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Steric and Complexation Effects on the 1,4-Addition Reaction of Lithium Dimethylcuprate with Rigid α,β-Unsaturated Ketones

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Abstract:

Reaction of lithium dimethylcuprate with a series of substituted 10-methyl-1(9)-octal-2-ones in diethyl ether give 1,4-addition products with the same ring junction stereochemistry as the parent, unsubstituted α,β-unsaturated ketone. The reactivity of the system is modified by groups positioned axially and 1,3 with respect to the β-carbon of the enone. Alkoxy substituents are generally activating, particularly if they are *syn* with respect to the incoming methyl group.

*Keywords:*Copper and compounds; Addition reactions; Enones

Introduction

The high 1,4- (conjugate) regioselectivity of organocuprate (R_2CuLi)† reactions with α,β-unsaturated carbonyl compounds has lead to extensive utilization of these reagents in synthetic procedures for creating carbon-carbon single bonds relatively remote from the carbonyl group [1-3]. A natural progression from this effort is the consideration of the stereoselectivity of these reactions. Although many organocuprate 1,4-additions are stereoselective [4], it would be clearly advantageous to be able to directly control the product stereoselectivity. A necessary prerequisite for obtaining stereochemical control of cuprate 1,4-additions to α,β-unsaturated carbonyl systems is a knowledge of the mechanism and, in particular, an understanding of how the cuprate and substrate interact during carbon-carbon bond formation. The mechanism of the 1,4-addition reaction has been extensively studied both experimentally and theoretically [5] and the current view is that it involves significant complexation between metal centres and the substrate. It has been shown [6] that lithium, from within the cuprate cluster if necessary, coordinates to the carbonyl oxygen and copper interacts with the double bond of the unsaturated system. All of these interactions precede the migration of R from copper to the organic

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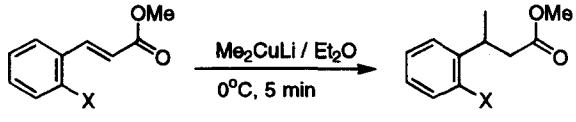
substrate and clearly the stereochemical aspects of these interactions, prior to the crucial bond formation, could influence the stereochemistry of the product. Recently, an in-depth theoretical analysis of the reaction [7] has signalled the possibility that the facial selectivity of the incoming organometallic and the irreversible C-C bond formation are separate steps and hence may respond differently to changes in the reaction environment.

Control of the reactivity, regio-, and stereoselectivity of reactions involving organometallic reagents can often be achieved by the inclusion of a remote functional group into the substrate to interact with and modify the organometallic reagent [8]. Many ligands coordinate with copper(I) to form relatively stable compounds and this feature has been utilized in the formation of mixed organocuprate reagents [9-11]. It is therefore conceivable that a group, appropriately positioned within the substrate, may be able to coordinate with the cuprate reagent, and influence the overall stereoselectivity and/or reactivity. Steroids have provided a convenient rigid framework for intramolecular coordination studies and 1,4- addition reactions of lithium dimethylcuprate (Me_2CuLi) with steroidal 4-en-3-ones afford 5β-methyl-3-ones with high stereoselectivity [2]. Related studies of organocuprates with 10-methyl-1(9)-octal-2-one (**1**) and derivatives have also been undertaken [12-16], and only the *cis* dialkyl ring junction products have been obtained. For ready comparison, the results of previous, relevant studies with octalone derivatives are summarised in the Table along with the results from this work.

The influence of a remote functional group or a bulky substituent on the reactivity and stereochemistry of cuprate 1,4-addition has been demonstrated in acyclic and monocyclic systems [20,21]. Reports of asymmetric applications involving unsaturated esters have also appeared [22-24]. It has been generally considered that steric factors are the decisive element for stereochemical control and stereoelectronic influences are important only when there is little steric hindrance [25]. Examples of reactivity modification by remote alkyl and alkenyl groups are illustrated in the reactions of Me_2CuLi with **2** - **5** listed in the Table.

Hydroxyl groups remotely positioned in steroid systems appear to be relatively innocuous as shown by the successful Me_2CuLi 1,4-additions with testosterone [19]. However, if the hydroxyl group is in certain positions relative to the reactive site then complete inhibition is noted *e.g.* 6β-hydroxycholest-4-en-3-one, 2α-hydroxycholest-4-en-3-one [17]. Some reagent dependence on the success of the 1,4-addition is evident, as reaction of Me_2CuLi with *cis*-5-hydroxy-10-methyl-1(9)-octal-2-one (**6**) was not observed in this work (*vide infra*) although the same substrate reportedly reacts with MeMgI in the presence of copper(II) [26].

Ethers are conceptually and synthetically attractive functionality to examine remote group effects on organocuprate reactions. A striking example is the report that a *o*-methoxymethylene group significantly modified the 1,4- reactivity of Me_2CuLi with cinnamate esters [27] (Scheme 1). The observed activation was explained by evoking intramolecular coordination of the remote group to a lithium atom in the π-complexed cuprate based on a "closed" [7] organometallic cluster. Our recent observations of the influence of alkyl ethers on organocuprate reactivity [28, 29] in nonpolar environments reinforces this interest. Silyl ethers *e.g.* (**7**) are also reported to react effectively with Me_2CuLi in diethyl ether (Et_2O) (Table) and give the *cis* ring products.



X = H (18%)
X = CH_2OMe (>98%)

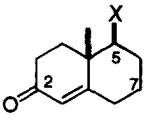
Scheme 1.

Acetals are also potentially useful as coordinating ligands and have been of particular interest for enantioselective cuprate additions [30]. Other relevant reports, summarized in the Table, indicate that, while reaction of Me_2CuLi with the acetal **8** proceeds well, the spiro acetals **9** and **10** are unreactive. The relative position of the acetal is clearly important given the successful reaction with **11** and the observation of effective reaction with **12** indicates that the close positioning of a saturated ketone is not inhibiting.

We have recently disclosed that alkyl ethers [28, 29] significantly modify the 1,4-/1,2-product ratio in the reactions of dibutylcuprates with α,β-unsaturated ketones such as **1** in a non polar solvent (toluene). This paper reports studies of the reactions of Me_2CuLi with substrates derived from **1** which were examined from the viewpoint of determining the influence of remote groups on the product stereochemistry and the overall reactivity. The remote functional groups were chosen on the basis of previous results [27,31] where increased reactivity and stereoselectivity in cuprate 1,4-addition had been observed. The reaction studies were carried out in Et_2O solvent to allow for valid comparison with the wide variety of published results from other groups using a common reagent (Me_2CuLi) and also in recognition that any intramolecular interactions should be competitive with intermolecular solvent interactions.

Results and Discussion

The initial investigation of the influence of a remote group on the cuprate addition was based on the *cis*-5-alkoxy octalone derivatives[‡], as some substrates of this general type have previously been used for mechanistic studies [19,32]. The *cis*-5-alkoxyoctal-2-ones **13**, **14** and **15** were prepared by reaction of **6** with appropriate alkylating agents (NaH/MeI in DMF; LiBr/*p*-TsOH in dimethoxymethane; benzyl 2,2,2-trichloroacetimidate [33] respectively) with care to avoid strongly basic reaction conditions to prevent a vinylogous *retro* aldol ring cleavage reaction [34]. Reaction of the *cis*-5-oxy derivatives; **6**, **13**, **14** and **15** with Me_2CuLi[†] in Et_2O were investigated and the results are presented in the Table. Compound **6** failed to undergo any significant reaction with excess Me_2CuLi, although a yellow precipitate was formed during the reaction. Reaction of one equivalent of Me_2CuLi with the hydroxyl group seems reasonable, however it appears that there is little nett negative charge on the alcohol oxygen as the starting material is recovered intact. When the alkoxide is generated from **6** using sodium hydride, little starting material is recovered due to the facile ring cleavage. As discussed earlier, alcohol groups do not induce complete decomposition of Me_2CuLi, as successful 1,4-additions can be achieved with molecules containing (albeit remote) hydroxyl groups.

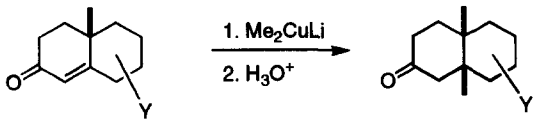


13 X = OMe
14 X = OCH_2OMe
15 X = OCH_2Ph

The structures of the major products resulting from the reaction of **13**, **14** and **15** with Me_2CuLi, were the 1,4- methyl addition products **16**, **17** and **18.** The structural assignments are based on evidence of a saturated carbonyl group: IR (ν_{max} *ca.* 1712 cm^{-1}), ^{13}C NMR (δ *ca.* 213) for each product. The stereochemistry of each of these 1,4-addition products and, in particular, the ring junction arrangement was established by procedures developed with **19,** the methyl 1,4-

Table

Reaction of Me_2CuLi with Substituted Octalones



Reactants		Products Yield (/%)[a,b]			Ref
structure	Y	substrate	1,4-[c]	1,2-[c]	
1	H		88		[6]
2	*cis* 7 -$CH(CH_3)_2$		62		[16]
3	*cis* 7 -$C(CH_3)=CH_2$	~60	40	trace	[15]
4	*trans* 7 -$CH(CH_3)_2$		5		[16]
5	*trans* 7 -$C(CH_3)=CH_2$	mostly	~3		[15]
6	*cis* 5 -OH	80(95)			[d]
7	*cis* 5 -$OSiMe_2tBu$		53(60)	0(40)	[12]
8	*cis* 5 -OTHP		88		[13]
9	5 -OCH_2CH_2O-	90	0		[17]
10	5 -SCH_2CH_2S-	93	0		[17]
11	6 -$OCH_2CH_2CH_2O$-		61		[18]
12	5 =O		83		[19]
13	*cis* 5 -OMe	0	**16** 46(73)	16(27)	[d]
14	*cis* 5 -OCH_2OMe	8(10)	**17** 50(90)	-	[d]
15	*cis* 5 -OCH_2Ph	-	**18** 51(92)	-	[d]
21	*trans* 5 -OCH_2OMe	27	-	**24** 58	[d]
28	*trans* 7 -OMe	8(10)	**31** 53(60)	17(30)	[d]
29	*trans* 7 -OCH_2OMe	23(25)	**32** 50(75)	-	[d]
30	*trans* 7 -OCH_2Ph	43(50)	**33** 44(50)	-	[d]
34,36[e]	7 -CH_2OCH_2OMe	17[f]	**43** 30, **44** 43	-	[d]
35[g]	7 -$CH_2CH_2OCH_2OMe$	68	**52** 15[h]	-	[d]

[a] isolated yield

[b] values in parentheses are indicative yields obtained from ^1H NMR spectra of the crude reaction mixtures

[c] structural formulae numbers shown in bold

[d] this work

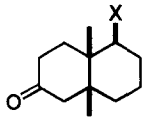
[e] 54:46 mixture

[f] 13:2 mixture

[g] 94:6 *trans:cis* mixture

[h] 3:1 mixture of isomers

addition product derived from **1.** The stereochemistry of **19** was verified by observing a ^1H NMR nOe [35] between the bridgehead methyl groups and also by variable temperature ^1H and ^{13}C NMR spectroscopy. In contrast to the rigid *trans* decalins [36], ketone **19** is mobile and interconverts between two major conformers which results in time averaged NMR spectra spectra at room temperature [37]. The ^{13}C NMR spectrum of **19** at room temperature showed some broad resonances but, after cooling to -50°C, sharp signals arising from both conformers are clearly visible [37,38]. A similar separation of the ^1H NMR resonances for each conformer was found at -50°C [38], most notably those assigned to the quaternary methyl groups. The ^1H NMR chemical shifts of the quaternary methyl resonances of 9,10-dimethyl-2-decalones show distinct chemical shift differences at room temperature [39]

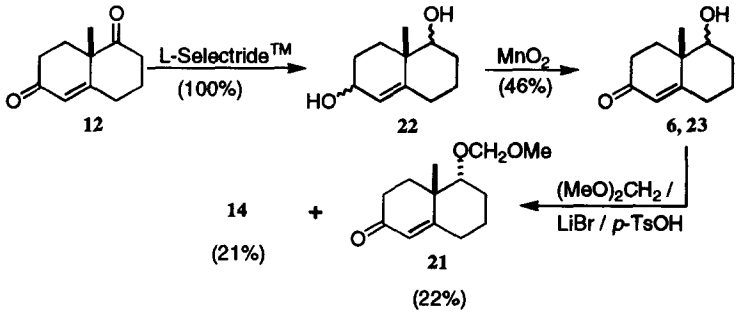


16 X = OMe
17 X = OCH_2OMe
18 X = OCH_2Ph
19 X = H
20 X = OH

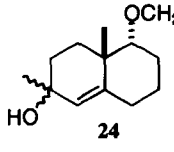
and this can also assist stereochemical assignment. The ring junction stereochemistry of **16**, **17** and **18** were all established as *cis* by nOe and room temperature ^{13}C NMR studies as described for **19**. The resonances in the ^{13}C NMR spectra of **16** and also **20**, obtained by debenzylation of **18**, generally sharpened on cooling and, at -50°C, each compound produced a single set of twelve sharp resonances [38] indicating a dominant conformer.

The results obtained from the *cis*-5-alkoxy series clearly indicated that any cuprate-alkoxy group interaction did not inhibit 1,4-addition and retained the stereochemical preference observed for **1.** While hydroxyl groups appropriately positioned close to the reactive site of the substrate appear to be inhibiting, all of the alkoxy groups had comparable activity and the methyloxymethyleneoxy was generally preferred for further studies. The investigation was then directed at examining the effect of *trans*-5-alkoxy substituents on cuprate 1,4-addition. While previous work had indicated a *trans* 5-alkoxy group as contained in an acetal (**9**) was inhibiting a study based on an alkoxy group attached to the cyclic skeleton by a single bond was considered worthwhile.

trans-5-(Methoxymethyl)oxy-10-methyl-1(9)-octal-2-one (**21**) [40] was prepared as outlined in Scheme 2. Reduction of **12** using L-Selectride gave a mixture of isomeric diols (**22**). Allylic oxidation [41] of **22** gave an inseparable 54:46 isomeric mixture of hydroxyketones (**6,23**).The *trans* arrangement of the minor isomer was supported by ^1H NMR spectroscopy, which showed a broad, one-proton peak (δ 3.66, $W_{h/2}$ = 6.8 Hz) assigned to the equatorial C-5 proton [42]. Methoxymethylenation of (**6,23**) gave a separable mixture of **21** and **14**. Reaction of **21** with Me_2CuLi at 0°C gave a mixture of recovered **21** and the 1,2- addition product **24** (Table). The structure of **24** was confirmed by IR [ν_{max} 3414(OH); 1661 (C=C) cm^{-1}] and ^{13}C NMR [δ 141.3, 129.7 (C=C); 70.1 (C-OH)] data.



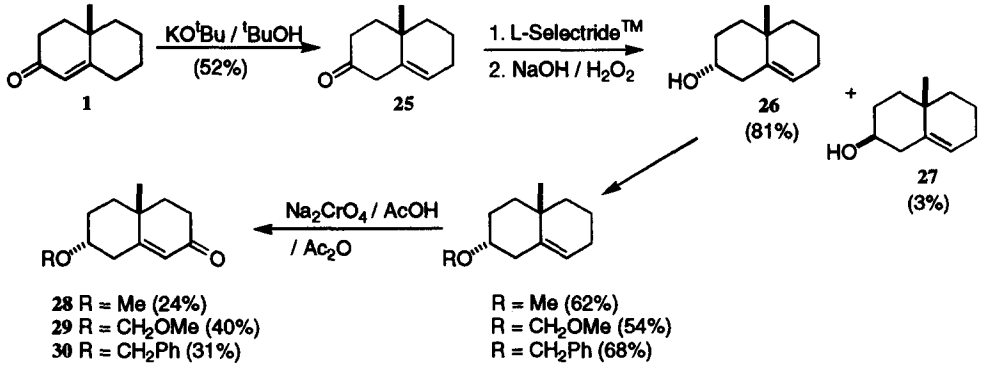
Scheme 2.



24

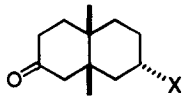
The results obtained from cuprate reactions with **21**, **9** and **10** lead to the conclusion that, in the octalone system, a heteroatom in the *trans*-5 position is sufficient to completely inhibit the 1,4-addition reaction. Investigations of the influence of a noncoordinating atom such as carbon situated in a *trans*-5 axial position in the octalone framework was curtailed due to the synthetic difficulties of introducing a suitable group The 7- position is equivalent in terms of bond connectivity to the 5- position in octalones with respect to the β-carbon of the enone and 7-substituted octalones were attractive as they offered easy synthetic access. Therefore an investigation of the effect of an alkoxy substituent at the axial *trans*-7 position was undertaken for the purpose of comparison with the *trans*-5 results.

trans-7-Alkoxyoctalone derivatives were prepared by taking advantage of the feature whereby the 2- and 7- positions could essentially be interchanged by migration of the alkenyl functional group. Functionalization of the 7- position was carried out as outlined in Scheme 3.



Scheme 3.

Deconjugation of **1** to give **25** followed by reduction with L-Selectride gave a mixture of **26** and **27**. The ^{1}H NMR spectrum of **26** confirmed the relative stereochemistry, with the resonance assigned to the C-2 carbinol proton (δ 4.02) appearing as a quintet (J = 3.0 Hz) [42]. The *trans* alcohol (**26**) was then converted into the methyl, methoxymethyl and benzyl ethers by standard routines. Finally, allylic oxidation [43] of the ethers gave a set of *trans*-7-alkoxy derivatives **28, 29** and **30** in usable amounts. Reaction of **28, 29** and **30** with Me_2CuLi were then carried out and in all cases the major products were the 1,4-addition products (Table). From the results it is apparent that the methyloxymethyleneoxy group effectively promotes 1,4-addition. The ring junction stereochemistry of the products, **31, 32** and **33**, were established as *cis* by nOe and room temperature ^{13}C NMR spectroscopy, as described previously. The ^{1}H NMR spectra of **31** and **32** at -50°C showed that two conformers were present in ratios of 86:14 and 91:9 respectively.

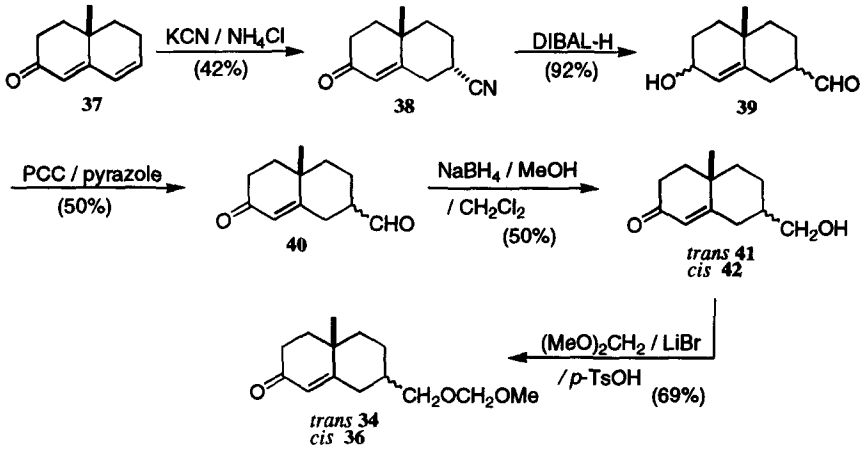


31 X = OMe
32 X = OCH_2OMe
33 X = OCH_2Ph
43 X = CH_2OCH_2OMe

The relative lack of 1,4-reactivity of **21** compared with **29** was probably not due to steric effects nor the proximity of a polar functional group since these aspects are comparable in the two substrates. A significant factor may be the orientation of the axial oxygen with respect to the enone π system which could lead to an ineffective atom match in the cuprate cluster-alkene intermediate complex [7]. The successful 1,4-addition of the *trans*-7-alkoxy derivatives was in contrast to the inhibition of the 1,4-addition reaction observed with **4** and **5** which have (bulky) carbon substituents at the *trans*-7 position. This would indicate that although substitution at the axial 7-position does inhibit 1,4-addition, there is a helpful effect from having oxygen rather than carbon at that locale. Attempts to separate the steric effect from any potential coordination advantage of appropriate ether oxygens induced a study of *trans*-7-alkyloxyalkyl systems. This arrangement has the 1,3 relationship of a non coordinating atom to the β-site of the enone and a potential ligand close by. Reactions of Me_2CuLi with substituents having this general spatial arrangement

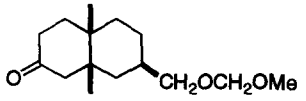
environment were undertaken using two *trans*-7-alkyl derivatives **34** and **35** and the *cis*-7-alkyl derivative **36.**

The general approach to the synthesis of *trans*-7-alkyloxyalkyl derivatives involved Michael addition of suitably stabilized carbanions to **37**, then subsequent modification of the functional groups. The Michael acceptor **37** was prepared [44] by the reaction of *p*-chloranil with **1** and a synthesis is outlined in Scheme 4. Reaction of equimolar amounts of **37**, KCN and NH_4Cl gave the *trans* isomer **38** whose ^1H NMR spectrum indicated an equatorial C-7 proton (δ 3.18, $W_{h/2}$ = 10 Hz). Reduction of **38** with at least six mole equivalents of DIBAL-H [45] gave **39**. Oxidation [46-48] of the allylic alcohol function in **39** gave the aldehydes **40** as a 60:40 mixture. A 55:45 mixture of stereoisomers **41** and **42** was then obtained by selective borohydride reduction of **40**. The stereochemistry of **41** was *trans* by ^1H NMR spectroscopy, as when the multiplet assigned to the C-7 proton (δ 2.15) was selectively decoupled from the hydroxymethylene proton resonance (δ 3.52), the residual coupling indicated an equatorial proton ($W_{h/2}$ = 12.9 Hz). The mixture of **41** and **42** was converted into a 54:46 isomeric mixture of **34** and **36** which proved to be inseparable on a preparative scale and made it necessary to carry out the examination of cuprate reactions directly on the mixture.



Scheme 4.

Reaction of Me_2CuLi with the **34,36** mixture gave 1,4-addition products and recovered starting material, which was enriched in the *trans* isomer **34** (Table). The two 1,4-addition products, **43** and **44** were shown to have *cis*-9,10-dimethyl partial structures by nOe measurements. While it was not possible to unambiguously establish the stereochemistry of the 7- alkyl substituent in these compounds a comparison of the chemical shifts of the quaternary methyl ^1H NMR resonances with those of 1,4-addition products with known stereochemistry [38] showed that **44** had a similar set of resonances to related *cis* compounds *e.g.* **16** and thus is tentatively assigned the all *cis* stereochemistry. Accepting this stereochemical assignment, leads to the suggestion that the



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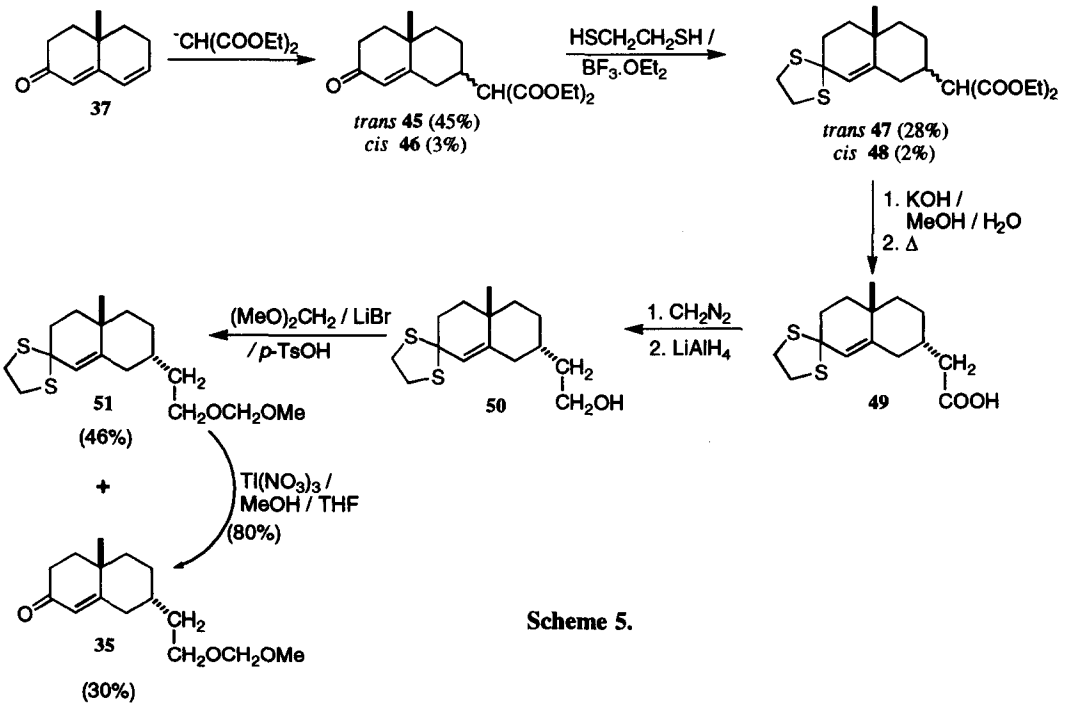
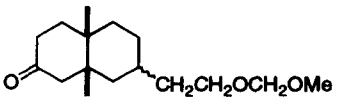
trans isomer **34** is less reactive than the *cis* isomer **36** and is in concert with the recovered substrate being enriched with (less reactive) **34**.

Preparation of a derivative with a two carbon pendant unit at the 7- position was accomplished by the Michael addition of the diethyl malonate carbanion to **37** [49, 50] (Scheme 5). The product was found to be predominantly the *trans* isomer (**45**) [51] and attempts to remove the minor, *cis* isomer **46** were unsuccessful. The *trans* arrangement in **45** was confirmed by ^{1}H NMR spectroscopy which showed a broad ($W_{h/2}$ = 10.6 Hz) resonance, assigned to the equatorial *cis* C-7 proton, after irradiation of the methine malonate ester resonance. As dealkylations of **45** and **46** were unproductive, they were converted into the ethylene dithioacetals **47** and **48** which allowed unambiguous stereochemical assignment by ^{1}H NMR spectroscopy. Reaction of **48** with $Tl(NO_3)_3$ [52] gave a pure sample of the minor *cis* isomer **46** for complete characterization. The remainder of the synthetic sequence was carried out with samples containing *ca.* 6% of the *cis* isomer. Hydrolysis of the dithioacetal mixture (**47,48**) and thermal decarboxylation gave **49**. As direct reduction of **49** with $LiAlH_4$ did not proceed well, **50** was obtained by esterification with diazomethane followed by treatment with $LiAlH_4$. Reaction of **50** with LiBr and *p*-TsOH in dimethoxymethane gave a mixture of **51** and **35**. Deprotection of **51** using $Tl(NO_3)_3$ [52] gave further **35**.



Scheme 5.

Reaction of **35** with Me_2CuLi in diethyl ether/dichloromethane, at 0°C, gave primarily recovered starting material, depleted of the small amount of the *cis* isomer contaminant, and **52** as a 3:1 isomeric mixture (Table). The ^{1}H NMR spectrum of **52** showed two sets of quaternary



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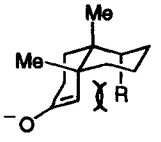
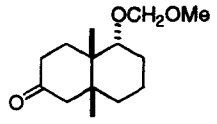
methyl resonances at 1.12, 1.00 ppm (75%) and 0.96, 0.84 ppm (25%) and, by comparison with the data for **43** and **44**, the major isomer is assigned as *cis*-9,10-dimethyl-*trans*-7-(2'-((methoxymethyl)oxy)ethyl)-2-decalone. Consideration of the molar amounts of material involved in the reaction indicates that all of the *cis* isomer had reacted and ca 12% of the *trans* compound **35** was consumed.



53

The reduced reactivity of *trans* 5- and, to a lesser extent, *trans* 7-substituted octalones can be rationalized if, following an initial complexation between the substrate and cuprate, production of the steroid-like β-alkyl enolate **53** involves a product-like transition state. The necessary bond reorganizations result in the development of unfavourable 1,3-diaxial interactions between the substituent and ring carbon(s) and these interactions could inhibit the orbital overlap necessary for the collapse of the cuprate-enone complex to the β-alkylated enolate. The interatomic distances between the axial oxygen and the C-1 and C-3 carbons, in the steroidal conformations of the 1,4-addition products, **32** and **54**, were estimated using PCMODEL [53] and a larger distance was found with **32.**



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Conclusion

In summary, it has been demonstrated that the influence of δ-alkoxy or -alkyloxyalkyl groups in octalones is not sufficient to produce a *trans* dimethyl ring junction product. However the stereochemistry of the remote group does influence the relative reactivity. The substrate with a remote group which is disposed *syn* with respect to the incoming methyl group is significantly more reactive compared with the corresponding *anti* compound.

These studies have demonstrated that in these rigid, sterically demanding, octalone systems the steric effects are predominant in determining the product stereochemistry. Any coordination between the cuprate and the ethereal oxygen(s) in the substrate, is demonstrably insufficient to overcome the inherent *cis* ring junction preference for 1,4-addition.

Experimental

Materials and Equipment

Melting points were determined on a Kofler hot stage and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 1600 spectrometer as films or Nujol mulls. UV spectra were recorded on a Shimadzu UV-240 spectrometer. ^{1}H NMR spectra were recorded on Varian Gemini 200 (200 MHz) or VXR 300 (300 MHz)spectrometers in dilute $CDCl_3$ solution using TMS (δ = 0) reference. Spectra are reported according to the convention: chemical shift, integrated area, multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), quintet, m (multiplet) and br (broad)], coupling constant (J), [largest coupling first, or band width at half the peak

height ($W_{h/2}$)], followed by the proton assignment. Nuclear Overhauser enhancements are reported as *NOE* followed by the irradiated peak. ^{13}C NMR spectra were recorded at 50 MHz on Varian Gemini 200 spectrometer or at 75 MHz on a Varian VXR 300 spectrometer in dilute $CDCl_3$ solution referenced to the central $CDCl_3$ resonance (δ = 77.08). Assignments listed with the same superscript ($^{\Diamond}$, $^{\nabla}$ or $^{\#}$) can be interchanged. Carbons types were determined by the DEPT pulse sequence. One bond and multiple bond heteronuclear correlations are reported as *HC* and *LRHC* respectively, followed by the chemical shift of the correlating proton. Column chromatography was performed using silica gel 60 (0.040 - 0.063mm) (Merck). Ether/hexane (E/H) mixtures were usually used as eluting solvents unless otherwise stated. Analytical thin layer chromatography (t.l.c.) was carried out on (Merck) t.l.c. aluminium foil coated with silica gel 60 F_{254} of 0.2 mm thickness. Components were visualized under 254 nm UV light if appropriate, followed by spraying with a 10% dodecamolybdophosphoric acid in ethanol, or by immersion in a *p*-anisaldehyde solution and heating. Preparative layer chromatography (p.l.c.)was achieved on glass plates (20 x 20cm) coated with 1mm of silica gel 60 PF_{254} (Merck).

Diethyl ether was distilled from $LiAlH_4$ and stored over sodium wire. 10-Methyl-1(9)-octal-2,5-dione (**12**) and L-Selectride (1M in THF)were obtained from Aldrich. Di*iso*butylaluminum hydride (DIBAL-H) (20% in hexane) was obtained from Merck. Methyllithium (MeLi) (5% in Et_2O) was obtained from commercial sources (Aldrich, Fluka) and analyzed by the Gilman double titration method [54] using 3-bromo-1-propene. Copper iodide (CuI) (Fluka) was purified by continuous extraction using THF [55] then dried *in vacuo* (2 mm Hg), powdered, and stored *in vacuo*. Reactions involving organometallic reagents were performed under an atmosphere of dry, oxygen free nitrogen or argon in Schlenk tubes, equipped with septum stoppers. The tubes were dried by heating with a flame under vacuum and cooling after flushing with dry nitrogen or argon. For all organometallic reactions the solvent was deoxygenated by alternate application of vacuum and argon.

High resolution mass spectra were obtained by Dr. H. Young, Horticulture Division, DSIR, Auckland, New Zealand or by Dr. B. Clark, Chemistry Department, University of Canterbury, Christchurch, New Zealand. Microanalyses were performed by Dr R.G. Cunninghame, M. Dick and R. McAllister, Campbell Microanalytical Laboratory, Chemistry Department, Otago University. Isomeric mixtures of tertiary allylic alcohols from 1,2-additions were generally sensitive to normal handling procedures and often did not give satisfactory microanalyses.

Preparation of Substrates

cis-5-Hydroxy-10-methyl-1(9)-octal-2-one (**6**) and *cis-5-Methoxy-10-methyl-1(9)-octal-2-one* (**13**)were prepared according to the literature[56, 57].

cis-5-(Methoxymethyl)oxy-10-methyl-1(9)-octal-2-one (**14**)

p-TsOH.H_2O (0.24 g, 1.26 mmol) was added to a stirred solution of **6** (0.91 g, 5.02 mmol) and LiBr (0.19 g, 2.2 mmol) in dimethoxymethane (50 mL) [58]. After stirring for 16 hours, sat. aqueous NaCl (80 mL) was added and the mixture was extracted with ether (3 x 150 mL). The combined ether extract was washed with H_2O (50 mL), dried ($MgSO_4$), filtered and the solvent

evaporated *in vacuo*. The residue was chromatographed on silica gel (50 g) with 33% E/H to afford **14** [40] (0.52 g, 46%) as an oil; IR ν_{max}/cm^{-1} 1682 (α,β-unsat. C=O), 1614 (conjugated C=C); UV λ_{max}(MeOH)/nm 237 (ε_{max} 18089); ^{1}H NMR/ppm 5.78 (1H, br s, H-1), 4.75, 4.62 (2H, AB system, J_{AB} = 6.9 Hz, OCH_2O), 3.39 (3H, s, OMe), 3.30 (1H, dd, J = 11.7, 3.9 Hz, H-5), 1.23 (3H, s, H-11); ^{13}C NMR/ppm 199.5 (C-2), 168.4 (C-9), 125.3 (C-1), 95.6 (OCH_2O), 83.7 (C-5), 55.6 (OMe), 41.3 (C-10), 34.3 (C-3)$^{\diamond}$, 33.7 (C-4)$^{\diamond}$, 32.1 (C-6)$^{\diamond}$, 27.1 (C-7)$^{\diamond}$, 23.0 (C-8)$^{\diamond}$, 16.2 (C-11).

cis-5-Benzyloxy-10-methyl-1(9)-octal-2-one (**15**)

Trifluoromethanesulfonic acid (0.5 mL) was added to a stirred solution of **6** (0.51 g, 2.85 mmol) and benzyl 2,2,2-trichloroacetimide [33] (50 mL, hexane solution, 7.5 mmol) in cyclohexane (10 mL) and CH_2Cl_2 (30 mL) at room temperature under nitrogen. After stirring for 18 hours at room temperature, the reaction mixture was washed sequentially with sat. aqueous $NaHCO_3$ (50 mL), H_2O (30 mL), dried ($MgSO_4$), filtered and the solvents evaporated *in vacuo*. Chromatography, on silica gel (100 g) and eluting with 50% E/H, gave impure **15**. Vacuum distillation at 150°C (60 mm Hg) to remove excess benzyl alcohol, followed by purification by p.l.c. (50% E/H) gave **15** (0.24 g, 31%) as a clear oil; IR ν_{max}/cm^{-1} 1667 (α,β-unsat. C=O), 1620 (C=C), 714, 698 (C-H bend); ^{1}H NMR/ppm 7.33 (5H, m, phenyl), 5.75 (1H, d, J = 1.5 Hz, H-1), 4.68, 4.43 (2H, AB system, J_{AB} = 13.2 Hz, OCH_2), 3.11 (1H, dd, J = 11.6, 4.2 Hz, H-5), 1.23 (3H, s, H-11); ^{13}C NMR/ppm 199.8 (C-2), 168.7 (C-9), 138.6 (phenyl *i* C), 128.3 (phenyl *o* C)$^{\nabla}$, 127.6 (phenyl *m* C)$^{\nabla}$, 127.6 (phenyl *p* C)$^{\nabla}$, 125.2 (C-1), 85.2 (C-5), 71.5 (OCH_2), 41.7 (C-10), 34.5 (C-3)$^{\diamond}$, 33.8 (C-4)$^{\diamond}$, 32.2 (C-6)$^{\diamond}$, 26.0 (C-7)$^{\diamond}$, 23.0 (C-8)$^{\diamond}$, 16.3 (C-11); Mass spectrum: *m/z* 270.1620 (M^+); Calcd. for $C_{18}H_{22}O_2$: 270.1620.

10-Methyl-1(9)-octal-2,5-diol (**22**)

A solution of L-Selectride (20 mL, 20 mmol) was added to a stirred solution of **12** (1.03 g, 5.80 mmol) in ether (25 mL), under nitrogen at -78°C [40]. The reaction mixture was stirred for 3 hours at -78°C, then warmed to room temperature over 1 hour. 8% Aqueous NaOH (10 mL) was slowly added, followed by the dropwise addition of 30% H_2O_2 (15 mL) and then the reaction mixture was stirred for 1 hour. The aqueous layer was saturated with solid K_2CO_3 and ether extracted (3 x 100 mL). The combined ether extract was washed with H_2O (60 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to give crude **22** (1.10 g) as an oil, which was used without further manipulation.

trans-5-(Methoxymethyl)oxy-10-methyl-1(9)-octal-2-one (**21**)

A mixture of crude **22** (1.10 g) and MnO_2 [59] (11.01 g, 0.127 mol) in $CHCl_3$ (100 mL) was shaken for 8 hours. The resultant mixture was filtered and the solid residues washed with $CHCl_3$ (5 x 25 mL). The solvent was evaporated *in vacuo* to give an inseparable mixture of **6** and **23** (0.52 g), as an oil, in a ratio of 54:46. This mixture was used without further purification; IR ν_{max}/cm^{-1} 3420 (OH), 1659 (α,β-unsat. C=O), 1616 (conjugated C=C); ^{1}H

NMR/ppm 5.87 (1H, s, H-1), 3.66 (1H, s, $W_{h/2}$ = 6.8 Hz, H-5), 1.25 (3H, s, H-11); ^{13}C NMR/ppm 199.8 (C-2), 168.1 (C-9), 126.9 (C-1), 75.3 (C-5), 40.9 (C-10), 34.0 (C-3)$^{\diamond}$, 31.8 (C-4)$^{\diamond}$, 30.8 (C-6)$^{\diamond}$, 28.7 (C-7)$^{\diamond}$ 21.8 (C-11), 19.9 (C-8)$^{\diamond}$. *p*-TsOH.H_2O (0.15 g, 0.79 mmol) was added to a stirred solution of the previous mixture (0.52 g, 2.88 mmol) and LiBr (0.078 g, 0.90 mmol) in dimethoxymethane (25 mL) and the resultant solution was stirred for 40 hours at room temperature [58]. Sat. aqueous NaCl (50 mL) was added to the reaction mixture and then ether extracted (3 x 100 mL). The combined ether extract was washed with H_2O (40 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. Separation of the products by p.l.c. (50% E/H) gave **12** (0.054 g, 10%), **14** (0.14 g, 21%), a mixture of **6** and **23** (0.14 g, 22%) and **21** [40] (0.14 g, 22%) as an oil; IR ν_{max}/cm^{-1} 1667 (α,β-unsat. C=O), 1619 (conjugated C=C); UV λ_{max}(MeOH)/nm 237 (ε_{max} 10916); ^1H NMR/ppm 5.83 (1H, br s, $W_{h/2}$ = 3.8 Hz, H-1), 4.72, 4.59 (2H, AB system, J_{AB} = 6.9 Hz, OCH_2O), 3.51 (1H, br s, $W_{h/2}$ = 6.2 Hz, H-5), 3.38 (3H, s, OMe), 1.26 (3H, s, H-11); ^{13}C NMR/ppm 199.4 (C-2), 167.8 (C-9), 126.4 (C-1), 95.7 (OCH_2O), 81.1 (C-5), 56.1 (OMe), 40.7 (C-10), 34.1 (C-3)$^{\diamond}$, 31.9 (C-4)$^{\diamond}$, 30.8 (C-6)$^{\diamond}$, 25.3 (C-7)$^{\diamond}$, 22.1 (C-11), 20.2 (C-8)$^{\diamond}$.

10-Methyl-8-octal-2-one (**25**)

The ketone **25** was prepared [60] by the reaction of **1** [61] (5.09 g, 0.031 mol) and KO^{t}Bu (34 g, 0.303 mol) in *t*-BuOH (150 mL). The residue was chromatographed on silica gel (250 g) with 40% E/H to afford **1** (1.02 g, 20%) and **25** (2.65 g, 52%) as an oil; IR ν_{max}/cm^{-1} 1711 (C=O), 1667 (C=C); ^1H NMR/ppm 5.39 (1H, q, J = 2.3 Hz, H-8, *NOE* 2.82), 3.23 (1H, d quartet, J = 16.1, 6.5 Hz, H-1 *cis*, *NOE* 1.25, 2.82), 2.82 (1H, dd, J = 16.1, 2.2 Hz, H-1 *trans*, *NOE* 5.39), 1.25 (3H, s, H-11); ^{13}C NMR/ppm 210.0 (C-2), 137.9 (C-9), 123.4 (C-8), 48.6 (C-1), 38.9 (C-3)$^{\diamond}$, 38.2 (C-4)$^{\diamond}$, 37.9 (C-5)$^{\diamond}$, 34.1 (C-10), 25.6 (C-6)$^{\diamond}$, 23.9 (C-11), 18.9 (C-7)$^{\diamond}$.

trans-10-Methyl-8-octal-2-ol (**26**)

L-Selectride (40 mL, 40 mmol) was added to a stirred solution of **25** (1.88 g, 0.011 mol) in ether (30 mL) at -78°C under argon and stirred for 3 hours at -78°C. The mixture was warmed to room temperature over 1 hour and 8% aqueous NaOH (30 mL) was slowly added, followed by the dropwise addition of 30% H_2O_2 (40 mL). The mixture was stirred for 2 hours, then the aqueous layer was saturated with solid K_2CO_3 and ether extracted (5 x 80 mL). The combined ether extract was washed with H_2O (50 mL), dried ($MgSO_4$), filtered and the solvents were evaporated *in vacuo*. The residue was chromatographed on silica gel (150 g) with 33% E/H to afford **27** (0.056 g, 3%) as an oil; IR ν_{max}/cm^{-1} 3353 (OH), 1660 (C=C); ^1H NMR/ppm 5.38 (1H, m, $W_{h/2}$ = 8.1 Hz, H-8), 3.53 (1H, m, $W_{h/2}$ = 23 Hz, H-2), 1.07 (3H, s, H-11); ^{13}C NMR/ppm 140.4 (C-9), 122.1 (C-8), 72.1 (C-2), 42.1 (C-1)$^{\diamond}$, 39.2 (C-3)$^{\diamond}$, 39.2 (C-4)$^{\diamond}$, 33.7 (C-10), 31.6 (C-5)$^{\diamond}$, 25.8 (C-6)$^{\diamond}$, 24.8 (C-11), 19.0 (C-7); Anal. Found: C, 79.76; H, 11.03%. Calcd. for $C_{11}H_{18}O$: C 79.46, H 10.91% and **26**, initially as an oil, which crystallized on standing (1 month) to give white crystals m.p. 77-78°C; (1.30 g, 81%); IR ν_{max}/cm^{-1} 3434 (OH), 1660 (C=C); ^1H NMR/ppm 5.44 (1H, m, $W_{h/2}$ = 8.4 Hz, H-8), 4.02 (1H, quintet, J = 3.0 Hz, H-

2), 2.52 (1H, d quintet, J = 14.3, 2.7 Hz, H-1 *cis*, *NOE* 1.08), 2.05 (1H, dt, J = 14.3, 2.6 Hz, H-1 *trans*), 1.08 (3H, s, H-11); ^{13}C NMR/ppm 138.7 (C-9), 124.3 (C-8), 67.4 (C-2), 39.7 (C-1)$^{\Diamond}$, 39.6 (C-3)$^{\Diamond}$, 35.4 (C-4)$^{\Diamond}$, 34.7 (C-10), 28.9 (C-5)$^{\Diamond}$, 26.0 (C-6)$^{\Diamond}$, 23.7 (C-11), 19.0 (C-7)$^{\Diamond}$; Anal. Found: C, 79.23; H, 11.25%. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91%.

trans-2-Methoxy-10-methyl-8-octalin

NaH (0.82 g, 60% mineral oil dispersion, 21 mmol) was added to a stirred solution of **26** (1.30 g, 7.83 mmol) in DMSO (25 mL), under argon at room temperature and stirred for 2 hours. MeI (3.2 mL, 51.4 mmol) was added and the solution was stirred for a further 3 hours. H_2O (50 mL) was added, dropwise initially, and the mixture was ether extracted (5 x 50 mL). The combined ether extract was washed with sat. aqueous NaCl (30 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. Separation using radial chromatography, eluting with 20% E/H, gave *trans*-2-methoxy-10-methyl-8-octalin (0.82 g, 62%) as an oil; IR ν_{max}/cm^{-1} 1707 (C=C); ^{1}H NMR/ppm 5.34 (1H, m, $W_{h/2}$ = 9.6 Hz, H-8), 3.48 (1H, t, J = 2.7 Hz, H-2), 3.29 (3H, s, OMe), 1.08 (3H, s, H-11); ^{13}C NMR/ppm 139.4 (C-9), 122.0 (C-8), 76.5 (C-2), 55.7 (OMe), 39.4 (C-1)$^{\Diamond}$, 36.3 (C-3)$^{\Diamond}$, 35.6 (C-4)$^{\Diamond}$, 34.4 (C-10), 25.8 (C-5)$^{\Diamond}$, 25.2 (C-6)$^{\Diamond}$, 23.9 (C-11), 18.9 (C-7)$^{\Diamond}$. Microanalysis and high resolution mass spectrum analysis gave inconclusive results due to the instability of the material.

trans-2-(Methoxymethyl)oxy-10-methyl-8-octalin

p-TsOH.H_2O (0.20 g, 1.05 mmol) was added to a stirred solution of **26** (0.53 g, 3.19 mmol) and LiBr (0.37 g, 4.35 mmol) in dimethoxymethane (40 mL) [58], and then stirred for 42 hours at room temperature. Sat. aqueous $NaHCO_3$ (50 mL) was added to the reaction mixture and then ether extracted (5 x 50 mL). The combined ether extract was washed with H_2O (50 mL), dried ($MgSO_4$), filtered and the solvents were evaporated *in vacuo*. The residue was chromatographed on silica gel (60 g) with 33% E/H to afford *trans*-2-(methoxymethyl)oxy-10-methyl-8-octalin (0.36 g, 54%) as an oil; IR ν_{max}/cm^{-1} 1709 (C=C); ^{1}H NMR/ppm 5.35 (1H, quintet, J = 2.4 Hz, H-8), 4.67 (2H, s, OCH_2O), 3.89 (1H, quintet, J = 2.9 Hz, H-2), 3.36 (3H, s, OMe), 1.08 (3H, s, H-11); ^{13}C NMR/ppm 139.3 (C-9), 122.2 (C-8), 94.4 (OCH_2O), 72.5 (C-2), 55.1 (OMe), 39.4 (C-1)$^{\Diamond}$, 37.0 (C-3)$^{\Diamond}$, 35.9 (C-4)$^{\Diamond}$, 34.4 (C-10), 26.5 (C-5)$^{\Diamond}$, 25.9 (C-6)$^{\Diamond}$, 23.9 (C-11), 18.9 (C-7)$^{\Diamond}$. Mass spectrum: *m/z* 211.1698 (MH^+); Calcd. for $C_{13}H_{23}O_2$: 211.1698.

trans-2-Benzyloxy-10-methyl-8-octalin

NaH (0.65 g, 60% mineral oil dispersion, 16.3 mmol) was added to a stirred solution of **26** (0.94 g, 5.65 mmol) in DMF (15 mL) under nitrogen at room temperature and stirred for 30 minutes. Benzyl bromide (0.75 mL, 6.3 mmol) was then added and the mixture was stirred for 54 hours at room temperature. Following addition of H_2O (30 mL) and ether (300 mL), the ethereal layer was washed with sat. aqueous NaCl (70 mL), H_2O (50 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. Column chromatography, on silica gel (120 g) and eluting with 25% E/H, gave an inseparable mixture of benzyl bromide (0.58 g) and *trans*-2-benzyloxy-10-methyl-8-octalin (0.99 g, 68%) as an oil; IR ν_{max}/cm^{-1} 3028 (C-H of phenyl),

1716 (C=C), 732, 696 (C-H bend); ^{1}H NMR/ppm 7.34 (5H, m, $W_{h/2}$ = 7.2 Hz, phenyl), 5.35 (1H, br s, $W_{h/2}$ = 9.7 Hz, H-8), 4.55, 4.47 (2H, AB system, J_{AB} = 12.6 Hz, H-12), 3.66 (1H, m, $W_{h/2}$ = 7.0 Hz, H-2), 1.08 (3H, s, H-11); ^{13}C NMR/ppm 139.5 (C-9)$^{\nabla}$, 139.4 (phenyl *i* C)$^{\nabla}$, 128.3 (phenyl *o* C)$^{\diamond}$, 127.4 (phenyl *m* C)$^{\diamond}$, 127.2 (phenyl *p* C), 122.2 (C-8), 73.7 (C-2), 69.2 (OCH_2), 39.5 (C-1)$^{\#}$, 36.3 (C-3)$^{\#}$, 35.9 (C-4)$^{\#}$, 34.5 (C-10), 26.1 (C-5)$^{\#}$, 26.0 (C-6)$^{\#}$, 24.0 (C-11), 19.1 (C-7)$^{\#}$.

trans-7-Methoxy-10-methyl-1(9)-octal-2-one (**28**)

Anhydrous Na_2CrO_4 (0.82 g, 5.06 mmol) was added portionwise to a stirred solution of *trans*-2-methoxy-10-methyl-8-octalin (0.52 g, 2.88 mmol) in AcOH (20 mL) and Ac_2O (10 mL) at 30-40°C under nitrogen [43]. The resultant mixture was stirred for 48 hours at 30-40°C, then poured into ice cold H_2O (300 mL) and ether extracted (5 x 50 mL). The combined ether extract was washed with sat. aqueous $NaHCO_3$, until pH>8, then H_2O (20 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel (150 g) with 66% E/H to afford impure **28**. Further separation by p.l.c. (75% E/H) gave **28** (0.14 g, 24%) as an oil; IR ν_{max}/cm^{-1} 1682 (α,β-unsat. C=O), 1621 (conjugated C=C); ^{1}H NMR/ppm 5.77 (1H, br s, H-1), 3.65 (1H, m, $W_{h/2}$ = 7.3 Hz, H-7), 3.30 (3H, s, OMe), 1.26 (3H, s, H-11); ^{13}C NMR/ppm 199.1 (C-2), 167.4 (C-9), 126.4 (C-1), 75.8 (C-7), 55.7 (OMe), 37.6 (C-3)$^{\diamond}$, 36.7 (C-4)$^{\diamond}$, 35.6 (C-10), 34.9 (C-5)$^{\diamond}$, 34.0 (C-6)$^{\diamond}$, 24.9 (C-8)$^{\diamond}$, 21.9 (C-11). Anal. Found: C, 74.04; H, 9.20%. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34%.

trans-7-(Methoxymethyl)oxy-10-methyl-1(9)-octal-2-one (**29**)

As for **28**, treatment of *trans*-2-(methoxymethyl)oxy-10-methyl-8-octalin (0.37 g, 1.76 mmol) in AcOH (15 mL) and Ac_2O (7 mL) with anhydrous Na_2CrO_4 (1.13 g, 7.00 mmol) gave impure **29**. Further separation by p.l.c. (75% E/H) gave **29** (0.16 g, 40%) as an oil; IR ν_{max}/cm^{-1} 1667 (α,β-unsat. C=O), 1620 (conjugated C=C); UV λ_{max}(MeOH)/nm 239 (ε_{max} 11803); ^{1}H NMR/ppm 5.78 (1H, br s, H-1), 4.67, 4.63 (2H, AB system, J_{AB} = 7.2 Hz, OCH_2O), 4.04 (1H, quintet, J = 2.9 Hz, H-7), 3.36 (3H, s, OMe), 1.26 (3H, s, H-11); ^{13}C NMR/ppm 199.2 (C-2), 167.4 (C-9), 126.6 (C-1), 94.8 (OCH_2O), 72.4 (C-7), 55.5 (OMe), 37.6 (C-3)$^{\diamond}$, 36.5 (C-10), 35.6 (C-4)$^{\diamond}$, 35.3 (C-5)$^{\diamond}$, 34.0 (C-6)$^{\diamond}$, 26.3 (C-8)$^{\diamond}$, 21.9 (C-11). Anal. Found: C, 69.46; H, 8.70%. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99%.

trans-7-Benzyloxy-10-methyl-1(9)-octal-2-one (**30**)

As for **28**, treatment of impure *trans*-2-benzyloxy-10-methyl-8-octalin (0.77 g, 3.02 mmol, 43% in benzyl bromide) in AcOH (10 mL) and Ac_2O (5 mL) with anhydrous Na_2CrO_4 (2.08 g, 12.84 mmol) afforded **30** (0.25 g, 31%) as an oil; IR ν_{max}/cm^{-1} 3029 (C-H of phenyl), 1667 (α,β-unsat. C=O), 1620 (conjugated C=C), 739, 698 (C-H bend); ^{1}H NMR/ppm 7.31 (5H, m, $W_{h/2}$ = 3.5 Hz, phenyl), 5.78 (1H, br s, H-1), 4.50 (2H, s, OCH_2), 3.84 (1H, m, $W_{h/2}$ = 7.6 Hz, H-7), 1.26 (3H, s, H-11); ^{13}C NMR/ppm 199.5 (C-2), 167.9 (C-9), 138.6 (phenyl *i* C), 128.4 (phenyl *o* C)$^{\nabla}$, 127.6 (phenyl *p* C), 127.4 (phenyl *m* C)$^{\nabla}$, 126.5 (C-1), 73.5 (C-7), 69.7 (OCH_2),

37.7 (C-3)$^{\diamond}$, 37.0 (C-4)$^{\diamond}$, 35.7 (C-10), 35.2 (C-5)$^{\diamond}$, 34.1 (C-6)$^{\diamond}$, 25.6 (C-8)$^{\diamond}$, 22.0 (C-11). Mass spectrum: *m/z* 270.1620 (M^+); Calcd. for $C_{18}H_{22}O_2$: 270.1620.

10-Methyl-1(9),7-hexal-2-one (**37**)

A mixture of **1** (10.10 g, 0.062 mol) and *p*-chloranil (80.34 g, 0.32 mol) in *t*-BuOH (400 mL) was heated under reflux. Vacuum distillation of the crude product gave **37** (5.00 g, 50%) as an oil; b.p. 95-96°C at 2.5 mm Hg (Lit [44] 70-71°C at 0.5 mm Hg); IR ν_{max}/cm^{-1} 1651 (α,β,δ,γ-unsat. C=O), 1614, 1585 (conjugated C=C); ^{1}H NMR/ppm 6.23 (1H, ddd, J = 9.6, 5.3, 2.2 Hz, H-7), 6.15 (1H, dd, J = 10.3, 2.1 Hz, H-8), 5.68 (1H, br s, $W_{h/2}$ = 4.5 Hz, H-1), 1.18 (3H, s, H-11); ^{13}C NMR/ppm 199.8 (C-2), 162.0 (C-9), 137.9 (C-7, *HC* 6.23), 127.7 (C-8, *HC* 6.15), 123.5 (C-1, *HC* 5.68), 36.9 (C-3)$^{\diamond}$, 35.8 (C-4)$^{\diamond}$, 34.2 (C-5)$^{\diamond}$, 33.2 (C-10), 23.5 (C-6)$^{\diamond}$, 21.2 (C-11).

trans-7-Cyano-10-methyl-1(9)-octal-2-one (**38**)

A stirred mixture of **37** (4.13 g, 25.5 mmol), KCN (1.53 g, 23.5 mmol) and NH_4Cl (1.09 g, 20.4 mmol) in DMF (150 mL) and H_2O (20 mL) was heated to 60-70°C for 3 days. The cooled reaction mixture was poured into H_2O (200 mL) and $CHCl_3$ extracted (6 x 75 mL). The combined $CHCl_3$ extract washed with sat. aqueous NaCl (40 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. Vacuum distillation at 70°C (2mm Hg) to remove excess DMF, followed by chromatography on silica gel (300 g) with 75% E/H gave **37** (1.11 g, 27%). Further elution with 5% $CHCl_3$/ether gave **38** as a white solid m.p. 95-96°C; (2.03 g, 42%); IR ν_{max}/cm^{-1} 2236 (C°N), 1673 (α,β-unsat. C=O), 1620 (conjugated C=C); ^{1}H NMR/ppm 5.86 (1H, d, J = 1.9 Hz, H-1), 3.18 (1H, m, $W_{h/2}$ = 10.0 Hz, H-7 *cis*), 2.66 (1H, ddd, J = 15.0, 5.3, 1.9 Hz, H-8 *trans*, *NOE* 1.26), 1.26 (3H, s, H-11); ^{13}C NMR/ppm 198.6 (C-2), 162.5 (C-9), 127.4 (C-1), 120.4 (C≡N), 37.5 (C-3)$^{\diamond}$, 37.0 (C-4)$^{\diamond}$, 35.4 (C-10), 34.4 (C-8, *HC* 2.66), 33.9 (C-5)$^{\diamond}$, 28.6 (C-7), 24.1 (C-6)$^{\diamond}$, 21.9 (C-11). Anal. Found: C, 76.15; H, 7.95; N, 7.63%. Calcd. for $C_{12}H_{15}ON$: C, 76.16; H, 7.99; N, 7.40%.

7-Formyl-10-methyl-1(9)-octal-2-ol (**39**)

A solution of DIBAL-H (36 mL, 36 mmol) was added to a stirred solution of crude **38** (1.08 g, 5.73 mmol) in CH_2Cl_2 (165 mL) at -40°C under argon [45]. After stirring for 1 hour, MeOH (11 mL) was added followed by 8% aqueous NaOH (120 mL) and the reaction mixture was extracted with $CHCl_3$ (6 x 75 mL). The combined $CHCl_3$ extract was dried ($MgSO_4$), filtered and the solvents evaporated *in vacuo*. ^{1}H NMR analysis, of the residue (1.02 g, 92%); ^{1}H NMR/ppm 9.66 (br s), 5.57 (m, $W_{h/2}$ = 7.6 Hz), 5.44 (br s, $W_{h/2}$ = 5.1 Hz), 5.35 (m, $W_{h/2}$ = 10.1 Hz), 4.17 (m, $W_{h/2}$ = 22.8 Hz), 1.14 (s); showed that no starting material remained. The residue was used without further manipulation.

7-Formyl-10-methyl-1(9)-octal-2-one (**40**)

Pyridinium chlorochromate (PCC) [48] (3.95 g, 18.3 mmol) was added to a stirred solution of crude **39** (1.02 g) and pyrazole (4.96 g, 72.8 mmol) in CH_2Cl_2 (110 mL) at 0°C under argon

[46,47]. After stirring for 30 minutes, sat. aqueous NaCl (120 mL) was added and the mixture was acidified with 10% HCl. The reaction mixture was extracted with $CHCl_3$ (5 x 100 mL) and the combined extract dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. The residue was then applied to a short column of silica gel (5 g) and eluted with $CHCl_3$ (150 mL) and E (150 mL) to give a crude mixture of isomeric keto aldehydes **40** (0.50 g) as a yellow oil; ^{1}H NMR/ppm: Isomer 1 (40%); 9.70 (s), 5.82 (s), 1.25 (s). Isomer 2 (60%); 9.67 (s), 5.85 (s), 1.27 (s), which was used without further purification.

7-Hydroxymethyl-10-methyl-1(9)-octal-2-one (**41,42**)

$NaBH_4$ (0.41 g, 10.8 mmol) was added to a stirred solution of crude **40** (0.50 g) in CH_2Cl_2 (33 mL) and MeOH (33 mL) at -78°C [56]. After stirring for 1 hour, acetone (11 mL) was added and the reaction mixture allowed to warm to room temperature over 1 hour. The reaction mixture was then diluted with CH_2Cl_2 (300 mL) and washed with 8% aqueous NaOH (35 mL). The combined CH_2Cl_2 extract was washed with H_2O (20 mL), dried ($MgSO_4$), filtered and the solvents were evaporated *in vacuo* to give a crude mixture of **41** and **42** (0.50 g); ^{1}H NMR/ppm: Isomer 1 (45%); 5.76 (s), 3.57 (d, J = 5.5 Hz), 1.24 (s). Isomer 2 (55%); 5.76 (s), 3.52 (d, J = 7.6 Hz), 1.28 (s). Multiple elution p.l.c. (75% E/H) of a sample gave a small amount of the oily *trans* isomer **41**; ^{1}H NMR/ppm 5.76 (1H, d, J = 1.8 Hz, H-1), 3.52 (2H, d, J = 7.6 Hz, CH_2O), 2.58 (1H, ddd, J = 14.9, 5.9, 2.0 Hz, H-8 *cis*), 2.15 (1H, m, $W_{h/2}$ (after selective irradiation of 3.52) = 12.9 Hz, H-7 *cis*), 1.27 (3H, s, H-11). The remaining crude mixture of **41** and **42** (0.19 g) was used without further purification; Mass spectrum: *m/z* 194.1309 (M^+); Calcd. for $C_{12}H_{18}O_2$: 194.1307.

7-((Methoxymethyl)oxy)methyl-10-methyl-1(9)-octal-2-one (**34,36**)

p-TsOH.H_2O (0.13 g, 0.66 mmol) and 1/8 in molecular sieve 4Å (10 beads) were added to a stirred solution of a 55:45 mixture of **41** and **42** (0.17 g, 0.88 mmol) and LiBr (0.20 g, 2.28 mmol) in dimethoxymethane (15 mL) at room temperature [58]. The resultant reaction mixture was stirred for 2 days at room temperature. The reaction mixture was then diluted with $CHCl_3$ (200 mL) and washed with H_2O (10 mL), dried ($MgSO_4$), filtered and the solvents evaporated *in vacuo*. The residue was separated by p.l.c. (75% E/H) and gave a 53:47 mixture of **41** and **42** (0.029 g, 17%) and an inseparable mixture of **34** and **36** (0.15 g, 69%); ^{1}H NMR/ppm: 5.76 (1H, t, J = 1.9 Hz, H-1), 4.63, 4.60 (2H, 2 x s, OCH_2O), 3.44 (1H, dd, J = 5.7, 1.7 Hz), 3.39 (1H, d, J = 7.6 Hz), 3.37, 3.35 (3H, 2 x s, OMe), 1.27, 1.24 (3H, 2 x s, H-11); Mass spectrum: *m/z* 238.1570 (M^+); Calcd. for $C_{14}H_{22}O_3$: 238.1569.

trans-7-Di(ethoxycarbonyl)methyl-10-methyl-1(9)-octal-2-one (**45**)

A mixture of KO^{t}Bu (2.82 g, 25.1 mmol) and diethyl malonate (7.64 mL, 0.05 mol) in EtOH (50 mL) was stirred for 30 minutes at room temperature. A solution of **37** (2.42 g, 14.9 mmol) in EtOH (10 mL) was added and stirring was continued for 7 days at room temperature [49,50]. The mixture was then acidified with AcOH (5 mL) and the solvent evaporated *in vacuo*. The residue was diluted with H_2O (150 mL) and ether extracted (5 x 100 mL). The combined ether extract was washed with sat. aqueous $NaHCO_3$, until pH>9, H_2O (50 mL), dried ($MgSO_4$),

filtered and the solvent evaporated *in vacuo*. The product was chromatographed on silica gel (250 g) with 66% E/H to afford an oily mixture containing **45** [51] (2.18 g, 45%); IR ν_{max}/cm^{-1} 1732 (C=O of ester), 1682 (α,β-unsat. C=O), 1620 (conjugated C=C); ^1H NMR/ppm 5.69 (1H, br s, $W_{h/2}$ = 3.5 Hz, H-1), 4.20, 4.19 (4H, 2 x q, J_q = 7.1 Hz, (quartets separated by 2.3 Hz, 2 x ester CH_2), 3.38 (1H, d, J = 11.7 Hz, $CH(CO_2R)_2$), 2.77 (1H, m, $W_{h/2}$ = 21.5 Hz after selective irradiation of malonate CH, H-7), 2.63 (1H, ddd, J = 15.3, 5.4, 1.8 Hz, H-8 *cis*, *NOE* 1.27), 2.22 (1H, dt, J = 15.3, 2.1 Hz, H-8 *trans*), 1.27 (9H, m, $W_{h/2}$ = 4.4 Hz, H-11 + 2 x ester Me); ^{13}C NMR/ppm 199.1 (C-2), 168.4 (ester C=O, *LRHC* 3.38), 166.7 (C-9), 126.9 (C-1), 61.6, 61.5 (2 x ester CH_2), 52.9 ($CH(CO_2R)_2$), 37.8 (C-3)$^{\diamond}$, 36.1 (C-4)$^{\diamond}$, 35.8 (C-10), 35.4 (C-8, *HC* 2.63, 2.22), 35.0 (C-7), 34.1 (C-5)$^{\diamond}$, 23.9 (C-6)$^{\diamond}$, 22.4 (C-11), 14.1 (2 x ester Me) and *cis*-7-di(ethoxycarbonyl)methyl-10-methyl-1(9)-octal-2-one (**46**) (0.15 g, 3%).

trans-7-Di(ethoxycarbonyl)methyl-2,2-ethylenedithio-10-methyl-1(9)-octalin (**47**)

$BF_3.OEt_2$ (10 drops) was added to a stirred solution of **45** (1.02 g, 3.17 mmol) and 1,2-ethanedithiol (1.28 mL, 15.3 mmol) in ether (10 mL) and then stirred for 16 hours. The reaction mixture was then diluted with ether (250 mL), washed sequentially with 8% aqueous NaOH (2 x 15 mL), sat. aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL), then dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. The product was chromatographed on silica gel (60 g) with 50% E/H to afford unreacted **45** (0.32 g, 31%) and slightly impure **47** (0.63 g, 50%); IR ν_{max}/cm^{-1} 1754, 1731 (ester C=O), 1646 (C=C); ^1H NMR/ppm 5.44 (1H, s, H-1), 4.21, 4.18 (4H, 2 x quartet, J = 7.1 Hz, 2 x ester CH_2), 3.47 (1H, d, J = 11.9 Hz, malonate CH), 3.37 (4H, m, $W_{h/2}$ = 2.5 Hz, SCH_2CH_2S), 2.60 (1H, m, $W_{h/2}$ = 21 Hz, after irradiation of CH, $W_{h/2}$ = 11 Hz, H-7 *cis*), 2.43 (1H, ddd, J = 14.7, 5.1, 1.8 Hz, H-8 *cis*, *NOE* 1.09), 1.94 (1H, dm, J = 14.7 Hz, $W_{h/2}$ = 4.4 Hz, H-8 *trans*), 1.29, 1.26 (6H, 2 x triplet, appears as quartet, J = 7.1 Hz, 2 x ester Me), 1.09 (3H, s, H-11); ^{13}C NMR/ppm 168.9, 168.7 (2 x ester C=O), 140.8 (C-9), 127.9 (C-1), 65.7 (C-2), 61.2 (2 x ester CH_2), 52.3 (ester CH, *HC* 3.47), 40.2, 39.5 (SCH_2CH_2S), 39.1 (C-3)$^{\diamond}$, 38.0 (C-4)$^{\diamond}$, 36.1 (C-5)$^{\diamond}$, 35.3 (C-7, *HC* 2.60), 34.6 (C-8, *HC* 2.43, 1.94), 34.0 (C-10), 24.1 (C-6)$^{\diamond}$, 23.7 (C-11), 14.2, 14.1 (2 x ester Me). Multiple elution of a fraction of this material(0.20 g) by p.l.c. (10% E/H) gave pure **47** (0.14 g) as an oil; Anal. Found: C, 60.09; H, 7.61; S, 16.12%. Calcd. for $C_{20}H_{30}O_4S_2$: C, 60.27; H, 7.56; S, 16.09% and pure, oily *cis*-7-di(ethoxycarbonyl)methyl-2,2-ethylenedithio-10-methyl-1(9)-octalin (**48**) (0.013 g) IR ν_{max}/cm^{-1} 1749, 1731 (ester C=O), 1646 (C=C), ^1H NMR/ppm 5.51 (1H, s, H-1), 4.20, 4.19 (4H, 2 x quartet, J = 7.1 Hz, 2 x ester CH_2), 3.37 (4H, m, $W_{h/2}$ = 5.3 Hz, SCH_2CH_2S), 3.19 (1H, d, J = 7.7 Hz, malonate CH), 1.28, 1.27 (6H, 2 x triplet, J = 7.1 Hz, 2 x ester Me), 1.04 (3H, s, H-11); ^{13}C NMR/ppm 168.5 (2 x ester C=O), 143.0 (C-9), 126.1 (C-1), 65.8 (C-2), 61.3 (2 x ester CH_2), 57.9 (ester CH), 40.8, 40.2 (SCH_2CH_2S, *HC* 3.37), 39.6 (C-3)$^{\diamond}$, 39.2 (C-7), 39.0 (C-4)$^{\diamond}$, 37.9 (C-5)$^{\diamond}$, 35.9 (C-6)$^{\diamond}$, 33.8 (C-10), 26.1 (C-8)$^{\diamond}$, 23.3 (C-11), 14.2 (2 x ester Me). Anal. Found: C, 60.46; H, 7.83; S, 16.21%. Calcd. for $C_{20}H_{30}O_4S_2$: C, 60.27; H, 7.56; S, 16.09%.

cis-7-Di(ethoxycarbonyl)methyl-10-methyl-1(9)-octal-2-one (**46**)

A solution of $Tl(NO_3)_3.3H_2O$ (0.021 g, 47.3 μmol) in MeOH (0.3 mL) was added to a stirred solution of **48** (0.010 g, 23.2 μmol) in MeOH (1.5 mL) and THF (0.5 mL) [52]. After 10 minutes CH_2Cl_2 (10 mL) was added and the resultant precipitate was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (75 mL), washed with H_2O (5 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. Isolation by p.l.c. (75% E/H) gave **46** (0.008 g, 98%) as an oil; ^1H NMR/ppm 5.74 (1H, s, H-1), 4.22 (4H, q, J = 7.1 Hz, 2 x ester CH_2), 3.27 (1H, d, J = 7.3 Hz, malonate CH), 1.28 (6H, t, J = 7.1 Hz, 2 x ester Me), 1.22 (3H, s, H-11). Anal. Found: C, 66.79; H, 7.74%. Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13%.

trans-7-Carboxymethyl-2,2-ethylenedithio-10-methyl-1(9)-octalin (**49**)

A mixture of **47** (0.43 g, 1.09 mmol) and KOH (0.45 g, 7.98 mmol) in MeOH (15 mL) and H_2O (3 mL) was stirred for 3 hours at room temperature [49], at which stage t.l.c. showed no starting material remained. The mixture was then acidified with 10% aqueous HCl (20 mL) and $CHCl_3$ extracted (4 x 25 mL). The combined $CHCl_3$ extract was washed with H_2O (10 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to give crude, oily *trans*-7-dicarboxymethyl-2,2-ethylenedithio-10-methyl-1(9)-octalin (0.53 g); ^1H NMR/ppm 5.53 (0.4H, s), 5.45 (0.6H, s), 3.38 (5H, m, $W_{h/2}$ = 2.5 Hz, SCH_2CH_2S, diacid CH), 1.09 (3H, s, H-11) which was heated to 200°C for 40 minutes under nitrogen. The crude **49** (0.32 g) obtained was used without further purification; ^1H NMR/ppm 5.50 (1H, s, H-1), 3.37 (6H, m, $W_{h/2}$ = 2.1 Hz, SCH_2CH_2S, CH_2CO_2), 1.08 (3H, s, H-11); Mass spectrum: *m/z* 298.1053 (M^+); Calcd. for $C_{15}H_{22}O_2S_2$: 298.1061.

trans-2,2-Ethylenedithio-7-(2'-hydroxyethyl)-10-methyl-1(9)-octalin (**50**)

Ethereal CH_2N_2 (20 mL) was added to a stirred solution of crude **49** (0.24 g) in ether (5 mL) at room temperature and stirred for 3 days at room temperature. AcOH (0.5 mL) was added and the solvents evaporated *in vacuo* to give crude methylated **49** (0.25 g) which was used without further manipulation. $LiAlH_4$ (0.050 g, 1.32 mmol) was added to a stirred solution of crude methylated **49** (0.25 g) in ether (10 mL) and THF (5 mL) at room temperature and stirred for 2 hours at room temperature. 10% Aqueous HCl (5 mL) was added, dropwise initially, then the reaction mixture was diluted with ether (200 mL) and washed with H_2O (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and the solvents were evaporated *in vacuo* to give crude **50** (0.43 g). The product was chromatographed on silica gel (30 g) with 66% E/H to afford **50** (0.19 g, 76%); IR ν_{max}/cm^{-1} 1644 (C=C); ^1H NMR/ppm 5.48 (1H, s, H-1), 3.64 (2H, t, J = 6.8 Hz, CH_2O), 3.37 (4H, m, $W_{h/2}$ = 1.3 Hz, SCH_2CH_2S), 2.40 (1H, ddd, J = 13.8, 5.1, 1.8 Hz, H-8 *cis*), 1.99 (1H, m, $W_{h/2}$ = 18.2 Hz, H-7, *HC* 31.1),1.09 (3H, s, H-11); ^{13}C NMR/ppm 142.3 (C-9), 126.7 (C-1), 66.0 (C-2), 61.2 (CH_2O), 40.4, 39.6 (SCH_2CH_2S, *HC* 3.37), 39.4 (C-3)$^\diamond$, 38.0 (C-4)$^\diamond$, 36.2 (C-5)$^\diamond$, 36.2 (C-8, *HC* 2.40), 34.2 (C-10), 33.7 (C-6)$^\diamond$, 31.1 (C-7), 25.9 (CH_2)$^\diamond$, 23.6 (C-11). Satisfactory microanalysis could not be obtained for this compound as samples decomposed during sublimation.

trans-2,2-Ethylenedithio-7-(2'-((methoxymethyl)oxy)ethyl)-10-methyl-1(9)-octalin (**51**) and *trans-7-(2'-((Methoxymethyl)oxy)ethyl)-10-methyl-1(9)-octal-2-one* (**35**)

p-TsOH.H_2O (0.16 g, 0.84 mmol) and 1/8 in molecular sieve 4Å (5 beads) were added to a stirred solution of **50** (0.19 g, 0.67 mmol) and LiBr (0.25 g, 0.29 mmol) in dimethoxymethane (15 mL) at room temperature [58]. The reaction mixture was stirred for 3 days at room temperature, then H_2O (20 mL) was added and ether extracted (4 x 50 mL). The combined ether extract was dried ($MgSO_4$), filtered and the solvents evaporated *in vacuo*. Isolation of the products by p.l.c. (66% E/H) gave impure **51** (0.10 g); ^{1}H NMR/ppm 5.48 (1H, br s, $W_{h/2}$ = 3.5 Hz, H-1), 4.62 (2H, d, J = 1.7 Hz, OCH_2O), 3.52 (2H, t, J = 6.6 Hz, CH_2O), 3.35 (7H, m, $W_{h/2}$ = 2.1 Hz, SCH_2CH_2S, OMe), 1.09 (3H, s, H-11) and pure *trans*-7-(2'-((methoxymethyl)oxy)ethyl)-10-methyl-1(9)-octal-2-one (**35**) (0.051 g) as an oil; ^{1}H NMR/ppm 5.75 (1H, d, J = 1.8 Hz, H-1), 4.61 (2H, s, OCH_2O), 3.53 (2H, t, J = 6.5 Hz, CH_2O), 3.36 (3H, s, OMe), 1.26 (3H, s, H-11); ^{13}C NMR/ppm 199.4 (C-2), 168.9 (C-9), 126.3 (C-1), 96.5 (OCH_2O), 65.7 (CH_2O), 55.3 (OMe), 38.0 (C-3)$^{\diamond}$, 37.1 (C-4)$^{\diamond}$, 36.1 (C-5)$^{\diamond}$, 36.0 (C-10), 34.2 (C-6)$^{\diamond}$, 31.6 (C-7), 31.3 (C-8)$^{\diamond}$, 25.6 (CH_2)$^{\diamond}$, 22.4 (C-11); Mass spectrum: *m/z* 252.1720 (M^+); Calcd. for $C_{15}H_{24}O_3$: 252.1725.

trans-7-(2'-((Methoxymethyl)oxy)ethyl)-10-methyl-1(9)-octal-2-one (**35**)

A solution of $Tl(NO_3)_3.3H_2O$ (0.092 g, 0.21 mmol) in MeOH (1 mL) was added to a stirred solution of impure **51** (0.064 g) in MeOH (6 mL) and THF (3 mL) at room temperature [52]. After stirring for 10 minutes, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ (75 mL), washed with H_2O (5 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. Isolation by p.l.c. (66% E/H) gave oily **35** (0.026 g) and an unidentified impurity (0.019 g).

Cuprate Reactions

Purified CuI (0.29 g, 1.50 mmol) was placed in a Schlenk tube containing a magnetic stirrer bar under nitrogen or argon which had been flame dried *in vacuo*,. Degassed dry ether (10 mL) was added and the suspension was stirred at 0°C, then MeLi (3.00 mmol) was added over 30 s to give a colorless or slightly yellow solution. The mixture was stirred for 10 minutes at 0°C before use. The 'workup as usual' procedure involved adding a mixture of saturated aqueous NH_4Cl/NH_3 (25 mL), prepared by mixing saturated NH_4Cl (25 mL) and 25% aqueous NH_3 (4 mL), to the reaction mixture at 0°C. The total reaction mixture was then poured into a separating funnel and the reaction Schlenk tube was consecutively washed with NH_4Cl/NH_3 solution (15 mL) and then ether (50 mL). The combined mixture was then shaken until a deep blue colour developed and all solids had dissolved. The aqueous layer was ether extracted (3 x 50 mL) and the combined ether extract was washed with H_2O (15 mL), dried ($MgSO_4$) and the solvent evaporated *in vacuo*.

Reaction of Me_2CuLi with Enones

cis-5-Hydroxy-10-methyl-1(9)-octal-2-one (**7**)

A solution of **7** (0.18 g, 1.01 mmol) in ether (2.0 mL) was added to a stirred solution of ethereal Me_2CuLi (2.5 mmol, ~15 mL) at 0°C. A yellow precipitate formed immediately and the resultant mixture was stirred for 45 minutes. Workup as usual and isolation by p.l.c. (90% E/H) gave **7** (0.15 g, 80%).

cis-5-Methoxy-10-methyl-1(9)-octal-2-one (**13**)

A solution of **13** (0.16 g, 0.85 mmol) in ether (1.0 mL) was added to a stirred solution of ethereal Me_2CuLi (1.30 mmol, ~7 mL) at 0°C. A yellow solution formed immediately followed by a yellow/orange precipitate after approximately 20 seconds and was stirred for 45 minutes. Workup as usual and isolation by p.l.c. (66% E/H) gave *cis*-9,10-dimethyl-*cis*-5-methoxy-2-decalone (**16**) (0.083 g, 46%); IR ν_{max}/cm^{-1} 1709 (C=O); ^1H NMR/ppm (25°C) 3.55 (1H, m, $W_{h/2}$ = 18.2 Hz, H-5), 3.40 (3H, s, OMe), 0.94 (3H, s, H-11, *NOE* 0.89)$^{\diamond}$, 0.89 (3H, s, Me, *NOE* 0.94)$^{\diamond}$; ^1H NMR/ppm (-50°C) 3.55 (1H, dd, J = 10.4 ,3.9 Hz, H-5), 3.45 (3H, s, OMe), 0.92 (3H, s, H-11)$^{\diamond}$, 0.89 (3H, s, Me)$^{\diamond}$; ^{13}C NMR/ppm (25°C) 212.7 (C-2), 78.5 (br), 57.5, 57.4, 49.4 (br), 42.4, 37.9, 35.1, 31.2 (br), 29.7, 25.1, 24.2, 19.9, 16.0; ^{13}C NMR/ppm (-50°C) 214.4 (C-2), 77.7 (C-5), 57.7, 49.0, 42.5, 40.1, 37.9, 34.7, 30.6, 24.9, 24.1, 19.9, 15.7; Anal. Found: C, 74.17; H, 10.58%. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54%. and an isomeric mixture of 2,10-dimethyl-5-methoxy-1(9)-octal-2-ol: higher R_f (0.028 g, 16%); IR ν_{max}/cm^{-1} 3354 (OH), 1654 (C=C); ^1H NMR/ppm 5.30 (1H, br s, $W_{h/2}$ = 3.7 Hz, H-1), 3.36 (3H, s, OMe), 2.74 (1H, dd, J = 11.3, 4.2 Hz, H-5), 2.14 (1H, tdd, J = 13.6, 4.8, 1.7 Hz, H-8 *cis*), 1.27 (3H, s, H-11), 1.04 (3H, s, Me): lower R_f (0.016 g, 9%); IR ν_{max}/cm^{-1} 3374 (OH), 1655 (C=C); ^1H NMR/ppm 5.34 (1H, br s, $W_{h/2}$ = 4.2 Hz, H-1), 3.37 (3H, s, OMe), 2.79 (1H, dd, J = 11.4, 4.2 Hz, H-5), 2.13 (1H, tdd, J = 14.0, 5.1, 2.1 Hz, H-8 *cis*), 1.27 (3H, s, H-11), 0.98 (3H, s, Me).

cis-5-(Methoxymethyl)oxy-10-methyl-1(9)-octal-2-one (**14**)

A solution of **14** (0.24 g, 1.08 mmol) in ether (2.0 mL) was added to a stirred solution of ethereal Me_2CuLi (2.03 mmol, ~12 mL) at 0°C. A yellow solution formed immediately followed by a yellow/orange precipitate after approximately 30 seconds and was stirred for 45 minutes. Workup as usual and isolation by p.l.c. (50% E/H) gave **14** (0.019 g, 8%) and *cis*-9,10-dimethyl-*cis*-5-(methoxymethyl)oxy-2-decalone (**17**) (0.13 g, 50%) as an oil; IR ν_{max}/cm^{-1} 1713 (C=O); ^1H NMR/ppm 4.80, 4.59 (2H, AB system, J_{AB} = 6.9 Hz, OCH_2O), 4.02 (1H, m, $W_{h/2}$ = 19.0 Hz, H-5), 3.39 (3H, s, OMe), 0.97 (3H, s, H-11, *NOE* 0.90)$^{\diamond}$, 0.90 (3H, s, Me, *NOE* 0.97)$^{\diamond}$; ^{13}C NMR/ppm 212.9 (C-2), 107.8, 95.1 (OCH_2O), 73.9 (br), 55.7 (OMe), 49.4 (br), 42.3, 40.1, 37.5, 34.9, 31.2 (br), 26.6, 24.2, 20.0, 16.0; Anal. Found: C, 69.88; H, 9.86%. Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07%.

cis-5-Benzyloxy-10-methyl-1(9)-octal-2-one (**15**)

A solution of **15** (0.13 g, 0.48 mmol) in CH_2Cl_2 (1.0 mL) was added to a stirred solution of ethereal Me_2CuLi (1.50 mmol, ~10 mL) at 0°C. A yellow precipitate formed immediately and the mixture was stirred for 45 minutes. Workup as usual and isolation by p.l.c. (66% E/H) gave *cis*-5-benzyloxy-*cis*-9,10-dimethyl-2-decalone (**18**) (0.07 g, 51%) as an oil; IR ν_{max}/cm^{-1} 1713 (C=O), 735, 698 (C-H bend); ^1H NMR/ppm 7.33 (5H, m, $W_{h/2}$ = 3.4 Hz, phenyl), 4.72, 4.42 (2H, AB system, J_{AB} = 12.0 Hz, OCH_2), 3.74 (1H, m, $W_{h/2}$ = 18.6 Hz, H-5), 2.68 (1H, br s, $W_{h/2}$ = 12.2 Hz), 2.25 (1H, ddd, J = 13.9, 6.1, 3.6 Hz), 1.00 (3H, s, H-11)$^{\diamond}$, 0.88 (3H, s, Me)$^{\diamond}$; ^{13}C NMR/ppm 212.9 (C-2), 138.9 (phenyl *i* C), 128.4 (phenyl *o* C)$^{\nabla}$, 127.7 (phenyl *m* C)$^{\nabla}$, 127.6 (phenyl *p* C)$^{\nabla}$, 70.8, 49.3 (br), 40.5, 37.6, 35.1, 31.3 (br), 25.5, 24.2, 19.9, 16.2; Mass spectrum: *m/z* 286.1921 (M^+); Calcd. for $C_{19}H_{26}O_2$: 286.1933. Variable temperature NMR studies on *cis*-9,10-dimethyl-*cis*-5-hydroxy-2-decalone (**20**), derived from **18** showed at 25°C; ^1H NMR/ppm 0.95, 0.91; ^{13}C NMR/ppm 212.9 (C-2), 68.8 (br), 49.2 (br), 42.1, 40.4, 37.7, 35.0, 31.1, 30.6, 29.7, 24.4, 20.2, 15.1. At -50°C a single set of peaks were detected; ^1H NMR/ppm 0.93, 0.91; ^{13}C NMR/ppm 214.7 (C-2), 68.2, 48.8, 42.7, 40.0, 37.6, 34.5, 30.7, 30.2, 24.4, 20.1. 14.9. Anal. Found: C, 73.24; H, 10.58%. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27%.

trans-5-(Methoxymethyl)oxy-10-methyl-1(9)-octal-2-one (**21**)

A solution of **21** (0.10 g, 0.45 mmol) in ether (1.0 mL) was added to a stirred solution of ethereal Me_2CuLi (1.20 mmol, ~10 mL) at 0°C. A yellow/orange precipitate formed immediately and the mixture was stirred for 45 minutes. Workup as usual using $CHCl_3$ and isolation by p.l.c. (75% E/H) gave starting material (0.027 g, 27%) and 2,10-dimethyl-5-(methoxymethyl)oxy-1(9)-octal-2-ol (**24**) (0.063 g, 58%); IR ν_{max}/cm^{-1} 3414 (OH), 1661 (C=C); ^1H NMR/ppm 5.35 (1H, br s, $W_{h/2}$ = 4.6 Hz, H-1), 4.58, 4.69 (2H, AB system, J_{AB} = 6.9 Hz, OCH_2O), 3.39 (3H, s, OMe), 3.36 (1H, br s, H-5), 1.32 (3H, s, H-11)$^{\diamond}$, 1.12 (3H, s, Me)$^{\diamond}$.

trans-7-Methoxy-10-methyl-1(9)-octal-2-one (**28**)

A solution of **28** (0.17 g, 0.87 mmol) in ether (2.0 mL) was added to a stirred solution of ethereal Me_2CuLi (2.54 mmol, ~15 mL) at -20°C. A yellow/orange precipitate formed immediately and the mixture was warmed to 0°C and stirred for 45 minutes. Workup as usual using $CHCl_3$ and isolation by p.l.c. (66% E/H) gave **28** (0.014 g, 8%) and *cis*-9,10-dimethyl-*trans*-7-methoxy-2-decalone (**31**) (0.097 g, 53%) as an oil; IR ν_{max}/cm^{-1} 1712 (C=O); ^1H NMR/ppm (25°C) 3.30 (3H, s, OMe), 1.10 (3H, s, H-11, *NOE* 0.97)$^{\diamond}$, 0.97 (3H, s, Me, *NOE* 1.10)$^{\diamond}$; ^1H NMR/ppm (-50°C) two sets of resonances in a ratio of 86:14 (a) 1.16 (3H, s, H-11)$^{\diamond}$, 1.03 (3H, s, Me)$^{\diamond}$ (b) 0.99 (s, H-11)$^{\nabla}$, 0.83 (s, Me)$^{\nabla}$; ^{13}C NMR/ppm 211.7 (C-2), 76.2 (C-7), 55.7, 52.4, 41.4, 39.7 (br), 34.7, 34.3, 32.8 (br), 29.7, 26.9, 24.0, 22.6; Anal. Found: C, 74.33; H, 10.42%. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54% and an isomeric mixture of 2,10-dimethyl-7-methoxy-1(9)-octal-2-ol: Higher R_f (0.032 g, 17%); IR ν_{max}/cm^{-1} 3398 (OH), 1654

(C=C); ^{1}H NMR/ppm 5.24 (1H, br s, H-1), 3.51 (1H, m, $W_{h/2}$ = 7.5 Hz, H-7), 3.27 (3H, s, OMe), 1.30 (3H, s, H-11)$^{\diamond}$, 1.11 (3H, s, Me)$^{\diamond}$: Lower R_f (0.015 g, 8%); IR ν_{max}/cm^{-1} 3433 (OH), 1659 (C=C); ^{1}H NMR/ppm 5.32 (1H, br s, H-1), 3.53 (1H, m, $W_{h/2}$ = 8.0 Hz, H-7), 3.28 (3H, s, OMe), 1.25 (3H, s, H-11)$^{\diamond}$, 1.04 (3H, s, Me)$^{\diamond}$.

trans-7-(Methoxymethyl)oxy-10-methyl-1(9)-octal-2-one (**29**)

A solution of **29** (0.073 g, 0.33 mmol) in ether (1.0 mL) was added to a stirred solution of ethereal Me_2CuLi (1.03 mmol, ~9 mL) at -20°C. A yellow/orange precipitate formed immediately and the mixture was warmed to 0°C and stirred for 45 mintues. Workup as usual and isolation by p.l.c. (66% E/H) gave **29** (0.017 g, 23%) and *cis*-9,10-dimethyl-*trans*-7-(methoxymethyl)oxy-2-decalone (**32**) (0.040 g, 50%) as an oil; IR ν_{max}/cm^{-1} 1714 (C=O); ^{1}H NMR/ppm (25°C) 4.63 (2H, s, OCH_2O), 3.34 (3H, s, OMe), 1.10 (3H, s, H-11, *NOE* 0.98)$^{\diamond}$, 0.98 (3H, s, Me, *NOE* 1.10)$^{\diamond}$; ^{1}H NMR/ppm (-50°C) two sets of resonances in a ratio of 91:9 (a) 1.15 (3H, s, H-11)$^{\diamond}$, 1.03 (3H, s, Me)$^{\diamond}$ (b) 1.00 (s, H-11)$^{\nabla}$, 0.84 (s, Me)$^{\nabla}$; ^{13}C NMR/ppm 211.6 (C-2), 94.8 (OCH_2O), 72.7 (C-7), 55.3, 52.5, 41.5, 40.9, 38.1, 34.6, 34.3 (br), 33.0 (br), 27.8, 23.9, 22.7; Anal. Found: C, 69.98; H, 9.80%. Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07%.

trans-7-Benzyloxy-10-methyl-1(9)-octal-2-one (**30**)

A solution of **30** (0.071 g, 0.26 mmol) in ether (1.0 mL) was added to a stirred solution of ethereal Me_2CuLi (0.52 mmol, ~6 mL) at -20°C. A yellow/orange precipitate formed immediately and the mixture was warmed to 0°C and stirred for 45 mintues. Workup as usual and isolation by p.l.c. (66% E/H) gave **30** (0.031 g, 43%) and *trans*-7-benzyloxy-*cis*-9,10-dimethyl-2-decalone (**33**) (0.032 g, 44%) as an oil; IR ν_{max}/cm^{-1} 1712 (C=O), 736, 697 (C-H bend); ^{1}H NMR/ppm 7.31 (5H, m, $W_{h/2}$ = 1.0 Hz, phenyl), 4.50 (2H, s, OCH_2), 3.60 (1H, m, $W_{h/2}$ = 20.2 Hz, H-7), 1.09 (3H, s, H-11, *NOE* 0.95)$^{\diamond}$, 0.95 (3H, s, Me, *NOE* 1.09)$^{\diamond}$; ^{13}C NMR/ppm 211.7 (C-2), 138.8, 128.4, 127.5, 74.4, 70.1, 52.5, 41.5, 40.2, 38.1, 34.8, 34.5 (br), 29.7, 27.3, 24.0, 22.7; Mass spectrum: *m/z* 286.1929 (M^+); Calcd. for $C_{19}H_{26}O_2$: 286.1933.

7-((Methoxymethyl)oxy)methyl-10-methyl-1(9)-octal-2-one (**34,36**)

A solution of **34** and **36** (0.059 g, 0.25 mmol) in ether (1.0 mL) was added to a stirred solution of ethereal Me_2CuLi (0.51 mmol, ~8 mL) at -20°C. A yellow/orange precipitate formed immediately and the mixture was warmed to 0°C and stirred for 45 mintues. Workup as usual and isolation by p.l.c. (66% E/H) gave the starting material mixture (0.010 g, 17%) enriched in **34** IR ν_{max}/cm^{-1} 1676 (α,β unsat. C=O), 1621 (conjugated C=C); ^{1}H NMR/ppm 5.75 (1H, d, J = 1.8 Hz, H-1), 4.60 (2H, s, OCH_2O), 3.40 (2H, d, J = 7.6 Hz, CH_2O), 3.35 (3H, s, OMe), 1.27 (3H, s, H-11); *cis*-9,10-dimethyl-*cis*-7-((methoxymethyl)oxy)methyl-2-decalone (**44**) (0.027 g, 43%) as an oil; IR ν_{max}/cm^{-1} 1713 (C=O); ^{1}H NMR/ppm (25°C) 4.61 (2H, s, OCH_2O), 3.36 (3H, s, OMe), 2.89 (1H, d, J = 13.9 Hz), 0.97 (3H, s, H-11, *NOE* 0.86)$^{\diamond}$, 0.86 (3H, s, Me, *NOE* 0.97)$^{\diamond}$; ^{1}H NMR/ppm (-50°C) 4.68 (2H, s, OCH_2O), 3.40 (3H, s, OMe), 2.89 (1H, d, J = 13.9

Hz), 0.99 (3H, s, H-11)$^{\diamond}$, 0.87 (3H, s, Me)$^{\diamond}$; Anal. Found: C, 70.73; H, 10.27%. Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30% and *cis*-9,10-dimethyl-*trans*-7- ((methoxymethyl)oxy)methyl-2-decalone (**43**) (0.019 g, 30%) as an oil; IR ν_{max}/cm^{-1} 1712 (C=O); ^{1}H NMR/ppm (25°C) 4.58 (2H, s, OCH_2O), 3.33 (3H, s, OMe), 3.30 (1H, d, J = 6.2 Hz), 1.14 (3H, s, H-11, *NOE* 1.02)$^{\diamond}$, 1.02 (3H, s, Me, *NOE* 1.14)$^{\diamond}$; ^{1}H NMR/ppm (-50°C) 4.64 (2H, s, OCH_2O), 3.36 (3H, s, OMe), 1.16 (3H, s, H-11)$^{\diamond}$, 1.04 (3H, s, Me)$^{\diamond}$; ^{13}C NMR/ppm 212.2 (C-2), 96.6 (OCH_2O), 73.3 (CH_2O), 55.2, 52.7, 40.8, 38.4, 38.3, 38.0, 37.2, 34.9, 34.5, 33.9, 33.8, 29.8, 24.2, 23.5, 23.2, 22.7; Anal. Found: C, 70.83; H, 10.58%. Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30%.

trans-7-(2'-((Methoxymethyl)oxy)ethyl)-10-methyl-1(9)-octal-2-one (**35**)

A solution of **35** (0.013 g, 0.050 mmol) in CH_2Cl_2 (2.0 mL) was added to a stirred solution of Me_2CuLi (0.33 mmol, ~6 mL), prepared in ether (3 mL) and then diluted with CH_2Cl_2 (4 mL), at -20°C. No precipitate formed even after 5 minutes, the solution was warmed to 0°C and then stirred for 45 minutes. Workup as usual using $CHCl_3$ and isolation by p.l.c. (66% E/H) gave **35** (0.009 g, 68%) and *cis*-9,10-dimethyl-7-(2'-((methoxymethyl)oxy)ethyl)-2-decalone (**52**) (0.002 g, 15%) as an oily inseparable mixture of two isomers; IR ν_{max}/cm^{-1} 1714 (C=O); ^{1}H NMR/ppm (a) *cis* isomer (25%); 4.61 (s), 3.36 (s), 0.96 (s), 0.84 (d, J = 0.96 Hz) and (b) *trans* isomer (75%); 4.60 (s), 3.52 (t, J = 6.7 Hz), 3.35 (s), 1.12 (s), 1.00 (s); Mass spectrum: *m/z* 268.2038 (M^+); Calcd. for $C_{16}H_{28}O_3$: 268.2038.

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References and Notes

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† this formula depicts the simplest stoichiometry and does not imply any particular molecular state.

‡ all octalone compounds used were racemic, only one enantiomer depicted in the diagrams.

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