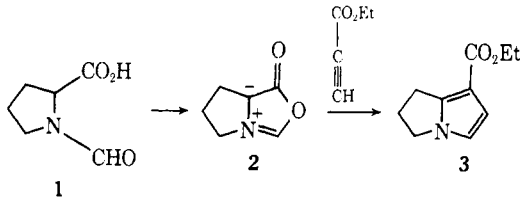
Stereospecific Synthesis of 1-Substituted Pyrrolizidines[1]

Summary: A two-step stereospecific route to 1-substituted pyrrolizidines was achieved from *N*-formyl-L-proline.

Sir: Interest in the 1-substituted pyrrolizidine skeleton derives chiefly from its presence in a number of widely distributed alkaloids[2] and from the pharmacological activity of these compounds.[3]

Previous syntheses of 1-substituted pyrrolizidines are multiple-step procedures.[4] This report describes a two-step stereospecific route that gives the thermodynamically less stable racemate **5** in 80% overall yield. Since complete epimerization at C_1 to the more stable racemate is known to proceed with high yield,[5] this is a preparative procedure to obtain derivatives of the heliotridane **4** and pseudoheliotridane **7** series, from a single intermediate **3**.

The synthesis was accomplished starting with the readily available *N*-formyl-L-proline[6] (**1**) [mp 88–91°, $[\alpha]^{20}D$ −125° (*c* 1, EtOH)] prepared in quantitative yield from L-proline and acetic-formic anhydride. Cycloaddition of ethyl propiolate to **1** (5 equiv of ethyl propiolate in acetic anhydride at reflux for 2 hr) afforded the ester **3**[6] in 90% yield after silica gel column chromatography using chloroform as eluent.



1 **2** **3**

4, R = CH_3 **7**, R = CH_3
5, R = CO_2Et **8**, R = CO_2Et
6, R = CH_2OH **9**, R = CH_2OH

It is reasonable to assume that a 1,3 dipole,[7] **2**, is the intermediate in the conversion of **1** to **3**.

Hydrogenation of **3** was carried out in ethanol as solvent under 3 atm of hydrogen for 24 hr with 10% palladium on carbon (amount equal weight of substrate **3**) to afford the stereochemically pure[8] ethyl (±)-isoretronecanolate (**5**)[6] in 93% yield, picrate mp 119–121° (lit.[4b] mp 119.5–120°), picrolonate mp 183–189° (lit.[4b] mp 186–189°). Reduction of **5** to (±)-isoretronecanol (**6**), picrate mp 187–189° (lit.[4b] 189.5–190°), picrolonate mp 174–176° (lit.[4b] 176–177°), as described[4b] provided final identification of the structure and stereochemistry of product **5**.

References and Notes

(1) This investigation was supported by grants from the National Research Council (Argentina).
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The Convenient Stereospecific Synthesis of Terminal Acetylenes *via* the Treatment of Lithium Ethynyltrialkylborates with Iodine

Summary: Lithium ethynyltrialkylborates, readily prepared from lithium acetylide–ethylenediamine and trialkylboranes, react readily with iodine to produce in high yield the corresponding terminal alkylacetylene with complete retention of the stereochemistry of the boron–carbon bond.

Sir: Treatment of lithium 1-alkynyltrialkylborates with iodine under very mild conditions produces the corresponding internal acetylenes in essentially quantitative yields[1] (eq 1). However, when we attempted to extend

$$Li[R_3BC{\equiv}CR'] + I_2 \longrightarrow RC{\equiv}CR' \qquad (1)$$

this synthesis to the preparation of the corresponding terminal acetylenes, the results were highly unsatisfactory. For example, treatment of monolithium acetylide[2] with tri-*n*-butylborane produced the lithium ethynyltri-*n*-butylborate (^{11}B nmr +17.3 ppm). Treatment of this complex with iodine at −78° provided 1-hexyne in a yield of only 24% (glpc analysis). However, when the commercially available lithium acetylide–ethylenediamine[3] was used, the reaction proved far more favorable. Addition of 1 molar equiv of tri-*n*-butylborane to a suspension of the reagent in tetrahydrofuran (THF) resulted in a slightly exothermic reaction and solution of the suspension. Addition of iodine at −78° followed by warming to room temperature produced 1-hexyne in a yield of 75%.

The reaction was then applied to representative organoboranes. Even better results, in the range of 84–94%, were obtained with the great majority of the trialkylboranes.[4] Representative results are summarized in Table I.

The following procedure for the preparation of cyclohexylethyne is representative. A dry 100-ml flask equipped with septum inlet and magnetic stirring bar was flushed with nitrogen. The flask was charged with 2.02 ml of 2.46 *M* borane in THF (5.0 mmol of borane) and 7 ml of dry THF. Cyclohexene (15.0 mmol) was added to the solution and the mixture stirred overnight at room temperature. (Alternatively, the solution may be heated at 50° for 3 hr to complete the hydroboration of this relatively sluggish olefin.) To the solution was added 0.50 g (5.09 mmol) of lithium acetylide–ethylenediamine (Ventron Corp.). (The lithium acetylide reacts slowly with air and moisture and should be handled in a glove bag.) The solution was

Table I
Synthesis of Terminal Acetylenes by the Treatment of Lithium Ethynyltrialkylborates–Ethylenediamine with Iodine

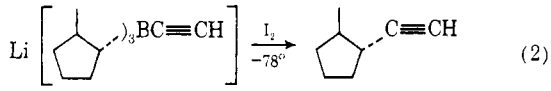
Olefin in R_3B	Product	Yield, %[a]
1-Butene	1-Hexyne	75
2-Butene	3-Methyl-1-pentyne	84
2-Methylpropene	4-Methyl-1-pentyne	94
Cyclopentene	Cyclopentylethyne	85
1-Methylcyclopentene	*trans*-2-Methylcyclopentylethyne	90
Cyclohexene	Cyclohexylethyne	92

[a] Analysis by glpc with yield based on R_3B.

stirred for 2 hr at room temperature and then cooled to −78°. Iodine, 1.27 g (5.0 mmol), in 6 ml of THF was added dropwise to the solution with vigorous stirring. After 90 min at −78°, the solution was brought to room temperature and treated with 5 ml of 40% potassium hydroxide, and the aqueous phase saturated with potassium carbonate. Analysis by glpc revealed the presence of 4.6 mmol (92% yield) of cyclohexylethyne.

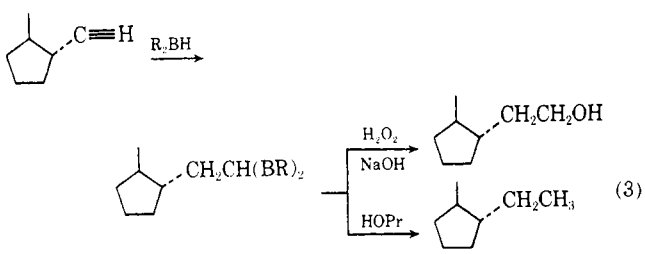
Many reactions of organoboranes proceed to provide products which retain the stereochemistry of the boron–carbon bond.[5] On the other hand, some reactions which proceed through free-radical intermediates involve the loss of such stereochemistry.[6] Accordingly, it appeared desirable to establish the stereochemistry of the present synthesis.

The trialkylborane from 1-methylcyclopentene was selected for this study. Oxidation with alkaline hydrogen peroxide produces 100% *trans*-2-methylcyclopentanol, with only a trace of 1-methylcyclopentanol.[5] The acetylene product obtained from this organoborane was indicated to be a single isomer, presumably the trans derivative (eq 2) by glpc analysis.



(2)

This conclusion was confirmed by dihydroborating the product with dicyclohexylborane (R_2BH). Oxidation with alkaline hydrogen peroxide[7] produced 2-(*trans*-2-methylcyclopentane)ethanol and protonolysis[8] with propionic acid produced *trans*-1-ethyl-2-methylcyclopentane (eq 3). In each case, the isomeric purity of the products was confirmed by glpc comparison with authentic samples of the *cis* and *trans* isomers. In both cases, only the trans isomers could be detected.



(3)

One of the major conventional methods for the preparation of terminal acetylenes involves nucleophilic displacement of halides or sulfates by the acetylide ion. The reaction proceeds in a satisfactory manner only with those primary derivatives which readily participate in S_N2 substitution processes. However, the present procedure accommodates, in addition to primary alkyl groups, highly branched groups, secondary, and alicyclic groups, groups which are often relatively resistant to nucleophilic substitution. Furthermore, the transfer of alkyl groups from boron to the acetylenic carbon with retention further extends the range of applicability of this procedure. Consequently, this development provides a general, stereospecific synthesis of monoalkyl- and monocycloalkylacetylenes under exceptionally mild conditions. The discovery that lithium acetylide–ethylenediamine may be used to prepare lithium ethynyltrialkylborates now makes possible the extension of the many interesting new reactions of the lithium 1-alkynyltriorganoborates[9] to the parent compound.

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(10) Graduate research assistant on Grant No. GM 10937 from the National Institutes of Health.

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Alkylation of the Dianion of β-Keto Sulfoxides. A Versatile Synthesis of Phenyl (2-Oxoalkyl) Sulfoxides. A General Route to Ketones, 1,4 Diketones, and Aldols

Summary: General synthetic routes to phenyl (2-oxoalkyl) sulfoxides, ketones, 1,4 diketones, and aldols have been realized *via* dianions of β-keto sulfoxides.

Sir: We wish to report that dianion 3 derived from phenyl (2-oxopropyl) sulfoxide (1) can be generated and undergoes specific alkylation at the γ carbon atom (eq 1). In addition, dianions derived from γ-substituted β-keto alkyl sulfoxides undergo exclusive alkylation at the γ carbon (eq 2). The specific alkylation at γ carbon of 1 and 4 *via* dianions 3 and 5, respectively, makes phenyl (2-oxopropyl) sulfoxide (1) a useful reagent in organic synthesis (*vide infra*) and provides a general high yield synthesis of β-keto sulfoxides. Russell[1] and Corey[2] have previously shown that esters react with dimethyl sulfoxide anion to produce β-keto sulfoxides (eq 3). In addition, it had been reported[2] that compounds such as I could be reductively cleaved (aluminum amalgam) to yield methyl ketones. More recently it has been demonstrated that lithiated chloromethyl phenyl sulfoxide reacts with aldehydes affording an adduct which upon treatment with methyllith-