INTERMOLECULAR RHODIUM CARBENOID INSERTIONS INTO THE N-H BOND OF \( \beta \)-LACTAMS.
SYNTHESIS OF 0-2-ISOCEPHEMS

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Abstract - A new, convergent synthesis of 0-2-isocephems is reported. Rhodium carbenoid insertion of \( \alpha \)-diazo-\( \beta \)-ketoesters into the N-H bond of a preformed \( \beta \)-lactam, followed by cyclization of the resulting enol-alcohols by Mitsunobu reaction gives the title compounds.

Introduction

The 0-2-isocephems \( \mathcal{I} \) are a class of \( \beta \)-lactam antibiotics that are effective against many pathogenic bacteria.\(^1\) The chemistry of these compounds, including total synthesis and structure/activity relationships has been studied extensively by the Bristol Canada group.\(^2\) Most reported syntheses of \( \mathcal{I} \) follow the same generalized route, that is, \( \beta \)-lactam formation by cycloaddition of an activated acetic acid derivative \( \mathcal{Z} \) to suitably substituted Schiff bases \( \mathcal{Z} \), (PG = protecting groups) followed by conversion of the 4-styryl group into a leaving group and final ring closure.

Using this generalized approach, chemists at Bristol Canada prepared many variations of \( \mathcal{I} \), however for each new analog synthesized a new Schiff base had to be prepared since the eventual C-3 side chain \( \text{R}_1 \) is an integral part of the starting imine. These syntheses lead to achiral products, with the exception of one example by Tenneson and Belleau\(^3\) who obtained a 90% optical yield of cis lactam \( \mathcal{I} \) \( \text{R}_1 = \text{CH}_3, \text{R}_2 = \text{CH}_2\text{Ph} \) by utilizing an imine derived from D-threonine in the cycloaddition reaction.

We envisioned a potentially more flexible, convergent synthesis of \( \mathcal{I} \) by means of a rhodium carbenoid insertion of an \( \alpha \)-diazo-\( \beta \)-ketoester, suitably substituted at \( \text{R}_1 \) into the N-H bond of a preformed \( \beta \)-lactam. The resulting enol \( \mathcal{A} \) would be cyclized and the carboxylate revealed giving \( \mathcal{I} \).
Potential advantages of this synthesis would include; a) a wide variety of \( R_1 \) analogs (C-3 in 1) could be simply prepared by acetoacetic ester dianion condensation prior to diazo transfer and insertion. b) the synthesis is highly convergent, requiring only cyclization and deprotection following assembly of the two precursors by rhodium carbenoid insertion. c) the synthesis would give rise to enantiomerically pure 1 by starting with an optically pure lactam\(^4\) since no chiral centers of the lactam are created or destroyed in the reaction sequence.

Intermolecular carbenoid insertions into the N-H bonds of \( \beta \)-lactams have been described on two previous occasions. Brooks,\(^5\) repeating the work of Cuffe,\(^6\) reported a 7.5% yield of 5 by insertion of \( \alpha \)-diazo-\( \beta \)-ketoester 6 into 4-acetoxyazetidin-2-one. Miller\(^7\) has reported the preparation of nocardicin analogues by insertion of an \( \alpha \)-diazo-\( \beta \)-aryl ester 7 into the N-H bond of 3-(tert-butoxycarbonylamino)-azetidin-2-one in 26-67% yield. These observations led us to believe that we could insert a variety of \( \alpha \)-diazo-\( \beta \)-ketoesters into the lactam N-H bond in preference to the amide side chain N-H, hence allowing us to have the side chain already in place prior to insertion.

**Discussion and Results**

The rhodium acetate catalyzed decomposition of a number of \( \alpha \)-diazo-\( \beta \)-ketoesters was carried out in the presence of the \( \beta \)-lactam 8. This lactam was readily prepared via cycloaddition of azidoacetic
acid-methanesulphonic acid mixed anhydride and cinnamylidene-N-(4-methoxyphenyl)imine. The desired 4-substituent was elaborated by ozonolysis, sodium borohydride reduction and silylation. The p-methoxyphenyl group was removed by ceric ammonium nitrate oxidation and the 3-azido function was reduced with hydrogen sulfide and acylated with phenoxyacetyl chloride (see Experimental section). Note that 8 and compounds derived from it are all racemic and the stereochemistry depicted for all p-lactams is relative and not absolute.

Reaction of the lactam 8 with t-butyl 2-diazo-3-oxobutyrate (1.2 eq) in dry refluxing benzene in the presence of 5 mole % Rh₂(OAc)₄ afforded the enol ester 9 in 54% isolated yield, thereby confirming the expectation of a selective insertion into the lactam N-H bond in the presence of the side chain N-H amide bond. The structure of 9 was assigned on the basis of its spectroscopic data (IR 3420, 1760, 1685 cm⁻¹; ci-ms 521 (M+1); ei-ms 464 (M'-56), 407 (M'-56-57); the nmr data was consistent with the assigned structure, including an enolic H resonance at 7 12.2, and by its cyclization to the 0-2-isocoumarin 11 via the following sequence: (i) acid catalyzed deprotection of the 4-hydroxymethyl group and, (ii) cyclization of the intermediate enol-alcohol 10 with diethyl azodicarboxylate-triphenylphosphine (DEAD-Ph₃P). The yield for the two-step sequence was 57%. The 0-2-isocoumarin 11 thus obtained showed infrared absorptions of 3405, 1772 and 1700 cm⁻¹, and nmr peaks at 1.50(9H), 2.20(3H), 3.68(1H), 3.90(1H), 4.45(1H), 4.52(2H), 5.45(1H), 6.86-7.34(5H) and displayed a ci-ms peak at m/z 389(M+1). Unfortunately, attempted removal of the t-butyl ester protecting group using trifluoroacetic acid failed to give significant amounts of the desired, known acid 12. (Scheme 1)
We therefore turned to the 2-(trimethylsilyl)ethyl group as a carboxylate protecting function, which is removable with fluoride ion in tetrahydrofuran under mild conditions. 2-(Trimethylsilyl)ethyl acetoacetate, prepared in 87% yield by reaction of 2-(trimethylsilyl)-ethanol with diketene, was subjected to the usual diazo transfer sequence (TsN₃, Et₃N) and the diazo ester (E=H) was inserted into the lactam N-H bond of to give in 40% yield. The desired N-H insertion product was accompanied by a 21% yield of the γ-lactone, the result of an intramolecular insertion into a C-H bond of the methylene group alpha to silicon; 21% of the starting lactam was also recovered.

Scheme 2

The adduct, a clear oil, was desilylated and cyclized as above to afford in 61% yield. Deprotection with tetrabutylammonium fluoride (TBAF) in dry THF gave the 0-2-isocephem acid as a white powder, mp 169-170°C (lit. mp 171-172°C). Its spectroscopic properties were identical to those reported by Doyle. A number of other α-diazo-γ-ketoesters related to were also prepared to test the scope of substituents which do not interfere with the insertion reaction. These esters were prepared by the reaction of the dianion of 2-(trimethylsilyl)ethyl acetoacetate with the appropriate electrophiles, followed by diazo transfer (Scheme 3). The results of both the insertion and subsequent cyclization steps are given in Table 1.

Scheme 3
Diazo esters $\text{13b, c } \text{ and } d$ gave useful yields of insertion products which could be elaborated into 0-2-isocephem. In the case of $\text{13e}$ the major reaction product, isolated in 53% yield, was the bicyclic thiophene derivative $\text{18}$, the result of a formal carbenoid insertion into the heteroaromatic C-H bond alpha to the sulfur atom. Such insertion reactions are relatively rare and only a few examples have been described.$^{16}$ The product $\text{18}$ exists essentially in the enol form; $\text{ir } 1640, 1593 \text{ cm}^{-1}; \text{ci-ms } 297 (M^+1), 269 (M^+1-28)$; $\text{nmr } \delta 1.1 (2H), 2.55 (4H), 4.2 (2H), 6.6 (1H), 6.9 (1H), 12.8 (1H)$. We have recently extended the rhodium carbenoid aromatic C-H insertion reaction to a series of $\alpha$-diazo-$\beta$-sulfonyl esters $\text{19}$ which afford 1,3-dihydrobenzo[c]thiophene-2,2-dioxides $\text{20}$.\(^{17}$

![Chemical structures](image)

Cephalosporins bearing 3-alkenyl substituents have shown exciting antibiotic properties.$^{19}$ Disappointingly, however, attempts to prepare 0-2-isocephem bearing a 3-propenyl group were not successful since the carbenoid derived from $\text{14f}$ gave preferentially the ketene $\text{21}$ which was trapped by the lactam to give $\text{22}$ rather than the desired insertion product.$^{18}$ The $\alpha$-diazo-$\beta$-keto-esters $\text{13c and d}$, prepared from the dianion of $\text{23}$ with acetaldehyde or benzaldehyde, followed by protection of the resulting alcohols as their acetate and TBDMS ether respectively, were investigated as alternate routes to the C-3 alkenyl derivatives. The insertion reactions proceeded reasonably well, and the diastereomeric products were elaborated to their respective 0-2-isocephem $\text{16c and 16d}$. We were unable to eliminate $\text{H}_2\text{O}$ or $\text{HOAc}$ at any stage after the diazo insertion.

Finally, an attempt to prepare 0-2-isocephem possessing a C-3 bromomethyl group (which would allow preparation of 3-alkenyl analogs via Wittig elaboration) was made. Insertion of $\text{13h}$ into $\text{8}$...
unfortunately gave a complex mixture of products, none of which were identifiable.

Table 1

<table>
<thead>
<tr>
<th>E</th>
<th>Yield 14</th>
<th>Yield 15</th>
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<tbody>
<tr>
<td>a -H</td>
<td>40 (51)</td>
<td>61</td>
</tr>
<tr>
<td>b -CH₃Ph</td>
<td>46 (61)</td>
<td>42</td>
</tr>
<tr>
<td>c -CH(OAc)CH₃</td>
<td>33 (53)</td>
<td>64</td>
</tr>
<tr>
<td>d -CH(O-TBDM)Ph</td>
<td>35 (40)</td>
<td>20%</td>
</tr>
<tr>
<td>e -3-thienylmethyl</td>
<td>172 (37)</td>
<td>68</td>
</tr>
<tr>
<td>f -CHCH₃</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>g -CH(O-TBDM)-3-pyridyl</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>h -Br</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

1) Yields refer to isolated yields; yield based on recovered lactam in brackets.
2) Most diazo compound reacted intramolecularly, see text.
3) Only products derived from Wolff rearrangement were observed.
4) Starting materials were recovered.
5) No identifiable products.
6) O-desilylated side chain.
7) Yields are for 2-steps from 14, and are isolated.

EXPERIMENTAL

Proton nmr spectra were recorded in CDCl₃ with a Varian XL 300 or EM 360 spectrometer (chemical shifts are given in ppm from tetramethylsilane) unless otherwise indicated, infrared spectra with a Perkin-Elmer 783 spectrophotometer, and mass spectra with a VG ANALYTICAL 7070E mass spectrometer (el-ms-70eV, ci-ms-70eV ionizing potential, ether was used as reagent gas). Flash chromatography was performed with Merck 9385 silica gel; HPLC separations were performed with a Waters PREP LC/ system 500 using a PrepPAK-500 silica column. Melting points were determined on a Gallenkamp apparatus, and are uncorrected. Solvents were dried prior to use; benzene and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl; methylene chloride from phosphorous pentoxide and stored over 4A* molecular sieves.

3-Phenoxyacetamido-4-tertbutylidimethylsilyloxymethylazetidin-2-one 8. Freshly distilled methanesulfonyl chloride (6.873 g, 60 mmole) was added dropwise to a stirred solution of azidoacetic acid hemihydrate (6.6 g, 60 mmole) and Et₃N (6.07 g, 60 mmole) in 50 mL of dry CH₂Cl₂ at 0°C. The mixed anhydride solution was stirred for 10 min and added to a stirred solution of cinnamylidene-N-(4-methoxyphenyl)imine (14.22 g, 60 mmole) and Et₃N (12.14 g, 120 mmole) in 200 mL of dry CH₂Cl₂ at 0°C. The resulting solution was stirred for 18h at room temperature and washed successively with H₂O, 5% HCl, 5% NaHCO₃, then dried over MgSO₄ and evaporated to give 17.3 g of crude β-lactam. Recrystallization from warm EtOAc gave 10.0 g β-lactam as a tan powder (52%); mp 104-105°C (lit. mp 106°C).
The β-lactam was dissolved in 250 ml of dry CH₂Cl₂. Et₃N (3.16 g, 1 equiv) was added and the mixture was stirred at 0°C while H₂S was bubbled in at a fast rate for 10 min. The solution was stored for 1 h and the solvent evaporated to give an orange solid. This solid was dissolved in 100 ml of dry CH₂Cl₂ containing 4-dimethylaminopyridine (DMAP) (381 mg, 0.1 equiv) and Et₃N (3.16 g, 1 equiv). The solution was cooled in ice and phenoxycarbonyl chloride (5.326 g, 1equiv) dissolved in 10 ml of dry CH₂Cl₂ was added over 20 min. The resulting thick white slurry was stirred for 3 h, then filtered to give 13.05 g of crude acylated material as a white powder (contaminated with sulfur). A small sample was recrystallized from CH₂Cl₂-hexane, mp 213-214°C; ir (KBr), 3305, 1760, 1665 cm⁻¹; el-ms 428 (M⁺), 277 (M⁺-151), 236 (M⁺-192); nmr δ 3.75 (s, OCH₃), 4.46 (ABq, OCS, J=15 Hz), 4.95 (m, C4-H), 5.54 (dd, olefinic H, J=6.6, 16.2), 6.7-7.40 (m, 15H). Anal. Calcd. for C₂₆H₂₈N₂O₂: C, 72.90; H, 5.61. Found: C, 72.54; H, 5.93.

The crude material was dissolved in a mixture of 700 ml of CH₂Cl₂ - 150 ml of CH₃OH, cooled to -78°C (dry ice-acetone) under N₂ and ozonized until blue. The excess O₂ was purged with N₂, and NaBH₄ (2.3 g, 60.8 mmole) was added. The dry ice bath was replaced by an ice bath and the mixture was stirred for 1 h, followed by neutralization with Amberlite IR-120(H⁺), filtration and evaporation. The resulting off-white solid was triturated with hexane-ether (1:1), filtered and dried to give 9.93 g of pure alcohol (89%, 2 steps from azido-lactam); mp 161-163°C; ir (CHCl₃) 3610, 3400, 1755, 1690 cm⁻¹; el-ms 356 (M⁺), 338 (M⁺-18); nmr (acetone d₆) δ 3.74-3.79 (m, 4H, OCH₃, CSH, δdB), 4.31 (dd, CHOH, J= 2.6, 12.7Hz), 4.49 (m, C4-H), 4.60 (ABq, PhOCH₂, J=15 Hz) 5.64 (dd, C3-H, J = 5.6, 10 Hz), 6.92 - 7.48 (m, 9H, aromatics), 8.25 (br.d., amide NH, J =10 Hz). Anal. Calcd. for C₁₉H₂₀N₂O₆: C, 64.04; H, 5.66. Found: C, 63.98; H, 5.93.

The alcohol was protected as a TBDMS ether by dissolution in 25 ml of dry DMF followed by addition of imidazole (4.75g, 2 equiv) and TBDMS-chloride (5.05 g, 1.2 equiv). The solution was allowed to stand at room temperature for 12 h, then poured into ether-water, separated, the organic layer dried over MgSO₄ and evaporated to give 14 g of crude silyl ether. This was recrystallized from warm hexane - EtOAc (25:15) to give 11.56 g of pure silyl ether (88%); mp 149-149°C; el-ms 470(M⁺), 413 (M⁺-57), 280(M⁺-190); ir (CHCl₃) 3400, 1755, 1680, 1512 cm⁻¹; nmr δ-0.33 (s, SiCH₃), -0.21 (s, SiCH₂), 0.75 (s, SiC(CH₃)₃), 3.69 (d, CHOSi, J=12 Hz), 3.77 (s, OCH₃), 4.15 (d, CHOSi, J=12 Hz), 4.30 (m, C4-H), 4.55 (ABq, PhOCH₂, J=15 Hz), 5.73 (dd, C3-H, J=5.2, 10.8 Hz), 6.84-7.34 (m, 9H, aromatics) 7.63 (d, amide NH, J=10.8 Hz). Anal. Calcd. for C₂₅H₃₄N₂O₅Si: C, 63.80; H, 7.28. Found: C, 64.11; H, 7.48.

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The silyl ether was N-dearylated by the method of Kronenthal. Thus, the silyl ether was dissolved in 250 ml of CH₃CN and cooled to -5°C. A solution of ceric ammonium nitrate (40.22g, 3 equiv in 365 ml of H₂O) was added over 5 min to the stirred solution of the silyl ether, then stirred for a further 25 min at 0°C. The mixture was diluted with 500 ml of H₂O and extracted with EtOAc (3x300 ml), the extract was washed with 5% NaHCO₃ and brine. The resulting organic layer was dried over MgSO₄ and evaporated to afford 9.6g of crude lactam as a brown solid.

Trituration with cold ether followed by filtration gave 5.2g of pure 8 (58%) as a white powder. A small sample was recrystallized from hexane - EtOAc (3:1); mp 125-126°C; ir(CHCl₃) 3410, 1775, 1685 cm⁻¹; el-ms 307 (M⁺-57), 264 (M⁺-57-43); nmr δ 0.1 [s, Si(CH₃)₂], 0.9 [s, SiCl(CH₃)₂], 3.7-4.0 (m, CH₂O,C₄-H), 4.4 (s, PhOC₂H), 5.5 (dd, C₃-H, J=5.7 Hz), 6.2 (br, lactam N-H), 6.7-7.6 (m, 6H, Ph, amide N-H). Anal. Calcd. for C₁₈H₂₆N₂O₄Si: C, 59.31; H, 7.74. Found: C, 59.52; H, 7.99.

General Procedure for Diazotransfer: Preparation of t-Butyl 3-oxo-2-diazo butyrate.

A solution of t-butyl acetoacetate (316.4mg, 2 mmole) in 8 ml of CH₃CN was stirred at room temperature and Et₃N (202mg, 2 mmole) was added, followed by addition of tosyl azide (394 mg, 2 mmole). The reaction mixture was stirred for 2h and the solvent was evaporated. The resulting residue was dissolved in 10 ml of ether, washed with 5 ml of 10% KOH, H₂O, dried over MgSO₄ and evaporated to give 318 mg of diazo ester (86%, yellow oil); ir (neat) 2120, 1712, 1655 cm⁻¹; nmr δ 1.5 [s, ClCH₂], 2.43 [s, CH₂], 2.23 [s, COCH₃], 3.33 [s, CH₂CO], 4.13 (dd, OCH₂).

2-(Trimethylsilyl)ethyl Acetoacetate 23

A mixture of 2-(trimethylsilyl)ethanol (4.0g, 33.8 mmole) and 20 mg of NaOAc was heated to 80°C, the heating bath was removed and diketene (3.0g, 1.06 equiv) was added dropwise with stirring. The stirring was continued for 30 min after addition, and the resulting brown solution was distilled under vacuum to give 5.94g of pale yellow oil (bp 74°C/0.15mm, 87%); ir (neat) 2960, 1740, 1650 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.96 (dd, CH₂Si), 2.23 [s,COCH₃], 3.33 [s, CH₂CO], 4.13 (dd, OCH₂).

Preparation of α-Diazo-β-ketoester 13a-h

The dianion of 23 was generated according to the method of Weiler (NaH, nBuLi), and was alkylated with the appropriate electrophiles:

Compound 13a (E=H) was prepared by diazo transfer reaction of 23 in 68% yield (after chromatography) as a yellow oil; ir (neat) 2955, 2120, 1715, 1660 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.95 (dd, SiCH₂), 2.46 [s, COCH₃], 3.66 (dd, CH₂O).
Compound 13b (E=CH₂Ph) was prepared by reaction of 8 mmole of dianion of 23 with 12 mmole of PhCH₂Cl for 30 min; yield 1.82g as clear oil (78%); bp 160-163°C/0.2mm; ir (neat) 2950, 1740, 1715, 1645 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.96 (dd, SiCH₂), 2.9 (s, PhCH₂CH₂), 3.4 (s, CH₂CO), 4.2 (dd, CH₂O), 7.2 (s, Ph).

Diazo transfer gave 13b in 96% crude yield which was used without further purification; ir (neat) 2950, 2115, 1710, 1655 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.96 (dd, SiCH₂), 2.6-3.2 (m, 4H), 4.2 (dd, CH₂O), 7.2 (s, Ph).

Compound 13c (E=CH(OAc)CH₃) was prepared by reaction of 15 mmole of dianion of 23 with 60 mmole of CH₂CHO for 40 min; yield 2.13g as clear oil (58%) of alcohol isolated by HPLC (2 hexane: 1 EtOAc); ir (neat) 3110, 2930, 1735, 1710 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.96 (dd, SiCH₂), 1.2 (d, CH₃, J=7Hz), 2.1-2.8 (m, 4H), 3.4 (s, CH₂CO), 4.2 (dd, CH₂O). Diazo transfer was accomplished in 95% crude yield, the product was used as such: ir (neat) 3450, 2100, 1710, 1650 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.96 (dd, SiCH₂), 1.2 (d, CH₃, J=7Hz), 2.0 (s, COCH₃), 2.9 (d, CH₂CO, J=7Hz), 4.2 (dd, CH₂O), 4.0 (br, CH). A 1.09g sample was acetylated by addition of 2 equiv CH₃COCl to a stirred solution of the alcohol and 1 equiv of pyridine in 15 ml of CH₂Cl₂. The solution was stirred for 15 min, poured into 15 ml of water, separated and the organic extracts were dried over MgSO₄, and evaporated. Chromatography with hexane-EtOAc (9:1) gave 1.04g of protected diazo alcohol 13c as a clear colorless oil (83%); ir (neat) 3295-3600, 2950, 1740, 1710, 1655 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.96 (dd, SiCH₂), 1.2 (d, CH₃, J=7Hz), 2.0 (s, COCH₃), 2.9 (d, CH₂CO, J=7Hz), 4.2 (dd, CH₂O), 5.2 (dd, CH). Compound 13d (E=CH(OAc)O(TBDMS)Ph) was prepared by reaction of 5 mmole of dianion of 23 with 3.5 mmole of PhCHO for 30 min; yield 972 mg of clear oil (63%) isolated by chromatography with (5:1) hexane EtOAc; ir (neat) 3350-3600, 2950, 1740, 1700 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.96 (dd, CH₂Si), 2.8 (d, CH₂CH₂, J=7Hz) 3.3 (s, CH₂CO), 4.2 (dd, CH₂O), 5.2 (t, CH), 7.2 (s, Ph). Diazo transfer was performed on 700mg of the above alcohol to give 695mg of crude diazo compound (91%) subsequently used as such: ir (neat) 3350-3600, 2950, 2120, 1740, 1710, 1650 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.96 (dd, CH₂Si), 3.2 (d, CH₂CO J=7Hz), 3.5 (br, OH), 4.3 (dd, CH₂O), 5.2 (t, CH), 7.2 (s, Ph). A 673mg of sample was 0-t-butyldimethylsilylated by dissolution in 8ml of CH₂Cl₂ at 0°C followed by treatment with 2 equiv of 2,6lutidine and 1.2 equiv of TBDMS-triflate for 30 min. The mixture was poured into 10 ml of cold 1% HCl, separated, the organic layer dried over MgSO₄, and evaporated. Column chromatography with hexane - EtOAc (95:5) gave 735mg (81%) of pure protected diazo compound 13d as a yellow oil: ir (neat) 2950, 2120, 1740, 1650 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃, Si(CH₃)₂], 0.9 [s, SiC(CH₃)₂], 0.96 (dd, CH₂Si), 2.8 (dd, 1H, CH₂CO J=14, 4 Hz), 3.6 (dd, 1H, CH₂CO, J=14, 8 Hz), 4.3 (dd, CH₂O), 5.2 (dd, H, J=8, 4Hz), 7.2 (s, Ph).

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Compound 13 **E=(3-thienylmethyl)** was prepared by reaction of 4 mmole of the dianion of 23 with 4.4 mmole of 3-bromomethylthiophene for 30 min: yield 490mg of yellow oil (41%) isolated by column chromatography hexane-EtOAc (9:1); ir (neat) 2950, 1740, 1715 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.9 (dd, SiCH₂), 2.8 (s, Th-CH₂CH₂), 3.3 (s, CH₂CO), 4.1 (dd, CH₂O), 6.8 (br.s., 2H), 7.1 (br.s., 1H). Diazo transfer was effected in 79% yield after column chromatography with hexane-EtOAc (9:1); ir (neat) 2950, 2115, 1710, 1655 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.95 (dd, SiCH₂), 2.8-3.2 (m, 4H), 4.3 (dd, CH₂O), 5.2 (d, CH₂CO), 7.2 (br.s., 1H).

Compound 13f (**E=CHCH₃**) was prepared by dehydration of the precursor of 13c. Thus 3.4 mmole of diazomethane in 10ml of dry CH₂Cl₂ was stirred at 0°C with 2 equiv. Et₃N and 1 equiv of CH₃SO₂Cl was added. The mixture was stirred at room temperature for 18h, washed with 10% HCl, water, and dried over MgSO₄ then evaporated to give 780mg of orange oil. This was chromatographed with hexane-EtOAc (95:5) to give 640mg of pure olefin (74%) as a yellow oil; ir (neat) 2950, 2118, 1715, 1660, 1615 cm⁻¹; nmr δ 0.1 [s, SiCH₃], 0.95 (dd, SiCH₂), 1.9 (d, CHCH₃, J=8.3 Hz), 4.2 (dd, CH₂O), 7.1 (s, CHCO), 7.2 (br.s., 5H, pyridyl). Diazo transfer afforded the diazo alcohol in 78% yield as a yellow oil; ir (neat) 3400-3500, 2120, 1705, 1640 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.96 (dd, CH₂Si), 3.2 (s, COCH₂CO), 4.3 (dd, CH₂O), 5.2 (t, CH), 7.0-8.5 (m, 5H, pyridyl). This diazo alcohol was O-t-butyldimethylsilylated (by the same procedure as for 13d) to give 13g as a yellow oil in 38% yield. ir (neat) 2950, 2120, 1710, 1650 cm⁻¹; nmr δ 0.1 [s, Si(CH₃)₃], 0.96 (dd, CH₂Si), 3.2 (d, CH₂CO), 4.2 (dd, CH₂O), 5.2 (t, CH), 7.0-8.5 (m, 5H, pyridyl!).

Compound 13h₂¹ **(E=Br)** was prepared by reaction of 13a (1 mmole) in 8ml of CCl₄ at 0°C with 1.2 equiv. Et₃N and 1.1 equiv. TMS-triflate, followed by stirring at room temperature for 30 min, after which a floating layer of Et₃N-triflate was removed by pipette. A solution of 1 mmole of Br₂ in 3ml of CCl₄ was added dropwise, the mixture stirred at room temperature for 5 min and evaporated. The crude product was eluted through a short plug of silica gel with hexane-EtOAc (95:5) to give 310mg of pure bromo compound 13h as a light yellow oil (100%); ir (neat) 2950, 2120, 1710, 1655 cm⁻¹ nmr δ 0.1 [s, Si(CH₃)₃], 1.08 (dd, CH₂Si), 4.38 (dd, CH₂O), 4.42 (s, CH₂Br); ci-ms 307,309 (M⁺+1).
General Procedure for Diazo Insertion Reactions: 14a (Insertion of 13a into 8)

A solution of 0.824 mmole of 8 in 7ml of dry benzene was warmed to effect dissolution. Diazocompound 13a (0.99mmole, 1.2 equiv) was added and the solution was brought to reflux, allowing some benzene vapours to escape (in an effort to remove possible traces of water) and Rh$_2$(OAc)$_4$ (18mg, 5 mole % based on lactam) was added in one portion. The solution was refluxed for 1h.

Vigorous gas evolution occurred during the initial stages of the reaction. The reaction mixture was cooled, filtered and evaporated to give 525mg of green oil. The oil was dissolved in 4ml of warm hexane-EtOAc (3:1) and allowed to cool, 65mg of pure 8 was recovered by filtration. The mother liquor was evaporated and subjected to column chromatography with hexane-EtOAc (2:1). Two fractions were recovered, $R_f = 0.62$ (41mg) 15 and $R_f = 0.41$ (187mg) 14a (40%). This compound crystallized on standing; mp 98-100°C; ir (CHCl$_3$) 3418, 2960, 1760, 1685 cm$^{-1}$; ci-ms 565 (M$^+1$), 537 (M$^+1-28$). Anal. Cald. for C$_{27}$H$_{44}$N$_2$O$_7$Si$_2$: C, 57.42; H, 7.85. Found: C, 57.56; H, 8.12.

Compound 14b (Insertion of 13b into 8) Treatment of 0.824 mmole of 8 with 0.99 mmole of 13b as above gave 71mg of 8 (23%) and 250mg of 14b (46%) as a yellow oil after chromatography; ir (CHCl$_3$) 3420, 2960, 1760, 1685 cm$^{-1}$; ci-ms 655 (M$^+1$), 627 (M$^+1-28$).

Compound 14c (Insertion of 13c into 8) Treatment of 1.86 mmole of 8 with 2.23 mmole of 13c as above gave 254mg of 8 (38%) and 400mg of 14c (33%) as a yellow oil after chromatography; ir (CHCl$_3$) 3400, 2950, 1760, 1725, 1675, 1650 cm$^{-1}$; ci-ms 651 (M$^+1$), 623 (M$^+1-28$).

Compound 14d (Insertion of 13d into 8) Treatment of 1.25 mmole of 8 with 1.5 mmole of 13d as above gave 60mg of 8 (13%) and 340mg of 14d (35%) as a white foam after chromatography; ir (CHCl$_3$) 3420, 2960, 1765, 1685, 1600 cm$^{-1}$; ci-ms 785 (M$^+1$), 757 (M$^+1-28$).

Compound 14e (Insertion of 13e into 8) Treatment of 0.775 mmole of 8 with 0.93 mmole of 13e as above gave 152mg of 8 (54%) and 89mg of 14e (17%) as an orange gum after chromatography; ir (CHCl$_3$) 3420, 2950, 1760, 1685, 1600 cm$^{-1}$; ci-ms 661 (M$^+1$), 633 (M$^+1-28$). Also isolated was 145mg (53%) of 18 as a green oil (See Text).

Compound 14f (Insertion of 13f into 8) Treatment of 1.9 mmole of 8 with 2.28 mmole of 13f as above gave 472mg of 82 (42%) as a yellow oil after chromatography, identified by ci-ms 591 (M$^+1$), 563 (M$^+1-28$); ir (CHCl$_3$) 3400, 2925, 2960, 1800, 1735, 1690, 1600 cm$^{-1}$.

Compound 14g (Insertion of 13g into 8) Treatment of 0.55 mmole of 8 with 0.66 mmole of 13g as above gave back unchanged starting materials.
Compound 14h (Insertion of 13h into 8).

Treatment of 0.168 mmole of 8 with 0.20 mmole of 13h as above gave 117 mg of green oil, from which no identifiable products could be isolated.

General Procedure for Desilylation-Cyclization Sequence: Preparation of 11

A 43\mu\text{L} aliquot of 6N HCl (0.26 mmole, 3 equiv) was added to a stirred solution of 45 mg of lactam 9 (0.087 mmole) in 2 ml of CH₃OH at room temperature, and stirred until TLC analysis revealed that the starting material was no longer present (~3h). Powdered NaHCO₃ (3.5 equiv) was added in one portion and the mixture was evaporated to dryness. The residue was taken up in CH₂Cl₂, filtered and evaporated to give the crude enol-alcohol 10 (~quant) which was used in the following step. The crude enol-alcohol 10 was dissolved in 1 ml of dry THF and stirred at room temperature. Solid Ph₃P (1 equiv) was added to the above solution followed by DEAD (1 equiv), and the reaction mixture was stirred for 30 min, then evaporated to give 79 mg of brown foam. Column chromatography with hexane-EtOAc (2:1) gave 19 mg of pure 11 (57%) as a white powder: mp 120-121°C; ir (CHCl₃) 3405, 1772, 1700 cm⁻¹; ci-ms 389 (M⁺+1), 333 (M⁺+1-56). Anal. Calcd. for C₉₀H₇₄N₂O₆: C, 61.86; H, 6.23. Found C, 62.16; H, 6.49.

Preparation of 16a (E=H)

Treatment of 164 mg of 14a as above gave 131 mg of crude enol-alcohol, cyclization gave 260 mg of brown foam. Chromatography with hexane-EtOAc (2:1) gave 77 mg of pure 16a (61%) as a clear colorless oil; ir (CHCl₃) 3400, 1775, 1710 cm⁻¹; ci-ms 432 (M⁺), 389 (M⁺-28-15).

Preparation of 16b (E=CH₂Ph)

Desilylation of 191 mg of 14b gave 220 mg of crude enol-alcohol. This was purified by chromatography to give 92 mg of pure enol-alcohol (58%) as a clear colorless oil which was cyclized to give 65 mg pure 16b (73%) as a clear colorless oil. ir (CHCl₃) 3405, 1773, 1698, 1610, 1600 cm⁻¹; ci-ms 523 (M⁺+1), 495 (M⁺+1-28).

Preparation of 16c (E=CH(OAc)CH₃)

Treatment of 385 mg of 14c as above gave 620 mg of crude cyclic material as a pink oil. Column chromatography with hexane-EtOAc(2:1) yielded 172 mg of pure 16c (56%) as a clear colorless oil; ir (CHCl₃) 3405, 1763, 1730, 1690, 1615, 1600 cm⁻¹; ci-ms 519 (M⁺+1), 491 (M⁺+1-28).

Preparation of 16d (E=CH(OH)Ph)

Desilylation of 326 mg of 14d with 6 equiv of 6N HCl gave 285 mg of pink foam, which was a mixture of products. Chromatography with hexane-EtOAc(2:1) provided 86 mg of pure enol-diol as a white foam (37%). This was cyclized as above to give 43 mg of pure 16d (52%) as a clear oil after chromatography; ir (CHCl₃) 3500-3300 br, 3000, 2950, 1775, 1730, 1685, 1610, 1600 cm⁻¹; ci-ms 539 (M⁺+1), 521 (M⁺+1-18), 511 (M⁺+1-28), 493 (M⁺+1-18-2).
Preparation of 16e (E=3-thienylmethyl)

Treatment of 83 mg of 14e as above gave 73 mg of crude enol-alcohol which was of purified prior to cyclization by column chromatography with hexane-EtOAc (1:1) to afford 55 mg pure enol-alcohol (80%) as a clear oil. This was cyclized to give 45 mg of pure 16e (85%) as a clear colorless oil after chromatography with hexane-EtOAc (2:1); IR (CHCl₃) 3405, 3000, 2960, 1775, 1700, 1610, 1600 cm⁻¹; CI-MS 529 (M⁺1), 501 (M⁺1-28).

General Procedure for Removal of 2-(Trimethysilyl)ethyl Protecting Groups: Preparation of 17a (E=H). A 72 μL aliquot (1.1 equiv) of 1.0 M TBAF solution in THF (Aldrich) was added to a stirred solution of 24 mg of 16a in 1 mL of dry THF. After 5h TLC analysis revealed presence of starting material, therefore another 0.5 equiv TBAF were added. The deprotection was complete in 30 min. The solution was poured into 4 mL of EtOAc and washed with 2 mL of 0.3 M H₂SO₄. The organic layer was dried over MgSO₄ and evaporated, leaving an off-white powder. Recrystallization from acetone-ether gave 18 mg of 17a (~ 98%) as a white powder; mp 169-170°C (lit. 171-172°C)¹⁵; IR (nujol) 3420, 1750, 1700, 1650, 1600 cm⁻¹; CI-MS 288 (M⁺-44).

Preparation of 17b (E=CH₂Ph)

Deprotection of 68.5 mg of 16b gave 46 mg (84%) of pure 17b as a white powder from acetone-ether; mp 161-163°C (lit. 162-163°C)¹⁵; IR (CHCl₃) 3400, 1775, 1690, 1600 cm⁻¹; CI-MS 423 (M⁺1), 379 (M⁺1-44), 329 (M⁺-93).

Preparation of 17e (E=3-Thienylmethyl)

Deprotection of 45 mg of 16c gave 30 mg of pure (83%) 17e as tan crystals after recrystallization from ether-acetone. mp 152-153°C (dec.); IR (CHCl₃) 3400, 3010, 1773, 1690, 1600, 1520 cm⁻¹; CI-MS 429 (M⁺1), 385 (M⁺1-44), 335 (M⁺-93).
TABLE 2

Nuclear Magnetic Resonance Data for Monocyclic p-Lactams

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>AROMATIC</th>
<th>C(3)H</th>
<th>PhOCH₂</th>
<th>C(4)H</th>
<th>CH₂OTBDMS</th>
<th>OTHERS</th>
</tr>
</thead>
</table>
| 9        | 6.88-7.30 (m,6H)
          |          | 5.44  | 4.51   | 4.10  | 3.73-3.85 (dd,J=12,4) | 0.02(s,6H), 0.82(s,9H), 1.48(s,9H), 2.12(s,3H), 12.23(s,1H) |
| 14a      | 6.86-7.34 (m,6H)
          |          | 5.50  | 4.51   | 4.15  | 3.73-3.85 (dd,J=12,4) | 0.02(s,6H), 0.03(s,9H), 1.04(m,2H), 2.14(s,3H), 4.24(m,2H), 12.2(s,1H) |
| 14b      | 6.88-7.34 (m,11H)
          |          | 5.54  | 4.51   | 4.12  | 3.69-3.82 (dd,J=12,4) | 0.02(s,6H), 0.03(s,9H), 0.73(s,9H), 1.07(t,2H), 1.86-3.20(m,4H), 4.30(m,2H), 12.56(s,1H) |
| 14c      | 6.89-7.33 (m,5H)
          |          | 5.53  | 4.55   | 4.13  | 3.75-3.90 (m,2H)      | 0.02(s,6H), 0.03(s,9H), 0.79(s,9H), 1.05(m,2H), 1.32(d,3H), 7.13(m,7), 2.00(s,3H), 2.9-3.25(m,2H), 4.27(m,2H), 5.10(m,1H), 7.8(d,J=8,9H), 12.19(s,1H) |
| 14d      | 6.95-7.42 (m,10H)
          |          | 5.48  | 4.56   | 4.28  | 3.73-4.03 (dd,J=12,4) | 0.03(s,9H), 2.51(d,1H), 3.16(dd,1H), 4.38(m,2H), 5.20(dd,1H), 7.11(d,J=14,4), 8.32(d,J=8,9H) |
| 14e      | 6.88-7.34 (m,9H)
          |          | 5.48  | 4.51   | 4.09  | 3.67-3.79 (dd,J=12,4) | 0.02(s,6H), 0.03(s,9H), 0.76(s,9H), 1.04(m,2H), 2.84-3.08(m,4H), 4.25(m,2H), 12.4(s,1H) |

1. Includes NH of amide
2. Mixture of diastereomers
3. O-desilylated, recorded in acetone d₆
### TABLE 3

**Nuclear Magnetic Resonance Data for Bicyclic \( \beta \)-Lactams**

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<tr>
<th>COMPOUND</th>
<th>AROMATIC</th>
<th>C(7)H</th>
<th>PhOC(6)A</th>
<th>C(1)H(_{6})</th>
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<td>6.86-7.34</td>
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<td>4.52</td>
<td>4.45, 3.68</td>
<td>3.90</td>
<td>1.50(s, 9H), 2.20(s, 3H)</td>
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<td></td>
<td>(m, 6H)(^1)</td>
<td>(t, J = 5)</td>
<td>(s)</td>
<td>(dd, J = 11.4)</td>
<td>(t, J = 11)</td>
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</tr>
<tr>
<td>16a</td>
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<td>6.86-7.34</td>
<td>5.44</td>
<td>4.51</td>
<td>4.44, 3.67</td>
<td>3.86</td>
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<td></td>
<td></td>
<td>(m, 5H)</td>
<td>(dd, J = 5, 6)</td>
<td>(s)</td>
<td>(dd, J = 10.8, 9.9)</td>
<td>(d, J = 7, 9.8)</td>
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<tr>
<td>16b</td>
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<td>4.52</td>
<td>4.45</td>
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<td>3.84</td>
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<td>(s)</td>
<td>(m)</td>
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<td>(t, J = 10)</td>
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<td>(s)</td>
<td>(dd, J = 10.8, 3.9)</td>
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<td></td>
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<td>(AB, J = 14)</td>
<td>(dd, J = 10.8, 9.8)</td>
<td>(m)</td>
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<td>17b(^3)</td>
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<td>(s)</td>
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\(^1\) includes NH of amide  
\(^2\) mixture of diastereomers  
\(^3\) recorded in acetone \( d_6 \)
ACKNOWLEDGEMENTS

The financial support of NSERC (Canada) is gratefully acknowledged. Helpful discussions with Dr. H. Mastalerz, Bristol Laboratories, Canada and the assistance of N. Etkin are greatly appreciated.

REFERENCES AND NOTES


Received, 13th April, 1987