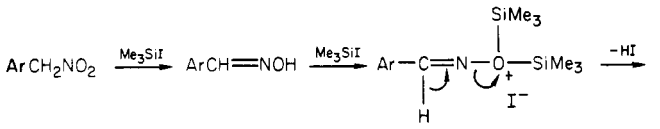
zinc–acetic acid,[7] photolysis,[8] etc. However, these methods either require the use of hazardous gases or acidic and harsh reaction conditions or are limited to special cases and therefore are not general in nature. Use of iodotrimethylsilane permits the reduction to occur under extremely mild and neutral conditions. The reaction stops at the oxime stage, and further reduction to the imine is not observed.

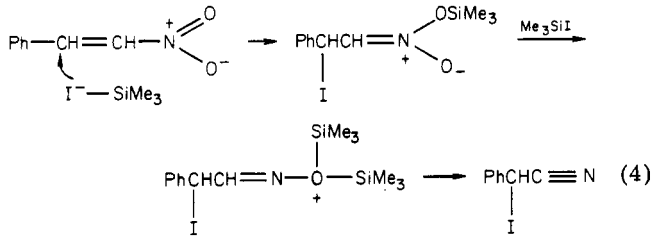
(3) Primary Nitroalkanes. The reaction of iodotrimethylsilane with primary nitroarylalkanes results in the formation of corresponding nitriles via deoxygenation followed by in situ dehydration of the resulting oximes (eq 3).



$$ArC{\equiv}N + Me_3SiOSiMe_3 \quad (3)$$

When α-nitrotoluene was treated with iodotrimethylsilane, benzonitrile was obtained in 98% yield. Due to the high acidity of benzylic hydrogens, the transformation of oxime to the nitrile via the oxime is very facile. 1-Nitrohexane yielded only a small amount of the nitrile, the main product being the oxime.

(4) ω-Nitrostyrene. The reaction of ω-nitrostyrene with iodotrimethylsilane provides an interesting combination of reactions. The final product, phenylacetonitrile, is obtained in 71% yield. The mechanism probably involves Michael addition, followed by deoxygenation, dehydration, and finally dehalogenation of the α-halonitrile (eq 4).



(4)

All these reactions have precedence in the literature. The Michael addition of iodotrimethylsilane to various Michael acceptors, the dehalogenation of α-halo ketones, and the reaction of acetonitrile with this reagent are well documented.[2]

The reaction of 1-nitrocyclohexene yielded a complex mixture of products even at low temperatures.

(5) Tertiary Nitrosoalkanes. 2-Methyl-2-nitrosopropane yielded 2-methyl-2-iodopropane in high yield in a reaction analogous to the reaction of 2-methyl-2-nitropropane (eq 5).

$$(Me)_3CNO \xrightarrow{2Me_3SiI} Me_3CI + Me_3SiOSiMe_3 \quad (5)$$

Conclusions

We have demonstrated the facile reaction of nitro- and nitrosoalkanes with iodotrimethylsilane, where the reaction is initiated by the formation of a strong bond between silicon and oxygen. The deoxygenation reactions occur due to the excellent reducing power of iodide. The strong affinity of silicon for oxygen and the reducing power of iodide has allowed us to develop a mild, neutral method to convert secondary nitroalkanes to oximes, which can be regarded as masked ketones.

(7) Baer, H. H.; Ramk, W. *Can. J. Chem.* **1972**, *50*, 1292.
(8) Saito, I.; Takami, M.; Matsuura, T. *Tetrahedron Lett.* **1975**, 3155.

Experimental Section

To a stirred solution of the 1-nitroadamantane (10 mmol) in dichloromethane (50 mL) was added iodotrimethylsilane (20 mmol) under a dry nitrogen atmosphere. The reaction mixture was allowed to stirr at 25 °C for 16 h. The reaction mixture was quenched with aqueous sodium bicarbonate solution (50 mL) and washed with aqueous sodium thiosulfate solution (2 × 25 mL) and NaCl solution (50 mL). The organic extract was dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure to give 1-iodoadamantane: 98% yield; mp 74 °C.

Acknowledgment. Support of our work by the U.S. Army Office of Research, Durham, NC, is gratefully acknowledged.

Registry No. Me_3CNO_2, 594-70-7; $CH_3CH(NO_2)CH_3$, 79-46-9; $C_2H_5CH(NO_2)CH_3$, 600-24-8; $PhCH_2NO_2$, 622-42-4; CH_3-*o*-$C_6H_4CH_2NO_2$, 38362-89-9; CH_3-*m*-$C_6H_4CH_2NO_2$, 38362-90-2; $CH_3(CH_2)_4CH_2NO_2$, 646-14-0; $PhCH{=}CHNO_2$, 102-96-5; Me_3CNO, 917-95-3; Me_3SiI, 16029-98-4; Me_3CI, 558-17-8; $(CH_3)_2C{=}NOH$, 127-06-0; $C_2H_5C(CH_3){=}NOH$, 96-29-7; PhCN, 100-47-0; CH_3-*o*-C_6H_4CN, 529-19-1; CH_3-*m*-C_6H_4CN, 620-22-4; $CH_3(CH_2)_4CN$, 628-73-9; $CH_3(CH_2)_4CH{=}NOH$, 6033-61-0; $PhCH_2CN$, 140-29-4; 1-nitroadamantane, 7575-82-8; nitrocyclohexane, 1122-60-7; 1-iodoadamantane, 768-93-4; cyclohexanone oxime, 100-64-1.

Synthesis of Enantiomerically Pure (*S*)-(+)-3-Hydroxytetrahydrofuran and Its *R* Enantiomer from Malic or Tartaric Acid

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In connection with the development of chiral analogues of tosylmethyl isocyanide (TosMIC),[1] a simple, enantiomerically pure, low molecular weight, secondary alcohol was need in quantity. The likeliest candidate, 2-butanol, is expensive,[2] probably because resolution of racemic 2-butanol is tedious.[3]

(−)-Menthol, a popular[4] and relatively cheap optically pure secondary alcohol, has certain disadvantages: (1) the molecular weight is twice that of 2-butanol; (2) in displacement reactions (for example, of menthyl tosylate), eliminations to menthenes sometimes are observed;[5] (3) only one enantiomer is normally available.

Our attention was drawn to 3-hydroxytetrahydrofuran (**4**), which is readily available by acid-catalyzed cyclodehydration of 1,2,4-butanetriol (**3**).[6] To our surprise, 3-hydroxytetrahydrofuran (**4**) had not been reported in optically active form. It seemed to us that both (*S*)-3-hydroxytetrahydrofuran (**4a**) and the *R* enantiomer (**4b**) ought to be accessible by using the enantiomers (**3a** or **3b**) of 1,2,4-butanetriol, *provided that cyclodehydration could be carried out without racemization of the secondary*

(1) Cf.: Van Leusen, D.; Rouwette, P. H. F. M.; van Leusen, A. M. *J. Org. Chem.* **1981**, *46*, 5159.
(2) Both enantiomers are commercially available. Prices for research quantities of (+)- and (−)-2-butanol of various degrees of purity range from 25 to 40 U.S. dollars per gram. The price tends to decrease for the higher homologues to $3–4 for (−)-2-octanol.
(3) Kantor, S. W.; Hauser, C. R. *J. Am. Chem. Soc.* **1953**, *75*, 1744.
(4) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; Prentice-Hall: Englewood Cliffs, NJ, 1971. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
(5) Hückel, W.; Maucher, D.; Fechtig, O.; Kurz, J.; Heinzel, M.; Hubele, A. *Justus Liebigs Ann. Chem.* **1961**, *645*, 115.
(6) Wynberg, H.; Bantjes, A. *Org. Synth.* **1958**, *38*, 37; "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 534.

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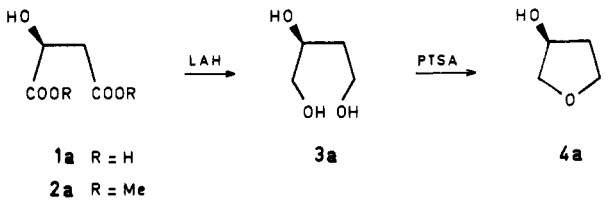
Scheme I



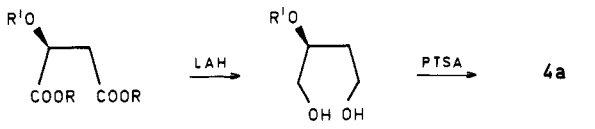
1a R = H
2a R = Me

3a

4a

(1b to 4b refer to (R)-enantiomers)

Scheme II



1a R = R' = H
5a R = Et, R' = H
6a R = Et, R' = EtOCHMe
7a R' = EtOCHMe
3a R' = H

alcohol function. We find this to be the case. Since both enantiomers of triol **3** are readily available by known chemistry[7,8] from (*S*)- or (*R*)-malic acid (**1**)[9] or from (*R,R*)- or (*S,S*)-tartaric acid,[10] we now report a convenient synthesis of optically pure 3-hydroxytetrahydrofurans **4a** and **4b** *that does not rely on resolution.*

We have investigated in detail two routes that lead to optically active 3-hydroxytetrahydrofuran (**4**). The first route (Scheme I) requires two steps to synthesize (*S*)-(+)-3-hydroxytetrahydrofuran (**4a**)[11] from (*S*)-(−)-dimethyl malate (**2a**) in 61% overall yield with an enantiomeric excess (ee) of 94%. The procedure of Nakanishi et al.[7] used for the first step (i.e., the $LiAlH_4$ reduction of **2a**) was improved to yield 72% of (*S*)-(−)-1,2,4-butanetriol (**3a**; reported[7] yield 50%). The cyclodehydration step was carried out by heating **3a** (neat) with a catalytic quantity of *p*-toluenesulfonic acid according to the literature procedure[6] used previously for the synthesis of racemic **4**.

The second route, outlined in Scheme II, took four steps to convert (*S*)-(−)-diethyl malate (**5a**) in 75% overall yield to **4a** with an ee of at least 99%. As compared with the first route, a larger ee and a higher overall yield were accomplished by protecting the secondary OH group during $LiAlH_4$ reduction of the ester functions. The method of Seebach et al.[8] was followed to prepare (*S*)-(−)-1,2,4-butanetriol (**3a**) from **5a**, via the 1-ethoxyethyl derivative **6a** and diol **7a**. The yield in the deprotection step to **3a** was improved to 96% (reported[8] yield 72%). Despite the additional two steps of protection and deprotection, the second route was more convenient and allowed us to prepare **4a** in batches of 15–20 g.

When enantiomerically pure (*S*)-(−)-1,2,4-butanetriol (**3a**) prepared by the second route (Scheme II) was cyclized under literature[6] conditions, an 87% yield of optically active 3-hydroxytetrahydrofuran, [$[\alpha]^{22}_D$ +16.23° (*c* 2.427, MeOH)] was obtained. The ee was found to be at least 99% as determined by ^{19}F NMR analysis of the diastereomeric esters prepared with Mosher's reagent.[12] This shows that no racemization at the *sec*-hydroxyl site takes place under the cyclodehydration conditions.[13] The lower ee (94%) of **4a** obtained in the two-step procedure of Scheme I is ascribed to some racemization during the $LiAlH_4$ reduction of unprotected dimethyl malate (**2a**) to **3a**.

Since complete inversion of configuration at C(3) during the cyclodehydration step seems highly unlikely, the absolute configuration of **4a** must reflect that of **3a**.[7] Independent proof of the absolute configuration has been obtained by X-ray analysis of the tosylate of **4a** (mp 34.5–35.5 °C).[14] The ring closure, proceeding most likely by an S_N2 mechanism,[15] does not affect the absolute configuration of **4a**.

Experimental Section

All $[\alpha]_D$ values were determined with the use of a Perkin-Elmer 241 polarimeter with 10-cm cells at room temperature.

(*S*)-(−)-Dimethyl malate[7] **(2a)** was obtained in 90% yield from (*S*)-(−)-malic acid (**1a**, Aldrich) and gave $[\alpha]^{22}_D$ −7.55° (*c* 3.734, MeOH) (lit.[16] $[\alpha]_D$ −6.85°); **(*S*)-(−)-diethyl malate (5a**, 85% yield) gave $[\alpha]^{22}_D$ −10.70° (neat) [lit.[8] $[\alpha]_D$ −10.4° (neat)].

(*S*)-(−)-1,2,4-Butanetriol (3a). Route 1. The procedure of Nakanishi et al.[7] for the $LiAlH_4$ reduction of **2a** (30 g) was improved by employing a Soxhlet extraction with absolute EtOH of the solid obtained after water decomposition of the reducing mixture. Thus the yield of **3a** was 14.2 g (72%, lit.[7] 50%): bp 97–99 °C (0.05 mmHg); $[\alpha]^{22}_D$ −24.60° (*c* 3.320, MeOH) [lit.[17] $[\alpha]^{27}_D$ −25.0° (2.6 M in MeOH)].

Route 2. Hydrolysis of **7a** (43.10 g, see below) according to the method of Seebach et al.[8] gave, after distillation, 24.53 g (96%, lit.[8] 72%) of **3a**: bp 121–123 °C (0.03 mmHg); $[\alpha]^{22}_D$ −25.50° (*c* 1.001, MeOH) [lit.[8] bp 150 °C (0.04 mmHg); $[\alpha]^{25}_D$ −29° (*c* 1.035, MeOH)].

(*S*)-(+)-3-Hydroxytetrahydrofuran (4a). The literature[6] procedure was followed by using 21.87 g (0.206 mol) of (*S*)-(−)-1,2,4-butanetriol (**3a**) of $[\alpha]^{22}_D$ −25.50° (*c* 1.001, MeOH) (above, route 2) and 0.20 g (1 mmol) of *p*-toluenesulfonic acid monohydrate (PTSA)[18] to give 15.73 g (87%) of **4a** as a colorless liquid: bp 80 °C (15 mmHg); $[\alpha]^{22}_D$ +16.23° (*c* 2.427, MeOH); IR (neat) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–2.4 (m, 2), 3.3–4.2 (m, 5), 4.4 (m, 1); ^{13}C NMR ($CDCl_3$) δ 75.2 (t, J = 145 Hz, C-2), 71.4 (d, J = 150 Hz, C-3), 35.2 (t, J = 135 Hz, C-4), 66.5 (t, J = 145 Hz, C-5); exact mass found m/e 88.054 (calcd m/e 88.052).

To determine the ee, **4a** was allowed to react with freshly distilled (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in the usual way[12] to give the corresponding ester as a colorless liquid. Comparison of the diastereomeric CF_3 signals at δ −72.15 and −72.33 relative to $CFCl_3$ in the ^{19}F NMR spectrum at 94.1 MHz showed the ee of **4a** to be at least 99%.

(*R*)-(−)-3-Hydroxytetrahydrofuran (4b) was prepared similarly to **4a** from (*R*)-(+)-butanetriol[17] (**3b**, prepared by route 1; $[\alpha]^{22}_D$ +24.60° (*c* 3.32, MeOH), lit.[17] $[\alpha]^{27}_D$ +24.6°): 85% yield; bp 68–70 °C (12 mmHg); $[\alpha]^{20}_D$ −14.36° (*c* 3.194, MeOH).

(*S*)-(−)-Diethyl 2-(1-ethoxyethoxy)succinate (6a) was prepared in quantitative yield according to the procedure of Seebach et al.[19]

(7) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749.
(8) Hungerbühler, E.; Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1981**, *64*, 1467.
(9) For a facile, totally synthetic route to both (*S*)- and (*R*)-malic acid, see: Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166.
(10) For availability of (*R,R*)- and (*S,S*)-tartaric acid, see: Seebach, D.; Hungerbühler, E. In "Modern Synthetic Methods 1980"; Scheffold, R., Ed.; Salle and Sauerländer: Frankfurt, 1980; p 115.
(11) For the sake of completeness we have shown that Scheme I also applies to the synthesis of the enantiomer (*R*)-(−)-3-hydroxytetrahydrofuran (**4b**) from (*R*)-malic acid.
(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(13) For kinetics of acid-catalyzed racemization of 2-butanol at temperatures around 100 °C, see: Bunton, C. A.; Konasiewicz, A.; Llewellyn, D. R. *J. Chem. Soc.* **1955**, 604. Bunton, C. A.; Llewellyn, D. R. *Ibid.* **1957**, 3402.
(14) van Bolhuis, F. Department of Chemical Physics of Groningen University, to be published elsewhere.
(15) Compare: Molnár, A.; Felföldi, K.; Bartók, M. *Tetrahedron* **1981**, *37*, 2149 and references cited therein.
(16) Freudenberg, K. *Chem. Ber.* **1914**, *47*, 2027.
(17) Tang, K. C.; Tropp, B. E.; Engel, R. *Tetrahedron* **1978**, *34*, 2873.
(18) For smaller scale operations (30 mmol) of **3a** it is essential for a successful experiment to use 5 mol % of PTSA, rather than 0.5 mol % as prescribed in ref 6.
(19) Hungerbühler, E.; Naef, R.; Wasmuth, D.; Seebach, D.; Loosli, H.-R.; Wehrli, A. *Helv. Chim. Acta* **1980**, *63*, 1960.

(S)-(−)-2-(1-Ethoxyethoxy)-1,4-butanediol (7a) was prepared in 91% yield by $LiAlH_4$ reduction of **6a** according to the procedure of Seebach et al.;[19] bp 108 °C (0.2 mmHg) [lit.[8] bp 99 °C (0.01 mmHg)].

Registry No. **1a**, 97-67-6; **2a**, 617-55-0; **3a**, 42890-76-6; **3b**, 70005-88-8; **4a**, 86087-23-2; **4a** (+)-α-methoxy-α-(trifluoromethyl)phenylacetate ester, 86014-40-6; **4b**, 86087-24-3; **5a**, 691-84-9; **6a**, 76494-95-6; **7a**, 72229-31-3; (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 20445-33-4.

Preparation of Methyl 2,5-Dioxohexanoate: A Highly Convenient Reagent for the Introduction of the 2-Carboalkoxy-1,5-dialkylpyrrole Nucleus

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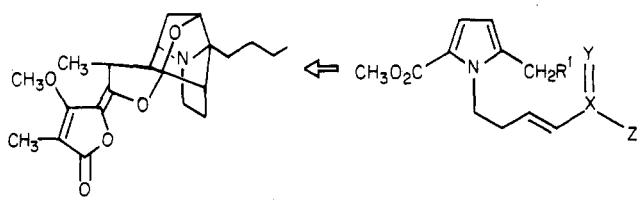
As part of an investigation directed at the synthesis of the potent natural insecticide stemofoline (**1**,[1] Scheme I) and structural variants, we required a general method for the rapid construction of 1,2,5-trisubstituted pyrroles (**2**) where either of the 2,5-substituents was an electron-withdrawing functionality. Our strategy was designed both to explore the intramolecular cycloaddition chemistry of pyrroles and to provide access to simpler structural analogues for biological evaluation.[2]

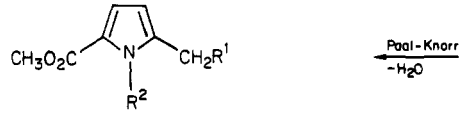
While a variety of useful methods for the synthesis of 1*H*-2-carboalkoxy-1,5-dialkylpyrroles have been developed, synthetic procedures for the 1-alkylated derivatives are scarce.[3-6] Since N-alkylation of 1,5-disubstituted pyrroles requires a sterically congested S_N2 transition state, low yields of products are obtained in the reaction of the 1-tetraalkylammonium or 1-metalated pyrroles with primary alkyl halides.[4]

While conceptually the carboalkoxy substituent could be introduced by metalation of a 1,2-dialkylated pyrrole,[3,4] this approach requires more synthetic manipulations when carbanion-sensitive functional groups are present in the target molecule. Construction of the pyrrole ring with the electron-withdrawing function affixed therefore increases the convergency of the synthesis as well as the inherent chemical stability of the products. Other methods which are amenable to the synthesis of 2-carboalkoxy-1,5-dialkylpyrroles such as the Hantzsch synthesis or the ring contraction of 1,2-oxazines suffer from the low chemical yields of pure products, lack of regioselectivity, or nongenerality.[5,6]

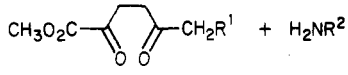
Scheme I



stemofoline, 1



2a, R^1 = H; R^2 = $CH_2CH_2CH_2OH$
b, R^1 = H; R^2 = $CH_2CH(OCH_3)_2$
c, R^1 = H; R^2 = CH_2Ph
d, R^1 = $CH_2CH_2CH_3$; R^2 = $CH_2CH_2CH_2OH$
e, R^1 = H; R^2 = (*R*)-$CH(CH_2OH)CH_2CH_3$
f, R^1 = H; R^2 = $CH_2CH_2CO_2H$



3

The most convergent approach for the preparation of these highly substituted pyrroles is the Paal–Knorr pyrrole synthesis[3] (Scheme I). The major obstacle to overcome in this approach is in the preparation of the 2,5-diketo esters **3**. Although the parent member of this potentially useful family of compounds, methyl 2,5-dioxohexanoate (**3a**), was first reported in 1973, we were unable to obtain synthetically useful quantities of pure material using the methodologies which the authors described.[7,8] While a lack of experimental details may have been a primary determinant in our difficulties, we elected to pursue an alternative, shorter route to the diketo ester **3a**, which obviates the necessity of handling offensive low-valent organosulfur intermediates.

The 1,4 conjugate addition of methyl nitroacetate[10] with methyl vinyl ketone (MVK) proceeds smoothly on using a catalytic amount of base to give methyl 2-nitro-5-oxohexanoate (**5a**) in 65–74% yield after distillation (eq 1). This result sharply contrasts with our experience with the reaction of the anion derived from methyl 2,2-diethylthioacetate with MVK, which consistently afforded low yields (>30%) of monomeric conjugate addition product.[7] The efficacy of the nitroacetate conjugate addition presumably results from the rapid protonation of the intermediate ketone enolate anion ($pK_B \simeq 20$) by proton transfer from the α-nitroacetate function ($pK_A = 5.82$),[11] giving rise to a thermodynamically more stable nitronate

(1) Sakata, K.; Aoki, K.; Chang, C.-F.; Sakurai, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457–63.

(2) We gratefully acknowledge the interest and cooperation of Willy D. Kollmyer of the Biological Chemistry Department of the Shell Development Co., Modesto, CA.

(3) For reviews on the synthesis of pyrroles: Jackson, A. H. In "Comprehensive Organic Chemistry"; Pergamon Press: New York, 1979; Vol. 4, Chapter 17.1, pp 275–320.

(4) Baltazzi, E.; Krimen, L. I. *Chem. Rev.* **1963**, *63*, 511–56.

(5) The Hantzsch pyrrole synthesis proceeds to give a maximum 50% yield of products, uses highly toxic α-halo ketones, and requires several steps for the 1,2,5-trisubstitution pattern: Roomi, M. W.; MacDonald, S. F. *Can. J. Chem.* **1970**, *48*, 1689–97.

(6) The ring contraction of 3-carboalkoxy-1,2-oxazines to 2-carboalkoxy-5-alkylpyrroles proceeds in excellent yields but is not useful for 1-alkyl derivatives which have protons on the carbon atom attached to the pyrrole nitrogen. The requisite starting material would be an alkyl nitroso compound bearing α-protons which are known to rapidly isomerize to the oximino tautomer. (a) Needleman, S. B.; Chang Kuo, M. C. *Chem. Rev.* **1962**, *62*, 405–31. (b) Belleau, B.; Au-Young, Y.-K. *J. Am. Chem. Soc.* **1963**, *85*, 64–71.

(7) The title compound, methyl 2,5-dioxohexanoate, was first reported to have been prepared "in excess of" 62% overall yield from dichloroacetic acid.[8] Conversion to methyl diethylmercaptoacetate is reported to proceed in 75% overall yield by using sodium ethyl mercaptide followed by methanolic hydrogen chloride. The best yield we were able to obtain overall for these conversions was ca. 30%. The key step in this methodology involves the 1,4-addition of the anion derived from methyl diethylmercaptoacetate to methyl vinyl ketone in a reported 93% yield.[8] We consistently obtained yields of less than 28% of pure distilled product. Finally, the hydrolysis of the diethyl thioketal using *N*-bromosuccinimide in aqueous acetonitrile[9] was reported to proceed "always in excess of 90%". While the procedure of Corey and Erickson was reproduced with no experimental difficulties, affording ethyl 3-phenylpyruvate from the corresponding acyl-1,3-dithiane in 78% yield, in the case of the 2,2-diethyl thioketal of methyl 2,4-dioxopentanoate, this procedure gave a 53% yield of product after evaporative distillation.

(8) Cregge, R. J.; Herrman, J. L.; Richman, J. E.; Romanet, R. F.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2595–8.

(9) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553–60.

(10) Shipchandler, M. T. *Synthesis* **1979**, 666–86.

(11) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439–43.

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