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FEATURE ARTICLE

Stereocontrolled synthesis of 1-oxabicyclic β-lactam antibiotics *via* [2 + 2]cycloaddition of isocyanates to sugar vinyl ethers

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[2 + 2]Cycloaddition of chlorosulfonyl and trichloroacetyl isocyanates to sugar vinyl ethers affords the corresponding azetidin-2-ones in moderate to good yields. Diastereofacial differentiation in these reactions is sterically dependent and usually provides excellent configuration control at C-4 of the azetidin-2-one ring. Deprotection of the amide nitrogen in those adducts, followed by suitable transformations of the sugar part, enables construction of a variety of β-lactam structures.

Introduction

Since the beginning of 1940's, when penicillin was introduced into clinical use, the continuing emergence of bacterial resistance has propelled the consecutive search for new antibiotics. A major driving force has been provided by the production of β-lactamases, bacterial enzymes that hydrolyse the β-lactam ring of antibiotics.

The isolation in 1976 by Beecham[1] of clavulanic acid **1**, a potent β-lactamase inhibitor used clinically in combination with penicillins, and the synthesis by the Merck group of 1-oxacephalothin **2**[2] and 1-oxacephamandol **3**,[3] which are congeners of known cephalosporins and demonstrate that the 1-sulfur atom is not necessary for high antibacterial activity, have prompted a concentrated research effort on 1-oxabicyclic β-lactams.

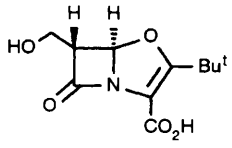
While a number of clavams have been isolated,[4–8] only **1** and its simple *O*-acyl derivatives are known so far to have the (5*R*)-configuration at the ring junction and offer strong β-lactamase inhibition and weak antibacterial activity. Other clavams, represented here by **4–7**, which possess (*S*)-configuration at C-5, exhibit activity against a number of species of fungi.[4–8] Several attempts at their synthesis have been reported.[9–11]

The oxapenem class of β-lactams (2,3-dehydroclavams), first described in 1977,[12] show interesting antibacterial and β-lactamase inhibitory activity but low stability.[13–16] The search for more stable oxapenems led to the synthesis of 2-*tert*-butyloxapenems, *e.g.* compounds **8–10**, which exhibit high activity and are relatively stable against chemical hydrolysis.[13–15] Surprisingly, both enantiomeric forms of **8** have been found to be active antibiotics and β-lactamase inhibitors.[13]

Wide-ranging investigations undertaken by Shionogi towards the synthesis of 1-oxacephem antibiotics led to the clinical use of two 1-oxacephamycins representing the third and fourth generation of β-lactam antibiotics: latamoxef **11**, the first antibiotic with an unnatural β-lactam skeleton, and flomoxef **12**.[16,17]

In 1988, the Merck and Meiji groups reported a new interesting 1-oxacephem OCP-9-176 **13** having a 2β-methyl substitutent, which displayed high antibacterial activity, but was stable to β-lactamases.[18]

[2 + 2]Cycloaddition of chlorosulfonyl isocyanate to vinyl acetates plays a special role in synthesis of β-lactams. It provides 4-acetoxyazetidin-2-ones, which, because the 4-acetoxy group can be replaced by a variety of nucleophiles, are recognized as the most convenient substrates for the synthesis



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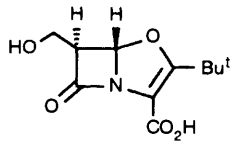

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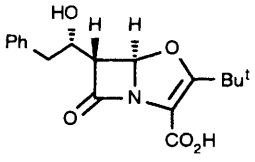

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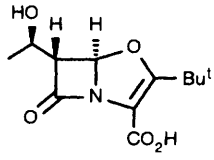

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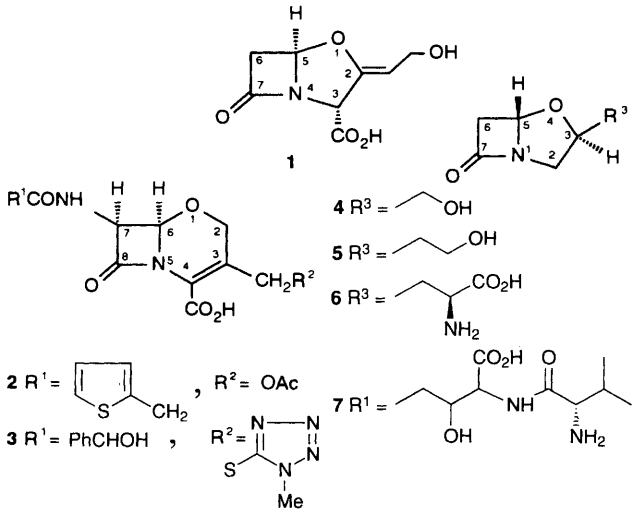

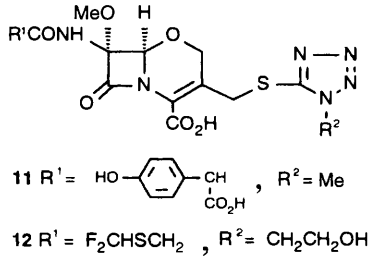

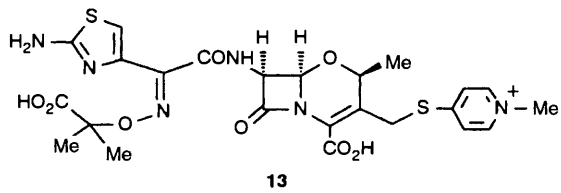

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of carbapenems, clavams, 1-oxapenems and 1-oxacephems.[13–19] In contrast to many literature reports concerning the cycloaddition of isocyanates to vinyl esters,[13–19] there are only a few reports on similar reactions involving vinyl ethers. The latter could provide a route to clavams and 1-oxacephems *via* a suitable transformation of the 4-alkoxy group. So far clavams have been synthesized from [2 + 2]cycloadducts of chlorosulfonyl isocyanate to vinyl esters[9–11,13–19] or to silyl vinyl ethers,[20] whereas 1-oxacephems have been obtained from 6-aminopenicillanic acid.[16–18]

Several years ago we initiated a synthetic project aimed at transforming sugars into 1-oxabicyclic β-lactams (Scheme 1). As a part of this study we decided to investigate the [2 + 2]-cycloaddition of isocyanates to vinyl ethers, especially to glycals and to the related dihydro-2*H*-pyrans and dihydrofurans.[21–23]

Nucleophilic alkenes such as vinyl ethers, vinyl acetates and enamines readily give [2 + 2]cycloadducts with highly electrophilic sulfonyl or acyl isocyanates, but only in a few cases were the adducts stable enough to be isolated.[21–26] The alkene electron-donating substituent and the isocyanate electron-withdrawing substituent which promote cycloaddition are also responsible for the low stability of the cycloadduct by facilitating the heterolytic cleavage of the N–C(4) bond of azetidin-2-one and the formation of α,β-unsaturated amide *via* a zwitterionic intermediate.[21,25,26] The tendency to such rearrangement is directly related to the electron-donating and electron-withdrawing character of the substituents present in both cycloaddition partners and the rearrangement is accelerated by the presence of an acid catalyst and by elevation of the reaction temperature. In order to obtain a stable β-lactam structure, it is necessary to remove the electron withdrawing-substituent Z from the nitrogen atom prior to the purification or to any other transformation of the [2 + 2]cycloadduct. This generally has been accomplished successfully in the case of chlorosulfonyl[19,24] and trichloroacetyl[21,22] groups. The present account focuses on various aspects of the cycloaddition of sulfonyl and acyl isocyanates to vinyl ethers and on transformations of the resulting [2 + 2]cycloadducts into 1-oxabicyclic β-lactam skeletons.

[2 + 2]Cycloaddition of sulfonyl isocyanates to vinyl ethers

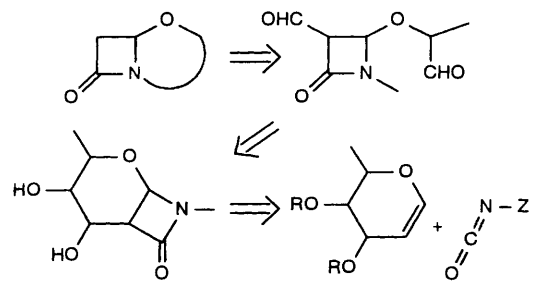
[2 + 2]Cycloaddition of tosyl isocyanate to vinyl ethers was studied in detail by Effenberger's group.[27] The concerted formation of the four-membered β-lactam ring, and a stepwise reaction proceeding *via* a zwitterionic intermediate resulting in epimerization at C-4 of the azetidin-2-one ring or in the rearrangement to the α,β-unsaturated amide were proposed.[27] The mechanistic proposition was based on the specificity of the reaction which transforms *cis* vinyl ethers into *cis* 3,4-disubstituted azetidinones and *trans* vinyl ethers into *trans* adducts. This proposal has recently been supported by *ab initio* calculations which predicted a concerted suprafacial mechanism for the [2 + 2]cycloaddition between isocyanates and alkenes.[28]

The reversibility of [2 + 2]cycloaddition of isocyanates to vinyl ethers often plays a decisive role in carrying out these reactions.[29,30] For example, the reaction of tosyl isocyanate with 3,4-dihydro-2*H*-pyran at low temperature (0 °C) leads to the formation of the bicyclic β-lactam **14**. Heating this adduct in benzene to 70 °C causes, after 20 min, the precipitation of the α,β-unsaturated amide, whereas in solution only the substrates can be found (Scheme 2). Tri-*O*-acetyl-D-glucal **15**, and other acetylated glycals, react with tosyl isocyanate under very high pressure (10 kbar; 1 bar = 10^5 Pa) to afford in each case a single adduct having the four membered ring located *anti* with respect to the 3-*O*-acetyl substituent.[31] At atmospheric pressure and room temperature adduct **16** undergoes retro-addition to afford the starting glucal.[29,31] The rate of the retro-addition increases with rising temperature and polarity of the solvent. Cycloadduct **16** can be transformed into the α,β-unsaturated amide only if high pressure and elevated temperature are applied (Scheme 2).[29]

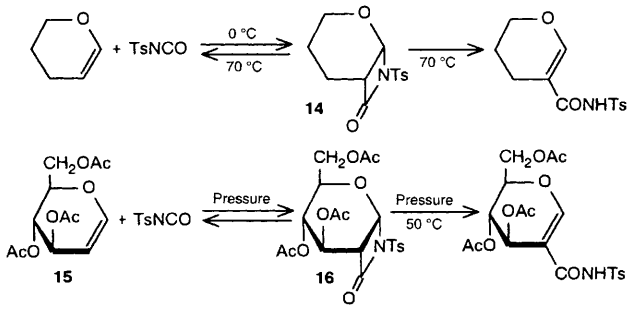
Neutral tosyl isocyanate affords relatively stable [2 + 2]-cycloadducts, suitable for mechanistic studies but useless for the synthesis of β-lactam antibiotics since the sulfonyl substituent is not easily removable from the nitrogen atom. Six years ago we reported the formation of a β-lactam ring *via* a stereoselective [2 + 2]cycloaddition of tosyl isocyanate to vinyl ether of diacetone glucose **17**.[32] The (4*R*)-diastereoisomer **18** has been obtained with 70% de. However, deprotection of the *N*-tosyl substituent with sodium in liquid ammonia, in order to form the stable β-lactam product, proceeded in low yield (Scheme 3).

Chlorosulfonyl isocyanate (CSI), being very active in [2 + 2]-cycloaddition, has been found to react with a variety of simple alkenes such as vinyl esters, vinyl silyl ethers, allenes, *etc.*[19,24,33] The chlorosulfonyl group can be easily removed from the nitrogen atom using a variety of reagents, thus providing an attractive entry into β-lactam antibiotics. This approach became more attractive after the discovery by Clauss, Grimm and Prossel[34] that 4-acetoxyazetidinones readily undergo a nucleophilic displacement at the C-4 carbon atom. Owing to the strong electron-withdrawing character of the chlorosulfonyl group and contamination of the reagent with sulfur trioxide and hydrogen chloride, cycloaddition of CSI to highly nucleophilic alkenes, such as vinyl ethers or enamines (except for cyclic acetals[33]) has not been previously reported.

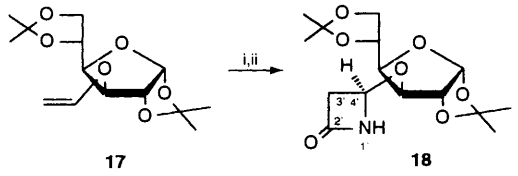
The reaction between **15** and CSI was studied in the past, but neither the cycloadduct nor the rearranged products were observed. The isocyanate acted only as the acid catalyst that induced the decomposition of the sugar.[35] Recently, we have shown that acidity of the commercially available chlorosulfonyl isocyanate originating from contamination is the cause of the



Scheme 1



Scheme 2



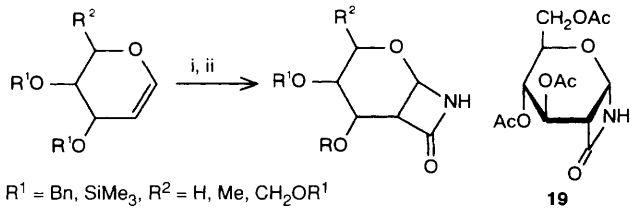
Scheme 3 *Reagents and conditions*: i, TsNCO; ii, Na–NH_3; 20%

reactivity of this reagent towards many functional groups. We have found that storage of the commercially available CSI over potassium carbonate, sodium carbonate or calcium carbonate, and addition of these bases to the reaction mixture enabled us to achieve [2 + 2]cycloaddition in many cases[36] which had resulted previously in decomposition of the alkene or the cycloadduct even at temperatures as low as −78 °C.[35] Following our de-acidification protocol, glycals with non-polar protecting groups on hydroxy groups have been found to react cleanly with chlorosulfonyl isocyanate (1 : 1.3 molar ratio; in toluene at −40 to −60 °C). In order to obtain stable β-lactams, the chlorosulfonyl substituent was removed from the nitrogen atom of the cycloadduct by treatment of the reaction mixture with Red-Al (Scheme 4).[33,36] In all cases CSI approached the glycal molecule exclusively *anti* with respect to the substituent at C-3.[36] Furanoid glycals, which are more reactive than pyranoid ones, either did not produce any β-lactam under the same conditions or afforded them in low yields only. Clearly, CSI caused decomposition of the sugar.[36]

Tri-*O*-acetyl-D-glucal **15**, which previously has been found not to form cycloadducts, reacted with a 4 molar excess of the isocyanate to afford, after reduction of the chlorosulfonyl substituent with lithium iodide, the β-lactam **19** in 35% yield.[36]

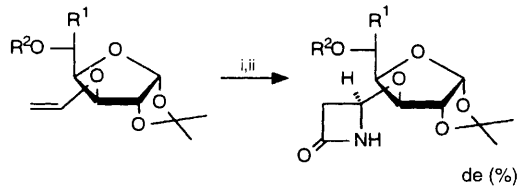
In the presence of carbonates CSI offered a successful procedure for a [2 + 2]cycloaddition to simple sugar vinyl ethers.[36–38] It was particularly important because tosyl isocyanate, due to difficulties with N-deprotection, is useless with such substrates, whereas acyl isocyanates give almost exclusively the [4 + 2]cycloadducts.[26,32] The CSI [2 + 2]cycloaddition to simple sugar vinyl ethers offers an alternative route to the commonly used condensation of readily available 4-acetoxyazetidinone with sugar alcohols popular in clavam synthesis.[9–11] A study of [2 + 2]cycloaddition of CSI/Na_2CO_3 to a variety of 1,2-*O*-isopropylidene-3-*O*-vinyl-D-glucofuranoses showed that the selectivity of these reactions was sterically controlled.[37] A large substituent at C-4 of the furanose ring blocks the isocyanate entry from the *Re* side and affords very high stereoselectivity in the case of compounds **22** and **23** (Scheme 5, Fig. 1.)[37]

[2 + 2]Cycloaddition of CSI to 5-*O*-vinyl derivatives of 1,2-*O*-isopropylidene-α-D-glycofuranoses **28–33** shows that in this case reaction stereoselectivity can also be controlled (Scheme 6).[23] The presence of a small substituent at the C-3 carbon atom on the top of the furanose ring, or even a large



R^1 = Bn, $SiMe_3$, R^2 = H, Me, CH_2OR^1 **19**

Scheme 4 *Reagents and conditions*: i, CSI, Na_2CO_3, toluene, −40 to −60 °C; ii, Red-Al



		de (%)
20 R^1 = H, R^2 = Ts	**24**	33
21 R^1 = H, R^2 = TIBS	**25**	54
22 R^1 = H, R^2 = Ph_3Si	**26**	> 95
23 R^1 = CH_2OTs, R^2 = Ts	**27**	> 95

TIBS = 2,4,6-triisopropylbenzenesulfonyl

Scheme 5 *Reagents and conditons*: i, CSI, Na_2CO_3; ii, Red–Al

substituent localized on the bottom, gave excellent asymmetric induction. This evident relationship between the magnitude of the asymmetric induction on one hand, and the substitution pattern and configuration at C-3 on the other hand indicates that the attack of CSI occurs from the side occupied by the substituent R^1. The (*S*)-configuration of the major diastereoisomer formed proves that the *Re* side of the alkene is turned to the substituent and the *Si* side is blocked by the TIBS group. This blocking might be due to complexation of the nucleophilic alkene by the electrophilic aryl substituent (Fig. 2).[38] We have not found in ^1H NMR spectra, however, any NOE interactions between aromatic and vinyl protons, that could support the complexation of both groups.

Low levels of asymmetric induction in the case of 3-*O*-vinyl-5-*O*-arylsulfonyl sugars **20**, **21** shows that similar complexation, if it exists, does not always play a decisive role.[37] Stereoselectivity of the cycloaddition to 5,6-di-*O*-tosyl compound **23** might, however, be ascribed to an interaction between 3-*O*-vinyl and 6-*O*-tosyl substitutents.[37] Investigation of the [2 + 2]cycloaddition of CIS to vinyl ethers **40–42** derived from malic acid and **46**, **47** derived from lactic acid provided similar inferences[39] (Scheme 7). High stereoselectivity found for compounds **42**, **46** and **47** should be assigned to the steric effect. Recently published *ab initio* calculations of conformational energies of isopropyl vinyl ether reported the synclinal s-*cis* conformation **50** as the most stable one.[40] Application of the conformation **50** having the silyloxy, benzyloxy or sulfonyloxy oxygen atom located antiperiplanar to the vinyloxy oxygen atom, explains the stereoselectivity direction.[39]

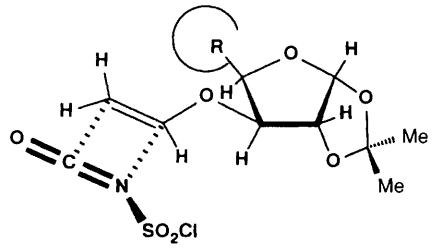
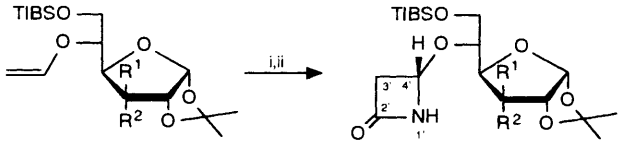


Fig. 1



		de (%)
28 R^1 = OBz, R^2 = H	**34**	4
29 R^1 = CH_2SMe, R^2 = H	**35**	38
30 R^1 = OBn, R^2 = H	**36**	72
31 R^1 = OMe, R^2 = H	**37**	92
32 R^1 = R^2 = H	**38**	>95
33 R^1 = H, R^2 = OCH_2SMe	**39**	>95

Scheme 6 *Reagents and conditions*: i, CSI, Na_2CO_3, toluene, −78 °C; ii, Red–Al

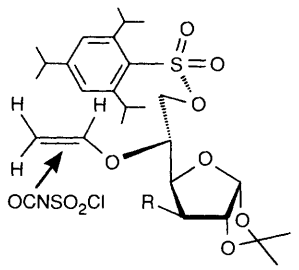


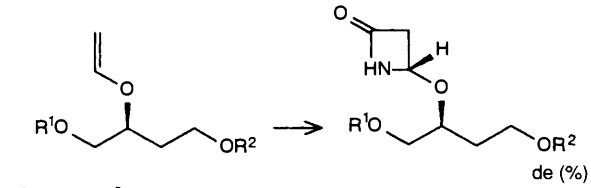
Fig. 2

The two isomeric 3-*O*-butenylglycofuranose derivatives **50** (*cis*) and **51** (*trans*) treated with CSI/Na_2CO_3 gave the *cis* and *trans* azetidinones **52** and **53** having (*R*) configuration at C-4′ (Scheme 9) with excellent stereoselectivity. This observation is in agreement with the results described above, showing steric control being responsible for the face-differentiation.[41]

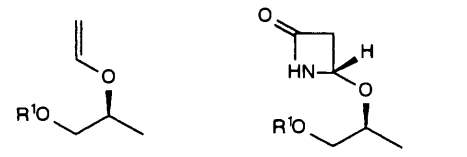
The β-lactams obtained from 3-*O*-vinyl and 5-*O*-vinyl ethers of 1,2-*O*-isopropylideneglycofuranose and those obtained from ethers **41**, **42**, **46**, **47** have been easily transformed into the respective 1-oxacephems **54–59** or clavams **60–64** by the intramolecular alkylation of the nitrogen atom.[37–39,41]

Cycloaddition of acyl isocyanates to vinyl ethers

Acyl isocyanates are generally less reactive in [2 + 2]cycloaddition reactions than sulfonyl isocyanates, except for trichloro- and trifluoro-acetyl isocyanate. Moreover, acyl isocyanates exhibit competitive formation of [4 + 2]cycloadducts which are usually thermodynamically preferred over the [2 + 2]cycloadducts.[21,26]

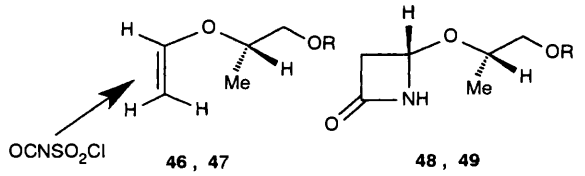


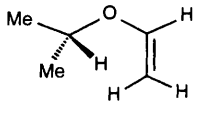
			de (%)
R^1 = TIBS, R^2 = Bn	**40**	**43**	39
R^1 = Bn, R^2 = TIBS	**41**	**44**	0
R^1 = Ph_3Si, R^2 = Bn	**42**	**45**	60



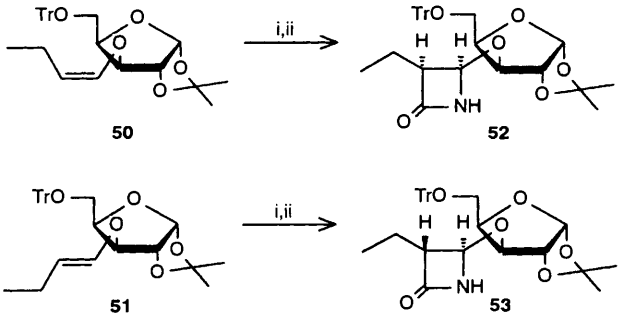
R^1 = Ph_3Si	**46**	**48**	74
R^1 = Pr^i_3Si	**47**	**49**	67

Scheme 7





Scheme 8

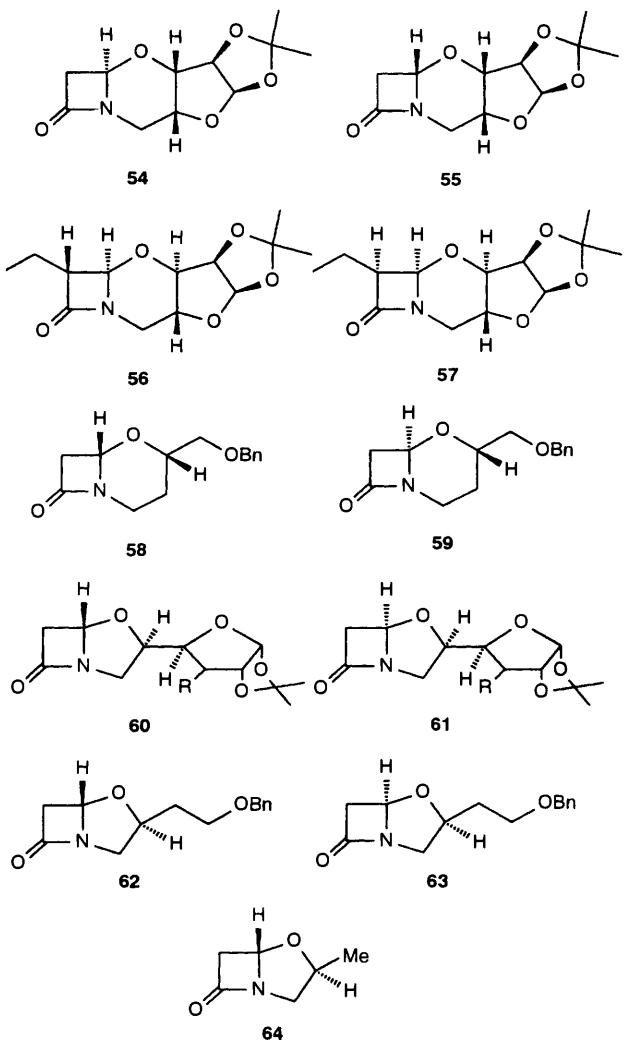


Scheme 9 *Reagents and conditions*: i, CSI, Na_2CO_3; ii, Red–Al

Chitwood, Gott and Martin[26] studied the cycloaddition reactions of trichloroacetyl isocyanate **65** with a variety of vinyl ethers. They found that α,β-unsaturated amides **68** were obtained in these reactions *via* intermediate formation of the unstable [2 + 2] and [4 + 2]cycloadducts **66** and **67** (Scheme 10).

The initial proportion of the adducts changed slowly to bring about the predominance of the six-membered ring compound **67**. Owing to their low stability, both intermediates **66** and **67** were detected only by NMR.

Our investigation of the cycloaddition of trichloroacetyl isocyanate to glycals[19,21,22] has shown consistency with the results of Chitwood *et al.*[26]



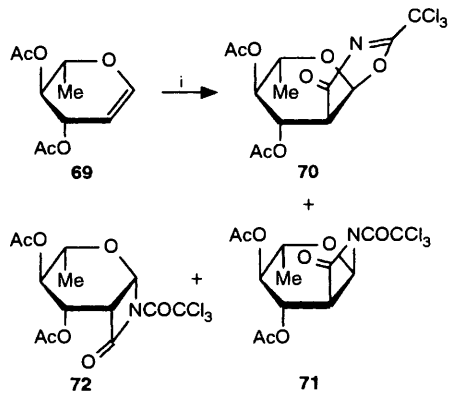
Scheme 10 *Reagents and conditions*: i, CCl_3CONCO **65**; ii, $CHCl_3$ or MeCN

Owing to the reversibility of the cycloaddition, acetylated glycals reacted with the isocyanate **65** only under high pressure or with a large excess of the cumulene to exhibit low chemo- and stereo-selectivity, yielding three products: the [4 + 2]-cycloadduct **70** and two β-lactams **71** and **72** (Scheme 11).[42] In contrast to the acetylated glycals, those having nonpolar protecting groups have been found to react readily under atmospheric pressure at room temperature with 2–3 equiv. of **65** to give mixtures of [2 + 2] and [4 + 2]cycloadducts (Scheme 12).[21,22] The reactions proceeded with high stereoselectivity to afford *cis* fused bicyclic systems *anti* with respect to the C-3 substituent. The rate of addition and the composition of the reaction mixture differed in dependence on the solvents and substrates used. The highest content of the [2 + 2]cycloadduct in the reaction mixture could be achieved when cycloaddition was performed in a polar solvent with the solution of benzylated or silylated glycal as concentrated as possible.[21] Addition of a primary amine to the reaction mixture quenched the reaction progress leading to the removal of N-protection and resulting in the formation of stable β-lactams **73** in the yields of up to 75%. The [4 + 2]cycloadducts absorbed a molecule of amine to afford a bicyclic system **74**.[43]

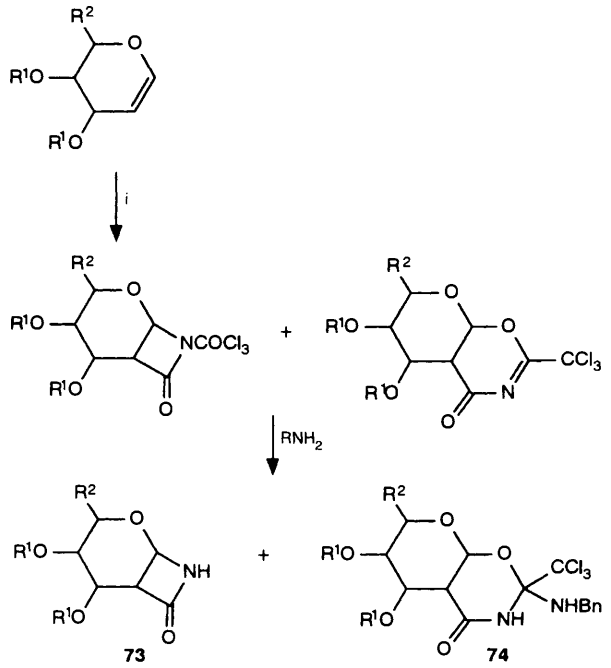
Using trichloroacetyl isocyanate and a variety of glycals, a number of bicyclic β-lactams **73** have been obtained. The same procedure could be applied to the cycloaddition to the furanoid glycals **75** and **76** (Scheme 13). The reaction proceeded with the same high stereoselectivity to produce [2 + 2] and [4 + 2]-cycloadducts having the new ring located *anti* with respect to the C-3 substituent. N-Deprotection led to the formation of stable compounds **77** and **78** (Scheme 13).[44]

In view of these results, trichloroacetyl isocyanate seems to be the most suitable acyl isocyanate that promotes cycloaddition, provides relative stability of cycloadducts, and offers an N-substituent readily removable under mild conditions. Trifluoroacetyl isocyanate which is more reactive than trichloroacetyl isocyanate produces the α,β-unsaturated amide from dihydropyran. However no β-lactam was formed.[25]

Isocyanates less electrophilic than trichloroacetyl isocyanate react wtih glycals only under high pressure to provide respective adducts with high stereoselectivity.[23] Aryloyl isocyanates afford considerable amounts of [4 + 2]cyclo- adducts whereas isocyanates derived from urethanes give [2 + 2]-cycloadducts and α,β-unsaturated amides. Benzyloxycarbonyl isocyanate is particularly attractive owing to the formation of the [2 + 2]cycloadduct in good yield. In the case of addition to arabinal **79**, adduct **80** was stable enough to be purified by flash chromatography. N-Deprotection of **80** by hydrogenolysis yielded with β-lactam **81** which had been previously obtained using CSI/Na_2CO_3, and the trichloroacetyl isocyanate methods (Scheme 14).[22] Each of the three routes results in the formation of the β-lactam **81** in about 60% yield.



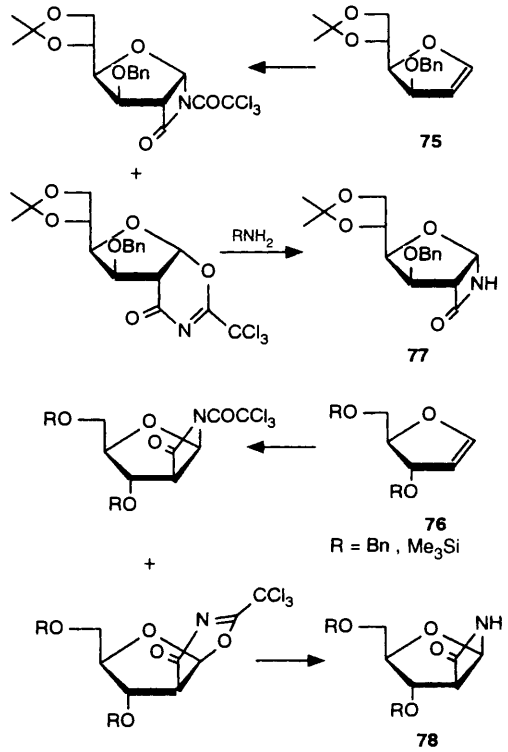
Scheme 11 *Reagent*: i, CCl_3CONCO



Scheme 12 *Reagents and conditions*: i, CCl_3CONCO, MeCN or $MeNO_2$

Synthesis of 1-oxabicyclic β-lactams from glycals and isocyanates

The [2 + 2]cycloaddition of isocyanates to glycals is stereoselective (isocyanate adds to a sugar molecule *anti* to the C-3 substituent) and a variety of glycal precursors are available. The synthetic strategy depicted in Scheme 1, therefore, could offer full sterocontrol of the configuration at C-4 of the azetidinone system. Mastering this stereocontrol is essential for the synthesis of biologically active β-lactam antibiotics. Thus, cycloaddition to D-glucal, D-galactal, L-arabinal and D-xylal provides azetidinones with the (*S*)-configuration at C-4, whereas cycloaddition to D-arabinal, L-xylal, L-rhamnal and D-allal leads to azetidinones with the opposite (*R*)-configuration.



Scheme 13

The relevance of the [2 + 2]cycloaddition of isocyanates and glycals to synthesis of 1-oxabicyclic β-lactam structures has been exemplified by the preparation of clavam and 1-oxacephems.[45–47] As the first goal, the recently discovered clavam **82**,[4] having the (*S*)-configuration at the hemiaminal carbon atom was chosen. The substrate **83** was subjected to the sequence of reactions shown in Scheme 15. Removal of the carbon atom from C-3 of the azetidin-2-one, or alternatively from the C-6 of clavam by an oxidation–decarboxylation procedure failed: the easy β-elimination process resulted in the opening of the β-lactam ring.[48] In consequence, product **84** had an additional acetoxymethyl group at C-6.[45]

The same substrate **83** served for construction of the 1-oxacephem skeleton (Scheme 16).[46] Owing to the stereochemical consequences of [2 + 2]cycloaddition to benzylated D-galactal, the configuration of the carbon atom bearing the oxygen and nitrogen atoms is opposite to that found in active cephems. It is obvious, however, that the synthesis could be repeated starting from the β-D-altro β-lactam **87**, easily available from D-allal, and in this way it would generate the 1-oxacephem skeleton having the proper configuration at the bridge-head carbon atom.[49] An alternative route towards 1-oxacephem from a glycal and an isocyanate had recently been demonstrated (Scheme 17).[47] Di-*O*-Me_3Si-β-D-arabino compound **88** was subjected to standard transformations to afford the ylide **89**. Subsequent intramolecular Witting reaction yielded the 1-oxacephem skeleton **90**. Basic conditions of the condensation caused partial epimerization at C-7 to afford, after reduction of the aldehyde group, a *cis–trans* mixture of **91** and **92**, 3 : 2.[47]

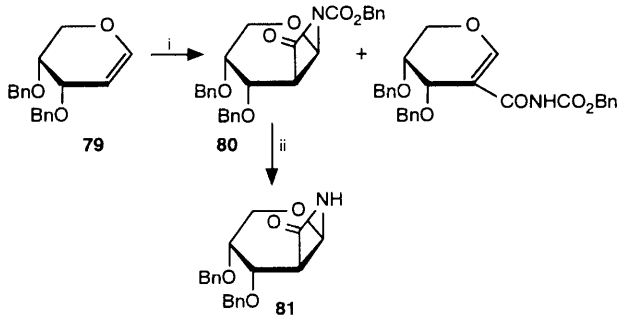
Stereocontrolled transformations of benzylated galactal **83** into **84** and **86** (Schemes 15 and 16) have been a consequence of the specificity of [2 + 2]cycloaddition and suitable protection of the terminal hydroxymethyl group. This protection allowed for retention of chirality at the carbon atom stemming from C-5 of the glycal molecule. In both syntheses shown in Schemes 15 and 16 we did not discriminate between the carbon atoms which were split during the glycolic cleavage step. Our attempts at discrimination *via* oxidation of the dialdehyde to the corresponding dicarboxylic acid, failed. Decarboxylation of the group that is in a malonyl array with the β-lactam carbonyl group was unsuccessful due to the β-elimination reaction.[48]

The discrimination of aldehyde groups obtained during a glycolic cleavage step have been achieved by trapping one of them with an intramolecular Wittig cyclization (Scheme 17).[47]

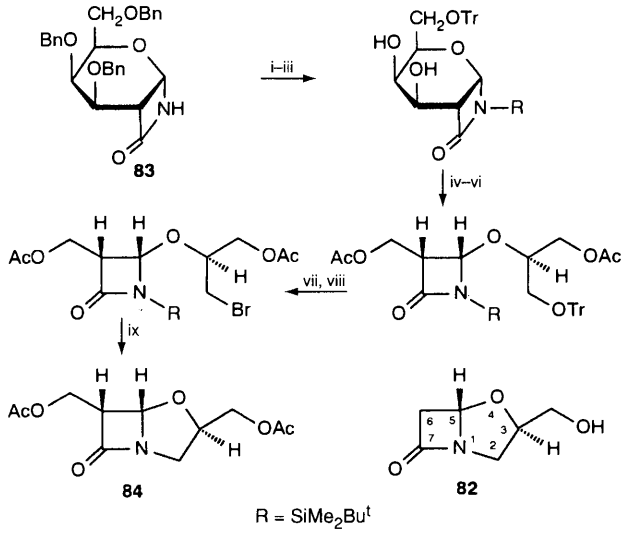
Syntheses of 1-oxbicyclic β-lactams shown in Schemes 15, 16 and 17 have employed a glycolic cleavage for opening of the sugar ring. This has led to the need for discrimination between carbon atoms which were split during the glycolic cleavage step. The two primary hydroxy groups in **93** and **94** could be differentiated easily by protecting one of them by a bulky silyl substituent or by intramolecular lactonization[50] (Scheme 18). Compound **94** could be an attractive precursor for the synthesis of 2β-methyl-1-oxacephems which have been found to possess high antibacterial and anti-β-lactamase activity.[18]

The opening of the sugar ring by other means then the glycolic cleavage has also been investigated. The retro-aldol route, which removes the substituent from C-3 of the azetidinone ring failed. Model studies of Beckmann rearrangement of the oxime, which could lead to the introduction of the amino function to C-3 of azetidinone, afforded the unstable iminoether **98** as the single product (Scheme 19).[51] Attempts to rearrange the tosyl oxime **97** in the presence of water failed, resulting in decomposition of the substrate.[51] Baeyer–Villiger oxidation of the ketone **95** led to breaking of the C(3)–C(4) bond of the furanose ring and, consequently, to formation of the cyclic ester **99**.[51]

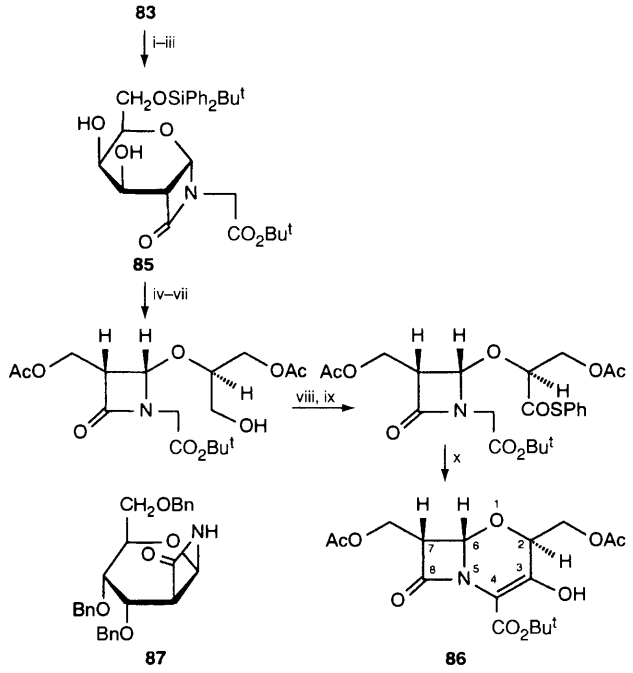
We have shown that vinyl ethers are useful substrates for [2 + 2]cycloadditions with isocyanates. The reactions proceeded in relatively good yield, even with very reactive chlorosulfonyl isocyanate and simple vinyl ethers, if the reaction conditions were properly controlled. In the case of



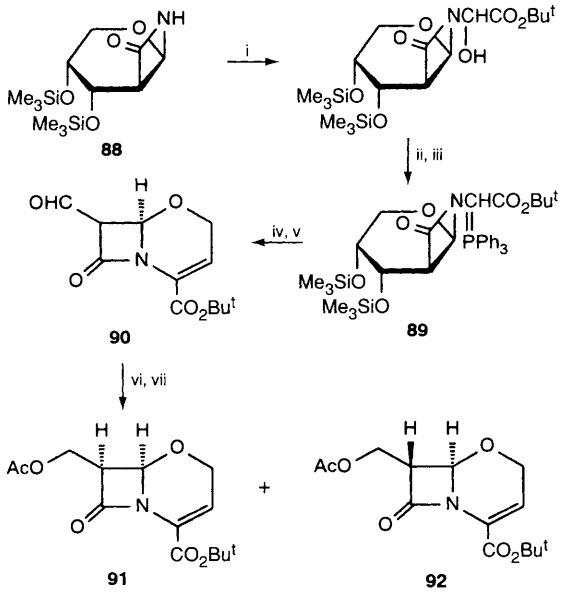
Scheme 14 *Reagents and conditions:* i, ZNCO, 10 kbar (1 bar = 10^5 Pa), MeCN; ii, H_2–Pd, AcOEt



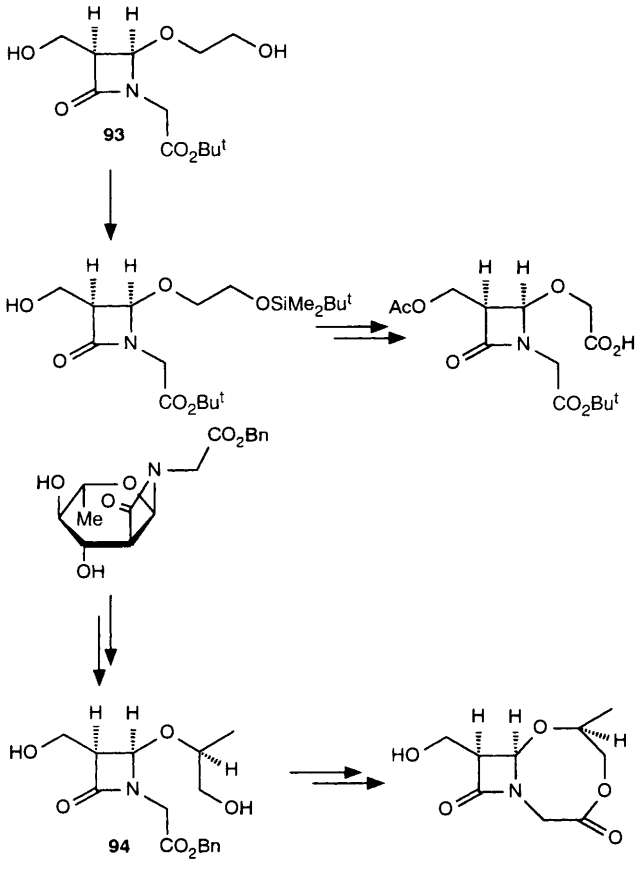
Scheme 15 *Reagents and conditions*: i, Bu^tMe_2SiCl, DMAP, DMF; ii, H_2, Pd–C; iii, TrCl, Py; iv, $NaIO_4$; v, $NaBH_4$; vi, Ac_2O, Py; vii, H_2, Pd–C; viii, CBr_4, PPh_3; ix, Bu_4NF



Scheme 16 *Reagents and conditions*: i, $BrCH_2CO_2Bu^t$, K_2CO_3, TBABr; ii, H_2, Pd–C; iii, Bu^tPh_2SiCl, Py; iv, $NaIO_4$; v, $NaBH_4$; vi, Ac_2O, Py; vii, HF–Py; viii, RuO_4; ix, PhSH, DCC; x, $LiN(SiMe_3)_2$

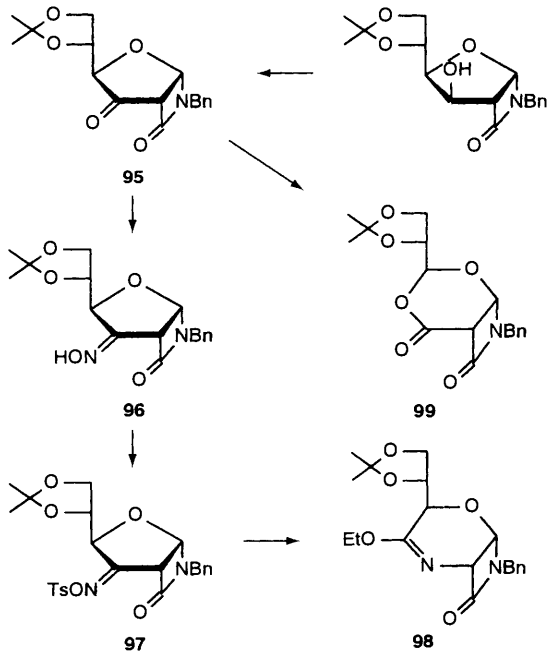


Scheme 17 *Reagents and conditions*: i, $OHCCO_2Bu^t$; ii, $SOCl_2$, Py; iii, PPh_3, 2,6-lutidine; iv, H^+; v, $NaIO_4$, $NaHCO_3$; vi, $NaBH_4$; vii, Ac_2O, Py



Scheme 18

glycals (cyclic vinyl ethers), stereoselectivity of the cycloaddition was excellent. In the case of simple vinyl ethers diastereoselectivity strongly depended on the location of the vinyl group and on neighbouring substituents; suitable substitution of the sugar substrate allowed excellent face-differentiation and control of the absolute configuration of the 4-alkoxyazetidinone ring. β-Lactams obtained in that way can serve as substrates for the synthesis of 1-oxabicyclic β-lactam structures such as clavams and 1-oxacephems as well as for the synthesis of a variety of sugars containing an azetidinone ring.



Scheme 19

Marek Chmielewski's research interests are in the synthesis and transformations of low molecular carbohydrates. After obtaining his MSc (Warsaw Technical University) he moved to the Institute of Organic Chemistry of the Polish Academy of Sciences (1969) and since then he has been associated with the Institute. He obtained his PhD in 1972 and Habilitation in 1981 to become Docent in 1984 and Professor in 1991. He undertook his postdoctoral work at Purdue (1974) and at Southern Illinois University at Carbondale (1980) and has been awarded the Kostanecki medal by the Polish Chemical Society.

Zbigniew Kałuża obtained his MSc from the Warsaw Technical University (1983) and his PhD from the Institute of Organic Chemistry of the Polish Academy of Sciences (1988). During his PhD studies he twice visited Odense University for short periods of research work. He spent two years at Stevens Institute of Technology as postdoctoral fellow and then returned to the Institute of Organic Chemistry (1991) to join Professor Chmielewski's research group.

Bartłomiej Furman obtained his MSc from the Warsaw Technical University (1994) and he is currently completing his PhD thesis on the work being part of this feature article.

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