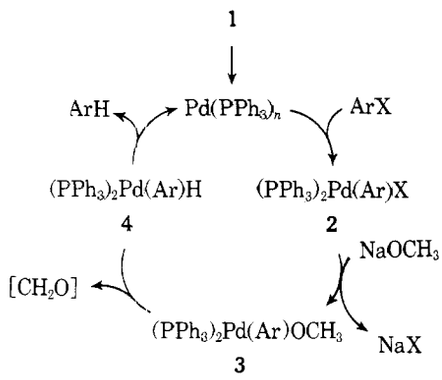
Scheme I



from the formaldehyde or possibly from the solvent, DMF. Also, the nature of the palladium species remaining after completion of the reaction has not been investigated. Therefore, we cannot rule out other possible mechanisms at this time.

The formation of the various side products is explainable on the basis of Scheme I. Biaryls have previously been obtained from arylpalladium complexes.[17] Reductive elimination from 3 would produce anisoles, and metathetical displacement of halide from 2 by the *N,N*-dimethylamide ion derived from DMF would lead to anilines. Formation of benzene may result from cleavage of a carbon–phosphorus bond of the triphenylphosphine ligand, a process for which several other workers have reported evidence.[18]

A typical procedure is given for the reduction of 2-bromonaphthalene (run 4). Into a round-bottom flask equipped with a magnetic stirring bar were placed 2-bromonaphthalene (0.414 g, 2.00 mmol), sodium methoxide (0.162 g, 3.00 mmol), and 1 (0.116 g, 0.100 mmol) at 25 °C. The mixture was then placed under nitrogen, DMF (4 mL) was added, and the heterogeneous yellow mixture was heated at 100 °C for 4 h. The resulting orange solution was cooled to 25 °C and diluted with ether, water, and pentane. The crude product was isolated from the organic layer and was purified by sublimation [75–140 °C (16 Torr)] to afford 0.218 g (85%) of naphthalene as white crystals, mp 79–80 °C (lit.[19] mp 80.2 °C).

Further work is in progress to explore other conditions for performing the reduction,[20] the generation of the catalyst in situ, the use of other transition metal species as catalysts, and the reduction of other types of organic halides and of other classes of compounds. We also intend to investigate conditions for obtaining the biaryls as the major products because of the important potential of this reaction to provide a metal-*catalyzed* method for the coupling of aryl halides as opposed to the usual methods which employ stoichiometric amounts of metal-containing reagents.[21–23]

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(22) An approach to optimization of biaryl formation is to employ a reducing agent which is capable of reducing Pd(II) to the catalytically active Pd(0) species but which does not lead to reduction of the aryl halides.
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1,2-Transposition of Ketones via Vinylsilanes

Summary: New methodology for shifting a ketone carbonyl by one carbon is described. The scheme, which involves sequential vinylsilane generation from an arenesulfonyl hydrazone, epoxidation, hydride reduction, and chromic acid oxidation, is both simple and efficient.

Sir: The carbonyl group plays a pivotal role in bringing latitude to organic synthesis. The need to relocate this functional group within a molecule occurs with such frequency that interest in efficient methods of carbonyl transposition remains high. Various procedures have been developed for effecting site exchange within saturated[1–9] and α,β-unsaturated ketones,[10–13] sometimes in tandem with an alkylation step,[14–17]

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Table I. Carbonyl Transposition Data[a,b]

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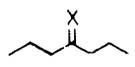
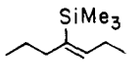
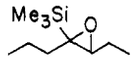
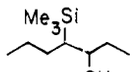
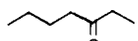
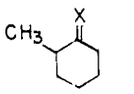
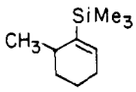
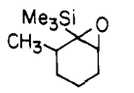
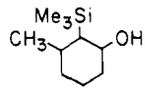
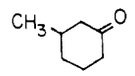
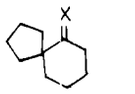
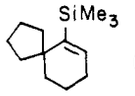
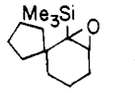
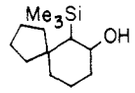
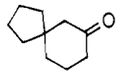
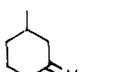
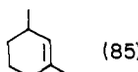
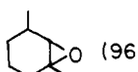
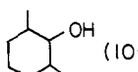
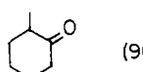
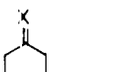
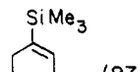
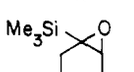
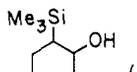
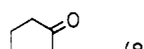
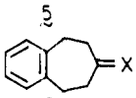
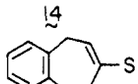
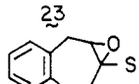
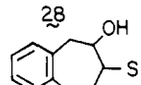
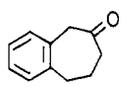
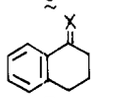
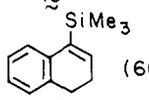
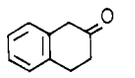
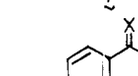
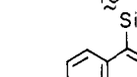
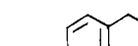
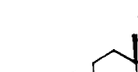
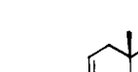
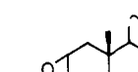
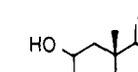
 1	 (96) 10	 (97.5) 19	 (88)	 (84)
 2	 (91) 11	 (89) 20	 (83) 26	 (84)
 3	 (67) 12	 (91) 21	 (95)	 (66)[f]
 4	 (85) 13	 (96) 22	 (100)	 (90)
 5	 (97) 14	 (87) 23	 (e) 28	 (83)
 6	 (89) 15	 (100) 24	 (100)	 (63)[g]
 7	 (66) 16	d	d	 (83)
 8	 (67) 17	d	d	 (96)
 9	 (33) 18	 (100) 25	 (43)[h]	(87)

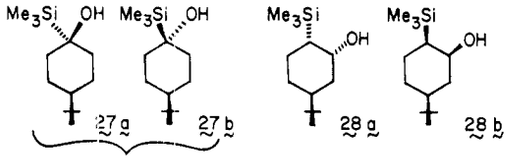
[a] All compounds were identified by IR, NMR, and accurate mass spectral measurements. Additionally, the vinylsilanes were characterized by combustion analysis. The transposed ketones were identified by comparison with authentic samples of the ketones or derivatives thereof. [b] The percentage yields which are provided in parentheses represent the isolated yields at each step. [c] For convenience purposes, these structures will be further defined as follows: **a**, X = O; **b**, X = $NNHSO_2C_6H_5$. [d] These intermediates were not isolated under the conditions employed (see text). [e] See text for discussion of results. [f] Reference 5. [g] G. Bodennec and M. St. Jacques, *Can. J. Chem.*, **55**, 1199 (1977). [h] The remainder of the product was the α-silyl alcohol.

and these have met with varying degrees of accepted usage. We now wish to describe a quite different approach to the 1,2-transposition of ketones which takes advantage of the chemical properties associated with covalently bonded silicon.

Previous work in this laboratory[18] and elsewhere[19] has demonstrated that vinyl carbanions generated through reaction of ketone arenesulfonyl hydrazones with alkyllithium reagents in TMEDA solution[20] condense with chlorotrimethylsilane to deliver vinylsilanes in very good yield. Where relevant, this transformation is regiospecific, deprotonation occurring perferentially for electronic reasons at the lesser substituted α position.[21] A representative selection of such conversions is provided in Table I.

The vinylsilanes undergo smooth oxidation to their epoxides[22] at 0 °C in dichloromethane solution with 1.1 equiv of *m*-chloroperbenzoic acid. Subsequent reductions with lithium aluminum hydride were performed in anhydrous tetrahydrofuran at room temperature (**19, 20,** and **23**) or under reflux conditions. In early work, Eisch and Trainor discovered that hydride attack on α-silyl epoxides occurs preferentially at the silicon-bearing carbon.[23] More recently, Robbins and Whitham have demonstrated that hydride reduction of the conformationally flexible 1,2-epoxy-1-trimethylsilylcyclohexane molecule is stereospecific as well, *cis*-2-trimethylsilylcyclohexanol being the only product isolated.[24] In the present study, we have found that the electronic directing effect of silicon is inadequate to overcome the normal kinetic bias for trans diaxial ring opening in conformationally rigid systems. When ring inversion is not severely impeded as in **20, 21, 22,**

Table II. Specificity of Mixed Hydride Reductions of 23a and 23b[a]



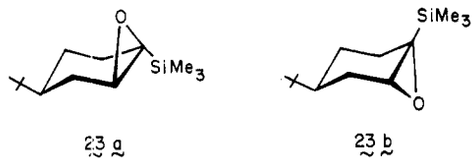
$LiAlH_4/AlCl_3$	Probable effective reagent	27a + 27b	28a	28b
1:0	$LiAlH_4$	76	24	
1:1.2	$AlHCl_2$	23	59	18
1:1	AlH_2Cl	5	64	31
2:1	$AlH_2Cl + AlH_3$	9	50	41
3:1	AlH_3	11	57	32

[a] Reactions conducted in anhydrous ether at 0 °C to room temperature. The percentage composition values given were obtained by vapor-phase chromatography (thermal conductivity detector), are uncorrected as to relative response to detection, and are normalized to exclude small amounts of recovered epoxide. [b] Structural assignments to these alcohols were made chiefly on the basis of their ^1H NMR spectra [W. K. Musker and G. L. Larson, *Tetrahedron Lett.*, 3481 (1968)].

and **24**, ring opening occurs by regiospecific α attack in the usual manner. For example, vinylsilane **11**, which is presumed to exist as a pair of rapidly equilibrating conformational isomers,[25] is converted to the epoxide mixture **20a** and **20b**

(38:62). These isomers were separated by vapor phase chromatography, identified by $Eu(fod)_3$ shifting of their ^1H NMR spectra,[26] and separately reduced to give only β-trimethylsilylated alcohol.

When the identical reduction procedure is applied to more rigid α-silyl epoxides such as **23** and **25**, mixtures result. Our findings with **23** are exemplary (Table II). Upon epoxidation of **14**, there was produced a 40:60 mixture of **23a** and **23b**



which, because it proved difficultly amenable to separation, was utilized as such. It is, of course, not feasible to estimate accurately the ground- and transition-state conformational interaction energies which gain importance within **23a** and **23b** as reduction proceeds. Nor can some degree of anomalous mechanistic behavior be ruled out in such reactions.[27] However, the level to which **27a** and **27b** are produced in the presence of $LiAlH_4$ alone is clearly not at all acceptable for our synthetic purposes. As a means of enhancing the electrophilic nature of the α carbon in such epoxides, we have examined the efficacy of various "mixed hydrides"[28] and uncovered remarkably enhanced specificity for α attack, particularly with AlH_2Cl (95% combined yield of **28a** and **28b**).[29]

Application of similar methodology to **25** likewise results in higher levels of α-bond fission, thereby illustrating the versatility of this modification.

Typically, the β-silylethanols are oxidized with a stoichiometric quantity of chromic acid under two-phase (ether/water) conditions[31] to deliver the pure transposed ketone. The rate of acid-promoted desilylation[32] of the intervening α-silyl ketones was found to be accelerated by increased amounts of acid and therefore 10 molar equiv of H_2SO_4 were routinely utilized.

In the case of the activated vinylsilanes **16** and **17**, treatment with buffered ($NaHCO_3$) *m*-chloroperbenzoic acid in dichloromethane led directly to the corresponding β-tetralone in high yield and there was no need for the customary reduction–oxidation sequence. The precise course of these one-step reactions has not been elucidated.

The present approach to 1,2-carbonyl transposition complements the existing methods. It employs a different substrate, a vinylsilane, as the relay intermediate. Since the ready availability of the latter from ketones is now well documented,[18,19] and since their subsequent chemical manipulation is exceptionally efficient, the scheme serves as a promising means for effecting the 1,2 migration of a carbonyl group. It is also minimally time consuming, since the intermediate products need not be isolated, but simply freed of solvent prior to further manipulation.

Acknowledgments. Support of our research program by the National Cancer Institute (CA-12115) and Eli Lilly and Company is acknowledged with gratitude. The authors thank Mr. Rhys Daniels for his efforts with the spiroketone **3**.

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(29) Reduction of **23** with AlD_2Cl afforded **28a** containing the isotopic label only at C_1, α to the silicon atom (^1H NMR analysis). Structural assignment to this alcohol was further secured by its reaction with sodium hydride in tetrahydrofuran to give 4-*tert*-butylcyclohexene-*1-d* (>92.5% d_1 by mass spectroscopy). Accordingly, the stronger Lewis acid character of AlH_2Cl and AlD_2Cl does not appear to bring into play a new mechanism such as initial electrophilic α C–O fission with concomitant intramolecular 1,2-hydride shift and subsequent normal reduction of 3-*tert*-butylcyclohexanone. The possible intervention of a pentacoordinated silicon hydride intermediate[30] which provides directionality to this epoxide-opening process has been neither established nor disproven.

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Peptide-Gap Inhibitors.[2] 2. Stereoselective Synthesis of Enantiomeric Dipeptide Analogues of Glycylleucine Which Contain Methylene Thioether Groups Substituted for Peptide Linkages

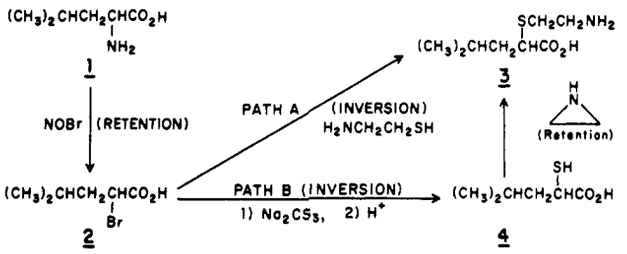
Summary: Stereoselective syntheses of (*R*)- and (*S*)-(*S*-cysteaminyl)-4-methylpentanoic acids have been developed which involve: (a) displacement of bromide in the appropriate enantiomers of 2-bromo-4-methylpentanoic acid by cysteamine; or (b) displacement of bromide of these substrates with thiocarbonate followed by aminoethylation of the resulting 2-mercapto-4-methylpentanoic acids.

Sir: Recently we reported from this laboratory that the dipeptide analogue *S*-2-(*S*-cysteaminyl)-4-methylpentanoic acid (**3**) binds several times more tightly to aminopeptidase M than the natural substrate glycyl-L-leucine.[1] **3** is a member of a class of peptide analogues which contain methylene thioether groups substituted for the peptide bond atoms. Model building as well as enzymatic studies indicate that such analogues may satisfy binding requirements while being resistant to enzymatic hydrolysis.[1] It is, therefore, clear that practical routes to such analogues would permit access to a broad new avenue for study and modulation of biological control. Accordingly, the purpose of this communication[2] is to describe for the first time two complementary synthetic paths which provide a general basis for gram scale preparation of peptide analogues of Gly–X, where X may be a variety of amino acids. The syntheses described are for the instances where X is L- or D-Leu.

Scheme I summarizes the routes. Treatment of D-leucine (**1**) (16.4 g, 125 mmol) with nitrosyl bromide,[3] followed by distillation of the crude product, gave 15.1 g (77.4 mmol) of purified (*R*)-2-bromo-4-methylpentanoic acid (**2**)[4]: bp 97–98 °C (0.25 mm); $[\alpha]_D^{22}$ +38.2 ± 1.8° (*c* 2, methanol) [lit. (*S* isomer),[4a] $[\alpha]_D^{27}$ −34° (methanol)]. The (*R*)-bromo acid (5.3 g, 27 mmol) was dissolved in 530 mL of nitrogen-purged 0.5 M $NaHCO_3$ and a threefold molar excess of 2-mercaptoethylamine hydrochloride (9.2 g, 81 mmol) was added (path A, Scheme I). The reaction vessel was flushed with nitrogen for 1 h and then sealed. After standing 24 h at room temperature, automatic amino acid chromatography revealed that 70% of **2** had been converted to **3**.

The solution was acidified with 6 N HCl and extracted twice

Scheme I



with ether. The ether extracts were discarded. The aqueous portion was neutralized with 2 N NaOH and diluted to 2 L with deionized water. This solution was desalted on a 5.5 × 30 cm column of Dowex 2-X8 resin according to Dréze et al.[5] The fractions from the 1 M acetic acid wash containing **3** were pooled and evaporated to dryness under reduced pressure. The residue was triturated with 20 mL of acetone (discarded) and then crystallized from 47.5% ethanol to give white needles (yield: 2.34 g, 12.1 mmol, 44.5%): mp 205–210 °C dec. For analytical purposes, **3** was subjected to gel filtration on Sephadex G-15 using 0.1 M acetic acid as eluent and was further crystallized: anal ($C_8H_{17}NO_2S$) C, H, N, S; mol wt 191, QM^+ (*m/e*) 192; $[\alpha]_D^{21}$ −23.2 ± 1.2° (*c* 2, H_2O); ^1H NMR (90 MHz, 2 N DCl in D_2O) multiplets centered at δ 0.902 (6 H), 1.622 (3 H), 2.919 (2 H), 3.221 (2 H), 3.475 (1 H) ppm (DSS as standard); TLC R_f 0.48 (1-butanol–acetic acid–H_2O, 12:3:5, silica gel). **3** is resistant to 6 N HCl hydrolysis (24 h, 110 °C, 91% recovery) and elutes near the position of arginine during automatic amino acid chromatography of the single column type[6] (ninhydrin constant, 0.82 times that of leucine).

Alternatively, the same enantiomer of **3** may be prepared in two steps (path B) from the bromo acid **2**. Bromide was displaced with trithiocarbonate and the resulting thioester was decomposed with acid.[7] The product was extracted with ether and the ether extract was dried over sodium sulfate. Removal of the ether at reduced pressure left an oil which was subjected to vacuum distillation to give purified (*S*)-2-mercapto-4-methylpentanoic acid (**4**): $[\alpha]_D^{22}$ −23.8 ± 1.8° (*c* 1.8, ether) [lit[4b] $[\alpha]_D^{20}$ −15.6° (ether)]. Treatment of **4** with ethylene imine[8] gave crude **3**. Purification by Dowex 2-X8 column chromatography and recrystallization from 47.5% ethanol gave a 56% yield of **3** based on **4** or an overall yield from D-leucine of 34%, $[\alpha]_D^{22}$ −16.3° (*c* 1, H_2O). This compound was otherwise indistinguishable in all respects from that prepared by path A.

When L-leucine was substituted for D-leucine in path A the enantiomeric (*R*) form of **3** was obtained: $[\alpha]_D^{22}$ +24.1 ± 1° (*c* 2, H_2O).

The assignment of the *S* configuration to the product (**3**) derived from D-leucine, which exhibits a negative rotation at 589 nm, is supported by the following. (1) Substitution of 2-bromo acids branched at C-4 with nitrogen as the nucleophilic atom produces inversion of configuration.[9] Accordingly, treatment with mercaptoethylamine, where displacement by sulfur predominates over nitrogen, would also be expected to cause inversion as would trithiocarbonate. Aminoethylation of the mercapto acid **4** would not be expected to alter the configuration. The properties of **3** obtained by paths A and B are indistinguishable with the exception of the specific rotation. The greater magnitude of the rotation of **3** obtained from the single step synthesis suggests that this product is of higher optical purity. (2) Brewster's studies[10] suggest that the (*S*)-2-mercapto-3-methylpentanoic acid would have a negative rotation at the sodium D line as would the final product **3**. (3) The conclusion that both paths involve a predominant overall inversion of configuration is consistent with the observed binding patterns of the *S* and *R* analogues with aminopeptidase M. This enzyme is known to cleave only those

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