Nucleophilic Attack on a Carbonyl Group Conjugated to a Chiral Centre: A Search For a Vinylogous Cram's Rule†

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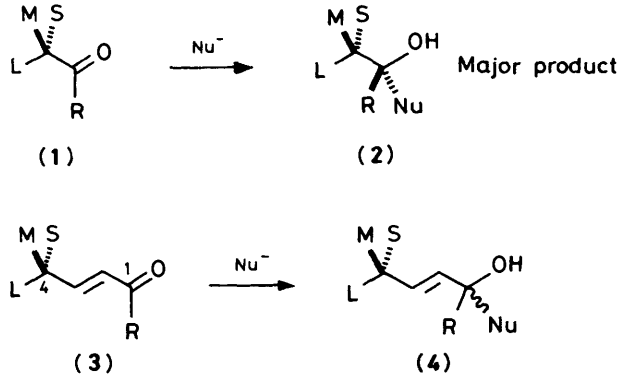
In a search for a vinylogous version of Cram's rule, 1,4-diphenylbut-2-ene-1,4-dione (**5**), 4-methoxy-1,4-diphenylbut-2-en-1-one (**9**), and hex-3-ene-2,5-dione (**13**) are found to be reduced with low or negligible diastereoselectivity. Similarly, the phenyl Grignard reagent showed no diastereoselectivity in its reaction with 4-methoxy-4-phenylbut-2-enal (**12**)

The diastereoselectivity of nucleophilic attack on a carbonyl group adjacent to a chiral centre is covered by Cram's rule.[1] The explanation for the diastereoselectivity, which usually takes place in the sense (**1**) ⟶ (**2**), has been much discussed, with notable contributions by Cornforth,[2] Karabatsos,[3] Felkin,[4] Anh,[5] and Houk.[6] However, there is much that is still uncertain and especially uncertain is the extent to which diastereoselectivity is governed by steric or electronic factors. We were intrigued by the possibility of a vinylogous Cram's rule, in the sense of a reaction of the type (**3**) ⟶ (**4**), in which the chiral centre (C-4) is held spatially away from the centre undergoing reaction (C-1), but is conjugated to it. In this situation, electronic information might reasonably be relayed to the prochiral centre (C-1), but steric information cannot (at least it cannot when the groups on the chiral centre are not unusually large).



Results and Discussion

The Search for a Vinylogous Cram's Rule.—There is, in the literature, one report of high diastereoselectivity of this type: the reduction of the diketone (**5**) with lithium aluminium hydride is reported[7] to give very largely a single diol, together with some 4-hydroxy-1,4-diphenylbutan-1-one (see Scheme 1). Later work[8] assigned the *meso* configuration (**7**) to this diol. It was this report which led us into the present work, so we repeated the lithium aluminium hydride reduction, but analysed the crude reaction mixture using ^{13}C n.m.r. spectroscopy. We find that the diols (**7**) and (**8**) are produced in the disappointingly low ratio of *ca.* 60:40. We also find the same diols in the same ratio when we use di-isobutylaluminium hydride in place of lithium aluminium hydride. The diol (**7**) is much less soluble than the diol (**8**), crystallising out from the reaction mixture with great ease. It seems likely that the earlier work gave a misleading impression, because one product was so much easier to isolate than the other. Indeed, the 'racemic' diol (**8**) has not been fully characterised before our work. Thus, there is very little transmission of chiral information through the double bond, as one might have expected from another report in the literature: in Corey's prostaglandin synthesis,[9] the C-15 ketone was reduced by zinc borohydride with no measurable diastereoselectivity, except when a most unusually large protecting group was used to shield one face of the ketone group in a clearly steric manner.

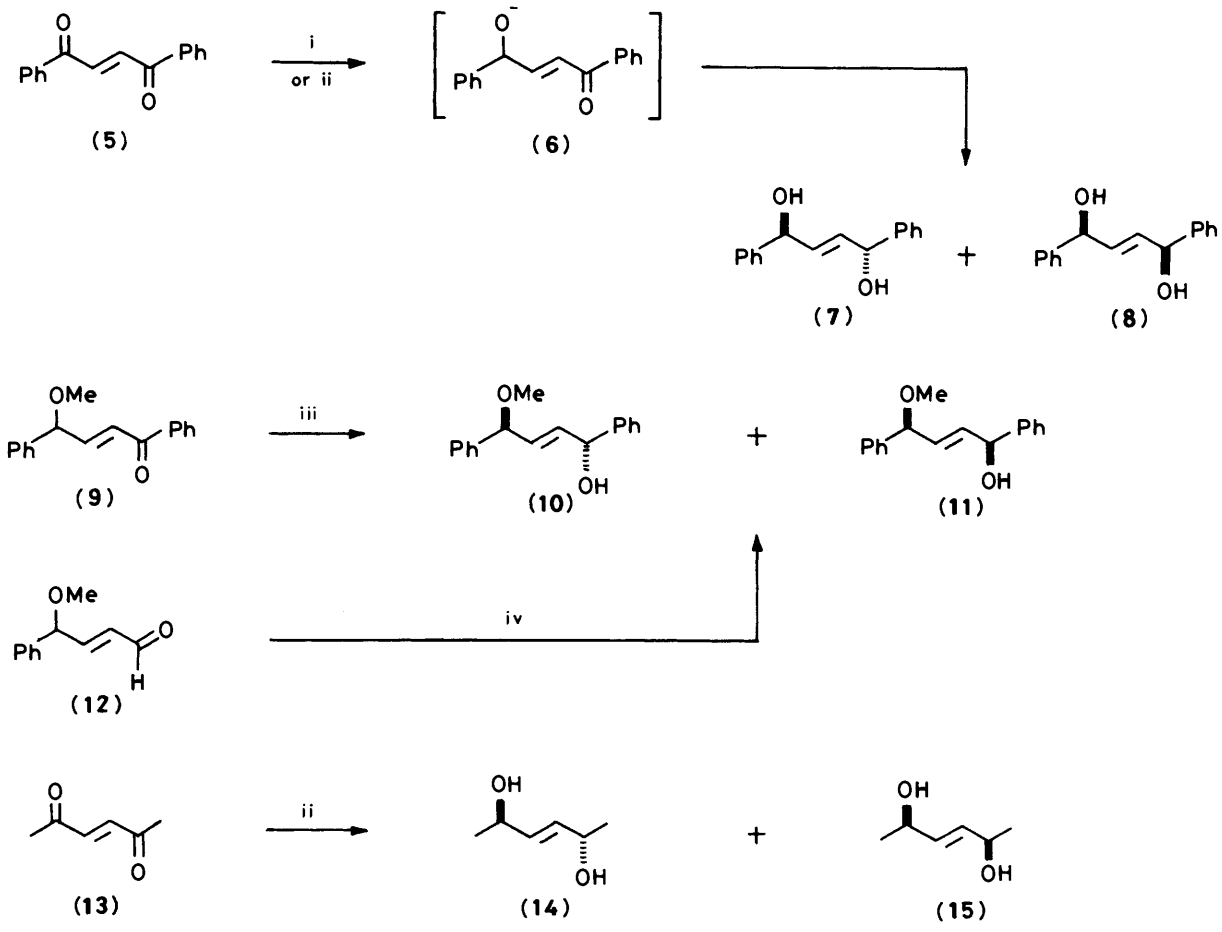
In spite of this discouragement, we have examined one other system. Presumably in the reduction of the diketone (**5**), the diastereoselective step will be the reduction of an alkoxide (**6**). We decided to look carefully at a less uncertain species, the corresponding methyl ether (**9**). Here we saw no diastereoselectivity at all: reduction of this ketone with zinc borohydride gave a 50:50 mixture of the alcohols (**10**) and (**11**) (together with some 4-methoxy-1,4-diphenylbutan-1-ol).

There remained the intriguing possibility that the diastereoselectivity in the individual steps of this reaction might actually have been high: if half the reaction took place in the s-*cis* conformation (the one drawn) and half in the s-*trans* conformation, and if attack took place in each case only from the top (or only from the bottom) face, the overall result would be the misleading appearance of no diastereoselectivity. We tested for this remote possibility by treating the aldehyde (**12**) with the phenyl Grignard reagent. The aldehyde (**12**) can reasonably be expected to exist very largely in the s-*trans* conformation (as drawn);[10] nevertheless, the diastereoselectivity was again zero, the alcohols (**10**) and (**11**) being produced in a 50:50 ratio. In one last reaction, carried out in case the phenyl groups had been an unfortunate choice of substituent, we reduced the diketone (**13**) with di-isobutylaluminium hydride. Once again, the diols (**14**) and (**15**) were produced in a 50:50 ratio.

We conclude that Cram's rule diastereoselectivity is either largely steric in origin or that chiral information is very inefficiently transmitted by conjugation. In any case, there is little prospect of there being a useful vinylogous version of Cram's rule, given that the three substituents on our chiral centre (carbon, hydrogen, and oxygen) are quite well differentiated electronically.

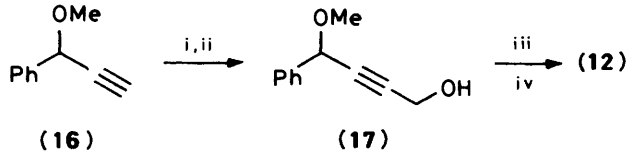
Preparation of Starting Materials.—We prepared authentic samples of the alcohols (**7**) and (**8**) by careful reduction of the corresponding acetylenic diols[11] using lithium aluminium hydride. Analysis of the mixture was possible using the just resolved signals (in CD_3OD) at 75.49 and 134.72 [compound (**7**)] and at 75.44 and 134.67 [compound (**8**)]. We prepared the ether (**9**) by methanolysis of the monoepoxide[12] of 1,4-diphenylbutadiene followed by oxidation and separation from the mixture of products. We prepared a sample of the ether (**10**) by

† No reprints available.



Scheme 1. *Reagents:* i, $LiAlH_4$; ii, Bu^i_2AlH; iii, $ZnBH_4$; iv, PhMgBr. Only one enantiomer of each pair is shown

monomethylation of the *meso*-acetylenic diol,[11] followed by careful reduction with lithium aluminium hydride. None of these reactions went in good yield. Analysis of the mixture of alcohols (**10**) and (**11**) was possible using the signals at 134.3 and 131.8 [compound (**10**)] and at 134.2 and 131.6 [compound (**11**)]. We prepared the aldehyde (**12**) from the prop-2-ynylic ether (**16**)[13] by way of the alcohol (**17**) (see Scheme 2). In all the reductions using lithium aluminium hydride, elimination [to give diphenylbutadiene from the acetylenic precursors of (**7**), (**8**), and (**10**), and phenylbutadiene from (**17**)] was a serious and unavoidable problem.[14]



Scheme 2. *Reagents:* i, EtMgBr; ii, CH_2O; iii, $LiAlH_4$; iv, MnO_2

Experimental

Reduction of the Diketone (**5**).—(*E*)-1,4-Diphenylbut-2-ene-1,4-dione[15] (472 mg) and lithium aluminium hydride (100 mg) were stirred in ether (50 ml) at room temperature for 20 min. Work-up using aqueous sodium potassium tartrate and preparative t.l.c. eluting with ethyl acetate–cyclohexane (1:1) gave 4-hydroxy-1,4-diphenylbutan-1-one (253 mg, 53%) and a mixture (114 mg, 24%) of a saturated diol (*ca.* 42%) and the two unsaturated diols (**7**) and (**8**) (*ca.* 58%). The bands were scraped off, care being taken to collect all the diol products. The proportion of the isomers (**7**) and (**8**) was estimated (from spectra taken in CD_3OD) by integration of the signals mentioned in the text. The ratio was 59:41 (lowfield peaks) and 63:37, (highfield peaks). We established the accuracy of the method with a mixture (59:41) made up from the pure isomers; this gave ratios of 63:37 (highfield) and 62:38 (lowfield) in the n.m.r. spectrum. In a second reduction, the diketone (236 mg) and di-isobutylaluminium hydride (2.8 mmol) were kept in benzene (25 ml) at 0 °C for 2 h. Work-up, and t.l.c. separation as before gave the hydroxy ketone (45 mg, 19%) and the unsaturated diols (**7**) and (**8**) (124 mg, 52%). The ratio was 59:41 on both peaks. The ratio 60:40 quoted in the text is probably accurate, therefore, to ±4%.

Reduction of the (E)-4-*Methoxy*-1,4-*diphenylbut*-2-*en*-1-*one* (**9**).—The ketone (217 mg) and zinc borohydride, prepared from sodium borohydride (0.7 g) and zinc chloride (1.0 g),[16] were stirred in ether (90 ml) at room temperature for 48 h. Work-up and preparative t.l.c. on silica, eluting with ethyl acetate–cyclohexane (2:3), gave a mixture (117 mg) of saturated hydroxy ketone and the allylic alcohols (**10**) and (**11**). The ratio of allylic alcohols, determined using the signals mentioned in the text, was 51:49 (lower field signals) and 49:51 (higher field signals).

Reaction of Phenyl Grignard Reagent on 4-*Methoxy*-4-*phenylbut*-2-*enal* (**12**).—The aldehyde (471 mg) in ether (5 ml) was added to the Grignard reagent prepared from bromobenzene (892 mg) and magnesium (136 mg) in ether (15 ml) and the mixture was kept at room temperature for 30 min and then refluxed for 10 min. Work-up and chromatography [SiO_2, ether–hexane, (1:3)] gave the mixture of (*E*)-4-methoxy-1,4-diphenylbut-2-en-1-ols (**10**) and (**11**) (676 mg, 99%), $\nu_{max.}$(film) 3 400 (OH), 3 020 (=CH), 1 600 (Ar), and 980 cm^{-1} (CH=CH); $\delta_H(CDCl_3)$ 7.38—6.91 (10 H, m, ArH), 5.72 (2 H, m, CH=CH), 5.02 (1 H, m, C*H*OH), 4.48 (1 H, m, C*H*OMe), 3.18 (3 H, 2 × s, OMe), and 2.25 (1 H, br s, OH); $\delta_C(CDCl_3)$ 142.7, 140.9, 134.3 (*RS,SR*), 134.2 (*RR,SS*), 131.8 (*RS,SR*), 131.6 (*RR,SS*), 128.7, 128, 128.1, 127.7, 127.2, 126.9, 126.3, 83.6, 74.4 (*RS,SR*) 74.3 (*RR,SS*), and 56.3 (OMe). The integration of the three sets of resolved signals gave ratios of 47:53, 51:49, and 48:52 respectively (Found: $M^+ - H_2$, 252.1172. $C_{17}H_{16}O_2$ requires $M - H_2$, 252.1150); *m/z* 252 (4%, $M^+ - H_2$), 147 (30, PhCHOH), 121 (30, PhCHOMe), and 105 (100, PhCO).

Reduction of (E)-*Hex*-3-*ene*-2,5-*dione* (**13**).—Di-isobutylaluminium hydride (25% w/w in toluene; 3.6 ml) was added to the enedione[17] (224 mg) in benzene (30 ml) at 0 °C and stirred for a further 2 h. Methanol (40 ml) was added, the precipitate filtered off, and the filtrate worked-up. Distillation gave a mixture of the diols (**14**) and (**15**)[18] (115 mg, 50%), $\delta_H(CDCl_3)$ 5.63—5.47 (2 H, m, =CH), 4.4—3.8 (2 H, m, *H*COH), 3.98 (2 H, s, OH), and 1.25 (6 H, d, *J* 6 Hz, CH*Me*); $\delta_C(CDCl_3)$ 133.9 and 133.6, 68.0 and 67.8, and 23.1. The ratio of isomers from the two peaks was 51:49 and 50:50 respectively. We did not prove which isomer was which.

The (E)-1,4-*Diphenylbut*-2-*ene*-1,4-*diols* (**7**) *and* (**8**).—The separated diphenylbutyne-1,4-diols[11] (1 mmol) were each refluxed in ether (15 ml) with lithium aluminium hydride (2 mmol) for 1 h. Work-up using aqueous sodium potassium tartrate gave the appropriate diol and 1,4-diphenylbutadiene, which were separated by fractional crystallisation from ether for compound (**7**) and by chromatography (SiO_2, ether–pentane) for compound (**8**): (*RS,SR*)-isomer (**7**) (50%), needles, m.p. 147—148 °C (from ethanol) (lit.,[7] m.p. 151 °C), and (E)-(RR,SS)-1,4-*diphenylbut*-2-*ene*-1,4-*diol* (**8**) (32%), thin plates, m.p. 112—113 °C [from chloroform–light petroleum (b.p. 40—60 °C)] (Found: C, 80.0; H, 6.6. $C_{16}H_{16}O_2$ requires C, 80.0; H, 6.7%); $\delta_H(CDCl_3)$ 7.28 (10 H, s, Ph), 5.97—5.83 (2 H, m, CH=CH), 5.22—5.04 (2 H, m, HCO), 2.2—1.85 (2 H, m, OH); $\delta_C(CDCl_3)$ 142.6, 133.2, 128.5, 127.7, 126.3, and 74.3. The n.m.r. spectra of the two isomers differed only in the signals mentioned in the text.

(E)-4-*Methoxy*-1,4-*diphenylbut*-2-*en*-1-*one* (**9**).—2-Phenyl-3-styryloxirane[12] (135 mg) was kept at room temperature in methanol (6 ml) with toluene-*p*-sulphonic acid (1 mg) for 1 day after which time ether was added. The mixture was then washed with aqueous sodium hydroxide and evaporated, and the residue oxidised in dichloromethane (5 ml) with pyridinium chlorochromate (260 mg) and sodium acetate (50 mg) over 2.5 h. Ether (25 ml) was added and the solution was filtered through Celite. Work-up and crystallisation from methanol and then from cyclohexane gave the enone (**9**) (32 mg, 21%) as plates, m.p. 98—98.5 °C (lit.,[19] m.p. 98—98.5 °C).

(RS,SR)-4-*Methoxy*-1,4-*diphenylbut*-2-*yn*-1-*ol*.—(*RS,SR*)-1,4-Diphenylbut-2-yne-1,4-diol[11] (476 mg) was stirred with sodium hydride (110 mg) in dry tetrahydrofuran at 0 °C for 2 h. The solvent was evaporated off, and the residue stirred with methyl iodide (10 ml) and tetrahydrofuran (10 ml) for 2 h. Work-up and preparative t.l.c. on silica eluting with ethyl acetate–cyclohexane (1:4) gave the *methoxybutynol* (100 mg, 20%), spectroscopically identical with a sample consisting of a mixture of the diastereoisomers, separately prepared from the acetylene (**16**)[13] and benzaldehyde, $\nu_{max.}(CCl_4)$ 3 585 (OH), 2 815 (OMe), and 2 220 cm^{-1} (C≡C); $\delta(CDCl_3)$ 7.5—6.8 (10 H, m, Ph), 5.35 (1 H, d, *J* 1.5 Hz, *H*COH), 5.02 (1 H, d, *J* 1.5 Hz, *H*COMe), 3.30 (3 H, s, OMe), and 3.10 (1 H, m, OH) (Found: M^+, 252.1136. $C_{17}H_{16}O_2$ requires *M*, 252.1150); *m/z* 252 (52% M^+), 145 (27), 115 (48), 105 (83), 91, and 77 (100).

(E)-(RS,SR)-4-*Methoxy*-1,4-*diphenylbut*-2-*en*-1-*ol* (**10**).—The prop-2-ynylic alcohol (97 mg) and lithium aluminium hydride (23 mg) were kept at 50 °C in tetrahydrofuran (5 ml) for 1 h. Work-up using sodium potassium tartrate gave the allylic alcohol and diphenylbutadiene. The latter crystallised and was filtered off; the former was then further purified by t.l.c. eluting with ethyl acetate–cyclohexane (1:3) to give the allylic alcohol (**10**) (16 mg, 16%), spectroscopically identical with the 50:50 mixture obtained earlier from the enone (**9**) and the enal (**12**) but now used to assign the peaks at δ 134.3 and 131.8 to the *RS,SR*-isomer. This was done by adding this authentic sample to the former mixture, and measuring an appropriate increase in intensity in these two peaks.

4-*Methoxy*-4-*phenylbut*-2-*yn*-1-*ol* (**17**).—The ethyl Grignard reagent was prepared from magnesium (2.55 g, 105 mmol) and ethyl bromide (10.90 g, 100 mmol) in dry ether (40 ml). 1-Methoxy-1-phenylpropyne[13] (7.30 g, 50 mmol) in dry ether (10 ml) was added dropwise under nitrogen to ethyl magnesium bromide (100 mmol) in ether (40 ml) with cooling in a water bath, and the mixture was stirred for 3 h at room temperature. Gaseous formaldehyde, generated from paraformaldehyde (3.47 g, 116 mmol), was passed through the mixture. Dry tetrahydrofuran (30 ml) was added and the mixture refluxed for 2 h. Aqueous work-up and distillation gave an alcohol (4.95 g, 56%) as a yellow viscous oil, b.p. 112—116 °C/0.2 mmHg, $\nu_{max.}$(neat) 3 400 (OH), 2.360 (C≡C), and 1 080 cm^{-1} (C–O); $\delta(CDCl_3)$ 7.28—6.88 (5 H, m, Ph), 4.85 (1 H, m, OC*H*Ph), 4.10 (2 H, d, *J* 1.6 Hz, CH_2), 3.25 (3 H, s, OMe), and 2.30 (1 H, br s, OH).

(E)-4-*Methoxy*-4-*phenylbut*-2-*en*-1-*ol*.—The alcohol (**29**) (4.37 g, 26.9 mmol) in dry ether (10 ml) was added dropwise under argon to a stirred suspension of lithium aluminium hydride (1.62 g, 42.6 mmol) in dry ether (20 ml) with cooling in an ice-bath, and stirring was continued for 2 h at 0 °C. Aqueous work-up and chromatography on silica gel eluting with benzene–hexane (1:1) then benzene–ethanol (20:1) gave 1-phenylbutadiene (1.21 g, 35%) and the butenol (2.74 g, 57%), $\nu_{max.}$(neat) 3 350 (OH), 3 020 (C=CH), 1 600 (C=C), 1 100 (C–O–C), and 980 cm^{-1} (CH=CH); $\delta(CDCl_3)$ 7.37—7.00 (5 H, m, Ph), 5.68 (2 H, m, CH=CH), 4.50 (1 H, m, C*H*OMe), 4.00 (2 H, m, CH_2OH), 3.23 (3 H, s, OMe), and 1.80 (1 H, br s, OH).

(E)-4-*Methoxy*-4-*phenylbut*-2-*enal* (**12**).—(*E*)-4-Methoxy-4-phenylbut-2-en-1-ol (1.42 g, 7.98 mmol) and manganese dioxide[20] (12.0 g, 138 mmol) in chloroform (60 ml) were stirred at room temperature for 20 h. The mixture was filtered and washed with chloroform. The combined filtrate was concentrated and the residue chromatographed on silica gel eluting with hexane–ether (3:1) followed by Kugelrohr distillation to give the *aldehyde* (**12**) (0.76 g, 54%), b.p. 90 °C/0.2 mmHg, $\nu_{max.}$(neat) 1 690 (C=O) and 1 100 cm^{-1} (C–O); $\delta(CDCl_3)$ 9.47 (1 H, d, *J* 7 Hz, CHO), 7.47—7.08 (5 H, m, Ph), 6.73 [1 H, dd, *J* 5.4 and 16.0 Hz, =C*H*CH(OMe)Ph], 6.18 (1 H, dd, *J* 7 and 16 Hz, =C*H*CHO), 4.80 (1 H, d, *J* 5.4 Hz, C*H*OMe), and 3.28 (3 H, s, OMe) (Found: M^+, 176.0836. $C_{11}H_{12}O_2$ requires *M*, 176.0837); *m/z* 176 (4%, M^+), 147 (100, M^+ − CHO), 121 (19, PhCHOMe), 115 (88, 147 − MeOH), and 91 (40, $PhCH_2$).

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