intramolecular alkylation; however, neither isomer afforded such an ether.[11]

Treatment of **6a** and **6b** with sodium cyanide (hexamethylphosphoramide, 25 °C, 20 h) yielded **7a** (100%, $R_f$ 0.50, silica gel plate, 1:1 acetone–methylene chloride) and **7b** (100%, $R_f$ 0.51) which were saponified (potassium hydroxide, aqueous methanol) to give the 2,3-dinor-$PGI_1$ isomers **8a** (81%, $R_f$ 0.32, silica gel plate, 1:1 acetone–methylene chloride containing 1% acetic acid) and **8b** (75%, $R_f$ 0.39), respectively. Each acid was subjected to lactone formation using dipyridyl disulfide and triphenylphosphine.[12] Only one acid (**8b,** endo) afforded a lactone **13** (24%, $R_f$ 0.41, silica gel plate, 6:4 ethyl acetate–hexane). To demonstrate lack of any unexpected rearrangements, the lactone was saponified back to its starting acid **8b.** Oxidation of **13** with manganese dioxide (ethyl acetate, 7 h) gave the expected unsaturated ketone **14** (69%, $R_f$ 0.58, silica gel plate, 1:1 ethyl acetate–hexane) demonstrating conclusively the point of lactone formation.

We next turned our attention to relating our di- and trinor-$PGI_1$ analogues to the previously reported C-6 isomers of $PGI_1$.[2-4] The more plentiful isomer **5a** (exo upper side chain) was converted to **10a** (73%) via the nitrile **9a**[13] using methods described above. Reduction of **10a** with lithium aluminum hydride and Pfitzner–Moffatt oxidation[14] of the intermediate alcohol **11a** afforded the aldehyde **12a** (73% from **10a,** $R_f$ 0.62, silica gel plate, 1:1 ethyl acetate–hexane). Reaction of **12a** with methyl (triphenylphosphoranylidine)acetate (tetrahydrofuran, 25 °C, 20 h) yielded **15a** (78%) which was hydrogenated with 5% palladium/carbon (ethyl acetate, atmospheric pressure, 0 °C) to yield **16a.**[15] Depyranylation of **16a** afforded (6*S*)-$PGI_1$ methyl ester (**17a**) (33% from **15a,** mp 42–43 °C, $R_f$ 0.25 compared to 0.30 for the 6*R* isomer, silica gel plate, ethyl acetate). Compound **17a** was shown to be identical with one of the previously described C-6 isomers of $PGI_1$ methyl ester by melting point, mixture melting point, comparisons of TLC mobilities, and NMR and mass spectra. The other previously described isomer must then be the 6*R* or endo isomer.[16]

As first noted by Johnson and verified in our own work, $PGI_1$ and its analogues having the upper side chain in the exo configuration (series "a" compounds) exhibit an ill-defined quartet centered at $\delta$ 4.4–4.5 ($J \simeq 6$ Hz) in their NMR spectra ($CDCl_3$). The corresponding endo isomers have not shown this absorption and presumably incorporate this H signal further upfield as part of other multiplets. We have also noted that the endo isomer (6$\beta$ H) of an isomer pair usually has a higher $R_f$ on silica gel plates than the exo isomer (6$\alpha$ H). While these generalities have been derived (with no exceptions) from inspection of 18 pairs of $PGI_1$ analogues isomeric at C-6, caution should be used in new situations, particularly if there are overlapping NMR absorptions or drastic changes in molecular configuration.

**Acknowledgment.** We are indebted to Dr. John C. Sih for supplying samples of (6*R*)- and (6*S*)-$PGI_1$ methyl ester for comparison purposes.

## References and Notes

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(6) The assignment of stereochemistry at C-6 of $PGI_1$ and derivatives has been based on stereochemical and mechanistic considerations and different conclusions have been arrived at by different authors; see ref 3, footnote 12 of ref 4, and the following footnote. Two recent references on conflicting assignments of C-6 configuration of dihydroprostacyclins were drawn to the attention of the author by referee (see ref 6a and 6b). Our work is in agreement with that of Fried and Barton who deduced stereochemical assignments on the basis of elegant mechanistic considerations, but appears to differ from Kovács' group who utilized $^{13}C$ NMR spectra for structural assignments. (a) J. Fried and J. Barton, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 2199 (1977). (b) I. Tömösközi, G. Galambos, V. Simonidesz, and G. Kovács, *Tetrahedron Lett.*, 2627 (1977).
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(11) It is possible to construct a 6,9-cyclic ether emanating from **6b** (endo upper side chain) using molecular models; however, in actual practice it may not be possible to achieve the required transition state for cyclic ether formation.
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(14) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661, 5670 (1965).
(15) Considerable overreduction occurred leading to 46% of the corresponding 2,3,13,14-tetrahydro compound.
(16) Our structural assignments for the C-6 isomers of $PGI_1$ methyl ester are in agreement with those of Johnson and colleagues[4] but appear to differ from those of Corey's group.[3]

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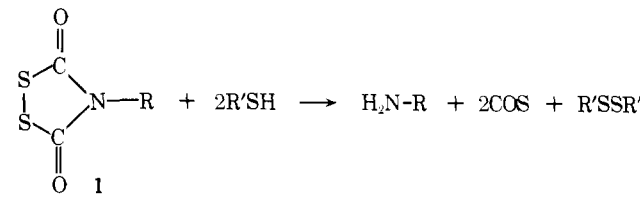
## A New Amino Protecting Group Removable by Reduction. Chemistry of the Dithiasuccinoyl (Dts) Function[1]

*Sir:*

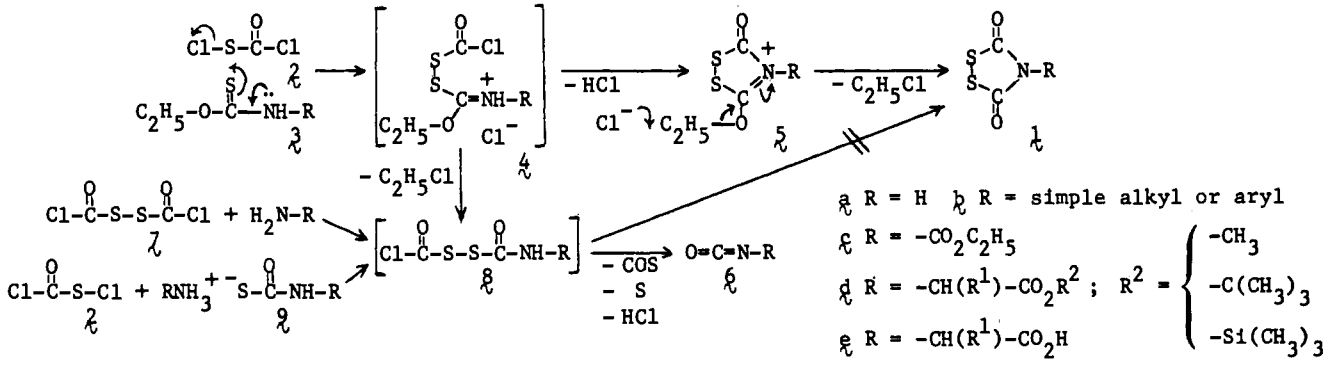
We wish to propose the 1,2,4-dithiazolidine-3,5-dione[2] heterocyclic system **1** as the basis of a new protecting group for peptide synthesis. These disulfide-containing amine derivatives are termed dithiasuccinoyl (Dts) amines by analogy with their carbocyclic analogues. Cleavage of the disulfide bond with thiols (or other reducing agents) generates the free amine (Scheme I). The reaction is driven to completion by loss of 2 equiv of gaseous carbonyl sulfide. The fact that both hydrogens of a primary amino function are replaced[3] is expected to be of particular advantage. Since the Dts-protecting group can be removed by mild reductive procedures, but is stable to acids and to photolysis above 330 nm, it is expected to lend itself to *orthogonal* systems[4] of peptide synthesis.

Some potential synthetic routes to Dts-amines are summarized in Scheme II. Chlorocarbonylsulfenyl chloride (**2**)[5] reacts[2a,d] in anhydrous solutions (optionally in the presence of tertiary amines) with ethyloxythiocarbonyl derivatives of primary amines **3**[6] to form an initial adduct **4**.[9] Ring closure to **5** followed by loss of ethyl chloride gives the Dts derivative **1.** The reactions proceed exceedingly rapidly at 0 to 45 °C, and in good yields.[10] Isocyanates **6** are the principal by-products. A new reagent, bis(chlorocarbonyl)disulfane (**7**)[11] was expected from a literature mechanism[2a] to react directly with primary amines to give the Dts derivative via the chlorocarbonyl carbamoyl disulfide intermediate **8.** However, the ring closure did not occur and isocyanates **6** were produced instead.

Scheme I



Scheme II. Synthetic Routes to Dithiasuccinoyl (Dts) Amines 1.




Reaction[9] of chlorocarbonylsulfenyl chloride (**2**) with thiocarbamate salts **9** gave the same results. These findings suggested that the sequence **2** + **3** → **4** → **5** → **1** represents the actual route for Dts-ring formation. Direct spectroscopic evidence (IR and NMR) was obtained for the occurrence of **5** as an intermediate in the formation of Dts-urethane (**1c**).[13] On the other hand, if the initial adduct **4** loses ethyl chloride, the intermediate **8** decomposes with loss of COS, elemental sulfur, and HCl to give **6** rather than **1**.

Dts derivatives could not be prepared directly from the ethyloxythiocarbonyl amino acids **3e**[6] containing a free carboxyl group. However, the corresponding methyl, *tert*-butyl, or trimethylsilyl esters reacted smoothly[10] with chlorocarbonylsulfenyl chloride. Cleavage of the appropriate ester by refluxing 12 N HCl–acetic acid (1:4), anhydrous HBr in acetic acid at 25 °C, or water, respectively, followed by extraction into bicarbonate and reacidification, gave the desired Dts-amino acids **1e** as crystalline compounds. The Dts moiety was entirely resistant to the strongly acidic and mildly basic reagents employed for these preparations. Furthermore, the optical purity of L-amino acids was retained. For example, Dts-phenylalanine, prepared in three steps from commercial HCl·L-Phe-OBu$^t$ was reduced with β-mercaptoethanol to free phenylalanine, which was shown to contain <0.2% D isomer by Manning–Moore assay.[14]

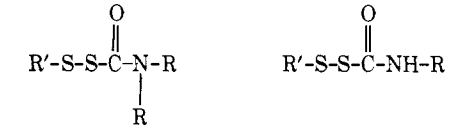
Dts-glycine (mp 140–141 °C, from ethyl acetate–carbon tetrachloride)[15] was characterized by its $^1$H NMR (singlet at δ 4.55 ppm); $^{13}$C NMR (two carbonyl singlets at 168.2 and 166.9 ppm, in ratio 2:1, in presence of chromium acetylacetonate); IR (1676 and 1729 cm$^{-1}$); UV ($\lambda_{max}$ 324 nm (ε 65), $\lambda_{min}$ 292 nm (ε 31), $\lambda_{max}$ 255 nm (ε 3.0 × 10$^3$), $\lambda_{min}$ 244 nm (ε 2.6 × 10$^3$), $\lambda_{max}$ 233 nm (ε 3.2 × 10$^3$), $\lambda_{min}$ 219 nm (ε 2.0 × 10$^3$)); electron ionization mass spectra (*m/e* 193 ($M^{+}\cdot$), 165 ($M^{+}\cdot$ − CO), 137 ($M^{+}\cdot$ − 2CO), 64 ($S_2^{+}\cdot$), assignments confirmed by high resolution mass measurements); and chemical ionization mass spectra (*m/e* 194 $(M + 1)^+$, 176 $(M + 1 - H_2O)^+$, 102 $(M + 1 - COS - S)^+$). Other derivatives, including Dts-L-alanine (mp 177–178 °C) and Dts-L-phenylalanine (mp 113 °C) showed corresponding spectral characteristics.

The Dts-amino acids were pure by thin layer chromatography,[16] analytical gas chromatography of volatile esters, and amino acid analysis.[17] Kinetic studies on the stability and reactivity of Dts compounds were conveniently carried out by both chromatographic and spectroscopic techniques.

Reductive deprotection (Scheme I) proceeded cleanly under a variety of conditions. Addition of tertiary amines markedly accelerated the thiolytic cleavage; for example, the reactions were generally complete within 5 min at 25 °C with excess 0.2 M β-mercaptoethanol and 0.5 M triethylamine in dichloromethane. A competing nucleophilic attack of the thiol at the carbonyl to give a thiourethane does not appear to occur (<5%, judged by IR), but this potential side reaction is being reexamined at higher levels of sensitivity. Prolonged treatment with bases such as the α-amino group of amino acid esters did not yield detectable cleavage products, but the Dts carbonyl is attacked by aliphatic amines or strong aqueous alkali to give the mixed urea or free parent amine.

Dts-glycine (8.6 mM solution) in benzene was recovered essentially quantitatively (>99% by UV, TLC, and amino acid analysis[17]) after irradiation under nitrogen for 66 h at 25 °C with a Hanovia Model L 450-W medium-pressure mercury lamp, using a uranium glass filter (λ >330 nm). A trace of free glycine (0.6%) was shown after aqueous workup. Further irradiation for 74 h using a Pyrex filter (λ >272 nm) gave 88% unchanged Dts-glycine and 12% free glycine. Irradiation (λ >330 nm) for 55 h in absolute ethanol gave predominantly (by NMR, IR) ethyloxycarbonylglycine.

The protection of secondary amines and imino acids should be feasible through the use of open-chain carbamoyl disulfide derivatives **12**, which are accessible[2a,9] by chemistry closely related to that described in Scheme II. The corresponding proposed primary amino protecting groups **13** are the intermediates in the thiolytic deprotection reaction of Dts derivatives (Scheme I).




**12** **13**

The preliminary application of Dts-amino acids **1e** to a simple model peptide synthesis has been reported.[1] The ideal general strategy for peptide synthesis will require at least three classes of protecting groups, each removable by a separate, selective chemical mechanism. The Dts group should be especially adaptable to a variety of such orthogonal[4] schemes. For example, a combination of the Dts functionality for $N^{\alpha}$-amino protection, *tert*-butyl based derivatives for side-chain protection, and a photolabile *o*-nitrobenzyl ester[18] for $C^{\alpha}$-carboxyl protection or anchoring to a solid support[19] would exploit three mutually complementary modes of chemical cleavage.

**Acknowledgments.** We thank Drs. Steven Wolff, T. P. King, Bruce W. Erickson, and Stephen B. H. Kent for helpful discussions.

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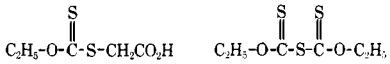
(4) An *orthogonal* system is defined as a set of completely independent classes of protecting groups. In a system of this kind, each class of groups can be removed in any order and in the presence of all other classes.
(5) Prepared by partial hydrolysis of trichloromethanesulfenyl chloride according to W. Weiss, German Patent 1 224 720 (Nov 11, 1964); *Chem. Abstr.*, **65**, 12112h (1966).
(6) Derivatives **3** were generally prepared in essentially quantitative yields by reaction of the parent amines with *O*-ethyl-*S*-carboxymethyl dithiocarbonate (**10**)[7] or bis(ethyloxythiocarbonyl) sulfide (**11**)[8]: G. Barany, B. W. Fulpius, and T. P. King, unpublished work.



**10** **11**

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(8) H. Welde, *J. Prakt. Chem.*, **15** (2), 43 (1877).
(9) Compare with the synthesis of carbamoyl disulfides: J. F. Harris, Jr., *J. Am. Chem. Soc.*, **82**, 155 (1960).
(10) Yields are intrinsically dependent on the nature of the substituent R. For amino acid ester derivatives **1d**, yields are typically 70–90%.
(11) We prepared **7**, bp 85–87 °C (27 mm), in excellent yield by thermolysis of the addition product between methyloxythiocarbonyl chloride[12] and chlorocarbonylsulfenyl chloride.[5] (b) Reported as part of partial hydrolysate mixture of bis(trichloromethyl)disulfane: N. Kobayashi, A. Osawa, and T. Fujisawa, *Chem. Lett.*, 1315 (1973).
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(14) J. M. Manning and S. Moore, *J. Biol. Chem.*, **243**, 5591 (1968).
(15) Satisfactory elemental analyses have been obtained for all new compounds. The reported melting points are uncorrected.
(16) Generally detected on basis of UV absorbance. An especially useful method designed to specifically distinguish Dts compounds involved spraying thin layer plates first with 5% $\beta$-mercaptoethanol in 1-butanol, followed by 0.2% ninhydrin in 1-butanol, to develop spots of the characteristic color.
(17) Dts compounds can be determined directly on standard amino acid analyzers. For example, Dts-glycine ethyl ester and Dts-glycine eluted, respectively, near lysine and aspartic acid, with integration constants ranging from 25 to 33% of a norleucine internal standard. Apparently, the active reducing agent is hydrindantin, and the released amine reacts in situ with ninhydrin to give a purple color.
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(19) (a) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963). (b) B. W. Erickson and R. B. Merrifield in H. Neurath and R. L. Hill, Ed., "The Proteins", Vol. 2, 3rd ed, Academic Press, New York, N.Y., 1976, pp 255–527.

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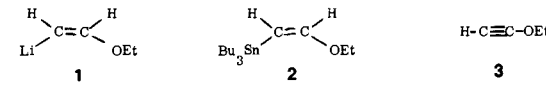
## A Nucleophilic Acetaldehyde Equivalent. Preparation and Synthetic Applications of *cis*-2-Ethoxyvinyllithium

*Sir:*

Reactions which convert aldehydes or ketones to $\alpha,\beta$-unsaturated aldehydes with simultaneous chain extension by two carbon atoms are highly useful synthetic operations. Unfortunately, a simple solution to this problem involving an aldol condensation between acetaldehyde and a carbonyl partner is not applicable owing to the facile self-condensation of acetaldehyde.[1,2] To overcome this restriction, a number of new reagents and processes have recently appeared. For example, the excellent process of Wittig involves masking of the nucleophilic aldehyde component as the metalated ethylidenecyclohexylamide.[2] Condensation with carbonyl compounds and subsequent hydrolysis has represented one of the most useful and simple procedures hitherto reported. The aldehyde component has also been masked as the corresponding dihydro-1,3-oxazine,[3] 2-oxazoline,[4] thiazole,[5] and thiazoline[6] and as the *N,N*-dimethylhydrazone.[7] Reactions based on Wittig-type condensations, for example, with the resonance-stabilized ylide formylmethylenetriphenylphosphorane,[8] diethyl carboxaldehydomethylphosphonate,[9] diethyl 2-(cyclohexylamino)vinylphosphonate,[10] and 1,3-dioxan-2-ylmethylenetriphenylphosphorane[11] have also been used for aldehyde synthesis. Recently, methods involving Lewis acid catalyzed condensations of an enol ether and a carbonyl group[12] or a ketal[13] were reported. In addition, aldehydes have been obtained by multistep procedures which involve addition of acetylide[14] and vinylmetallic reagents[15] to carbonyl groups.

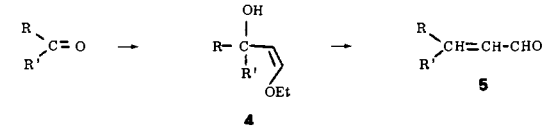
Despite the availability of this array of approaches, the known reagents are frequently unsatisfactory either as a result of their low reactivity or the necessity for subsequent acidic or multistep procedures to free the initially masked aldehyde, often resulting in poor overall yields.

We wish to report our finding that *cis*-2-ethoxyvinyllithium (**1**)[16] is a conveniently prepared and relatively stable nucleophilic acetaldehyde equivalent of considerable synthetic value. Formation of anion **1** proceeds smoothly and essentially quantitatively by reaction of *cis*-1-ethoxy-2-tri-*n*-butylstannylethylene (**2**), prepared by hydrostannation of the commercially available compound ethoxyacetylene (**3**, 94%),[17] with 1.1 equiv of *n*-butyllithium in THF at −78 °C for 1 h.[18] At −78 °C, the anion **1** reacts with aldehydes and ketones to produce the allylic alcohols **4** in excellent yields (Scheme I).



**1** **2** **3**

Scheme I



**4** **5**

The most notable advantage of our procedure for carbonyl homologation compared with the Wittig directed aldol approach is the ease by which the intermediate enol ethers of type **4** are converted into $\alpha,\beta$-unsaturated aldehydes under essentially nonacidic conditions. Thus, chromatography of these substances on silica gel or Florisil is sufficient to cause complete allylic rearrangement to the aldehydes **5** (Table I).[19] By contrast, the intermediate aldimine adducts prepared by the Wittig approach[2] require fairly vigorous acid hydrolysis for conversion to aldehydes. These acidic conditions not only result in lower overall yields but may also be incompatible with complex synthetic intermediates, particularly with functional groups protected as acid labile derivatives.

The reaction of **1** with halides was also investigated. In THF at −78 °C, alkylation of **1** with 1-bromo- or 1-iododecane requires HMPA as cosolvent (1 equiv). In the absence of HMPA the starting halides were completely recovered under similar conditions or even after slow warming to room temperature over 5 h.[20] The allylic halide, geranyl bromide, is more reactive and can be smoothly alkylated without HMPA as cosolvent. These intermediate enol ethers are converted by mild acid treatment (3:2:1 acetic acid–THF–water, 40 °C) to their corresponding carbonyl compounds, dodecanal and *trans*-5,9-dimethyl-4,8-decadienal,[21] in >95% isolated yields. We were, however, unsuccessful in alkylating **1** with benzyl bromide which gave only 1,2-diphenylethane, presumably by initial metal–halogen exchange to generate benzyllithium as an intermediate.