SYNTHESIS OF GIBBERELLINS†

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Synthetic studies on gibberellins have been developed during the past twenty years. This review deals with several works concerning synthesis of gibberellin derivatives, total synthesis of gibberellins, and chemical conversions of natural products into gibberellins.

1 Introduction

Gibberellin, the plant growing hormon, has originated from metabolism of fungi (mainly *Gibberella fujikuroi*) and higher plants. Fifty kinds of gibberellins have been isolated so far, and their structures determined. They are biosynthesized from *ent*-kaur-16-ene (1) and have a common *ent*-gibberellane skeleton (2) which is biosynthesized by the ring B contraction with extrusion of C-7 from a kaurene-type precursor. They are classified into C_{20} and C_{19} gibberellins, and the latter is produced by the loss of one carbon atom (C-20) from the former.

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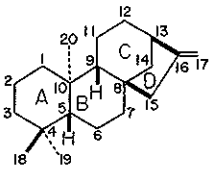
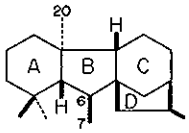
† This article is dedicated to Professor R. B. Woodward on the occasion of his sixtieth birthday.

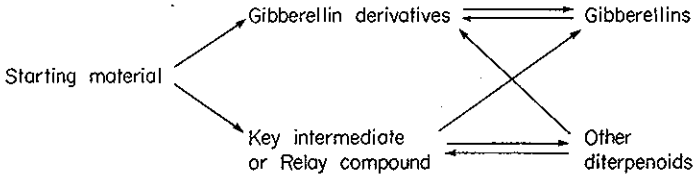


(1)



(2)

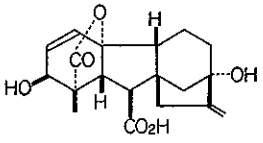
The synthesis of gibberellins has been carried out through several routes, which are outlined in Scheme 1.



Scheme 1

2 Synthesis of compounds derived from gibberellins

The synthetic studies on gibberellins began with the total synthesis of compounds which were derived from gibberellin A_3 (gibberellic acid) (3) and made a big contribution in its structure determination. They are gibberic acid (4), epigibberic acid (5), epiallogibberic acid (6), and gibberone (7). Compounds (4) and (5) had been obtained from (3) by its treatment with acid. The compound (6) had been derived by treatment of (3) with hydrazine. Gibberone (7) had been derived from (4) by dehydrogenation with palladium-carbon.



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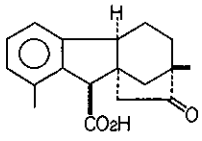

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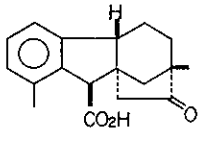

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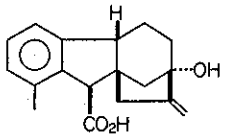

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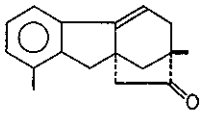
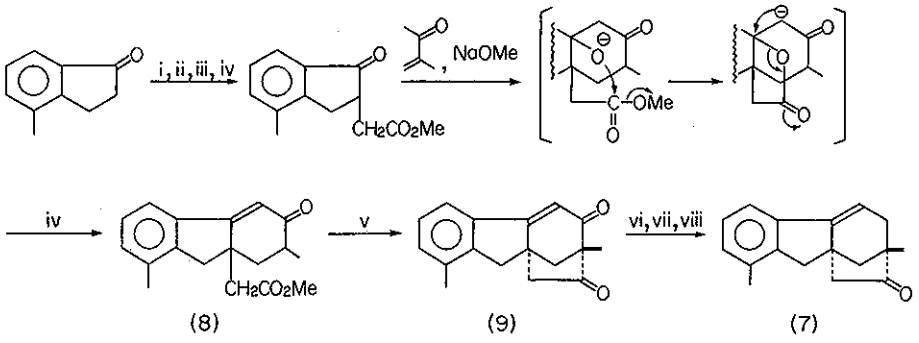


(7)

The total synthesis of gibberone (7) was carried out by Loewenthal *et al.*[1] as shown in Scheme 2 : the starting material, 4-methylindan-1-one, was converted into compound (8) *via* introduction of a C_2 unit into the 2-carbon atom and condensation with isopropenyl methyl ketone (consturction of the ring C) ; intramolecular acid-catalyzed cyclization of (8) led to diketone (9) in good yield (construction of the ring D) ; the ketone on the ring C, after protection of the ketone on the ring D, was subjected to the Wolff-Kishner reduction followed by acid hydrolysis to give *rac*-gibberone (7).

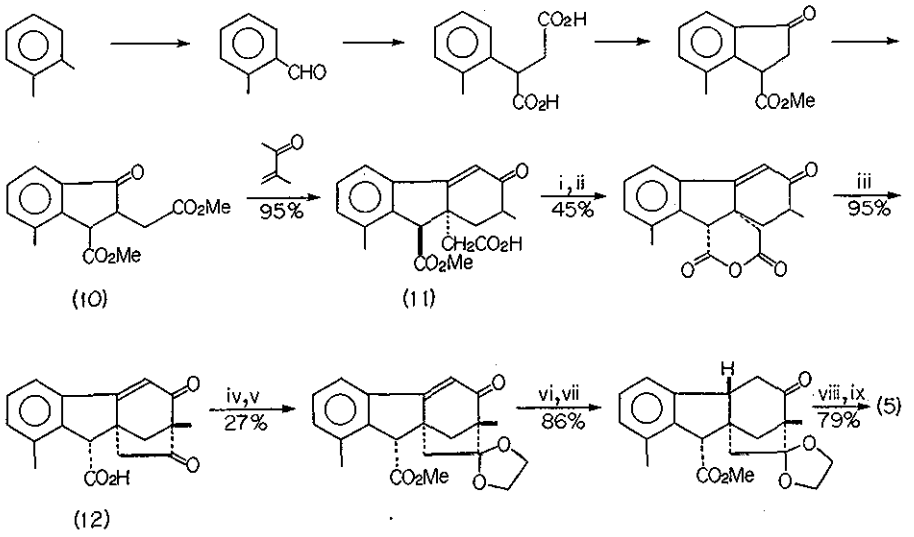


i Br_2 ; ii $NaCH(CO_2tBu)_2$; iii H^+ ; iv CH_2N_2 ; v BF_3, Ac_2O ; vi $HO(CH_2)_2OH, H^+$; vii Wolff-Kishner reduction

Scheme 2

rac-Gibberic acid (4) was also synthesized by Loewenthal *et al.*[3] The total synthesis of *rac*-epigibberic acid (5) was reported by Mori *et al.*[4] Since the both syntheses are fundametally similar, only the latter which was connected with the total synthesis of gibberellin A_4 *etc.* is outlined. As shown in Scheme 3, *o*-xylene was converted into compound (10), which was

transformed to a *trans*-halfester (11). This compound was later found to be the thermodynamically more stable product, which was produced by epimerization of the initial product formed under the kinetically controlled conditions. Acid anhydride derived from it was cyclized by BF_3 to give compound (12), whose reduction at the ring C afforded *rac*-epigibberic acid (5).



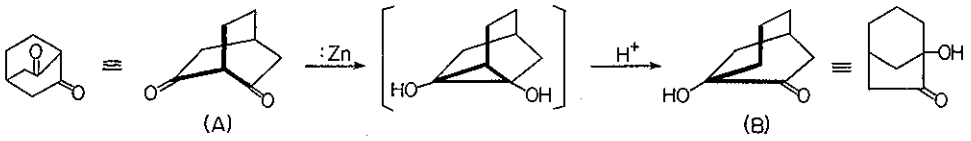
i OH^- ; ii Ac_2O ; iii BF_3 ; iv CH_2N_2 ; v $HO(CH_2)_2OH, H^+$; vi Raney Ni ; vii CrO_3 ; viii Huang-Minlon reduction ; ix H_3O^+

Scheme 3

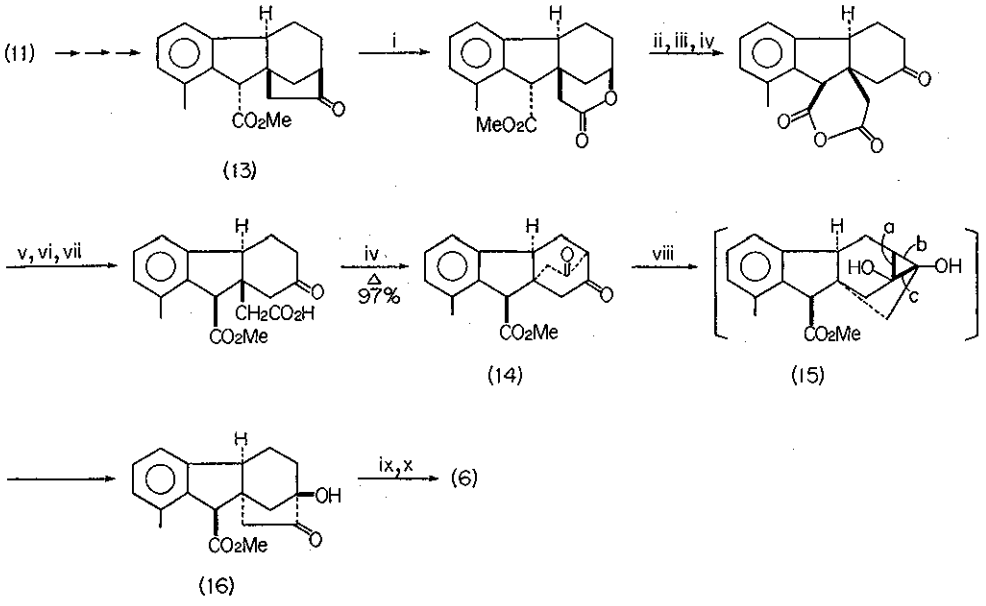
The total synthesis of *rac*-epiallogibberic acid (6) was first accomplished by Mori[6] and later by House *et al.*[7] This synthesis can be regarded as a model synthesis for the construction of the rings B, C, and D of gibberellin A_3 ; the introduction of the 13-hydroxyl group is the most important and difficult point.

Mori[6] synthesized compound (13) from compound (11) similarly to the

procedure used in the synthesis[4] of epigibberic acid (5). As the key reaction for the 13-hydroxylation, a new method[8] developed in the chemical conversion of gibberellin A_3 into epiallogibberic acid (6), that is, reductive rearrangement of diketone (A) into ketol (B) with zinc and acetic acid was applied. (See Scheme 4)



Scheme 4

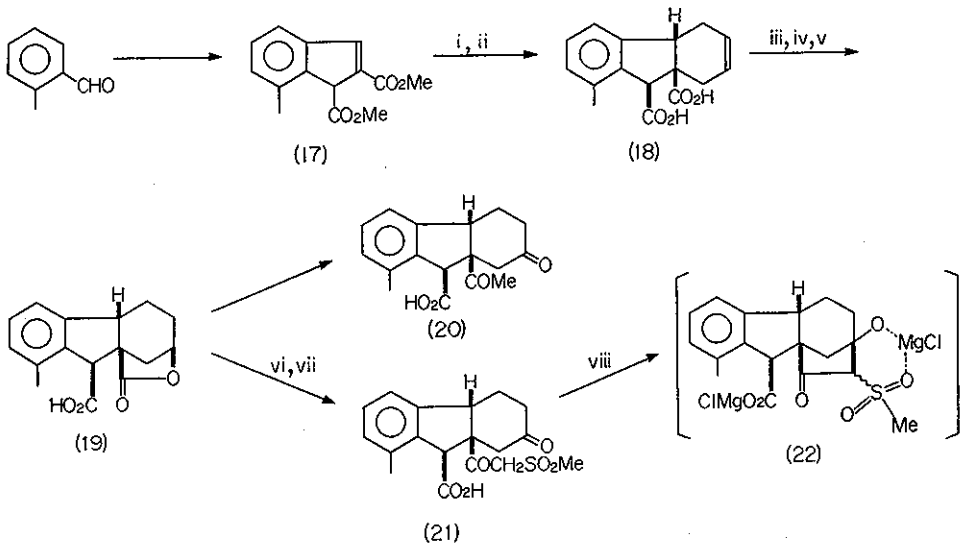


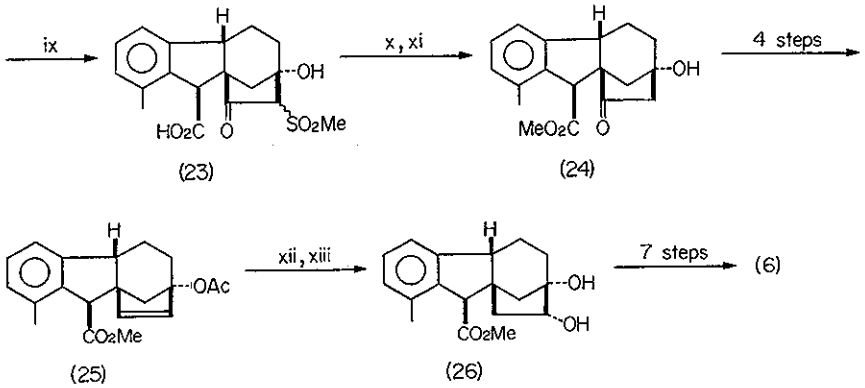
i CF_3CO_3H ; ii $LiAlH_4$; iii CrO_3 ; iv Ac_2O ; v $C_6H_5CH_2OH$; vi CH_2N_2 ; vii H_2, Pd-C ; viii Zn, AcOH ; ix Witting reaction ; x NaOH

Scheme 5

Thus, compound (13) was transformed into a type-A compound (14), which was heated with zinc in acetic acid to give the desired ketol (16) in 48% yield together with two minor products. These products are probably formed from cyclopropane diol (15), an intramolecualr pinacol condensation product, by acid-catalyzed cleavage at a, b, or c shown in (15). The Wittig reaction followed by the treatment with alkali converted the compound (16) into epiallogibberic acid (6). (See Scheme 5)

The sequence by House *et al.*[7] is shown in Scheme 6. *o*-Tolualdehyde was converted to an indene derivative (17) through ten steps. This compound was subjected to the Diels-Alder reaction with butadiene followed by hydrolysis to give dicarboxylic acid (18), which was converted into lactone (19) by iodolactonization utilizing the angular carboxylic acid. Since the intramolecular aldol condensation with diketone (20) which was derived from (19) was not successful, compound (19) was transformed into β-ketosulfone (21), whose intramolecular aldol condensation using two equivalents of t-butylmagnesium chloride was successfully developed to give the desired product (23) in 96% yield. The Mg^{++} is probably served to stabilize the intermediate by chelating as shown in formula (22). The methyl ester of (23) on treatment with aluminum amalgam gave hydrogenolyzed product (24), which was converted into the endocyclic 15-ene derivative (25) by the method of Nagata *et al.*[9] Oxymercuration of (25) occurred selectively at C-16 by the intramolecular participation of 13-acetoxyl group, and consequently 13,16-diol (26) was yielded. Finally the compound (26) was transformed into the desired compound, *rac*-epiallogibberic acid (6), but the direct conversion of the 16-ol of (26) into exomethylene by oxidation followed by Wittig reaction was not successful, and a somewhat roundabout way *via* repeated protections was necessary.





i butadiene ; ii NaOH ; iii I_2 , $NaHCO_3$; iv HCl ; v $(nBu)_3SnH$; vi $LiCH_2SO_2Me$; vii Jones oxidation ; viii 2x tBuMgCl ; ix aq. AcOH ; x CH_2N_2 ; xi Al-Hg ; xii $Hg(OAc)_2$; xiii $NaBH_4$, NaOH

Scheme 6

The foregoing total syntheses of the derivatives of gibberellin A_3 not only played the role for the structure determination of gibberellins which was the initial purpose, but they made a considerable contribution to the total synthesis of gibberellins. Thus the chemical conversion of epigibberic acid to gibberellins was accomplished by Mori *et al.* (*vide infra*). The chemical conversions of epiallogibberic acid into gibberellin A_1 or gibberellin A_3 might be possible and they would constitute the formal total synthesis of these gibberellins.

3 Total synthesis of gibberellins

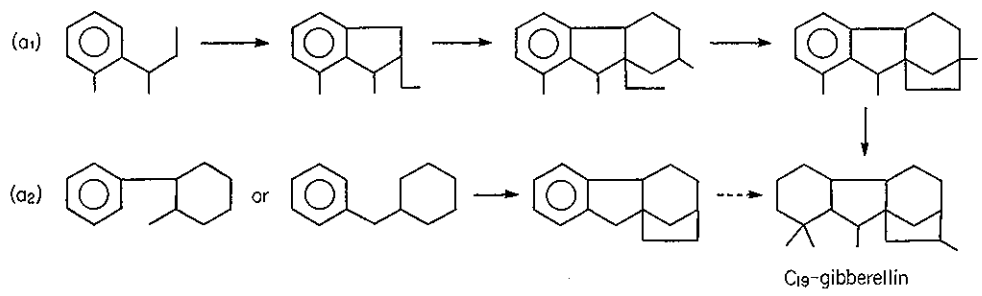
In the synthesis of the gibberellane skeleton, the most characteristic problem is how to construct the ring B. On the basis of the method, the synthesis can be classified into the route (a) *via* an indane intermediate and the route (b) *via* a decalin intermediate. Generally, the route (a) is convenient for the synthesis of C_{19}-gibberellins, while the route (b) for that of C_{20}-gibberellins.

The route (a) can be further divided into route (a_1) in which the rings A, B, C, and D are constructed in this order and route (a_2) in which the ring B is finally formed from the intermediate having rings A and C or rings A, C, and D. So far no total synthesis through route (a_2) has been reported. The route (b) can also be divided into (b_1) and (b_2). The latter is regarded as the pathway which is parallel to the biosynthesis, because it goes by way of kaurane derivative. These sequences are shown in Scheme 7.

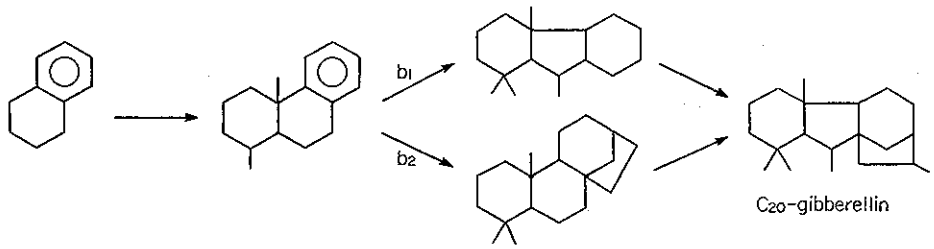
In the synthesis of C_{19}-gibberellins, the A/B-*trans* system can be produced by the lactonization to the 10-carbocation derived from a hydrindane derivative, as shown in Scheme 8, while the synthesis of *trans*-hydrindane system having a carbon atom on C-10 is generally difficult. Thus,

for the synthesis of C_{20}-gibberellins, the route through any indane derivative is not preferable, but the procedure, in which the ring B contraction of a *trans*-decalin derivative gives a *trans*-hydrindane derivative under keeping the A/B-*trans* juncture, is suitable.

Route (a)



Route (b)

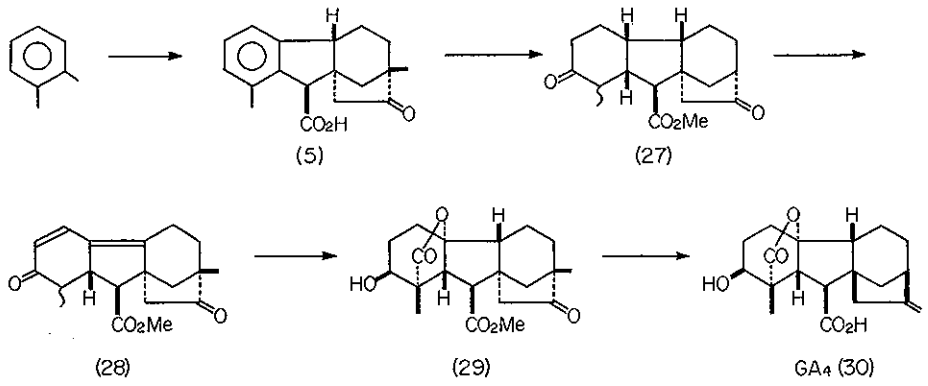


Scheme 7

Scheme 8

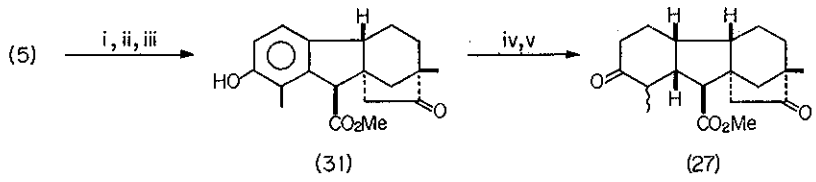
3-1 Total synthesis of C_{19}-gibberellins (GA_2, GA_4, GA_9 and GA_{10})

As the first total synthesis, the formal relay synthesis of gibberellin A_4 done through the route (a_1) by Mori *et al.*[10], is described. The outline is shown in Scheme 9.



Scheme 9

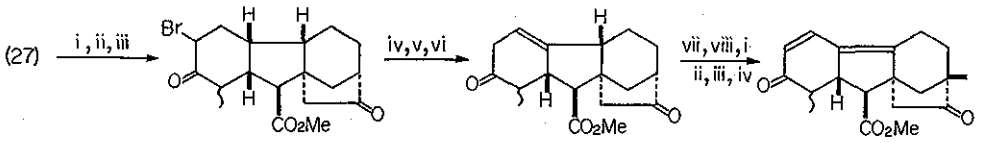
The synthesis of *rac*-epigibberic acid (5) has been mentioned in Chapter 2. The next steps are functionalization at C-3 and reduction of aromatic ring. Nitration at C-3 of (5), reduction, diazotization, and hydrolysis converted (5) into phenol (31) in overall 37% yield. The successive reduction of the aromatic ring, Jones oxidation, and separation of four products by chromatography resulted in the isolation of the desired diketo-ester (27) in low yield. This compound derived from gibberellin A_3 (*vide infra*) was used as the relay compound. (Scheme 10)



i HNO_2, Ac_2O ; ii H_2, Pd-C ; iii $NaNO_2$, H_2SO_4 ; iv RhO_2, PtO_2 ; v CrO_3

Scheme 10

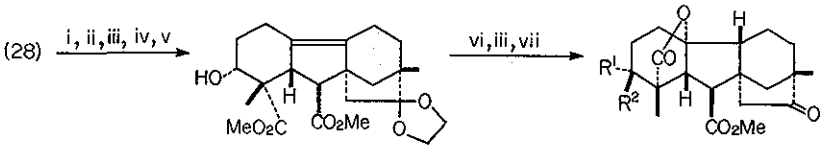
The third step is formation of dienone system starting from the 3-carbonyl group of (27). (Scheme 11) On formylation and bromination at C-2 followed by deformylation, (27) gave bromoketone (32), which on dehydrobromination, migration of the double bond accompanied by hydrolysis of ester, and reesterification gave βγ-unsaturated ketone (33). Migration of the double bond to the γδ-position for the carbonyl group followed by introduction of the αβ-double bond transformed the compound (33) into the desired dienenone ketoester (28).



i HCO_2Et, NaOMe ; ii Br_2 ; iii NaOH ; iv LiBr, $LiCO_3$; v dil HCl ; vi CH_2N_2 ; vii H_2, Pd/c ; viii CrO_3

Scheme 11

The fourth step is the conversion of (28) into gibberellin C methyl ester (29). (Scheme 12)



(35) R^1=OH, R^2=H

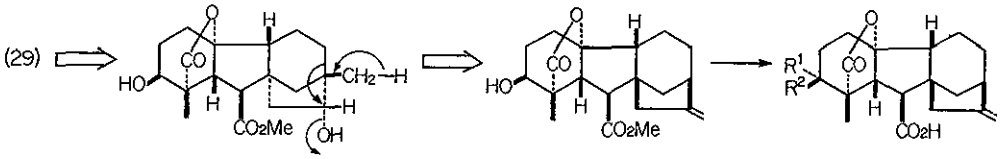
(29) R^1=H, R^2=OH

i $HO(CH_2)_2OH$, H^+ ; ii CO_2, Ph_3CNa ; iii CH_2N_2 ; iv $NaBH_4$; v H_2, Pd-C ; vi H_2SO_4 ; vii NaOH

Scheme 12

Ethylene acetalization at 16-carbonyl group, carboxylation at C-4, and esterification converted compound (28) into diester, which on sodium borohydride reduction and hydrogenation afforded γδ-unsaturated alcohol (34). Lactonization and epimerization of 3-ol by alkali transformed compound (34) into (29) *via* (35).

The final step is the rearrangement between rings C and D. Cross *et al.*[11] had treated the diol (36), derived from (29) by sodium borohydride reduction, with phosphorus pentachloride to give gibberellin A_4 methyl ester (37) though in a low yield. So, the remaining problem was only the hydrolysis of this methyl ester. Mori *et al.*[10] derived the ester (37) from gibberellin A_7 and treated it with 0.1 N NaOH to give gibberellin A_4 (30) (4%) and its 3-epimer (38) (27%). Since gibberellin A_4 had been converted into gibberellins A_2[12], A_9[13], and A_{10}[14] (*vide infra*), this synthesis constituted their formal total synthesis. (Scheme 13)



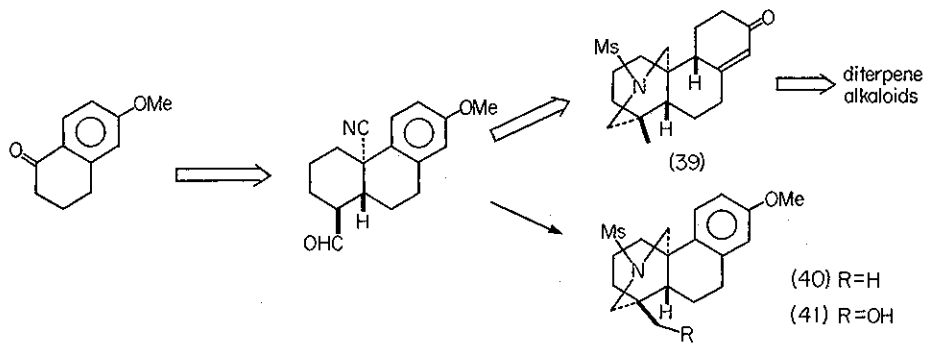
Scheme 13

3-2 Total synthesis of C_{20}-gibberellins (GA_{12}, GA_{15}, and GA_{37})

The first total synthesis of C_{20}-gibberellin is that of gibberellin A_{15} by Nagata *et al.*[15] through the route (b_1). Subsequently, the syntheses of gibberellins A_{15} and A_{37} by the authors[16] and of gibberellin A_{12} by Mori *et al.*[27] were accomplished *via* route (b_2).

3-2-1 Total synthesis of gibberellin A_{15} by Nagata *et al.*[1]

Nagata *et al.* had synthesized the diterpene alkaloids, and the key intermediate and related compounds, (39), (40), and (41), in the synthesis of atisine[17] appeared to be potential starting materials for the total synthesis of gibberellin A_{15}, because ApSimon *et al.*[18] had converted azomethines into lactones. On the basis of the preliminary experiments for the functionalization of the ring B required for the transformation of the six-membered ring B into a five-membered ring, the compound (39) was adopted as the suitable material. (Scheme 14)

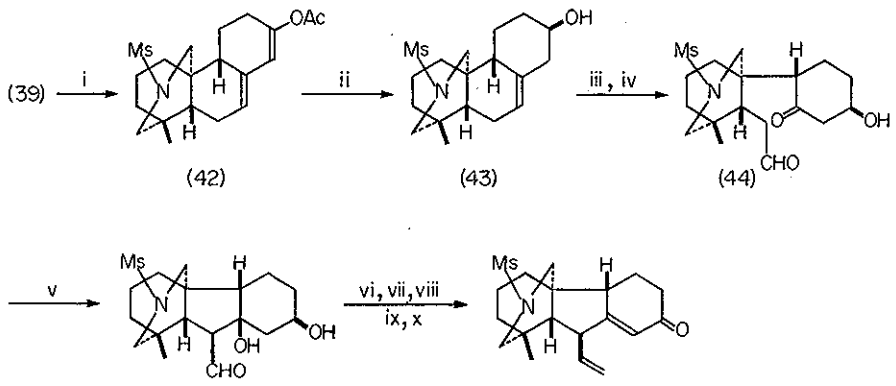


Scheme 14

The compound (39) has the same stereochemistry as gibberellin A_{15} in four asymmetric centers (C-4, C-5, C-9, and C-10). Three questions which must be solved are ring B contraction, ring D construction, and transformation of the piperidine ring into δ-lactone.

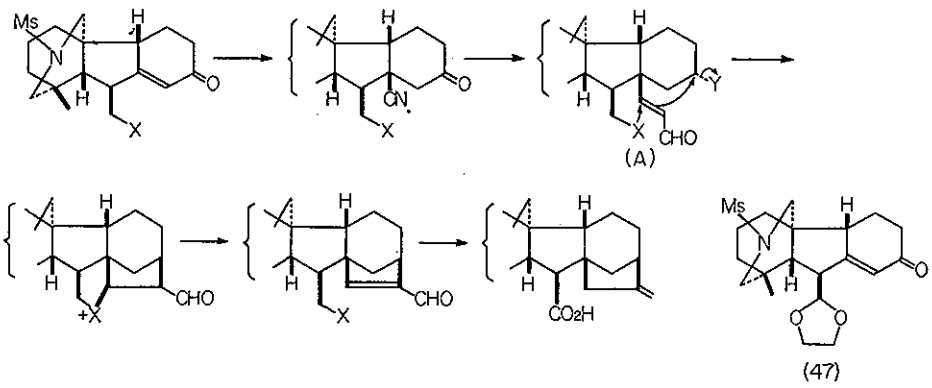
The key compound (39) was converted into dienol acetate (42), which was treated with sodium borohydride in alkaline medium to give 7-en-13-ol (43). Ozonolysis of (43) gave keto-aldehyde (44), whose aldol condensation afforded ring B contraction product (45). Acetylation of the secondary

alcohol, Wittig reaction on the aldehyde, alkaline hydrolysis of acetate, Jones oxidation of the alcohol, and dehydration converted the compound (45) into dienone (46). (Scheme 15)



Scheme 15

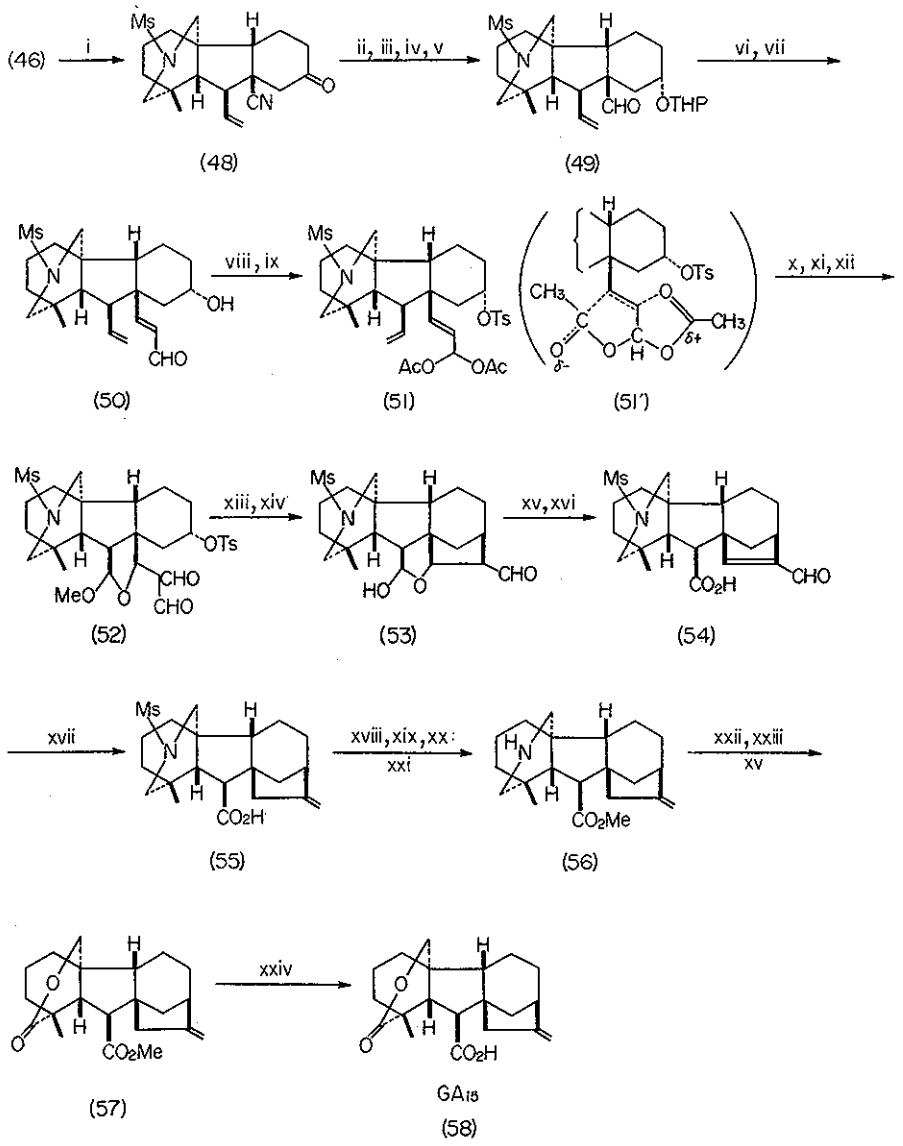
For the ring D construction, they made a plan shown in Scheme 16.



Scheme 16

The first attempt for the hydrocyanation to the acetal (47) was not successful, probably due to the steric hindrance and participation of the lone pair of the acetal oxygen atom, hence the aldyhyde was protected as the vinyl group as shown in (46) in Scheme 15. The hydrocyanation of the compound (46) proceeded smoothly with a new reagent (diethylaluminum cyanide)[19] and gave the B/C *cis*-product (48) as expected in good yield. (Scheme 17) The compound (48) was converted into (49) *via* a few steps including two types of reductions, and the latter was subjected to formylolefination[20] by their new reagent, diethyl β-(cyclohexylamino)-vinylphosphonate, followed by elimination of the protecting group to yield the compound (50). This compound was then transformed into (51) as shown. The double bond at C-15 of the compound (51) resisted to the ozonolysis, because of the intramolecular participation of two acetoxyl groups to this double bond as shown in formula (51'). Thus a selective ozonolysis on a double bond at C-7 occurred and gave 7-al, which was converted into methyl acetal (52) by treatment with potassium hydroxide in dry methanol. Now, cyclization *via* (A) shown in Scheme 16 was a little modified and an intramolecular S_N 2-type substitution *via* enamine was carried out. Subsequent hydrolysis yielded ring-D construction product (53), which was converted into exomethylene compound (55) *via* the 15-en-16-al (54). The finally remaining transformation of the piperidine ring into δ-lactone was accomplished as follows. Reductive elimination of the mesyl group, protection by trifluoroacetyl group of the amine, esterification, and elimination of the protecting group on the nitrogen atom converted the compound (55) into the imino ester (56), which was transformed into gibberellin A_{15} methyl ester (57) *via* conversion to azomethine followed by the procedure of ApSimon *et al.*[18] The corresponding lactone isomer was also

formed. Finally, demethylation of the ester was done by treatment of (57) with lithium iodide and triphenylphosphine in refluxing collidine, thus the first total synthesis of gibberellin A_{15} was accomplished. (Scheme 17)



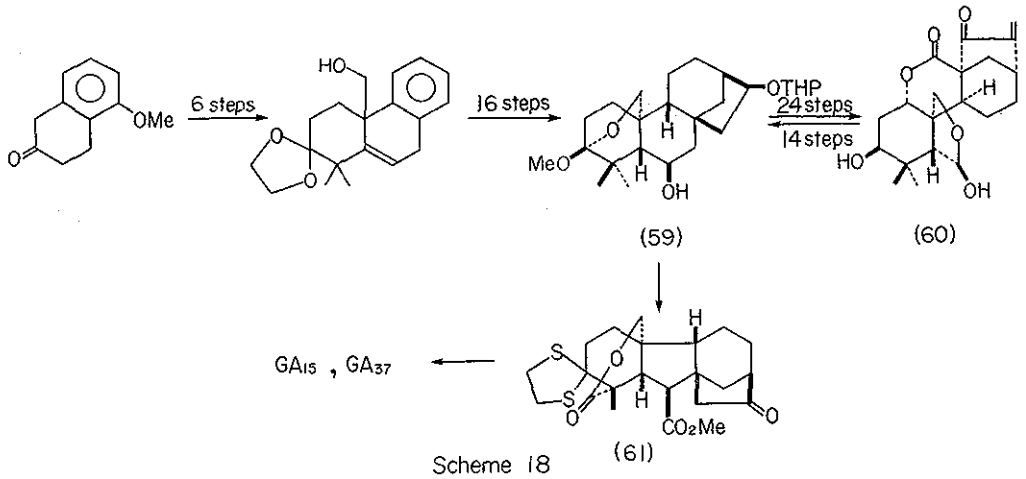
i Et_2AlCN ; iii $Al(iPrO)_3$; iii i-Bu_2AlH ; iv AcOH-AcONa ; v dihydropyran ; vi $(EtO)_2P(=O)CH=CH-NH-\langle\bigcirc\rangle$, NaH ; vii aq. oxalic acid ; viii tosyl chloride, pyridine ; ix $Ac_2O, ZnCl_2$; x O_3 ; xi Zn-AcOH ; xii KOH/MeOH ; xiii pyrrolidine (2 eq.) ; xiv 50% AcOH ; xv Collins oxidation ; xvi K_2CO_3 ; xvii Wolff-Kishner reduction ; xviii Li-liq. NH_3 ; xix $(CF_3CO)_2O$, pyridine ; xx CH_2N_2 ; xxi K_2CO_3 ; xxii $Pb(OAc)_4$; xxiii HNO_2 ; xxiv LiI, Ph_3P, collidine.

Scheme 17

3-2-2 Total Synthesis of gibberellins A_{15} and A_{37} by the authors

The authors[16] converted the key intermediate (59)[21] in the total synthesis of enmein (60) into compound (61), a common intermediate, which they transformed into gibberellins A_{15} and A_{37}. (Scheme 18)

In the course of the synthesis of enmein, there are many kaurane derivatives possessing functional groups in the ring B, and they may be regarded as the potential precursors for the synthesis of the gibberellins. None of them, however, has the oxygenated carbon atom at the 19 position. Preliminary experiments with several kaurane and gibberellane derivatives led to a conclusion that the hypoiodite reaction with the *ent*-kaurane derivatives which had the rigid boat conformation of the ring A and a 6β-hydroxyl group gave satisfactory results for the oxygenation at the 19-carbon atom. Thus, the foregoing compound (59) was picked up as the most suitable compound among the intermediates in the total synthesis of enmein (60). This compound has the same stereochemistry as in the gibberellin A_{37} in five of eight asymmetric centers. Furthermore it can be relatively easily derived from enmein (60) as illustrated in Scheme 18.[23]



Scheme 18

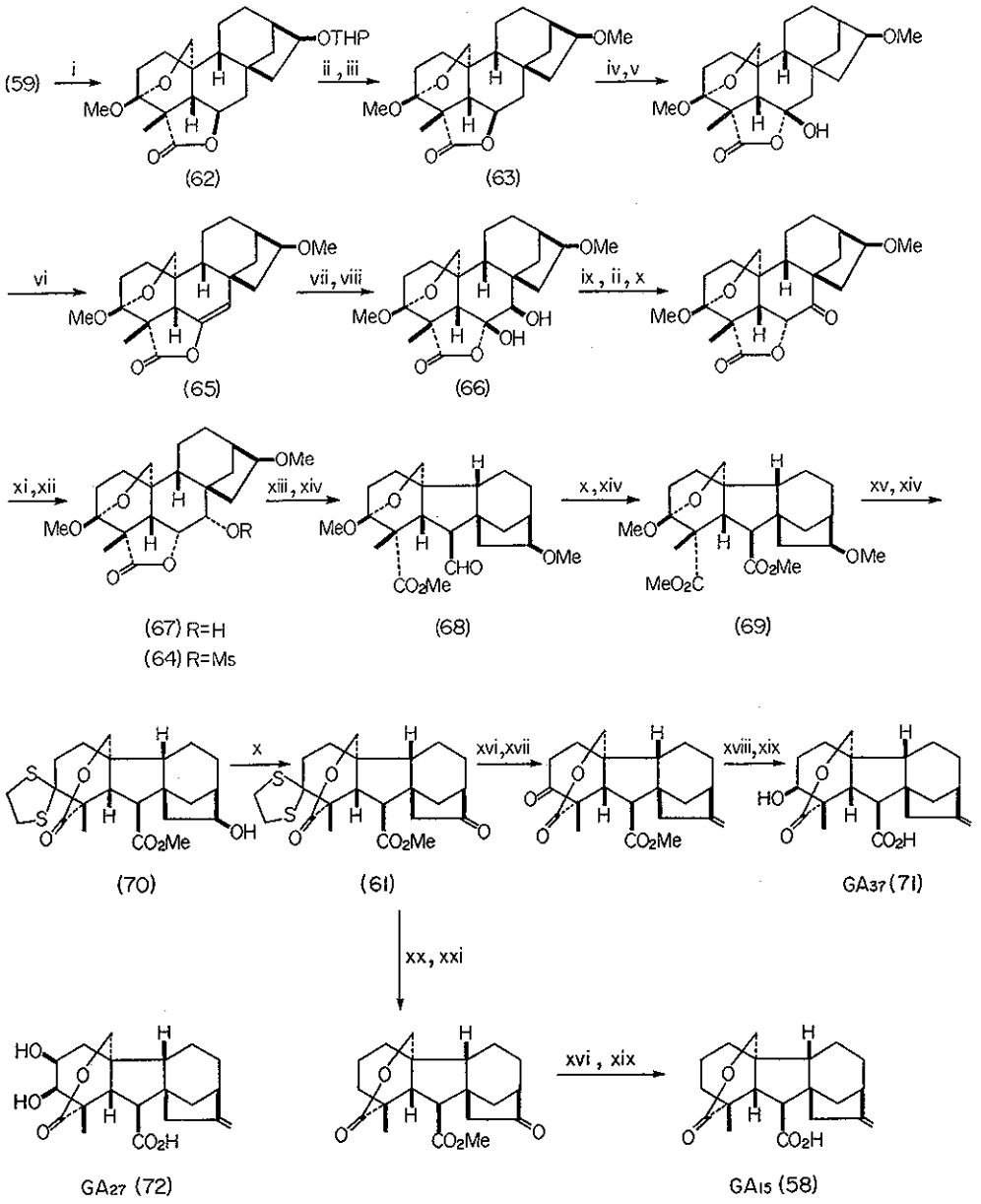
The hypoiodite reaction with compound (59) using lead tetraacetate and iodine under irradiation yielded lactone (62), as expected on the basis of the foregoing preliminary experiments.

The introduction of the exocyclic methylene group was attempted near the end; its earlier introduction seemed unwise because of its sensitivity to several reagents. Before the introduction of this group, the presence of a 16β-methoxyl group was maintained. Since the aliphatic methyl ethers are stable under acidic and basic conditions, they seem to be very suitable for the protection of alcohols. But generally, demethylation for recovering the original alcohol is not easy, so that the O-methyl group has scarcely been used as the protecting group. The authors investigated demethylation of several methyl ethers and found a good method using thiol and boron trifluoride etherate under mild conditions.[24] (*Vide infra*) Thus, the 16-ol tetrahydropyranyl ether (62) was converted into the methyl ether (63).

Subsequently, the ring B contraction for the conversion of the kaurane type into the gibberellane type compounds was investigated. As the result of the priliminary experiments[25], compound (64) was found to be the most

suitable material for the ring B contraction. Hence, the chemical transformation of compound (63) into (64) was carried out. As shown in Scheme 19, hydrolysis followed by oxidation converted the 6β-lactone (63) into 6α-lactone-6β-ol, which on dehydration, epoxidation, and acidic hydrolysis (with boron trifluoride in wet benzene) of the resulting β-epoxide afforded 6β,7β-glycol (66) *via* an enol-lactone (65). Compound (66) on reduction with lithium aluminum hydride afforded selectively the 6α-ol which on acidic treatment gave 6α-lactone. The 7-carbonyl group produced from 7β-ol by Jones oxidation was transformed by the sodium borohydride reduction to the α-ol (67) in good yield. Subsequent mesylation led to the formation of the desired mesylate (64), which on treatment with potassium hydroxide in aqueous t-butanol yielded the gibberellane aldehyde (68) quantitatively. Jones oxidation followed by methylation converted aldehyde (68) into methyl ester (69), which on treatment with ethanedithiol in the presence of boron trifluoride etherate followed with diazomethane gave a dithioacetal lactone alcohol (70) under simultaneous occurrence of demethylation of the C-16 methoxyl group, dithioacetalization at the C-3 atom, and lactonization between the 20-ol and the 19-carbonyl group. The 16β-ol of the compound (70) was oxidized to the ketone (61), an important common intermediate for the synthesis of gibberellins A_{15} and A_{37}. The transformation of the 16-oxo group into the exocyclic methylene group, dethioacetalization to the 3-ketone, Meerwein-Ponndorf reduction to the 3β-ol, and final demethylation of the methoxycarbonyl group on C-6 by the procedure of Johnson *et al.*[26] were successively carried out to give the desired gibberellin A_{37} (71). Thus a relay total synthesis of gibberellin A_{37} was performed. The gibberellin A_{15} (58) was derived from (61) by successive reductive desulfurization, Wittig reaction, and demethylation.

The common intermediate (61) would also be convertible to gibberellin A_{27} (72).

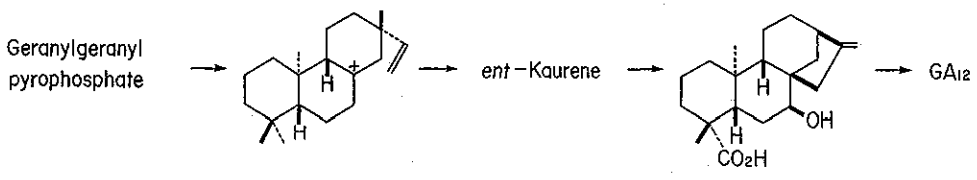


i $Pb(OAc)_4$, I_2, $h\nu$; ii dil. HCl ; iii CH_2N_2, BF_3 ; iv $HClO_4$; v Collins oxidation ; vi $SOCl_2$; vii *m*-chloroperbenzoic acid ; viii BF_3, H_2O ; ix $LiAlH_4$; x Jones oxidation ; xi $NaBH_4$; xii MsCl, pyridine ; xiii KOH, aq. *t*-BuOH ; xiv CH_2N_2 ; xv BF_3, $HSCH_2CH_2SH$; xvi Wittig reaction ; xvii N-chlorosuccinimide ; xviii $Al(iPrO)_3$; xix PrSLi in hexamethylphosphoramide ; xx Raney Ni ; xxi H_2, Pt

Scheme 19

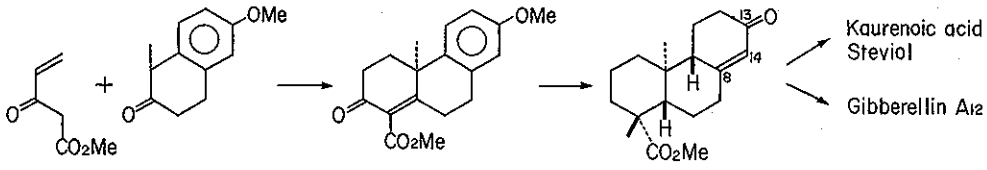
3-2-3 Total synthesis of gibberellin A_{12}

Mori *et al.*[27] carried out a formal total synthesis through a biosynthesis-like route ; they used the type-A and type-B compounds as the key intermediates in the synthesis. As shown in Scheme 20, (A) and (B) are the key intermediates in the biosynthesis of gibberellin A_{12}.



Scheme 20

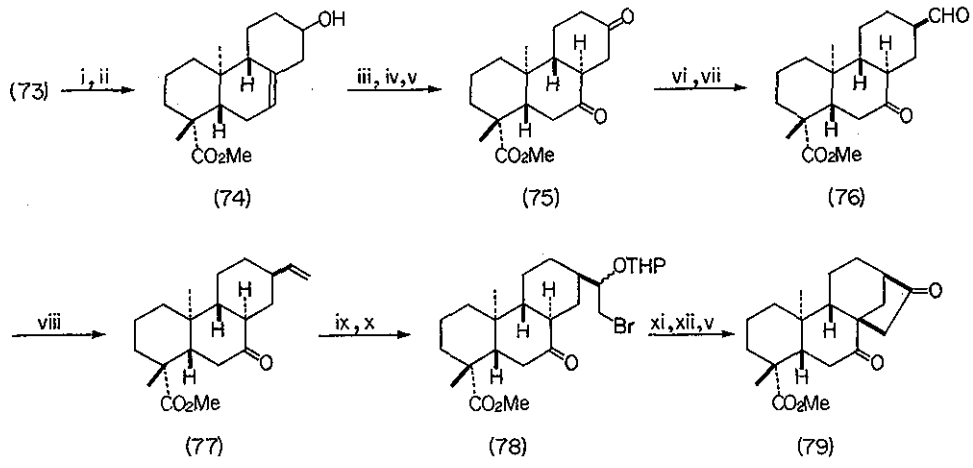
The compound (73), the material used for their total synthesis of kaurenoic acid [28] and steviol[28,29], was adopted as the starting material for the synthesis of gibberellin A_{12}. (Scheme 21)

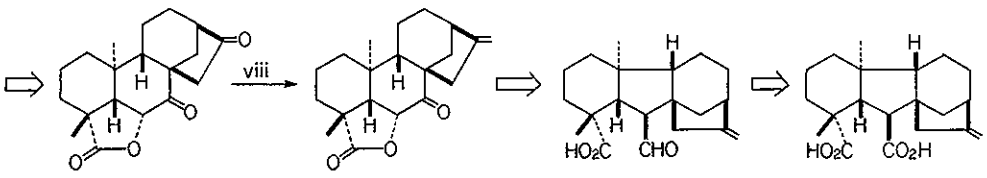


Scheme 21

The migration of the 8(14)-double bond to the 7-position was carried out by the same way as in the Nagata's total synthesis of gibberellin A_{15} and thus this compound (73) was converted to a βγ-unsaturated alcohol (74). On hydroboration and Jones oxidation, the compound (74) gave diketone (75), the 13-ketone of which was subjected to Wittig reaction followed by acid hydrolysis to give ketoaldehyde (76) in very low yield. The Wittig reaction with (76) gave 13-vinyl derivative (77), the foregoing type-A compound, which was converted into methyl norkaurane-7,16-dionoate (79), the foregoing type-B compound, *via* bromohydrin tetrahydropyranyl ether (78), as shown in Scheme 22.

Galt and Hanson[30] had converted the compound (79) into lactone (80). Mori *et al.* transformed the compound (80) derived from *ent*-7α,18-dihydroxykaur-16-en-6β,19-olide, a metabolite of *Gibberella fujikuroi*, into *ent*-kaur-16-en-7-on-6β,19-olide (81) by the Wittig reaction. Since the conversion of (81) into (82) and of (82) into gibberellin A_{12} (83) had been done by Galt and Hanson[30] and by Cross and Norton[31], respectively, the formal total synthesis of gibberellin A_{12} was now completed.





(80) (81) (82) GA12 (83)

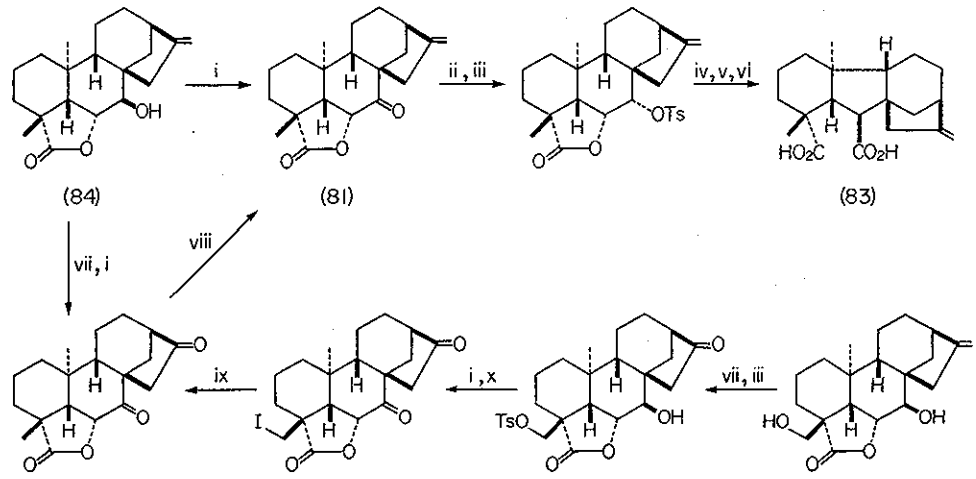
i AcCl, Pyridine ; ii $NaBH_4$; iii B_2H_6 ; iv H_2O_2 ; v Jones oxidation ;
vi $Ph_3P{=}CHO$–⟨⟩–Me ; vii $HClO_4$; viii Wittig reaction ; ix NBS, H_2O ;
x dihydropyran ; xi NaH ; xii Toluene-*p*-sulfonic acid

Scheme 22

4 Chemical conversions into gibberellins

4-1 From other natural products

4-1-1 From kaurenolides ‡



(84) (81) (83)

(80) (85)

i Jones oxidation ; ii $NaBH_4$; iii Toluene-*p*-sulfonyl chloride, pyridine ;
iv KOH ; v CrO_3 ; vi Li, liq. NH_3 ; vii O_3 ; viii Wittig reaction ; ix Zn, AcOH ;
x NaI

Scheme 23

‡ Chemical conversion into gibberellin A_{15} 17-nor-16-one has been published. [B. E. Cross and I. L. Gatfield, *J. Chem. Soc. (C)*, 1971, 1539.]

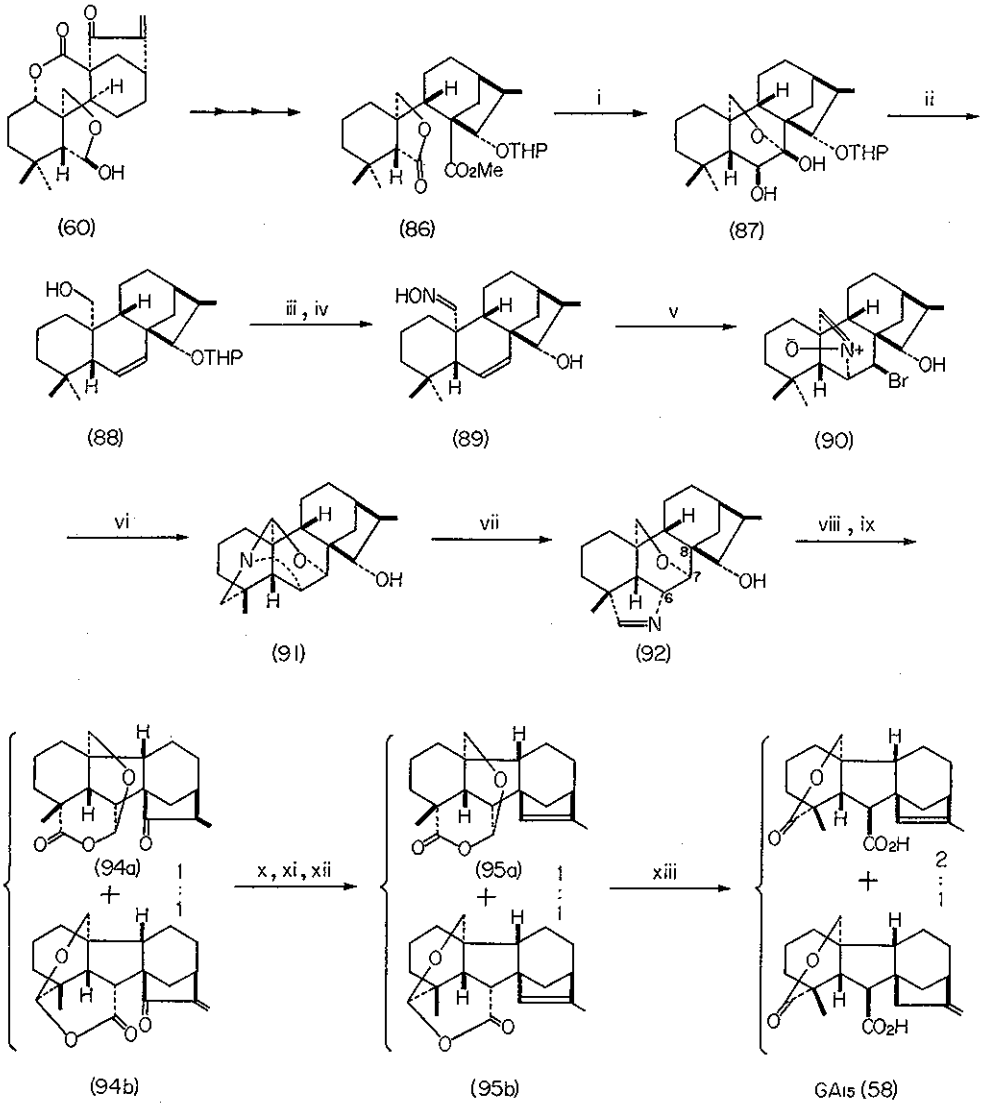
The chemical conversion of *ent*-7α-hydroxykaur-16-en-6β,19-olide ("7β-hydroxykaurenolide") (84) and *ent*-7α,18-dihydroxykaur-16-en-6β,19-olide ("7β,18-dihydroxykaurenolide") (85), metabolits of *Gibberella fujikuroi*, into gibberellin A_{12} (83) have been accomplished (in a formal sense) : Hanson, Cross, *et al.* converted (84) into (83) *via* (81)[30,31,32], and also (85) into (80)[33] ; Mori *et al.*[27] converted (80) into (81) as described in 3-2-3. (Scheme 23)

4-1-2 From enmein

The chemical conversions of enmein (60) into gibberellins have been achieved by two research groups. Somei and Okamoto[34] accomplished the chemical transformation of enmein (60) into gibberellin A_{15} (58). The authors[16] performed the chemical conversions of enmein (60) into gibberellins A_{15} (58) and A_{37} (71). The synthetic sequence is unique in each school. The former group carried out this work as the individual chemical conversion, while the latter group attempted these conversions for supplying the important intermediate (68) in their relay total synthesis of gibberellins A_{15} and A_{37}.

a) The procedure by Okamoto's school[34]

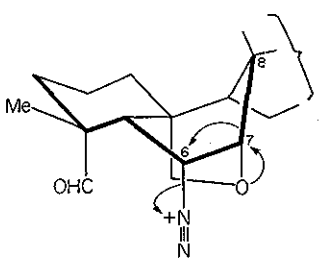
The lactone ester (86) which was derived from enmein (60) in good yield was converted into acyloin (87). The Wolff-Kishner reduction converted (87) into olefin (88). The most difficult step, that is, the functionalization on the C-19 atom was solved by the photolysis of the nitrone. Thus alcohol (88) was transformed into an oxime (89), which was converted into the nitrone (90). Subsequent photolysis of (90) led to the formation of a 19-functionalized product (91). Thermolysis of this compound afforded imine (92). The ring B of this compound has the boat conformation, in which the



i Na, toluene ; ii NH_2NH_2, KOH ; iii CrO_3 ; iv NH_2OH ; v BrN_3 ; vi *hν* ; vii heating ; viii HNO_2 ; ix Jones oxidation ; x $NaBH_4$; xi mesyl chloride, pyridine ; xii heating in collidine ; xiii KOH, diethylene glycol

Scheme 24

bonds of C-6,N and C-7,C-8 are antiparallel each other. Hence the formation of the diazonium salt by its treatment with nitrous acid brought about the rearrangement into the gibberellane skeleton simultaneously. As shown in formula (93), this rearrangement takes place with the extrusion of the C-7 atom under a biosynthetic mode to give dialdehyde, whose oxidation affords a mixture of (94a) and (94b). The mixture was transformed into the 15-ene derivatives (95a) and (95b) as shown in Scheme 24. This mixture was refluxed with potassium hydroxide in diethylene glycol to give a mixture of gibberellin A_{15} (58) and its 15-ene isomer in 15.4% yield under simultaneous autoxidation of aldehyde, isomerization of the double bond, and epimerization of the C-6 atom. Finally, the desired gibberellin A_{15} (58) was isolated by chromatography from its *endo* double bond isomer.

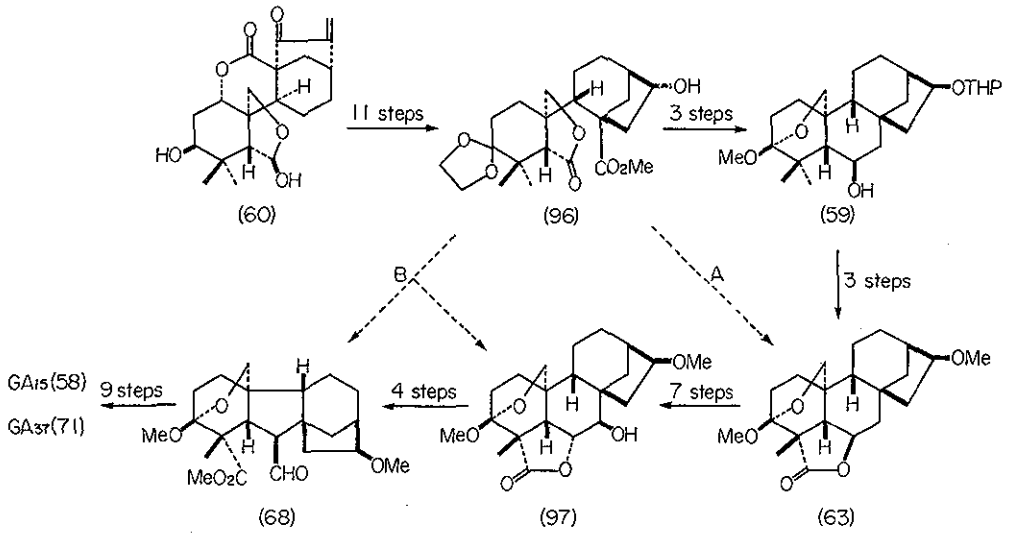


(93)

b) The procedure by the authors[16]

The total synthesis of gibberellins A_{15} and A_{37} described in 3-2-2 has utilized the compound (59) derived from enmein (60) as the relay compound, hence the performance of the foregoing relay total synthesis of gibberllins A_{15} (58) and A_{37} (71) has constituted the chemical conversion of enmein (60) into these gibberellins. Here the chemical conversions through other routes which were attempted for supplying several intermediate compounds between the relay compound (59) and the gibberellins are described.

First, the authors investigated the more effective chemical conversion of lactone ester (96) into lactone (63), the route A in Scheme 25. Thus the alcohol (96) was converted to its methyl ether, whose modified acyloin

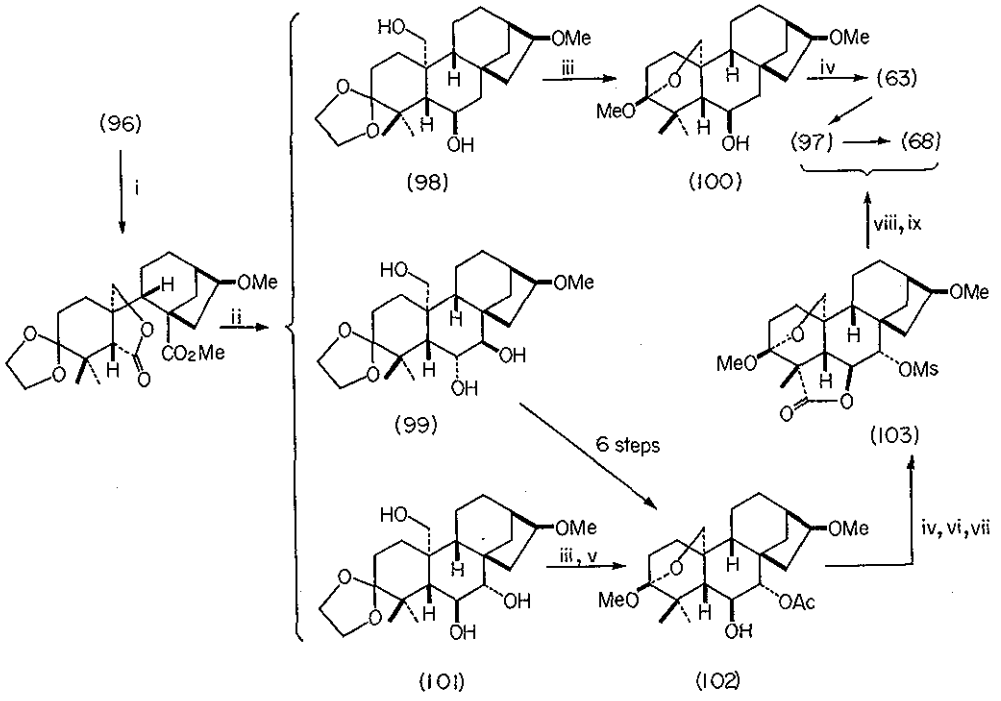


Scheme 25

condensation was explored using sodium in liquid ammonia in order to obtain better yield of the diol (98). Consequently, highest yield (50%) was given when 25 to 35 atom equivalents of sodium was used. Under these conditions, triol (99) was accompanied (25-36%). The methyl acetal (100) derived from (98) on hypoiodite reaction gave lactone (63) in 75% yield. The improved synthesis of (63) was thus achieved. (Scheme 26)

Secondly, the improved synthesis of (68) from (96) (route B in Scheme 25) was achieved in two ways. The by-product (99) in the foregoing modified acyloin condensation was converted into compound (102) through six steps of reactions. But the more detailed investigation of the modification of the acyloin condensation resulted in the formation of the more convenient epimeric triol (101) in a satisfactory yield.§ This triol was much more

§ The details will be published elsewhere.



i MeI, NaH, DMF ; ii Na, liq. NH_3 ; iii MeOH, H_2SO_4 ; iv $Pb(OAc)_4$, I_2, $h\nu$; v Ac_2O, pyridine ; vi Na_2CO_3 ; vii MsCl, pyridine ; viii KOH, aq. t-BuOH ; ix CH_2N_2

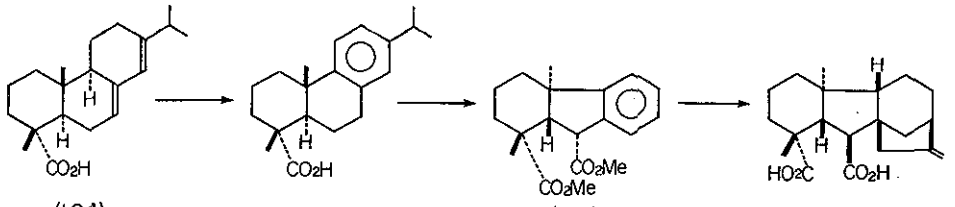
Scheme 26

easily and effectively converted into compound (102). Hypoiodite reaction and subsequent mesylation converted (102) into lactone mesylate (103), which on alkaline treatment followed by methylation gave gibberellane aldehyde (68) in 50% yield. Simultaneously, hydroxyl lactone (97) was formed in 43% yield, and this compound was also effectively converted into (68), which was transformed into the desired gibberellins as described in 3-2-2. Thus, the direct chemical conversions of enmein (60) into gibberellins were accomplished. Since enmein (60) had been synthesized by Fujita (one of the authors) and collaborators[21], the present chemical conversion constituted

the formal total synthesis of gibberellins A_{15} and A_{37}.

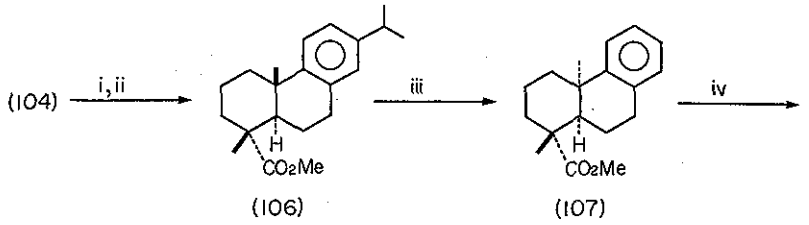
4-1-3 From abietic acid

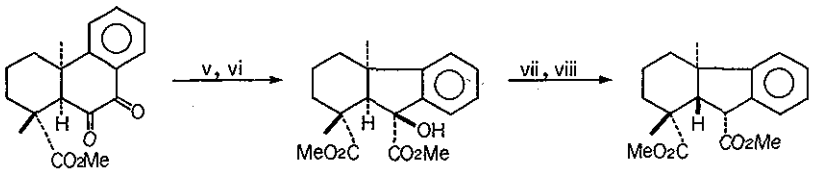
(the late) Tahara *et al.*[35] carried out the formal chemical conversion of abietic acid (104), a main component of the pine rosin, into gibberellin A_{12} (83). They synthesized hydrofluorene (105) from abietic acid (104) and then constructed the rings C and D from the aromatic ring of (105). (Scheme 27)



Scheme 27

The first half, the conversion of (104) to (105), was done as follows[37] : dehydrogenation of abietic acid (104) and esterification gave methyl dehydroabietate (106) ; retro-Friedel-Crafts reaction with (106) reported first by Ohta *et al.*[36] afforded product (107) which was formed by deisopropylation and epimerization at the C-10 methyl group ; the diketone (108) was derived from (107) by oxidation and subjected to benzylic acid rearrangement by alkaline treatment to yield compound (109) ; dehydration followed by hydrogenation gave the desired A/B *trans* derivative (105). (Scheme 28)



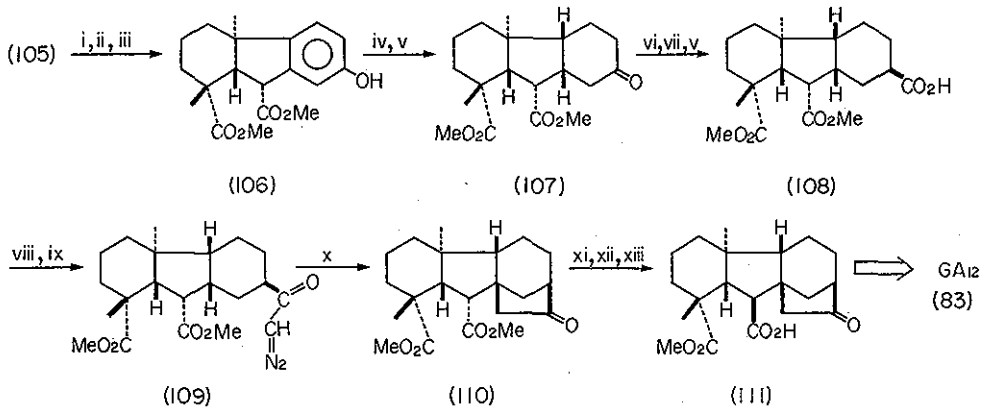


(108) (109) (105)

i Dehydrogenation on Pd-C ; ii MeOH, H_2SO_4 ; iii $AlCl_3$; iv CrO_3, AcOH ; v KOH ; vi CH_2N_2 ; vii H_2SO_4, AcOH ; viii H_2, Pd-C

Scheme 28

The latter half, the construction of the rings C and D, was done as shown in Scheme 29. The compound (105) on Friedel-Crafts reaction gave a product which was acetylated regioselectively on the 13-carbon atom. Baeyer-Villiger reaction and subsequent hydrolysis converted this acetyl compound into a phenol (106), which on catalytic hydrogenation under high pressure yielded a B/C *cis* alcohol. On Jones oxidation the alcohol afforded ketone (107). Wittig reaction, hydroboration, and Jones oxidation converted (107) into carboxylic acid (108), whose acid chloride was treated with diazomethane to give diazoketone (109). Its photolysis produced a carbene, which was inserted into the carbon-hydrogen bond at the C-8 position to give compound (110), the ring D closure product. Finally the half acid (111) was derived from (110). Since the compound (111) had been transformed into gibberellin A_{12} (83) by Cross *et al.*[38], this work means the accomplishment of the chemical conversion of abietic acid (104) into gibberellin A_{12} (83), although in a formal sense. Furthermore, this constitutes the formal total synthesis of gibberellin A_{12} (83), because abietic acid (104) had been synthesized.[39]



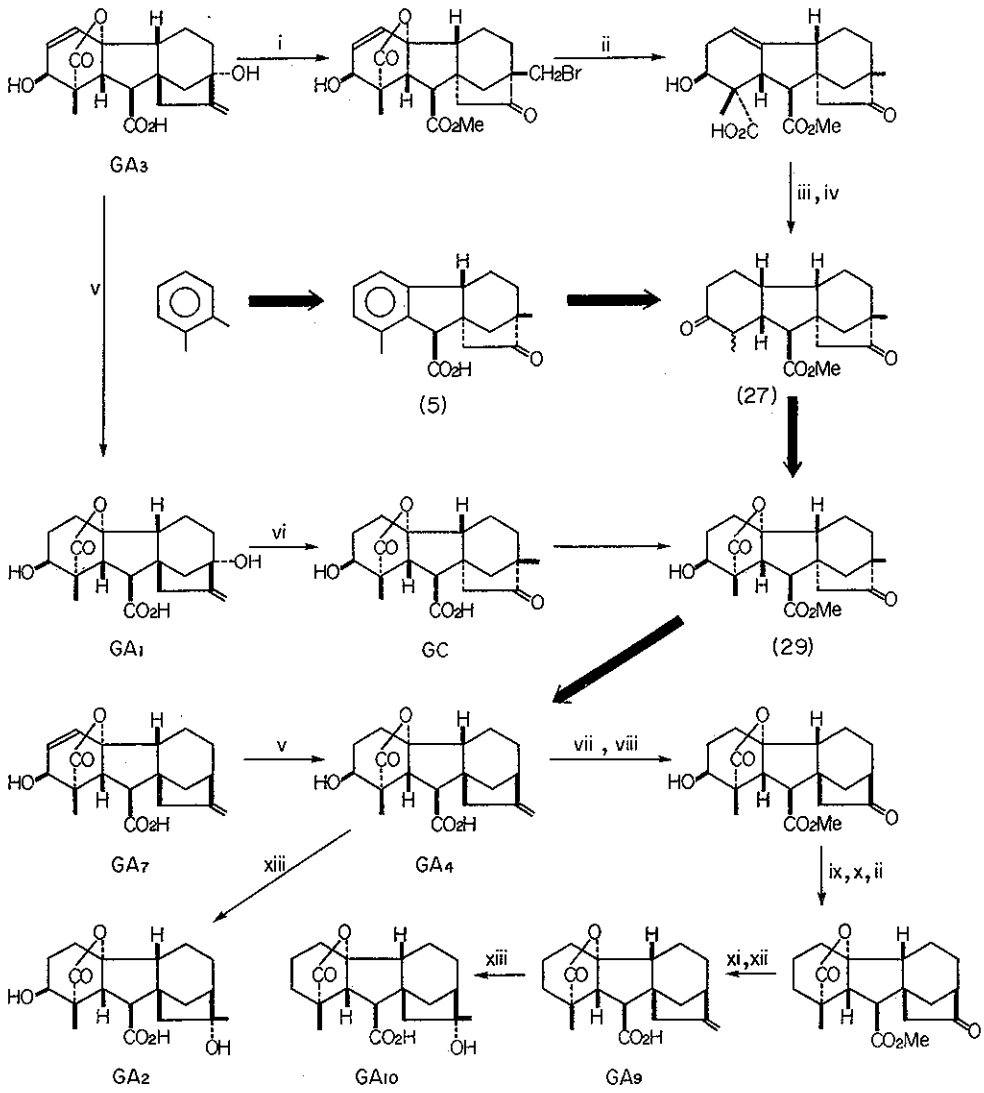
i AcCl, AlCl3 ; ii *m*-chloroperbenzoic acid ; iii MeOH, H_2SO_4 ; iv RuO_2, H_2 ; v Jones oxidation ; vi Wittig reaction ; vii B_2H_6 ; viii $SOCl_2$; ix CH_2N_2 ; x $h\nu$, $CuSO_4$; xi $HO(CH_2)_2OH$, H^+ ; xii KOH, $HO(CH_2)_2OH$; xiii H_3O^+

Scheme 29

4-2 Interconversions of gibberellins

The authors mainly describe here the chemical interconversions of gibberellins relating to their total synthesis.

Mori *et al.*[10] have carried out the formal total synthesis of gibberellin A_4 as described in 3-1. The route is indicated by the heavy arrow mark in Scheme 30. The relay compound (27) was synthesized by Mori *et al.*[10] from gibberellin A_3 as shown in Scheme 30. Thus the formal chemical conversion of gibberellin A_3 into gibberellin A_4 has been accomplished. Gibberellin A_3 had been converted into gibberellin A_1.[40] Gibberellin A_1 has also been transformed into compound (29) and gibberellin A_4 methyl ester[11] *via* gibberellin C.[41] Hence, the route gibberellins $A_3 \rightarrow A_1 \rightarrow C \rightarrow A_4$ has been performed. Furthermore, gibberellin A_4 had been chemically correlated with gibberellins A_2[12], A_7[11], A_9[13], and A_{10}[13,14] as shown in Scheme 30. Thus,

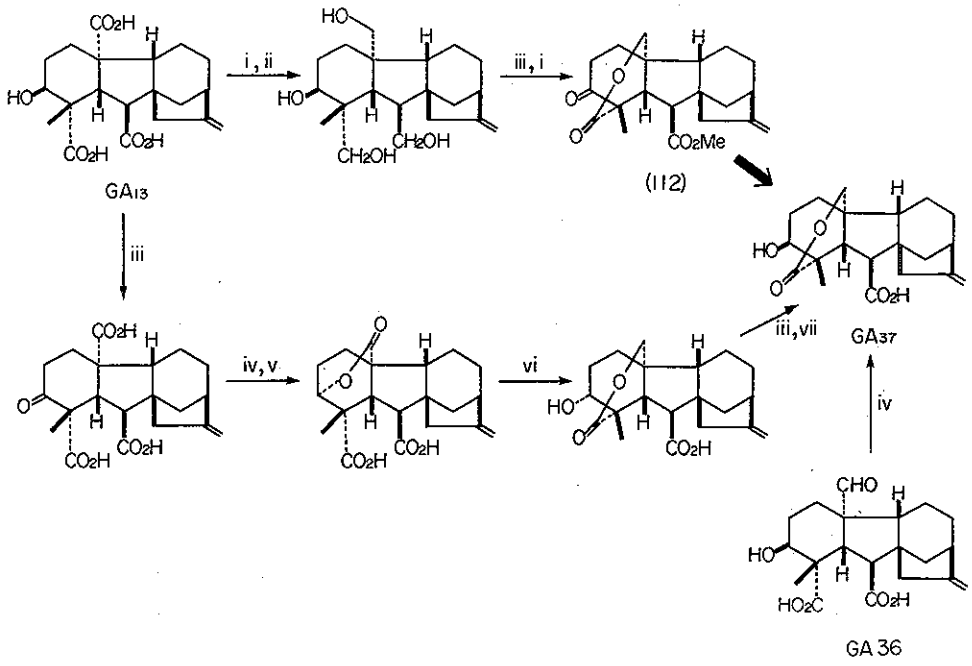


i $C_5H_5\overset{+}{N}H\ Br_3^-$; ii H_2, Pd-C ; iii H_2, PtO_2 ; iv Jones oxidation ; v H_2, Pd, $BaSO_4$, pyridine ; vi H^+ ; vii O_3 ; viii CH_2N_2 ; ix TsCl ; x heating in collidine ; xi Wittig reaction ; xii OH^- ; xiii H_3O^+

Scheme 30

the chemical conversions of gibberellins A_3, A_1, and A_7 into gibberellins A_2, A_4, A_9, and A_{10} have been accomplished.

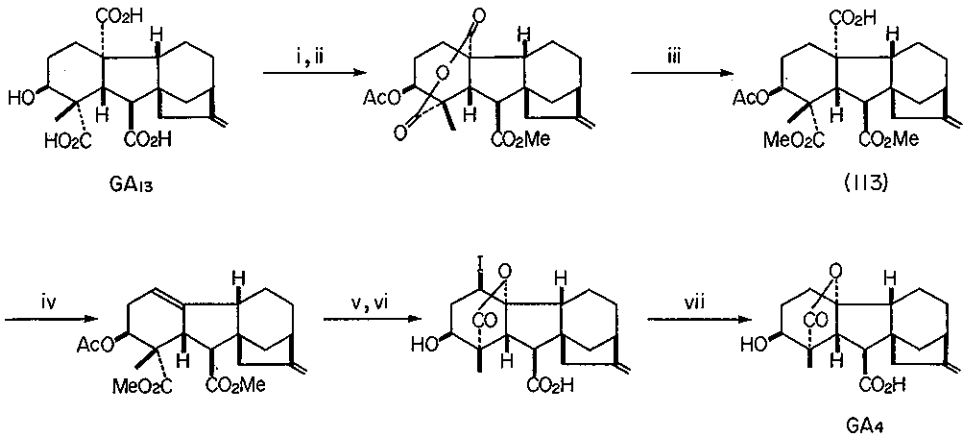
As shown in Scheme 31, Cross *et al.*[42a] had carried out the chemical conversion of gibberellin A_{13} into compound (112), which was converted into gibberellin A_{37} by the authors[16] as described in 3-2-2. Thus, the chemical transformation of gibberellin A_{13} into gibberellin A_{37} was accomplished. This conversion through another route was also completed by MacMillan *et al.*[42b] The transformations of gibberellin A_{36} into gibberellin A_{37} and of gibberellin A_{24} into gibberellin A_{15} were also done by MacMillan *et al.*[43]



i CH_2N_2 ; ii $LiAlH_4$; iii Jones oxidation ; iv $NaBH_4$; v H^+ ; vi $LiBH_4$; vii $Al(iPrO)_3$

Scheme 31

Although there are no relations with the total synthesis, MacMillan *et al.* report the chemical conversions of C_{20} gibberellins. These routes are parallel to the biosynthetic pathway, and the selective elimination of the C-20 atom is synthetically interesting. Hence, the authors picked up them. MacMillan *et al.*[44] treated gibberellin A_{13} with lead tetraacetate in dimethylformamide to give gibberellin A_4 and its isomeric lactone in a ratio 3 : 2. On the other hand, Takahashi *et al.*[45] converted gibberellin A_{13} into compound (113) which had a carboxyl group selectively on the C-10 atom, and treated it with lead tetraacetate. Thus a selective decarboxylation occurred. The following three steps of reactions led to the formation of gibberellin A_4 as shown in Scheme 32.



i Ac_2O, pyridine ; ii CH_2N_2 ; iii NaOMe ; iv $Pb(OAc)_4$, $Cu(OAc)_2$; v NaOH, 100° ; vi I_2, $NaHCO_3$; vii $NaBH_4$ in DMSO

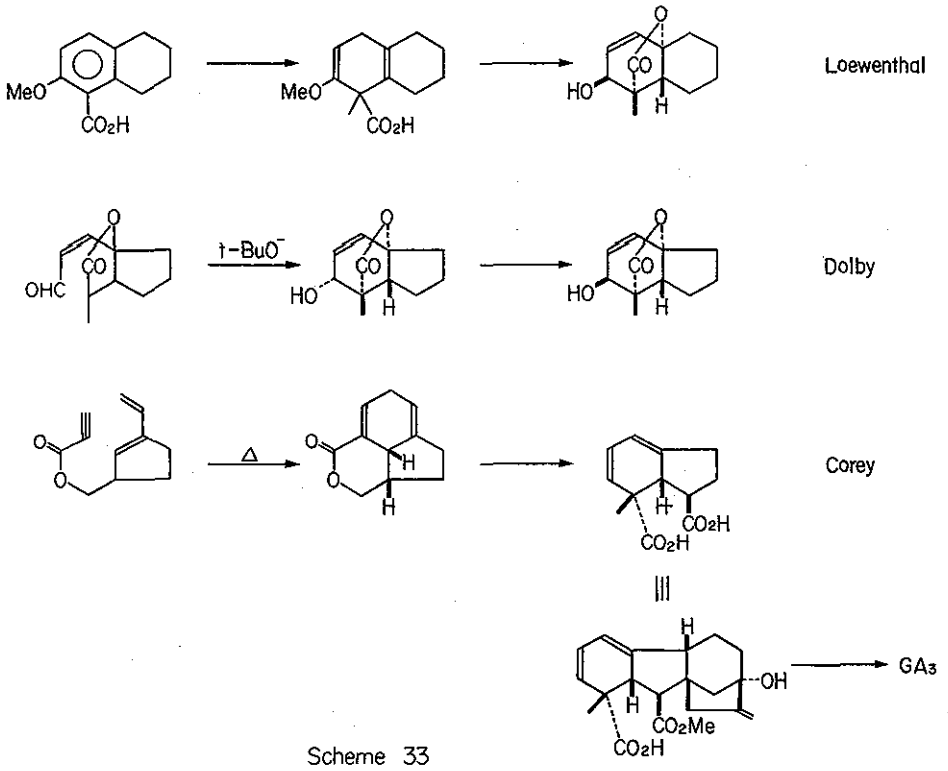
Scheme 32

Except for the foregoing examples, several interconversions of gibberellins have been published in the structure determinations and in the syntheses of the isotope labeled gibberellins for the biosynthetic studies, but they are

omitted in this review.

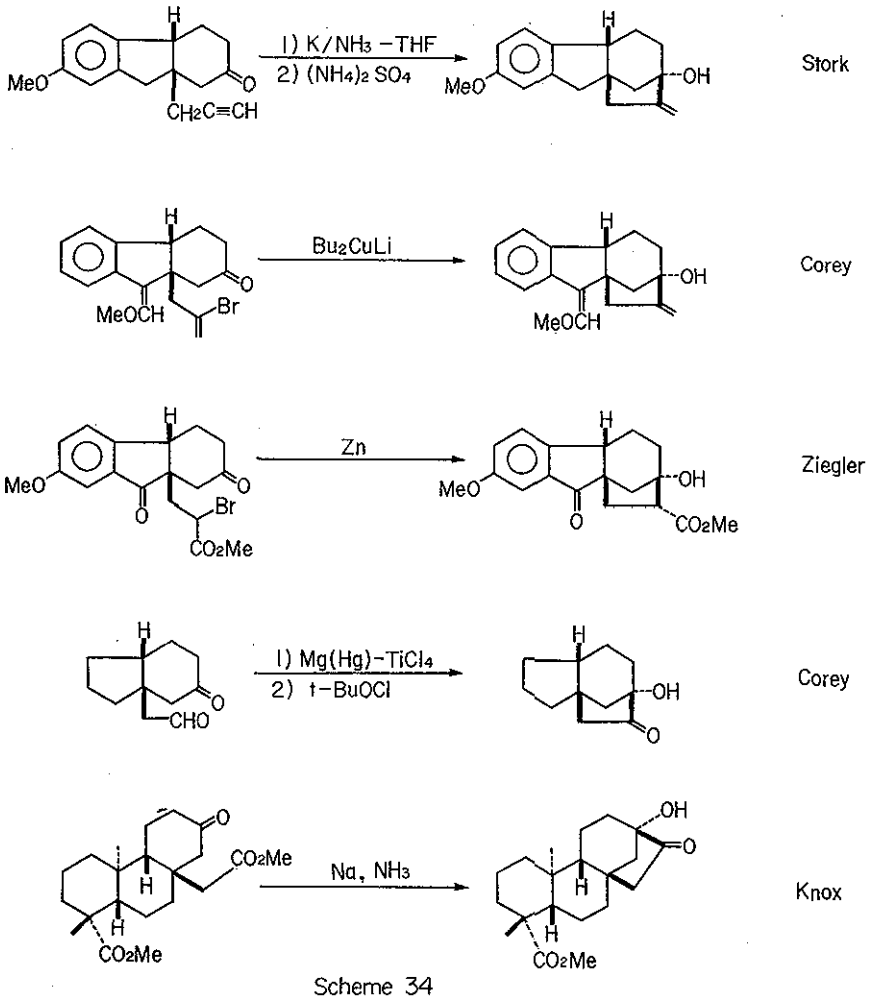
5 The other

In the chapter 3, the total syntheses accomplished so far were described. In addition ot these, many works which had been in their way to success have been published. Some of those works are outlined. As the model syntheses of the ring A of gibberellin A_3, modification of the aromatic ring by Loewenthal *et al.*[46], a procedure applying the aldol condensation by Dolby *et al.*[47], and the intramolecular Diels-Alder reaction with the acetylene derivatives by Corey *et al.*[48] have been developed. These are outlined in Scheme 33.



Scheme 33

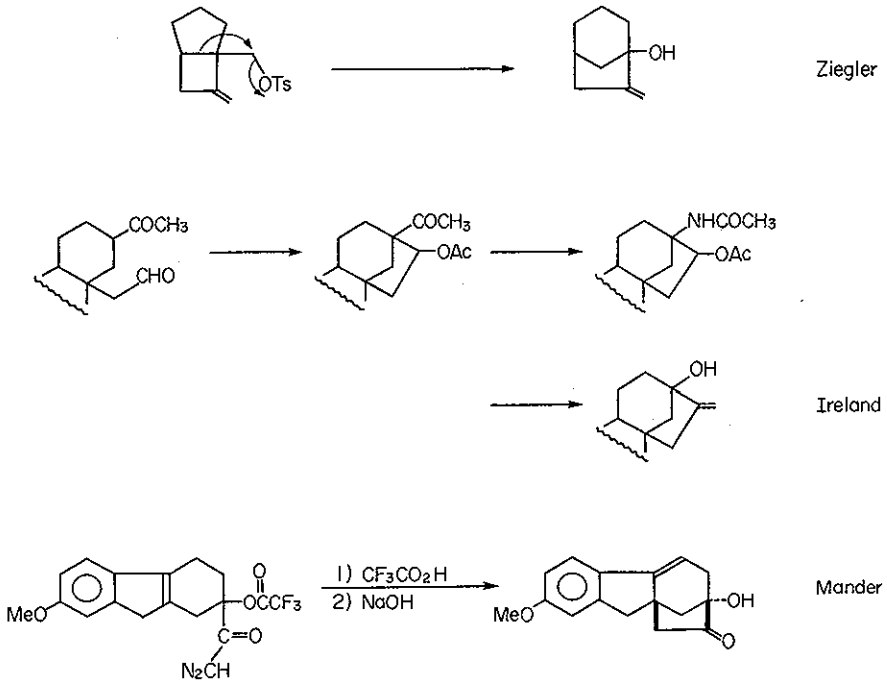
As the model syntheses of the 13-hydroxylated C/D rings of gibberellin A_3, several examples using the reductive cyclization have been found : the intramolecular reductive cyclizations between the ketone on the ring C and an acetylene function (by Stork *et al.*[49]), a vinyl bromide (by Corey *et al.*[50]), an α-bromoester (by Ziegler *et al.*[51]), an aldehyde (by Corey *et*



Scheme 34

al.[52]), and an ester (by Knox *et al.*[53]). The outline including the reducing agent is shown in each case in Scheme 34.

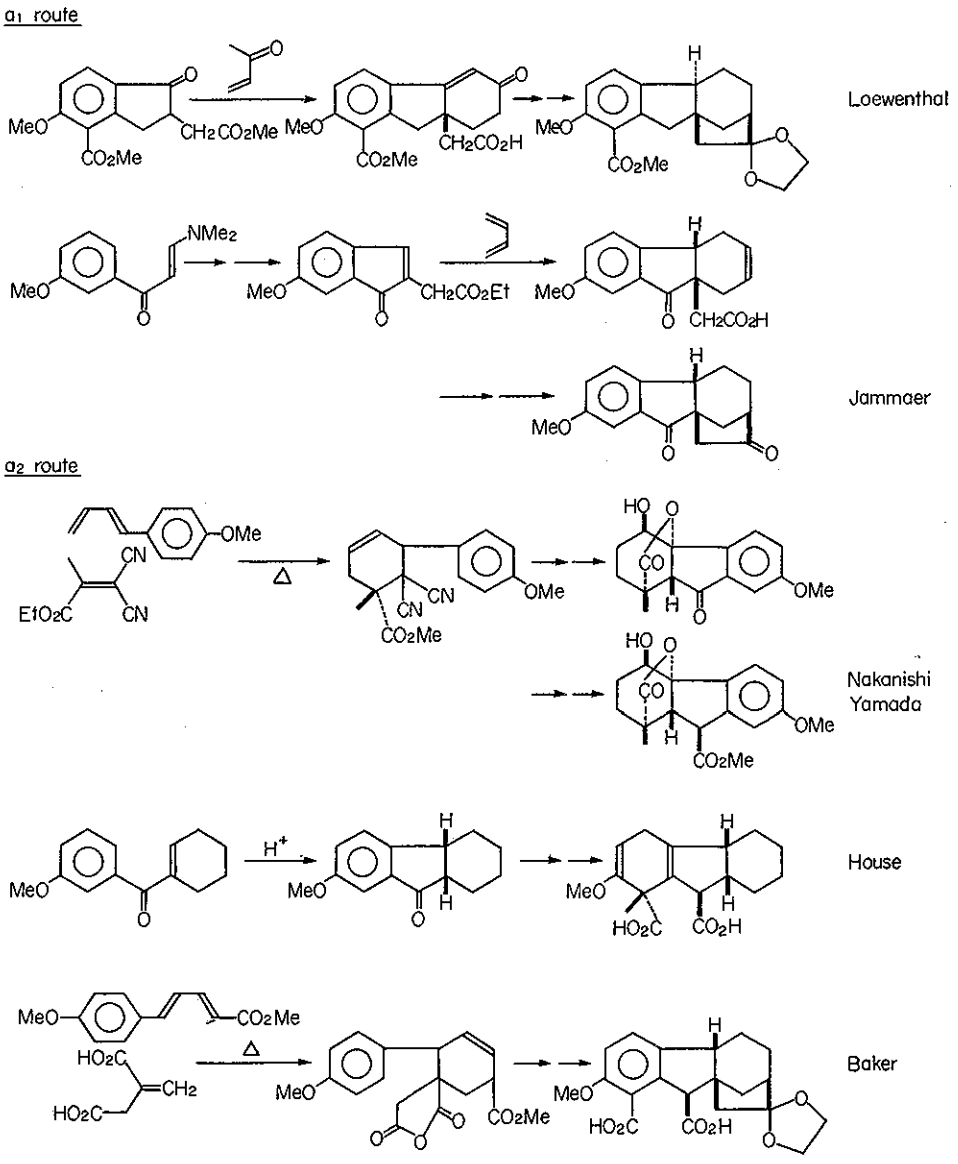
In addition to the foregoing examples, the methods applying a rearrangement by Ziegler *et al.*[54], the Beckmann rearrangement by Ireland, Mander *et al.*[55], and the acid catalyzed cyclization between an olefin and a diazoketone by Mander *et al.*[56] have been published. (Scheme 35) The procedures used by Mori *et al.* and House *et al.* in their total synthesis of epiallogibberic acid are described in Chapter 2.



Scheme 35

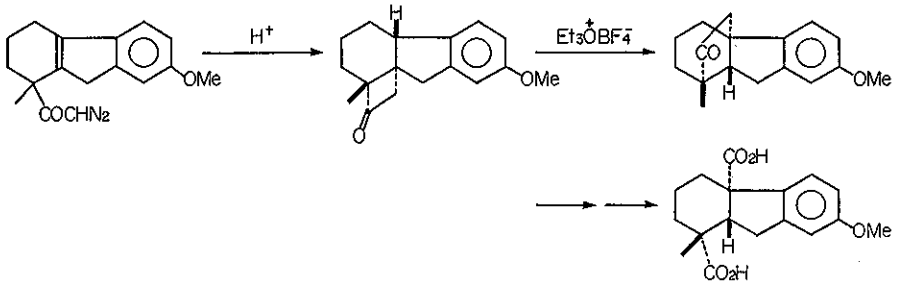
In the synthetic studies on the C_{19} gibberellins, both of the a_1 and a_2 types classified in Chapter 3 have been developed. The studies by Loewenthal *et al.*[57] and Jammaer *et al.*[58] belong to the former. Many works[59] have been published for the a_2 route syntheses. Among them, three works by Nakanishi *et al.*[60] and Yamada *et al.*[61], House *et al.*[62], and Baker *et al.*[63]

are picked up and outlined. (Scheme 36)



Scheme 36

In the synthetic studies on the C_{20} gibberellins, Ghatak *et al.* published another synthesis[64] of the key intermediate in the total synthesis of gibberellin A_{15} by Nagata *et al.* and an attempt for the synthesis by a route shown in Scheme 37.[65]



Scheme 37

6 Conclusion

In this review, the authors put emphasis on the total syntheses, and also picked up and outlined their related syntheses mainly. Therefore, they are afraid that many other valuable synthetic works were not introduced.

The recent development outlined in Chapter 5 will promise the accomplishment of the total syntheses of some gibberellins in the near future. Since gibberellins have a variety of structures and of extents of the biological activity, they seem attractive for the synthesis and/or chemical modification. Hence, the synthetic studies will be further developed for several purposes.

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