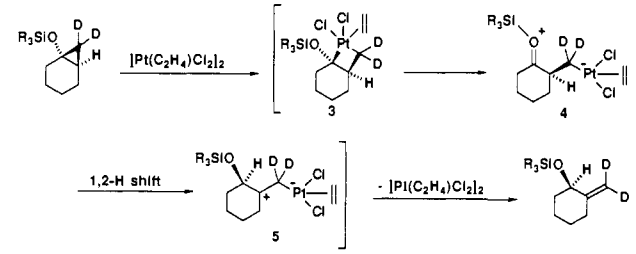
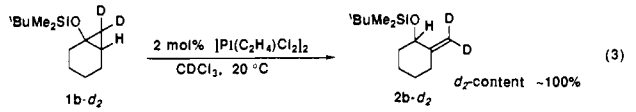
Scheme I



ization of a variety of 2-alkyl-substituted siloxycyclopropanes **1** and found the reaction to be quite general. Reaction of a chloroform solution of **1** with 2–10 mol % of Zeise's dimer at room temperature for 0.5–10 h afforded allyl silyl ethers **2** in good to excellent yields (Table I). Olefin formation was regioselective, and no other isomeric enol silyl ethers were detected.[8] Bicyclic siloxycyclopropanes **1a** and **1b** having 5- and 6-membered rings underwent a particularly rapid isomerization to **2a** and **2b**, respectively (entries 1 and 2). 2-Alkyl-substituted **1f**, prepared from 3-methylbutanal in two steps, was similarly converted to **2f** (entry 6). In all cases studied, the ring opening of **1** took place only between the methylene and the siloxy carbons. Other solvents (CH_2Cl_2, CH_3CO_2Et, THF, Et_2O, and PhH) can also be used to affect the isomerization.

To gain some insight into this reaction, an experiment using a deuterium-labeled substrate was carried out. The reaction of **1b**-d_2, possessing two deuteriums at a peripheral carbon in the cyclopropane ring, with 2 mol % of Zeise's dimer in $CDCl_3$ afforded **2b**-d_2 with ~100% d_2 content (eq 3). The two deuteriums were located exclusively on the exocyclic methylene carbon.[9]



The reaction of chiral siloxycyclopropane **1i** is noteworthy in terms of its stereochemistry and mechanism. The isomerization of **1i** afforded an optically active allyl silyl ether **2i** in which the observed stereochemistry of the siloxy carbon corresponded to ~100% inversion of configuration (entry 9).[10] Diastereoselective isomerization of **1j** also proceeded with inversion at the siloxy carbon (entry 10).[11] It is known that β-hydrogen abstraction causes the decomposition of platinacyclobutanes into olefins.[12] However, this mechanism seems less likely in our case, since β-hydride elimination and subsequent reductive elimination at the siloxy carbon should cause retention of configuration. Thus, we propose the reaction pathway involving a zwitterion (Scheme I) to explain the above stereochemical outcome. First, the insertion of platinum between the methylene and siloxy carbons takes place to form platinacycle **3**. Heterolytic cleavage of the platinum–siloxy carbon bond to give a zwitterion **4**, followed by a 1,2-hydrogen shift at the β-carbon to platinum, gives the allyl silyl ether. The key factor in this reaction would be stabilization of **4** by the siloxy group which permits the catalytic process.

We anticipate that the mildness and efficiency of the Pt(II)-promoted isomerization of siloxycyclopropanes to allyl silyl ethers will find considerable use in organic chemistry.[13]

Acknowledgment. We thank Professor S. Murai at Osaka University and Professors A. Tai and T. Sugimura at Himeji Institute of Technology for helpful discussions. We also thank Professor H. Alper at the University of Ottawa for his valuable comments. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture of Japan.

Supplementary Material Available: Typical experimental procedure and spectral data for all compounds prepared (4 pages). Ordering information is given on any current masthead page.

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(13) A number of natural products contain the 2-methylene alcohol moiety. For recent syntheses of such natural products, see: (a) Salomon, R. G.; Basu, B.; Roy, S.; Sachinvala, N. D. *J. Am. Chem. Soc.* **1991**, *113*, 3096. (b) Majetich, G.; Song, J.-S.; Ringold, C.; Nemeth, G. A.; Newton, M. G. *J. Org. Chem.* **1991**, *56*, 3973. (c) Posner, G. H.; Nelson, T. D. *J. Org. Chem.* **1991**, *56*, 4339. (d) Kabat, M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1991**, *32*, 2343. (e) Nagasawa, K.; Zako, Y.; Ishihara, H.; Shimizu, I. *Tetrahedron Lett.* **1991**, *32*, 4937. (f) Smith, R. J.; Mahiou, B.; Deinzer, M. L. *Tetrahedron* **1991**, *47*, 933. (g) Vedejs, E.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 4357. (h) Kobayashi, S.; Shibata, J.; Shimada, M.; Ohno, M. *Tetrahedron Lett.* **1990**, *31*, 1577.

Chemistry of Isoprenylated Cysteinyl Containing Peptides. [2,3] Sigmatropic Rearrangement of *S*-Farnesylcysteinyl Sulfoxides. Studies toward a Mild Method of Deprenylating Lipopeptides

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The recent identification of posttranslational modifications which involve the S-isoprenylation of cysteinyl residues to form thioether-containing lipoproteins has received a great deal of attention, most notably due to the role of farnesylated proteins in cancer mediated by *ras* oncogenes.[1] The chemical literature of isoprenylated cysteine systems is sparse,[2,3] and present methods for deprenylation of proteins/peptides, and hence structural identification, are limited and involve fairly harsh conditions (Raney nickel desulfurization, sulfonium ion formation).[4] Though these procedures may suffice for simple isoprenoids, they may ultimately be inadequate should lipid components be isolated which contain more delicate functionalities[5] (such as allylic alcohols as

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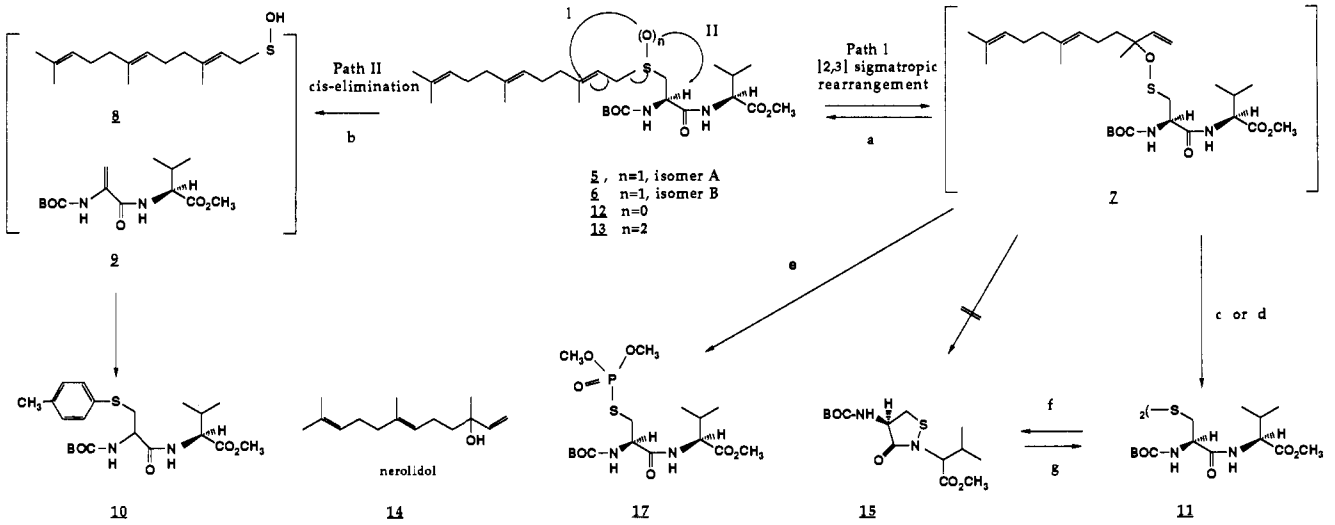
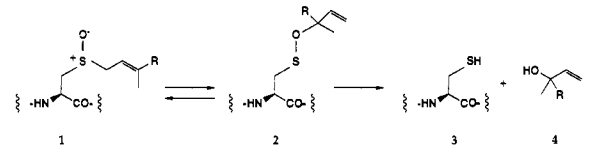
Scheme I[a]



[a] (a) Benzene, 80 °C. (b) Benzene, 80 °C, 4 days, excess *p*-thiocresol. (c) Boc-Cys-Val-OMe, benzene/pyridine 10:1, 80 °C, 24 h (>50%). (d) Triphenylphosphine, benzene, 80 °C, 24 h (31% **11**, 3.5% **12**, 1% **13**, 54% **14**). (e) Trimethyl phosphite, benzene, 80 °C, 24 h (63.5% **17**, 5% Boc-*S*-methyl-Cys-Val-OMe, 28% **14**). (f) Bromine (2.4 equiv), pyridine/methylene chloride 2:1, −78 °C, 24 h. (g) Boc-Cys-Val-OMe, benzene/pyridine, 26 °C, 24 h.

found in the lipopeptide tremerogen A-10). Herein, we report new chemistry of isoprenoid cysteinyl peptides, which may be applied toward the development of a mild deprenylation method.

Isoprenylated cysteines are allylic sulfides, and their corresponding sulfoxides (i.e., **1**) are expected to undergo reversible [2,3] sigmatropic rearrangement via the sulfoxide/sulfenate equilibrium.[6] If the sulfoxide/sulfenate equilibrium could be established (**1** to **2**), precedent suggests that addition of thiophilic nucleophiles should cleave the sulfenate (**2**) and thus lead, overall, to a mild deprenylation sequence for S-prenylated lipoproteins/peptides (i.e., **3** and **4**). In addition, however, to path I (Scheme I), cis elimination[7] (path II) is a potential competing pathway in the thermolysis of peptidyl S-isoprenylated cysteine sulfoxides (i.e., **5** and **6**), leading to a dehydroalanyl peptide (**9**) and isoprenylsulfenic acid (**8**), an unstable entity expected to spontaneously undergo further transformations (i.e., dimerization, cyclization, etc.[8]).



1 2 3 4

Since the Cys[186]–Val[187] sequence is present in human p21 H-*ras*, the sulfoxide(s) of Boc-*S*-farnesylcysteinylvaline methyl ester was chosen as a prototype model system to investigate the above. Synthesis of the model proceeded in a straightforward manner from *S*-farnesylcysteine[9] to produce two chromatographically separable, diastereomeric sulfoxides (**5** and **6**) (MCPBA, 23% and 31%, respectively). Heating of either sulfoxide in benzene gave rise to an equilibrium mixture of the pair, indicating that epimerization was likely[10] proceeding via sulfenate **7**. Under these conditions, the intervention of path II did not materialize, and the formation of **8** or **9** was not observed.[11]

A variety of thiophilic nucleophiles were employed to trap **7** and initiate deprenylation. *p*-Thiocresol reacted only slowly with **5** and **6** in refluxing benzene (4 days) to produce small quantities of aryl sulfide **10**, suggesting a slow cis elimination to give **9** followed by a Michael-type addition of thiol. Under these conditions, Boc-Cys-Val-OMe also reacted slowly with **5** and **6**, however, addition of a small quantity of pyridine caused a rapid conversion to disulfide **11** (>50%) and nerolidol (**14**).[12] The presence of nerolidol is an expected consequence of sulfenate cleavage and hence confirms the [2,3] sigmatropic rearrangement pathway. In the absence of external thiophiles and in the presence of a base, sulfenate **7** could undergo a base-assisted displacement by the neighboring amido nitrogen on sulfenate. We speculate that the interesting peptidyl isothiazolidones (i.e., **15**) which would result from such *intramolecular* attack might be important intermediates in protein folding/refolding mechanisms, since in principle they could mediate facile disulfide interchange as mild peptidyl sulfenyl donors.[13] We prepared authentic peptidyl isothiazolidone **15** by bromination of disulfide **11**,[14] but did not observe this substance when sulfenate **7** was generated in the presence of nonnucleophilic bases.[15]

In contrast to thiol nucleophiles, reaction of isoprenyl sulfoxides with phosphorous-based reagents was rapid in hot benzene. Reaction of **5** and **6** with triphenylphosphine afforded disulfide **11** (31%) as the major product, along with isoprenoid sulfide **12** (1%), sulfone **13** (3.5%, authentic sample obtained by oxone

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(10) In addition to the sulfoxide/sulfenate equilibrium, sulfoxides may also thermally epimerize by pyramidal inversion (Rayner, D. R.; Gordon, A. J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4854) or by homolysis and recombination (Miller, E. G.; Rayner, D. R.; Thomas, H. T.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4861).

(11) An authentic sample of dehydroalanyl **9** was prepared by tosylation/elimination of Boc-Ser-Val-OMe (ref 14a).

(12) Identical with an authentic racemic sample from Aldrich Chemical Co. Decay of chiral information from the pure sulfoxides is expected to be rapid due to the facility of the sulfoxide/sulfenate equilibrium; hence, it is not expected that sulfinyl asymmetry will be transferred to the nerolidol component.

(13) Allison, W. S. *Acc. Chem. Res.* **1976**, *9*, 293–299.

(14) Over-oxidation of **11** with excess bromine leads to mixtures containing mostly isothiazolones and the diastereomeric *S*-oxides of **15**: (a) Gordon, E. M. Ph.D. Thesis, University of Wisconsin, Madison, WI, 1973. (b) Lake, J. R. Ph.D. Thesis, University of Wisconsin, Madison, WI, 1974. (c) Morin, R. B.; Gordon, E. M.; Lake, J. R. *Tetrahedron Lett.* **1973**, 5213–7.

(15) Consistent with an expected sulfenyl donor role, Boc-Cys-Val-OMe reacts with **15** under mild conditions to regenerate **11**.

oxidation of **5** and **6**), and nerolidol **14** (54%). Alternatively, treatment of **5** and **6** with trimethyl phosphite smoothly produced thiophosphate **17** (63.5%), Boc-*S*-methyl-Cys-Val-OMe (5%), and nerolidol (**14**) (28%). The peptidyl reaction products are accounted for by the inter- or intramolecular decomposition of the expected thiophosphonium reaction intermediate.[16] Of special relevance for structure identification of unknown prenylated proteins/peptides is that the isoprene unit can be cleaved from the peptide and identified while *simultaneously* tagging the cysteinyl residue with phosphite. Thus, the mild removal of an isoprenoid from cysteine recommends the further development of these methods and also suggests that allylic sulfides/sulfoxides might find utility in peptide chemistry as orthogonally removable thiol protecting groups.

(16) Mikolajczyk, M.; Krzywanski, J.; Ziemnicka, B. *J. Org. Chem.* **1977**, *42*, 190 and references therein.

(17) All compounds described herein exhibited ^{1}H NMR, ^{13}C NMR, infrared, and mass spectra, as well as combustion analyses or high-resolution mass spectra, which were consistent with the assigned structures.

Complete Elimination of Spin Diffusion from Selected Resonances in Two-Dimensional Cross-Relaxation Spectra of Macromolecules by a Novel Pulse Sequence (SNOESY)

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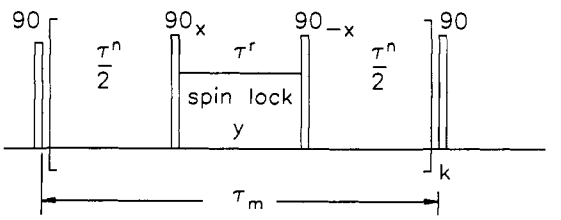
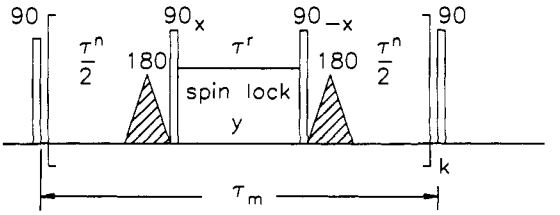
Spin diffusion represents a serious obstacle to the determination of highly accurate NMR solution structures. In ordinary NOESY (or ROESY) experiments, indirect magnetization transfer (spin diffusion) takes place simultaneously with direct magnetization transfer, but only the latter can be readily interpreted in terms of molecular geometry. The new method we report here (SNOESY) permits the evaluation of cross relaxation between a selected spin (or group of isolated spins) and *all* of its neighbors. Magnetization transfer between all other spin pairs is prevented, and thus spin diffusion is eliminated completely. Since longer mixing times can be used with SNOESY than with NOESY (or ROESY) without incurring complications from spin diffusion, SNOESY may permit the observation of pure, direct magnetization transfer between more distant spins and improve the quality of solution structures of macromolecules.

Several approaches have been taken to the spin diffusion problem. The amplitudes of spin-diffusion contributions can be diminished by using short cross-relaxation times in NOE spectroscopy.[1] Spin-diffusion effects can be evaluated by analysis of build-up curves,[2-4] by complete relaxation matrix analysis,[5] or

Scheme I



Scheme II



by linear combinations of laboratory-frame and rotating-frame cross-relaxation data (DNOESY).[6] All of these approaches are passive, since spin diffusion takes place during the experiment and is removed only later during data processing and evaluation.

An appealing alternative approach is to suppress spin diffusion in real time during the experiment. Experiments have been described where one[7,8] or a few[8] particular cross-relaxation pathways have been eliminated from the complete cross-relaxation network. These experiments can be used to uncover particular spin-diffusion steps, but they selectively suppress only one pathway, and they fail to prevent cross relaxation through the many remaining pathways. The selective NOESY experiment proposed here, which is derived from methods reported earlier,[8,9] exploits the difference between cross-relaxation rates in the rotating frame (σ^r) and the laboratory frame (σ^n) in macromolecules (eq 1).[10]

$$\sigma^r = -2\sigma^n \tag{1}$$

In a normal NOESY (or ROESY) experiment, cross relaxation takes place simultaneously between all pairs of neighboring spins. Since many pathways are active, it is not easy to separate the contribution of a given direct cross-relaxation step. For example, cross relaxation between spins s and k can occur directly or through a number of indirect pathways (e.g., $s \rightarrow l \rightarrow k$). In the compensated experiment (Scheme I), magnetization is flipped rapidly between the rotating and laboratory frames during the mixing time, τ_m; all effective cross-relaxation rates are zero, and spin diffusion cannot take place. The effective cross-relaxation rate between spins k and l is given by the following:[11]

$$\sigma_{kl}^{eff} = \sigma_{kl}^{n}\frac{\tau^n}{\tau_m} + \sigma_{kl}^{r}\frac{\tau^r}{\tau_m} \tag{2}$$

where $\tau_m = \tau^n + \tau^r$. If $\tau^n = 2\tau^r$, eqs 1 and 2 yield $\sigma_{kl}^{eff} = 0$; thus, there is no cross relaxation and, consequently, no spin diffusion.

If sequence I (given in Scheme I) is modified such that resonance s is selectively inverted each time the reference frame is

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† University of Belgrade.
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§ University of Wisconsin.

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(8) Fejzo, J.; Westler, W. M.; Macura, S.; Markley, J. L. *J. Magn. Reson.* **1991**, *92*, 195.

(9) Fejzo, J.; Westler, W. M.; Macura, S.; Markley, J. L. *J. Magn. Reson.* **1991**, *92*, 20.

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(11) (a) Griesinger, C.; Otting, G.; Wüthrich, K.; Ernst, R. R. *J. Am. Chem. Soc.* **1988**, *110*, 7870. (b) Bearden, D. W.; Macura, S.; Brown, L. R. *J. Magn. Reson.* **1988**, *80*, 534.

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