Stereoselective Synthesis of *Unnatural* 6α-*trans*-2-Oxaisocephams and $\Delta^{1(6)}$-2-Oxaisocephems

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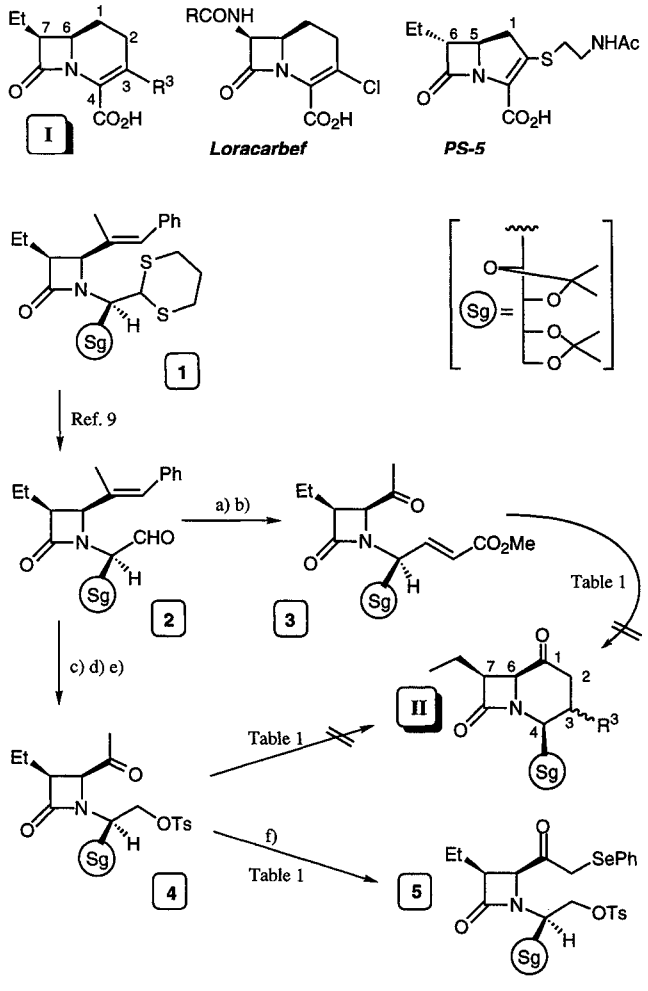
Abstract: Several 4β-acetyl-3β-ethyl-*N*-substituted 2-azetidinones have been synthesized by the Staudinger reaction with D-glucosamine as chiral auxiliary. Attempts to perform an intramolecular cyclisation between the C-4 and N-substituents under ionic conditions at low temperature failed, but at room temperature (thermodynamic control) the bicyclic β-lactams 4-(1,2;3,4-di-*O*-isopropylidene-1,2,3,4-*arabino*-tetrahydroxybutyl)-7β-ethyl-1-methylene-6α-2-oxaisocepham and the $\Delta^{1(6)}$ isomer were obtained.

For the past few years we have been developing an enantioselective approach to the synthesis of β-lactams,[1] which relies on the use of D-glucosamine[2] as chiral auxiliary in the Staudinger reaction[3] to make the monocyclic azetidin-2-ones required to prepare bicyclic β-lactam antibiotics.

Our interest in exploring new synthesis of chiral β-lactams has led us to consider the new 3,7-disubstituted carbacephems **I** as a synthetic target because the carbocycles such as loracarbef[4] and PS-5 showed a broad antibiotic spectrum against Gram-positive and Gram-negative bacteria and also because PS-5, with an ethyl group attached at C-6, was stable to β-lactamases.[5]



Reagents: a) Ph_3P=CH-COOMe / THF / r.t.; b) O_3- Red19 / CH_2Cl_2 / -78°C; c) $NaBH_4$ / EtOH /0°C; d) TsCl / pyr. / 0-4°C; e) O_3 / CH_2Cl_2 / -78°C; f) PhSeCl.

Scheme 1

Two synthetic strategies for elaborating the precursor carbacephams **II** from the readily available 1,3,4-trisubstituted azetidin-2-one **1**[6] are shown in Scheme 1. Both strategies involve the conversion of **1** into the key intermediates **3** and **4**, which have in N-1 appropriate substituents that may behave in cyclisation reactions as a Michael acceptor[7] or as a leaving group.[8] Several ways of removing the 1,3-dithiane ring system from **1** have been examined[9] and the highest yields for the preparation of aldehyde **2** (90 %) were obtained by treating the monobactam **I** with 4 eq. of $HgCl_2$ and 4 eq. of $CaCO_3$.

Compounds **3** and **4** were prepared in 45% and 57% yield respectively, from aldehyde **2** by known chemical manipulations: Wittig reaction followed by selective ozonolysis[10] or reduction, tosylate formation and ozonolysis.

Unfortunately, the conversion of monobactams **3** and **4** into the respective 3,7-disubstituted carbacephams **II** under kinetic conditions was not possible. All attempts to get the desired carbocycles were unsuccessful and only the starting material and/or the product of HOTs elimination (Entries 1-7, Table 1) were isolated.[11]

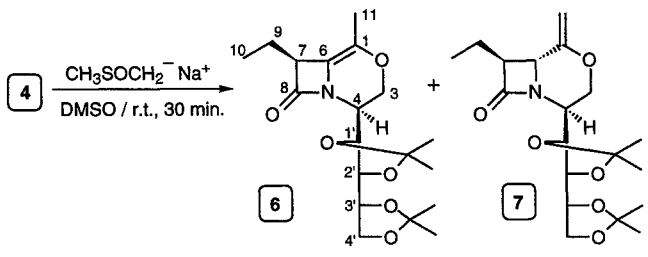
Table 1. Reaction conditions for intramolecular cyclisation of **3** and **4**

Entry		Base (n	T. (°C)	t (h.)	Reaction products (%)
1	**3**	LDA (1.2)	-78	2	complex mixture
2	**3**	LiHMDS (1.2)	-78	3 or 4	**3** (80 or 70)
3	**3**	LiHMDS (1.2)	-98→-50	1→1	complex mixture
4	**4**	LiHMDS (1.5; 2.2)	-78→r.t.	3→12	**4**; **4**(50)+complex mixt.
5	**4**	LiHMDS (1.2), HMPA (1.2)	-78→r.t.	1→12	**4**(20) + HOTs elimination
6	**4**	NaHMDS (1.2)	-78	3	**4**(50) +complex mixt.
7	**4**	NaHMDS (2.2)	-78→r.t.	1→12	HOTs elimination (85)
8	**4**	LDA (1.1)	-78	2	**5** (20)
9	**4**	LiHMDS (1.1)	-78→r.t.	3→12	**5** (16)

The conformation of compounds **3** and **4** in the kinetic controlled conditions, is presumably unfavorable for intramolecular cyclisation. In fact, the kinetic enolate anion of **4** was formed and could be trapped as the phenyl selenide **5** (Entries 8-9, Table 1).[12]

In order to explore the intramolecular cyclisation of compounds **3** and **4** under thermodynamic conditions, we used dimethylsulphinyl carbanion as a base.[13]

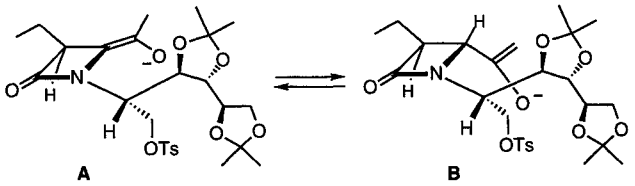
Treatment of monobactam **4** with a 0.5M solution of dimethylsulphinyl carbanion in DMSO (Scheme 2) at room temperature, gave in a 57% non-optimized yield the bicyclic isomers **6** and **7** as a 1:1 mixture, together with a smaller amount (14%) of the starting material.



Scheme 2

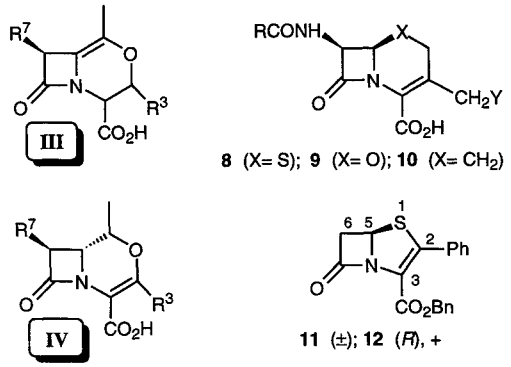
The structures of both bicyclic isomers **6** and **7** were rigorously established by IR and NMR spectroscopy.[14] The *trans* configuration for the unnatural 2-oxaisocepham **7** was deduced from the coupling constants of the H-6 and H-7 β-lactam protons: $J_{6,7}$ = 1.9 Hz.[15]

Compounds **6** and **7** should arise from the thermodynamic enolate anion **A** (Scheme 3). The formation of 2-oxaisocepham **7** could be due to the equilibration of the anion **A** with the *trans*-enolate anion **B**, which may adopt a suitable conformation for intramolecular cyclisation to give the *trans*-β-lactam **7**.



Scheme 3

These two new bicyclic β-lactams **6** and **7** are good precursors to reach the optically active $\Delta^{1(6)}$-2-oxaisocephem **III** and 2-oxaisocephem **IV** (Scheme 4), whose synthesis are now underway.



Scheme 4

According to Bachi et al.,[16] the antibacterial activitiy[17] of compounds **8**, **9** and **10** can be correlated to the enamine moiety of the bicyclic β-lactams, hence we reasoned that some $\Delta^{1(6)}$-2-oxaisocephems **III** with a similar enamine system in their structures could also exhibit antibiotic activity.

Moreover, some 6α unnatural *trans*-2-oxaisocephems **IV** could display better antibiotic and/or antielastase activity than the natural 6β *trans*-2-isooxacephems[18] in analogy with the antielastase properties[19] showed for the racemic penem **11** (IC_{50}=3 μM) more active than the 5β natural chiral penem **12** (IC_{50}>20 μM).

References and Notes

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(11) *General procedure for intramolecular cyclisation.* (Reactions were carried out on a 0.3-0.5 mmol scale). A solution of monobactams **3** or **4** in dry THF was added dropwise under nitrogen atmosphere to a solution of the base in dry THF as specified in Table 1. Direct work up or quenching with phenylselenyl chloride followed by usual work up, give the reaction products.

(12) All new compounds were characterised by elemental analyses and spectral data (IR, ^{1}H NMR and ^{13}C NMR).

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(14) *4β[(1',2';3',4'-Di-O-isopropylidene)-1,2,3,4-D-arabino-tetrahydroxybutyl]-7β-ethyl-1-methyl-$\Delta^{1(6)}$-2-oxaisocephem* **(6).** IR (neat) 1767, 1685, 1220, cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 1.04 (t, 3H, H_{10}, *J*=7.4 Hz); 1.33, 1.34, 1.37, 1.42 (4s, 12H, $CH_{3isopr.}$); 1.79 (s, 3H, H_{11}); 1.60-2.00 (m, 2H, H_9); 3.80 (t, 1H, $H_{4'a}$, *J*=7 Hz); 3.85-4.30 (m, 8H, H_3, H_4, H_7, $H_{1'-4'b}$); ^{13}C NMR (50.33 MHz, $CDCl_3$); δ= 11.1 (C_{10}); 14.8 (C_{11}); 21.3 (C_9); 25.5, 26.5, 27.3 (4C, $CH_{3isopr.}$); 52.6 (C_7); 57.1 (C_4); 66.4 (C_3); 68.0 ($C_{4'}$); 77.6, 79.2, 79.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$); 110.1 (2C, $C_{isopr.}$); 116.5 (C_6); 128.1 (C_1); 166.3 (C_8).

4β[(1',2';3',4'-Di-O-isopropylidene)-1,2,3,4-D-arabino-tetrahydroxybutyl]-7β-ethyl-1-methylidene-trans-2-oxaisocepham **(7).** IR (neat) 3.080, 1757, 1670, 1215, 885, cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 1.08 (t, 3H, H_{10}, $J_{10,9}$=7.2 Hz); 1.35, 1.37, 1.52 (3s, 12H, $CH_{3isopr.}$); 1.60-2.00 (m, 2H, H_9); 3.03 (ddd, 1H, H_7, $J_{7,9a}$=7.7 Hz, $J_{7,9b}$=5.8 Hz, $J_{7,6}$=1.9 Hz); 3.79-4.19 (m, 8H, H_3, H_4, $H_{1'-4'}$); 4.04 (d, 1H, H_{11a}, $J_{11a,11b}$=1.7 Hz); 4.07 (dd, 1H, H_{11b}, $J_{11b,11a}$=1.7 Hz, $J_{11b,6}$=1.5 Hz); 4.53 (dd, 1H, H_6, $J_{11b,6}$=1.5 Hz, $J_{6,7}$=1.8 Hz). Compound **7** is quite labile and it easily decomposed in $CDCl_3$ solution during the acquisition time to record the ^{13}C NMR spectrum.

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