The Diastereoselectivity of Electrophilic Attack on Trigonal Carbon Adjacent to a Stereogenic Centre: Diastereoselective Alkylation and Protonation of Open-chain Enolates having a Stereogenic Centre at the β Position

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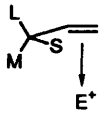
Methylation of the enolates **7**, **24**, **28** and **33** and protonation of the enolates **10**, **27**, **31** and **36** are diastereoselective in conformity to a general rule, summarised in the drawing **1**, governing the stereochemistry of electrophilic attack on a double bond adjacent to a stereogenic centre. The sense of the selectivity is, with one exception, opposite to that of the corresponding nucleophilic attack on a carbonyl group adjacent to a stereogenic centre, which, with the same exception, follows Cram's and the Felkin–Anh rule, summarised in the drawing **2**. The exception is probably the reduction **40** → **38** + **39**, with **39** as the major product. This result is inconsistent with Cram's and the Felkin–Anh rule if the isopropyl group is counted as 'larger' than the phenyl group, whereas the Grignard reaction **37** → **38** + **39**, where **39** is again the major product, and the corresponding electrophilic reactions **33** → **34** + **35**, with **34** as the major product, and **36** → **34** + **35**, with **35** as the major product, are all consistent with isopropyl being effectively larger than phenyl.

For some years we have been studying the diastereoselectivity of electrophilic attack on a C=C double bond adjacent to a stereogenic centre in the general sense **1**. Our interest in this



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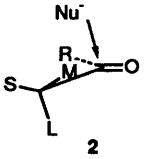

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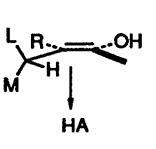
type of diastereoselectivity stems from our discovery, in several types of open-chain structure, of high levels of selectivity, with many applications in organic synthesis, when the large group, L, is a silyl group, and the small group, S, is hydrogen. Our interest was further stimulated by the realisation that this type of diastereoselectivity, even without a silyl group being present, was much less well studied, in spite of its fundamental nature, than the corresponding nucleophilic attack on trigonal carbon—the reaction of nucleophiles with carbonyl groups having an adjacent stereogenic centre, first systematised by Cram 30 years before we began our work, and explained with a transition structure **2**, with successive refinements by Karbatsos,[2] Felkin,[3] and Anh and their co-workers.[4] We present, in this and the following eight papers, all of our work to date in this area, with the exception of that which has already appeared in full,[5] and that which relates to natural product synthesis, which will follow in a second series of papers. To set the scene, we discuss here the *steric* factors that are either known or expected to affect the diastereoselectivity, and we also report our experiments on a simple enolate system with only carbon groups on the stereogenic centre, designed to provide a paradigm for this type of selectivity, and reported already in preliminary form.[6]

At the end of the present series we append a tenth paper summarising our results and conclusions. Less dedicated readers might like to turn to that paper now.†

Results and Discussion

Electrophilic Attack on Trigonal Carbon Adjacent to a Stereogenic Centre.—Early work in this area[7] was largely confined to cyclic systems, in which the double bond was either part of a ring or exocyclic to it. In these cases, the various constraints imposed by the ring system were dominant, and it was not sensible to generalise from them to open-chain systems. The first attempt to provide a general rule for open-chain systems was by Zimmerman,[8] who was looking at the kinetic protonation of enols and enolates. His rule, based on the argument that an exothermic reaction would have a transition structure close in geometry to that of the starting material,[9] and using, therefore, calculations of the preferred geometry of enols, suggested that attack by a protic acid would take place in the sense **3**, when the R group was large, and in the sense **4**, when the



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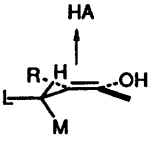

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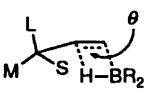
R group was small. Most of the available evidence at that time (and since) supports the idea embedded in the pictures **1** and **3**, that the small group, H, eclipses, or partially eclipses the double bond, with electrophilic attack taking place, in the absence of complicating stereoelectronic effects, on the side of the double bond opposite to the large group, L. A similar explanation was used by Barton for the addition of bromine to a double bond between C-22 and C-23 of steroids, where the medium-sized group, M, was the C-21 methyl group, and the large group, L, was the steroid residue.[10] Subsequently, the bromination of alkenes, and related reactions like bromolactonisation and sulfenylation, have been found to be more complicated stereochemically, because the diastereoselectivity of the initial attack by the electrophile is not the only factor determining the overall stereochemistry—the relative ease of opening of the two possible diastereoisomeric bridged intermediates can be decisive, when they are in rapid equilibrium with each other.[11,12]

Nevertheless, the picture **1** has many applications, and has been supported substantially by Houk and his co-workers,[13] who modified it, from an argument based solely on the ground-state, to take into account the preference in the transition structure for all the bonds, both those already in existence and

† I. Fleming, *J. Chem. Soc., Perkin Trans 1*, 1992, **24**, 3363.

that which is being formed, to be staggered. Their computations for the transition structure of hydroboration suggested a model **5**, in which the small group is tilted somewhat down, and the hydrogen atom of the borane approaches antiperiplanar to the large group. However, this picture is not always successful in accounting for the diastereoselectivity of other reactions having electrophilic character, even when the groups only differ significantly in size. Houk has found, for example, that nitrile oxide cycloadditions take place predominantly in the opposite sense.[14] For this reaction his calculations suggest a transition structure with a conformation **6**. The change in comformation from **5** to **6** is occasioned by the change in approach angle θ for



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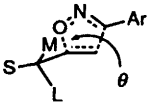

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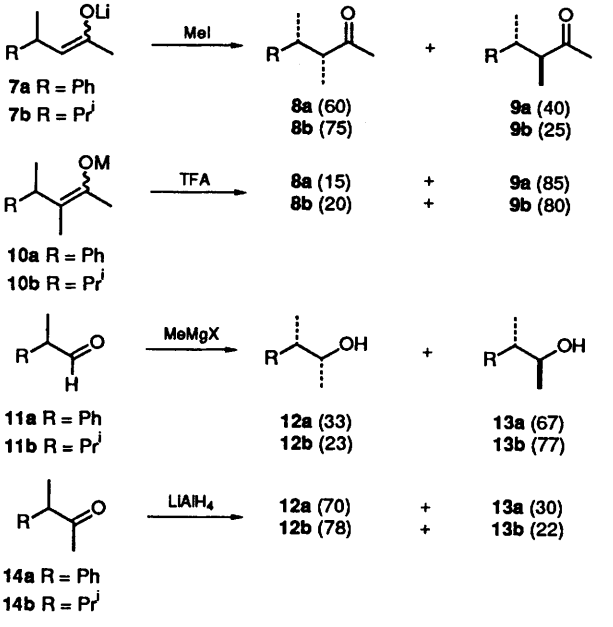
the new bond from acute for hydroboration, making the 'inside' position more hindered than the 'outside', to obtuse for nitrile oxide cycloaddition. In the latter reaction, there is more room for the medium-sized group to fit in the 'inside' position and more reason for the small group to be 'outside', where it is forced more nearly to eclipse the single bond on the adjacent trigonal carbon. This argument would seem to place great importance on the approach angle: whether it is acute or obtuse determining the sense of the diastereoselectivity. Unfortunately, the angle θ subtended by the bond forming to an incoming electrophile is not as predictably obtuse as it is for the corresponding nucleophilic reactions on carbonyl groups.[15] Whereas, some electrophiles, such as those involved in bromination, epoxidation, the Simmons-Smith reaction and hydroboration, can be expected to use acute angles, most reactions with protons or carbon electrophiles are likely to use obtuse angles,[16] because the product structure has tetrahedral geometry at this site, and the pathway to that tetrahedral geometry seems unlikely to be as devious as to begin with an acute approach followed by a large swing to the final tetrahedral angle. Fortunately, not knowing the approach angle is rarely a problem, because in most cases it appears not to be critical in determining the sense of the diastereoselectivity. Transition structures like **6**, with the medium-sized group on the 'inside', appear only to be favourable when *both* the medium-sized group *and* the substituent on the double bond *cis* to the stereogenic centre are small. When the medium-sized group is larger than a methyl group, or when the substituent *cis* to the stereogenic centre is larger than a hydrogen atom, there is much evidence that transition structures more like **5**, or its less specific relatives **1** and **3**, are followed as a consequence of allylic 1,3 strain.[17] Certainly these transition structures, or something very like them, are the most frequently invoked to explain the diastereoselectivity in such reactions as halogeno-lactonisation,[11] halogenations,[12] epoxidations,[18] osmylations,[18] sulfenylations,[19] oxypalladiation,[20] Diels–Alder reactions,[21] hydroborations[22] and the alkylation and protonation of enolates discussed below.

When the groups on the stereogenic centre also differ electronically, the story becomes more complicated, and we defer discussion of this topic to the third paper in the present series, which will be the first to deal in full with our results on compounds having a silyl group on the stereogenic centre.

We were struck by the absence of enolate alkylations from the group of reactions listed above, an absence that had also been noted by Evans.[23] Since enolate alkylations and protonations are usually carried out on ketone and ester enolates, rather than on aldehyde enolates, the substituent on the enolate double bond *cis* to the stereogenic centre is usually larger than a hydrogen atom, and transition structures like **6**, with the medium-sized group 'inside', are likely to be higher in energy than the transition structures with the small group 'inside'. While we were working on the problem, and since, several enolate alkylations and protonations taking place adjacent to a stereogenic centre carrying only carbon and hydrogen substituents have been reported,[19,24] most of which fit reasonably well with the picture **1** having the small group 'inside'. We now report the details of our own work, in which we specifically compare the sense of the diastereoselectivity of electrophilic attack on a carbon–carbon double bond **1** and the diastereoselectivity of the corresponding nucleophilic attack on a carbonyl group **2**.

Results from the Protonation and Methylation of the Enolates of Methyl Ketones.—The most straightforward reactions were the alkylations **7** → **8** + **9**, and the complementary protonations **10** → **8** + **9**, where the groups on the stereogenic centre can be unambiguously ranked, with hydrogen as the small group, methyl as the medium-sized group and either phenyl (the **a** series) or isopropyl (the **b** series) as the large group. In both cases, with the isomer **8** as the major product in the alkylations, and its diastereoisomer **9** as the major product in the protonations, the reactions follow the rule illustrated as **1**.

We prepared the enolates **7** and **10** by conjugate addition of cuprate reagents to enones. In the case of **7a**, we used both possible cuprates: conjugate addition of lithium dimethylcuprate to 4-phenylbut-3-en-2-one, and of lithium diphenylcuprate to pent-3-en-2-one, and the ratio 60:40 of alkylation products **8a**:**9a** was the same. Similarly, in the case of **10a**, we used the conjugate addition of the same cuprates to 3-methyl-4-phenylbut-3-en-2-one and 3-methylpent-3-en-2-one, respectively, again with the same result: a 15:85 ratio of the ketones **8a** and **9a** after protonation.



We measured the ratio of the products **8a** to **9a** in all these experiments by integrating the well-resolved acetyl singlets in the ^{1}H NMR spectra, and we proved the relative stereochemistry of the alkylation products by carrying out a Baeyer–Villiger reaction on the 60:40 mixture of ketones **8a** and **9a**, followed by reduction of the derived acetates using lithium aluminium hydride, to give the known alcohols **12a** and **13a**, respectively, also in a ratio of 60:40, as determined by GC. The

alcohols **12a** and **13a** were separable by column chromatography, and we identified them by comparison with IR data reported for them by Cram.[25] The yield in the Baeyer–Villiger reaction (79%) was high enough for there to be little ambiguity in correlating the major product from the alkylation reaction **8a** with the major alcohol **12a** at the end of this sequence, but we were further reassured by the recovery from the reaction mixture of a small amount of unchanged starting material **8a** + **9a**, still present in a ratio of 60:40.

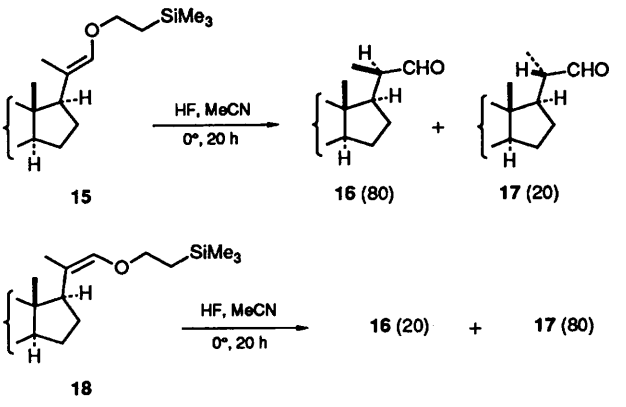
The alkylation products **8b** and **9b** were not well enough resolved in their ^{1}H NMR spectra for an accurate measurement of their ratio, and the analysis was, therefore, carried out indirectly by GC on the mixture of known alcohols **12b** and **13b** derived from them by Baeyer–Villiger reaction and reduction, as in the **a** series. We prepared an authentic sample of the alcohol **12b** by hydroboration–oxidation of (*E*)-3,4-dimethylpent-2-ene.[26] For the protonation experiments, the metal in the enolate **10b** was magnesium rather than lithium, because this enolate was prepared by the copper-catalysed addition of the isopropyl Grignard reagent to 3-methylpent-3-en-2-one.

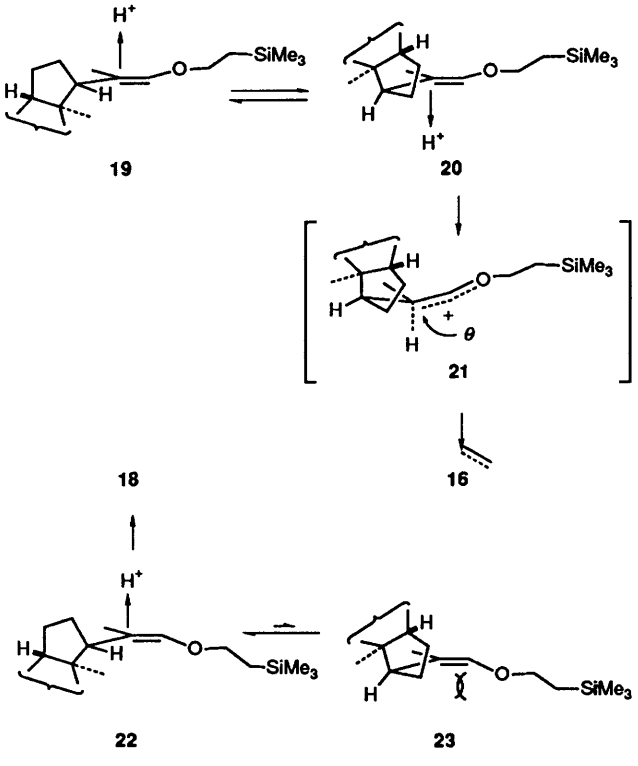
The results are almost certainly those of kinetic control, and they are certainly not the result of complete equilibration, neither in the protonation nor in the alkylation experiments. We deliberately equilibrated the ketones **8** and **9**, and obtained different ratios from those found in the alkylations and protonations—the ketones **8a** and **9a** were present at equilibrium in a ratio of 40:60, and the ketones **8b** and **9b** in a ratio of 65:35. In both cases these numbers fall between the alkylation and the protonation ratios.

The enolates undergoing the alkylations and protonations are inseparable mixtures of geometrical isomers, but it is likely that both stereoisomers will react in the same sense, although not necessarily to exactly the same degree. With either double-bond geometry, the substituent on the enolate double bond *cis* to the stereogenic centre is a group larger than a hydrogen atom—either a methyl group or the enolate oxygen. It should make little difference which of these groups is on which side, so that the argument and the calculation in favour of transition structure **3**, for example, is little affected if the enol is changed from the *E*- to the *Z*-isomer. We managed to secure some experimental support for this assertion in the case of the methylation of the enolate **7a**. When we prepared this enolate using the conjugate addition of lithium dimethylcuprate prepared from copper(I) iodide, we obtained the enolates in a ratio *E*:*Z* of 70:30, but when we prepared the enolates using lithium dimethylcuprate prepared from copper(I) cyanide, we obtained the enolates in a ratio of 50:50. Both mixtures gave the ketones **8a** and **9a** in the same ratio (60:40). Although none of these ratios is measured with great accuracy, it is clear that in this case, at least, there is no gross change in diastereoselectivity when the double bond geometry is changed.

In both series, we compared our results with the corresponding nucleophilic reactions already known, namely the attack of the methyl Grignard reagent on the aldehydes **11**[1,26,27] and the reduction of the ketones **14** with lithium aluminium hydride,[1,3,26,27] which all follow the Cram and Felkin–Anh rules. As expected, they are opposite in sense to the corresponding electrophilic reactions described above, and the pictures **1** and **2** explain the change. Thus, to pick out just one example, the reduction of the ketone **14a** by hydride attack gave the alcohols **12a** and **13a** in a ratio of 70:30, whereas the corresponding enolate undergoing protonation **10a** gave the ketones **8a** and **9a** in a ratio of 15:85.

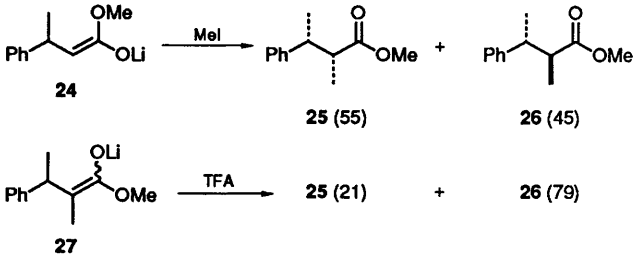
Discussion of a Related Reaction in the Literature.—There is one report of the stereochemistry of enol protonation being significantly affected by the geometry of the enol—when it was treated with acid, the enol ether **15** gave the aldehyde **16** as the major product, whereas the enol ether **18** gave largely the aldehyde **17**, with the natural steroid configuration at C-20.[28] In our preliminary communication, we drew attention to this curious result, but were unable at that time to offer an explanation. We can now suggest that this hitherto unexplained phenomenon is a consequence of the enol ether **15** having a hydrogen atom *cis* to the stereogenic centre, whereas the enolate **18** does not. The *E*-enol ether **15** can take up either conformation **19** or conformation **20** without a severe energetic penalty for the latter, and the latter will give the unnatural steroid configuration **16** if it is protonated on the lower surface. Why it should undergo protonation in a transition structure close to **20** rather than in a transition structure close to **19**, is explained by Houk's more detailed transition structure **6**, which can be translated to the present situation in the structure **21**, where a small electrophile, approaching with an obtuse angle θ, leaves room for the medium-sized group, the C-16 methylene group in this case, to fit 'inside'. The *Z*-enol ether **18**, on the other hand, will much more readily adopt the conformation **22** than the conformation **23**, and the transition structure leading from it will similarly have the hydrogen atom 'inside', because the oxygen atom of the enol ether will repel the C-16 methylene group from this position. Houk's calculations did not take this



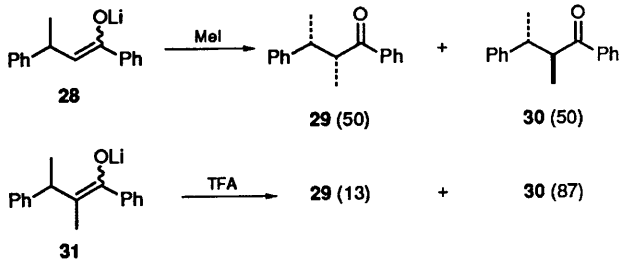


problem into account, since they dealt only with double bonds having a hydrogen atom *cis* to the stereogenic centre.

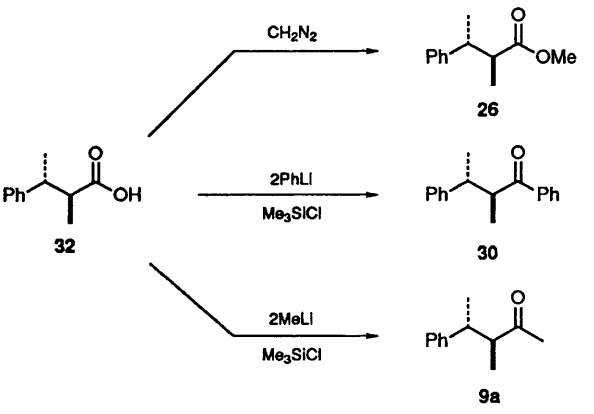
Results and Discussion of other Enolate Protonations and Methylations.—Using the stereogenic centre of the **a** series, we also looked at the alkylations and protonations of the corresponding methyl esters and phenyl ketones. In the ester series, we prepared the enolates **24** and **27** from the saturated



esters using lithium diisopropylamide, and, to guard against the possibility that there was incomplete formation of the enolate **27**, we used deuteriation in place of protonation, finding an 81% incorporation of deuterium. We measured the ratio of the isomers **25** and **26** by integration of the well-resolved methoxy signals in the ^{1}H NMR spectra, and we assigned structures by making the methyl ester **26** of an authentic sample[29] of the corresponding carboxylic acid **32**. The equilibrium ratio for the esters **25** and **26** was 34:66. In the phenyl ketone series, we prepared the enolate **28** by conjugate addition of lithium

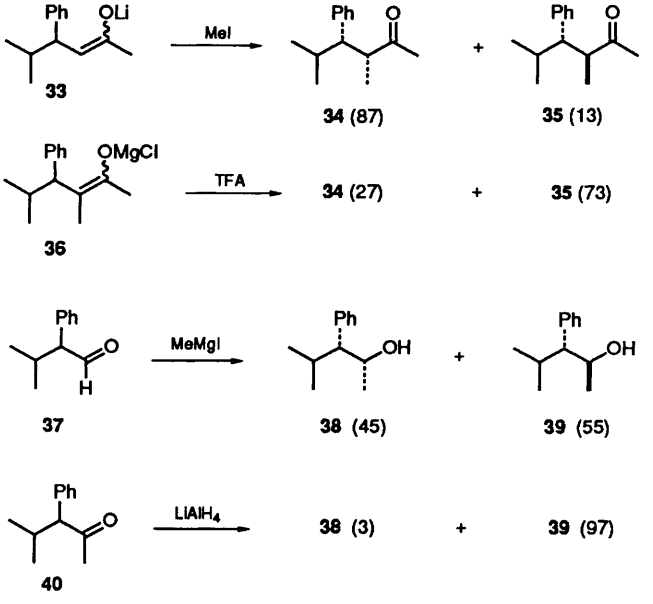


dimethylcuprate to chalcone, trapping the intermediate enolate with trimethylsilyl chloride, and regenerating it with methyllithium, but the ratio of the methylation products **29** and **30** proved to differ from run to run in the range 50:50 to 35:65, which implied that we were seeing some, or even complete, equilibration during the methylation step. Generating the enolate by deprotonation of 1,3-diphenylbutan-1-one, followed by methylation, gave the ketones in a ratio of 43:57. The equilibrium ratio was 35:65. We quote, therefore, the ratio, 50:50, obtained after the shortest reaction time, which is also the ratio furthest from the equilibrium ratio. It seems likely that the true kinetic ratio would have the ketone **29** as the major product. The protonation experiments were more straightforward, nor surprisingly, since equilibration was much less likely. Conjugate addition of lithium dimethylcuprate to 2-methyl-1,3-diphenylpropenone, and quenching with trifluoroacetic acid, gave the ketones **29** and **30** in a ratio of 13:87. We measured the ratio of the isomers **29** and **30** directly by GC, and we assigned structures by making the phenyl ketone **30** from the authentic sample[29] of the corresponding carboxylic acid **32** by treating it with phenyllithium. To make absolutely sure of some of our earlier assignments, we also converted this acid into the methyl ketone **9a**. The overall results are that the methyl ketone enolates **7a** and **10a**, the methyl ester enolates **24** and **27**, and the phenyl ketone enolates **28** and **31**, all show the same pattern in conformity with the generalised rule **1**. The small falling off in the ratio of methylation products from 60:40 in the



methyl ketone series **7a** to 50:50 in the phenyl ketone series is probably not significant, and there is no falling off in the corresponding protonations, which are very similar to each other: 15:85 in the methyl ketone series and 13:87 in the phenyl ketone series. Our results, therefore, do not support Zimmerman's suggestion in his early electrophilic rule, which has phenyl ketones adopting conformation **4**, and methyl ketones adopting conformation **3**.

We carried out a third set of experiments, in which the stereogenic centre carries a phenyl group, an isopropyl group and a hydrogen atom. We prepared the enolate **33** by conjugate



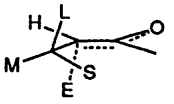
addition of lithium diphenylcuprate to 5-methylhex-3-en-2-one, and the enolate **36** by copper(I)-catalysed conjugate addition of the isopropyl Grignard reagent to 4-phenylbut-3-en-2-one. The alkylation and protonation, respectively, of these enolates gave the mixtures of ketones **34** and **35**, which were just resolved using the signals from the benzyl protons in the ^{1}H NMR spectra. The ratios were confirmed by Baeyer–Villiger oxidation of the mixtures of ketones, followed by reduction with lithium aluminium hydride, giving the alcohols **38** and **39**, in the same ratios, as measured by GC, and we assigned configurations by synthesising a pure sample of the alcohol **38** by hydroboration–oxidation of (*Z*)-4-methyl-3-phenylpent-2-ene.[30] The alkylation and protonation results were, as usual, complementary—the ketone **34** was the major product (87:13) from the alkylation, the ketone **35** was the major product (27:73) from the protonation, and the equilibrium ratio **34**:**35**

was in between (60:40). However, these reactions, do not have the groups on the stereogenic centre unambiguously ranked—hydrogen is the small group, but it is not clear whether it is the phenyl or the isopropyl group that should be counted as the large group. The results are consistent with the isopropyl group being the large group and phenyl being the medium-sized group. Conformational *A* values, which are traditionally used to rank the size of groups empirically, are known to be unreliable in this capacity, and a better measure is probably that of Sternhell, in which groups are ranked by the resistance they impart to the rotation of a biphenyl derivative.[31,†] With this measure, the isopropyl group is very much the large group (Sternhell's parameter, r^*: Ph = 1.6, Pr^i = 2.2), but the *A* values are the other way round (Ph = 2.7, Pr^i = 2.1).[32,33] It seems likely that the high *A* value for phenyl is the anomaly.

As it happens, in this series, the corresponding nucleophilic reactions were incomplete in the literature, and proved to be inconsistent with each other when we filled in the gap. The attack of the methyl Grignard reagent on the aldehyde **37** was known[34] to give the alcohol **39** as the major product but with little selectivity (55:45) over its diastereoisomer **38**. This result is consistent with Cram's and the Felkin–Anh rule, if we continue to treat isopropyl as 'larger' than phenyl. However, when we carried out the missing experiment, the reduction of the ketone **40** with lithium aluminium hydride, we obtained the same alcohol **39** with very high selectivity (97:3), the highest of any experiment in this paper. This result is only consistent with Cram's and the Felkin–Anh rule if we count phenyl as larger than isopropyl. We suggest that this remarkable result is a consequence of the same problem that has always made explaining Cram's rule difficult. Because the carbonyl group has no substituent on the oxygen, other than a Lewis acid, which is likely to be *trans* to the stereogenic centre, the ketone can adopt a conformation with any of the three substituents, L, M, or S, eclipsing the carbonyl group without a high energetic penalty. Furthermore, it has been suggested that a methyl group often prefers to be *gauche* to a phenyl rather than *anti* to it.[35] This would lead the ketone **40** to adopt a conformation with the isopropyl group eclipsing the carbonyl oxygen, even though we have been assuming that it is, marginally, the large group. To suggest that the large group should sometimes adopt this position is not unprecedented.[36] Of course, there can be no simple ranking of size in the sense required in this work, since the amount of steric hindrance offered by one group relative to that offered by another is a function of the size of the attacking reagent, its shape, its electronic nature, the approach angle and the force constants for deformation from the preferred approach angle. In the face of all these largely independent variables, it is hardly surprising that no single measure of size can safely be carried over from one reaction to another, especially if the reactions are of very different kinds.

In conclusion, we have found a representative set of enolate alkylations and protonations, which we offer as a paradigm for the stereochemistry of electrophilic attack adjacent to a stereogenic centre having groups that differ significantly only in size. We note that the electrophilic rule covering these reactions is opposite in sense from Cram's and the Felkin–Anh rule, which cover the corresponding nucleophilic reactions. The only exception to this pattern comes in a reaction that appears to be anomalous by Cram's and the Felkin–Anh rule, not by the electrophile rule.

Although we have for a number of years consistently used the general picture **1** to illustrate the diastereoselectivity of all kinds of electrophilic attack on a double bond, we would suggest, following Houk's argument, that it needs to be modified in detail for the specific cases of enolate alkylation and protonation, which are likely to have transition structures closer to **41**. In this picture, some rotation has taken place



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about the bond between the stereogenic centre and the double bond, allowing the groups on the stereogenic centre and the bonds, both existing and developing, at the reaction site to be staggered in a more favourable arrangement. We shall continue to use the picture **1** for the general case, while acknowledging that it is not, in detail, adequate for more specific reactions.

Experimental

Light petroleum refers to the fraction boiling between 30 and 40 °C.

2-(4-*Phenylpent*-2-*enyloxy*)*trimethylsilane*.—(*E*)-4-Phenylbut-3-en-2-one (1.2 g, 8 mmol) in ether (10 cm^3) was added to lithium dimethylcuprate (14 mmol from CuI) at −23 °C under nitrogen. After 20 min, triethylamine (4.2 cm^3, 30 mmol) and chlorotrimethylsilane (3.8 cm^3, 30 mmol) were added. After being stirred for 16 h, the mixture was poured into aqueous ammonium chloride (30 cm^3) and extracted with ether (20 cm^3). The extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Bulb-to-bulb distillation gave a mixture of the *silyl enol ethers* (1.75 g, 91%), b.p. 80 °C/0.1 mmHg; R_f (light petroleum–Et_2O, 9:1) 0.68; ν_{max}(film)/cm^{-1} 1670 (C=C); δ (250 MHz; CD_2Cl_2) (*E*): 7.4–7.1 (5 H, m, Ph), 4.85 (1 H, br d, *J* 11, CH=C), 3.55 (1 H, dq, *J* 7 and 11, PhC*H*), 1.8 (3 H, br s, MeC=C), 1.35 (3 H, d, *J* 7, *Me*CH) and 0.2 (9 H, s, $SiMe_3$); (*Z*): 7.1–7.4 (5 H, m, Ph), 4.65 (1 H, br d, *J* 11, CH=C), 3.8 (1 H, dq, *J* 7 and 11, PhC*H*), 1.85 (3 H, br s, MeC=C), 1.3 (3 H, d, *J* 7 *Me*CH) and 0.2 (9 H, s, $SiMe_3$) (Found: C, 71.9; H, 9.4. $C_{14}H_{22}SiO$ requires C, 71.7; H, 9.46%). The *E*:*Z* ratio was 70:30, with configurations assigned by NOE difference spectra irradiating at the frequency of the C=CMe group, and detecting an enhancement in the signals of the benzyl-H and the vinyl-H, respectively. A repeat of the experiment with cuprate made using copper(I) cyanide gave a 60% yield and an *E*:*Z* ratio of 50:50.

3-*Methyl*-4-*phenylpentan*-2-*one* **8a** *and* **9a** *by Methylation*.—Methyllithium in ether (1.4 mol dm^{-3}; 15 cm^3, 21 mmol) was added to the silyl enol ethers (1.6 g, 7 mmol) in THF (40 cm^3) at 0 °C under nitrogen. After 30 min, methyl iodide (1.9 cm^3, 30 mmol) was added. This mixture was maintained at −5 °C for 48 h. The solvent was evaporated under reduced pressure, and the residue was partitioned between ether (20 cm^3) and water (20 cm^3). The aqueous phase was separated and extracted with ether (20 cm^3). The ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel (100 g) eluting with ether–light petroleum (1:99) to give a mixture of the *ketones* (0.70 g, 58%); R_f (light petroleum–Et_2O, 7.3, 0.47); ν_{max}(film)/cm^{-1} 1710 (C=O); δ (250 MHz; $CDCl_3$) (3*RS*, 4*RS*)-**8a**: 7.3–7.14 (5 H, m, Ph), 3.02 (1 H, quintet, *J* 7, Ph C*H*), 2.78 (1 H, quintet, *J* 7, CHCO), 1.85 (3 H, s, COMe), 1.23 (3 H, d, *J* 7, PhCH*Me*) and 1.23 (3 H, d, *J* 7, COCH*Me*); (3*RS*, 4*SR*)-**9a**: 7.3–7.14 (5 H, m, Ph), 2.9 (1 H,

† For another measure of size, calculated rather than empirical, but in agreement with isopropyl being a more sterically hindering group than phenyl, see M. Charton, *J. Am. Chem. Soc.*, 1975, **97**, 1552, *J. Org. Chem.*, 1976, **41**, 2217; 1977, **42**, 2528.

quintet, *J* 7, PhC*H*), 2.7 (1 H, quintet, *J* 7, CHCO), 2.18 (3 H, s, COMe), 1.19 (3 H, d, *J* 7, PhCH*Me*) and 0.83 (3 H, d, *J* 7, COCH*Me*), in the ratio 60:40 (Found: C, 82.1; H, 9.3. $C_{12}H_{16}O$ requires C, 81.8, H, 9.15%). Alkylation of the lithium enolates generated from the 50:50 *E*:*Z* mixture of silyl enol ethers gave the same ratio of diastereomers as above in 50% yield.

Other Alkylation Procedures giving the Ketones **8a** *and* **9a**.—(A) (*E*)-4-Phenylbut-3-en-2-one (0.5 g, 3.4 mmol) in ether (5 cm^3) was added to lithium dimethylcuprate (5 mmol) under nitrogen at −23 °C. After being stirred for 10 min, the mixture was centrifuged at room temperature. The supernatant was transferred by a canula to a dry flask under nitrogen. The solvent was evaporated in a stream of nitrogen and the residue dissolved in THF (10 cm^3). Methyl iodide (2.5 g, 15 mmol) was added, and the solution was maintained at −5 °C for 48 h. Work-up as before gave the ketones (0.31 g, 51%) in the same ratio as before, as shown by NMR (60 MHz). (B) (*E*)-Pent-3-en-2-one (0.5 g, 6 mmol) in ether (5 cm^3) was added to lithium diphenylcuprate (from CuCN, 12 mmol) at −78 °C under nitrogen. After 1 h, the mixture was allowed to warm to room temperature. Triethylamine (3.5 cm^3, 25 mmol) and chlorotrimethylsilane (3.2 cm^3, 25 mmol) were added, and the mixture was stirred at room temperature for 18 h. Work-up and distillation as before gave the silyl enol ethers (1.9 g). This product was dissolved in THF, and treated with methyllithium (1.4 mol dm^{-3}; 9 cm^3, 20 mmol) at 0 °C for 2 h. Methyl iodide (1.4 cm^3) was added, and the mixture was maintained at −5 °C for 48 h. Work-up as before gave the ketones (0.34 g, 33%) in the same ratio as before, as shown by NMR (60 MHz). (C) A solution of (*E*)-pent-3-en-2-one (0.5 g, 6 mmol) in ether (5 cm^3) was added to a solution of lithium diphenylcuprate (from CuBr, 20 mmol) in ether at 0 °C under nitrogen. The mixture was then treated as in experiment (A) above to give the ketones (0.45 g, 42%) in the same ratio as before, as shown by NMR (60 MHz).

3-*Methyl*-4-*phenylpentan*-2-*one* **8a** *and* **9a** *by Protonation*.—(A) 3-Methyl-4-phenylbut-3-en-2-one[37] (1.5 g, 9.4 mmol) in ether (15 cm^3) was added to lithium dimethylcuprate (15 mmol) at −23 °C under nitrogen. After 20 min, the mixture was cooled to −78 °C, and trifluoroacetic acid (TFA) (1.5 cm^3, 20 mmol) was added. After 5 min, the mixture was diluted with aqueous ammonium chloride (30 cm^3) and extracted with ether (30 cm^3). The ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel (100 g) eluting with ether–light petroleum (1:99) to give the mixture of ketones (1.40 g, 85%) in a ratio of 15:85. (B) A solution of (*Z*)-3-methylpent-3-en-2-one[38] (0.5 g, 5 mmol) in ether (5 cm^3) was added to a solution of lithium diphenylcuprate (from CuBr, 10 mmol) at 0 °C under nitrogen. After 45 min, the mixture was cooled to −78 °C, and TFA (1.1 cm^3, 15 mmol). Work-up and purification as for (A) gave the mixture of ketones (0.63 g, 70%), in the same ratio, as shown by NMR (60 MHz).

3,4,5-*Trimethylhexan*-2-*one* **8b** *and* **9b** *by Methylation*.—5-Methylhex-3-en-2-one (2.0 g, 18 mmol) in ether (10 cm^3) was added to lithium dimethylcuprate (22 mmol) at −23 °C under nitrogen. After 20 min, the ether was removed in a stream of nitrogen and the residue dissolved in THF. After the solution had been cooled to 0 °C, methyl iodide (3.1 cm^3, 50 mmol) was added and the mixture kept at −5 °C for 16 h. Work-up and purification in the usual way gave the *ketones* **8b** and **9b** together with 4,5-dimethylhexan-2-one[39] (1.7 g, 67%); R_f (light petroleum–Et_2O, 9:1) 0.36; ν_{max}(film)/cm^{-1} 1710 (C=O); δ (250 MHz; $CDCl_3$) (3*RS*, 4*SR*) **8b**: 2.37 (1 H, dq, *J* 10 and 7, CHCO), 2.1 (3 H, s, COMe), 1.9–1.4 (2 H, m, Me_2CH_2) and 1.04–0.69 (12 H, m, remainder); (3*RS*, 4*RS*)-**9b**: 2.58 (1 H, quintet, *J* 6.7, CHCO), 2.1 (3 H, s, COMe), 1.9–1.4 (2 H, m, Me_2CH_2) and 1.04–0.69 (12 H, m, remainder) (Found: C, 75.8; H, 12.95. $C_9H_{18}O$ requires C, 76.0; H, 12.70%). The NMR spectrum also had the signals, see below, of the unmethylated ketone, in a ratio (GC, Carbowax 20 M column, 70 °C, carrier flow of 300 kp, with retention times of 15 min for the unmethylated ketone, and 25 min for the mixture of methylated ketones) **8b** + **9b**: unmethylated ketone of 80:20, and (NMR) **8b**:**9b** consistent with the ratio of 75:25 deduced more accurately by GC analysis of the alcohols after the Baeyer–Villiger reaction.

4,5-*Dimethylhexan*-2-*one*.—5-Methylhex-3-en-2-one (0.5 g, 4.5 mmol) was added to a solution of lithium dimethylcuprate (5.0 mmol) at −23 °C under nitrogen. After 20 min, the reaction mixture was worked up, and the product purified in the usual way to give the unmethylated ketone[39] (0.4 g, 71%); R_f (light petroleum–Et_2O, 9:1) 0.36; ν_{max}(film)/cm^{-1} 1710 (C=O); δ (250 MHz; $CDCl_3$) 2.45–2.1 (2 H, m, CH_2CO), 2.11 (3 H, s, COMe), 2.0–1.85 (1 H, m, CH_2CH), 1.6–1.45 (1 H, m, Me_2CH) and 1.9–1.8 (6 H, m, Me_2CH).

3,4,5-*Trimethylhexan*-2-*one* **8b** *and* **9b** *by Protonation*.—Isopropylmagnesium chloride (2 mol dm^{-3}; 10 cm^3, 20 mmol) in ether (30 cm^3) was added dropwise to a mixture of copper(I) iodide (0.4 g), 3-methylpent-3-en-2-one (1.5 g, 15 mmol) and ether (20 cm^3) over 30 min at 0 °C under nitrogen. After 1 h, the mixture was cooled to −78 °C and TFA (1.9 cm^3, 25 mmol) was added. Work-up and purification in the usual way gave a mixture of the ketones (1.60 g, 74%) in a ratio (NMR) consistent with the ratio of 20:80 deduced by GC analysis of the alcohols.

Methyl 2-*Methyl*-3-*phenylbutanoate* **25** *and* **26** *by methylation*.—Methyl 3-phenylbutanoate (0.50 g, 2.8 mmol) in THF (5 cm^3) was added to LDA (3.1 mmol) at −78 °C under nitrogen. After 30 min, methyl iodide (0.31 cm^3, 5 mmol) was added. After a further 30 min at −78 °C, the solvent was removed under reduced pressure and the residue partitioned between water (30 cm^3) and ether (20 cm^3). The ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was distilled to give the esters[40] (0.53 g, 98%), b.p. 80 °C/1 mmHg (bulb-to-bulb); R_f (light petroleum-Et_2O, 9:1) 0.5; ν_{max}(film)/cm^{-1} 1720 (C=O); δ (250 MHz; $CDCl_3$) (2*RS*, 3*RS*)-**25**: 7.3–7.14 (5 H, m, Ph), 3.46 (3 H, s, OMe), 3.05 (1 H, quintet, *J* 7, PhC*H*), 2.66 (1 H, quintet, *J* 7, CHCO), 1.25 (3 H, d, *J* 7, PhCH*Me*) and 1.16 (3 H, d, *J* 7, *Me*CHCO); (2*RS*,3*SR*)-**26**: 7.33–7.14 (5 H, m, Ph), 3.7 (3 H, s, OMe), 2.87 (1 H, dq, *J* 10 and 7, PhC*H*) 2.6 (1 H, dq, *J* 10 and 6.8, CHCO), 1.23 (3 H, d, *J* 7, PhCH*Me*) and 0.92 (3 H, d, *J* 6.8, *Me*CHCO), in a ratio of 55:45.

Methyl 2-*Methyl*-3-*phenyl*[2-^{2}H]-*butanoate* **25** *and* **26**.—The esters **25** and **26** (0.3 g, 1.6 mmol) in THF (5 cm^3) were added to LDA (2.4 mmol) in THF at 0 °C under nitrogen. After 30 min, the solution was cooled to −78 °C and MeOD (0.4 cm^3, 10 mmol) was added. The solution was allowed to warm to room temperature after which the solvent was removed under reduced pressure. The residue was diluted with water (20 cm^3) and extracted with ether (2 × 10 cm^3), and the extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the esters (0.28 g, 93%). Integration of signals in the 250 MHz NMR spectrum of the product showed 81% incorporation of deuterium, and a ratio of 21:79.

1,3-*Diphenylbut*-1-*enyloxy*(*trimethyl*)*silane*.—Chalcone (1 g, 5 mmol) in ether (5 cm^3) was added to lithium dimethylcuprate (15 mmol) at 0 °C under nitrogen. After 15 min, triethylamine (5 cm^3, 36 mmol) and chlorotrimethylsilane (4.6 cm^3, 36 mmol)

were added. After being stirred at room temperature for 16 h, the mixture was poured into aqueous ammonium chloride (30 cm^3) and extracted with ether (20 cm^3). The extracts were dried ($MgSO_4$), and evaporated under reduced pressure. Distillation gave a mixture of the *silyl enol ethers* (1.36 g, 96%), b.p. 120 °C/0.1 mmHg (bulb-to-bulb); R_f (light petroleum–Et_2O, 9:1) 0.6; ν_{max}(film)/cm^{-1} 1640 (C=C); δ (250 MHz; $CDCl_3$) 7.53–7.2 (10 H, m, Ph), 5.2 (1 H, d, *J* 9.7, C=CH), 4.05 (1 H, dq, *J* 9.7 and 7, PhC*H*), 1.43 (3 H, d, *J* 7, Me) and 0.13 (9 H, s, $SiMe_3$) (Found: C, 77.1, H, 8.2. $C_{19}H_{24}OSi$ requires C, 77.0, H, 8.10%).

2-*Methyl*-1,3-*diphenylbutan*-1-*one* **29** *and* **30** *by Methylation: Method A*.—Methyllithium in ether (1.8 mol dm^{-3}; 5.5 cm^3, 10 mmol) was added to the silyl enol ethers (1.1 g, 3.7 mmol) in THF (30 cm^3) at 0 °C under nitrogen. After 30 min, methyl iodide (1.2 cm^3, 20 mmol) was added and the solution kept at −5 °C for 48 h. The solvent was evaporated under reduced pressure and the residue partitioned between water (20 cm^3) and ether (20 cm^3). The ether extract was dried ($MgSO_4$) and evaporated under reduced pressure and the residue was distilled to give the ketones[41] (0.84 g, 95%) b.p. 140 °C/0.1 mmHg (bulb-to-bulb); R_f (light petroleum–Et_2O, 9:1) (2*RS*,3*SR*) 0.49 and (2*RS*,3*RS*) 0.43; ν_{max}(film)/cm^{-1} 1680 (C=O); δ (250 MHz; $CDCl_3$; 60 MHz) (2*RS*,3*SR*)-**29**: 8.0–7.0 (10 H, m, 2 × Ph), 3.8–3.0 (2 H, m, CHCH), 1.15 (3 H, d, *J* 7, *Me*CHCO), 1.0 (3 H, d, *J* 7, *Me*CHPh); (2*RS*,3*RS*)-**30**: 8.0–7.0 (10 H, m, 2 × Ph), 4.0–3.0 (2 H, m, CHCH), 1.3 (3 H, d, *J* 7, *Me*CHCO) and 1.2 (3 H, d, *J* 7, *Me*CHPh), in a ratio of 50:50 (GC, Carbowax 20 M column, 180 °C, flow rate 410 kp, with retention times of 104 min and 92 min, respectively).

1,3-*Diphenylbutan*-1-*one*.—Chalcone (0.5 g, 2.4 mmol) in ether (5 cm^3) was added to lithium dimethylcuprate (10 mmol) at 0 °C under nitrogen. The reaction was worked up in the usual way to give the ketone (0.51 g, 95%) as plates, m.p. 73–75 °C (from hexane) (lit.,[42] 73–75 °C); R_f (light petroleum–Et_2O, 9:1), 0.4; ν_{max}(Nujol)/cm^{-1} 1680 (C=O); δ (250 MHz; $CDCl_3$) 8.0–7.0 (10 H, m, 2 × Ph), 3.6–3.2 (3 H, m, CH_2CH) and 1.45 (3 H, d, *J* 6, Me).

2-*Methyl*-1,3-*diphenylbutan*-1-*one* **29** *and* **30** *by Methylation: Method B*.—1,3-Diphenylbutan-1-one (0.3 g, 1.3 mmol) in THF (5 cm^3) was added to LDA (1.8 mmol) in THF (15 cm^3) at −78 °C under nitrogen. After 15 min, methyl iodide (0.31 cm^3, 5 mmol) was added, and the solution kept at −5 °C for 48 h. Work-up as before gave the ketones (0.32 g) in a ratio of 43:57.

2-*Methyl*-1,3-*diphenylbutan*-1-*one* **29** *and* **30** *by Protonation*.—2-Methyl-1,3-diphenylprop-2-en-1-one[43] (0.5 g, 2.3 mmol) in ether (5 cm^3) was added to lithium dimethylcuprate (7.5 mmol) at −78 °C under nitrogen. After 30 min, the mixture was cooled to −78 °C and TFA (0.8 cm^3, 10 mmol) was added. The product was worked up in the usual way to give the mixture of ketones (0.49 g, 91%) in a ratio of 13:87.

3,5-*Dimethyl*-4-*phenylhexan*-2-*one* **34** *and* **35** *by Methylation*.—5-Methylhex-3-en-2-one (0.70 g, 6.3 mmol) in ether (5 cm^3) was added to lithium diphenylcuprate (from CuCN, 10 mmol) under nitrogen at −78 °C. After 2 h, the ether was removed in a stream of nitrogen, and the residue dissolved in THF. The mixture was cooled to 0 °C, and methyl iodide (1.4 cm^3, 22 mmol) added and the mixture maintained at −5 °C for 16 h. Work-up and purification in the usual way gave the mixture of *ketones* (0.69 g, 54%); R_f (light petroleum–Et_2O, 7:3) 0.54; ν_{max}(film)/cm^{-1} 1715 (C=O); δ (250 MHz; $CDCl_3$) (3*RS*,4*SR*) **34**: 7.3–7.05 (5 H, m, Ph), 3.05 (1 H, dq, *J* 7 and 9.5, CHCO), 2.70 (1 H, dd, *J* 6 and 9.5, PhC*H*), 2.15 (3 H, s, COMe), 1.87 (1 H, m, C*H*Me_2) and 1.2–0.75 (9 H, m, remainder); (3*RS*,4*RS*)-**35**: 7.3–7.05 (5 H, m, Ph), 3.07 (1 H, dq, *J* 7 and 10.5, CHCO), 2.73 (1 H, dd, *J* 4.5 and 10.5, PhC*H*), 2.15 (1 H, m, C*H*Me_2), 1.85 (3 H, s, COMe) 1.18–0.75 (9 H, m, remainder), in a ratio of 87:13 (Found: C, 82.6; H, 9.95. $C_{14}H_{20}O$ requires C, 82.3; H, 9.80%).

3,5-*Dimethyl*-4-*phenylhexan*-2-*one* **34** *and* **35** *by Protonation*.—Isopropylmagnesium chloride (2 mol dm^{-3}; 10 cm^3, 20 mmol) in ether (40 cm^3) was added dropwise to a mixture of copper(I) iodide (0.4 g), 3-methyl-4-phenylbut-3-en-2-one (1.5 g, 9.4 mmol) and ether (20 cm^3) over 35 min at 0 °C under nitrogen. After 1 h, the mixture was cooled to −78 °C and TFA (1.9 cm^3, 25 mmol) was added. Work-up and purification in the usual way gave a mixture of the ketones (1.48 g, 77%) in a ratio of 27:73.

Equilibrations.—Three of the ketone pairs were kept at room temperature in a solution of sodium ethoxide in ethanol (*ca.* 1 mol dm^{-3}) for the following times, by which time equilibration was complete: **8a** and **9a**, 4 h, 40:60; **29** and **30**, 48 h, 35:65; **34** and **35**, 72 h, 60:40. 3,4,5-Trimethylhexan-2-one was equilibrated using sodium methoxide in methanol (0.5 mol dm^{-3}) for 48 h, giving **8b**:**9b** 65:35, and methyl 2-methyl-3-phenylbutanoate was equilibrated using potassium *tert*-butoxide in *tert*-butyl alcohol (0.2 mol dm^{-3}) giving **25**:**26** 34:66. Yields of equilibrated mixtures were >90%, except for 3,4,5-trimethylhexan-2-one, where the recovery was only 83%.

Baeyer–Villiger Oxidation[44] *of the Methyl Ketones*.—Trifluoroacetic anhydride (0.3 cm^3, 2 mmol) was added to a mixture of hydrogen peroxide (90%; 0.06 g) in dichloromethane (3 cm^3) at 0 °C. After 10 min, the solution was added to a mixture of ketone (1 mmol), disodium hydrogen phosphate (0.43 g, 3 mmol) and dichloromethane (4 cm^3) at 0 °C. The mixture was allowed to warm to room temperature over 2 h after which it was stirred for an additional 16 h and then poured into aqueous sodium hydrogen carbonate and extracted with dichloromethane (2 × 5 cm^3). The organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was chromatographed on silica gel (30 g) eluting with ether–light petroleum (1:99) to give the following acetates. The yields are given first for the acetates derived from the alkylation mixture and second from the protonation mixture.

3-*Phenylbut*-2-*yl Acetates* (77%, 79%); R_f (light petroleum–Et_2O, 7:3), 0.53; ν_{max}(film)/cm^{-1} 1730 (C=O); δ (250 MHz; $CDCl_3$) (2*RS*,3*SR*): 7.33–7.17 (5 H, m, Ph), 5.0 (1 H, dq, *J* 7.9 and 6.3, CHCO), 2.84 (1 H, m, PhC*H*), 2.06 (3 H, s, COMe), 1.27 (3 H, d, *J* 7, PhCH*Me*) and 1.04 (3 H, d, *J* 6.3, *Me*CHO); (2*RS*,3*RS*): 7.3–7.17 (5 H, m, Ph), 5.1 (1 H, quintet, *J* 6.4, CHCO), 2.9 (1 H, m, PhC*H*), 1.9 (3 H, s, COMe), 1.27 (3 H, d, *J* 7.2, PhCH*Me*) and 1.15 (3 H, d, *J* 6.4, *Me*CHCO) (Found: C, 75.2; H, 8.41. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.35%).

2,3-*Dimethylpentan*-2-*yl Acetates* (71%, 63%, and, from the equilibrated mixture, 68%); R_f (light petroleum–Et_2O, 9:1), 0.50; ν_{max}(film)/cm^{-1} 1725 (C=O); δ (250 MHz; $CDCl_3$) (2*RS*,3*SR*): 4.9 (1 H, quintet, *J* 6, MeC*H*O), 2.0 (3 H, s, COMe), 1.7–1.6 (1 H, m, Me_2CH), 1.4–1.3 (1 H, m, Me_2CHCH), 1.18 (3 H, d, *J* 6.3, *Me*CHCO) and 0.9–0.77 (9 H, m, remainder); (2*RS*,3*RS*): 4.85 (1 H, dq, *J* 7.3 and 6.3, MeC*H*O), 2.0 (3 H, s, COMe), 1.7–1.6 (1 H, m, Me_2CH), 1.6–1.5 (1 H, m, Me_2CHCH), 1.12 (3 H, d, *J* 6.3, *Me*CHO) and 0.9–0.77 (9 H, m, remainder) (Found: C, 68.7; H, 11.05. $C_9H_{18}O_2$ requires C, 68.4; H, 11.3%).

4-*Methyl*-3-*phenylpentyl Acetates* (73%, 75%) R_f (light petroleum–Et_2O, 7:3) 0.55; ν_{max}(film)/cm^{-1} 1730 (C=O); δ

(250 MHz; $CDCl_3$) (2*RS*,3*RS*): 7.3–7.1 (5 H, m, Ph), 5.35 (1 H, dq, *J* 8.8 and 6.3, CHO), 2.65 (1 H, dd, *J* 6.3 and 8.8, PhC*H*), 2.1–2.0 (1 H, m, Me_2CH), 2.04 (3 H, s, COMe) and 1.04–0.67 (9 H, m, remainder); (2*RS*,3*SR*): 7.3–7.1 (5 H, m, Ph), 5.4 (1 H, m, CHCO), 2.25 (1 H, dd, *J* 4.6 and 9.2, PhC*H*), 2.1–2.0 (1 H, m, Me_2CH), 2.00 (3 H, s, COMe) and 1.04–0.67 (9 H, m, remainder) (Found: C, 76.4; H, 9.0. $C_{14}H_{20}O_2$ requires C, 76.4; H, 9.10%).

Cleavage of the Acetates with Lithium Aluminium Hydride.—The acetate (1 mmol) in ether (2 cm^3) was added to a mixture of lithium aluminium hydride (LAH) (1 mmol) in ether (5 cm^3) at 0 °C. After 15 min, the mixture was diluted with water (10 cm^3) and extracted with ether (2 × 10 cm^3) and the extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was distilled (Kugelrohr) to give the following alcohols.

3-*Phenylbutan*-2-*ols*[25] **12a** *and* **13a** (96%, 94%). R_f (light petroleum–Et_2O, 7:3), 0.16; ν_{max}(film)/cm^{-1} 3300 (OH); δ (250 MHz; $CDCl_3$) (2*RS*,3*SR*)-**12a**: 7.35–7.18 (5 H, m, Ph), 3.9 (1 H, br quintet, *J* 6.3, C*H*OH), 2.7 (1 H, br quintet, *J* 7, PhC*H*), 1.5 (1 H, br s, OH), 1.32 (3 H, d, *J* 7, PhCH*Me*) and 1.08 (3 H, d, *J* 6.3, *Me*CHOH); (2*RS*,3*RS*)-**13a**: 7.36–7.18 (5 H, m, Ph), 3.84 (1 H, dq, *J* 8.6 and 6.3, C*H*OH), 2.67 (1 H, m, PhC*H*), 1.46 (1 H, br s, OH), 1.26 (3 H, d, *J* 7, PhCH*Me*) and 1.22 (3 H, d, *J* 6.3, *Me*CHOH). A sample of the mixture of alcohols was separated by chromatography on silica, eluting with ether–light petroleum (1:99). The two diastereoisomers were identified by the comparison of IR spectra with those recorded in the literature. GC was performed on a Carbowax 20 M column at 160 °C, with a carrier flow of 410 kp. Peak retention times were (2*RS*,3*RS*) 15.8 min, and (2*RS*,3*SR*) 19 min.

3,4-*Dimethylpentan*-2-*ol*[26] **12b** *and* **13b** (85%, 91% and, from the equilibrated mixture, 87%) R_f (light petroleum–Et_2O, 7:3) 0.22; ν_{max}(film)/cm^{-1} 3350 (OH); δ (250 MHz; $CDCl_3$) (2*RS*,3*SR*)-**12b** 3.8 (1 H, quintet, *J* 6.3, C*H*OH), 1.85–1.6 (1 H, m, Me_2CHCH), 1.3–1.1 (2 H, m, Me_2CH and OH), 1.17 (3 H, d, *J* 6.3, *Me*CHCO) and 0.94–0.73 (9 H, m, remainder), and (2*RS*,3*RS*)-**13b** 3.7 (1 H, m, C*H*OH), 2.0–1.85 (1 H, m, Me_2CHCH), 1.3–1.1 (2 H, m, Me_2CH and OH), 1.13 (3 H, d, *J* 6.3, *Me*CHCO) and 0.94–0.70 (9 H, m, remainder). GC was performed on a Carbowax 20 M column at 70 °C, with a carrier flow of 370 kp. Peak retention times were (2*RS*,3*SR*) 19.5 min and (2*RS*,3*RS*) 23 min. The alcohols derived from the enolate alkylation reaction were separated from the impurity derived from the unmethylated ketone by GC on an OV 17 column at 35 °C with a carrier flow of 200 kp, which showed that 25% of product was unmethylated.

4-*Methyl*-3-*phenylpentan*-2-*ol*[45] **38** *and* **39** (91%, 98%). R_f (light petroleum–Et_2O, 7:3) 0.18; ν_{max}(film)/cm^{-1} 3400 (OH); δ (250 MHz; $CDCl_3$) (2*RS*,3*RS*)-**38**: 7.3–7.1 (5 H, m, Ph), 4.1 (1 H, m, C*H*OH), 2.45 (1 H, br t, *J* 7, PhC*H*), 2.2 (1 H, m, Me_2CH), 1.3 (1 H, br s, OH) and 1.07–0.7 (9 H, m, remainder); (2*RS*,3*SR*)-**39**: 7.3–7.1 (5 H, m, Ph), 4.18 (1 H, m, C*H*OH), 2.2 (2 H, m, PhC*H* and Me_2CH), 1.3 (1 H, br s, OH) and 1.1–0.7 (9 H, m, remainder). GC was performed on a FFAP/W column at 125 °C, with a carrier flow of 410 kp. Peak retention times were (2*RS*,3*SR*) 11 min, and (2*RS*,3*RS*) 15 min.

3-*Methyl*-2-*phenylbutanol* **37**.—2-Phenylbut-2-enal[46] (2 g, 14 mmol) in ether (10 cm^3) was added to lithium dimethylcuprate 18 mmol) at −23 °C under nitrogen. After 15 min, the reaction was worked up in the usual way, and the product chromatographed on silica gel (100 g) eluting with ether–light petroleum (1:99) to give the aldehyde[45] (1.7 g, 78%); R_f (light petroleum–Et_2O, 9:1) 0.34; ν_{max}(film)/cm^{-1} 1710 (C=O), δ (60 MHz; $CDCl_3$) 9.6 (1 H, d, *J* 4, CHO) 7.4–6.9 (5 H, m, Ph), 3.2 (1 H, dd, *J* 4 and 9, PhC*H*Me), 2.6–2.2 (1 H, m, Me_2CH) and 1.3–0.8 (6 H, m, Me_2CH).

4-*Methyl*-3-*phenylpentan*-2-*ol* **38** *and* **39** *by Grignard Addition to the Aldehyde* **37**.—Methyl iodide (0.3 cm^3, 5 mmol) in ether (10 cm^3) was added to a suspension of magnesium (0.3 g, 5 mmol) in ether (10 cm^3) at such a rate as to maintain a gentle reflux. The mixture was refluxed for 30 min, and then cooled. The aldehyde (0.5 g, 3 mmol) in ether (10 cm^3) was added dropwise over 10 min at 0 °C to methylmagnesium iodide (5 mmol) in ether (10 cm^3). After 20 min, the mixture was poured into water (20 cm^3) and extracted with ether (20 cm^3), and the extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the alcohols (0.52 g, 95%) in a ratio of 45:55.

4-*Methyl*-3-*phenylpentan*-2-*one* **40**.—The alcohols **38** and **39** (0.95 g, 5 mmol) and pyridinium dichromate (2.6 g, 7.0 mmol) in dimethylformamide (15 cm^3) were stirred at room temperature for 24 h. The mixture was poured into water (50 cm^3) and extracted with ether (2 × 20 cm^3). The ether extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure, and the residue chromatographed on silica gel (50 g) eluting with ether–light petroleum (1:99) to give the ketone[47] (0.6 g, 65%); R_f (light petroleum–Et_2O, 7:3) 0.59; ν_{max}(film)/cm^{-1} 1705 (C=O); δ (250 MHz; $CDCl_3$) 7.3–7.2 (5 H, m, Ph), 3.3 (1 H, br d, *J* 10.4, PhC*H*), 2.4 (1 H, m, Me_2CH), 2.07 (3 H, s, COMe) and 0.97 and 0.65 (6 H, 2 × d, *J* 6.4 and 6.7, Me_2CH).

4-*Methyl*-3-*phenylpentan*-2-*ol* **38** *and* **39** *by Reduction of the Ketone* **40**.—The ketone (0.3 g, 1.7 mmol) in ether (5 cm^3) was added dropwise to a suspension of LAH (0.2 g) in ether (15 cm^3) at −78 °C under nitrogen. After 30 min, the mixture was diluted with water (25 cm^3), extracted with ether (20 cm^3), and the extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the alcohols (0.3 g, 99%) in a ratio of 3:97.

(*Z*)-4-*Methyl*-3-*phenylpent*-2-*ene*.—(Ethyl)triphenylphosphonium bromide (5 g, 13.5 mmol) was added in portions to butyllithium (1.5 mol dm^{-3}; 10 cm^3, 15 mmol) in hexane (15 cm^3) and ether (10 cm^3) under nitrogen, and the mixture refluxed for 1 h. Isobutyrophenone (2.4 g, 16 mmol) in ether (10 cm^3) was added dropwise over 30 min and the mixture was refluxed for 3 h, poured into water (50 cm^3) and extracted with ether (2 × 20 cm^3). The ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was triturated with light petroleum and filtered. The filtrate was evaporated under reduced pressure and the residue chromatographed on silica (100 g) in 0.5 g samples, eluting with light petroleum to give the (*Z*)-alkene[30] (0.48 g, 19%, >95% *Z* by GC); R_f (light petroleum) 0.56; δ (250 MHz; $CDCl_3$) 7.4–7.1 (5 H, m, Ph), 5.5 (1 H, m, C=CH), 2.5 (1 H, m, Me_2CH), 1.48 (3 H, d, *J* 6.7, C=CMe) and 1.0 (6 H, d, *J* 6.8, Me_2CH). The stereochemistry was established by NOE enhancement of the methine hydrogen when the sample was irradiated at the frequency of the olefinic hydrogen signal. A mixture of (*E*)- and (*Z*)-alkenes (1.1 g, 54%) was also isolated from the column. GC was performed on an Apiezon L column at 100 °C, with a carrier flow of 330 kp. Peak retention times were (*Z*)-alkene, 22 min, and (*E*)-alkene, 30 min.

Preparation of 4-*Methyl*-3-*phenylpentan*-2-*ol* **38** *by Hydroboration of* (*Z*)-4-*Methyl*-3-*phenylpent*-2-*ene*.—Borane in THF (1 mmol dm^{-3}; 1 cm^3, 1.0 mmol) was added over 10 min to the (*Z*)-alkene (0.3 g, 1.9 mmol) in THF (15 cm^3) at room temperature under nitrogen. After 1 h, water (1 cm^3), aqueous sodium hydroxide (3 mol dm^{-3}; 0.3 cm^3) and hydrogen peroxide (30%; 0.3 cm^3) were added. The mixture was stirred for 30 min and then most of the THF was removed under reduced pressure. The residue was diluted with water (15 cm^3) and extracted with ether (2 × 10 cm^3). The ether extracts were dried ($MgSO_4$) and

evaporated under reduced pressure to give the (2*RS*,3*RS*)-alcohol (0.32 g, 96%).

3,4-*Dimethylpentan*-2-*one* **14b**.—3-Methylpent-3-en-2-one (3.0 g, 31 mmol) in ether (15 cm^3) was added to lithium dimethylcuprate (35 mmol) in THF at −23 °C under nitrogen. After 15 min, the reaction mixture was worked up in the usual way. The product was distilled using a spinning band column to give the ketone (1.6 g, 45%) (b.p. 80–100 °C); R_f (light petroleum–Et_2O, 9:1) 0.54; ν_{max}(film)/cm^{-1} 1710 (C=O); δ (60 MHz; $CDCl_3$) 2.3–1.8 (2 H, m, CHCH), 2.1 (3 H, s, COMe) and 1.0–0.7 (6 H, m, remainder).

3,4-*Dimethylpentan*-2-*ols* **12b** *and* **13b** *by Reduction of the Ketone* **14b**.—The ketone (0.4 g, 3.5 mmol) in ether (10 cm^3) was added dropwise to a suspension of LAH (0.2 g) in ether (20 cm^3) at 0 °C under nitrogen. After being stirred for 30 min, the mixture was worked up in the usual way to give the alcohols (0.30 g, 75%) in a ratio of 80:20, confirming the earlier work.[26]

2-*Methyl*-3-*phenylbutanal*.—α-Methylcinnamaldehyde (2.0 g, 14 mmol) in ether (10 cm^3) was added to lithium dimethylcuprate (17 mmol) at −23 °C under nitrogen. After 15 min, the mixture was cooled to −78 °C and TFA (2.7 cm^3, 35 mmol) was added. The product was worked up in the usual way, and purified by chromatography on silica gel (100 g), eluting with ether–light petroleum (1:99) to give the aldehydes (1.83 g, 83%); R_f (light petroleum–Et_2O, 9:1 v/v) 0.49; ν_{max}(film)/cm^{-1} 1710 (C=O); δ (250 MHz; $CDCl_3$) (2*RS*,3*SR*): 9.68 (1 H, d, *J* 3.3, CHO), 7.35–7.15 (5 H, m, Ph), 3.15 (1 H, quintet, *J* 7.1, PhC*H*), 2.61 (1 H, m, C*H*CHO), 1.3 (3 H, d, *J* 6.5, PhCH*Me*) and 0.88 (3 H, d, *J* 7.9, *Me*CHCHO); (2*RS*,3*RS*): 9.58 (1 H, d, *J* 2.1, CHO), 7.35–7.15 (5 H, m, Ph), 3.0 (1 H, m, PhC*H*) 2.55 (1 H, m, C*H*CHO), 1.27 (3 H, d, *J* 7.2, PhCH*Me*) and 1.08 (3 H, d, *J* 6.9, *Me*CHCHO); *m*/*z* 162 (2%, M^+) and 105 (100, PhCHMe) in a ratio of 50:50 (Found: M^+, 162.1033. $C_{11}H_{14}O$ requires *M*, 162.1044).

(2RS,3SR)-2-*Methyl*-3-*phenylbutanoic Acid* **32**.—The aldehydes (1.70 g, 10.5 mmol) and pyridinium dichromate (14 g) in DMF (20 cm^3) were stirred at room temperature for 16 h. The mixture was diluted with water (50 cm^3) and extracted with ether (2 × 20 cm^3). The ether extracts were extracted with aqueous sodium carbonate (2 × 20 cm^3). The aqueous extracts were acidified with hydrochloric acid and extracted with ether (2 × 20 cm^3), and the extracts were washed with water (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was triturated with light petroleum, and the solid filtered off to give the acid (0.53 g, 27%) as granules, m.p. 131–132 °C (from cyclohexane) (lit.,[29] 130–131 °C); R_f (EtOAc) 0.52; ν_{max}(Nujol)/cm^{-1} 1710 (C=O); δ (250 MHz; $CDCl_3$) 7.33–7.14 (5 H, m, Ph), 2.90 (1 H, dq, *J* 10 and 7, PhC*H*), 2.60 (1 H, dq, *J* 10 and 7, CHCO), 1.23 (3 H, d, *J* 7, PhCH*Me*) and 0.92 (3 H, d, *J* 7, *Me*CHCO).

(2RS,3SR) *Methyl* 2-*Methyl*-3-*phenylbutanoate* **26**.—Diazomethane in ether was added to the acid **32** (0.1 g, 0.56 mmol) in ether (10 cm^3) until a strong yellow colour persisted. The ether was evaporated under reduced pressure to give the ester (104 mg, 96%), identical (NMR, TLC) with the sample described above.

(2RS,3SR)-2-*Methyl*-1,3-*diphenylbutan*-1-*one* **30**.—The acid **32** (105 mg, 0.56 mmol) in ether (15 cm^3) was added to phenyllithium (0.65 mol dm^{-3}; 3.1 cm^3, 2 mmol) in ether (15 cm^3) at 0 °C under nitrogen. The mixture was stirred for 24 h after which time chlorotrimethylsilane (0.5 cm^3, 4 mmol) was added.[48] The mixture was then stirred for a further 1 h after which it was diluted with water (20 cm^3) and extracted with ether (10 cm^3). The extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel (10 g), eluting with ether–light petroleum (1:99), to give the ketone (130 mg, 96%), identical (NMR, TLC) with the sample described above.

(2RS,3SR)-3-*Methyl*-4-*phenylpentan*-2-*one* **9a**.—The acid **32** (102 mg, 0.56 mmol) in ether (5 cm^3) was added to methyllithium (1.4 mol dm^{-3}; 1.4 cm^3, 2.0 mmol) in ether (20 cm^3) at 0 °C under nitrogen, and the mixture kept for 24 h at room temperature. Chlorotrimethylsilane (0.6 cm^3, 5 mmol) was added[48] to the mixture which was then worked up, as described above, to give the ketone (92 mg, 92%), identical (NMR, TLC) with the sample described above.

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