

Chiral Allenic Alcohols from Addition-Elimination Reactions of Acetylenes with Lithium Aluminium Hydride*

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(*R*)-(-)-3,4-Hexadien-1-ol, (-)-2,3-pentadien-1-ol and (-)-2-methyl-3,4-hexadien-2-ol with the maximum enantiomeric purities of 75, 90–95 and 90 %, respectively, were formed in lithium aluminium hydride reactions of mono-tetrahydropyranyl derivatives of the appropriate chiral acetylenic diols according to known reactions. (*S*)-(-)-4-Methoxy-2-pentyn-1-ol was also used in the same reaction. The yields varied between 35 and 65 %. Resolved (*S*)-(-)-3-butyn-2-ol was used as the starting material. It was shown that the allene-forming reactions around 0 °C proceed *via* a *trans*-addition of lithium aluminium hydride across the triple bond followed by a highly *anti*-selective 1,2-elimination of metal alkoxide. The overall stereoselectivity increases with the donor properties of the solvent, from diisopropyl ether through diethyl ether to tetrahydrofuran.

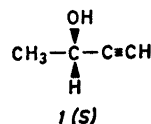
Chiral β -allenic alcohols are accessible through Landor's method, in which a 5-alkyl-2-penten-4-yn-1-ol is reduced with a chiral lithium aluminium hydride (LAH) complex,^{1,2} and through the LAH reduction of chiral 5-(tri-alkylammonio)-3-alkyn-1-ols.³ One chiral α -allenic alcohol (*3c*) was also prepared according to the last mentioned principle.³

The above methods give allenic alcohols of low enantiomeric purity (< 33 %) and the overall yields are usually moderate. Clearly, compounds of low enantiomeric purity are of limited usefulness in biochemical-pharmacological experiments in which enantioselective activity is to be determined. We have continued the search for more stereoselective prep-

arations of α - and β -allenic alcohols from a common intermediate and report here that the tetrahydropyranyl (THP) derivative of resolved 3-butyn-2-ol confers high enantiomeric purity to the final allenic products. The procedure gives α -allenic alcohols in good yields and with enantiomeric excess (ee) greater than 90 %; the method is less attractive for β -allenic alcohols although the stereochemical yield of the one prepared is the highest reported (75 % ee).

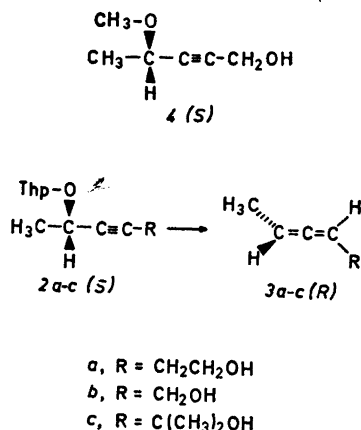
RESULTS

3-Butyn-2-ol was resolved via the (*S*)-(-)- α -methylbenzylammonium salt of the phthalic acid half ester.⁴ The enantiomeric purity of the liberated (*S*)-(-)-alcohol (*1*) was determined by NMR on the diastereomeric esters with (-)- α -methoxyphenylacetic acid. Methanol-*d*₄ as the solvent gave the largest difference in shifts of the diastereotopic terminal acetylenic hydrogens (δ 2.90 and 2.76); acetone-*d*₆, DMSO-*d*₆, benzene-*d*₆, pyridine, CDCl₃, CCl₄ and CD₃CN were inferior. The alcohol *1* had > 95 % ee, $[\alpha]_D^{25}$ -51.8° (c 3.8, dioxane). Weidman *et al.*⁴ reported $[\alpha]_D^{24}$ -40.3° (c 3.2, dioxane) for the same alcohol of 100 % ee as determined in NMR with a chiral shift reagent. Our alcohol had α_D^{25} -39.9° (neat), $[\alpha]_D^{25}$ -44.8° (neat, density 0.891).



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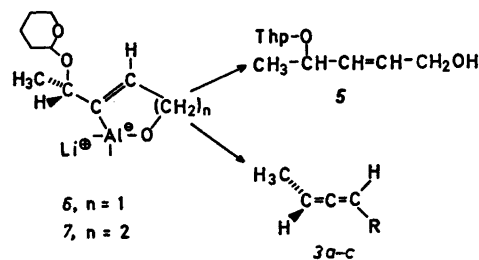
The resolved (*S*)-butynol was converted into the derivatives *2a-c* and *4* using standard procedures.⁵⁻⁷ The latter compounds were treated with LAH according to conditions given in Table 1. The reactions, which are all known from preparations of the racemic allenic compounds,^{5,8,9} gave the chiral allenes *3a-c*.

The absolute configuration of the allene *3a* is known.¹ Alcohols *3b* and *3c* can be assigned the (*R*)-configuration according to the Lowe-Brewster empirical rule¹⁰ (*cf.* Discussion).

The enantiomeric purity of the allenic alcohols *3a* and *3c* was determined with Eu(hfbc)₃ as described.³ The α -allenic alcohol *3c* had an enantiomeric excess of 90% while the β -allenic compound *3a* was less pure, 75% ee (estimated accuracy $\pm 3\%$). The application of the same shift reagent to the (*-*)-alcohol *3b* was less successful. A ratio of shift reagent to alcohol of 0.24 shifted the α -protons to δ 10.5 (broad

multiplet). Increased ratio resulted in considerable peak broadening. Decoupling of the C-2 proton at δ 8.5 simplified the signal to an apparent AB-system ($J_{AB}=11$ Hz) while decoupling of the C-4 proton revealed an ABX-system for the C1-C2 protons. In addition to the above pattern for the (*-*)-alcohol the racemic alcohol *3b* exhibits a narrow multiplet at δ 10.6. However, it might be concluded that the enantiomeric purity of *3b* ($[\alpha]_D^{25} -87.6^\circ$) prepared from *2b* in diethyl ether ought to be of the same order as that of *3c* (90% ee) which means that *3b*, $[\alpha]_D^{25} -90.7^\circ$ (run 2) would have around 94% ee.

Another LAH-reduction of racemic *2b* in ether at -10°C gave 14% of the allenol (\pm)-*3b* and 65% of compound *5* upon hydrolysis of the reaction mixture after 1 h. Through GLC-comparison with synthetic *cis-5* the isolated product *5* was shown to have the *trans*-configuration ($>97\%$). However, when the acetylene *2b* is treated with LAH in refluxing diethyl ether only allenol *3b* can be indicated.



The result indicates that at the lower temperature the reaction proceeds *via* an organometallic

Table 1. Lithium aluminium hydride reductions of compounds *2a-c* and *4* into the chiral allenes *3a-c*.

Run	Cpd	Solvent	Temp /°C	Allene yield %	$[\alpha]_D^{25}$ (c, MeOH)
1	<i>2a</i>	THF	Reflux	<i>3a</i> (35) ^a	-62.5° (7.7)
2	<i>2b</i>	THF	24°	<i>3b</i> (50) ^a	-90.7° (9.5)
3	<i>2b</i>	Et ₂ O	Reflux	<i>3b</i> (65)	-87.6° (9.5)
4	<i>2b</i>	(i-C ₄ H ₉) ₂ O	20°	<i>3b</i> (50) ^a	-83.9° (9.1)
5	<i>2c</i>	Et ₂ O	Reflux	<i>3c</i> (60)	-87.1° (12.2)
6	<i>2c</i>	Et ₂ O	0°	<i>3c</i> (54)	-87.4° (12.3)
7	<i>4</i>	Et ₂ O	Reflux	<i>3b</i> (40) ^a	-73.6° (8.4)

^a Purified further by preparative GLC.

intermediate **6** having the indicated *trans* stereochemistry over the double bond. The reaction of **2b** in diisopropyl ether at 0 °C also takes place *via* the intermediate **6** (>96% *trans*).

DISCUSSION

The overall stereochemical course of the reaction (*S*)-**2a**→(*R*)-**3a** is a predominant (to approximately 87%) attack by hydride on the same side of the propargylic system from which the leaving group departs *i.e.* overall *cis*-substitution. Provided the (*R*)-configurations assigned to **3b** and **3c** are correct the same stereochemistry predominates in their formation from **2b**, **2c** and **4**, for **3c** from **2c** to the extent of more than 95%. The assignment of absolute configurations to disubstituted allenes according to the Lowe-Brewster rule has so far only failed for 1,2-cyclononadiene.¹¹ The allenes **3b** and **3c**, unlike 1,2-cyclononadiene, do not present any conformational complications and therefore there is no reason to question the present conclusion based on the Lowe-Brewster rule. Also the reasonable assumption that the same mechanism should be operative in, *e.g.*, **2b**→**3b** as in **2a**→**3a** leads to the same assignment of configurations to the allenes **3b** and **3c**.

We recently have reported that compounds like **2a** upon treatment with LAH in THF are converted into β -allenic alcohols *via* intermediates like **7**. In contrast to **6** these latter intermediates decompose slowly even in refluxing THF.⁵ We have chosen to depict the intermediates **6** and **7** as cyclic compounds but this may not be their true nature; indeed, the very different stabilities of **6** and **7** give reason to suspect dissimilar structures.

LAH adds across the acetylenic triple bond of the present derivatives in a *trans* fashion (>96%) which is the normal course of this type of reaction;¹² *cis*-addition has been observed with diethyl ether as the solvent but never in THF alone.^{12b,c} In our cases this *trans*-addition leading to a transient intermediate may be operative also when no organometallic intermediate can be indicated, *viz.* for compounds **2b**, **2c** and **4** in refluxing ether. The fact that the stereoselectivity of the reaction **2c**→**3c** is the same at 0 and 33 °C (runs 5 and 6) indicates

that the mechanism has not changed with temperature. We have observed variation of the stereoselectivity with temperature for other types of leaving groups (to be published).

The addition of LAH to the triple bond is followed by a 1,2-elimination which for the THP-compounds **2b**–**c** follows a nearly exclusive *anti*-mechanism ($\geq 95\%$). Methoxy as the leaving group does not give the same uniform elimination mechanism as THP-oxy when occupying the same position (*cf.* runs 3 and 7). This difference can possibly be understood as facilitated interaction of the THP-oxy group, with its two oxygens, with the metal atom bound in the vinylic position (**6**). As revealed by studies of models little bridging *via* metal ions (aggregate formation) would be needed for the THP-oxy group to depart in an *anti* mode; the methoxy group clearly has difficulties in this respect leading to slightly increased *syn*-elimination. Research on *E2* reactions in low polar solvents has evidenced the importance of contact between the leaving group and the metal atom of the base.^{13,14} The formation of aggregates (of potassium butoxide) was used to explain preferred *anti*-eliminations in toluene.¹⁴

The β -allenic alcohol **3a** is formed with lower stereoselectivity (75% ee) than the α -allenic alcohols (90–95% ee) from similar THP derivatives *i.e.* the *syn/anti* ratios of the elimination step are different. This difference might be due to the unknown factors which make the intermediates **6** and **7** differ greatly in stability. Compound **7** is stable for hours in refluxing THF⁵ while **6** starts to decompose around 0 °C.

Obviously, the compounds **2a**–**c** are mixtures of diastereomers;⁸ however, this has no observable influence on the stereochemical yields.

The influence on stereoselectivity of the donor properties of the ether solvent is seen in the runs 2–4. This nice correlation represents varying *syn/anti* ratios in the 1,2-elimination reaction since the addition of LAH to the triple bond is *trans* (>96% at 0 °C) in all three cases. Obviously, THF is the solvent of choice for achieving high stereoselectivity. At the same time, however, THF seems to facilitate the LAH reduction of the α -allenic alcohols to conjugated dienes,²⁴ thus lowering the isolated yields.

The results presented here strongly support the proposed mechanism of the LAH-reduction of a 4,5-epoxy-2-alkyn-1-ol in THF.¹⁵ The authors obtained overall *cis*-substitution over the propargylic system and reasoned in agreement with the herein proven mechanism. Varying results (*cis* or *trans* substitution) have been obtained with other leaving groups (trialkylammonio, tosyloxy and hydroxy) in substitution reactions with LAH in propargylic systems.^{3,16} We will comment on these findings in future publications.

EXPERIMENTAL

General. The general IR and NMR instrumentation has been described.⁶ These spectra were routinely recorded and are in full agreement with the proposed structures. 100 MHz ¹H NMR spectra were taken with a JEOL JNM-FX 100.

The mass spectra were recorded as described.¹⁷ GLC analyses were run on a Varian 1700 instrument, equipped as described.¹⁷ Microanalyses were carried out at the Microanalytical laboratory, Royal Agricultural College, Uppsala. Unless otherwise stated optical rotations were measured in methanol with a Perkin-Elmer 141 spectropolarimeter. All reactions involving LiAlH₄ and Grignard reagents were performed under a nitrogen atmosphere.

Materials. (*S*)-(-)- α -Methylbenzylamine was of commercial origin, $[\alpha]_D^{20} - 36^\circ$ to -39° (neat). Eu(hfbc)₃ was purchased from Aldrich Chemical Co. This reagent was handled under a dry nitrogen atmosphere and NMR-solutions in CDCl₃ containing this shift reagent, were centrifuged prior to running the spectra. α -Methoxyphenylacetic acid was resolved *via* the (-)-ephedrine salt¹⁸ to give (*R*)-(-)- α -methoxyphenylacetic acid, $[\alpha]_D^{22} - 148.7^\circ$ (c 0.6, absolute ethanol). This acid was converted to the acid chloride and 3-butyn-2-ol was acylated according to a method described in the literature.¹⁹

(*S*)-(-)-3-Butyn-2-ol-(1) was prepared according to the literature.^{4,20} Reaction of this alcohol with (*R*)-(-)-methoxyphenylacetyl chloride (see *Materials*) gave the diastereomeric esters. NMR in methanol-d₄ indicated an enantiomeric purity of the alcohol of > 95 % (see Results).

(*S*)-(-)-3-Methoxy-1-butyne was prepared as described for similar compounds⁶ from 1 and dimethyl sulfate. Yield 46 %. B.p. 68 °C. $[\alpha]_D^{22} - 130.5^\circ$ (c 7.7). The racemic ether is known.²³

(*S*)-(-)-4-Methoxy-2-pentyn-1-ol (4) was prepared according to standard procedures,⁸ from the Grignard derivative of (-)-3-methoxy-1-butyne and gaseous formaldehyd. Yield 68 %,

b.p. 90 °C/2 kPa. $[\alpha]_D^{22} - 122.9^\circ$ (c 9.6). Anal. C₆H₁₀O₂: C, H.

(-)-3-(2-Tetrahydropyranyloxy)-1-butyne was prepared according to Ref. 7 from 1. Yield 86 %. $[\alpha]_D^{22} - 122.3^\circ$ (c 10.8).

(-)-5-(2-Tetrahydropyranyloxy)-3-hexyn-1-ol (2a) was prepared as described.²¹ Yield 75 %. $[\alpha]_D^{22} - 121.0^\circ$ (c 11.3).

(-)-4-(2-Tetrahydropyranyloxy)-2-pentyn-1-ol (2b) was prepared according to literature procedures.²¹ Yield 80 %. $[\alpha]_D^{22} - 118.7^\circ$ (c 11.4).

(-)-2-Methyl-5-(2-Tetrahydropyranyloxy)-3-hexyn-2-ol (2c) was prepared in analogy with similar compounds⁸ from (-)-3-(2-tetrahydropyranyloxy)-1-butyne (12.0 g; 0.08 mol) and acetone (4.5 g; 0.08 mol). Yield 79 %, b.p. 93 °C/40 Pa. $[\alpha]_D^{22} - 106.8^\circ$ (c 9.1). Anal. C₁₂H₂₀O₃: C, H.

Reactions of 2a-c and 4 with LiAlH₄.^{5,8} Approximately 0.03 mol of the acetylenes 2a-c and 4 in the appropriate solvent (see Table 1) was slowly added to a stirred suspension of LiAlH₄ (1.4 equiv. for the THP-oxy derivatives and 1.0 equiv. for the methoxy compound). The mixture was then kept at the indicated temperature and the reactions were followed by GLC. Work-up and distillation yielded the products 3a-c in Table 1. Some of these were isolated on GLC (20 % Carbowax 20 M) before measuring the rotation (Table 1). Reaction of racemic 2b with LiAlH₄ in ether at -10 °C for 1 h gave 14 % racemic 3b and 65 % of *trans*-4-(tetrahydro-2-pyranyloxy)-2-penten-1-ol (*trans*-5), which was isolated by preparative GLC (20 % SE-30) and identified by IR, NMR and MS.

cis-4-(2-Tetrahydropyranyloxy)-2-penten-1-ol (*cis*-5) was prepared by hydrogenation²² of racemic 2b. The product was isolated and characterized as described for the *trans*-compound. Comparison of *cis*- and *trans*-5 was made by GLC on 5 % OV 25; the ratio of retention times *trans/cis* at 165 °C was 1.5.

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Note added in proof: Dr. G. R. Sullivan of Stanford Magnetic Resonance Laboratory, Stanford University, has obtained resolution of the α -protons of the α -allenic alcohol 3b using Eu(dcm)₃ [Whitesides *et al.* *J. Am. Chem. Soc.* 96 (1974) 1038] in deuteriochloroform (enantiomeric shift difference 24 Hz). The enantiomeric purity of 3b, $[\alpha]_D - 83.90$, was estimated to be 80-90 %, *i.e.* the same alcohol with $[\alpha] - 90.7^\circ$ (run 2) should be very close to 100 % optically pure. We are most grateful to Dr. Sullivan for running the spectrum.

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