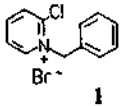
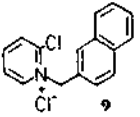
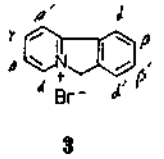
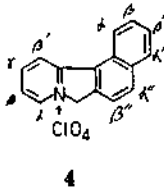


**Table 1.** Spectroscopic Properties of *N*-Arylmethyl-2-chloropyridinium and Substituted Isoindolium Salts

Compound	<sup>1</sup> H NMR (80 MHz) (TFA-D, vs. TMS, in ppm)	Ms ( <i>m/e</i> , intensity)	UV (λ <sub>max</sub> , log ε H <sub>2</sub> O)	IR (KBr, cm <sup>-1</sup> )
	6.02(s, 2H, CH <sub>2</sub> ) 7.42-7.80(m, 5H, ArH) 8.00-8.70(m, 3H, PyH) 8.90(d, J = 6.0 Hz, 1H, α-PyH)	115(17%, C <sub>5</sub> H <sub>4</sub> N <sup>37</sup> Cl <sup>+</sup> ) 113(50%, C <sub>5</sub> H <sub>4</sub> N <sup>35</sup> Cl <sup>+</sup> ) 91(100%, C <sub>7</sub> H <sub>7</sub> <sup>+</sup> )	275.8 nm (3.89)	3078 3035 2970 1612 1570
	6.20(s, 2H, CH <sub>2</sub> ) 7.40-8.50(m, 10H, Ar) 9.80(d, J = 6.3 Hz, 1H, Pyr. α-H)	141(36%, C <sub>11</sub> H <sub>9</sub> <sup>+</sup> ) 115(10%, C <sub>5</sub> H <sub>4</sub> N <sup>37</sup> Cl <sup>+</sup> ) 113(30%, C <sub>5</sub> H <sub>4</sub> N <sup>35</sup> Cl <sup>+</sup> )	274.0 nm (4.04)	3078 3055 2970 2935 1612
	6.00(s, 2H, CH <sub>2</sub> ) <sup>*</sup> 7.80(m, 1H, β-pyrH) 7.83(m, 2H, β'-pyrH + β'-ArH) 7.95(t, J = 6.0 Hz, 1H, γ-pyrH) 8.22(d, J = 9.0 Hz, 1H, α'-ArH) 8.47(d, J = 9.0 Hz, 1H, α-ArH) 8.60(t, J = 9.0 Hz, 1H, β-ArH) 9.11(d, J = 6.0 Hz, 1H, α-pyrH)	168(10%, M <sup>+</sup> -Anion) 167(100%, M <sup>+</sup> -1, Pseudo Aromatic)	255.0 nm (4.11) 312.4 nm (4.01)	3020 2943 2893 1632 1562
	6.00(s, 2H, CH <sub>2</sub> ) <sup>*</sup> 7.76(m, 1H, β-pyrH) 7.91(t, J = 6.0 Hz, 1H, γ-pyrH) 7.88(m, 2H, β'-pyrH + α''-ArH) 8.12(m, 1H, β'-ArH) 8.30(d, J = 9.0 Hz, 1H, β''-ArH) 8.56(d, J = 9.0 Hz, 1H, α'-ArH) 8.64(t, J = 9.0 Hz, 1H, β-ArH) 8.88(d, J = 9.0 Hz, 1H, α-ArH) 9.11(d, J = 6.0 Hz, 1H, α-pyrH)	218(20%, M <sup>+</sup> -Anion) 217(100%, M <sup>+</sup> -1, Pseudo Aromatic)	253.8 nm (4.16) 326.8 nm (3.70)	3086 3070 3051 2928 1628 1589

\* : 300 MHz <sup>1</sup>H NMR.

(4) (see Figure 2 and Table 1). A doublet peak for α-proton of pyridinium ring appeared in the low field (at δ, 9.11, J = 6.0 Hz) and a multiplet peak for β-proton of pyridinium ring appeared in high field somehow (at δ, 7.76). A triplet peak for γ-proton of pyridinium ring appeared at high field (at δ, 7.91) with J equal 6.0 Hz. The remaining three doublet peaks at δ, 8.88, 8.56 and 8.30 indicated α-, α'- and β''-proton of naphthyl ring respectively (all J = 9.0 Hz). A triplet peak at δ, 8.64 coupled with α-proton of naphthyl ring indicated β-proton of naphthyl ring. Two multiplet peaks at δ, 8.12 (1H) and 7.88 (2H) appeared for β'- and α''-proton of naphthyl ring and β'-proton of pyridinium ring respectively. The molecular cation constitution was also confirmed by mass determination of the molecular ion at *m/e* 218 which revealed the composition of C<sub>16</sub>H<sub>12</sub>N (218.275).

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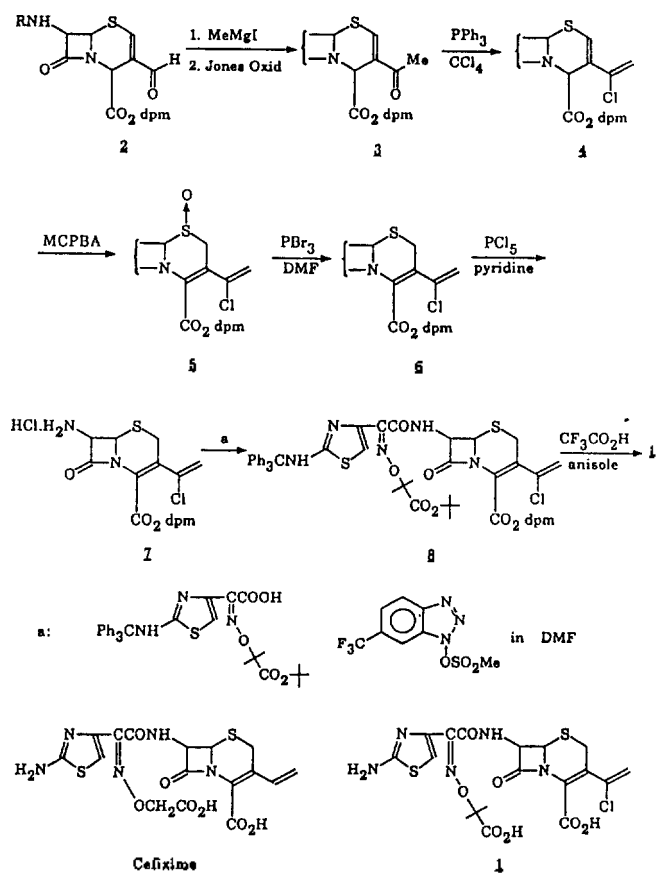
### Synthesis of a Novel 3-(1'-Chloroethenyl) - cephem

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Since the introduction of cefixime<sup>1</sup> as an orally absorbable cephalosporin in 1983, the preparation of cefixime analogs has been reported in the literature.<sup>2</sup> In this laboratory we were interested in the modification of C-10 position in vinyl group by substitution with chlorine atom. To our best knowledge, the preparation of 3-(1-chloroethenyl)cephem has not yet been reported in the literature.<sup>3</sup> Here we wish to report a synthesis of 7-[(Z)-2-amino-4-thiazole]-2-[(1-carboxy-1-methyl)ethoxyimino]acetamido]-3-(1'-chloroethenyl)-3-

R = PhCH<sub>2</sub>CO, dpm = CHPh<sub>2</sub>

cephem-4-carboxylic acid (1) starting from the readily available 3-formyl-2-cephem.<sup>4</sup>

The aldehyde 2 was converted to the methyl ketone 3 via methylmagnesium iodide addition followed by Jones oxidation in overall 62% yield.<sup>5</sup> Conversion of ketone 3 to chloroethenyl cephem 4 was achieved by refluxing in CCl<sub>4</sub> in the presence of triphenylphosphine<sup>6</sup> for 24 h to give the desired 3-(1'-chloroethenyl)-2-cephem 4, mp 118–120 °C in 15% purified yield.<sup>7</sup> The starting ketone 3 could be recovered in ca. 50% yield. In the proton NMR spectrum two geminal vinylic proton signals appeared as doublets at 5.33, 5.28 ppm with a 2.5 Hz coupling constant. Also, the carbon-13 NMR spectrum showed the vinylic carbon resonances at 124.5 (Cl-C=) and 112.5 (=CH<sub>2</sub>) ppm. This 2-cephem 4 was transformed to 3-cephem 6, mp 163–165 °C,<sup>8</sup> by the two-step procedure<sup>9</sup> using *m*-chloroperbenzoic acid oxidation (1 equiv., CH<sub>2</sub>Cl<sub>2</sub>, -5 °C, 2 hr, 55%), followed by phosphorus tribromide reduction (DMF, 0 °C, 1 h, 61%) of the resulting 3-cephem sulfoxide 5, mp 217–220 °C (dec.).<sup>10</sup> Subsequently, deprotection of the phenylacetyl group by PCl<sub>5</sub>-pyridine-methanol<sup>11</sup> gave the amine hydrochloride 7, mp 128–130 °C,<sup>12</sup> in 72% yield, which was acylated with commercially available (*Z*)-2-(2-*N*-tritylaminothiazole)-2-(*t*-butoxycarbonyl-1-methyl)-ethoxyiminoacetic acid using 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole<sup>13</sup> as a condensing agent to afford cephem 8 in 90% yield.<sup>14</sup> Finally deprotection with trifluoroacetic acid/anisole gave the final product 1 in 70% yield.<sup>15</sup>

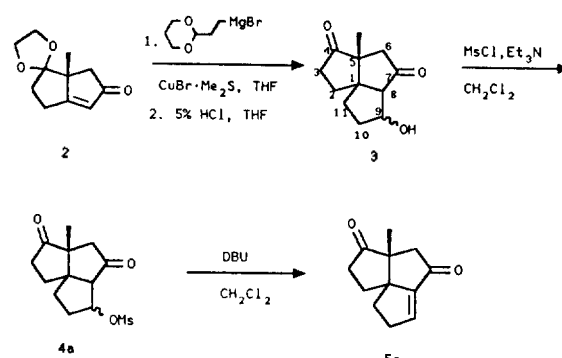
Minimum inhibitory concentrations (μl/mg) of 1 against bacterial strains, determined by agar dilution method in Mueller-Hinton agar are compared with those of cefixime (given in parenthesis): *Streptococcus pyogenes* A308, 0.007 (0.098); *Staphylococcus aureus* SG511, 50 (12.5); *Escherichia coli* 0.55, 12.5 (0.195); *Pseudomonas aeruginosa* 9027, >100 (100); *Salmonella typhimurium*, 12.5 (0.049); *Klebsiella oxytoca* 1082E, 6.25 (0.025); *Enterobacter cloacae* p99, >100 (>100). Thus, cephem 1 showed inferior activity than cefixime.

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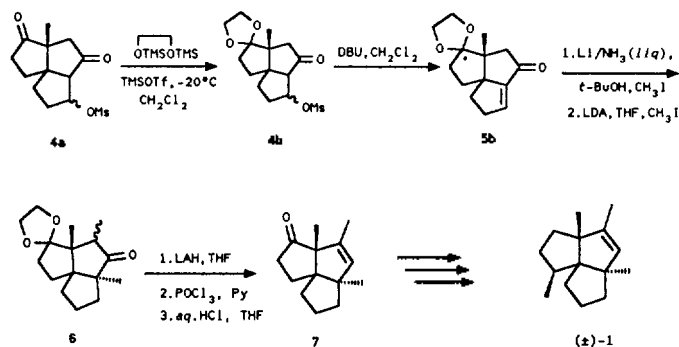
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- Compound 4; IR (KBr): 1770, 1730 cm<sup>-1</sup>; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.40–7.20 (m, 15 H), 6.89 (s, 1H), 6.86 (s, 1H), 6.10 (d, 1H, J = 8 Hz, NH), 5.59 (dd, 1H, J = 4, 8 Hz, C-7), 5.37 (s, 1H, C-4), 5.33, 5.28 (2xd, 2H, J = 2.5 Hz, =CH<sub>2</sub>), 5.15 (d, 1H, J = 4 Hz, C-6), 3.65 (ABq, 2H, PhCH<sub>2</sub>); <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>): δ 171.0, 165.5, 164.0, 139–127, 124.5 (Cl-C=), 112.5 (=CH<sub>2</sub>), 60.0, 53.5, 50.0 (C-4), 43.5 (PhCH<sub>2</sub>); MS: *m/z* = 545.
- Compound 6; IR (KBr): 1770, 1720, 1650, 1220 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.40–7.20 (m, 15H), 7.30 (s, 1H, CHPh<sub>2</sub>), 6.15 (d, 1H, J = 9 Hz, NH), 5.88 (dd, 1H, J = 9, 5 Hz, C-7), 5.01 (d, 1H, J = 5 Hz, C-6), 5.00, 4.90 (2xd, 2H, J = 2 Hz, =CH<sub>2</sub>), 3.65 (ABq, 2H, J = 16 Hz, PhCH<sub>2</sub>), 3.50 (ABq, 2H, J = 18 Hz, C-2).
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- Compound 5; IR (KBr): 1780, 1720, 1650 cm<sup>-1</sup>; <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>): δ 8.60 (d, 1H, NH), 7.50–7.15 (m, 15H), 7.00 (s, 1H, CHPh<sub>2</sub>), 5.95 (dd, 1H, C-7), 5.30, 5.15 (2xbs, 2H, =CH<sub>2</sub>), 4.90 (d, 1H, C-6), 3.85 (ABq, 2H, PhCH<sub>2</sub>), 3.60 (ABq, 2H, C-2).
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- Compound 7; IR (KBr): 3380, 3010, 1770, 1720, 1220 cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 7.45–7.20 (m, 10H), 6.93 (s, 1H, CHPh<sub>2</sub>), 5.20, 5.11 (2xd, 2H, J = 2 Hz, =CH<sub>2</sub>), 5.10 (d, 1H, J = 5 Hz), 4.92 (d, 1H, J = 5 Hz), 3.65 (ABq, 2H, C-2).
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- Compound 8; IR (KBr): 1780, 1720, 1510, 1380, 1280, 1220, 1140 cm<sup>-1</sup>; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.39 (1H, d = 9 Hz, NH), 7.04 (s, 1H, CHPh<sub>2</sub>), 6.74 (s, 1H), 6.06 (dd, 1H, J = 9, 5 Hz, C-7), 5.11 (d, 1H, J = 5 Hz,

C-6), 4.98, 4.86 (2xd, 2H,  $J = 2$  Hz,  $=CH_2$ ), 3.69, 3.41 (ABq, 2H,  $J = 18$  Hz, C-2), 1.65 (s, 3H), 1.59 (ds, 3H), 1.39 (s, 9H).

15. Compound 1: IR (KBr): 3200, 1780, 1700, 1380, 1200, 1140  $cm^{-1}$ ;  $^1H$ -NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.58 (d, 1H,  $J = 9$  Hz, NH), 6.78 (s, 1H), 5.93 (bs, C-7), 5.49 (bs, 2H,  $=CH_2$ ), 5.25 (d, 1H,  $J = 5$  Hz, C-6), 3.69 (bs, 2H, C-2), 1.46 (s, 3H), 1.44 (s, 3H).



Scheme 1



Scheme 2

### Synthesis of Isocomene Via Selective Monoketalization of Tricyclo[6.3.0.0<sup>4,8</sup>]undecadione

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It has been well known that bicyclo[3.3.0]octenones can be utilized as potential intermediates in the synthesis of structurally complicated polyquinanes such as coriolin and gymnomitrol.<sup>1,2</sup> However, only one example of the construction of tricyclo[6.3.0.0<sup>4,8</sup>]undecane ring system from bicyclo[3.3.0]octenones has been reported so far.<sup>3</sup> We herein describe the construction of tricyclo[6.3.0.0<sup>4,8</sup>]undecane ring, i.e., isocomene (1) from the monoketal of bicyclo[3.3.0]octenone (2), which was easily prepared from 2-methyl-1,3-cyclopentadione in four steps by analogous method described by Dauben and Hart.<sup>4</sup>

Treatment of 2 with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane in the presence of the cuprous bromide-dimethyl sulfide complex resulted in smooth 1,4-addition in 92% yield.<sup>5</sup> Subsequent aldol condensation under acidic condition employing 3% aqueous HCl in refluxing THF for 5 hrs gave a deketalized aldol product 3 in 83% yield. Compound 3 was mesylated with methanesulfonyl chloride in pyridine to obtain 4a in 83% yield and the elimination using DBU provided enone 5a (Scheme 1). But it was necessary to protect the carbonyl group adjacent to the angular methyl in order to introduce methyl group following Birch reduction of the enone 5a. Adopting this strategy, we tried chemoselective monoketalization utilizing conventional method or transketalization,<sup>6</sup> but we could not obtain the desirable results because of either poor selectivity or decomposition of the product under the reaction conditions.

Therefore, we decided to take on the ketalization prior to the elimination reaction of 4a. Now we could obtain monoketal 4b in 79% yield, which was ketalized at the carbonyl of C-4 adjacent to the angular methyl, by submitting the methanesulfonate derivative 4a to a mild condition of 1,2-bis(trimethylsilyloxy)ether in the presence of TMSOTf at  $-20^\circ C$  for 20 hrs in anhydrous dichloromethane.<sup>7</sup> Perhaps rationale for this selective monoketalization is that bulky methanesulfonate group at C-9 increases the steric crowded-

ness around the carbonyl group at C-7 and this factor facilitates the introduction of ketal at the carbonyl of C-4. Also molecular model of 3 supports this conjecture.

With ketal 4b in our hands, we could smoothly perform the elimination to acquire enone 5b in 89% yield by treating with DBU in anhydrous dichloromethane (Scheme 2). The chemical transformations including Birch methylation and succeeding methylation with LDA and methyl iodide furnished compound 6 in 52% from 5b. The submission of 6 to the reduction with lithium aluminum hydride, the dehydration condition utilizing phosphorus oxychloride and pyridine for 3 days, and deprotection of a ketal group under acidic condition gave eventually the desired product 7<sup>8,9</sup> in overall yield of 45% from 6. Thus this work constitutes a formal total synthesis of racemic isocomene, because the ketone 7 was already converted to racemic isocomene (1).<sup>9</sup>

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