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A METHOD FOR THE STEREOSPECIFIC SYNTHESIS OF CHIRAL <u>CIS</u>-2-ALKYLCYCLOPROPYLLITHIUM REAGENTS

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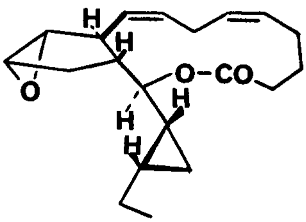
Summary: A general synthetic route to optically active *cis*-1,2-disubstituted cyclopropanes has been developed from the key intermediates **3** and **4**.

In connection with recent studies in these laboratories[1,2] on the stereochemistry and total synthesis of the novel marine eicosanoid hybridalactone (**1**) we needed the chiral organolithium reagent **2**. A survey of the literature failed to reveal either examples of synthesis of such chiral *cis*-2-alkylcyclopropyllithium reagents or methodology suitable for stereospecific synthesis. We report herein a simple and effective solution of this general problem. The chiral lithium reagent **2** has been synthesized with the absolute configuration shown and has been applied successfully to a total synthesis of hybridalactone which allowed unambiguous assignment of the complete stereochemistry shown in **1**.



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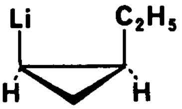
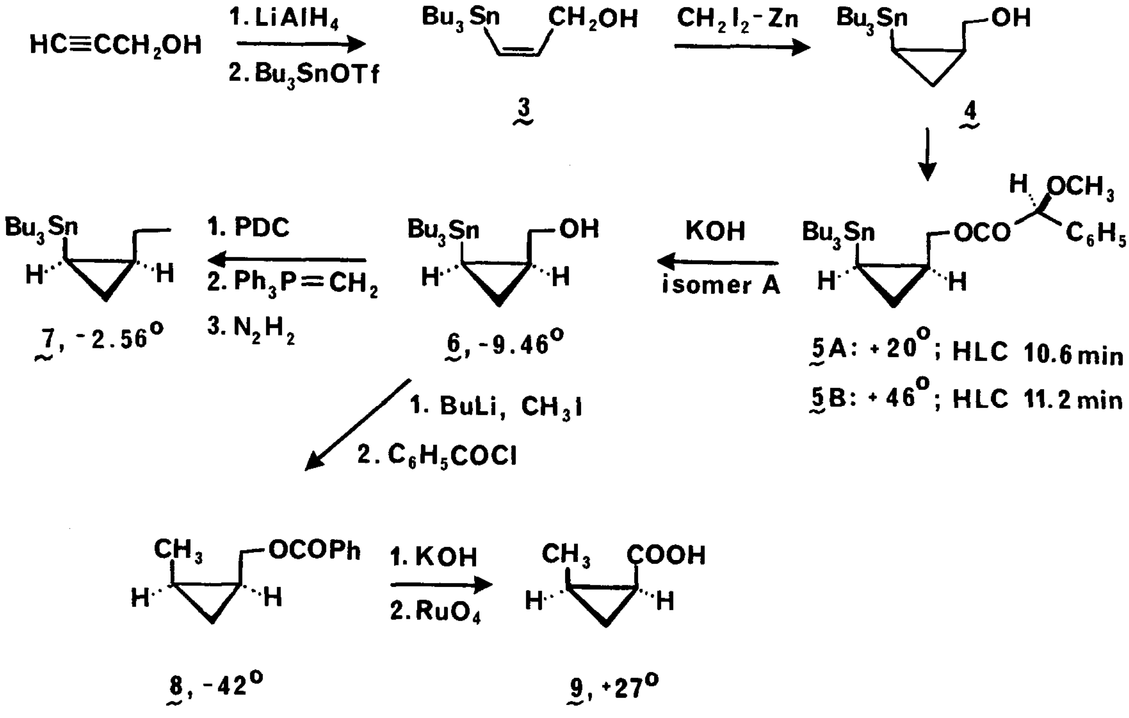


2

The first step in the sequence leading to *cis*-1,2- functionalized cyclopropanes is the synthesis of the *Z*-1,2- functionalized olefin **3**, which is also an extremely useful precursor of more complex *Z*-olefins such as the essential fatty acids.[3] Addition of propargyl alcohol (1.5 mole) to a stirred suspension of lithium tetrahydroaluminate (0.75 mole) in tetrahydrofuran (THF, 2.5 l) at 0-5° afforded a clear solution which upon further stirring at 23° for 23 hr led to a suspension of a *Z*-3-alumino-2-propen-1-oxide species (from *trans* hydroalumination). The suspension was cooled to -78°, and treated with a solution of tri-*n*-butyltin triflate (0.43 mole) in ether for *ca*. 5 hr at -78° to give after quenching at -78° (gaseous ammonia, followed by methanol) and extractive isolation 80% yield of 98+% pure *Z*-alcohol **3**.[4,5] Reaction of **3** with the Simmons-Smith reagent[6] (obtained by reaction of diiodomethane and zinc copper couple in dimethoxyethane at 23°) in the presence of diisopropylethylamine (used to complex with zinc iodide) at 23° for 2 hr. afforded the *cis*-cyclopropyl carbinol **4** in 70% yield. Esterification of **4** with (*S*)-O-methyl mandelyl chloride[7] and 4-dimethylaminopyridine in methylene chloride at 23° for 1 hr afforded **5** (99%) as a mixture of diastereomers: A, $[\alpha]^{21}_{D}$ + 20.0° (c = 0.08 in $CHCl_3$), R_T 10.6 min (HPLC using a Dupont Zorbax silica gel column with 89:10:1 hexane-methylene chloride-THF for elution); and B, $[\alpha]^{22}_{D}$ + 46.6° (c = 0.013 in $CHCl_3$), R_T 11.2 min. The diastereomers A and B were separated cleanly (baseline separation) on a Zorbax preparative column and saponified with 5*N* potassium hydroxide in 4:1 methanol-water at 23° for 15 min to give in >96% yield a levo alcohol (**6**, from A) $[\alpha]^{19}_{D}$ -9.46°, and a dextro alcohol (from B) $[\alpha]^{19}_{D}$ +9.52° (both in $CHCl_3$). The absolute configurations were assigned by chemical correlation as described below. Oxidation of **6** (the enantiomer required for the synthesis of hybridalactone) with pyridinium dichromate[8] at 23° in methylene chloride in the presence of powdered 4Å molecular sieves and anhydrous magnesium sulfate afforded the corresponding aldehyde, $[\alpha]^{22}_{D}$ -2.17° (c = 2.0 in $CHCl_3$), in 89% yield. This aldehyde was transformed by reaction with methylene triphenylphosphorane in THF (at 0° for 30 min and 22° for 1 hr) into *cis*-1-tributylstannyl-2-vinylcyclopropane (90%), $[\alpha]^{23}_{D}$ -42.9° (c = 5.5 in $CHCl_3$). Diimide reduction of this vinylcyclopropane with hydrazine and air in 4:1 methanol-THF with promotion by copper sulfate[9] produced *cis*-1-tributylstannyl-2-ethylcyclopropane (**7**, 93%) as a colorless oil, $[\alpha]^{22}_{D}$ -2.56° (c = 4.56 in $CHCl_3$).[10] The conversion of **7** to the cis-2-ethylcyclopropyllithium could be effected cleanly by reaction with 1 equiv of n-butyllithium in THF for 3 hr at 0°.[2]

The generality of the methodology described herein as a route for the stereocontrolled synthesis of optically active cis-1,2-disubstituted cyclopropanes is evident. A wide variety of Wittig reagents can be substituted for methylene triphenylphosphorane in the aldehyde coupling process and the tributyltin grouping can be replaced (via the lithium or copper derivative) by countless other substituents.



The absolute configuration of alcohol **6** was established as follows. Sequential reaction of **6** in THF with n-butyllithium (2 equiv at 0° for 30 min), methyl iodide (1.1 equiv, at 0° for 30 min and 23° for 2 hr) and benzoyl chloride (1.5 equiv at 0° for 30 min and 23° for 30 min) afforded after extractive isolation and chromatography on silica gel benzoate **8**, $[\alpha]_D^{18}$ -42.0° (c = 1.32 in $CHCl_3$). Saponification of **8** using 5N potassium hydroxide in 4:1 methanol-water at 23° provided the corresponding alcohol, $[\alpha]_D^{19}$ -36.0° (c = 0.32 in $CHCl_3$), which upon oxidation with ruthenium tetroxide[11] gave cis-2-methylcyclopropane carboxylic acid **(9)**, $[\alpha]_D^{20}$ +27.1° (c = 0.29 in 95% ethanol). The unambiguous assignment of the (1S),(2R) absolute configuration to this dextro acid **(9)** has been made previously.[12,13]

References and Notes

1. E. J. Corey, B. De, J. W. Ponder, and J. M. Berg, **Tetrahedron Letters**, in press.
2. E. J. Corey and B. De, **J. Am. Chem. Soc.**, in press.
3. E. J. Corey and T. M. Eckrich, accompanying paper.
4. Satisfactory spectroscopic data (infrared, pmr, mass) were obtained for each intermediate described herein.
5. Tri-n-butylstannyl trifluoromethanesulfonate, mp 41-43°, was prepared by reaction of tri-n-butyltin oxide with trifluoromethanesulfonic anhydride at <40° followed by distillation at 155-167° and 0.08 mm.
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7. C. P. R. Jennison and D. MacKay, **Tetrahedron**, 29, 1255 (1973).
8. E. J. Corey and G. Schmidt, **Tetrahedron Letters**, 399 (1979).
9. E. J. Corey, W. L. Mock and D. J. Pasto, **Tetrahedron Letters**, 347 (1961).
10. Catalytic reduction of unsaturated tin derivatives over Pd or Rh catalysts has not been satisfactory in our experience.
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12. R. G. Bergman, **J. Am. Chem. Soc.**, 91, 7405 (1969).

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