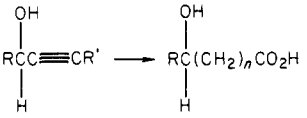
Communications

Asymmetric Synthesis of Hydroxy Carboxylic Acids

Summary: Optically-active hydroxy carboxylic acids of the general formula $RCHOH(CH_2)_nCO_2H$ are prepared from optically-active propargyl alcohols.

Sir: Optically-active hydroxy carboxylic acids are important biological molecules as well as intermediates for organic synthesis. Conventional routes for the asymmetric synthesis of these compounds involve the asymmetric reduction of ketones,[1] the use of chiral oxazolines,[2] and aldol-type condensations.[3] Although great strides have been made in these areas in specific cases, the methods suffer from the lack of generality and/or low enantiomeric induction. Herein we report general methods for the conversion of propargyl alcohols to optically-active hydroxy carboxylic acids in which the chiral hydroxy center may be placed at any position in a linear aliphatic chain.

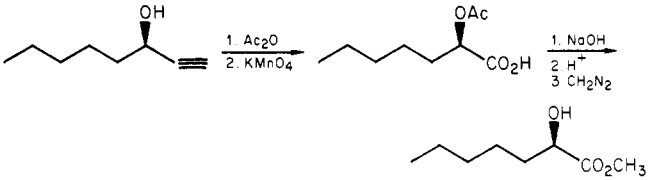


$n \geq 0$

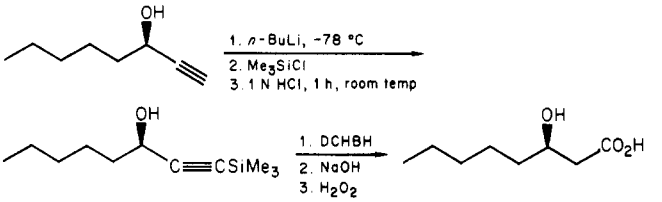
Optically-active propargyl alcohols of either configuration are readily available in high optical purity by asymmetric reduction of propargyl ketones with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane.[4] While methods exist for the

conversion of acetylenes to acids, applications of these methods to propargyl alcohols either result in low yields or interference by the hydroxyl group. We therefore sought to develop effective methods for converting either carbon of an acetylene to a carboxylic acid.

It has been reported that terminal propargyl alcohols (R′ = H) are oxidized to α-hydroxy carboxylic acids by potassium permanganate.[5] However our attempts to repeat this reaction led to oxidation of the alcohol. Simple protection of the alcohol as an acetate followed by oxidation by the method of Krapcho[6] (3 equiv of potassium permanganate, acetic acid, 0 °C, 5 h) gave 2-acetoxyheptanoic acid[7] in 92% yield. Deprotection (sodium hydroxide/methanol, 25 °C, 12 h) gave the α-hydroxy acid which was recrystallized from hexane (mp 59.8–60.2 °C, lit.[8] mp 61–61.6 °C). The acid was esterified[9] (diazomethane) for analysis by NMR in the presence of the optically-active shift reagent tris[3-((heptafluoropropyl)-hydroxymethylene)-*d*-camphorato]europium(III). None of the minor *S* enantiomer could be detected. Since the starting 1-octyn-3-ol was 92% enantiomerically pure, enrichment of the α-hydroxy carboxylic acid presumably occurred during recrystallization.



The terminal carbon of an acetylene may be converted to an acid by conversion to a trimethylsilyl (Me_3Si) acetylene followed by hydroboration with dicyclohexylborane (DCHBH) and oxidation.[10] However, when *O*-trimethylsilyl propargyl alcohols (R′ = Me_3Si) are subjected to the reaction, an elimination occurs to produce an α,β-unsaturated acid.[10] We have discovered that prior removal of the silyl group from the oxygen allows the sequence to occur without elimination, thus preserving the stereochemistry at C-3. The acid is obtained in 82% yield from



the bis-trimethylsilylated product. The acid was converted to the methyl ester for NMR analysis, which revealed an 86% enantiomeric purity.[11]

Through these two processes either carbon of a terminal acetylene may be converted into a carboxylic acid. The recent discovery that potassium 3-aminopropylamide (KAPA)[12] isomerizes internal propargyl alcohols to ter-

(1) For examples, see (a) Ojima, I.; Kogure, T.; Kamagai, M. *J. Org. Chem.* **1977**, *42*, 1671. (b) Tai, A.; Nakahata, M.; Harada, T.; Izumi, Y.; Kusumoto, S.; Inage, M.; Shiba, T. *Chem. Lett.* **1980**, 1125. (c) Ohno, A.; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Am. Chem. Soc.* **1979**, *101*, 7036. For general reviews of asymmetric synthesis, see: Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions", Reprint Edition; American Chemical Society: Washington, D.C., 1976. Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329. Kagan, H. B., Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175. Opsimon, J. W.; Seguin, R. P. *Tetrahedron*, **1979**, *35*, 2797.

(2) Meyers, A. I.; Knaus, G. *Tetrahedron Lett.* **1974**, 1333.

(3) For recent examples, see Evans, D. A.; Bartroli, J.; Shih, T. L., *J. Amer. Chem. Soc.* **1981**, *103*, 2127. Masamune, S.; Choy, W.; Kerdesky, F. A. J., Imperialli, B. *Ibid.* **1981**, *103*, 1566. Heathcock, C. H.; White, C. T.; Morrison, J. J.; Van Derveer, D. J. *Org. Chem.* **1981**, *46*, 1296. Meyers, A. I.; Reider, P. J. *J. Am. Chem. Soc.* **1979**, *101*, 2501. Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *Ibid.* **1980**, *102*, 7964.

(4) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, 102, 867. For alternative methods, see: Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339. Vigneron, J.-P.; Bloy, V. *Tetrahedron Lett.* **1979**, 2683. Nishizawa, M.; Yamada, M.; Noyori, R. *Ibid.* **1981**, 247. Mori, K.; Akao, H. *Tetrahedron* **1981**, *36*, 91. Mukaiyama, T.; Suzuki, K. *Chem. Lett.* **1980**, 255.

(5) Bergel'son, I. D.; Batrakov, S. G.; Grigoryan, A. N. *Izv. Akad. Nauk SSSR*, **1962**, 1617.

(6) Krapcho, A. P.; Larson, J. R.; Eldridge, J. M. *J. Org. Chem.* **1977**, *42*, 3749.

(7) Optically-active 2-hydroxyhepanoic acid has been previously prepared by resolution for use in a prostaglandin synthesis. See: Hauser, F. M.; Coleman, M. L.; Huffman, R. C.; Carroll, F. I. *J. Org. Chem.* **1974**, *39*, 3426.

(8) Horn, D. H. S.; Pretorius, Y. Y. *J. Chem. Soc.* **1954**, 1460. Racemic material melted at 65.5–65.9 °C (lit.[7] mp 65–66 °C).

(9) Esterification is necessary for analysis by shift reagent since the carboxylic acid destroys the shift reagent. In each case racemic hydroxy ester was added to the sample of optically-active ester to verify assignment of peaks. The assignment of absolute configuration is based on the mode of reduction.[4]

(10) Zweifel, G.; Backlund, S. *J. Am. Chem. Soc.* **1977**, *99*, 3184.

(11) One attempt to prepare the methyl ester directly by MCPBA oxidation in methylene chloride/methanol (2:1) failed. (See Ortiz de Montellano, P. R.; Kunze, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 7373, for the use of this method.)

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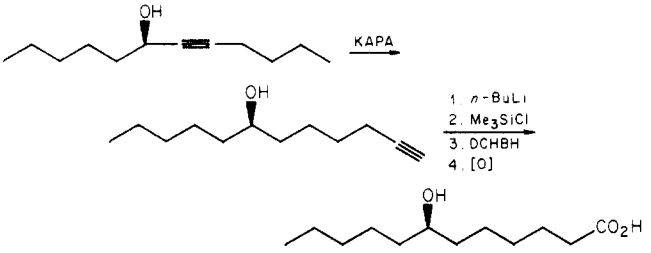
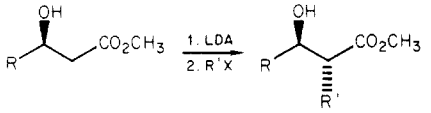
minal acetylenes without racemization[13] now provides a general route to optically-active hydroxy carboxylic acids in which the hydroxy center may be placed at any position in the aliphatic chain. Thus 5-dodecyn-7-ol (78% ee) was converted to 7-hydroxydodecanoic acid[14] through the trimethylsilyl acetylene in 76% yield. Analysis of the methyl ester with the NMR shift reagent revealed an enantiomeric purity of 82%.[15]



The reduction of propargyl ketones with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane generally proceeds in 74–100% ee. The limiting factor in obtaining high optical purity is usually the optical purity of the α-pinene.[16] Methods exist for obtaining (+)- or (−)-α-pinene of essentially 100% optical purity.[17] Alternatively, many α- and β-hydroxy carboxylic acids may be enriched by simple recrystallization.[18]

These acids are useful intermediates for organic synthesis. For example, the dianion of β-hydroxy esters may be alkylated with a very high degree of threo selectivity.[19]



It should be noted that the relative configuration is the opposite of that obtained in most aldol-type condensations.[3]

Acknowledgment. We thank the National Institutes of Health and the Committee on Research, University of California, Riverside, for financial support.

Registry No. (*R*)-1-Octyn-3-ol, 32556-70-0; (*R*)-1-octyn-3-ol acetate, 54315-41-2; (*R*)-2-acetoxyheptanoic acid, 78672-88-5; (*R*)-2-hydroxyheptanoic acid, 52437-20-4; (*R*)-methyl-2-hydroxyheptanoate, 78672-89-6; (*R*)-3-hydroxyoctanoic acid, 44987-72-6; (*R*) methyl 3-hydroxyoctanoate, 78672-90-9; (*R*)-5-dodecyn-7-ol, 78672-91-0; (*R*)-7-hydroxydodecanoic acid, 78737-61-8; (*R*) methyl 7-hydroxydodecanoate, 78672-92-1.

(12) Brown, C. A.; Yamashita, A. *J. Chem. Soc., Chem. Comm.* **1976**, 959.
(13) Midland, M. M.; Halterman, R. L.; Brown, C. A.; Yamaichi, A., *Tetrahedron Lett.*, in press.
(14) It has been discovered recently that this acid is produced by various *Mucor* species of fungi. See Tahara, S.; Hosokawa, K.; Mizutani, J. *Agric. Biol. Chem.* **1980**, *44*, 193.
(15) In this case the methyl ester signal was split by the NMR shift reagent.
(16) With use of commercially available α-pinene (92% ee), most propargyl alcohols are obtained in 80–90% ee.
(17) Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1976/1977**, *15*, 12. Cocker, W.; Shannon, P. V. R.; Staniland, P. A. *J. Chem. Soc. C* **1966**, 41. Also, research in progress with R. Graham.
(18) For an example, see ref 1b.
(19) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825, 2829.
(20) A. P. Sloan Foundation Fellow, 1978–1982.

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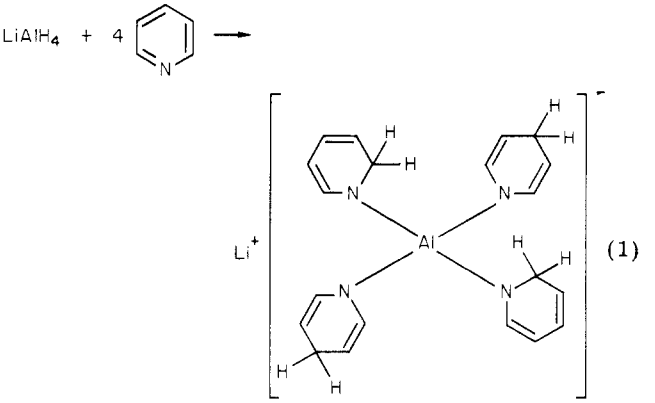
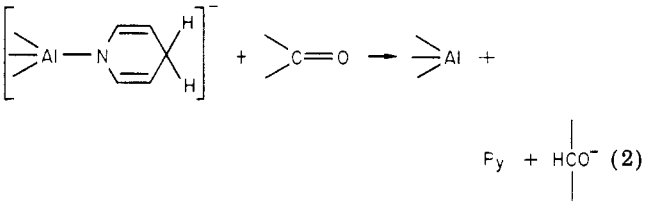
Evidence of Single Electron Transfer in the Reduction of Various Organic Substrates by Lithium Tetrakis(*N*-dihydropyridyl)aluminate

Summary: Aromatic ketones, polynuclear hydrocarbons, and alkyl halides react wih $LiAl(PyH)_4$ by a single electron transfer process.

Sir: In the early 1960's, Lansbury and co-workers[1-3] investigated reactions of $LiAlH_4$ dissolved in pyridine with organic substrates and made some unusual observations. Sometime later the same workers discovered that $LiAlH_4$ reacted with pyridine to form lithium tetrakis(*N*-dihydropyridyl)aluminate (LDPA, I) as a result of $LiAlH_4$ attack on the pyridine ring[4] (eq 1) and also found that LDPA was the responsible reducing agent when $LiAlH_4$ was allowed to react in pyridine. Further work by Lansbury and co-workers demonstrated that the 1,2- or 1,4-hydrogens on the dihydropyridyl group were transferred to the organic substrate (e.g., ketone) via a polar mechanism during the course of reduction (eq 2).





Recently, we demonstrated that simple and complex metal hydrides of the main group elements reduce certain aromatic ketones via a single electron transfer (SET) mechanism,[5] although the mechanism of this reaction was also considered previously to be of a polar nature. In view of these recent findings, we decided to investigate the possible involvement of SET mechanisms in reactions of

(1) P. T. Lansbury, *J. Am. Chem. Soc.*, **83**, 429 (1961).
(2) P. T. Lansbury, J. R. Rogozinski, and F. L. Coblentz, *J. Org. Chem.*, **26**, 2277 (1961).
(3) P. T. Lansbury and R. Thedford, *J. Org. Chem.*, **27**, 2383 (1969).
(4) P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.*, **83**, 3537 (1961); **86**, 1756 (1962); **85**, 2236 (1963).
(5) E. C. Ashby, A. B. Goel, and R. N. DePriest, *J. Am. Chem. Soc.*, **102**, 7779 (1980).
(6) E. C. Ashby, A. B. Goel, R. N. DePriest, and H. S. Prasad, *J. Am. Chem. Soc.*, **103**, 973 (1981).
(7) E. C. Ashby, R. N. DePriest, and A. B. Goel, *Tetrahedron Lett.*, in press (1981).
(8) E. C. Ashby, A. B. Goel, and R. N. DePriest, *J. Org. Chem.*, **46**, 2429 (1981).
(9) E. C. Ashby and A. B. Goel, *Tetrahedron Lett.*, in press (1981).
(10) EPR spectrum consists of four sets (or a quartet) of well-resolved peaks. The appearance of a quartet is consistent with the large splitting (≃4–5 G) displayed by the ortho and para protons of the phenyl ring.
(11) D. H. Paskovich, A. H. Reddoch, and D. F. Williams, *J. Chem. Soc., Chem. Commun.*, 1195 (1972).

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