# Ethynyl Alcohol Precursors to Methylene Lactones

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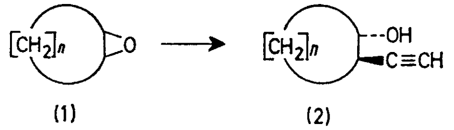
*Summary* *trans*-2-Ethynyl substituted alcohols can be obtained by treatment of epoxides with ether-stabilised methyl ethynyl alanes; a *cis* analogue, obtained by oxidation and stereoselective reduction, has been converted into the corresponding *cis* ring-fused methylene lactone.

SINCE our palladium-catalysed synthesis[1] of α-methylene lactones requires 2-ethynyl substituted alcohols as substrates, we have explored general synthetic routes to them. While the more reactive cyclic epoxides may be converted into *trans*-2-ethynyl alcohols by Li(en)C≡CH (en = ethylenediamine) in dimethylsulphoxide[2] or hexamethylphosphoramide,[1,3] the strongly basic conditions and generally slow reaction rates preclude its use as a general synthetic method. A more promising approach is suggested by the work of Fried, *et al.*, in which dialkyl alkynyl alanes ($R^1_2AlC{\equiv}CR^2$, $R^1$ = Me, Et, $R^2 \neq H$) in non-polar solvents rapidly convert epoxides into *trans*-2-alkynyl substituted alcohols.[4]

The acidic proton on an ethynyl group makes it impossible to prepare an analogous reagent with $R^2$ = H, and attempts to prepare uncomplexed $R^1_2AlC\equiv CH$ invariably produce polymeric materials.[5–8]

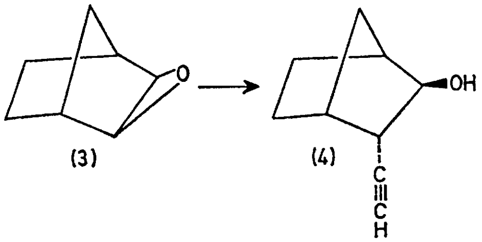
However, a number of ethynyl aluminium complexes are stable when complexed with donor ligands.[6,8,9] We have prepared several ethynyl alkyl aluminium compounds in complexing solvents, and have investigated their ability to convert epoxides into *trans* ethynyl alcohols. Diethyl ether was the most useful complexing agent, presumably because it is readily displaced by epoxides; methyl aluminium chlorides were the most useful and readily available precursors. The resulting solutions of $Me_nAl(C\equiv CH)_{3-n}$-$Et_2O$ ($n$ = 1 or 2) react rapidly at room temperature with most epoxides.

Yields varied somewhat among the methyl aluminium chlorides obtained from different sources. However, a standardized and effective reagent can be prepared from $Me_3Al_2Cl_3$ (checked for purity by n.m.r. spectroscopy: Me–Al signals at $\tau$ 10·51 and 10·73 in ether solution).[10] After treatment with NaC≡CH in ether for 5 h at room temperature and removal of NaCl, n.m.r. spectra showed sets of signals at $\tau$ 8·12 and 10·87, and 8·03 and 10·80, assigned to the etherates of $Me_2AlC\equiv CH$ and $MeAl(C\equiv CH)_2$, respectively. Addition of toluene and removal of all but the co-ordinated ether yielded a solution of the ethynylaluminium reagent into which a solution of epoxide (mole ratio epoxide : Al 1 : 1·4) in toluene was then added dropwise. The reaction is more effective at concentrations >5 M.



(1) (2)

a; $n$ = 3
b; $n$ = 4
c; $n$ = 5
d; $n$ = 6



(3) (4)

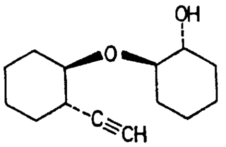
TABLE

| Epoxide | Time | % Yield of *trans* ethynyl alcohol[a] |
|---|---|---|
| (**1a**) | 40 min | 36(44) |
| (**1b**) | 40 min | 53(66)(62)[b] |
| (**1c**) | 2 h | 20(27) |
| (**1d**) | 24 h(50 °C) | 4(9) |
| (**3**) | 2 h | 44(53) |

[a] Yield from g.l.c. analysis with reagents characterized as described in the text; yields in parentheses were the highest obtained with dimethylaluminium chloride, from various sources, as starting material. [b] Isolated yield.

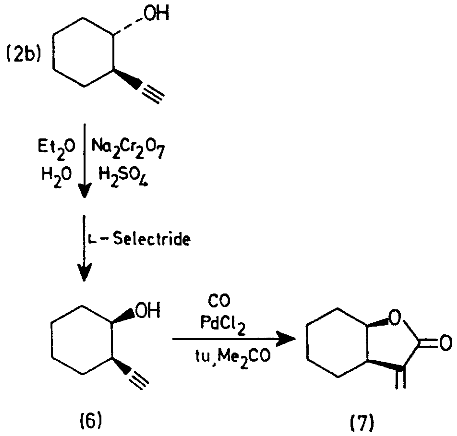
Examples are shown in the Table. While the best results were obtained with cyclohexene oxide (**1b**), the reagent even produces some ethynyl alcohol from epoxides prone to transannular reactions under basic conditions and for which Li(en)C≡CH is therefore unsuitable. For example, *exo*-norbornene oxide (**3**) gave no *trans*-2-ethynyl alcohol (**4**) even after prolonged stirring with Li(en)C≡CH in dimethylsulphoxide; a similar lack of success has been reported with (**1d**).[2c]

The major byproducts with the alane reagent were ethers such as (**5**), presumably formed by the attack of the product alkoxide on the unchanged epoxide. The ethynyl alcohols are easily separated by distillation. It is unclear why this side reaction (which addition of the epoxide to the alane minimizes but does not eliminate) should occur more readily with ethynyl alanes than with longer-chain alkynyl groups.[4]



(5)

*cis*-Ring fused methylene lactones are also important natural products,[11] and these may be made *via* inversion of the stereochemistry of the *trans*-compounds. *E.g.*, *trans*-2-ethynylcyclohexanol (**2b**) was first oxidised (two-phase chromic acid)[2b,12] to the unstable ketone, which was then reduced with L-Selectride[13] to *cis*-2-ethynyl cyclohexanol (**6**) (51% yield; stereoselectivity *ca.* 95%).† Palladium



(tu = thiourea)

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† B.p. 45 °C at 0·2 mmHg; m.p. of 3,5-dinitrobenzoate 104—105 °C. All new compounds were characterized by n.m.r. and i.r. spectra and elemental analysis or high-resolution mass spectrometry.

chloride, thiourea, and carbon monoxide in acetone[1] converted (**6**) into the known *cis* ring-fused methylene lactone (**7**) (62%). The overall yield of (**7**) from cyclohexene oxide (**1b**) was 21%.

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[1] J. R. Norton, K. E. Shenton, and J. Schwartz, *Tetrahedron Letters*, **1975**, 51.

[2] (a) E. Casadevall, J.-C. Jallageas, L. Mion, M. Mion, and P. Moreau, *Compt. rend.*, 1967, **265**, 839; (b) R. G. Carlson and D. E. Henton, *Chem. Comm.*, 1969, 674; (c) R. G. Carlson, J. H.-A. Huber, and D. E. Henton, *ibid.*, 1973, 223.

[3] A. B. Holmes, R. A. Raphael, and N. K. Wellard, *Tetrahedron Letters*, **1976**, 1539.

[4] J. Fried, J. C. Sih, C. H. Lin, and P. Dalven, *J. Amer. Chem. Soc.*, 1972, **94**, 4343; J. Fried and J. C. Sih, *Tetrahedron Letters*, **1973**, 3899; J. Fried, C.-H. Lin, and S. H. Ford, *ibid.*, **1969**, 1379.

[5] P. Parrini and P. Pansini, Fr. P. 1,343,923 (*Chem. Abs.*, 1964, **61**, 1892g).

[6] G. Wilke and W. Schneider, *Bull. Soc. chim. France*, 1963, 1462.

[7] H. Demarne and P. Cadiot, *Bull. Soc. chim. France*, 1968, 205.

[8] H. Lehmkuhl and K. Ziegler, in Houben-Weyl, 'Methoden der Organischen Chemie,' Vol. XIII, Part 4, Georg Thieme Verlag, Stuttgart, 1970, pp. 157 and 158, and refs. therein.

[9] T. Mole and E. A. Jeffery, 'Organoaluminium Compounds,' Elsevier, Amsterdam, 1972, pp. 274—281; H. Demarne and P. Cadiot, *Bull. Soc. chim. France*, 1968, 211; 216.

[10] J. Mole, *Austral. J. Chem.*, 1964, **17**, 1050.

[11] S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Medicin. Chem.*, 1971, **14**, 1147.

[12] H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, 1961, **83**, 2952.

[13] H. C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, 1972, **94**, 7159.