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AZO ANIONS IN SYNTHESIS. USE OF TRITYL- AND DIPHENYL-4-PYRIDYLMETHYLHYDRAZONES FOR REDUCTIVE C-C BOND FORMATION.

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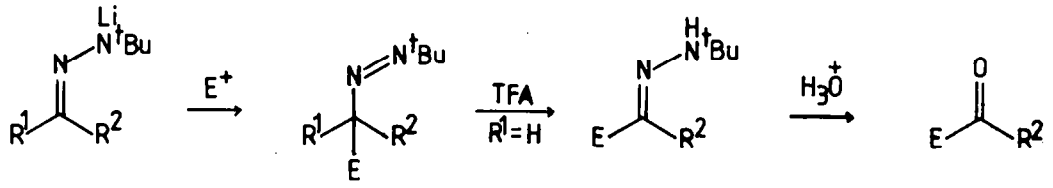
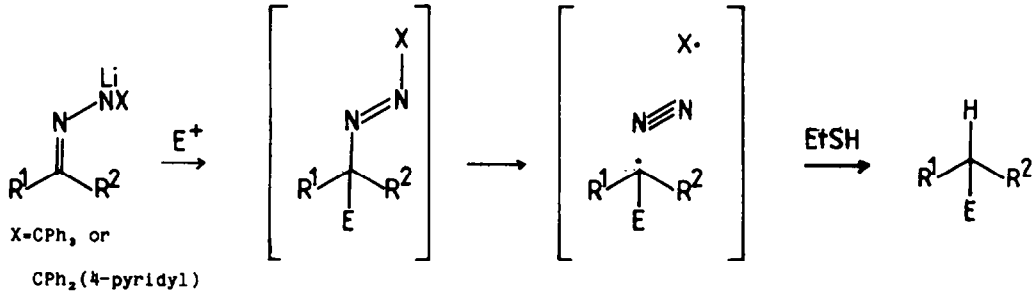
Abstract: The lithium salts of trityl- and diphenyl-4-pyridylmethyl-hydrazones of both aldehydes and ketones react with electrophiles (alkyl halides, aldehydes, ketones, crotonates) at low temperature to form C-trapped azo compounds; these intermediates decompose homolytically with loss of nitrogen below room temperature and can be diverted in a synthetically useful way to alkanes, alkenes, alcohols or saturated esters.

Recently we demonstrated that the lithium salts of hindered hydrazones, e.g. t-butylhydrazones, undergo reaction with electrophiles at carbon.[1] The so-formed azo- products from aldehyde t-butylhydrazones could be tautomerised, and thereafter hydrolysed, to yield ketonic products, thus illustrating the potential of hindered hydrazones as a new acyl anion equivalent (Scheme 1). The

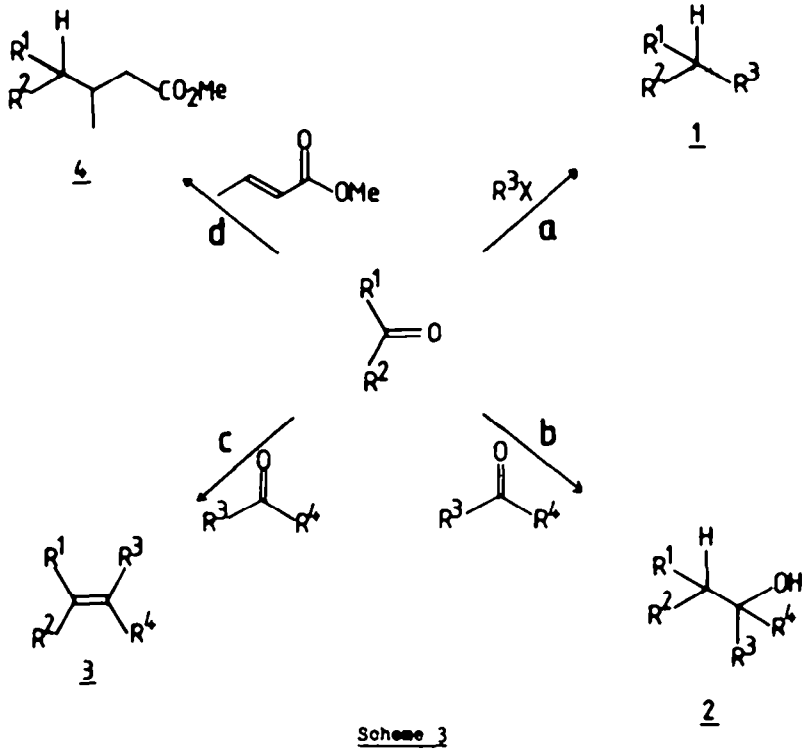


Scheme 1

use of such hindered hydrazones was advanced by the development of trityl- and diphenyl-4-pyridylmethyl-(DPP)hydrazones. The lithium anions of these hydrazones could also be trapped on carbon to produce thermally labile azo- products which decomposed homolytically, below room temperature, with evolution of nitrogen gas forming a radical pair. Quenching of these radicals with thiols led to a reductive carbon-carbon bond forming sequence (Scheme 2).[2] This methodology was developed [1c,2] using various electrophiles ($E^{\oplus}$) to create new practical methods for the preparation of alkanes (1)(path a), alcohols (2)(path b), olefins (3)(path c), and saturated esters (4)(path d)(Scheme3). Herein we describe details of these novel reductive carbon-carbon bond forming procedures.



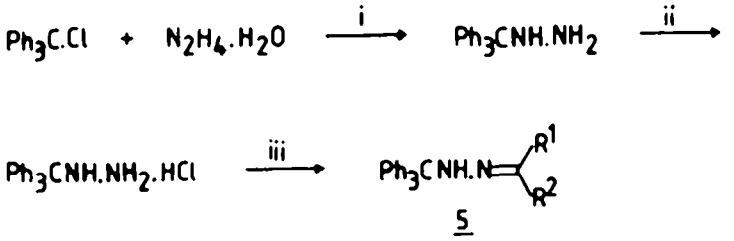
Scheme 2



Scheme 3

Preparation of Trityl- and Diphenyl-4-pyridylmethylhydrazones

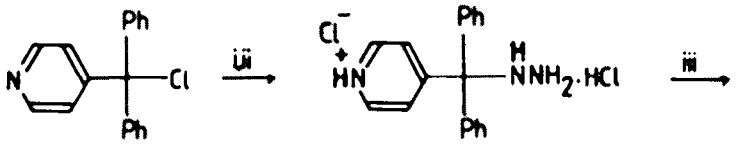
Tritylhydrazones (5) were prepared from tritylhydrazine hydrochloride, which itself was prepared[9] from tritylchloride and hydrazine hydrate (Scheme 4). Diphenyl-4-pyridylmethylhydrazones (DPP)(6) were prepared by analogous methods from diphenyl-4-pyridylmethylchloride[6] (Scheme 5). Typically the solid hydrazone derivatives (5),(6) precipitated from the reaction mixtures (Table 1). They were filtered off, dried at room temperature under vacuum (18hrs.), and used without further purification.[8] Those that could not be precipitated were extracted into organic solvent (e.g. CH_2Cl_2), dried over sodium sulphate (s), and concentrated to give oils. Further purification could be achieved by rapid flash chromatography on silica gel.

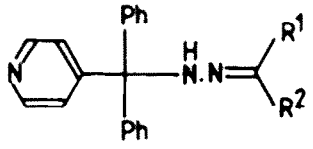


Reagents: (i) THF, reflux, 6-18h.; (ii) MeOH, HCl(g) (1 equiv.); (iii) HCO_2Na (1.5 equiv.), MeOH, H_2O, $R^1.CO.R^2$.

Scheme 4

[8] These Compounds are metastable at room temperature in the absence of air.





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Reagents: (i) NH_2NH_2, THF, reflux, 18h.; (ii) Et_2O, HCl(g) (2 equiv.); (iii) HCO_2Na (1.5 equiv.), MeOH, H_2O, $R^1.CO.R^2$.

Scheme 5

			Tritylhydrazone (5)		DPP- hydrazone (6)	
Entry	R^1	R^2	Yield(%)	m.p.(°C)	Yield(%)	m.p. (°C)
a	Me	H	81	112-114	-	-
b	Me	Me	90	119-120	65	124-5
c	i-Pr	H	81	oil	-	-
d	n-Bu	H	87	wax	-	-
e	$-(CH_2)_4-$		83	127-130.5	-	-
f	$-(CH_2)_5-$		86	135-137	57	127-9
g	$n-C_6H_{13}$	Me	-	-	57	114-5
h	$-(CH_2)_{11}-$		87	142-143	81	139.5-140.5
	$c-C_6H_{11}$	Me	88	55		

Table 1

Preparation of Alkanes (1)

For an alkane synthesis, the lithium anions of the tritylhydrazones were reacted with an alkyl halide (1.2 equivs.) at -30° for 3h.† Thereafter treatment with acetic acid (1.2 equivs.) and ethanethiol (excess) in sequence followed by warming to room temperature led to nitrogen evolution at -10° to +20°C (equivalent to the alkane yield) and alkane production (Scheme 3, path a, table 2). These optimal conditions probably reflect a need for extensive azo-anion alkylation (at -30°C) prior to radical fragmentation at (-10°C), which itself requires thiol quenching to avoid undesired olefin forming [see preparation of alcohols (2)] and possible radical coupling pathways. Reactions in which alkylation was attempted at higher temperatures gave lower yields of alkanes, as did the use of DPP-hydrazones (6) under the optimal conditions.

† Longer reaction times were not tried due to experimental inconvience.

Hydrazone (5)	Alkyl halide (R_2X)	Yield of (1) (%)
a	n-$C_{12}H_{25}I$	27
b	$PhCH_2Br$	42
b	n-$C_{12}H_{25}I$	38
d	n-$C_{12}H_{25}I$	47
e	n-$C_{12}H_{25}I$	27
f	n-C_4H_9I	40
f	n-$C_7H_{15}I$	67
f	$PhCH_2Br$	68
h	n-C_4H_9I	51*
h	$PhCH_2Br$	44

* : Yield estimated by g.c. analysis

Table 2

Preparation of Alcohols (2)

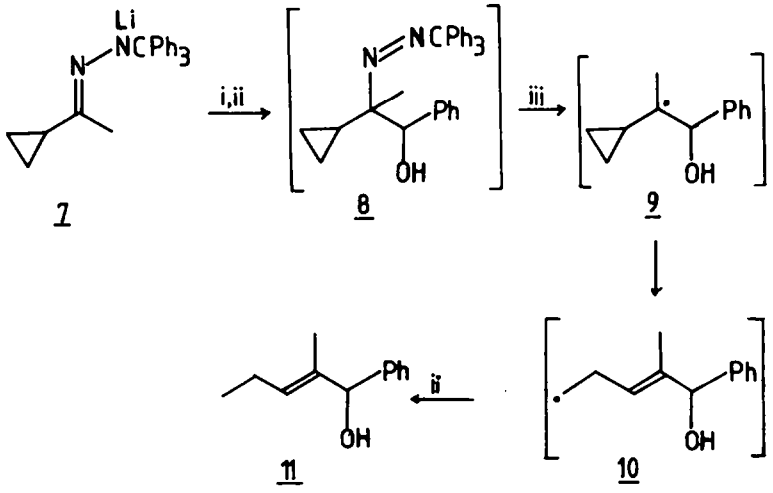
For the reductive coupling of carbonyls to form alcohols (2), the azo-anion from a tritylhydrazone (5) or DPP- hydrazone (6) was treated with an aldehyde or ketone ($R^3.CO.R^4$, 1.1 equiv.) at -40° to -25°C followed by the addition of acetic acid (1.1 equiv.) and ethanethiol (>10 equiv.) at -25°C in sequence. Warming to room temperature led to nitrogen evolution and alcohol (2) production (Scheme 3, path b, Table 3). In Table 3, the results of a comparison between the use of trityl-(5)- or DPP-hydrazone(6)-are given. In general yields from the two methods are comparable but the DPP-hydrazones offer the advantage that basic residues obtained from the reaction can be removed with a dilute acid wash . Like the azo-anions from t-butylhydrazones[1], the azo-anions from (5) or (6) formed from alkyl lithium reagents are significantly basic and lower yields of alcohols (2) were obtained with enolisable carbonyl electrophiles.

When attempts were made to exchange the lithium counter ion of such azo-anions [eg. from (5b)] with other metal counter ions (eg. Zn^{2+}, Ti^{4+}, and $BF_3.Et_2O$) which were then tried as azo anions for an alcohol synthesis with acetophenone, these procedures gave lower yields of the desired alcohol than the standard conditions.

Hydrazone (5) or (6)	$R^3.CO.R^4$		Yield of (2) (%)	
	R^3	R^4	Tritylhydrazone (5)	DPP-hydrazone (6)
a	Ph	H	60	-
a	Ph	Me	54	-
a	$-(CH_2)_5-$		39	-
b	Ph	H	<72	65
b	Ph	Me	46	-
d	Ph	H	40	-
d	Ph	Me	51	-
d	$-(CH_2)_5-$		42	-
f	Me_2CH	H	-	40
f	$-(CH_2)_5-$		35	40
f	Ph	H	63	72
f	Ph	Me	50	-
g	Ph	H	-	63
g	Me_2CH	H	-	65
h	Ph	H	82	82

Table 3

Direct evidence for the free radical intermediate postulated in the decomposition of the azo adduct (Scheme 2) was obtained from the reaction of the anion of cyclopropylmethylketone tritylhydrazone (7) with benzaldehyde. Warming (-35°→ +20°) of the so-formed azo-adduct (8) in the presence of ethanethiol gave the ring opened alcohol (11)(52%, E :Z 93:7). The intermediate radical (9) would, as is known [8], be expected to undergo rapid ring opening to the isomeric homoallylic radical (10), which was then trapped by thiol to give (11) (Scheme 6).



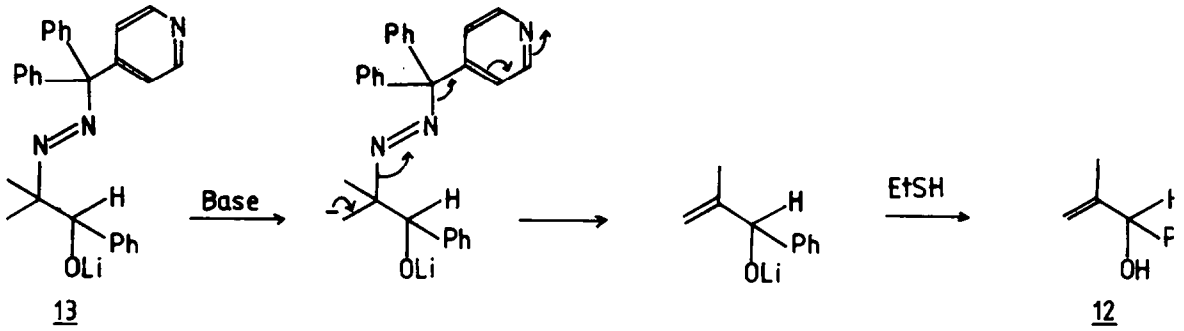
7 8 9 10 11

Reagents: (i) PhCHO, -35°; (ii) EtSH; (iii) -35° → +20°C

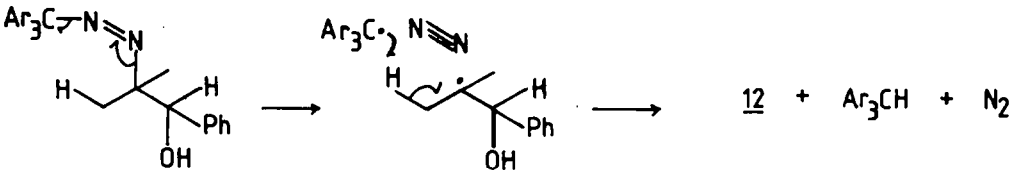
Scheme 6

The preparation of 2-methyl-1-phenylpropan-1-ol (2, R^1=R^2=Me,R^3,R^4=Ph,H) from the tritylhydrazone (5b) and benzaldehyde followed by acid quench and a standard ethanethiol work up led to the production of 2-methylene-1-phenylpropan-1-ol (12) as a minor by-product (ca 5%). This by-product, which could be obtained by Shapiro reaction methodology from acetone 2,4,6-tri-isopropylbenzenesulphonylhydrazone [6], was more significant when the DPP-hydrazone (6b) was used (ca 15%). As the diphenyl-4-pyridylmethyl carbanion is a potentially better leaving group than its trityl counterpart, it could be argued that a Shapiro like pathway accounted for the by-product (12) formation (Scheme 7). However, treatment of the intermediate (13) with excess base (MeLi, 1.1 equivs.) gave not only lower overall alcohol yields, but did not change the ratio of (2, R^1=R^2=Me,R^3,R^4= Ph,H) to the allylic alcohol (12). The origin of the allylic by-product (12) was found when the reaction was warmed to room temperature without addition of ethanethiol. In this reaction the ratio of (2,R^1=R^2=Me,R^3,R^4= Ph,H) : (12) changed dramatically to <5 : >95.[♦] A possible mechanism for the by-product formation is given in Scheme 8. This undesired olefinic by-product forming reaction was only found to be significant when hydrazones from methyl ketones were used, and in these reactions and in the case of the alkane (1) synthesis (path a, Scheme 3), a bromine wash was employed in the work up procedure to aid product purification.

♦ The overall yield of combined (12) and (2, R^1=R^2=Me,R^3,R^4=Ph,H) was also lowered by this procedure (ca 50%).



Scheme 7



Scheme 8

Preparation of Alkenes (3)

For an alkene synthesis, the lithium anions (14) formed from the adduct of the tritylhydrazones (5) with carbonyl electrophiles were treated with phosphorus trichloride. Thus addition at -78°C to the adduct (14) in THF: TMEDA (4:1) of PCl_3 (1.2 equivs.) gave, upon warming to +20°C, the alkenes (3) (path c, Scheme 3, Table 4). The DPP-hydrazones (6) offer no advantage over the tritylhydrazone (5) in this synthesis, as the alkene products are readily separated from the trityl residues by silica gel chromatography.

Hydrazone	R^3.CO.R^4		Yield of (3) (%)
	R^3	R^4	
5a	Ph	H	20
5b	Ph	H	52
5f	Ph	H	48
5f	Ph	Me	34
5f	$-(CH_2)_5-$		23 + (18, 18%)
6g	Ph	H	60 (E:Z 65:35)
6g	n-C_7H_{15}	H	55 (E:Z 60:40)
5h	Ph	H	37

Table 4

Using the preparation of benzylidene cyclohexane from (5f) and benzaldehyde as a model reaction, reagents other than PCl_3 were tried for alkene preparation. However, in all cases lower yields were obtained than with PCl_3 (Table 5). It should be noted that whereas phenylphosphorus dichloride can be used to generate olefin by this methodology, diphenylphosphorus chloride can not.

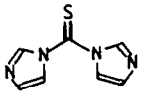
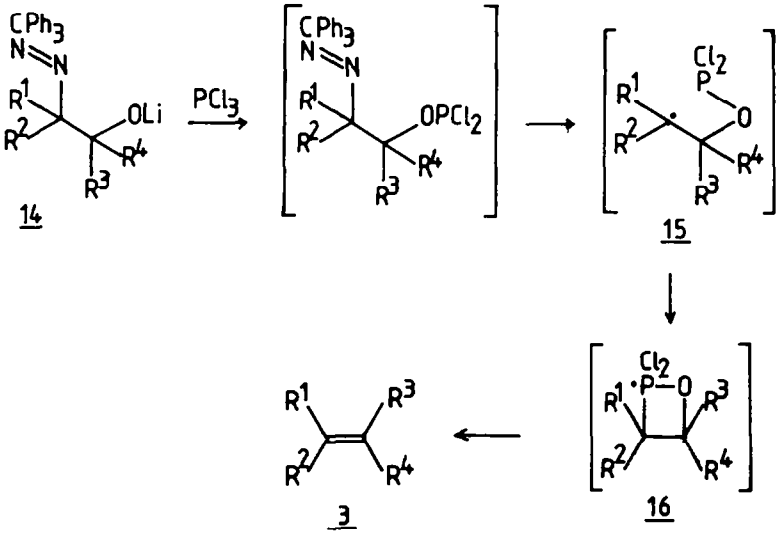
Reagent	Yield (%)
PCl_3	48
$PO.Cl_3$	39
$PhPCl_2$	25
PBr_3	12
$(EtO)_2PO.Cl$	6
Ph_2PCl	0
CS_2/MeI	26
$Cl.CS_2Et$	26
$Cl.CS_2Et/EtSH$	25
$Cl.CS_2Et$, then reflux in THF	20
	0
$SnCl_4$	0

Table 5

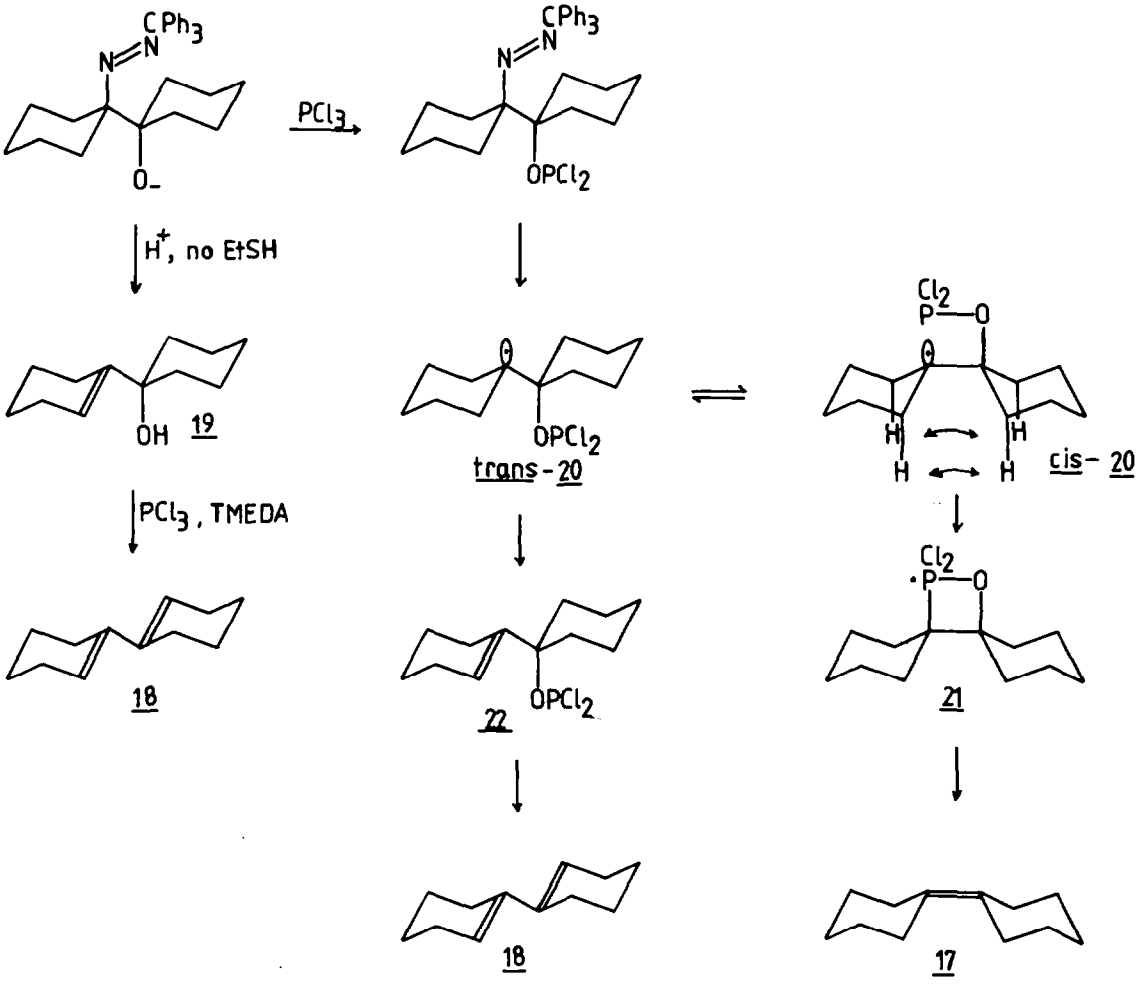
The mechanism of the PCl_3 mediated olefin formation is uncertain, but a possible mechanism is given in Scheme 9. Thus the intermediate radical (15) could close to the 4 membered ring (16) which could cis-eliminate to the olefin (3) in a similar manner to the Wittig reaction.



Scheme 9

Evidence for 4 membered ring (16) follows from the following observations. Firstly, the preparation of cyclohexylidene cyclohexane (17)(23%) gave as a by-product, the diene (18)(18%). Secondly, whereas the standard alcohol preparation from (6f) and cyclohexanone gave the alcohol (2, R^1,R^2,and R^3,R^4=-$(CH_2)_5$-) (40%), if the thiol work-up was omitted, then the allylic alcohol (19)(37%) was obtained. Treatment of the allylic alcohol (19) with PCl_3 and TMEDA gave the diene (18). These observations are consistent with the following explanation (Scheme 10). During the olefin forming sequence, the first formed radical intermadiate as (20) can only form the olefin (17) from a cis-elimination process, via (21). As this requires four membered ring formation from a sterically demanding conformation as cis-(20), then a low yield of the olefin (17) would be expected. Alternatively, the sterically favoured conformation as trans-(20) could generate the allylic species (22)(via a method similar to that in Scheme 8) which under the reaction conditions (TMEDA as base) could generate the observed diene (18).

This general method for olefin formation enables the discriminated coupling of two different carbonyl compounds as opposed to the pinacol related processes [7] which necessarily yield both symmetrically coupled and cross-over products. The coupling of two ketones to give a tetrasubstituted olefin is also noteworthy.



Scheme 10

Preparation of Saturated Esters (4)

The lithium anions of tritylhydrazones (5) could also be quenched with methyl crotonate to give a C- addition product. Thus treatment of (5) with n-butyl lithium (0.95 equiv.) in 1,2-dimethoxyethane at -78° gave an azo-anion which was warmed to -50° and treated with methyl crotonate (2.0 equiv. added over 1h., -50°C). TFA (1.0 equiv.) and ethanethiol (5 equiv.) were added in sequence and the solution warmed to 20°C. Purification by chromatography on silica gel gave the saturated esters (4) (Scheme 3, path d, table 6). The yields in this sequence were disappointingly low and the major reaction pathway in these processes appeared to be a basic deprotonation of methyl crotonate by the azo-anions to give recovered tritylhydrazone (5). The DPP- hydrazones (6) gave lower yields than the corresponding tritylhydrazones (5) with methyl crotonate. Substitution of methyl crotonate by methyl acrylate, methyl β,β-dimethylacrylate, or acrylonitrile led to negligible yields of C-addition products.

Hydrazone (5)	Ester (4) (%)
c	23
d	20
f	35

Table 6

General Experimental

Standard laboratory practice as previously described[8] was observed. All ^1H N.M.R. spectra were recorded at 300MHz upon a Bruker WH 300 N.M.R. spectrometer using deuteriochloroform as solvent referenced to residual $CHCl_3$ = 7.27 p.p.m. unless otherwise stated. Coupling constants J were measured to the nearest 0.5Hz. All ^{13}C N.M.R. spectra were recorded at 62.85 MHz on a Bruker AM 250 spectrometer using deuteriochloroform as solvent, referenced to $CDCl_3$ = 77.00 p.p.m. unless otherwise stated. Some ^{13}C peaks (especially in the case of geometric isomers) are unresolved. Only selected I.R., ^1H, and ^{13}C N.M.R. signals are assigned. Accurate mass measurements were recorded from the electron impact (E.I.) mode only. G.L.C. was run on a Pye series 104 chromatograph with a 5'x 0.25" I.D., 3% OV1 on gas chrome Q (100-120 mesh) column.

Compounds reported in tables 1 - 4 but not described in the experimental section gave satisfactory spectral and analytical data consistant with their structures; this data has been omitted in order for brevity in the presentation of this manuscript.

Preparation of Tritylhydrazine Hydrochloride

Triphenylmethyl chloride (100g, 0.35 mol.) was added to a solution of hydrazine hydrate (120 ml, excess) in THF (500ml.) and the mixture stirred under reflux for 6-18 h. The solution was cooled to 25°, concentrated to half volume, and extracted into diethyl ether (2 x 150ml.). The organic layer was washed with brine (2 x 30ml.), dried (Na_2SO_4), filtered and treated with a solution prepared from hydrogen chloride (g) in methanol (55ml, 6.5M, 1.0 equiv.). The solution was cooled to 0° for 24h., and the solid filtered off and washed with diethyl ether to give tritylhydrazine hydrochloride (96.0g, 86%), m.p. 109-112°C (Lit.,[3] 108-113°C).

General procedure for the preparation of Tritylhydrazones (5)

The following procedure for the preparation of acetone tritylhydrazone (5b) is typical.

Tritylhydrazine hydrochloride (10.0g, 32 mmol.) was dissolved in methanol (200ml.) and a solution of sodium formate (3.28g, 48 mmol) in water (15ml) was added. Acetone (2.60ml, 35 mmol) was added and the mixture stirred under argon for 2h. in the dark. The solid precipitate was filtered off, washed with water and light petroleum (10ml) in sequence, then dried under vacuum to yield acetone tritylhydrazone (5b) as a while solid (9.10g, 90%), m.p. 119-120°C; νmax. ($CHCl_3$) 3060 w, 2960 s, 2930 s, 2860 s, 1597 m, 1487 m, 1445 s, 760 s, 720 s, and 705 s cm^{-1}; δH 1.74 (3H, s, Me), 1.80 (3H, s, Me), 5.38 (1H, br, NH), and 7.19 - 7.46 (15H, m, Ar-H); δC 15.63 (q, Me), 25.30 (q, Me), 75.50 (s, CPh_3), 126.43, 127.60, 129.16 (3 x d, phenyl CH), 145.66, 146.17 (2 x s, phenyl-ipso-C, C=N); m/e (NH, C.I.) 315 (MH^+, 11%), 243 ($Ph_3C^{\oplus}$, 100), and 165 (27); (E.I.) 243 (100%), 165 (60).

Those hydrazones which did not crystallise were extracted into dichloromethane, dried (Na_2SO_4), and evaporated to give oily products. Further purification could be achieved by rapid flash chromatography on silica gel.

Preparation of Diphenyl-4-pyridylmethylhydrazine dihydrochloride

A solution of 4-benzoylpyridine (25.0g, 0.13 mol) in dry diethyl ether (330ml) was added to a solution of phenylmagnesium bromide [from bromobenzene (0.28 mol.) and magnesium (0.26 mol.) in diethyl ether (150ml)] at a rate to maintain reflux. The solution was then refluxed for 2h., stirred at 20° for 10h., then poured into ice-cold, hydrochloric acid (110ml, 0.65 mol.). The aqueous layer was seperated, then basified to pH 9 with 0.880 ammonia. The solid product was filtered off, washed with water and benzene then dried to give diphenyl-4-pyridylmethanol (29.3g, 82%), m.p. 230-232°C. (Lit.[9] 235°C), νmax. (nujol) 3150 m (O-H) cm^{-1}.

Diphenyl-4-pyridylmethanol (25.0g, 96 mmol) was converted to diphenyl-4-pyridylmethylchloride hydrochloride (25.4g, 84%) by a modification to the procedure of Young[6] in which a shorter reaction time (16h.) was employed, m.p. 174-6°C (Lit., [6] 134-5°C), δH (D_2O, HOD = 4.60 p.p.m.) 7.10 - 7.15 (4H,m, phenyl-H), 7.22 - 7.25 (6H,m, phenyl-H), 7.86 (2H,d,J 7Hz,pyridyl-H), and 8.53 (2H,d,J 7Hz, pyridyl-H).

Diphenyl-4-pyridylmethylchloride hydrochloride (24.0g, 76 mmol) was dissolved in dry THF (250ml) and excess anhydrous hydrazine (24ml) added. The mixture was stirred at 65° for 12h., cooled and extracted into diethyl ether (2 x 100ml). The organic layer was washed with brine (2 x 100ml), dried (Na_2SO_4), and treated with a solution prepared from hydrogen chloride (g) (175 mmol) in diethyl ether. The white solid was filtered off, washed with diethyl ether (200ml) and dried to yield diphenyl-4-pyridylmethylhydrazine dihydrochloride (25.40g, 96%); m.p. 182-4° C; ν_{max}. (nujol) 3400 wbr, 3090 m, 3060 m, 3020 m, 1600 m, 765 m, and 700 m cm^{-1}; δH (CD_3OD, CHD_2OD=3.305 p.p.m.) 7.39 - 7.56 (10H,m, phenyl-H), 8.32 (2H,d,J 6Hz, pyridyl-H), 8.86 (2H,d,J 6Hz, pyridyl-H), m/e (positive argon F.A.B.) 276 ($C_{18}H_{18}N_2^+$, 17%), 262 (75), and 246 (100).

General procedure for the preparation of Diphenyl-4-pyridylmethylhydrazones (6)

The following method for the preparation of acetone diphenyl-4-pyridylmethylhydrazone (6b) is typical.

Diphenyl-4-pyridylmethylhydrazine dihydrochloride (10.0g, 29 mmols.) was dissolved in methanol (100ml) and a solution of sodium formate (4.80g, 72.5 mmols) in water (20ml.) was added. Acetone (35 mmol.) was added and the mixture stirred under argon for 2h. in the dark. The resultant solid was filtered off, washed with water (50ml.), and light petroleum (10ml) in sequence to give acetone diphenyl-4-pyridylmethylhydrazone (6b) (5.88g, 65%); as a white solid m.p. 124-5°C; ν_{max}. (nujol) 3200 m, 1595 s, 760 m, and 700 s cm^{-1}; δH 1.74 (3H,s,Me), 1.80 (3H,s,Me), 5.30 (1H,s,NH), 7.24 -7.33 (12H,m,aryl-H), 8.50 (2H,d, J 6Hz, pyridyl-H); δC 15.63 (q, Me), 25.22 (q, Me), 72.02 (s, CAr_3), 124.29, 126.93, 127.88, 128.75 (4 x d, aryl CH), 144.72, 146.81 (2 x s), 149.26 (d, aryl CH), and 154.66 (s); m/e (NH_3 C.I.) 316 (MH^+, 10%), 244 (Ar_3C^+, 100) and 165 (10).

General procedure for the preparation of Alkanes (1)

The following procedure for the preparation of alkanes (1) from tritylhydrazones (5) is typical.

To a solution of tritylhydrazone (5f) (5.0 mmol) in THF (30ml) at -40°C was added methyl lithium (5.5 mmol). After 20 min., benzyl bromide (6.5 mmol) was added, the reaction warmed to -30°C and stirred for 3h. The reaction was quenched with acetic acid (5.5 mmol), then ethanethiol (2ml) was added and the reaction warmed to 20°C over 30 min. during which nitrogen evolution occurred. Diethyl ether (40ml) was added and the solution washed with aqueous sodium hydroxide (2M, 2 x 100ml), brine (60ml), dried, filtered, and evaporated. The crude product was then initially purified by filtration through silica gel (50g) using light petroleum as eluant. The product was dissolved in dichloromethane (20ml), reacted briefly with bromine until present in excess, washed with saturated sodium thiosulphate solution (2 x 15ml.),dried, filtered, and evaporated. Final purification by p.l.c. (Merck Kieselgel 60. P254 20 x 20 x 0.1 cm plates, using light petroleum as eluant) gave benzylcyclohexane (594 mg, 68%); b.p. 129° at 14 mm Hg; g.c. retention time 5.6 min at 155°; ν_{max}. (film) 3090 w, 3065 w, 3025 w, 2925 s, 1285 m, 1607 w, 1496 w, 1450 m, 743 m, and 698 m cm^{-1}; δH 0.98 - 1.73 (11H, m, C_6H_{11}), 2.51 (2H, d, J 7Hz, CH_2Ph), and 7.11 - 7.37 (5H, m, aryl-H); δC 26.33, 26.60, 33.17 (3 x t, CH_2), 39.78 (d, CH), 44.14 (t, CH_2Ph), 125.52, 127.99, 129.14 (3 x d, aryl CH), and 141.33 (s, aryl-ipso-C); m/e (E.I.) 174 (M^+, 24%), 92 (100), 91 (39), 83 (40), 82 (12), 67 (12), 65 (11), 55 (60), and 41 (24); (Found : C, 89.4%; H, 10.2%; 174.1408. $C_{13}H_{18}$ requires C, 89.6%; H, 10.4%; 174.1408.).

General procedure for the preparation of Alcohols (2)

The following procedure is typical for the preparation of alcohols (2) from trityl-(5) or DPP-(6) hydrazones.

Hydrazone (6h.) (4.0 mmol) was dissolved in THF:TMEDA (4:1, 50ml.) and the solution cooled to -55°C. Methyl lithium (5.25 mmol in diethyl ether) was added and the solution stirred for 20 min. before addition of benzaldehyde (5.25 mmol.). After 20 min. the reaction was quenched with acetic acid (5.25 mmol) and ethanethiol (5ml) added. The mixture was warmed to 20° over 30 min., during which time nitrogen evolution occured. The mixture was extracted into diethyl ether (100ml.), washed with sodium hydroxide solution (1M, 2 x 20ml.), hydrochloric acid (2M, 2 x 20ml.), dried (Na_2SO_4), filtered, and evaporated to yield a crude product. Purification by flash column chromatography on silica gel and p.l.c. [using diethyl ether : light petroleum (3:17) as eluant] gave 1-cyclododecyl-1-phenylmethanol (899 mg, 82%); m.p. 82-3°; t.l.c. [diethyl ether : light petroleum (3:17)] Rf 0.35; ν_{max}. (nujol) 3400 m (O-H), 3085 w, 3060 w, 3030 w, 765 s, and 705 s cm^{-1}; δH 1.17 - 1.57 (22H, m, CH_2), 1.74 - 1.94 (1H, m, CH), 4.55 (1H, d, J 5Hz, CHOH), 7.20 -7.41 (5H, m, phenyl-H); δC 21.77, 22.10, 23.23, 23.58, 24.24, 24.80, 24.89, 25.71, 25.80 (9 x t, CH_2), 41.64 (d, CH), 77.10 (d, CHOH), 126.55, 127.27, 128.18 (3 x d, phenyl CH), 144.08 (phenyl-ipso-C); m/e (E.I.) 274 (M^+, 1%), 257 (22), 107 (100), 79 (36), 77 (21), 55 (15), 41 (20), 39 (11); (Found : C, 83.41%; H, 11.00%. $C_{19}H_{30}O$ requires C, 83.15%; H, 11.02%).

For alcohols derived from methyl ketone hydrazones, a brief bromine wash was employed prior to final p.l.c. purification (to facilitate seperation from olefinic by-products).

Also prepared 2-methyl-1-phenylpropan-1-ol [from (6b, 5.0 mmol) and benzaldehyde] (488 mg, 65%); t.l.c. [diethyl ether : light petroleum (3:7)] Rf 0.3; ν_{max}. (film) 3400m (O-H), 3090 w, 3070 w, 3030 w, 2965 s, 2935 s, 2880 s, 760 s, 705 s cm^{-1}; δH 0.80 (3H, d, J 7Hz, Me), 1.01 (3H, d, J 7Hz, Me), 1.91 - 2.02 (1H, m, $CHMe_2$), 4.36 (1H, d, J 7Hz, CHOH), 7.23 - 7.37 (5H, m, phenyl-H); δC 18.19 (q, Me), 18.96 (q, Me), 35.21 (d, $CHMe_2$) 79.97 (d, CHOH), 126.50, 127.32, 128.10 (3 x d, phenyl CH), 143.59 (s, phenyl-ipso-C); m/e 150 (M^+, 4%), 132(21), 117(31), 115(12), 107(100), 91 (17), 79(51), 77(28), 51(13), 40(17), 39(13); (Found : 150.1044. $C_{10}H_{14}O$ requires 150.1045) along with 2-Methylene-1-phenylpropan-1-ol (12); (111 mg, 15%); t.l.c. [SiO_2, light petroleum (4:1)] Rf 0.6; ν_{max}. (film) 3360 br (O-H), 3060 m, 3030 m, 2970 m, 1450 s, 1045 s, 1025 s, 905 s, and 700 s cm^{-1}; δH 1.63 (3H, s, Me), 2.09 (1H, br s, OH), 4.97 (1H, multiplet s, vinyl-H), 5.14 (1H,s, CHOH), 5.22 (1H, multiplet s, vinyl-H), and 7.27 - 7.41 (5H, m, phenyl-H), m/e (E.I.) 148 (MH^+, 100%), 133(70), 105(86), and 79(96).

2-Methyl-1-phenylpropan-1-ol was also prepared from isopropyl magnesium bromide and benzaldehyde and shown to have identical spectral properties.

An authentic sample of 2-methylene-1-phenylpropan-1-ol (12) was prepared via acetone 2,4,6-tri-isopropylbenzenesulphonylhydrazone [4] and benzaldehyde and shown to have identical spectral properties.

Preparation of 2-Methyl-1-phenylpent-2-en-2-ol (11)

(7) (1.50g, 4.41 mmol.) was dissolved in dry THF (15ml), the solution cooled to -35° and treated with n-butyl lithium (5.0 mmol). The solution was stirred for 20 min. at -35°C, quenched with benzaldehyde (5.0 mmol) then stirred for 5 min. Ethanethiol (4ml) was then added and the solution warmed slowly to 20° during which nitrogen evolution was observed. The solution was evaporated, extracted into diethyl ether (100ml), washed with water (50ml), dried, filtered, and evaporated. Purification by chromatography on flash silica gel [60g, using dichloromethane as eluant] gave the title compound (11) (404mg, 52%); as an oil; E:Z = 93:7; t.l.c. (dichloromethane) Rf 0.3; νmax. (neat film) 3380 br m (O-H), 3090 w, 3060 w, 3030 w, 2960 m, 2930 m, 2870 m, 1605 w, 1490 m, 1450 m, 1190 w, 1020 s, 915 w, 870 w, 740 m, and 700 s cm^{-1}; δH 1.05 (3H,t, J 7Hz,$MeCH_2$), 1.47 and 1.56 (3H, 2 x multiplet s, ratio 93:7, vinyl Me), 2.00 - 2.20 (3H,m, CH_2Me and OH), 5.10 (1H,s, CHOH), 5.65 (1H,t, J 5Hz, vinyl-H), 7.20 - 7.40 (5H,m, phenyl-H); m/e (E.I.) 176 (M^+, 40%), 147(90), 129(40), 107(60), 105(60), 79(100), 77(95), 69(40), and 41(60) (Found : 176.1200. $C_{12}H_{16}O$ requires 176.1201). In a n.O.e experiment irradiation of the vinyl methyl group at δH 1.47 gave n.O.e of the CH_2Me protons, δH 2.0 - 2.2 (3%) but not to the vinylic proton δH 5.65 (< 0.5%), whereas irradiation of the vinyl proton, δH 5.65 gave n.O.e of the CHOH proton, δH 5.10 (6%) but not to the vinyl methyl group, δH 1.47 (< 0.1%).

Preparation of 2-Methylene-1-phenylpropen-1-ol (12) in the absence of ethanethiol

The standard procedure for alcohol (2) formation was employed using (6b) (1.5 mmol) and benzaldehyde (1.5 mmol) except that the ethanethiol addition was omitted. Standard work up and chromatography gave (12) (110mg, 49%) t.l.c., n.m.r. as before along with minor (< 5%) amounts of 2-Methyl-1-phenylpropan-1-ol.

General procedure for the preparation of Alkenes (3)

The following procedure for the preparation of β,β-dimethylstyrene is typical.

(5b) (5.0 mmol) was dissolved in THF:TMEDA (4:1, 50ml.) and the solution cooled to -55°C. Methyl lithium (5.25 mmol in diethyl ether) was added, the solution stirred for 20 min., then treated with benzaldehyde (5.25 mmol). After 20 min the solution was cooled to -78°C and phosphorus trichloride (6.25 mmol.) was added. The mixture was allowed to warm to 20° over 90 min., then stirred for a further 60 min. Diethyl ether (100ml.) was added, the solution washed with sodium hydroxide solution (1M, 2 x 20ml.), hydrochloric acid (1M, 2 x 20ml), dried ($MgSO_4$), filtered, and evaporated to give a viscous oil (3.2g). Purification by flash chromatography on silica gel (75g) using light petroleum as eluant gave β,β-dimethylstyrene (343mg, 52%); as an oil; t.l.c. (light petroleum) Rf 0.6; νmax (film) 3080 w, 3060 w, 3020 w, 2970 s, 2930 s, 2910 s, 2850 s, 1650 m (C=C), 745 s, and 700 s cm^{-1}; δH 1.90 (3H,s, Me), 1.94 (3H,s, Me), 6.31 (1H,s, vinyl-H), and 7.25 - 7.37 (5H,m, phenyl-H), δC 19.36 (q,Me), 28.84 (q,Me), 125.11, 125.72, 127.96, 128.69 (4 x d, vinyl, phenyl CH), 135.37, 138.66 (2 x s, CMe_2, phenyl-ipso-C); m/e (E.I.) 132 (M^+., 80%), 117(100), 115(21), 91(22); (Found 132.0939. $C_{10}H_{12}$ requires 132.0938).

Also thus prepared cyclohexylidene cyclohexane [from (5f, 4.5 mmol.) and cyclohexanone] (170 mg, 23%); m.p. 55-60° (lit., [10] 53°) t.l.c. (light petroleum) Rf 0.75; νmax (nujol) 1265 w, 1240 w, 1015 w, 890 m, and 850 m cm^{-1}; δH 1.43 - 1.65 (12H, br, CH_2), 2.13 - 2.27 (8H, br, allylic CH_2); δC 27.30, 28.71, 30.13 (3 x t, CH_2), and 129.40 (s, C=C); m/e (E.I.) 164 (M^+., 73%), 135(12), 121(20), 107(17), 93(23), 91(15), 82(100), 81(66), 79(40), 67(75), 55(41), 39(40), 37(22); (Found 164.1565. $C_{12}H_{20}$ requires 164.1565) along with the diene (18) (131mg, 18%) as an oil; t.l.c. (light petroleum) Rf 0.8; νmax (film) 2930 s, 2860 s, 2835 s, 1450 m, 1435 m, 1335 w, 1135 w, 925 w, and 795 m cm^{-1}, δH 1.50 - 1.63 (4H,m), 2.05 - 2.26 (8H,m), 5.80 (2H, br s); δC 22.54; 23.16, 25.54, 25.86 (4 x t, CH_2), 121.30 (d, vinyl CH), 136.82 (s, vinyl C); m/e (E.I.) 162 (M^+, 100%), 147(14), 133(30), 119(30), 105(32), 94(60), 91(70), 79(75), 65(18), 51(19), 41(45), and 39(41).

Also thus prepared 2-Methyl-1-phenyloct-1-ene [from (6g, 4.0 mmol.) and benzaldehyde] [485mg, 60%, E : Z = 65:35] as an oil; t.l.c. (light petroleum) Rf 0.65; νmax (film) 3085 w, 3060 w, 3030 w, 2960 s, 2930 s, 2860 s, 1650 m (C=C),745 m, and 700 s cm^{-1}; δH 0.89 - 0.96 (3H,m, CH_2Me), 1.30 -1.39 (6H,m, CH_2), 1.52 - 1.55 (2H,m, CH_2), 1.88 and 1.91 (3H, 2 x multiplet s, ratio 65:35, vinyl-Me), 2.17 - 2.27 (2H,m, allylic CH_2), 6.30 (1H,s, vinyl-H), 7.17 - 7.38 (5H,m, phenyl-H); δC 14.09 (q, Me), 17.72 (q, Me), 22.65 (t, CH_2), 24.09 (q, Me), 27.99, 28.10, 29.01, 29.36, 31.71, 31.81, 32.54, 40.76, (8 x t, CH_2), 124.67, 125.29, 125.67, 127.94, 128.52, 128.78 (6 x d, vinyl CH, phenyl CH), 138.72, 139.34, 139.79 (3 x s, C=C, phenyl-ipso-C); m/e (E.I.) 202 (M^+, 49%), 131(100), 117(21), 115(11), 91(57) 69(11), and 55(9), (Found : C, 89.29; H, 11.16; 202.1721. $C_{15}H_{22}$ requires C, 89.04; H, 10.96%; 202.1721).

In an n.O.e experiment, irradiation of the vinyl proton, δH 6.30 gave n.O.e of the vinyl methyl resonances δH 1.91 (2.2%) and δH 1.88 (< 0.5%).

Preparation of the Allylic alcohol[13](19)

The standard procedure for alcohol (2) formation was employed using (5f) (4.5 mmol) and cyclohexanone except that the ethanethiol addition was omitted. Standard work up and p.l.c. [SiO_2, using light petroleum : diethyl ether (17:3)] gave (19) (303mg, 37%), t.l.c. [light petroleum : diethyl ether (17:3] Rf 0.3; m.p. 64-5°C (Lit.[13] 69°C); νmax 3280 s, 3220 s (O-H), 1295 m, 1195 m, 1055 s, 960 s, 925 m, 905 m, 855 s; δH 1.22 - 1.32 (2H, m), 1.45 - 1.71 (12H, m), 2.00 - 2.05 (4H, m), 5.75 -5.81 (1H, m); m/e (E.I.) 180 (M^+, 24%), 137(100), 119(18), 109(25), 91(21), 81(37), 67(21), and 55(22) [Found 180.1514. $C_{12}H_{20}O$ requires 180.1514].

Conversion of the Allylic alcohol (19) to the Diene (18)

The allylic alcohol (19) (1.3 mmol) was dissolved in THF:TMEDA [(4:1), 15ml] and cooled to -78°. Methyl lithium (1.4 mmol) was added, the solution stirred for 10 min, and treated with phosphorus trichloride (1.6 mmol). The mixture was warmed to 20° over 90 min, and stirred for 30 min. Diethyl ether (50ml) was added, the solution washed with hydrochloric acid (2N, 10ml), brine (2 x 10ml), dried, filtered, and evaporated. Purification by chromatography on silica gel [(70g); using light petroleum as eluant] gave the diene (18) (132mg, 62%), t.l.c., n.m.r. as before.

General procedure for the preparation of Saturated Esters (4)

The following procedure for the preparation of methyl-3-cyclohexylbutanoate is typical.

(5f) (5.0 mmol.) was dissolved in dry 1,2-DME (60ml) and the solution cooled to -55°. n-Butyl lithium (4.75 mmol in hexane) was added, the solution stirred for 20 min., and a solution of methyl crotonate (10.0 mmol) in 1,2-DME (8ml) was added over 1h. Trifluoroacetic acid (5.0 mmol) was added, followed by ethanethiol (5ml), the solution warmed to 20° and evaporated. The residue was triturated with light petroleum (4 x 20ml), and the extracts evaporated to give an oil (1.40g). Kügelrohr distillation b.p. ca 150° at 20 mmHg, (Lit.[18], 149-50° at 25 mmHg) gave a colourless oil (640mg) which was purified by p.l.c. [using diethyl ether : light petroleum (3:17) as eluant] to give methyl-3-cyclohexylbutanoate[18] (323mg, 35%) as an oil, t.l.c. [diethyl ether : light petroleum (3:17)] Rf 0.75; ν_{max} (film) 2965 s, 2860 s, 1745 s (C=O), 1450 m, and 1140 m, cm^{-1}; δH 0.88 (3H,d, J 7Hz,Me), 0.88 - 1.24 (6H, m, CH_2), 1.57 - 1.80 (5H,m, CH_2 and C(4)H), 1.80 - 1.91 (1H,m, C(3) H), 2.03 - 2.15 (1H,m, AB part of ABX, CH_2CO), 2.33 - 2.43 (1H,m, AB part of ABX, CH_2CO), 3.66 (3H,s, OMe); δC 16.52 (q, Me), 26.66, 28.98, 30.30 (3 x t, CH_2), 35.39 (d, CH), 39.05 (t, CH_2CO), 42.63 (d, CHMe), 51.33 (q, OMe), 174.23 (s, CO); m/e (E.I.) 185 (MH^+, 5%), 153(17), 111(100), 101(95), 87(62), 74(72), 55(90), and 41(67); (Found: C, 71.83%; H, 10.92%). $C_{11}H_{20}O_2$ requires C, 71.63%; H, 10.93%).

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