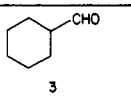
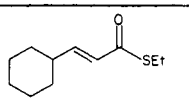
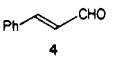
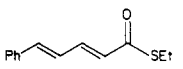
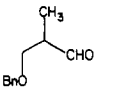
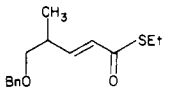
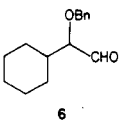
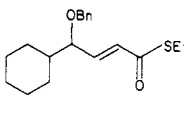
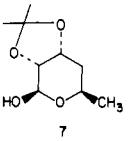
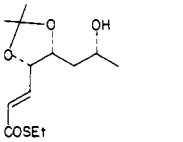
(1:9) to afford 177.1 mg (77%) of pure **1d** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.61 (4 H, m), 7.31 (6 H, m), 5.25 (1 H, dm, $J \simeq 8$, 1.5 Hz), 1.89 (1 H, dd, $J \simeq 8$, 6 Hz), 1.83 (1 H, br s), 1.69 and 1.67 (3 H and 3 H, overlapping s), 1.24 (3 H, s), 1.21 (3 H, s), 1.12 (9 H, s); IR (NaCl, film) ν_{max} 3068, 3048, 2955, 2925, 2885, 1718, 1473, 1465, 1430, 1392, 1379, 1365, 1175, 1146, 1118, 1080, 824, 742, 699 cm^{-1}.

(±)-*cis*-Chrysanthemic Acid (1a). A solution of silyl ester **1c** (50.3 mg, 0.17 mmol) in acetonitrile (4 mL) was cooled to 0 °C, and to this was added a solution of hydrofluoric acid in acetonitrile (0.12 mL of a 3 M solution in acetonitrile, prepared from 48% aqueous HF, 0.35 mmol). After 0.5 h at 0 °C, aqueous K_2CO_3 (1.5 mL, 3 M) was added to the reaction mixture, and the solution was stirred for 5 min followed by addition of ether (5 mL). The aqueous layer was separated and washed with ether (5 mL), neutralized with concentrated hydrochloric acid, and extracted with ether (4 × 10 mL). The combined organics were washed with brine and dried over $MgSO_4$. Removal of the solvents gave 28 mg (94%) of **1a** as white prisms, mp 115–116 °C (lit.[5g] mp 115–116 °C), whose ^{1}H NMR spectra were identical with that in ref 13.

Acknowledgment. We appreciate the financial and material support provided by the National Institutes of Health (Grant No. GM2866301). Mass spectra were obtained through the National Science Foundation Regional Mass Spectrometry Center at the University of Nebraska (Grant CHE-82-11164).

Registry No. (±)-**1a**, 2935-23-1; (±)-**1c**, 94500-32-0; (±)-**1d**, 94500-33-1; **2**, 67099-40-5; **3**, 94500-34-2; **4**, 94500-35-3; **5c**, 94500-36-4; **5d**, 94500-37-5; acetone, 67-64-1.

Table I

aldehyde	product	yield,[a,b] %	trans/cis ratio[a,c]
 3		91 (93)	96:4 (95:5)
 4		87 (84)	96:4 (86:14)
 5		80 (89)	97:3 (97:3)
 6		78 (81)	91:9 (75:25)
 7		79 (71)	80:20 (56:44)

[a] Values in parentheses refer to results obtained for preparation of the corresponding methyl esters using carbomethoxymethylenetriphenylphosphorane under identical conditions. [b] All yields are isolated yields of cis-trans mixtures. Satisfactory C, H combustion analyses were obtained on the trans thiol ester products derived from aldehydes **3**, **4**, and **5**. [c] Trans-cis ratios were determined by capillary VPC analysis except with substrate **7**, where these ratios were determined by isolation.

A Useful Wittig Reagent for the Stereoselective Synthesis of Trans α,β-Unsaturated Thiol Esters

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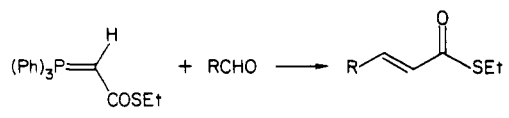
The reaction of aldehydes with Wittig reagents of the general structure $(Ph)_3PCHCO_2R$ constitutes an extremely powerful method for two-carbon chain extension which has seen wide application. The corresponding phosphonates, $(RO)_2P(O)CH_2CO_2R'$, are also very useful reagents in the same context. However, several problems can arise upon application of the above reagents to complex systems. For instance, the phosphoranes often exhibit low trans selectivity, particularly with α-alkoxy aldehydes, where trans–cis ratios of ca. 1:1 are not uncommon.[2] Moreover, the lithio or sodio derivatives of the corresponding phosphonates are generally not useful with base-sensitive substrates.[3] Finally, if the corresponding carboxylic acids are the ultimate goal of such Wittig processes, rather harsh hydrolytic conditions may be required to accomplish the requisite hydrolysis. We record here the preparation and reactions of a Wittig reagent (compound **1**) which has proven very useful in our laboratories. This material serves to allow for two-carbon chain extension resulting in the production of a latent "active" ester, from which either carboxylic acids or simple esters are readily accessible under mild and specific conditions.[4] Moreover, the application of such thiol esters to macrocyclic lactonization, as espoused by Masamune,[5] may further contribute to the utility of the reagent.



1

Reagent **1** is readily available in 78% overall yield from bromoacetic acid by the sequence: (1) thiol ester formation (ethanethiol) using dicyclohexylcarbodiimide (DCC) and catalytic 4-(dimethylamino)pyridine (4-DMAP) as described by Steglich;[6] (2) treatment with triphenylphosphine in benzene; and (3) exposure of the phosphonium salt so produced to aqueous sodium carbonate.

We summarize in Table I the Wittig reactions of **1** with five representative aldehydes. It should be noted that the higher trans selectivity exhibited by **1** as compared to, e.g., carbomethoxymethylenetriphenylphosphorane (**2**) *can be increased even further by exposure of the product to catalytic amounts of 4-(dimethylamino)pyridine (4-DMAP)*. For instance, substrate **7** yields a 60:40 mixture of unsaturated esters upon reaction with carbomethoxymethylenetriphenylphosphorane while **1** gives an 80:20 mixture of unsaturated thiol esters. Exposure of the isolated cis thiol ester product to 4-DMAP in CH_2Cl_2 at room temperature results in essentially quantitative isomerization to the trans thiol ester isomer; the cis unsaturated methyl ester obtained from carbomethoxymethylenetri-

(1) Fellow of the Alfred P. Sloan Foundation, 1981–1985.
(2) For a recent example, note: Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231–2234.
(3) For a very recent solution to this problem, note: Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
(4) (a) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523–5526. (b) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23–32. (c) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756–6758.
(5) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515–3516. Note also ref 4b and 4c.
(6) Steglich, W.; Neises, B. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–524.

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phenylphosphorane is unaffected by this treatment.

The results delineated in Table I suggest that the phosphorane 1 should prove useful in organic synthesis, particularly in carbohydrate-based synthesis and in the "chain extension" approaches of Kishi[7] and Sharpless/Masamune.[8] The preparation of 1 is detailed below.

Experimental Section

Preparation of Phosphorane 1. A solution of 13.93 g of recrystallized bromoacetic acid, 9.65 mL (1.3 eq) of ethanethiol,[9] and 1.22 g (0.1 equiv) of 4-(dimethylamino)pyridine in 450 mL of CH_2Cl_2 was cooled to 0 °C with stirring under an atmosphere of nitrogen. Dicyclohexylcarbodiimide (21.71 g, 1.05 equiv) was added in three portions, and the solution slowly warmed to room temperature overnight. The solution was then filtered through Celite, and the cake was washed several times with CH_2Cl_2. The filtrate was then washed with saturated aqueous $NaHCO_3$ solution, water, and brine, then dried over Na_2SO_4, and concentrated in vacuo to give 17.50 g (95%) of a light yellow oil. This oil was allowed to stand with 26.3 g of triphenylphosphine in 150 mL of benzene at room temperature for 2 days[10] to yield 35.54 g (83.5%) of colorless saltlike crystals after filtering and washing with toluene. The crystals were dissolved in 150 mL of CH_2Cl_2 and vigorously stirred with 100 mL of 10% aqueous Na_2CO_3 solution for 30 min. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were partially concentrated in vacuo and then diluted with pentane to yield 25.2 g of saltlike crystals (mp 82–83 °C). A second crop was similarly isolated (3.16 g, mp 79–83 °C) to give a combined yield of 98% (78% overall).

General Procedure for Reaction of 1 with Aldehydes. A solution of approximately 0.20 g of aldehyde and 1.3 equiv of ylide 1 in 15–20 mL of reagent grade $HCCl_3$ was heated at reflux for 12–18 h. The solution was concentrated in vacuo and chromatographed on a 25 cm × 1.2 cm silica gel column (slurry packed in hexane), eluting with hexane and then with 10% ether in hexane. Characteristic spectral data that is indicative of the formation of a trans α,β-unsaturated thiol ester (e.g., from 3) is as follows: IR 1670 and 1630 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 6.83 (dd, J = 6, 16, 1 H), 6.02 (dd, J = 16, 2, 1 H), 2.90 (q, J = 8, 2 H).

Acknowledgment. Support of this research by the Alfred P. Sloan Foundation and the National Institutes of Health (through NIH Grant No. GM 28961) is gratefully acknowledged.

Registry No. 1, 32443-51-9; 2, 2605-67-6; 3, 2043-61-0; 4, 14371-10-9; 5, 73814-73-0; 6, 89869-02-3; 7, 94498-98-3; (*E,E*)-PhCH=CHCH=CHC(O)SEt, 94498-99-4; (*Z,E*)-PhCH=CHCH=CHC(O)SEt, 94499-00-0; (*E*)-$PhCH_2OCH_2CH(CH_3)$-CH=CHC(O)SEt, 94499-01-1; (*Z*)-$PhCH_2OCH_2CH(CH_3)CH$=CHC(O)SEt, 94499-02-2; $BrCH_2C(O)SEt$, 60277-18-1; Ph_3P, 603-35-0; *t*-BuSH, 75-66-1; *S*-ethyl (*E*)-3-cyclohexyl-2-propenethioate, 94499-03-3; *S*-ethyl (*Z*)-3-cyclohexyl-2-propenethioate, 94499-04-4; (*S*)-ethyl (*E*)-4-(benzyloxy)-4-cyclohexyl-2-butenethioate, 94499-05-5; *S*-ethyl (*Z*)-4-(benzyloxy)-4-cyclohexyl-2-butenethioate, 94499-06-6; 4(*S*)-[3-(ethylthio)-3-oxo-1(*E*)-propenyl]-5(*R*)-[2(*R*)-hydroxypropyl]-2,2-dimethyldioxolane, 94499-07-7; 4(*S*)-[3-(ethylthio)-3-oxo-1(*Z*)-propenyl]-5(*R*)-[2-(*R*)-hydroxypropyl]-2,2-dimethyldioxolane, 94595-41-2.

(7) See: Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873–3888, and references therein.

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(9) The use of *tert*-butyl mercaptan was also examined. However, the derived phosphorane could not be obtained in crystalline form, and also reacted only very sluggishly with substrate 7.

(10) (a) Choice of temperature is important here. At benzene reflux, the phosphonium salt decomposes with formation of methyltriphenylphosphonium bromide. (b) The mixture should not be stirred, as this results in the formation of poor quality crystals.

Intramolecular Photoreduction of α-Keto Esters. Total Synthesis of (±)-Isoretronecanol[1]

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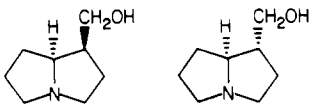
There is much interest in pyrrolizidine alkaloids[2] and their derivatives because of their wide range of physiological properties.[3]

The two simplest members of this group are the diastereoisomers of 1-(hydroxymethyl)pyrrolizidine: isoretronecanol (1) and trachelanthamidine (2). Many syntheses of 1 and 2 have been reported.[4] We now describe a new, short, and efficient synthesis of isoretronecanol (1).



1 2

In this approach, the second ring is created in a key photochemical step based on the intramolecular photoreduction of an α-keto ester. We already reported that the hydrogen α to the nitrogen of an amide function was easily abstracted by the n,π* excited triplet state of an aryl ketone.[5] The coupling of the two radicals resulting from this process created a carbon–carbon bond α to a nitrogen atom. The intramolecular version of this reaction should be an efficient method to generate heterobicyclic systems with a nitrogen in a bridgehead position: irradiation of aryl ketones such as 3 leads via the diradical 4 to 1-azabicyclo[x.3.0]alkanes 5.[6] In the absence of hydrogen in the γ position, the hydrogen in the δ position is efficiently abstracted to lead to a five-membered ring (Scheme I).

However, the applicability of this reaction is limited by the difficulty in transforming the aromatic ring (Scheme II). The most useful function is the α-keto ester group which is easily photoreduced by various hydrogen donors.[7]

(1) Presented at "Journées de Chimie Organique de la Société Chimique de France", Palaiseau, Sept 12–14, 1983.

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(3) (a) Warren, F. L. In "The Alkaloids Chemistry and Physiology"; Manske, R. H. F., Ed.; Academic Press: New York, 1970; Vol. XII, p 319. (b) Mac Lean, E. K. *Pharmacol. Rev.* **1970**, *22*, 429.

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(5) (a) Gramain, J. C.; Remuson, R.; Troin, Y. *Tetrahedron* **1979**, *35*, 753. (b) Jeandrau, J. P.; Gramain, J. C.; Lemaire, J. *J. Chem. Res., Synop.* **1979**, 186.

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(7) (a) Schonberg, A.; Latif, N.; Moubasher, R.; Singe, A. *J. Chem. Soc., Chem. Commun.* **1961**, 1364. (b) Huyser, E. S.; Neckers, D. C. *J. Org. Chem.* **1964**, *29*, 276. (c) Kendall, D. S.; Leermakers, P. A. *J. Am. Chem. Soc.* **1966**, *88*, 2766. (d) Pappas, S. P.; Pappas, B. C.; Blackwell, J. E., Jr. *J. Org. Chem.* **1967**, *32*, 3066.

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