Tetrahedron Vol. 42, No. 19, pp. 5443 to 5450, 1986
Printed in Great Britain.

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

STEREOSELECTIVE SYNTHESIS OF (E)-2-ALKENE-1,4-DIOLS VIA METALLATED ALLYLIC SULPHOXIDES

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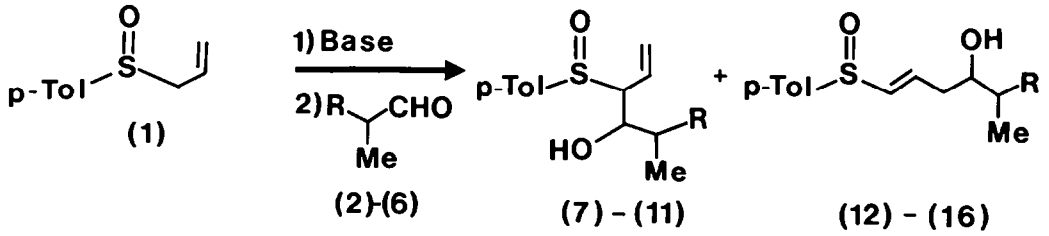
(*Received in UK* 28 *July* 1986)

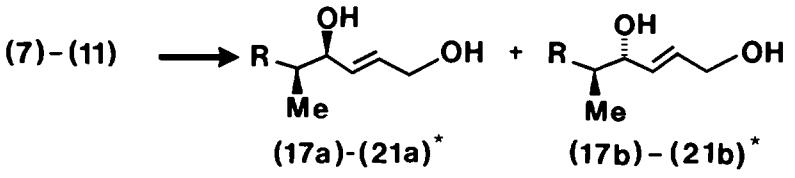
Abstract - Reaction of allyl sulphinyl anion with chiral α-methylaldehydes affords α- or γ-adducts in highly regiocontrolled fashion, depending on reaction conditions. From the α-adducts syn (E)-2-alkene-1,4-diols are obtained as major (d.r. 2:1 ~ 28:1) products by thiophile promoted desulphurization.

Allylic sulphoxides are a versatile class of reagents, their synthetic applications being related to the facile allylic sulphoxide-sulphenate rearrangement, the Mislow-Evans rearrangement.[1,2] Although the equilibrium is usually shifted far to the sulphoxide side,[1-4] in the presence of sulphenate esters trapping agents, rearranged allylic alcohols can cleanly be obtained from the corresponding sulphoxides.[1,2]

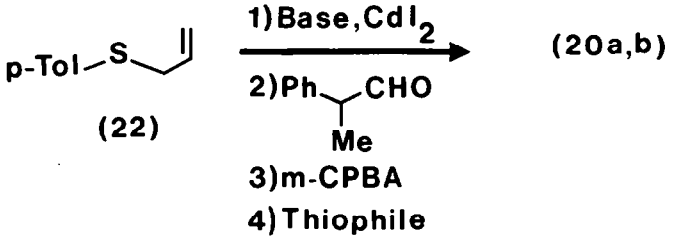
The elegant work by Evans[1] established the synthetic equivalence of an allyl sulphoxide anion with an allylic alcohol γ-anion: reaction with alkylating agents gives predominantly the α-product which on quenching with a thiophile affords the (E)-allylic alcohol since 1,3 allylic interactions unfavour the transition state leading to the (Z)-isomer.[1,2] Recently it has been shown[5-7] that, in the presence of HMPA, lithium derivative of allylic sulphoxides adds to cyclopentenone and related substrates exclusively in the γ-fashion affording the corresponding Michael-type adducts with excellent degrees of stereoselections.[5-7]

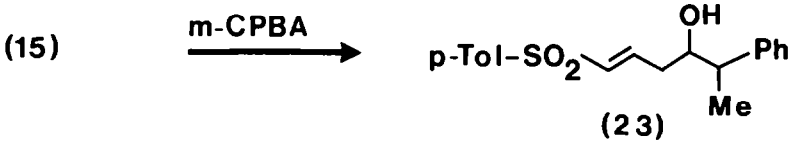
In contrast to the huge amount of work devoted to alkylation or reaction with Michael-acceptors of allylic sulphoxides, very little has been reported on their behaviour towards carbonyl compounds.[8,9] As described in a preliminary note,[10] we envisaged that the Mislow-Evans rearrangement could provide a key to the stereocontrolled insertion of an allylic alcohol moiety into organic molecules. In this line we reacted a series of chiral but racemic α-methyl aldehydes (2)-(6) with metallated allyl p-tolyl sulphoxide (1). The reaction affords mixtures of α(7)-(11) and γ(12)-(16) adducts. Treatment with $(MeO)_3P$ or Et_2NH of the α adducts (7)-(11) gave 2-alkene-1,4-diols (17a,b)-(21a,b) as mixtures





(2), (7), (12), (17a,b) R = Et
(3), (8), (13), (18a,b) R = i-Pr
(4), (9), (14), (19a,b) R = c-C_6H_{11}
(5), (10), (15), (20a,b) R = Ph
(6), (11), (16), (21a,b) R = 6-Methoxy-2-naphthyl





of diastereoisomers which, as expected,[1,2] were obtained exclusively in the (E)-configuration.

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* In the case of compounds (17a,b)-(21a,b) only one enantiomer is shown for simplicity.

The effective use of (1) as a synthon of $^{-}CH=CH-CH_2OH$ in the reaction with aldehydes requires that a useful degree of α / γ regiocontrol is achieved. To establish the conditions which maximize the formation of the α-product, a series of reaction was carried out on hydratropic aldehyde (5) in the presence of additives such as HMPA, DABCO, or crown ethers, at different temperatures, and with a variety of counterions (Table 1).

The experimental data indicate that the presence of substantial amounts of HMPA are essential in order to obtain a predominance of the α-product, while the use of metals "softer" than lithium leads to increasing amount of the γ-product, to the point that a complete reversal in regioselectivity was observed in the case of the allyl cadmium species. This trend is opposite to that reported for the reaction of carbonyl compounds with metallated allyl sulphides, since in this case the lithium derivative affords mainly the γ-adduct, while the α-product is the major one in the case of copper and zinc derivatives, and especially with boron, aluminium, titanium, tin, and cadmium species.[12-18]. For sake of completeness we examined the reaction of hydratropic aldehyde with metallated allyl p-tolyl sulphide (22): reaction of the cadmium derivative[16] with the carbonyl compound, followed by oxidation (mCPBA, -78°C, CH_2Cl_2) of the crude adduct to the sulphoxide level, and interception of the allylic sulphoxide-sulphenate rearrangement afforded the unsaturated diol (20a,b) with a stereoselection comparable to that observed in the reaction of (1) (see below), but in much lower chemical yield.

Table 1. Reaction of metallated (1) with (5) at -78°C

Solvent	Additive (mol.eq.)	Yield	α/γ ratio	(20a/20b)
THF[a]	-	83	1.1 :1	15:1
THF[a]	HMPA (1.1)	76	1.5 :1	28:1
THF	HMPA (1.1)	63	4.0 :1	28:1
Et_2O	HMPA (1.1)	78	3.0 :1	19:1
THF[b]	HMPA (1.1)	59	6.4 :1	14:1
THF	HMPA (4.4)	75	9.0 :1	28:1
THF	DABCO (1)	65	4.0 :1	12:1
THF	18-crown-6 (1)	61	1.3 :1	25:1
Et_2O	$MgBr_2$ (6)	45	1 :1.4	-[c]
Et_2O	CuI (6)	68	1 :1.5	-[c]
Et_2O	$ZnCl_2$ (6)	35	1 :7.8	-[c]
THF	CdI_2 (6)	68	1 :14.0	-[c]

[a] At -90°C. [b] At -40°C. [c] Not determined.

Having in hand the problem of regiocontrol, the question of stereoselection was addressed. Among the conditions employed for the reaction of hydratropic

aldehyde with metallated allyl sulphoxide, those which provide useful α/γ ratios also secure an excellent level of diastereoface selection (Table 1), and were thus employed for a series of chiral but racemic α-methyl aldehydes (Table 2).

Isolation of the α-adducts (7)-(11) (method A) usually resulted in slightly lower yields,[8,9] with respect to direct quenching with a thiophile of the crude α-γ mixture (method B); this, however, could not be extended to diols (18), (20) and (21), since these could not be separated from the γ-products (13), (15) and (16), respectively. The stereochemical result was unchanged on passing from method A to method B.

With the α-methyl aldehydes (2)-(6) employed, satisfactory levels of regioselection in favour of the α-adduct were always achieved, thus opening access to a series of (E)-2-alkene-1,4-diols.[=/=] The extent of stereoselection in the addition of metallated (1) to (2)-(6) is clearly related to the stereoelectronic effect of the R substituent at the stereocenter of (2)-(6), ranging from 2:1 (R=Et) up to 28:1 (R = Ph).

The syn[19] configuration of the major diastereoisomers (17a)-(21a) is suggested by spectroscopic evidences. Indeed compounds (17a)-(21a) always feature smaller values of CHOH-CHMe coupling constants (J = 5.1-6.0 Hz) with respect to their stereoisomeric counterparts (17b)-(21b) (J = 6.6-7 Hz), a trend previously observed for related compounds.[20]

Table 2. Synthesis of diols (17a,b)-(21a,b) from metallated (1) in THF in the presence of HMPA (4.4 molar equiv.) at -78°C.

Aldehyde	Product	Method	α/γ ratio[a]	Yield[b] %	a/b ratio
(2)	(17a,b)	A	6.1:1	40	2.1:1
(2)	(17a,b)	B	-	65	2.2:1
(3)	(18a,b)	A	10.0:1	40	5.1:1
(4)	(19a,b)	A	5.6:1	57	6.4:1
(4)	(19a,b)	B	-	61	6.4:1
(5)	(20a,b)	A	9.0:1	67	28.0:1
(6)	(21a,b)	A	9.0:1	40	10.0:1

[a] Ratio of α (7)-(11)/ γ (12)-(16) adducts. [b] Overall yield of (17a,b)-(21a,b) from (1).

Furthermore a trend was observed in the chemical shift values of some diagnostic signal of all the major (and minor) diastereoisomeric products: e.g. the Me-CH doublet resonates at lower field in the syn (major) products with respect to the anti (minor) ones, a behaviour not unprecedented.[20,21]

[=/=] The extent of regioselectivity strongly depends on the nature of the aldehyde: a lower α/γ ratio has been observed in the case of benzaldehyde and of isobutyraldehyde, an achiral equivalent of (2)-(6).

Finally in the case of compound (17a,b) a two-dimensional n.O.e. effect, observed using variable mixing times (0.1-0.4 s), strongly suggest the syn configuration for the predominant diastereoisomer.

These data, together with the observed increase in the extent of diastereoface selectivity in the reaction of (1) with aldehydes (2)-(6) on increasing the stereolectronic requirement of the R substituent, indicate that the major stereochemical path involves the attack at the carbonyl carbon of the electron rich and sterically demanding α-allyl sulphinyl anion in a Felkin-Ahn[22] mode. In line with this is the fact that definitely higher stereoselectivities were achieved in the case of metallated sulphoxide (1) with respect to the values observed in the addition of alkyl or allyl lithium derivatives to α-methyl aldehydes.[23,24]

Furthermore, m-CPBA oxidation of γ-adduct (15) afforded sulphone (23) as a 3.5:1 mixture of diastereoisomers: this shows that the less sterically requiring γ-allyl sulphinyl anion of (1) adds to (5) with the value of diastereoface selection generally observed for a "Cram-type" addition of an allyl lithium species to hydratropic aldehyde.[23,24]

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian XL 300 instrument, using tetramethylsilane as internal standard and $CDCl_3$ 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 and Et_2O were distilled from $LiAlH_4$, MeOH from Mg turnings, HMPA and diisopropylamine from CaH_2. All reactions employing anhydrous solvents were run under Argon. Aldehydes were distilled immediately before use. Compounds (2) and (5) are commercial products; aldehyde (3) was prepared according to a literature method;[25] aldehyde (4) was obtained in racemic form from (5) as described elsewhere;[19,26] aldehyde (6) (m.p. 59-61°C) was obtained in 60% yield by the corresponding carboxylic acid[27] by $LiAlH_4$ reduction to the alcohol and subsequent Swern oxidation. Found: C% 78.29; H% 6.63. $C_{14}H_{14}O_2$ requires: C% 78.48; H% 6.58. Sulphide (22) and sulphoxide (1) were prepared as described.[8]

General procedure for the condensation of (1) with aldehydes. To a stirred solution of diisopropylamine (1.1 mmol, 0.140 ml) in THF or Et_2O (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, 180 mg) was added dropwise. After 30 min stirring at -78°C a solution of the proper additive was added (see Table 1 for sulphoxide/additives molar ratios) and the mixture stirred for additional 15 min at -78°C. Finally, 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, which could be separated by flash chromatography (SiO_2, diethylether as eluant) or directly converted into diols (17)-(21). As mentioned in the text compound (10) was also prepared in 30% overall yield from sulphide (22) by metallation (THF, n-BuLi 1.1 mol equiv.) addition of CdI_2 (6.0 mol equiv.), condensation with (5) (3.0 mol equiv.) and mCPBA oxidation of the crude reaction mixture (CH_2Cl_2, -78°C).

General procedure for the synthesis of diols (17)-(21). A stirred solution of α- and γ-adducts mixture (or of pure α-adducts) in MeOH (5 ml) and trimethylphosphite or diethylamine (2 ml) was 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 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-Methyl-2-heptene-1,4-diol (17a,b). Found: C% 66.41; H% 11.27; $C_8H_{16}O_2$ requires: C% 66.62; H% 11.17. ^{1}H NMR: δ 5.62-5.84 (m, 2H, $J_{CH=CH}$= 15.0 Hz, HC=CH); 4.06 (d, 2H, J 4.7 Hz, CH_2-O); 3.87-3.96 (m, 1H, CH-O); 2.85 (bs, 1H, OH); 0.96-1.58 (m, 3H, CH-Me and CH_2-Me); 0.87 (t, 3H, J = 6.8 Hz, CH_2-Me); 0.85 and 0.83 (2d in 2.2:1 ratio, 3H, J = 6.7 Hz, Me-CH of (17a) and (17b), respectively). Selected ^{13}C values: δ 14.0 and 14.5 (Me-CH of (17a) and (17b), respectively); 40.5 (CH-Me); 75.7 and 76.1 (CH-O of (17a) and (17b), respectively).

(E)-5,6-Dimethyl-2-heptene-1,4-diol (18a,b). Found: C% 68.22; H% 11.55; $C_9H_{18}O_2$ requires: C% 68.31; H% 11.46. ^{1}H NMR: δ 5.66-5.88 (m, 2H, $J_{CH=CH}$= 15.0 Hz, HC=CH); 4.14 (d, 2H, J = 4.9 Hz, CH_2-O); 4.10 and 4.00 (2t in a 5.1:1 ratio, 1H, $J_{CHOH-CHME}$= 6.0 and 7.0 Hz, CH-O of (18a) and (18b), respectively); 2.05 (bs, 1H, OH); 1.21-1.95 (m, 2H, CH-Me and $CH(Me)_2$); 0.82-0.95 (two sets of two d, 6H, Me_2-CH); 0.82 and 0.73 (2d in 5.1:1 ratio, 3H, J = 6.5 Hz, Me-CH of (18a) and (18b), respectively). Selected ^{13}C values: δ 9.7 and 10.2 (Me-CH of (18a) and (18b), respectively); 44.6 (CH-Me); 74.4 (CH-OH).

(E)-5-Cyclohexyl-2-hexene-1,4-diol (19a,b). Found: C% 72.49; H% 11.17; $C_{12}H_{22}O_2$ requires: C% 72.68; H% 11.18. ^{1}H NMR: δ 5.68-5.86 (m, 2H, $J_{CH=CH}$= 16.0 Hz, HC=CH); 4.18 and 4.05 (2t, in a 6.4:1 ratio, 1H, $J_{CHOH-CHMe}$= 5.1 and 7.0 Hz, CH-O of (19a) and (19b), respectively); 4.16 (d, 2H, J = 4.7 Hz, CH_2-O); 3.43-3.58 (m, 1H, CH-Me); 0.90-2.00 (m, 12H, C_6H_{11} and OH); 0.87 and 0.74 (2d in 6.4:1 ratio, 3H, J = 6.6 Hz, Me-CH of (19a) and (19b), respectively). Selected ^{13}C values: δ 10.6 and 11.5 (Me-CH of (19a) and (19b), respectively); 43.9 (CH-Me); 73.8 and 74.0 (CH-O of (19a) and (19b), respectively).

(E)-5-Phenyl-2-hexene-1,4-diol (20a,b). Found: C% 75.00; H% 8.50; $C_{12}H_{16}O_2$ requires: C% 74.96; H% 8.39. ^{1}H NMR: δ 7.19-7.40 (m, 5H, aromatic protons); 5.54-5.75 (m, 2H, $J_{CH=CH}$= 15.4 Hz, HC=CH); 4.15 (t, 1H, $J_{CHOH-CHMe}$= 5.9 for (20a), CH-O); 3.93 (d, 2H, J = 4.5 Hz, CH_2-O); 2.76-3.00 (m, 2H, OH and CH-Me); 1.29 and 1.22 (2d in 28:1 ratio, 3H, J = 7.5 Hz, Me-CH of (20a) and (20b), respectively). Selected ^{13}C values: δ 15.8 and 17.7 (Me-CH of (20a) and (20b),

respectively); 45.7 and 46.1 (CH-Me of (20a) and (20b), respectively); 76.3 (CH-OH).

(E)-5-(6-Methoxy-2-naphthyl)-2-hexene-1,4-diol (21a,b). Found: C% 74.49; H% 6.95; $C_{16}H_{18}O_3$ requires: C% 74.39; H% 7.02. ^{1}H NMR: δ 7.11-7.71 (m, 6H, aromatic protons); 5.65-5.84 (m, 2H, $J_{CH=CH}$= 15.7 Hz, HC=CH); 4.32 and 4.24 (2t in 10:1 ratio, 1H, $J_{CHOH-CHMe}$= 5.8 and 7.0 Hz, CH-O of (21a) and (21b), respectively); 4.07 (d, 2H, J = 4.4 Hz, CH_2-O); 3.91 (s, 3H, CH_3-O); 2.98-3.07 (m, 1H, CH-Me); 1.63 (bs, 1H, OH); 1.40 and 1.32 (2d in 10:1 ratio, 3H, J = 7.7 Hz, Me-CH of (21a) and (21b), respectively). Selected ^{13}C NMR values: δ 15.8 and 17.3 (Me-CH of (21a) and (21b), respectively); 45.6 and 46.5 (CH-Me of (21a) and (21b), respectively); 76.2 (CH-OH).

(E)-6-(4-Methylphenyl)-sulphonyl-2-phenyl-5-hexene-3-ol (23). Sulphoxide (15) (0.1 mmol, 32 mg) was oxidized with mCPBA in CH_2Cl_2 at -78°C monitoring the reaction by TLC; usual work-up gave 26 mg of sulphone (23). Found: C% 69.30; H% 6.81; $C_{19}H_{22}O_3S$ requires: C% 69.06; H% 6.71. ^{1}H NMR: δ 7.05-7.73 (m, 9H, aromatic protons); 6.86 (m, 1H, C=CH-CH_2); 6.27 (d, 1H, $J_{CH=CH}$= 15.0 Hz, SO_2-CH=C); 3.67-3.95 (m, 1H, CH-O); 2.54-2.85 (m, 1H, CH-Me); 2.44 (s, 3H, Me-Ar); 2.10-2.36 (m, 2H, CH_2-CH); 1.25 and 1.16 (2d in 3.5:1 ratio, 3H, J = 6.7 Hz, Me-CH).

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.

REFERENCES

1 D.A. Evans and G.C. Andrews, Acc. Chem. Res., 1974, 7, 147, and references therein.

2 R.W. Hoffmann, Angew. Chem., Int. Ed. Engl., 1979, 18, 563, and references therein.

3 R. Tang and K. Mislow, J. Am. Chem. Soc., 1970, 92, 2100.

4 R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, and A. Restelli, Gazzetta, 1985, 115, 637.

5 M.R. Binns, R.J. Goodridge, R.K. Haynes, and D.D. Ridley, Tetrahedron Lett., 1985, 26, 6381, and references therein.

6 J. Nokami, T. Ono, S. Wakabayashi, A. Hazato, and S. Kurozumi, Tetrahedron Lett., 1985, 26, 1985.

7 D.H. Hua, G. Sinai-Zingde, and S. Venkataraman, J. Am. Chem. Soc., 1985, 107, 4088.

8 D.J. Antonjuk, D.D. Ridley, and M.A. Smal, Aust. J. Chem., 1980, 33, 2635.

9 D.D. Ridley and M.A. Smal, Aust. J. Chem., 1983, 36, 1049.

10 R. Annunziata, M. Cinquini, F. Cozzi, and L. Raimondi, J.Chem. Soc., Chem. Commun., 1986, 366.

[11] V.K. Aggarwal and S. Warren, Tetrahedron Lett., 1986, 27, 101.
[12] Y. Yamamoto, Y. Saito, and K. Maruyama, J. Organometal. Chem., 1985, 292, 311.
[13] Y. Yamamoto, H. Yatagai, Y. Saito, and K. Maruyama, J. Org. Chem., 1984, 49, 1096.
[14] Y. Ikeda, K. Furuta, N. Meguriya, N. Ikeda, and H. Yamamoto, J. Am. Chem. Soc., 1982, 104, 7663.
[15] K. Oshima, H. Yamamoto, and H. Nozaki, Bull. Chem. Soc. Japan, 1975, 48, 1567.
[16] P. Brownbridge and S. Warren, J. Chem. Soc., Perkin Trans. I, 1977, 1131.
[17] L. Widler, T. Weber, and D. Seebach, Chem. Ber., 1985, 118, 1329, and references therein.
[18] J.F. Biellmann and J.B. Ducep, Org. React., 1982, 27, 1.
[19] C.H. Heathcock,in "Asymmetric Synthesis", J.D. Morrison, Ed., Academic Press, Orlando, 1984, vol. 3, p. 111.
[20] F. Sato, M. Kusakabe, T. Kato, and Y. Kobayashi, J. Chem. Soc., Chem. Commun., 1984, 1331, and references therein.
[21] Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, and K. Maruyama, Tetrahedron, 1984, 40, 2239.
[22] N.T. Anh, Top. Curr. Chem., 1980, 88, 145.
[23] J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions", Prentice Hall, New York, 1971.
[24] Y. Yamamoto, T. Komatsu, and K. Maruyama, J. Am. Chem. Soc., 1984, 106, 5031, and references therein.
[25] G. Stork and S.R. Dowd, J. Am. Chem. Soc., 1963, 85, 2178.
[26] D.J. Cram and F.D. Greene, J. Am. Chem. Soc., 1953, 75, 6005.
[27] S.W. Markowicz, Pol. J. Chem., 1979, 53, 157.