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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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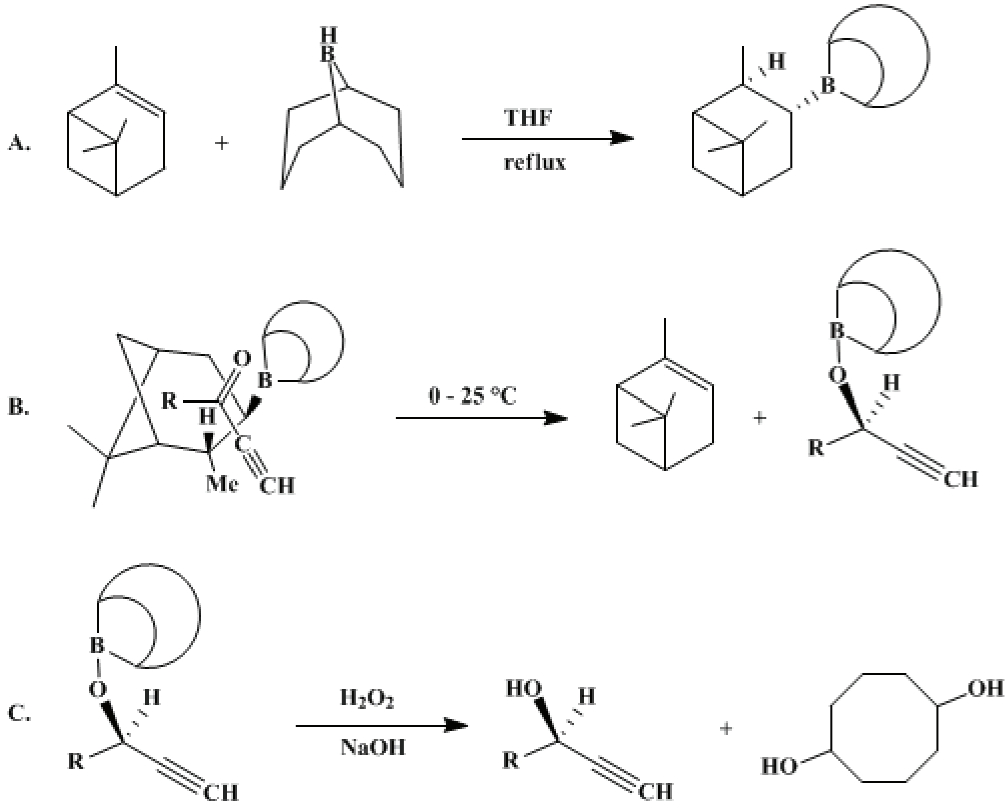
ASYMMETRIC REDUCTION OF α,β-ACETYLENIC KETONES WITH *B*-3-PINANYL-9-BORABICYCLO[3.3.1]NONANE: (*R*)-(+)-1-OCTYN-3-OL

[1-Octyn-3-ol, (*R*)-]



Submitted by M. Mark Midland and Richard S. Graham[1].
Checked by Joel M. Hawkins and K. Barry Sharpless.

1. Procedure

A. A 2-L, round-bottomed flask equipped with a septum-capped sidearm, magnetic stirring bar, reflux condenser, and stopcock adapter connected to a mercury bubbler is flame-dried while being flushed with nitrogen. A nitrogen atmosphere is maintained during the procedure through the oxidation step. After the apparatus is cooled, it is charged, via a double-ended needle,[2] with 800 mL of a 0.5 M tetrahydrofuran (THF) solution of 9-borabicyclo[3.3.1]nonane (9-BBN, 0.4 mol, (Note 1)). Then 61.3 g (71.5 mL, 0.45 mol) of (+)-α-pinene (Note 2) is added. After the solution is refluxed for 4 hr, the excess α-pinene and THF are removed by vacuum (Note 3) to provide a thick clear oil of neat B-3-pinanyl-9-borabicyclo[3.3.1]nonane, **1** (Note 4).

B. The flask is cooled to 0°C (ice bath) and 35.3 g (0.285 mol) of 1-octyn-3-one (Note 5) is added. After an initially exothermic reaction, the reaction is allowed to warm to room temperature. The reduction can be monitored by gas chromatography (Note 6), but generally 8 hr is required for completion. The color of the reaction mixture is initially light yellow and darkens to red at the end of the reduction.

C. Excess **1** is destroyed by adding 22 mL (0.3 mol) of freshly distilled propionaldehyde and stirring for 1 hr at room temperature. Liberated α-pinene is then removed by vacuum (Note 7). Tetrahydrofuran, 200 mL, is added, followed by 150 mL of 3 *M* aqueous NaOH. Hydrogen peroxide (150 mL, 30%) is added dropwise (see *Caution* in (Note 8)). Oxidation is complete in 3 hr at 40°C. The reaction mixture is transferred to a separatory funnel and extracted with three 50-mL portions of ethyl ether. The ether layers are combined and dried with copious amounts of anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give an oil. Distillation at 60–65°C (3.0 mm) yields 31 g (0.245 mol) of 1-octyn-3-ol, 86% yield (Note 9). The distillation pot residue is a thick oil consisting for the most part of *cis*-1,5-cyclooctanediol. An NMR lanthanide shift study showed the alcohol to be 93% (R) and 7% (S), 86% e.e. (Note 10) and (Note 11).

2. Notes

1. A 0.5 *M* THF solution of 9-BBN is available from Aldrich Chemical Company in 800 mL bottles.
2. (+)-α-Pinene (90–92% e.e.) is available from Aldrich Chemical Company. The pinene was distilled from lithium aluminum hydride before use.
3. Most of the THF is removed by water aspirator vacuum. Excess pinene (0.05 mol, ∼8 mL) is removed by applying a 0.05-mm vacuum for 2 hr while warming to 40°C with a water bath. The vacuum should be bled with nitrogen to maintain an inert atmosphere in the reaction flask. Recently Brown's group[3] has shown that reduction occurs at an enhanced rate with neat organoborane **1**. Excess **1**, 1.4 equiv per equivalent of l-octyn-3-one, is used to provide a slight excess of reducing agent to increase the rate for this bimolecular process.
4. *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane, **1**, is also available from Aldrich Chemical Company under the tradename "R-Alpine-Borane."
5. 1-Octyn-3-one was obtained by standard Jones oxidation[4] of racemic 1-octyn-3-ol (in ∼80% yield). Racemic 1-octyn-3-ol is available from Aldrich Chemical Company. It is essential to check the ketone for unreacted starting alcohol since racemic alcohol will contaminate the final, optically active product.
6. GLC can be used to monitor the disappearance of the acetylenic ketone. 1-Octyn-3-one is eluted just after α-pinene from a SE-30 6-ft column at 80°C. The checkers followed the disappearance of ketone by TLC (15% ethyl acetate in hexane).
7. This is the most convenient time for removal of α-pinene since α-pinene and 1-octyn-3-ol have similar boiling points, making separation by distillation difficult. Application of a 0.05-mm vacuum while the flask is warmed to 40°C for several hours will remove most of the α-pinene (0.4 mol, ∼63.5 mL). Because of the volume of α-pinene, cold traps in the vacuum system may become plugged; therefore, the traps will have to be emptied several times. This provides a convenient method for recovery of liberated (+)-α-pinene.
8. Hydrogen peroxide oxidation of organoboranes is exothermic. Careful, dropwise addition of 30% hydrogen peroxide to the organoborane will provide sufficient heating to maintain a reaction temperature in the 40–50°C range.
9. 1-Octyn-3-ol has the following properties: bp 60–65°C (3.0 mm); IR (neat) cm^{-1}: 3315, 2950, 2860, 2120, 1475, 1380, 1120, 1060, 1025, 650; ^{1}H NMR (CDCl$_3$) δ: 0.86 (t, 3 H, $J = 6.6$, CH$_3$), 1.3-1.4 (m, 6 H), 1.65 (m, 2 H), 2.42 (d, 1 H, $J = 2$, C≡C-H), 3.0 variable (broad, 1 H, OH), 4.33 (m, 1 H); ^{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); $[\alpha]_D^{25}$ + 7.50° (neat, density 0.864 g/mL). It has been shown that optical rotation is an unreliable criterion of enantiomer purity of 1-octyn-3-ol.[5]
10. Commercially available Eu (hfc)$_3$, tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium III, NMR shift reagent, was used as received from Aldrich Chemical Company. The proton on the chiral carbinol carbon was shifted downfield to ∼11 ppm in CDCl$_3$. The R isomer was shifted ∼0.5 ppm further downfield than the *S* isomer.
11. 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 salt is made by heating equal molar amounts of 1-octyn-3-ol and phthalic anhydride. This half acid phthalate derivative is a waxy solid that 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 three to four recrystallizations from methylene chloride to resolve enantiomers.[6] The first recrystallization may take several days, with successive recrystallizations becoming easier. If the 86% e.e. 1-octyn-3-ol is used to make the phthalic amine salt only one facile recrystallization is needed to provide optically-pure alcohol. The pure amine salt melts at 132–134°C.

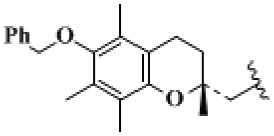
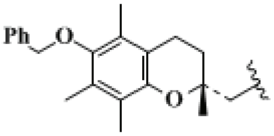
The enantiomeric purity of the salt may be determined by NMR by observing the ethynyl hydrogen doublets at δ 2.48 (minor) and 2.52 (major) ($CDCl_3$ solvent).

3. Discussion

In this procedure, we describe a general method for the synthesis of alkynyl alcohols of high enantiomeric purity. The one-pot asymmetric reduction of 1-octyn-3-one with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane provides a mild and efficient method for the preparation of optically active 1-octyn-3-ol. The reduction occurs in good chemical yield and is virtually (>95%) stereospecific (correcting for the use of 90% e.e. α-pinene). The availability of optically pure α-pinene is a limiting factor in this method, but recently Brown's group has developed a process that provides enantiomerically pure α-pinene.[7] The reduction can be applied to prepare both enantiomers of 1-octyn-3-ol, since both enantiomers of α-pinene are commercially available; although commercial (−)-α-pinene is only 81.3% e.e.,[7] (−)-α-pinene of 92% e.e. is easily obtained by isomerizing commercial (−)-β-pinene (92% e.e.).[8] [9] (Reducing agent **1**, made with (−)-α-pinene, will provide (*S*)-(−)-1-octyn-3-ol). The α-pinene liberated (by β-hydride elimination) in the reduction may be recycled without loss of optical purity. Another attractive feature of this reduction is that organoborane **1** is a mild reagent and seldom affects other functional groups present within the acetylenic ketone. For base-sensitive systems that cannot tolerate the standard sodium hydroxide–hydrogen peroxide oxidation, an alternative workup using ethanolamine is available.[10] Table I illustrates the application of this reduction to other propargyl ketones.[10] In these cases, tetrahydrofuran was not removed prior to reduction. Removal of tetrahydrofuran provides a faster reaction and slightly higher optical purity.[3].

TABLE I

REDUCTIONS OF ALKYNYL KETONES WITH B-(3)-α-PINANYL-9-BBN

Ketone RCOC≡CR'			Enantiomeric Excess (%)[b]
R	R'	Yield (%)[a]	
Ph	Bu	72	89[c]
Me	Ph	98	72(78)
Pr	C_6H_{13}	68	77[c]
2-Pr	H	78	91(99)
	Me	77	85:15[d]
	H	75	91:9[d]
Me	COOEt	59	71(77)
C_5H_{11}	COOEt	72	85(92)
Ph	COOEt	64	92(100)
t-Bu	Me	0	
Me	*t*-Bu	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% e.e. 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.

The most popular methods of preparing optically active 1-octyn-3-ol involve asymmetric reduction of 1-octyn-3-one with optically active alcohol complexes of lithium aluminum hydride or aluminum hydride.[11] [9] [12] [13] These methods give optical purities and chemical yields similar to the method reported above. A disadvantage of these metalhydride methods is that some require exotic chiral alcohols that are not readily available in both enantiomeric forms. Other methods include optical resolution of the racemic propargyl alcohol (100% e.e.)[6] (and (Note 11)) and microbial asymmetric hydrolysis of the propargyl acetates (∼15% e.e. for 1-heptyn-3-ol).[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 95

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

9-BBN

propargyl acetates

tris [3-(heptafluoropropylhydroxy-methylene)-d-camphorato]europium III

ethyl acetate (141-78-6)

ethyl ether (60-29-7)

sodium hydroxide,
NaOH (1310-73-2)

Propionaldehyde (123-38-6)

nitrogen (7727-37-9)

phthalic anhydride (85-44-9)

hydrogen peroxide (7722-84-1)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

ethanolamine (141-43-5)

(+)-α-methylbenzylamine (3886-69-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

propargyl alcohol (107-19-7)

aluminum hydride

propargyl (2932-78-7)

9-borabicyclo[3.3.1]nonane (280-64-8)

α-pinene,
(+)-α-pinene (7785-70-8)

pinene (18172-67-3)

1-octyn-3-ol,
(+)-1-octyn-3-ol (818-72-4)

B-3-Pinanyl-9-borabicyclo[3.3.1]nonane (73624-47-2)

1-octyn-3-one,
l-octyn-3-one

1-heptyn-3-ol (7383-19-9)

1-Octyn-3-ol, (R)-,
(R)-(+)-1-OCTYN-3-OL (32556-70-0)

cis-1,5-cyclooctanediol