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ASYMMETRIC REDUCTIONS OF PROPARGYL KETONES

AN EFFECTIVE APPROACH TO THE SYNTHESIS OF OPTICALLY-ACTIVE COMPOUNDS

M. MARK MIDLAND, ALFONSO TRAMONTANO, ALEKSANDER KAZUBSKI, RICHARD S. GRAHAM, DAVID J. S. TSAI and DANIEL B. CARDIN
Department of Chemistry, University of California, Riverside, CA 92521, U.S.A.

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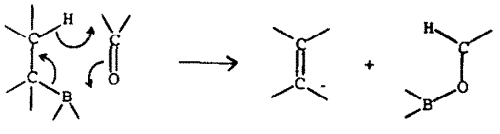
Abstract—Propargyl ketones are readily reduced by the asymmetric reducing agent *B*-3-pinanyl-9-borabicyclo[3.3.1]-nonane (Alpine–borane). The reagent prepared from (+)-α-pinene and 9-BBN provides the *R* enantiomer while the *S* enantiomer can be obtained from (-)-α-pinene. Alternatively the *S* enantiomer can be prepared from the reagent derived from 9-BBN and the benzyl ether of nopol (6,6-dimethyl-bicyclo[3.1.1.]hept-2-ene-2-ethanol). The limiting factor in obtaining high enantiomeric induction is often the enantiomeric purity of the α-pinene. With 100% enantiomerically pure α-pinene, propargyl alcohols of essentially 100% ee can be obtained. A predictive rationalization of the transition state leading to this remarkable selection is presented. The acetylene unit of the propargyl alcohol provides a convenient handle for transformations to other useful, optically-active products. The use of propargyl alcohols for the synthesis of optically-active α- and β-substituted γ-lactones, and δ-lactones is illustrated.

Chirality often plays an important role in determining the biological activity of molecules. Often small amounts of the minor enantiomer can change the activity of a compound.[1] Hence the preparation of optically-active molecules in a high state of enantiomeric purity is an important endeavor.[2] One of the simplest methods of producing optically-active compounds is the asymmetric reduction of prochiral ketones. Although this reaction has been studied for over 30 years,[3] it has only been in the past few years that exceptional progress has been achieved.[4] However, one notes that almost all studies of asymmetric reducing agents use acetophenone as a substrate. There is a good reason for selection of this substrate. Most asymmetric reducing agents uniformly fail for the non-aromatic ketones of interest to synthetic chemists!

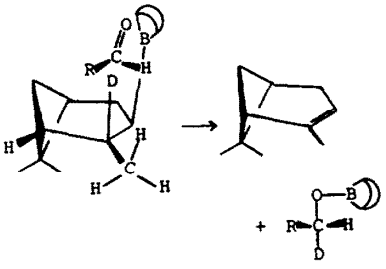
To overcome the problem of lack of generality and usefulness, several groups have investigated the reduction of propargyl ketones.[5] Since the acetylene unit provides a convenient handle for further elaborations, the resulting optically-active propargyl alcohols are very useful in organic synthesis.[6]

We have reported that certain trialkylboranes are efficient reducing agents.[7] For example, *B*-3-pinanyl-9-BBN (Alpine–borane[8]) is an extremely effective reagent for the asymmetric reduction of aldehydes.[9] The reaction is thought to proceed by a bimolecular, 6-membered transition state in which the β-hydrogen of the organo-borane is transferred to the carbonyl C (eqn 1).[10]



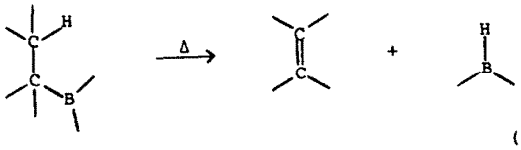
(1)

Reduction of deuterio aldehydes consistantly provides the *S* primary alcohol, while reduction with deuterio Alpine–borane provides the *R* product. A simple model can be used to predict the results.



(2)

The reagent is extremely sensitive to steric effects.[11] Initial attempts to reduce acetophenone led to prolonged reaction times and low (< 10%) asymmetric inductions. Under forcing conditions (refluxing tetrahydrofuran, THF) an alternative pathway of dehydroboration-reduction becomes important.[12]



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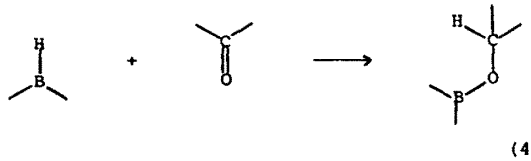


(4)

In order to achieve reductions of ketones, the sterically less conjested propargyl ketones were investigated.[13] We report herein full details of this reaction.

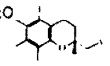
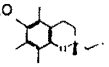
RESULTS AND DISCUSSION

Our initial investigation examined reductions using 0.5 M solutions of Alpine–borane in THF. (Aldrich supplies 0.5 M solutions of 9-BBN). Reductions of aldehydes with this solution are generally complete within an hr or so at room temp. Reductions of α, β-acetylenic ketones are slow in comparison with aldehydes. Nevertheless complete reduction can be accomplished in reasonable time by using 2 equiv of the trialkylborane. Terminal acetylenic ketones and acetylenic keto esters were completely reduced after 8 hr at room temp. Internal acetylenic ketones required 1–4 days at room temp or until no starting material was detectable by GLC or NMR. This kinetic differentiation may be due to a steric and/or electronic influence of the substituent on the acetylene. Recourse to heating as a means of accelerating the rate should be avoided. Enantiomeric purities were significantly lowered when the mixtures were refluxed for 8 hr at room temp. The loss of selectivity may be attributed to the competitive dehydroboration-reduction mechanism. (eqns 3–4).

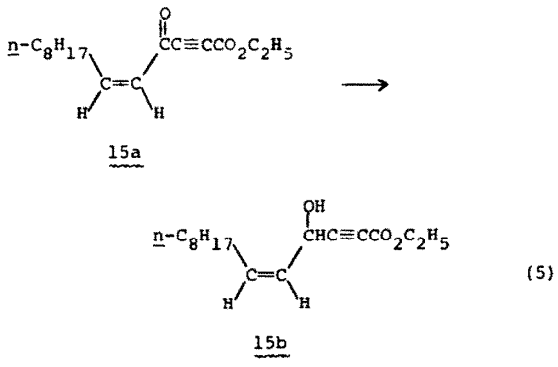
The reagent is widely applicable as seen by the variety of substrates in Table 1. Chemical yields are generally good. The enantiomeric purities of the products range from 73 to 100%. The enantiomeric excess is somewhat sensitive to the size of the substituent on the ketone. In general methyl ketones give the lowest selectivity as would be expected from steric considerations. Note, for example, the increasing enantioselectivity in the series of acetylenic keto esters in proceeding from the methyl ketone **10** to the phenyl ketone **13**. The bulky t-butyl ketone **1** was the only substrate which failed to undergo reduction.

The optically-active chromanyl substrates (**7** and **8**) were reduced to investigate the effect of a proximate chiral center on the selectivity of the reduction. These examples showed that intramolecular interactions between a chiral center in the substrate and the reaction site do not appreciably enhance or detract from the enantioselective forces. These substrates gave diastereomeric alcohols with (*R*, *R*); (*R*, *S*) ratios of 85:15 for the internal and 91:9 for the terminal acetylene. These values were obtained using (+)-α-pinene of 100% ee. The reagent from (−)-α-pinene (90% ee) gave a 22:78 ratio of the two diastereomeric internal propargyl alcohols (18:82 when corrected for purity of (−)-α-pinene). These results are in sharp contrast to the results obtained with the $LiAlH_4$/Darvon alcohol complex. With this reagent *S*-**7**, gave a 67:33 (*S*, *R*):(*S*:*S*)ratio while the enantiomer of Darvon alcohol gave a 5:95 (*S*, *R*):(*S*:*S*) ratio.[5a]

Table 1. Reductions of alkynyl ketones with Alpine–borane

	ketone RCOC≡CR'			
	R	R'	% yield[a]	% e.e.[b]
1	C_6H_5	n-C_4H_9	72	89[c]
2	CH_3	C_6H_5	98	72(78)
3	n-C_3H_7	n-C_6H_{13}	68	77[c]
4	n-C_5H_{11}	n-C_4H_9	66	78(85)
5	n-C_5H_{11}	H	70	92[c]
6	$CH(CH_3)_2$	H	78	91(99)
7		CH_3	77	85:15[d]
8		H	75	91:9[d]
9	$CH_3O_2CCH_2CH_2$	n-C_8H_{17}	75	90(98)
10	CH_3	$CO_2C_2H_5$	59	71(77)
11	CH_3CH_2	$CO_2C_2H_5$	58	88(96)
12	n-C_5H_{11}	$CO_2C_2H_5$	72	85(92)
13	C_6H_5	$CO_2C_2H_5$	64	92(100)
14	Z-$C_5H_{11}CH{=}CHCH_2$	$CO_2C_2H_5$	73	90
15	Z-$C_8H_{17}CH{=}CH$	$CO_2C_2H_5$	62	98
16	$C(CH_3)_3$	CH_3	0	
17	CH_3	$C(CH_3)_3$	62	73[c]

[a]Isolated yield based on starting ketone. [b]Determined by analysis of the $Eu(dcm)_3$ shifted NMR spectrum. The numbers in parentheses are corrected for 92% ee α-pinene. [c]100% optically pure (+)-α-pinene was used. [d]Diastereomeric ratio (*R*, *R* to *R*, *S*) determined by LC or NMR analysis of the mixture.

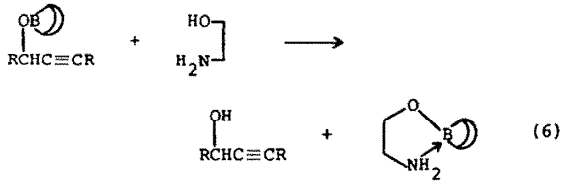


15a

15b (5)

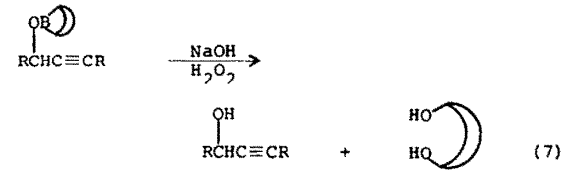
To illustrate the mildness and selectivity of the reagent the reduction of the vinyl acetylenic ketone **15a** was investigated. This compound is extremely sensitive to acid or base catalysed isomerization of the *cis* double bond. The reagent from (+)-α-pinene (100% ee) provide the alcohol in >98% ee (the *S* enantiomer could not be detected by NMR/lanthanide shift reagent) while the reagent from (−)-α-pinene (90% ee) gave material of 87% ee.

To facilitate isolation of the product the excess Alpine–borane is treated with a volatile aldehyde such as acetaldehyde or propionaldehyde to liberate α-pinene. This process minimizes alcohol contaminents in the final product. The α-pinene may then be removed under vacuum and recycled if desired. In our initial experiments the product was then isolated by liberating the propargyl alcohol and precipitating the 9-BBN as the ethanol amine adduct.[14] This process works well for base-sensitive



(6)

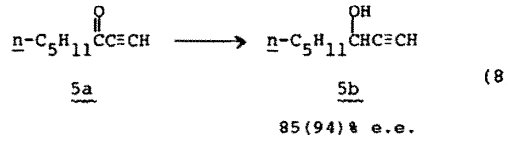
propargyl alcohols. However, problems in isolating pure alcohol are often encountered. The product may be contaminated with boron containing material or become entrapped in the precipitate. To overcome these problems an alternative oxidative workup can



(7)

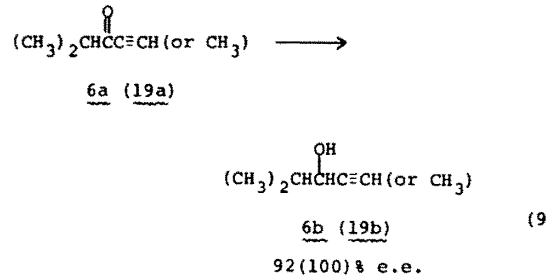
be used. The propargyl alcohol may then be separated from the *cis*-1,5-cyclooctanediol by distillation or precipitation of the diol from hexane or ether.

The longer reaction times often required when using 0.5 M solutions of alpine-borane can lead to diminished %ee because of competing dehydroboration–reduction (eqns 3–4). The method introduced by Brown[15] of running the reactions neat leads to a greatly increased reaction rate. For example Brown has found that 4-phenyl-3-butyne-2-one (**2**) is reduced in 4 h to product of 96.5% optical purity. Reactions are usually complete within a few hours but generally they are run overnight. Several examples which we have investigated are illustrated below (% ee corrected for % ee of α-pinene is given in parenthesis).



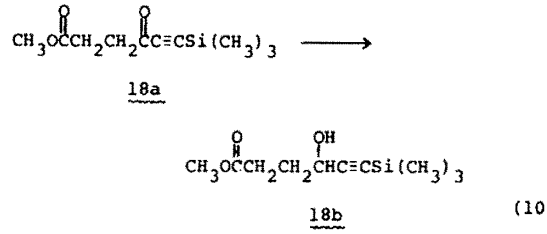
5a 5b

85(94)% e.e. (8)



6a (19a) 6b (19b)

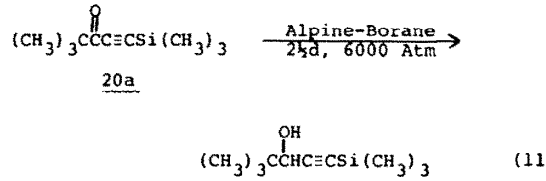
92(100)% e.e. (9)



18a 18b

82(89)% e.e. (10)

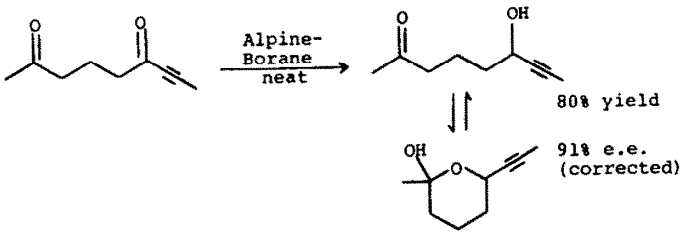
Of the various structural changes in the alkynyl ketone so far investigated, only ketones with a t-Bu group adjacent to the ketone fail to undergo reduction. Even running the reaction in the absence of solvent does not give a satisfactory result. Reduction presumably occurs by the dehydroboration–reduction pathway to provide racemic products. However we have found that these ketones are reduced by Alpine–borane when subjected to high



20a 20b (11)

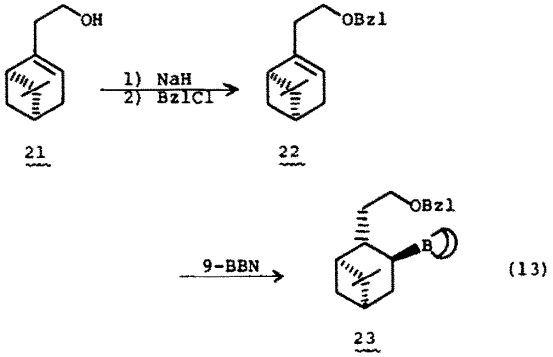
pressure. The reaction in eqn (11) proceeds with 100% enantiomeric efficiency.[16]

Alpine–borane is an extremely chemoselective reducing agent. Benzoyl chloride, γ-valerolactone, ethyl propiolate and phthalic anhydride are not reduced by neat Alpine–borane over a period of several days.[17] Aldehydes are reduced up to 10^3 times faster than ketones.[11] This chemoselectivity allows one to selectively reduce a propargyl ketone in the presence of a methyl ketone.



(12)

Alpine–borane prepared from (+)-α-pinene provides the (*R*)-propargyl alcohols while (−)-α-pinene provides the (*S*)-alcohols. When we initiated this investigation (−)-α-pinene was rather expensive and of low optical purity. To overcome these problems alternative analogs of (−)-α-pinene were sought. The readily available nopol (**21**), was an ideal substitute.[18] Hydroboration of the benzyl ether of nopol (**22**) provides the reducing agent (**23**) which is called NB-Enantrane (the corresponding borohydride is



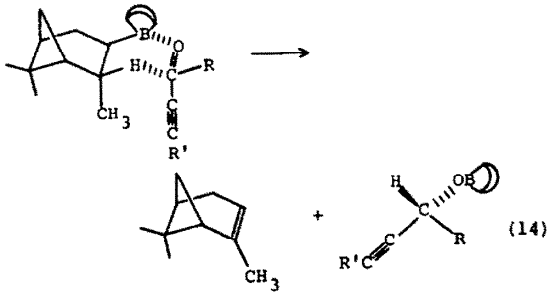
(13)

called NB-Enantride[19]). Hydroboration of the nopol benzyl ether is slow in comparison to hydroboration of α-pinene but can be completed upon reflux in tetrahydrofuran (THF) overnight.

Reductions of α, β-acetylenic ketones with NB-Enantrane are slow in comparison to Alpine–borane reductions. Nevertheless, complete reduction can be accomplished in 24–48 hr at room temperature by using a two-fold excess of organoborane and running the reaction without solvent. The slower rate of reduction is evidently caused by the very subtle steric effects that are observable with the organoborane reagents. Changing the Me group on α-pinene to the ethanol group of nopol apparently increases the steric congestion of the reducing agents enough to effect the rate of reduction. Asymmetric inductions obtained in these reductions, using commercial nopol as a starting material, were about 85–89%. For example, 1-octyn-3-one was reduced to (*S*)-1-octyn-3-ol in 89% ee. Upon examination it was found the commercial nopol is approx. 94% optically pure. We have found that it is possible to improve the optical purity of nopol to about 98% by recrystallization of nopol as the (−)-α-methyl-benzylamine salt of the half phthalate derivative.

A series of α, β-acetylenic ketones were examined with the purified NB-Enantrane (Table 2). In general, both chemical and enantiomeric yields are high. In each case the (*S*)-propargyl alcohol is obtained.

The stereochemical outcome of the reduction may be predicted by the simple model developed for aldehydes (eqn 2). Based on our mechanistic studies[10] the original model has been slightly modified. We envision that the hydride transfer occurs from a boat-like transition state in which the acetylene occupies the axial position. The model for Alpine–borane prepared from (+)-α-pinene is depicted below.



(14)

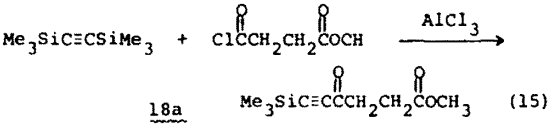
Table 2. Reduction of α, β-Acetylenic Ketones with NB-Enantrane

	ketone RCOC≡CR'		% yield[a]	% e.e.[b]
	R	R'		
2	CH_3	C_6H_5	87	86
5	n-C_5H_{11}	H	74	95
12	n-C_5H_{11}	$CO_2C_2H_5$	74	91
24	n-C_5H_{11}	CH_3	79	91
25	n-C_5H_{11}	$Si(CH_3)_3$	81[c]	96
26	C_2H_5	C_2H_5	77	94
27	cyclohexyl	n-C_5H_{11}	84	96

[a]Isolated yield. [b]Determined by analysis of the Eu(hfc)$_3$ shifted NMR spectrum.
[c]During the oxidative workup the trimethylsilyl group was removed.

The transition state leading to the minor component is therefore destabilized by the diaxial interaction of the pinanyl Me group and the *R* group of the ketone. The selectivity of the reagent appears to be based purely on steric grounds rather than on an electronic effect. Note for example that the phenyl alkynyl ketones **1** and **13** are effective substrates. (However, electronic effects do change the rate of reduction, electron withdrawing substituents increase the rate.) These results are to be contrasted to the $LiAlH_4$ based reagents in which an electronic effect of the acetylene appears to be very important. The acetylene unit predictively behaves as if it were the aromatic group of acetophenone with the $LiAlH_4$ reagents.[5] In fact little selectivity is observed for alkynyl aromatic ketones with these reagents.[5c]

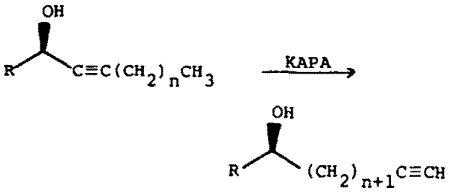
The ketones required for the reduction are generally prepared by standard literature procedures such as oxidation of the propargyl alcohol with Jones reagent. The racemic alcohols are in turn either commercially obtained or prepared by addition of a lithium acetylide to an aldehyde. The racemic ester alcohols **10–15** were prepared by adding lithium ethyl propiolate to the aldehyde.[20] Alternative methods for preparing the ketones directly have also been used in several cases. For example, Sn,[21] Si[22] or Cu[23] acetylides can be reacted with acid chlorides to provide the ketones.



18a (15)

As we have indicated, the enantiomeric efficiency of the reduction often approaches 100%. The optical purity of the α-pinene then becomes the limiting factor in obtaining a high purity product. Since methods exist for obtaining high optical-purity (+)- or (−)-α-pinene,[24] this problem is solved.

The acetylene handle may be moved through a series of CH_2 units using potassium 3-aminopropylamide (KAPA) without affecting the chiral center.[27]



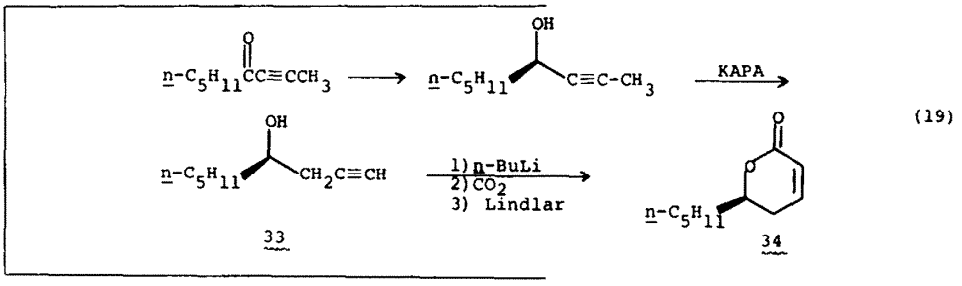
(17)

Reduction of the acetylene can produce the optically-active *cis* or *trans* allylic alcohols. The chirality of the alcohol center may then be transferred by sigmatropic rearrangements to remote C centers.[28]

(18)

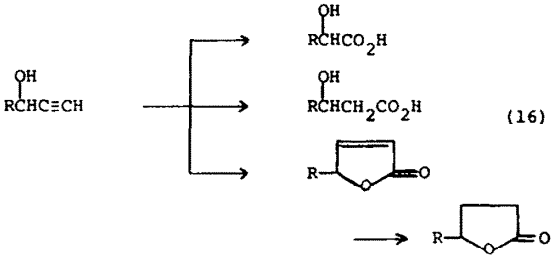
To illustrate these possibilities, we have explored the synthesis of some simple substituted lactones. We have previously demonstrated the synthesis of optically-active γ-substituted γ-lactones and butenolides[26] and the synthesis of the γ-lactone pheromone of the Japanese beetle in 100% optical purity.[29] To obtain α- or β-substituted lactones, a combination of chirality transfer and ozonolysis may be used (Scheme 1).

In these cases the alkyl group adjacent to the CO in the propargyl ketone eventually is discarded. By choosing the isopropyl group we can obtain maximum asymmetric induction so that the chirality of the α-pinene is ultimately transferred to the β-position of the lactone with essentially 100% efficiency. However there is a small loss in enantiomeric purity of the α-substituted lactone which occurs in the last step.



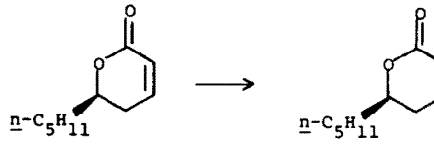
33 34 (19)

In many ways we feel that the ability to effectively reduce propargyl ketones is far more useful than being able to reduce acetophenone. Because of the acetylene unit, the propargyl alcohols can be converted into a variety of useful products.[6] For example the acetylene may be converted into other functional groups such as acids,[25] butenolides or lactones.[26]



(16)

Larger ring lactones may be prepared by isomerization of the acetylene. Carboxylation of the acetylene followed by Lindlar reduction provides the α, β-unsaturated lactone in eqn (19) in 85% optical purity.[30] The *R* enantiomer (massoilactone) has been identified as the defense allomone of the formicine ant.[31] Pirkle has demonstrated that such compounds will undergo stereoselective organocuprate additions.[30]



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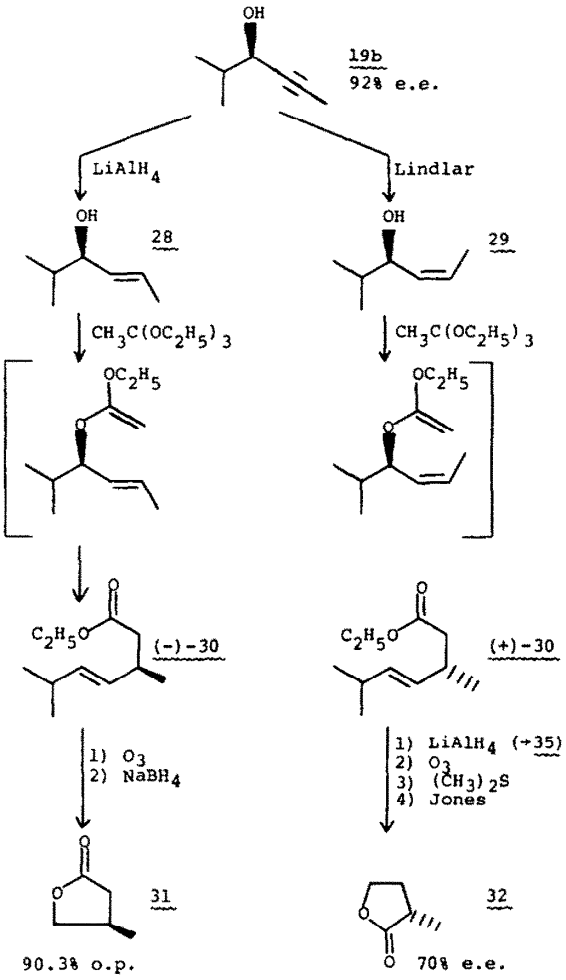

Scheme 1.

CONCLUSION

Alpine–borane is an attractive reagent for the preparation of chiral secondary propargylic carbinols of high enantiomeric purity. Reduction of certain acetylenic keto esters and terminal eynones proceeds with virtually quantitative asymmetric induction. This is a rare event in prochiral nonaromatic systems. Alpine–borane compares favorably with other reagents and often gives superior results. The reagent is commercially available or can be readily prepared from (+)- or (−)-α-pinene. The reduction is easy to perform and large-scale reactions pose no problem. The pinene liberated in the reduction may be recycled without loss of optical purity. Finally, *B*-alkyl-9-BBN compounds are mild reagents which will tolerate the presence of other functional groups.

EXPERIMENTAL

All operations involving air-sensitive reagents were performed under a dry nitrogen atmosphere using syringe techniques.[32] All glassware was dried at 135° for at least 4 hr, assembled hot, and cooled while being purged with N_2. ^1H NMR spectra were obtained on a Varian EM-390 (90 MHz) instrument or JEOL FX-200 (200 MHz) FT instrument. ^{13}C NMR spectra were obtained on the JEOL FX-200 (50 MHz) instrument. Areas of *R* and *S* proton signals in the presence of Eu(hfc)$_3$ or Eu(dcm)$_3$ were determined by cutting and weighing expanded spectra. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter.

THF was distilled under N_2 from potassium benzophenone ketyl and stored under a positive N_2 pressure. (+)-α-pinene ($[\alpha]_D^{22}$ + 46.6° (neat, d = 0.858, lit.[33] $[\alpha]_D^{20}$ + 51.8°); (−)-β-pinene ($[\alpha]_D^{22}$ − 21.0° (neat, d = 0.859), lit.[34] $[\alpha]_D$ − 22.1°) and 0.5M 9-BBN in THF where obtained from Aldrich Chemical Company. Acetylenes were obtained from Aldrich or Farchan. Bis-trimethylsilylacetylene was obtained from Strem Chemical Company. (−)-α-Pinene was prepared by isomerization of (−)-β-pinene according to the method of Cocker.[35] The Eu(dcm)$_3$, shift reagent was prepared according to the method of Whitesides.[36]

R-(+)-4-*Phenyl*-3-*butyn*-2-*ol* (**2b**). This experiment is representative of reductions in 0.5 M THF using the ethanolamine work up. An oven-dried 50-ml round-bottom flask, equipped with a septum-capped side arm, magnetic stirring bar, reflux condenser, and stopcock adaptor connected to a mercury bubbler was assembled hot and flushed with a stream of N_2.[32] Then 18.5 ml of a 0.54 M THF soln (10.0 mmol) of 9-BBN was added by syringe followed by 1.78 mL (11.0 mmol) of (+)-α-pinene ($[\alpha]_D^{25}$ +47.28°, 92% ee, distilled from LiAlH$_4$). The soln was stirred at reflux for 2.5 hr. The soln was cooled to room temp and 0.73 mL (5.0 mmol) of 4-phenyl-3-butyn-2-one (Aldrich) was injected into the flask. A yellow-orange color at this stage is characteristic in these reductions. Stirring at room temp was continued for 48 hr. Then 0.5 mL of acetaldehyde (excess) was added to the soln and stirring continued for 15 min. With the flask in a water bath, the solvent was removed by applying a water aspirator and stirring vigorously as a stream of N_2 was passed over the soln. This operation was completed by stirring the residue at 40° under aspirator pressure for 10 min. The α-pinene may be removed at this stage by applying a 0.05 mm vacuum for 2 hr while the flask is heated to 40°. The flask was then filled with N_2 and the liquid was dissolved in 12 mL of anhyd diethyl ether. This soln was cooled in an ice bath and then treated with 0.66 mL (11 mmol) of ethanolamine. A white ppt formed and the mixture was stirred for 15 min at 0°c. The flask was then opened to air and the mixture filtered with suction. The solid was washed with 4 mL of cold ether. The combined filtrate was then washed with 20 mL of sat aq NaCl dried over MgSO$_4$, filtered, and concentrated to a clear oil. This was distilled from a Kugelrohr oven [pot temp, 100°, (0.02 mm Hg)] to provide 0.72 g (98%) of 4-phenyl-3-butyn-2-ol ($[\alpha]_D^{25}$ + 51.8° (neat). ^1H NMR (CCl_4) δ: 1.45 (d, 3H, J = 7), 2.1 (bs, OH), 4.61 (q, 1H, J = 6), 7.15 – 7.48 (m, 5H). Examination of the NMR spectrum in the presence of tris(dicampholylmethanato) europium(III), Eu(dcm)$_3$,[36] indicated an enantiomeric mixture of 86% *R*, 14% *S* (72% ee). In reductions of **10–15**, isolation of the γ-hydroxy-α, β-acetylenic esters was facilitated by elution of the crude products through a short silica gel column prior to distillation. Unless this precaution is taken, the pot contents rapidly decompose upon heating.

S-(−)-4-*Heptyn*-3-*ol* (**26b**). (Reduction with NB-Enantrane and oxidative workup). The 50-ml reaction flask (see above) was assembled and flushed with N_2. Then 10.64 mL (5 mmol) of a 0.47 M THF solution of 9-BBN was added by syringe followed by a soln of 1.408 g (5.5 mmol) of nopol benzyl ether in 5 mL of THF. The soln was refluxed overnight. The THF was then evaporated by applying a water aspirator and stirring vigorously as a stream of N_2 was passed over the soln. The flask was then filled with N_2 and 0.275 g (2.5 mmol) of 4-heptyn-3-one[37] was added. The slightly yellow mixture was stirred for 48 hr at room temp. Then, 0.43 mL (6 mmol) of freshly distilled propionaldehyde was added and the mixture stirred for 1 hr. The soln was diluted with 10 mL of THF and the organoborane oxidized (1.7 mL of 3M NaOH, 1.2 mL of

30% H_2O_2, 2 hr, 40–50°). After saturation with anhyd K_2CO_3 the organic phase was separated, the water layer was extracted with ethyl ether, and the combined extracts were dried over K_2CO_3. After evaporation of the solvents, the crude mixture was partly purified by a Kugelrohr distillation (pot temp 150°, at 54 mm) and finally by column chromatography over silica gel (70–200 mesh), using hexane/diethyl ether (6:1). Thus, 0.215 g, (76.8%) of 4-heptyn.3.ol[b.p. 110° (45 mm); $[\alpha]_D^{20}$ −4.85° ($c = 4$, $CHCl_3$)] was obtained. Examination of the NMR spectrum in the presence of tris[3-((heptafluoropropyl) hydroxymethylene)-*d*-camphorato] europium(III) ($Eu(hfc)_3$) indicated an enantiomeric mixture of 97.2% *S* and 2.8% *R* (94.4% ee).

R-(+)-1-*Octyn*-3-*ol* (**5b**). (Reduction with neat Alpine-borane and oxidative work up). A 2-1 round-bottom flask equipped with a septum-capped side arm, magnetic stirring bar, refluxing condenser and stopcock adapter connected to a Hg-bubbler, was flame-dried while being flushed with N_2. A N_2 atmosphere was maintained throughout the procedure up through the oxidation step. After the apparatus cooled, it was charged, via double-ended needle,[32] with 800 ml of a 0.5 M THF soln of 9-BBN (0.4 mole). Then 61.3 g (71.5 ml, 0.45 mole) of (+)-α-pinene was added. After the soln had refluxed for 4 hr, the excess α-pinene and THF were removed, first by a water aspirator and then by vacuum pump at 40° to provide a thick clear oil of neat Alpine–borane. The vacuum was released with N_2. The flask was then cooled to 0° (icebath) and 35.3 g (0.285 mole) of 1-octyn-3-one[37] added. The reduction can be monitored by gas chromatography, but typically 8 hr is required for completion. During this time, the ice-bath was allowed to warm to room temp. The color of the mixture was initially light yellow and darkened to red at the end of the reduction. Excess Alpine–borane was destroyed by adding 22 ml (0.3 mole) of freshly distilled propionaldehyde and stirring for 1 hr at room temp. Liberated α-pinene was then removed by vacuum.[38] Then 200 ml of THF was added followed by 150 ml of 3 M NaOH. Then 150 ml of 30% H_2O_2 was added dropwise (CAUTION! exothermic). The oxidation was stirred for 3 h at 40°. The mixture was extracted with three 50 ml portions of ethyl ether. The ether layers were combined and dried with $MgSO_4$, filtered, and then concentrated by rotary evaporation to give an oil. Distillation at 60°–65° at 3.0 mm Hg provided 31 g (0.245 mole) of 1-octyn-3-ol, 86% yield, IR(neat)cm^{-1}: 3315, 2950, 2860, 2120, 1475, 1380, 1120, 1060, 1025, 650. ^1H NMR ($CDCl_3$) δ: 0.86 (t, 3H, J = 6.6, CH_3), 1.3 – 1.4 (m, 6H), 1.65 (m, 2H), 2.42 (d, 1H, J = 2, C≡C-H), 3.0 (variable, broad, 1H, OH), 4.33 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ: 72.6 (C-1), 85.1 (C-2), 62 (C-3), 37.4 (C-4), 31.3 (C-5), 24.6 (C-6), 22.4 (C-7), 13.9 (C-8). Optical rotation $[\alpha]_D^{25} = 7.50°$ (neat, density 0.864 g/ml). It has been shown that optical rotation is an unreliable criteria of enantiomer purity of 1-octyn-3-ol.[39] The distillation pot residue was a thick oil consisting mainly of *cis*-1,5-cyclooctane diol. Lanthanide shift study showed the alcohol to be 93%(*R*) and 7%(*S*), 86% ee.[40]

4,4-*Dimethyl*-1-*trimethylsilyl*-1-*pentyn*-3-*ol* (**20b**). 4,4-Dimethyl-1-trimethylsilyl-1-pentyn-3-one **20a** (1.82 g) was introduced into neat Alpine–borane (20.0 mmol, 2.0 eq.) at room temp: The soln was mixed until homogeneous. The clear soln was taken-up in a 10 ml disposable syringe, capped and transferred to the high pressure cell.[41] After 2d at 6000 atm. (83% reduction)[42] the mixture was quenched with acetaldehyde (2.0 eq.) followed by workup in the usual manner with ethanolamine in ether (0°). The product (1.3 g, 71% yield) was isolated via preparative gas chromatography (80°, 10% XE-60 chromosorb W, 6 ft). Enantiometric purity was determined by $Eu(dcm)_3$ chiral shift study (92% ee, 100% ee when corrected for the purity of the (+)-α-pinene). Alternatively, the desilated alcohol, 4,4-dimethyl-1-pentyne-3-ol, may be isolated following the usual oxidative workup.

Nopol-benzyl ether (**22**). A 500 ml reaction flask was charged with 5.80 g of 57% NaH (148 mmol) in mineral oil and the mineral oil removed by washing with hexane. Then 200 ml of dry THF was added followed by 16.66 g (100 mmol) of nopol (**21**). The reaction was stirred at room temp for 1 hr. Benzyl chloride, 15.4 g (122 mmol) was added and the mixture refluxed overnight. After cooling to room temp, the mixture was poured into water and extracted with ether. The ether was washed with water, followed by sat NaCl aq and then dried ($MgSO_4$). The solvent was removed and the product distilled; BP 118–120°, 0.8 mm, yield 23.6 g (92%), $[\alpha]_D^{25}$ −26.47° ($c = 10.4$, $CHCl_3$). ^1H NMR: 0.8 (s, 3H, Me), 1.2 (d, 1H), 1.3 (s, 3H, Me), 2.2 (m, 7H), 3.5 (t, 2H, CH_2O), 4.5 (s, 2H, $PhCH_2O$), 5.3 (m, 1H, olefin), 7.3 (s, 5H, aromatic).

The optical purity of the nopol ($[\alpha]_D^{20}$ −37.45° (neat, d = 0.9602)) could be improved in the following manner: nopol, 50 g (0.3 mol) and phthalic anhydride, 44.4 g (0.3 mol) were refluxed in 350 ml of toluene for 4 hr. The toluene was removed under vacuum and the residue dissolved in a soln of 48 g anhyd Na_2CO_3 in 2.5 l of water. The water was extracted with ether and then acidified to pH 1 with HCl. The soln was extracted with ether. The ether dried ($MgSO_4$) and removed. The solid was dissolved in $CHCl_3$ and the undissolved material (phthalic acid) removed by filtration. After removal of the $CHCl_3$ the solid was recrystallized from hexane to give 64.2 g (68%) of nopol half phthalate, m.p. 76–80°, $[\alpha]_D^{25}$ −26.81° ($c = 10.195$, $CHCl_3$). The nopol half phthalate (89.2 g, 0.284 mol) was dissolved in 400 ml of acetone and (−)-α-methylbenzylamine; 34.3 g, (0.284 mol) was added dropwise. The slurry was stirred at room temp for 1 hr and then filtered. The crude material (m.p. 137–138°, $[\alpha]_D^{25}$ −20.39° ($c = 3.04$, $CHCl_3$)) was recrystallized from MeCN/MeOH (10/1). (m.p. 138–139°$[\alpha]_D^{25}$ − 21.32°($c = 3.00$, $CHCl_3$)) to give 94.9 g (76%). The salt was treated with 200 ml of HCl (1:3) and extracted with ether. The extract was dried over $MgSO_4$, the ether removed and the residue recrystallized from hexane–EtOAc (10:1) to give 58.59 g (86%) of the nopol half phthalate m.p. 81–82°, $[\alpha]_D^{25}$ −28.11° ($c = 10.175$, $CHCl_3$) the half phthalate was stirred with a soln of 22.4 g of NaOH in 200 ml of water at 50–60° for 2 hr. The water was saturated with NaCl and extracted with ether. The ether was washed with $NaHCO_3$ aq and dried over K_2CO_3. Distillation gave 29 g of nopol, 96% b.p. 63–65°, 0.05 mm. $[\alpha]_D^{25}$ −39.36° (neat). This material gave nopol benzyl ether of $[\alpha]_D^{25}$ −27.8° ($c = 10$, $CHCl_3$).

(−)-(2E, 4R)-5-*Methyl*-2-*hexen*-4-*ol* (**28**). (*R*)-**19b**, (4.12 g, 36.7 mmol) prepared by the procedure for 1-octyn-3-ol in 92% ee., 70% yield, was added dropwise to a stirred soln of LAH (1.4 g, 35.1 mmol) in 25 ml of THF at room temp. The mixture was refluxed for 3 hr. After cooling, the mixture was treated by successive addition of water (2 ml), NaOHaq (15%, 1.5 ml) and water (4.5 ml) to form a ppt. After filtration, ethyl ether (50 ml) was added and the filter cake was refluxed for 1 hr and filtered again. The combined filtrate was dried over anhydrous $MgSO_4$ and the solvent removed by rotovac. Distillation at 58°/25 mm Hg produced 3.13 g (74.7%) of **2** as a colorless oil. Optical rotation: $[\alpha]_D^{23}$ −24.11°, (neat, d = 0.8338); lit[43] $[\alpha]_D^{25}$ +19.36° (neat, d = 0.8327). IR (film) 3400, 1674 cm^{-1}; ^1H NMR (200 MHz) ($CDCl_3$), 5.64 (dq, J − 15.4 and 6.4, 1H), 5.43 (dd, J = 15.4, 7.3 and 1.0, 1H), 3.71 (t, J = 6.8, 1H), 2.00 (br, 1H), 1.67 (d, J = 6.4, 3H), 1.50 1.80 (m, 1H), 0.88 (d, J = 6.8, 3H), 0.83 (d, J = 6.4, 3H); ^{13}C NMR (50 MHz) ($CDCl_3$), 132.41 (d), 127.35 (d), 78.12 (d), 33.70 (d), 18.09 (q), 17.60 (q).

(−)-(2Z, 4R)-5-*Methyl*-2-*hexen*-4-*ol* (**29**). A vigorously stirring soln of 7.5 g (67 mmol) of **19b** in 10 ml of hexane, 200 mg of Lindlar catalyst and 1 ml of 2,6-lutidine was exposed to H_2 atmosphere until H_2 uptake ceased, as monitored by Hg-bubbler column (about 20 min). The mixture was then filtered to remove the catalyst and washed with dil HCl to remove lutidine. The organic layer was dried ($MgSO_4$), filtered and the solvent removed by rotary

evaporation. The resulting oil was distilled at 80° (water aspirator ~30 mm) to afford **29** in 89% yield, 6.8 g (60 mmol). None of the transisomer could be detected by ^{13}C NMR. The enantiomeric purity was measured by Eu(hfc)$_3$ NMR shift study and determined to be 90% ee $[\alpha]_D^{24}$ −14.4° (*c* = 6.8, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.84 (dd, 6H, J = 6.9), 1.6 (d, 3H, J = 6.4), 2.2 (b, 1H, OH), 4.09 (dd, 1H, J = 6.8), 5.33 (m, 1H), 5.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 131.7, 126.4, 71.9, 33.9, 18.1, 17.6, 13.2.

(−)-*Ethyl* (R)-(E)-3,6-*dimethyl*-4-*heptenoate* (**30**). The Johnson ortho ester Claisen rearrangement was used.[28b] A soln of **28** (2.57 g, 22.5 mmol) and propanoic acid (0.19 g, 2.60 mmol) in triethyl orthoacetate (18.0 g, 111.0 mmol) was distilled through a short column under N_2 until no more EtOH was present, then refluxed overnight. The excess triethyl orthoacetate was removed and distillation at 93°/25 mm Hg gave 2.61 g (62.9%) of **30** as a colorless oil. Optical rotation: $[\alpha]_D^{24}$ −17.67°; (*c* = 3.18, $CHCl_3$). IR (film) 1742, 970 cm^{-1}; ^1H NMR ($CDCl_3$) 5.38 (dd, J = 15.6 and 6.4, 1H), 5.23 (dd, J = 15.6 and 6.8, 1H), 4.09 (q, J = 7.31, 2H), 2.58 (m, 1H), 2.35 (m, 3H), 1.22 (t, J = 7.3, 3H), 1.00 (d, J = 6.8, 3H), 0.92 (d, j + 6.8, 6H); ^{13}C NMR ($CDCl_3$) 172.60 (s), 136.60 (d), 130.86 (d), 59.97 (t), 42.07 (t), 33.65 (d), 30.83 (d), 22.51 (q), 20.42 (q), 14.24 (q). The (+) isomer was prepared from **29** $[\alpha]_D^{25}$ +18.17° (C = 10.5, $CHCl_3$).

(3R)-(+)-3-*Methyl*-γ-*butyrolactone* (**31**). (−)-Ethyl ester **30** (1.43 g, 7.76 mmol) was ozonized in a 1:1 soln of EtOH and $CHCl_3$ (60 ml) at −78° until the color of the soln turned blue. $NaBH_4$ (0.50 g, 13.2 mmol) was added slowly to the ozonide mixture in two portions at −78° and 0° while the soln was gently bubbled with N_2. After standing 1.5 hr at room temp, the mixture was acidified with HCl (3N, 35 ml), the organic layer separated, and the aqueous layer further extracted with ethyl ether. The combined extracts were dried over $MgSO_4$, filtered, and bulb to bulb distillation produced 0.57 g (73.5%) of **31** (>95% pure). The product was further purified by prep. GC (10% XE-60, 160°). Optical rotation: $[\alpha]_D^{24}$ +23.00° (*c* = 4.0, MeOH); lit[44] $[\alpha]_D^{25}$ −24.7° (*c* = 4, MeOH, 97% ee) has been reported for (*S*)-**31**. IR (film) 1780, 1178 cm^{-1}; ^1H NMR ($CDCl_3$) 4.21 (dd, J = 8.8 and 7.3, 1H), 3.88 (dd, J = 8.8 and 6.3, 1H), 2.72 − 2.58 (m, 2H), 2.00 2.20 (m, 1H), 1.17 (d, J − 6.4, 3H). ^{13}C NMR ($CDCl_3$) 177.22, 74.62, 36.04, 30.30, 17.84.

(+)-(4E, 3S)-3,6-*Dimethyl*-4-*hepten*-1-*ol* (**35**). (+)-Ester **30** was added to 50 ml of THF containing 1.5 g (40 mmol) LAH. This mixture was refluxed for 2 hr then cooled (ice bath) and carefully quenched with dil NaOH aq. The resulting Al salt slurry was dissolved by adding conc HCl, followed by ether extraction. The ether layer was dried ($MgSO_4$), filtered and the solvent removed by rotary evaporation. Distillation (90°–100°, 30 mm) yielded **35** in 80%, 4.1 g (29 mmol). $[\alpha]_D^{24}$ +27.4° (*c* = 6.4, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.95 (m, 9H, $3CH_3$), 1.5 (bm, 2H), 2.2 (bm, 2H), 2.5 (1H, OH), 3.6 (dd, 2H, J = 3.4), 5.2–5.4 (m, 2H, vinyl); ^{13}C NMR ($CDCl_3$) δ: 136.7, 132.5, 61.29, 39.78, 33.8, 30.9, 22.6, 21.15.

(−)-(2S)-2-*Methyl*-γ-*butyrolactone* (**32**). A cold (−78°, Dry ice/acetone) soln containing 1.4 g of the above **35** (9 mmol) and 50 ml CH_2Cl_2 was treated with O_3 until the soln became blue (excess O_3). The excess O_3 was flushed from the O_3-apparatus with N_2. Then an excess of Me_2S (~5 ml) was added and the mixture was allowed to warm to room temp. The solvent was removed by rotary evaporation and the oily residue was washed with water/ether (water removes DMSO). The ether layer was dried ($MgSO_4$), filtered and the solvent removed by vacuum to afford a thick oily product which was thought to be the lactol, although it was never fully characterized by NMR. Without further purification the lactol was oxidized with Jones reagent to give the lactone. To an acetone soln of 0.8 g (7.8 mmol) of crude lactol in 100 ml of acetone was added 3 ml of 2.67 M Jones reagent,[37] the soln was stirred for 3 hr at ice bath temp. The mixture was filtered and washed with NaCl aq and ether. The ether layer was washed with aq $NaHCO_3$, then dried $MgSO_4$, filtered and the solvent removed by rotary evaporation. Bulb to bulb distillation gave 0.4 g (4 mmol) of **32**. The enantiomeric purity was determined to be 70% by Eu(hfc)$_3$ NMR shift study. (The (*S*) Me group shifts faster downfield than the (*R*) Me group). $[\alpha]_D^{24}$ −14.7° (*c* = 6.3, EtOH), lit[44] $[\alpha]_D^{24}$ −22.9° (*c* = 2 EtOH). ^1H NMR ($CDCl_3$) δ: 1.25 (d, 3H, J = 7.33), 1.9 (m, 1H), 2.4 (m, 1H), 2.6 (m, 1H), 4.18 (m, 1H), 4.3 (dt, 1H, J = 2.93, 8.3); ^{13}C NMR ($CDCl_3$) δ: 174.25, 66.2, 34.09, 30.6, 15.07.

(R)-1-*Nonyn*-4-*ol* (**33**). (KAPA isomerization). A dry 500-ml reaction flask was charged with 5.2 g of KH (130 mmol) 24% in mineral oil. The oil was removed by washing with hexane (3 × 40 ml). Then 100 ml of 3-amino propylamine (APA) was added and the mixture stirred for 3 hr (H_2 evolution). The mixture was cooled to 0° and 5.5 g (*R*)-2-nonyn-4-ol (39 mmol) 88% ee., prepared by the procedure used for 1-octyn-3-ol in 85% yield, was added to the flask. After 10 min the soln was warmed to room temp over 30 min. The reaction was then quenched with isopropanol and then water. The mixture was extracted with ether and the ether washed 3 times with 1N HCl. The ether was dried over $MgSO_4$ and the ether removed on a rotovac. The product was dried at 0.1 mm and provided 5.0 g (91%) of 1-nonyn-4-ol.

(R)-5-*Hydroxy*-2-*decynoic acid*. A 250-ml reaction flask was charged with 80 ml of THF and 3.04 g (21.5 mmol) of 1-nonyn-4-ol. The soln was cooled to −78° and 43 mmol (26.8 ml of 1.6 M) n-BuLi was added dropwise and then stirred for 10 min. Solid dry ice was added to an Erlenmeyer flask and the flask capped with a septum penetrated by a double-ended needle. Gaseous CO_2 was transferred by the double-ended needle to the reaction flask. After 15 min, addition was stopped and the reaction flask removed from the −78° bath. After reaching 0°, water was added followed by $NaHCO_3$ aq to ensure a pH above 8. The soln was extracted with ether and the ether washed with $NaHCO_3$ aq. The aqueous phase was then acidified with 3N HCl. The product was extracted with ether, dried with $MgSO_4$ and the ether removed on a rotovac. The product was dried at 0.02 mm Hg, 35° for 20 min. The yield was 2.94 g, 74%.

(R)-(−)-2-*Decen*-5-*olide* (**34**). A 100-ml 24/10 flask was charged with 1.72 g. of 5-hydroxy-2-decynoic acid, 2.0 ml of quinoline, 35 ml of THF and 400 mg of 5% Pd on $BaSO_4$. The flask was attached to a Brown□ hydrogenator.[45] The system was flushed with H_2. A 250-ml gas syringe was filled with H_2 and the needle inserted into the septum of the apparatus. Upon initiation of stirring, the level of the Hg-bubbler was maintained by adding H_2 from the syringe. The reaction was stopped when 95% of the theoretical amount of H_2 was absorbed. The mixture was filtered through celite, ether added and the soln washed 3 times with 1 N HCl. The ether was removed on a rotovac and replaced with 45 ml of cyclohexane. The soln was refluxed in a Dean Stark apparatus for 1 hr to remove water. The cyclohexane was removed and the product distilled at 58–60°, 0.02 mm, yield 1.2 g, 76%. A sample was purified by chromatography over silica gel eluting with 10% isopropanol in hexane $[\alpha]_D^{25}$ −92.9° (*c* = 4.76, $CHCl_3$) lit[30] $[\alpha]_D^{22.6}$ −110.5° (*c* = 2.5, $CHCl_3$).

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[40]Optically-pure (+)-1-octyn-3-ol may be obtained by recrystallization of the half acid phthalate with (+)-α-methylbenzylamine (Aldrich Chemical Company). The half acid phthalate is made by heating equal molar amounts of 1-octyn-3-ol and phthalic anhydride. This half acid phthalate derivative is a waxy solid which does not lend itself to recrystallization. Attempts to form crystalline salts of the phthalate derivative with achiral alkyl amines only lead to waxy solids or thick oils. The phthalic amine salt made with racemic 1-octyn-3-ol requires 3-4 recrystallizations from methylene chloride to resolve enantiomers. (J. Fried, C. H. Lin, M. M. Mehra, W. L. Kao, and P. Dalven *N. Y. Acad. Sci.* **180**, 38 (1971). The first recrystallization may take several days, with successive recrystallizations becoming easier. If the 86% ee

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