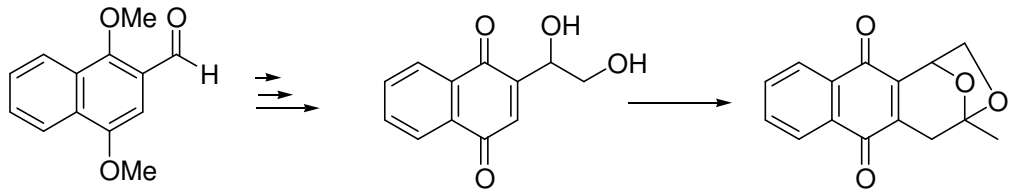
LITERATURE REVIEWS

Recently, a new type of tetracyclic naphthoqiunone, named isagarin (11), was isolated from the hexane extract of dried roots of *Pentus longiflora* and subsequently synthesized (Kimpe *et al.* 1999). Kimpe's synthesis relies on the conjugate addition of an acetyl pyridinium ylide, generated *in situ* from *N*-acetylmethyl pyridinium chloride and trimethylamine, to give an unisolated intermediate naphthoquinone containing keto diol functional groups which undergo spontaneous ketalisation to afford isagarin (11)**.**

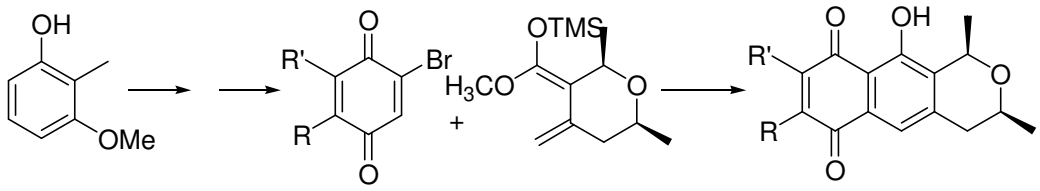


Isagarin (11)

The synthesis of marticin (13) and isomarticin (14) has not been reported. Therefore we proposed syntheses of these form a core naphthoquinone and then building up the cyclic ketal via Wacker reaction.

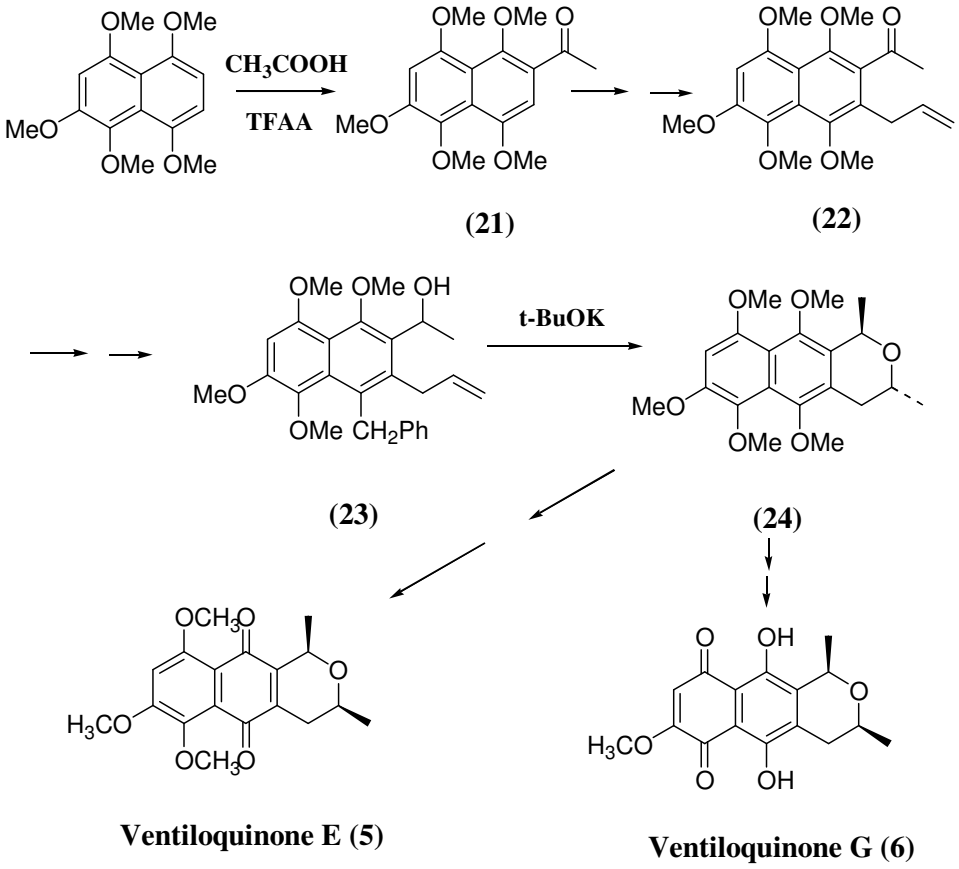
Ring construction of core pyranonapthoquinone

Many approaches have been proposed for the synthesis of naturally occurring benzoisochroman-5, 10-quinone. In 1990, Brassard succeeded in the synthesis of (+)-ventilagone (19) and ventiloquinone H (20) by Diels-Alder reaction of bromobenzoquinone (17) which was prepared by 3-methoxy-2-methyl phenol (16) and heterocyclic diene (18).



(16) **(17)** **(18)** **R=OH, R'= CH_3 (19)**
R=OCH_3, R'= OCH_3 (20)

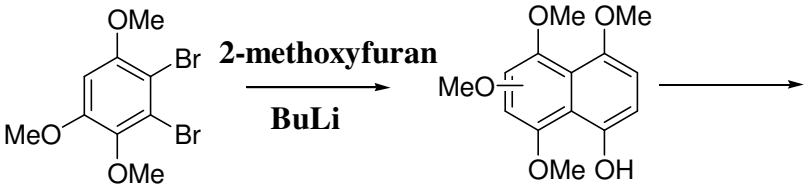
(-)-Ventiloquinone E (5) was synthesized using a different approach (Giles *et al*., 1991). The ortho acetyl naphthalene (21) precursor was easily prepared from 1,2,4,5,8-pentamethoxynaphthalene. Allylation of (21) followed by reduction and cyclisation afforded the trans-dimethylnaphthopyran (24). Oxidation of (24) with CAN provided ventiloquinone E (5) but when (24) was oxidized using silver(I) oxide and then treated with ethanolic hydrochloric acid ventiloquinone G (6) was formed (Scheme 2).



Ventiloquinone E (5) **Ventiloquinone G (6)**

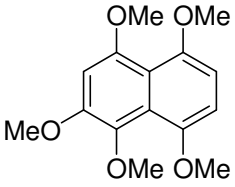
Scheme 2

The synthesis of 1,2,4,5,8-pentamethoxynaphthalene was achieved from 2,3-dibromo-1,4,5-trimethoxybenzene (25) as starting material (Giles *et al.*, 1988). Reaction of compound (25) with *n*-butyl lithium generated a benzyne intermediate which reacted *in situ* with commercially available 2-methoxyfuran to afford the naphthol (26). Methylation of naphthol (26) using dimethylsulfate and potassium carbonate in acetone gave 1,2,4,5,8-pentamethoxynaphthalene (Scheme 3).



2,3-Dibromo-1,4,5-trimethoxybenzene (25)

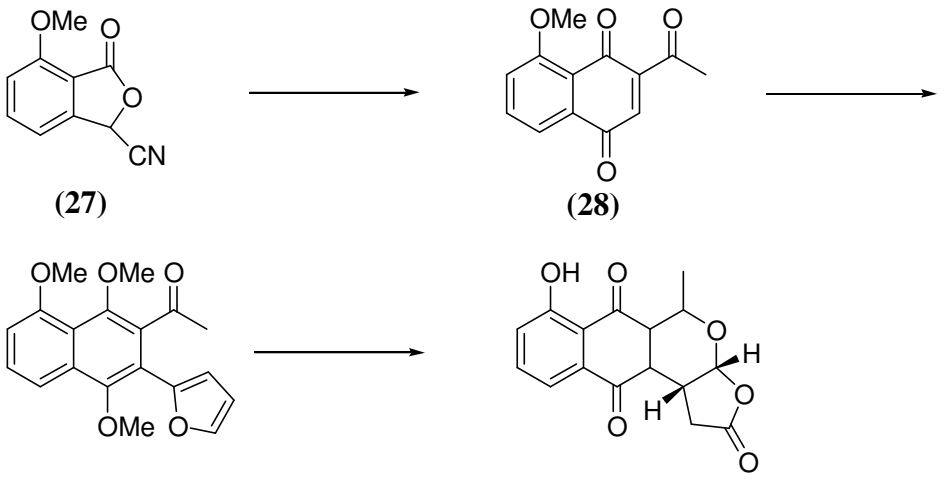
Naphthol (26)



1,2,4,5,8-Pentamethoxynaphthalene

Scheme 3

The synthesis of kelafungin (30) described another method to construct the naphthoquinone ring (Kraus *et al*., 1983). The key step involved 1,4-addition of a phthalide precursor (27) (Scheme 4).



(27) **(28)**

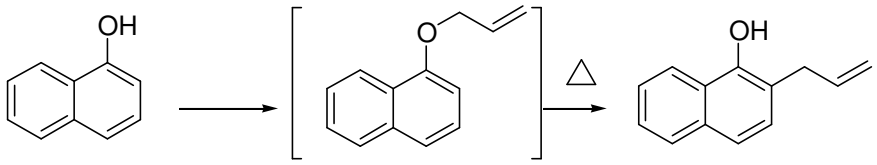
(29) **Kalafungin (30)**

Scheme 4

Introduction of an allyl group onto the naphthalene ring

Generally, C-Allylation can be carried out by Claisen rearrangement of naphthol derivatives or 1,4-addition of an allylmetal reagent to p-naphthoquinone.

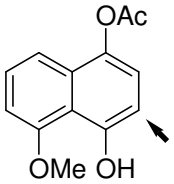
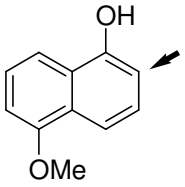
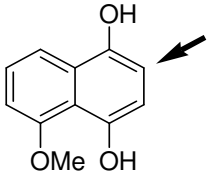
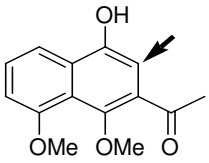
The Claisen rearrangement is a powerful carbon-carbon bond-forming chemical reaction discovered by Rainer Ludwig Claisen in 1912. Heating an allyl vinyl ether (32) initiates a [3,3]-sigmatropic rearrangement to give (33) (Scheme 5)**.** Many reports of C-allylation of to naphthalenes via Claisen rearrangement have been published some of which are shown in Table 1.



(31) **(32)** **(33)**

Scheme 5

Table 1 Claisen rearrangement of naphthalene derivatives[a]

Substrates	Conditions	References
 **(34)**	1. Allyl bromide, K_2CO_3, acetone, reflux 2. 200 ^{0}C, 71 %	Kraus *et al.*, 1987.
 **(35)**	1. Allyl bromide, K_2CO_3, acetone, reflux 2. 200 ^{0}C, 81 %	Schmid *et al.*, 1958.
 **(36)**	1. Allyl bromide, K_2CO_3, acetone, reflux 2. Me_2SO_4, K_2CO_3 3. DMF, 140 ^{0}C, 73 %	Masquelin *et al.*, 1995.
 **(37)**	1. Allyl bromide, K_2CO_3, acetone, reflux 2. 220 ^{0}C, 35 min, 75%	Green *et al.*, 1996

[a] Arrows indicated side of allylation

1,4-Addition reaction represents a versatile method to introduce an allyl group into the naphthoquine ring. Normally, the reaction uses but-3-enoic acid or an allylmetal such as allyltin, allylsilane or allylzine as nucleophilic reagents. These methods have been further studied and applied by several groups to synthesize pyranonaphthoquinone class (Table 2).

Table 2 Allylation of naphthoquinone derivatives via 1,4-addition reaction

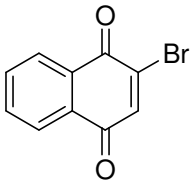
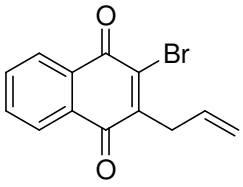
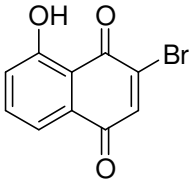
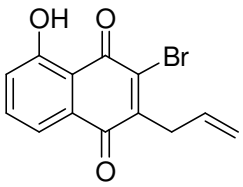
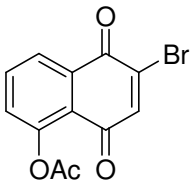
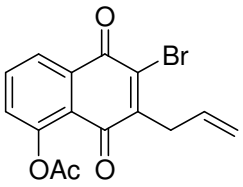
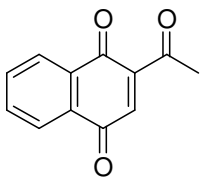
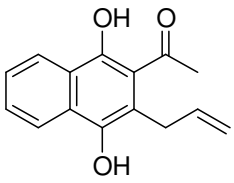
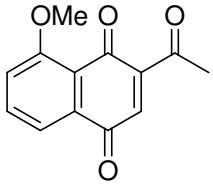
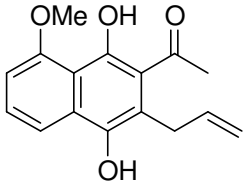
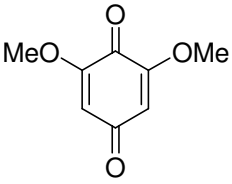
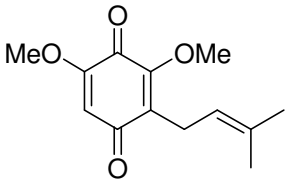
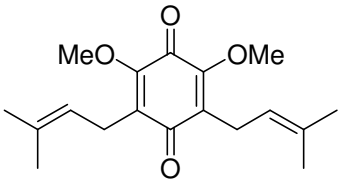
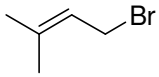
Substrates	Products	Reaction Conditions/ References
 **(38)**	 **(39)**	$AgNO_3$, 3-butenoic acid 70 ^{0}C Ammonium peroxodisulphonate 78 % (Masato *et al*., 1981)
 **(40)**	 **(41)**	$AgNO_3$, 3-butenoic acid 70 ^{0}C Ammonium peroxodisulphonate 65 % (Kometani *et al*., 1989)
 **(42)**	 **(43)**	$AgNO_3$, 3-butenoic acid 70 ^{0}C Ammonium peroxodisulphonate 69 % (Masato *et al*., 1983)

Table 2 (cont'd)

Substrates	Products	Reaction Conditions/ References
 **(44)**	 **(45)**	Allyltrimethyltin, $BF_3.OEt_2$, CH_2Cl_2, -78 ^{0}C , 74 % (Uno *et al*., 1986)
 **(46)**	 **(47)**	Allyltrimethyltin, $BF_3.OEt_2$, CH_2Cl_2, -78 ^{0}C ,73 % (Uno *et al*., 1981)
 **(48)**	 **(49)**  **(50)**	Zn, THF, 60 ^{0} C  55 % (Oliveira *et al*., 1997)

Acylation of naphthalene derivatives

Friedel-Crafts acylation and Fries rearrangement are classical methodology to connect acyl groups onto an aromatic ring to afford aromatic ketones. Normally, the reactions involve an acid chloride or acid anhydride as acylating reagents and a Lewis acid such as $AlCl_3$, $BF_3.OEt_2$, $TiCl_4$ or $SnCl_4$ as catalyst. Some naphthalene examples of Friedel-Crafts acylation and Fries rearrangement are shown in Table 3.

Table 3 Friedel-Crafts acylation and Fries rearrangement of naphthalene derivatives

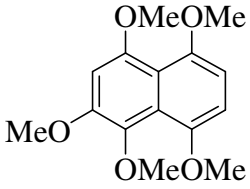
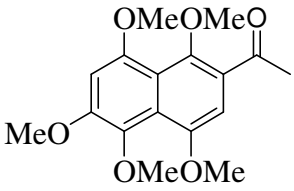
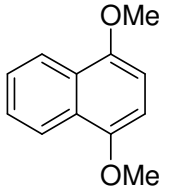
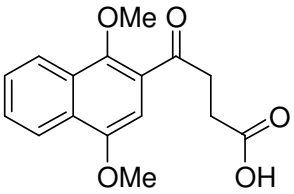
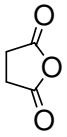
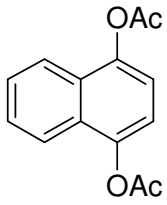
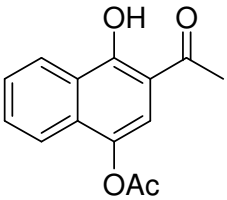
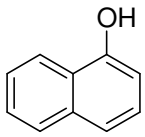
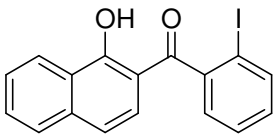
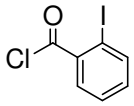
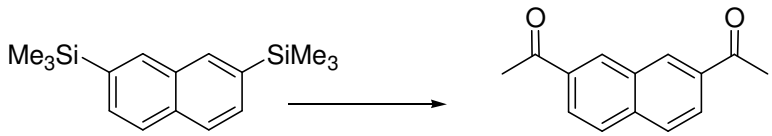
Substrates	Products	Reaction Conditions/ References
 **(51)**	 **(52)**	CH_3COOH, TFAA 12h. 78 % (Giles *et al.*, 1991)
 **(53)**	 **(54)**	$AlCl_3$, nitrobenzene  82 % (Fieser *et al.*, 1963)
 **(55)**	 **(56)**	$BF_3.OAc$ 85 % (Wigle *et al.*, 2000)

Table 3 (Cont'd)

Substrates	Products	Reaction Conditions/ References
 **(57)**	 **(58)**	$TiCl_4$, 120 ^{0}C  **(59)** 87 % (Jones *et al*., 2000)

A novel coupling approach to acylation of aromatic rings has been achieved by using silylnaphthalene (60), acetyl chloride and aluminum trichloride as a catalyst to give diketone (61) in a good yield (Scheme 6) (Katz *et al*., 1997).



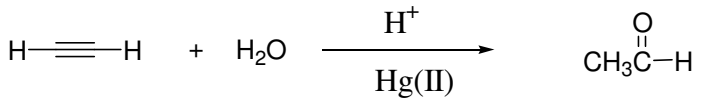
(60) **(61)**

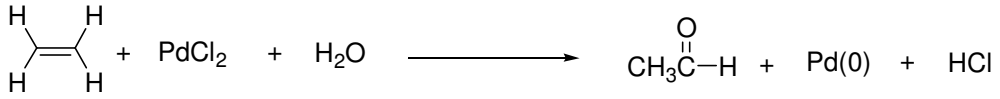
Scheme 6

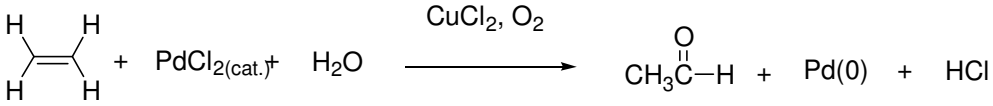
Palladium cyclization by Wacker reaction

Acetaldehyde was originally prepared from hydration of acetylene. This synthesis is now obsolete because of problems associated with the acetylene. Acetylene is produced by heating a hydrocarbon stream to high temperature, sometimes in the presence of electric arc. All processes for producing acetylene require large amounts of energy. Acetylene is also thermodynamically unstable, it must be handled with extreme care in order to prevent explosion.

The incentive existed to develop production of acetaldehyde from a cheaper and less hazardous starting material. It had long been known that acetaldehyde formed directly from ethylene and water in the presence of a stoichiometric amount of $PdCl_2$ and a commercially feasible process was developed by Smidt that employed Pd in catalytic amounts ($PdCl_2$, $CuCl_2$, O_2).

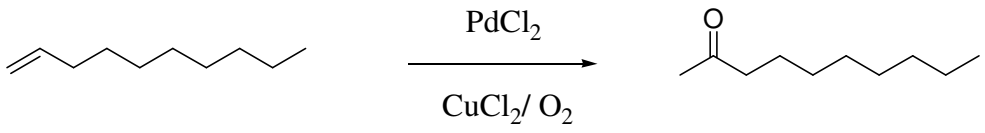




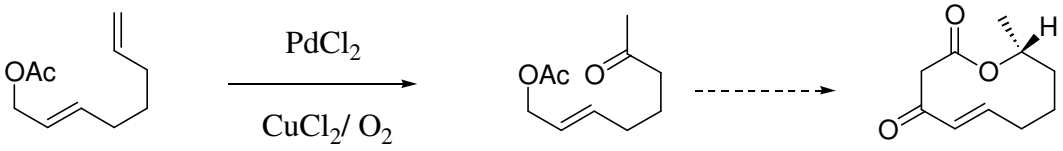


This chemistry was also applied to prepare methyl ketones from terminal olefins. 2-Undecanone (63) was synthesized via palladium catalyst from oxidation of 1-undecene (62) (Miller *et al*., 1992). In diplodialide synthesis, the diene ester (64) was oxidized to the corresponding methyl ketone (65) a in good yield by the Wacker process (Tsuji, 1979). Only the terminal olefin was oxidized because internal double bonds are much less reactive due to steric hindrance.

On the basis of mechanism, alcohols could be used as nucleophiles in Wacker reaction to afford ketals. By using dry ethlylene glycol as solvent, ketal (68) was prepared from olefin (67) in a good yield (Hunt *et al*., 1972).



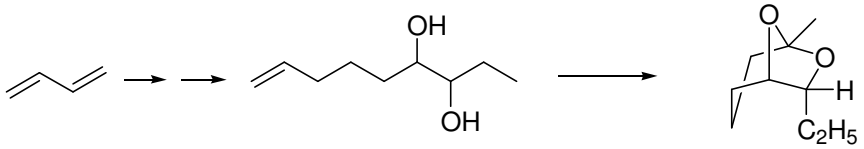
(62) **(63)**



(64) **(65)** **Diplodialide (66)**

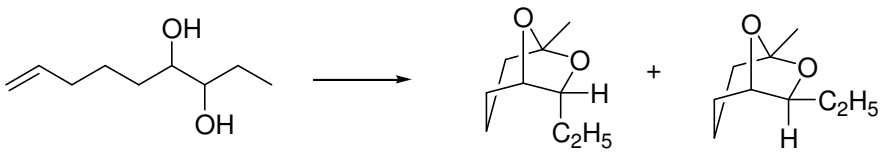
(67) **(68)**

In 1976, Wacker reaction was first modified for intramolecular cyclization reactions. An insect pheromone, endo-brevicomin (70) was simply prepared from the palladium catalyzed cyclization of the olefinic diol (69) by Grigg *et al*.



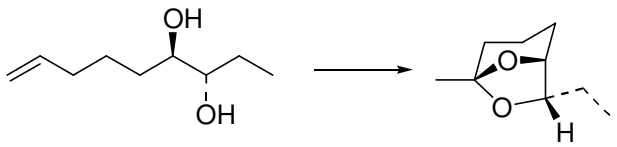
(69) **(70)**

By careful study, it was reported later that the above synthesis route, in fact, provided both endo-and exo-brevicomin (71, 72) in ratio of 1:5 (Grigg *et al*., 1984).

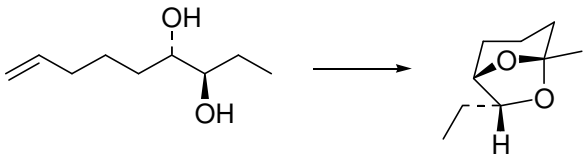


(69) **(71)** **(72)**

In the following year, Mori and Seu (1985) reported the enantioselective synthesis of (1R, 5S, 7S)-(+)-endo-brevicomin (71a) and its (1S, 5S, 7R)-(-)-isomer (71b) from diols 69a and 69b, respectively by using palladium catalyzed cyclization as the key step.

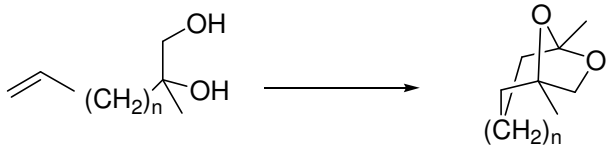


(69a) **(1R,5S,7S)-(+)-endo-brevicomin (71a)**



(69b) **(1S,5R,7R)-(+)-endo-brevicomin (71b)**

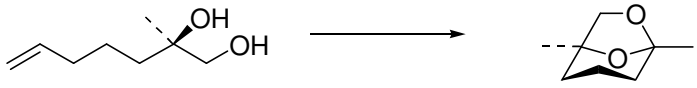
In 1985, Kongkathip *et al.,* applied this reaction to synthesize frontalin (74), an insect pheromone of *Dendroctonus frontalis*, and its analogue (76) from corresponding diols (73) and (75).



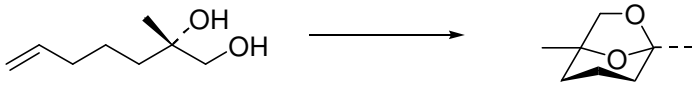
73 : n = 3 **74 : n =1**

75 : n = 4 **76 : n = 2**

During the same period, Hosokawa *et al*. (1985), reported the synthesis of both (S)-(-)-frontalin (78) and unnatural (R)-(+)-frontalin (80) in high enantiomeric excess from olefinic diols (77) and (79), respectively.

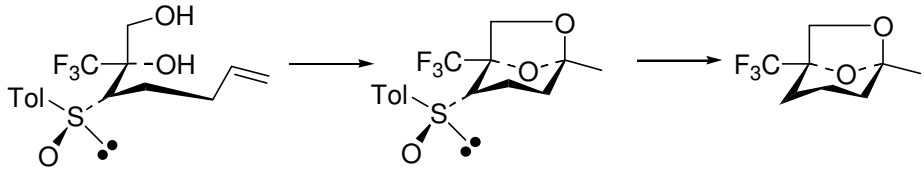


(77) **(78)**



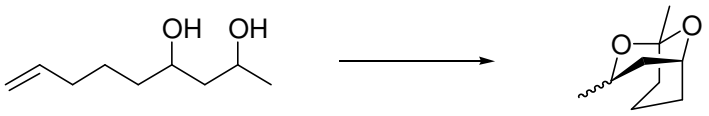
(79) **(80)**

In 1999, Bravo *et al*. developed the synthetic approach of enantiomerically pure (-)-(1S,5S)-1-trifluoromethyl frontalin (83) by using a chiral building block approach.



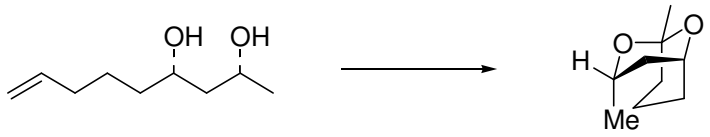
(81) **(82)** **(83)**

The insect attractant, 1,3-dimethyl-2-9 dioxabicyclo [3.3.1] nonane (85) was synthesized from the corresponding 1,3-diol (84) by this method (Kongkathip *et al*., 1984).

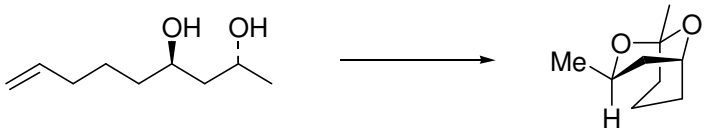


84 **85**

In 1986, Sutherland *el al*., reported the stereospecific synthesis of exo- and endo-1,3-dimethyl-2,9-[3.3.1] nonane (87 and 89) from 1,3-diols (86) and (88), respectively.

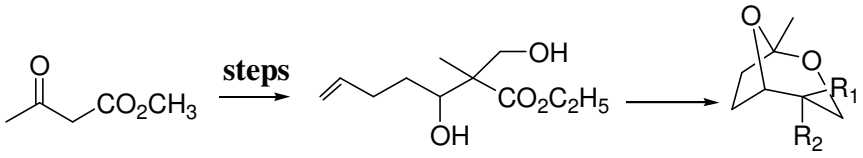


(86) **(87)**



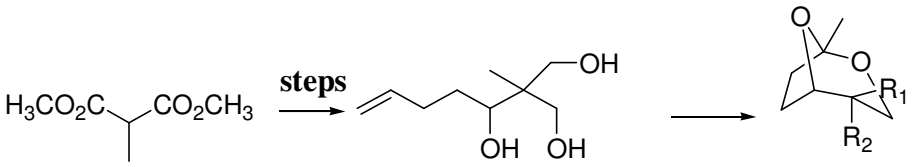
(88) **(89)**

Both diastereoisomers of 2,8-dioxabicyclo [3.2.1] octane derivatives (92, 93), and the 4-hydroxy methyl analogues (96, 97) were synthesized from ethyl acetoacetate (90) and diethyl malonate (94), respectively. The key step of this process involved intramolecular cyclization using palladium chloride as catalyst. (Kongkathip *et al*., 1999)



(90) **(91)**

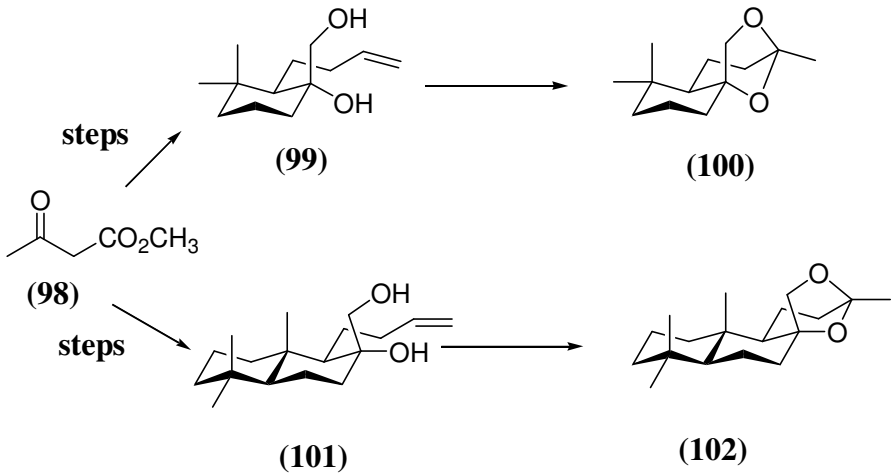
(92) $R_1 = CO_2C_2H_5$; $R_2 = CH_3$
(93) $R_1 = CH_2OH$; $R_2 = CO_2C_2H_5$



(94) **(95)**

(96) $R_1 = CO_2OH$; $R_2 = CH_3$
(97) $R_1 = CH_3$; $R_2 = CH_2OH$

In the same year, amberketal (100) and acetal homologue (102) were synthesized from a commercially available methyl acetoacetate (98) (Kongkathip *et al*., 1999).



In 1999, Perlmutter *et al*., reported a rapid method for enantioselective construction of 2,8-dioxabycyclo[3.2.1]octanes of relevance to zaragozic acid. Asymmetric aldol condensation of (103) with aldehyde (104) provided the partially protected enediol (105) as a single isomer. Direct ring closure of mono silylether (105) proceeded efficiently to (106), obviating the need for desilylation prior to ring closure. Presumably, the HCl generated during the Wacker oxidation is sufficient to promote desilylation of the primary silylether.