upon reaction with bromine under a variety of conditions.
(3) This investigation has been reported at a recent symposium. See G. A. Koppel, "Recent Advances in β-Lactam Chemistry," Cambridge, England, 1976.
(4) G. A. Koppel and R. E. Koehler, *J. Am. Chem. Soc.*, **95**, 2403 (1973).
(5) All new compounds were characterized by satisfactory mass spectral and elemental analyses.
(6) It has not been demonstrated whether or not C_7 oxidation precedes or is competitive with the C_3-olefin chlorination.
(7) Cephem was obtained from the corresponding cephem sulfoxide (prepared from penicillin by the Kukolja rearrangement, see ref 1) in 92–95% yield by reduction with PCl_3–DMF.
(8) In contrast, the reaction of cephem with bromine in THF at 0 °C affords a quantitative yield of 5-bromothienyl-3-*exo*-methylenecephem sulfide.
(9) Formerly, the only source of 3-iodomethyl was the iodide exchange with the 3-halomethylcephem. See Belgian Patent 755256.
(10) Cephem **5e** is identical with that made from 7-ACA.
(11) C. F. Murphy, R. E. Koehler, and C. W. Ryan, Abstracts, 14th Interscience Conference on Antimicrobial Agents and Chemotherapy, 425 (1974).

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A New Synthesis of β-Lactams

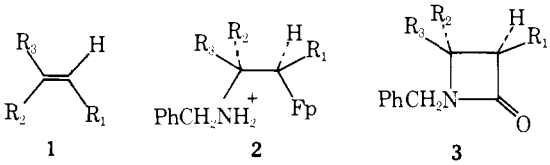
Sir:

We recently reported the regiospecific addition of heteroatomic nucleophiles to a number of Fp(olefin) cations[1] (Fp = η^5-$C_5H_5Fe(CO)_2$). Furthermore, it has been shown that oxidatively induced ligand transfer in FpR complexes (R-Fe-CO → FeCOR) leads to carboxylation of R with retention of configuration at the migrating carbon center.[2] We now show that an appropriate combination of these processes provides a facile and stereospecific synthesis of mono- and bicyclic β-lactams from olefins.

The readily available propylene complex (**1b**)[3] adds benzylamine at −25 °C to give the ammonium salt (**2b**)[1] in high yield. This on oxidation at −78 °C in methylene chloride solution with Cl_2, followed by addition of triethylamine gives the β-lactam (**3b**)[4,5] in 47% yield: IR (neat) 1750 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (s, 5, Ph), 4.65, 4.06 (2d, 2, J = 15 H, $PhCH_2$), 3.56 (m, 1, CHN), 3.05 (dd, 1, J = 4.9, 14.5 Hz, CH_2CO), 2.48 (dd, 1, J = 2.5, 14.5 Hz, CH_2CO), 1.17 (d, 3, J = 6 Hz, CH_3).

This sequence, which proceeds through the β-amino acid chloride,[2b] is particularly well suited for the conversion of unstable Fp(olefin)-amine adducts, derived from disubstituted olefins. These also provide useful substrates for examining the stereochemistry and stereospecificity of the sequence. Thus, the addition of an equivalent of benzylamine to a solution of the *cis*-2-butene complex (**1d**) in nitromethane-chloroform (3:1) at −24 °C affords a mixture of the adduct (**2d**, 45%), displacement product ($FpNH_2CH_2Ph$)(BF_4) (40%), and unreacted olefin complex. Oxidation of this solution at −78 °C with chlorine gave *trans*-3,4-dimethylazetidinone (**3d**)[5] as the single isomer (GLC analysis) in 34% yield based on **2d**; IR (neat) 1745 cm^{-1}; NMR δ 7.28 (s, 5, Ph), 4.62, 4.05 (2d, 2, J = 15 Hz, CH_2Ph), 3.16 (dq, 1, J = 6, 2 Hz NCH), 2.74 (dq, 1, J = 6, 2 Hz, CHCO), 1.25, 1.17 (2d, 6, J = 6 Hz, CH_3).

Similar experiments with the *trans*-2-butene complex (**1c**),



1 2 3

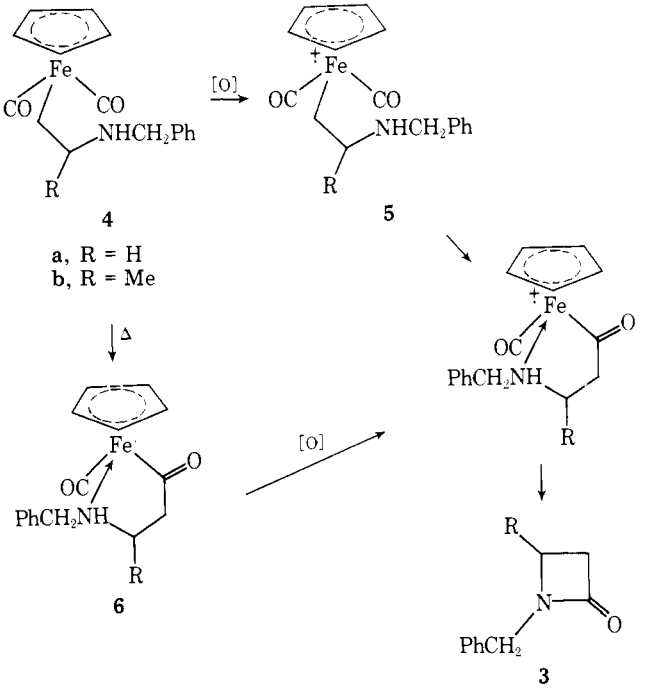
a, R_1,R_2,R_3 = H
b, R_1,R_2 = H; R_3 = Me
c, R_1,R_3 = Me; R_2 = H
d, R_1,R_2 = Me; R_3 = H

gave only the *cis*-3,4-dimethylazetidinone (**3c**) in approximately 10% yield: NMR δ ($CDCl_3$) 7.23 (m, 5, Ph), 4.52, 4.0 (d, 2, J = 15.5 Hz, CH_2Ph), 3.51 (m, 1, J = 6.3, 6.0 Hz, CHN), 3.13 (m, 1, J = 7.5, 6.0 Hz, CHCO), 1.11 (d, 3, J = 7.5 Hz, CH_3), 1.01 (d, 3, J = 6.3 Hz, CH_3).

These results are in accord with a stereochemical sequence involving trans addition to the olefin complex,[6] followed by carboxamidation with retention of configuration at the C-Fe bond.[2]

Milder oxidizing reagents such as Cu^{2+} and Ag^+ are without effect on the benzylammonium salts, but the free amine, (**4b**) obtained from **2b** by treatment at 0 °C with 1 N NaOH solution, was smoothly transformed to the β-lactam (69%) by freshly prepared lead dioxide[7] or by silver oxide in THF solution (25 °C, 16 h). Similarly, oxidation of the free amine derived by deprotonation of **2a**, gave the β-lactam (**3a**)[5,8] in 30% yield:[9] IR (neat) 1745 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (s, 5, Ph), 4.36 (s, 2, CH_2), 3.25–2.75 (m, 4, CH_2CH_2).

These changes may be depicted in terms of a mechanism involving initial oxidation at the metal atom.[2a,10] Alkyl ligand transfer in the resulting radical cation (**5**) is apparently rapid and is probably promoted by decreased electron density at the metal and hence also at the carbonyl carbon.[11] Ligand transfer in the uncharged alkylamino complex **4**, which affords the stable chelate **6**[12] (ν_{CO}(THF) 1920, 1620 cm^{-1}), is by contrast relatively slow. Hence **6** cannot be an intermediate in the oxidative conversion of the alkylamino complexes to β-lactam.



4 5 6 3

a, R = H
b, R = Me

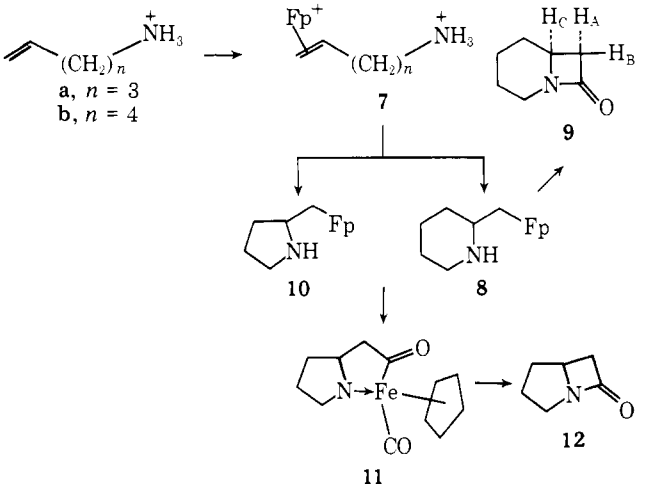
Nevertheless, these chelate complexes constitute alternative and advantageous intermediates since their conversion to β-lactams, on exposure to PbO_2 or Ag_2O, is even more facile than the corresponding β-aminoalkyl complexes. This sequence is particularly advantageous with heat sensitive β-lactams. Thus, rearrangement of **2a** to **6a** (CH_3CN, 70 °C, 20 h) in the presence of 10% PBu_3, followed by oxidation with Ag_2O (70 °C, 1 h) gave β-lactam (**3a**) in 59% yield.

Similarly **2b** is converted to **6b** by heating in THF solution (70 °C, 5 h, 10% Bu_3P), and then by the addition of Ag_2O to the β-lactam in 82% yield.

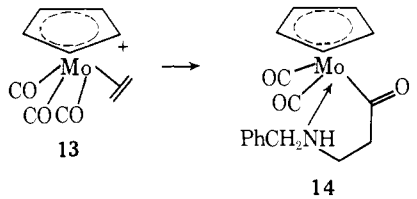
The synthetic sequence may readily be extended to the construction of fused ring β-lactams starting with amino olefins. Complex **7b** is obtained in 80% yield from the exchange reaction involving 1-hexenylammonium tetrafluoroborate and Fp(isobutene) tetrafluoroborate. Successive deprotonation

with tri-*n*-butylamine followed by potassium *tert*-butoxide gave the piperidine complex **8**, which was converted with Ag_2O (THF, 65 °C, 20 h) to the lactam **9** in 30% overall yield from the uncomplexed olefin: IR 1755 cm^{-1}; NMR ($CDCl_3$) δ 3.8 (dd, 1, J_{ab} = 14 Hz, J_{ac} = 2 Hz, H_A).[13]

A similar sequence, employing 1-pentenylammonium tetrafluoroborate gave the pyrrolidine complex **10.** An attempt to convert this directly to β-lactam by oxidation led instead to a polyamide (ν_{CO} 1590 cm^{-1}) due to the high reactivity of this lactam. However, when **10** was heated in THF for 4 h in the presence of 10 molar % of triphenylphosphine, it was smoothly converted to the chelate (**11**, ν_{CO} 1620, 1930 cm^{-1}) in 80% yield. Treatment of this with freshly precipitated Ag_2O for 5 min at 25 °C led to the disappearance of chelate carbonyl absorptions and formation of β-lactam (**12**) (ν_{CO}(THF) 1775 cm^{-1}).[14] Initial attempts to isolate this substance have led to polymerization.



Finally, these transformations are not confined to iron complexes. The closely related group 6 metal-ethylene complexes are known to add amines with ease.[15] Thus the molybdenum-ethylene complex (**13**) smoothly adds benzylamine, affording the chelate complex (**14**) directly in 90% yield. Preliminary experiments show that oxidation of this substance with Ag_2O gives the β-lactam (**3a**) in 10% yield.



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References and Notes

(1) P. Lennon, M. Madhavarao, A. Rosan, and M. Rosenblum, *J. Organomet. Chem.*, **108**, 93 (1976).
(2) (a) K. M. Nicholas and M. Rosenblum, *J. Am. Chem. Soc.*, **95**, 4449 (1973); (b) P. L. Bock, D. J. Boschetto, J. R. Rasmussen, J. P. Demers, and G. M. Whitesides, *ibid.*, **96**, 2814 (1974).
(3) A. Cutler, D. Ehntholt, W. P. Giering, P. Lennon, S. Raghu, A. Rosan, M. Rosenblum, J. Tancrede, and D. Wells, *ibid.*, **98**, 3495 (1976).
(4) W. A. Gould and F. F. Blicke, *J. Org. Chem.*, **23**, 1102 (1958).
(5) A correct elemental analysis was obtained for this substance.
(6) A. Sanders, C. V. Magatti, and W. P. Giering, *J. Am. Chem. Soc.*, **96**, 1610 (1974); K. M. Nicholas and A. M. Rosan, *J. Organomet. Chem.*, **84**, 351 (1975).
(7) L. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 533.
(8) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, **71**, 2124 (1949).
(9) The rate of this heterogeneous reaction is considerably more rapid with freshly prepared silver or lead oxides than with commercial reagents.
(10) S. N. Anderson, C. W. Fong, and M. D. Johnson, *J. Chem. Soc., Chem. Commun.*, 163 (1973).
(11) A similar promotion of carboxylation reactions is observed in $RFe(CO)_4^-$, J. P. Collman, S. R. Winter, and R. B. Komoto, *J. Am. Chem. Soc.*, **95**, 249 (1973), and in p-$FC_6H_4CH_2Mo(CO)_3Cp$, ref 10.
(12) Related chelate complexes have been prepared by metalation of β-aminoalkyl halides. R. B. King and M. B. Bisnette, *Inorg. Chem.*, **5**, 293 (1966).
(13) F. Moll, *Z. Naturforsch. B*, **21**, 297 (1966).
(14) F. Moll, *Z. Naturforsch. B*, **24**, 942 (1969).
(15) W. H. Knoth, *Inorg. Chem.*, **14**, 1566 (1975).

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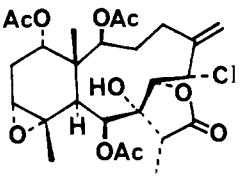
Stylatulide, a Sea Pen Toxin

Sir:

The sea pen *Stylatula* sp.[1] is a slender, whip-like coelenterate which was collected in the intertidal zone at Isla Partida, Gulf of California. The bioluminescent properties of *S. elongata* and other sea pens have been investigated,[2] but there are no other reports of secondary metabolites from sea pens. We found that extracts of *Stylatula* were toxic to larvae of the copepod *Tisbe furcata johnsonii*. We wish to report the structure of stylatulide (**1**), the major toxic metabolite of *Stylatula* sp.

Florisil chromatography of an acetone extract of homogenized *Stylatula* resulted in the isolation of one major (0.8% of dry weight) and five minor metabolites. The major metabolite, stylatulide (**1**), crystallized from 1:1 hexane:dichloromethane, mp 179–181 °C, $[\alpha]_D$ +65° (c 1.8). Stylatulide (**1**)



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had the molecular formula $C_{26}H_{35}O_{10}Cl$.[3] The ^1H NMR spectrum contained three acetate signals at δ 1.95, 2.00, and 2.27 ppm which, together with an IR band at 1740 cm^{-1}, indicated that stylatulide was a diterpene triacetate. The IR spectrum also contained bands at 3500 cm^{-1} (hydroxyl) and 1780 cm^{-1} (γ-lactone). All signals in the richly detailed ^1H NMR spectrum have been assigned: δ ($CDCl_3$) 1.10 (3 H, s, 15-H), 1.29 (3 H, s, 20-H), 1.31 (3 H, d, J = 7 Hz, 18-H), 1.70 (1 H, m, 3-H), 2.10 (1 H, d, J = 18 Hz, 13-H), 2.27 (1 H, m, 13-H), ~2.4 (2 H, m, 4-H), 2.59 (1 H, m, 3-H), 2.97 (1 H, d, J = 4 Hz, 12-H), 3.04 (1 H, s, 10-H), 3.18 (1 H, q, J = 7 Hz, 17-H), 3.36 (1 H, s, -OH), 4.63 (1 H, td, 6-H), 4.71 (1 H, d, J = 4 Hz, 7-H), 4.90 (1 H, d, J = 6.5, 14-H), 5.50 (1 H, s, 9-H), 5.79 (1 H, bs, 16-H), 5.93 (1 H, d, J = 9, 2-H) and 6.00 (1 H, bs, 16-H). The structure of stylatulide (**1**) was determined by single-crystal x-ray diffraction analysis.

Preliminary x-ray photographs showed tetragonal symmetry for stylatulide. Accurate lattice constants, determined by least-squares fitting of 15 accurately measured 2θ values, were $a = b$ = 11.543 (4) and c = 20.293 (7) Å. The systematic extinctions (00l, absent if $l \neq 4n$) conformed to the tetragonal space group $P4_1$ (or its enantiomorph $P4_3$) and the density indicated four molecules of $C_{26}H_{35}ClO_{10}$ in the unit cell or one per asymmetric unit. All unique diffraction maxima with $2\theta \leq 114.1°$ were recorded on a computer-controlled four-circle diffractometer using graphite monochromated Cu Kα (1.541 78Å) radiation. Of the 1889 reflections surveyed, 1844 (98%) were judged observed ($F_o^2 \geq 3\sigma(F_o^2)$) after correction for Lorentz, polarization, and background effects.