which converts carbonyl groups to vinylsilane groups, even in enolizable compounds.

Lithium reagent 1 is formed in quantitative yield by the regiospecific lithium–hydrogen exchange of (methoxydimethylsilyl)(trimethylsilyl)methane (2) with *tert*-butyllithium in hydrocarbon solvent at room temperature (see Scheme I). This was confirmed by quenching of 1 with D_2O, which gave the monodeuterated product 4 in 98% yield based on 2.[15] Notably the formation of 1 is not complicated by substitution reactions at the methoxy-substituted silicon atom or by metalation at the silyl methyl groups under these conditions. As we reported previously,[16] compound 2 is readily obtained by trapping [(methoxydimethylsilyl)methyl]lithium with trimethylchlorosilane.

As shown in Table I, 1 reacts with each of the carbonyl compounds in this study (cyclohexanone, 2-cyclohexen-1-one, 3-pentanone, and benzaldehyde) to produce good yields of the corresponding alkenylsilane. In each case,[17] 1 was prepared by adding a pentane solution of *tert*-butyllithium to a solution of 2. The reaction mixture was cooled to −78 °C and the carbonyl compound was added dropwise. The reaction mixture was allowed to warm slowly with stirring to room temperature overnight. An aqueous workup was followed by removal of the solvent and heating of the crude product for 2 h at 100 °C. Flash chromatography yielded the alkenylsilane 3.

When the ketone was added at 0 °C or in the presence of diethyl ether, the yield of the alkenylsilane was reduced. Analysis of the crude product before chromatography by ^{13}C NMR indicated the absence of the other possible olefin, 5, derived from elimination of the trimethylsilyl group. This result is consistent with the increased electrophilicity of silicon on replacement of alkyl groups with alkoxy groups.[18]

In a few instances for reactions with cyclohexanone, an additional unidentified compound was observed. This compound was cleanly converted to the alkenylsilane upon heating to 100 °C for 2 h. Although apparently an intermediate, the ^{13}C NMR data is not consistent with the anticipated β-hydroxy silane intermediate.[19] Work is currently in progress to identify this intermediate and to study the conditions under which it may be isolated reproducibly. In any case, the desired alkenylsilane **3a** was produced exclusively after heating.

Treatment of reagent 1 with 2-cyclohexen-1-one or benzaldehyde resulted in a mixture of *E* and *Z* isomers. The stereochemical assignments were made on the basis of 300-MHz ^1H NMR spectra. The fair selectivity for the reaction with cyclohexenone (2:1, *E*:*Z*)[20] and with benzaldehyde (3:1, *E*:*Z*)[21] contrasts with the lack of stereoselectivity generally observed with other Peterson-type olefinations.

The effectiveness of the described procedure with enolizable compounds should make available many useful, but previously unattainable, alkenylsilanes. Efforts are currently underway to isolate and identify reaction intermediates and to establish the mechanism of these and related reactions.

Acknowledgment. We thank the Robert A. Welch Foundation for financial support of this work.

Supplementary Material Available: Spectral and analytical data for new compounds **3b** and **3c** shown in Table I (2 pages). Ordering information is given on any current masthead page.

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(15) The yield was determined by integration of the methylene carbon resonances, in the proton-decoupled ^{13}C NMR spectra, of 3 and 4, which appear as a singlet at 4.1 ppm and a 1:1:1 triplet at 3.7 ppm, respectively.

(16) Bates, T. F.; Thomas, R. D. *J. Organomet. Chem.* **1989**, *359*, 285.

(17) Using the reaction with cyclohexanone as a typical example: 12.0 mmol of *tert*-butyllithium (7.06 mL, 1.7 M in pentane) was added to 12.0 mmol of 2 in 15 mL of dry pentane. After being stirred for 2 h, the reaction mixture was cooled to −78 °C and 10.0 mmol of cyclohexanone was added dropwise by syringe. The reaction mixture was allowed to warm slowly to room temperature while being stirred overnight. This was hydrolyzed with 15 mL of saturated NH_4Cl followed by washing with 15 mL of H_2O, extraction of the aqueous portions with 10 mL of pentane, and drying of the combined organic fractions with $MgSO_4$. After removal of the solvent, the crude product was heated for 2 h at 100 °C. Flash chromatography (silica gel/pentane) yielded 1.15 g (68%) of 3a.

(18) Eaborn, D. *Organosilicon Compounds*; Butterworths: London, 1960; p 301.

(19) The unidentified compound was observed by NMR in several reactions following the aqueous workup. ^{13}C NMR: −1.0, 1.0, 22.5, 23.0, 25.0, 28.0, 31.0, 119.0, 135.5 ppm.

(20) A complete listing of the ^1H NMR chemical shifts and the vinylic proton coupling patterns and coupling constants is included in the supplementary material.

(21) The stereochemical assignments were made by comparing the ^1H NMR spectra to those previously reported for each isomer. Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520.

An Organozinc Aid in Alkylation and Acylation of Lithium Enolates

Summary: The presence of dimethylzinc in the reaction of lithium enolates and electrophiles effectively suppresses undesired α-proton exchange reaction and enhances the efficiency of enolate alkylation and acylation.

Sir: Reaction of lithium enolates and electrophiles is one of the most fundamental synthetic operations.[1] The utility, however, is often hampered by undesired proton exchange between the starting enolates and ketonic products. For example, enolates of ketones such as cyclopentanones containing highly acidic protons are prone to undergo polyalkylation reactions with alkyl halides,[1,2] and also the yields of the C-acylation products with acyl halides hardly exceed 50% because of the high acidity of the resulting β-dicarbonyl compounds,[1a,3] We here report

(1) Reviews: (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; Chapters 9–11. (b) Augustine, R. L. *Carbon-Carbon Bond Formation*; Marcel Dekker: New York, 1979; Vol. 1.

(2) For some examples, see: (a) Tardella, P. A. *Tetrahedron Lett.* **1969**, 1117. (b) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361. (c) Borowitz, I. J.; Casper, E. W. R.; Crouch, R. K.; Yee, K. C. *Ibid.* **1972**, *37*, 3873. (d) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.

(3) Review: Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59.

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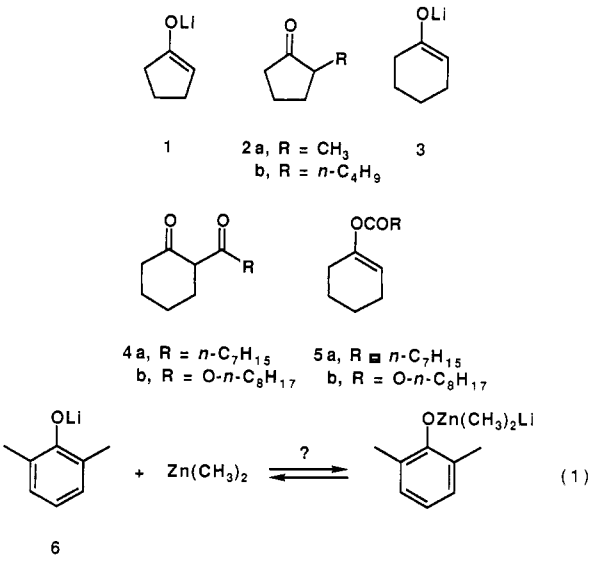
that addition of dimethylzinc notably increases the synthetic efficiency of enolate reactions in this context. Some examples are given below.

Reaction of lithium enolate **1**, generated from equimolar amounts of the corresponding enol trimethylsilyl ether and methyllithium in THF, with 5 equiv of methyl iodide (0 °C, 3 h) produced ca. 15% of polymethylated cyclopentanones (2,2-, *cis*- and *trans*-2,5-, and 2,2,5-) in addition to 79% of the desired 2-methylcyclopentanone (**2a**). Addition of 3 equiv of HMPA accelerated the alkylation as expected,[4] and, after 10 h at −78 °C, **2a** and the 2,2- and 2,5-dimethylation products were obtained in 94 and 3.3% yields, respectively. When the reaction was conducted with 0.2 equiv of dimethylzinc under the same conditions, the yield of **2a** was increased to 98%[5] and formation of the dimethylation products was suppressed to 0.5%. In the presence of 1 equiv of dimethylzinc, the reaction rate was halved but only **2a** was produced in 91% yield; no trace of poly-C- or O-methylated product was detected by capillary column GLC analysis.[6] In like manner, reaction of enolate **1** and *n*-butyl iodide (5 equiv) in THF containing HMPA (10 equiv) at −60 °C for 10 h gave a mixture of monobutyl ketone **2b** (63%), di- and tributylated ketones (29%), and O-butylation products (1.1%), whereas addition of 1 equiv of dimethylzinc led to desired **2b** in 96% yield contaminated with 0.6% of the 2,5-dibutylated ketone and 0.7% of O-butylation product. Both dimethylzinc and HMPA are necessary to obtain smooth, selective monoalkylation.

When a 1:1:1 molar mixture of cyclohexanone enolate **3**,[7] dimethylzinc, and octanoyl chloride in THF was allowed to stand at −78 °C for 30 min, β-diketone **4a** was obtained in 88% yield together with 8% of O-acylated product **5a**. The highest reported yield of a related C-acylation (without dimethylzinc) was 65%.[8] Reaction of enolate **3**[7] with an equimolar amount of *n*-octyl chloroformate in the presence of 1 equiv of dimethylzinc (−78 to −30 °C, 4 h) gave keto ester **4b** and O-oxycarbonylation product **5b** in 85 and 8% yields, respectively. This procedure thus compares well with the recently devised recipe using acyl nitriles[9] or cyanoformates[10] as electrophiles. An HMPA/dimethylzinc combination affects strongly the chemoselectivity; the C- to O-acylation ratio, **4a**/**5a**, varied from 11:1 (0.2–1 equiv of dimethylzinc) to 1.4:1 (3 equiv of HMPA and 1 equiv of dimethylzinc).

A mixture of a lithium alkoxide[11] and a dialkylzinc may form a lithium alkoxydialkylzincate in a reversible manner. Although ^1H and ^{13}C NMR chemical shifts of dimethylzinc were not influenced to a noticeable extent by the addition of an equimolar amount of lithium 2,6-dimethylphenoxide (**6**), the ^7Li spectra varied with coexisting dimethylzinc, suggesting the presence of some interaction between the two metallic agents (eq 1). The ^7Li signal of **6** in THF



(0.44 M, LiCl as external standard, −40 °C) appearing at δ 0.09 ppm was shifted to δ −0.42 and −0.67 ppm by addition of 1 and 2 equiv of dimethylzinc, respectively. In the presence of 3 equiv of HMPA, the signal appearing at δ 0.18 ppm moved to δ −0.75 and −0.85 ppm upon addition of 1 and 2 equiv of dimethylzinc. Although lithium enolates would thus have a dynamic interaction with dialkylzincs, we feel that the major reactive species undergoing alkylation with alkyl iodides is a simple lithium enolate, because addition of organozinc agents does not accelerate the reaction.[12] In any event, the organozinc additive increases opportunities for effecting efficient nucleophilic reactions.

The utility of this protocol is greatly amplified by combination with organozincate conjugate addition to an enone,[13] as illustrated by the three-component coupling synthesis of prostaglandins (PGs).[14] Although conjugate transfer of sp^2 carbons to enones using lithium triorganozincates (empirical formulas) is unknown,[15] we have found that the reagent formed by mixing dimethylzinc and (*E*)-vinylic lithium **8** in a 1:1 mole ratio undergoes selective vinyl transfer to the chiral enone **9**,[14c] giving the 3,4-trans product **11** exclusively as judged by ^{13}C NMR analysis.[14,16] An equimolar mixture of dimethylzinc and **8** [generated from enantiomerically pure **7**[17] and *n*-butyllithium (1:1) in THF] was treated sequentially with siloxy enone **9** (1 equiv, −78 °C, 1 h) and propargylic iodide **10** (5 equiv in 10 equiv of HMPA, −78 to −40 °C, 24 h) and, after aqueous workup and chromatographic separation, the desired PG

(4) (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. (b) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934. (c) Johnson, C. R.; Penning, T. D. *Ibid.* **1988**, *110*, 4726 and references cited therein.

(5) Use of 1 equiv of methyl iodide (−50 °C, 1 h) gave 90% yield.

(6) 1,3-Dimethyl-2-oxohexahydropyrimidine (DMPU), *N*-methyl-2-pyrrolidone, or DMSO is also helpful but somewhat less effective than HMPA. $(n\text{-}C_4H_9)_3SnCl$, $(C_6H_5)_3SnCl$, or $Ti(O\text{-}i\text{-}C_3H_7)_3Cl$ (0.2 equiv) combined with 3 equiv of HMPA is also effective for this purpose. Diethylzinc did not give satisfactory results, however.

(7) The lithium enolate was generated from equimolar amounts of the enol trimethylsilyl ether and methyllithium in THF.

(8) Beck, A. K.; Hoekstra, M. S.; Seebach, D. *Tetrahedron Lett.* **1977**, 1187.

(9) Howard, A. S.; Meerholz, C. A.; Michael, J. P. *Tetrahedron Lett.* **1979**, 1339.

(10) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

(11) For structures of lithium enolates, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(12) For chemistry of chlorozinc enolates, see: (a) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310. (b) Heng, K. K.; Smith, R. A. J. *Tetrahedron* **1979**, *35*, 425. (c) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. For alkylzinc enolates, see: (d) Kataoka, K.; Tsuruta, T. *Polym. J.* **1977**, *9*, 595. (e) Hansen, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069.

(13) (a) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679. (b) Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581. (c) Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 3593. (d) Kjonaas, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133 and references cited therein.

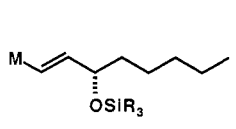
(14) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348. (c) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Ibid.* **1988**, *110*, 4718.

(15) For vinyl conjugate addition using a dimethylzinc/vinylmagnesium bromide mixed reagent, see ref 13b.

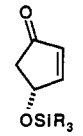
(16) This reaction is in principle catalytic with respect to dimethylzinc. The reaction of **8** and **9** with added 10 mol % of dimethylzinc afforded **11** in 37% yield.

(17) For a convenient way to **7**, see: Kitano, Y.; Matsumoto, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Chem. Lett.* **1987**, 1523.

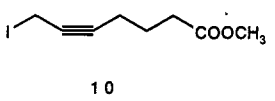
synthetic intermediate **12**[14] was obtained in 71% yield. No cyclopentenones corresponding to the β-siloxy ketone **11** or **12** were formed. The present procedure thus results in considerable simplification of the PG synthesis; particularly isolation of the product is much easier than in our earlier synthesis using a phosphine-complexed organocopper reagent and triphenyltin chloride.[14b,c,18,19]



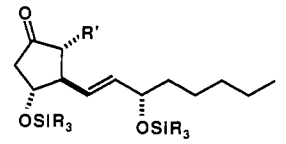
7, M = $Sn(n\text{-}C_4H_9)_3$
8, M = Li



9



10



11, R' = H
12, R' = $CH_2C{\equiv}C(CH_2)_3COOCH_3$

SiR_3 = $Si(CH_3)_2$-*tert*-C_4H_9

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Supplementary Material Available: Experimental procedures and spectroscopic data for the new compounds (10 pages). Ordering information is given on any current masthead page.

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Received December 8, 1988

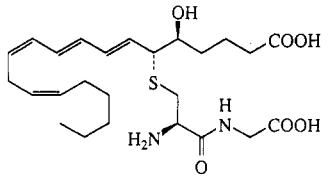
(18) (a) Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299. (b) Tanaka, T.; Hazato, A.; Bannai, K.; Okamura, N.; Sugiura, S.; Manabe, K.; Toru, T.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron* **1987**, *43*, 813.

(19) Product **12** was most conveniently separated from unreacted **10** on preparative high-performance liquid chromatography using a Japan Analytical Industry Model LC-09 chromatograph (column, JAIGEL AJ2H × 2; eluant, $CHCl_3$; flow rate, 3.5 mL/min; detection UV-254H and RI-2).

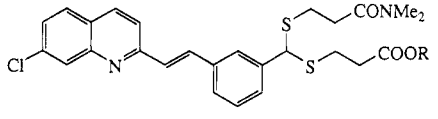
Synthesis of Chiral Dithioacetals: A Chemoenzymic Synthesis of a Novel LTD_4 Antagonist

Summary: An enantioselective enzymatic hydrolysis of prochiral diester **3**, having four bonds between the prochiral center and ester group, serves as the key step in a short and efficient synthesis of both enantiomers of the selective LTD_4 antagonist, MK-0571.

Sir: Aryl and alkyl dithioacetals of mercaptopropionic acid derivatives are potent receptor antagonists of leukotriene D_4 (**1**) and are being developed as therapeutic agents for bronchial diseases.[1] One of the most promising candidates currently in clinical trials is MK-0571 (**2a**), a racemic compound. Due to the similarity of the two thioalkyl side chains, attempts to resolve **2a** by classical methods, such as crystallization of diastereomeric salts or chromatographic separation of diastereomeric derivatives, proved difficult. Recently, the synthesis of both enantiomers of **2a** and analogues has been reported.[2] This synthesis entails chromatographic separation of a 50/50 mixture of diastereomers early in the synthesis followed by transformation of each diastereomer into the appropriate enantiomer. However, scale up of such a process would be difficult. Thus, we directed our efforts to enzymatic resolutions, resulting in a straightforward route to both enantiomers of **2a**, described herein.



1



2 (a) R = H
(b) R = Me

There is little or no literature precedent[3] for enzymatic resolutions of compounds such as **2**, wherein there is a 4-bond distance between carboxylic acid and the chiral center, and the thioalkyl chains are similar and have unrestricted conformational flexibility. Nonetheless, two enzymatic approaches were examined: (1) selective hydrolysis of racemic esters of **2a** and (2) hydrolysis of prochiral diesters **3**. Several enzymes were screened with a variety of esters before finding that lipase from *Pseudomonas* species cleanly hydrolyzed the Me and CH_2CONH_2 prochiral diesters **3a** and **3b** with >98% enantiomeric excess and 90% yield.[4-6] Over hydrolysis to the diacid

(1) (a) Perchonock, C. D.; McCarthy, M. E.; Erhard, K. F.; Gleason, J. G.; Wasserman, M. A.; Muccitelli, R. M.; DeVan, J. F.; Tucker, S. S.; Vickery, L. M.; Kerchner, T.; Weichman, B. M.; Mong, S.; Crooke, S. T.; Newton, J. F. *J. Med. Chem.* **1985**, *28*, 1145; **1986**, *29*, 1442–1452; **1987**, *30*, 959. (b) Saksena, A. K.; Green, M. J.; Mangiaracina, P.; Wong, J. K.; Kreutner, W.; Gulbenkian, A. R. *Tetrahedron Lett.* **1985**, *26*, 6427. (c) Young, R. N.; Guindon, Y.; Jones, T. R.; Ford-Hutchinson, A. W.; Belanger, P.; Champion, E.; Charette, L.; DeHaven, R. N.; Denis, D.; Fortin, R.; Frenette, R.; Gauthier, J.-Y.; Gillard, J. W.; Kakushima, M.; Letts, L. G.; Masson, P.; Maycock, A.; McFarlane, C.; Piechuta, H.; Pong, S. S.; Rosenthal, A.; Williams, H.; Zamboni, R.; Yoakim, C.; Rokach, J. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **1986**, *16*, 37.

(2) (a) Therien, M.; Gauthier, J. Y.; Young, R. N. *Tetrahedron Lett.* **1988**, *29*, 6733–6736. (b) Young, R. N.; Gauthier, J. Y.; Therien, M.; Zamboni, R. *Heterocycles*, in press.

(3) Whitesides, G. M.; Wong, C.-H. *Angew. Chem., Ind. Ed. Engl.* **1985**, *24*, 617–638. Jones, J. B. *Tetrahedron*, **1986**, *42*, 3351–3403.

(4) The enantiomeric ratios were determined by HPLC analysis of samples derivatized with (*R*)- or (*S*)-1-(1-naphthyl)ethylamine. For **4a**, HPLC conditions were: Zorbax C8 column, 25 cm; eluent consisting of 80:20 CH_3CN–0.1% aqueous H_3PO_4; flow 2.0 mL/min; ambient temperature; detection at 350 nm. The two diastereomeric amides elute at 25 and 27 min with base-line resolution. When the amides are prepared with (*R*)-1-(1-naphthyl)ethylamine, the diastereomer from (*R*)-**4a** elutes first. The amides prepared from **2a** elute at similar times under these conditions. The rotations of both enantiomers of **2a** were identical with those reported in ref 2b. ^1H NMR spectral data of the enantiomers match those of racemic material reported in ref 9.

(5) These results are with purified *Pseudomonas* lipase from Sigma. With crude lipase from Amano Enzyme Co., the ee was 95%, the chemical yield was 85%, and 5% diacid was formed from the prochiral dimethyl ester. With pure lipase from Beohringer-Mannheim, no reaction occurred.

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