High Diastereofacial Selectivity in the Conjugate Addition of Phenylmagnesium Bromide to Acyclic α-Enones with an Asymmetric Carbon at the γ-Position

Carlos Alvarez Ibarra,*[a] María Selma Arias Pérez,*[b] Irene de Castro[b] and María Jose Fernandez[b]

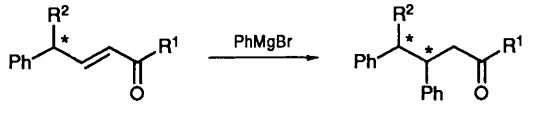
[a] *Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain*

[b] *Departamento de Química Orgánica, Universidad de Alcalá de Henares, 28871 Alcalá de Henares, Madrid, Spain*

Moderately high diastereofacial preference has been observed in the conjugate addition of phenylmagnesium bromide to the acyclic α-enones with an asymmetric carbon at the γ-position (4*E*,6*RS*)-2,2,7,7-tetramethyl-6-phenyloct-4-en-3-one (**1**), (2*E*,4*RS*)-5,5-dimethyl-1,4-diphenylhex-2-en-1-one (**2**), and (4*E*,6*RS*)-2,2-dimethyl-6-phenylhept-4-en-3-one (**3**). The *RR,SS* selectivity is practically unaffected by the addition of copper(I) salts. These results are in qualitative agreement with the selectivity predicted by a Felkin-like transition state model. The method is shown to be useful for the stereoselective preparation of acyclic ketones having two chiral centres.

Acyclic stereocontrol plays a crucial role in synthetic organic chemistry for the preparation of compounds with several stereocentres having the desired configuration.[1] In the last few years, considerable attention has been focused on theoretical[2–5] and experimental[6–15] stereochemical studies of nucleophilic additions. Excellent diastereofacial preferences in the conjugate additions of organometallic reagents to acyclic α,β-unsaturated carbonyl compounds and other Michael acceptors have been achieved, mainly with substrates and/or reagents bearing polar groups.[8–15]

In order to attain the diastereoselective synthesis of acyclic ketones with two asymmetric carbon atoms at the β,γ-positions we have studied the Michael additions of phenylmagnesium bromide in the presence or absence of added copper(I) salts to the acyclic α-enones **1–3** bearing a chiral centre at the γ-position. We report herein the high diastereofacial preferences observed in these processes which offer an improvement in the stereoselective preparation of the ketones **4–6**[16,17] (Scheme 1).



(*E*), (*RS*) (*RR, SS*) + (*RS, SR*)

1 R^1 = Bu^t, R^2 = Bu^t **4** R^1 = Bu^t, R^2 = Bu^t
2 R^1 = Ph, R^2 = Bu^t **5** R^1 = Ph, R^2 = Bu^t
3 R^1 = Bu^t, R^2 = Me **6** R^1 = Bu^t, R^2 = Me

Scheme 1 Conjugate addition of phenylmagnesium bromide to acyclic α-enones with an asymmetric carbon at the γ-position

The *RR,SS* diastereofacial preference observed in all cases has been explained using a Felkin-like transition state model. The selected α-enones **1–3** present an alkyl and a phenyl substituent at the γ-asymmetric carbon and the inversion of the conformational preference of the phenyl group has been verified when a methyl group is replaced by a *tert*-butyl group.

Results and Discussion

The Michael addition of phenylmagnesium bromide to the acyclicα-enones(4*E*,6*RS*)-2,2,7,7-tetramethyl-6-phenyloct-4-en-3-one (**1**), (2*E*,4*RS*)-5,5-dimethyl-1,4-diphenylhex-2-en-1-one (**2**), and (4*E*,6*RS*)2,2-dimethyl-6-phenylhept-4-en-3-one (**3**) was carried out using 0.30 mol dm^{-3} solutions of the Grignard reagent in the presence or absence of copper(I) salts. In each case, a mixture of the two diastereoisomeric racemates of the respective ketones **4–6** were obtained (Scheme 1). The yields and diastereoselectivities obtained are summarized in Table 1. When low conversion was observed, the starting α-enone and some unidentified products were found along with the desired adduct in variable ratios. α-Enone **2** led to the ketone **5** in low yield (<50%; Table 1, entries 6–8). When the reaction was performed in tetrahydrofuran (THF) only traces of **5** were detected and 5,5-dimethyl-1,1,4-triphenylhexa-1,3-diene, obtained by dehydration of the 1,2-addition product, was found (Table 1, entry 7).

In all cases studied, the organometallic conjugated addition gave predominantly the (*RR,SS*) isomer, regardless of the α-enone. Moreover, the diastereoselectivities are uniformly good and practically unaffected by the presence of copper(I) salts. These results contrast advantageously with those observed for the 1,4-addition of 2,2-dimethyl-1-phenylpropylmagnesium chloride and 1-phenylethylmagnesium chloride to α-enones (*E*)-1,3-diphenylprop-2-en-1-one and (*E*)-4,4-dimethyl-1-phenylpent-1-en-3-one. By this way, practically no diastereofacial selectivity was observed in the preparation of **4** and **5**[16] (diastereoisomeric ratio *ca.* 50:50) and **6** was achieved with lower *RR,SS* preference[17] (63% of *RR,SS* and 37% of *RS,SR*).

The diastereoselection exhibited in these reactions is in good agreement with the selectivity predicted by a modified Felkin model.[2–5,10] Thus, to rationalize the stereoselectivity, these processes can be considered as normal additions, regardless of whether the reactive species might be a nucleophile or a radical.

Assuming a modified Felkin model, the observed diastereofacial preferences may be explained as a consequence of the competition between transition states **7** and **8** (Fig. 1). As the attack angle, θ, of the reactive species is >90°, steric factors in the outside region become important in controlling the selectivity[2,4,5,10] and the hydrogen atom occupies the hindered outside position. Therefore, the major isomer *RR*, is produced *via* **7** for the α-enones **1** and **2** (R^2 = Bu^t), whereby the *tert*-butyl group adopts an *anti*-arrangement to the incoming reactive species. Nevertheless, for α-enone **3** (R^2 = Me) the transition structure prefers a conformation in which the phenyl group occupies the *anti*-position in preference to the methyl group and thus the transition state **8** is selectively stabilized over **7**. These

Table 1 Diastereoselectivity of conjugated addition of phenylmagnesium bromide to α-enones **1–3**

Entry	α-Enone	Reagent/solvent[a]	T/°C	t/h	Ketone, yield (%)[b]	Diastereoisomer ratio[b] *RR,SS/RS,SR*
1	1	$PhMgBr/Et_2O$, (1.5)	25	2	**4**, 88	86/14
2	1	PhMgBr/THF, (2.5)	25	3	**4**, 70	80/20
3	1	PhMgBr–Cu(I)/Et_2O, (3)	25	3	**4**, 70	81/19
4	1	PhMgBr–Cu(I)/Et_2O, (3)	0	3	**4**, 100	83/17
5	1	PhMgBr–Cu(I)/Et_2O, (3)	0	3	**4**, 66	85/15
6	2	$PhMgBr/Et_2O$, (3)	25	3	**5**, 40	86/14
7	2	PhMgBr/THF, (2.5)	25	3	**5**, —[c]	—
8	2	PhMgBr–Cu(I)/Et_2O, (3)	0	3	**5**, 45	90/10
9	3	$PhMgBr/Et_2O$, (1.5)	25	2	**6**, 95	75/25
10	3	PhMgBr–Cu(I)/Et_2O, (3)	0	2	**6**, 80	72/28

[a] Equiv. of PhMgBr are indicated in parentheses. Molar ratio [PhMgBr]:[CuI], 20:1; except for entry 5 which was 2:1. [b] Determined by GC and ^1H NMR spectroscopy (±3%). [c] Only traces of ketone were observed along with 5,5-dimethyl-1,1,4-triphenylhexa-1,3-diene.

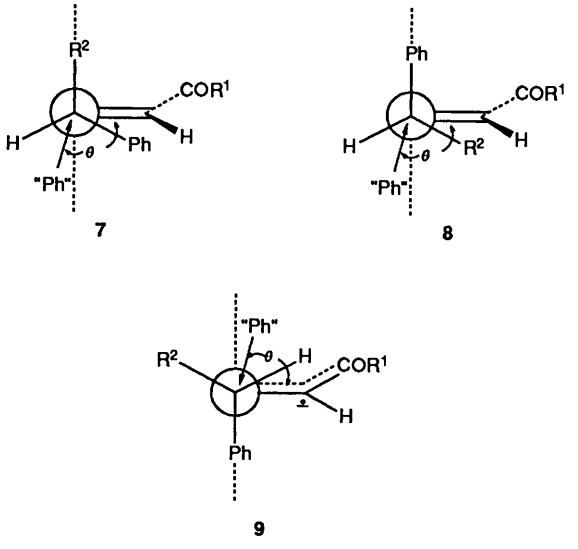


Fig. 1 Proposed transition states for the conjugate addition of phenylmagnesium bromide to α-enones **1–3**, **7** and **8** assuming a nucleophilic process and **9** for an electron-transfer path-way

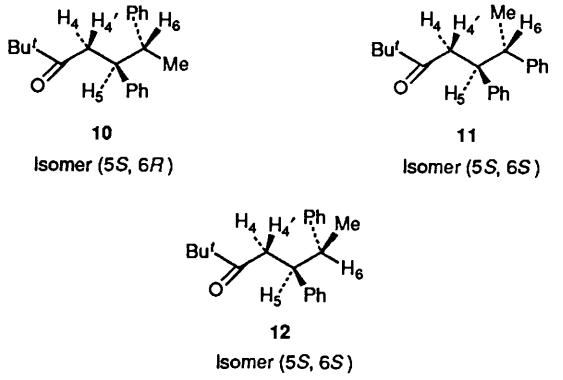


Fig. 2 Significant conformers for diastereoisomers (5*S*6*R* and 5*S*6*S*) of **6**

results are also in agreement with the qualitative order of ligand preferences for the *anti* position, Bu^t > Ph > Me > H, proposed on the basis of a balance between electronic and steric effects for nucleophilic additions to chiral carbonyl compounds[6] and conjugate additions to different Michael acceptors bearing a γ-stereocentre.[4,5]

The Grignard and copper-catalysed additions may also involve an electron-transfer process[18] and the diastereoselectivity may be explained by the intermediacy of the radical anion of the Michael acceptor.[2,12] As in the radical anion intermediate the interaction between the HOMO of the substrate and the phenyl group dictates the stereoselectivity, with electrophilic attack occurring with an angle $\theta < 90°$ and the inside region stereodetermining.[2,12] The major isomer arises from **9** (Fig. 1) in all cases and *SS* isomers result from **1** and **2** and the *SR* isomer results from **3**. So a marked stereochemical contrast between a nucleophilic process and an electron-transfer pathway is predicted in the addition to **3**, as has been reported previously for related process.[2,12] These predictions do not agree with the experimental results (Table 1) which point out the predominant formation of the (*RR,SS*) isomer in all cases. Therefore, it is not probable that the additions studied take place by an electron-transfer pathway.

The stereochemical results reported herein provide the first example of high diastereoselectivity in the Grignard conjugated additions to acyclic α-enones without polar groups and suggest the non-operativity of an electron-transfer mechanism.

The assignment of relative configurations *RR,SS* and *RS,SR* to the diastereoisomeric racemates of ketones (±)-2,2,7,7-tetramethyl-5,6-diphenyloctan-3-one (**4**), and (±)-5,5-dimethyl-1,3,4-triphenylhexan-1-one (**5**), has previously been reported.[19] The relative configurations 5*R*6*R*,5*S*6*S* and 5*R*6*S*,5*S*6*R* of (±)-2,2-dimethyl-5,6-diphenylheptan-3-one (**6**), have been assigned following the same method,[19,20] by analysis of the ^1H–^1H vicinal coupling constants and the consideration of prior selection of the significant conformers in each diastereoisomer.

The conformational analysis of the 5*S*6*R* and 5*S*6*S* isomers has been carried out according to the method previously applied to other acyclic ketones.[19,20] The study of Dreiding models and the evaluation of relative conformational free energies, computing energy values[19,20] of the differential steric interactions present in each conformer, has led to the selection of the significant conformers (Fig. 2). Those conformers with a participation in the conformational equilibrium of < 5% have been disregarded.

According to this analysis, the monoconformational character of the 5*S*6*R* isomer can be reasonably asserted, while the other diastereoisomer (5*S*6*S*) can be described as a mixture of two conformers, **11** and **12**.

The magnetic parameters of most interest for the assignment of relative configurations to the diastereoisomeric racemates of **6**, arbitrarily designated α and β, are the vicinal coupling constants of the protons attached to C-4, C-5 and C-6 (Fig. 2) which appear as a seven-spin system ($AMNRX_3$ for the α-isomer and $ABCRX_3$ for the β-isomer). The AMNR and ABCR systems were analysed by means of the LAOCOON III program,[21] deducting the coupling between 6-H and CH_3 protons. The magnetic parameters together with the most probable errors deduced from this analysis, are shown in Table 2.

Table 2 ^{1}H NMR parameters for the diastereoisomeric racemates of (±)-2,2-dimethyl-5,6-diphenylheptan-3-one **6**

Chemical[a] shifts	α-Isomer δ(ppm)	β-Isomer δ(ppm)	Coupling constants	α-Isomer J/Hz	β-Isomer J/Hz
4-H	2.331 ± 0.001	2.786 ± 0.001	4(H)-4′(H)	−16.91 ± 0.04	−17.17 ± 0.08
4′-H	2.816 ± 0.001	2.948 ± 0.001	4(H)-5(H)	3.44 ± 0.04	5.40 ± 0.04
5-H	3.402 ± 0.001	3.485 ± 0.001	4′(H)-5(H)	10.06 ± 0.04	8.39 ± 0.04
6-H	2.910 ± 0.001	3.043 ± 0.001	4(H)-6(H)	−0.28 ± 0.04	−0.08 ± 0.04
Me (d)	0.99	1.27	4′(H)-6(H)	−0.21 ± 0.04	−0.08 ± 0.04
Bu^t (s)	0.77	0.99	5(H)-6(H)	10.46 ± 0.04	5.54 ± 0.04
Ph (m)	7.19[b] 7.12[b]	6.84 − 7.18	6(H)-CH_3	6.78	7.00

[a] Abbreviations: d, doublet; m, multiplet; s, singlet. Directly measured on the spectra with an error of ±0.01 ppm, except for the cases indicated in which they were calculated by means of the LAOCOON III program. [b] Apparent singlet.

As the C4–C5 rotational system exhibits similar behaviour in all the selected conformers (Fig. 2), $^3J_{5(H)\text{-}6(H)}$ is the key vicinal coupling constant for the assignment of relative configurations to the α and β isomers. According to the results deduced from prior conformational analysis (Fig. 2) the (5*S*,6*R*) isomer with only one significant conformer **10**, must show a large antiperiplanar coupling constant, $^3J_{5(H)\text{-}6(H)}$, because of the relative positions of the vicinal 5-H and 6-H protons.[22] This condition is precisely observed in the α-isomer (Table 2). On the other hand, in the (5*S*,6*S*) isomer $^3J_{5(H)\text{-}6(H)}$ should have an average value between a large antiperiplanar and a small synclinal coupling constant[22] due to its conformational heterogeneity. This condition is observed in the β-isomer (Table 2). Therefore, the relative configurations 5*R*6*S*,5*S*6*R* and 5*R*6*R*,5*S*6*S* can be unmistakably assigned to the α and β isomers, respectively.

Experimental

GLC analysis were performed on a Perkin-Elmer Sigma-3 instrument provided with a flame-ionization detector and a Sigma-10 data collector. The columns used were: A, (0.25 in × 0.90 m) 10% BDS on Chromosorb W-AW-DMCS; B, (0.125 in × 2 m) 5% UCC-982 on Chromosorb W-AW-DMCS; and C, (0.125 in × 2 m) 12% Carbowax-20M on Chromosorb W-AW-DMCS. IR spectra were measured as KBr pellets on a Perkin-Elmer 883 spectrophotometer. Mass spectra were recorded on a Hewlett-Packard 5890 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian FT-80 A (PFT) spectrometer at 303 K using Me_4Si as the internal reference. The recording conditions were: ^{1}H NMR (79.542 MHz), 7% w/v $CDCl_3$ solutions, acquisition time 2.047 s, spectral width 800 Hz and pulse width 7 μs; ^{13}C NMR (20 MHz) proton noise-decoupled and off-resonance decoupled spectra were recorded using 25% w/v $CDCl_3$ solutions, acquisition time 1.638 s, delay time 1.64 s, spectral width 5000 Hz and pulse width 5 μs.

THF and diethyl ether were purified in the usual manner and distilled from sodium/benzophenone immediately prior to use. Copper(I) iodide was purified as described previously.[23] Enones **1–3** were prepared and purified following the method previously described by us.[24] The phenylmagnesium bromide solutions were prepared under a nitrogen atmosphere using standard Schlenk techniques and titrated using the method of Kjonaas and Vawter.[25]

Condensation Reactions.—A dry three-necked flask equipped with a magnetic stirrer and rubber septum was charged with an excess of a 0.30 mol dm^{-3} solution of phenylmagnesium bromide (1.5–3.0 equiv.) under a N_2 atmosphere and thermostatted at the reaction temperature (Table 1). The α-enone (2×10^{-4} mol), dissolved in the minimum amount of solvent (ether or THF), was then added by syringe and stirring was continued at the same temperature for the appropriate reaction time (Table 1). The reaction was quenched with brine. The organic layer was decanted and the aqueous layer extracted with several portions of ether. The ethereal extracts were dried ($MgSO_4$), and after removal of the solvent under reduced pressure, the crude product was analysed by GLC and ^{1}H NMR spectroscopy. Reactions in the presence of copper(I) salts were carried out with the above procedure. The organometallic reagent was prepared by adding the phenylmagnesium bromide solution to copper(I) iodide.

The yields of the conjugate addition product were determined by ^{1}H NMR spectroscopy and GLC (Table 1). The following conditions were used: column A, column temperature 185 °C, gas flow (N_2) 50 cm^3 min^{-1} for **4**, retention time 25.3 min (unresolved isomers); column B, column temperature 210 °C, gas flow (N_2) 30 cm^3 min^{-1} for **5**, retention time 107.1 min (unresolved isomers); column C, column temperature 180 °C, gas flow (N_2) 35 cm^3 min^{-1} for **6**, retention times: 76.4 and 65.2 min for the *RR*,*SS* and *RS*,*SR* diastereoisomeric racemates, respectively. Estimation of diastereoisomer ratio (Table 1) was carried out by ^{1}H NMR spectroscopy for ketones **4** and **5** and by GLC and ^{1}H NMR spectroscopy for **6**.

2,2-*Dimethyl*-5,6-*diphenylheptan*-3-*one* **6**.—Ketone **6** was described previously as a mixture of the two diastereoisomeric racemates. Silica gel chromatography [30:1 (w/w) adsorbent:product ratio] using hexane–ethyl acetate (97:3) as the eluent provided samples with 90% and 94% (GLC) of the (5*R*6*S*,5*S*6*R*) and (5*R*6*R*,5*S*6*S*) isomers, respectively. Characterization was carried out by mass spectrometry, IR, and ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR magnetic parameters are collected in Table 2. The molecular ion was hardly observed in the mass spectra and this behaviour was attributed to a very favourable McLafferty rearrangement with loss of pinacolone ($M^+ - 100$).

(5R6S,5S6R) *Isomer* (Found: C, 85.55; H, 8.9. $C_{21}H_{26}O$ requires C, 85.7; H, 8.8%); ν_{max}/cm^{-1} 1694 (CO); *m*/*z* 195 (18%), 194 ($M^+ - 100$, 61), 115 (14), 105 (72), 104 (44), 103 (20), 91 (43), 85 (80), 79 (12), 78 (15), 77 (23) and 57 (100); δ_C 21.19 (C-7), 25.83 (C-1), 42.36 (C-4), 43.93 (C-2), 45.48 (C-6), 47.62 (C-5), 126.29, 126.38, 127.67. 128.24, 128.42, 128.57 (*o*-, *m*- and *p*-C of Ph groups), 143.93, 145.98 (C-*ipso* of Ph groups) and 213.96 ppm (C-3).

(5R,6R;5S,6S) *Isomer* (Found: C, 85.9; H, 8.65. $C_{21}H_{26}O$ requires C, 85.7; H, 8.8%); ν_{max}/cm^{-1} 1696 (CO); *m*/*z* 195 (13%), 194 ($M^+ - 100$, 52), 115 (11), 105 (68), 104 (42), 103 (19), 91 (32), 85 (75), 79 (12), 78 (15), 77 (22) and 57 (100); δ_C 19.35 (C-7), 26.30 (C-1), 40.26 (C-4), 44.15 (C-2), 44.48 (C-6), 46.66 (C-5), 125.96, 127.61, 127.76, 128.18, 128.74 (*o*-, *m*- and *p*-C of Ph groups), 142.91, 144.61 (C-*ipso* of Ph groups) and 213.96 ppm (C-3).

5,5-*Dimethyl*-1,1,4-*triphenylhexa*-1,3-*diene*.—δ_H 1.02 (9 H, s, Bu^t), 6.15 and 6.32 (2 H, AB system, *J*/Hz 11.20, 2-H and 3-H) and 7.02–7.32 (15 H, m, Ph).

References

1 E. L. Eliel, *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1983, vol. 2, p. 125.
2 K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y. D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li and R. J. Loncharich, *Science*, 1986, **231**, 1108.
3 S. D. Kahn, K. D. Dobbs and W. J. Hehre, *J. Am. Chem. Soc.*, 1988, **110**, 4602.
4 A. E. Dorigo and K. Morokuma, *J. Am. Chem. Soc.*, 1989, **111**, 6524.
5 A. Bernardi, A. M. Capelli, C. Gennari and C. Scolastico, *Tetrahedron Asymmetry*, 1990, **1**, 21.
6 E. P. Lodge and C. H. Heathcock, *J. Am. Chem. Soc.*, 1987, **109**, 3353.
7 C. Alvarez Ibarra, R. Pérez-Ossorio, M. L. Quiroga, M. S. Arias-Pérez and M. J. Fernández-Domínguez, *J. Chem. Soc., Perkin Trans. 2*, 1988, 101.
8 D. Kruger, A. E. Sopchick and C. A. Kingsbury, *J. Org. Chem.*, 1984, **49**, 778.
9 C. H. Heathcock and D. E. Vehling, *J. Org. Chem.*, 1986, **51**, 279.
10 Y. Yamamoto, *Acc. Chem. Res.*, 1987, **20**, 243.
11 K. Maruoka, T. Itoh, M. Sakurai, K. Nomoshita and H. Yamamoto, *J. Am. Chem. Soc.*, 1988, **110**, 3588.
12 Y. Yamamoto, S. Nishii and T. Ibuka, *J. Am. Chem. Soc.*, 1988, **110**, 617.
13 K. Takaki, T. Maeda and M. Ishikawa, *J. Org. Chem.*, 1989, **54**, 58.
14 D. A. Care and C. H. Heathcock, *Topics in Stereochemistry*, eds. E. L. Eliel and S. H. Wilen, Wiley, New York, 1989, p. 227.
15 M. Larcheveque, G. Tamagnan and Y. Petit, *J. Chem. Soc., Chem. Commun.*, 1989, 31.
16 C. Alvarez Ibarra, M. S. Arias-Pérez, J. M. Esteban and E. Moya, *Org. Prep. Proced. Int.*, 1987, **19**, 25.
17 C. Alvarez Ibarra, M. S. Arias-Pérez, E. Moya and M. A. Rodriguez-Barranco, *Org. Prep. Proced. Int.*, 1990, **22**, 77.
18 (*a*) E. C. Ashby, *Pure Appl. Chem.*, 1980, **52**, 545; (*b*) T. Holm, *Acta Chem. Scand., Ser. B*, 1983, **37**, 569; (*c*) C. Walling, *J. Am. Chem. Soc.*, 1988, **110**, 6846.
19 C. Alvarez Ibarra, M. S. Arias-Pérez and E. Moya, *Magn. Reson. Chem.*, 1990, **28**, 617 and references therein.
20 C. Alvarez Ibarra, M. S. Arias-Pérez, A de Andrés and J. L. Balcázar, *Magn. Reson. Chem.*, 1986, **24**, 568.
21 S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, 1963, **41**, 3863.
22 L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd edn. Pergamon Press, London, 1978.
23 (*a*) G. B. Kauffman and L. A. Teter, *Inorg. Synth.*, 1963, **7**, 9; (*b*) G. H. Posner and J. J. Sterling, *J. Am. Chem. Soc.*, 1975, **97**, 107.
24 (*a*) C. Alvarez Ibarra, S. Arias, G. Bañón, M. J. Fernández, M. Rodriguez and J. Sinisterra, *J. Chem. Soc., Chem. Commun.*, 1987, 1509; (*b*) C. Alvarez Ibarra, S. Arias, M. J. Fernández and J. V. Sinisterra, *J. Chem. Soc., Perkin Trans. 2*, 1989, 503.
25 R. A. Kjonaas and E. J. Vawter, *J. Org. Chem.*, 1986, **51**, 3993.

Paper 0/04748A
Received 23*rd October* 1990
Accepted 16*th November* 1990