Proc. Indian Acad. Sci. (Chem. Sci.), Vol. 100, Nos 2 & 3, April 1988, pp. 235–252.

Carbon-carbon bond formation and annulation reactions using trimethyl and triethyl orthoformates

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Abstract. Synthetic utility of trimethyl and triethyl orthoformates for carbon-carbon bond formation is briefly surveyed, particularly in relation to dialkoxymethylation, carbonyl transposition-homologation, and cycloalkenone annulation reactions recently reported from the authors' and other laboratories. The complex mechanisms involved in the one-step and two-step annulations of rigid β, γ- and γ, δ-unsaturated ketones have been discussed.

Keywords. Trimethyl orthoformate; triethyl orthoformate; cyclopentenone and cyclohexenone annulations; carbonyl transposition and homologation; bridged bicyclo [3.3.1] nonanes; intramolecular hydride transfer; polycyclic synthesis.

1. Introduction

The carbon-oxygen bond formation involving orthoesters, such as trimethyl-or triethyl orthoformate with aldehydes and ketones is a well-established reaction (Fieser and Fieser 1967). On the other hand, carbon-carbon bond formation reactions with orthoesters have not been adequately explored. However, the synthetic potential of these reactions cannot be ignored. Even ring annulation can be achieved in specially designed substrates under proper reaction conditions. In general, carbon-carbon bonds are formed by the reaction of orthoesters with compounds having active methylene or methyl groups, diazoketones and diazo esters, and by electrophilic addition and substitution reactions of dialkoxy carbonium ions derived from orthoesters under the influence of Lewis acids (Dewelfe 1970; Perst 1971), with suitable substrates.

2. Reactions of orthoesters with activated methylene or methyl groups

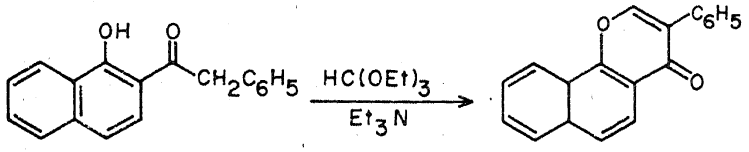
Compounds having active methylene groups like acetyl acetone, ethyl acetoacetate and diethylmalonate react with triethyl orthoformate in presence of acetic anhydride to form ethoxymethylene derivatives (Claisen 1893),

$$XYCH_2 + HC(OEt)_3 + 2(CH_3CO)_2O \rightarrow XYC = CH(OEt) + 2CH_3CO_2H + 2CH_3CO_2Et \quad (1)$$

$X = Y = COCH_3$; $X = COCH_3$, $Y = CO_2Et$; $X = Y = CO_2Et$.

*For correspondence

One of the successful applications of this reaction is found in the synthesis of chromone (2) (Sathe *et al* 1949) by the reaction of the hydroxy ketone (1) with triethyl orthoformate in presence of triethylamine.



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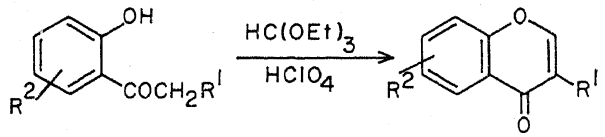
More recently, chromones (4) have also been synthesised in high yields in perchloric acid catalysed reactions of *o*-hydroxy aromatic acyl ketones (3) with triethyl orthoformate (Dorofeenko and Mezheritskii 1968; Dorofeenko and Tkachenko 1972; and Becket *et al* 1978).



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The application of the reaction of diazoketones or ethyl diazo-acetate with trialkyl orthocarboxylates in presence of borontrifluoride etherate to form an alkoxyacetal (2) (Schonberg and Praefeke 1964, 1966; Schonberg *et al* 1966) has remained practically unexplored.

$$RCOCHN_2 + R^1C(OR^2)_3 \xrightarrow[-N_2]{BF_3.Et_2O} RCO-\underset{\displaystyle CR^1(OR^2)_2}{\overset{\displaystyle |}{CH(OR^2)}} \qquad (2)$$

3. Electrophilic substitution with orthoesters

3.1 *Reaction of orthoesters with acetylenes.*

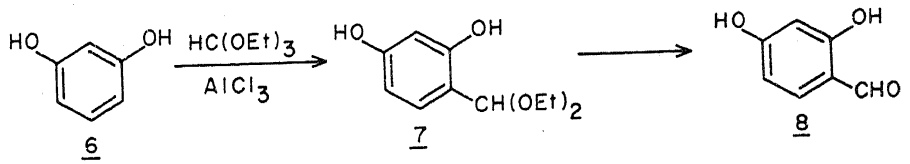
According to Howk and Sauer (1958, 1963), the terminal alkynes react with triethyl orthocarboxylates in presence of Lewis acids such as zinc chloride, zinc iodide, cadmium chloride, magnesium chloride or mercuric bromide to form acetylenic acetals, ketals and orthoesters are illustrated by the preparation of phenyl propargyl aldehyde (5).

$$C_6H_5C{\equiv}CH + HC(OEt)_3 \xrightarrow[-C_2H_5OH]{ZnI_2} \underset{\displaystyle \downarrow H_3O^+}{\overset{\displaystyle C_6H_5C{\equiv}C-CH(OEt)_2}{}} \underset{\displaystyle \underline{5}}{\overset{\displaystyle C_6H_5.C{\equiv}C-CHO}{}}$$

The carbon-carbon bond-forming step in this reaction probably initiates through an attack by a dialkoxy carbonium ion on the triple bond of the acetylene, and is thus an electrophilic substitution reaction.

3.2 *Aromatic substitution with orthoesters*

Phenols and aromatic tertiary amines react with triethyl orthoformate in the presence of Lewis acids to form substituted benzaldehyde diethyl acetals through electrophilic attack by the diethoxy carbonium ion on an activated position of the aromatic ring. A number of phenols were converted to substituted *o*- and *p*-hydroxy benzaldehydes in 40–96% yields with triethyl orthoformate and aluminium chloride in dichloromethane (Gross *et al* 1963) e.g. resorcinal (6) produces 2,4-dihydroxy benzaldehyde (8) after hydrolysis of the intermediate



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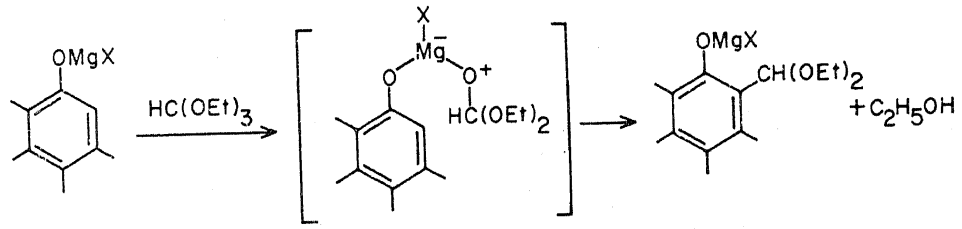
diethyl acetal (7). Phenols with electron withdrawing substituents are relatively unreactive or do not react at all.

Aryloxy magnesium halides having an unsubstituted ortho position react with triethyl orthoformate to yield, after hydrolysis, *o*-hydroxy aromatic aldehydes with no detectable amount of the *p*-hydroxy isomers (Casnati *et al* 1965). The reaction is sensitive to the electronic and steric properties of substituents on the aromatic ring of the phenol. The specifity observed in this reaction suggests that it involves electrophilic attack on the ortho position of the phenol by the acyl carbon of an orthoformate molecule in an aryloxy magnesium halide-orthoformate complex (9) or by a diethoxy carbonium ion of an ion-pair derived from such a complex.



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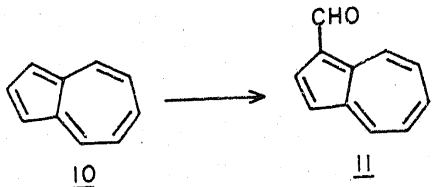
An application of this type of reaction is found in the conversion of azulene (10) to azulene aldehyde (Treibe 1967; Kirby and Raid 1961; Hafner *et al* 1961).



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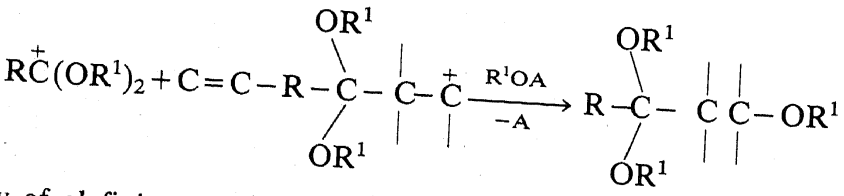
4. Addition of orthoesters to double bonds

The orthoesters may add to double bonds in the presence of Lewis acids to form 1,1,3-trialkoxy derivatives (3). Probably, a dialkoxy carbonium ion is generated initially which then adds to double bond to form the final product.

$$RC(OR^1)_3 + A \rightarrow \overset{+}{R}C(OR^1)_2 + R^1OA[A=\text{Lewis acid}]$$

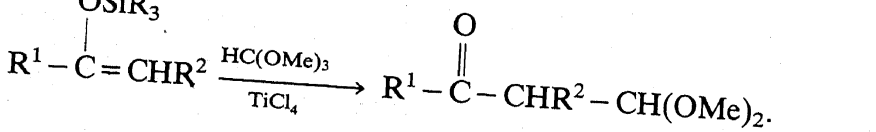


(3)

A variety of olefinic compounds such as ketenes, alkenes, cycloalkenes, enol ethers and enol acetates undergo Lewis-acid-catalysed addition (Perst 1971).

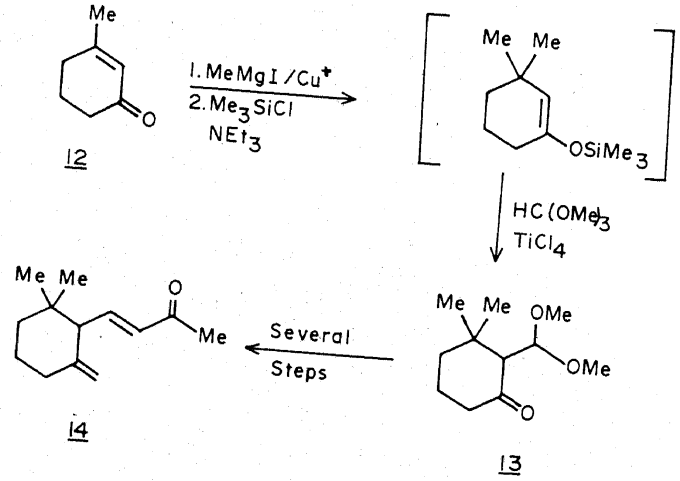
5. Alkylation of enolates with orthoformates

Mukaiyama and Hayashi (1974) have shown that silyl enol ether on reaction with trimethyl orthoformate in the presence of $TiCl_4$ produces the β-ketoacetal (4).

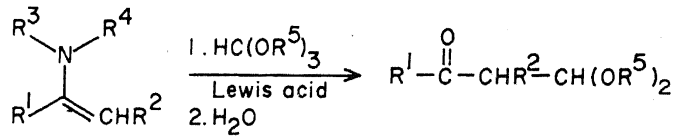


(4)

Exploiting this strategy a simple synthesis of γ-ionone (14) has been achieved from 3-methyl cyclohexenone (12), through the β-keto acetal (13).

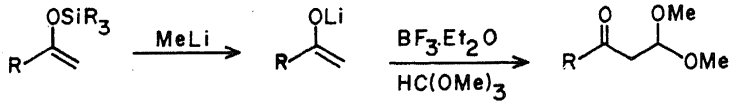


More recently this group has extended (Takazawa and Mukaiyama 1982) this reaction to achieve alkylation on enamines (5).



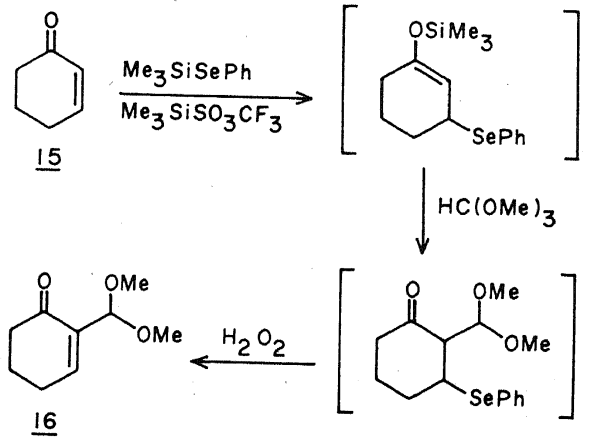
(5)

Suzuki *et al* (1982) have developed a similar route to β-keto acetals by regiospecific α-dialkoxymethylation of preformed enolates with trialkyl orthoformates in presence of Lewis acids, the enolates being generated by addition of methyl lithium to the corresponding silyl enol ethers (6).



(6)

Suzuki *et al* (1981) have also developed a sequence for the introduction of a dialkoxy alkyl group at the sp^2 hybridised α-position of α, β-unsaturated ketones as exemplified by the transformation of cyclohexenone (15) to 2-dimethoxymethyl-2-cyclohexen-1-one (16).



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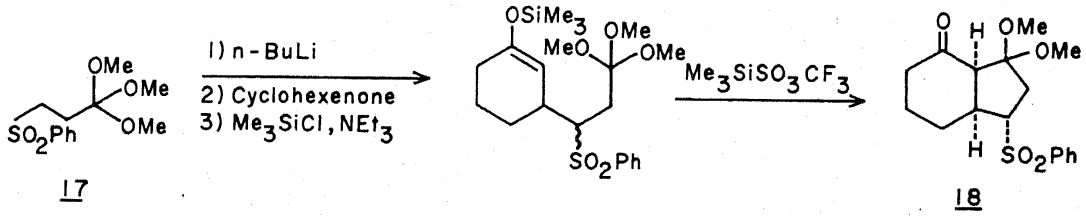
An intramolecular enolate alkylation with orthoformate (e.g. (17) → (18) has been developed by Lombert *et al* (1986) for cyclopentannulation to enones.



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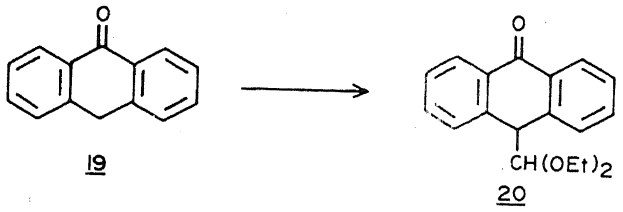
Recently, Miller (1981) has shown that anthrone (19) on refluxing with 10 molar excess of the orthoester in presence of sulphuric acid resulted in the formation of 10-(diethoxymethyl)-9-anthrone (20) in 65% yield.



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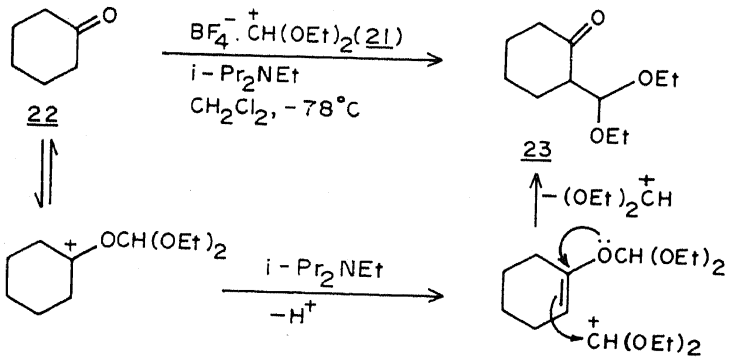
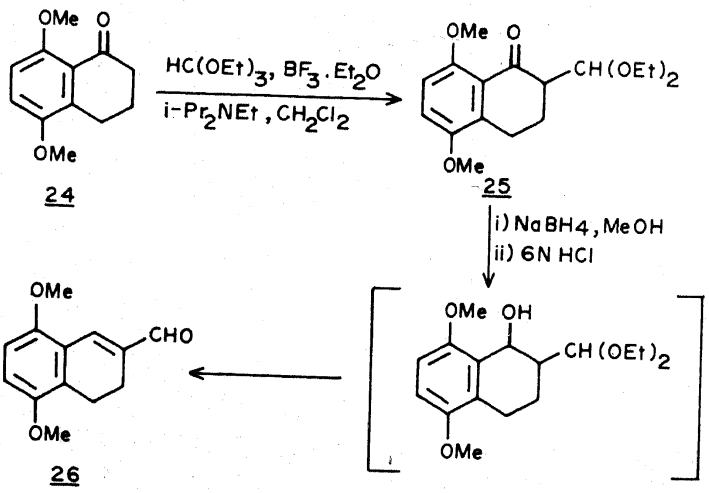
A reaction analogous to dialkoxyalkylation of enolates and enamines of ketones has been achieved by Mock and Tsou (1981) in a single step by reaction of aliphatic and aromatic ketones with diethoxy carbonium fluoroborate (21), generated *in situ*



from triethyl orthoformate and boron trifluoride etherate. For example, cyclohexanone (22) is transformed to the β-keto acetal (23) by reaction with (21) in the presence of N,N-diisopropylethylamine in methylene chloride at $-78°C$. The regioselectivity observed for unsymmetrically substituted ketones provides a clue to the mechanism for this reaction. The ketone is activated by some form of O-alkylation and is then deprotonated to an enol ether which subsequently yields the observed reaction products by electrophilic addition of diethoxy carbonium ion to the double bond.

Based on this one step α-dialkoxyalkylation of ketones, a simple synthesis of α,β-unsaturated aldehydes by 1,3-carbonyl transposition through one carbon



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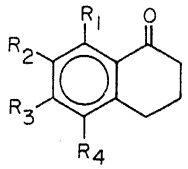
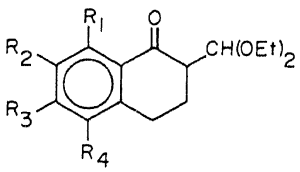
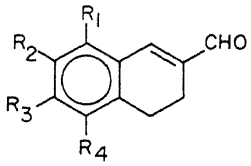
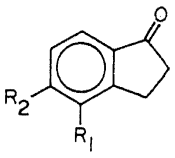
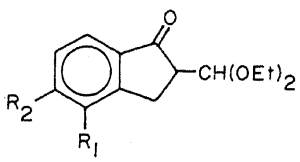
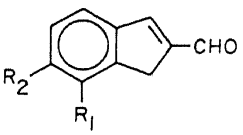
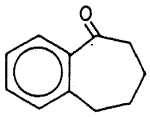
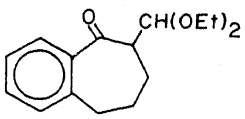
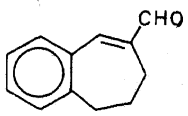
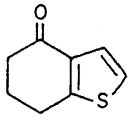
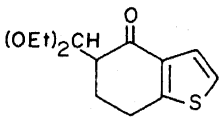
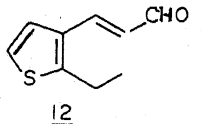
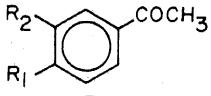
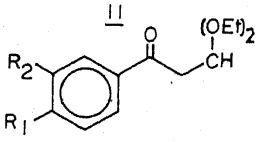
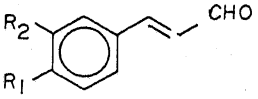
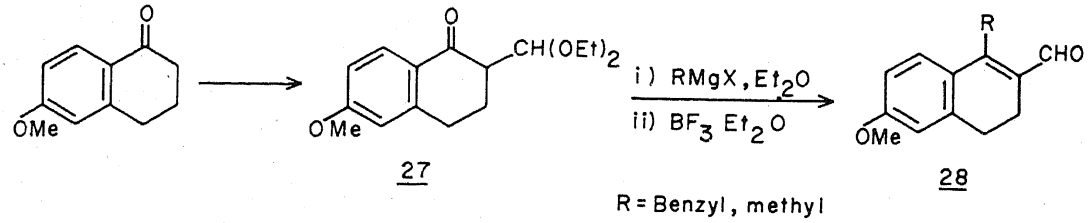
homologation has been achieved (table 1) from the authors' laboratory (Dasgupta and Ghatak 1985). A typical example is the conversion of the tetralone (24) via the β-ketoacetal (25) into the dihydronaphthaldehyde (26), a key intermediate in the synthesis of anthracyclines.

The synthesis of α,β-unsaturated aldehydes with an alkyl group at the β-position (28) has also been achieved (Chakraborti *et al* 1985a) from the reaction of β-keto acetal (27) with organometallics.

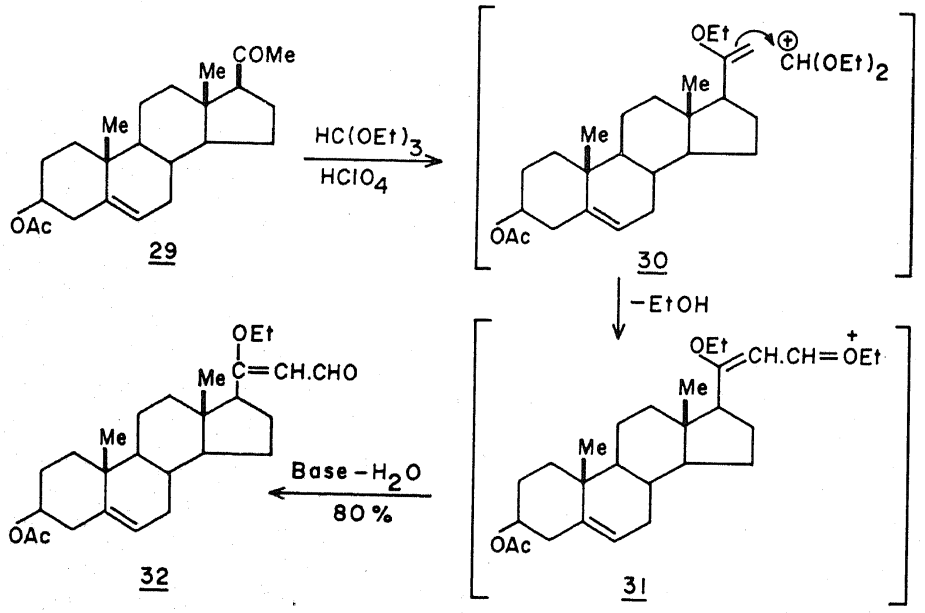
Table 1. Transformations of the ketones to α, β-unsaturated aldehydes.

Entry	Starting Ketone	β-Ketoacetal	α,β-Unsaturated Aldehyde	Yield (%)
	 1	 2	 3	
1		a, $R_1=R_2=R_3=R_4=H$		92
2		b, $R_1=R_2=R_4=H$, $R_3=OMe$		73
3		c, $R_1=R_3=R_4=H$, $R_2=OMe$		68
4		d, $R_2=R_3=H$, $R_1=R_4=OMe$		80
	 4	 5	 6	
5		a, $R_1=R_2=H$		50
6		b, $R_1=Me$, $R_2=H$		75
7		c, $R_1=OMe$, $R_2=H$		79
8		d, $R_1=H$, $R_2=OMe$		82
9	 7	 8	 9	
10	 10	 11	 12	
	 13	 14	 15	
11		a, $R_1=OMe$, $R_2=H$		62
12		b, $R_1=H$, $R_2=OMe$		67



6. Direct formylation of ketones

Dusza *et al* (1964) first developed a direct alkylation of steroid ketones using acid-catalysed reaction with orthoformates. Thus, in the presence of perchloric acid pregnenolone acetate (29) reacts with triethyl orthoformate to give the intermedi-

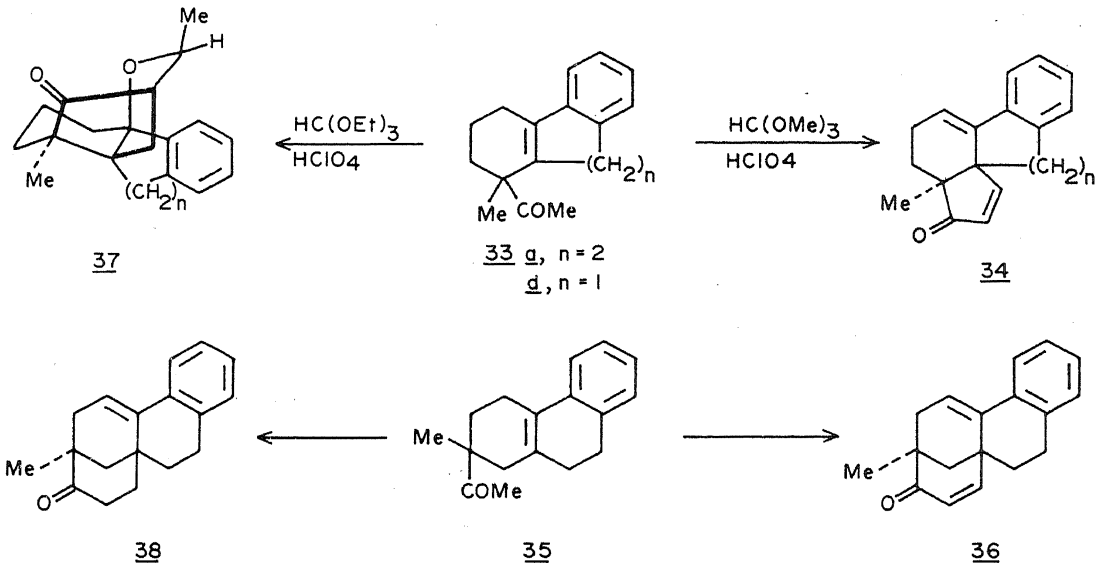


ate oxonium salt (30) which on hydrolysis produces the C-21 formyl derivative (32) in excellent yield. Presumably, the reaction involves the addition of diethoxycarbonium salt to the double bond of the intermediate enol ether (30).

The formyl derivative (32) has been utilised by Pettit *et al* (1970) for the synthesis of bufadienolides.

7. Ring annulations through orthoformates

A remarkable annulation reaction leading to cycloalkenones has been discovered by Ghatak *et al* (1980) involving a one-pot perchloric acid catalysed formylation-cyclisation reaction of rigid β,γ- and γ,δ-unsaturated methyl ketones. For example, when the β,γ-unsaturated methyl ketones (33a,d) are exposed to an excess of trimethyl orthoformate in the presence of perchloric acid, the tetracyclic ketones

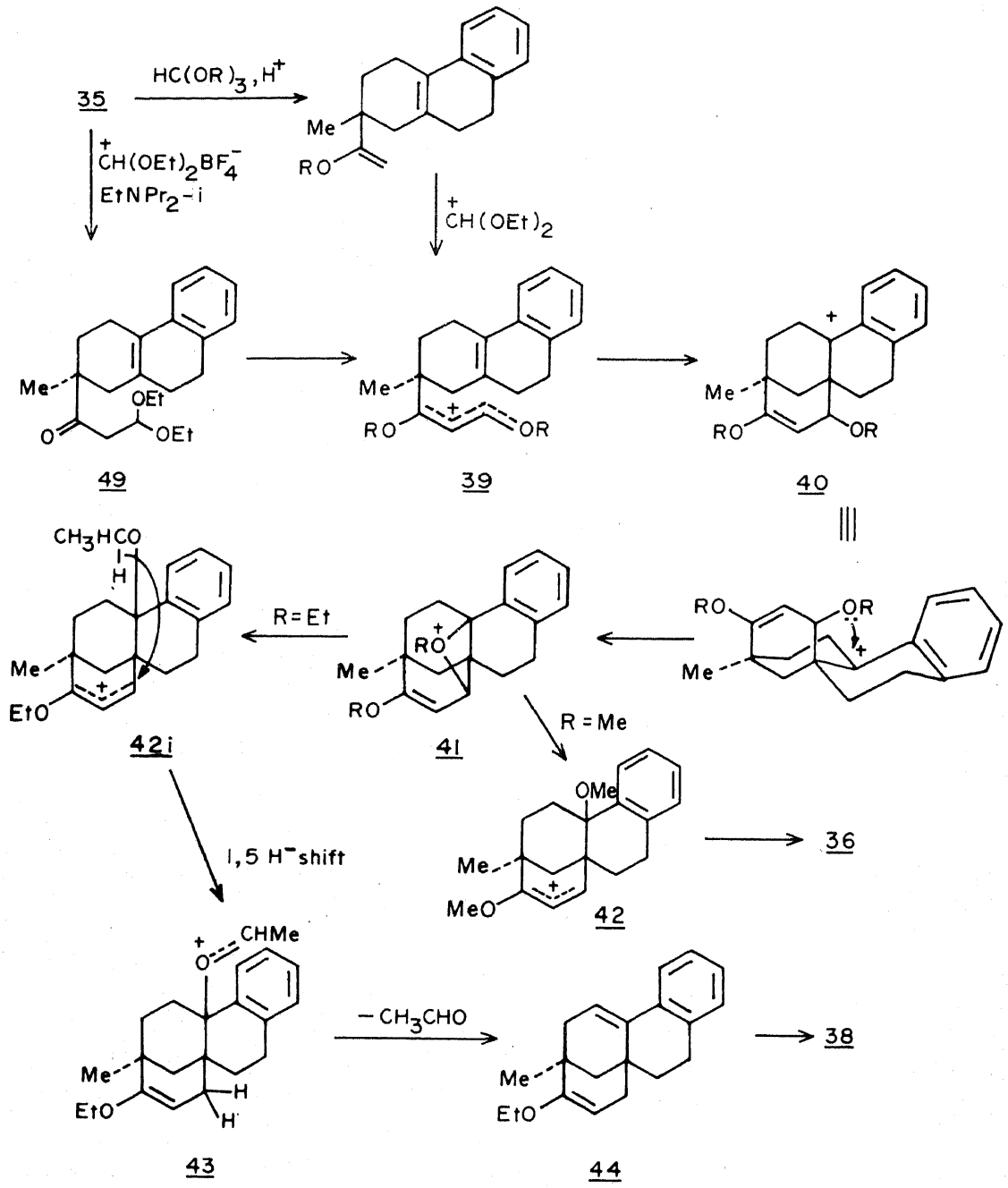


37 — 33 a, n = 2; d, n = 1 — 34

38 — 35 — 36

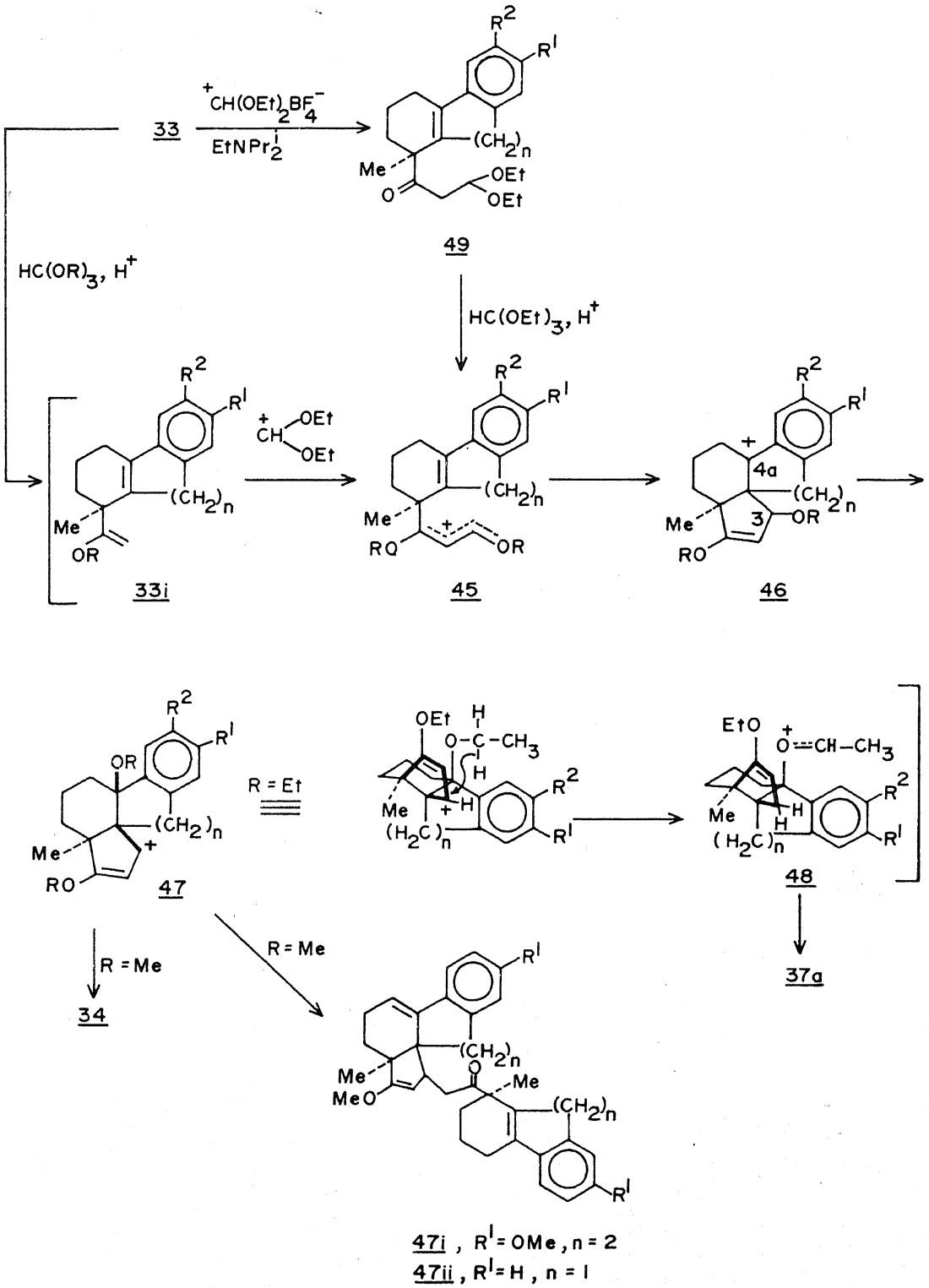
(34a,d) are formed, while the γ,δ-unsaturated methyl ketone (35) under identical conditions affords the bridged [3.3.1]nonadienone (36). Interesting results are obtained when the formylation-cyclisation processes are carried out with triethyl orthoformate acting as the ortho ester reagent. The β,γ-unsaturated methyl ketones (33a,d) afford the pentacyclic keto ethers (37a,d) and the γ,δ-one (35) produces the bridged [3.3.1]-nonenone (38). The incorporation of the ethoxy group in the products (37a,d) obtained from the methyl ketones (33a,d), and the formation of the ketone (38), the dihydroderivative of the conjugated ketone (36), obtained from (35) with triethyl orthoformate, suggests the involvement of an ethoxy group which through intramolecular donation of a hydride from its oxymethylene component, gives rise to the observed products. The greater stability of the resultant oxycarbonium ion $(R^1O–CHR)^+$ emanating from ethoxy group (R=Me) as compared to the one from the methoxy function (R=H) is the basis for the different reaction behavior of triethyl and trimethyl orthoesters. The following schemes represent a mechanistic portrayal of the proposed reaction pathways (schemes 1 and 2).

Initially, the dialkoxy allyl cations (39,45) are formed during formylation process which cyclise leading to γ-alkoxyallyl ether (40,46) whose spatial orientation places the saturated alkoxy group in close proximity to the benzyl cation centre, facilitating the intramolecular transfer of the alkoxy unit to the latter via an oxetane cation intermediate (e.g. 40 → 41 → 42 and 46 → 47). In the case of the trimethyl orthoformate reactions, the resultant benzyl methyl ethers e.g. (42) and (47) (R=Me), merely lose methanol and yield (36) and (34a). The benzyl ethyl ether intermediate e.g. (42i) and (47) (R=Et) in the triethyl orthoformate reaction undergo an intramolecular 1,5-hydride shift from the oxymethylene of the ethoxy group at the benzylic position to the ethoxyallyl cation resulting in (43,48). Loss of acetaldehyde from (43) finally furnishes the ketone (38). Instead of losing acetaldehyde, the carbocation in (48) interacts with the proximate enol ether furnishing the pyrano ketone (37a).



Scheme - I

The isolation of dimeric products (47i) and (47ii) (Ghosh 1978) in appreciable yield from the reaction of the respective methyl ketones (33b) and (33d) with excess of trimethyl orthoformate in presence of perchloric acid clearly suggests that the rate-determining step in the reaction is the intermolecular electrophilic reaction of the intermediate enol ether (33i) with dialkoxymethyl cation. The rapid subsequent cyclisation step, followed by alkoxy migration leading to the allylic cation (47), facilitates further reaction of the latter with the intermediate enol ethers (33i) which probably exist in sufficient concentration in the reaction mixture.



Scheme – 2

Direct evidence in support of the proposed mechanism is gained from the observation that the dialkoxyethyl ketone (49a) prepared from the methyl ketone (35a) by interaction with diethoxycarbonium fluoroborate, according to Mock and Tsou (1981), on cylisation with perchloric acid (70%) in benzene gives the dienone

(38a) in 87% yield (Dasgupta *et al* 1983; Chakraborti *et al* 1985). As expected, repeating the cyclisation of (49a) with an excess of ethyl orthoformate under identical conditions gives the enone (36a) in 89% yield. Obviously, in the perchloric acid catalysed reaction of (35a), the dienone (38a) originates by normal electrophilic cyclisation followed by elimination of the β-ethoxy group from the cyclised ketone, whereas in the presence of ethyl orthoformate the sequence of reactions involving the alkoxy transfer, and 1,5-hydride shift can only account for the formation of (36a) as shown in scheme 1.

In order to evaluate the synthetic potential of both the single-step and the modified two-step formylation cyclisation methods for the construction of bicyclo[3.3.1]nonane derivatives, cyclisation of a number of γ,δ-unsaturated dialkoxyethyl ketones (49b–f) (table 2) and (50a–c and 51a–d) (table 3) are studied. In accord with the previous findings, the ketones (49b–d) (entries 2–6, table 2) afford the cyclodienones (38b–f) and cycloalkenones (36b–f) when subjected to cyclisation with perchloric acid and excess triethyl orthoformate-perchloric acid, respectively, in good to excellent yields.

The presence or absence of an α'-methyl group in the methyl ketone substrates has profound influence on the course of the formylation-cyclisation reactions. Thus, perchloric acid (70%) catalysed cyclisation of diethoxy ethyl derivatives (50a–c) and (51a,c) (entries 1, 2, 3, 4, 6 in table 3) having no α'-methyl group, in the presence or the absence of triethyl orthoformate give only the respective dienones. Direct reaction of the methyl ketones corresponding to entries 1, 2, 3 (table 3) with triethyl orthoformate and perchloric acid again afford the same dienones in comparable yields. That alkoxy transfer is retarded in this series, is supported by the isolation of the β-methoxy ketone (54) in perchloric acid

Table 2. Synthesis of bicyclo [3.3.1] nonanes.

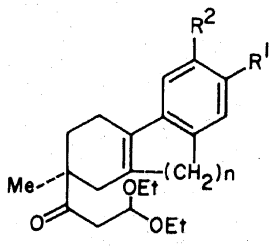
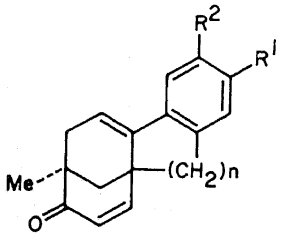
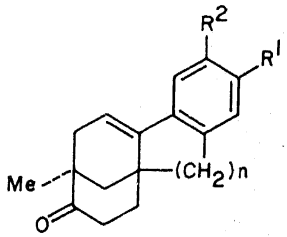
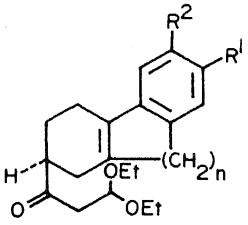
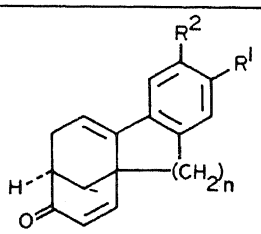
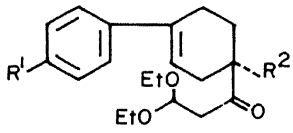
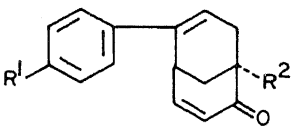
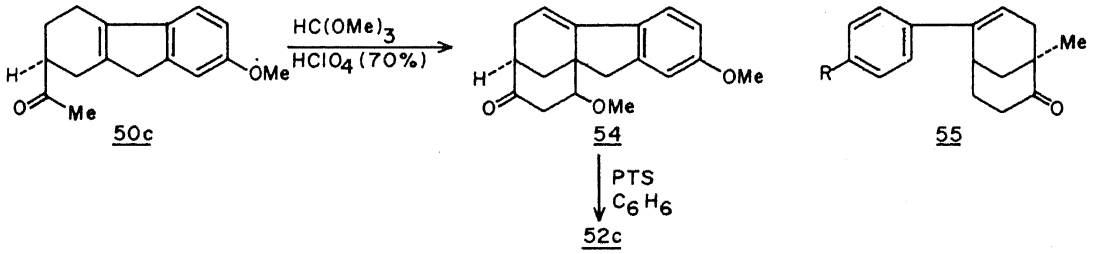
Entry	Diethoxyethyl Ketone	Bicyclo [3.3.1] nonane (yield %)	
		By perchloric acid (70%)	By excess $HC(OEt)_3$ and perchloric acid (70%)
	 49	 38	 36
1	a, $R^1=R^2=H$, n = 2	87 (41)*	89 (85)*
2	b, $R^1=H$, $R^2=OMe$, n=2	74	81
3	c, $R^1=OMe$, $R^2=H$, n=2	80	83
4	d, $R^1=R^2=H$, n = 1	60	83
5	e, $R^1=H$, $R^2=OMe$, n=1	73	70
6	f, $R^1=OMe$, $R^2=H$, n=1	70	75

*Figure in parenthesis represents the yield obtained from the reaction of corresponding methyl ketone with excess triethyl orthoformate and perchloric acid (70%)

Table 3. Synthesis of bicyclo [3.3.1] nonanes.

Entry	Diethoxyethyl Ketones	Bicyclo[3.3.1]nonane	Yield (%)
	 50	 52	
1	a, $R^1=R^2=H$, n = 2		70
2	b, $R^1=OMe$, $R^2=H$, n = 2		64
3	c, $R^1=OMe$, $R^2=H$, n = 2		55
	 51	 53	
4	a, $R^1=R^2=H$		60
5	b, $R^1=H$, $R^2=Me$		80
6	c, $R^1=OMe$, $R^2=H$		65
7	d, $R^1=OMe$, $R^2=Me$		50



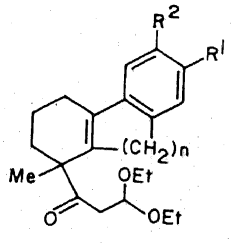
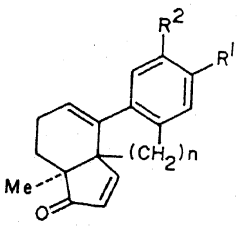
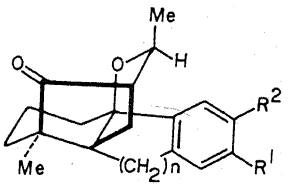
catalysed reaction of (50c) with trimethyl orthoformate. This is smoothly converted to the dienone (55) by treatment with *p*-toluenesulphonic acid in boiling benzene.

That the rigid geometry of the substrates plays an important role in the alkoxy transfer and in the hydride shift steps is demonstrated by the failure of the ketones (51b and d) (entries 5 and 7, table 3) to produce the enones (55) when treated with excess triethyl orthoformate and perchloric acid. Only dienones are obtained in the presence or the absence of ethyl orthoformate and perchloric acid.

Thus, the formylation cyclisation of the methyl ketones to the bridged dienones coupled with stereospecific catalytic hydrogenation (Chakraborti *et al* 1987) and chemoselective hydrogenation of the ketone-conjugated double bond (Chakraborti, Ranu and Ghatak, unpublished work) offers excellent routes to the stereospecific construction of bicyclo[3.3.1]nonane derivatives.

This two-step formylation-cyclisation annulation reaction has been extended for the construction of angularly fused cyclopentenones (Ranu *et al* 1988). The intermediacy of the 1,3-dialkoxyallyl cation (45) in the acid-catalysed orthoformate-induced annulation of the methyl ketone (33a) (scheme 2) is clearly evident from this two-step reaction. Thus, the β-diethoxyethyl ketones (49a–d) (entries 1–4, table 4) prepared from the corresponding methyl ketones (33a–d) on cyclisation with perchloric acid (70%) in benzene give the angularly fused cyclopentenones (34a–d) in 77, 56, 62 and 55% yield, respectively. Obviously, unlike the complex path followed in the formation of cyclopentenones directly from the methyl ketones, where the excess of trimethyl orthoformate has an important role in transforming (33a) to the presumed intermediate (45) through the enol ether prior to its cyclisation, perchloric acid-catalysed reaction of the β-diethoxyethyl ketone (49) involves a simple electrophilic cyclisation of (49i) followed by elimination of the β-ethoxy group from the intermediate (49j) (scheme 3). In contrast, cyclisation of the diethoxy ethyl ketones (49a and 49c) (entries 1, 3, table 4) with an excess of triethyl orthoformate in the presence of perchloric acid afford the pentacyclic keto ethers (37a and 37c) in 80 and 69% yield, respectively, while the ketone (49b) (entry 2) under similar condition produces the cyclopentenone (34b). Thus, in the presence of triethyl orthoformate, a 1,3-diethoxyallyl cation (45) is generated which then undergoes electrophilic cyclisation. The 1,3-migration of the OC_2H_5 group from C-10 to C-4b in the intermediate (46) is possibly facilitated by the geometry and the stability of the cation (47) over that of (46). However, the presence of a *p*-methoxy group in the aromatic substrate (for example 49b) decreases the electrophilicity (or increases stability) of the benzylic cation relative to (46) and would thus possibly block the transfer of the alkoxy group from C-10 to C-4b. So, in contrast to the demethoxy and the 3-methoxy derivatives (49a) and (49c), the *p*-methoxy styrenoid substrate

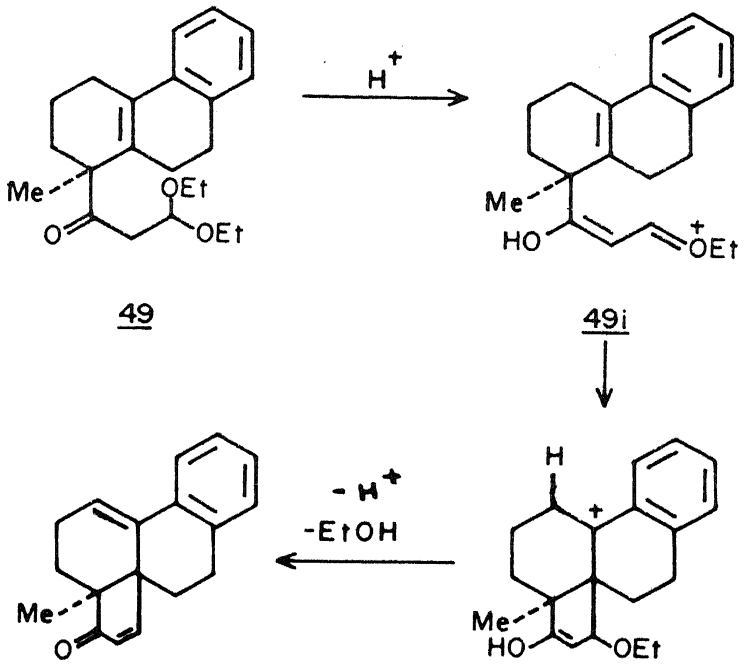
Table 4. Synthesis of cyclopentenones and pentacyclic keto ethers.

Entry	Diethoxyethyl Ketones	Cyclopentenones	% yield	Pentacyclic Keto ether	% yield
					
	49	34		37	
1		a, $R^1 = R^2 = H$, n = 2	77[a] (41)[b]		80[b,c]
2		b, R^1 = OMe, R^2 = H, n = 2	56[a] (50)[c]		
3		c, R^1 = H, R^2 = OMe, n = 2	62[a]		69[c]
4		d, $R^1 = R^2$ = H, n = 1	55[a] (14)[b]		37[b]

[a] Yield by reaction of diethoxyethyl ketone with perchloric acid (70%) in benzene

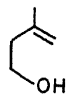
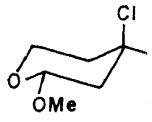
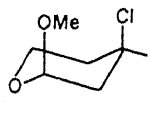
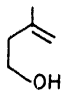
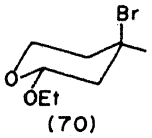
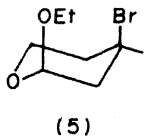
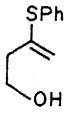
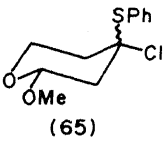
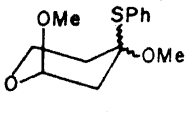
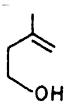
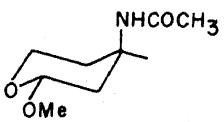
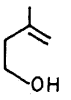
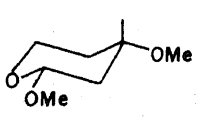
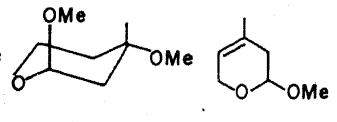
[b] Yield by reaction of the corresponding methyl ketone with excess triethyl orthoformate and perchloric acid (70%).

[c] Yield by reaction of diethoxyethyl ketone with excess triethyl orthoformate and perchloric acid (70%).



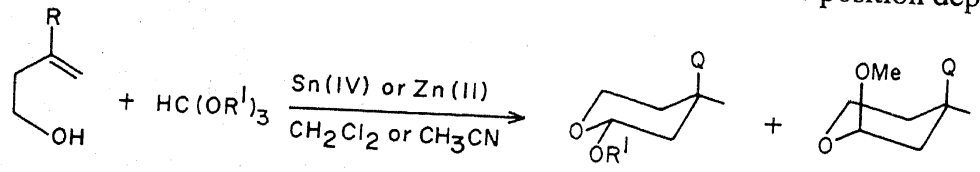
Scheme - 3

Table 5. Results of dioxenium cation–olefin cyclisations.

Olefinic alcohol	Ortho ester	Conditions	Product (s) (yield)	
	$HC(OMe)_3$	1.1 equiv $SnCl_4$ CH_2Cl_2/-78 °C	 (85)	 (5)
	$HC(OEt)_3$	0.5 equiv $SnBr_4$ CH_2Cl_2 /-20 °C	 (70)	 (5)
	$HC(OMe)_3$	1.6 equiv $SnCl_4$ CH_2Cl_2 /-20 °C	 (65)	 (15)
	$HC(OMe)_3$	1.1 equiv $SnCl_4$ CH_3CN/-20 °C	 (77)	
	$HC(OMe)_3$	2 equiv $ZnBr_2$ CH_2Cl_2 /25 °C	 (8)	 (41)

(49b) failed to give the corresponding pentacyclic keto ether due to the inability of the corresponding benzylic cation (46) to facilitate the alkoxy migration, thereby resulting in only the dienone. The abnormal behavior of the hydrofluorene analogue (49d) might be due to the strain involved in the intramolecular process of ethoxy transfer in the relatively flattened hydrofluorene system in comparison with that of the geometrically favourable strain-free hydrophenanthrene systems.

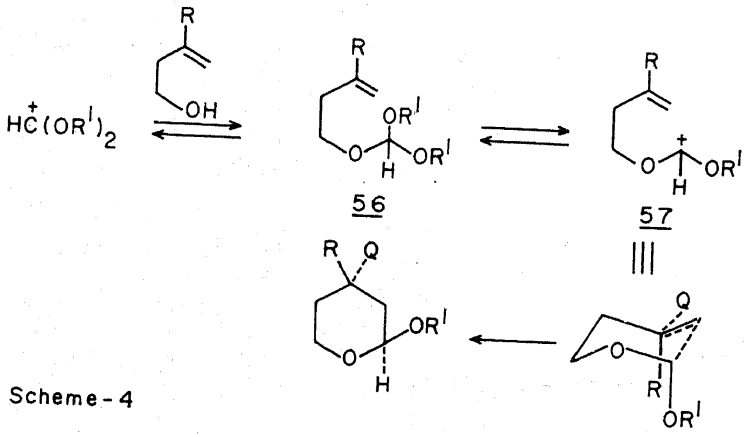
Very recently Perron and Albizati (1987) have described an analogous cyclisation involving dioxenium cation onto unactivated olefins resulting in the formation of 4-heterosubstituted pyranosides (table 5). When a dichloromethane solution of an ortho ester is treated with Lewis acid followed by addition of a homoallylic alcohol, 4-hetero-substituted pyranosides are formed (7) at temperatures as low as $-78°C$. A number of heteroatomic groups can be incorporated at the 4-position depending



(7)

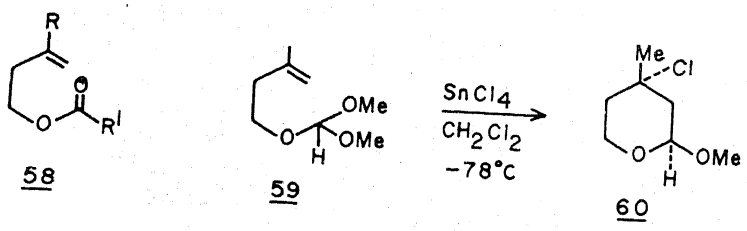
on the solvent and the Lewis acid chosen. A predominance of one isomer is generally observed in the reactions with Sn(IV).

The mechanism postulated in scheme 4 proceeds through the combination of the dioxenium cation with the homoallylic alcohol to give the mixed orthoester (56) which is presumably in equilibrium with a second dioxeneum cation (57). In



Scheme - 4

Sn(IV) catalysed reaction cyclisations are preferentially occurring via the transition state A in which the dioxenium cation and the terminating group approach the olefin in a *trans*-antiperiplanar fashion and in which the alkoxy group has adopted



an axial orientation, thus maximising any benefit derived from an anomeric effect. Isolation of esters of the general structure (58), presumably arising by hydration of the intermediate cation (57) supports this mechanism. In addition, the mixed orthoester (59) when treated with $SnCl_4/CH_2Cl_2$ at $-20°C$ cyclises to (60).

8. Conclusions

Although carbon-carbon bond formation through reactions of orthoesters is known for long time, its applications in the synthesis of complex polycyclic compounds has remained unexplored. The extensive investigations carried out in the authors' laboratory resulting in a novel formylation-cyclisation route for the synthesis of functionalised polycyclic bridged-bicyclo[3.3.1]nonanes and cyclopentenones and a few isolated results from other laboratories have greatly increased the synthetic potential of carbon-carbon bond formation reaction through orthoformates. The reactions specially the annulations involving the orthoformates reviewed in this article may find use in the synthesis of natural products.

References

Becket G J P, Ellis G P and Trindade M I 1978a *J. Chem. Res.* (*S*) 47
Becket G J P, Ellis G P and Trindade M I 1978b *J. Chem. Res.* (*M*) 865
Casnati G, Grisafulli M and Ricca A 1965 *Tetrahedron Lett.* 243
Chakraborti R, Deb S and Ghatak U R 1985a *J. Indian Chem. Soc.* **42** 883
Chakraborti R, Ranu B C and Ghatak U R 1985b *J. Org. Chem.* **50** 5268
Chakraborti R, Ranu B C and Ghatak U R 1987 *Synth. Commun.* **17** 1539
Claisen L 1893 *Chem. Ber.* **26** 2729
Dasgupta R and Ghatak U R 1985 *Tetrahedron Lett.* **26** 1581
Dasgupta R, Ranu B C and Ghatak U R 1983 *Indian J. Chem.* **22B** 619
Dewelfe R H 1970 *Carboxylic ortho acid derivatives* (New York and London: Academic Press) p. 223
Dorofeenko G N and Mezheritskii V V 1968 *J. Org. Chem.* **4** 1260
Dorofeenko G N and Tkachenko V V 1972 *Chem. Heterocycl. Comp.* **8** 935
Dusza J P, Joseph J P and Bernstein S 1964 *J. Am. Chem. Soc.* **86** 3908
Fieser M and Fieser L 1967 *Reagents for organic synthesis* (New York: Wiley-Interscience) p. 1204
Ghatak U R, Sanyal B, Ghosh S, Sarkar M, Raju M S and Wenkert E 1980 *J. Org. Chem.* **45** 1081
Ghosh S 1978 *Synthetic studies in condensed cyclic systems* Ph.D. dissertation, University of Calcutta
Gross H, Rieche A and Matthey G 1963 *Chem. Ber.* **96** 308
Hafner K, Peleter H and Schneider J 1961 *Liebigs Ann. Chem.* **650** 62
Howk B W and Sauer J C 1958 *J. Am. Chem. Soc.* **80** 4607
Howk B W and Sauer J C 1963 *Organic Synth. Coll. Vol.* **4** 801
Kirby E C and Raid D H 1961 *J. Chem. Soc.* 1724
Lombert S D, Nemery I, Roekens B, Carretero J C, Kimmel T and Ghosez L 1986 *Tetrahedron Lett.* **27** 5099
Miller B 1981 *J. Org. Chem.* **46** 2795
Mock W L and Tsou H R 1981 *J. Org. Chem.* **46** 2557
Mukaiyama T and Hayashi M 1974 *Chem. Lett.* 15
Perron F and Albizati K F 1987 *J. Org. Chem.* **52** 4130
Perst H 1971 *Oxonium ions in organic chemistry* (London: Verlag Chemie, Academic Press)
Pettit G R, Knight J C and Herald C L 1970 *J. Org. Chem.* **35** 1593
Ranu B C, Chakraborti R and Ghatak U R 1988 *J. Chem. Soc., Perkin Trans.* 1 (in press)
Sathe V R and Venkatraman K 1949 *Curr. Sci.* **18** 373
Schonberg A and Praefcke K 1964 *Tetrahedron Lett.* 2043

Schonberg A and Praefcke K 1966 *Chem. Ber.* **99** 196
Schonberg A, Praefcke K and Kohtz J 1966 *Chem. Ber.* **99** 2433
Suzuki M, Kawagishi T and Noyori R 1981 *Tetrahedron Lett.* **22** 1809
Suzuki M, Yamagisawa A and Noyori R 1982 *Tetrahedron Lett.* **23** 3395
Takazawa O and Mukaiyama T 1982 *Chem. Lett.* 1307
Treibe W 1967 *Tetrahedron Lett.* 4707