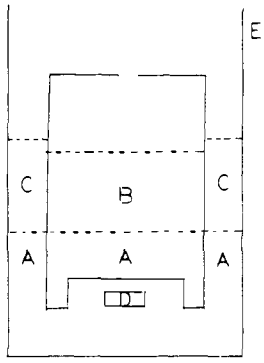

Figure 1. Apparatus used for transport studies. (A) Lower layer, 150 mL of 0.7 mM ionophore in CH_2Cl_2; (B) inner layer, 40 mL of 0.05 or 0.0125 M KSCN in deionized, distilled water; (C) outer layer, 50 mL of 0.02 M $Fe(NO_3)_3$ in 0.2 M aqueous HNO_3; (D) stirring bar; (E) 600-mL beaker.

Table I. Variation with Temperature of the Cation Flux[a] of KSCN through CH_2Cl_2 by Various Ionophores

	cation flux, J_m[a,b]		
T, °C	Tween 80, 0.05 M KSCN	18-crown-6, 0.0125 M KSCN	PEG-1000, 0.05 M KSCN
30	1.95 ± 0.14	6.54 ± 0.44	1.98 ± 0.19
23	2.60 ± 0.12	8.67 ± 0.47	3.10 ± 0.15
16	4.22 ± 0.23	12.54 ± 0.59	4.30 ± 0.28
2	7.03 ± 0.31	17.68 ± 1.17	6.67 ± 0.27
	Plot, J_m vs. T		
10^9 slope	-1.879	-4.076	-1.680
r	0.9921	0.9961	0.9999

[a] J_m = (mol 10^8)/(s m^2). [b] A minimum of three determinations were run at each temperature.

periments were conducted in a constant temperature bath at a stirring rate of 125 rpm.

Our results are summarized in Table I. Rates and fluxes at each temperature were determined from the slopes of lines (minimum $r = 0.9982$) resulting from the plotting of thiocyanate concentration in the outer layer vs. time. No transport was observed in the absence of ionophore. The lack of a reverse transport of ferric ions from the outer to the inner layer was shown by the total absence of the colored complex in the inner layer, even after several days. Thus, the thiocyanate transport accurately reflects the potassium ion transport. Note the large macrocyclic effect reflected by the 18-crown-6 rates compared to those of the two noncyclic ionophores.

A possible reason for this unusual temperature relationship may be found in the recent statement of Grandjean and Laszlo[4] that "many authors have shown that the rate determining step in ionic transport phenomena occurs at the water–membrane interface". Two interactions of the potassium ions at that interface can be cited: that with the solvent molecules in the water layer and that with the ionophore in the organic layer. Each of these attractions will increase at lower temperatures. If the strength of the potassium ion–ionophore interaction (within the ion pair KL^+ (org), SCN^- (org)) increases faster with a fall in temperature than the strength of the potassium ion–water molecule interaction, the partition coefficient would rise in favor of the ionophore complex and the rate of transport would also rise. This explanation is substantiated by the work of Ouchi et al.,[5] who found that the degree of extraction of potassium and sodium ions from water into CH_2Cl_2 with the help of crown ethers increased with decreasing temperature.

These variations merit further investigation, since ion transport figures so prominently in many important biochemical processes.

Registry No. 1, 9005-65-6; **2**, 17455-13-9; **3**, 25322-68-3; CH_2Cl_2, 75-09-2; K, 7440-09-7.

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A New Synthetic Strategy for the Penems. Total Synthesis of (5*R*,6*S*,8*R*)-6-(α-Hydroxyethyl)-2-(hydroxymethyl)penem-3-carboxylic Acid

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Woodward's original concepts regarding the penems[1] as well as their synthesis[2] stand as hallmarks of excellence in the area of β-lactam antibiotics.[3] Notable improvements have been recently reported with regard to the Wittig-type ring closure to 2-substituted thiazolines,[3] by resorting to reductive, thermal cyclizations of oxalimides, in the presence of trialkyl phosphites, or via anionic and other types of cyclizations.[4-8]

We wish to report on an operationally novel and practical process for the stereocontrolled assembly of an optically active penem nucleus, as exemplified in the total synthesis of the title compound, and its highly bioactive 2-*O*-carbamoyl derivative (FCE 22101).[9] The synthetic strategy is shown in the retrosynthetic analysis depicted in Scheme I. Two key features involve the exploitation of L-threonine as a versatile chiral template[10,11] for an optically active azetidinone precursor to the penem and the utilization of a unique ketene dithiol reagent[12] having ambident sites of reactivity, in a conceptually novel type of access to the thiazoline ring via in an intramolecular Michael addition.

The readily available L-threonine was converted into an epoxy acid $[\alpha]_D$ -9° (MeOH) via the corresponding α-bromide[10] in a modified, one-pot sequence and then to the epoxyamide **1**, mp 79–80 °C, $[\alpha]_D$ +176.4° (MeOH), in good overall yield. Treatment of **1** with potassium carbonate in DMF resulted in a remarkably facile ring closure to give the azetidinone **2**, mp 77–79 °C, $[\alpha]_D$ -68.2° (MeOH).[13,14] Protection of the hydroxyl group and removal of the *N*-(*p*-methoxyphenyl) group[15] led to **4**, mp 158–160 °C, $[\alpha]_D$ -28.2° ($CHCl_3$). Baeyer–Villiger oxidation

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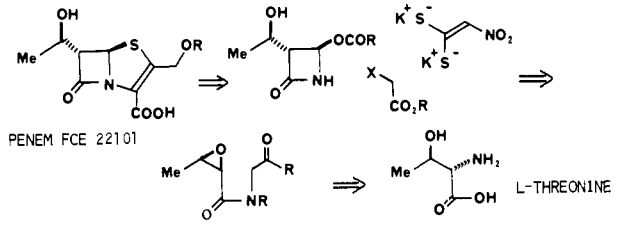
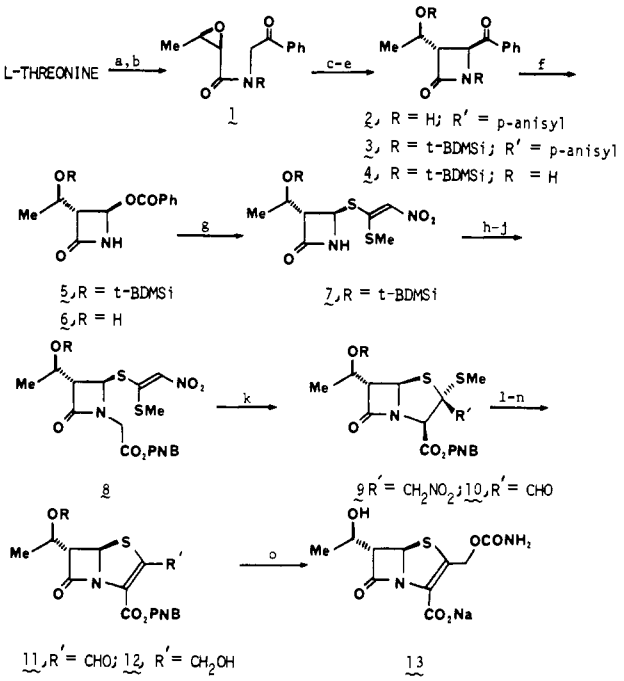
Scheme I



Scheme II[a]



[a] (a) aqueous $NaNO_2$, KBr H_2SO_4, 0 °C, 70%, then NaOH, and acidification, (b) *p*-$MeOC_6H_4NHCH_2COPh$, ClCOO-*i*-Bu, *N*-methylmorpholine 4-Å sieves, THF, −20 °C, then 25 °C, 70%; (c) K_2CO_3, DMF, 60 °C, 3–4 h, 75%; (d) *tert*-butyldimethylsilyl chloride, DMF, imidazole, 80%; (e) ceric ammonium nitrate, MeCN, −10 °C, 87%; (f) monoperphthalic acid, EtOAc, 18 h, 89%; (g) KS(KS)C=$CHNO_2$, aqueous EtOH, 0 °C, 10 min, 1 h Me_2SO_4, 76%; (h) $ClCOCO_2pNB$, CH_2Cl_2, Et_3N, $(i\text{-}Pr)_2NEt$, 0 °C, 75%; (i) $P(OMe)_3$, 25 °C, 90%; (j) PTS, aqueous THF, 1 h, 75%; (k) $LiN(SiMe_3)_2$, THF, −78 °C, 10 min, 56–60% (l) $LiN(Me_3Si)_2$, −78 °C; then add MeI, then ozone; 63%; (m) MCPBA, $CHCl_3$, 10 min, 0 °C, then aqueous $NaHCO_3$ 80%; (n) L-Selectride, THF, −78 °C, 61%; Cl_3CCNO, CH_2Cl_2, then Bu_4NF, THF, then Pd/C, H_2, EtOAc, aqueous $NaHCO_3$, then chromatography, LiChroprep RP-18 (Merck), 40% overall three steps.

then gave the crystalline azetidinone **5**, mp 100–102 °C, $[\alpha]_D$ −66° ($CHCl_3$). Alternatively, de-N-protection of **2** followed by a Baeyer–Villiger oxidation gave the crystalline azetidinone **6**, mp 146–147 °C, $[\alpha]_D$ +97.2 (MeOH). Reaction of **5** with the dipotassium salt of 1,1-dithio-2-nitroethene[12] followed by S-methylation led to the crystalline adduct **7**, mp 144–146 °C, dec, $[\alpha]_D$ +230.5° ($CHCl_3$). Direct reaction of **7** with methyl bromoacetate in the presence of a variety of bases led to mixtures. Hence, the acetic acid moiety was introduced in an uneventful three-step sequence[16] in good overall yield, to give **8**. The critical intramolecular Michael addition of the anion generated from **8** afforded the cyclized product **9** as a crystalline solid, mp 105–106 °C, $[\alpha]_D$ +216.9° ($CHCl_3$),[14] in which the methylthio and ester groups had an anti orientation.[14] With the bicyclic system in hand, there remained to manipulate functionality and adjust oxidation states en route to the target. Thus, the treatment of the nitronate salt derived from **9** with methyl iodide afforded the corresponding methoxy nitronate, which upon treatment with ozone gave the corresponding aldehyde **10** as a colorless oil. Sequential treatment with *m*-CPBA and then aqueous sodium bicarbonate led to spontaneous elimination and the formation of the desired penem intermediate **11** as an amorphous solid, λ_{max} 265, 390 nm. Finally, reduction with L-Selectride (Aldrich) gave the penem **12** ($[\alpha]_D$ +33.5° ($CHCl_3$); mass spectrum, *m/e* 495 (M + 1); λ_{max} ($CHCl_3$) 265, 324 nm), identical in all respects with authentic material prepared by a known route.[6,9] By a sequence of known steps[9] penem **12** was converted into the bioactive carbamate **13**, $[\alpha]_D$ +143° (H_2O), identical with an authentic sample.[9]

The presently described synthesis constitutes a tactically and conceptually new approach for the construction of the optically active azetidinones and penems. It has the attractive features of utilizing readily available, inexpensive starting materials, and it involves a novel ring-forming step under mild conditions in comparison to the original Woodward[2] or other recently reported methods.[4–8]

Acknowledgment. We thank Farmitalia-Carlo Erba for sabbatical leaves to A.B., C.B. and N.M. and for also financial assistance. We thank Dr. Phan-Viet Minh Tan for recording 400-MHz NMR spectra and M. Evans for the mass spectra. We are grateful to A. Glamyan for skillful technical assistance and F. Bélanger-Gariépy for X-ray structure determinations.

Supplementary Material Available: NMR, IR, and mass spectra of **1–3**, **5–8**, and **10–12** and stereoviews of **6** and **9** (38 pages). Ordering information is given on any current masthead page.

(16) For the conversion of related oxalimide esters to acetates, see ref 4–6.

Molecular and Electronic Structures of Metallaspiropentanes

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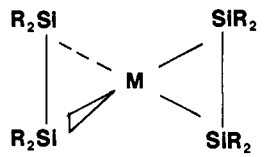
Recent efforts in this laboratory have concentrated on synthesizing metallaspiropentane compounds (I) with M = C, Si, Ge,



Sn, Ni, and Zn. To date, the molecule with M = Si and R = methyl has been successfully prepared,[1] while attempts to synthesize the corresponding carbon compound have not reached fruition. This paper presents initial ab initio calculations on the species with M = C and Si and with R = H.

Geometries for all species were calculated with the 3-21G[2] basis set at the closed-shell Hartree–Fock level of computation. Subsequently, single-point 6-31G*[3] calculations were carried out at the 3-21G geometries. All calculations were performed using an IBM version of GAUSSIAN80.[4]

The 3-21G molecular structures of the two parent species are displayed in Figure 1. for both species the most stable structure is the twisted (distorted pyramidal) form, with the planar structure being higher in energy by 66.2 and 32.3 kcal/mol for M = Si and C, respectively, at the 6-31G* level. For both molecules, the

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