Reactions of 4-Substituted-2′-Halogenoacetophenones with Grignard Reagents

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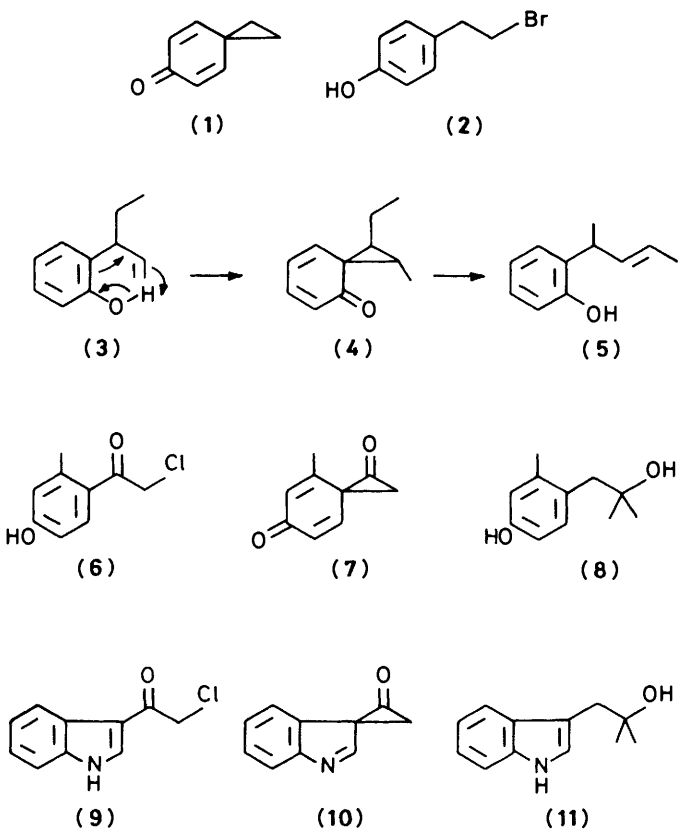
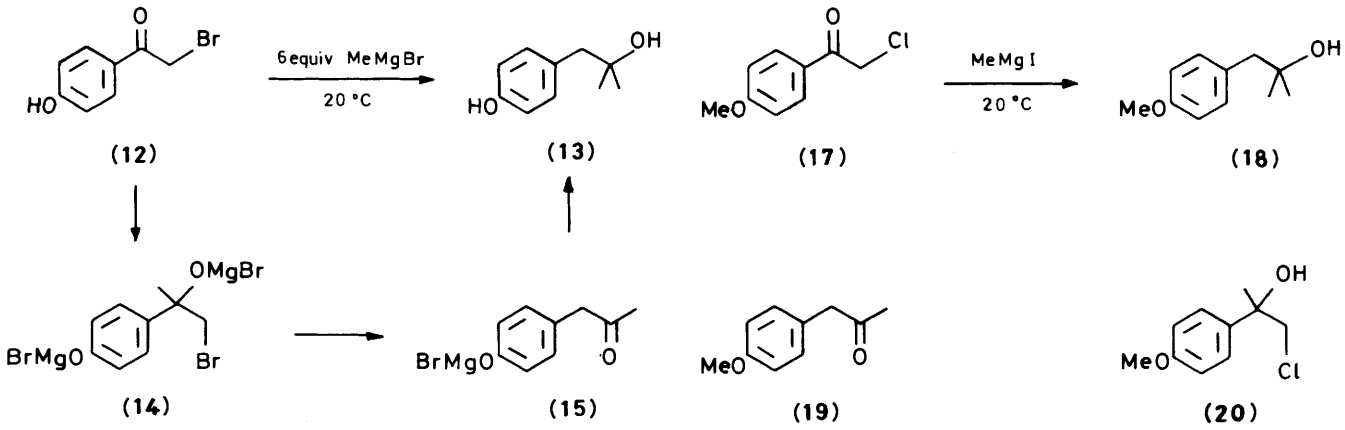
The initial reaction of 4-substituted 2′-halogenoacetophenones with an excess of methyl Grignard reagent is shown to be an attack at the 1′-carbonyl to form a halohydrin salt. The various reactions which then follow are substituent dependent. In the 4-hydroxy case [(**12**) and (**16**)] the only product is 1-(4-hydroxyphenyl)-2-methylpropan-2-ol (**13**) which arises *via* a [1,2]-aryl shift with simultaneous elimination of magnesium halide. When the substituent is 4-methoxy, a second pathway becomes important involving epoxide formation and a subsequent [1,2]-hydride migration to the benzylic position, or attack of the Grignard reagent at the benzylic carbon of the epoxide, When the substituent is 4-bromo, the reaction proceeds exclusively *via* the epoxide and, following a [1,2]-hydride shift, leads to the isomeric butanols (**33**) and (**34**). The reasons underlying such diversity of reactivity are discussed.

In connection with synthetic studies of certain natural products, we recently became interested in the generation of dienones based on a spiro[5.2]octane system (**1**). Spectral evidence for the formation of (**1**) by Ar_13 participation during the solvolysis of (**2**) was obtained many years ago [1] and species such as (**4**) have been reported as intermediates in the formation of 'abnormal' Claisen rearrangements leading from (**3**) to (**5**).[2] Bohlmann has reported that 2′-halogenoacetophenones [(*e.g.* (**6**)] containing electron-releasing *para* substituents, such as OH, OMe, or NMe_2, yield rearranged products (**8**) when treated with an excess of Grignard reagent, and has postulated attack by methylmagnesium iodide on an intermediate cyclopropanone (**7**) as responsible for the outcome.[3] A rather similar reaction, for which cyclopropanone (**10**) was postulated as the intermediate, was found by Bergman[4] who treated 3-chloroacetylindole (**9**) with methylmagnesium bromide and isolated α,α-dimethyltryptophol (**11**). In this paper we report a study of the reaction of 4-substituted-2′-halogenoacetophenones with Grignard reagents, originally initiated with a view to trapping an intermediate such as (**7**). A surprising diversity of paths emerged and we believe that a satisfactory rationalisation of the chemistry can now be presented.

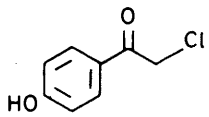
Our first experiments were carried out using 2′-bromo-4-hydroxyacetophenone (**12**). In agreement with Bohlmann's findings,[3] treatment of (**12**) with six equivalents of methylmagnesium bromide in tetrahydrofuran (THF) at room temperature for 16 h gave the alcohol (**13**) as the sole product in 85% isolated yield. When a similar reaction was terminated after 2 h, ^1H n.m.r. analysis revealed the presence of 12% of the ketone (**15**) (as the phenol). In an effort to isolate earlier





Scheme 1.

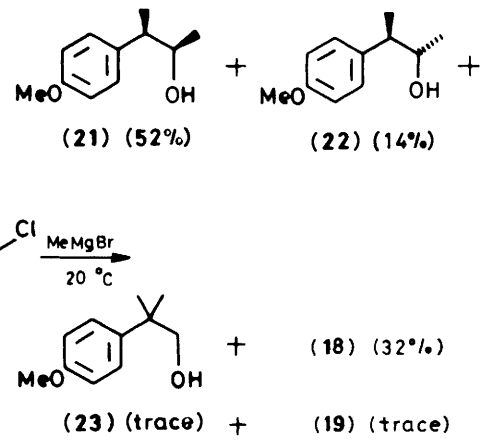
intermediates, the acetophenone (**12**) was treated with MeMgBr at −78 °C for 0.5 h. After work-up, ^{1}H n.m.r. analysis of the product showed it to be a mixture of the bromohydrin [*cf.* (**14**)] (74%) and the starting acetophenone (**12**) (16%). The bromohydrin proved to be rather unstable and was not fully characterised but its identity is assured on the basis of comparisons with other more stable halohydrins, prepared subsequently (*vide infra*). When (**12**) was treated with MeMgBr at −78 °C, followed by warming to 0 °C during 0.5 h, the product was found to be a mixture of (**12**) (trace), (**14**) (70%), (**15**) (*ca.* 5%), and (**13**) (25%). It therefore seems that the basic reaction pathway is, in fact, as outlined in Scheme 1. The precise nature of the species involved in the rearrangement step [(**14**) ⟶ (**15**)] is discussed later. However, it can be concluded that the mechanism proposed by Bohlmann [3a] (and an earlier carbene version [3b]) is not followed, although the rearrangement step may involve an intermediate related to structure (**7**). This type of reaction with 4-hydroxyacetophenones seems to be relatively insensitive to the nature of the 2′-halogen substituent. Thus, reaction between the chloroacetophenone (**16**) and an excess of methylmagnesium iodide at ambient temperature for 2 h also gave the alcohol (**13**). A ^{1}H n.m.r. examination of the crude reaction product revealed the presence of the halohydrin corresponding to (**14**) (trace) and the ketone (**15**) (5%).



(**16**)

By contrast, reactions of the corresponding 4-methoxyacetophenone derivatives with methyl Grignard reagents proved to be dependent on the nature of the halogen of the Grignard. We first examined the reaction between 2′-chloro-4-methoxyacetophenone (**17**) and MeMgI. As in the cases of the 4-hydroxyacetophenones described above, the product obtained using an excess of the Grignard reagent at ambient temperature for 16 h was the alcohol (**18**), in agreement with Bohlmann's findings.[3a] The crude reaction mixture also contained a small amount (*ca.* 10%) of the ketone (**19**). In view of the presence of an excess of Grignard reagent and the length of the reaction period, it seems unlikely that the free ketone could survive and hence is probably present in the reaction mixture as the corresponding enolate. Subsequent experiments showed that the reaction pathway from (**17**) to (**18**) is similar to that outlined in Scheme 1. Treatment of (**17**) with MeMgI at room temperature for only 2 h gave a mixture of the alcohol (**18**) (60%), the ketone (**19**) (5%) and the chlorohydrin (**20**) (35%), while reaction of (**17**) with MeMgI at −78 °C for 1.5 h gave only the chlorohydrin (**20**). Subsequent reaction between the isolated chlorohydrin (**20**) and an excess of MeMgI (20 °C/24 h) gave the alcohol (**18**) along with the ketone (**19**). In addition, small traces of two other components were detected by ^{1}H n.m.r. but the identification of these compounds as 3-(4-methoxyphenyl)-butan-2-ols was not achieved until our next experiments.

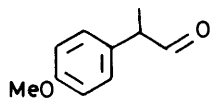
When the Grignard reagent was changed to MeMgBr and the chloroacetophenone (**17**) was treated with an excess (20 °C/24 h), a much more complex mixture was obtained which was composed of the *erythro*- and *threo*-butanols (**21**) and (**22**) [(52%) and (14%) respectively] together with the alcohol (**18**) (32%), its isomer (**23**) (trace) and the ketone (**19**) (trace) (Scheme 2). The compounds were separated by semi-preparative h.p.l.c.,



Scheme 2.

and were quantified by the weights obtained which agreed (±5%) with the values arrived at by integration of the ^{1}H n.m.r. spectrum of the crude reaction product. The *erythro*/*threo* ratio of (**21**) and (**22**) is closely similar to that reported [5] for the reaction of methylmagnesium iodide with 2-(4-methoxyphenyl)-propanal (**24**), suggesting that the latter is the final precursor to these compounds.

A similar pattern of reactivity was observed with 2′-bromo-4-methoxyacetophenone (**25**); relative percentages of the products arising from reactions between (**25**) and MeMgBr or MeMgI at ambient temperature for 24 h are shown in Scheme 3. A previously unobserved product which was formed in the latter reaction was the diketone (**26**). Presumably this arises by attack



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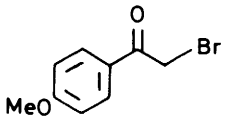

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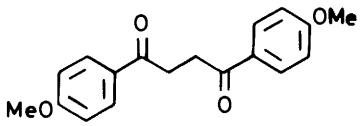


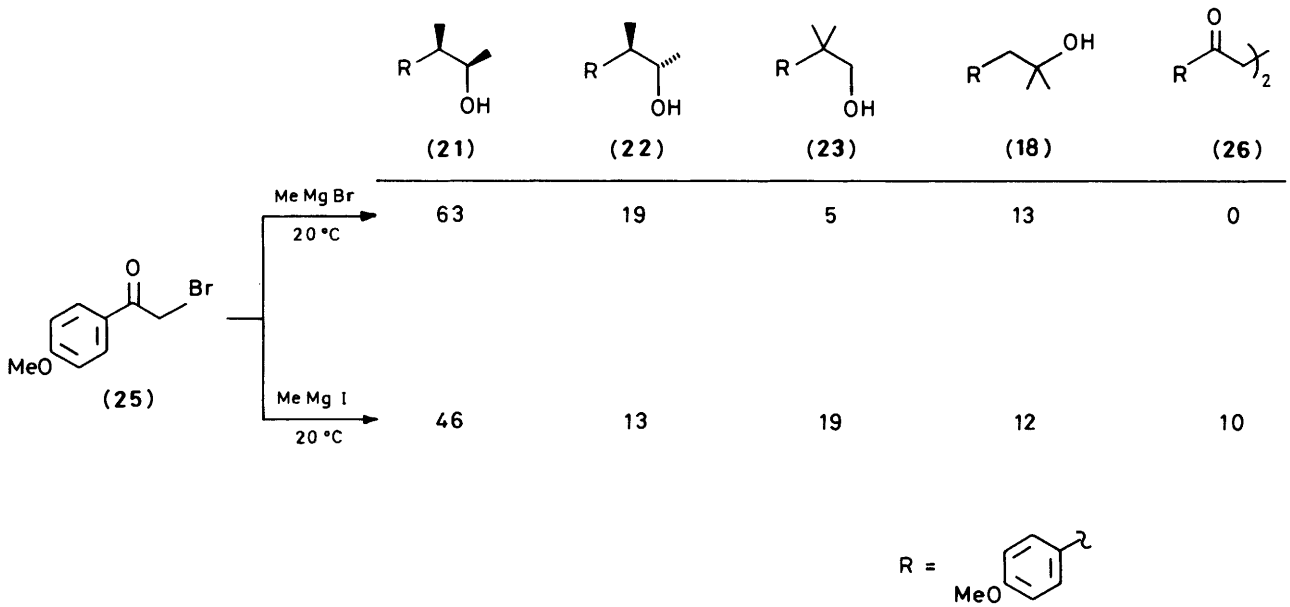
(26)

of the Grignard reagent at the bromine rather than the ketone group in (25), resulting in debromination to give the acetophenone enolate which is then alkylated by (25); alternatively a radical dimerisation may be envisaged. Similar dehalogenations of halogenoacetophenones by Grignard reagents have been observed previously,[6] but usually in cases where the substrates are much more sterically hindered than in (25).

Table 1. Products from treatment of epoxide (28) with Grignard reagents (relative percentages)

(28)	$\xrightarrow{\text{MeMgX}}$	(21)	+	(22)	+	(23)
	X = Br	73		26		Trace
	X = I	61		21		18

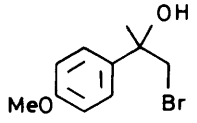
with methanolic potassium hydroxide, and on treatment with MeMgBr at ambient temperature for 24 h gave *only* the butanols (21) and (22) (73 and 26% respectively) together with a trace of the alcohol (23). An analogous reaction between the epoxide (28) and MeMgI gave *only* the same three alcohols, although in slightly different relative amounts (Table 1). Attempts to intercept the epoxide from Grignard reactions of the original halogenoacetophenones were not successful, indicating that (28) is very reactive under the conditions used. When the bromoacetophenone (25) was treated with MeMgBr for 1 h at ambient temperature, a closely similar ratio of products to those shown in Scheme 3 was found by isolation, containing in addition the bromohydrin (27) (16%). Similarly,



Scheme 3.

The initially formed precursor to all of the products shown in Scheme 3 [except dione (26)] was clearly established as the bromohydrin (27). Thus, reaction between acetophenone (25) and MeMgBr at −78 °C for 0.5 gave the pure bromohydrin (94%); no other compound was detected by ^{1}H n.m.r. analysis. Compound (27) was also the sole product isolated when a similar reaction mixture was warmed to 0 °C during 0.75 h before work-up. Furthermore, treatment of the bromohydrin with an excess of MeMgBr at ambient temperature for 24 h gave the same product distribution as that observed in the same reaction of acetophenone (25) (Scheme 3).

As it has already been established that the halohydrins can lead to alcohols such as (8) and (13) by a [1,2]-aryl migration (*cf.* Scheme 1), it seemed likely that a different reaction pathway was followed in the formation of the butanols (21) and (22) and propanol (23), which could proceed *via* the epoxide (28). The latter was prepared by brief treatment of the bromohydrin (27)



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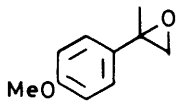


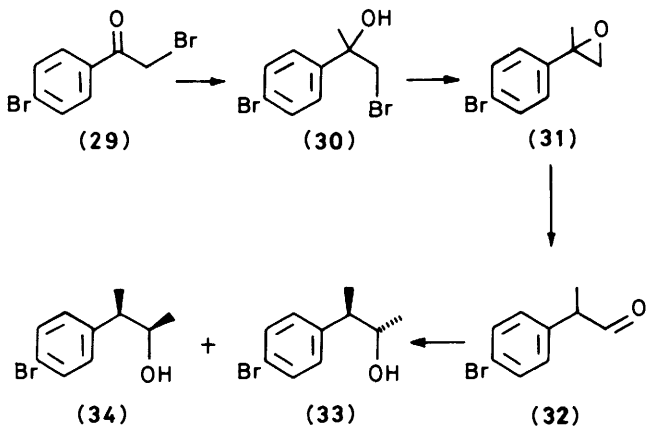
(28)

reaction between the bromoketone (25) and MeMgI for 2 h at ambient temperature gave the product distribution shown in Scheme 3 together with the bromohydrin (27) (51%). The reactions of (27) with MeMgI are thus rather slower than with the corresponding magnesium bromide. In neither case was the epoxide (28) detected.

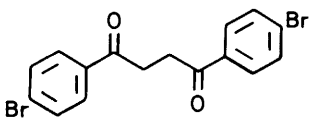
The reactions of α-halogenoacetophenones with Grignard reagents can therefore proceed *via* two pathways, following

Table 2. Reactions of 2′,4-dibromoacetophenone (**29**) with an excess of MeMgBr

Conditions	Products (Relative %) (30)	(31)	(32)	(33)	(34)	(35)
−78 °C/0.5 h	100					
20 °C/1 h	41	28	11	5	13	2
60 °C/2 h			39	15	44	2
60 °C/6 h				26	72	2

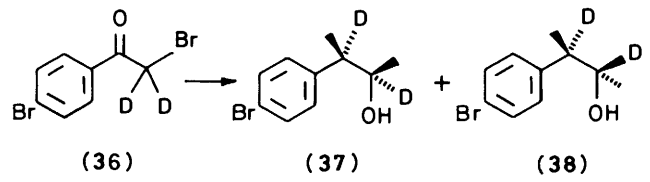


Scheme 4.



initial formation of the halohydrin salt [*e.g.* (**14**)]. The first involves a [1,2]-aryl shift (Scheme 1) while the second proceeds *via* epoxide formation. In our final set of experiments, we have found that such Grignard reactions of 2′,4-dibromoacetophenone (**29**) follow exclusively the latter pathway. As expected, treatment of (**29**) with MeMgBr at −78 °C resulted in the rapid formation of the bromohydrin (**30**). A reaction at ambient temperature for 1 h gave a mixture of all the possible products, while after refluxing for 6 h only the butanols (**33**) and (**34**) were obtained. These results are summarised in Table 2. We therefore conclude that the overall reaction pathway is as outlined in Scheme 4. The isolation of considerable amounts of the intermediate aldehyde (**32**) indicates that it may well not be present as the free compound in the reaction mixture.

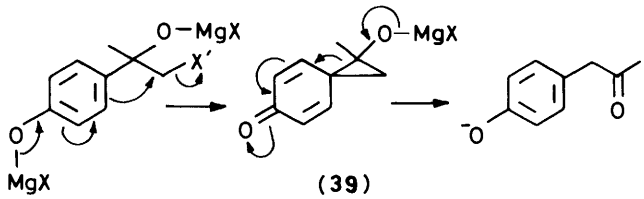
To further define the later stages of this reaction, we have also examined the reaction of the deuteriated acetophenone (**36**) with an excess of MeMgBr. After 24 h at ambient temperature, the *erythro*- and *threo*- butanols (**37**) and (**38**) each containing 2 atoms of deuterium were isolated, indicating that the



isomerisation of the epoxide (**31**) to the aldehyde (**32**) involves a [1,2]-hydride shift.

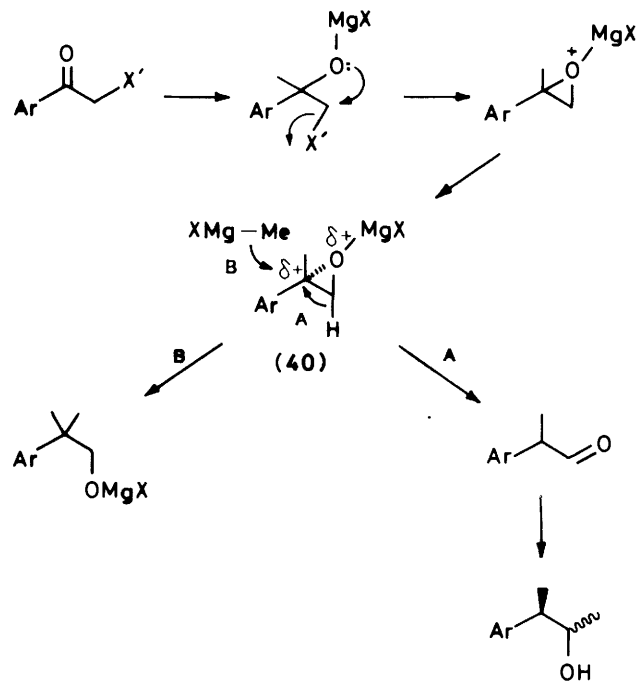
In summary, we have shown that in all cases examined, reaction between a 2′-halogenoacetophenone and a Grignard reagent MeMgX occurs initially at the carbonyl group to give a halohydrin salt. (In some cases a very small amount of apparent dehalogenation accompanies this reaction.) There is ample literature precedent for this[7] and other hard nucleophiles, such as acetylides,[8] α-lithiovinyl ethers,[9] 2-furyl-lithium[10] and sodamide,[11] also initally attack the carbonyl function in 2′-halogenoacetophenones. It follows that the postulated cyclopropanone (**7**)[3a] is not an intermediate in this reaction. As has been pointed out by Geissman and Akawie,[12] such halohydrin salts can undergo further reactions to form a ketone or an epoxide. The former pathway is followed when the migrating group is the very electron-rich 4-hydroxyphenyl group,[13] the [1,2]-aryl shift occurring very rapidly to the exclusion of other paths open to the intermediate halohydrin salt (Scheme 1).

Whilst the intermediacy of a spiro-cyclopropane species such as (**7**) is not in accord with our results, it is possible that the [1,2]-aryl shift could involve a related species, represented in an extreme form as the intermediate (**39**) (Scheme 5). Similar



Scheme 5.

intermediates have been postulated to account for products formed in the reduction of 2′-bromo-4-hydroxy-3,5-di-t-butylacetophenone and related derivatives with $LiAlH_4$,[14] as well as base-induced rearrangements of 3-(α-halogeno-acyl)indoles[4] mentioned above.



Scheme 6.

In the case of the relatively less electron rich 4-methoxyphenyl group, the [1,2]-aryl shift mechanism, while still operative, is not the exclusive pathway by which the initially formed halohydrin salt reacts further, (*cf.* Schemes 2 and 3), except in the reaction of 2′-chloro-4-methoxyacetophenone (**17**) with MeMgI. The even less electron rich 4-bromophenyl group does not undergo a [1,2]-aryl shift at all, but instead leads, *via* an expoxide, eventually to the butanols (**33**) and (**34**) (*cf.* Table 2 and Scheme 4). These results, together with the deuterium labelling experiments can be accounted for by the mechanism outlined in Scheme 6. When Ar is a 4-methoxyphenyl group, the developing electron deficient centre at the benzylic position in (**40**) is stabilised sufficiently by the aryl substituent to allow some attack of the Grignard reagent (Path *B*) before the hydride shift (path *A*) occurs. When Ar is 4-bromophenyl, this stabilisation is much reduced and hence the hydride shift occurs rapidly to the exclusion of path *B*. Similar [1,2]-shifts, promoted by Lewis acids, have been previously reported to occur in a variety of reactions involving epoxides substituted with phenyl or t-butyl groups.[15] It is not at present clear whether the different product ratios arising from the reaction of an α-halogenoacetophenone with MeMgBr or MeMgI reflect different Lewis acid character or differing nucleophilicities.

Experimental

General Details.—Melting points were determined using a Kofler hot stage apparatus and are uncorrected. I.r. spectra were measured using chloroform solutions, unless otherwise stated, with a Perkin-Elmer 710B spectrometer. All n.m.r. spectra were determined using dilute solutions in deuteriochloroform with tetramethylsilane as internal standard, unless stated otherwise. ^{1}H N.m.r. spectra were obtained at 90 MHz using a Perkin-Elmer R32A spectrometer while ^{2}H and ^{13}C spectra were measured at 250 MHz using a Bruker WM-250 spectrometer. Resonances were singlets unless otherwise stated and splittings (*J*) are given in Hz. Molecular weights and mass spectra were determined at 70 eV using an AEI MS902 spectrometer.

All reactions were carried out under a slight pressure of dry nitrogen. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride immediately prior to use. Unless otherwise stated, the Grignard reactions were carried out in THF (40 ml per 1 g of acetophenone) using 6 equivalents of the Grignard reagent (0.38M in THF). Reactions at 20 °C were left for 16 h, while those at −78 °C were worked up after 0.5 h. Work-up consisted of dilution of the reaction mixture with aqueous ammonium chloride followed by ether extraction. The combined ethereal extracts were dried over anhydrous magnesium sulphate, and evaporated.

Semi-preparative h.p.l.c. was performed using a Waters 600A pump, an R401 refractive index detector and a 7.8 mm × 30 cm stainless-steel column packed with μ-Porasil, operating at a flow rate of 3 ml min^{-1}. Preparative scale h.p.l.c. was carried out using a Waters Prep. LC 500 machine and a PREP PAK 500-Silica column.

2′-Chloro-4-hydroxy- and 2′-chloro-4-methoxy-acetophenone [(**16**) and (**17**)] were prepared by Friedel-Crafts acylations using chloroacetyl chloride,[16] while 2′-bromo-4-hydroxyacetophenone (**12**) was obtained by bromination of the corresponding acetophenone with dioxane dibromide.[17] 2′-Bromo-4-methoxy- and 2′,4-dibromo-acetophenone [(**25**) and (**29**)] are commercially available.

Reaction of 2′-Bromo-4-hydroxyacetophenone (**12**) *with Methylmagnesium Bromide at* 20 °C; *Preparation of* 1-(4-*Hydroxyphenyl*)-2-*methylpropan*-2-*ol* (**13**).—Crystallisation of the crude product from ethyl acetate–hexane gave the *alcohol* (**13**) (84%), as colourless needles, m.p. 122—125 °C, $\nu_{max.}$ 3 575 and 3 375 cm^{-1}; δ 1.16 (6 H, 2 × CH_3), 2.69, (2 H, ArCH_2), 4.80 (1 H, br, OH), 6.79 (2 H, d, *J* 8.5), and 7.11 (2 H, d, *J* 8.5), *m*/*z* 166 (M^+, 3%), 151 (10), 121 (14), 108 (100), 107 (77), and 77 (11) (Found: C, 72.0; H, 8.5. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.4%). (Found: M^+, 166.0990. $C_{10}H_{14}O_2$ requires *M*, 166.0947).

Reaction of 2′-Bromo-4-hydroxyacetophenone (**12**) *with Methylmagnesium Bromide at* −78 °C.—The product consisted of the bromohydrin [*cf.* (**14**)] (84%), δ[$(CD_3)_2CO$] 1.62, (3 H, CH_3), 3.68 (2 H, CH_2Br), 6.82 (2 H, d, *J* 8.5), and 7.39 (2 H, d, *J* 8.5) and starting acetophenone (26%) δ 4.56 (2 H, CH_2Br), 7.04 (2 H, d, *J* 8.5), and 8.05 (2 H, d, *J* 8.5). Attempts to further purify the bromohydrin failed.

Reaction between 2′-Chloro-4-hydroxyacetophenone (**16**) *and Methylmagnesium Iodide at* 20 °C.—After 2 h, the product was found to contain 1-chloro-2-(4-hydroxyphenyl)propan-2-ol (trace; δ 1.64 and 3.83) and 1-(4-hydroxyphenyl)propan-2-one (**15**) (5%; δ 2.04 and 3.60), as well as the alcohol (**13**). Crystallisation from ethyl acetate–hexane gave 1-(4-hydroxyphenyl)-2-methylpropan-2-ol (**13**) (90%), m.p. 122—125 °C, identical with the sample prepared as described above.

Reaction of 2′-Chloro-4-methoxyacetophenone (**17**) *with Methylmagnesium Iodide at* 20 °C; *Preparation of* 1-(4-*Methoxyphenyl*)-2-*methylpropan*-2-*ol* (**18**).—^{1}H N.m.r. analysis of the crude product showed the presence (*ca.* 10%) of 1-(4-methoxyphenyl)propan-2-one (**19**) [δ 2.12 (CH_3CO) and 3.63 ($ArCH_2$)]. Crystallisation from hexane gave the pure alcohol (**18**) (85%) as colourless needles, m.p. 40—41 °C (lit.,[18] m.p. 42.5 °C); $\nu_{max.}$(film) 3 425, 1 600, 1 500 and 1 245 cm^{-1}; δ 1.22 (6 H, 2 × CH_3), 1.60 (1 H, br s, OH), 2.73 (2 H, $ArCH_2$), 3.82 (3 H, OCH_3), 6.87 (2 H, d, *J* 8.5), and 7.17 (2 H, d, *J* 8.5); *m*/*z* 180 (M^+, 9%), 165 (12), 122 (100), and 121 (36) (Found: C, 73.2; H, 9.1. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.9%). The sample was identical (^{1}H n.m.r.: t.l.c.: m.p. and mixed m.p.) with authentic material.[18]

Reaction between 2′-Chloro-4-methoxyacetophenone (**17**) *and Methylmagnesium Iodide at* −78 °C; *Preparation of* 1-*Chloro*-2-(4-*methoxyphenyl*)*propan*-2-*ol* (**20**).—The only product was the *chlorohydrin* (**20**) (92%), an oil, $\nu_{max.}$(film), 3 475, 1 620, 1 520, and 1 260 cm^{-1}; δ 1.62 (3 H, CH_3), 2.60 (1 H, br s, OH), 3.79 (2 H, CH_2Cl), 3.82 (3 H, OCH_3), 6.87 (2 H, d, *J* 8.5), and 7.42 (2 H, d, *J* 8.5); *m*/*z* 202 [M^+, (^{37}Cl), 10%], 200 [M^+, (^{35}Cl), 35], 152 (40), 151 (100), 135 (44), 121 (30), and 121 (30) (Found: M^+, 200.0597. $C_{10}H_{13}{}^{35}ClO_2$ requires *M*, 200.0603).

Reaction between 1-*Chloro*-2-(4-*methoxyphenyl*)*propan*-2-*ol* (**20**) *and Methylmagnesium Iodide at* 20 °C.—The only product was the alcohol (**18**), (83%), which was identical with previously prepared material.[18]

Reaction between 2′-Chloro-4-methoxyacetophenone (**17**) *and Methylmagnesium Bromide at* 20 °C.—The crude product mixture was separated by semi-preparative h.p.l.c., using 15% ethyl acetate–n-hexane as eluant, into the following (in order of elution): (i) threo-3-(4-*methoxyphenyl*)*butan*-2-*ol* (**22**) (14%), R_t 14.5 min, a colourless oil (lit.,[5] oil), $\nu_{max.}$ 3 580, 1 605, 1 460, 1 035, and 910 cm^{-1}, δ 1.21 (3 H, d, *J* 6 $CHCH_3$), 1.24 (3 H, d, *J* 6 $CHCH_3$), 1.40 (1 H, br s, OH), 2.63 (1 H, m, ArCH), 3.80 (1 H, m, *CH*OH), 3.81 (3 H, OCH_3), 6.91 (2 H, d, *J* 8.5), and 7.19 (2 H, d, *J* 8.5), *m*/*z* 180 (M^+, 10%), 136 (42), 135 (100), 121 (42), 103 (15), and 91 (13) (Found: M^+, 180.1149. $C_{11}H_{16}O_2$ requires *M*, 180.1150); (ii) erythro-3-(4-*methoxyphenyl*)*butan*-2-*ol* (**21**) (52%), R_t 16 min, a colourless solid, m.p. 57.5—58.5 °C (lit.,[5]

m.p. 58.8—59.2 °C), $\nu_{max.}$ 3 600, 1 610, 1 460, 1 033, and 910 cm^{-1}; δ 1.08 (3 H, d, *J* 6, $CHCH_3$), 1.30 (3 H, d, *J* 6, $CHCH_3$), 1.45 (1 H, br s, OH), 2.71 (1 H, m, ArCH), 3.80 (3 H, OCH_3), 3.84 (1 H, m, *CH*OH), 6.88 (2 H, d, *J* 8.5), and 7.16 (2 H, d, *J* 8.5); *m/z* 180 (M^+, 13%), 136 (42), 135 (100), 121 (31), 103 (15), and 91 (7) (Found: M^+, 180.1150); (iii) 2-(4-*methoxyphenyl*)-2-*methylpropan*-1-*ol* (**23**) (*ca.* 1%), R_t 17 min, which was identified by comparison (^1H n.m.r.; R_t; t.l.c.) with a fully characterised sample isolated from a later experiment, and (iv) 1-(4-methoxyphenyl)-2-methylpropan-2-ol (**18**) (32%), R_t 17.5 min, as a colourless solid, m.p. 39.5—40.5 °C, identical (^1H n.m.r., t.l.c., m.p., mixed m.p.) with an authentic sample.[18]

Reaction of 2′-Bromo-4-methoxyacetophenone (**25**) *with Methylmagnesium Bromide at* 20 °C.—The composition of the product mixture is shown in Scheme 3, and was calculated by integration of the ^1H n.m.r. spectrum; the identities of the components were confirmed by comparative t.l.c. and h.p.l.c. analysis against authentic samples. A repeat run, together with internal checks of the integration values showed that the data shown in Scheme 3 is accurate to within ±10% of the percentages given.

Reaction between 2′-Bromo-4-methoxyacetophenone (**25**) *and Methylmagnesium Iodide at* 20 °C.—The crude product was triturated with ether (2 ml). A colourless crystalline solid remained undissolved and, after cooling the mixture in ice, was filtered off and identified as 1,4-*bis*(4-*methoxyphenyl*)*butane*-1,4-*dione* (**26**) (10%), m.p. 149—150 °C (lit.,[19] m.p. 150—151 °C); $\nu_{max.}$ 1 670, 1 595, and 1 170 cm^{-1}; δ[$(CD_3)_2CO$], 3.38 (4 H, 2 × CH_2), 3.90 (6 H, 2 × OCH_3), 7.05 (4 H, d, *J* 8.5), and 8.05 (4 H, d, *J* 8.5); *m/z* 298 (M^+, 10%) 135 (100), and 77 (11) (Found: M^+, 298.1195. $C_{18}H_{18}O_4$ requires *M*, 298.1205).

The composition of the mixture (Scheme 3) was determined by intergration of the ^1H n.m.r. spectrum of the crude product before trituration.

Reaction between 2′-Bromo-4-methoxyacetophenone (**25**) *and Methylmagnesium Bromide at* −78 °C; *Preparation of* 1-*Bromo*-2-(4-*methoxyphenyl*)*propan*-2-*ol* (**27**).—Work-up gave the bromohydrin (**27**) (94%) as an oil, $\nu_{max.}$ 3 475, 1 619, 1 510, 1 260, and 840 cm^{-1}; δ 1.67 (3 H, CH_3), 2.58 (1 H, br s, OH), 3.70 (2 H, CH_2Br), 3.81 (3 H, OCH_3), 6.93 (2 H, d, *J* 8.5), and 7.42 (2 H, d, *J* 8.5); *m/z* 228 (96%), 226 (100, $M(^{79}Br) - H_2O$), 147 (44), 132 (33), 115 (32), and 91 (37). No other resonances were observed in the ^1H n.m.r. spectrum, but attempts to secure an analytical sample resulted in extensive decomposition.

Reaction between 1-*Bromo*-2-(4-*methoxyphenyl*)*propan*-2-*ol* (**27**) *and Methylmagnesium Bromide at* 20 °C.—The product was separated by semi-preparative h.p.l.c. in 15% ethyl acetate–n-hexane to give the alcohols (**21**) (63%), (**22**) (12%), (**23**) (5%), and (**18**) (20%). Each component was identical with an authentic sample. The amounts of each component were calculated both from the weights obtained and from integration of the ^1H n.m.r. spectrum of the crude product.

1,2-*Epoxy*-2-(4-*methoxyphenyl*)*propane* (**28**).—Freshly prepared 1-bromo-2-(4-methoxyphenyl)propan-2-ol (2.3 g, 10 mmol) was treated with 5% methanolic potassium hydroxide (100 ml). As soon as mixing was complete, water (500 ml) was added and the mixture extracted with ether (2 × 400 ml). The combined extracts were dried and evaporated to leave the unstable epoxide (**28**) (1.4 g), $\nu_{max.}$ 1 590, 1 495, and 1 400 cm^{-1}; δ 1.70 (3 H, CH_3), 2.78 (2 H, dd, J_{AB} 8.9, CH_AH_BO), 3.82 (3 H, OCH_3), 6.93 (2 H, d, *J* 8.5), and 7.34 (2 H, d, *J* 8.5) which was used directly in the following reactions.

Reaction between 1,2-*Epoxy*-2-(4-*methoxyphenyl*)*propane* (**28**) *and Methylmagnesium Bromide at* 20 °C.—The crude product mixture was separated by semi-preparative h.p.l.c. using 15% ethyl acetate in n-hexane as eluant into the *erythro*-alcohol (**21**) (73%) and the *threo*-alcohol (**22**) (26%), identical with previously characterised samples. A ^1H n.m.r. spectrum of the crude product revealed the presence of a trace (*ca.* 1—2%) of the alcohol (**23**) (δ 3.58).

Reaction between 1,2-*Epoxy*-2-(4-*methoxyphenyl*)*propane* (**28**) with *Methylmagnesium Iodide at* 20 °C.—Separation of the product mixture as described in the foregoing experiment gave the *erythro*-alcohol (**21**) (61%), the *threo*-alcohol (**22**) (21%), and 2-(4-*methoxyphenyl*)-2-*methylpropan*-1-*ol* (**23**) (18%) as a colourless solid, m.p. 44—45 °C (lit.,[20] m.p. 45—46.5 °C); $\nu_{max.}$ 3 500, 1 610, and 1 040 cm^{-1}, δ 1.30 (6 H, 2 × CH_3), 1.45 (1 H, br s, OH), 3.58 (2 H, CH_2OH), 3.81 (3 H, OCH_3), 6.90 (2 H, d, *J* 8.5), and 7.35 (2 H, d, *J* 8.5); *m/z* 180 (M^+, 56%), 165 (13), 150 (56), and 149 (100) (Found: M^+, 180.1145. $C_{11}H_{16}O_2$ requires *M*, 180.1150).

Reaction between 2′,4-Dibromoacetophenone (**29**) *and Methylmagnesium Bromide at* −78 °C; *Preparation of* 1-*Bromo*-2-(4-*bromophenyl*)*propan*-2-*ol* (**30**).—The only product was the *bromohydrin* (**30**) (92%), an oil $\nu_{max.}$(film) 3 480 and 1 605 cm^{-1}; δ 1.66 (3 H, CH_3), 2.58 (1 H, br s, OH), 3.71 (2 H, CH_2Br), 7.36 (2 H, d, *J* 8.5), and 7.54 (2 H, d, *J* 8.5); *m/z* 296 (1%), 294 (3), 292 (1), 201 (97), and 199 (100) (Found: M^+, 295.8968. $C_9H_{10}{}^{81}Br_2O$ requires *M*, 295.9056).

Reaction between 2′,4-Dibromoacetophenone (**29**) *and Methylmagnesium Bromide at* 20 °C *for* 1 h.—After 1 h at ambient temperature, the reaction mixture was worked up to give an oil, the composition of which was determined from ^1H n.m.r. spectra, using the resonances given in parentheses, and by comparison with authentic samples using h.p.l.c.—bromohydrin (**30**) (41%; δ 1.66 and 3.71) epoxide (**31**) (28%; δ 1.68), aldehyde (**32**) (11%; δ 1.44 and 9.72), *threo*-butanol (**33**) (5%; δ 1.19), *erythro*-butanol (**34**) (13%; δ 1.05), dione (**35**) (2%; δ 3.44).

Reaction between 2′,4-Dibromoacetophenone (**29**) *and Methylmagnesium Bromide at reflux for* 6 h.—The crude product on trituration with cold ether gave a solid, identified as 1,4-*bis*-(4-*bromophenyl*)*butane*-1,4-*dione* (**35**) (2%), m.p. 181—182 °C (lit.,[19] m.p. 180—181 °C) $\nu_{max.}$ 1 680, 1 585, and 990 cm^{-1}, δ 3.44 (4 H, CH_2CO), 7.68 (4 H, d, *J*8.5), and 7.95 (4 H, d, *J* 8.5); *m/z* 398 (4%), 396 (9), 394 (5), 213 (7), 185 (97), and 183 (100) (Found: C, 48.6 H, 3.3. $C_{16}H_{12}Br_2O_2$ requires C, 48.5; H, 3.0%).

The remainder of the product was separated by preparative scale h.p.l.c., using 10% ethyl acetate in n-hexane as eluant, into (i) threo-3-(4-*bromophenyl*)*butan*-2-*ol* (**33**) (26%) (eluted first), as a colourless oil, b.p. 90 °C (oven temp.) at 0.5 mmHg, $\nu_{max.}$(film) 3 375, 1 490, and 1 050 cm^{-1}; δ 1.19 (3 H, d, *J* 6, $CHCH_3$), 1.24 (3 H, d, *J* 7 $CHCH_3$), 1.55 (1 H, br s, OH), 2.65 (1 H, m, ArC*H*), 3.83 (1 H, m, C*H*OH), 7.13 (2 H, d, *J* 8.5), and 7.47 (2 H, d, *J* 8.5); δ ^{13}C 16.2(q), 21.1(q), 46.7(d), 72.0(d), 120.1(s), 129.6(d), 131.4(d), and 143(s); *m/z* 230 (1%), 228 (1), 186 (52), 185 (21), 184 (55), 183 (19), and 171 (16) (Found: C, 52.5; H, 5.6. $C_{10}H_{13}BrO$ requires C, 52.4; H, 5.7%); and (ii) erythro-3-(4-*bromophenyl*)*butan*-2-*ol* (**34**) (72%) (eluted second), as a colourless oil, b.p. 90 °C (oven temp.) at 0.55 mmHg, $\nu_{max.}$(film) 3 380, 1 490, and 1 050 cm^{-1}; δ 1.05 (3 H, d, *J* 6, $CHCH_3$), 1.27 (3 H, d, *J* 7, $CHCH_3$), 1.70 (1 H, s, OH), 2.69 (1 H, m, ArC*H*), 3.83 (1 H, m, C*H*OH), 7.11 (2 H, d, *J* 8.5), and 7.46 (2 H, d, *J* 8.5); δ ^{13}C 17.6(q), 20.7(q), 47.2(d), 72.0(d), 120.3(s), 129.8(d), 131.5(d), and 142.7(s); *m/z* 230 (1%), 228 (1), 186 (54), 185 (23), 184 (58), 183 (20), 171 (16) (Found: C, 52.8; H, 5.9%).

The 1-*naphthylurethane* derivative had m.p. 156—158 °C (from CCl_4) (Found: C, 63.4; H, 5.1; N, 3.4. $C_{21}H_{20}BrNO_2$ requires C, 63.3; H, 5.0; N, 3.5%).

Reaction between 2',4-Dibromoacetophenone (**29**) *and Methylmagnesium Bromide at reflux for* 2 h.—Trituration of the product with cold ether left the dione (**35**) (2%), m.p. 180—181 °C. The remainder was separated by semi-preparative h.p.l.c., using 18% ethyl acetate in n-hexane to give 2-(4-bromophenyl)propanal (**32**) (39%), R_t 5 min, $\nu_{max.}$(film) 1 720 cm^{-1}; δ 1.44 (3 H, d, *J* 7, $CHCH_3$), 3.62 (1 H, m, $CHCH_3$), 7.13 (2 H, d, *J* 8.5), 7.55 (2 H, d, *J* 8.5), and 9.72 (1 H, d, *J* 2, CHO); [The 2,4-dinitrophenylhydrazone derivative showed m.p. 117—119 °C (from EtOH) (lit.,[21] m.p. 118—121 °C)]; the *threo*-butanol (**33**) (15%), R_t 9 min and the *erythro*-butanol (**34**) (44%), with R_t 10 min. The latter two samples were identical with previously characterised material.

1,2-*Epoxy*-2-(4-*Bromophenyl*)*propane* (**31**).—1-Bromo-2-(4-bromophenyl)-propan-2-ol (2.28 g) was treated with 5% methanolic potassium hydroxide (100 ml). After 5 min, the solution was diluted with water (500 ml) and extracted with ether. The dried extracts were evaporated and the residue chromatographed over silica with 10% ethyl acetate in n-hexane as eluant to give the *epoxide* (**31**) (1.34 g), an oil, $\nu_{max.}$(film) 1 590, 1 490, and 1 400 cm^{-1}; δ 1.68 (3 H, CH_3), 2.81 (2 H, dd, *J* 5.5, CH_AH_BO), 7.24 (2 H, d, *J* 8.5), and 7.48 (2 H, d, *J* 8.5); *m/z* 214 (10%), 212 (14), 185 (60), 183 (63), 104 (69), and 103 (29) (Found: M^+, 211.9769, $C_9H_9{}^{79}BrO$ requires *M*, 211.9738).

2',4-*Dibromo*[2',2'-$^2H_2$]-*acetophenone* (**36**).—A solution of 20% deuterium chloride in deuterium oxide (2.65 ml) was added to a solution of ethyl 4-bromobenzoylacetate (4.4 g)[22] in THF (30 ml) and deuterium oxide (30 ml). The mixture was stirred at ambient temperature for 24 h when the organic layer was separated and the aqueous layer extracted with ether (30 ml). The combined organic solutions were dried, evaporated, and distilled to give the deuteriated *keto-ester* (4.1 g), b.p. 105 °C (oven temp.) at 0.1 mmHg, $\nu_{max.}$(film) 1 735 and 1 680 cm^{-1}; δ 1.24 (1.5 H, t, *J* 7, O·CH_2CH_3 keto tautomer), 1.33 (1.5 H, t, *J* 7, OCH_2CH_3, enol), 4.22 (1 H, q, *J* 7, OCH_2CH_3, keto), 4.30 (1 H, q, *J* 7, enol) and 7.58—7.91 (4 H, m); δ[^2H] 3.93 (CD_2), 5.67 (:CD) and 12.41 (:C·OD).

A mixture of the deuteriated β-keto ester (0.54 g) and 2M-sodium deuterioxide (1.5 ml) was stirred and refluxed for 1 h, then cooled and extracted with ether. The dried extracts were evaporated to leave 4-bromo[2',2',2'-$^2H_3$]acetophenone (0.27 g), m.p. 47—50 °C (lit.,[23] m.p. 49—50.5 °C for non-deuteriated material, $\nu_{max.}$ 1 670 cm^{-1}; δ 7.68 (2 H, d, *J* 8.5) and 7.91 (2 H, d, *J* 8.5); δ[^2H] 2.56 (CD_3).

A solution of bromine (0.17 g) in carbon tetrachloride (3 ml) was added dropwise to a solution of the foregoing acetophenone (0.2 g) in carbon tetrachloride (5 ml). The solution was stirred at ambient temperature for 24 h and then washed with deuterium oxide (5 ml), dried and evaporated to leave a solid residue which after crystallisation from EtOD gave 2',4-dibromo[2',2'-$^2H_2$]-acetophenone (**36**) (0.18 g), m.p. 106—108 °C, (lit.,[24] m.p. 110—111 °C for the non-deuteriated compound), $\nu_{max.}$ 1 665 cm^{-1}; δ 7.66 (2 H, d, *J* 8.5) and 7.89 (2 H, d, *J* 8.5); δ[^2H] 4.38 (CD_2Br). No undeuteriated compound was detected by ^1H n.m.r. spectroscopy.

Reaction between 2',4-Dibromo-2',2'-Dideuterioacetophenone (**36**) *and Methylmagnesium Bromide at* 20 °C.—The product was separated, using semi-preparative h.p.l.c. with 18% ethyl acetate in n-hexane as eluant, into (i) *threo*-3-(4-bromophenyl)[2,3-$^2H_2$]butan-2-ol (**38**) (24%), $\nu_{max.}$(film) 3 380 cm^{-1}; δ 1.18 (3 H, CH_3), 1.14 (3 H, CH_3), 7.12 (2 H, d, *J* 8.5), and 7.46 (2 H, d, *J* 8.5); δ[^2H] 2.66 (1 D, ArC*D*), and 3.84 (1 D, C*D*·OH); and (ii) *erythro*-3-(4-bromophenyl)[2,3-$^2H_2$]butan-2-ol (**37**) (76%), $\nu_{max.}$(film) 3 380 cm^{-1}; δ 1.05 (3 H, CH_3), 1.26 (3 H, CH_3), 7.10 (2 H, d, *J* 8.5), and 7.45 (2 H, d, *J* 8.5); δ[^2H] 2.69 (1 D, ArC*D*) and 3.84 (1 D, C*D*OH).

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