SYNTHESIS OF α-METHYLENE-γ-BUTYROLACTONES

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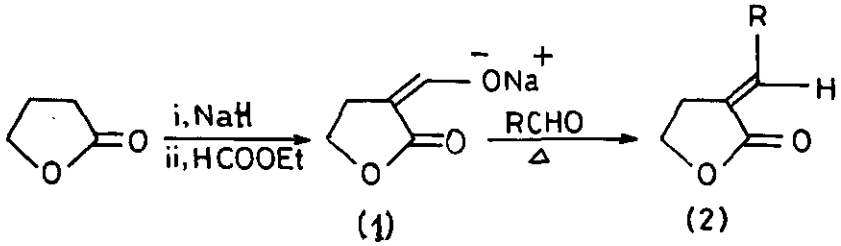
Abstract - Synthesis of α-methylene-γ-butyrolactone moiety present in numerous natural products displaying a wide range of biological activity has been reviewed here embracing the period from 1980 to the middle of 1985.

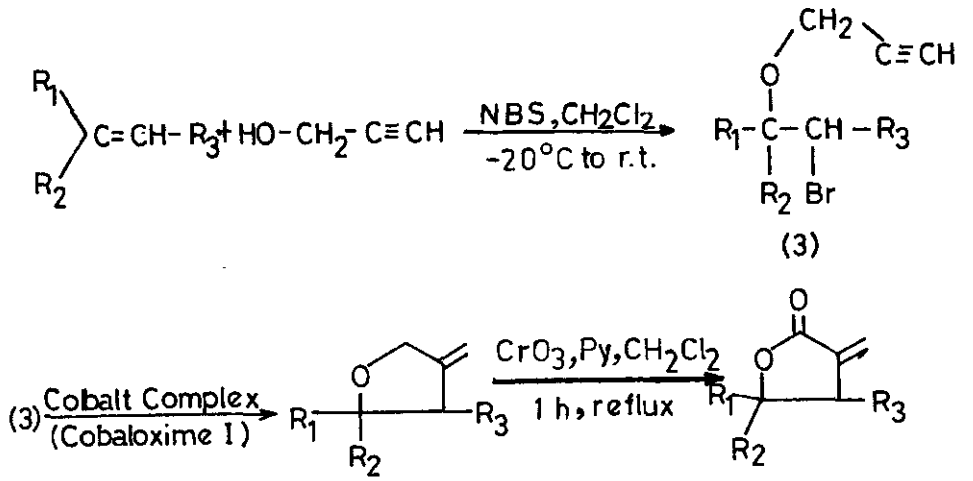
The wide range of biological activity (e.g. antitumor[1], carcinogenic[2,3], microbial growth inhibitor[4], schistosomicidal[5], allergic contact dermatitis[6-11] antifeedant[5,12], vertebrate poisoning[13,14], plant growth inhibitors[15] and antiinflammatory[16]) displayed by a large number of compounds possessing α-methylene-γ-butyrolactone moiety has attracted the attention of synthetic organic chemists for the synthesis of this moiety during the past two decades. Several reviews have already appeared[17], the present article deals with the literature accumulated during the last five years.

1. In a preformed γ-lactone moiety the formyl group has been introduced using sodium hydride and ethyl formate and the resulting enolate (1) on refluxing with formaldehyde for 3 h furnishes the α-methylene-γ-lactone (2a), in 98% yield[18]. The reaction with benzaldehyde and propionaldehyde results in the formation of a mixture of the corresponding α-<u>trans</u> and α-<u>cis</u> (substituted ylidene)-γ-butyrolactones (2b).



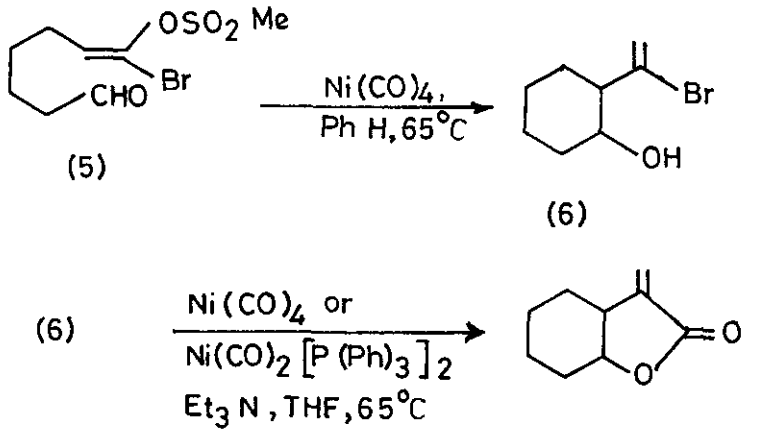
SCHEME 1

2. Tade et al.[19] have employed the strategy for the synthesis of α-methylene-γ-butyrolactones which requires the introduction of carbonyl group at the last stage. Thus they have developed a new method for the synthesis of 3-methylene oxolanes (4) through the reductive cyclization of 2-[(2-propynyl)oxy] ethyl bromides (3) by a cobalt complex.



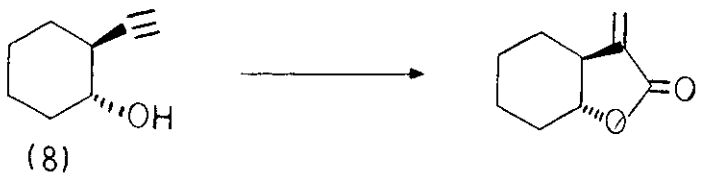
SCHEME 2

3. The allylic methanesulfonic ester (5) is converted in situ to the vinyl bromide (6) by treatment with nickel carbonyl which undergoes carbonylation to give the α-methylene-γ-lactone (7)[20].

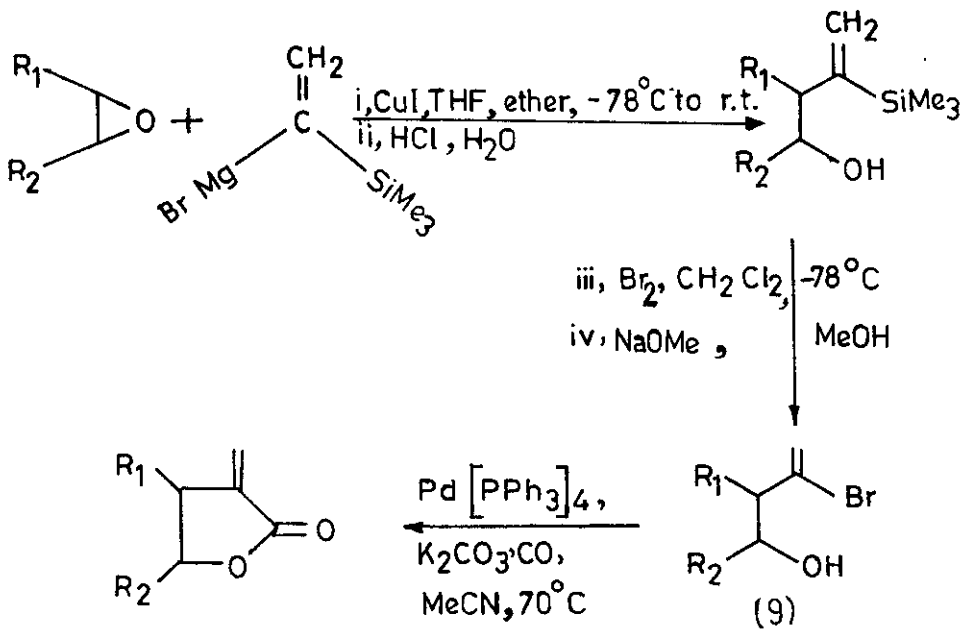


SCHEME 3

4. Palladium-catalyzed carbonylation of homopropargyl alcohols (8) is one of the most useful and well-documented transition metal catalyzed synthesis of α-methylene-γ-butyrolactones[21], but Stille and Martin have reported the same could be obtained in high yield from the palladium-catalyzed carbonylation reaction of alkyl-substituted 3-bromo-but-3-en-1-ols (9) as shown in scheme 4[22] below. Optically active epoxides furnish the corresponding lactones in an optically pure state.

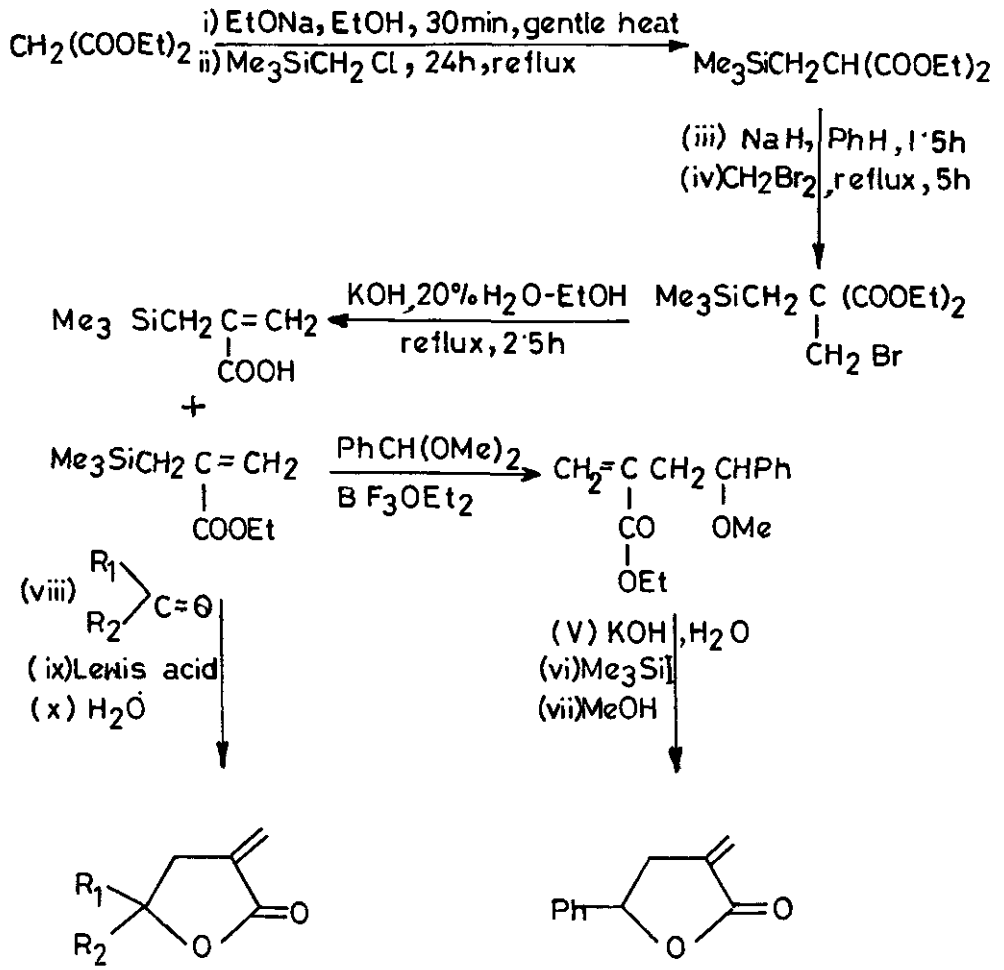


(8)



SCHEME 4

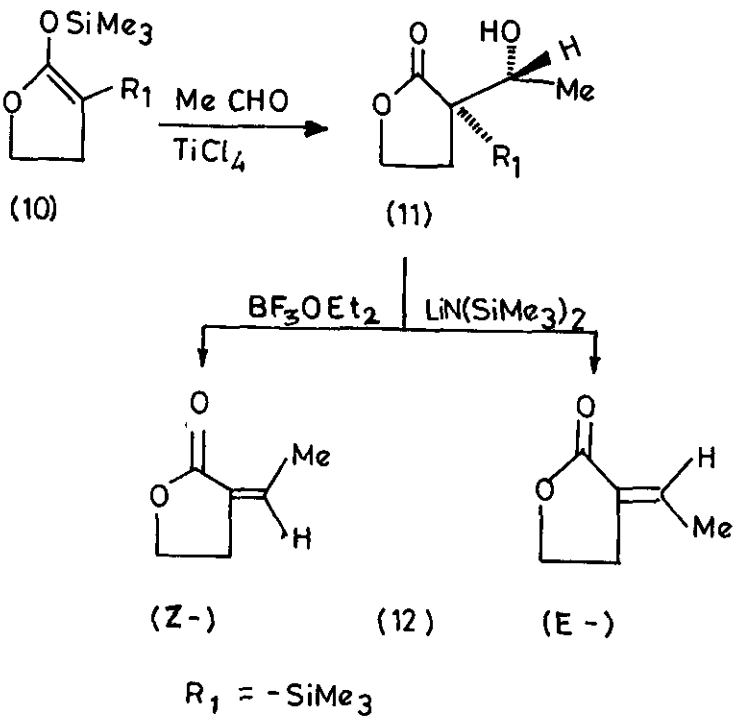
5. 2-Carbethoxy-allylation of carbonyl compounds is one of the widely used procedure for the construction of α-methylene-γ-butyrolactone moiety[23]. Sakurai et al.[24] while demonstrating the use of allylsilanes have developed a new method for the preparation of 2-alkoxycarbonylallytrimethylsilanes which has been employed for the introduction of 2-alkoxycarbonylallyl group into electrophilic centres in a single step by reaction with acetals or carbonyl compounds.



SCHEME 5

In a similar method reported by Okuda et al.[25], allylic chromium species derived from the reaction of ethyl α-(bromomethyl)acrylate with Cr(II) reagent is condensed with aldehydes to obtain α-methylene-γ-butyrolactones.

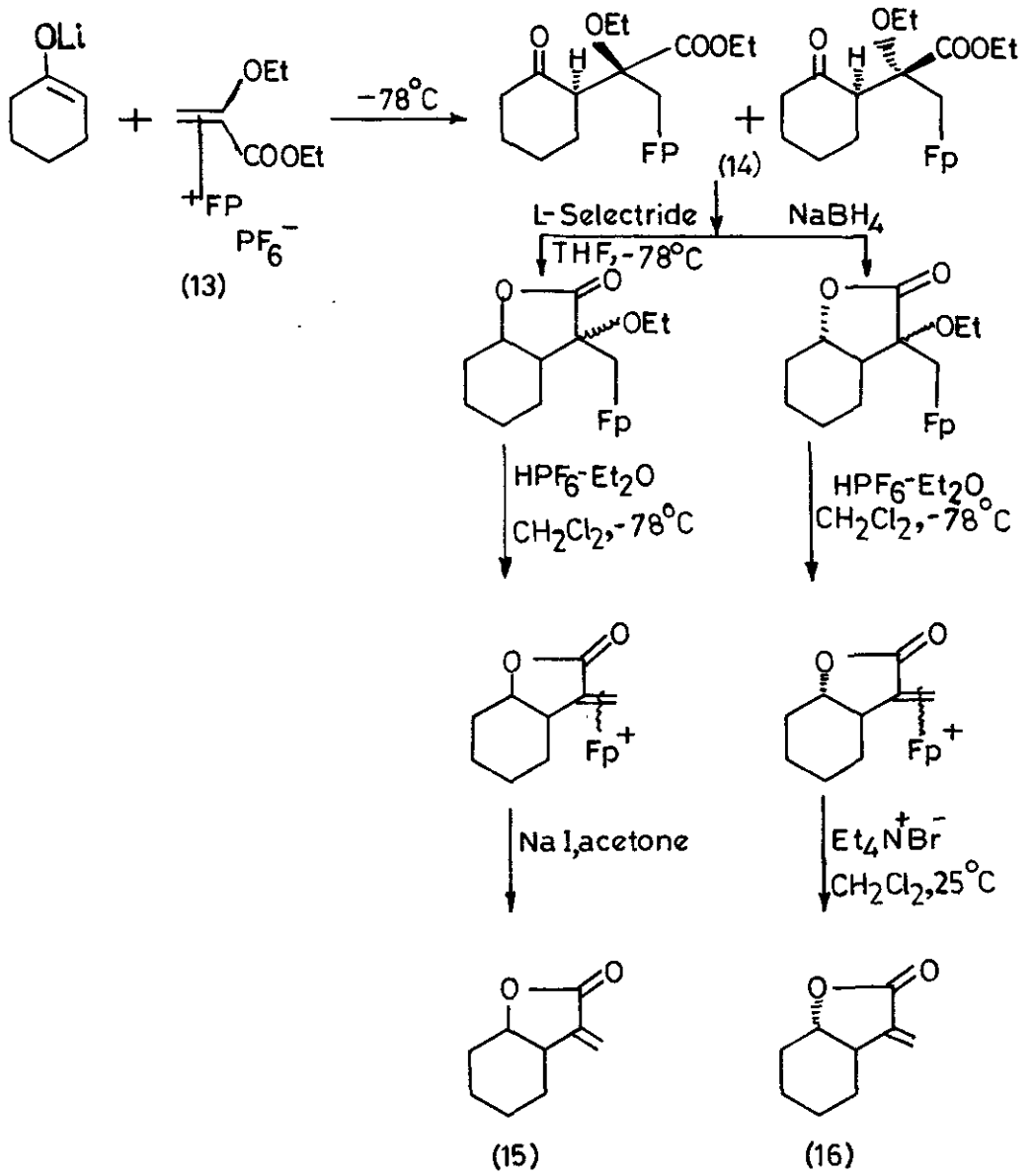
6. Yamamoto et al.[26] have made use of the preformed lactone moiety for the preparation of (Z) and (E)-alkylidene-γ-butyrolactone moiety. Titanium (IV) chloride mediated reaction of 4,5-dihydro-2-(trimethylsiloxy)-3-(trimethylsilyl) furan (10) with acetaldehyde gave diastereomerically pure (3S*, 1'R*)-4,5-dihydro-3-(1'-hydroxyethyl)-3-(trimethylsilyl)-2(3H)-furanone (11) which afforded selectively either (Z)-or (E)-α-ethylidene-γ-butyrolactone (12) under appropriate reaction conditions.



SCHEME 6

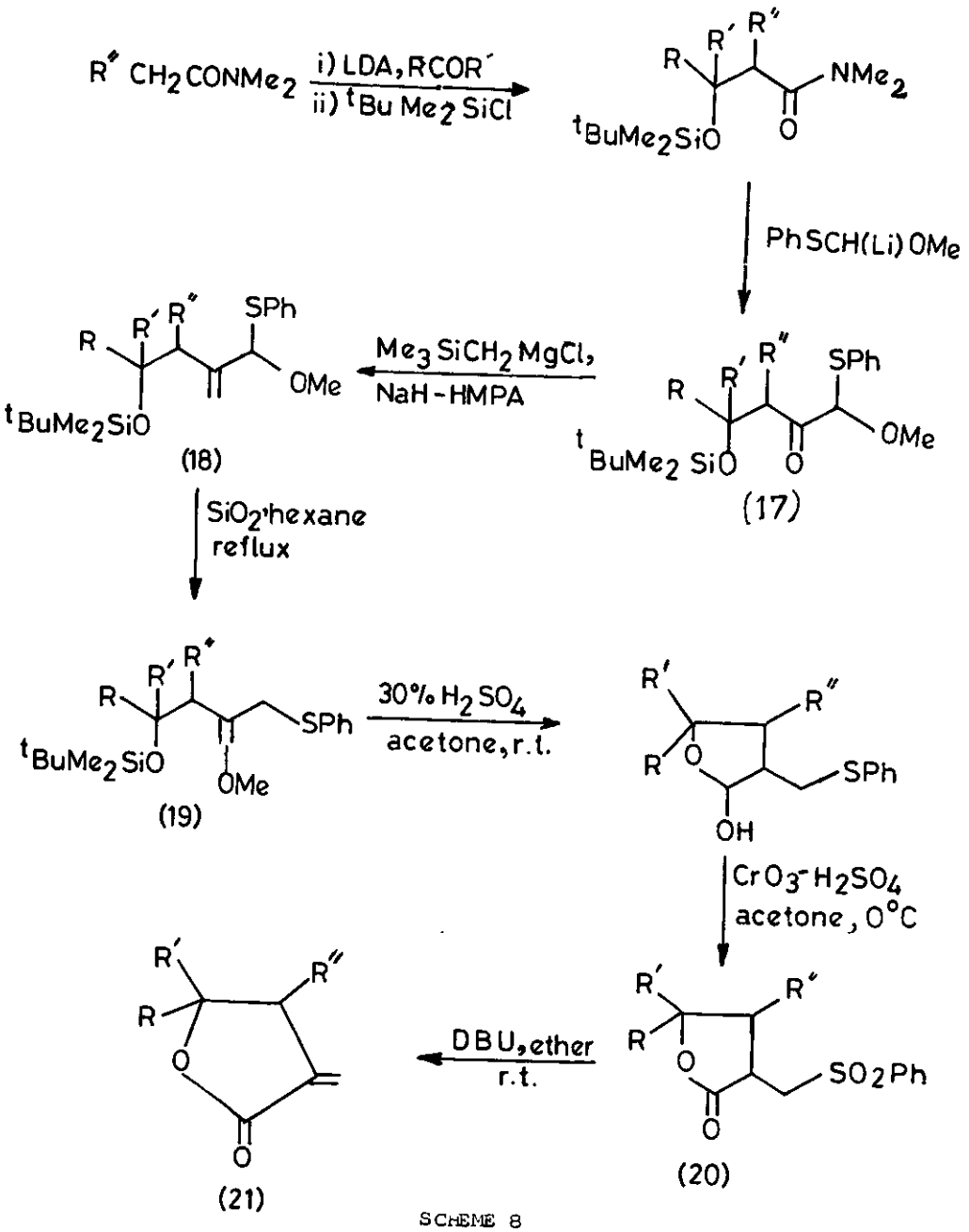
7. An α-acrylic ester cation equivalent (13) has been employed in the construction of α-methylene-γ-butyrolactone moiety[27].

Cyclohexanone lithium enolate reacts at -78°C with the suspension of (13) in THF solution to give diastereomeric adducts (14) which under suitable reaction conditions can be transformed into cis and trans-α-methylene-γ-butyrolactones (15) and (16) as shown in the scheme 7.



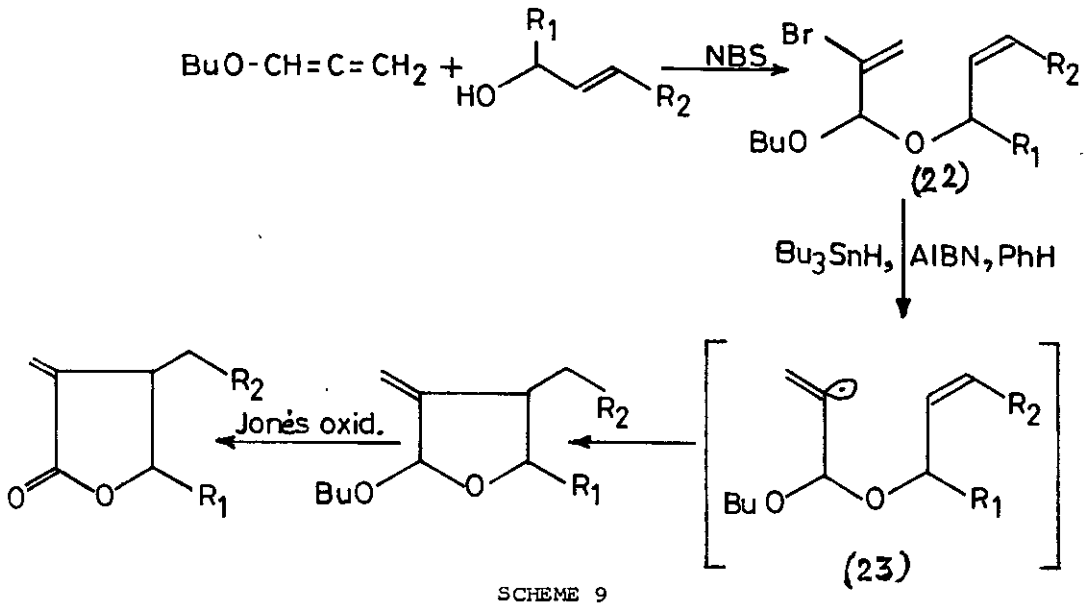
SCHEME 7

8. Otera et al.[28] have employed acid-catalyzed thioallylic rearrangement as the key step in the construction of α-methylene-γ-lactone moiety. β-Siloxyketones (17) were converted into α-methoxyallyl sulfides (18) through the Peterson olefination whose hexane solution when refluxed in the presence of silica gel gave (19). On subsequent treatment of (19) with 30% H_2SO_4 followed by Jones oxidation furnished (20) whose desulfonylation was effected with DBU in ether to give the desired compound (21).



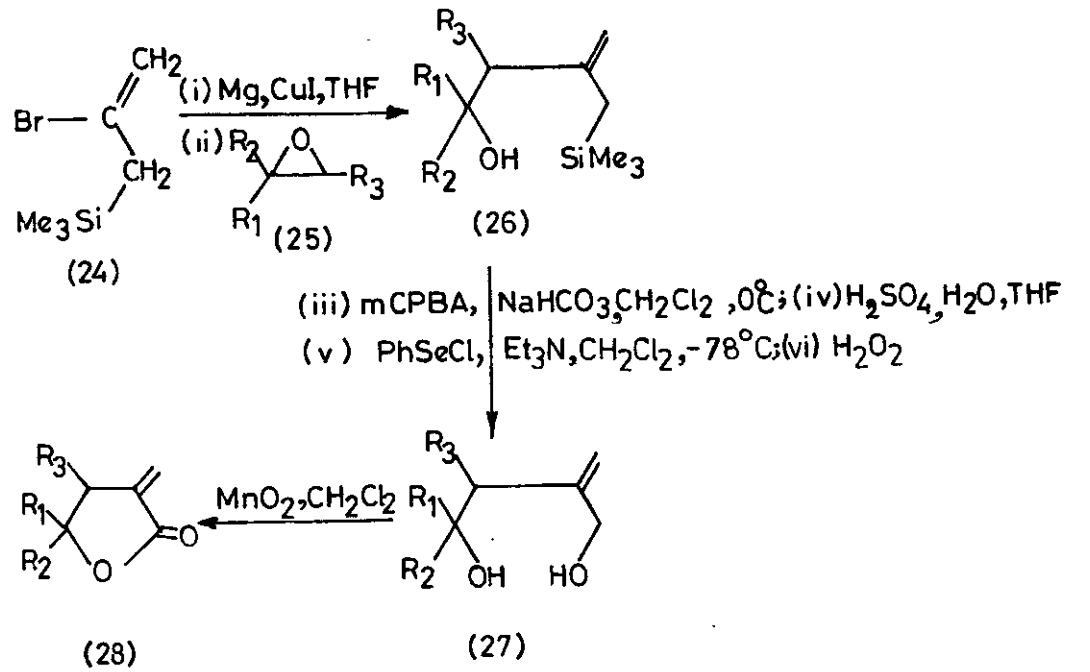
SCHEME 8

9. Stereoselective radical cyclization of (22) is the key feature in the method developed by Moriya et al.[29] for the synthesis of α-methylene-γ-lactone moiety. The bromoacetals (22) were prepared by the reaction of butoxyallene with excess allylic alcohols in presence of NBS. The vinyl radical (23) was generated by tri-n-butyltin hydride.



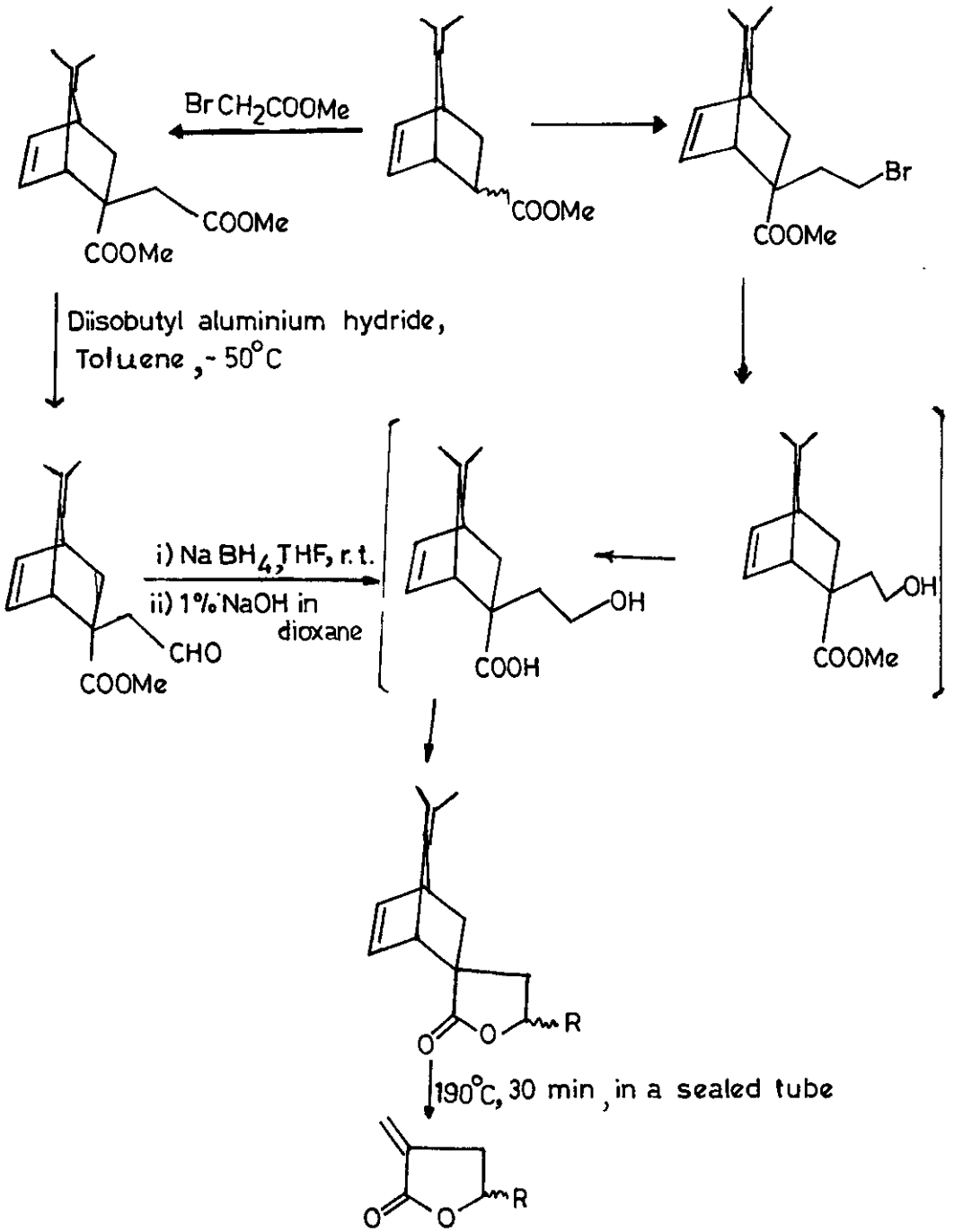
SCHEME 9

10. The utility of allylsilanes in the preparation of α-methylene-γ-butyrolactones has been demonstrated by Itoh et al.[30] 2-Bromoallyltrimethylsilane (24) was converted into a Grignard reagent which on reaction with epoxides (25) provides 2-(2-hydroxyethyl)allylsilanes (26) which could be easily elaborated to the diols (27) and then to the lactones (28) as shown in the scheme 10.



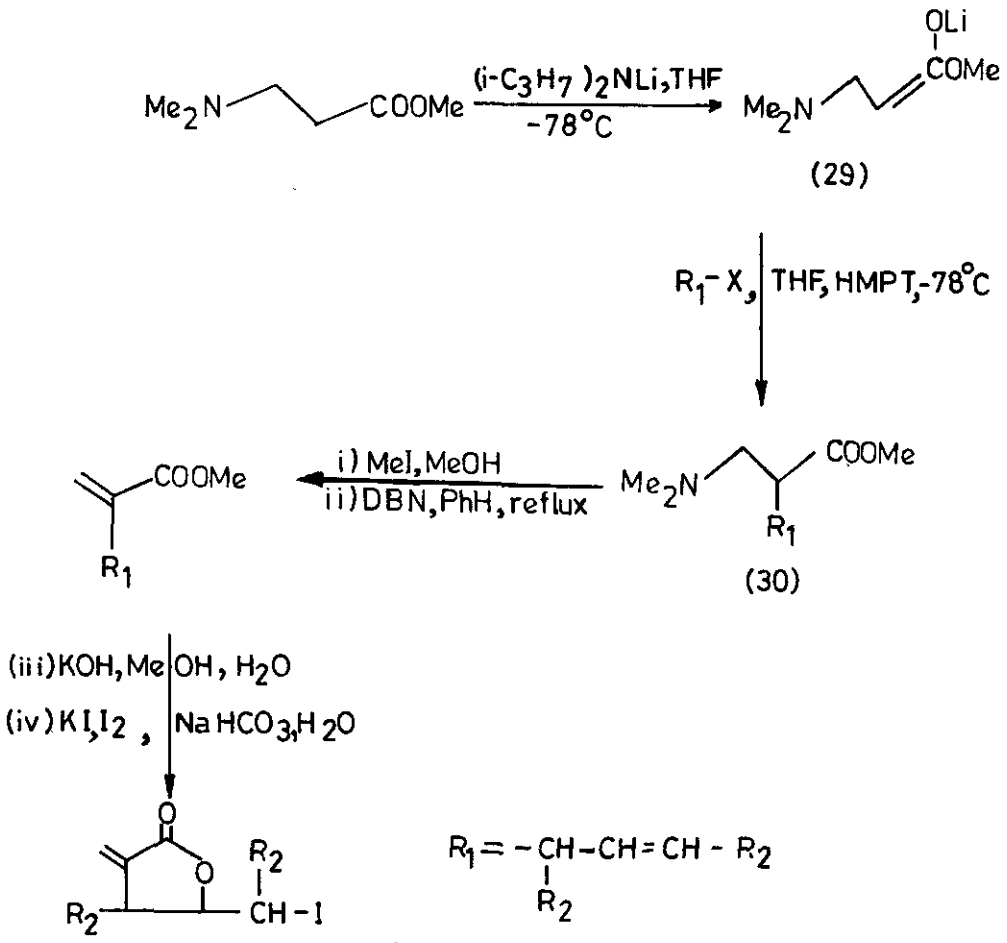
SCHEME 10

11. Ichihara et al.[31] have successfully demonstrated the use of retro-Diels-Alder reaction in putting the exomethylene group in a γ-butyrolactone as shown in scheme 11.



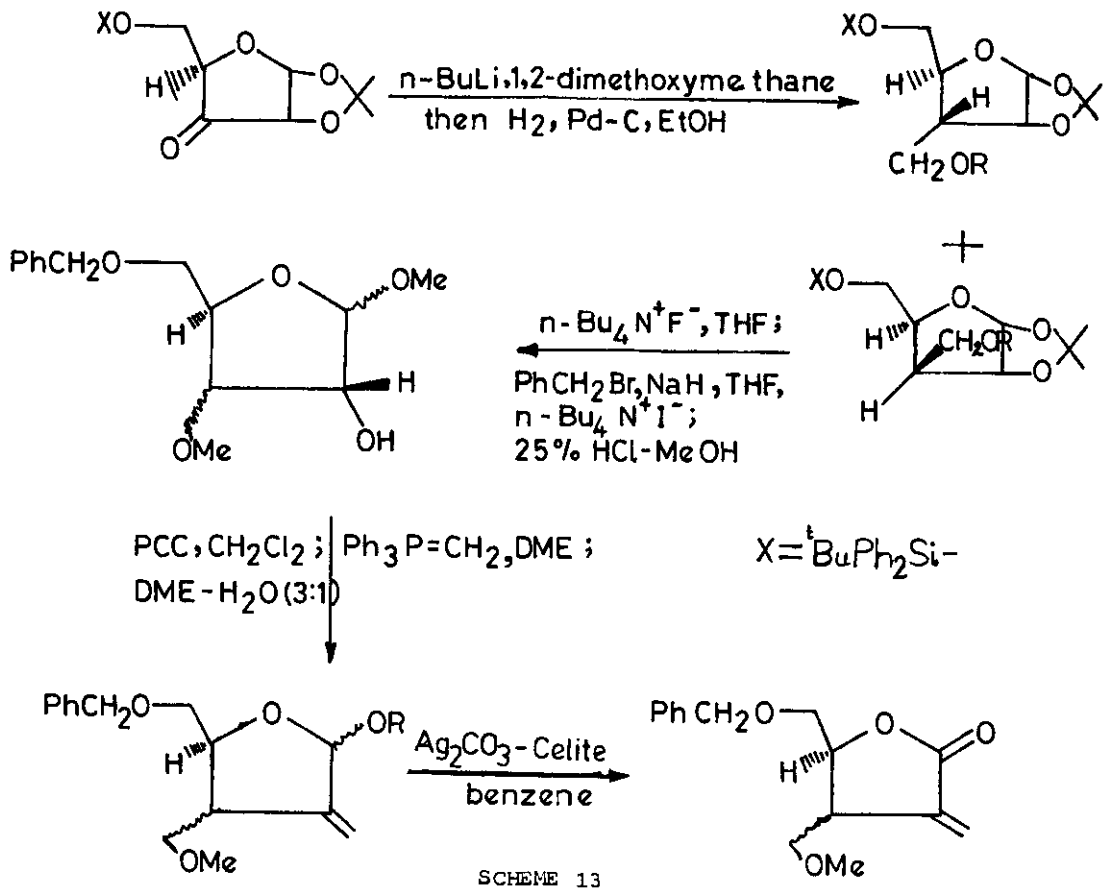
SCHEME 11

12. Helquist et al.[32] have demonstrated the utility of β-amino ester enolate such as (29) which can be alkylated with a variety of allylic halides to furnish protected acrylate esters (30) which may be conveniently converted into α-methylene-γ-lactones.



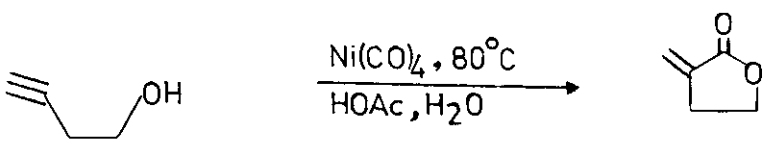
SCHEME 12

13. 1,2-O-Isopropylidene furanose derivatives have been converted into syn or anti forms of α-methylene-γ-butyrolactones via 2-C-methylene glycofuranosides which are hydrolysed under neutral conditions[33].



SCHEME 13

14. Many years ago it was reported that cyclocarbonylation of acetylenic alcohols (31) by a stoichiometric $Ni(CO)_4$ reaction leads to poor yields of α-methylene-γ-butyrolactone (32)[34].



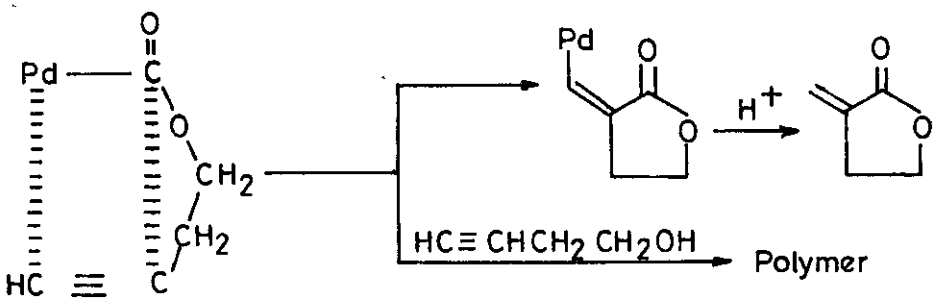
(31) (32)

Murray et al.[35] report that palladium-catalyzed cyclocarbonylation of acetylenic alcohols provides good yields of the corresponding lactones. The general procedure used for the preparation of ethynyl alcohol is shown in equation (1). These authors have studied various catalytic systems but the best

cyclocarbonylation catalyst system has proved to be palladium chloride, anhydrous stannous chloride and 2 equivalents of a tertiary phosphine in acetonitrile.

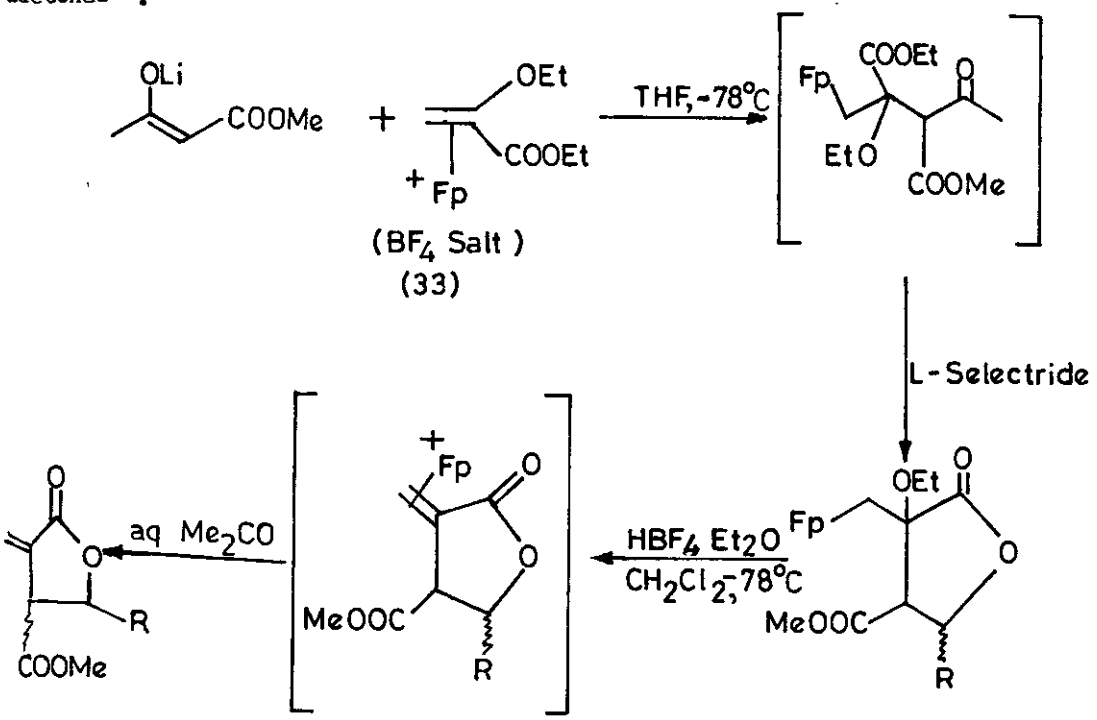
Olefin $\xrightarrow{[O]}$ Epoxide $\xrightarrow{\text{ethynylation}}$ Ethynyl alcohol $\xrightarrow{CO}$ α-Methylene-γ-lactone..(1)

$$Pd(II) + CO + HOCH_2\,CH_2\,C\equiv CH \longrightarrow PdCO_2CH_2CH_2C\equiv CH + H^+$$



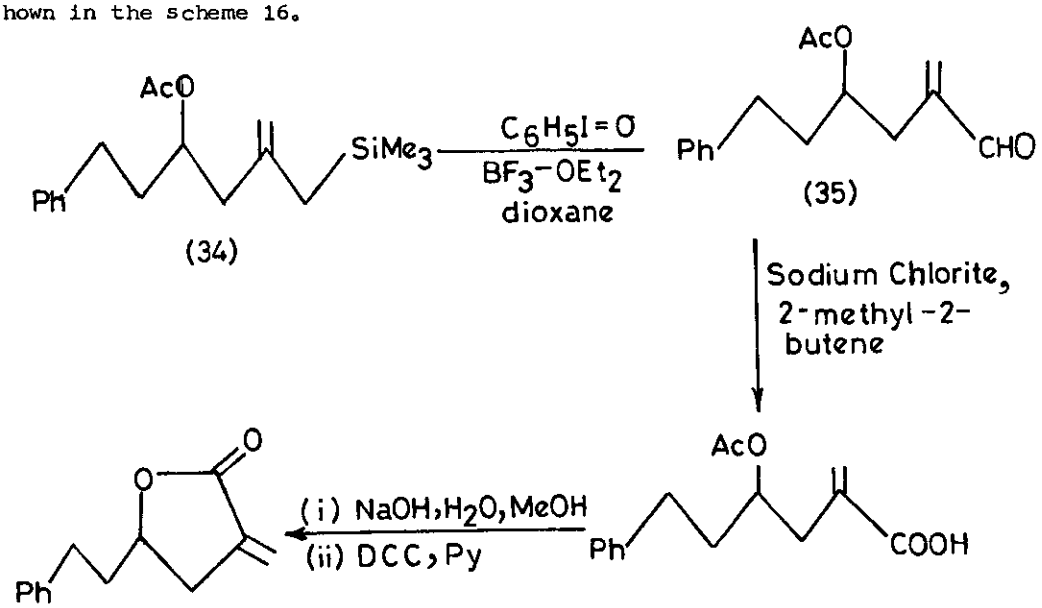
SCHEME 14

15. The reaction of lithium enolates derived from β-ketoesters with complex cation (33) provides a facile route to 3,4-disubstituted α-methylene-γ-butyrolactones[36].



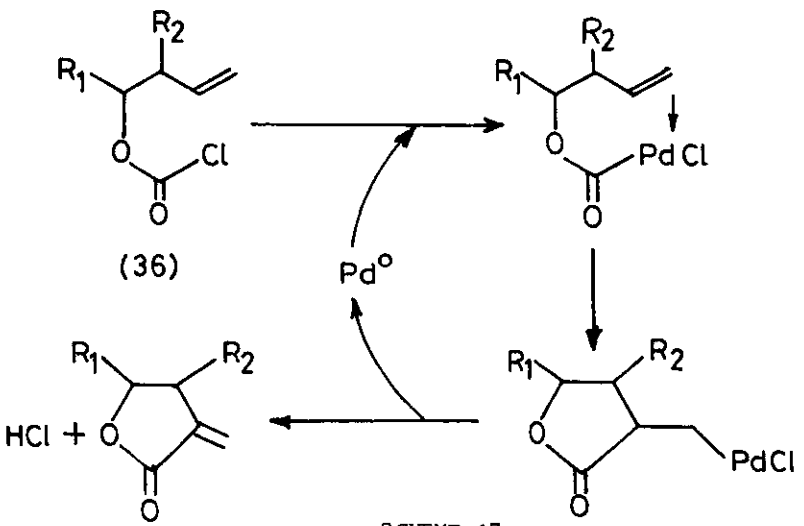
SCHEME 15

16. Another application of allylsilanes for the preparation of α-methylene-γ-lactones has been cited by Fujita et al.[37] 2-Substituted allylsilane (34) on treatment with iodosobenzene and BF_3 etherate in dioxane furnishes the conjugated enal (35) in good yield, from which α-methylene-γ-butyrolactone was synthesised as shown in the scheme 16.



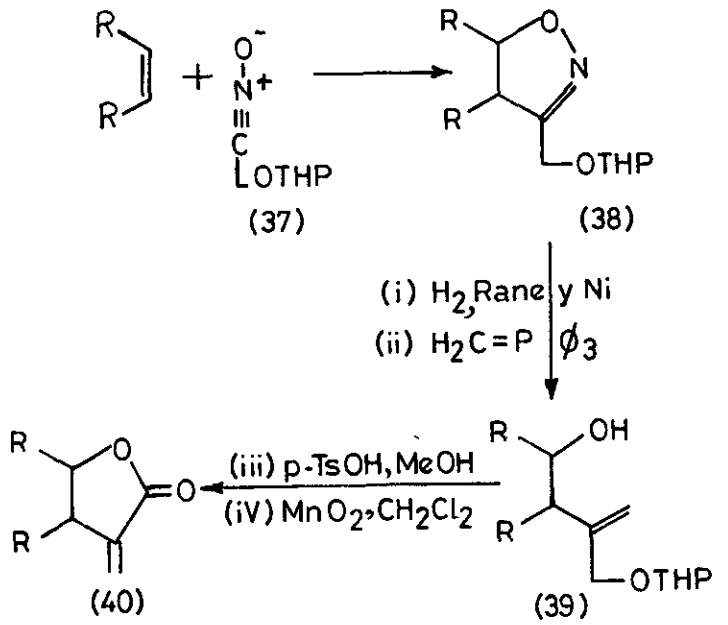
SCHEME 16

17. Palladium-catalyzed intramolecular carboalkoxylation of homoallylic chloroformates furnished α-methylene-γ-lactones in poor to moderate yields[38]. The starting material (36) can be made from the homoallylic alcohols and phosgene.



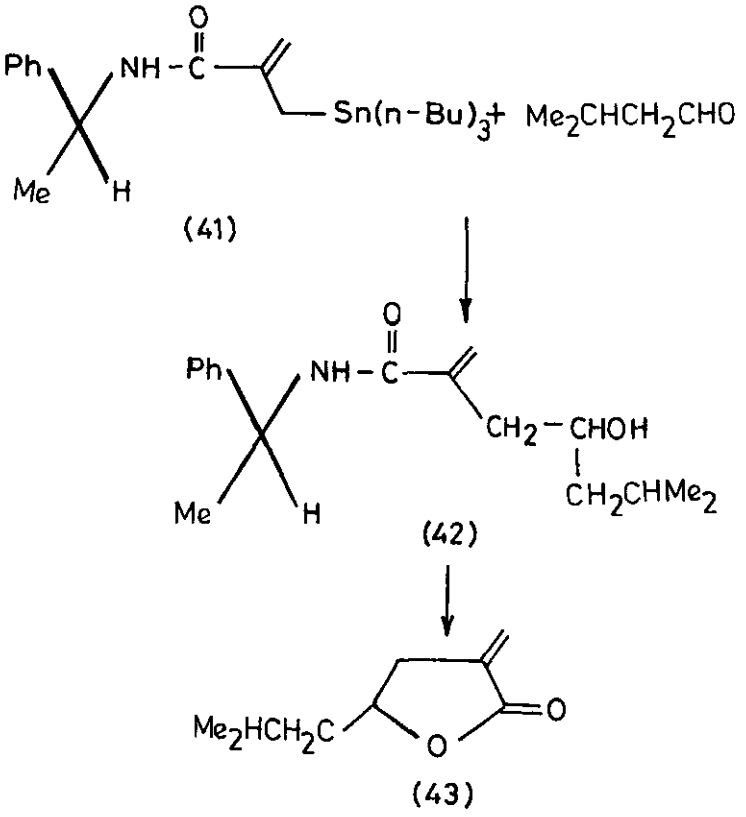
SCHEME 17

18. α-Methylene-γ-butyrolactones have been prepared through isoxazolines as shown in scheme 18[39]. Cycloaddition reaction of the nitrile oxide (37) with the appropriate alkene furnishes the isoxazoline product (38) which is cleaved by hydrogenolysis and the resulting β-hydroxyketone on methylenation provides homoallylic alcohol (39). Cleavage of the tetrahydropyranyl group followed by manganese dioxide oxidation of the diol furnishes α-methylene-γ-lactone (40).



SCHEME 18

19. New chiral reagents such as 2-[(tributylstannyl) methyl] propenamides have been used for asymmetric synthesis of γ-alkyl-α-methylene-γ-butyrolactones[40]. Reaction of N-[(S)-α-methylbenzyl]-2-[(tributylstannyl)methyl] propenamide ((S)-(-)-41) with isovaleraldehyde in the presence of 4 equivalents of BF_3 OEt_2 furnished γ-hydroxy-α-methyleneamide (42) in 80% yield, which on acidic hydrolysis furnished γ-isobutyl-α-methylene-γ-butyrolactone (43) in 81% yield.



SCHEME 19

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