Tetrahedron Vol. 42, No. 19, pp. 5451 to 5456, 1986
Printed in Great Britain.

0040-4020/86 $5.00+.00
Pergamon Journals Ltd.

STEREOSELECTIVE SYNTHESIS OF POLYOLS PRECURSORS BY ALLYL SULPHINYL ANION ADDITION TO CHIRAL ALKOXY ALDEHYDES

RITA ANNUNZIATA, MAURO CINQUINI,* FRANCO COZZI,* LAURA RAIMONDI and STEFANIA STEFANELLI

Centro CNR e Dipartimento di Chimica Organica e Industriale dell'Università, Via Golgi 19, I-20133 Milano, Italy.

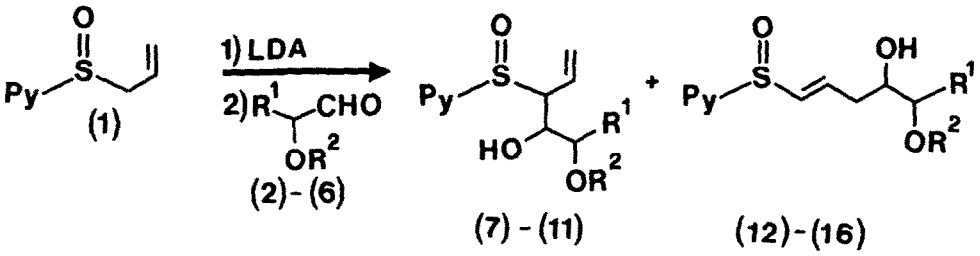
(*Received in UK* 28 *July* 1986)

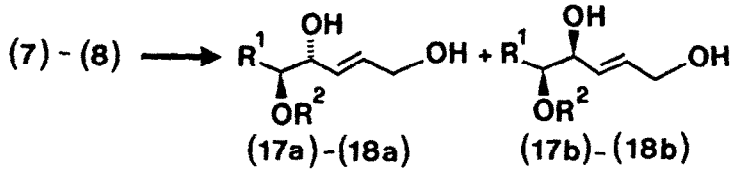
Abstract. Tandem condensation of chiral α-alkoxy and α,β-dialkoxy aldehydes with allylic sulphinyl anion, and thiophile promoted desulphurization of the resulting α-substituted allylic sulphoxide afford (E)-5-alkoxy-(or 5,6-dialkoxy)-2-alkene-1,4-diols, advanced polyols precursors, the major stereochemical path occuring via a Felkin-Ahn (non chelation control) mode.

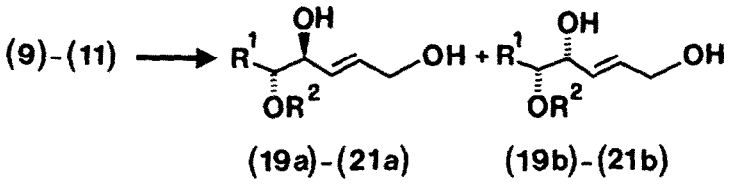
A variety of stereocontrolled modifications of allylic alcohols[1] makes the stereodefinite introduction of this functional group in organic substrates a useful synthetic tool. Among the available routes for the synthesis of allylic alcohols, the approach which exploits allylic sulphoxides (Mislow-Evans reaction)[2,3] appears simple and versatile. We here report that this method can be used to insert stereoselectively a $CH=CH-CH_2OH$ moiety in chiral α-alkoxy and α,β-dialkoxy aldehydes, to give the corresponding (E)-2-alkene-1,4-diols, advanced precursors for the synthesis of polyols and sugars.

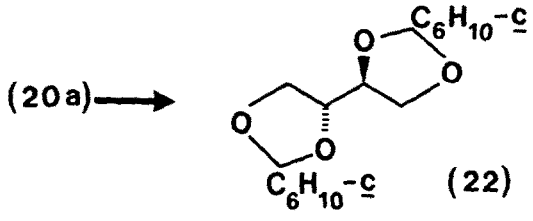
In line with the analogous reaction sequence reported for chiral but racemic α-methyl aldehydes,[4] in preliminary experiments we tested allyl-p-tolyl sulphoxide. Unfortunately this substrate did not allow a good level of α-regiocontrol in the condensation with alkoxy aldehydes, and chemical yields were poor. Having in mind that noticeable improvement in selectivity had been achieved in the alkylation of allylic sulphides by using ligands at sulphur capable of cation coordination,[2,5] we then turned our attention to allyl 2-pyridyl sulphoxide (1), which proved to be a suitable substrate. Indeed, metallation of (1), at -78°C, followed by addition of 3.0 mol. equiv. of aldehydes (S)-(2), (S)-(3), (R)-(4), (R)-(5), and (±)-(6) gave α-adducts (7)-(11) together with minor amounts of their γ-counterparts (12)-(16) with α:γ adducts ratios ranging from 6:1 to 10:1 by ^{1}H-NMR analysis of the mixture.

In order to avoid diastereoisomeric enrichment which can occur in the isolation of the α-adducts, and to minimize retroaldol-type processes,[4] the crude α/γ mixtures were treated with an excess of trimethylphosphite which quenched the allylic sulphoxide-sulphenate equilibrium, to afford diastereo-









Py = 2-pyridyl

(2), (7), (12), (17a,b)	R^1 = Me	R^2 = CH_2Ph
(3), (8), (13), (18a,b)	R^1 = Me	R^2 = $SiMe_2Bu$-t
(4), (9), (14), (19a,b)	R^1 = CH_2OCH_2Ph	R^2 = CH_2Ph
(5), (10), (15), (20a,b)	R^1,R^2 = CH_2-O-(C_6H_{10}-c)-	
(6), (11), (16), (21a,b)*	R^1,R^2 = CH(Me)-O-(C_6H_{10}-c)-	

* For the compounds derived from (6) only one enantiomer is shown for simplicity.

isomeric mixtures of (E)-diols (17a,b)-(21a,b). Chemical yields and diastereoisomeric ratios are collected in Table 1.

The stereochemical outcome of the process requires a few comments. As mentioned above the diols (17a,b)-(21a,b) are obtained exclusively in the (E) form, in agreement with most of the observation for the synthesis of allylic alcohols from allylic sulphoxides.[2-4] Diols (17a,b)-(21a,b) are produced in diastereoisomeric ratios that range from 2.5:1 for (17a,b) to 6.5:1 for (20a,b), evaluated by high field ^{1}H or ^{13}C NMR spectroscopy.

The stereoselectivity of the process seems to depend mainly on the steric bulkiness of the α-alkoxy substituent rather than on the presence of one or two alkoxy groups on the aldehyde. Thus the diastereoface selection is similar for (2) and (4) (R^2= CH_2Ph) and doubles on passing to aldehyde (3) that features a bulkier R^2 group (R^2= $SiMe_2Bu^t$) and to the sterically demanding acetal-type substituent of (5) and (6).

These values favourably compare with those observed by Uenishi[6] in the reaction of aldehyde (3) with alkyl p-tolyl sulphoxides, diastereoisomeric ratios ranging from 1:1 to 2.2:1 depending on the nature of the alkyl group and the absolute configuration of the sulphoxide.

In order to rationalize the stereochemical outcome of the process, we tentatively propose that the predominant isomers of diols (17a,b)-(21a,b) are produced by the attack of a large and sterically requiring α-allyl sulphinyl anion[4] on the aldehyde in a Felkin-Anh (non-chelation controlled) mode[7] which leads to anti[8] products. This interpretation is in agreement with previous observations for additions of lithium reagents to chiral alkoxy aldehydes.[9] Furthermore, the presence of strongly coordinating pyridine nitrogen and sulphinyl oxygen[2,10] should markedly decrease the chelating ability of lithium cation towards alkoxy aldehydes.

The anti configuration of the major isomers of (17a,b) and (18a,b) was confirmed by the ^{13}C chemical shift values of the methyl signal which resonates at higher fields with respect to that of the minor ones, as already observed in related substrates.[11]

Further evidence of the stereochemical result was achieved by the unambiguous determination of the relative configuration of the major diol (20a), obtained starting from (R)-(5). Ozonization of pure (20a), $[\alpha]_{436}^{23}$ - 1.7° (c 1 in $CHCl_3$), followed by reductive work-up and ketalization with cyclohexanone gave the expected meso-(22), m.p. 89-90°C, in 60% overall yield, thus showing the anti configuration of the precursor (20a).

Thus allyl 2-pyridyl sulphoxide can efficiently be used as a synthon for the regio- and stereocontrolled insertion of an allylic alcohol moiety into α-alkoxy or α,β-dialkoxy aldehydes O-protected with bulky groups,[=/=] with predictable anti stereochemistry of the resulting unsaturated diols. The natural tendency of

[=/=] Unfortunately the extension of this method to chiral, protected α-amino aldehydes resulted in poor chemical yields.

alkoxycarbonyl compounds to react via a chelation controlled model[6,9,11] is such that the achievement of good extent of Felkin-Ahn (non chelation controlled) stereoselectivity is a difficult task to address, and only recently successful examples have been reported.[9]

Table 1. Synthesis of (E)-diols (17a,b)-(21a,b) from (1).

Product	R^1	R^2	Yield %[a]	(a/b) ratio
(17a,b)	Me	CH_2Ph	51	2.5:1[b]
(18a,b)	Me	$SiMe_2Bu$-t	40	5.5:1[b]
(19a,b)	CH_2OCH_2Ph	CH_2Ph	68	3.0:1[b]
(20a,b)	-CH_2O-(c-C_6H_{10})-		60	6.5:1[c]
(21a,b)	-CH(Me)O-(c-C_6H_{10})-		60	6.0:1[b,c]

[a] Overall isolated yield from (1).
[b] As determined by ^{1}H-NMR spectroscopy on the (a,b) mixtures.
[c] As determined by ^{13}C-NMR spectroscopy on the (a,b) mixtures.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian XL 300 instrument, using tetramethylsilane as internal standard and $CDCl_3$ (for ^{1}H) or CD_2Cl_2 (for ^{13}C) as solvent. Infrared spectra were recorded on a Perkin-Elmer 457 spectrometer. Elemental analyses were performed with a Perkin Elmer 240 instrument. Silica gel was used for analytical and flash chromatography; organic extracts were dried over sodium sulphate and filtered before removal of the solvent under reduced pressure. THF was distilled from $LiAlH_4$, MeOH from Mg turnings, diisopropylamine from CaH_2. All reactions employing anhydrous solvents were run under Argon. Aldehydes were purified immediately before us. Aldehydes (S)-(2),[12] (S)-(3),[13] (R)-(4),[14] (R)-(5)[15] were prepared as described. Racemic cis-1,4-dioxaspiro-4,5-decane-2-carboxyaldehyde-3-methyl (6)[16,17] was prepared by osmylation of (E)-ethylcrotonate (cat. OsO_4, trimethylamine N oxide, THF:H_2O 9:1, RT, 5 h), diol protection (cyclohexanone, cat. PTSA, toluene, reflux), $LiAlH_4$ reduction, and Swern oxidation. Sulphoxide (1) was prepared by periodate oxidation of the corresponding sulphide.[18] It had n_D^{29}= 1.5690. Found: C% 57.41; H% 5.38; N% 8.43. C_8H_9NOS requires: C% 57.46; H% 5.42; N% 8.38. ^{1}H NMR: δ 7.25-8.60 (m, 4H, aromatic protons); 5.05-5.95 (m, 3H, CH=CH_2); 3.49-4.05 (m, 2H, CH_2-SO).

General procedure for the synthesis of (17a,b)-(21a,b).

To a stirred solution of diisopropylamine (1.1 mmol, 0.140 ml) in THF (10 ml), n-BuLi (1.1 mmol; approximately 1.3 M in hexane) was added dropwise. After 10 min stirring at 0°C a THF (2 ml) solution of (1) (1.0 mmol, 167 mg) was added dropwise. After 30 min stirring at -78°C aldehyde (3.0 mmol) was added in one

portion; after 2 min the reaction was quenched by addition of glacial acetic acid (0.100 ml) and the mixture warmed up to room temperature. Usual work up afforded mixture of α- and γ-adducts. This was dissolved in MeOH (5 ml) and trimethylphosphite (2 ml) and heated at 50°C overnight under Argon. The reaction mixture was concentrated under vacuum and the crude product purified by flash chromatography (SiO_2, diethylether/ethyl acetate as eluant). Diols (17a,b)-(21a,b) were obtained as mixture of diastereoisomers: they were thick oils that eventually solidified in the freezer.

(E)-5-Benzyloxy-2-hexene-1,4-diol (17a,b). Found: C% 70.13; H% 8.23. $C_{13}H_{18}O_3$ requires: C% 70.24; H% 8.16. ^{1}H NMR: δ 7.26-7.36 (m, 5H, aromatic protons); 5.63-5.97 (m, 2H, $J_{CH=CH}$= 14.8 Hz, HC=CH); 4.43-4.68 (m, 2H, CH_2Ar); 4.20-4.25 and 3.95-4.01 (2m in 2.5:1 ratio, 1H, CH-OH of (17a) and (17b), respectively); 4.11 (d, 2H, J = 5.0 Hz, CH_2-OH); 3.55-3.62 and 3.38-3.47 (2m in 2.5:1 ratio, 1H, CH-Me); 2.28 (bs, 2H, OH); 1.17 and 1.14 (2d in 1:2.5 ratio, 3H, J = 6.4 Hz, Me-CH of (17b) and (17a) respectively). Selected ^{13}C values for (17a) and (17b), respectively: δ 74.2, 75.9 (CH-OH); 78.2, 78.8 (CH-OR); 129.9, 130.1 (HC-CH=); 132.0, 132.8 (=CH-CH_2).

(E)-5-Dimethyl-t-butylsilyloxy-2-hexene-1,4-diol (18a,b). Found: C% 58.61; H% 10.57. $C_{12}H_{26}O_3Si$ requires: C% 58.49; H% 10.63. ^{1}H NMR: δ 5.63-5.97 (m, 2H, $J_{CH=CH}$= 15.6 Hz, HC=CH); 4.15 (d, 2H, J = 5.1 Hz, CH_2-OH); 4.03-4.06 and 3.63-3.68 (2m in 5.5:1 ratio, 1H, CH-OH of (18a) and (18b) respectively); 3.78-3.86 (m, 1H, CH-Me); 1.86 (bs, 2H, OH); 1.14 and 1.07 (2d in 1:5.5 ratio, 3H, Me-CH of (18b) and (18a) respectively); 0.86 (s, 9H, Me_3C); 0.06 (s, 6H, Si-Me_2). Selected ^{13}C values for (18a) and (18b), respectively: δ 71.6, 72.1 (CH-OH); 76.0, 76.5 (CH-OR); 129.8, 130.4 (CH-CH=); 131.8, 132.3 (=CH-CH_2).

(E)-5,6-Dibenzyloxy-2-hexene-1,4-diol (19a,b). Found: C% 73.06; H% 7.46. $C_{20}H_{24}O_4$ requires: C% 73.14; H% 7.37. ^{1}H NMR: δ 7.30-7.41 (m, 10H, aromatic protons); 5.72-5.95 (m, 2H, $J_{CH=CH}$= 16.0 Hz, HC=CH); 4.47-4.79 (m, 4H, CH_2-Ar); 4.35 and 4.26 (2m in 3.0:1 ratio, CH-OH); 4.11 (d, 2H, J = 5.2 Hz, CH_2-OH); 3.53-3.74 (m, 3H, CH-OR and CH_2-OR); 2.86 (bs, 2H, OH). Selected ^{13}C values for (19a) and (19b), respectively: δ 72.5, 71.9 (CH-OH); 80.7, 80.9 (CH-OR); 129.8, 129.9 (HC-HC=); 131.6, 132.0 (=CH-CH_2).

(E)-5,6-O,O-Cyclohexylidendioxy-2-hexene-1,4-diol (20a,b). Found: C% 63.01; H% 8.81. $C_{12}H_{20}O_4$ requires: C% 63.13; H% 8.83. ^{1}H NMR: δ 5.63-5.95 (m, 2H, $J_{CH=CH}$= 15.2 Hz, HC=CH); 4.16-4.22 (m, 1H, CH-OH); 4.10 (d, 2H, J = 5.0 Hz, CH_2-OH); 3.83-4.06 (m, 3H, CH-OR and CH_2-OR); 3.01 (bs, 2H, OH); 1.26-1.63 (m, 10H, C_6H_{10}). Selected ^{13}C values for (20a) and (20b) respectively: δ 71.8, 73.5 (CH-OH), 78.1; 78.6 (CH-OR); 128.7, 129.4 (HC-CH=); 132.0, 133.0 (=CH-CH_2); the average (20a): (20b) signal ratio is 6.5:1.

(E)-5,6-O,O-Cyclohexylidendioxy-2-hepten-1,4-diol (21a,b). Found: C% 64.49. H% 9.21. $C_{13}H_{22}O_4$ requires: C% 64.44; H% 9.15. ^{1}H NMR: δ 5.68-6.00 (m, 2H, $J_{CH=CH}$= 15.7 Hz, HC=CH); 4.31-4.35 (m, 1H, CH-OH); 4.17 (d, 2H, J = 5.1 Hz, CH_2OH); 4.06 (dq, 1H, J = 8.0 Hz, 6.0 Hz, CH-Me); 3.59 and 3.52 (2dd in 6.0:1 ratio, 1H, J = 8.0 Hz and J = 4.5 and 5.1 Hz, CH-OR of (21a) and (21b), respectively); 2.14 (bs, 2H, OH); 1.35-1.65 (m, 10H, C_6H_{10}); 1.28 and 1.25 (2d in 6.0:1 ratio, 3H, J

= 7.0 Hz, Me-CH of (21a) and (21b), respectively). Selected ^{13}C values for (21a) and (21b) respectively: δ 71.0, 71.8 (CH-OH); 84.1, 84.5 (CH-OR); 128.7, 129.7 (HC-CH=); 131.6, 132.2 (=CH-CH_2).

Conversion of (20a) to meso 1,2-3,4-bis-cyclohexylidene-butanetetrol (22). Flash chromatography of (20) with a 6:4 mixture of diethylether:ethylacetate as eluant afforded pure (20a), $[\alpha]_{436}^{23}$ = -1.7 (c1 in $CHCl_3$); 100 mg of (20a) were dissolved in absolute ethanol and treated at -78°C with a stream of ozone monitoring the reaction by TLC. After 20 min the reaction was over. Excess ozone was eliminated and to the crude mixture was added 5 fold excess of $NaBH_4$. After 2h at RT usual work-up afforded the crude diol which was converted into (22) by reaction with cyclohexanone (5 ml) in the presence of cat. $ZnCl_2$ at 60°C for 12 h. The product (74 mg, 60%) was obtained by flash chromatography (hexane:ethylacetate 9:1 mixture as eluant). It had m.p. 89-90°C and was optically inactive (c2 in $CHCl_3$) at all wavelenghts from 589 to 310 nm. Found: C% 68.25; H% 9.37. $C_{16}H_{26}O_4$ requires: C% 68.05; H% 9.28. ^1H NMR: δ 4.06- -4.12 (m, 2H, CH-O); 3.88-3.98 (m, 4H, CH_2-O); 0.93-1.63 (m, 20H, C_6H_{10}). Selected ^{13}C values: δ 23.8, 24.0, 25.1, 34.8, 36.5 67.2, 76.5, 109.9.

Acknowledgement. We thank Ministero Pubblica Istruzione - Rome for partial financial support of this work. One of us (S.S.) is the recipient of a fellowship from Accademia dei Lincei - Fondazione Donegani.

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