(m, 2 H, -CH_2O-), 7.21 (d, 1 H, J = 8 Hz, Ar H), 7.52 (d, 1 H, J = 8 Hz, Ar H). **13:** mp 127–128 °C; IR ($CHCl_3$) 3580, 3360, 1755, 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 3 H, $\geqslant C-CH_3$), 1.23 (d, 3 H, J = 7Hz, -$CHMe_2$), 1.27 (d, 3 H, J = 7 Hz, -$CHMe_2$), 1.5–3.2 (m, 7 H), 3.33 (septet, 1 H, J = 7 Hz, -$CHMe_2$), 4.78 (m, 2 H, -CH_2O-), 5.18 (m, 1 H, $W_{1/2}$ = 16 Hz, H-C-OH), 6.87 (d, 1 H, J = 8 Hz, Ar H), 7.17 (d, 1 H, J = 8 Hz, Ar H). **14:** mp 80–83 °C; IR ($CHCl_3$) 1755, 1680, 1660, 1637, 1582 cm^{-1}; UV (MeOH) 343 nm (ϵ 4954); ^1H NMR ($CDCl_3$) δ 1.10 (d, 6 H, J = 7 Hz, -$CHMe_2$), 1.15 (s, 3 H, $\geqslant C-CH_3$), 1.5–2.6 (m, 7 H), 2.93 (septet, 1 H, J = 7 Hz, -$CHMe_2$), 4.07 (m, 1 H, epoxy H), 4.70 (m, 2 H, -CH_2-O-), 6.42 (d, 1 H, J = 7 Hz, C_{11} H), 6.99 (d, 1 H, J = 7 Hz, C_{12} H).

(9) Ketone **11** and the corresponding isomer with cis A-B ring fusion are each obtained in ~15% yield, and the cis isomer is the more stable isomer. Quinone resulting from oxidation of the aromatic ring is also produced (35%). Separation was effected by column chromatography on silica gel and recrystallization. Efforts to improve the oxidation procedure are in progress.

(10) Bis epoxidation of **14** with m-CPBA to afford **3** in one step (22%) has been observed and is under further study.

(11) The structure of racemic **1** (mp 255–256 °C) and **3** (mp 225–226 °C) was established by comparison of spectral data with those of the natural substances. We thank the late Professor S. M. Kupchan for providing IR and ^1H NMR spectral data.

Richard S. Buckanin, Samuel J. Chen, Donna M. Frieze
Frank T. Sher, Glenn A. Berchtold*
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

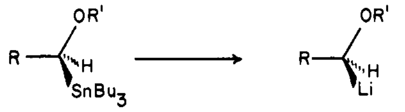
Received September 18, 1979

α-Alkoxyorganolithium Reagents. A New Class of Configurationally Stable Carbanions for Organic Synthesis

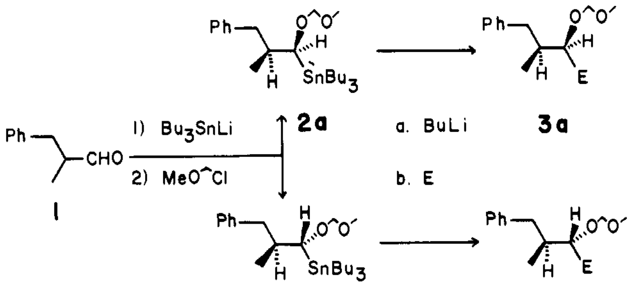
Sir:

Recent preparations of stereochemically defined organolithium reagents have provided a most useful approach to the stereospecific construction of carbon-carbon bonds. These reagents have however been limited largely to vinyl- and cyclopropyllithiums.[1] We report here the preparation of a new class of configurationally stable organolithiums which are sp^3 hybridized, acyclic, and may be obtained as diastereomerically or enantiomerically pure reagents.

Early attempts to prepare chiral organometallics from metals and optically active alkyl halides led to extensively racemized products, a result presumably due to the intermediacy of free radicals on the reaction pathway.[2] Later investigations showed however that the exchange reaction of alkyllithiums with resolved *sec*-butylmercuric chloride proceeded with clean retention of configuration.[3] Although the exchange reported is not a synthetically useful one owing to the presence of other lithium reagents in the product, the experiment did show that sp^3 organolithiums should be configurationally stable once formed. Since α-alkoxyorganolithium reagents may be prepared by a fast, low-temperature exchange from the corresponding organostannanes,[4] we felt that this route to organolithiums should be a stereospecific one.[5]

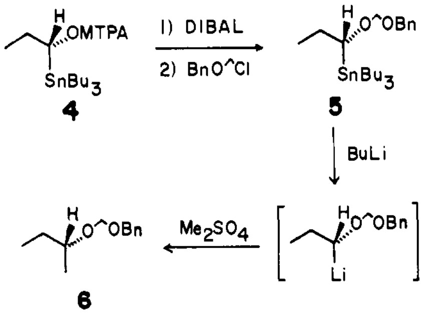


We therefore examined the stereochemistry of the exchange reaction in the following way. 2-Benzylpropanal (**1**) was first treated at −78 °C with tri-n-butylstannyllithium (from n-Bu_3SnH and $LiNiPr_2$) and then protected with chloromethyl methyl ether (i-Pr_2NEt, 0 °C, 1 h) to produce a 1:1 mixture of diastereomers **2a** and **2b** (75% yield). Although the compounds did not resolve on TLC, they could be cleanly separated on a preparative scale by medium-pressure liquid chromatography (MPLC) on silica gel.[6a] Compounds **2a** and **2b** were then individually treated with n-butyllithium (THF, −78 °C) and after 15 min the intermediate α-alkoxyorganolithium reagents were quenched with acetone. Careful high pressure liquid chromatographic (HPLC) examination of the products showed the reactions to be totally stereospecific. Thus **2a** produced a single acetone adduct (90% yield) which was different from the single product afforded by **2b.** These reactions were repeated at −30 °C (THF, 15 min) and again no loss of stereochemistry was observed.[7] Analogous results were obtained with trapping by trimethylchlorosilane.



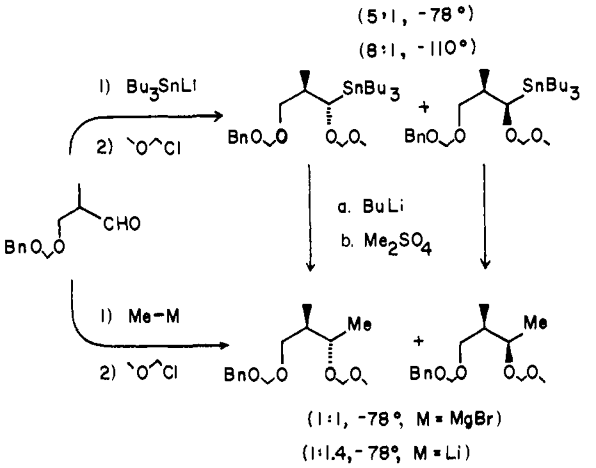
While the above experiments demonstrate the stereospecific nature of the exchange and trapping, they do not distinguish between retention and inversion. The expected net retention of configuration was verified in one case by trapping the intermediate α-alkoxyorganolithium reagent with a tin halide. Thus, while the lithium reagent prepared from **2a** was unreactive with tri-n-butyltin chloride, it did add to tri-n-butyltin iodide at −50 °C. The resulting α-alkoxyorganostannane was shown to be the product of retention by its correlation with the starting material, **2a.**

We have also prepared enantiomerically pure α-alkoxyorganolithium reagents from aldehydes by chromatographic resolution of suitable derivatives of the intermediate stannylcarbinols. An example of this operation starts with propanal. Addition of tri-n-butylstannyllithium and then esterification with (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(−)-MTPA-Cl][8] gave quantitatively a pair of diastereomeric esters which could be separated by MPLC.[6b,9] The more mobile R[13] ester **4** was converted into the resolved stannylcarbinol by reduction (i-Bu_2AlH, $PhCH_3$, −78°C, 90% yield) and was then protected with benzyl chloromethyl ether (i-Pr_2NEt, 0 °C, >95% yield) to give **5.** Finally the lithium reagent was prepared as usual (n-BuLi, THF, −78 °C) and was alkylated with dimethyl sulfate to yield **6.** Hydrogenolysis (10% Pd/C, Et_2O) gave optically active 2-butanol. Whereas the (−)-MTPA ester of racemic 2-butanol displayed the carbinol methyl resonances in the NMR ($CDCl_3$) as a pair of doublets at δ 1.25 and 1.33, the (−)-MTPA ester from **6** showed only the lower field doublet.[10] This ester was shown to be identical with that prepared from authentic (R)-(−)-2-butanol.



The results described above involve separations of diastereomeric organostannanes as a pathway to stereochemically defined organolithium reagents. Since stereoselective preparations of α-alkoxyorganostannanes would be of considerable value in this area, we briefly examined α induction in the addition of tributylstannyl nucleophiles to several α-substituted chiral aldehydes. Our results indicate that, for α induction based only on the relative sizes of α-substituents (Cram's rule),[11] the tributylstannyl anion exhibits much the same stereoselectivity as unhindered Grignard reagents. Thus 2,3-dimethylbutanal (THF, −110 °C) gives essentially the same stereochemical product distribution with either tributylstannyllithium (3:1) or methylmagnesium bromide (2.5:1). In the case of the former addition, the product stannylcarbinol mixture was protected ($BnOCH_2Cl$, i-Pr_2NEt), lithiated (BuLi, THF, − 78 °C), and methylated (Me_2SO_4) to give the same major methylcarbinol produced by the Grignard addition. This result would seem to indicate that methylation proceeds with retention unless steric α induction with methylmagnesium bromide is opposite that observed with tributylstannyllithium.

Stereoselectivity is somewhat improved with aldehydes substituted at the β position by oxygen. With α-asymmetric aldehydes of this type, the cyclic chelate mechanism[12] would presumably be operative and anti-Cram products would be predicted. When the β-alkoxy aldehyde **7** was treated with tributylstannyllithium in THF, a 5:1 (−78 °C) or 8:1 (−110 °C) mixture of diastereomeric stannylcarbinols was produced. After protection ($MeOCH_2Cl$, i-Pr_2NEt), the major diastereomer was purified by MPLC on silica gel. Lithiation (BuLi, −78 °C, THF) and methylation (Me_2SO_4) then gave the anticipated[13] threo product[14] stereospecifically. For comparison, both methyllithium and methylmagnesium bromide add to **7** (THF, −78 °C) in an essentially stereorandom manner. Although the generality of stereoselection in tin anion additions remains to be established, these preliminary results suggest that tributylstannyllithium may be added to aldehydes with moderate stereoselectivity and that the direction of the addition is that predicted either by Cram's rule or by the cyclic chelation model.[15]



References and Notes

(1) Other configurationally fixed organoalkali metal compounds have been prepared by equilibration and sometimes separation, for example, D. E. Applequist and G. N. Chmurny, *J. Am. Chem. Soc.*, **89**, 875 (1967); W. M. Glaze and C. M. Selman, *J. Org. Chem.*, **33**, 1987 (1968); W. M. Glaze and C. M. Selman, *J. Organomet. Chem.*, **11**, P5 (1968); F. R. Jensen and K. L. Nakamaye, *J. Am. Chem. Soc.*, **88**, 3437 (1966).

(2) R. L. Letsinger, *Angew. Chem.*, **70**, 151 (1958), and references cited therein; E. Grovenstein, Jr., and Y.-M. Cheng, *Chem. Commun.*, 101 (1970); M. J. S. Dewar and J. M. Harris, *J. Am. Chem. Soc.*, **91**, 3652 (1969).

(3) D. Y. Curtin and W. J. Koehl, *J. Am. Chem. Soc.*, **84**, 1967 (1962).

(4) W. C. Still, *J. Am. Chem. Soc.*, **100**, 1481 (1978).

(5) Other factors which would be expected to raise the barrier to organolithium inversion include intramolecular chelation (which stabilizes the position of lithium) and α-heteroatom substitution [which is known to raise pyramidal inversion barriers for example in the isoelectronic hydroxylamines: reviews by J. B. Lambert, *Top. Stereochem.*, **6**, 19 (1971) and H. A. Bent, *Chem. Rev.*, **61**, 275 (1961); see also H. M. Niemeyer, *Tetrahedron*, **33**, 2267 (1977)].

(6) A 25 × 500 mm LiCroprep.Si60 (25-40 μ, E. Merck No. 9390) was used, 15 mL/min: (a) 2% ethyl acetate-petroleum ether; (b) 0.3% ethyl acetate-petroleum ether.

(7) A similar sequence with **2a** at 0 °C gave mainly decomposition of the lithium reagent. The small portion of the reagent which did survive gave a 1:1 mixture of **3a** and **3b** [E = $C(CH_3)_2OH$] on trapping with acetone. It is not clear whether or not the isomerization is due to pyramidal inversion of the anion or due to some other process related to decomposition of the reagent.

(8) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969); S. L. Chen, K. Nakanishi, M. Morisaki, N. Ikehawa, and Y. Shimizu, *J. Am. Chem. Soc.*, **97**, 5297 (1975), and references cited therein.

(9) Optical resolution of the tributyltin adduct of propanal could also be effected via formation of a urethane with (−)-α-phenylethylamine [(a) $COCl_2$, i-Pr_2NEt; (b) (−)-$PhCH(CH_3)NH_2$]. With this derivative the MPLC separation was more difficult and the *S* urethane analogous to **4b** eluted first. Conversion to the stannyl carbinol was effected without loss of optical activity using $HSiCl_3$-EtY_3N; cf. W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42**, 1939 (1977);W. H. Pirkle and P. L. Rinaldi, *ibid.*, **43**, 3803 (1978).

(10) Although no peaks resulting from the (−)-MTPA ester of the enantiomeric alcohol could be seen, proportions of that material as large as 5% could have escaped detection.

(11) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828, 5851 (1952). See also N. T. Ahn and O. Eisenstein, *Nouv. J. Chim.*, **1**, 61 (1977).

(12) D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959); D. J. Cram and D. R. Wilson, *ibid.*, **85**, 1245 (1963).

(13) Assuming retention of stereochemistry during methylation.

(14) Authentic threo material was prepared from tiglic acid as follows: (1) $LiAlH_4$, Et_2O; (2) $BnOCH_2Cl$, i-Pr_2NEt; (3) BH_3, THF; NaOH, H_2O_2; (4) $MeOCH_2Cl$, i-Pr_2NEt.

(15) This work was supported by NSF Grant CHE 78-01769.

(16) Alfred P. Sloan Fellow, 1978-1980.

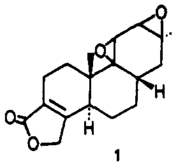
W. Clark Still,*[16] C. Sreekumar
Department of Chemistry, Columbia University
New York, New York 10027

Received June 7, 1979

Total Synthesis of Stemolide

Sir:

Falling in the same class as the potent cytotoxic agents triptolide, tripdiolide, and triptonide,[1] the diterpenoid bisepoxide stemolide (**1**), possessing the novel 18(4→3)*abeo*-abietane skeleton, was recently isolated and described by Manchand and Blount.[2] Herein we report a total synthesis of this natural product, the first route to a representative of this structural type.[3]



1

To prepare for the later incorporation of the bis epoxide moiety, the starting material, methyl dehydroabietate,[4] was first functionalized in the aromatic ring by treatment with acetyl chloride in CS_2 in the presence of Al_2Cl_6, providing methyl 12-acetyldehydroabietate (80%). Baeyer-Villiger oxidation with 3,5-dinitroperbenzoic acid[5]-methanesulfonic acid (CH_2Cl_2, room temperature), saponification, and O-alkylation with MeI-NaH (THF, room temperature) led to methoxy ester **2**,[6] convertible by EtSLi[7] (HMPA-THF, room temperature) into the corresponding acid **3**[6] (76% from **2**). Following the approach of Huffman and and Stockel,[8] the substituted dehydroabietic acid **3** was transformed into the dehydroabietene **7** (mp 75-77 °C) by Curtius degradation to isocyanate **4**, $LiAlH_4$ reduction followed by Eschweiler-Clarke methylation to **5**, N-oxidation to **6**, and Cope elimination (72% from **3**). The α-epoxide resulting from m-chloroperbenzoic acid oxidation of **7**, on treatment with Et_2Al-N-i-Pr_2[9] (C_6H_6/PE, 50 °C), generated allyl alcohol **8**. After conversion (n-Bu_3P/CCl_4, 0 °C) of **8** to halide **9**, displacement by lithium thiophenoxide (THF, room temperature) gave thioether **10** (81% from **7**). The corresponding sulfonium fluoroborate **11** was converted by BuLi (THF, −78 °C) into ylide **12**, which underwent in situ electrocyclic conversion at 0 °C into the