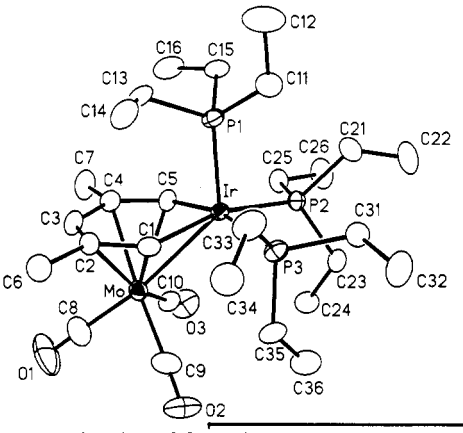

Figure 2. ORTEP drawing of $[(\overline{Ir{-}CH{-}C(Me){-}CH{-}C(Me){-}CH})(PEt_3)_3]Mo(CO)_3$ (**5**). Selected bond distances: Ir-Mo, 2.978 (1) Å; Ir-P(1), 2.274 (2) Å; Ir-P(2), 2.365 (2) Å; Ir-P(3), 2.369 (2) Å; Ir-C(1), 2.025 (8) Å; Ir-C(5), 2.038 (9) Å; C(1)-C(2), 1.399 (13) Å; C(2)-C(3), 1.411 (14) Å; C(3)-C(4), 1.429 (13) Å; C(4)-C(5), 1.393 (12) Å; Mo-C(1), 2.397 (8) Å; Mo-C(2), 2.404 (9) Å; Mo-C(3), 2.318 (10) Å; Mo-C(4), 2.355 (9) Å; Mo-C(5), 2.349 (9) Å.

is rapid (15 min) and probably involves initial transfer of an electron from **1** to O_2.

Treatment of **1** in acetone solution with iodine (I_2) leads to the rapid production of $(\overline{Ir{-}CH{-}C(Me){-}CH{-}C(Me){-}CH})(PEt_3)_2(I)_2$ (**4**), in which the aromatic ring is retained (see Scheme I).[9] Thus, **1** undergoes oxidative addition of I_2 at the iridium center rather than electrophilic aromatic substitution at carbon.[10] Although the detailed mechanism of this oxidative addition reaction is still unknown, both one-electron and two-electron processes can be envisaged. The ^1H NMR signals for ring protons H1/H5 and H3 in **4** are shifted dramatically downfield, appearing at δ 13.95 and 7.86, respectively. These shifts reflect the influence of a strong aromatic ring current, together with the electronic effect of two electronegative iodine atoms in the ring plane.

Finally, **1** cleanly displaces *p*-xylene from (*p*-xylene)$Mo(CO)_3$ in tetrahydrofuran (THF) solvent, producing the metal-coordinated metallabenzene complex, $[(\overline{Ir{-}CH{-}C(Me){-}CH{-}C(Me){-}CH})(PEt_3)_3]Mo(CO)_3$ (**5**) (see Scheme I and ORTEP drawing, Figure 2).[11,12] As is normally the case when arenes coordinate to metal fragments, the ^1H NMR signals for the ring protons in **5** shift upfield from their positions in the parent metallabenzene, **1**. Protons H1/H5 in **5** appear at δ 8.16 (vs δ 10.91 in **1**), while H3 resonates at δ 6.31 (vs δ 7.18 in **1**).[11] Furthermore, the metallabenzene moiety in **5** rotates with respect to the $Mo(CO)_3$ fragment. Hence, the carbonyl carbon atoms in **5** give rise to just one signal in the $^{13}C\{^1H\}$ NMR spectrum, even at -80 °C.

The infrared CO stretching bands exhibited by **5** in THF solution appear at very low energies (1918, 1836 cm^{-1}) compared to other (arene)$Mo(CO)_3$ complexes,[13] reflecting the extremely electron-rich nature of **1**. Since the stability of (arene)$Mo(CO)_3$ complexes increases with increasing arene basicity, it is not surprising that **1** readily displaces organic arenes from (arene)-$Mo(CO)_3$ complexes in THF solvent.[14]

Through this preliminary study, several reactivity features of metallabenzene complex **1** have emerged. First, the electron-rich metal center directs much of the chemistry by undergoing ligand-dissociation, oxidative-addition, and electron-transfer processes. Second, the aromaticity of the ring system appears to be quite fragile and is, in fact, disrupted in several of the reactions reported herein. Future work will continue to explore the chemistry of metallabenzenes via-ã-vis their conventional organic counterparts.

Acknowledgment. Support from the National Science Foundation (Grants CHE-8520680 and CHE-9003159), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Johnson-Matthey, Inc. ($IrCl_3 \cdot 3H_2O$ loan) is gratefully acknowledged. Washington University's X-ray Crystallography Facility was funded by the NSF Chemical Instrumentation Program (Grant CHE-8811456).

Supplementary Material Available: Detailed descriptions of syntheses and spectra of compounds **2-5**, structure determination summaries, ORTEP drawings, and tables of final atomic coordinates, thermal parameters, bond lengths, and bond angles for **3** and **5** (22 pages); listings of observed and calculated structure factor amplitudes for **3** and **5** (53 pages). Ordering information is given on any current masthead page.

(9) Spectroscopic data for **4**: ^1H NMR ($CD_3C(O)CD_3$, 17 °C, 300 MHz) δ 13.95 (s, 2, H1/H5), 7.86 (s, 1, H3), 2.37 (s, 6, ring CH_3's), 2.12-1.90 (m, 12, PEt_3 CH_2's), 1.00-0.78 (m, 18, PEt_3 CH_3's); $^{13}C\{^1H\}$ NMR ($CD_3C(O)CD_3$, 17 °C, 75 MHz) δ 215.1 (s, C1/C5), 161.6 (s, C3), 134.8 (s, C2/C4), 25.4 (s, ring CH_3's), 19.3 (virtual t, J_{C-P} = 36.4 Hz, PEt_3 CH_2's), 8.6 (s, PEt_3 CH_3's); $^{31}P\{^1H\}$ NMR ($CD_3C(O)CD_3$, 17 °C, 121 MHz, referenced to external H_3PO_4) δ -22.6 (s). The structure of **4** has been confirmed by an X-ray diffraction study.

(10) The same product is obtained when the reaction is run in the presence of a Friedel-Crafts catalyst.

(11) Spectroscopic data for **5**: ^1H NMR ($CD_3C(O)CD_3$, 17 °C, 300 MHz) δ 8.16 (br d, J_{H-P} = 20.4 Hz, 2, H1/H5), 6.31 (s, 1, H3), 2.10 (s, 6, ring CH_3's), 2.20-2.00 (m, 12, PEt_3 CH_2's), 1.83-1.71 (m, 6, PEt_3 CH_2's), 1.29-1.20 (m, 18, PEt_3 CH_3's), 0.96-0.85 (m, 9, PEt_3 CH_3's); $^{13}C\{^1H\}$ NMR (C_4D_8O, 17 °C, 75 MHz) δ 229.8 (s, CO's), 135.7 (d of d, J_{C-P} = 74.5, 9.4 Hz, C1/C5), 107.9 (s, C2/C4), 99.5 (s, C3), 29.3 (s, ring CH_3's), 24.8-24.3 (m, PEt_3 CH_2's), 22.0-21.6 (m, PEt_3 CH_2's), 10.4 (s, PEt_3 CH_3's), 9.0 (s, PEt_3 CH_3's); $^{31}P\{^1H\}$ NMR ($CD_3C(O)CD_3$, 17 °C, 121 MHz, referenced to external H_3PO_4) δ 19.9 (t, J_{P-P} = 3.5 Hz, 1, axial PEt_3), -19.4 (d, J_{P-P} = 3.5 Hz, 2, basal PEt_3's).

(12) Crystal data for **5**: monoclinic, space group $P2_1/n$, a = 9.897 (1) Å, b = 16.213 (3) Å, c = 20.937 (3) Å, β = 96.68 (1)°, V = 3336.7 (9) Å^3, Z = 4.

(13) By comparison, the ν(CO) bands for (hexamethylbenzene)$Mo(CO)_3$ come at 1958 and 1882 cm^{-1}: Barbeau, C.; Turcotte, J. *Can. J. Chem.* **1976**, *54*, 1612.

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Investigations of the Biosynthesis of *trans*-(+)-*S*-1-Propenyl-L-cysteine Sulfoxide. Elucidation of the Stereochemistry of the Oxidative Decarboxylation Process

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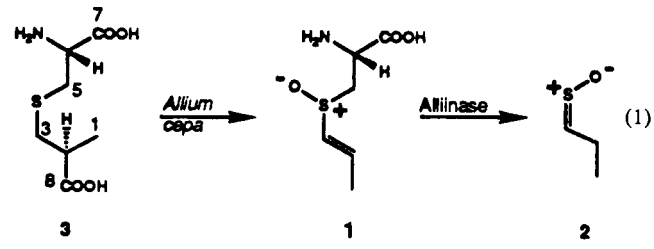
The novel amino acid *trans*-(+)-*S*-1-propenyl-L-cysteine sulfoxide (**1**) (PCS) is the constituent of the onion plant (*Allium cepa*)[1] that has been shown[1] to be the precursor of (*Z*)-propanethial *S*-oxide (**2**), the lachrymatory substance characteristic of this plant (eq 1).[2] Previous investigations in our laboratory[3]



(1)

3 1 2

have demonstrated that **1** is derived from (2*S*,6*R*)-(-)-*S*-(2-carboxy-*n*-propyl)cysteine (CPC) (**3**) by an oxidative decarboxylation process that proceeds with the loss of one hydrogen atom from C-3 of CPC and none from C-2. This observation indicated

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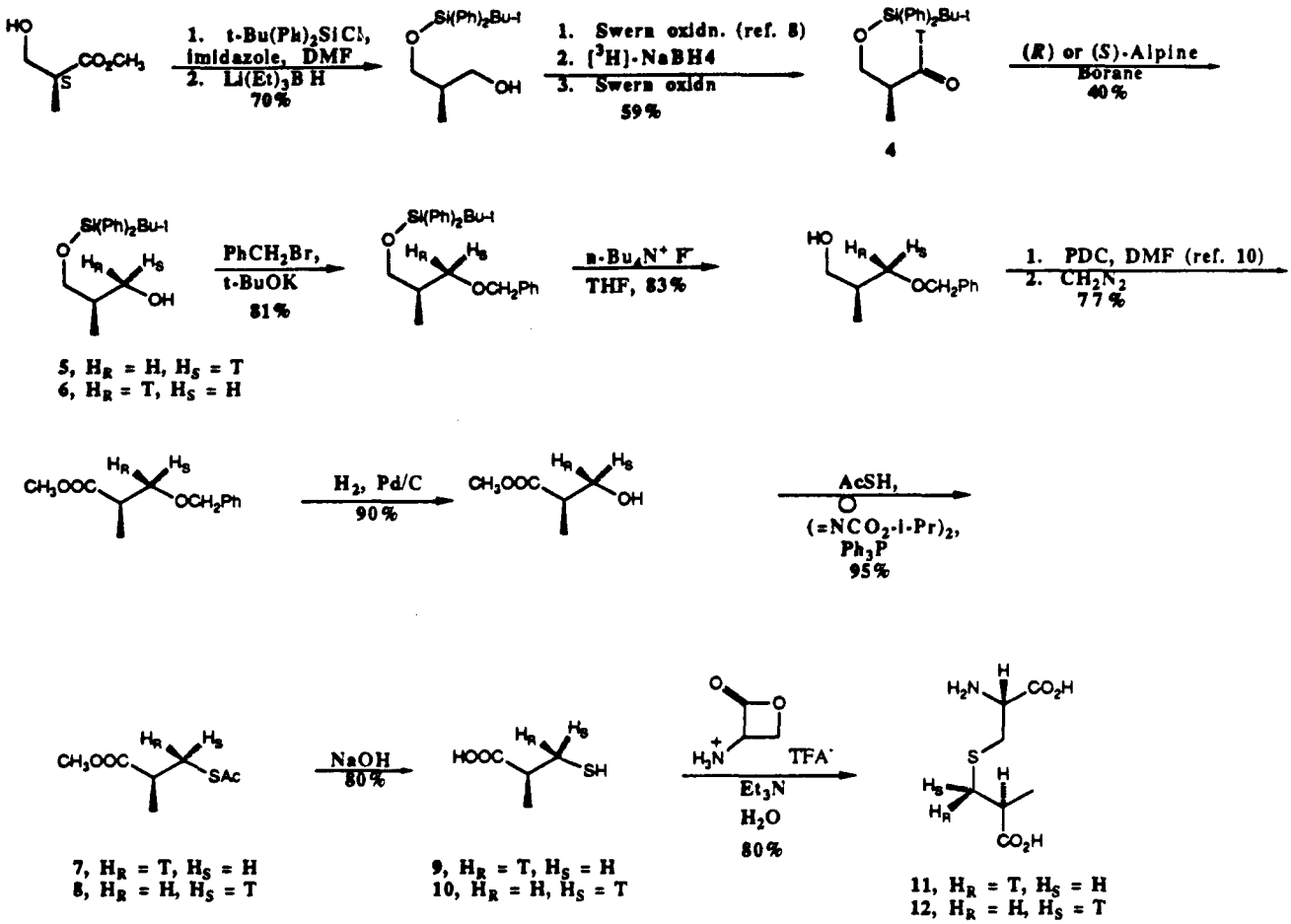
Scheme I



that the biosynthesis of PCS may be mechanistically related to the formation of vinyl groups in heme and chlorophyll from propionic acid side chains[4] and to the formation of uneven-numbered 1-alkenes from fatty acids in higher plants.[5] Since both of the latter decarboxylation reactions have been shown to proceed with anti geometry,[4,6] we decided to elucidate the stereochemistry of the decarboxylation reaction associated with PCS formation in order to determine the degree of kinship between this transformation and the other decarboxylation processes. We now report the results of these investigations.

Since naturally occurring (−)-*S*-(2-carboxy-*n*-propyl)-L-cysteine has previously been shown to possess the 2*S* configuration,[7] the stereochemistry of the decarboxylation reaction can be elucidated by means of precursor incorporation experiments with CPC that is stereospecifically tritiated at C-3. The synthesis of these compounds was accomplished as outlined in Scheme I. This synthesis included three crucial steps. The first was the reduction of the tritiated aldehyde **4** with *R*- or *S*-Alpine-Borane (Aldrich) to form the tritiated alcohols **5** and **6**, whose isotopic labels were assigned the *S* and *R* configurations, respectively, on the basis of literature precedent (vide infra).[9] The second was formation of the thiolacetates **7** and **8** using the Mitsunobu reaction; the configurations assigned to **7** and **8** are based upon the fact that the thiolacetate version of the Mitsunobu reaction has been shown to proceed with inversion of configuration.[11] The last critical step was treatment of the thiols **9** and **10** with the TFA salt of 2-amino-β-propiolactone[12] to form **11** and **12**. For reasons that are unclear, the β-propiolactone ring opening reaction could only be accomplished in the presence of triethylamine; the use of sodium hydroxide as the base proved completely unsatisfactory.

In order to be absolutely certain of the configuration of the tritium labels in **11** and **12**, the stereochemical outcome of the *S*-Alpine-Borane reduction was verified by synthesis of the deuterated analogue of aldehyde **4** and reduction of this compound with *S*-Alpine-Borane. The resulting deuterated alcohol was then converted to (*1R*)-(1-$^2H_1$)isobutanol, whose chirality was analyzed by the method of Gerlach.[13]

Precursor incorporation experiments with the stereospecifically tritiated forms of CPC required the use of an internal reference. (2*S*,6*R*)-[^{35}S]CPC was synthesized in three steps for this purpose. (*R*)-(−)-Methyl 3-hydroxy-2-methylpropionate was subjected to the Mitsunobu reaction using [^{35}S]thiolacetic acid[14] to give (*S*)-[^{35}S]-2-methyl-3-(thioacetoxy)propionate, base-catalyzed deprotection of this thiol ester gave the corresponding thiol, and the latter was then treated with the TFA salt of 2-amino-β-propiolactone. The resulting (2*S*,6*R*)-[^{35}S]CPC was mixed with **11** and **12** and the doubly labeled amino acid administered to 3-week-old onion plants by the cotton wick method. After 3 days, PCS was isolated by isotope dilution and treated with dilute ammonium hydroxide to give cycloalliin.[15] The mixture was then

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Table I. Administration of Labeled (2*S*,6*R*)-*S*-(2-Carboxy-*n*-propyl)cysteine to *A. cepa*

expt no.	labeling pattern in precursor **3**	isotopic ratio $^3H/^{35}S$ in precursor **3**	isotopic ratio $^3H/^{35}S$ in product **1**[a]	% ^3H retention
1	(3*S*)-[3-^{3}H,^{35}S]	6.94	4.87	70
2	(3*R*)-[3-^{3}H,^{35}S]	5.17	0.53	10

[a] The ratios are corrected for ^{35}S decay.

treated with sodium 2,4,6-trinitrobenzenesulfonate to remove primary amino compounds from the crude cycloalliin.[15] The recovered cycloalliin was converted to its hydrochloride salt, purified chromatographically, and then recrystallized repeatedly to constant isotopic ratio and constant specific activity. The results of the two incorporation experiments (Table I) demonstrate that CPC is converted into PCS with loss of the 3 *pro-R* hydrogen atom.[16] Since the configuration at C-2 of CPC is *S*, these results indicate that the oxidative decarboxylation reaction involved in the conversion of CPC to PCS proceeds with anti geometry. The formation of PCS from CPC therefore exhibits the same stereochemical preference as the decarboxylations associated with porphyrin and terminal alkene biosynthesis, and it appears that the mechanisms of these three decarboxylation processes may be closely related.[17]

Acknowledgment. We are pleased to acknowledge financial support of this research by the National Science Foundation (CHE8604611) and The Robert A. Welch Foundation (C-729).

(16) The tritium retention figure for (3*R*)-[3-^{3}H]CPC, which is derived from *R*-Alpine-Borane, is close to the theoretical value since the optical purity of *R*-Alpine-Borane is ca. 91%. However, that for (3*S*)-[3-^{3}H]CPC is somewhat lower than expected since the optical purity of *S*-Alpine-Borane is ca. 87%. This is undoubtedly due to the fact that the optical purity of the tritium label in the 3*S* isomer is low. NMR analysis of the chirality of the (1*R*)-(1-^{2}H$_1$)isobutanol obtained from the product of *S*-Alpine-Borane reduction of the deuterated aldehyde indicated that only about 70% of the deuterium label was in the *pro-R* position. This degree of stereoselectivity is lower than is usually encountered in Alpine-Borane reductions. Since the reductions were carried out with an excess of the reagent, the lower optical purity of the alcohol obtained from the *S*-Alpine-Borane reduction may be due to a difference in the rate of reduction of the chiral aldehydes by the two enantiomeric forms of Alpine-Borane.

(17) It is interesting to note that the same hydrogen atom in an absolute stereochemical sense is removed from C-3 of CPC and from C-3 of fatty acids by the corresponding plant enzyme systems.

Enhanced Transport of Nucleosides and Nucleoside Analogues with Complementary Base-Pairing Agents

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Recently, nucleoside analogues have been the focus of attention because of their potential utility in antiviral chemotherapy.[1] For example, 9-[(2-hydroxyethoxy)methyl]-9*H*-guanine (acyclovir, **1**)[2] is used to treat herpes infections, and a broad family of nucleosides containing a 2′,3′-dideoxyribose, including 2′,3′-dideoxycytidine (ddC, **2**)[3] and 3′-azido-2′,3′-dideoxythymidine (AZT, **3**)[4] (an approved drug for the treatment of AIDS), have been shown to have anti-HIV activity.[5] Mechanistically, after these substances enter the cells by simple diffusion[6] or with help of membrane-bound transport proteins,[7] phosphorylation in the cytoplasm produces active nucleotide analogues which can inhibit an essential viral enzyme, such as DNA polymerase, and/or terminate the growing virus DNA chain.[8] Therefore, a first requirement for drug activity is the transport of these nucleoside analogues into diseased cells through the lipophilic membrane barrier.[9] If selective carriers were available for various nucleoside-type prodrugs, they could be used to enhance into-cell transport of these substances. We now report a new approach to through-membrane transport based on complementary base-pairing.

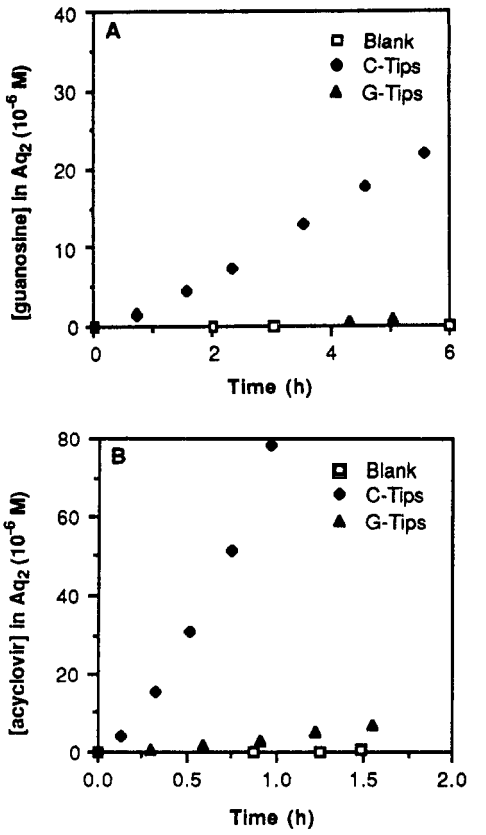

Figure 1. Time course of guanosine (frame A) and acyclovir (frame B) transport through a liquid chloroform membrane effected by using the silylated species C-Tips (**6**) and G-Tips (**7**). Blank refers to control experiments carried out without any added carrier.

Prior studies with various three-phase [Aq$_1$]-[hydrophobic membrane]-[Aq$_2$] systems (Aq = aqueous) have shown that substrate binding, substrate–carrier complex diffusion, and sub-

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