Tetrahedron Vol. 36, pp. 2163 to 2196
Pergamon Press Ltd., 1980. Printed in Great Britain

TETRAHEDRON REPORT NUMBER 90

STERIC CONTROL IN PROSTAGLANDIN SYNTHESIS INVOLVING BICYCLIC AND TRICYCLIC INTERMEDIATES

ROGER F. NEWTON*
Chemical Research Department, Glaxo Group Research Ltd., Ware, Herts. SG12 0DJ, England

and

STANLEY M. ROBERTS
Department of Chemistry and Applied Chemistry, Salford University, Salford M5 4WT, England

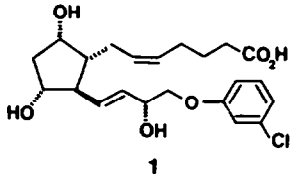
(*Received* 15 *January* 1980)

CONTENTS

1. INTRODUCTION

The potent and diverse biological activity of prostaglandins[1] (Fig. 1) has attracted the attention of numerous scientists from academic and industrial laboratories. Many novel synthetic routes to the naturally occurring materials have been devised following the pioneering work of Professors Corey and Fried.

The more adaptable syntheses have been used to prepare a host of analogues of the natural compounds in an effort to find an orally active prostanoid of specific biological activity that might find use as a drug. Partial modification of the C-12 side chain has been particularly rewarding and I.C.I. are marketing Estrumate[2] (1) and Equimate[2] (2) as veterinary aids.



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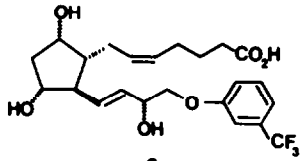

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Since our main interest in the prostaglandins lies in their pharmacological activity we required short flexible and stereospecific routes so that a wide range of compounds could be synthesised as potential drugs. In addition the syntheses had to start from cheap and commercially available chemicals and be amenable to plant scale preparations.

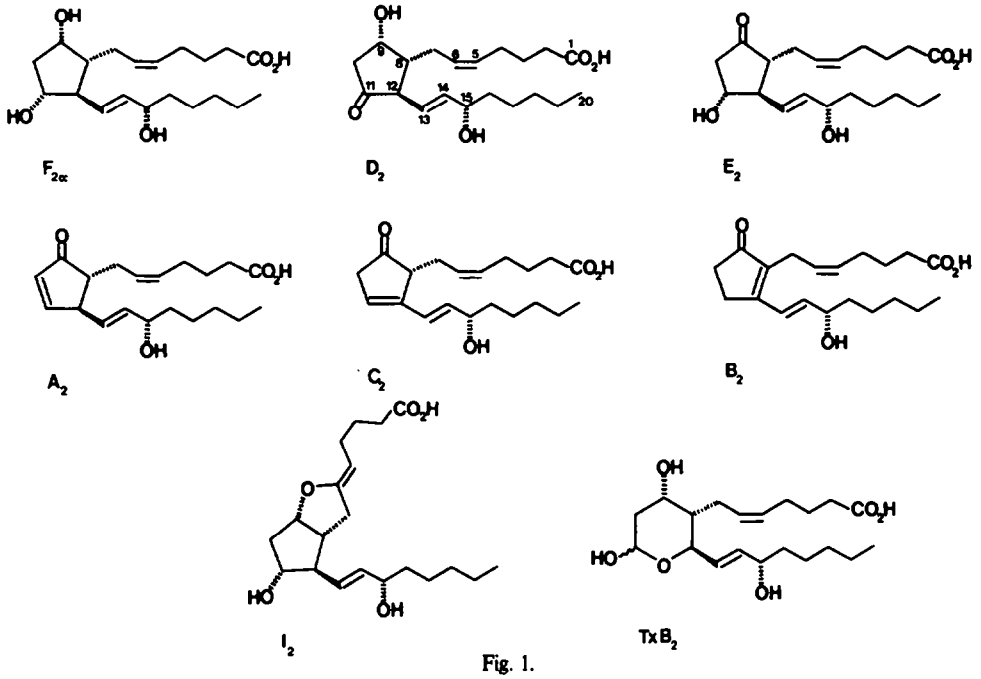


Fig. 1.

Of the numerous synthetic approaches to the prostaglandin system two have proved to be popular:

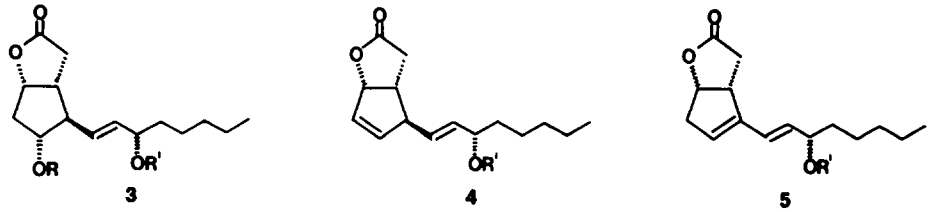
(a) Conjugate addition to substituted cyclopentenones using an organometallic reagent to deliver the protected octenol side chain.

(b) Syntheses using bicyclic intermediates.

In this report we will concentrate on recent developments in prostaglandin synthesis relying on the latter strategy since other texts are available that detail the other approaches.[3]

Bicyclic and tricyclic systems are particularly attractive prostaglandin intermediates because their inherent locked stereochemistry may be used to define the stereospecificity of the synthesis. In addition the subtle influences which one ring often has on the chemistry of another may be employed to give additional regio and stereochemical control.

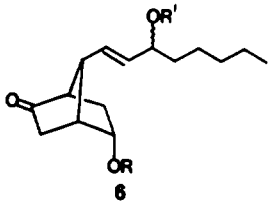
By 1973 Corey and Jenny had established that the bicyclic lactone (**3**) was convertible into prostaglandins D_2, E_2 and $F_{2\alpha}$ and that the lactones (**4** and **5**) were valuable intermediates in the synthesis



3 **4** **5**

of prostaglandin A_2 and prostaglandin C_2 respectively. Prostaglandin B_2 is available from the last mentioned prostaglandins on treatment with base, while later work by a group in the Upjohn laboratories showed that lactone systems related to **3** could easily be transformed into thromboxane B_2[4]. Furthermore prostaglandin $F_{2\alpha}$ yields prostaglandin I_2 methyl ester in three steps[5] so that most of the natural prostaglandins are available from the bicyclic lactones **3–5**.

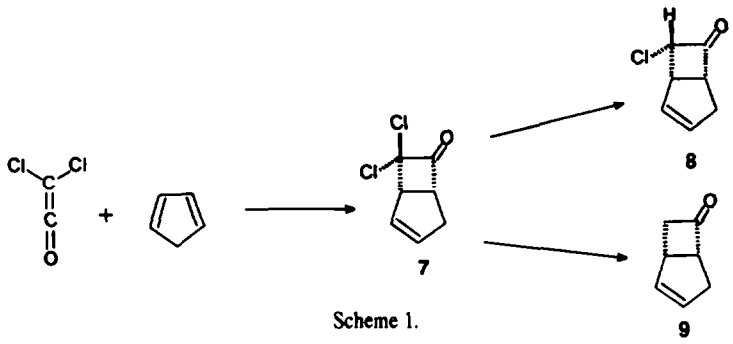
We set out, therefore, to define short, flexible routes to the lactones **3–5** and also to the ketone (**6**) since this represents a useful precursor to prostaglandins D_2 and C_2.



6

Although cyclopentadiene is an obvious and convenient starting material we were not attracted to the usual method of functionalization of this molecule via a [4+2]-cycloaddition reaction due to the inherent difficulties in this strategy[6]†. We preferred to employ the [2+2]-cycloaddition of dichloroketen and the diene[7] to give the dichlorobicycloheptenone (**7**; Scheme 1) for the following reasons. First, this reaction is regiospecific, high yielding and amenable to large scale work. Reduction of the dichloroketone (**7**) can be controlled to give either the monochloroketone (**8**) or the parent bicyclo[3.2.0]hept-2-en-6-one (**9**).

Secondly, the cyclobutanone ring so formed can be modified (viz. expanded, contracted or cleaved) in many ways.



Scheme 1.

Thus the compound **9** can be readily converted into the tricyclo[3.2.0.$0^{2,7}$]heptan-6-one system (Section 2), the 3-oxatricyclo[4.2.0.$0^{2,4}$]octan-7-one system (Section 3), the 6-oxabicyclo[3.1.0]hex-2-ene system (Section 4) and the bicyclo[3.1.0]hex-2-ene system (Section 5) and all these systems can be used to prepare prostaglandins and prostanoids (Fig. 2).

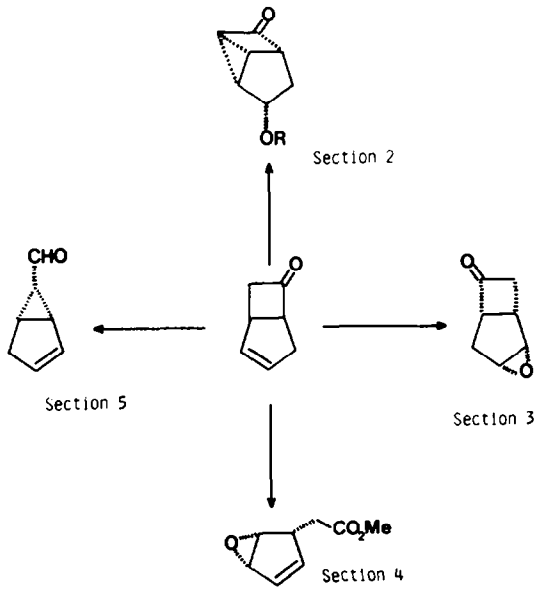
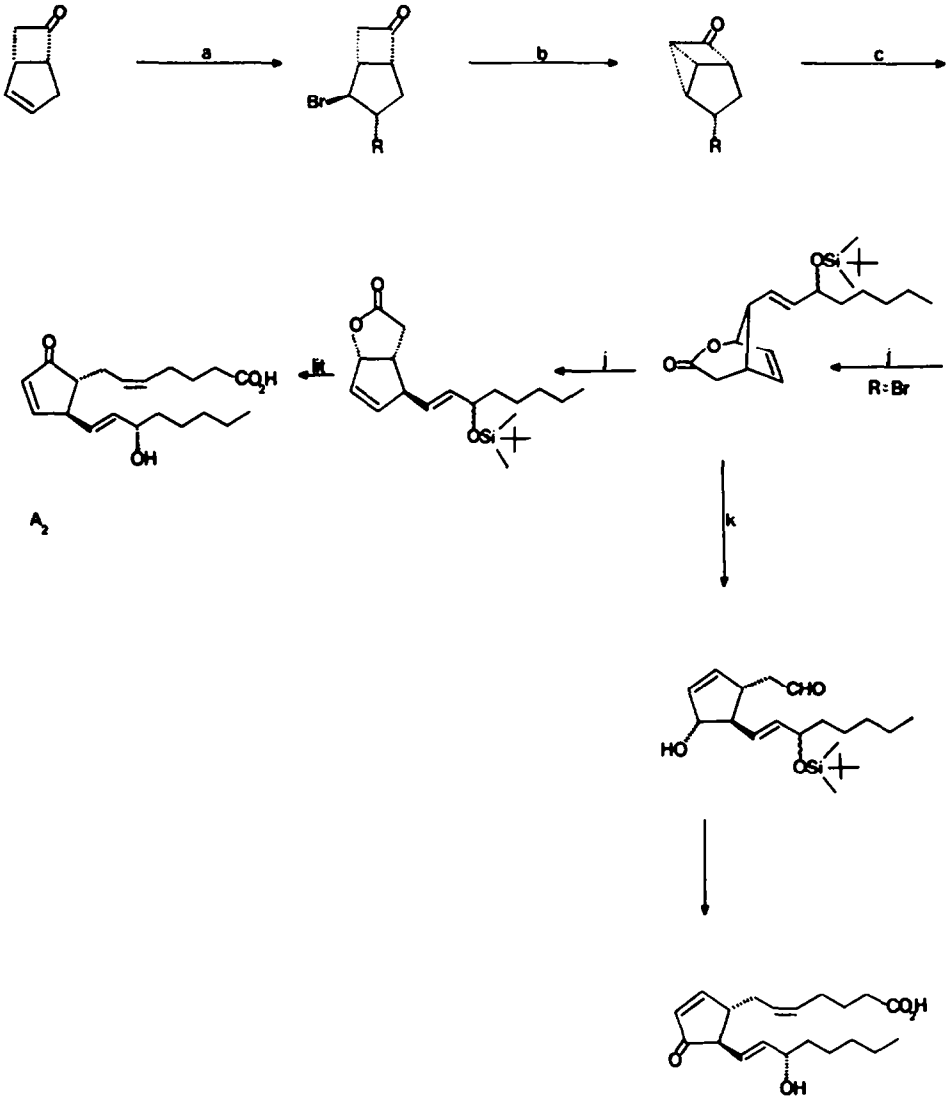


Fig. 2.

Our early synthetic work (Sections 2–5) utilised the racemates of the ketones (**7–9**) although the reaction schemes will depict only that enantiomer which affords the naturally occurring prostaglandin system. Resolution of the ketone (**9**) and enantiospecific prostaglandin synthesis will be described in Section 6.

†The [4+2]-cycloaddition suffers from two major disadvantages. The first is that a 5-substituted cyclopentadiene is required, the 5-substituent eventually becoming the β-sidechain of the prostaglandin. Such compounds may be prepared via alkylation of sodium or lithium cyclopentadienide with for instance chloromethyl ethers, however they readily isomerise leading to mixtures of cycloadducts after the Diels-Alder reaction. An alternative procedure employs the thallous salt of cyclopentadiene but although this minimises isomerisation thallous salts are very toxic. One of the best ways of overcoming this problem is to use acetoxy fulvene since the exocyclic double bond in the molecule prevents isomerisation.

The second disadvantage is that the ketone function required for further elaboration of the norbornene cannot be introduced directly. Various dienophiles e.g. 2-chloroacrylonitrile, 2-acetoxyacrylonitrile and α-chloroacrylyl chloride have been used to generate substituted norbornenes which are subsequently converted to the required norbornenone.

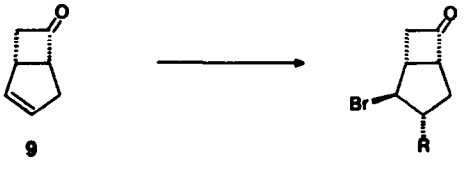


Scheme 2.

2. SYNTHESIS OF PROSTAGLANDINS A_2, C_2, D_2, E_2 AND $F_{2\alpha}$ FROM TRICYCLO[3.2.0.0^{2,7}]HEPTAN-6-ONES

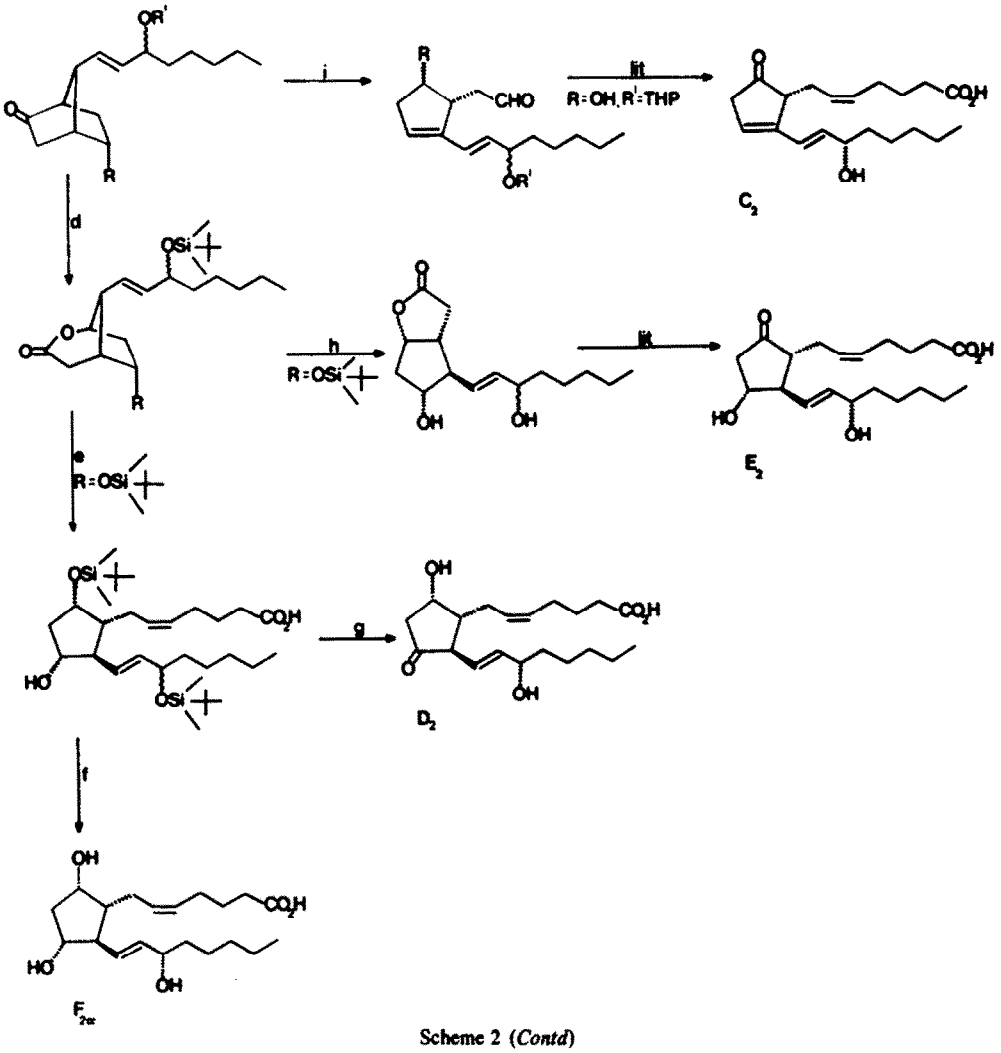
Homoconjugate addition of a cuprate reagent to a readily available tricyclo [3.2.0.0^{2,7}]heptanone is the key step in this synthetic route to prostaglandins as illustrated in Scheme 2. Some aspects of the individual steps are described in the appropriate sub-sections (a to k).

Section 2a



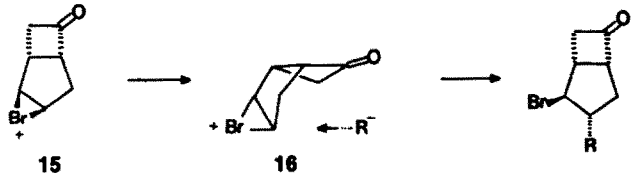
9

10: R = Br
11: R = OMe
12: R = OCH_2Ph
13: R = OH
14: R = OCOMe
18: R = $OSiMe_2{}^tBu$



Scheme 2 (*Contd*)

Bromination of the ketone (**9**) occurs in a highly stereoselective manner furnishing the dibromoketone (**10**) as the only isolated product.[8] On conducting the bromination of **9** in methanol benzyl alcohol, water, or acetic acid, the bromoethers (**11** or **12**), the bromohydrin (**13**) or the bromoester (**14**) respectively were obtained almost exclusively (Table 1)[9] indicating that the *exo*-bromonium ion (**15**) is formed preferentially and is attacked regioselectively by the attendant nucleophile at C-3 (Scheme 3)



15 **16**

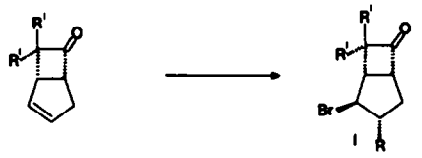
Scheme 3.

through the favoured transition state (**16**) which has the cyclopentane ring in an *endo*-envelope conformation. The *endo*-envelope conformation is calculated to be the most stable form for the parent molecule (**17**)[10] and X-ray data corroborates NMR evidence[9] that the bromohydrin (**13**) exists in this conformation.

17

A detailed study of the addition of HOBr to the alkenone (**9**) showed that while the bromohydrin (**13**) was the major product the three other possible stereoisomers were also present (each 3–4%).

Table 1. Reaction of some bicyclo[3.2.0]hept-2-en-6-ones with some brominating agents



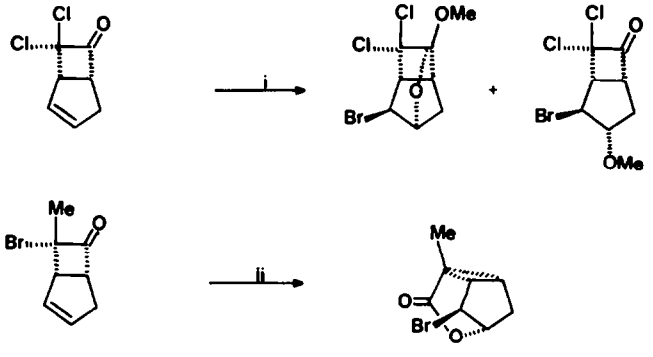
R^1	Brominating Agent	Solvent	Yield of I (%)	(R)[a]
Cl	Br_2	CCl_4	79	(Br)
Cl	NBA[b]	$MeCO_2H$	86	(OCOMe)
H	NBA	MeOH	90	(OMe)
H	NBA	$PhCH_2OH$	90	(OCH_2Ph)
H	NBS[c]	H_2O/Me_2CO	60	(OH)
H	NBA	$MeCO_2H$	90	(OCOMe)
Me	NBA	MeOH	75	(OMe)
Me	NBA	H_2O/Me_2CO	87	(OH)

a after chromatography and/or crystallization

b N-Bromoacetamide

c N-Bromosuccinimide

7-Substituted bicycloheptenones behave in much the same way as the parent system (Table 1) except in certain cases when an adjacent halogen atom activates the carbonyl group so that transannular interactions are translated into chemical bonds leading to the formation of tricyclic compounds (Scheme 4)[9,11]



Scheme 4. Reagents: i, MeCONHBr, MeOH, ii, MeCONHBr, H_2O, Me_2CO.

In relation to the synthesis of prostaglandins C_2, D_2, E_2 and $F_{2\alpha}$ the highly selective formation of the bromohydrin (**13**), or congener, from the ketone (**9**) is crucial since the hydroxyl group is destined to become the 9-oxy-substituent of the prostanoid ring.

The crystalline bromohydrin (**13**) can be derivatised in a number of ways: for instance the *t*-butyldimethylsilyloxyketone (**18**) can be synthesised in the standard manner.[12]

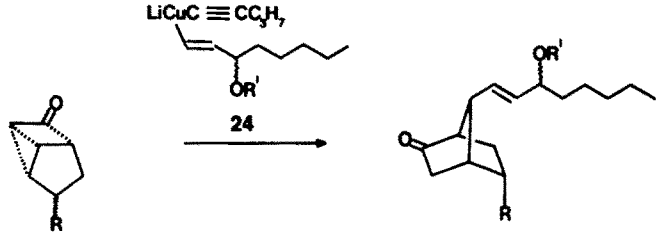
Section 2b

10:	R = Br	**19**
11:	R = OMe	**20**
12:	R = OCH_2Ph	**21**
14:	R = OCOMe	**22**
18:	R = $OSiMe_2{}^tBu$	**23**

Abstraction of a proton from the activated C–7 methylene group of the bromoketones (**10–12**), (**14** and **18**) by a non-nucleophilic base followed by intramolecular displacement of bromide ion gave the corresponding tricyclo[3.2.0.$0^{2,7}$]heptanone derivative (**19–23**) which could be isolated and stored for long periods. This tricyclic system had previously been prepared (but not isolated) by Dreiding[8] and others[13] whilst more recently Gilbert *et al.*[14] obtained X-ray data on the crystalline bromo compound (**19**).

2-Bromo-7-substituted bicycloheptanones could be dehydrohalogenated to the corresponding tricyclic ketone in a similar manner.[15,16]

Section 2c

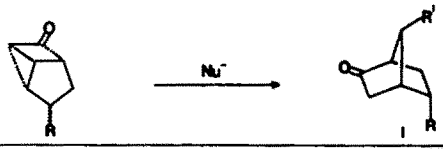


19: R = Br
20: R = OMe
21: R = OCH_2Ph
22: R = OCOMe
23: R = $OSiMe_2{}^tBu$

25: R = Br, R' = $SiMe_2{}^tBu$
26: R = OMe, R' = $SiMe^tBu$
27: R = OCH_2Ph, R' = $SiMe_2{}^tBu$
28: R = OH, R' = THP
29: R = $OSiMe_2{}^tBu$, R' = $SiMe_2{}^tBu$.

Weak nucleophiles (e.g. water and methanol) and powerful nucleophiles (e.g. cyanide ion and thiophenoxide ion) open the tricyclic ketone stereospecifically, with cleavage of the C1–C7 bond being observed in all cases (Table 2).

Table 2. Reaction of some tricycloheptanones with some nucleophiles



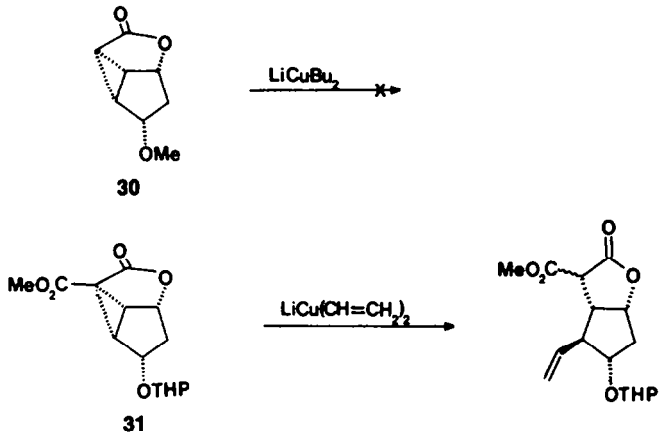
R	Nucleophile	Yield of I. (%)	(R')
Br	MeOH	80	(OMe)
OCH_2Ph	CN^-	87	(CN)
OMe	$LiCuBu_2$	60	(Bu)
OCH_2Ph	$LiCuC{\equiv}CC_5H_7$ (CH=CHCHC$_5$H$_{11}$, OSiMe$_2{}^t$Bu) **24**	75	(CH=CHCHC$_5$H$_{11}$, OSiMe$_2{}^t$Bu)
$OSiMe_2{}^tBu$	$LiCuC{\equiv}CC_5H_7$ (CH=CHCHC$_5$H$_{11}$, OSiMe$_2{}^t$Bu) **24**	88	(CH=CHCHC$_5$H$_{11}$, OSiMe$_2{}^t$Bu)

Likewise, the heterocuprate reagent (**24**) reacted with the tricycloheptanones (**19–23**) to give the corresponding norbornanone (**25–29**) in high yield.[17]

The reaction of the tricyclic ketone with nucleophiles is the key step in this approach to prostaglandin synthesis. Its flexibility allows the stereospecific synthesis of a wide variety of 7-substituted norbornanones and the reaction with the heterocuprate reagents means that the complete β-sidechain of the natural prostaglandins may be introduced in one step and in very high yields.

The majority of other syntheses that utilise bicyclic and tricyclic intermediates rely on introducing a simple group such as a protected hydroxymethyl moiety which is subsequently modified to give the β-sidechain. This type of approach involves several extra synthetic steps and lacks flexibility.

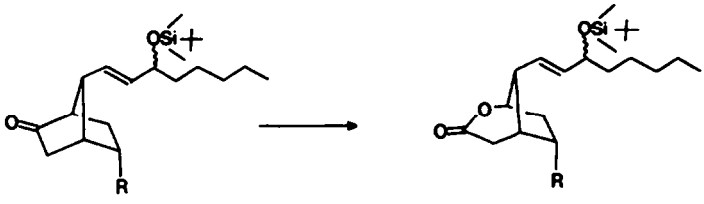
Homoconjugate addition to monoactivated cyclopropyl systems is usually difficult[18] unless the cyclopropyl ring is strained[19] as is the case in the present example. As expected the relatively unstrained oxa-bicyclooctanone system (**30**)[20] proved inert to nucleophilic attack whilst the closely related di-activated system (**31**) has been shown to react smoothly with a cuprate reagent (Scheme 5).[21]



Scheme 5.

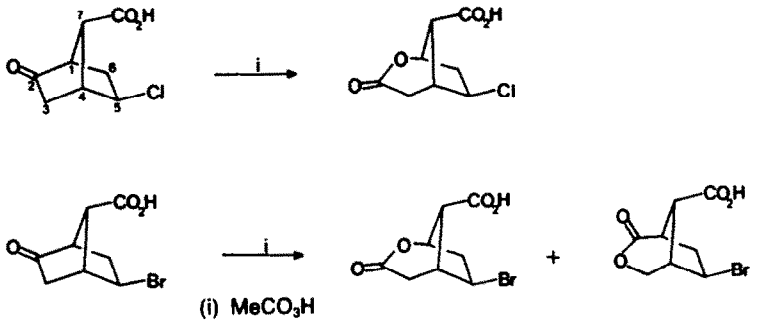
The regiospecificity of the nucleophilic ring opening of the tricyclo[3.2.0.0^{2,7}]heptanone system may be due in part to a weakness in the C1–C7 bond[14] but force-field calculations[22] suggest that the approach of nucleophilic species to C–2 is so hindered that this may be the sole factor dictating the specificity of the ring-opening process.

Section 2d

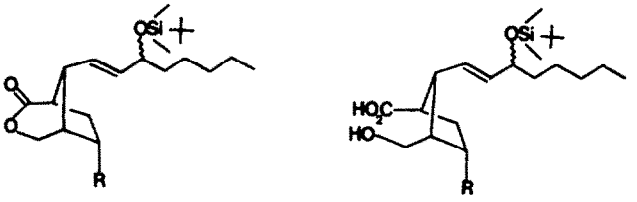


25: R = Br **32**
27: R = OCH_2Ph **33**
29: R = $OSiMe_2{}^tBu$ **34**

By analogy with earlier work involving the oxidation of 5-*exo*-chloro-[23] and 5-*exo*-bromo-7-*anti* substituted norbornanones[24] (Scheme 6) we expected that the norbornanones (**25, 27** and **29**) would be readily converted into the appropriate lactones (**32–34**) which can be regarded as late-stage intermediates to prostaglandins and prostanoids. However, only the bromoketone (**25**) gave the corresponding lactone (**32**) in high yield on reaction with *m*-chloroperoxybenzoic acid; the non-halogenated norbornanones (**27** and **29**) gave unacceptable mixtures of the desired product together with the isomeric lactones (**35** and **36**) respectively resulting from migration of the methylene group rather than the methine group.



Scheme 6.



35: R = OCH_2Ph
36: R = $OSiMe_2{}^tBu$

37

Model studies[25] indicated that the following factors increased the amount of product resulting from undesirable methylene group migration:

(i) an electron withdrawing substituent in the *anti*-configuration at C–7

(ii) the use of a peracid derived from a strong acid

(iii) employment of relatively high reaction temperatures.

On the other hand a substituent at C–5 *endo* capable of forming a hydrogen bond (e.g. Br) tended to promote the migration of the bridge-head carbon atom (Fig. 3).

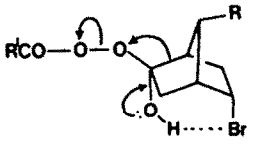
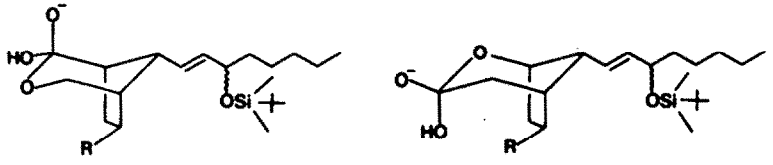


Fig. 3.

Guided by these results we reacted the ketone (**29**) with peracetic acid in acetic acid buffered with sodium acetate to give the lactone (**34**) in 65% yield after chromatography to remove the isomer (**36**).[17] Later work indicated that oxidation of the ketone (**29**) with peracetic acid in acetic acid at −20° gave a mixture of the lactone (**34**) and the isomer (**36**) in the ratio 79:21. Partial hydrolysis of this mixture using 0.2 N NaOH gave, after filtration through a column of silica gel, pure lactone (**34**; 70%) and the acid (**37**; 14%).

Similarly, peracetic acid oxidation of the benzyloxyketone (**27**) over ten days gave the lactone (**33**; 68%) and the lactone (**35**; 1%). On working up this reaction at an earlier stage the required lactone (**33**; 70%) was isolated along with the undesired isomer (**35**; 30%).

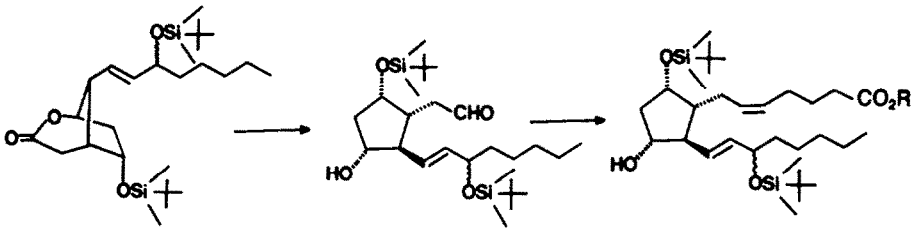
We attribute the more rapid hydrolysis of the 3-oxabicyclooctanone system (**35**, **36**) relative to the 2-oxabicyclooctanone system (**33**, **34**) under acidic or basic reaction conditions to less severe congestion within the tetrahedral intermediate formed from the former system (**38a**) compared with that from the latter (**38b**).[26]



38a **38b**

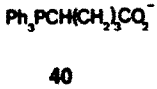
In summary, reaction of the ketone (**29**) with peracetic acid followed by treatment with dilute aqueous sodium hydroxide furnished the prostanoid synthon (**34**) in 70% yield without recourse to extensive chromatography.

Section 2e



34 **39** **41**: R = Me
43: R = H

The δ-lactone (**34**) was reduced to the hydroxyaldehyde (δ-lactol; **39**) in virtually quantitative yield using diisobutylaluminium hydride. The hydroxyaldehyde (**39**) was reacted with ylid (**40**) derived from carboxybutyltriphenylphosphonium bromide using potassium *t*-butoxide in tetrahydrofuran or benzene over 24 hr to give (after esterification) not only the expected 9,15-diprotected prostaglandin-$F_{2\alpha}$ ester (**41**, 53%) but also the isomer (**42**, 28%) resulting from migration of the silyl group. The propensity



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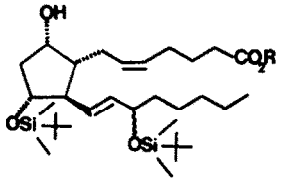
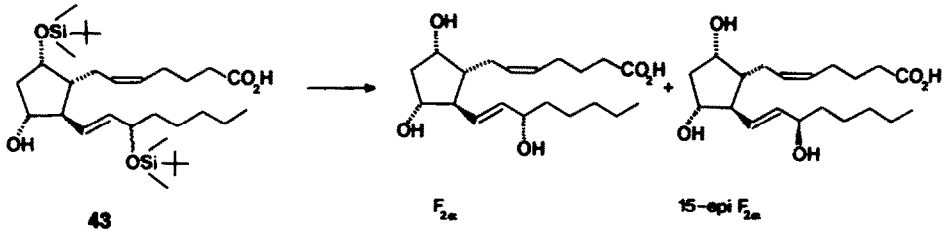


42: R = Me
44: R = H

of the silyl group to shift in this fashion has also been observed by other workers.[27] In order to overcome this problem the Wittig reaction involving **39** and **40** was carried out in benzene at ambient temperature and quenched after 5 min, whereupon the cyclopentanol (**43**) and the isomer (**44**) were obtained in 79% and 2% yield respectively.[28]

Section 2f



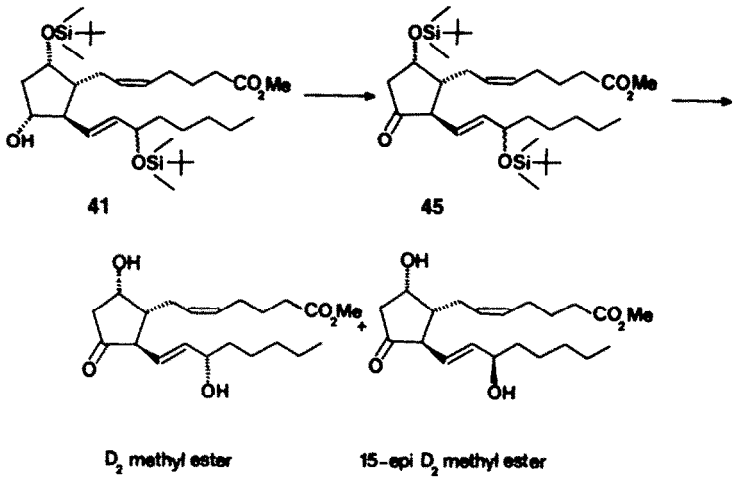
43 $F_{2\alpha}$ 15-epi $F_{2\alpha}$

Removal of the *t*-butyldimethylsilyl protecting groups from **43** using the standard conditions of aqueous acetic acid in tetrahydrofuran gave prostaglandin $F_{2\alpha}$ and 15-*epi*-prostaglandin-$F_{2\alpha}$ in practically quantitative yield.

Summary

Using the sequence a–f (Scheme 2), prostaglandin $F_{2\alpha}$ (16%) and 15-epi-prostaglandin $F_{2\alpha}$ (16%) were prepared from the ketone 9.

Section 2g

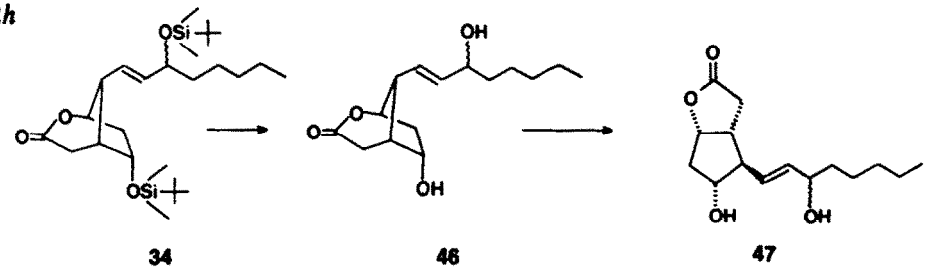


Oxidation of the 9,15-diprotected prostaglandin $F_{2\alpha}$ derivative (**41**) using pyridinium chlorochromate proceeded in 89% yield. Removal of the silyl protecting group on the sidechain of the ketone (**45**) presented no difficulty. Unfortunately, attempted removal of the O-C-9 silyl group using aqueous hydrochloric acid, aqueous acetic acid, or tetrabutylammonium fluoride failed to provide prostaglandin D_2 ester due to concurrent dehydration of the β-ketol. However treatment of the bissilyl ketone (**45**) with aqueous HF in acetonitrile[29] gave prostaglandin D_2 methyl ester and the C-15 epimer in 76% yield.[30]

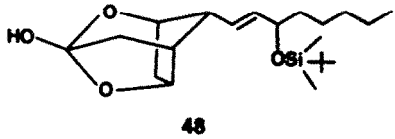
Summary

The sequence a–e, g (Scheme 2) represents the most practicable route to prostaglandin D_2 (a potent inhibitor of blood platelet aggregation)[31] yet devised[32] and involves nine steps from the bicyclic ketone (**9**).

Section 2h



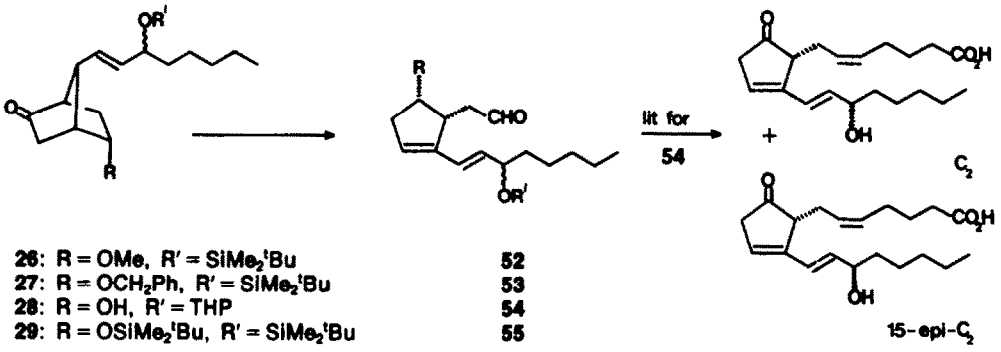
An entry into the E class of prostaglandins was obtained on establishing that the hydroxy δ-lactone (**46**) rapidly rearranged to the hydroxy γ-lactone (**47**).[33] This rearrangement, which is not peculiar to compounds having the prostaglandin side chain attached to C–8,[34] can be accomplished under acidic (aqueous hydrochloric acid) or basic (tetrabutylammonium fluoride) conditions in 70–80% yield presumably through the intermediacy of the tricyclic species (**48**). The γ-lactone (**47**) was converted into prostaglandin E_2 using improved literature methods (see Section 3d).



Summary

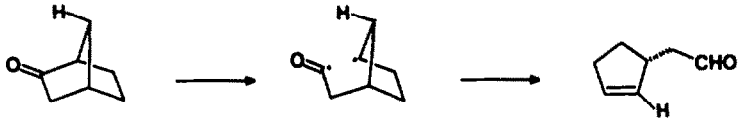
The well known prostaglandin E_2 precursor (**47**) *is available from the bicycloheptenone* (**9**) *in five steps (a–d), (h) (Scheme 2).*

Section 2i



26: R = OMe, R' = $SiMe_2{}^tBu$ **52**
27: R = OCH_2Ph, R' = $SiMe_2{}^tBu$ **53**
28: R = OH, R' = THP **54**
29: R = $OSiMe_2{}^tBu$, R' = $SiMe_2{}^tBu$ **55**

The photochemistry of simple norboranones has been extensively investigated by Yates.[35] The parent compound (**49**) behaves typically (Scheme 7) undergoing Norrish Type 1 cleavage to give the alkyl-acyl diradical (**50**). Abstraction of H-7 *syn* by the acyl radical leads to the formation of cyclopent-2-en-1-ylacetaldehyde (**51**) in good yield Similarly, photolysis of the 5-*endo*- 7-*anti*- nor-

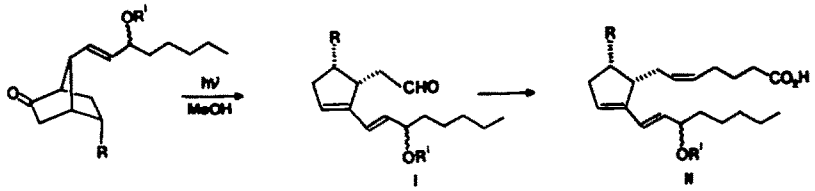


49 **50** **51**

Scheme 7.

bornanones (**26–29**) gave the corresponding 2-alkyenyl-5-substituted cyclopent-2-en-1-ylacetaldehyde (**52–55**) cleanly (Table 3). Each aldehyde was subjected to a Wittig reaction and further modified

Table 3. Conversion of some 5,7-disubstituted norbornanones into prostaglandin C_2 analogues

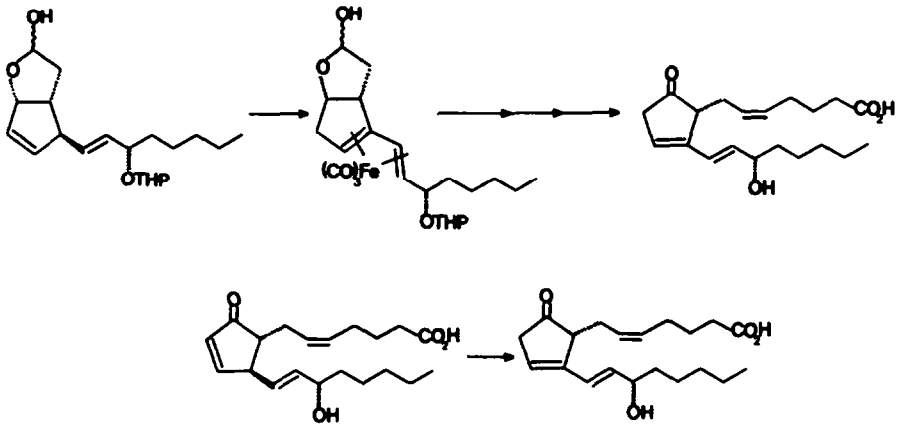


R^1	R	Yield of I[a] (%)	Yield of II[a] (%)
$SiMe_2{}^tBu$	$OSiMe_2{}^tBu$	37	22[b]
$SiMe_2{}^tBu$	OMe	39	69
$SiMe_2{}^tBu$	OCH_2Ph	45	70
THP	OH	53	-

a after chromatography

b not optimized

according to literature procedures to give prostaglandin C_2 from **54**[33,36] and analogues from **52**, **53** and **55**.[36,37]

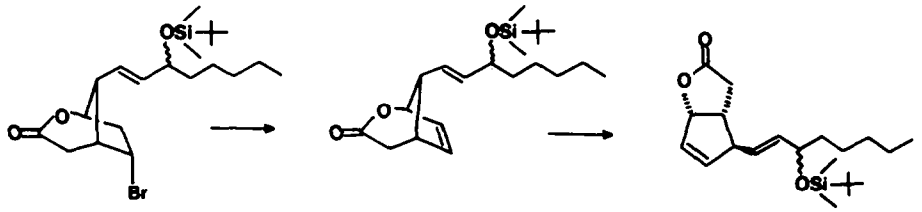


Scheme 8.

Summary

The photolysis step in this pathway (a)–(c), (i) (Scheme 2) to the known prostaglandin C_2 precursor (54) effects the introduction of the C11–C12 *double bond and simultaneously generates an aldehyde unit which can be elaborated to form the α-side chain of the prostaglandin. This strategy avoids the troublesome double bond isomerization that is essential in other published routes (Scheme 8).*[38]

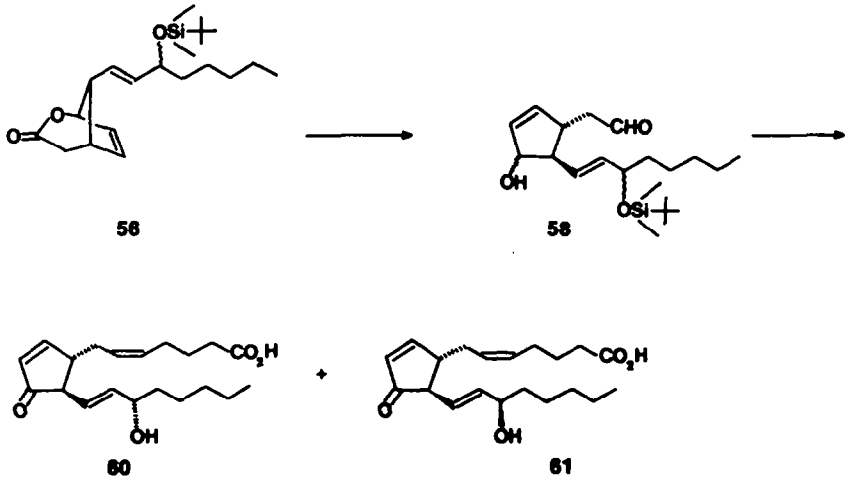
Section 2j



32 56 57

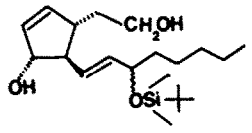
Dehydrobromination of the bromolactone (**32**) was achieved using diazabicycloundecene (DBU) in boiling toluene. The unsaturated lactone **56** was isolated 78% yield and was rearranged to the γ-lactone **57** (65%) on heating in dimethylformamide:[39] de-silylation occurred to a small extent under the latter reaction conditions. The γ-lactone **57** has been converted into prostaglandin A_2 (see Section 4d).

Section 2k



56 58 60 61

Partial reduction of the lactone (**56**) using di-isobutylaluminium hydride gave the hydroxyaldehyde (**58**, 65%)[40] after chromatography to remove the diol (**59**). A Wittig reaction followed by a Collins



59

oxidation and removal of the silyl group gave 9-deoxa-9,10-dehydro-prostaglandin D_2 (**60**)[41] and the C-15 epimer (**61**).[42]

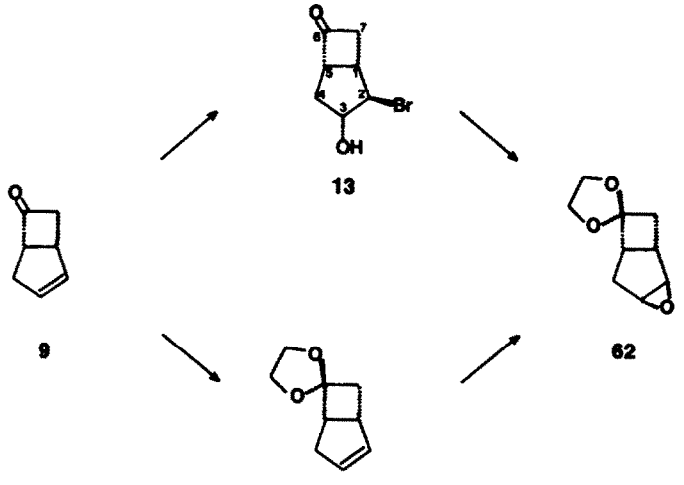
Summary

The prostanoid (**60**) *has not been isolated from natural sources as yet, but does possess potent biological activity. This route* (*a*)–(*d*), (*j*), (*l*) *provides this interesting molecule in nine steps from the ketone* (**9**) (*see also Section* 5).

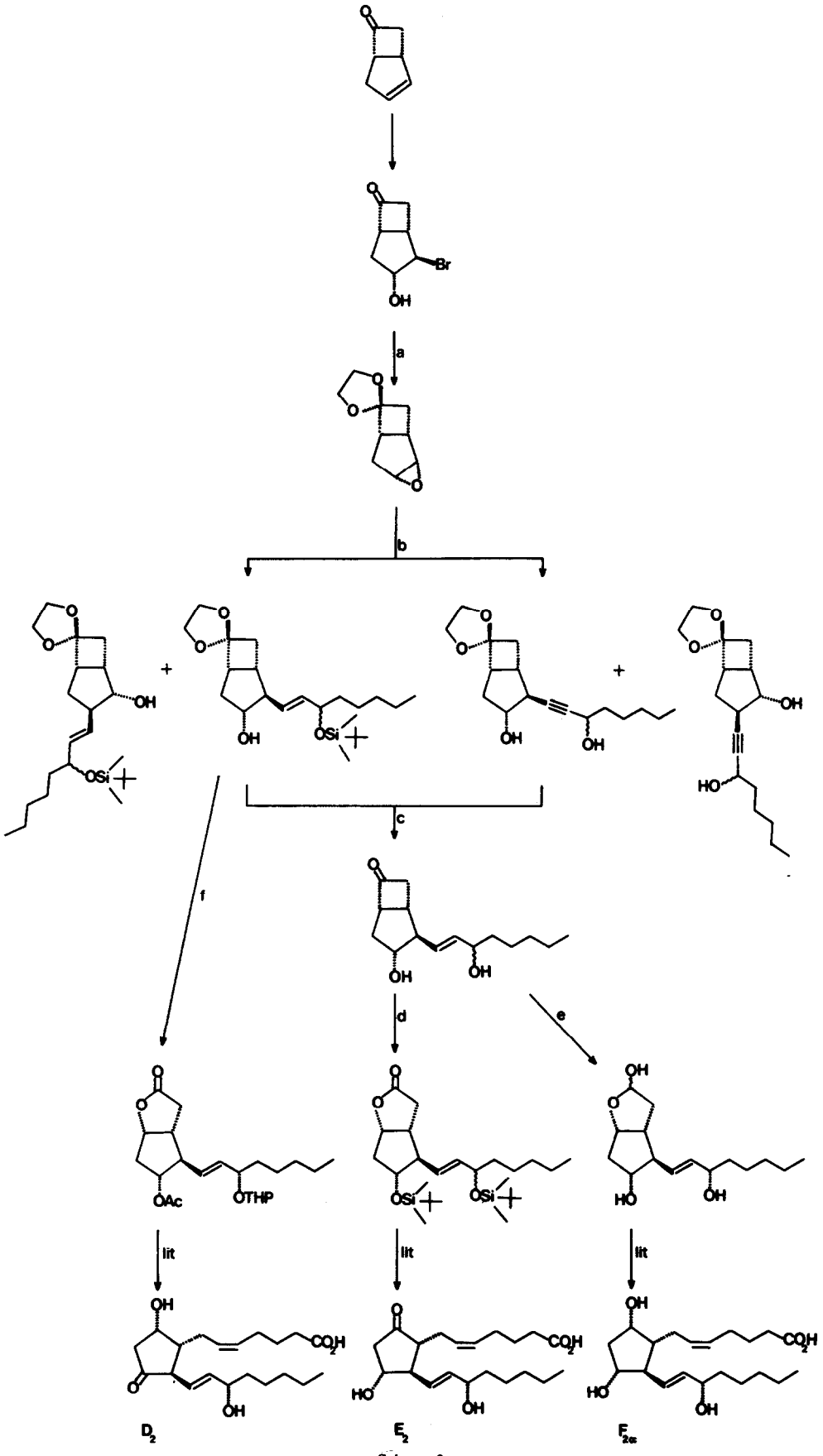
3. SYNTHESIS OF PROSTAGLANDINS D_2, E_2 AND $F_{2\alpha}$ FROM 3-OXATRICYCLO[4.2.0.0^{2,4}]OCTAN-7-ONE KETAL

The bromoketone (**13**) is readily available (Section 2a). Conversion into advanced prostaglandin intermediates involves replacement of the bromine atom at C–2 with the octenol side chain (in whole or in part) with retention of configuration. In Section 2 we illustrated that this can be achieved by protection of the OH group before performing two S_N2 (inversion) reactions at C–2 using a carbanion formed at C–7 for the initial displacement followed by *cine*-substitution using a cuprate reagent. In this section we show that the oxygen atom bonded to C–3 can be used for the initial nucleophilic attack: subsequent epoxy-ring opening by organometallic reagents is partially stereo-controlled by the adjacent 4-membered ring as indicated in Scheme 9 and described in detail in this section. These complementary synthetic approaches to prostaglandin $F_{2\alpha}$ from the same intermediate have some interesting stereochemical consequences which are discussed in Section 6.

Section 3*a*

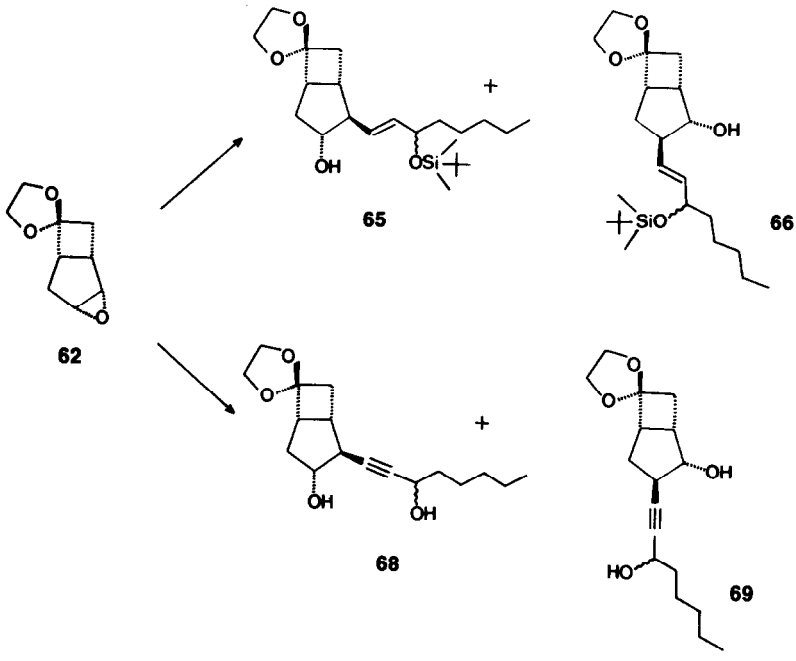


Ketalization of the bromohydrin (**13**) followed by base treatment formed the epoxyketal (**62**).[43] A more practicable route to this epoxy-ketal involved ketalization of bicycloheptenone (**9**) followed by a "one-pot" bromohydroxylation-dehydrobromination procedure which gave the desired compound **62** in 72% yield[44] from the ketone **9**.

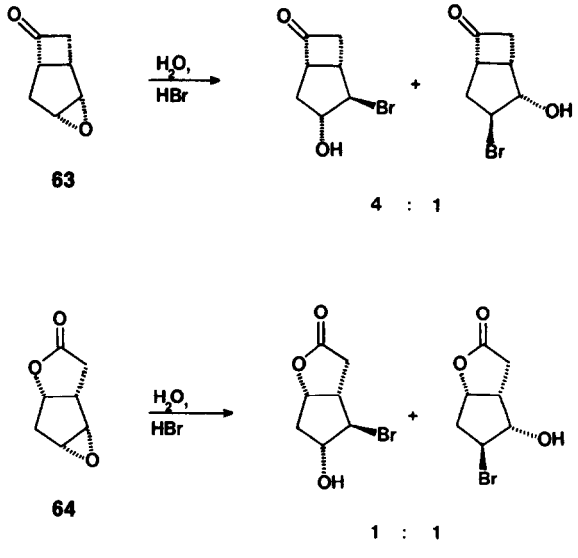


Scheme 9.

Section 3b



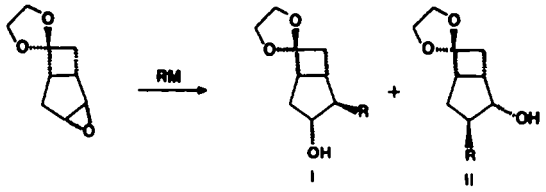
Regioselective ring-opening of the epoxide (**62**) was crucial in this synthetic route. Earlier work involving acid-catalysed epoxy-ring opening of the epoxyketone (**63**) and the epoxylactone (**64**) indicated that the 4-membered ring exerted some control of the regioselectivity of the nucleophilic attack (Scheme 10).[45]



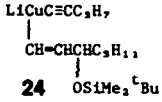
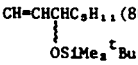
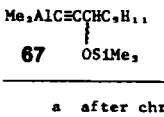
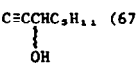
Scheme 10.

Similarly the epoxyketal (**62**) was attacked by a wide variety of organometallic reagents with pronounced regioselectivity in the desired sense (Table 4).[46]

Table 4. Reaction of 3-oxatricyclo[4.2.0.0^{2,4}]octan-7-one ketal with some organometallic reagents



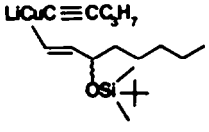
I II

Organometallic Reagent	Temp.	Yield (%)	Products formed (ratio)
C_4H_9MgCl/CuI	-30°	98	(I)(II) R = C_4H_9 (80:20)
	-20°	91[a]	(I)(II) R =  (73:27)
LiCH(SMe)CH=CHSMe	-78°	72[a]	(I)(II) R = CH(SMe)CH=CHSMe (83:17)
 **24**	-30°	86[a]	(I)(II) R =  (80:20)
 **67**	80°	97[b]	(I)(II) R =  (67:33)

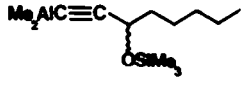
a after chromatography

b after desilylation and chromatography

Two reactions of the epoxide **62** are particularly noteworthy; first with the cuprate reagent **24** to give the prostaglandin synthon **65** (69%) and isomer **66** (17%) and secondly with the alane **67** to give after desilylation and chromatography the desired alkynol **68** (65%) and the isomer **69** (32%).

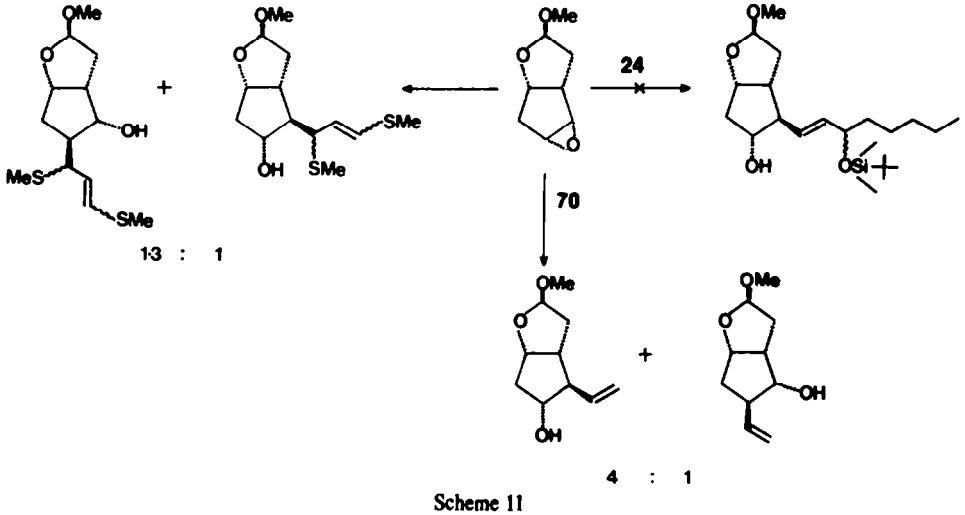


24



67

In contrast the epoxyacetal (**70**) reacted regioselectively with LiCu $(CH{=}CH_2)_2$,[47] but non-selectively with $LiCH(SCH_3)CH{=}CHSCH_3$[48] and not at all with the reagent **24** (Scheme 11).[49]



1·3 : 1

4 : 1

Scheme 11

We believe that epoxy-ring opening in the bicyclo[3.2.0]heptane system is controlled by the presence of the relatively inflexible 4-membered ring such that the preferred diaxial opening of the oxirane ring takes place through transition state (a) rather than transition state (b), while in the more flexible oxabicyclo[3.3.0]octanone system there is little difference in energy between the two possible transition

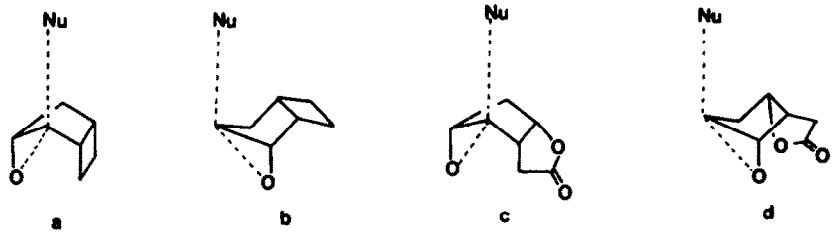
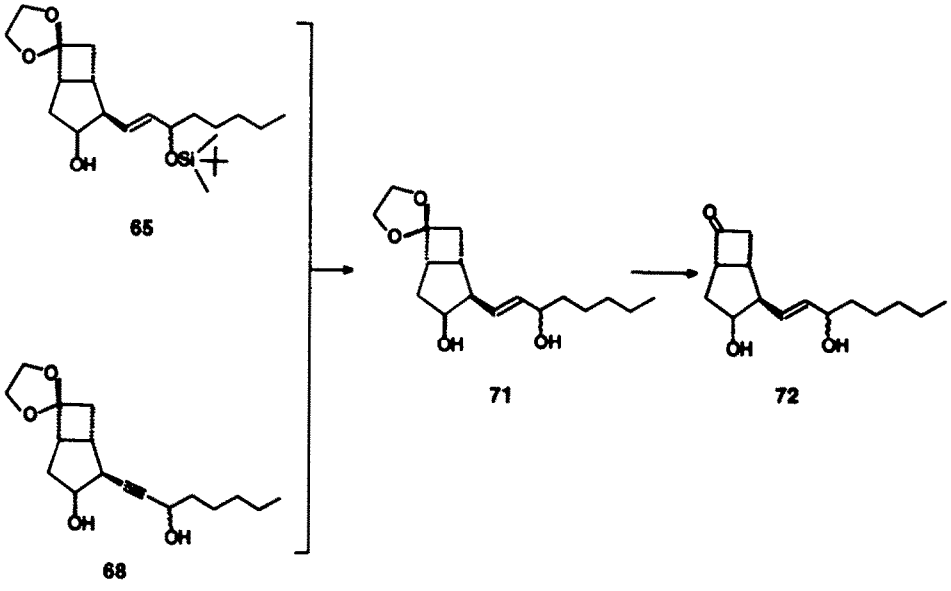


Fig. 3.

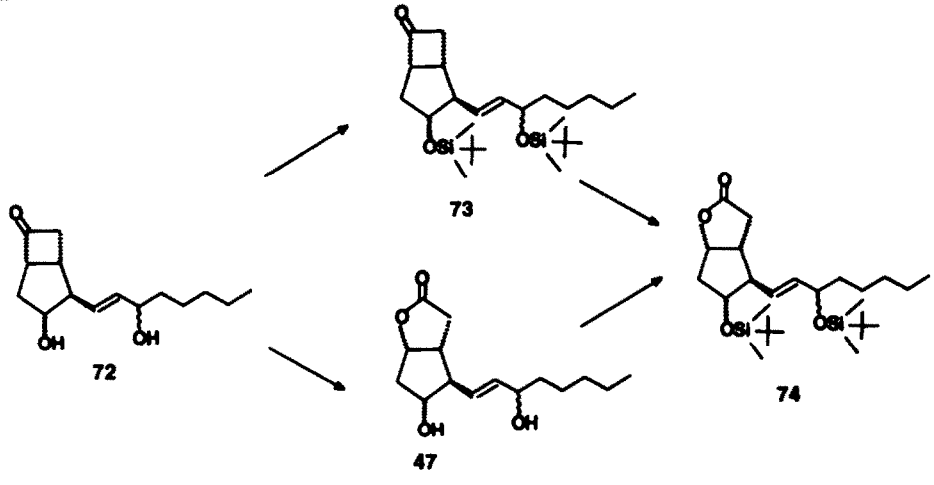
states (c) and (d) generally leading to a regiorandom substitution pattern (Fig. 3).

Section 3c

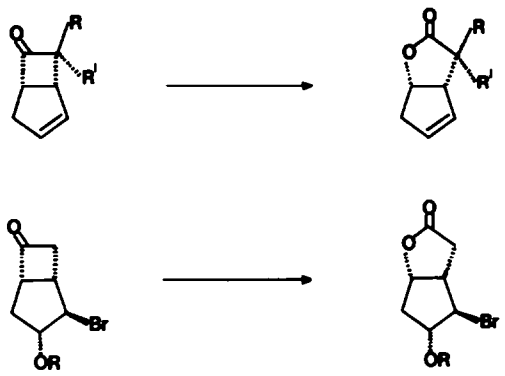


Desilylation of the ketal (**65**) or lithium aluminium hydride reduction of the alkyne (**68**) afforded the dihydroxyketal (**71**) in high yield, the 15(*S*)- and 15(*R*)- components of which were readily separated. The dihydroxyketal **71** gave the ketone **72** upon treatment with aqueous acid.

Section 3d

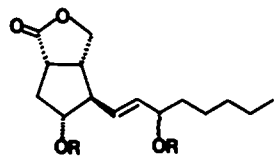


Simple bicyclo[3.2.0]hepten-6-ones[50,51] and bicyclo[3.2.0]heptan-6-ones[20] undergo Baeyer–Villiger oxidation with peracid to give the ring expanded product resulting from highly selective migration of the methine group (Scheme 12).



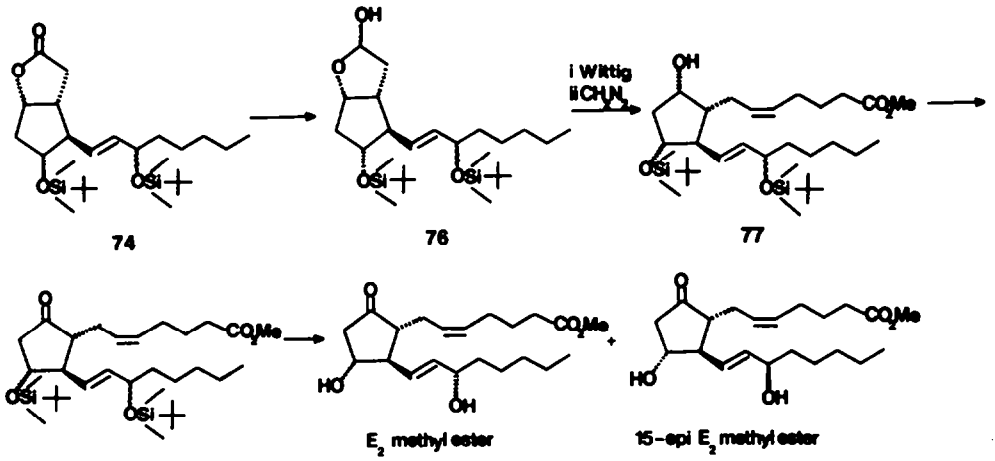
Scheme 12.

The dihydroxyketone (72) readily formed the bis-silyoxyketone (73) but oxidation of either ketone using a variety of peracids at ambient temperature led to the formation of unacceptable quantities (up to 20%) of the isomeric lactone system (75). This problem was overcome by oxidizing the ketone (72) with *m*-chloroperoxybenzoic acid at low temperature to give a 96% yield of the lactone (47). Silylation of the OH groups gave the lactone (74).



75 R = H or $SiMe_2{}^tBu$

The bis-silyloxylactone (74) was converted into prostaglandin E_2 according to prescribed procedures (Scheme 13)[33,35] but with two important improvements. First the Wittig reaction was carried out in



Scheme 13.

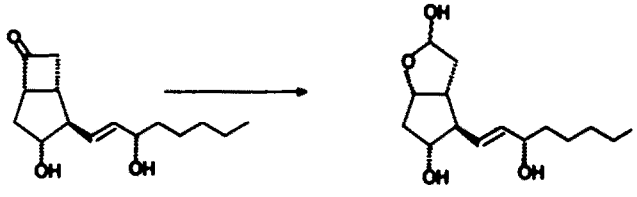
benzene at 75° using potassium-t-butoxide as the base and was quenched after 10 mins to give the bis-11, 15-silyl derivative (77) in 77% yield along with only 4% of the corresponding bis-9,15-silyl isomer resulting from silyl migration. Secondly the final deprotection step was carried out using aqueous HF in acetonitrile. In this way prostaglandin E_2 and 15-*epi*-prostaglandin E_2 were obtained in virtually quantitative yield. Using the literature method (THF, H_2O, CH_3CO_2H) for deprotection we obtained the

required products in 40% yield along with considerable amounts of prostaglandin A_2 and 15-*epi* prostaglandin A_2.

Summary

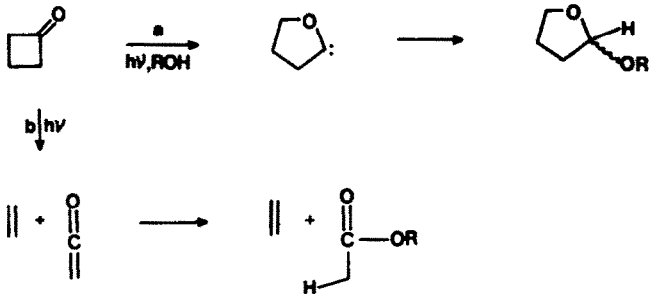
Prostaglandin E_2 is available from bicyclo[3.2.0]hept-2-en-6-one (9) in eleven steps (a–d) (Scheme 9).

Section 3e



72 78

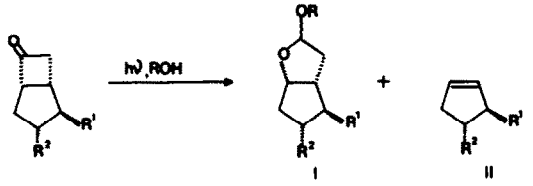
An attractive alternative to the Baeyer–Villiger reaction for the conversion of a cyclobutanone into a 2-substituted tetrahydrofuran involves photolysis of the former species in an appropriate protic solvent.[53] An oxacarbene is the proposed intermediate[54] (Scheme 14, path a): the major side reaction that can occur is the formation of an ester and an alkene *via* a cycloelimination process (Scheme 14, path b).



Scheme 14.

Photolysis of 2-*exo*, 3-*endo*-disubstituted bicyclo[3.2.0]heptan-6-ones in methanol led to only modest yields of the required acetals (Table 5).[43,55] Roughly equimolar quantities of the cyclopentene derived by retro[2 + 2]-cycloaddition were formed concurrently.

Table 5. Photolysis of some Bicyclo[3.2.0]heptan-6-ones in methanol or water



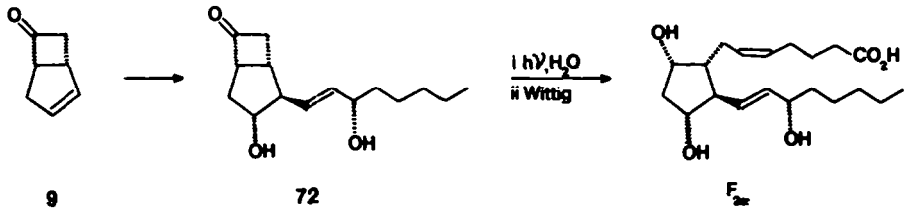
I II

R^1	R^2	R	Yield of I[a] (%)	Yield of II[a] (%)
CH(SMe)CH=CHSMe	OH	Me	33	18
CH=CHCHC$_5$H$_{11}$ (OH)	OH	Me	31	37
		H	40[b]	15
CH=CHCHC$_5$H$_{11}$ (OTHP)	OAc	Me	35	28
		H	50[b]	15

a after chromatography

b unstable compound

The synthetic potential of the photolysis procedure was dramatically improved by conducting the photo-reactions in aqueous acetonitrile or aqueous tetrahydrofuran (Table 5).[56] In these solvent systems photolysis of the ketone (72) gave only a small quantity of the non-polar alkene and a moderate amount of the required lactol (78) was isolated by chromatography. In view of the instability of this γ-lactol it seemed prudent to perform the subsequent Wittig reaction directly on the crude photolysis product. Using this strategy the readily available dihydroxyketone (72) gave prostaglandin $F_{2\alpha}$ in a highly satisfactory 48% yield[57] (Scheme 15).



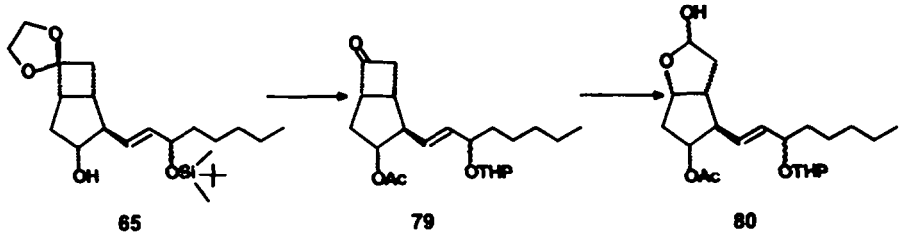
Scheme 15.

In short the photolytic procedures using methanol afforded acetals. Yields were modest and the acetals needed further treatment to generate the required lactols. However the lactols could be obtained directly and in good yield from the cyclobutanone on conducting the photolyses in an aqueous medium.

Summary

The synthetic pathway a–c, e (Scheme 9) represents the shortest synthesis of prostaglandin $F_{2\alpha}$ yet devised.

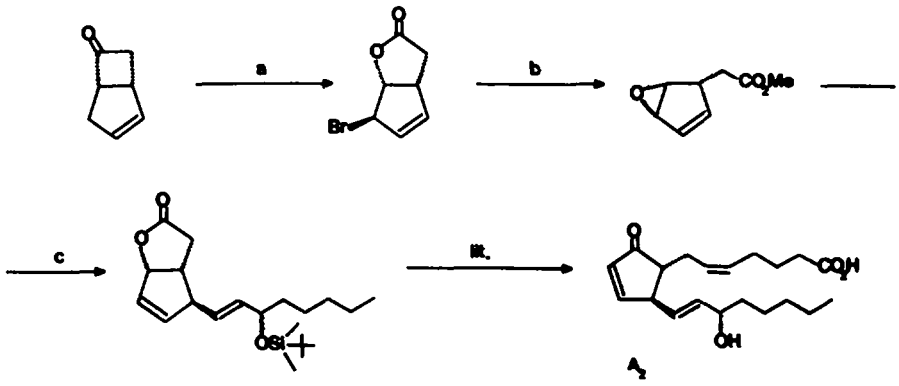
Section 3f



By redeployment of protecting groups the ketoester (79) is available from the hydroxyketal (65). Photolysis of the cyclobutanone (79) in aqueous tetrahydrofuran afforded the lactol 80 (Table 5) a known precursor to prostaglandin D_2.[58]

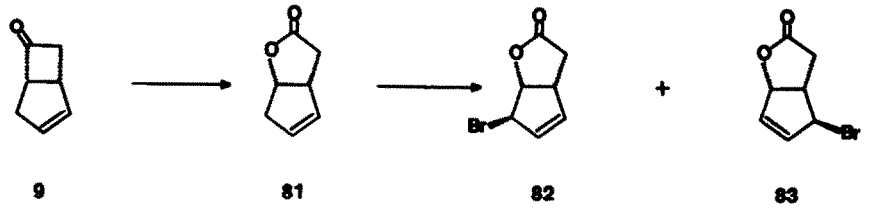
4. SYNTHESIS OF PROSTAGLANDIN A_2 AND ANALOGUES FROM 6-OXABICYCLO[3.1.0]HEX-2-ENE DERIVATIVES

In the synthetic route to prostaglandin A_2 described below (Scheme 16) the ability of a cuprate reagent to perform an S_N' *anti* reaction with an allyl epoxide is utilized.



Scheme 16.

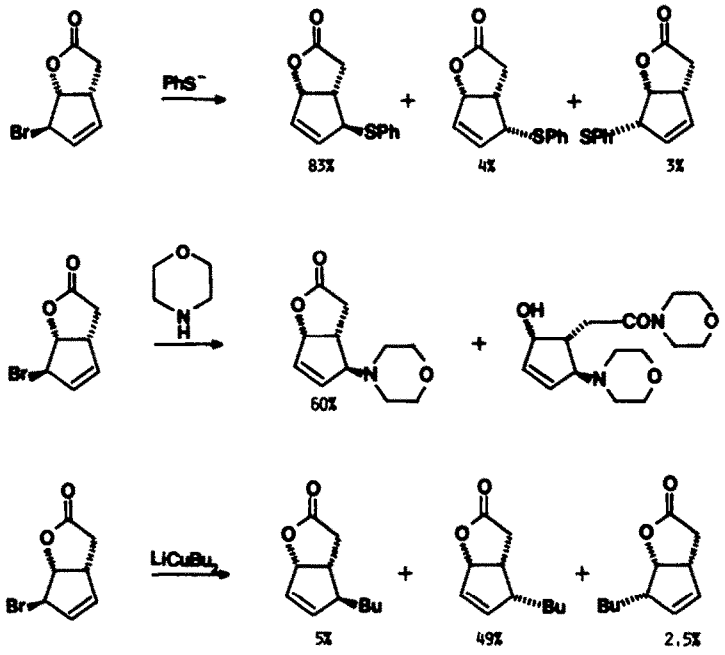
Section 4a



9 81 82 83

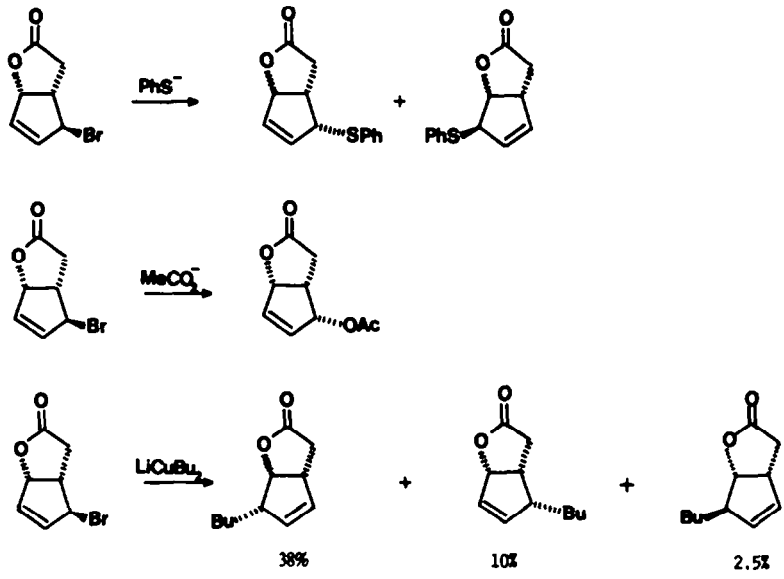
2-Oxabicyclo[3.3.0]oct-6-en-3-one (**81**) is available from the ketone (**9**) by peracetic acid oxidation.[50] Allylic bromination of the lactone (**81**) using N-bromosuccinimide in carbon tetrachloride under floodlamp irradiation gave a mixture of the isomeric lactones (**82** and **83**; ratio 3:2) from which the required isomer (**82**) could be isolated (35%) by fractional crystallization.[59] Further quantities of this material were obtained by refluxing in toluene the mother liquors of the crystallization which contained a mixture of bromolactones (**82**, **83**) that was rich in the unwanted isomer (**83**). A 1,3-halogen shift occurred to give a reconstituted mixture of **82** and **83** (ratio 4:1); this ratio was also attained on refluxing pure samples of the lactones (**82** and **83**) in toluene indicating that the observed ratio probably results from a thermodynamic control. In this way the bromolactone (**82**) was produced from the ketone (**9**) in 50% overall yield.

The bromolactone (**82**) reacted with simple nucleophiles e.g. thiophenoxide ion and morpholine primarily in the S_N' *syn* manner (Scheme 17).[60] It should be noted that attack at C–8 from the *endo*-face



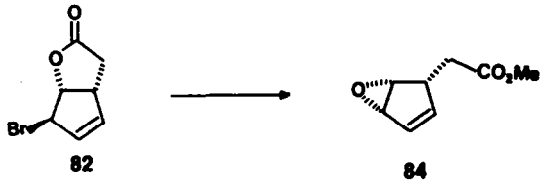
Scheme 17.

(S_N2 reaction) is made unfavourable by the adjacent lactone ring. In contrast lithium dibutyl cuprate reacted with the lactone (**82**) in S_N' *anti* fashion preferentially (Scheme 17). Others workers have recently shown that cycloalk-2-enyl epoxides[61,62] and esters[63] and allyl ethers[64] react with cuprate reagents to give rearranged (S_N') and/or unrearranged (S_N2) products with complete inversion of configuration. The isomeric bromolactone (**83**) reacts with thiophenoxide ion in S_N2 and S_N' *syn* fashion to an equal extent and with the less bulky acetate ion through S_N2 displacement only, while lithium dibutyl cuprate again reacted in S_N' *anti* fashion preferentially (Scheme 18).



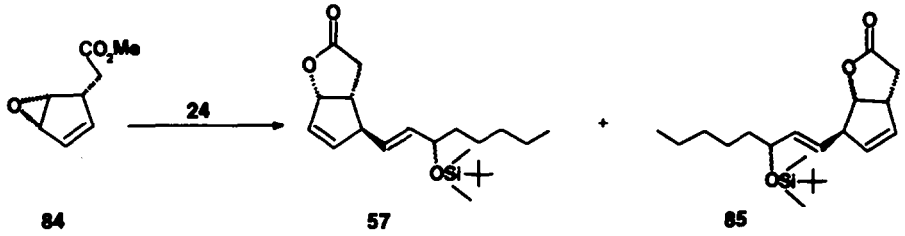
Scheme 18.

Section 4b



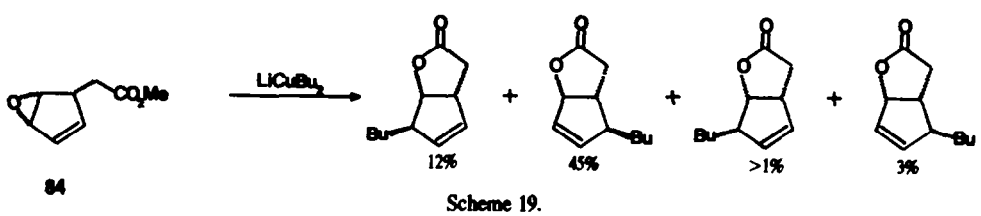
The above results highlight the tendency for cuprate reagents to perform S_N' *anti* reactions. Hence in order to use such reagents to introduce the octenol side chain of the prostaglandin the leaving group on the cyclopentene ring must be appropriately situated and *cis* to the acid side chain precursor. This was quite simply arranged by treating the bromolactone (**82**) with potassium carbonate in methanol whereupon the epoxyester (**84**) was formed in 83% yield. Unfortunately the bromolactone (**83**) could not be converted into the desired epoxide via an intramolecular S_N' *anti* reaction under these or more forcing conditions.

Section 4c



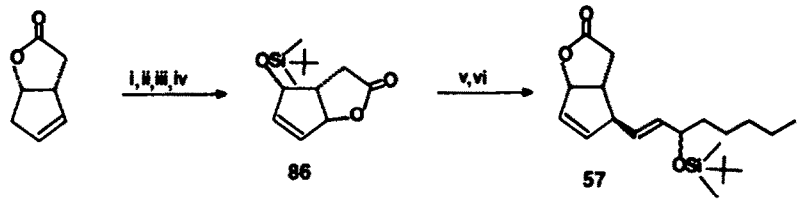
The alkenylcuprate reagent (**24**) reacted with the epoxy ester (**84**) to give two products, the desired prostaglandin A_2 precursor (**57**; 43%) and the isomer (**85**; 14%).

Similarly treatment of the epoxyester (**84**) with the more reactive lithium dibutyl cuprate gave a mixture of four butyllactones with the product formed from the S_N' *anti* mode of reaction being predominant (Scheme 19).



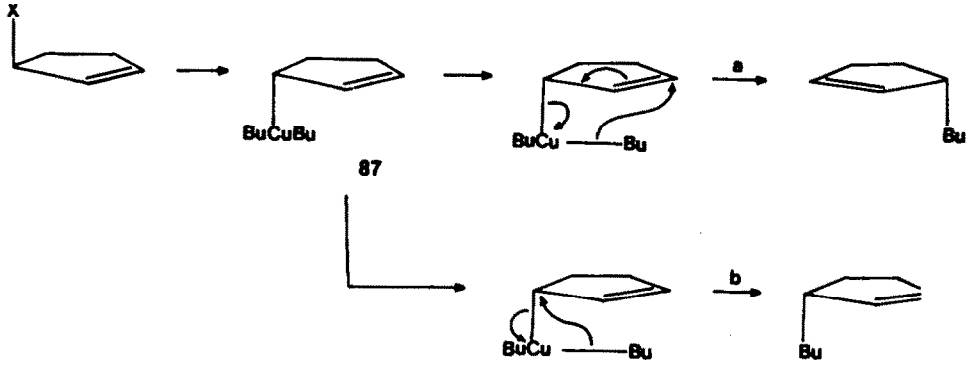
Scheme 19.

Corey *et al.* prepared the lactone (**57**) through an S_N2 reaction of the silyloxylactone (**86**) with a homocuprate reagent (Scheme 20).[65]



Scheme 20. Reagents: i, OH^-; ii, KI_3; iii, $^tBuSiMe_2Cl$; iv, DBN; v, $LiCu[CH{:}\ CHCH(OSiMe_2{}^tBu)C_5H_{11}]_2$; vi, H^+.

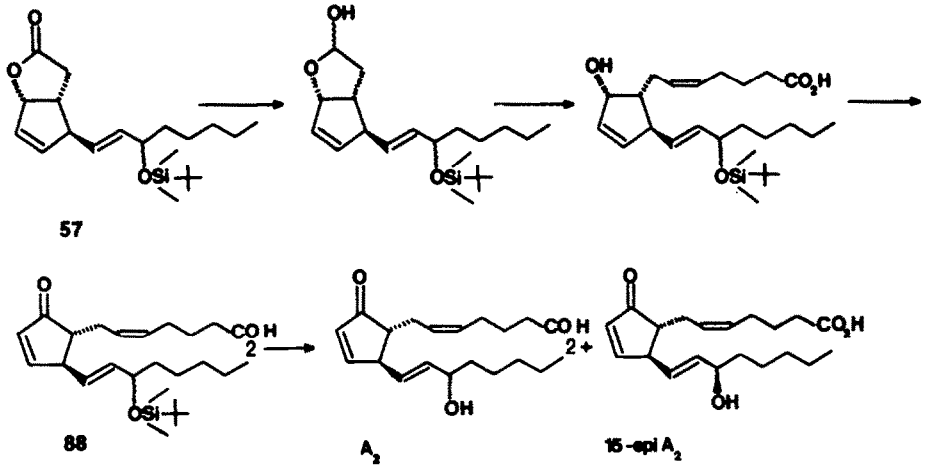
These workers did not report the isolation of the lactone (**85**) derived by an S_N' *anti* reaction† although the same lactone (**86**) reacted with lithium dibutyl cuprate to give roughly equimolar amounts of the products derived from S_N2 and S_N' reactions.[66]



Scheme 21.

We believe[60] that the allyl bromides (**82** and **83**) and the allyl epoxide (**84**) suffer nucleophilic substitution by the cuprate reagents with inversion of configuration to give either an allyl copper (III) intermediate (**87**)[67] or a π-allyl complex which maintains stereochemical integrity.[64] Migration of the alkyl ligand can take place with (path a) or without (path b) rearrangement of the double bond to give the products of S_N' *anti* and S_N2 alkylation respectively (Scheme 21). Other workers results[61–64] may also be interpreted in this way.

Section 4d



†Added in proof: We have repeated this experiment and in contrast to the literature report we consistently obtain a mixture of lactones (**57**) and (**85**) (60% yield) in the ratio 1:3.

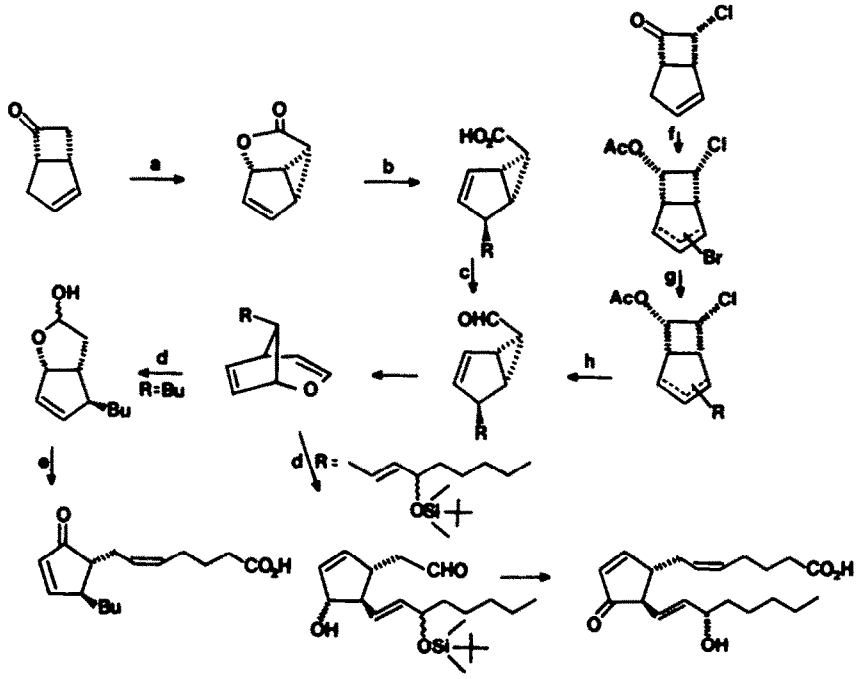
Previously reported methods[68] were used to convert the lactone **57** into the 15-protected prostaglandin A_2 (**88**); the final desilylation step was performed in quantitative yield using aqueous HF in acetonitrile. Prostaglandin A_2 and its C–15 epimer are readily separated by chromatography.

Summary

The synthesis of prostaglandin A_2 described in Scheme 16 is simple and efficient and the number of steps involving the protection and deprotection of functional groups is minimized.

5. SYNTHESIS OF 9-DEOXA-9,10-DEHYDROPROSTAGLANDIN-D_2 AND PROSTAGLANDIN-A_2 ANALOGUES USING 4-SUBSTITUTED BICYCLO[3.1.0] HEX-2-EN-6-*ENDO*-CARBOXALDEHYDES

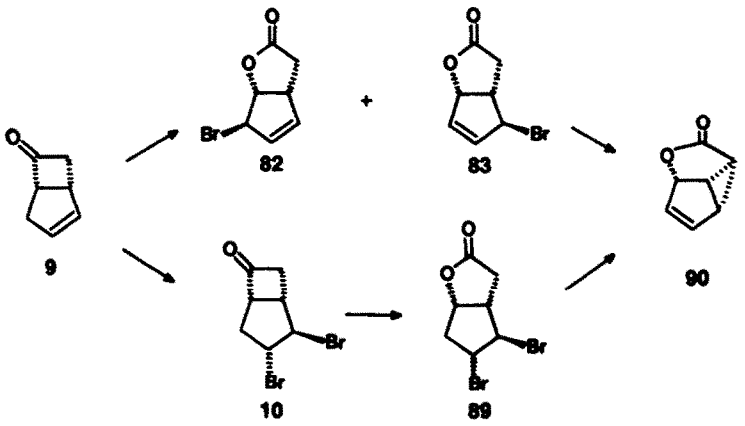
2-Oxatricyclo[3.3.0.$0^{4,6}$]oct-7-en-3-one undergoes acyloxy group displacement on reaction with a cuprate reagent (Scheme 22). The 4-substituted bicyclo[3.1.0]hex-2-en-6-*endo* carboxylic acid so formed



Scheme 22.

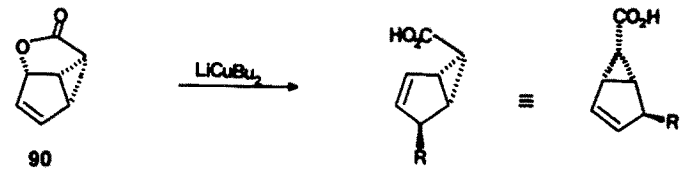
is converted into the corresponding carboxaldehyde which undergoes a Cope rearrangement to form an 8-substituted 2-oxabicyclo[3.2.1]octa-3,6-diene (Scheme 22). An alternative very efficient route to this aldehyde enol-ether system involves hydrolysis and subsequent rearrangement of the readily available 6(7)-acetoxy-4-substituted 7(6)-chlorobicyclo[3.2.0]hept-2-enes. Acid hydrolysis of the aldehyde⇌enol ether mixture leads to a γ-lactol which can be converted into a prostaglandin A_2 analogue *or* into an hydroxy aldehyde which is a precursor to 9-deoxa-9,10-dehydroprostaglandin D_2.

Section 5a



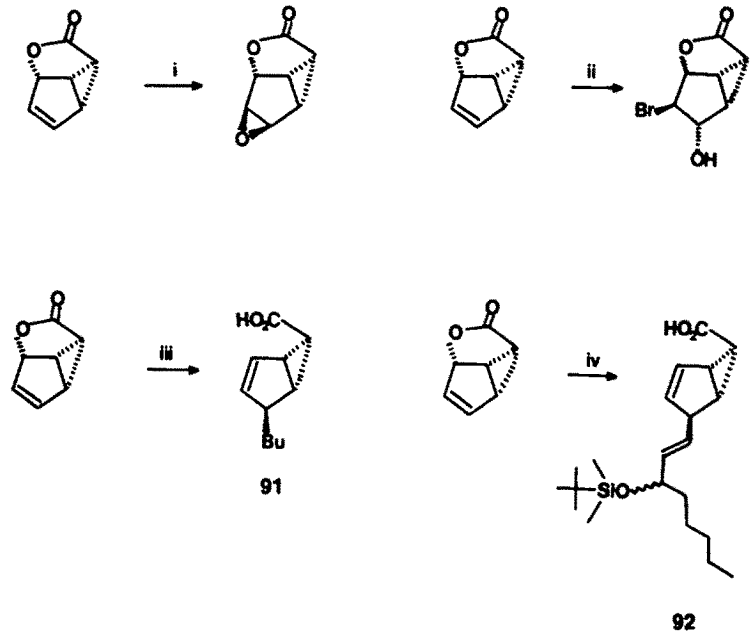
The ketone (**9**) is readily converted into the lactones **82** and **83** (Section 4a). The dibromolactone (**89**) is prepared by Baeyer-Villiger oxidation of the ketone **10** (Section 3c). Treatment of the allyl bromides (**82** and **83**) with potassium *t*-butoxide or treatment of the dibromolactone (**89**) with DBU gave the strained tricyclic ketone (**90**)[69] (the formal adduct of carbon dioxide and benzene).

Section 5b



90

The alkene unit within the tricyclic lactone (**90**) is attacked by electrophilic reagents from the exposed *exo*-face while cuprate reagents react by displacement of the activated acyloxy unit (Scheme 23). Thus the butyl compound (**91**) and the prostanoid precursor (**92**) can be prepared in 60–70% yield.[42]

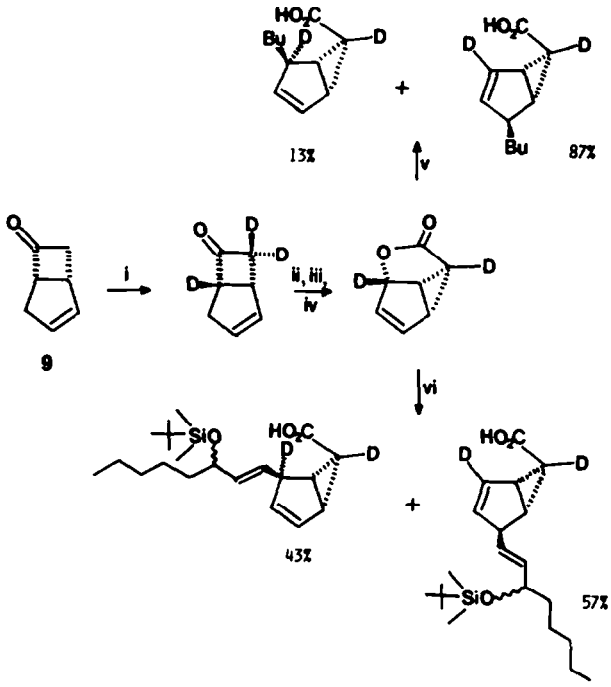


91

92

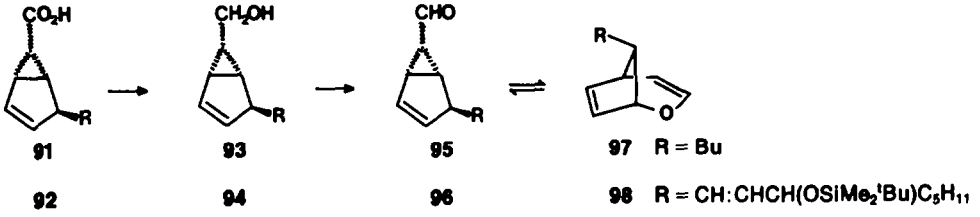
Scheme 23. Reagents. (i) *m*-Chloroperoxybenzoic acid (ii) NBA, H_2O, Me_2CO, (iii) $LiCuBu_2$ (iv) $LiCu[CH:CHCH(OSiMe_2{}^tBu)C_5H_{11}]_2$

Deuteration studies (Scheme 24) indicate that the cuprate reagents react with the lactone (**90**) primarily through an S_N' mechanism, although with the octenyl cuprate reagent the products of the two mechanistic pathways are formed in almost equal amounts.[66] In the light of the recent observation that lithium cyanocuprate reagents show a greater tendency to perform S_N' reactions than simple cuprate reagents,[62] it seems that the proportion of product resulting from the S_N' route could be further increased in the above reactions.



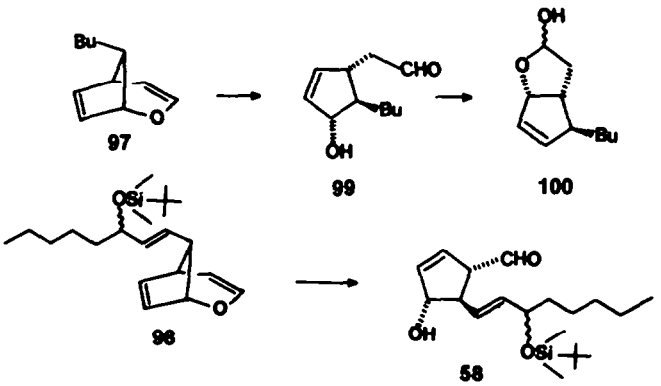
Scheme 24. Reagents. i, D_2O, NaOD, CH_2Cl_2, ii, Br_2, iii *m*-chloroperoxybenzoic acid, iv, DBU, v, $LiCuBu_2$, vi $LiCu[CH:CHCH(OSiMe_2{}^tBu)C_5H_{11}]_2$

Section 5c

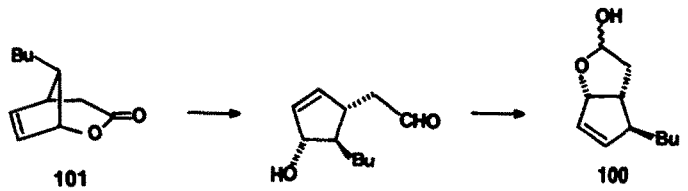


The acids (**91** and **92**) were converted into the corresponding aldehydes (**95** and **96**) by a two-step procedure involving lithium aluminium hydride reduction to the corresponding alcohols (**93** and **94**) followed by a controlled oxidation using Collin's reagent. Like the parent aldehyde[70] the 4-substituted compounds (**95** and **96**) exist in equilibrium with the appropriate enol ethers (**97** and **98**) through a Cope rearrangement: the ratio of aldehyde to enol ether as judged by NMR spectroscopy was *ca* 4:1 in favour of the aldehyde in both cases.

Section 5d



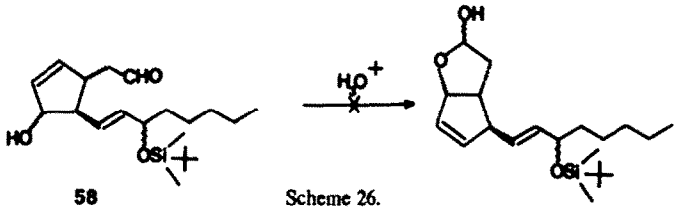
The butyloxabicyclooctanone (**97**) was hydrolysed (aqueous oxalic acid) to the butyllactol (**100**) presumably through the intermediacy of the δ-hydroxyaldehyde (**99**). Indeed the latter aldehyde (**99**) was prepared from the lactone (**101**) by partial reduction and was converted into the lactol (**100**) under the same acid conditions (Scheme 25).



101 99 100

Scheme 25.

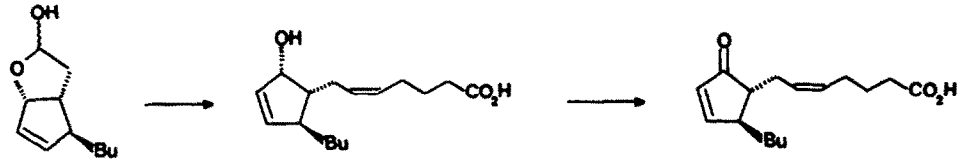
In contrast, the enol ether (**98**) afforded the hydroxyaldehyde (**58**) on treatment with an ether-aqueous HCl two-phase system and neither this hydroxylaldehyde (**58**) nor the desilylated material could be induced to rearrange to the corresponding γ-lactol (Scheme 26) under a variety of acidic conditions.



58 Scheme 26.

Instead, the aldehyde (**58**) was converted into 9-deoxa-9,10-dehydroprostaglandin D_2 (**69**) as described above (Section 2k).

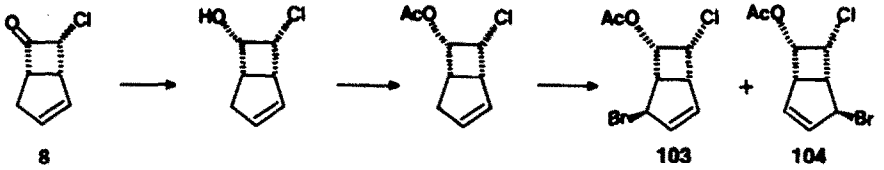
Section 5e



100 102

Standard methodology (*viz.* a Wittig reaction followed by a Jones oxidation) was employed to convert the lactol (**100**) into the desired prostaglandin A_2 analogue (**102**).[71]

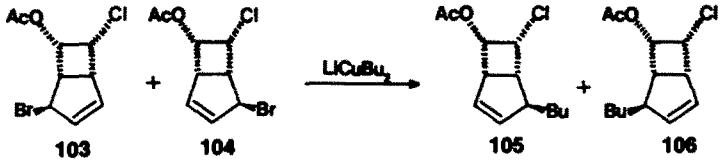
Section 5f



8 103 104

Conversion of the readily available chloroketone (**8**)[72] into the dihaloesters (**103** and **104**) involved stereospecific borohydride reduction,[73] acetylation and allylic bromination. The two isomers (**103** and **104**) could be separated by crystallization and chromatography but this operation was non-essential from a synthetic viewpoint.

Section 5g



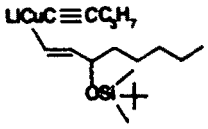
103 104 105 106

Reaction of the mixture of bromoesters (**103** and **104**; ratio 1:1) with lithium dibutyl cuprate gave a mixture of the butylbicycloheptenes (**105** and **106**; ratio 1:1). By performing the same cuprate reaction

on each pure isomer it was shown that a regiospecific S_N' *syn* reaction was occurring.[74] We believe that this takes place through a concerted process (Scheme 27) that does not involve a Cu^{III} intermediate (cf Scheme 21, Section 4d).

Scheme 27.

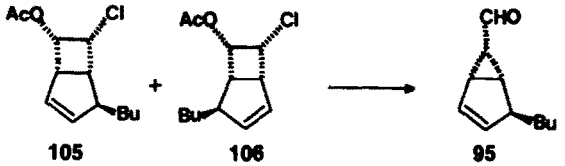
An initial S_N2 reaction to form the Cu^{III} species is thwarted by the presence of the pendant chloro-and acetoxy-substituents. The cuprate reagent (**24**) did not react with the bromoesters (**103** and



24

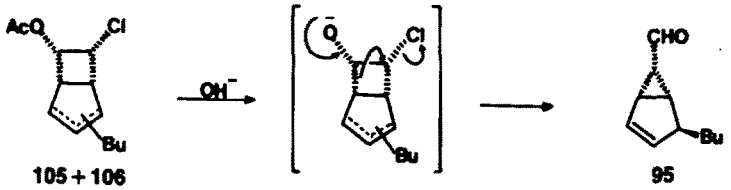
104) in a satisfactory manner.

Section 5h



105 **106** **95**

The butyl compound (**95**) was prepared from the mixture of the bicycloheptenes (**105** and **106**) by hydroxide ion mediated ester cleavage and a subsequent rearrangement (Scheme 28). Such rearrangements have been observed previously on base treatment of simple 7-halobicyclo[3.2.0] hept-2-en-6-ols.[75]



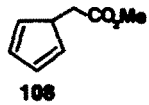
105 + 106 **95**

Scheme 28.

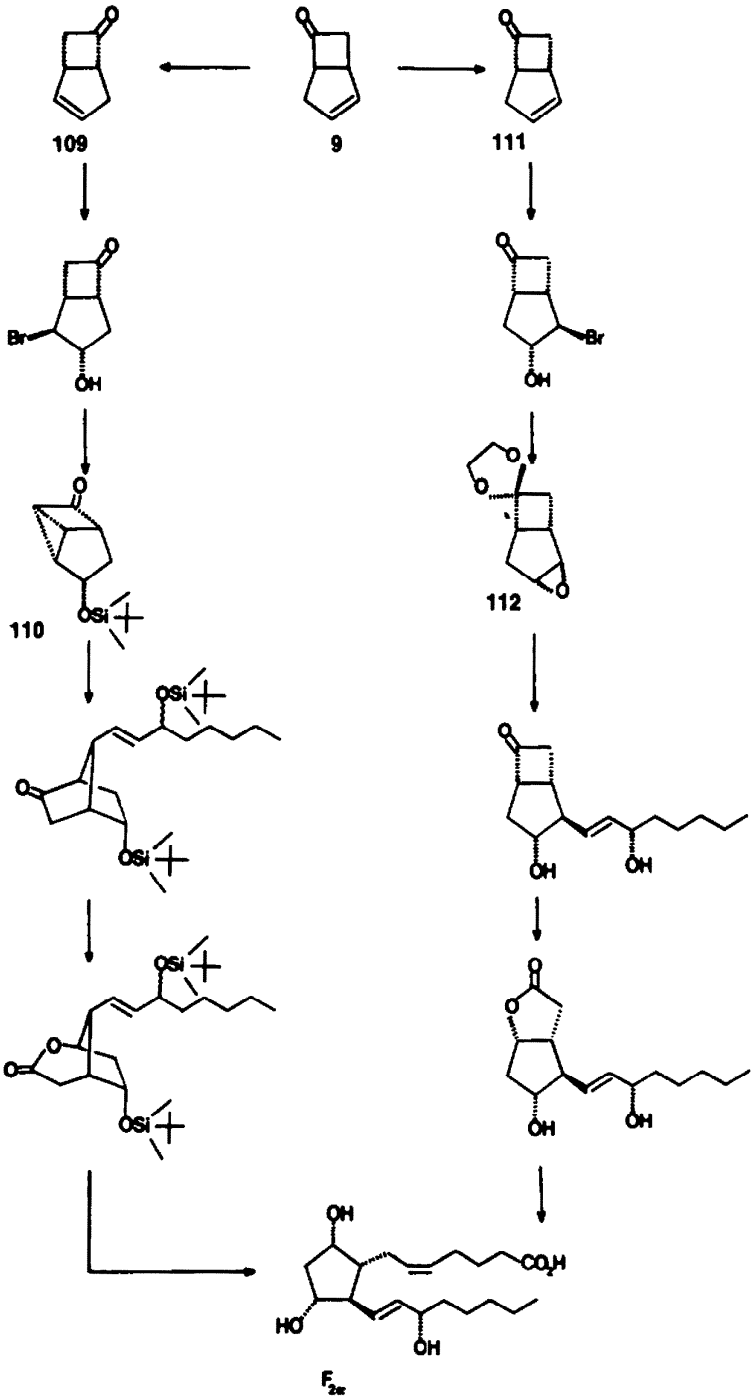
6. ENANTIOSPECIFIC SYNTHESIS OF PROSTAGLANDINS $F_{2\alpha}$, E_2, D_2 AND A_2

The majority of enantiospecific prostaglandin syntheses make use of a classical resolution step and discard the unwanted enantiomer;[76] however this is an expensive and wasteful procedure. Alternatively naturally occuring optically active compounds may be used as starting materials.[77] Several workers have employed optically active reagents to induce asymmetry into prostaglandin precursors. For instance Partridge *et al.*[78] obtained the optically pure lactone intermediate (**107**) via an asymmetric hydroboration reaction on the diene (**108**) using (+)-di-3-pinanylborane. An elegant alternative is to use an enantio convergent synthesis.[79]

107



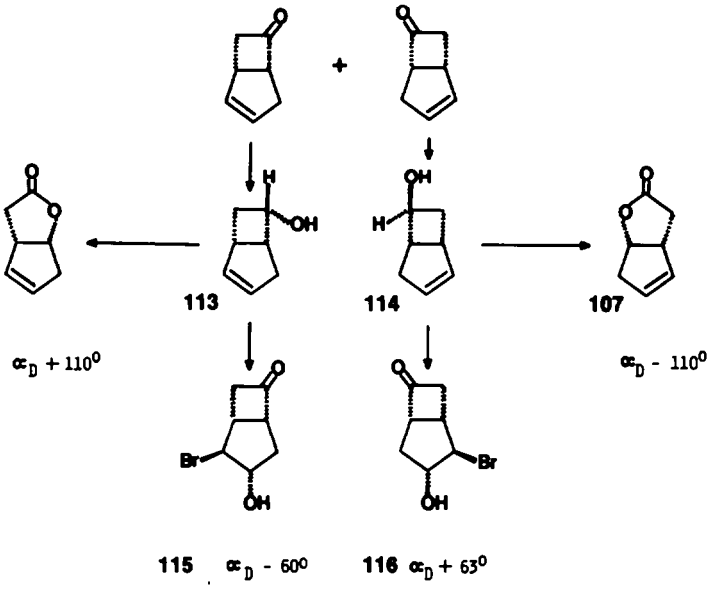
108



Scheme 29.

Our two major routes to prostaglandin $F_{2\alpha}$ are summarised in Scheme 29 and, as can be seen, they are complementary with respect to the enantiospecific synthesis of this prostaglandin. Thus enantiomer (**109**) of bicyclo[3.2.0]hept-2-en-6-one may be converted into natural prostaglandin $F_{2\alpha}$ via the tricyclic ketone (**110**) and enantiomer (**111**) may also be converted into natural prostaglandin $F_{2\alpha}$ but via the epoxide (**112**). A cheap method of resolution was therefore required which could be adapted to large scale preparations of either the enantiomeric bicyclo[3.2.0]hept-2-en-6-ones or the corresponding enantiomeric bromohydrins.

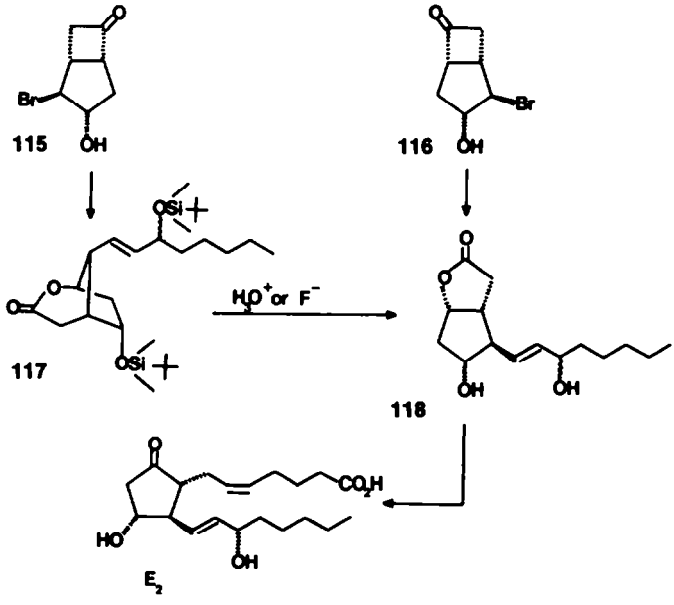
Reduction of the unresolved ketone (**9**) using actively fermenting bakers yeast furnished a mixture of two alcohols (**113** and **114**) which were separable by column chromatography or careful distillation on a spinning band column (Scheme 30).[80] The less polar alcohol (**113**) was shown to have an *endo*-OH group and the more polar isomer (**114**) an *exo*-OH group by NMR spectroscopy. The expected *S*-configuration



Scheme 30.

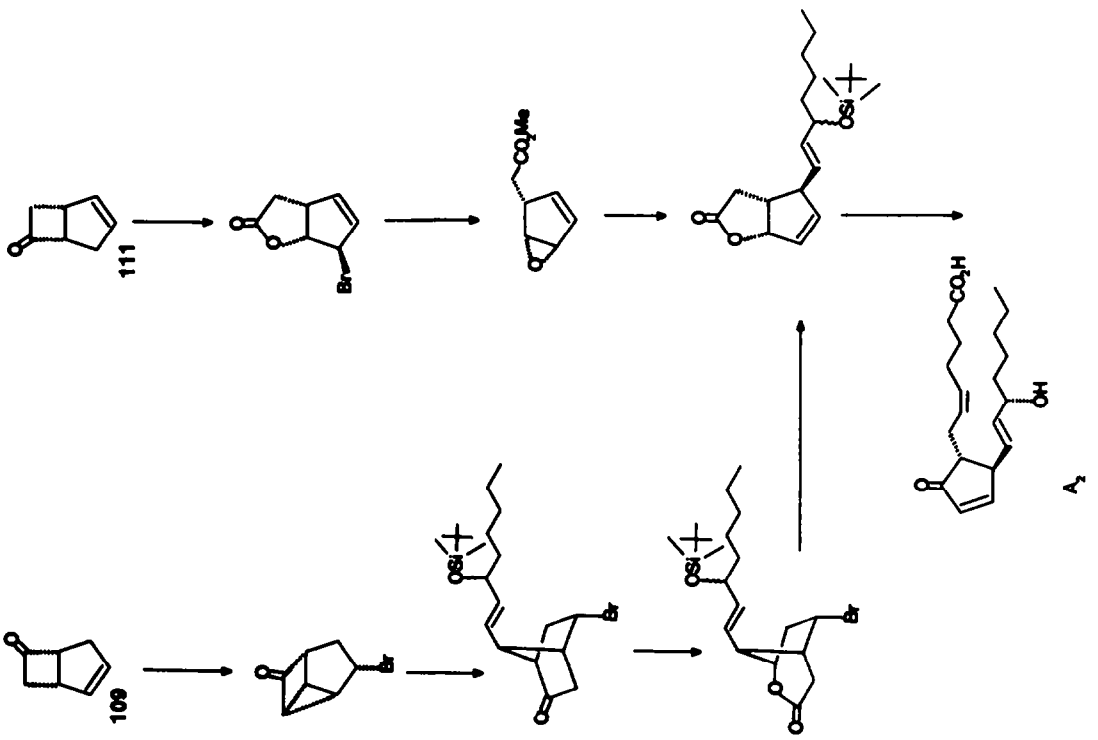
of the alcohols[81] at C–6 was proved by Jones oxidation to the corresponding ketones and subsequent Baeyer–Villiger oxidation. In this way the *exo*-alcohol afforded the known enantiomeric lactone (**107**).[78] Treatment of the alcohols (**113** and **114**) with N,N-dibromo-5,5'-dimethylhydantoin in aqueous acetone containing a trace of acetic acid afforded the corresponding bromohydrins (**115** and **116**) respectively which after one crystallisation were 98 and 100% optically pure. Additional proof of absolute stereochemistry was obtained by an X-ray analysis[10] of the bromohydrin (**115**). This resolution is economical and gives excellent optical and chemical (77%) yields of the alcohols (**113** and **114**). In addition fermentation processes of this type may be carried out on an industrial scale.

Both enantiomeric bromohydrins may also be converted into natural prostaglandin E_2 since rearrangement of the δ-lactone (**117**; Scheme 31) derived from enantiomer (**115**) gives the γ-lactone (**118**)

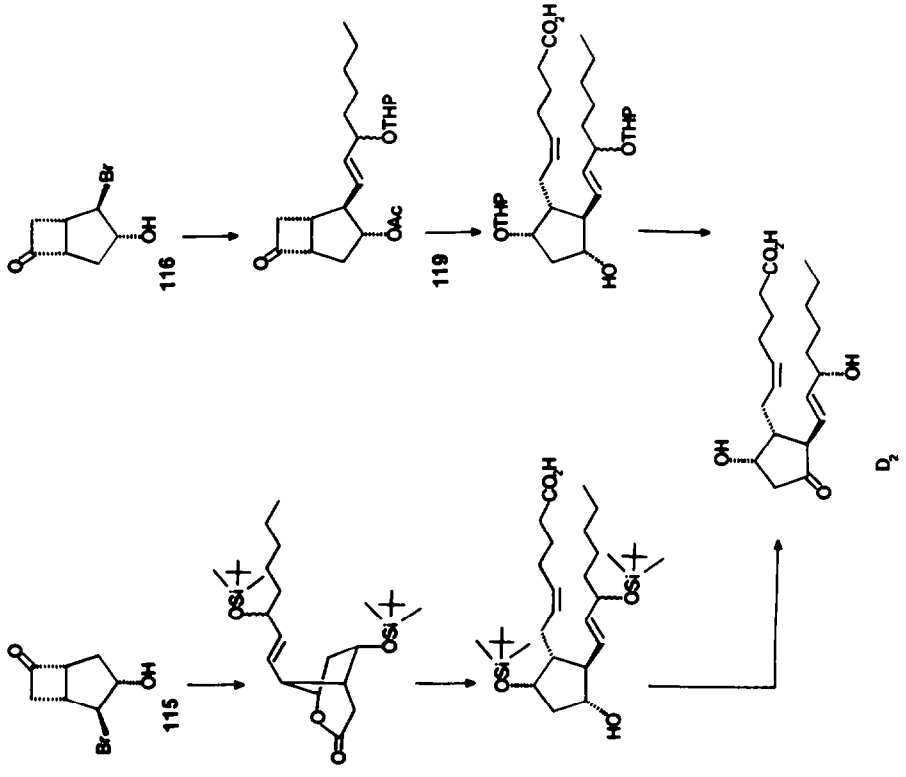


Scheme 31.

which may also be obtained from enantiomer (**116**; Section 2h). Similarly natural prostaglandin D_2 is available from either of the enantiomeric bromohydrins (Scheme 32) although the photolytic route via the acetoxy cyclobutanone (**119**) is not an efficient process (Sections 2g and 3f).



Scheme 33.



Scheme 32.

As can be seen from Scheme 33 natural prostaglandin A_2 may also be prepared from either of the bicyclo[3.2.0]hept-2-en-6-one enantiomers. However since neither of these routes proceeds via the bromohydrins (**115** and **116**) it is necessary to obtain the bicyclic ketones (**109** and **111**) from the corresponding alcohols (**113** and **114**) respectively using a Jones oxidation (Sections 2j and 4c).

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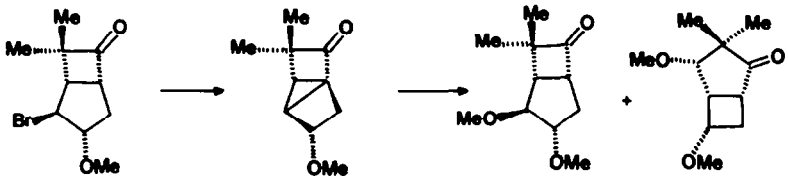

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