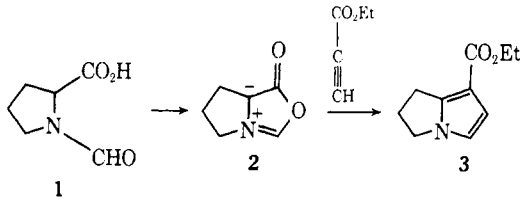
Stereospecific Synthesis of 1-Substituted Pyrrolizidines[1]

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).
(2) N. J. Leonard, in "The Alkaloids," R. H. Manske, Ed., Vol. VI, Academic Press, New York, N. Y., 1959, p 35.
(3) A. R. Pomeroy and C. Raper, *Eur. J. Pharmacol.*, **14**, 374 (1971), and references cited therein.
(4) (a) N. D. Nair and R. Adams, *J. Org. Chem.*, **26**, 3059 (1961); (b) N. J. Leonard and T. Sato, *J. Org. Chem.*, **34**, 1066 (1969), and references cited therein.
(5) A. M. Likhosherstov, V. N. Kulkov, and N. K. Kochetkov, *Zh. Obshch. Khim.*, **34**, 2798 (1964).
(6) Satisfactory ir and nmr spectra and C, H, and N analytical data have been obtained for this substance.
(7) H. O. Bayer, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, **103**, 2356 (1970).
(8) Thin layer chromatography is the best procedure for detection of impurities in this type of compounds; see A. H. Chalmers, C. C. J. Culvenor, and W. Smith, *J. Chromatogr.*, **20**, 270 (1965).

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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