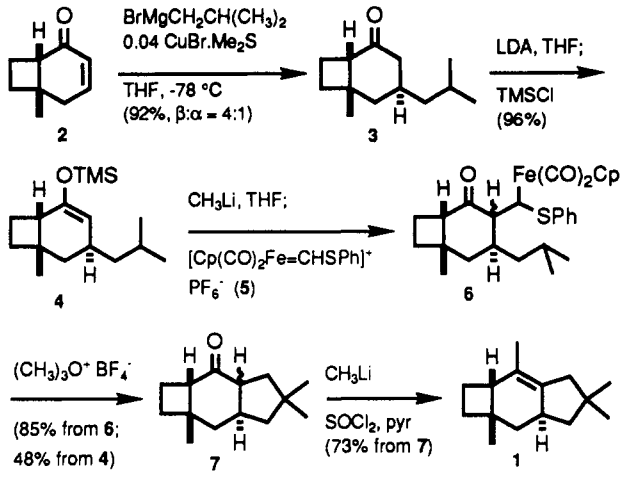
Scheme I



cis-6-Methylbicyclo[4.2.0]oct-3-en-2-one (**2**)[3] undergoes copper-catalyzed conjugate addition[4] of isobutylmagnesium bromide to give the ketone **3** as a 4:1 mixture of the β and α isomers favoring the desired β-substituted isomer. Enolate generation followed by addition of $[Cp(CO)_2Fe{=}CHSPh]^+PF_6^-$ (**5**, Cp = η^5-C_5H_5)[5] gives the intermediate **6** which when treated with trimethyloxonium tetrafluoroborate gives the epimeric tricyclic ketones **7**[6] (Scheme I). This product is obtained in 80–90% yields from **6**, but the overall cyclopentane annulation is made operationally simpler when **6** is not isolated or purified, in which case the overall yield of **7** is 48% from the enol silyl ether **4**. The main limitation in the yield for the overall annulation process appears to be incomplete reaction of the enolate generated from **4** in that 20–30% of the ketone **3** is recovered after the reaction of the enolate with **5**. The synthesis is completed as in Little's route[2b] by addition of methyllithium and dehydration of the resulting tertiary alcohol. The sterpurene thus obtained is identical to the previously obtained material according to direct comparison of ^1H and ^{13}C NMR spectra.[1,2d]

This synthesis provides sterpurene by an attractively simple, short route, and it demonstrates the utility of the new organoiron-based cyclization reaction.[6]

Acknowledgment. We thank Professors Ayer and Okamura for generously providing us with copies of NMR spectra of sterpurene. We also thank Dr. Bruce Plashko (Notre Dame) for mass spectrometric measurements. We are grateful to the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of *trans*-**7** and the synthetic sterpurene (8 pages). Ordering information is given on any current masthead page.

(3) Enone **2** was obtained as previously reported from the photocycloaddition of ethylene to 3-methyl-2-cyclohexenone followed by bromination/dehydrobromination: (a) Zurflüh, R.; Dunham, L. L.; Spain, V. L.; Siddall, J. B. *J. Am. Chem. Soc.* **1970**, *92*, 425. (b) Cargill, R. L.; Dalton, J. R.; Morton, G. H.; Caldwell, W. E. *Org. Synth.* **1984**, *62*, 118. (c) Jacques, J.; Marquet, A. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 175. (d) House, H. O.; Bashe, R. W. II *J. Org. Chem.* **1965**, *30*, 2942.

(4) (a) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025. (b) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045. Direct trapping of the enolate resulting from the conjugate addition was performed using TMSCl, and direct trapping of the enolate resulting from proton abstraction from ketone **3** was performed using iron reagent **5**, but superior results were obtained with the more stepwise route described in the text.

(5) (a) Knors, C.; Kuo, G.-H.; Lauher, J. W.; Eigenbrot, C.; Helquist, P. *Organometallics* **1987**, *6*, 988. (b) Knors, C.; Helquist, P. *Organomet. Synth.* **1988**, *4*, 205.

(6) Zhao, S.-K.; Knors, C.; Helquist, P. *J. Am. Chem. Soc.* **1989**, *111*, 8527.

Addition of Amino Lactams to Vinyl Vicinal Tricarbonyls. Formation of Tricyclic 2-Azadethiapenams and 3-Azadethiacephams

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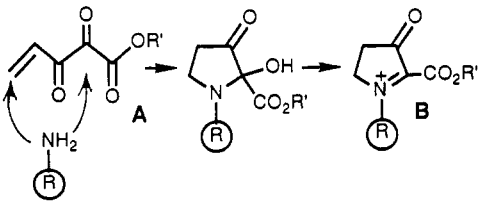
Summary: Amino lactams react as trinucleophiles with vinyl vicinal tricarbonyl esters to form tricyclic derivatives. Products of particular interest resulting from this reaction sequence are 2-azadethiapenams and 3-azadethiacephams.

We have recently shown[1] that the addition of primary amines to vinyl tricarbonyl reagents A generates ketopyrrolinium carboxylates B (Scheme I), which may serve as powerful electrophilic acceptors for nucleophilic residues attached to the primary amine (Figure 1). These nucleophiles have included indole groups, activated aromatic rings, enol ethers, vinylsilanes, propargylsilanes, and pyrroles.[1-3] We now report that the amide NH of a lactam

Scheme I



residue will add to the intermediate iminium group, forming fused-ring 2-(acylamino)-1-oxopyrrolidinecarboxylates.[4] This process constitutes a facile route to

(1) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371–372.

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(3) Wasserman, H. H.; Cook, J. D.; Vu, C. B. *J. Org. Chem.* **1990**, *55*, 1701–1702.

0022-3263/90/1955-5821$02.50/0

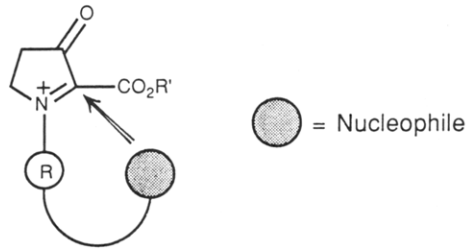


Figure 1.

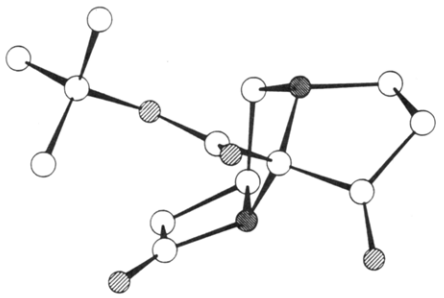
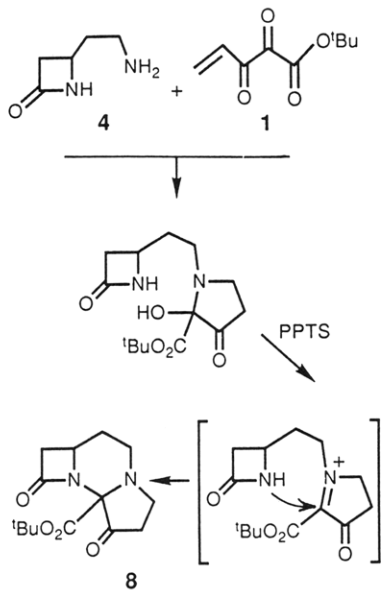


Figure 2. UPLOT drawing of the tricyclic product 9.

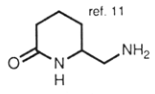
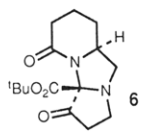
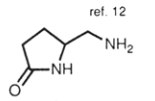
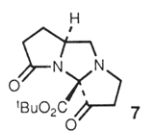
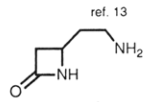
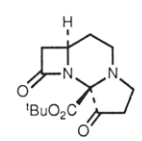
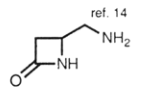
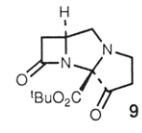
Scheme II



tricyclic systems incorporating lactam residues and is illustrated by the addition of 4-(aminoethyl)-2-azetidinone **4** to the vinyl tricarbonyl derivative **1** forming the polycyclic system **8** (72%) (Scheme II). Table I lists the amino lactams studied and the yields of the tricyclic lactam products.[5]

Of particular interest are the reactions of the amino β-lactams **4** and **5** which add to the vinyl tricarbonyl *tert*-butyl ester **1** to form tricyclic systems **8** and **9** related to the carbacephams and carbapenams. We have assigned the β-configuration to the carboxylate group in these products based on an X-ray crystallographic analysis of compound **9** containing the 4-5-5 fused ring system. Figure 2 is a UPLOT representation of **9**. The orientation of the carboxylate group at this position is known to play a significant role in the biological activity of β-lactam antibiotics.[6] Investigations of structure–activity relationships have led to the synthesis of tricyclic cepham[7] and penam[7,8] analogues which lock the carboxylate in the α- and β-orientations, and these studies have shown higher activity for the β-carboxylate isomers. In addition, Pearson has found that an azadethiocepham with a β-carboxylate group has higher antibacterial activity then the corresponding α-carboxylate compound.[9] We are pursuing the preparation of tricyclic systems of type **8** and **9** substituted with 3-(acylamino) and 3-(1-hydroxyethyl) groups as analogues of biologically active fused-ring β-lactams.[10]

Table I. Conversion of Amino Lactams to Tricyclic Products

amino amide[a]	product	yield,[b] %
 ref. 11 **2**	 **6**	84
 ref. 12 **3**	 **7**	76
 ref. 13 **4**	 **8**	72
 ref. 14 **5**	 **9**	30

[a] The corresponding azido amide was hydrogenated (Pd/C catalyst) to the amino amide shown and used directly. [b] Based on the azido amide.

(4) For intramolecular addition of β-lactams to tricarbonyl groups forming bicyclic products, see: (a) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3743–3746. (b) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3747–3750. (c) Wasserman, H. H.; Han, W. T. *J. Am. Chem. Soc.* **1985**, *107*, 1444–1446.

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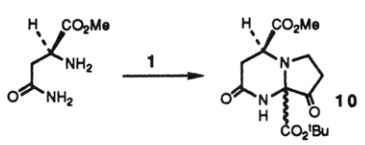

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(9) For other biologically active azadethiacepham, -cephem, and -penam analogues, see: (a) Azadethiacephem: Gleason, J. G.; Bryan, D. B.; Holden, K. G. *Tetrahedron Lett.* **1980**, *21*, 3947–3950. (b) Azadethiacepham: Branch, C. L.; Pearson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1077–1095. (c) Azadethiacepham and -cephem: Pfaendler, H. R.; Strasser, R. *Leibigs Ann. Chem.* **1987**, 911–919. (d) Aza-dethiapenam: Huffman, W. F.; Holden, K. G.; Buckley, T. F.; Gleason, J. G.; Wu, L. *J. Am. Chem. Soc.* **1977**, *99*, 2352–2353.

(10) For other biologically active tricyclic analogues, see: Branch, C. L.; Finch, S. C.; Pearson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1491–1498. Lammert, S. R.; Kukolja, S. *J. Am. Chem. Soc.* **1975**, *97*, 5583–5584.

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(12) Prepared by iodolactamization: Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006–4014.

In a typical reaction, the amino amide (0.5 mmol) in methanol (10 mL) was added dropwise over 5 min to the stirred solution of vinyl tricarbonyl reagent 1 (0.5 mmol) in methylene chloride (40 mL). After 30 min, the solvent was removed in vacuo, leaving a clear oil which was dissolved in methylene chloride (40 mL). Pyridinium *p*-toluenesulfonate (0.5 mmol) in methylene chloride (10 mL) was added to the solution, and the reaction was heated to reflux. After 25 min to 1 h, the solution was allowed to cool to room temperature, diluted with 20 mL of methylene chloride, and then washed twice with 20-mL portions of saturated $NaHCO_3$ (aqueous) solution. The aqueous layers were extracted with methylene chloride, and the organic solutions were combined, washed successively with water and brine, dried over Na_2SO_4, and then concentrated to yield a yellow oil. The crude material was purified by flash chromatography (ethyl acetate–methylene chloride) to yield the product.

Acknowledgment. This research was supported by Grants GM31350 and GM07874 from the NIH.

Supplementary Material Available: Complete spectroscopic and combustion analytical data for **6**, **7**, and **8**. X-ray crystallographic and spectroscopic data for compound **9** (11 pages). Ordering information is given on any current masthead page.

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Articles

Synthesis of *N*-(*tert*-Butyloxycarbonyl)-CBI, CBI, CBI-CDPI$_1$, and CBI-CDPI$_2$: Enhanced Functional Analogues of CC-1065 Incorporating the 1,2,9,9a-Tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (CBI) Left-Hand Subunit

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Full details of the synthesis of *N*-(*tert*-butyloxycarbonyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one [*N*-BOC-CBI (**6**)] constituting a more stable functional analogue of the CC-1065 left-hand subunit are described. The resolution of an immediate CBI synthetic precursor, (+)- and (−)-**14**, the unambiguous establishment of the absolute configuration, and the incorporation of (±)-, (+)-, and (−)-**14** into the synthesis of racemic and optically active CBI (**5**), *N*-BOC-CBI (**6**), CBI-CDPI$_1$ (**7**), and CBI-CDPI$_2$ (**8**), enhanced functional analogues of CC-1065, are detailed. The chemical solvolytic behavior of the CBI-based agents and their cytotoxic properties are described.

(+)-CC-1065 (**1**, NSC-298223), an antitumor antibiotic isolated from cultures of *Streptomyces zelensis*, possesses exceptionally potent in vitro cytotoxic activity, broad spectrum antimicrobial activity, and confirmed in vivo antitumor activity.[2,3] In a series of extensive investigations the site and mechanism of the (+)-CC-1065 antitumor activity have been related to its covalent alkylation of sequence-selective minor groove sites [5′-d(A/GNTTA)-3′ and 5′-d(AAAAA)-3′] that has been demonstrated to proceed by 3′-adenine N-3 alkylation of the electrophilic cyclopropane present in the left-hand subunit (CPI).[4,5] The initial demonstration that (+)-*N*-acetyl-CPI exhibits a comparable albeit substantially less intense (ca. 10000×) sequence-selective alkylation of DNA has led to the conviction that the left-hand subunit of (+)-CC-1065 plays a dominant role in controlling the properties of the agents.[6] However, the demonstration that simplified agents including CDPI$_3$ methyl ester[7] exhibit a substantial preference for A-T rich noncovalent minor groove binding[8] at-

(1) (a) National Institutes of Health research career development award recipient, 1983–1988 (CA 01134). Alfred P. Sloan Foundation research fellow, 1985–89. (b) On sabbitcal from Kyorin Pharmaceutical Co., Ltd., Tochigi, Japan, 1988–1990.
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