

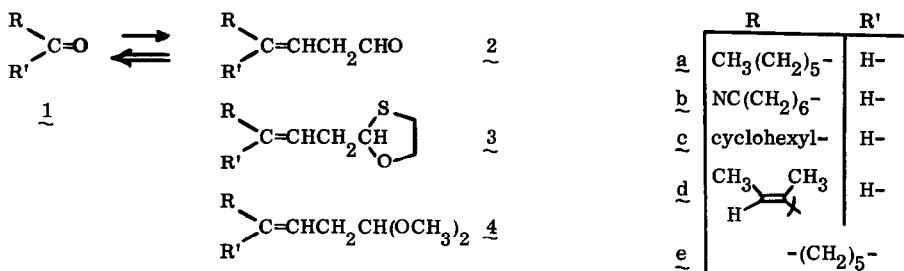
**cis- AND trans-2-METHOXYCYCLOPROPYLLITHIUM: NOVEL REAGENTS
FOR THE STEREOSELECTIVE SYNTHESIS OF trans- β,γ -UNSATURATED ALDEHYDES**

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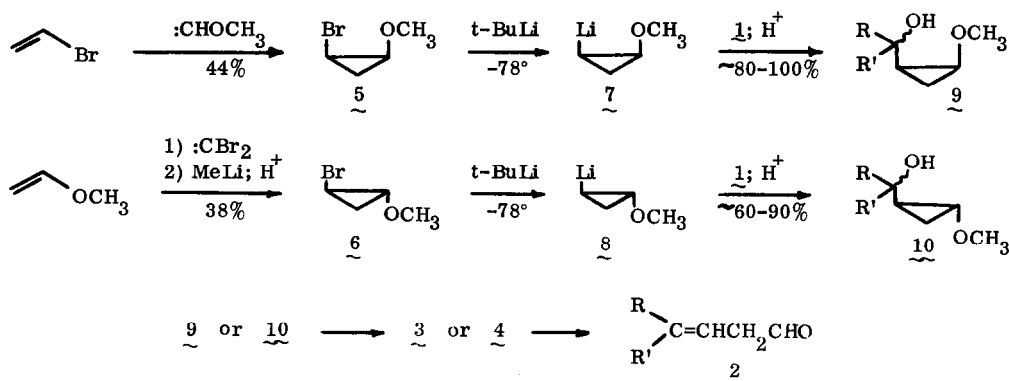
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In connection with other projects we have been seeking a general route to trans- (or E) β,γ -unsaturated aldehydes, in both free and protected form, via a three carbon chain extension which is equivalent to a hypothetical Wittig process from the unknown reagent $R_3P=CHCH_2CHO$. We report here the successful realization of this objective. Two new organolithium reagents, cis- and trans-2-methoxycyclopropyllithium 7 and 8 have been generated and shown to react with carbonyl compounds to give

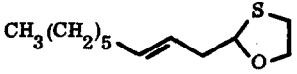
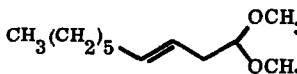
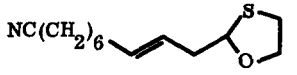
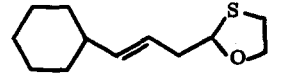
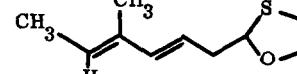
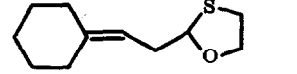


carbinols 9 and 10, which are readily converted to the β,γ -unsaturated acetals 4, the hemithioacetals 3, and the free aldehydes 2.²



The readily available bromo ethers 5^{3,5} and 6^{4,5} (1.1 equiv. in ether⁶), on treatment at -78° with 1.2 equiv. of *t*-butyllithium (in pentane) for 2 hr, undergo metal-halogen exchange with retention of configuration to give solutions of 7 and 8, respectively; 7 treatment of either solution with 1 equiv. of a carbonyl compound 1 gives on aqueous work-up the corresponding carbinol 9 or 10 in good to excellent

Table. β , γ -Unsaturated Aldehydes by Three Carbon Homologation⁵

Carbinol <u>9</u> or <u>10</u> , % yield from <u>1</u>	Acetal <u>3</u> or <u>4</u> , % yield, ^a <u>E</u> : <u>Z</u> ratio ^b	β , γ -Unsaturated aldehyde <u>2</u> , % yield ^{c, d}
<u>10a</u> , 85 ^a	 <u>3a</u> , 77, ^f 83:17	<u>2a</u> , 93; ^{i, j}
<u>10a</u> , 85 ^a	 <u>4a</u> , 97, ^g 83:17	<u>2a</u> , 96 ^{k, l} , 10
<u>10b</u> , 58 ^{a, e}	 <u>3b</u> , 82, ^f 83:17	<u>2b</u> , 93 ⁱ
<u>9c</u> , 100 ^c	 <u>3c</u> , 77, ^h >97:3 ¹¹	<u>2c</u> , 91 ⁱ
<u>9d</u> , 96 ^c	 <u>3d</u> , 61, ^h >97:3 ¹¹	<u>2d</u> , 67 ^l
<u>9e</u> , 92 ^c	 <u>3e</u> , 81, ^h ---	<u>2e</u> , 95 ⁱ

a) After chromatography on silica gel. b) By pmr (100 MHz). c) As isolated, >95% pure by pmr, ir, tlc. d) Less than 2% α , β isomer, unless noted. e) 30% 1b recovered. f) From 10 mesylate,⁹ 2-mercaptoethanol (1.05 equiv., -40°, 10 min) and BF₃·Et₂O (2.1 equiv., -40°, 10 min; 0°, 1 hr). g) From 10a mesylate⁹ and methanol (10 equiv., -40°, 10 min). h) From 9, 2-mercaptoethanol (1.05 equiv.) and BF₃·Et₂O (2.1 equiv.) in CH₂Cl₂, 0°, 1 hr (9c), or -20°, 1 hr (9d), or in ether, 0°, 2 hr (9e). i) From 3, HgCl₂ (2 equiv.) and CaCO₃ (2 equiv.) in aqueous 85% acetonitrile (0°, 1 hr; ether--aqueous ammonium acetate work-up, florisil filtration). j) Buffered hydrolysis of 10a mesylate; product purity 90%, E:Z ratio 83:17. k) Purity ca. 90%; 5% α , β isomer. l) Hydrolysis of methyl sulfonium salt.

yield.⁸

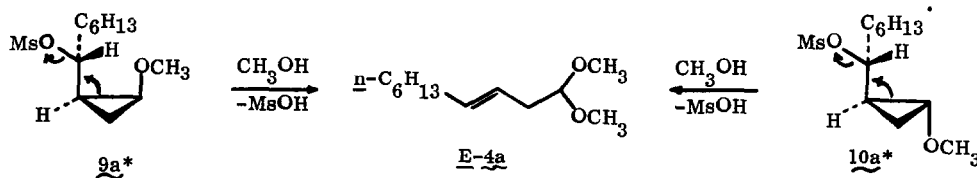
Mesylates⁹ of the alcohols 9 or 10 can often be hydrolyzed directly to aldehydes 2 under buffered conditions (acetone--water--oxalic acid--ammonium hydrogen oxalate, -40°, 15 min), but the process is less satisfactory with some very labile mesylates (e.g., of 9d). An alternative, more flexible approach proceeds via the stable, readily purified acetals 3 and 4. Treatment of a solution of mesylate⁹ of 9 or 10 with excess methanol at -40° gives clean, rapid formation of the dimethyl acetals 4 (85-97% isolated), which can be hydrolyzed to 2 by a reported method.¹⁰ More interesting to us was the formation of ethylene hemithioacetals 3 in good yield on treatment of 9 or 10 or their mesylates (in situ) with 2-mercaptoethanol and boron trifluoride etherate (see Table). Such hemithioacetals can be especially useful because, although relatively acid resistant, they are readily hydrolyzed under neutral conditions with

mercuric ion assistance (see Table) or via an S-methyl sulfonium derivative (1 M solution of 3 in acetonitrile, 2 equiv. of methyl fluorosulfonate, 0.2 equiv. of calcium carbonate, -20° , 2 hr; mixture added to acetone--water--excess calcium carbonate, 0° , 15 min); the latter method was particularly useful in the case of 3d in which the 1,3-diene unit is susceptible to mercuration.

With carbinols 9 or 10 derived from aldehydes (1, R' = H), the various solvolytic conditions provide β , γ -unsaturated derivatives 2, 3, or 4 with very high trans-selectivity¹¹ as long as R is other than primary alkyl (e.g., R = cyclohexyl (1c), 1-methyl-trans-propenyl (1d), isopropyl, phenyl). However, when R is primary alkyl (e.g., n-hexyl (1a), 7-cyanoethyl (1b), isobutyl), the stereoselectivity is diminished (ca. 5:1 E:Z from 10) or absent (ca. 1:1 E:Z from 9).

The rearrangements of the heptanal adducts 9a and 10a were studied in greater detail. Preparative layer chromatography (E. Merck Silica Gel 60) separated the carbinyl epimers of 9a (15:85 EtOAc--CH₂Cl₂, 3 elutions) and of 10a (8:92 Me₂CO--CH₂Cl₂, 3 elutions). Mesylation and methanolysis of each epimer at -40° gave the following results (carbinol no., R_f of epimer, percent in mixture, E:Z ratio in 4a product): 9a^{*}, 0.48, 77%, 35:65; 9a^{*}, 0.56, 23%, >97:3; 10a^{*}, 0.50, 50%, 67:33; 10a^{*}, 0.55, 50%, >97:3 (* and * refer to more and less polar epimer, respectively).

Thus the mesylates of the less polar alcohol epimers form the trans olefinic unit very selectively. We suggest that these diastereomers which give trans olefin can assume an uncrowded S-trans conformation in the concerted elimination-rearrangement represented below.



The stereochemical course of the various solvolyses showed little dependence on the nucleophile (methanol, 2-mercaptoethanol, water, formate ion) or on the temperature (-78° to 25°), but the nature of the carbinyl leaving group was critical. The more labile aryl sulfonates of 9a and 10a, which should allow more nearly complete heterolysis of the leaving group in the solvolytic transition state, give somewhat higher E:Z ratios on methanolysis than do the mesylates (up to 93:7 for the 2,4-dinitrobenzene-sulfonate of 10a), but the extreme sensitivity of these arylsulfonates is a drawback. Direct acid- or BF₃-catalyzed solvolysis of the alcohols 9a or 10a gave no higher trans-selectivity than that obtained via the mesylates.¹²

References and Notes

1. These are apparently the first reported 2-alkoxycyclopropyllithium reagents not of the α -halogenated (carbenoid) type. See K. G. Taylor, W. E. Hobbs, and M. Saquet, J. Org. Chem., **36**, 369 (1971); K. G. Taylor, W. E. Hobbs, M. S. Clark, and J. Chaney, ibid., **37**, 2436 (1972); J. D. White and L. G. Wade, Jr., ibid., **40**, 118 (1975).
2. M. Julia and coworkers prepared analogs of 9 and 10 by a totally different approach and studied their behavior in aqueous acid; β, γ -unsaturated aldehydes could be isolated only in certain favorable cases (e. g., when α -hydrogens were lacking). See M. Julia and G. LeThullier, Bull. Soc. Chim. Fr., 717, 729 (1966); M. Julia and M. Baillarge, ibid., 734, 743 (1966); see also E. Wenkert, R. A. Mueller, E. J. Reardon, S. S. Sathe, D. J. Scharf, and G. Tosi, J. Amer. Chem. Soc., **92**, 7428 (1970).
3. Methylithium--lithium iodide (1 M in ether) was added to vinyl bromide and methoxydichloromethane (12 equiv. :1 equiv.) in ether (1 vol.) under argon at -20° over 80 min, until a haloform test was negative. Work-up and distillation gave a mixture of 5 and 6 (91:9) (58%); redistillation (10 cm Vigreux) gave pure 5 (44% based on $\text{Cl}_2\text{CHOCH}_3$; bp $48.5\text{--}50.0^\circ$ at 24 mm; pmr $J = 5.2$ Hz for H-CBr-COMe-H). See U. Schöllkopf and J. Paust, Chem. Ber., **98**, 2221 (1965).
4. Bromoform (1 equiv.) was added to potassium t-butoxide (1.4 equiv., from potassium hydride and t-butyl alcohol) in 1:1 v/v methyl vinyl ether (10 equiv.)--pentane at -25° over 2 hr affording 1,1-dibromo-2-methoxycyclopropane⁵ (58%, bp $41\text{--}44^\circ$ at 4.5 mm); stereospecific Br-Li exchange¹ and protonation (methylithium--lithium bromide in ether, -78° , 10 min; methanolysis) gave pure 6 (65%, bp $31\text{--}36^\circ$ at 24 mm; pmr $J = 1.8$ Hz for H-CBr-COMe-H).
5. All new compounds exhibited ir, pmr, and mass spectra consistent with the assigned structures.
6. Approx. 0.5 M solution of 5, or 0.2 M solution of 6.
7. t-Butyl bromide, formed in the rapid initial exchange, destroys the excess t-butyllithium.
8. The carbinols 9 usually do not require purification. The carbinols 10 may be chromatographed on silica gel to remove about 5% of less polar, bromine containing impurities.
9. Mesylates were prepared in dichloromethane at -40° (-10° for t-ROH) by the method of R. K. Crossland and K. L. Servis, J. Org. Chem., **35**, 3195 (1970).
10. Acetone--water--oxalic acid, 45° , 30 min: see M. Winter, Helv. Chim. Acta, **46**, 1792 (1963).
11. Less than 3% of Z isomer by pmr or ir analysis.
12. This work was assisted financially by the National Science Foundation.