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HIGHLY ENANTIOSELECTIVE REDUCTION OF ALKYNYL KETONES BY A BINAPHTHOL-MODIFIED ALUMINUM HYDRIDE REAGENT. ASYMMETRIC SYNTHESIS OF SOME INSECT PHEROMONES[1]

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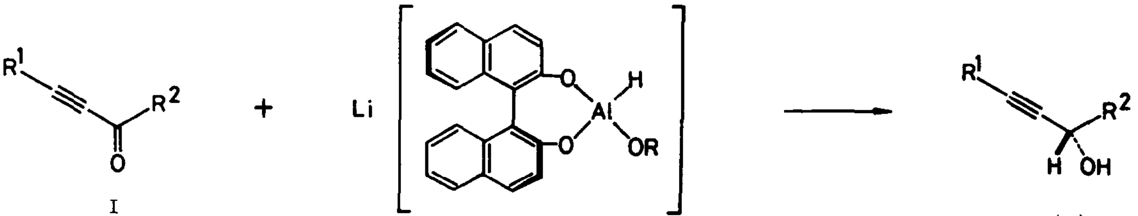
Summary: Alkynyl ketones can be reduced to chiral propargylic alcohols by a complex aluminum hydride modified by chiral 2,2'-dihydroxy-1,1'-binaphthyl. The synthetic utility has been demonstrated by the synthesis of the Japanese beetle and rove beetle pheromones.

Chiral propargylic alcohols are important as building blocks of various natural products[2–7] and precursors of ortherwise difficult-to-make optically active compounds.[8,9] Disclosed herein is an effective general way for obtaining diverse propargylic alcohols of high enantiomeric purity.

This method is based on the asymmetric reduction[10] of prochiral alkynyl ketones[11] with a binaphthol-modified complex aluminum hydride (abbreviated to BINAL-H).[1,12,13] The reducing agent formulated as III (empirical formula) was prepared in situ by mixing lithium aluminum hydride, a hydroxylic compound (ROH), and optically pure 2,2'-dihydroxy-1,1'-binaphthyl (II) (1:1:1 mol ratio) in dry THF at room temperature. When an alkynyl ketone I was treated with 3 equiv of this reagent in THF at -100 °C for 1 h and then at -78 °C for 2 h, the corresponding propargylic alcohol IV was obtained after ordinary aqueous workup in a high yield and in an optical active form. The optical purity was determined by high-pressure liquid chromatography after conversion of the GLC- or column chromatography-purified material to the diastereomeric (S)-β,β,β-trifluoro-α-methoxy-α-phenylpropionate[14a] or 3β-acetoxyetienate[14b] derivative. As the hydroxylic modifying agent, ROH, methanol or ethanol gave the most satisfactory result.



I

(S)-BINAL-H[(S)-III]

(S)-IV

a, $R^1 = H$; $R^2 = \underline{n}\text{-}C_5H_{11}$
b, $R^1 = H$; $R^2 = \underline{n}\text{-}C_8H_{17}$
c, $R^1 = H$; $R^2 = \underline{n}\text{-}C_{11}H_{23}$
d, $R^1 = H$; $R^2 = CH(CH_3)_2$
e, $R^1 = \underline{n}\text{-}C_4H_9$; $R^2 = CH_3$
f, $R^1 = \underline{n}\text{-}C_4H_9$; $R^2 = \underline{n}\text{-}C_5H_{11}$
g, $R^1 = \underline{n}\text{-}C_8H_{17}$; $R^2 = CH_2CH_2COOCH_3$
h, $R^1 = COOCH_3$; $R^2 = \underline{n}\text{-}C_8H_{17}$

Table I. Asymmetric Reduction of Alkynyl Ketones with BINAL-H[a]

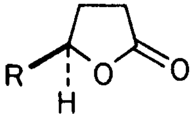
	BINAL-H		carbinol product IV			
ketone	OR	binaphthol[b] confign	% yield[c]	$[\alpha]_D^{21}$, deg (c)[d]	optical purity % ee[e]	confign[f]
Ia	OCH_3	S	87	-18.8 (1.30)	84	S
Ia	OC_2H_5	S	71	-18.5 (1.36)	84	S
Ib	OCH_3	S	80	-16.5 (0.86)[g]	96	S
Ib	OCH_3	R	69	h	94	R[e]
Ib	OC_2H_5	S	74	h	90	S[e]
Ib	OAl[i]	R	64	h	92	R[e]
Ic	OCH_3	S	90	-13.8 (0.76)[g]	92	S
Id	OCH_3	S	84[j]	-15.4 (0.81)[g]	57	S
Ie	OCH_3	R	79	+33.0 (1.62)[g]	84	R
If	OCH_3	S	85	-12.3 (1.35)[k]	90	S
Ig	OCH_3	R	82	h	84[l]	R[m]
Ih	OCH_3	S	80	-6.1 (1.08)	87[n]	S[o]

[a] Reduction was carried out using 3 equiv of BINAL-H at -100 °C for 1 h and then at -78 °C for 2 h. [b] Optical rotation values of binaphthols were: (R)-II:$[\alpha]_D^{21}$ +37.1° (c 1.00, THF). (S)-II: $[\alpha]_D^{21}$ -35.7° (c 1.08, THF). [c] Isolated yield. [d] Determined in ether solution using a JASCO DIP-4 polarimeter with digital read-out and a 1-dm cell. [e] Determined by HPLC analysis of the diastereomeric (S)-β,β,β-trifluoro-α-methoxy-α-phenylpropionate (MTPA) derivatives (ref 14a) (Aldrich, 99+%), with a JASCO FLC-350 instrument equipped with a JASCOSIL SS-05 column and a UV detector (250 nm) using petroleum ether—acetonitrile (99.5:0.5) mixed solvent system. [f] Determined by the comparison of optical rotation with reported data (ref 2,4,5a,11). [g] Rotation measured at 23 °C. [h] Not determined. [i] Water (0.5 equiv) was used for the preparation of BINAL-H. [j] GLC yield. [k] $[\alpha]_D^{23}$ -2.6° (c 0.50, $CHCl_3$). [l] Determined by NMR analysis of the MTPA derivative in the presence of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium(III). [m] Determined by the conversion to 5-tetradecyn-4-olide. [n] Determined by HPLC analysis of the diastereomeric 3β-acetoxyetienate derivative (ref 14b), with a Waters 6000A instrument equipped with a radial pack B column and a UV detector (220 nm) using hexane—THF (25:1) mixed solvent system. [o] Determined by the conversion to (S)-(-)-2-acetoxydecanoic acid, $[\alpha]_D^{23}$ -7.79° (c 0.68, $CHCl_3$). Authentic (R)-(+)-enantiomer, $[\alpha]_D^{23}$ +7.25° (c 1.44, $CHCl_3$), was prepared by acetylation and ozonolysis of (R)-(+)-1-undecyn-3-ol (ref 5a).

Examples are given in Table I. The optical purity of the products was generally high, regardless of the nature of the substituents attached to the acetylenic moiety. Notably, (S)-BINAL-H afforded generally the S alkynylcarbinols, whereas the R reagent produced the R alcohols.

This process is operationally simple and can be applied to a wide variety of ynones. Both (S)- and (R)-II are easily available in optically pure form,[15] and therefore one can prepare both enantiomers of propargylic alcohols by choosing the chiral inducing ligand. The chiral auxiliary ligand II can be recovered without loss of optical purity from the reaction mixture. Thus this method fully satisfies the requirements for an efficient asymmetric synthesis.

When (R)-IVg (84% ee) was exposed to p-toluenesulfonic acid in benzene (reflux, 1 h), the γ-lactone (R)-V ($[\alpha]_D^{26}$ -3.5° (c 0.86, $CHCl_3$), 85% ee)[5b] was obtained. The catalytic hydrogenation of the alkynyl lactone over Lindlar catalyst led to the Japanese beetle pheromone (R)-VI ($[\alpha]_D^{20}$ -51.2° (c 3.0, $CHCl_3$), 75% ee)[5b] in 90% yield. A pheromone of the rove beetle, VII,[4] may be prepared from the chiral alcohols IVb and IVh. For instance, diimide reduction of (S)-IVh (87% ee) (KOOCN=NCOOK—CH_3COOH) followed by treatment with p-toluenesulfonic acid (benzene, reflux) gave (S)-VII ($[\alpha]_D^{22}$ -28.7° (c 0.30, CH_3OH), 86% ee) in 60% yield. Although the absolute stereochemistry of this pheromone has not yet been determined, it must possess the (S)-(-) or (R)-(+) configuration.



(R)-V, R = C≡C-n-C_8H_{17}
(R)-VI, R = (Z)-CH=CH-n-C_8H_{17}
(S)-VII, R = n-C_8H_{17}

The acetylenic alcohol (R)-IVb can be transformed to a pheromone of the dried bean beetle[16] and avenaciolide.[3] (S)-IVa serves as a building block for prostaglandin synthesis.[2] In addition, reaction of acetate of (S)-IVa with lithium dimethylcuprate is known to lead to (R)-2,3-nonadiene efficiently.[8a]

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