Tetrahedron Vol. 49, No. 25, pp. 5549-5563, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

SYNTHESIS OF OPTICALLY ACTIVE AMINO AZAPENAMS BY THE PHOTOLYTIC REACTION OF CHROMIUM AMINOCARBENE COMPLEXES WITH N-PROTECTED IMIDAZOLINES

Baptiste Ronan and Louis S. Hegedus*, Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523.

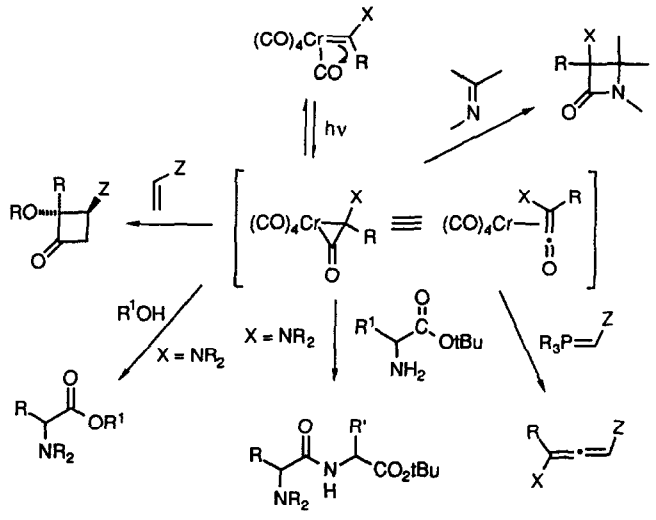
(Received in USA 28 January 1993)

Abstract: Photolysis of optically active aminocarbene chromium complexes with N-protected imidazolines produced α-amino-N-protected azapenams in good yield and with high diastereoselectivity. Removal of the protecting group resulted in cleaving of the β-lactam to give N-acylimidazolines.

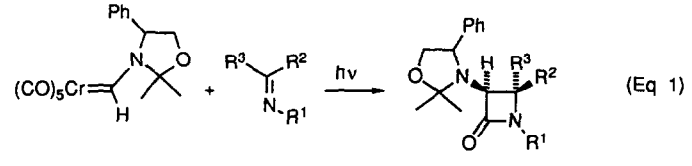
Introduction

Despite an enormous amount of research directed towards the synthesis of new classes of β-lactams, there are very few reports dealing with the synthesis of azapenams and azapenems (nitrogen analogs of the penicillin family). Racemic azapenems, having an sp^2 hybridized center in the five membered ring, have been prepared by intramolecular addition of a 4-azido group to an N-allylazetidinone,[1] or N-propargylazetidinone,[2] by the base induced cyclization of an ester enolate to a 4-isothiocyanato group,[3] by palladium(0) catalyzed carbonylation of aryl azirines,[4] and by triphenyl phosphine desulfurization of a 2-azacepham.[5] Optically active azapenems have been prepared by the base induced ester enolate – isothiocyanate cyclization of an optically active monocyclic β-lactam.[6] Azapenams are considerably less common. The reaction of azido ketene with an imidizoline was claimed to produce an unstable, unisolated azapenam.[7]

Over the past several years, photochemical reactions of chromium carbene complexes have been intensively studied in these laboratories. Irradiation of chromium carbene complexes (visible light, Pyrex) appears to drive a reversible insertion of carbon monoxide into the metal carbon double bond, generating a short lived species which has the reactivity of a ketene (Scheme 1).[8] These species undergo reaction with electron rich alkenes to give cyclobutanones,[9] with alcohols to give α-amino acids,[10] with amino acid esters to give dipeptides,[11] with stabilized ylides to give allenes[12] and with imines to give β-lactams.[13] With optically active chromium aminocarbene complexes, optically active amino β-lactams are produced in excellent yield and with very high stereoselectivity (Eq. 1).[3e,f,h] Although a very wide range of β-lactams were made by this procedure, azapenams were not attempted because of their reported unstability. However, the reaction of simple chromium alkoxy carbene complexes with N-protected imidazolines produced alkoxy azapenams which were quite stable and isolable,[14] although they underwent a novel cleavage/dimerization/cleavage reaction[15] in the presence of acids (Eq. 2). Herein we describe studies combining the chemistry presented in Eq. 1 and Eq. 2 for the synthesis of amino azapenams.

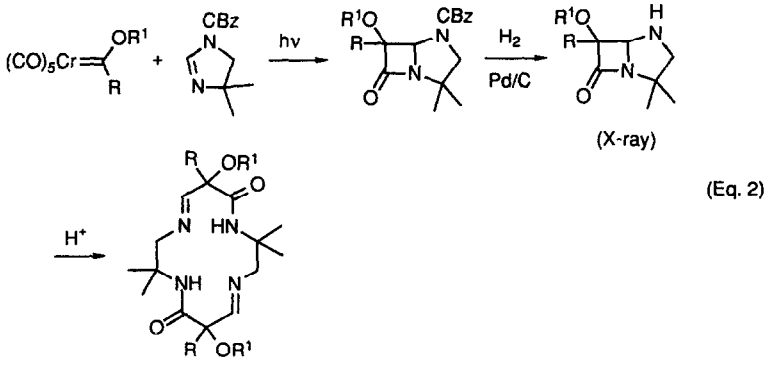


Scheme 1



(Eq 1)

≥97% de
≈80-95% yield



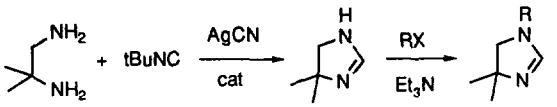
(X-ray)

(Eq. 2)

Results and Discussion

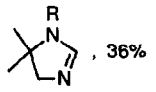
The requisite N-protected imidazolines were prepared from the known[14,16] 4,4-dimethyl-Δ^2-imidazoline **1** by treatment with the appropriate electrophile (Eq. 3). The protected imidazolines **2a**, **2c** and **2e** were obtained in good yield from di-*tert*-butyldicarbonate, *p*-toluenesulfonyl chloride, and benzyl chloroformate, respectively, whereas benzyl bromide gave **2b** in only 20% yield, and benzyl sulfonyl chloride gave a 1:1

mixture of isomeric imidazolines **2d** and **2d'**. (Protection of the free NH was required to prevent its reaction with the photogenerated ketenes).



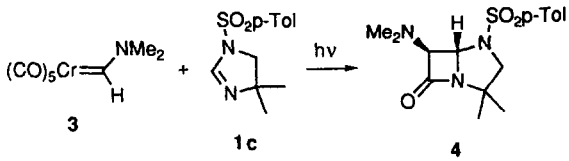
(Eq. 3)

1a	R = tBOC	87%
1b	R = Bn	26%
1c	R = pTs	87%
1d	R = $BnSO_2$	36%*
1e	R = CBz	72%



, 36%

This range of protecting groups was deemed necessary because the β-lactam-forming reaction is sensitive to the structural features of both the carbene complex and imidazoline,[17] and not all combinations are successful. Indeed, imidazolines **1a**, **1b**, and **1e** failed to form β-lactams when irradiated in the presence of the simple N,N-dimethylaminocarbene chromium complex **3**. Only N-tosylimidazoline **1c** converted cleanly to the desired protected α-amino azapenam **4** (Eq. 4) and the yield of the reaction was dependent on reaction conditions (Table 1). As expected,[13] compound **4** was produced as a single, (racemic) *trans* isomer.



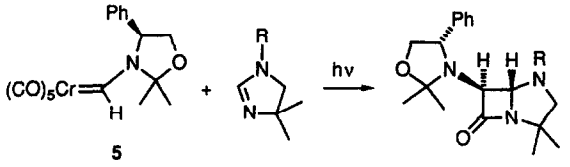
(Eq 4)

Table 1

Conditions	4 yield,[a] %
CH_3CN, Ar atm, 19 hr	36[b]
CH_3CN, Ar atm, 74 hr	45[b]; 38[c]
Et_2O, CO atm, 24 hr	43[b]
Et_2O, CO atm, 71 hr	82[b]

(a) After oxidation in sun light or in the light box and filtration through Celite to remove chromium residues. (b) Determined by ^1H NMR spectroscopy on the crude product. (c) After purification of the crude product by preparative chromatography on silica gel (ethyl acetate).

In contrast, optically active aminocarbene complex **5** was generally reactive towards imidazolines **1a-e**. Irradiation of **5** with **1a-e** under the optimum conditions developed in Table 1 led to fair to excellent yields of *trans*-amino azapenams **6a**, **6c**, **6d**, **6d'**, and **6e** with fair to excellent stereoselectivity (Eq. 5). Only N-benzyl imidazoline **1b** failed to produce a β-lactam, converting instead to an unidentified by-product. The N-tosylimidazoline **1c** gave the best yield as well as excellent diastereoselectivity. Reaction of the t-BOC protected imidazoline also proceeded with very high diastereoselectivity, although two rotamers about the carbamate group were obtained. The CBz-protected imidazoline gave similar yields, but with reduced diastereoselectivity, and, again, two rotamers about the carbamate bond were obtained. In all cases, the major diastereoisomer could be isolated pure and in good yield. With these materials in hand, removal of the nitrogen protecting groups was next addressed.



5 (Eq. 5)

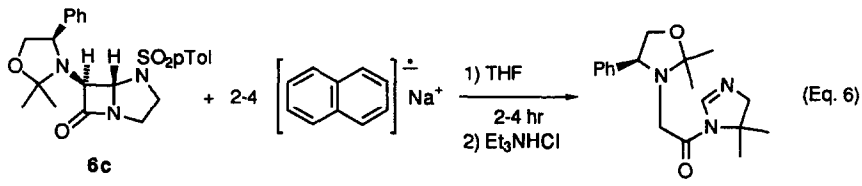
1a R = tBOC	**6a** 78%[a]	>97% de
1b R = Bn	---	
1c R = pTs	**6c** 93%	96% de
1d R = $BnSO_2$	**6d** 86%	80% de
1d' (isomer)	**6d'** (isomer) 79%	90% de
1e R = CBz	**6e** 80%	84% de

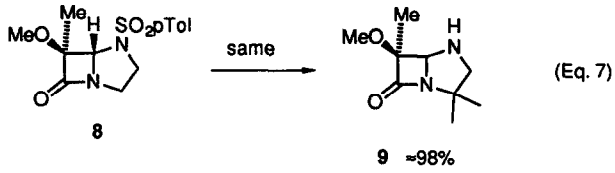
[a] Yield of pure, single diastereoisomer after separation.

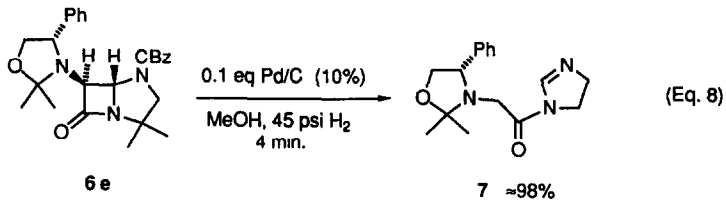
The sulfonamide is among the most stable nitrogen protecting groups and its removal from sensitive compounds can be problematic. Photolytic cleavage (U.V. hν, *i*-PrOH,[18] U.V. hν/EtOH/H_2O/$NaBH_4$/DME,[19] U.V. hν/Et_2O[20]) under relatively mild conditions is often successful. Unfortunately, subjecting azapenam **6c** to a variety of these conditions resulted in extensive degradation.

Removal of tosyl groups from amines can also be accomplished by reductive cleavage by sodium naphthalenide.[21] The procedure consists of mixing a solution of the sulfonamide in THF with 3-6 equivalents of sodium naphthalenide at -60°C, stirring for a few hours, and quenching with aqueous triethylammonium chloride. Subjecting N-tosyl azapenam **6c** to these conditions cleanly removed the tosyl group. However, the resulting azapenam was not obtained. Rather cleavage of the β-lactam ring to produce the N-acyl imidazoline **7** occurred in high yield (Eq. 6). This unexpected cleavage was initially attributed to the strongly basic, strongly reducing conditions of the detosylation procedure. However, detosylation of the corresponding α-alkoxy-N-tosylazapenam **8**, (synthesized as in Eq. 2) under identical conditions gave the free azapenam **9** in virtually quantitative yield (Eq. 7). A confirmation that this unusual cleavage was *not* due to the reductive deprotection conditions was the observations that the very mild hydrogenolytic cleavage of the CBz-protected azapenam gave the same product (Eq. 8). Protolytic cleavage of the t-BOC protected azapenam **6a** (trifluoroacetic acid/CH_2Cl_2/25°) resulted in unidentified degradation products, another indication of the sensitivity of α-amino

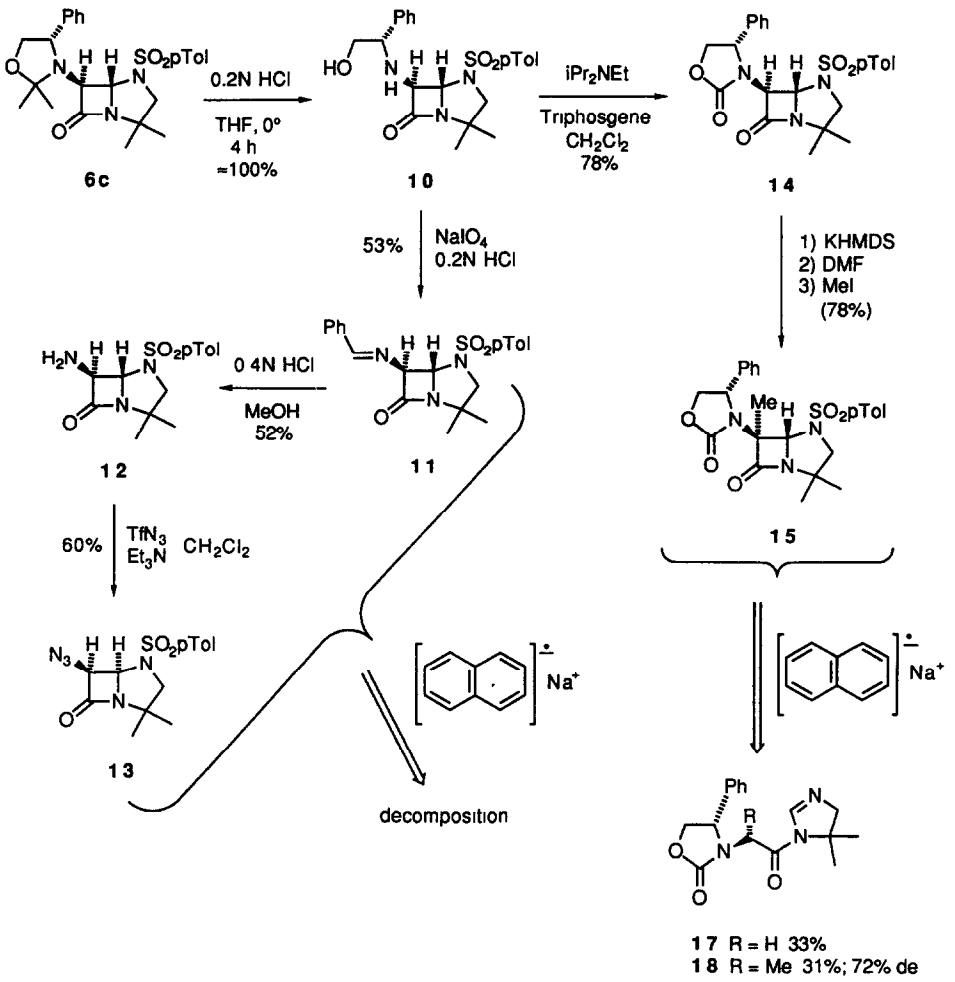
azapenams, relative to the much more stable α-alkoxy azapenams. The reasons for this difference in stability were next addressed.







α-Aminoazapenams **6** differ from α-alkoxy azapenams **8** (and those in reference 14) in at least two ways: (1) azapenams **6** have bulky, nitrogen substituents α to the carbonyl group while azapenams **8** has a relatively small alkoxy group; (2) the α-carbon of azapenams **6** are tertiary, while that of **8** is quaternary. To try to clarify which of these features accounts for the differences in stability between **6** and **8** the transformations in Scheme II were carried out, and each intermediate **10-15** was subjected to the standard sodium naphthalenide cleavage procedure. Aminoalcohol **10**, imine **11**, amine **12**, and azide **13**, underwent degradation to mixtures of unidentified products, while carbamate **14** and quaternary system **15** underwent the same undesired β-lactam cleavage as the parent compound. Thus, regardless of the oxidation state of the nitrogen, the steric bulk of the amine substituent, or the presence of lack of a quaternary β-carbon, stable α-amino azapenams could not be generated. Attempts to synthesize stable α-amino azapenams continue.



Scheme II

Experimental Section

General. NMR spectra were recorded on a Bruker/IBM 270 or a Bruker/IBM 300 NMR spectrometer in deuteriochloroform ($CDCl_3$), and the chemical shifts are expressed in δ ppm relative to tetramethylsilane (^1H NMR, δ = 0 ppm) or to $CDCl_3$ (^{13}C NMR, δ = 77 ppm) as an internal standard. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer and the signals are given in cm^{-1}. Mass spectra were recorded on a VG Micromass Ltd., Model 16F spectrometer. Melting points were determined on Mel-Temp apparatus and are uncorrected (open capillary). Optical rotations were measured on a Perkin-Elmer 24 polarimeter at 589 nm (sodium D line) in a 1.0 dm cell with a total volume of 1 ml. Specific rotations ($[\alpha]_D$) are reported in degree per decimeter at room temperature and the concentration (c) is given in grams per 100 ml in the specified solvent. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

4,4-Dimethyl-Δ^2-imidazoline,[16] 1-benzyloxycarbonyl-4,4-dimethyl-Δ^2-imidazoline **6e**, *tert*-butylisocyanide,[22] pentacarbonyl[(dimethylamino)methylene]-chromium **3**,[8a] pentacarbonyl[((5S)-2,2-dimethyl-5-phenyl-1-aza-3-oxacyclopentyl)methylene]-chromium **5**,[8a] pentacarbonyl[(methoxy)(methyl)-carbene]chromium complex[23] and triflic azide[24] were prepared by literature procedures.

1-*tert*-Butyloxycarbonyl-4,4-dimethyl-Δ^2-imidazoline (1a). The imidazoline (0.49 g, 5.0 mmol) and triethylamine (0.79 ml, 5.7 mmol) were dissolved in tetrahydrofuran (10 ml) and cooled in an icebath. Di-*tert*-butyl dicarbonate (1.16 g, 5.30 mmol) was added dropwise as a solution of 2 ml of tetrahydrofuran. After 15 min at 0°C the reaction was stirred 4 h at r.t. A part of the solvent was evaporated and ethyl acetate was added. The solution was washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent was evaporated to yield 0.86 g of **1a** as a colorless oil (4.34 mml, 87%); ^1H NMR δ 7.35 (s, 1H), 3.36 (s, 2H), 1.52 (s, 9H), 1.30 (s, 6H); ^{13}C NMR δ 149.8 (CO), 145.4 (C=N), 81.6 (CMe_2), 55.2 (CH_2), 28.7 (CH_3), 27.9 (CH_3); IR (neat) ν 1719 (CO), 1619 (C=N); MS (NH_3, CI) m/e 198 (M^+).

1-Benzyl-4,4-dimethyl-Δ^2-imidazoline (1b). The imidazoline (0.49 g, 5 mmol) and triethylamine (0.79 ml, 5.7 mmol) were dissolved in tetrahydrofuran (10 ml) and cooled in an icebath. Benzyl bromide (0.63 ml, 5.3 mmol) was added dropwise. After 15 min at 0°C the reaction was stirred 4 h at r.t. A part of the solvent was evaporated and ethyl acetate was added. The solution was washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent was evaporated to yield 0.33 g of a pink solid which was washed with hexane. The filtrate was concentrated to yield 0.19 g of **1b** as an orange oil (1 mmol, 20%); ^1H NMR δ 7.34-7.20 (m, 5H), 6.87 (s, 1H) 4.27 (s, 2H), 2.87 (s, 2H), 1.23 (s, 6H); IR (neat) ν 1671 (C=N).

1-*p*-Toluenesulfonyl-4,4-dimethyl-Δ^2-imidazoline (1c). The imidazoline (0.49 g, 5.00 mmol) and triethylamine (0 79 ml, 5.70 mmol) were dissolved in dichloromethane (10 ml) and cooled in an icebath. *p*-Toluenesulfonyl chloride (0.95 g, 5.0 mmol) was added dropwise as a solution in 8 ml of dichloromethane. After 15 min at 0°C the reaction was stirred overnight at r.t. The solution was washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent was evaporated to yield 1.09 g of **1c** as a white solid (4.32 mmol, 87%); mp 70°C; ^1H NMR δ 7.72-7.68 (d, 2H), 7.36-7.32 (d, 2H), 7.24 (br s, 1H), 3.14 (s, 2H), 2.44 (s, 3H), 1.16 (s, 6H); ^{13}C NMR δ 145.01 (CH=N), 144.69, 129.99, 127.26, 126.87 (Ar), 70.00 (C), 56.45 (CH_2), 28.51 (CH_3), 21.45 (CH_3, Ar); IR (KBr) ν 1615 (CH=N), 1356, 1166, 1093 (SO_2N); MS (NH_3, CI) m/e 97 (32%), 252 (100%) (M^+); Anal. Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10; S, 12.71 Found. C, 57.27; H, 6.27; N, 11.16, S, 12.56.

1-Benzylsulfonyl-4,4-dimethyl-Δ^2-imidazoline (1d) and 1-benzylsulfonyl-5,5-dimethyl-Δ^2-imidazoline (1d'). The imidazoline (0.49 g, 5.0 mmol) and triethylamine (0.79 ml, 5.7 mmol) were dissolved in dichloromethane (10 ml) and cooled in an icebath. Benzylsulfonyl chloride (0.95 g, 5.0 mmol) was added dropwise as a solution in 8 ml of dichloromethane. After 15 min a 0°C the reaction was stirred overnight at r.t. The solution was washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent was evaporated to yield 1.19 g of a white solid (**1d/1d'** = 1:1). Flash chromatography on silica gel (AcOEt/hexane = 3:2) gave, in order of elution, 0.46 g of **1d** as a white solid (1.82 mmol, 36%); mp 86°C, and 0 46 g of **1d'** as a yellow oil (1.82 mmol, 36%); (**1d**): ^1H NMR δ 7.40-7.24 (m, 5H), 6.68 (s, 1H), 4.37 (s, 2H), 3.16 (s, 2H), 1.21 (s, 6H); IR (KBr) ν 1622 (CH=N), 1347, 1139, 1096 (SO_2N). (**1d'**): ^1H NMR δ 7.40-7.32 (m, 5H), 6.50 (s, 1H), 4.34 (s, 2H), 3.67 (s, 2H), 1.49 (s, 6H); IR (neat) ν 1683, 1628 (CH=N), 1360, 1143, 1074 (SO_2N).

General procedure for the photoreaction of chromium aminocarbene complexes with imidazolines.

The chromium aminocarbene complex (0.5 mmol) and the imidazoline (0.5 mmol) were dissolved in 20 ml of diethyl ether in a pressure Pyrex tube equipped with a Matheson/Whitey Brand 100 psi pressure head and a pressure release valve. The solution was pressurized with CO to ~60 psi and then the pressure was released, three times. Finally, the solution was pressurized to 60 psi CO and carefully transported, using a protective shield, to an irradiation box and exposed to a 450W UV lamp (Conrad-Hanovia 7825 medium mercury lamp, Pyrex well) for the time desired. The progress of the reaction was monitored by use of analytical TLC (silica gel). Then, the pressure was released, the solvent was evaporated and the residue was oxidized in a mixture of ethyl acetate/hexane = 1:1 either on the roof in the sun light or in the light box. Filtration through Celite and evaporation of the solvent gave the crude product which was purified either by preparative plates on silica gel (ethyl acetate) or by flash chromatography on silica gel (ethyl acetate/hexane = 1:2). A similar procedure could be achieved in acetonitrile under Ar pressure but the photoreaction was slower. The oxidation of residue after photolysis was not necessary and purification could directly be achieved.

***trans*-2,2-Dimethyl-6-N,N-dimethylamino-4-*p*-toluenesulfonyl-1,4-diazabicyclo[3.2.0]heptan-7-one (4).** The chromium aminocarbene complex **3** (0.13 g, 0.50 mmol) and the imidazoline **1c** (0.14 g, 0.60 mmol) were dissolved in acetonitrile (20 ml) and irradiated under Ar pressure. After 74 h, the solvent was evaporated under reduced pressure and the residue was oxidized in a mixture of ethyl acetate/hexane = 1:1 (70 ml). The solid was removed by filtration through Celite and the filtrate was concentrated to yield 0.13 g of a yellow oil. A crude ^{1}H NMR spectrum showed that only single *trans* racemic diastereomer was formed as sole product (45% yield by ^{1}H NMR conversion). This was purified by preparative plates on silica gel (ethyl acetate) to give 0.064 g (0.19 mmol, 38%) of **4** as a white solid; mp 110°C; ^{1}H NMR δ 7.76-7.72 (d, 2H), 7.36-7.32 (d, 2H), 4.97 (s, 1H), 3.74 (s, 1H), 3.32 (AB, 2H, J_{AB} = 10Hz), 2.45 (s, 6H), 2.43 (s, 3H), 1.53 (s, 3H), 0.75 (s, 3H); ^{13}C NMR δ 171.50 (CO lactam), 129.96, 127.79, 127.47, 127.36 (Ar), 80.76 (NCHN), 71.57 (NCHCO), 62.33 (CH_2N), 42.63 (C-N), 25.75 (CH_3N), 22.15 (CH_3), 22.03 (CH_3), 21.41 (CH_3Ar); IR (KBr) ν 1775 (CO lactam), 1346, 1158 (SO_2N); MS (NH_3, CI) m/e 97 (46%), 252 (100%), 337 (2%) (M^+), 338 (0.3%) (MH^+); Anal. Calcd for $C_{16}H_{23}N_3O_3S$: C, 56.95; H, 6.87; N, 12.45; S, 9.50. Found: C, 56.86; H, 6.96; N, 12.26; S, 9.54.

(5S,6S,5'S)-6-(2',2'-Dimethyl-5'-phenyl-1'-aza-3'-oxacyclopentyl)-2,2-dimethyl-4-t-butyloxycarbonyl-1,4-diazabicyclo[3.2.0]heptane-7-one (6a). The chromium aminocarbene complex **5** (0.16 g, 0.42 mmol) and the imidazoline **1a** (0.08 g, 0.42 mmol) were dissolved in diethylether (10 ml) and irradiated under CO pressure (45 psi). After 69 h, the solvent was evaporated under reduced pressure and the residue was oxidized in a mixture of ethyl acetate/hexane = 1:1 (50 ml). The solid was removed by filtration through Celite and the filtrate concentrated to give 0.16 g of a yellow oil. A crude ^{1}H NMR spectrum showed that only one of the two possible *trans* diastereomers was formed as a mixture of two rotamers in 75:25 ratio. These were purified by flash chromatography on silica gel (AcOEt/hexane = 1:4) to yield 0.136 g (0.33 mmol, 78%) of **6a** (as a mixture of two rotamers in 75:25 ratio) as a white solid; ^{1}H NMR (major rotamer) δ 7.42-7.24 (m, 5H), 4.24 (m, 2H), 4.09 (s, br, 1H), 3.87 (s, br, 1H), 3.75 (t, br, 1H), 3.46 (d, 1H, J = 10.4 Hz), 3.06 (d, 1H, J = 10.2 Hz), 1.53 (s, 3H), 1.49 (s, 3H), 1.47 (s, 9H), 0.85 (s, 3H); ^{1}H NMR (minor rotamer) δ 4.56 (s, br, 1H), 4.41 (m, 1H), 4.24 (m, 1H), 3.87 (m, 1H), 3.69 (m, 1H), 3.33 (m, 1H), 3.06

(m, 1H). ^{13}C NMR δ 173.30 (CO lactam), 152.67 (CO carbamate), 142.12/128.24/127.96 (Ar), 96.02 (O-C-N), 80.61 (C-O), 73.86 (N-CH-N), 72.41 (N-CH-CO), 71.19 (CH_2O), 62.52 (N-CH-Ph), 60.47 (C-N), 59.90 (CH_2N), 28.46 (CH_3 t-Bu), 27.75 (CH_3), 25.66 (CH_3), 24.10 (CH_3), 21.91 (CH_3); IR (KBr) δ 1755 (CO lactam), 1706 (CO carbamate); MS (NH_3, Cl) m/e 83 (13%), 98 (17%), 99 (45%), 104 (15%), 142.9 (100%), 177.9 (17%), 189.9 (12%), 198.9 (69%), 216.9 (11%), 217.9 (78%), 218.9 (12%), 415.4 (5%) (M).

(5S,6S,5'S)-6-(2',2'-Dimethyl-5'phenyl-1'-aza-3'-oxacyclopentyl)-2,2-dimethyl-4-*p*-toluenesulfonyl-1,4-diazabicyclo[3.2.0]heptane-7-one (6c). The chromium aminocarbene complex **5** (0.19 g, 0.50 mmol) and the imidazoline **6c** (0.13 g, 0.50 mmol) were dissolved in diethylether (20 ml) and irradiated under CO pressure. After 16 h, the solvent was evaporated under reduced pressure and the residue was oxidized in a mixture of ethyl acetate/hexane = 1:1 (70 ml). The solid was removed by filtration through Celite and the filtrate was concentrated to yield 0.17 g of a yellow oil. A crude ^1H NMR spectrum showed that only *trans* diastereomers were formed as a mixture of two *trans* isomers in 98:2 ratio. This was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:2) to give 0.22 g (0.47 mmol, 93%) of **6c** optically pure as a white solid; mp 134-135°C; ^1H NMR δ 7.48-7.21 (m, 9H), 4.29-4.20 (m, 3H), 3.98 (d, 1H, J = 1Hz), 3.78 (dd, 1H, J_1 = 5Hz, J_2 = 7Hz), 3.26-3.05 (AB, 2H, J_{AB} = 10Hz), 2.41 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 0.36 (s, 3H); ^{13}C NMR δ 172.31 (CO lactam), 144.36, 142.56, 134.10, 130.00, 128.41, 128.03, 127.82, 127.34 (Ar), 96.28 (O-C-N), 74.10 (N-CH-N), 73.85 (OC-CH-N), 72.31 (CH_2O), 62.56 (C-N), 62.43 (Ph-CH-N), 60.77 (CH_2N), 27.69 (CH_3), 25.64 (CH_3), 24.23 (CH_3), 22.44 (CH_3), 21.67 (CH_3Ar); IR (KBr) ν 1765 (CO lactam), 1359, 1163 (SO_2N); MS (NH_3, CI) m/e 57.9 (10%), 96.9 (15%), 98.9 (48%), 217.9 (14%), 252.8 (100%), 253.8 (28%), 254.8 (11%), 269 (0.5%) (M^+), Anal. Calcd for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95; S, 6.83. Found: C, 63.13; H, 6.50; N, 8.99; S, 7.00. $[\alpha]_D$ = +26.3 (c = 0.54, CH_2Cl_2). Minor *trans* isomer: ^1H NMR δ 7.60-7.10 (m, 9H), 4.67 (br s, 1H), 4.54 (m, 1H), 4.30 (t, 1H, J = 8Hz), 4.19 (s, 1H), 3.69 (m, 1H), 3.23 (AB, 2H, J_{AB} = 11Hz), 2.38 (s, 3H), 1.55 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H), 0.39 (s, 3H).

(5S,6S,5'S)-6-(2',2'-Dimethyl-5'-phenyl-1'-aza-3'-oxacyclopentyl)-2,2-dimethyl-4-benzylsulfonyl-1,4-diazabicyclo[3.2.0]heptane-7-one (6d). The chromium aminocarbene complex **5** (0.09 g, 0.25 mmol) and the imidazoline **1d** (0.06 g, 0.25 mmol) were dissolved in diethylether (10 ml) and irradiated under CO pressure. After 15 h, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate/hexane = 1:2) to give 0.10 g (0.21 mmol, 86%) of a white solid. A crude ^1H NMR spectrum showed that only *trans* diastereomers were formed as a mixture of two *trans* isomers in 90:10 ratio. Major *trans* isomer: ^1H NMR δ 7.43-7.17 (m, 10H), 4.28-4.18 (m, 3H), 4.16-4.04 (AB, 2H, J = 14Hz), 3.89 (s, 1H), 3.71 (t, 1H, J = 6Hz), 3.04-2.83 (AB, 2H, J = 10Hz), 1.43 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 0.76 (s, 3H). Minor *trans* isomer: ^1H NMR δ 7.50-7.12 (m, 10H), 5.14 (s, 1H), 4.30-3.65 (m, 6H), 3.15 (d, 1H, J = 10Hz), 2.70 (d, 1H, J = 10Hz), 1.50 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H), 0.90 (s, 3H). Major and minor *trans* isomers: IR (KBr) ν 1765 (CO lactam), 1333 (SO_2N); MS (NH_3, CI) m/e 90.9 (56%), 97.0 (70%), 98.9 (25%), 107.9 (14%), 172.9 (11%), 177.9 (16%), 188.9 (20%), 189.9 (11%), 217.9 (32%), 252.9 (100%), 253.9 (55%), 254.9 (21%), 468.9 (0.5%) (M^+). Major *trans* isomer: mp 117°C; $[\alpha]_D^{25}$ = +21.5 (c = 0.53, CH_2Cl_2); ^{13}C NMR δ 172.05 (CO lactam), 141.28 (C, Ar), 130.51/128.97/128.46/127.69 (CH, Ar), 95.90 (O-C-N), 77.18 (CH), 74.10 (CH), 73.08 (CH_2O), 61.54

(CH), 61.03 (C), 58.97 (CH_2), 53.08 (CH_2), 27.69 (CH_3), 25.64 (CH_3), 24.36 (CH_3), 22.05 (CH_3); Anal. Calcd for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95; S, 6.83. Found: C, 64.06; H, 6.85; N, 9.10; S, 7.02.

(5S,6S,5'S)-6-(2',2'-Dimethyl-5'-phenyl-1'-aza-3'-oxacyclopentyl-3,3-dimethyl-4-benzylsulfonyl-1,4-diazabicyclo[3.2.0]heptane-7-one (6d'). The chromium aminocarbene complex **5** (76 mg, 0.20 mmol) and the imidazoline **1d'** (51 mg, 0.20 mmol) were dissolved in diethyl ether (10 ml) and irradiated under CO pressure. After 15 h, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate/hexane = 1:2) to give 74 mg (0.16 mmol, 79%) of a white solid. A crude ^1H NMR spectrum showed that only *trans* diastereomers were formed as a mixture of two *trans* isomers in 95:5 ratio. Another chromatography flash on silica gel (ethyl acetate/hexane = 1:2) gave 52 mg (0.11 mmol, 56%) of **6d'** optically pure as a white solid; mp = 124°C; ^1H NMR δ 7.42-7.12 (m, 10H), 4.27-4.20 (m, 2H), 4.19 (d, 1H, J = 0.8Hz), 4.07 (s, 2H),m 3.93 (d, 1H, J = 0.7Hz), 3.70 (dd, 1H, J_1 = 9.5Hz, J_2 = 11.6Hz), 3.55 (d, 1H, J = 11.8Hz), 2.48 (d, 1H, J = 11.9Hz), 1.50 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.05 (s, 3H); ^{13}C NMR δ 175.53 (CO lactam), 142.76, 130.58, 128.96, 128.83, 128.66, 128.53, 127.77, 127.68 (Ar), 96.21 (O-C-N), 76.06 (N-CH-N), 76.01 (N-CH-CO), 72.30 (CH_2O), 67.83 (C-NSO_2), 62.76 (N-CH-Ph), 60.00 (CH_2N), 58.06 (SO_2CH_2Ar), 29.87 (CH_3), 27.37 (CH_3), 24.84 (CH_3), 24.15 (CH_3); IR (KBr) ν 1775 (CO lactam), 1341 (SO_2N); MS (NH_3, CI) m/e 90.9 (36%), 97 (14%), 99 (34%), 107.9 (18%), 172.9 (19%), 177.9 (29%), 188.9 (15%), 189.9 (14%), 217.9 (74%), 252.9 (100%), 253.9 (54%), 469.9 (0.3%) (M^+); $[\alpha]_D$ = +36.2 (c = 0.61, CH_2Cl_2); Anal. Calcd for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95; S, 6.83. Found: C, 63.79; H, 6.85; N, 8.86; S, 6.89. Minor *trans* isomer: ^1H NMR δ 7.52-7.09 (m, 10H), 4.40 (dd, 1H), 4.23 (t, 1H, J = 8Hz), 4.19-4.06 (m, 3H), 3.84 (s, 1H),m 3.64-3.59 (m, 2H), 2.54 (d, 1H), 1.47 (s, 3H), 1.32 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H).

(5S,6S,5'S)-6-(2',2'-Dimethyl-5'-phenyl-1'-aza-3'-oxacyclopentyl)-2,2-dimethyl-4-t-benzyloxycarbonyl-1,4-diazabicyclo[3.2.0]heptane-7-one (6e). The chromium aminocarbene **5** (0.153 g, 0.40 mmol) and the imidazoline **1e** (0.093 g, 0.40 mmol) were dissolved in diethylether (10 ml) and irradiated under CO pressure (45 psi). After 63 h, the solvent was evaporated under reduced pressure and the residue was oxidized in a mixture of ethyl acetate/hexane = 1:1 (50 ml). The solid was removed by filtration through Celite and the filtrate concentrated to give 0.186 g of a yellow oil. A crude ^1H NMR spectrum showed that only two *trans* diastereomers were formed in 92:8 ratio (de = 84%) and that major *trans* diastereomer was formed as a mixture of two rotamers in a 75:25 ratio. These were purified by flash chromatography on silica gel (AcOEt/hexane = 1:4) to give *trans* diastereomers in a quantitative yield. The major *trans* diastereomer was isolated as a mixture of two rotamers in a 75:25 ratio as a white solid (0.143 g, 0.32 mmol, 80%); ^1H NMR (major *trans* rotamer) δ 7.45-7.18 (m, 10H), 5.15-5.05 (AB, 2H, J_{AB} = 12 Hz), 4.19 (m, 3H), 3.90 (s, 1H), 3.68 (m, 1H), 3.53 (d, 1H, J = 10 Hz), 3.16 (d, 1H, J = 10 Hz), 1.54 (s, 3H), 1.33 (s, 3H), 1.23 (s, 3H), 0.87 (s, 3H); ^1H NMR (minor *trans* rotamer) δ 5.24-4.93 (AB, 2H, J = 12Hz), 4.49 (s, br, 1H), 4.38 (m, 1H), 4.19 (m, 1H), 3.93 (s, br, 1H), 3.72 (m, 1H), 3.45 (m, 1H), 3.11 (m, 1H); ^1H NMR (minor *trans* diastereomer) δ 7.50-7.15 (m, 10H), 5.24-4.93 (AB, 2H, J_{AB} = 13 Hz), 4.30-4.10 (m, 3H), 3.91 (s, br, 1H), 3.72-3.59 (m, 2H), 3.66 (d, 1H, J = 13 Hz), 1.53 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (rotamers) δ 173.0 (CO lactam), 153.3 (CO carbamate), 136.1/128.5/128.3/127.9 (Ar), 96.0 (N-C-O), 73.8 (N-C-N), 72.3 (N-C-CO), 71.5 (CH_2O), 67.5 (O-CH_2-Ph), 62.6 (Ph-CH-N, C-N), 60.4 (CH_2N), 27.4 (CH_3), 25.9 (CH_3), 24.2 (CH_3), 22.0 (CH_3); IR (KBr) δ 1764 (CO lactam), 1712 (CO carbamate); MS (NH_3,

CI) m/e 90.9 (58%), 107.9 (18%), 177.9 (11%), 217.9 (38%), 232.9 (27%), 233.0 (100%), 234.0 (28%), 449.4 (1%) (M).

(±)-2,2,6-Trimethyl-6-methoxy-4-*p*-toluenesulfonyl-1,4-diazabicyclo-[3.2.0]heptane-7-one (8). The (methoxy)(methyl)chromium carbene complex (95 mg, 0.40 mmol) and the imidazoline **1c** (101 mg, 0.40 mmol) were dissolved in acetonitrile (10 ml) and irradiated (450W UV lamp) under 1 atm argon at room temperature. After 18 h, the solvent was evaporated and the residue was oxidized in a mixture of ethyl acetate/hexane = 1:1 (70 ml) in a light box. Filtration through Celite and evaporation of the solvent gave 135 mg of crude product as a yellow solid. A crude ^1H NMR spectrum showed that only *trans* isomer was formed. The crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:3) to yield 91 mg (0.27 mmol, 67%) of **8** as a white solid; mp = 115°C; ^1H NMR δ 7.78 (d, 2H, J = 8.3Hz), 7.37 (d, 2H, J = 8Hz), 4.96 (s, 1H), 3.48 (s, 3H), 3.49-3.20 (AB, 2H, J_{AB} = 10.6Hz), 2.46 (s, 3H), 1.53 (s, 3H), 1.42 (s, 3H), 0.63 (s, 3H); IR (KBr) ν 1782 (CO lactam), 1343/1157 (SO_2N); ^{13}C NMR δ 172.79 (CO lactam), 144.47 (C, Ar), 134.96 (C, Ar), 130.04 (2CH, Ar), 127.34 (2CH, Ar), 90.72 (C-O), 76.29 (N-CH-N), 62.12 (CH_2N), 60.91 (C-N), 53.48 (CH_3-O), 25.19 (CH_3), 21.88 (CH_3), 21.57 (CH_3), 14.15 (CH_3); MS (NH_3, CI) *m/e* 98.9 (32%), 182.9 (10%), 252.7 (100%), 310.7 (40%), 338.7 (76%) (M), 339.7 (14%) (MH^+), 356.8 (1%) (MNH_4^+).

General procedure for the cleavage of the *p*-toluenesulfonamide group with sodium naphthalenide.

A solution of sodium naphthalenide (0.4M/THF) was prepared by addition of Na (0.23 g, 0.01 mol) over solid naphthalene (1.28 g, 0.01 mol) followed by 25 ml of tetrahydrofuran at room temperature under argon. The dark green solution was stirred at room temperature under argon overnight before use. Protected azapenam was dissolved in tetrahydrofuran and cooled under argon at -60°C. A solution of sodium naphthalenide (2-4 eq.) in tetrahydrofuran was added dropwise and the mixture stirred at -60°C for 2-4 h. An aqueous solution of $Et_3NH^+Cl^-$ was added, the product was extracted by CH_2Cl_2 and dried over $MgSO_4$. After filtration and removal of the solvent on a rotatory evaporator, the product was chromatographed on silica gel (AcOEt).

Cleavage of the *p*-toluenesulfonamide group in 6c. Azapenam **6c** (23 mg, 0.05 mmol) was dissolved in tetrahydrofuran (1 ml) and cooled under argon at -60°C. Sodium naphthalenide (0.4M/THF) (0.5 ml, 0.2 mmol) was added dropwise and the mixture stirred at -60°C for 3 h. After the usual workup, 16 mg of **7** (0.05 mmol, 100% yield) was obtained as a colorless oil; $[\alpha]_D^{25}$ = +20.5 (c = 0.88, CH_2Cl_2); ^1H NMR δ 7.57 (s, br, 1H), 7.37-7.24 (m, 5H), 4.21 (t, 1H, J = 7.9 Hz), 3.89 (t, 1H, J = 7.3 Hz), 3.77 (t, 1H, J = 7.5 Hz), 3.55-3.35 (ABd, 2H, J = 2 Hz, J_{AB} = 15.2 Hz), 3.45-3.26 (AB, 2H, J_{AB} = 13.3 Hz), 1.61 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 0.93 (s, 3H); ^{13}C NMR δ 166.66 (C=O), 148.25 (Ar), 139.89 (CH=), 128.76/128.26/128.13 (Ar), 96.44 (O-C-N), 71.91 (CH_2O), 70.46 (N-$\underline{CH_2}$-CO), 67.41 (C-N), 61.18 (N-$\underline{CH}$-Ph), 54.89 (CH_2N), 27.13 (CH_3), 25.13 (CH_3), 24.66 (CH_3), 19.92 (CH_3); IR (KBr) δ 1678 (CO carbonyl), 1618 (N-CH=N); MS (NH_3, CI) *m/e* 98.9 (40%), 131.9 (23%), 189.8 (37%), 217.9 (19.9%), 315.8 (100%) (M), 316.8 (20%) (MH^+); Anal. Calcd for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.52; H, 8.06; N, 13.12.

Cleavage of the *p*-toluenesulfonamide in 8. Alkoxy azapenam **8** (17 mg, 0.05 mmol) was dissolved in tetrahydrofuran (1 ml) and cooled under argon at -60°C. A solution of sodium naphthalenide

(0.4M/THF) (0.375 ml, 0.15 mmol) was added dropwise and the mixture was stirred at -60°C for 30 min. An aqueous solution of $Et_3NH^+Cl^-$ was added, the product was extracted with ethyl acetate, dried over $MgSO_4$, filtrated and concentrated to give 16 mg of a yellow solid. This was purified by flash chromatography on silica gel (ethyl acetate) to yield 9 mg (0.05 mmol, 100%) of **9** as a colorless oil; identical in all respects to material prepared as in reference 14.

Hydrogenation of 6e to 7. Azapenam **6e** (45 mg, 0.10 mmol) was dissolved in methanol (5 ml) in a small pressure tube under Argon. Hydrogenation was performed under 45 psi H_2 at room temperature for 8 min. Filtration through Celite, and removal of the solvent on a rotatory evaporator gave **7** (32 mg, 0.10 mmol, ≈100% yield) as a yellow oil.

Hydrolysis of the oxazolidine group in 6c; synthesis of 10. A tetrahydrofuran solution (4 ml) of **6c** (72 mg, 0.15 mmol) was treated with 0.2 N HCl (4 ml) at room temperature and stirred for 3 h. The reaction was monitored by TLC (AcOEt/hexane = 1:1). Upon complete hydrolysis the tetrahydrofuran was removed on a rotatory evaporator and the aqueous solution was brought to pH 7.0 with aqueous sodium bicarbonate. The product was then extracted with CH_2Cl_2 and dried over $MgSO_4$. After filtration and removal of the solvent **10** was obtained as a white solid (64 mg, 0.15 mmol, 100% yield, 100% de); mp 132°C; $[\alpha]_D^{25}$ = +92.5 (c = 0.92, CH_2Cl_2); ^1H NMR δ 7.56-7.22 (m, 9H), 4.72 (s, 1H), 4.14-4.09 (m, 1H), 4.01 (s, 1H), 3.76 (dd, 1H, J^1 = 11 Hz, J^2 = 4 Hz), 3.58 (dd, 1H, J^1 = 11 Hz, J^2 = 9 Hz), 3.20 (AB, 2H, J = 10Hz), 2.41 (s, 3H), 2.15 (s, br, 1H), 2.01 (s, br, 1H), 1.48 (s, 3H), 0.69 (s, 3H); IR (KBr) δ 3427 (NH, OH), 1772 (CO, lactam), 1352/1160 (SO_2N); MS (NH_3, CI) *m/e* 97 (37%), 98.9 (26%), 252.6 (100%), 253.6 (15%); ^{13}C NMR δ 172.11 (CO lactam), 144.24/139.65/134.69 (C, Ar), 129.94/128.78/127.92/127.64/127.26 (CH, Ar), 75.63 (CH), 72.21 (CH), 67.05 (CH_2O), 62.12 (CH_2N), 62.06 (CH, Ph), 61.42 (C), 25.58 (CH_3), 22.20 (CH_3), 21.54 (CH_3).

Oxidation of 10; Preparation of 11. The amino alcohol azapenam **10** (63 mg, 0.15 mmol) was dissolved in tetrahydrofuran (4 ml) and 0.2N HCl (10 ml). The mixture was stirred at room temperature for 5 min before solid $NaIO_4$ (66 mg, 0.31 mmol) was added. The mixture was stirred at room temperature for 25 min and neutralized by adding of a saturated aqueous solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 and dried over $MgSO_4$. Filtration and removal of the solvent on a rotatory evaporator gave 50 mg of a yellow oil. Chromatography flash on silica gel (AcOEt/hexane = 2:1) gave 31 mg of **11** (0.08 mmol, 53% yield, 100% de) as a colorless oil which gave a yellow solid; mp 42°C; $[\alpha]_D^{25}$ = -10.5, (c = 0.285, CH_2Cl_2); ^1H NMR δ 8.35 (s, 1H), 7.79-7.34 (m, 9H), 5.06 (s, 1H), 4.70 (s, 1H), 3.42 (s, 2H), 2.44 (s, 3H), 1.61 (s, 3H), 0.84 (s, 3H); IR (KBr) δ 1775 (CO lactam), 1636 (HC=N), 1352/1161 (NSO_2); MS (NH_3, CI) *m/e* 90.9 (11%), 97.0 (99%), 98.9 (22%), 252.3 (100%), 253.3 (32%), 254.2 (13%); ^{13}C NMR δ 170.5 (CO lactam), 164.9 (CH=N), 144.3/135.3/134.3 (C, Ar), 131.3/130.0/128.65/128.58/127.4 (CH, Ar), 81.2 (CH), 74.7 (CH), 62.4 (CH_2), 61.7 (C), 25.7 (CH_3), 22.3 (CH_3), 21.6 (CH_3).

(5S,6S)-6-Amino-2,2-dimethyl-4-*p*-toluenesulfonyl-1,4-diazabicyclo-[3.2.0]heptane-7-one (12). The amino alcohol azapenam **11** (75 mg, 0.18 mmol) was dissolved in tetrahydrofuran (4 ml) and stirred at room temperature with HCl 0.2N (11 ml), and $NaIO_4$ (0.19 g, 0.88 mmol) was added. The mixture was stirred at room temperature for 1 h and neutralized by adding of a saturated aqueous solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 and dried over $MgSO_4$. Filtration and removal of the

solvent on a rotatory evaporator gave 77 mg of crude **12** as a yellow oil. This was dissolved with methanol (10 ml) and stirred at room temperature in the presence of HCl 0.4N (15 ml) overnight. The solvent and benzaldehyde were removed on a rotatory evaporator. Water (25 ml) was added, the mixture was neutralized by adding a saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated to give 54 mg of a yellow oil which was purified by flash chromatography on silica gel (ethyl acetate/hexane = 2:1), giving 28 mg (0.09 mmol, 52%) of **12** as a yellow oil which gave a yellow solid; mp = 43°C; $[\alpha]_D^{25}$ = +21.4 (c = 0.295, CH_2Cl_2); ^1H NMR δ 7.74 (d, 2H, J = 8.2Hz), 7.34 (d, 2H, J = 8.1Hz), 4.62 (s, 1H), 4.07 (s, br, 1H), 3.28 (AB, 2H, J_{AB} = 9.8Hz), 2.42 (s, 3H), 1.72 (s, br, 2H), 1.51 (s, 3H), 0.77 (s, 3H); ^{13}C NMR δ 167.0 (CO lactam), 144.43 (C, Ar), 134.69 (C, Ar), 130.02 (2CH, Ar), 127.32 (2CH, Ar), 77.53 (CH), 68.36 (CH), 62.07 (CH_2), 61.39 (C), 25.78 (CH_3), 22.30 (CH_3), 21.57 (CH_3); IR ν 1769 (CO lactam), 1347/1160 (NSO_2); MS (NH_3, CI) m/e 96.9 (20%), 98.9 (20%), 252.4 (100%), 253.4 (15%), 309.2 (0.4%) (M); Anal. Calcd for $C_{14}H_{19}N_3O_3S$: C, 54.35; H, 6.19 N, 13.58; S, 10.36. Found: C, 54.58; H, 6.29; N, 13.56; S, 10.51.

(5S,6S)-6-Azido-2,2-dimethyl-4-*p*-toluenesulfonyl-1,4-diazabicyclo-[3.2.0]heptane-7-one (13). The amino azapenam **12** (77 mg, 0.25 mmol) was dissolved under argon with CH_2Cl_2 (4.5 ml) and cooled in an ice-bath. A freshly prepared solution of triflic azide[24] in CH_2Cl_2 (1M solution) (5 ml, 5 mol) was added dropwise following by triethylamine (0.11 ml, 0.75 mmol). After being stirred with ice cooling for 15 min, the mixture was allowed to stand at room temperature for 21 h with stirring. The solvent was removed on a rotatory evaporator to give a yellow oil which was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:2) to yield 84 mg (100%) of **13** as a colorless oil. This was taken up in 5% aqueous solution of $NaHCO_3$ (15 ml), extracted with CH_2Cl_2, dried over $MgSO_4$, filtrated and concentrated to give 49 mg (0.15 mmol, 58%) of an analytical sample **13** as a white solid; mp = 93°C; $[\alpha]_D^{25}$ = +31.5 (c = 0.355, CH_2Cl_2); ^1H NMR δ 7.75 (d, 2H, J = 8.3Hz), 7.38 (d, 2H, J = 7.9Hz), 4.78 (d, 1H, J = 0.8Hz), 4.45 (s, 1H), 3.33 (AB, 2H, J = 9.9Hz), 2.45 (s, 3H), 1.54 (s, 3H), 0.82 (s, 3H); ^{13}C NMR δ 167.05 (CO lactam), 144.87 (C, Ar), 134.28 (C, Ar), 130.23 (2 CH, Ar), 127.34 (2CH, Ar), 73.91 (CH), 70.79 (CH), 62.17 (C), 62.01 (CH_2), 25.60 (CH_3), 22.25 (CH_3), 21.60 (CH_3); IR ν 2115 (N_3C), 1782 (CO lactam), 1353/1161 (NSO_2); MS (NH_3, CI) *m/e* 83.0 (19%), 90.9 (25%), 97.0 (100%), 99.0 (100%), 108.0 (23%), 124.0 (18%), 139.9 (19%), 152.0 (100%), 168.9 (78%), 188.8 (16%), 253.1 (100%), 307.9 (38%), 335.9 (11%) (M), 352.9 (2.3%) (MNH_4^+); Anal. Calcd for $C_{14}H_{17}N_5O_3S$: C, 50.14; H, 5.11; N, 20.88; S, 9.56. Found: C, 50.14; H, 5.29; N, 20.85; S, 9.31.

(5S,6S,5'S)-6-(5'-phenyl-1'-aza-3'-oxacyclopentyl-2-onyl-2,2-dimethyl-4-*p*-toluenesulfonyl-1,4-diazabicyclo[3.2.0]heptane-7-one 14. Azapenam **10** (0.46 g, 1.08 mmol) was dissolved in CH_2Cl_2 (43 ml) and cooled in an icebath. Diisopropyl ethyl amine (0.75 ml, 4.32 mmol) was added and the mixture was stirred at 0°C for 10 min before triphosgene (0.39 g, 1.30 mmol) was added in portions. The mixture was stirred at 0°C for 2 h and filtered through SiO_2. The solvent was removed on a rotatory evaporator to give a yellow oil (0.652 g) which was chromatographed on silica gel (AcOEt/hexane = 1:1) to yield 0.38 g (0.84 mol, 78% yield, 100% de) of **14** as a white solid; mp 65-70°C; $[\alpha]_D^{25}$ = +86.9 (c = 0.47, CH_2Cl_2); ^1H NMR δ 7.67-7.30 (m, 9H), 5.00 (t, 1H, J = 8.5 Hz), 4.82 (s, 1H), 4.70 (t, 1H, J = 8.4 Hz), 4.31 (s, 1H), 4.20 (t, 1H, J = 8.5Hz), 3.20 (AB, 2H, J_{AB} = 9.8 Hz), 2.43 (s, 3H), 1.47 (s, 3H), 0.68

(s, 3H); IR (KBr) δ 1762 (CO lactam), 1352/1161 (SO_2N); MS (NH_3, CI) m/e 97.0 (15%), 98.9 (65%), 106 (10%), 163.9 (14%), 180.9 (34%), 219.9 (17%), 252.8 (100%), 253.9 (15%), 455.2 (0.4%) (M).

(5S,6S,5'S)-6-(5'-phenyl-1'-aza-3'-oxacyclopentyl-2-onyl)-2,2,6-trimethyl-4-*p*-toluenesulfonyl-1,4-diazabicyclo[3.2.0]heptane-7-one 15. Azapenam **14** (46 mg, 0.10 mmol) was dissolved in tetrahydrofuran (1.5 ml) and cooled at -78°C. Potassium bis(trimethylsilyl) amide (0.5M/toluene) (0.80 ml, 0.40 mmol) was added dropwise and then the solution was stirred for 1.15 h at -78°C. N,N-dimethylformamide (0.5 ml) was added followed 5 min after by iodomethane (0.1 ml). The mixture was stirred at -78°C for 3 h and aqueous solution of NH_4Cl (10 ml) was added. The product was extracted with CH_2Cl_2 and dried over $MgSO_4$. Filtration and removal of the solvent on a rotatory evaporator gave 52 mg of a yellow oil. A crude ^1H NMR spectrum showed that only one diastereomer was obtained with 67% of conversion. Chromatography flash on silica gel (AcOEt/hexane = 1:1) gave a mixture of the starting azapenam **14** (11.5 mg, 25% yield, 100% de) and methylated compound **15** (24.5 mg, 52% yield, 100% de) as a yellow oil; ^1H NMR (**31**) 7.79-7.32 (m, 9H), 5.08 (s, 1H), 5.01 (t, 1H, J = 8.5 Hz), 4.71 (t, 1H, J = 8.5 Hz), 4.13 (t, 1H, J = 8.5 Hz), 3.29 (AB, 2H, J_{AB} = 10.6 Hz), 2.46 (s, 3H), 1.47 (s, 3H), 1.24 (s, 3H), 0.58 (s, 3H).

Cleavage of the *p*-toluenesulfonamide group in 14. Azapenam **14** (23 mg, 0.05 mmol) was dissolved in tetrahydrofuran (1 ml) and cooled under argon at -60°C. Sodium naphthalenide (0.4 M/THF) (0.38 ml/0.15 mmol) was added dropwise and the mixture stirred at -60°C for 2 h. After usual workup, 5 mg of **17** (0.017 mmol, 33% yield) was obtained as a colorless oil; ^1H NMR δ 7.44-7.25 (m, 6H), 5.15 (t, 1H, J = 8.3 Hz), 4.75 (t, 1H, J = 8.8 Hz), 4.47 (d, 1H, J = 16.8 Hz), 4.18 (q, 1H, J^1 = 8.7 Hz, J^2 = 7.6 Hz), 3.73-3.68 (m, 2H), 3.47 (d, 1H, J = 16.8 Hz), 1.56 (s, 3H), 1.51 (s, 3H); IR (KBr) δ 1762 (C=O oxazolidinone), 1686 (C=O carbonyl), 1622 (N-CH=N).

Cleavage of the *p*-toluenesulfonamide group in 15. Azapenam **15** (24 mg, 0.05 mmol) was dissolved in tetrahydrofuran (1 ml) and cooled under argon at -60°C. Sodium naphthalenide (0.4M/THF) (0.5 ml, 0.2 mmol) was added dropwise and the mixture was stirred at -60°C for 4 h. After usual workup, 5 mg of **18** (0.016 mmol, 31% yield, 72% de) was obtained as a colorless oil; ^1H NMR (major diastereomer) δ 7.49-7.26 (m, 6H), 5.19 (q, 1H, J^1 = 9 Hz, J^2 = 5.5 Hz), 4.84 (q, 1H, J^1 = 14.7 Hz, J^2 = 7.3 Hz), 4.70 (t, 1H, J = 8.8 Hz), 4.19 (q, 1H, J^1 = 8.6 Hz, J^2 = 5.4 Hz), 3.74 (m, 2H), 1.56 (s, 3H), 1.51 (s, 3H), 1.01 (d, 3H, J = 7.4 Hz); ^1H NMR (minor diastereomer) δ 4.62 (t, 1H, J = 8.8 Hz), 3.52 (AB, 1H, J_{AB} = 15 Hz).

Acknowledgement: Support for this research under Grant No. GM26178 from the National Institutes of General Medical Sciences (Public Health Service) is gratefully acknowledged. Baptiste Ronan would like to thank Rhone Poulenc for support in the form of a fellowship.

References

1. Nagakura, I. *Heterocycles* **1981**, *16*, 1495.
2. (a) Davies, D.; Pearson, M.J. *J Chem. Soc., Perkin Trans. I* **1981**, 2539. (b) Davies, D.; Pearson, M.J. *Special Publication - Ryal Society of Chemistry* **1981**, *38* (Recent Adv. Chem. β-Lactam Antibiot.), 88.
3. Johnson, G.; Rees, P.M.; Ross, B.C. *J. Chem. Soc., Chem. Comm.* **1984**, 970.
4. Shibata, T.; Sugimura, Y.; Sato, S.; Kawazoe, K. *Heterocycles* **1985**, *23*, 3069.

5. (a) Alper, H.; Perera, Ch.P.; Ahmed, F.R. *J. Am. Chem. Soc.* **1981**, *103*, 1289. (b) Alper, H.; Perera Mahatantila, Ch. *Organometallics* **1982**, *1*, 70. (c) Ahmed, F.R. *Acta Cryst.* **1983**, *C39*, 735.
6. (a) Johnson, G.; Ross, B.C. *J. Chem. Soc., Chem. Comm.* **1981**, 1269. (b) Ross, B.C.; Johnson, G. Eur. Pat. Appl. EP 31,509 (Cl. C07D487/04), 08 July 1981 (CA **96**: 35240n).
7. Bose, A.K.; Kapur, J.C.; Fahey, J.L.; Manhas, M.S. *J. Org. Chem.* **1973**, *19*, 3437.
8. (a) Hegedus, L.S.; deWeck, G.; D'Andrea, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122. (b) For reviews on amino carbene complex chemistry see: Schwindt, M.A.; Miller, J.R.; Hegedus, L.S. *J. Organomet. Chem.* **1991**, *413*, 143; Grotjahn, D.B.; Dötz, K.H. *Synlett.* **1991**, 381.
9. ref. 3 allene paper
10. (a) Hegedus, L.S.; Schwindt, M.A.; DeLombaert, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264. (b) Hegedus, L.S.; Lastra, E.; Narukawa, Y.; Snustad, D.C. *J. Am. Chem. Soc.* **1992**, *114*, 2991. (c) Vernier, J.M.; Hegedus, L.S.; Miller, D.B. *J. Org. Chem.* **1992**, *57*, 6914. (d) Lastra, E.; Hegedus, L.S. *J. Am. Chem. Soc* **1993**, *115*, 0000.
11. Miller, J.R.; Pulley, S.R.; Hegedus, L.S.; DeLombaert, S. *J. Am. Chem. Soc.* **1992**, *114*, 5602.
12. Sestrick, M.R.; Miller, M.; Hegedus, L.S. *J Am. Chem. Soc.* **1992**, *114*, 4079.
13. ref. 2 allene (f) Hegedus, L.S.; Montgomery, J.; Nerukawa, Y.; Snustad, D.C. *J. Am. Chem. Soc.* **1991**, *113*, 5784. (g) Thompson, D.K.; Suzuki, N.; Hegedus, L.S.; Satoh, Y. *J. Org. Chem.* **1992**, *57*, 1461. (h) Narukawa, Y.; Juneau, K.N.; Snustad, D.; Miller, D.B.; Hegedus, L.S. *J. Org. Chem.* **1992**, *57*, 5453.
14. Betschart, C.; Hegedus, L.S. *J. Am. Chem. Soc.* **1992**, *114*, 5010.
15. This exceptional rearrangement is precedented in studies of Bischler-Naperelski cyclizations to form 7-membered cyclic imines: Goldman, I.M.; Larson, J.K; Trelter, J.R.; Andrews, E.G. *J. Am. Chem. Soc.* **1969**, *91*, 4941.
16. Ito, Y.; Inubushi, Y.; Zenbayashi, M.; Tomita, S.; Saegusa, T. *J. Am. Chem. Soc.* **1973**, *95*, 4447.
17. The reaction of ketenes with imines is a two step process, requiring the imine to be a nucleophile in the first step, and the imines ion to be an electrophile in the second. Thus the electronic nature of the protecting group on nitrogen can and does have a profound influence on reactivity. For a detailed discussion see reference 13.
18. (a) Searless, S.; Nukina, S. *Chem. Rev.* **1959**, *59*, 1077. (b) Muth, F. in *Methoden Der Organischen Chemie*, Vol. 9, E. Muller, Ed., Houben-Wezl, Stuttgard, 1959, 605.
19. Hamada, T., Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140.
20. (a) Abad, A.; Mellier, D.; Pète, J.P. C. Portella, C. *Tetrahedron Lett.* **1971**, 4555. (b) Yuan, W.; Fearson, K.; Gelb, M.H. *J. Org. Chem.* **1989**, *54*, 906.
21. (a) Sungchul, Ji; Gortler, L.B.; Waring, A.; Battista, A.; Bank, S.; Closson, W.D. *J. Am. Chem. Soc.* **1967**, *89*, 5311. (b) McIntosh, J.M.; Matassa, L.C. *J. Org. Chem.* **1988**, *53*, 4452. (c) Heathcock, C.H.; Blumenkopf, T.A.; Smith, K.M. *J. Org. Chem.* **1989**, *54*, 1548.
22. Ugi, I.; Meyr, R.; Lipinski, M.; Bodesheim, F.; Rosendahl, F. *Organic Synthesis*, *41*, 13.
23. Aumann, R.; Fischer, E.O. *Chem. Ber.* **1988**, *101*, 959.
24. Cavender, C.J.; Shiner, V.J., Jr. *J. Org. Chem.* **1972**, *37*, 3567.