(27) (46 mg, 0.07 mmol) in 5 mL of DME was added and the final mixture refluxed for 1 h. The resulting residue was further purified by chromatography on a silica gel column, 20% methylene chloride/petroleum ether being used for elution. The main compound was collected and recrystallized from methylene chloride/methanol to give 32 mg (72%) of the title dimer: mp 199-200 °C; vis λ_{max} 347 nm (ϵ 45 600), 412 (118 100), and 630 (51 610); NMR δ_H (ppm) 8.90, 8.87, 8.83, 8.82, 7.85, and 7.83 (all s, 6 meso H), 7.60 and 7.58 (both d, 2 H_a, J = 15.1 Hz), 6.44 (dd, 2 H_c, J_1 = 7.2 Hz, J_2 = 3.0 Hz), 5.81 (ddd, 2 H_b, J_1 = 15.0 Hz, J_2 = 7.2 Hz, J_3 = 3.0 Hz), 4.10 (m, 2 H, 8,8'-H), 3.88 (m, 2 H, 7,7'-H), 3.25-3.57 (overlapping q, 24 H, CH_2 of Et), 1.76 (overlapping q, 8 H, 7,7',8,8'-CH_2 of Et), 1.46-1.68 (overlapping t, 36 H, CH_3 of Et), 0.98 and 0.93 (t, 12 H, 7,7',8,8'-CH_3 of Et); MS, m/e 1261.9 (100). Anal. Calcd for $C_{78}H_{98}N_8Ni_2$: C, 74.17; H, 7.66; N, 8.87. Found: C, 74.20; H, 7.58; N, 8.88.

***trans,trans,trans*-1,6-Bis{δ-[nickel(II) benzochlorin]}-1,3,5-hexatriene (57).** The same general procedure was followed. $TiCl_3(DME)_{1.5}$ (336 mg, 1.16 mmol), Zn-Cu (311 mg, 4.38 mmol), and DME (10.0 mL) were used. After 2 h of refluxing, nickel(II) γ-(2-formylvinyl)octaethylbenzochlorin (14) (76 mg, 0.11 mmol) in 15 mL of DME was added and the final mixture was refluxed for 1 h. The resulting residue was chromatographed on a silica gel column, 40% methylene chloride/petroleum ether being used for elution. The second least polar band was collected and recrystallized from methylene chloride/methanol to give 42 mg (56%) of the title compound: mp 239-241 °C; vis λ_{max} 371 nm (ϵ 54 500), 434 (95 700), 618 (28 800) and 706 (42 400); NMR δ_H (ppm) 8.66 (d, 2 benzo H, J = 8.1 Hz), 8.63 and 8.27 (s, 2 H each, 4 meso H), 7.86 (d, 2 H_a, J = 14.7 Hz), 7.68 (t, 2 benzo H), 7.60 (d, 2 benzo H, J = 6.9 Hz), 6.35 (dd, 2 H_c, J_1 = 7.2 Hz, J_2 = 3.0 Hz), 5.55 (ddd, 2 H_b, J_1 = 15.0 Hz, J_2 = 7.2 Hz, J_3 = 3.0 Hz), 3.27-3.55 (m, 24 H, CH_2 of Et), 2.77 and 2.32 (q, 4 H each, CH_2 of *gem*-Et_2), 1.56, 1.53, and 1.36 (t, 36 H, CH_3 of Et), 0.07 and 0.04 (t, 6 H each, CH_3 of *gem*-Et_2); MS, m/e 1334.5 (100). Anal. Calcd for $C_{84}H_{98}N_8Ni_2 \cdot H_2O$: C, 74.56; H, 7.30; N, 8.28. Found: C, 74.60; H, 7.36; N, 8.12.

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Preparation of 3-Alkyl β-Lactams via the Ketene-Imine Cycloaddition Reaction Using α-(Phenylthio)alkanoyl Halides as Starting Materials: Application to the Synthesis of (±)-Carbapenem Building Blocks and Related Compounds

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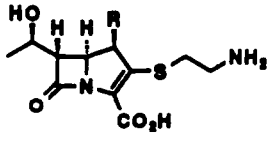
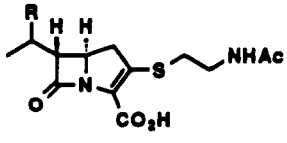
Preparation of appropriately substituted 3-alkyl β-lactams via the ketene (or equivalent)-imine cycloaddition reaction is described. The dehydrochlorination reaction of α-(phenylthio)alkanoyl chlorides with triethylamine in the presence of imines derived from cinnamaldehydes and *p*-anisidine produced a high-yield formation of α-phenylthio β-lactams, which upon desulfuration furnished a variety of 3-alkyl β-lactams in a highly stereoselective fashion. In contrast, reaction between α-haloalkanoyl chlorides and cinnamylideneamines in the presence of triethylamine furnished the corresponding [4 + 2] cycloadducts as main products. Preparation of highly functionalized α-alkylidene β-lactams through thermal decomposition of the corresponding β-lactam sulfoxides or by cycloaddition of α,β-unsaturated acid chlorides to imino esters in the presence of triethylamine is also described. Addition of Flemming's silylcuprate reagent to α-alkylidene β-lactams furnished the corresponding 3-(1'-(dimethylphenylsilyl)ethyl) β-lactams as (±)-thienamycin intermediates.

Carbapenem antibiotics, such as thienamycin (1), 1-β-methylthienamycin (2), and the closely related structures PS-5 (3) and PS-6 (4), have attracted a great deal of interest from both a biological and a synthetic point of view.[1]



1 R: H Thienamycin
2 R: Me 1-β-Methylcarbapenems



3 R: H PS-5
4 R: Me PS-6

Because of the inherent chemical instability of the bicyclic ring system, the main strategies toward their synthesis (Figure 1) usually involve the preparation of an appropriately substituted monocyclic 3-alkyl β-lactam with the correct stereochemistry at C_3-C_4 of the β-lactam ring, followed by chemical manipulations at N_1 and C_4 and subsequent ring closure to form the bicyclic carbapenem system in the last steps of the synthesis.[2] Of the existing methods to carry out an efficient ring closure, the carbene insertion reaction developed by the Merck group[3] for thienamycin synthesis (Figure 2) seems to be the most widely employed method for the construction of bicyclic

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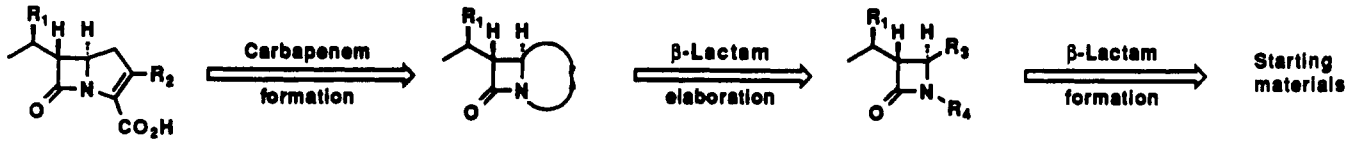
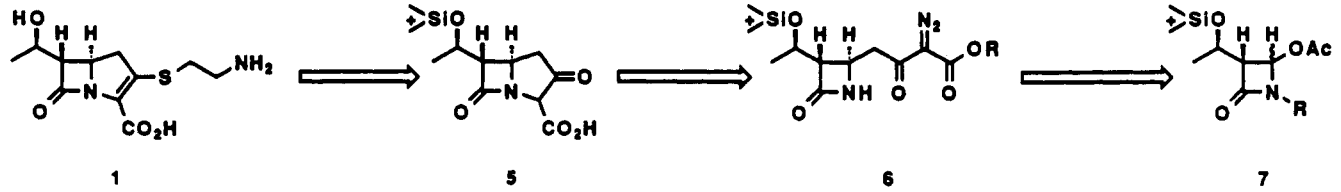


Figure 1.



1 5 6 7

Figure 2.

β-lactams.[1,2] Thermolysis of diazo ketone 6 in the presence of rhodium acetate provides the cyclized β-keto ester 5 in excellent yield, which can be converted into thienamycin in three steps.[4] For this strategy, 4-(acyloxy)azetidin-2-ones of type 7 are recognized as the most useful intermediates for synthetic work in β-lactam chemistry.[5] The replacement of the acyloxy group by a variety of nucleophiles provides an easy access to a wide variety of bicyclic β-lactam precursors, including penems[6] and related systems.[7] Consequently, the development of short and highly stereocontrolled methods for the synthesis of 3-alkyl-4-acetoxyazetidin-2-ones or β-lactams containing alternative leaving groups at C_4 position is of crucial importance in β-lactam chemistry.

The most direct access to 4-acetoxyazetidin-2-ones is the addition of chlorosulfonyl isocyanate (CSI) to the corresponding vinyl acetate.[8] However, the lack of stereoselectivity in the cycloaddition step[9] and the reactivity of CSI toward several functional groups[10] necessitated the development of new approaches to 3-alkyl-4-acetoxyazetidin-2-ones. Several groups have demonstrated that 3-alkyl-4-styrylazetidin-2-ones are appropriate starting materials for a further chemical elaboration leading to the required precursors in a few steps.[1,2,4] Following this strategy, we have recently described[11] a short synthesis of 4-acetoxy β-lactams by using the α-bromo ester–imine condensation as an approach to 3-alkyl-4-styrylazetidin-2-ones.

Among many other methods for the synthesis of β-lactams,[12] the enolate–imine condensation[13] and the hydroxamate approach[14] have received considerable attention in carbapenem synthesis. Surprisingly, the most widely employed method to construct β-lactams, the Staudinger reaction[15] or its variant the acid chloride–imine approach,[16] has received very little attention within the context of carbapenem synthesis. This approach is potentially quite versatile since the needed substrates, acetic acids, and Schiff bases are easily accessible and therefore a number of β-lactams with functional groups at N_1 and C_4 positions can be prepared. Although from this method the steric course of the β-lactam formation does not appear to be predictable, it can be controlled by the experimental conditions used[17] and by the choice of Schiff bases with bulky substituents.[18] This approach has found wide applicability in α-amino β-lactam synthesis[16,19] or in β-lactams

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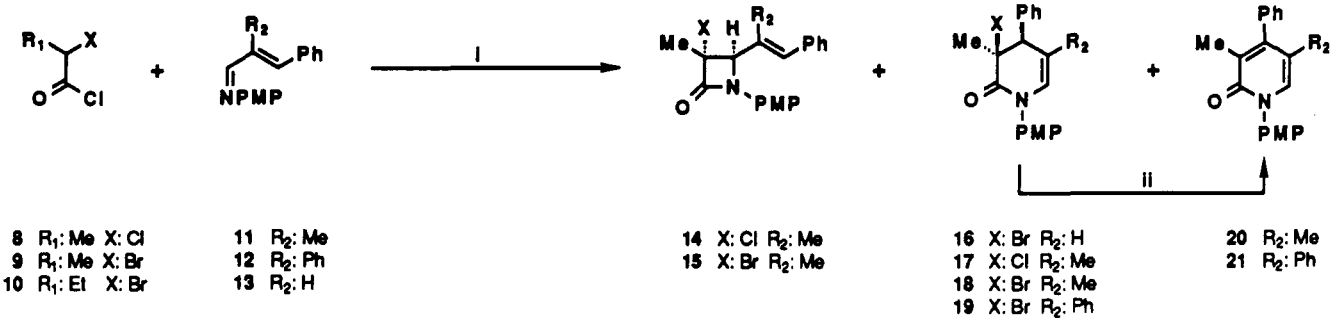
Scheme I[a]



8 R_1: Me X: Cl
9 R_1: Me X: Br
10 R_1: Et X: Br

11 R_2: Me
12 R_2: Ph
13 R_2: H

14 X: Cl R_2: Me
15 X: Br R_2: Me

16 X: Br R_2: H
17 X: Cl R_2: Me
18 X: Br R_2: Me
19 X: Br R_2: Ph

20 R_2: Me
21 R_2: Ph

[a] Reagents and conditions: (i) NEt_3, solvent, rt, 20–24 h; (ii) DBU, benzene, rt.

bearing electron-withdrawing groups at C-3 position;[20] however, only a few reports have been appeared concerning the utility of this approach to the synthesis of 3-alkyl β-lactams.[21-23] For example, Plumet and co-workers[22] reported the cycloaddition reaction of monoalkylketenes, generated from aliphatic acid chlorides, with imines derived from phenylglyoxal and then a Merck group employed such an approach to the synthesis of (+)-thienamycin.[23] An analogous approach has recently appeared in which acetylketene, presumably generated from diketene, reacted with both imino esters and chiral imines derived from (S)-(benzyloxy)propanals to provide carbapenem building blocks.[24] Since it is well known that reaction between an acid halide and an imine in the presence of triethylamine to furnish the azetidinone nuclei only works well with electron-withdrawing substituents at the α-position of the acid halide,[25] these procedures seem to be limited in scope.

Recently we have applied the Staudinger reaction to the synthesis of appropriately substituted 3-alkyl β-lactams for the preparation of carbapenem building blocks.[26] Herein, we wish to report full details of our preliminary work that demonstrate the synthetic potential of the acid chloride–imine methodology in carbapenem synthesis.

Results and Discussion

As mentioned above, dehydrohalogenation of simple aliphatic acid chlorides is fraught with potential difficulties that are probably associated with the inherent instability of monoalkylketenes.[25] Therefore, we decided to explore an indirect general route to 3-alkyl β-lactams that would involve the formation of β-lactams bearing electron-withdrawing groups at the α-position of the β-lactam ring able to undergo further reductive elimination.[27]

It has been described that α-halopropanoyl chlorides[28] and α-(phenylthio)propanoyl chloride[29] efficiently reacted with both imines and olefinic compounds in the presence of triethylamine to give the corresponding [2 + 2] cycloadducts in a straightforward manner. Consequently we thought that we could utilize this methodology for preparing valuable monocyclic β-lactams for carbapenem synthesis. Since a *N*-*p*-methoxyphenyl group in β-lactams can be removed under mild conditions according to the Kronenthal method,[30] the reaction was examined with imines derived from cinnamaldehydes and *p*-anisidine. For our study (Scheme I), we examined the behavior of α-haloalkanoyl chlorides **8–10** toward Schiff bases **11–13**. When **8** was allowed to react at room temperature with imine **11** in methylene chloride in the presence of triethylamine, the expected β-lactam **14** was only produced in 40% yield together with the dehydrochlorinated [4 + 2] cycloadduct **20** in 42% yield. Under these conditions α-bromopropanoyl chloride (**9**) reacted with the imine **11** to produce the pyridone **20** as the main product. Similar results were found in all of the other cases tested, except in the reaction between α-bromobutanoyl chloride (**10**) and the imine **13**, which under the above reaction conditions did not afford any of these cycloadducts.[31] The relative stereochemistry at C_3 and C_4 positions in pyridones **16** and **19** was established on the basis of their nuclear Overhauser enhancement of the ^1H NMR signal corresponding to the C_4-H methine when the 3-methyl group was irradiated. The 8–10% NOE observed could be attributed to a cis stereochemistry between the C_3 and C_4 substituents. Dehydrohalogenation of these cycloadducts by means of 1,8-diazabicyclo[5.4.0]undec-7-ene[32] (DBU) gave the pyridones **20** and **21**, in agreement with the stereochemistry assigned for the above compounds.

As previously described,[26] our finding is that the change of the halo group in the starting carboxylic acid by an arylthio group efficiently produced the expected 3-alkyl 3-arylthio β-lactam in excellent yield (Scheme II). Thus, reaction between α-(phenylthio)propanoyl chloride (**22**)

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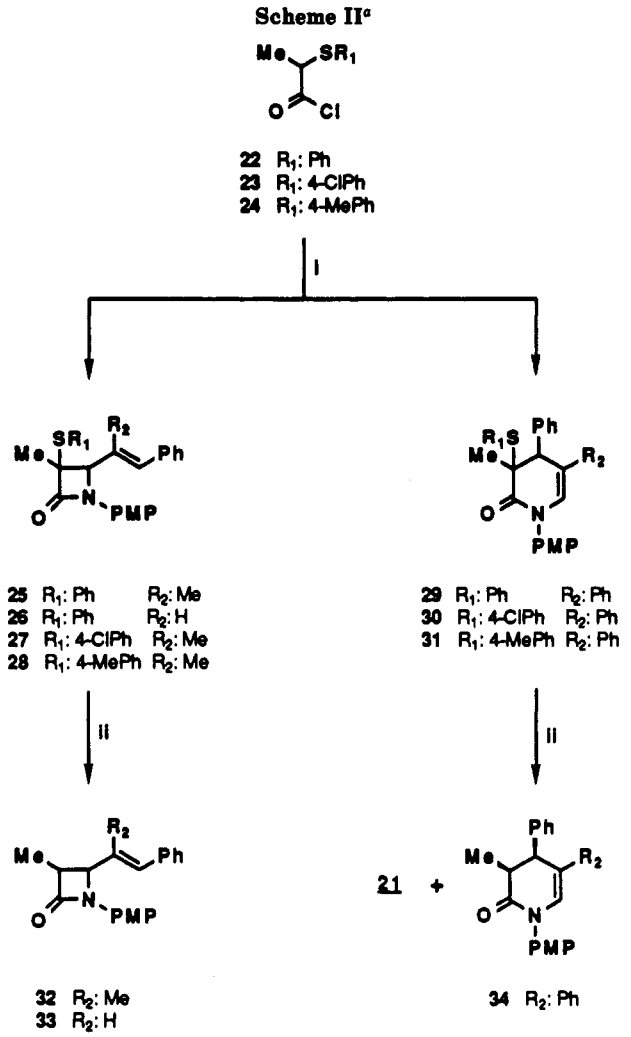
Table I. Preparation of β-Lactams 25–28[a]

compd[b]	solvent	yield, %[d]	cis:trans[e]	^{1}H NMR trans isomer, δ[f] (C-3)-CH_3	(C-4)-H	^{1}H NMR cis isomer, δ[f] (C-3)-CH_3	(C-4)-H	mp, °C[g]
25	CH_2Cl_2	97	80:20	1.50	4.38	1.63	4.48	oil
	benzene	95	91:9					
	CH_3CN	80	72:28					
26[c]	benzene	85	74:26	1.51	4.49	1.65	4.55	99–100
	CH_2Cl_2	60	60:40					
27	CH_2Cl_2	91	85:15	1.47	4.36	1.63	4.48	132–135
28	CH_2Cl_2	97	79:21	1.47	4.38	1.60	4.46	104–107

[a] Reactions carried out at room temperature overnight and conducted on a 10-mmol scale by addition of the acid chloride to a solution of the imine and triethylamine. [b] All compounds are racemic. [c] Reaction carried out in refluxing benzene for 2.5 h. [d] Yields based on weight of isolated material by column chromatography. [e] Determined by 300 MHz NMR spectroscopy. [f] Chemical shifts downfield relative to internal tetramethylsilane. [g] Cis isomer crystallized from EtOH.



[a] Reagents and conditions: (i), 11, 12, or 13, NEt_3, solvent, rt, 20–24 h or reflux; (ii) n-Bu_3SnH, AIBN, toluene, reflux, 1.5 h.

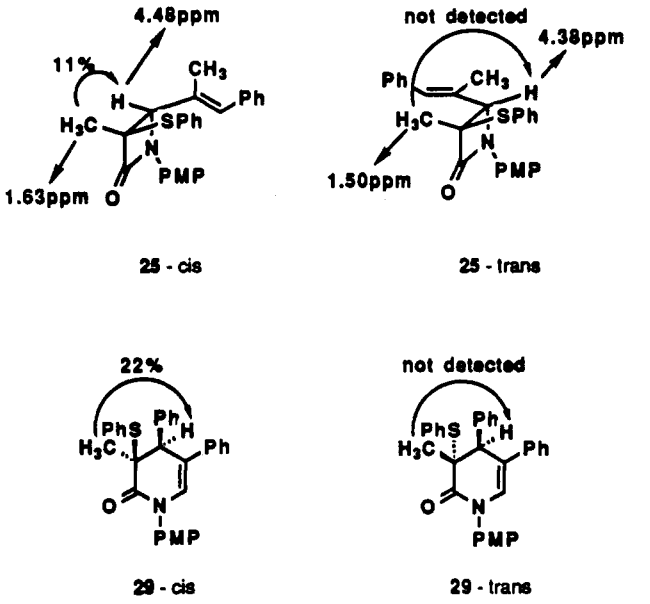
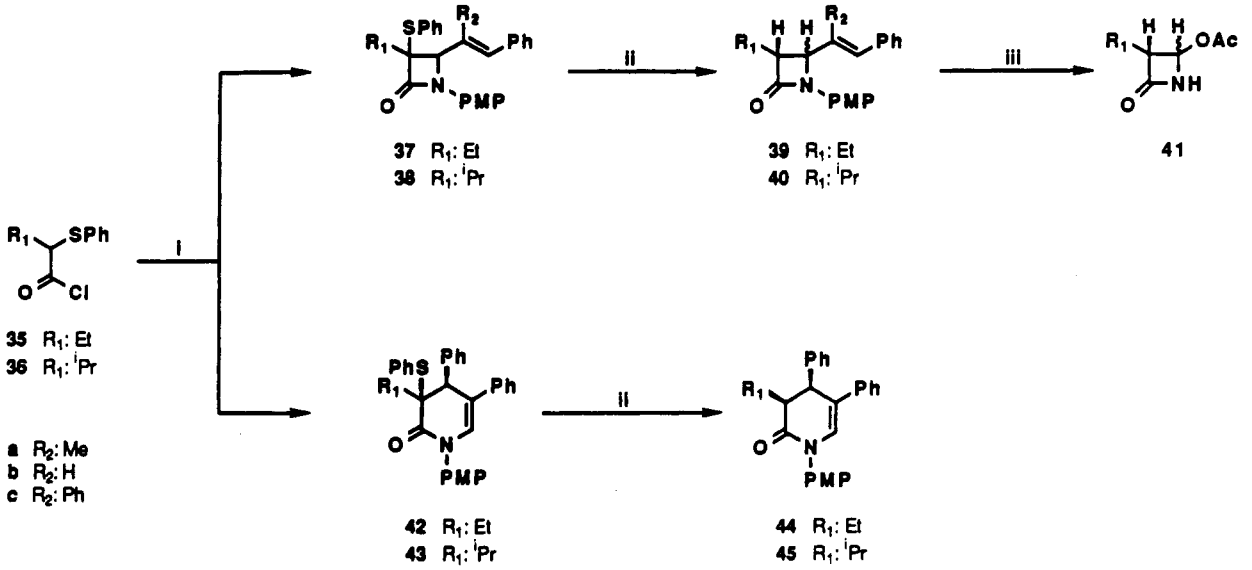


Figure 3.

and the imine 11 in methylene chloride as solvent, under standard conditions,[29] furnished the desired β-lactam 25 in 97% yield as a mixture of cis and trans isomers in a ratio of 80:20, respectively. In the case of imine 13 the reaction was carried out under reflux conditions to achieve high-yield formation of the desired β-lactam 26. Results of the cycloaddition of some (arylthio)propanoyl chlorides to Schiff bases 11 and 13 are summarized in Table I. These results suggest that there is not a remarkable influence on the chemical yield and stereochemical outcome by the substitution pattern of the aromatic ring in the starting carboxylic acid. α-((4-Chlorophenyl)thio)propanoyl chloride (23) and α-((4-methylphenyl)thio)propanoyl chloride (24) reacted with the imine 11 in the presence of triethylamine to produce the corresponding β-lactams 27 and 28 in yields and cis:trans ratios similar to those obtained starting from α-(phenylthio)propanoyl chloride (22). Particularly noteworthy is that the change of the reaction solvent from methylene chloride to a more polar one like acetonitrile caused a loss of stereoselectivity, and the best results were obtained when benzene was the solvent of choice.

The relative stereochemistry at C-3 and C-4 of the 3-methyl-3-(phenylthio)-2-azetidinones 25–28 was determined by measuring the nuclear Overhauser enhancement of the ^{1}H NMR signal corresponding to the C_4-H methine when the 3-methyl group was irradiated for 15 s. For example, when the NOE experiments were performed on the crude mixture of *cis*- and *trans*-1-(4-methoxyphenyl)-3-methyl-4-(1-methylstyryl)-3-(phenylthio)-2-azetidinone (25) (Figure 3) by presaturation of the 3-methyl group of the major isomer, an 11% NOE was observed in the signal corresponding to the C_4-H proton, whereas in the case of the minor isomer, no enhancement could be detected. The same results were obtained when NOE experiments were performed on β-lactams 26–28. Therefore, the cis stereochemistry was assigned to the major isomer in view of the minor internuclear distance between 3-methyl and 4-methine groups. On the basis of this assumption, the signals corresponding to the methyl and methine protons of the trans isomer appear at higher field than those of the cis isomer. This assignment of cis or trans stereochemistry is also in agreement with the data

Scheme III[a]



[a] Reagents and conditions: (i) 11–13, NEt_3, solvent, rt or reflux, 20–24 h; (ii) *n*-Bu_3SnH, toluene, reflux, 2–2.5 h; (iii) ref 11.

reported by Agawa and co-workers[29] on related molecules. However, when imine **12**, derived from α-phenylcinnamaldehyde and *p*-anisidine, was used in the cycloaddition reaction, the product obtained was the pyridone **29** instead of the expected β-lactam. Similar results were obtained when the reaction was tested with acid chlorides **23** and **24**, and the corresponding pyridones **30** and **31** were obtained as a mixture of cis and trans isomers (Scheme II). The relative stereochemistry at C_3 and C_4 positions in these pyridones was established by NOE experiments as previously done in cycloadducts **17** and **18**.

At this stage we examined the reductive elimination of the phenylthio group to produce the desired 3-alkyl β-lactam. The reaction was examined by using tributyltin hydride under azobis(isobutyronitrile) (AIBN) catalysis in benzene as solvent under standard conditions.[27,33] However, the reaction was more efficient when carried out in refluxing toluene, which gives the desired 3-alkyl β-lactams **32** and **33** in better yields. Under these conditions, a 80:20 cis:trans mixture of β-lactam **25** produced an 80% yield of compound **32** as a mixture of cis and trans isomers in a 92:8 cis:trans ratio. Similarly compound **26** afforded the β-lactam **33** in 80% yield as a mixture of cis and trans isomers in a 80:20 ratio. The yield and cis:trans ratios did not vary either by using β-lactam **27** or **28** as starting materials. The high degree of cis stereoselectivity could be explained by assuming that the hydride attack takes place preferentially at the less hindered face of the starting α-arylthio β-lactam. Under similar conditions, compounds **29–31**, upon treatment with tributyltin hydride under AIBN catalysis, afforded the pyridone **34** together with traces of pyridone **21**. The stereochemistry of β-lactams **32–33** was established on the basis of their ^1H NMR spectral data. Thus, the proton at C_4 in the corresponding cis isomer shows as a doublet at 4.60 ppm (J = 5.4 Hz) while the corresponding one in the trans isomer appears at 4.16 ppm (J = 2.4 Hz). In the case of β-lactam **33**, possessing the styryl group at the C_4 position, the proton at C_4 in the trans isomer shows a doublet of doublets at higher field than the corresponding C_4-H proton in the cis isomer.

The established methodology was next extended to the preparation of valuable β-lactams for (±)PS-5 and (±)PS-6 synthesis, starting from α-(phenylthio)alkanoyl chlorides **35** and **36** respectively, Scheme III. For example, reaction between α-(phenylthio)butanoyl chloride (**35**) and the imine **11** in benzene as solvent in the presence of triethylamine for 20–24 h furnished the β-lactam **37a** in 90% yield as a 91:9 mixture of cis and trans isomers. As expected, the ratio of the cis isomer decreased when the reaction was carried out in a more polar solvent like methylene chloride or acetonitrile. The use of cyclohexane or mixtures of benzene and hexane did not increase the ratio of the cis isomer. Particularly, in the case of imine **13** derived from cinnamaldehyde, the reaction might be accomplished in refluxing benzene to achieve a high-yield formation of the desired β-lactam **37b**. In a similar way, reaction between 3-methyl-2-(phenylthio)butanoyl chloride (**36**) and imine **11** under the same conditions as those used for the preparation of **37a** gave **38a** as a mixture of cis and trans isomers in which the highest cis:trans ratio was also produced when benzene was the solvent. As expected, reaction between **35** and the imine **12**, derived from α-phenylcinnamaldehyde, produced the pyridone **42** together with traces of the corresponding β-lactam **37c**. The stereochemistry of all these β-lactams was determined by correlation of their spectral data with those obtained from the corresponding methyl analogues. From this correlation, the C_4-H proton in a trans isomer appears at higher field than the corresponding C_4-H proton in the respective cis isomer. The cis:trans β-lactam **37a**, upon reductive removal of the phenylthio group by means of tributyltin hydride under AIBN catalysis, furnished the 3-ethyl β-lactam **39a** in 97% yield as a mixture of cis and trans isomers in a ratio of 92:8, respectively. When the desulfuration was examined for β-lactam **37b**, which incorporates a less bulky group at C_4 position of the β-lactam ring, the ratio of the cis isomer decreased to 76%. Under similar conditions as above, β-lactam **38a** produced the expected 3-isopropyl β-lactam **40a** in 91% yield as a mixture of cis and trans isomers in a ratio of 88:12, respectively. Similarly, **38b** produced the corresponding cis and trans isomers of **40b** in a ratio of 73:27, respectively. These isomers could be separated by crystallization or by column chromatography and further elaborated to the corresponding (±)PS-5 and (±)PS-6 carbapenems according to our method[11] or

(33) For recent reviews on tributyltin hydride, see: (a) Newman, W. P. *Synthesis* **1987**, 665. (b) Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987.

Table II. Preparation of β-Lactams 55–57[a]

compd[b]	R_2	R_3	solvent	yield, %[d]	cis:trans[f]	mp, °C[g]
55a	PhCO	PMP	benzene	76	22:78	131–133
56a	PhCO	PMP	CH_2Cl_2	95	19:81	138–140
57a	PhCO	PMP	CH_2Cl_2	93	9:91	118–120
55b	CO_2Me	PMP	CH_2Cl_2	96	14:86	66–67
56b	CO_2Me	PMP	benzene	89	7:93	77–79
57b	CO_2Me	PMP	benzene	74	17:83	129–130
55c	PhC≡C	PMP	benzene	83	57:43	97–99[h]
56c	PhC≡C	PMP	CH_2Cl_2	82	28:72	*i*
56c	PhC≡C	PMP	benzene	90	60:40	
55d	PhCH=CMe	CH_2CO_2Me	CH_2Cl_2	64[e]	85:15	*i*
56d	PhCH=CMe	CH_2CO_2Me	CH_2Cl_2	70[e]	81:19	85–87[j]
56d	PhCH=CMe	CH_2CO_2Me	benzene	80[e]	92:08	*i*
56e	PhCH=CH	CH_2Ph	benzene[c]	60	65:35	*i*

[a] Reactions carried out at room temperature overnight and conducted on a 10-mmol scale, by addition of the acid chloride to a solution of the imine and triethylamine at 0 °C. [b] All compounds are racemic. [c] Reaction carried out under reflux conditions for 2.5 h. [d] Yields based on weight of isolated product by column chromatography. [e] In these cases the corresponding imines were prepared in situ and not purified. [f] Determined by 300-MHz NMR spectroscopy. [g] Trans isomer crystallized from EtOH unless otherwise state. [h] Crystallized from hexane. [i] Isomers not separated. [j] Cis isomer crystallized from EtOH.

Table III. Selected ^1H NMR Data of 3-Methyl-3-phenyl-2-azetidinones

			cis isomer[a]			*trans* isomer[a]		
compd	R_2	R_3	$\delta(CH_3)$	$\delta(C_4\text{-H})$	NOE (%)[b]	$\delta(CH_3)$	$\delta(C_4\text{-H})$	NOE (%)[b]
55a	PhCO	4-$MeOC_6H_4$	1.88	5.39	23	1.38	5.09	2
55b	CO_2Me	4-$MeOC_6H_4$	1.65	4.52	37	1.55	4.34	6
55c	PhC≡C	4-$MeOC_6H_4$	1.68	4.84	37	1.80	4.66	n.d.[c]
55d	PhCH=C(Me)	$MeOOCCH_2$	1.65	4.38	14	1.40	4.25	n.d.

[a] Signal assigned from mixtures of cis and trans isomers. [b] Enhancement observed in the signal corresponding to C_4-H previous saturation of the methyl group. [c] n.d. = not detected.

by established protocols.[34] Although β-lactams **39c** and **48** could not be obtained through this methodology, these compounds were directly produced as a mixture of cis:trans isomers in 83% yield and 85% yield, respectively, by using the α-bromo ester–imine condensation[11] (eq 1).

46 R: Me
47 R: Et
12
48 R: Me
39c R: Et

The structures of these β- and δ-lactams were unambiguously elucidated on the basis of their IR and MS properties. For instance, the cis β-lactam **48** showed a strong carbonyl absorption at 1735 cm^{-1}, whereas the IR C=O band of δ-lactam **34** was detected at 1671 cm^{-1}, corresponding to a less constrained six-membered cyclic amide. Moreover, the respective mass spectra were very different (Scheme IV). The base peak in the spectrum of **34** was the imine fragment **49**, corresponding to an aza-Diels–Alder cycloreversion, whereas the base peak of β-lactam **48** was the olefinic fragment **53**, attributed to a well-known[35] fragmentation of the β-lactam ring, followed by a loss of methyl radical. As expected, the relative intensity of the molecular peak in the strained four-membered ring **48** was lower than that in the case of **34**. The same trends were observed in compounds **44** and **39** (R = Et) and **45** and **40c** (R = ^{i}Pr).

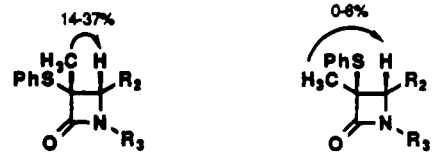
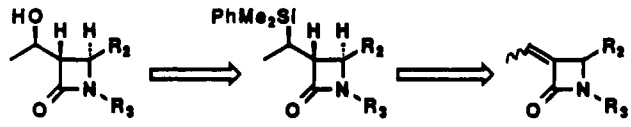


Figure 4.



61 **62** **63**

Figure 5.

Extension of this method to other imino compounds is shown in Scheme V and results are summarized in Table II. As shown from the data listed in the table, a variety of β-lactams bearing suitable functionalities at N_1 and C_4 positions can be obtained in good to excellent yields. The assignment of the relative stereochemistry of the β-lactams **55** was made on the basis of their ^1H NMR spectra and the nuclear Overhauser effect detected in the signal corresponding to the C_4-H methine after saturation of the signal corresponding to the 3-methyl group of each isomer (Figure 4). As in the case of β-lactams **25–28**, a significant NOE (14–37%) was measured for one isomer, whereas a very small or undetectable enhancement was observed for the other isomers. In the former compounds, both the methyl group and the methine proton at the C_4 position were assumed to be in a cis relationship. Consequently, in the trans isomers that showed a smaller NOE, these groups are on opposite sides of the plane of the β-lactam ring. The assignments made in this study are tabulated in Table III. Inspection of the table reveals that the chemical shifts corresponding to the methyl groups of cis isomers are at lower fields than the chemical shifts of the methyl groups of trans β-lactams, except in the case of β-lactam **55c** because of the deshielding effect of the triple

(34) For recent methods, see: (a) Bodurow, C.; Carr, M. A. *Tetrahedron Lett.* **1989**, *30*, 4081. (b) Palomo, C.; Aizpurua, J. M.; Cossío, F. P.; García, J. M.; López, M. C.; Oiarbide, M. *J. Org. Chem.* **1990**, *55*, 2070. For a recent review on PS-5 and PS-6 synthesis, see: Palomo, C. In *Recent Progress in The Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; p 565.

(35) (a) Manhas, M. S.; Bose, A. K. *Synthesis of Penicillin, Cephalosporin C and Analogs*; Bekker: New York, 1969; pp 23–26. (b) De Petris, G. *Org. Mass Spectrom.* **1989**, *24*, 514. (c) Bose, A. K.; Tabei, K.; Raju, V. S. *Tetrahedron Lett.* **1990**, *31*, 1661. (d) Bourgeois, G.; Picard, J. P.; Cossío, F. P.; Palomo, C. *Adv. Mass Spectrom.* **1989**, *11A*, 876.

Scheme IV

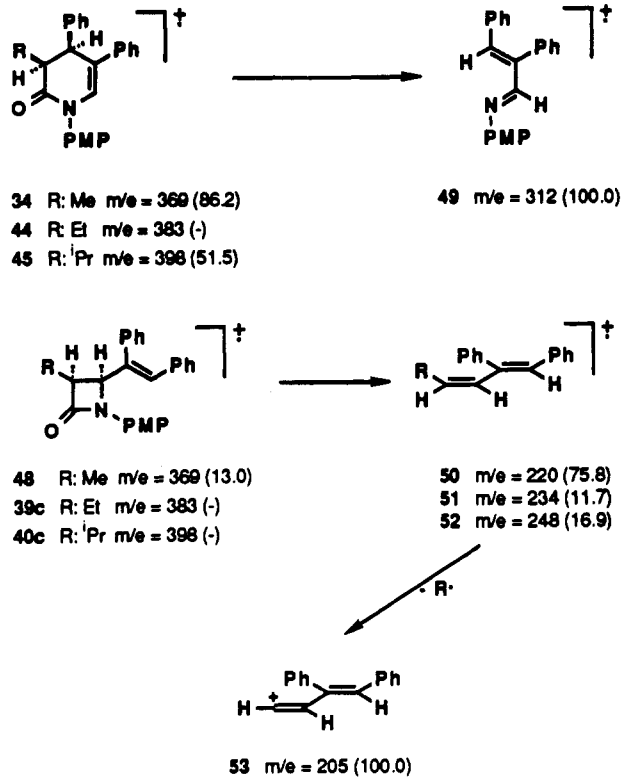


Table IV. Reductive Desulfuration of β-Lactams 55–57[a]

compd[b]	yield, %[c]	cis:trans[d]	mp, °C[e] (solvent)	δ CH-4 cis	δ CH-4 trans
58b	95	78:22	74–76 (Et_2O–hexane)	4.61	4.12
58d	77	86:14	oil[f]	4.49	4.02
59b	92	71:29	81–82 (cyclohexane)	4.60	4.19
59d	75	82:18	oil[f]	4.48	4.12
59e	88	68:32	oil[f]	4.15	3.73
60b	78	72:28	119–120 (cyclohexane)	4.58	4.22

[a] Reactions carried out in refluxing toluene and conducted on a 10-mmol scale. [b] All compounds are racemic. [c] Yields based on weight of isolated product by column chromatography. [d] Determined by 300-MHz NMR spectroscopy. [e] Cis isomer. [f] Isomers not separated.

bond. The assignment of cis or trans stereochemistry in β-lactams **56** and **57** was determined by correlating the corresponding C_4-H chemical shifts with those assigned to β-lactams **55**. With the exception of **55a** and **55c**, all these β-lactams upon treatment with tributyltin hydride under AIBN catalysis afforded the expected 3-alkyl β-lactams **58–60** in excellent yields as a mixture of cis and trans isomers,[36] and results are summarized in Table IV.

The next question that we examined was the preparation of β-lactams of type **61**, which carry the 1′-hydroxyethyl side chain at C_3 as precursors for the synthesis of thienamycin (1) (Figure 5). For this purpose, we focused our attention on the work of Fleming and Kilburn[37] on the use of the dimethylphenylsilyl group as a masked form of the hydroxy group. We thought that addition of Fleming's silylcuprate reagent to β-lactams of type **63** should render the desired silyl β-lactams **62**. Compounds of type **62** have also been prepared by Hart and co-workers[38] via the lithium ester enolate–imine condensation. However, this approach fails when imino esters are used as imino components in the reaction.[39] Since the α-methylstyryl moiety at C_4 of the β-lactam ring can be appropriately elaborated according to our protocol,[11] the reaction sequence depicted in Scheme VI was first studied with β-lactam **65a**. Compound **65a** was prepared by following the method reported by Agawa[29] starting from 3-phenylthio β-lactam **37a**. Thus, oxidation of a 91:9 mixture of *cis*- and *trans*-3-(phenylthio)azetidine-2-one (**37a**) with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride at 0 °C gave the corresponding sulfoxide **64a** without concomitant side products. The crude sulfoxide was directly subjected to vacuum thermolysis to give the desired 3-alkylidene β-lactam **65a** in 65% overall yield as a mixture of *Z* and *E* isomers about the double bond in a 32:68 ratio, respectively. These isomers were separated by column chromatography and their stereochemistry was determined by measuring the nuclear Overhauser enhancement of the ^1H NMR signal corresponding to the C_4-H methine when the alkylidene methyl group was irradiated for 15 s. On the basis of this assignment, the vinylic proton in the *Z* isomer appears at higher field than that in the *E* isomer. This assignment is also in agreement with the calculated value following the Pascual equation.[40]

Table V. $J_{1',3}$ Coupling Constants of Trans and Cis β-Lactams 66–69[a,b]

		trans		cis	
65[c]	R	anti 68	syn 66	anti 67	syn 69
E	PhCH=CMe	4.5 (5)	7.0 (78)	12.2 (17)	4.0 (-)[d]
Z	PhCH=CMe	(61)	(7)	(1)	(31)
E	CO_2Me	4.9 (23)	6.8 (60)	12.4 (12)	(5)
Z	CO_2Me	(64)	(20)	(3)	(13)

[a] Determined by 300-MHz NMR spectroscopy. [b] The number in parentheses indicates the ratio of isomers. [c] *E* and *Z* denote the stereochemistry of the 3-exocyclic double bond in the respective starting β-lactam **65**. [d] Not detected.

The *E* isomer was then allowed to react with Fleming's silylcuprate reagent at 0 °C in tetrahydrofuran as solvent to give after protonation a mixture of three of the four possible diastereomers **66a–68a** in 90% total yield. These compounds were characterized by NMR spectroscopy from the coupling constants between H-3 and H-1′. Thus, in similar compounds the $J_{1',3}$ for the anti-cis isomer is greater than that for the syn-cis isomer and the $J_{1',3}$ for the anti-trans isomer is lower than that for the syn-trans isomer.[38] According to this observation, compounds **66a–68a** were produced in a ratio of 78:17:5, respectively. When the cuprate addition was performed on the *Z* isomer, a mixture of four diastereomers **66a–69a** was produced in 78% yield. The relative stereochemistry of such isomers was determined as above and their relative proportions are listed in Table V. However, attempted conversion of these diastereomers to the corresponding (±)-thienamycin intermediate by treatment with tetrafluoroboric acid–diethyl ether complex[41] and further peracetic oxidation[37] to the desired 3-(1′-hydroxyethyl) β-lactam was unfruitful.

In view of this result, we next examined the same sequence with β-lactam **65b** as the starting material, which carrys an alkoxycarbonyl group at C_4, suitable for an easy

(36) Reductive desulfuration of 3-alkyl-3-arylthio β-lactams by tributyltin hydride has recently been reported to produce the inverse ratio of isomers, see: Sugano, Y.; Naruto, S. *Chem. Lett.* **1989**, 1331.

(37) Fleming, I.; Kilburn, J. D. *J. Chem. Soc., Chem. Commun.* **1986**, 1198. For a review, see: Fleming, I. *Pure Appl. Chem.* **1988**, *60*, 71. See also: Palomo, C.; Aizpurua, J. M.; Urchegui, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1390.

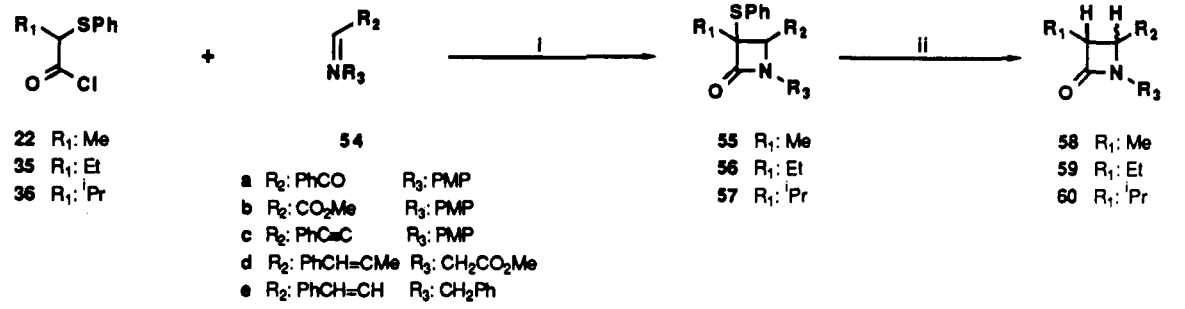
(38) Burnett, D. A.; Galluci, J. G.; Hart, D. J. *J. Org. Chem.* **1985**, *50*, 5120.

(39) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.

(40) Pascual, C.; Meier, J.; Simon, W. *Helv. Chim. Acta* **1966**, *49*, 164.

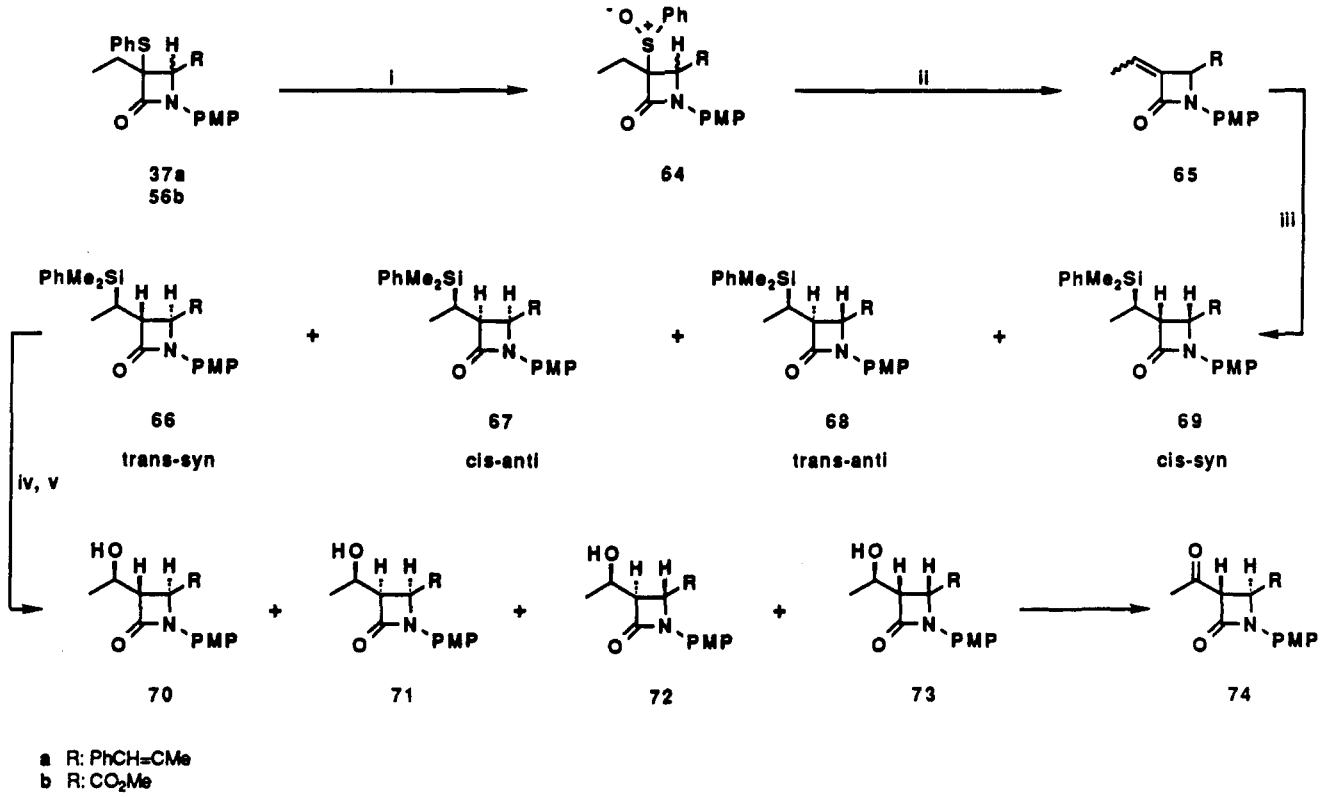
(41) Fleming, I.; Hill, J. H. M.; Parker, D.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1985**, 318.

Scheme V[a]



[a] Reagents and conditions: (i) NEt_3, benzene, rt; (ii) n-Bu_3SnH, AIBN, toluene, 2.5 h, reflux.

Scheme VI[a]



a R: PhCH=CMe
b R: CO_2Me

[a] Reagents and conditions: (i) MCPBA, CH_2Cl_2, 0 °C; (ii) 160 °C/0.1–0.2 mmHg; (iii) $(PhMe_2Si)_2CuCNLi_2$, THF, 0 °C; (iv) $HBF_4(Et_2O)_2$, CH_2Cl_2, rt; (v) AcO_3H, AcOH, NEt_3.

functionalization. β-Lactam **65b** was prepared as described for **65a**, in 70% overall yield starting from **56b**. Compound **65b** was produced as a mixture of *E* and *Z* isomers about the double bond in a ratio of 43:57 respectively, which were separated by column chromatography. The *E* isomer was then treated with Fleming's silylcuprate reagent, to give a mixture of four diastereomers **66b–69b** in which the trans-syn β-lactam **66b** predominates. Similarly, when the *Z* isomer of **65b** was subjected to treatment with Fleming's silylcuprate reagent, the same mixture of diastereomers was produced. The assignment for syn and anti isomers was made according to the aforementioned observations, and their relative proportions are tabulated in Table V. As can be seen from the data listed in the table, the overall proportion of trans β-lactams predominates over the cis β-lactams. Treatment of this mixture of diastereomers under the same conditions as those used in the case of **65a–68a** gave the desired 3-(1′-hydroxyethyl)azetidin-2-ones **70b–73b** in 90% yield. The relative stereochemistry of these compounds was determined by NMR spectroscopy by measuring $J_{1',3}$. In 3-(1′-hydroxyethyl) β-lactams, $J_{1',3}$ for the anti-cis isomer is lower than that for the syn-cis isomer and $J_{1',3}$ for the anti-trans isomer is greater than that for the syn-trans isomer according to the assignments made by Cainelli and Panunzio on related compounds.[42] Separation of both anti **72b** and syn **70b** epimers was followed by conversion into their corresponding mesylates **75**, and further stereospecific elimination[43] provided the respective (*Z*)-**76** and (*E*)-**76** alkenes, thus confirming unambiguously the above stereochemical assignments (Figure 6). Although from this approach no great diastereoselection was produced, oxidation of the hydroxy group in these racemic β-lactams by means of an NDC–pyridine system[44] leads to the thermodynamically more stable 3-acetyl β-lactam **74** in quantitative yield. Such compound

(42) Cainelli, G.; Panuncio, M.; Basile, T.; Bongini, A.; Giacomini, D.; Martelli, G. *J. Chem. Soc., Perkin Trans. I* **1987**, 2637.

(43) (a) Corbett, D. F.; Coulton, S.; Southgate, R. *J. Chem. Soc., Perkin Trans. I* **1982**, 3011. (b) Pecquet, F.; d'Angelo, J. *Tetrahedron Lett.* **1982**, *23*, 2777. (c) Palomo, C.; Aizpurua, J. M.; Urchegui, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1390.

(44) Cossío, F. P.; López, M. C.; Palomo, C. *Tetrahedron* **1987**, *43*, 3963. For the structure of NDC, see: Matikainen, J. K. T.; Kaltia, S. A. A.; Hase, T. A.; Saundberg, M. R.; Kivekas, R. *J. Chem. Res., Synop.* **1990**, 150.

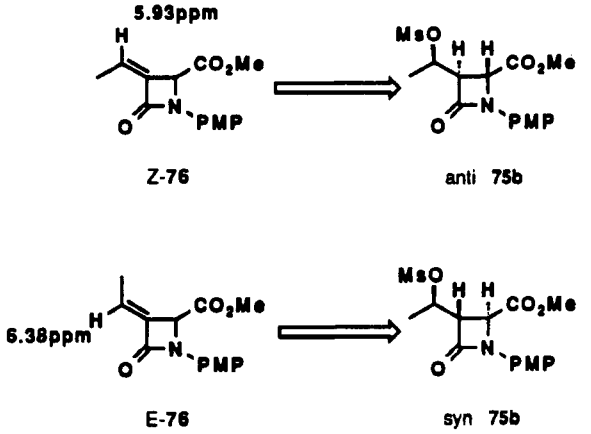
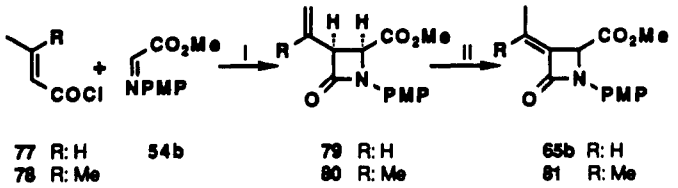


Figure 6.

Scheme VII[a]



77 R: H 54b 79 R: H
78 R: Me 80 R: Me

[a] Reagents and conditions: (i) NEt_3, CH_2Cl_2, 40 °C; (ii) DBU, benzene, 80 °C.

could be transformed into the (±)-thienamycin precursor 7 according to Merck's methodology.[45]

At this stage we envisaged alternative approaches to α-alkylidene β-lactams of type **63**. In view of the easy epimerization at C_3 of the β-lactam ring in 3-acetyl β-lactams, we reasoned that an α-vinyl β-lactam like **79** (Scheme VII) could also be easily isomerized into an α-alkylidene β-lactam, thus providing an alternative approach to Agawa's method.[29] In fact, while our work was in progress, Manhas and co-workers[46] reported the same strategy to produce α-alkylidene β-lactams[47] like **65b** and **81**, which were converted into the corresponding 3-alkyl β-lactams **41** as (±)PS-5 and (±)PS-6 intermediates.

Conclusion

From the results reported here the cycloaddition reaction between α-(phenylthio)alkyl ketenes, generated from their corresponding α-(phenylthio)alkanoyl halides, and imines in the presence of triethylamine seems to be of general utility since a wide range range of structurally different imines could be used. The β-lactams prepared could be easily elaborated to carbapenem precursors and the method may be readily extended to further applications not only in β-lactam chemistry but also in chemistry that employs β-lactams as starting materials.

Experimental Section

Commercially available compounds were used without further purification unless otherwise noted. Hexane was purified by distillation. Tetrahydrofuran was distilled over sodium with benzophenone as indicator. Methylene chloride was shaken with concentrated H_2SO_4, dired over K_2CO_3, and distilled. Ozonization reactions were carried out on a Fisher 502 ozone generator. Melting points were determined on either Büchi SMP-20 or Mettler FP61 instruments and are uncorrected. Proton magnetic resonance (^1H NMR) spectra were recorded on a Varian VXR 300 spectrometer; chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. The nuclear Overhauser enhancement experiments were run at 300 MHz by preirradiating the desired signals for 15 s with the decoupler channel turned on at 20 db below 1 W and acquiring the spectrum with the decoupler turned off. A control experiment was created by setting the irradiation away from any signal. The acquisitions were carried out in groups of four for each irradiated signal, until 32 accumulations were performed. The FIDs, acquired with 16K (3000-Hz sweep width), were Fourier transformed with 32K (zero filling). The NOEs were measured by integration of the signals resulting from the respective difference spectra. Infrared spectra were obtained on a Shimadzu IR-435 spectrometer. Mass spectra were obtained on a Shimadzu GCMS-QP2000 spectrometer operated at 70 eV and 250 °C. For new compounds, microanalytical data were obtained in these laboratories on a Perkin-Elmer Model 240 C instrument. All compounds prepared in this work are racemic.

Reaction between α-Haloalkanoyl Chlorides 8–10 and Imines 11–13. General Procedure. To a stirred solution of the corresponding imine (10 mmol) and triethylamine (2.8 mL, 20 mmol) in benzene (25 mL) was added a solution of α-haloalkanoyl chloride (15 mmol) in the same solvent (10 mL) dropwise at 0–5 °C. The reaction mixture was stirred overnight at room temperature and then was poured into water (25 mL), and methylene chloride (25 mL) was added. The organic layer was separated and washed with 1 N HCl (25 mL) and aqueous $NaHCO_3$ (25 mL, saturated solution) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:3 as eluent).

Preparation of 3-Alkyl 3-Arylthio Lactams. Procedure A. To a stirred solution of the corresponding imine (10 mmol) and triethylamine (2.8 mL, 20 mmol) in benzene as solvent (25 mL) was added a solution of the corresponding α-(arylthio)alkanoyl chloride (15 mmol) in the same solvent (10 mL) dropwise at 0–5 °C. The reaction mixture was stirred overnight at room temperature and then was poured into water (25 mL). Methylene chloride (25 mL) was added and the organic layer was separated and washed with 0.1 N HCl (25 mL) and aqueous $NaHCO_3$ (25 mL, saturated solution) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:3 as eluant).

Procedure B. To a stirred solution of the corresponding imine (10 mmol) and triethylamine (2.8 mL, 20 mmol) in refluxing benzene (25 mL) was added dropwise a solution of the corresponding α-(arylthio)alkanoyl chloride (15 mmol) in the same solvent (10 mL). The reaction mixture was stirred under reflux for 2.5 h and then cooled at room temperature and poured into water (25 mL). Methylene chloride (25 mL) was added and the organic layer was separated and washed with 0.1 N HCl (25 mL) and aqueous $NaHCO_3$ (25 mL, saturated solution) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:3 as eluant).

3-Ethyl-1-(4-methoxyphenyl)-3-(phenylthio)-4-styrylazetidin-2-one (37b). The title compound was prepared from *N*-cinnamylidene-*p*-anisidine (**13**) (2.37 g, 10 mmol) and α-(phenylthio)butanoyl chloride (**35**) (3.22 g, 15 mmol), following procedure B. The crude title compound was purified by column chromatography to give a 77:23 ratio of cis and trans isomers of **37b**, yield 3 g (72%). Crystallization from ethanol gave the cis isomers of **37b**: mp 120–122 °C (EtOH); IR (KBr) ν 1741 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.55–7.70 (m, 2 H, Ar), 7.44–7.24 (m, 10 H, Ar), 6.85–6.77 (m, 3 H, Ar, =CH), 6.37 (dd, 1 H, J = 15.9 Hz, J' = 8.4 Hz, =CH), 4.61 (d, 1 H, J = 8.4 Hz, CH), 3.75 (s, 3 H, OCH_3), 1.96–1.88 (m, 2 H, CH_2), 1.08 (t, 3 H, J = 7.3 Hz, CH_3). Anal. Calcd for $C_{26}H_{25}NO_2S$: C, 75.15; H, 6.06; N, 3.37. Found: C, 74.88; H, 5.95; N, 3.33.

3-Isopropyl-1-(4-methoxyphenyl)-4-(α-methylstyryl)-3-(phenylthio)azetidin-2-one (38a). Procedure A was followed, starting from *N*-(α-methylcinnamylidene)-*p*-anisidine (**11**) (2.51 g, 10 mmol) and α-(phenylthio)isovaleryl chloride (**36**) (3.43 g,

(45) Reider, J. P.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293.
(46) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575. Also, see: Palomo, C.; Aizpurua, J. M.; López, M. C.; Aurrekoetxea, N.; Oiarbide, M. *Tetrahedron Lett.* **1990**, *31*, 6425.
(47) For other methods to prepare α-alkylidene β-lactams, see: (a) Tufariello, J. J.; Pinto, D. J. P.; Milowsky, A. S.; Reinhardt, D. V. *Tetrahedron Lett.* **1987**, *28*, 5481. (b) Alcaide, B.; Plumet, J.; Rodriguez-López, J.; Sánchez-Cantalejo, Y. M. *Tetrahedron Lett.* **1990**, *31*, 2493.

15 mmol). The crude title compound was purified by column chromatography to give a 86:14 ratio of cis and trans isomers of **38a** as an oil, yield 4.30 g (97%). Crystallization from hexane gave the cis isomer of **38a**: mp 111–112 °C (EtOH); IR (KBr) ν 1733 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.66–7.63 (m, 2 H, Ar), 7.36–7.18 (m, 8 H, Ar), 7.00 (d, 2 H, J = 9 Hz, Ar), 6.69 (d, 2 H, J = 9 Hz, Ar), 6.65 (s_b, 1 H, =CH), 4.32 (s, 1 H, CH), 3.71 (s, 3 H, OCH_3), 2.67–2.54 (m, 1 H, CH), 1.98 (s, 3 H, CH_3), 1.41 (d, 3 H, J = 6.7 Hz, CH_3), 1.09 (d, 3 H, J = 6.7 Hz, CH_3). Anal. Calcd for $C_{28}H_{29}NO_2S$: C, 75.81; H, 6.60; N, 3.16. Found: C, 75.96; H, 6.63; N, 2.99.

3-Isopropyl-1-(4-methoxyphenyl)-3-(phenylthio)-4-styrylazetidin-2-one (38b). Procedure A was followed, starting from *N*-cinnamylidene-*p*-anisidine (**13**) (2.37 g, 10 mmol) and α-(phenylthio)isovaleryl chloride (**36**) (3.43 g, 15 mmol), using methylene chloride as solvent. The crude title compound was purified by column chromatography to give a 27:73 ratio of cis and trans isomers of **38b** as an oil, yield 1.72 g (40%). The trans isomer was crystallized from ethanol: mp 123–125 °C (EtOH); IR (CH_2Cl_2) ν 1739 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.67–6.66 (m, 15 H, Ar), 6.30 (dd, 1 H, J = 15.9 Hz, J' = 8.3 Hz, =CH), 4.40 (d, 1 H, J = 8.3 Hz, CH), 3.70 (s, 3 H, OCH_3), 2.62–2.49 (m, 1 H, CH), 1.39 (d, 3 H, J = 6.8 Hz, CH_3), 1.09 (d, 3 H, J = 6.8 Hz, CH_3). Anal. Calcd for $C_{27}H_{27}NO_2S$: C, 75.49; H, 6.33; N, 3.26. Found: C, 75.46; H, 6.32; N, 3.30.

***cis*-3-Isopropyl-1-(4-methoxyphenyl)-4-(α-phenylstyryl)-3-(phenylthio)azetidin-2-one (38c).** Procedure B was followed, starting from *N*-(α-phenylcinnamylidene)-*p*-anisidine (**12**) (3.13 g, 10 mmol) and α-(phenylthio)isovaleryl chloride (**36**) (3.43 g, 15 mmol). The crude title compound was purified by column chromatography to give a 21:79 of **38c** and **43**, respectively, as an oil, yield 4.13 g (84%). The β-lactam **38c** was separated by crystallization from ethanol: mp 181–183 °C (EtOH); IR ($CHCl_3$) ν 1742 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.82–7.79 (m, 2 H, Ar), 7.53–6.88 (m, 17 H, Ar), 6.60 (s_b, 1 H, =CH), 4.80 (s, 1 H, CH), 3.78 (s, 3 H, OCH_3), 2.02–1.93 (m, 1 H, CH), 0.86 (d, 3 H, J = 6.8 Hz, CH_3), 0.60 (d, 3 H, J = 6.8 Hz, CH_3). Anal. Calcd for $C_{33}H_{31}NO_2S$: C, 78.38; H, 6.18; N, 2.77. Found: C, 77.73; H, 6.19; N, 2.69. Compound **43**: mp 116–119 °C (EtOH); IR (KBr) ν 1674 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.67–7.97 (m, 19 H, Ar), 6.54 (s, 1 H, =CHN), 4.37 (s, 1 H, CH), 3.83 (s, 3 H, OCH_3), 2.70–2.58 (m, 1 H, CH), 1.30 (d, 3 H, J = 6 Hz, CH_3), 1.11 (d, 3 H, J = 6 Hz, CH_3). Anal. Calcd for $C_{33}H_{31}NO_2S$: C, 78.38; H, 6.18; N, 2.77. Found: C, 78.08; H, 6.15; N, 2.79.

Tributyl Hydride Reduction of 3-Alkyl 3-Arylthio Lactams. General Procedure. To a stirred solution of the corresponding cis:trans 3-alkyl 3-arylthio lactam (10 mmol) in toluene (10 mL) were added tributyltin hydride (3.23 mL, 12 mmol) and azobis(isobutyronitrile) (0.16 g, 1 mmol), and the resulting solution was stirred under reflux for 1.5 h. Then, the reaction mixture was cooled at room temperature and poured into a mixture (large excess) of $CuSO_4$ (20 g) and KF (20 g) in water (50 mL). Diethyl ether (50 mL) was added, the organic layer was separated and filtered off through silica gel, the pad was washed with diethyl ether (3 × 50 mL), and the combined organic solutions were dried (Na_2SO_4). Evaporation of the solvents under reduced pressure gave a residue, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:2 as eluant).

3-Ethyl-1-(4-methoxyphenyl)-4-(α-methylstyryl)azetidin-2-one (39a). To a stirred solution of *N*-(α-methylcinnamylidene)-*p*-anisidine (**11**) (2.51 g, 10 mmol) and triethylamine (2.8 mL, 20 mmol) in benzene as solvent (25 mL) was added a solution of α-(phenylthio)butanoyl chloride (**35**) (3.22 g, 15 mmol) in the same solvent (10 mL) dropwise at 0–5 °C. The reaction mixture was stirred overnight at room temperature. After standard workup and isolation by column chromatography, the intermediate β-lactam **37a** was obtained as a mixture of cis and trans isomers in a ratio of 91:9, respectively: yield 3.87 g (90%); ^1H NMR ($CDCl_3$) δ 7.78–7.15 (m, 12 H, Ar, both isomers), 6.86 (d, 2 H, J = 9 Hz, Ar) and 6.75 (d, 2 H, J = 9 Hz, Ar), 6.54 (s_b, 1 H, =CH) and 6.36 (s_b, 1 H, =CH), 4.50 (s, 1 H, CH) and 4.37 (s, 1 H, CH), 3.76 (s, 3 H, OCH_3) and 3.72 (s, 3 H, OCH_3), 2.05 (d, 3 H, J = 1.2 Hz, CH_3, both isomers), 1.92–1.84 (m, 2 H, CH_2, both isomers), 1.22 (t, 3 H, J = 7.3 Hz, CH_3) and 1.07 (t, 3 H, J = 7.3 Hz, CH_3). This mixture of isomers was dissolved in toluene (9 mL) and tributyltin hydride (2.9 mL, 10.8 mmol) and azobis(isobutyronitrile) (0.14 g, 0.9 mmol) were added. Following the above general procedure a mixture of cis and trans isomers of **39a** was obtained in a ratio of 92:8, respectively, yield 2.8 g (87% from **11**, 97% from **37a**). The physical and spectroscopic properties of the isomeric β-lactams **39a** agreed with the previously reported data.[11]

3-Ethyl-1-(4-methoxyphenyl)-4-styrylazetidin-2-one (39b). Following the general procedure starting from **37b** (4.15 g, 10 mmol), a mixture of cis and trans isomers of **39b** was obtained in a ratio of 76:24, respectively, yield 2.67 g (87%). The cis isomer could be separated by crystallization from ethanol: mp 80–82 °C (EtOH); IR (KBr) ν 1727 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.41–7.25 (m, 7 H, Ar), 6.82 (d, 2 H, J = 9.3 Hz, Ar), 6.76 (d, 1 H, J = 8.1 Hz, =CH), 6.27 (dd, 1 H, J = 15.9 Hz, J' = 8.1 Hz, =CH), 4.72 (ddd, 1 H, J = 8.1 Hz, J' = 5.7 Hz, J'' = 0.7 Hz, CH), 3.76 (s, 3 H, OCH_3), 3.42–3.35 (m, 1 H, CH), 1.91–1.72 (m, 1 H, HC*H*), 1.69–1.62 (m, 1 H, *H*CH), 1.05 (t, 3 H, J = 7.5 Hz, CH_3). Anal. Calcd for $C_{25}H_{23}NO_2$: C, 78.15; H, 6.89; N. 4.56. Found: C, 78.69; H, 6.99; N, 4.62.

3-Isopropyl-1-(4-methoxyphenyl)-4-(α-methylstyryl)azetidin-2-one (40a). Following the general procedure starting from β-lactam **38a** (4.44 g, 10 mmol), a mixture of cis and trans isomers of **40a** was obtained in a ratio of 88:12, respectively, yield 3.05 g (91%). The physical and spectroscopic properties of the isomeric β-lactams **40a** agree with the previously reported data.[11]

3-Isopropyl-1-(4-methoxyphenyl)-4-styrylazetidin-2-one (40b). Following the general procedure starting from **38b** (4.3 g, 10 mmol), a mixture of cis and trans isomers of **40b** was obtained in a ratio of 73:27, respectively, yield 2.86 g (89%). The physical and spectroscopic properties of the isomeric β-lactams **40b** agreed with the previously reported data.[11]

3-Ethylidene-4-(methoxycarbonyl)-1-(4-methoxyphenyl)-azetidin-2-one (65b). To a stirred solution of the cis–trans mixture of the β-lactam **56b** (1.86 g, 5 mmol) in methylene chloride (15 mL) was added dropwise at 0 °C a solution of MCPBA (0.90 g, 5.2 mmol) in methylene chloride (25 mL), and the solution was stirred for 1 h at 0 °C. The mixture was poured into water and the organic layer was washed with aqueous $NaHSO_3$ (2 × 30 mL, 40% solution) and aqueous $NaHCO_3$ (2 × 30 mL, saturated solution), dried ($MgSO_4$), and evaporated under reduced pressure to give **64b** as oil: yield of diastereomer mixture 1.80 g (93%); IR (neat) ν 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ (one diastereomer) 7.75–7.39 (m, 5 H, Ar), 6.85 (d, 2 H, J = 9.0 Hz, Ar), 6.70 (d, 2 H, J = 9.0 Hz, Ar), 4.56 (s, 1 H, H-4), 3.81 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 2.26 (m, 1 H, CH_aH_b), 2.14 (m, 1 H CH_aH_b), 1.37 (t, 3 H, J = 7.4 Hz, CH_3); (other diastereomer) 7.75–7.39 (m, 5 H, Ar), 7.26 (d, 2 H, J = 8.9 Hz, Ar), 6.84 (d, 2 H, J = 8.9 Hz, Ar), 5.06 (s, 1 H, H-4), 3.77 (s, 3 H, OCH_3), 3.55 (s, 3 H, OCH_3), 1.77 (m, 1 H, CH_aH_b), 1.64 (m, 1 H, CH_aH_b), 1.26 (t, 3 H, J = 7.5 Hz, CH_3). This mixture of isomers was subjected to thermolysis at 160 °C (0.2 mmHg) to give a mixture of *E* and *Z* isomers of **65b**, in a 43:57 ratio, respectively, which were separated by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane). Yield of *E* isomer 0.36 g (28% from **56b**): mp 108–109 °C (EtOH); IR (KBr) ν 1741 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.26 (d, 2 H, J = 8.9 Hz, Ar), 6.88 (d, 2 H, J = 8.9 Hz, Ar), 6.38 (dq, 1 H, J = 7.3 Hz, J' = 1.6 Hz, CH=C), 4.96 (s, 1 H, H-4), 3.79 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 1.87 (d, 3 H, J = 7.3 Hz, CH_3). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.74; N, 5.36. Found: C, 64.23; H, 5.87; N, 5.62. Yield of *Z* isomer 0.48 g (37% from **56b**): mp 146–147 °C (EtOH); IR (KBr) ν 1736 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.28 (d, 2 H, J = 9.1 Hz, Ar), 6.88 (d, 2 H, J = 9.1 Hz, Ar), 5.93 (dq, 1 H, J = 7.2 Hz, J' = 1.2 Hz, CH=C), 4.82 (d, 1 H, J = 1.0 Hz, H-4), 3.79 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 2.11 (dd, 3 H, J = 7.2 Hz, J' = 0.9 Hz, CH_3). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.74; N, 5.36. Found: C, 63.92; H, 5.85; N, 5.27.

Preparation of β-Lactams 66–69. General Procedure. (Dimethylphenylsilyl)lithium (THF solution, 4 mmol) was added to copper(I) cyanide (0.18 g, 2 mmol) at 0 °C under nitrogen, and the mixture was stirred at this temperature for 0.5 h. The corresponding β-lactam **65** (2 mmol) was added, and the mixture was stirred at 0 °C for 0.5 h, poured into a mixture of NH_4Cl (25 mL, saturated solution) and NH_4OH (25 mL, 25% aqueous solution), and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were filtered off over Celite, dried ($MgSO_4$), and evaporated under reduced

pressure to give a mixture of diastereomers **66–69**, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane).

***trans*-3-Acetyl-4-(methoxycarbonyl)-1-(4-methoxyphenyl)azetidin-2-one (74).** To a solution of β-lactams **66b–69b** (1 mmol) in CH_2Cl_2 (5 mL) was added at 0 °C a solution of the HBF_4·Et_2O (1.2 mmol, 85% solution in Et_2O), and the mixture was stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2 (25 mL), washed with H_2O (1 × 25 mL) and NaCl (2 × 25 mL, saturated solution), and dried ($MgSO_4$). Evaporation of the solvent gave the corresponding silyl fluoride as an oil, which was mixed with a 32% solution of peracetic acid in acetic acid (4 mL) at 0 °C. Triethylamine (0.16 mL, 1.2 mmol) was slowly added, and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with 2 N HCl (1 × 20 mL), 40% aqueous $NaHSO_3$ (3 × 20 mL, 40% w/v solution), and aqueous $NaHCO_3$ (3 × 20 mL, saturated solution), dried ($MgSO_4$), and evaporated under reduced pressure to give the corresponding 3-(1′-hydroxyethyl) β-lactams **70b** and **72b** as main products and traces of **71b** and **73b**: yield 0.25 g (90%); IR (neat) ν 3439 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ **70b** 7.25 (d, 2 H, J = 7.3 Hz, Ar), 6.87 (d, 2 H, J = 7.3 Hz, Ar), 4.43 (d, 1 H, J = 2.4 Hz, H-4), 4.20 (qd, 1 H, J = 6.6 Hz, J' = 5.4 Hz, O—CH), 3.79 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.37 (dd, 1 H, J = 5.4 Hz, J' = 2.4 Hz, H-3), 2.52–2.23 (s_b, 1 H, OH), 1.42 (d, 3 H, J = 6.6 Hz, CH_3); **72b** 7.25 (d, 2 H, J = 7.3 Hz, Ar), 6.87 (d, 2 H, J = 7.3 Hz, Ar), 4.60 (d, 1 H, J = 2.7 Hz, H-4), 4.33 (qd, 1 H, J = 6.5 Hz, J' = 4.1 Hz, O—CH), 3.79 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.35 (dd, 1 H, J = 4.1 Hz, J' = 2.7 Hz, H-3), 2.52–2.23 (s_b, 1 H, OH), 1.33 (d, 3 H, J = 6.5 Hz, CH_3). To a suspension of chromic nicotinic anhydride (NDC) (0.81 g, 3.68 mmol) in CH_2Cl_2 (3 mL) and pyridine (0.57 mL, 7 mmol) was added the crude mixture of β-lactams **70b–73b** obtained as above (0.35 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred overnight at room temperature and then was diluted with CH_2Cl_2 (25 mL) and filtered off through a pad of silica gel. The organic layer was washed with 6 N HCl (4 × 25 mL) and aqueous $NaHCO_3$ (2 × 25 mL, saturated solution), dried ($MgSO_4$), and evaporated under reduced pressure to afford the title compound: yield 0.095 g (98%); mp 103–104 °C (EtOH); IR (neat) ν 1754, 1716 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.24 (d, 2 H, J = 9.2 Hz, Ar), 6.87 (d, 2 H, J = 9.2 Hz, Ar), 4.97 (d, 1 H, J = 2.4 Hz, H-3), 4.40 (d, 1 H, J = 2.4 Hz, H-4), 3.80 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 2.41 (s, 3 H, CH_3). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.46; N, 5.05. Found: C, 61.04; H, 5.47; N, 5.10.

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Supplementary Material Available: Preparation and characterization data of additional compounds (16 pages). Ordering information is given on any current masthead page.

An Investigation of Intermediates in the Hydrolysis of Ortho Esters Derived from D-Glucose and D-Mannose

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The hydrolysis of a series of 1,2-ortho esters derived from α-D-glucopyranose and β-D-mannopyranose have been investigated by NMR and UV spectroscopy. When the hydrolysis of 1,2-*O*-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose (**6**) in CD_3CN (97.2 v %) and D_2O (2.8 v %) containing DCl (2.8×10^{-4} M) was followed by ^1H NMR spectroscopy, an intermediate was detected that may be the corresponding hemi ortho ester. Evidence was also obtained for the incursion of a hemi ortho ester in the hydrolysis of 1,2-*O*-(α-*exo*,4-dimethoxybenzylidene)-α-D-glucopyranose (**14**) under similar conditions. The proportions of the hydrolysis products of **6**, 1-*O*-acetyl-α-D-glucopyranose (**13**), and 2-*O*-acetyl-α-D-glucopyranose (**12**) depend on acid concentration with more of the former being formed at the higher acid concentrations. When the hydrolysis of **14** was studied at higher acid concentrations (DCl, 0.17 M) the intermediate cation **15** was detected. Evidence was obtained by ^{18}O-labeled studies for decomposition of this by attack of water at C-1 of the glucopyranose ring and by an attack at the *pro*-acyl carbon of the dioxolanylium ion depending on the reaction conditions. In the hydrolysis of the ortho esters derived from β-D-mannopyranose, tricyclic 1,2,6-ortho esters were detected in solvents of low water content and when the concentration of DCl was 0.33 M, the intermediate cation was also detected. The kinetics of hydrolysis of the two series of ortho esters were studied by UV spectrophotometry, and evidence was obtained that the 1,2-*O*-(α-*exo*-alkoxy-4-methoxybenzylidene)-α-D-glucopyranoses reacted with rate-limiting breakdown of intermediate hemi ortho ester at high acid concentrations. Evidence for similar behavior was obtained for the hydrolysis of the analogous glucose orthobenzoate esters and mannose 4-methoxyorthobenzoate esters, but the other compounds studied showed no evidence for a change in the rate-determining step of their hydrolyses or else showed complex kinetics on hydrolysis indicative that formation and breakdown of the hemi ortho ester were proceeding at comparable rates.

Introduction

Although there have been many kinetic and mechanistic studies on the hydrolysis of ortho esters,[1-3] there have been few investigations of this type on ortho esters derived from carbohydrates, despite these being important synthetic intermediates.[4-7] Apart from several early investigations carried our polarimetrically,[8-10] there appear to have been

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