Syn-axial steric and counter-ion coordination factors in the methylation of 6-membered cyclic esters

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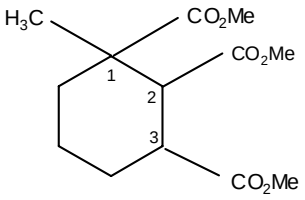
It was found in an earlier study that one (**A**) of the four possible configurational isomers of trimethyl 1-methylcyclohexane-1,2,3-tricarboxylate yields, in regiospecific and highly stereospecific manner, trimethyl *trans*, *meso* 1,2-dimethylcyclhexane-1,2,3-tricarboxylate on exposure to the methylation condition of treatment with tritylsodium (ether)/methyl iodide. Isomer **A** changes to isomer **C** via enolate formation unexpectedly slowly even though what was needed for the transformation was only a ring inversion. Equally unexpectedly, it was found in an independent experiment that an α-enolate is not formed at all directly from **C** on treatment with tritylsodium. The role that coordination of counter-ion (Na^+) may play in the first case and manner in which 1,3-syn axial steric effect may operate in the second was sought to be tested by employing methyl 9-ethoxycarbonyl- and methyl 9-methyl-*trans*-decalin-2-carboxylates as test systems having no possibility of ring-inversion. The 9-methyl system, analogue of **C**, did not form an α-enolate ion, as expected. On the other hand, the 9-ester, analogue of **A**, readily formed an enolate that does not undergo methylation under conditions when **A** does. It did undergo the reaction, practically non-stereoselectively however, when the strong de-coordinating agent hexamethyl phosphoric triamide was added before the addition of methyl iodide.

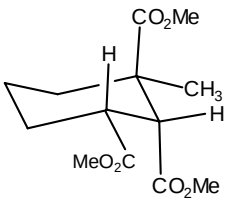
The synthesis, separation and characterization of three of the four possible configurational isomers, **A**, **B** and **C**, of trimethyl 1-methylcyclohexane-1,2,3-tricarboxylate **1** were reported some years ago[1]. ^{1}H NMR evidence[2] had shown that these isomeric triesters prefer, in order, conformations **2A**, **2B** and **2C** in the solution phase (CCl_4). Treatment of triester **A** with Ph_3C^- Na^+ in ether, quickly followed by quenching with methyl iodide, gives the C-3 methylated product **3** of *trans*, *meso* configuration as the overwhelmingly predominant product, showing that enolate-formation is regiospecific at C-3 and methylation highly stereoselective.

Triesters **2A** and **2C** were expected to form a common C-3 enolate ion **E** for the reason that the C-1 and C-2 ester groups are in the same configurational (*trans*) relationship in the two. To our great surprise, **2C** was found not to react with Ph_3C^- at all, as was apparent from absence of decolourisation as addition of the reagent proceeded, in contrast with instantaneous decolourisation seen in the case with **2A** (until the point of addition of one molar equiv. had been passed). Two reasons, differently based, could be advanced for this contrast in behaviour: Following from the concept of "steric approach control",[3] steric hindrance offered by the *syn* axial methyl at C-1 in **2C** could prevent Ph_3C^-

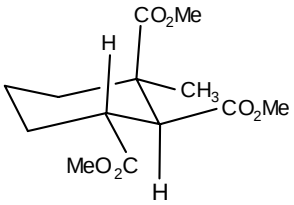
from approaching within a distance optimal for the abstraction of the C-3 proton. Or, the C-3 proton in **2A** could be activated (i.e. its acidity enhanced)[4] by the *syn* axial ester function at C-1 and rendered prone to facile removal.



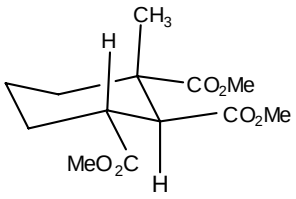
1



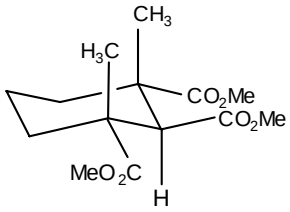
2A



2B

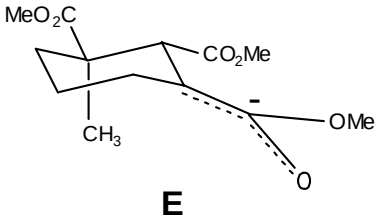


2C



3

(*trans, trans*; meso)



E

Equally surprisingly, it was found that the enolate derived from **2A** gets transformed into a form that yields **2C** on protonation, not instantaneously (as one might expect) but at a rate slow enough to allow being conveniently followed by a conventional technique. Quenching samples of the enolate mixture, drawn at known intervals, with water, sample preparation and GLC analysis (details given in 'Experimental' of ref. 2) showed a gradual increase in the proportion of **2C** at the expense of **2A**, attainment of apparent equilibrium taking as long as *ca* 8 hr!

It appeared that the slowness of the **2A** → **2C** enolate-ion transformation could be explained on a basis that the **A**-enolate co-ordinates sodium ion in some specific manner to form a metastable entity (Type **A** enolate; **Figure 1**[5]; interestingly, recent studies have pictured aromatic amino acid - Na^+/K^+ complexes[6] looking very similar to what we envisaged several years earlier[1a] for the triester **A** enolate - Na^+ complex). Transformation to Type **C** enolate requires the counter-ion to be de-coordinated first, before it can re-coordinate, perhaps not as tightly as before, with the ester function at C-2, following

ring-inversion. The process may need prior de-aggregation of ion aggregates formed in the ether medium, possibly through solubilisation of the initially precipitated aggregate.[7]

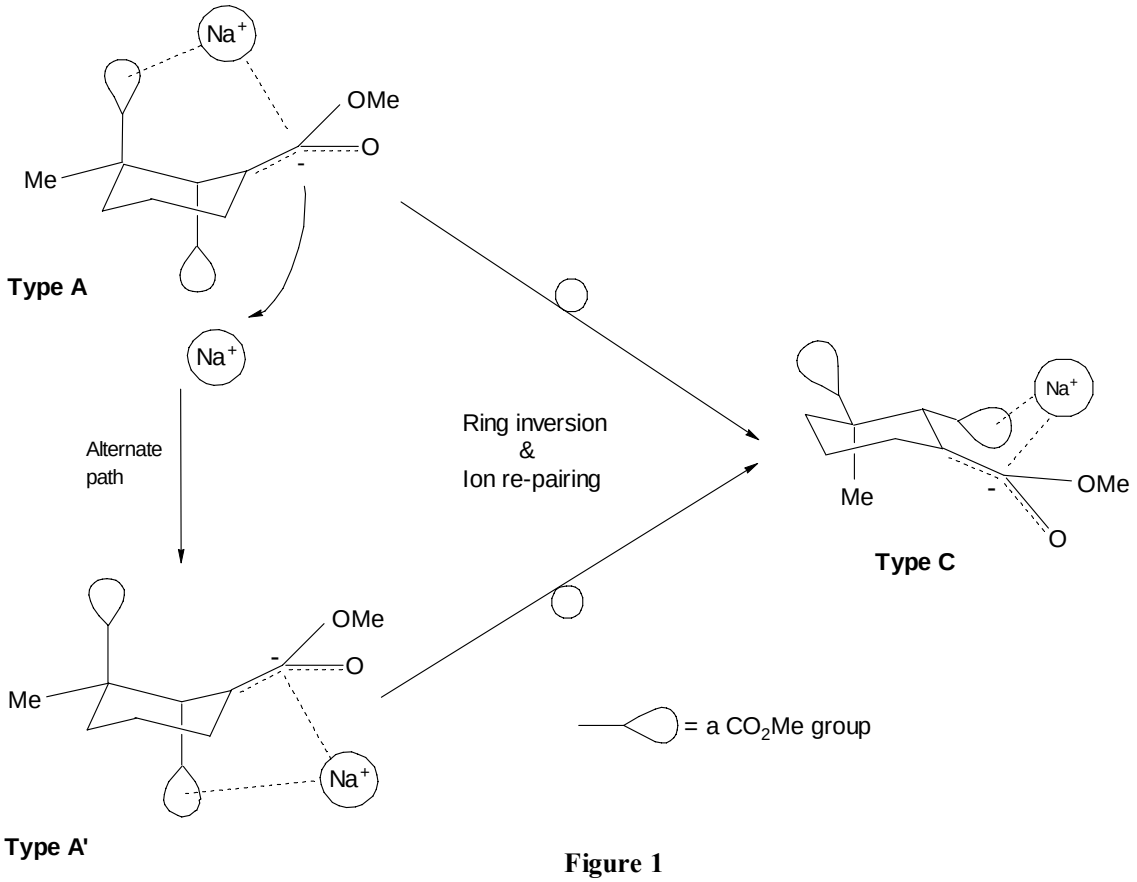


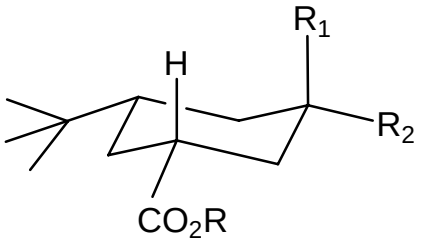
Figure 1

Alternatively, in case the ion-trappimg or coordination involves the C-2 ester function even initially, the tranformation would require re-approach and re-coordination from the opposite side after ring inversion (Type **A'** → Type **C**). Were tight ion-pairing indeed the reason for the slow attainment of Type **A** ⇆ Type **C** equilibrium, the stereoselectivity observed in the methylation of **2A** may well be due to the methylating agent being constrained to approach Type **A** enolate from the side not containing the counterion (i.e. it adopts "equatorial approach").

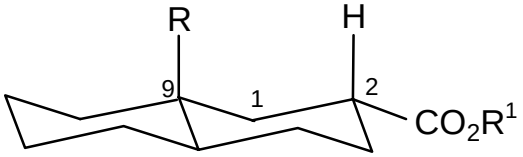
Transformation of the **A**-enolate into the **C**-enolate was not observed unless Ph_3C^- was present in excess. Because ring inversion would be unimpeded presumably only when the enolate is momentarily 'free' during a process of de-coordination and re-coordination, the rate-determining step in the Type **A** ⇆ Type **C** equilibration could very well be the ion-de-pairing event. The amount of Na cation available in excess could control this rate (as sought to be indicated by the 'Alternate path' in **Figure 1**). An important factor here could be that coordination of the counter-ion, while being intrinsically weak in conformationally mobile monocyclic systems, could be weaker still in Type **A'** or Type **C** enolates than in Type **A** enolates.

Present work

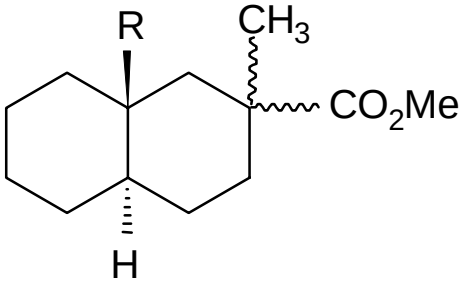
A way to examine these suggestive possibilities, especially the role the C-2 ester group may play, appeared to lie in a study of the behaviour of such systems as the 1,3-diesters **4** or the *trans* decalin esters **5a** and **5b** where ring inversion and conformational changes are much less likely or wholly restricted. Anticipating much difficulty in isolating the *tert*-butyl systems **4** in configurationally pure forms, we opted for the *trans*-decalin systems **5**.



4a:$R_1=CO_2R;R_2=CH_3$
4b:$R_1=CH_3;R_2=CO_2R$



5a:$R=CH_3$
5b:$R=CO_2Et$



6a:$R=CH_3$
6b:$R=CO_2Et$

Formation of the C-2 anion (decalin numbering) from the *trans*-decalin diester **5b** was expected to be facile, in accordance with the aforementioned criterion that the presence of a *syn*-diaxial ester function at C-1 in triester **2A** could enhance the acidity of the C-3 proton or otherwise facilitate its removal. For the reason that replacement of the *syn*-axial ester group at C-9 by a methyl removes this criterion, one may anticipate difficulty in generating an enolate ion from **5a**, let alone making it undergo methylation.

Systems **5a** and **5b** were synthesized following well-known procedures (see **Scheme I** in the Experimental section). Two methods were available for assigning configurations to products **6** of methylation of **5**, the "solvent-shift method"[8] for **6a** and a method based on the degree of anisochrony of the *O*-methylene protons of the C-9 ethyl ester function[9] for **6b**.

Methylation experiments

We found the red colour of tritylsodium was not discharged at all when we attempted to methylate **5a** employing the Ph_3CNa (ether)/MeI sequence; the starting material was recovered unchanged.

When anion-formation from **5b** was attempted next, rapid discharge of the Ph_3CNa colour was observed until the end-point had passed. Methyl iodide was dropped in after allowing an interval of ~15 min. The product was found to consist only of the unchanged starting material, however. Our immediate interpretation of these results was that, while **5a** does not form an anion at all at C-2, **5b** does form one in a facile manner but methylation is slow because the ion complex tends to maintain its aggregation.

A further attempt to methylate **5b** was predicated on an observation that quenching of α-lithio carbanions derived from diastereo-isomeric 4-*tert*.-butylsulphoxides with methyl iodide and methylation with trimethyl phosphate occur predominantly from opposite directions.[10] As illustrated for the case at hand **5b** (**Figure 2**), methyl iodide can be envisaged as being directed to approach the counter-ion paired enolate from the α-side because of the large steric hindrance offered by Na^+, very likely externally solvated by ether or tetrahydrofuran and coordinated to the C-9 ester carbonyl (Path 1). We found, however, that methylation of **5b** does not take place, possibly because the negative charge of the enolate, engaged by Na^+, becomes too weak to displace iodide.

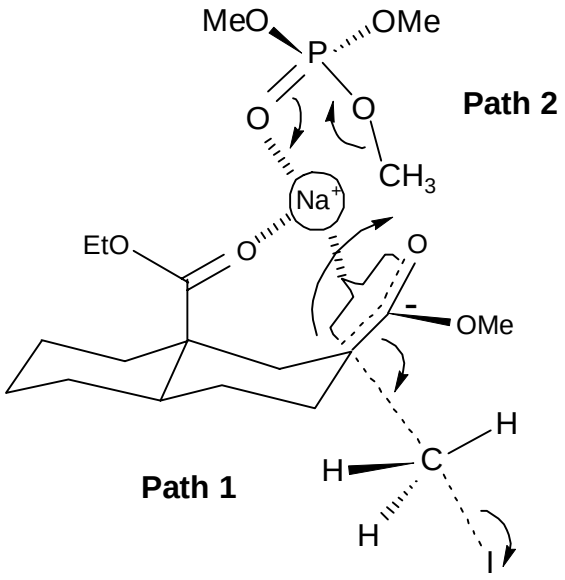


Figure 2

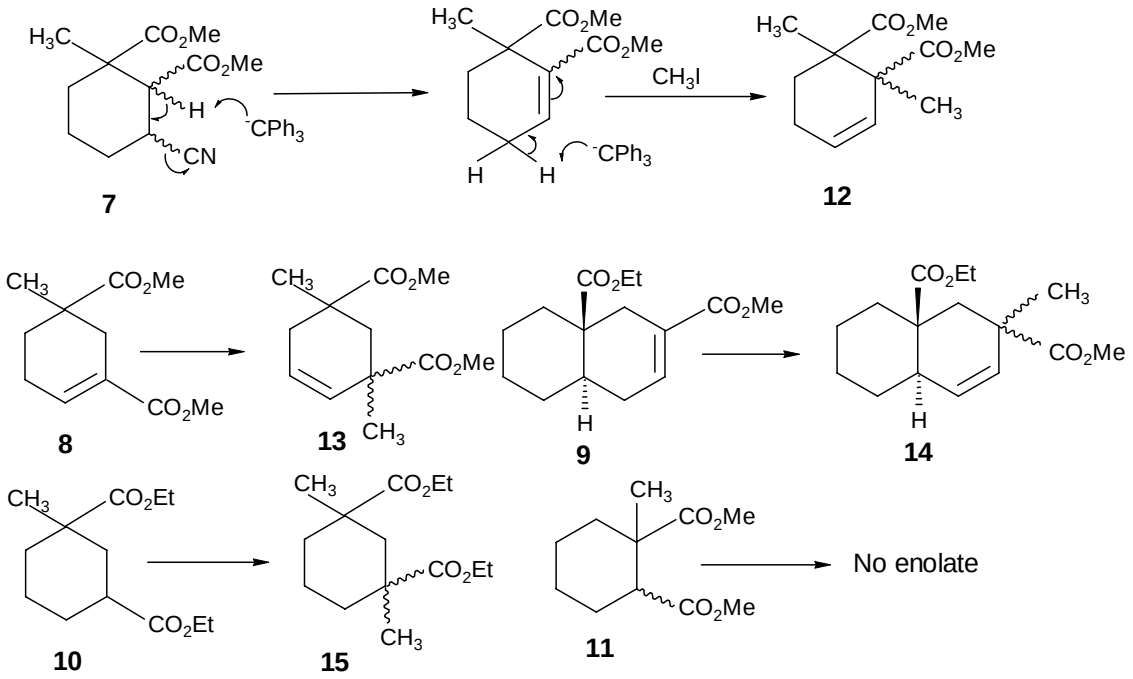
Trimethyl phosphate, capable of chelating on its own, was thought to have the capacity to loosen the coordination. Were it to replace, largely, ether or tetrahydrofuran as the external solvating agent, transfer of the methyl group could occur from the same side (β-side) as the coordinated Na^+ ion (Path 2).

All attempts to methylate the enolate from **5b** employing either trimethyl phosphate or dimethyl sulphate (but retaining ether or tetrahydrofuran as the medium) resulted only in the recovery of the starting material. One implication of these results, at least, was that the chelated structure of the 1,3-

enolate derived from **5b** remains stable in the solvents employed, the methylating agents evidently failing to displace the counter ion.

In a further effort to depair the cation, a crown ether was added before the addition of the methylating agent. 15-Crown-5, known to solvate Na^+ ions specifically,[11] was expected to leave the enolate much freer and greatly enhance its rate of alkylation. This strategy also failed - it seemed that chelation of Na^+ by the carbonyl oxygen of the C-9 ester function in the ion-paired enolate derived from the conformationally rigid system **5b** was strong, rendering competitive complexation by the crown ether especially slow.[12]

Time came now to validate the negative results obtained so far, whether the conditions we had employed were really conducive to methylation, through a study of systems modeled on **5b**.



Systems **8** – **11** were chosen for the model studies. Earlier work in these Laboratories[13] had disclosed that the isomeric cyano-diesters **7** undergo elimination and methylation sequentially on being subjected, individually or as a mixture of stereoisomers, to the Ph_3CNa (ether)/MeI treatment. The mechanism shown involves vinylogous activation).[2] With the reagents employed in excess, the product was found to be a 2:5 mixture of the *cis* and *trans* isomers of dimethyl 1,2-dimethylcyclohex-3-ene-1,2-dicarboxylate **12**. Were a similar mechanism to hold for the unsaturated diester **8**, the 1,3-analogue of diester **7**, the expected product would be the double-bond migrated, α-methylated diester **13**. The bicyclic analogue **9** could form an enolate with a potential to coordinate the counter-ion. However, even while this system bears a seemingly good structural analogy with the bicyclic system **5b** the coordination could have a different stereochemical relationship with the *tert*. methoxycarbonyl group because of the presence of an endocyclic double bond.

In both cases, **8** and **9**, the delocalised anions resulting from the removal of an allylically activated proton were conceived of as retaining higher negative charge densities at C-α, C-γ and the ester carbonyl oxygen (the HOMO is ψ_3 of a pentadienyl anion). Alkylation was expected to occur at C-α in a situation loosely paired compared with that in a structurally similar saturated enolate where delocalisation of the negative charge can involve only the α-carbon, as should be the case with the enolate derived from the saturated analogue **10**.

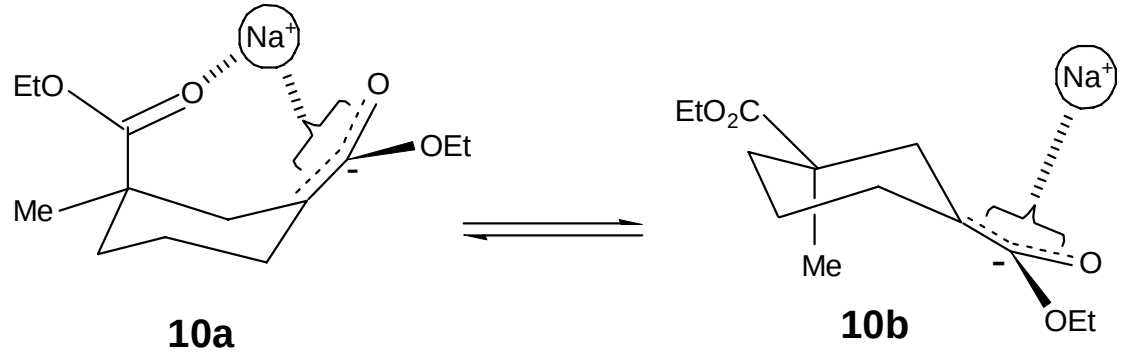
System **10** represents triester **1** with the ester function at C-2 removed and the last, **11**, had, in the absence of an ester function at C-3, a possibility of forming an anion at C-2. The starting materials taken for the methylation experiments were mixtures of *cis*:*trans* isomers in both the cases (1:4 in **10** and 2:9 in **11**; by VPC).

The experiments with the model systems gave mixed results. Enolate-formation was facile in the systems **8** - **10**, as was evident from the rapid discharge of the tritylsodium colour in all three cases. With **8** and **9**, methylation did take place but none of the methods tried could cleanly separate the two configurationally isomeric methylated products from each other and from the starting unsaturated esters (unchanged or the derived deconjugated). Nevertheless, the ^{1}H NMR spectra of the product mixtures, after the necessary preliminary clean up, gave clear evidence of methylation having taken place.

Methylation was a clean reaction in the case of the saturated 1,3-diester **10**. The components could be separated easily and identified with the known *cis* and *trans* diesters **15** that had been prepared earlier in these Laboratories through another route,[14] demonstrating that methylation had occurred at C-3.

The 1,2-diester **11** failed to form an anion, there being no discharge of the Ph_3CNa colour.

Trimethyl phosphate, used as the methylating agent in a repeat attempt, failed to methylate the 1,3-diester isomer mixture **10**. Interestingly, an increase in the proportion of the *trans* isomer (from a *cis*:*trans* ratio of ~1:4 to ~1:5; ^{1}H NMR and VPC evidence; see Experimental section) was noticed in the mixture recovered from this attempt. It is reasonable to assume that this increase represents the outcome of axial and equatorial modes of protonation of the mixture of counter-ion paired enolates **10a** and **10b** (which may not have reached equilibrium composition, however, at the time the reaction was terminated; see later discussion).

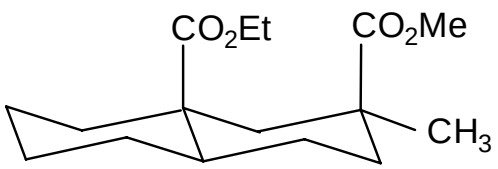


10a **10b**

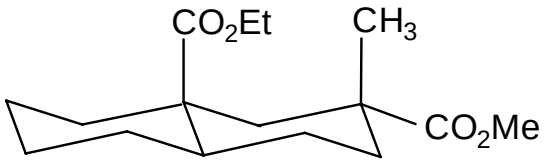
The successful attempt

We have already alluded to studies[7] that have shown that alkali metal enolates associate to form ion-aggregates of high molecular weight whose degree of polymerisation may vary widely with solvent and structure. Polar solvents can alter the aggregated structures by lengthening or cleaving the electrostatic liaisons in 'contact' or 'tight' ion-pairs. Direct experimental evidence is available from some cases[15] showing that contact and solvent-separated ion-pairs are in rapid equilibrium

We took our ability to methylate some of the model systems as strongly indicating that tight ion-pairing is the chief reason for the failure to methylate **5b**. In poorly solvating media like tetrahydrofuran (μ= 1.7 D)[16] or diethyl ether (μ = 1.15 D)[17] the free-energy of solvation of the alkali cation is, perhaps, too small to overcome the strong Coulombic attraction between it and the enolate ion, even if the latter were an entity with the negative charge delocalized. It is known that hexamethyl phosphoric triamide (HMPT) can completely dissociate ion pairs, even when present at low concentration.[18] Its powerful influence probably derives from its being a strong dipolar aprotic solvent (μ = 4.30 D).[19]



6b α



6b β

Based on these considerations we attempted to alkylate system **5b** by replacing diethyl ether, in which the enolate was formed, with HMPT (see Experimental section). This attempt met with immediate success. The product was a 3:2 mixture of the α- and β-methylated products (**6b α** and **6b β**). The configurations of the components separated by TLC were established by an NMR method[9] based on the magnitudes of the relative chemical shifts of the anisochronous *O*-methylene protons of the ethyl ester function at C-9.

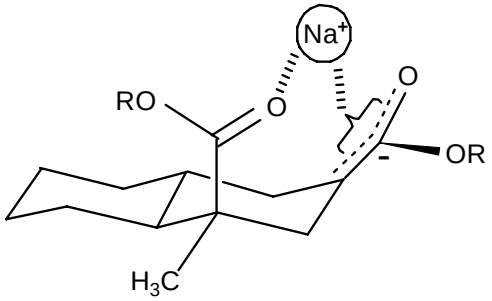
Conclusion

We believe that this result clearly demonstrates that the enolate derived from **5b** forms ion-pair aggregates when ether solvents are the medium. Methylation of these aggregates is extremely slow and methylated products are not formed to a detectable limit. The aggregation is disrupted by complexation with the powerful coordinating agent HMPT. The ‘solvent-separated’ ion-pairs are of higher reactivity and the 'free' carbanion undergoes facile methylation. Polarisation induced in methyl iodide on approaching the enolate from the equatorial side is not sufficient to displace the counter-ion coordinated to the C-9 ester function (**Figure 1**) even though it is likely to be externally solvated. Trimethyl phosphate, guided to approach the enolate from the same side as the counter-ion, is unable to disrupt the coordination, possibly due to its own inability to coordinate with the counter-ion effectively. Crown ether is unable to trap the counter-ion because the energy released on complex forma-

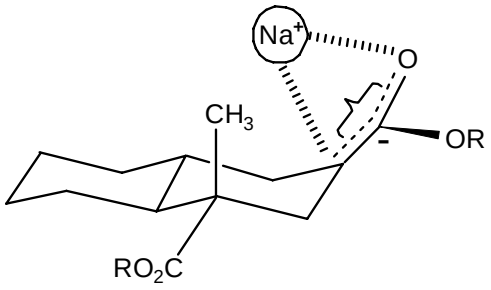
tion is not sufficient to overcome the strong coordination of the counter ion in the chelated structure (**Figure 1**). Together, these could imply that binding of the sodium ion by the crown ether is much weaker than that by the phosphoramide while that by the enolate (as shown in **Figure 1**) is of an intermediate strength.

One can now confidently state that the enolate derived from triester **2a** does coordinate sodium ion and conversion of the Type **A** (or Type **A'**) coordinated structure (**Figure 1**) to the Type **C** structure is slow because the ring inversion necessarily involves both de-aggregation and de-pairing.

Finally, we wish to point out that the substrate from the 1,3-diester **10** that undergoes methylation is a system that would tend to reach equilibrium between the two types of counter-ion paired enolates **10a** and **10b**. If the (qualitatively apparent) strong binding of the counter-ion in the case of **5b** is any indication, the equilibrium is likely to be displaced much in favour of form **10a**, that is, much beyond that based solely on the conformational free-energy difference between CH_3 and CO_2Me groups [~ 0.6 (≅ 1.7 – 1.1) kcal mole^{-1} represents a 7:3 preponderance of **10a** over **10b** at room temperature].[20] Such could be the case despite that Type **A** enolate-Na^+ complex evidently enters an equilibrium with Type **C** enolate-Na^+ complex where the latter predominates since the behaviour of these triester complexes could be quite different from that of the diester **10** complexes (e.g. in their solubility, aggregation, etc.).



11a



11b

It appears reasonable to expect that information on the faciality of methylation of each of forms **10a** and **10b** can be had from the ratio of axial and equatorial methylation of the bicyclic analogues **11a** and **11b.** The latter, though bearing close structural analogies with **10a** and **10b**, cannot, themselves, enter conformational equilibrium. If, now, the ratio of *cis* and *trans* methylation products of **10** is widely different from that expected on observations made with the bicyclic diester **11**, the case for coordination of the counter-ion playing a part in guiding the faciality of methylation would receive support.

Experimental section

General. IR spectra (of liquid films unless stated otherwise) were recorded with a Perkin-Elmer model 137 (NaCl Optics) or a model 397 (grating) IR spectrophotometer. ^{1}H NMR spectra were recorded with a Varian A-60, HA 100D or a Bruker WH-270 spectrometer employing TMS as the in-

ternal standard. TLC tests and separations by PLC were carried out on glass plates (20 x 5 cm and 20 x 20 cm, respectively) coated with silica gel (*ca* 0.2 mm**;** commercial grade containing 10% calcium sulphate). The coated plates were activated at 80-90° C for 12 hr prior to use; spots and bands were rendered visible with iodine vapour. Hexane refers to the petroleum fraction boiling in the range 40-60° C.

Esterifications of carboxylic acids with diazomethane or diazoethane were carried out employing the reagents co-distilled with ether. Reactions involving the use of ether solutions of triphenylmethyl-sodium were carried out in a special apparatus that permitted transfer of measured quantities of the reagent of predetermined strength into the reaction vessel under pressure of dry, oxygen-free nitrogen gas.

Samples were cleaned up to analytical grade by molecular (short-path) distillation. The temperature range ("bath temp.") within which the bulk of the sample distilled over and the lowest pressure attained have been given. It is to be understood that isomer mixtures normally being handled in all those cases where configurational isomerism was possible unless a separation procedure, followed by configurational assignment, has been specifically described.

The following conditions were maintained for all VPC tests/separations:

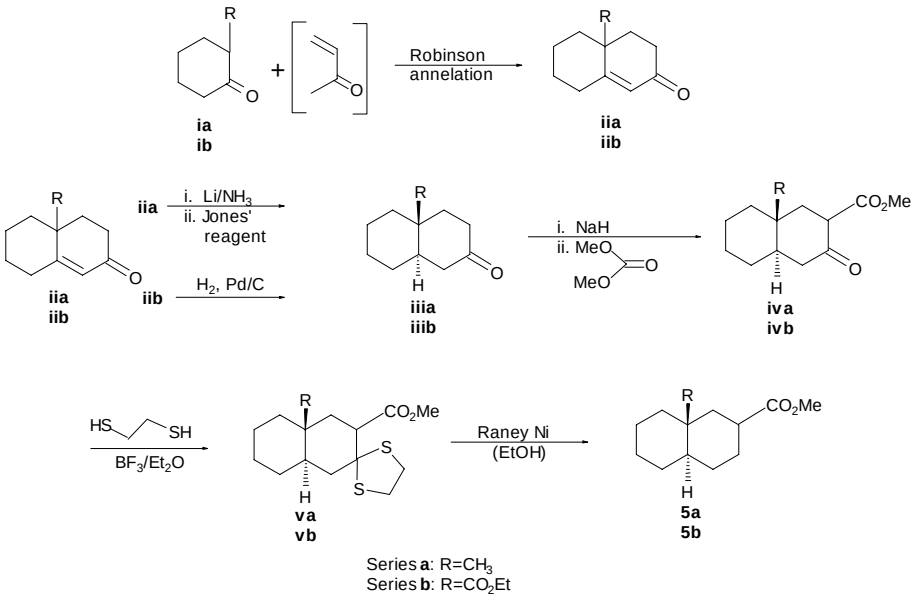
i. 'AIMIL' vapour phase chromatograph with a flame ionisation detector.

ii. Nitrogen as carrier gas; flow pressure 1.2kg/cm^2.

iii. Column: 2mx3.2 mm, packed with 10% Carbowax 20M on Chromosorb W.

iv. Temperatures: Oven 210°; Injector 170°; Detector 200°.

The bicyclic esters **5a** and **5b**, the subjects of the present investigations, were synthesized following the sequence of **Scheme I**:



Scheme I

Methyl 9-methyl-*trans*-decalin-2-carboxylate 5a

a) **2-Methylcyclohexanone ia**. Freshly distilled *o*-cresol (laboratory grade certified free from the *p*-isomer; 214 g), dissolved in dry methanol (300 mL) was hydrogenated over W-2 Raney nickel (10 g) at 180° C in a high pressure hydrogenation apparatus at a pressure of 200 atm.[21] After filtering off the catalyst at the end of uptake of hydrogen, the solution was concentrated and the residue distilled. The resulting colourless mixture of stereoisomeric 2-methylcyclohexanols (200 g) had b.p. 158-61° C (Lit.[22] 2-methyl-cyclohexanol *cis* 165° C; *trans* 166.5° C)

A solution of potassium dichromate (60.8 g) in diluted sulphuric acid (66 mL in 360 mL water) was added to a stirred suspension of 2-methylcyclohexanol (63 g) in water (70 mL) at such a rate that the temperature of the reaction mixture did not rise above 40 °C.[23] The reaction mixture was stirred thereafter for 2 hr., cooled and extracted several times with ether. The combined extracts were washed free from acid with water, dried and concentrated. The residue, on distillation, furnished 2-methylcyclohexanone (51 g); b.p. 72-76° C/27 mm, taken up for the next step of Robinson annelation.

b) **10-Methyl-1(9)-octal-2-one iia**: To a mixture of 2-methylcyclohexanone (50.7 g) and 1-*N*,*N*-diethylaminobutan-3-one (25 g) containing hydroquinone (50 mg) placed in a 3-neck flask provided with an oil bath and a mechanical stirrer was added sodium metal (1.4 g) in small pieces.[24] After the sodium had dissolved, the temperature of the bath was raised slowly (to ~150° C; 5 hr) until the reaction mixture began to reflux steadily while being stirred. It was then allowed to cool overnight, neutralized (10% HCl) and extracted with ether. The ether layer was washed with water, dried and concentrated. The dark brown liquid residue was fractionally distilled, first at 24 mm to recover left over 2-methylcyclohexanone (33 g). The pressure was then lowered (3 mm) to distil out the formed octalone **iia** (10 g); colourless. liquid; b.p. 115-25° C /3 mm (Lit.[25] b.p. 139° C/15 mm). IR: ν_{max} 1670 (α,β-unsatd. C=O), 1630 cm^{-1}; UV (EtOH): λ_{max} 241 mμ (ε 14,100); ^{1}H NMR (60 MHz, $CC1_4$): δ 1.27 (*s*, 3H, C-C*H*$_3$), 1.3-2.8 (*m*, 12H, ring *H*'s) and 5.63 (*s*, 1H, vinylic *H*) ppm.

c) **10-Methyl-*trans*-decal-2-one iiia**. A solution of octalone **iia** (8.47 g; 0.052 mole) in ether (70 mL) was added to a solution of lithium (1.5 g; 0.216 g.a.) in liquid ammonia (400 mL) during 5 min. The mixture was stirred for 30 min and solid ammonium chloride was added slowly until the blue colour of the solution was discharged.[26] Ammonia was allowed to evaporate off (under exhaust) and the residue was rendered acidic by cautious addition of 2% HCl. Extraction with ether and its removal yielded 10-methyl-*trans*-decal-2-ol as a viscous oil, taken for the next step of oxidation without further purification.

A suspension of the oil (8 g) in water, cooled to 0° C, was oxidized by dropwise addition of 8*N* chromic acid (chromium trioxide 5.4 g in dil. H_2SO_4 4.5 mL in H_2O 20 mL) over 15 min. Excess oxidant remaining over was destroyed by adding isopropanol. Usual work-up yielded the *trans* decalone **iiia** as a colourless oil (6.2 g); bath temp. 95-97° C/1 mm. ^{1}H NMR (60 MHz, $CC1_4$): δ 1.0 (*s*, 3H, C-*CH*$_3$) and 0.8-2.6 (***m*,** 15H, ring *H*'s) ppm.

d) **3-Methoxycarbonyl-10-methyl-*trans*-decal-2-one iva**. Sodium hydride (50% mineral oil mull; 10 g), washed thrice with dry benzene, was suspended in the same solvent (50 mL). The reaction vessel was flushed with dry nitrogen and dimethyl carbonate (5 mL) in dry benzene (5 mL) was run in, followed by a solution of decalone **iiia** (5 g) in dry benzene (10 mL).[27] At the end of 45 hr of heating under reflux the mixture was cooled externally with ice and treated cautiously with acetic acid (10 mL) followed by sufficient ice-water to dissolve the solid material. The organic layer was separated and the aqueous layer was extracted twice with ether. The combined extracts were washed with water, dried and concentrated. The crude product (6 g) was adsorbed on a column of silica gel (175 g.) and eluted with hexane followed by 5% ether in hexane. The β-ketoester **iva** (4 g) was obtained as a colourless, highly refractory liquid on short-path distillation; bath temp 105° C/4 mm; positive to alcoholic $FeCl_3$ test (purple). IR: ν_{max} 3300 (enolic OH), 1720 (CO), 1660, 1620 (enolic) cm^{-1}; ^1H NMR (60 MHz, $CC1_4$): δ 0.8 (*s*, 3H, C-C*H*$_3$), 0.9-2,2 (*m*, 3H, ring *H*'s), 3.68 (*s*, 3H. CO_2CH_3) and 12.19 (*s*, 1H, enolic *H*) ppm.

e) **10-Methyl-3-methoxycarbonyl-2,2-ethylenedithio-*trans*-decalin va**. Freshly distilled BF_3 etherate (b. p. 124 °C; 4 mL) was added with stirring to a mixture of the β-ketoester **iva** (4 g) and ethanedithiol (4 mL). The reaction mixture was let stand at room temperature for 3 days protected from moisture. A saturated solution of sodium chloride (50 mL) was added and the mixture extracted with ether. The ether extract was washed with an ice-cold solution of potassium hydroxide (3%) followed by water. The residue obtained on concentration of the extract was dried and cleaned up by PLC. Thioketal **va** was obtained as a colourless crystalline solid; m.p. 78-79 °C. IR (crystalline matrix): ν_{max} 1730 (CO_2Me), 665 and 690 (C-S stretching) cm^{-1}; ^1H NMR (60 MHz, $CC1_4$): δ 0.9 (*s*, 3H, C-C*H*$_3$), 1.0 – 3.1 (*m*, 14H, ring *H*'s), 3.2 (*s*, 4H, -SC*H*$_2$C*H*$_2$S-) and 3.6 (*s*, 3H, CO_2CH_3) ppm.

f) **Methyl 9-methyl-*trans*-decalin-2-carboxylate 5a**. W-2 Raney nickel (30 g) was suspended in a solution of the thioketal (**va**; 5 g) in absolute ethanol (200 mL) and the mixture was heated under reflux for 36 hr.[28] and the catalyst was filtered off. The filtrate, on concentration, yielded the decarbonylated ester **5a** (4 g); bath temp. 121° C/2 mm. IR (liquid film): ν_{max} 1710 (C=O), 1425, 1360, 1240, 1165, 1010 and 740 cm^{-1}; ^1H NMR (270 MHz, $CDC1_3$): δ 0.85 (*s*, 3H, C_9 –CH_3), 1.07-2.60(*m*, ring H's) and 3.65 (*s*, 3H, CO_2CH_3) ppm. (Anal. Found: C, 74.03; H, 10.50. $C_{13}H_{22}O_2$ requires C, 74.28; H, 10.48%)

Methyl 9-ethoxycarbonyl-*trans*-decalin-2-carboxylate 5b.

Procedures closely resembling those just described for the preparation of **5a** were followed for the preparing the *trans* decalin diester **5b** starting from 2-ethoxycarbonyl-cyclohexanone.

a) **10-Ethoxycarbonyl-1(9)-octal-2-one iib**. A solution of 2-ethoxycarbonyl-cyclohexanone (29 g; 0.17 mol.)[29] in dry ethanol (100 mL) was added with stirring to a solution of sodium ethoxide (prepared from 4.6 g Na; 0.2 m in dry ethanol 100 mL). The solution of the sodium enolate, thus prepared, was cooled in ice and the methiodide prepared from N,N-diethylaminobutan-3-one (25 g) and

methyl iodide (23 g) in ethanol (100 mL) was added slowly while the mixture was being stirred.[30] After letting stand for 12 hr at rt, the mixture was heated under reflux for 4 hr and allowed to cool down. The pH was adjusted to 7 by adding acetic acid (40 mL in water 100 mL) and the organics were extracted with ether after adding more water (*ca* 300 mL). The ether extracts were washed successively with 10% sodium carbonate solution and water, dried and concentrated. Octalone **iib** (20 g) was obtained as a colourless liquid; b.p. 145° C/2 mm. IR: ν_{max} 1710 (CO_2Et), 1680 (α,β-unsatd. C=O), 1630 (C=C) cm^{-1}; UV (EtOH): λ_{max} 239 mμ (ε 13,900); ^1H NMR (60 MHz, $CC1_4$): δ 1.28 (*t*, 3H, OCH_2CH_3), 1.30-2.67 (*m*, ring *H*'s), 4.2 (*q*, 2H, OCH_2CH_3) and 5.75 (*s*, 1H, vinylic *H*) ppm.

b) **10-Ethoxycarbonyl-*trans*-2-decalone iiib**. Unsaturated ketoester **iib** (5 g) was hydrogenated over 5% Pd/C (600 mg) in dry ethanol (60 mL) containing suspended calcium carbonate (1 g).[31] Decalone ester **iiib** was obtained as a colourless oil (560 mg); bath temp 118° C/1 mm. IR: ν_{max} 1705, 1455, 1205, 1150 and 1035 cm^{-1}; ^1H NMR (60 MHz, $CC1_4$): δ 1.30 (*t*, 3H, OCH_2CH_3), 1.0-3.0 (*m*, ring H's) and 4.17 (*q*, 2H, OCH_2CH_3) ppm.

c) **3-Methoxycarbonyl-10-ethoxycarbonyl-*trans*-2-decalone ivb**. To a stirred suspension of sodium hydride (50% mineral oil mull; washed thrice with dry benzene, 4 g) in dry benzene (40 mL) was added a solution of dimethyl carbonate (10 mL) in benzene (10 mL) after flushing the reaction vessel with dry nitrogen. The contents of the flask were heated to 70° C and decalone **iiib** (7 g), dissolved in benzene (25 mL), was added during 30 min. After heating under reflux for 2 hr the reaction mixture was cooled and cold dil. acetic acid was added to destroy any remaining sodium hydride. Cold water added to dissolve the suspended solids, the organic layer extracted with ether, the extracts washed with water, dried and concentrated. The residue (4.5 g) was cleaned up by column chromatography over silica-gel by successive elution with hexane and 5% ether in hexane. The combined main fractions, on concentration, gave β-ketoester **ivb** as a colourless oil. IR: ν_{max} 3400 (enolic OH)**,** 1730 (C=O), 1670, 1625 (enolic) cm^{-1}; ^1H NMR (60 MHz, $CC1_4$): δ 1.20 (*t*, 3H, OCH_2CH_3), 1.0-3.0 (*m*, ring *H*'s), 3.76 (*s*, 3H, CO_2Me), 4.13 (*q*, 2H, OCH_2CH_3) and 12.1 (*b*, enolic *H*) ppm.

d) **10-Ethoxycarbonyl-3-methoxycarbonyl-2,2-ethylenedithio-*trans*-decalin vb**. Thioketalisation of decalone diester **ivb** was carried out with ethanedithiol and BF_3 etherate following the procedure described for **iva**. Thioketal **vb** was obtained as a colourless viscous liquid; bath temp. 230° C/2 mm. IR (liquid film): ν_{max} 1720 (C=0), 1430, 1190, 1015 and 1750 cm^{-1}; ^1H NMR (60 MHz, $CC1_4$): δ 1.27 (*t*, 3H, OCH_2CH_3), 1.0-2.8 (*m*, ring *H*'s), 3.27 (*s*, 4H, $-SCH_2CH_2S-$), 3.63 (*s*, 3H, CO_2CH_3) and 4.17 (*q*, 2H, OCH_2CH_3) ppm. (Anal. Found: C, 57.15; H, 7.554. $C_{17}H_{26}0_4S_2$ requires C, 56.98; H, 7.26%).

e) **Methyl 9-ethoxycarbonyl-*trans*-decalin-2-carboxylate 5b**. The decalin diester **5b** (3 g) was obtained on desulphurisation of thioketal **vb** (4 g) in the manner already described for **5a**.; bath temp. 135-37° C/3 mm. IR: ν_{max} 1710, 1425, 1360, 1170, 1010, 950, 830 and 755 cm^{-1}; ^1H NMR (270 MHz,

$CDC1_3$): δ 1.262 (*t*, 3H, OCH_2CH_3), 1.147-2.338 (*m*, ring *H*'s), 3.653 (*s*, 3H, CO_2CH_3) and 4.152 (*q*, 2H, OCH_2CH_3) ppm. (Anal. Found: C, 67.26; H, 9.198. $C_{15}H_{24}0_4$ requires C, 67.16; H, 8.95%).

General procedure for the alkylation experiments

To a magnetically stirred solution of the substrate ester (100-300 mg) in dry ether or tetrahydrofuran (50-100 mL), taken in a reaction vessel through which a continuous stream of dry, oxygen-free nitrogen was being passed, was added dropwise a solution of tritylsodium in ether[32] from a pressure-equalised, graduated dropping funnel. Enough of the solution of known strength had previously been transferred into this dropping funnel by nitrogen pressure to constitute a 15% excess over 1:1 (substrate ester: tritylsodium) molar ratio. In all cases where enolate-formation was facile, the initial instantaneous decolourisation of the reagent slowed as the addition progressed but a definite point could usually be discerned after which one felt that no further decolourisation would occur. After letting stand for known periods after completing this addition (see text) a measured volume of 1:1 (v/v) solution of the alkylating agent (CH_3I, trimethyl phosphate or dimethyl sulphate) in ether, to constitute at least twice the molar equivalent, was added in one lot. The mixture was stirred for varying periods but not less than 5 hr and let stand overnight. Cold acidified water (*ca*. 200 mL containing 1 mL of conc. HCl) was then added and the ethereal layer containing the organics was separated, washed with sodium chloride solution and concentrated. The bulk of the aromatic hydrocarbons was separated by precipitation with methanol and filtering off over a Celite bed. The filtrate was concentrated and subjected to chromatographic analyses (TLC/column), as described.

In order to determine the ratio of isomeric alkylated products the NMR spectrum of the crude material was recorded prior to chromatographic separation but after the removal of aromatic hydrocarbons (see above). Assignments of the prominent resonances in the spectra of the crude materials were based on the described criteria.

Trial with methyl 9-methyl-*trans*-decalin-2-carboxylate 5a.

In behaviour reminiscent[1] of the triester **2C**, it was found that the red colour of the triphenylmethylsodium reagent was not being discharged at all on treating a solution of the bicyclic ester **5a** in ether with the reagent, in the manner described above. This was taken as clear indication that the enolate ion was not being formed at all from **5a**.

Trial with methyl 9-ethoxycarbonyl-*trans*-decalin-2-carboxylate 5b.

Rapid discharge of the triphenylmethylsodium colour was noted until addition of the reagent in slight excess of 1:1 molar ratio had been reached. At the end of ~ 10 min methyl iodide solution (in ether) was dropped in one lot. Work-up procedure led to the total recovery of the stating material.

The methylation trials were repeated twice, employing, first, trimethyl phosphate and, second, dimethyl sulphate as the methylating agents. In neither case could methylation be effected.

Preparation of the model systems 8 - 11

Dimethyl 5-methylcyclohex-l-ene-1,5-dicarboxylate 8.

Reduction of 4-methyl-2,4-dimethoxycarbonylcyclohexanone[33] with sodium borohydride in methanol medium furnished 2,4-dimethoxycarbonyl-4-methylcyclohexanol as a colourless viscous liquid; bath temp.132° C/2mm. [IR: ν_{max} 3500 (broad, OH), 1710 (C=O) cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 1.2 (*m*, 3H, C-*CH*$_3$'s), 1.0-3.0 (*m*, ring methylenes), 3.6 (*m*, 6H, CO_2CH_3's) and 5.6 (broad, OH) ppm. (Anal. Found: C, 57.89; H, 7.504. $C_{ll}H_{18}O_5$ requires C, 57.40; H, 7.83%)] This hydroxy-diester was dehydrated with phosphorus oxychloride in the manner described earlier to obtain the ene-diester **8** as a colourless liquid. IR (liquid film): ν_{max} 1700, 1645cm^{-1}; UV (EtOH) λ_{max}: 219 mμ (ε 11,000); ^1H NMR (60 MHz, CCl_4): δ 1.2 (s, 3H, C-*CH*$_3$'s), 1.0-3.0 (*m*, ring *H*'s), 3.62(s, 3H, C_1-CO_2CH_3), 3.67 (*s*, 3H, C_3-CO_2CH_3) and 6.8 (broad signal, 1H, vinylic *H*) ppm.

Methyl 9-ethoxycarbonyl-*trans*-2-octalin-2-carboxylate 9.

Sodium borohydride (325 mg) was added to a solution of 10-ethoxycarbonyl-3-methoxycarbonyl-*trans*-decal-2-one (**ivb**; 1.6 g) in methanol (60 mL).[34] The mixture was allowed to stand at rt for 30 min and then heated under reflux on a water-bath for 3 hr. The organics that separated on removing the solvent under reduced pressure after rendering the residue acidic with ice-cold dilute hydrochloric acid were extracted with ether. Removal of the ether after washing with the extract with brine followed by drying gave the decalol 10-ethoxycarbonyl-3-methoxycarbonyl-*trans*-decal-2-ol (1.2 g) as a gummy product, cleaned up by TLC. IR: ν_{max} 3425 (broad, OH), 1720 (C=O), 1460, 1380, 1210 and 1030cm^{-1}; UV (EtOH): λ_{max} 217 mμ (ε 10,500); ^1H NMR (270 MHz, $CDC1_3$): δ 1.27 (*t*, 3H, OCH_2CH_3), 0.8-2.8 (*m*, ring methylene *H*'s), 3.7 (*s*, 3H, CO_2CH_3), 4.15 (*q*, 2H, OCH_2CH_3), and 4.8 (broad, 1H, O*H*) ppm. (Anal. Found: C, 63.49; H, 8.081. $C_{15}H_{24}0_5$ requires C, 63.39; H, 8.45%).

To a cooled stirred solution of this decalol (1.2 g) in dry pyridine (25 mL) was added dropwise phosphorus oxychloride (5 mL). Stirring was continued for 12 hr at rt. The mixture was then heated to 100° C at which temperature it was maintained for 45 min. After cooling, it was poured cautiously onto crushed ice containing sulphuric acid (10 mL) and extracted thrice with ether. The ethereal extracts were combined, dried and concentrated to obtain the unsaturated diester **9** (0.7 g) as a light yellow oil. IR: ν_{max} 1720 (C=O), 1645 (C=C), 1445, 1370, 1255, 1190, 1125, 1060, 1020 and 725 cm^{-1}; ^1H NMR (270 MHz, $CDC1_3$): δ 1.198 (t, 3H, OCH_2CH_3), 1.256-3.661 (m, ring *H*'s), 3.719 (s, 3H, CO_2CH_3), 4.08 (2H, AB pattern for OCH_2CH_3 $\Delta\nu_{AB}$ = 9.249 Hz) and 6.976 (m, 1H, vinylic *H*) ppm. (Anal. Found: C, 67.30; H, 8.352. $C_{15}H_{22}O_4$ requires C, 67.67; H, 8.27%.

Isomeric diethyl 1-methylcyclohexane-1,3-dicarboxylates 10.

A solution of 2-methyl-2,6-diethoxycarbonylcyclohexanone[35] (3.5g) in dry ethanol (150mL) was saturated with dry hydrogen chloride and pieces of freshly prepared zinc amalgam (15g) were added over a period of 1 hr while the mixture was externally cooled with an ice-bath. It was then brought to rt and heated under reflux for 6 hr. Most of the alcohol was then distilled off and the residue was diluted with water and extracted with ether. The ether layer was washed with sodium carbonate solu-

tion, dried and concentrated. Diethyl 1-methylcyclohexane-1,3-dicarboxylate **10** (3g), thus obtained as a colourless oil on short-path distillation, was shown by GLC test to consist of an estimated 1:4 mixture of *cis* and *trans* isomers. ^{1}H NMR (270 MHz, $CDC1_3$): δ 1.25-1.35 (overlapping *t*'s, OCH_2CH_3's), 1.34 (singlet and shoulder, C-CH_3's) 1.20-2.2 (m, ring *H*'s), 2.3 (br, C-3 *H*), 3.6-4.6 (overlapping AB patterns for OCH_2CH_3) ppm, consistent with mixture of *cis* and *trans* isomers of diester **10**.

Isomeric dimethyl 1-methylcyclohexane-1,2-dicarboxylates 11.

A solution of lithium metal (0.5 g) in liquid ammonia (150 mL) was treated with a solution of 3-methylcyclohex-1-ene-2,3-dicarboxylic acid[36] (1 g) in THF (20 mL). The resulting blue solution was stirred for 1 hr and solid ammonium chloride was added as the protonating agent. After letting the ammonia evaporate (under a hood provided with an exhaust system) the residue was taken up in ethyl acetate after acidification. The extract was dried and the solvent distilled off. Esterification with diazomethane of the crystalline residue gave a 2:9 mixture of *cis*- and *trans*-dimethyl 1-methylcyclohexane-1,2-dicarboxylates **11** (GLC test and NMR); bath temp. 90°C/2mm. IR (liquid film)**:** ν_{max} 1725, 1435, 1180, 1010, 880 and 745 cm^{-1}; NMR (60MHz, CCl_4): δ 1.15 and 1.22 (*s*, 3H, C-CH_3 of *cis* and *trans* isomers), 1.0-3.0 (*m*, ring *H*'s) and 3.53, 3.57 and 3.60 (*s*, 6H, CO_2CH_3 of *cis* and *trans* isomers) ppm.

Methylation trials

Formation of the corresponding enolate ions was facile in the following three cases (compounds **8** - **10**) as indicated by the rapid discharge of the Ph_3CNa colour until the end point had been passed. Quenching of the enolate with methyl iodide within about 10 min of its formation resulted in methylation, as described below.

Isomeric dimethyl 3,5-dimethylcyclohex-l-ene-3,5-dicarboxylates 13. TLC could not resolve this mixture, from the alkylation experiments with the unsaturated diester **8**, into the individual isomers. IR and NMR spectra were recorded for the mixture. Though ^{1}H NMR spectroscopy failed resolve the individual methyl singlets expected of a spectrum of a mixture of the isomeric diesters **13** comparison with the NMR spectrum of the starting diester **8** clearly indicated that methylation had indeed taken place by the appearance of a new 3H (methyl) singlet shifted downfield. IR: ν_{max} 1725, 1425, 1190, 1125, 980 and 695 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4): δ 1.18 and 1.22 (*s*'s, 3H & 3H, C-CH_3's), 0.73-3.13 (*m*, ring CH_2's), 3.5 and 3.57 (*s*'s, 3H & 3H, CO_2CH_3's) and 5.6 (broad *s*, 2H, vinylic *H*'s) ppm.

Isomeric methyl 3-methyl-10-ethoxycarbonyl-*trans*-l-octalin-3-carboxylates 14.

The product mixture from the methylation of methyl 9-ethoxycarbonyl-*trans*-2-octalin-2-carboxylate **9** could not be clearly resolved into its components by the TLC methods tried. The NMR spectrum of the cleaned up mixture showed two singlets in the C-CH_3 region, two singlets assignable to the CO_2CH_3 groups in addition to the $CO_2CH_2CH_3$ quartets in the *O*-methylene region. Individual

assignments of these peaks to the α- and β-isomers of **14** were not made. The vinylic region, while showing evidence for the formation of the methylated and concomitantly deconjugated product (two broadened resonances at δ 5.64 and 5.68), showed also the presence of unsaturated as well as un-methylated, deconjugated materials.

Isomeric diethyl 1,3-dimethylcyclohexane-1,3-dicarboxylates 15. VPC analysis of the mixture of isomers from the methylation of diester **10** disclosed the presence of two major components formed in an approximate 1:1 ratio, identified as *cis* and *trans* diethyl 1,3-dimethylcyclohexane-1,3-dicarboxylates **15** by comparison with authentic samples prepared in these Laboratories earlier through an alternative procedure.[14] In a second attempt using trimethyl phosphate as the alkylating agent, no alkyated product was detected but VPC analysis showed a change in the *cis*:*trans* isomer ratio from ~1:4 in the starting sample **10** to ~1:5 in the recovered material.

Attempt to methylate isomeric dimethyl 1-methylcyclohexane-1,2-dicarboxylates 11. It was clear that an enolate ion was not being formed from the 1,2-diester **11** from the absence of any discharge of the triphenylmethylsodium colour.

Attempt to α-methylate methyl 9-ethoxycarbonyl-*trans*-decalin-2-carboxylate 5b in the presence of coordinating agents. Assuming that, in the experiments conducted thus far, the methylating agents were failing to displace the counter ion from coordination with the 1,3-enolate derived from **5b**, a solution of the Na^+-specific crown ether 15-crown-5 in anhydrous ether was added to the reaction mixture in one experiment prior to the addition of the methylating agent. This attempt also failed to generate any methylated product.

In a final effort, tritylsodium was added to a solution of the ester in HMPT (25mL/100.mg) till the red colour started to persist. Ether was distilled off from the reaction mixture with the stream of nitrogen using a bath of warm water as the heat source. The alkylating agent (methyl iodide) was added after allowing the reaction mixture to cool down. The reaction mixture was worked up at the end of 5 hr. A ^1H NMR spectrum of the preliminarily cleaned up product showed evidence that the bicyclic 1,3-diester had indeed undergone methylation, the attempt to trap the counter ion having proved successful.

It was found possible to separate the α- and β-methylated products, found formed in the approximate ratio 2:3, by TLC (EtOAc-Hexane 5:95). Anal. (of isomer mixture): Found: C, 68.42; H,9.303. $C_{16}H_{26}0_4$ requires, C, 68.05; H, 9.28%.

α-Isomer (**6b α**): IR: ν_{max} 1725, 1450, 1365, 1155 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.111 (s, 3H, C-*CH_3*), 1.262 (t, 3H, OCH_2*CH_3*), 0.879-2.595 (m, ring methylenes), 3.595 (s, 3H, CO_2*CH_3*) and 3.902-4.190 (2H, AB pattern for O*CH_2*CH_3, J_{AB} = 10.93 Hz, Δν = 44.20 Hz) ppm.

β-Isomer (**6b β**): IR: ν_{max} 1725, 1465, 1375, 1130 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.122 (s, 3H, C-*CH_3*), 1.267 (t, 3H, OCH_2*CH_3*), 0.896-2.310 (m, ring methylenes), 3.657 (s, 3H, CO_2O*CH_3*) and 4.015-4.177 (2H, AB pattern for O*CH_2*CH_3, J_{AB} = 10.93 Hz, Δν = 15.13 Hz) ppm.

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[5] Though not strictly relevant to what may happen in solution phases, it is necessary to point out that computations employing powerful theoretical methods and mass spectrometry-based experimental determinations have yielded "vacuum phase" values of binding energies of Na^+ complexes. These values provide a basis for setting up a scale of affinities of Na^+ for small molecules [Hoyau S, Norrman K, McMahon T B & Ohanessian G, *J Am Chem Soc*, 121, **1999**, 8864.] Even though the "vacuum stability" of the bidentate Na^+-Type **A** enolate can be expected, naturally, to be much higher than the Na^+-Type **C** enolate, the situation in the solution phase could be entirely different for reasons set down in footnote 7 whereby Na^+-Type **C** enolate predominates in the equilibrium with Na^+-Type **A** enolate.

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