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COMPLETE 1,3-ASYMMETRIC INDUCTION IN THE REACTIONS OF ALLENYLBORONIC ACID WITH β-HYDROXY KETONES

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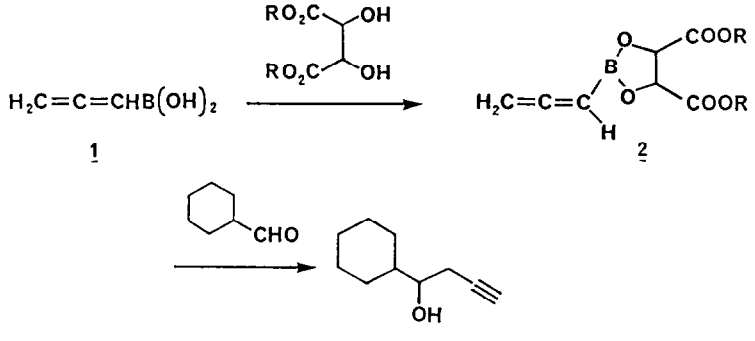
Summary: A novel reaction system is described for the complete stereoselective addition of carbanionic nucleophiles to β-hydroxy ketones.

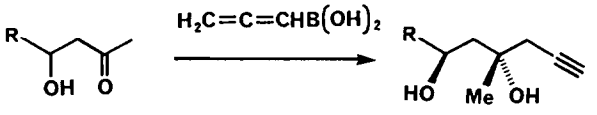
Controlling 1,n-asymmetric induction in nucleophilic addition to acyclic carbonyl compounds is one of the most powerful and useful synthetic methods in organic chemistry. Recently there has been extensive investigation in this area, and rather reliable methods now exist for achieving good stereoselectivity in additions to α- and β-alkoxy aldehydes.[1] Unfortunately, however, simple aldol products, for which good progress has been made in finding ways to control stereochemistry,[2] generally show poor degrees of diastereofacial selectivity. This paper describes a promising new method for effecting such asymmetric induction with β-hydroxy ketones.

The reaction of allenylboronic acid (**1**) with dialkyl tartrate and aldehyde described previously,[3] leads to a chiral homopropargylic alcohol with high optical purity. Possible first step in the reaction is the formation of intermediate **2** which can lead to coupling with aldehydes. Of crucial



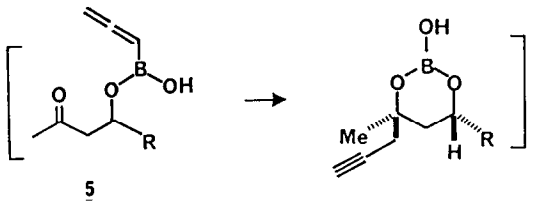
importance to the present studies was the observation that the reaction of allenylboronic acid with carbonyl compound is slow relative to the reaction of allenylboronic esters.[3] These results suggested the possiblity that hydroxy carbonyl compounds might undergo asymmetric addition under the proper conditions. Verification of this hypothesis has been obtained as follows.

The reaction of allenylboronic acid (1.2 equiv) with β-hydroxy ketones in anhydrous ether at room temperature in the presence of molecular sieves 5A for 20 h, followed by treatment of basic hydrogen peroxide, yielded the threo diol **4** with unprecedented levels of 1,3-asymmetric induction (>99%). Results are summarized in Table 1. The yields in all cases amounted to >90%. The reaction of propargylmagnesium bromide with **3** in ether affords a mixture of the threo and erythro diols, in agreement with related nonselective processes.[4]



3 **4**

In these cases we are not certain whether the organometallics uses are in fact the reacting species or whether rapid ester exchange first generates the intermediate **5**, which then reacts intramolecularly with carbonyl group of the molecule. However, the observed complete stereoselectivities strongly suggested the existence of the covalently bonded organometallics rather than the usual chelated cyclic transition state. Indeed, treatment of a mixture of cyclohexanone and sec-phenethyl alcohol with allenylboronic acid give none of the homopropargylic alcohol under the above reaction conditions. Furthermore, a mixture of the ketone **3** (R = cyclohexyl) and 2-hexanone was treated with allenylboronic acid to produce the diol **4** as a sole product.



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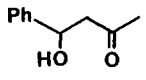
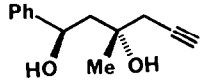
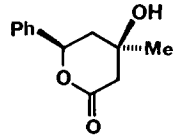
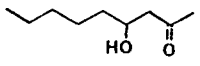
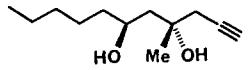
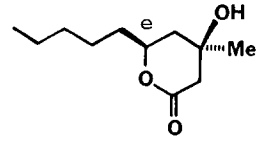
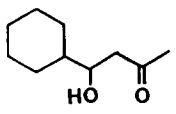
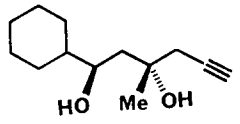
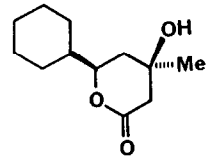
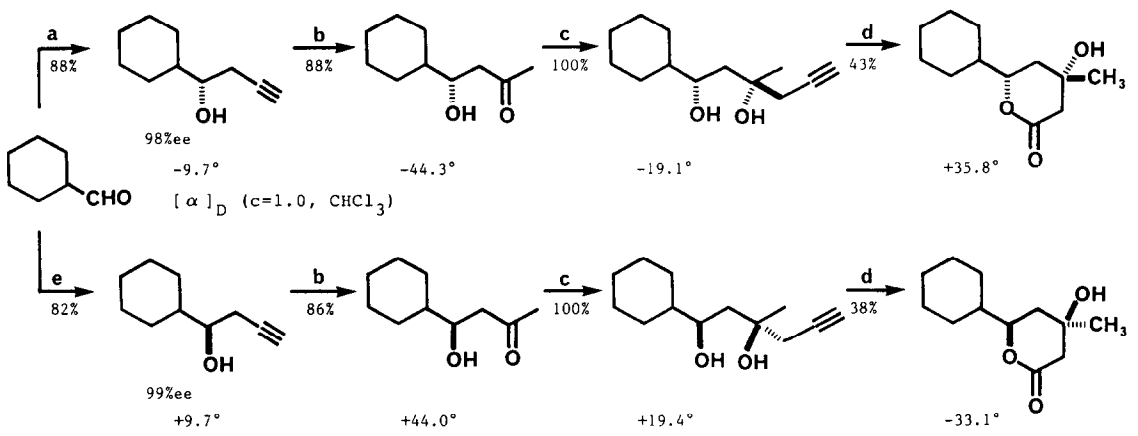
The threo diol **4** was reacted with ruthenium trichloride-sodium periodate[5] to give the corresponding lactone (Table 1). The relative configuration follows from direct comparison (^{1}H NMR) of the lactone thus obtained with the spectral data of the corresponding threo and erythro lactones.[6]

Table 1. Reaction of Allenylboronic Acid with β-Hydroxy Ketones[a]

Entry	β-hydroxy ketone[b]	1,3-diol	yield (%)[c]	diastereomeric ratio[d]	δ-lactone	yield (%)
1			95	>99 (72:28)		83
2			>95	>99 (54:46)		42
3			96	>99 (58:42)		56

[a]See text for the reaction conditions. [b]Prepared from the corresponding aldehydes with lithium enolate of acetone. [c]Based on the isolated pure product. [d]Determined by gc analyses. The ratios in parentheses indicate the corresponding ratios with the Grignard reagent. [e] ^{1}H NMR ($CDCl_3$) δ4.16 (br m, C(6)H).

The use of the present method for the preparation of the β-hydroxy-δ-lactone may be illustrated as follows. Mevinolin and related fungal metabolite is selective inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA reductase) and have attracted considerable attention both from synthetic and biological chemists.[6,7] Studies concerning potent HMG-CoA reductase inhibitors possessing more varied structural modifications have been less well reported due to a lack of effective methods for the construction of appropriately substituted β-hydroxy-δ-lactones. Our strategy for the synthesis of this important functionality is outlined below. Unfortunately, however, the product has the configuration of 4S,6R rather than the most active 4R,6R configuration.[6]



a:(+)-Bis(2,4-dimethyl-3-pentyl) tartrate-allenylboronic acid; b:$HgSO_4$, H_2SO_4-THF-H_2O c:Allenylboronic acid, ether, molecular sieves 5A, r.t., 20h; d:$RuCl_3$-$NaIO_4$, CCl_4-H_2O-CH_3CN; e:(-)-Bis(2,4-dimethyl-3-pentyl) tartrate, allenylboronic acid

References and Notes

1. W. C. Still and J. H. McDonald, III, Tetrahedron Lett., **21**, 1031 (1980). S. Kiyooka and C. H. Heathcock, ibid., **24**, 4765 (1983) and references therein. M. T. Reetz and A. Jung, J. Am. Chem. Soc., **105**, 4833 (1983); M. T. Reetz, K. Kesseler, and A. Jung, Tetrahedron Lett., **25**, 729 (1984); See also, R. W. Hoffmann and S. Froech, Tetrahedron Lett., **26**, 1673 (1985).
2. For a review of aldol stereoselection, see: C. H.Heathcock in "Asymmetric Organic Reaction, Vol. 3," J. D. Morrison, Ed., Academic Press, New York, 1984.
3. R. Haruta, M. Ishiguro, N. Ikeda, and H. Yamamoto, J. Am. Chem. Soc., **104**, 7667 (1982); N. Ikeda, I. Arai, and H. Yamamoto, ibid., in press.
4. For studies of propargyl Grignard reagent with 4-tert-butyl-2-methoxycyclohexanone: D. Guillerm-Dron, M. L. Capmau and W. Chodkiewicz, Tetrahedron Lett., 37 (1967).
5. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, J. Org. Chem., **46**, 3936 (1981). Ruthenium dioxide-periodate procedure was also effective for this oxidation: E. J. Corey and N. W. Boaz, Tetrahedron Lett., **25**, 3059 (1984).
6. (a) T. Lee, W. J. Holtz, and R. L. Smith, J. Org. Chem., **47**, 4750 (1982); See also, (b) H. Ferres, I. K. Hatton, L. J. A. Jennings, A. W. R. Tyrrell, and D. J. Williams, Tetrahedron Lett., **24**, 3769 (1983).
7. J. D. Prugh, C. S. Rooney, A. A. Deana, and H. G. Ramjit, Tetrahedron Lett., **26**, 2947 (1985); M. Sletzinger, T. R. Verhoeven, R. P. Volante, J. M. McNamara, E. G. Corley, and T. M. H. Liu, ibid., **26**, 2951 (1985) and references cited therein.

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