (s) and 22.0 (s), m/e 44, 39, 41, 59, 67, 53, 55, 79, 82 and 61. (Found: C, 69.0; H, 9.5; N, 10.1. $C_8H_{13}NO$ requires C, 69.1; H, 9.4; N, 10.1%

2) The above experiment was repeated except that no zinc was used. After 1 week the β-lactam (25) was recovered unaltered.

Experiment 66

The N-Deblocking of 1-(2,2,2 Trichloroethylsulphonyl)-1-azaspiro-[3,5]-nonan-2-one (45a) by Zinc under Neutral conditions

1) The β-lactam (45a) (0.33g, 1mmol) was dissolved in THF (4ml) and added to ammonium chloride (0.11g, 2eq) dissolved in the minimum of water. Activated zinc dust (0.1g) was then added with vigorous stirring. After five weeks the mixture was filtered through a celite pad and the filtrate extracted with diethyl ether (50ml). The ethereal layer was washed with water (10ml), dried (magnesium sulphate) and evaporated under reduced pressure to give an oil (0.12g). Separation of the products by column chromatography on silica with a petroleum, dichloromethane mixture gave a colourless oil, 1-azaspiro-[3,5]-nonan-2-one (86) (0.026g, 19%), identical with an authentic sample[2], and cyclohex-1-eneacetamide (87) (0.094g, 68%), m.p. 146-148°C, ν_{max} ($CHCl_3$) 3520 (m), 3490 (m), 2915 (m), 1675 (s), 1575 (m), 1360 (m), 1125 (m) and 905 (s) cm^{-1}, δH ($CDCl_3$), 6.8-5.5 (3H, m), 2.85 (2H, s), 2.01 (4H, br) and 1.63 (4H, br), m/e 44, 39, 41, 59, 67, 53, 55, 79, 82 and 61, (Found: C, 69.0; H, 9.5; N, 10.1. $C_8H_{13}NO$ requires C, 69.03; H, 9.41; N, 10.06%).

2) The above experiment was repeated except that no zinc was employed. After five weeks a small amount of decomposition had occurred but most of the β-lactam (45c) (0.29g) was recovered.

Experiment 67

The N-Deblocking of 1-(2,2,2 -Trichloroethylsulphonyl)-1-azaspiro-[3,5]-nonan-2-one (45a) by Sodium Dithionite

1) The β-lactam (45a) (0.033g, 0.1mmol) was added to a mixture of sodium dithionite (0.035g, 2 eq) and tetra-n-butyl ammonium iodide (3 crystals) in DMF (0.4ml). After stirring at room temperature for 2 weeks no further change was evident and the solvent was removed under reduced pressure to give an oil. Separation of the components of the oil by PLC using a 50% petroleum ether, dichloromethane mixture gave the starting material (45a) (0.0055g, 17%) m.p. 135°C and 1-azaspiro-[3,5]-nonan-2-one (86) (0.0033g, 24%) which was identical with an authentic sample.

2) The above reaction was repeated using 15-Crown-5 as the phase transfer catalyst. Separation of the products on PLC using a 50% petroleum ether, dichloromethane mixture gave the starting material (45a) (0.071g, 21%) m.p. 135°C and 1-azaspiro- 3,5 -nonan-2-one (86) (0.01g, 72%) which was identical with an authentic sample.

Experiment 68

The Attempted Deprotection of 8-(2-Nitrobenzenesulphonyl)-8-aza-2-oxabicyclo[4.2.0]-octan-7-one (43b)

3,4 -Dihydropyran (0.42g, 5mmol) was added to a solution of 2-nitrobenzenesulphonyl isocyanate (42) (1.14g, 5mmol) in chloroform (4ml) at 0°C. After 3h the infra red spectrum indicated that the amount of β-lactam (43b) formed had reached its maximum and the solvent was removed under reduced pressure at low temperature. The residue, which still contained β-lactam, was redissolved

in THF (30ml) and to this solution was added 10% palladium on carbon catalyst (0.5g). Hydrogenation of the mixture resulted in the uptake of hydrogen (114ml) over 1.5h. The catalyst was removed by filtration through a pad of silica and the resulting solution examined by infra red. No β-lactam was present in the product which was shown by TLC to be a complex mixture of components.

Experiment 69

The Attempted N-Deblocking of 1-(2-Nitrobenzenesulphonyl)-1-azaspiro[3,5]-nonan-2-one (45b)

The β-lactam (45b) (0.324g, 1mmol) was dissolved in diethyl ether (10ml) and to this was added 10% palladium on charcoal catalyst (0.1g). The mixture was hydrogenated at atmospheric pressure and stopped after 12hr when it had taken up 123cm^3 of hydrogen. The catalyst was removed by filtration through a celite pad and the solvent was removed under reduced pressure. Recrystallisation of the residue from diethyl ether afforded 1-(2-aminobenzenesulphonyl)-1-azaspiro-[3,5]-nonan-2-one (89) as a crystalline solid (0.261g, 78%), m.p. 215-216°C, ν_{max} ($CHCl_3$), 3485 (m), 3430 (m), 1795 (s), 1625 (m), 710 (m) and 630 (m) cm^{-1}, δH ($CDCl_3$), 8.8-6.6 (4H, m), 5.5-5.0 (2H, br), 2.75 (2H, s) and 2.4-1.0 (10H, br), m/e 122, 121, 91, 198, 208, 98, 137, 65, 92 and 96 (Found: C, 57.27; H, 6.17; N, 9.52, $C_{14}H_8N_2O_3S$ requires C, 57.12; H, 6.16; N, 9.52%).

Experiment 70

The Attempted Reduction of 1-(2,2,2 -trichloroethyloxy-sulphonyl)-7-phenyl-1-azaspiro-[3,5]-nonan-2-one (111) to 2-oxo-7-phenyl-1-azaspiro-[3,5]-nonane-1-sulphonic acid (113b)

1) A solution of bis-ethylenediamine chromium II perchlorate complex[3] in DMF (0.50 mmol, 4ml, 2 eq) was added to a solution of the β-lactam (111) (0.42 g, 1mmol) in DMF (1ml) at room temperature. The purple colour of the complex was discharged instantaneously. After stirring overnight the solution was partitioned between diethyl ether (100ml) and water (50ml). The ethereal layer was dried (sodium sulphate), and the solvent removed under reduced pressure, the residue being recrystallised from THF and petroleum to give 7-phenyl-1-azaspiro-[3,5]-nonan-2-one (112b), (0.081g, 38%), m.p. 155-157°C, ν_{max} (nujol mull) 3180 (m), 1740 (s) and 700 (m) cm^{-1}, δH ($CDCl_3$), 7.61 (1H, br), 7.25 (5H, septet, J=7.8Hz), 2.73 (2H, s), 2.55 (1H, dt, J=12, 3.6Hz), 2.10-1.7 (4H, m), and 1.7-1.5 (4H, m), m/e 104, 91, 172, 143, 79, 130, 115, 116, 105 and 78.

2) The β-lactam (111) (0.39g, 0.9mmol) was added to a mixture of zinc/copper couple (0.1g) and THF (4ml)[4]. After stirring overnight at room temperature the mixture had solidified and no further stirring was possible. The mixture was added to THF (50ml) at reflux, when all the white precipitate had dissolved it was filtered through a pad of celite. The THF was removed under reduced pressure to give a white solid (0.34g) which was purified by column chromatography on silica to give the starting

β-lactam (111) (0.014g, 4%) and 7-phenyl-1-azaspiro-[3,5]-nonan-2-one (112b), (0.052g, 26%), m.p. 156°C which was identical with an authentic sample.

3) The above experiment was repeated except that the mixture was stirred at 55°C for 2 days. Column chromatography on silica gave 7-phenyl-1-azaspiro-,3,5.-nonan-2-one (112b) (0.082g, 42%), m.p. 156°C.

4) The β-lactam (111) (0.42g, 1mmol) was added to a mixture of zinc/copper couple (0.1g) and THF (4ml). After stirring at 45°C overnight the solvent was removed under reduced pressure and the residue was added to water (20ml). Concentrated hydrochloric acid was added until the white precipitate had all dissolved whereupon the solution was extracted with diethyl ether (2 x 50ml). After washing the ethereal layer with water, it was dried (sodium sulphate) and evaporated under reduced pressure, the residue being recrystallised from THF and petroleum to give 7-phenyl-1-azaspiro-[3,5]-nonan-2-one (112b), (0.077g, 37%), m.p. 156°C.

5) The above experiment was repeated using a larger excess of zinc/copper couple (0.5g). Stirring overnight at 45°C gave 7-phenyl-1-azaspiro-[3,5]-nonan-2-one (112b) (0.081g, 41%), m.p. 156°C.

Experiment 71

The Attempted Reduction of 1-(2,2,2 -Trichloroethoxy-sulphonyl)-4-phenyl-azetidin-2-one (109) to 2-Oxo-4-phenylazelidine-1-sulphonic acid (113a)

1) The β-lactam (109) (0.175g, 0.5mmol) was added to a mixture of zinc/copper couple (0.04g) and THF (4ml).

After stirring overnight at 45°C the mixture was filtered through a pad of celite. The filtrate was washed with a saturated ammonium chloride solution, dried and evaporated under reduced pressure to give a solid residue which was recrystallised from ethyl acetate and petroleum to give 4-phenylazetidin-2-one (112a) (0.071g, 97%), m.p. 105°C (lit m.p. 108-109°C)[5], ν_{max} (CH_2Cl_2), 3400 (m) and 1755 (s) cm^{-1}, δH ($CDCl_3$) 7.4 (5H, s), 6.7-5.9 (1H, br), 4.66 (1H, dd, $\underline{J}$=4, 3Hz), 3.4-2.82 (2H, ABX system, $\underline{J}_{AB}$=15Hz, $\underline{J}_{AX}$= 4Hz, $\underline{J}_{BX}$=3Hz).

2) The above experiment was repeated except using less zinc/copper couple (0.02g). After 3 days the work up described above gave an oil which was purified by column chromatography on silica using a petroleum ether, dichloromethane mixture to give the starting β-lactam (109) (0.044g, 25%), m.p. 102°C and 4-phenylazetidin-2-one (112a) (0.040g, 54%), m.p. 105°C, which was identical with an authentic sample.

3) The above experiment was repeated using zinc powder (0.07g) and the β-lactam (109) (0.08g). After 3 days column chromatography on silica gave the starting β-lactam (109) (0.011g, 14%), m.p. 102-104°C and 4-phenylazetidin-2-one (112a) (0.025g, 76%), m.p. 105°C; this was identical with an authentic sample.

4) The above experiment was repeated using less zinc/copper couple (0.02g) and diethyl ether (4ml). No reaction was evident after 1 week and the starting β-lactam (109) was recovered.

Experiment 72

The Attempted Reduction of 1-(2,2,2 -Trichloroethoxy-sulphonyl)-4-phenylazetidin-2-one (109) to 1-oxo-4-phenylazetidine-1-sulphonic acid (113a) using a chromium (II) complex.

1) To a stirred solution of the β-lactam (109) (0.175g, 0.5mmol) in DMF (1ml) was added a solution of bis-ethylenediamine chromium (II) perchlorate in aqueous DMF (2ml, 1mmol, 0.5 molar solution).[3] The purple colour of the complex was discharged immediately and the resulting green solution was added to diethyl ether (20ml) and was extracted with water (10ml). The ether layer was dried and evaporated under reduced pressure. The residue was recrystallised from THF and petroleum to give 4-phenyl-azetidin-2-one (112a) (0.064g, 87%), m.p. 105°C, (lit. m.p. 108-109°C)[5], ν_{max} (CH_2Cl_2) 3400 (m) and 1760 (s) cm^{-1}. δH ($CDCl_3$), 7.4 (5H, s), 6.7-5.9 (1H, br), 4.66 (1H, dd, $\underline{J}$=4, 3Hz), 3.4, 2.82 (2H, ABX system, $\underline{J}_{AB}$=15Hz, $\underline{J}_{AX}$=4Hz, $\underline{J}_{BX}$=3Hz).

2) The above experiement was repeated using a solution of chromium (II) perchlorate in water (0.612ml, 1mmol, 1.63 molar). Reaction was complete after 2 mins and a similar work up gave 4-phenylazelidin-2-one (112a) (0.069g, 94%), m.p. 105°C which was identical with an authentic sample.

Experiment 73

The Attempted N-Deprotection of 8-chlorosulphonyl-6-methyl-8-aza-2-oxabicyclo [4.2.0]octan-7-one (94a)

1) A solution of the crude β-lactam (94a) (0.24g, 1mmol) from experiment in chloroform (4ml) at -18°C was added to a rapidly stirred mixture of water (0.1g), ice (0.45g), sodium sulphite (0.17g) and sodium hydrogen carbonate (0.24g) at 0°C. After stirring vigorously for 1h no starting material remained. The mixture was extracted into diethyl ther, dried and evaporated under reduced pressure to give a complex mixture of products none of which contained the β-lactam moiety.

2) The above reaction was repeated except that a solution of the crude β-lactam (94a) (0.24g, 1mmol) in THF (4ml) at -18°C was used. Again, there was no sign of any β-lactam in the intractable mixture of products.

3) Thiophenol (0.2ml, 1 eq) was added to a solution of the crude β-lactam (0.24g, 1mmol) in chloroform (4ml) at 0°C. Pyridine (0.1ml, 2 eq) was then added to this slowly, with stirring. After stirring for 2h a fine precipitate had formed. The solution infra red spectrum revealed that no β-lactam remained in the mixture which contained a complex mixture of products.

4) A solution of propane-1,3-dithiol (0.11g, 1 eq) and ethyldi-isopropylamine (0.13g, 1 eq) in THF (5ml) was added slowly to a solution of the crude β-lactam (94a) (0.24g, 1mmol) in dichloromethane (5ml) at -78°C. After 1h no β-lactam remained in the solution which contained a complex mixture of products.

Experiment 74

The Attempted N-Deblocking of 8-(2,2,2 -Trichloroethoxy-sulphonyl)-6-methyl-8-aza-2-oxabicyclo[4.2.0]octan-7-one (94b)

1) Zinc/copper couple[4] (0.1g) was added to a rapidly stirred solution of the crude β-lactam (94b) (0.35g, 1mmol), from experiment no in THF (4ml) at room temperature. After stirring for 3 weeks the mixture was filtered through a pad of celite and the solvent was removed under reduced pressure to give a mixture of a solid and an oil. The oil (0.11g) dissolved in chloroform and was separated from the solid (0.14g), it proved to be unstable on silica and was destroyed when attempting to purify by column chromaotgraphy. The solid contained a carbonyl stretch at 1720cm^{-1} but was insoluble in deuterated solvents and could not be identified.

2) The above reaction was repeated except it was performed at 50^{o}C. After stirring overnight the reaction was worked up as above and gave the white solid (0.13g) and an oil (0.19g). The oil again proved unstable on silica and the white solid appeared to be identical to the one obtained above.

3) Freshly prepared aluminium amalgam[1](0.5g) was added to a solution of the crude β-lactam (94b) (0.35g, 1mmol) in THF (4ml) with rapid stirring at room temperature. After 18h, no β-lactam remained in the solution which contained a complex mixture of compounds.

Experiment 75

The Attempted Reduction of 1-(2,2,2-Trichloroethoxysulphonyl)-4-phenylazetidin-2-one (109) with Aluminium Amalgam

To a solution of 1-(2,2,2-Trichloroethoxysulphonyl)-4-phenylazetidin-2-one (109) (0.21g, 0.6mmol) in THF (4ml) was added freshly prepared aluminium amalgam[1] (excess). After stirring under nitrogen for 3 weeks at room temperature, no reaction had occurred.

Experiment 76

The Preparation of 6-Methyl-8-aza-2-oxabicyclo[4.2.0] octan-7-one (95)

1) Benzylamine (0.12g, 1.3 eq) was added to a solution of crude 6-methyl-8-trifluoroacetyl-8-aza-2-oxabicyclo [4.2.0]octan-7-one (94c) (0.24g, 1mmol) in dichloromethane (10ml) at -78°C. After stirring for 1h, the solvent was removed under reduced pressure and the residue purified by column chromatography on silica using a dichloromethane, petroleum ether mixture to give the title compound (95) (0.058g, 41%), m.p. 45-48°C, ν_{max} (CH_2Cl_2) 3380 (m), 2850 (m), 1750 (s) and 1600 (w) cm^{-1}, δH ($CDCl_3$), 7.0-6.3 (1H, br), 4.85 (1H, s), 3.8 (2H, t, J=9Hz), 2.0-1.5 (4H, m), and 1.25 (3H, s), m/e 98, 83, 41, 69, 42, 39, 43, 68 and 55 (Found: C, 59,77; H, 7.80; N, 9.85. $C_7H_{11}NO_2$ requires C, 59.56; H, 7.85; N, 9.92%).

2) Crude 6-methyl-8-trifluoroacetyl-8-aza-2-oxabicyclo[4.2.0]octan-7-one (94a) (0.24g, 1mmol) was chromatographed on florisil (10g) using diethyl ether

(400ml). The ether was removed under reduced pressure and the residue repurified by column chromatography on silica using a dichloromethane, petroleum ether mixture to give the title compound (95) (0.087g, 62%), m.p. 45-48°C, which was identical to the sample obtained previously.

Experiment 77

The Preparation of 6-Benzyl-8-aza-2-oxabicyclo[4.2.0] octan-7-one (104)

1) Crude 8-(trifluoroacetyl)-6-benzyl-8-aza-2-oxa-bicyclo[4.2.0]octan-7-one (103) (0.31g, 1mmol) was chromatographed on florisil (10g) with diethyl ether (500ml) as eluant. The ether was removed under reduced pressure and the residue purified by column chromatography on silica using a dichloromethane, petroleum ether mixture to give starting enol ether (102) (0.045g, 25%), and the title compound (104) (0.088g, 40%), m.p. 95-99°C ν_{max} ($CHCl_3$) 3410 (m), 2950 (w), 1765 (s), 1650 (w), 1360 (m), and 1105 (m), δH 7.23 (5H, s), 6.2 (1H, br), 4.96 (1H, s), 3.76 (2H, t, J=6Hz), 3.03 and 2.72 (2H, Abq, J=14Hz), and 2.2-1.3 (4H, m), m/e 91, 174, 115, 118, 117, 83, 129, 173, 128 and 175 (Found: C, 71.52; H, 6.96; N, 6.47. $C_{13}H_{15}NO_2$ requires C, 71.87; H, 6.96; N, 6.45%).

2) The above experiment was repeated using the crude β-lactam (0.31g). Column chromatography on silica using a dichloromethane, petroleum ether mixture gave the title compound (104) (0.091g, 41%) which was identical with the above product.

Experiment 78

The N-Deblocking of 1-(Trifluoroacetyl)-1-azaspiro[3,5] nonan-2-one (83)

1) Reaction of trifluoroacetyl isocyanate (79) (0.70g, 5mmol) with methylenecyclohexane (0.48g, 5mmol) in chloroform (5ml) yielded a mixture of N-trifluoroacetyl compounds. On removing the solvent under reduced pressure the resulting oil was passed down a column of florisil (10g) with diethyl ether (500ml). The diethyl ether was removed under reduced pressure to give an oil (1.068g), the components of which were separated by chromaography on silica using a dichloromethane, petroleum ether mixture. The major components were identified as cyclohex-1-eneacetamide (87) (0.244g, 31%) m.p. 146-148°C, identical with the previous sample, and 1-azaspiro-[3,5]-nonan-2-one (86) (0.257g, 37%) as an oil, identical with the previous sample.

2) Reaction of trifluoroacetylisocyanate (79) (0.70g, 5mmol) with methylenecyclohexane (0.48g, 5mmol) in chloroform (5ml) yielded a mixture of N-trifluoroacetyl compounds. On removing the solvent under reduced pressure, the resulting oil was redissolved in dichloromethane (10ml) and cooled to -78°C. Benzylamine (0.59g, 1.1 eq) was added and the mixture stirred for a further 2h after which it was warmed up to room temperature. The solvent was removed under reduced pressure to give an oil which was separated by column chromatography on silica using a petroleum ether, dichloromethane mixture to give N-benzyltrifluoroacetamide, (0.512g, 51%), m.p. 74-75°C,[6] cyclohex-1-eneacetamide (87)

(0.075g, 11%), m.p. 146-148°C and 1-azaspiro-[3,5]-nonan-2-one (86) (0.238g, 34%), oil, all of which were identical authentic samples.

Experiment 79

The Deprotection of 3R-(Trimethylsilyloxymethyl)-4R,5R-(Trimethylsilyloxy)-8-(Trifluoroacetyl)-2-oxa-8-aza-bicyclo[4.2.0]octan-7-one (106b).

1) The crude β-lactam (106b) from experiment no. 48 (0.32g) was chromatographed on florisil (10g) using diethyl ether (500ml) as eluant. The solvent was removed under reduced pressure to give an oil (0.122g) from which a solid crystallised (0.032g). This was insoluble in deuterated solvents but was shown by infra red spectrum not to be a β-lactam. The oil, however, did contain the deprotected β-lactam moiety and Trimethylsilyloxy groups. The oil was dissolved in THF (20ml) and trifluoroacetic acid (10mg) was added. After 2h the solvent was removed under reduced pressure to give an insoluble gum which was shown by infra red to contain a complex mixture of products, ν_{max} ($CDCl_3$) 3420 (s), 2970 (s), 1755 (s), 1670 (s), 1590 (w), 1180 (s) and 1080 (s) cm^{-1}. δH ($CDCl_3$) 5.25 (d, J=5Hz), 4.2-3.2 (m) and 0.0 (s).

2) The crude mixture from experiment no 48 (0.32g) was chromatographed on florisil with diethyl ether (500ml) as eluant. Removal of the solvent under reduced pressure gave an oil which was shown to contain a complex mixture of products but no β-lactam.

3) The crude product from experiment no 48 (0.31g) was chromatographed on florisil (10g) with diethyl ether

(500ml) as eluant. Removal of the solvent under reduced pressure gave an oil (0.315g) which contained β-lactam absorbtions in the infra red spectrum. Examination of the mixture by TLC on alumina and silica plates revealed an inseparable mixture of products and the experiment was abandoned.

Experiment 80

The Preparation of 4-Phenylmethylenecyclohexane (110)

Methyltriphenylphosphonium bromide (71.4g, 0.2mmol) was added slowly to a solution of butyllithium (0.22mmol) in diethyl ether (400ml) with rapid stirring. After 4h, 4-phenylcyclohexanone (38.33g, 0.22mmol) was added slowly to the red solution which became colourless and formed a precipitate. The mixture was refluxed overnight and after cooling to room temperature, the precipitate was filtered off, the solid being washed with diethyl ether (100ml). The combined ethereal filtrates were extracted with water (100ml) until neutral and were dried over calcium chloride. Removal of the ether by distillation through a vigreux column followed by fractional distillation under vacuum gave the title compound (110) (12.72g, 37%), b.p. 124°C at 17mmHg, ν_{max} (neat) 2940 (s), 1710 (s), 1600 (m), 1495 (m), 1450 (m), 760 (s) and 700 (s) cm^{-1}, δH ($CDCl_3$) 7.15 (5H, s), 4.6 (2H, s) and 2.85-1.1 (9H, m), m/e 57, 56, 104, 172 ($M^{+\cdot}$), 143, 71, 55, 86, 130 and 117, (Found: C, 90.34; H, 9.64; $C_{13}H_{16}$ requires C, 90.64; H, 9.36%).

Experiment 81

The Preparation of 1-(Chlorosulphonyl)-7-phenyl-1-aza-spiro-[3,5]-nonan-2-one

Chlorosulphonyl isocyanates (1.41g, 10mmol) was added to methylene-4-phenylcyclohexane (110) (1.7g, 10mmol) in diethyl ether (3ml) at $0^{o}C$. The mixture immediately became hot and formed a white precipitate which was collected by suction filtration. Recrystallisation from THF and petroleum afforded the title compound (2.1g, 67%), m.p. 90-91^{o}C, ν_{max} (nujol) 1815 (s), 1405 (s), 1190 (s), 1145 (s), 1080 (s), 1060 (s), 940 (m) and 770 (s) cm^{-1}, δH ($CDCl_3$/d^6DMSO) 7.25 (5H, s), 3.1 (2H, s), and 3.1-1.5 (9H, m), m/e 104, 91, 64, 313 (M^{+}), 36, 28, 48, 80, 172 and 79, (Found: C, 53.3; H, 5.0; N, 4.5. $C_{14}H_{16}ClNO_3S$ requires C, 53.6; H, 5.1; N, 4.5%).

Experiment 82

The Preparation of 7-Phenyl-1-azaspiro-[3,5]-nonan-2-one (112b)

1-(Chlorosulphonyl)-7-phenyl-1-azaspiro- 3,5 -nonan-2-one (1.8g, 6mmol) dissolved in THF (20ml) was added to a stirred mixture of water (6.8ml), sodium hydrogencarbonate (2.83g) and sodium sulphite (2.23g) at room temperature. After stirring vigorously overnight the mixture was extracted with diethyl ether (2 x 100ml) and the combined ethereal layer was washed with water, dried (sodium sulphate) and evaporated under reduced pressure. The residue was recrystallised from ethyl acetate and petroleum to give the title compound (112b)

(0.96g, 78%), m.p. 155-157°C, ν_{max} (nujol mull) 3180 (m), 1740 (s), and 700 (m) cm^{-1}, δH ($CDCl_3$, 250 MH_3), 7.61 (1H, br), 7.25 (5H, m), 2.73 (2H, s), 2.6-2.3 (1H, m), 2.10-1.7 (4H, m), and 1.7-1.5 (2H, m), m/e 104, 91, 172, 143, 79, 130, 115, 116, 105 and 78, (Found, C, 77.9; H, 8.2; N, 6.3. $C_{14}H_7NO$ requires C, 78.1; H, 7.9; N, 6.5%).

Experiment 83

The Preparation of 2-Oxo-7-phenyl-1-azaspiro-[3,5]-nonane-1-sulphonic acid (113b)

Pyridine-sulphur trioxide (0.95g, 2 eq) was added to the azetidinone (112b) (0.62g, 3mmol) in DMF (5ml) with stirring. After stirring at room temperature overnight the solution was poured into diethyl ether (60ml) with rapid stirring. The white precipitate which formed was filtered off and dried in air. After dissolving in water the compound was chromatographed on ambertyst IR 120 H with water and the residue, after removing the eluent under reduced pressure was recrystallised from THF and petroleum to give the title compound (113b) (0.65g, 88%), m.p. 187°C, ν_{max} (THF) 1715 (s) and 1625 (s) cm^{-1}, δH (CD_3OD), 8.25 (5H, s), 3.25 (2H, s) and 3.1-1.7 (9H, m), m/e 91, 95, 78, 105, 77, 115, 94, 92, 156 and 172.

Experiment 84

The Preparation of 2-Oxo-4-phenylazetidine-1-sulphonic acid (113a)

1) 4-Phenylazetidin-2-one (112a) (1.5g, 10mmol) dissolved in DMF (20ml) was added to sulphur trioxide-pyridine (3.2g, 2 eq). After 8h at room temperature, the solution was poured into diethyl ether (200ml) with stirring to give a white solid (3.7g). This was then dissolved in water (2ml) and was chromatographed on Amberlyst IR120H eluting with water. The solvent was removed under reduced pressure and the residue recrystallised from THF and petroleum to give the title compound (113a) (2.05g, 91%), m.p. 161°C, ν_{max} (THF), 2450 (m), 1715 (s) and 1300 (m) cm^{-1}, δH (CD_3OD), 8.3 (5H, s), 5.45 (1H, dd, J4Hz, 11Hz), and 3.6-3.15 (2H, m), m/e 77, 51, 47, 103, 102, 50, 104, 131, 64 and 78.

2) The above experiment was repeated except that the intermediate pyridinium sulphonate (0.40g) was dissolved in a mixture of dichloromethane and water (1:1, 20ml). The pH of the aqueous solution was raised to pH 6.5 with potassium hydroxide solution (2 Molar) and the aqueous layer was extracted with dichloromethane (3 x 20ml). The extract was evaporated to dryness under reduced pressure and the residue was extracted with methanol (20ml), the

residue of potassium sulphate being removed by filtration. The methanol was removed under reduced pressure and the residue was retreated with methanol. Recrystallisation of the residue from THF and petroleum afforded the title compound (113a) (100mg, 45%), which was identical to the sample prepared previously.

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APPENDIX I

Biological activity was tested for by ICI Pharmaceuticals. A standard solution of each compound was prepared ($256\mu g ml^{-1}$) and was then diluted, sequentially by a factor of two to give a range of concentrations. These solutions were then used to prepare culture plates onto which various strains of bacteria were introduced. Following a period of incubation, the concentration of compound at which each strain of bacteria failed to thrive was noted, in order to ascertain the level of anti-bacterial activity, if any. The bacteria used are arranged into five groups as follows.

GROUP 1

A1	STREP PYOGENES	streptococcus
A2	STREP FAECALIS	streptococcus
A3	STAPH AUREUS (B-LASE +)	staphylococcus
A4	STAPH AUREUS (B-LASE +)	staphylococcus
A8	E.COLI	E scherischia
A25	E.COLI	E scherischia
A20	S DUBLIN	Salmonella
A10	K AEROGENES	Klebsiella
A24	K PNEUMONIAE	Klebsiella
A13	E COLAACAE	Enterobacter
A16	S MARCESCENS	Serralia
A18	P MIRABILIS	Proteus
M11	P VULGARIS	Proteus
M5	P MORGANII	Proteus
PR2	P RETTGERI	Proteus

PV9	PROV STUARTII	Proviclencia
A21	PS AERUGINOSA	Pseudomonas
SL	SARCINA LUTEA	
A23	C ALBICANS	Candida

GROUP 2 - Mouse Virulent Strains

E18	E COLI (B-LASE +)
E1	E COLI
E13	E COLI
K17	K PNEUMONIAE
F1	E CLOACAE
F4	E CLOACAE
S3999	S MARCESCENS
P15	D VULGARIS
P19	P MIRABILIS

GROUP 3 - H Influenzae, B fragilis and Cwelchii strains

H7	H INFLUENZAE	HAEMOPHILUS
H21	H INFLUENZAE	
46453	H INFLUENZAE	
55560	H INFLUENZAE	
B5	B FRAGILIS	
B6	B FRAGILIS	
B7	B FRAGILIS	
B8	B FRAGILIS (B-LASE+)	

CW1	C WELCHII	
CW2	C WELCHII	
CW3	C WELCHII	

GROUP 4

X1	E CLOACAE (18410P, P99+)	1A BLASE+
X2A	E CLOACAE (18410M, P99N)	BLASE-
X3	E COLI (TEM+)	3A BLASE+
X4	E COLI (R-1570E)	BLASE-
X51	K AEROGENES (K1, 1082E)	4C BLASE+
X6	K AEROGENES (K, 1522E)	BLASE-
X7	PS AERUGINOSA (PS19, 15923E)	1D BLASE+
X8	PS AERUGINOSA (PS19/8 1593E)	BLASE-
X9	PS AERUGINOSA (185H)	BLASE + CONSTITUTIVE
X10	E COLI (DC0, UB1005)	
X11	E COLI (DCZ)	ENVELOPE MUTANT
X14	PS AERUGINOSA (799WT)	
X15	PS AERUGINOSA (799/61)	ENVELOPE MUTANT
K-12	E COLI (K12, J53.2)	BLASE-
K12T1	E COLI (K12, J53.2R6K TEM1+)	3A BLASE+
ECT1	E COLI (2025E TEM+)	3A BLASE+
K1251	E COLI (K12, J53.2R100 SHV1+)	BLASE +
K1201	E COLI (K12, J53.2R455 OXA1+)	BLASE+
K1202	E COLI (K12, J53.2R467S OXA2+)	BLASE+
K1203	E COLI (K12, J53.2R576 OXA3+)	BLASE+

GROUP 5

A01	STAPH AUREUS	A17	P.VULGARIS
A02		A18	
A05		A21	
A06		A22	
A8		A23	
A25		A04	
A20		B27	Ps AERUGMOSA
A10		LISV	LISUREIA MONOCYTOGENES
A24		A26	STREP MUTANS
A13		A27	STREP SANGUIS
A16			
X10			
X11			

RESULTS OF TESTS ON COMPOUNDS PREPARED IN THIS THESIS

A) β-lactams

COMPOUND NO		RESULT
1)	25	Not active in Groups 1, 4 at 256μgml^{-1}
2)	112a	Not active in Groups 1, 2, 4 at 256μgml^{-1}
3)	111	active A1, A2, A4, A6, SL at 128μgml^{-1} not active all others in groups 1, 2, 4.
4)	112b	not active in Groups 1, 2, 4 at 256μgml^{-1}
5)	109	not active in Groups 1, 2, 4 at 256μgml^{-1}
6)	113b	not active in Groups 1, 2, 4 at 256μgml^{-1}

7)	113b	active A, A2, at 256µgml^{-1} not active in all other groups 1, 2, 4.
8)	104	not active Groups 1, 2, 4 at 64µgml^{-1}
9)	95	not active Groups 1, 2, 4 at 64µgml^{-1}.

B) non β-lactams

1)	35	active A1, A2, A5, A6, A8, A25, A20, A16, A4, LIST 11, A26, A27 at 1000µgml^{-1} not active all others in Group 5 at 1000µgml^{-1}
2)	17c	active all group 5 at 1000µgml^{-1}
3)	75	active A17, LIST, A26, A27 1000µgml^{-1} not active all others group 5.
4)	80	not active in group 5 1000µgml^{-1}
5)	74	active A1, A17, A26, A27 1000µgml^{-1} not active all others group 5 1000µgml^{-1}
6)	24	active A1, A2, A5, A6, A17, A4, A26, X11 at 1000µgml^{-1} active A27 200µgml^{-1} LIST 40µgml^{-1} not active all others group 5 1000µgml^{-1}

2,2,2-Trichloroethylsulphonyl, 2,2,2-Trichloroethoxysulphonyl, and Trifluoroacetyl Isocyanates in β-Lactam Synthesis

Anthony G. M. Barrett,*[a] Ashley Fenwick,[a] and Michael J. Betts[b]

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[b] *Imperial Chemical Industries PLC, Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.*

Condensation of the title isocyanates with olefins and subsequent dissolving-metal reduction (sulphonyl derivatives) or chromatography on Florisil (trifluoroacetyl derivatives) gave several *N*-unsubstituted β-lactams including two 8-aza-2-oxabicyclo[4.2.0]octan-7-one derivatives.

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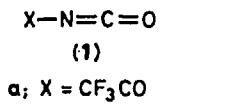
Chlorosulphonyl isocyanate (CSI) has been widely used for the preparation of β-lactams by reaction with olefins followed by mildly reductive dechlorosulphonylation.[1] For example, the synthetically versatile[2] 4-acetoxyazetidin-2-one is thus readily available from vinyl acetate albeit in modest yield.[3] However, CSI has several limitations including the failure to convert vinyl ethers directly into 4-alkoxyazetidin-2-ones.[4] Such a transformation would be of use in the concise synthesis of oxacephems and related systems. Recently, Ganem has reported a novel β-lactam synthesis which involved the halogen-mediated cyclisation of *N*-toluene-4-sulphonyl- and *N*-2,2,2-trichloroethoxysulphonyl-but-3-enamides.[5] In con-

Table 1

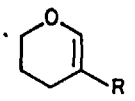
Entry[a]	Isocyanate	Olefin	β-Lactam (%, m.p.)	Other product (%, m.p.)	Deprotection step[b] β-Lactam (%, m.p.)	Deprotection step[b] Other product (%, m.p.)
1	(1a)	(2a)	—	(3) (63, 95 °C)	—	—
2	(1b)	(2a)	—	(4a) (87, 123—125 °C)	—	—
3	(1c)	(2a)	—	(4b) (78, 132—133 °C)	—	—
4	(1a)	(2b)	(5d)[c]	—	(5a) (61, 45—48 °C)	—
5	(1a)	(2c)	(5e)[c]	—	(5b) (40, 95—99 °C)	—
6	(1b)	(6a)	(8a) (89, 135 °C)	—	(8c) (22, oil)	(11) (71, 146—148 °C)
7	(1c)	(6a)	(8b) (99, 137 °C)	—	(8c) (29, oil)	(11) (9)
8	(1c)	(6b)	(10a) (67, 149—151 °C)	—	(10b) (42, 155—157 °C)	—
9	(1c)	(7)	(9a) (60, 102—104 °C)	—	(9b) (98, 105 °C)	—

[a] The isocyanate olefin condensations were carried out at room temperature in chloroform (entries 1—6), carbon tetrachloride (7), diethyl ether (8), or diethyl ether at reflux (9). [b] The deprotection reactions were carried out using Florisil and diethyl ether (entries 4,5); zinc dust and ammonium chloride in aqueous tetrahydrofuran (THF) (6,7) or zinc–copper couple in dry THF (8,9). [c] The intermediate β-lactams were not isolated but directly deprotected.



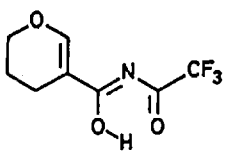
(1)

a; X = CF_3CO
b; X = $CCl_3CH_2SO_2$
c; X = $CCl_3CH_2OSO_2$

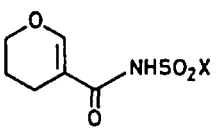


(2)

a; R = H
b; R = Me
c; R = $PhCH_2$

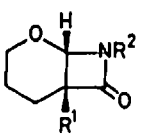


(3)



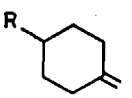
(4)

a; X = CCl_3CH_2
b; X = CCl_3CH_2O



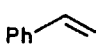
(5)

a; R^1 = Me, R^2 = H
b; R^1 = $PhCH_2$, R^2 = H
c; R^1 = H, R^2 = Ts
d; R^1 = Me, R^2 = CF_3CO
e; R^1 = $PhCH_2$, R^2 = CF_3CO

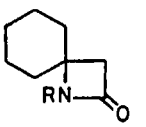


(6)

a; R = H
b; R = Ph

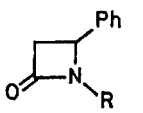


(7)



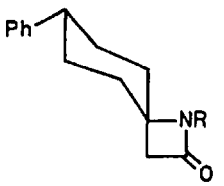
(8)

a; R = $CCl_3CH_2SO_2$
b; R = $CCl_3CH_2OSO_2$
c; R = H



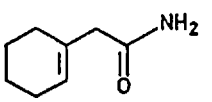
(9)

a; R = $CCl_3CH_2OSO_2$
b; R = H



(10)

a; R = $CCl_3CH_2OSO_2$
b; R = H



(11)

nection with the design of CSI surrogates we have had occasion to study the preparation and reactions of 1-(2,2,2-trichloroethoxysulphonyl)azetidin-2-one derivatives and related β-lactams. Herein we report our preliminary observations.

Isocyanates that are used for β-lactam synthesis must satisfy two criteria: the *N*-substituent must be electron-withdrawing to permit cycloaddition[1,6] and also must be readily removable under mild conditions. In this context we have examined the condensation reactions of trifluoroacetyl,[7] 2,2,2-trichloroethylsulphonyl, and 2,2,2-trichloroethoxysulphonyl[8] isocyanates (**1a**, **b**, and **c**) with olefins. We considered that after cycloaddition the *N*-substituent should be readily removable using Florisil[9] for the β-lactams derived from (**1a**) or by dissolving metal reduction for those from (**1b** or **c**).

The hitherto unknown isocyanate (**1b**)† was prepared from *N*-2,2,2-trichloroethylsulphonamide[10] by reaction with n-butyl isocyanate and aluminium chloride in nitrobenzene followed by phosgene in chlorobenzene at 120 °C (56%). The isocyanates (**1a**, **b**, and **c**) were condensed with several olefins (Table 1). Dihydropyran (**2a**) reacted with (**1a**, **b**, and **c**) to give the α,β-unsaturated amides (**3**) and (**4a** and **b**);[11] no β-lactam was isolated. However, the substituted dihydropyrans (**2b** and **c**) reacted smoothly with trifluoroacetyl isocyanate to give, after chromatography of the reaction mixture on Florisil in diethyl ether solution, the required β-lactams (**5a** and **b**). Although toluene-4-sulphonyl isocyanate has previously been condensed with dihydropyran (**2a**) giving the bicyclic β-lactam (**5c**)[12] *N*-deprotection could not be achieved. In contrast, trifluoroacetyl isocyanate provides a convenient entry to the *N*-unsubstituted 8-aza-2-oxabicyclo[4.2.0]octan-7-one (**5**, R^2 = H) system.

The isocyanates (**1b** and **c**) condensed cleanly and in good yield with methylenecyclohexane (**6a**), 4-phenylmethylenecyclohexane (**6b**), and styrene (**7**) to give the β-lactams (**8a** and **b**), (**9a**), and (**10a**). Reduction of these using either zinc dust or zinc–copper couple gave the desulphonylated β-lactams (**8c**),[13] (**9b**),[14] and (**10b**), albeit in modest yields (Table 1). The β,γ-

† All new compounds were fully characterised by spectral data and microanalyses. The isocyanate (**1b**) was microanalysed as *N*-methoxycarbonyl-*N*-2,2,2-trichloroethylsulphonamide, m.p. 108 °C, produced from (**1b**) and methanol (99%).

unsaturated amide (**11**) was formed in addition to (**8c**) on the reduction of both β-lactams (**8a** and **b**).

Clearly, trifluoroacetyl isocyanate (**1a**) and the sulphonyl isocyanates (**1b** and **c**) are convenient reagents for β-lactam synthesis. The isocyanate (**1a**) is especially useful for the preparation of the sensitive products (**5a** and **b**). We have yet to apply this reagent (**1a**) for the synthesis of β-lactams from acyclic vinyl ethers.

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