Pergamon

Tetrahedron Vol. 50, No. 42, pp. 12049-12064, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00719-5

Synthesis and Biological Evaluation of 6-Azabicyclo[3.2.0]hept-2-ene Derivatives as Potential Anti-bacterial Agents and β-lactamase Inhibitors

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Abstract : This paper describes the synthesis of a series of 6-azabicyclo[3.2.0]hept-2-ene compounds and subsequent results obtained from biological testing, for anti-microbial potency and β-lactamase inhibition activity. It was determined that a number of compounds possessed some β-lactamase inhibition efficacy.

Introduction

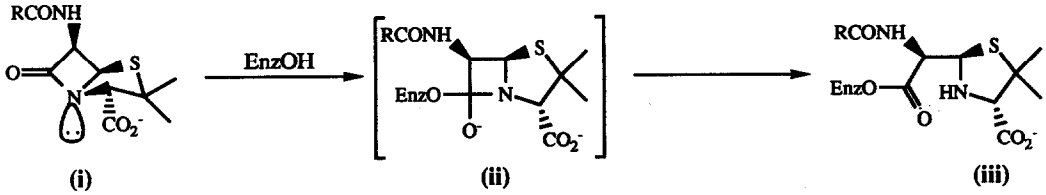
β-lactam antibiotics act by acylating enzymes essential in bacterial cell wall[1] synthesis, such enzymes are referred to as penicillin binding proteins (PBPs). More specifically β-lactams affect the biosynthesis of the peptidoglycan, a cross-linked polymer that encloses the cell.[2] One of the reactions in the biosynthesis of the peptidoglycan is a transpeptidation process catalyzed by a DD-transpeptidase[3] and it is this enzyme that is acylated by the β-lactams acting as structural analogs of the natural substrates[4]. This leads to the synthesis of a defective peptidoglycan resulting in cell lysis because the cell becomes osmotically compromised. The interaction of β-lactams with target enzymes can be represented by **equation (1)**.

$$E + A \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} EA \xrightarrow{k_2} EA^* \xrightarrow{k_3} E + P(s) \qquad \textbf{equation (1)}$$

where E is the enzyme, A the antibiotic, EA a non-covalent Michaelis complex, EA^* a covalent acyl enzyme complex and P(s) the hydrolysis product(s) of the antibiotic-enzyme covalent intermediate.

Thus, inactivation of the enzyme results from a rapid and irreversible formation of the covalently bound complex, EA^*, characterized by a low k_3 (i.e. stable EA^*) and high k_2. Attempts have been made to correlate the activity of β-lactam antibiotics to the strain of the 4-membered ring[5] which is expected to lead to a reduction in the planarity of the amide functionality and thus to a minimization in the amide resonance[6]. This increases the susceptibility of the amide carbonyl group to nucleophilic attack and hence $k_2 >> k_{-1}$. **Scheme 1** illustrates this with penicillin **(i)** as an example where the β-lactam ring is opened by a serine hydroxy group originating from the transpeptidase enzyme and the resultant tetrahedral intermediate **(ii)** proceeds to the formation of a penicilloyl-enzyme intermediate[7] **(iii)**.

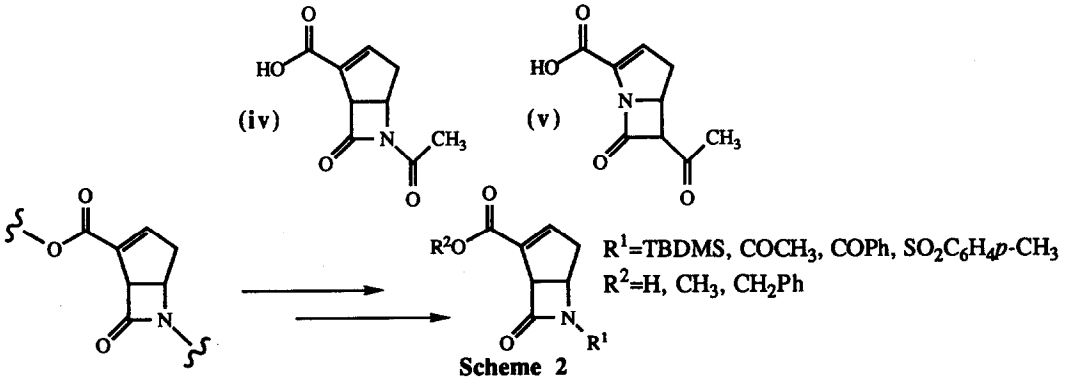
The loss of activity of β-lactams against bacteria which have become resistant may also be caused by the presence of β-lactamases, enzymes that hydrolyze the amide bond of the 4-membered ring (i.e. large value of k_3) thereby rendering them inactive.[8]



Scheme 1

Transition-state analogs[9] can serve as an approach in the design of inhibitors of both the transpeptidases and the related β-lactamases. Some work has been performed with cyclobutanones in order to determine the influence of the β-lactam nitrogen on the activity of penicillin. Due to the reactivity of the cyclobutanone carbonyl such a system is expected to form a stable hemiketal with the serine residue of a PBP or β-lactamase[10,11] and the anticipated greater stabilization could in principle afford an increase in the anti-bacterial activity or β-lactamase inhibition by favoring the forward process in **equation (1)**. Cocuzza[12] and Gordon[13] in separate studies have investigated carbocyclic derivatives as potential anti-bacterial agents and β-lactamase inhibitors. The compounds from the former author showed activity against Gram-positive bacteria in addition to some β-lactamase inhibition and the latter publication reported anti-bacterial activity against only non-β-lactamase producing microorganisms. A recent publication by Page[14] has reviewed the various approaches applied to the design and development of antibiotics and β-lactamase inhibitors.

A structurally alternative attempt to influence the rate of the forward reaction in **equation (1)** would be to rearrange the nitrogen to the other side of the carbonyl group and thus generate a azabicyclo[3.2.0]hept-2-ene system. We obtained an excellent superimposition between the energy minimized form [using MOPAC 6.0 AM1] of the 6-azabicyclo[3.2.0]hept-2-ene type derivative (**iv**) and a carbapenem penicillin analog (**v**), **Figure 1**. Thus we decided to synthesize these carbapenem analogs and evaluate them for anti-bacterial and β-lactamase inhibition activity. **Scheme 2** summarizes the initial series of compounds that represented our goal.



Scheme 2

Synthesis

The starting substrate for the synthesis of the desired compounds was readily available 7-azabicyclo[4.2.0]oct-3-en-8-one **1**, which was prepared by the cycloaddition of chlorosulfonyl isocyanate and 1,4-cyclohexadiene (**Scheme 3**). In our hands this reaction proceeded more cleanly in the absence of any solvent as compared to the published procedure.[15] Azetidinone **1** was silylated with *tert*-butyldimethylsilyl chloride and catalytic quantity of 4-dimethylaminopyridine (DMAP) in acetonitrile at room temperature overnight.

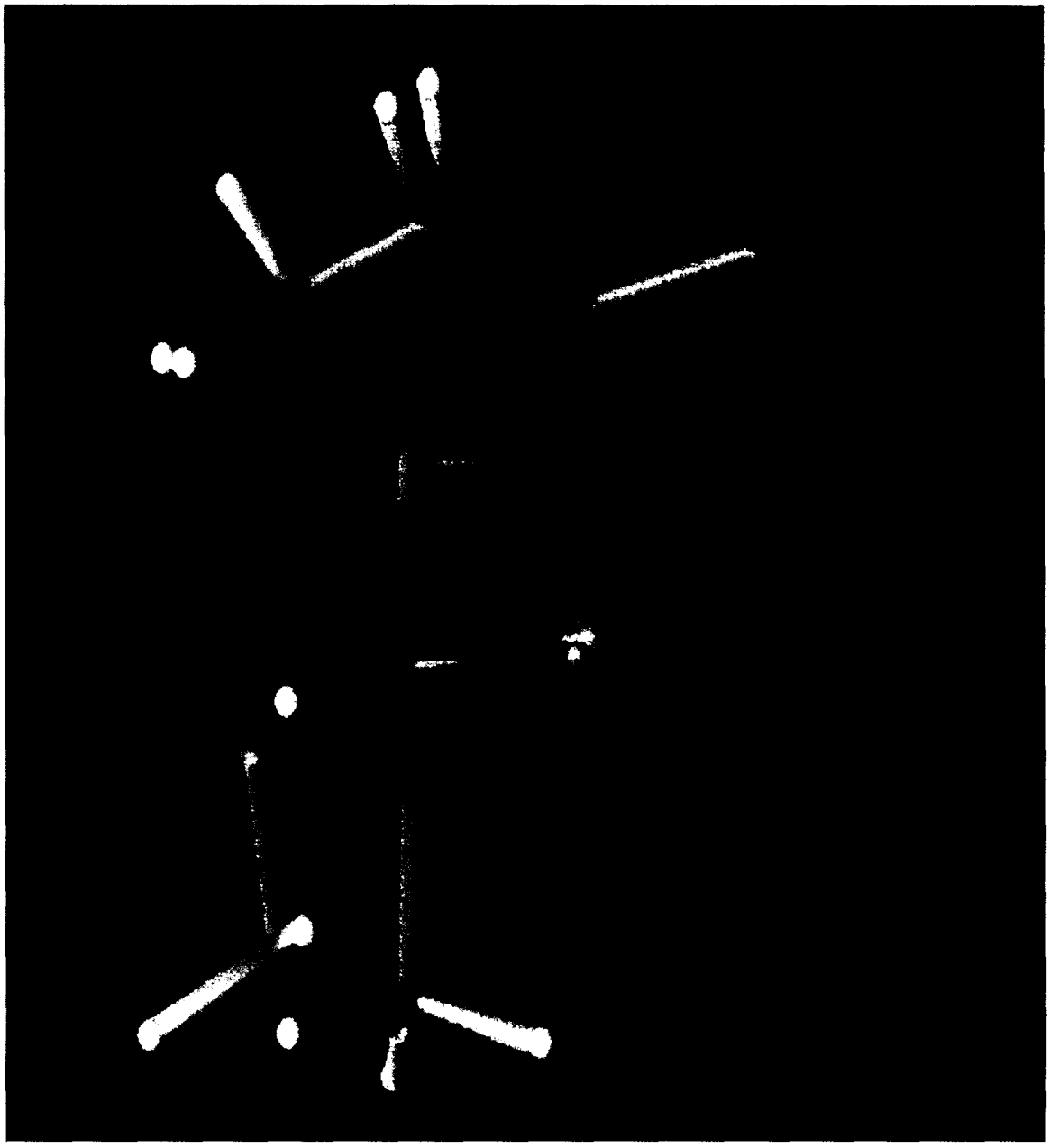
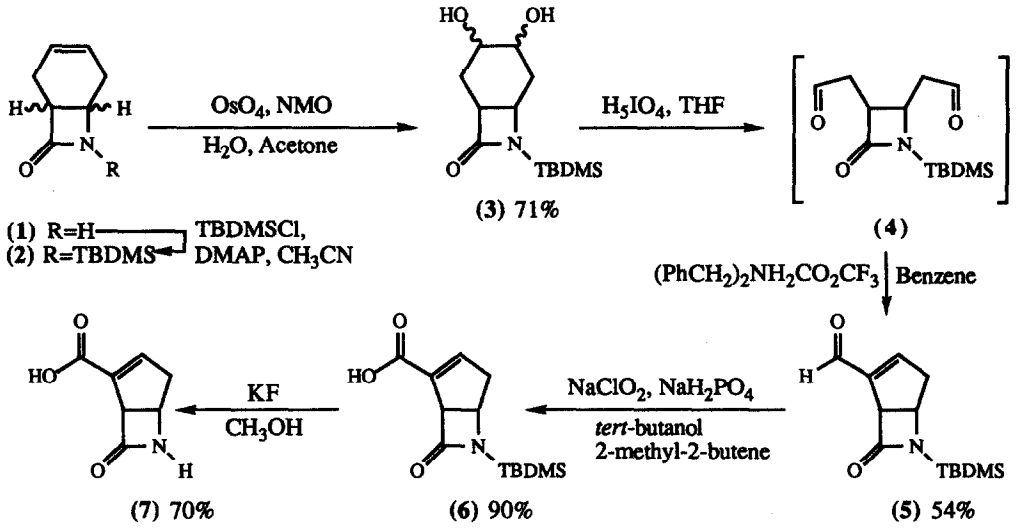


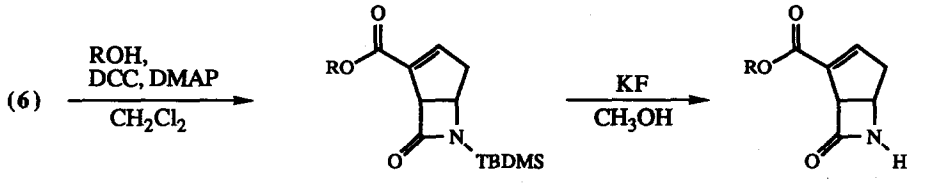
Figure 1

The desired material **2** was obtained in 78% yield after purification by flash chromatography. The alkene component was routinely dihydroxylated using standard conditions of osmium tetroxide with 4-methylmorpholine *N*-oxide (NMO) in an aqueous mixture of *tert*-butanol and acetone to afford diol **3**.[16] Diol **1** was then cleaved with periodic acid in anhydrous THF at 0°C to give the intermediate dialdehyde **4** which was used immediately in the internal aldol condensation.[16] The regioselectivity of the aldol product was fully controlled with dibenzylammonium trifluoroacetate[17] as base in anhydrous benzene at 60°C for 50 min. The desired α,β-unsaturated bicycloaldehyde **5** was afforded in 54% yield and in general we observed that the yield varied from one particular run to another, probably due to the inherent instability to aqueous workup and silica gel. The most favorable system for a combination of high yield and clean product for the oxidation of α,β-unsaturated aldehyde **5** to the corresponding acid **6** was that of sodium chlorite buffered with sodium phosphate, in *tert*-butanol and 2-methyl-2-butene[18] at room temperature overnight. Under these conditions, oxidation of compound **6** proceeded in 90% yield and the product was used in subsequent reactions without further purification (**Scheme 3**). Acid derivative **6** was de-silylated to give compound **7** which was tested for anti-bacterial and β-lactamase inhibition activity.



Scheme 3

Azetidinone **6** was benzylated with *N,N'*-dicyclohexylcarbodiimide (DCC), benzyl alcohol and catalytic DMAP in dichloromethane at 0°C to afford ester **8**. It is worth noting that experiments involving phase transfer conditions[19] were also attempted to carry out this transformation but the reaction proceeded at a very slow rate. The *tert*-butyldimethylsilyl group of structure **8** was cleaved in 86% yield with potassium fluoride in methanol at 0°C to generate substrate **10**. Exactly the same methodology was employed to prepare the corresponding methyl ester **9** with subsequent deprotection to afford β-lactam **11** in 88% yield (**Scheme 4**).

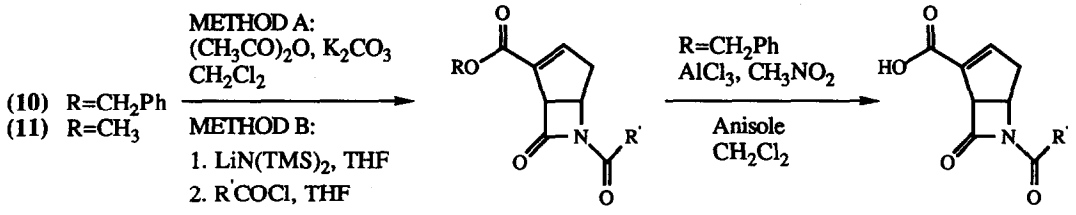


(8) R=CH_2Ph 67%
(9) R=CH_3 70%

(10) R=CH_2Ph 86%
(11) R=CH_3 88%

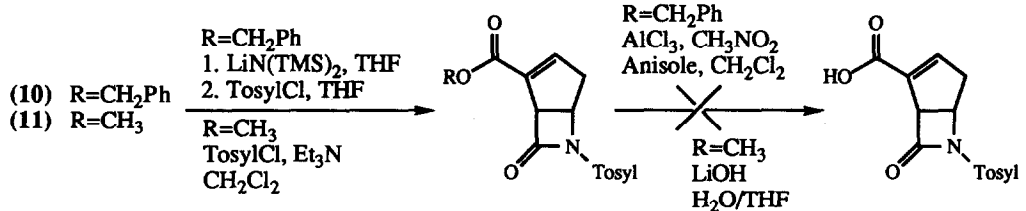
Scheme 4

The ester derivatives **10** and **11** were converted to their respective *N*-acetyl compounds **12** and **13** by either utilizing acetic anhydride in the presence of anhydrous potassium carbonate in dichloromethane or lithium bis(trimethylsilyl) amide as base and quenching the resultant anion with acetyl chloride in THF. However, both procedures were found to proceed in similar yields, **Scheme 5**.



(12) R=CH_2Ph, R'=CH_3 55%
(13) R=CH_3, R'=CH_3 60%
(14) R=CH_2Ph, R'=Ph 64%
(15) R=CH_3, R'=Ph 55%

(16) R'=CH_3 67%
(17) R'=Ph 85%



(18) R=CH_2Ph 40%
(19) R=CH_3 35%

Scheme 5

The analogous derivatives possessing the *N*-benzoyl moiety were prepared with application of the latter conditions. The debenzylation of **12** and **14** did not proceed without incident, attempted hydrogenation in the presence of 5% Pd-C under 1 atmosphere of hydrogen led not only to the required conversion but also reduction of the double bond. Whereas, catalytic transfer[20] hydrogenation with 1,4-cyclohexadiene and 10% Pd-C was found to be very sluggish. Attempted hydrolysis with aqueous potassium carbonate in THF failed to give any of the desired material.[21] Eventually debenzylation was achieved successfully by the application of methodology reported by Tsuji *et. al.*, which employs the use of aluminum trichloride in conjunction with nitromethane, anisole and dichloromethane at 0°C.[22] Thus, compounds **16** and **17** was obtained in 67% and 85% yield respectively (**Scheme 5**).

The preparation of the (*N*)-*p*-toluenesulfonyl series of compounds proved to be somewhat problematic with tosylations of compounds **10** and **11** proceeding in very disappointing yields, as illustrated in **Scheme 5.**

Results, discussion and conclusions from biological results

The rate of base catalyzed hydrolysis of β-lactams with sodium hydroxide has been used to develop a pattern as to their reactivity towards PBPs, attempting to mimic the acylation of the serine-hydroxyl group of the PBPs by β-lactams.[23] We measured the rates of base catalysed hydrolysis, (methodology described in the experimental section), in order to gain insight regarding the effect of varying substituents on the chemical reactivity of these novel derivatives. In addition, the infrared carbonyl stretching frequencies of β-lactams have been employed in an attempt to relate the degree of strain in such systems to their chemical reactivity and in general high absorption frequencies correspond to a decrease in chemical stability.[24] However, there is literature precedent that debates this correlation.[25] The stability data and infrared spectral data for some of these new β-lactams are shown in **Table I.** Even though some of these new derivatives possess higher absorption frequencies relative to the control substrate [penicillin V *p*-nitrobenzyl ester] the rates of hydrolysis do not reflect a corresponding decrease in hydrolytic stability. Thus this study provides an example where the strain in the β-lactam ring, as indicated by the infrared carbonyl stretching frequency, cannot be correlated to the chemical reactivity.

Table I. Stabilities of 6-Azabicyclo[3.2.0]hept-2-ene derivatives

Compound	k, s^{-1}	$t_{1/2}$, s	IR, cm^{-1}
8	2.93×10^{-4}	2.37×10^{3}	1741
12	9.50×10^{-4}	7.29×10^{2}	1795
15	2.94×10^{-4}	2.36×10^{3}	1797
19	5.50×10^{-5}	1.26×10^{4}	1794
Standard[a]	1.47×10^{-3}	4.71×10^{2}	1790

[a]Standard employed was PenV *p*-nitrobenzyl ester.

These compounds were screened for *in vitro* minimal inhibitory concentration (MIC) activity by published methodology.[26] In addition to this, all derivatives were screened for activity against two different β-lactamases, P99 [a cephalosporinase] and TEM-1 [penicillinase], the former is produced by *Enterobacter cloacae 265A* and the latter by *Escherichia coli 58.* Surprisingly all of the carboxylic acid derivatives were inactive both as antibiotics or as inhibitors of β-lactamases. For some derivatives the β-lactamase activity proved to be more encouraging than the corresponding MIC values. For example, compound **12** was found to possess 73% inhibitory activity against P99 at a concentration of 0.2mM. The N-tosyl derivatives **18** and **19** proved to be better with 92% and 42% inhibition, respectively, against P99 at a concentration of 0.2mM, **Table II** summarizes these results.[27,28]

Table II. β-lactamase Inhibitory activity against P99 and TEM

	% Inhibition	
	P99	TEM
Substrate	0.2mM	0.2mM
15	44	0
18	43	0
19	92	0
12	73	9
10	0	3
9	0	20
6	8	0
7	0	5
5	0	5
Li Clavulanate	19	90

These compounds were inactive as antibiotics, however their stability was sufficient to survive the test conditions. Furthermore there was an excellent over-lap from modelling experiments, **Figure 1**, between a penicillin analog and these new derivatives, which when combined with the crystal structure, **Figure 2**, of derivative **17**[29] would seem to indicate that these compounds are configured very similarly to carbapenem derivatives. Two possible explanations for this lack of activity could be either the lack of bacterial cell wall penetration or binding by a PBP. In an attempt to answer these questions a number of derivatives were also tested for binding ability with PBPs of *Escherichia coli* K-12 according to the procedure developed by Preston, *et. al.*[30] The only activity detected was shown by compound **16** at a concentration of 100μM against low molecular weight PBP 6. This PBP has not been considered to be a lethal target in bacteria thus it would appear that lack of recognition by the lethal PBP targets is the cause of the poor biological activity.

In conclusion, these compounds did not show any anti-microbial activity, although some derivatives however, did exhibit β-lactamase inhibition and some binding ability for a low molecular weight non-lethal PBP. The fundamental processes involved in the interaction of the β-lactam antibiotics with the bacterial cell wall and the mechanism of its lethality to bacteria still remains an area lacking a thorough understanding.

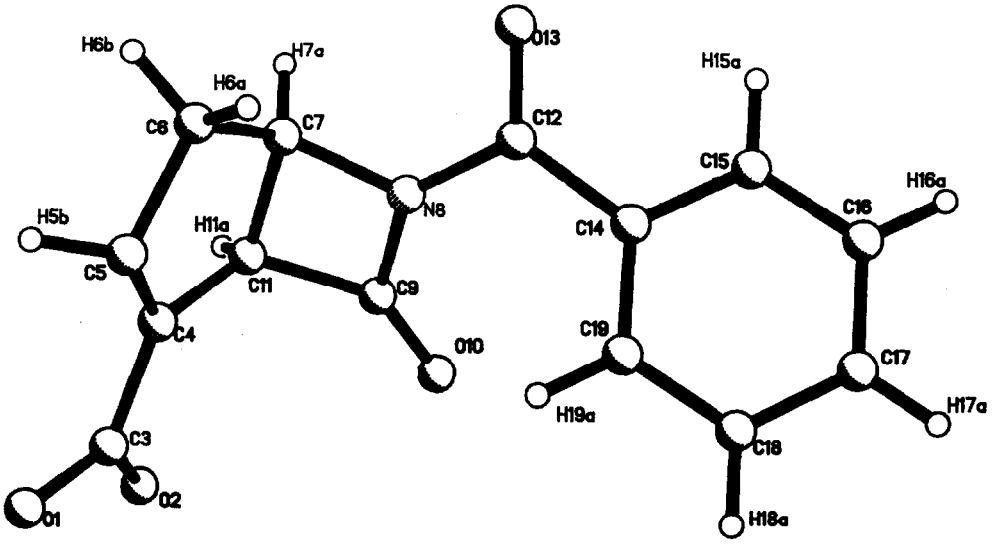


Figure 2, crystal structure of compound **17**.

EXPERIMENTAL

Melting points were recorded on a Gallenkamp apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Nicolet MX-1 FT-IR spectrometer, using conditions as stated *vide infra*. ^{1}H and ^{13}C NMR were obtained using General Electric QE-300MHz machine at 300 and 75.4MHz, respectively, in chloroform-d_1, unless otherwise stated. Chemical shifts are quoted in parts per million (δp.p.m.) using chloroform as an internal reference and the coupling constants (J) are given to the nearest 0.5Hz. Mass spectra (Field Desorption) were recorded on either a CEC-21-140 or a Varian MAT-731 spectrometer. Microanalyses were performed in Lilly Research Laboratories.

All reactions were performed under an atmosphere of nitrogen unless otherwise indicated. Standard solvents employed in reactions were distilled prior to use: tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl and benzene from calcium hydride. All other solvents and reagents were used as purchased from the manufacturer. The drying agent used after workup procedure refers to sodium sulfate. Flash chromatography was performed on silica gel (Mallinckrodt SilicAR 230-400 Mesh 40-63 microns).

Determination of Base-Catalysed-Hydrolysis Rates.

The rates of hydrolysis were determined by following the loss of the parent β-lactam. The pH was monitored with a Corning pH meter 125 and was maintained at the value indicated for the relevant substrate by the addition of 1N NaOH. The hydrolysis was followed by reverse-phase HPLC on a Hitachi LC-Organizer, which consisted of a Hitachi L-6200 intelligent pump, Hitachi L-4000 UV detector set at 256nm and Hitachi D-

2000 integrator. The stationary phase was 8 x 20 Waters reverse-phase column and the flow rate was 1.5 mL/min. The pH and the mobile phases (v / v) were as follows: MeCN/H_2O: **(8)** pH 11.4, (75 : 25); **(16)** pH 11.2, (75:25); **(17)** pH 11.2, (75:25); **(19)** pH 11.2, (75:25); standard pH 11.5, (75:25).

7-Azabicyclo[4.2.0]oct-3-en-8-one (1)

To 1,4-cyclohexadiene (17g, 210mmol) was added chlorosulfonyl isocyanate (1.0 equiv. 30g). The resultant mixture was stirred at 80°C for 4h and then allowed to cool to room temperature. A mixture of ice (250 ml) and acetone (250 ml) was added to the reaction material and then adjusted to pH 7 with slow addition of 5N NaOH, maintaining the temperature below 35°C. The aqueous solution was extracted with dichloromethane (3x150 ml). The combined extracts were washed with brine, dried, filtered and concentrated *in vacuo* to afford a yellow solid **(1)**(17.4g, 58%). This material was used in crude form for the next step. A small sample was recrystallized from THF for characterization. mp 122.4-124.6°C, Lit[15]. 121.5-122.5°C; IR ($CHCl_3$) 3690 (w), 3412 (m), 3013 (m), 1752 (s), 1603 (w); ^1H NMR δ 2.05 - 2.25 (2H, m), 2.27 - 2.50 (2H, m), 3.45 (1H, t, *J*= 5.5Hz), 4.00 (1H, t, *J*=4.5Hz), 5.65 - 5.90 (2H, m), 6.37 (1H, br); ^{13}C NMR δ 21.4, 27.1, 47.1, 48.1, 124.3, 126.1, 176.8; *m/z* 124 (MH^+, 100%).

7-tert-Butyldimethylsilyl-7-azabicyclo[4.2.0]oct-3-en-8-one (2)

Azetidinone **(1)**(17.4g, 140mmol) was taken up in acetonitrile (500 ml), TBDMSCl (1.0 equiv. 21.3g), triethylamine (1.0 equiv. 20 ml) and DMAP (0.2 equiv. 3.5g) were added successively. The resultant mixture was allowed to stir overnight and diluted with dichloromethane (300 ml), washed with water, brine, dried, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate:hexanes 1:5) and the desired product was obtained as a viscous clear oil which solidified on standing **(2)**(26.3g, 78%). mp 35.6-37.5°C; IR ($CHCl_3$) 3012 (m), 2954 (m), 2933 (m), 2886 (m), 2860 (m), 1729 (s), 1471 (m), 1338 (m); ^1H NMR δ 0.2 (3H, s), 0.25 (3H, s), 0.95 (9H, s), 2.00 - 2.20 (2H, m), 2.30 - 2.50 (2H, m), 3.35 - 3.45 (1H, m), 3.85 - 3.93 (1H, m), 5.65 - 5.75 (1H, m), 5.85 - 5.90 (1H, m); ^{13}C NMR δ 18.3, 21.6, 25.7, 26.2, 27.6, 48.3, 48.8, 124.4, 126.9, 175.1; *m/z* 237 (M^+, 100%), 181 (7), 157 (17), 137 (7), 120 (12).

(1S*,6R*)-3,4-cis-7-tert-Butyldimethylsilyl-3,4-dihydroxy-7-azabicyclo[4.2.0]oct-8-one (3)

This compound was prepared according to the literature reference[16]. The material was obtained as a white solid **(3)**(10.1g, 71%) from compound **(2)**(13.5g, 570mmol). mp 81-83°C, Lit[16]. 83-85°C; IR ($CHCl_3$) 3500 - 3200 (br), 3022 (m), 2957 (m), 2932 (m), 2899 (w), 2860 (w), 1723 (s), 1470 (w); ^1H NMR δ 0.2 (3H, s), 0.25 (3H, s), 0.95 (9H, s), 1.85 - 2.25 (4H, m), 3.37 - 3.46 (3H, m), 3.83 - 4.00 (3H, m); ^{13}C NMR δ 18.4, 26.2, 33.1, 33.3, 46.2, 47.6, 67.4, 67.6, 176.9; *m/z* 272 (MH^+, 100%), 214 (54), 157 (16).

(1S*,5R*)-6-tert-Butyldimethylsilyl-2-formyl-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (5)

To a solution of **(3)**(4.01g, 14.8mmol) in anhydrous THF (150 ml) at 0°C was added periodic acid (1.25 equiv. 4.2g), the resultant mixture was stirred until a white suspension was formed and stirring was continued at room temperature for 45min. Water was added to the reaction, then extracted with dichloromethane, combined extracts washed with water, dried, filtered and concentrated *in vacuo*. This material was used immediately in the next

step. Thus, the crude dialdehyde (4)(3.91g, 14.8mmol) was taken up in freshly distilled benzene (280 ml), dibenzylammonium trifluoroacetate[17] (0.2 equiv. 919mg) was added and the resultant mixture stirred at 60°C for 50min. After allowing to cool to room temperature the solvent was removed *in vacuo* to afford a dark coloured solid and this was taken up in a mixture of ethyl acetate:1N HCl. The organic layer was separated following filtration through celite and the aqueous portion extracted with ethyl acetate. The combined extracts were washed with water, brine, dried, filtered and concentrated *in vacuo* to afford a brown residue which was purified by flash column chroamatography (ethyl acetate:hexanes 1:4). The required material (5)(1.90g, 54%) was obtained as lightly yellow coloured solid. mp 103.4-105.5°C; (Found: C, 62.14; H, 8.61; N, 5.64. $C_{13}H_{21}NO_2Si$ requires C, 62.11; H, 8.42; N, 5.57%); IR ($CHCl_3$) 3021 (m), 2958 (m), 2932 (m), 2861 (m), 1741 (s), 1686 (s), 1471 (m); ^1H NMR δ 0.21 (6H, s), 0.95 (9H, s), 2.70 - 2.90 (2H, m), 4.18 (1H, ABX_2, J=1.5, 6.0Hz), 4.45 - 4.50 (1H, m), 6.82 (1H, t, J=1Hz), 9.80 (1H, s); ^{13}C NMR δ 18.3, 26.2, 38.7, 51.6, 61.2, 143.6, 149.9, 175.2, 187.7; *m/z* 252 (MH^+, 100%), 194 (78), 157 (75).

(1S*,5R*)-6-tert-Butyldimethyl-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (6)

Aldehyde (5)(1.27g, 5.06mmol) was dissolved in *tert*-butanol (100 ml), and 2-methyl-2-butene (40 ml) was added followed by the dropwise addition of a mixture of $NaClO_2$ (2.0 equiv. 10.1 ml, 1.0N solution) and NaH_2PO_4 (3.0 equiv. 12.1 ml, 1.25N solution). The resultant mixture was allowed to stir overnight and then concentrated *in vacuo* to approximately 15ml. The oily residue was taken up in water (80 ml), washed with hexanes (2x40 ml), acidified to pH 3 with 1N HCl and extracted with diethyl ether. The desired product was obtained as a white solid (6)(1.22g, 90%) which was used without purification in subsequent steps. A small sample was recrystallized from dichloromethane/hexanes for characterization. mp 155.5-157.5°C; (Found: C, 58.14; H, 7.97; N, 5.21. $C_{13}H_{21}NO_3Si$ requires C, 58.43; H, 7.87; N, 5.24%); IR ($CHCl_3$) 3200 - 2400 (br), 2958 (m), 2932 (m), 1736 (s), 1695 (m); ^1H NMR δ 0.22 (6H, s), 0.76 (9H, s), 2.35 - 2.60 (2H, m), 3.90 (1H, ABX_2, J=1.5, 6.0Hz), 4.15 - 4.22 (1H, m), 6.55 (1H, t, J=1.0Hz); ^{13}C NMR δ 19.1, 27.1, 39.1, 53.1, 64.0, 135.1, 143.4, 166.4, 174.6; *m/z* 268 (MH^+, 100%), 157 (11).

(1S*,5R*)-2-Carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (7)

A solution of (6)(200mg, 0.749mmol) in methanol (20 ml) was cooled to 0°C. Potassium fluoride (1.1 equiv. 49mg) was added and the resultant mixture stirred for 60min. The reaction mixture was concentrated *in vacuo*, taken up in ethyl acetate with a trace of methanol and then extracted with dilute $NaHCO_3$. The aqueous extracts were acidified to pH 3 with 1N HCl, extracted with ethyl acetate, dried, filtered and concentrated *in vacuo* to afford a cream coloured solid. The crude material was purified by recrystallization from methanol/1,2-dichloroethane and the desired product was isolated as a white solid (7)(80mg, 70%). mp 200°C-decomposition; (Found: C, 54.78; H, 4.60; N, 8.88. $C_7H_7NO_3$ requires C, 54.90; H, 4.61; N, 9.15%); IR (KBr) 3400 - 2800 (br), 2975 (m), 1732 (s), 1677 (m), 1627 (w), 1425 (m); ^1H NMR δ (CD_3OD) 2.57 - 2.80 (2H, m), 4.20 - 4.35 (2H, m), 6.81 (1H, s); ^{13}C NMR δ (D_2O) 36.8, 52.4, 62.7, 136.9, 142.4, 172.0, 175.7; *m/z* 154 (MH^+, 80%), 136 (8), 110 (100).

Benzyl-(1S*,5R*)-6-tert-butyldimethylsilyl-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (8)

Substrate (**6**)(1.97g, 7.38mmol) was dissolved in dichloromethane (20 ml), cooled to 0°C. Then benzyl alcohol (1.05 equiv. 0.8 ml), DCC (1.1 equiv. 1.67g) and DMAP (0.1 equiv. 90mg) were added successively. The mixture was stirred at 0°C for 90min, then stirring continued at room temperature for 30min and the resultant solid was removed by filtration. The filtrate was diluted with diethyl ether, washed with water (4x), dried, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (ethyl acetate:hexanes 1:4) and the product (**8**)(1.77g, 67%) was obtained as a white solid. mp 112.8-114.2°C: (Found: C, 67.21; H, 7.69; N, 4.03. $C_{20}H_{27}NO_3Si$ requires C, 67.18; H, 7.61; N, 3.92%); IR (KBr) 3019 (m), 2958 (m), 2932 (m), 2860 (m), 1741 (s), 1325 (m), 1234 (m); ^{1}H NMR δ 0.20 (6H, s), 0.70 (9H, s), 2.35 - 2.55 (2H, m), 3.90 (1H, dd, *J*=1.5, 4.5Hz), 4.20 (1H, m), 5.00 (2H, s), 6.61 (1H, t, *J*=1.5Hz), 7.05 - 7.22 (5H, m); ^{13}C NMR δ 18.3, 26.0, 26.1, 38.2, 38.3, 52.1, 63.1, 66.4, 128.1, 128.2, 128.5, 133.5, 135.9, 143.5, 163.4, 173.4; *m/z* 358 (MH^+, 7%), 200 (100), 157 (17).

Methyl-(1S*,5R*)-6-tert-butyldimthylsilyl-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (9)

Substrate (**6**)(1.30g, 4.87mmol) was dissolved in dichloromethane (20 ml) and cooled to 0°C. Methyl alcohol (1.3 equiv. 0.26 ml), DCC (1.05 equiv. 1.05g) and DMAP (0.1 equiv. 60mg) were added successively. The mixture was stirred at 0°C for 90min and the resultant solid was removed by filtration. The filtrate was diluted with diethyl ether, washed with water (4x), dried, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (ethyl acetate:hexanes 1:4) and the product (**9**)(953mg, 70%) was obtained as a white solid. mp 79.6-81.2°C; (Found: C, 60.01; H, 8.21; N, 4.76. $C_{14}H_{23}NO_3Si$ requires C, 59.75; H, 8.24; N, 4.98%); IR ($CHCl_3$) 3029 (m), 2955 (m), 2932 (m), 2861 (m), 1740 (s), 1472 (m), 1438 (m), 1326 (m); ^{1}H NMR δ 0.21 (6H, s), 0.92 (9H, s), 2.35 - 2.55 (2H, m), 3.57 (3H, s), 3.90 (1H, dd, *J*=4.5, 6.5Hz), 4.15 - 4.20 (1H, m), 6.6 (1H, t, *J*=2.5Hz); ^{13}C NMR δ 18.3, 26.0, 26.2, 38.2, 51.9, 52.2, 63.0, 133.4, 143.1, 164.1, 173.5; *m/z* 282 (MH^+, 26%), 224 (12), 157 (63), 124 (100).

Benzyl-(1S*,5R*)-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (10)

A solution of (**8**)(1.23g, 3.45mmol) in methanol (40 ml) was cooled to 0°C. Potassium fluoride (1.1 equiv. 220mg) was added and the resultant mixture stirred for 60min. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (neat ethyl acetate). The desired compound (**10**)(716mg, 86%) was afforded as a white solid. mp 119.9-121.4°C; (Found: C, 69.34; H, 5.52; N, 5.90. $C_{14}H_{13}NO_3$ requires C, 69.13; H, 5.39; N, 5.76%); IR (KBr) 3229 (m), 3168 (m), 1748 (s), 1711 (s), 1618 (m), 1227 (m); ^{1}H NMR δ 2.57 - 2.75 (2H, m), 4.20 (1H, m), 4.40 (1H, m), 5.25 (2H, s), 6.55 (1H, br), 6.81 (1H, s), 7.23 - 7.45 (5H, m); ^{13}C NMR δ 38.3, 51.8, 63.9, 67.2, 128.8, 128.9, 129.3, 133.7, 136.7, 144.8, 164.2, 170.8; *m/z* 243 (M^+, 40%), 200 (100), 171 (5).

Methyl-(1S*,5R*)-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (11)

A solution of (**9**)(953mg, 3.39mmol) in methanol (30 ml) was cooled to 0°C. Potassium fluoride (1.1 equiv. 217mg) was added and the resultant mixture stirred for 60min. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (neat ethyl acetate). The desired compound was afforded as a white solid (**11**)(499mg, 88%). mp 132.1-134.8°C; (Found: C, 57.47; H, 5.46; N, 8.20. $C_8H_9NO_3$ requires C, 57.48; H,

5.43; N, 8.38%); IR ($CHCl_3$) 3414 (m), 3021 (m), 2977 (m), 2955 (m), 1764 (s), 1721 (s), 1627 (w), 1438 (m); ^1H NMR δ 2.60 - 2.75 (2H, m), 3.80 (3H, s), 4.20 - 4.30 (1H, m), 4.35 - 4.42 (1H, m), 6.60 (1H, br), 6.80 (1H, s); ^{13}C NMR δ 38.2, 51.8, 52.7, 63.8, 133.6, 144.5, 164.8, 170.9; *m/z* 168 (MH^+, 33%), 124 (100).

Benzyl-(1S*,5R*)-6-acetyl-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (12)

METHOD A. To a solution of **(10)**(250mg, 1.03mmol) in dichloromethane (20 ml) was added acetic anhydride (10 equiv. 0.98 ml) and potassium carbonate (10 equiv. 1.42g). The resultant suspension was allowed to stir for 24h, filtered, concentrated *in vacuo* and purified by flash column chromatography (ethyl acetate:hexanes 1:1). The desired material **(12)**(160mg, 55%) was afforded as a white solid.

METHOD B. A solution of **(10)**(250mg, 1.03mmol) in THF (10 ml) was cooled to -78°C and lithium bis(trimethylsilyl)amide (1.0 equiv. 1.03 ml, 1M solution) added dropwise. The resultant mixture was stirred for 20min and a solution of acetyl chloride (2.0 equiv. 0.15 ml) in THF (2 ml) was introduced to the reaction mixture dropwise. Stirring was continued at -78°C for 30min, then warmed to room temperature and quenched with water. The solution was extracted with diethyl ether and the combined extracts were washed with brine, dried, filtered and concentrated *in vacuo*. The crude material was subjected to flash chromatography (ethyl acetate:hexanes 1:1) and the product **(12)**(155mg, 53%) was obtained as a white solid. mp 79.1-80.7°C; (Found: C, 67.43; H, 5.50; N, 4.91. $C_{16}H_{15}NO_4$ requires C, 67.36; H, 5.30; N, 4.91%); IR ($CHCl_3$) 3028 (m), 3014 (m), 1795 (s), 1706 (s), 1380 (m), 1332 (s); ^1H NMR δ 2.35 (3H, s), 2.73 - 3.05 (2H, m), 4.40 - 4.50 (1H, m), 4.60 (1H, t, *J*=5.5Hz), 5.25 (2H, d, *J*=2.5Hz), 6.90 (1H, t, *J*=1.0Hz), 7.30 - 7.43 (5H, m); ^{13}C NMR δ 23.8, 36.1, 53.5, 60.8, 66.7, 128.1, 128.3, 128.5, 128.7, 131.1, 145.7, 162.8, 164.9, 168.1; *m/z* 285 (M^+, 22%), 200 (100).

Methyl-(1S*,5R*)-6-acetyl-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (13)

To a solution of **(11)**(167mg, 1mmol) in dichloromethane (20 ml) was added acetic anhydride (10 equiv. 0.94 ml) and potassium carbonate (10 equiv. 1.38g). The resultant suspension was allowed to stir for 24h, filtered, concentrated *in vacuo* and purified by flash column chromatography (ethyl acetate:hexanes 1:2). The desired material **(13)**(125mg, 60%) was afforded as a white solid. mp 78.7-80.7°C; (Found: C, 57.18; H, 5.18; N, 6.65. $C_{10}H_{11}NO_4$ requires C, 57.41; H, 5.30; N, 6.69%); IR (KBr) 3020 (w), 1787 (s), 1717 (m), 1695 (s), 1447 (m), 1331 (m); ^1H NMR δ 2.30 (3H, s), 2.74 - 3.00 (2H, m), 3.78 (3H, s), 4.39 - 4.42 (1H, m), 4.59 - 4.63 (1H, m), 6.88 (1H, t, *J*=1.5Hz); ^{13}C NMR δ 23.8, 36.0, 52.1, 53.6, 60.7, 131.1, 145.4, 163.5, 164.9, 168.1; *m/z* 210 (MH^+, 32%), 166 (7), 124 (100).

Benzyl-(1S*,5R*)-6-benzyloxy-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (14)

A solution of **(10)**(486mg, 2mmol) in THF (20 ml) was cooled to -78°C and lithium bis(trimethylsilyl)amide (1.05 equiv. 2.1 ml, 1M solution) added dropwise. The resultant mixture was stirred for 20min and a solution of benzoyl chloride (1.05 equiv. 0.24 ml) in THF (2 ml) was added to the reaction mixture dropwise. Stirring was continued at -78°C for 30min, then warmed to room temperature and quenched with water. The solution was extracted with diethyl ether and the combined extracts washed with brine, dried, filtered and concentrated *in vacuo*. The crude material was subjected to flash chromatography (ethyl acetate:hexanes 1:3) and the product

(14)(447mg, 64%) was obtained as a thick oil which solidified to give a low melting point material on cooling. (Found: C, 72.38; H, 5.10; N, 4.14. $C_{21}H_{17}NO_4$ requires C, 72.61; H, 4.93; N, 4.03%); IR ($CHCl_3$) 3032 (m), 3014 (m), 1796 (s), 1717 (s), 1672 (s), 1629 (w), 1451 (w); ^{1}H NMR δ 2.83 - 3.10 (2H, m), 4.40 - 4.50 (1H, m), 4.85 (1H, t, *J*=5.0Hz), 7.00 (1H, t, *J*=1.0Hz), 7.30 - 8.00 (10H, m); ^{13}C NMR δ 36.9, 53.3, 59.3, 66.8, 128.2, 128.3, 128.6, 129.8, 129.9, 131.5, 131.8, 133.3, 146.1, 162.6, 163.7, 166.8; *m/z* 348 (MH^+, 15%), 200 (100).

Methyl-(1S*,5R*)-6-benzyloxy-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (15)
Compound **(15)**(127mg, 55%) was obtained as a low melting white solid from **(11)**(162mg, 0.97mmol), after purification by flash column chromatography, using the procedure described for **(14)**. (Found: C, 66.71; H, 4.62; N, 4.89. $C_{15}H_{13}NO_4$ requires C, 66.42; H, 4.83; N, 5.16%); IR ($CHCl_3$) 3028 (m), 3014 (m), 1797 (s), 1745 (s), 1673 (s), 1604 (m), 1452 (m); ^{1}H NMR δ 2.90 - 3.10 (2H, m), 3.81 (3H, s), 4.40 - 4.10 (1H, m), 4.85 (1H, t, *J*=5.0Hz), 7.00 (1H, t, *J*=1.0Hz), 7.40 - 7.70 (5H, m); ^{13}C NMR δ 36.9, 52.2, 53.3, 59.3, 128.2, 128.8, 130.2, 133.3, 133.8, 145.8, 163.6, 163.8, 166.5; *m/z* 272 (MH+, 7%), 124 (100).

(1S*,5R*)-6-acetyl-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (16)
A solution of **(12)**(607mg, 2.13mmol) in dichloromethane (20 ml) and anisole (4.0 equiv. 0.95 ml) was added dropwise to a solution of aluminum trichloride (3.0 equiv. 852mg) in nitromethane (20 ml) at 0°C. The resultant highly coloured solution was allowed to stir at 0°C for 90min and then at room temperature for 20min. After diluting with ethyl acetate, the solution was washed with 1N HCl and then extracted with dilute $NaHCO_3$ solution. The aqueous extracts were acidified to pH 3, extracted with ethyl acetate, dried, filtered and concentrated *in vacuo*. The crude solid was recrystallized from acetonitrile/hexanes to afford a white solid **(16)**(281mg, 67%). mp 188.8-191.1°C; (Found: C, 55.63; H, 4.80; N, 7.14. $C_9H_9NO_4$ requires C, 55.39; H, 4.65; N, 7.18%); IR (KBr) 3000 (m), 1806 (s), 1714 (s), 1660 (s), 1618 (s), 1350 (m); ^{1}H NMR δ 2.36 (3H, s), 2.75 - 3.05 (2H, m), 4.40 - 4.50 (1H, m), 4.65 (1H, t, *J*=5.5Hz), 6.87 (1H, t, *J*=1.0Hz); ^{13}C NMR δ 23.8, 36.0, 53.7, 60.9, 144.8, 165.1, 165.3, 168.2, 171.2; *m/z* 196 (MH^+, 100%), 178 (10), 152 (11), 110 (37).

(1S*,5R*)-6-benzyloxy-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (17)
Acid **(17)**(367mg, 85%) was obtained as a white solid after recrystallization of the crude product obtained from the debenzylation of **(14)**(580mg, 1.67mmol) employing the method used for the preparation of derivative **16**. mp 194.1-196.1°C; (Found: C, 65.08; H, 4.37; N, 5.36. $C_{14}H_{11}NO_4$ requires C, 65.37; H, 4.31; N, 5.44%); IR (KBr) 3000 (w), 1793 (s), 1673 (s), 1617 (w), 1452 (m), 1420 (m); ^{1}H NMR δ (CD_3OD) 2.80 - 3.00 (2H, m), 3.20 - 3.37 (1H, m), 4.35 - 4.50 (1H, m), 6.90 (1H, t, *J*=1.0Hz), 7.30 - 7.90 (5H, m); ^{13}C NMR δ 35.5, 52.9, 58.8, 106.5, 127.1, 128.5, 131.2, 131.6, 131.9, 144.9, 163.9, 164.3; *m/z* 258 (MH^+, 60%), 240 (10), 151 (15), 106 (100).

Benzyl-(1S*,5R*)-6-(*p*-toluylsulfonyl)-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (18)

A solution of **(10)**(252mg, 1.03mmol) in THF (10 ml) was cooled to -78°C and lithium bis(trimethylsilyl)amide (1.1 equiv. 1.14 ml, 1M solution) was added dropwise. The resultant mixture was stirred for 20min and a solution of *p*-toluenesulfonyl chloride (1.1 equiv. 217mg) in THF (3 ml) was introduced to the reaction mixture dropwise. Stirring was continued at -78°C for 45min, then warmed to room temperature and quenched with water. The solution was extracted with diethyl ether and the combined extracts were washed with brine, dried, filtered and concentrated *in vacuo*. The crude material was subjected to flash chromatography (ethyl acetate:hexanes 1:2) and the product **(18)**(165mg, 40%) was obtained as a white solid. mp 160.2-162.5°C; (Found: C, 63.26; H, 5.02; N, 3.22; S, 8.01. $C_{21}H_{19}NO_5S$ requires C, 63.46; H, 4.82; N, 3.52; S, 8.07%); IR (KBr) 1792 (s), 1715 (s), 1620 9m), 1366 (m); ^{1}H NMR δ 2.45 (3H, s), 2.75 - 2.85 (1H, m), 3.05 - 3.15 (1H, m), 4.35 - 4.42 (1H, m), 4.60 (1H, t, *J*=5.0Hz), 5.20 (2H, dd, *J*= 8.0, 12.0Hz), 6.90 (1H, t, *J*=1.0Hz), 7.20 - 7.40 (4H, m), 7.80 - 8.00 (2H, m); ^{13}C NMR δ 21.6, 36.8, 57.4, 61.8, 66.8, 127.3, 128.1, 128.3, 128.5, 128.5, 130.1, 131.2, 135.9, 144.9, 145.4, 162.5, 163.3, 174.6; *m/z* 398 (MH^+, 11%), 200 (100), 155 (29).

Methyl-(1S*,5R*)-6-(*p*-toluylsulfonyl)-2-carboxylate-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (19)

To a solution of **(11)**(653mg, 3.91mmol) in dichloromethane (20 ml) was added triethylamine (1.2 equiv. 0.65 ml) and *p*-toluenesulfonyl chloride (1.1 equiv. 820mg). The resultant mixture was allowed to stir overnight at room temperature, then diluted with diethyl ether, washed with water, brine, dried, filtered, concentrated *in vacuo* and purified by flash chromatography (ethyl acetate:hexanes 1:2) to afford **(19)**(439mg, 35%) as a foam. (Found: C, 55.70; H, 4.73; N, 4.44; S, 10.22. $C_{15}H_{15}NO_5S$ requires C, 56.06; H, 4.70; N, 4.36; S, 9.98%); IR ($CHCl_3$) 3029 (m), 3019 (m), 1794 (s), 1723 (s), 1438 (w); ^{1}H NMR δ 2.42 (3H, s), 2.73 - 2.82 (1H, m), 2.99 - 3.06 (1H, m), 3.73 (3H, s), 4.34 (1H, t, *J*=1.5Hz), 4.61 (1H, t, *J*=5.5Hz), 6.80 (1H, s), 7.33 (2H, d, *J*=8.0Hz), 7.82 (2H, d, *J*=8.0Hz); ^{13}C NMR δ 21.7, 36.7, 52.1, 57.5, 61.8, 127.2, 130.1, 131.0, 135.9, 144.7, 145.4, 163.2, 163.5; *m/z* 322 (MH^+, 10%), 197 (15), 124 (100).

Acknowledgements: We would like to thank Jana Grissom-Arnold, Jane Flokowitsch and Penny Lubbehusen for biological testing, Jennifer Olkowski for the X-ray crystallographic data and the Physical Chemistry department for spectral data.

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29. Crystal data for **16** : $C_{14}H_{11}NO_4$; M_r = 256.2, monoclinic, C2/c, a = 24.228(5)Å, b = 7.708(2)Å, c = 14.975(4) Å, β = 115.50(2)°, V = 2524.1(11)Å^3, Z = 8, D_χ = 1.349Mg/m^3, λ (CuKα) = 1.54178Å, μ = 0.841 mm^{-1}, F(000) = 1064, T = 295K, R = 3158. Crystallographic data have been deposited at the Cambridge Crystallographic Data Center.

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(*Received in USA* 30 *June* 1994; *revised* 11 *August* 1994; *accepted* 12 *August* 1994)