The Chemistry of Gibberellins: An Overview

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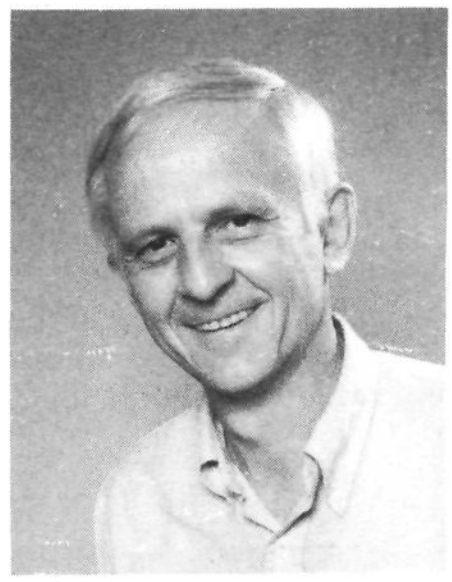
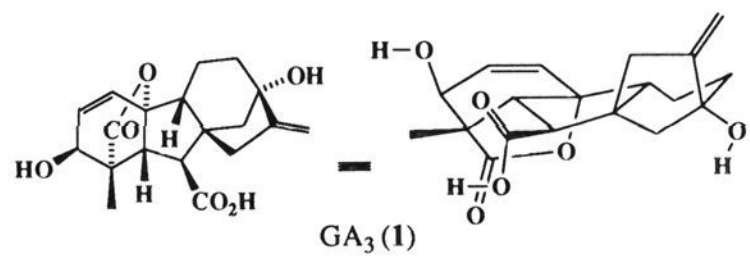


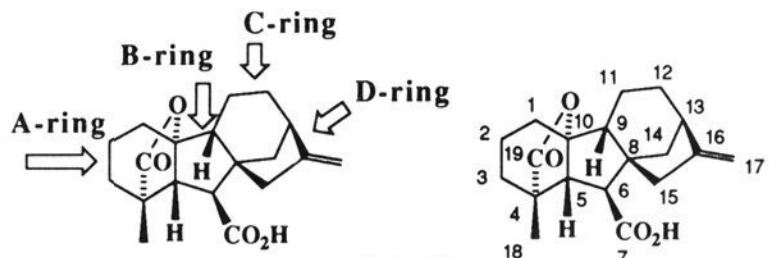
Lew Mander was born in Auckland, New Zealand, completed his BSc and MSc degrees at the University of Auckland, the latter with R. C. Cambie, and obtained his PhD in 1964 at the University of Sydney under the supervision of C. W. Shoppee, E. Ritchie, and W. C. Taylor. After two years of post-doctoral studies with R. E. Ireland, initially at the University of Michigan and then at the California Institute of Technology, he returned to Australia as a lecturer in organic chemistry at the University of Adelaide. He moved to the Australian National University in 1975 as a senior fellow in the Research School of Chemistry and was appointed as Professor in 1980, serving also as Dean for a five-year period. He was a Nuffield Fellow at Cambridge University in 1972 with A. R. Battersby, and a Fulbright Senior Scholar at the California Institute of Technology in 1977 and at Harvard University in 1986 (with D. A. Evans on both occasions). His research interests are concerned with the development of methods and strategies for the assembly and manipulation of complex organic molecules with a special interest in plant growth and development.

I. Introduction

The gibberellins presently form a group of ~90 highly functionalized diterpenoids, which are distributed widely throughout the plant kingdom and which play an important role in plant growth and development.[1-5] The gibberellins (with "GA" being the widely accepted abbreviation) are typified by gibberellic acid (1), which is produced commercially in ton quantities by the fermentation of the fungus *Gibberella fujikuroi*. The quest for an understanding of the biology and biochemistry of GAs has been greatly advanced by the ease of availability of this molecule and a few related compounds. This has made it possible to explore the complex chemistry of GAs in considerable detail, to explore their biosynthesis, to confirm tentative new structures by partial synthesis, and to provide sufficient quantities of rare derivatives for biological investigations. The complex biology and structures of GAs have also made them popular targets for total synthesis. The aim of this review is to provide an overview of this chemistry. It is divided into three roughly equal parts, the first providing a summary of structural, biological, and biosynthetic aspects, the second devoted to the manipulation of the GA molecule, and the third devoted to total synthesis.



GA_3 (1)



GA_9 (2)

To avoid problems with trivial names, once the structure for a new gibberellin has been established, it

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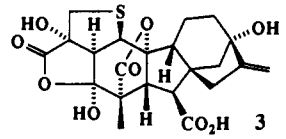
is given a code name A_n (n = 1,2,3...).[6] Thus, gibberellic acid (1) is also known as gibberellin A_3, or GA_3. A complete set of the 86 structures for which structures have been unequivocally established is provided in Figure 1.

The gibberellins are conveniently divided into two subgroups, the larger of which (ca. 60 members) is based on a 19 carbon atom pentacyclic skeleton. The 7-carboxyl, 17-methylene group, and 19,10-γ-lactone function are features common to the majority of these "C-19 GAs", for which GA_9 (2) may be regarded as the parent structure. The differences in constitution are largely accounted for by the location and number of hydroxy groups (up to four). These are most commonly attached to C(3) and/or C(13), but may also be located on C(1), C(2), C(11), C(12), C(15) and C(18) as summarized in Figure 2.

Further variations in structure for the C-19 GAs are indicated in Figure 3. Hydroxylation at C-16 or C-17 corresponds formally to hydration of the 17-methylene group and is relatively uncommon. Twelve of the C-19 GAs incorporate an additional double bond [six with Δ^1, five with Δ^2, and one with $\Delta^{9(11)}$], two possess an epoxy function (one with a 19,2-lactone group), two have oxo groups (C-3 and C-12, respectively), and two an additional carboxy group (C-18).

Many compounds have been obtained as glucosides or glucosyl esters.[7] GA_3-3-acetate has been isolated from *G. fujikuroi*,[8] GA_3 *n*-propyl ester from *Cucumis sativus*,[9] and gibberethione (3) (an adduct of 3-oxo-GA_3 (4) and 3-thiolopyruvic acid) from Japanese morning glory (*Pharbitis nil*).[10] GA_9 methyl ester (5) has been isolated from gametophytes of the fern *Lygodium japonicum*,[11] in which it cooccurs with the $\Delta^{9(11)}$-didehydro derivative, GA_{73} methyl ester (6).[12,13] Both compounds have been shown to be antheridium-inducing factors ("antheridiogens") in *Lygodium japonicum*.[14]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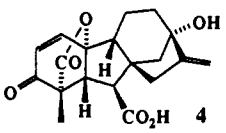
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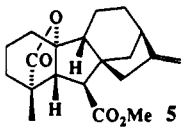
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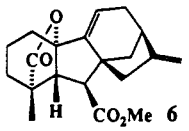
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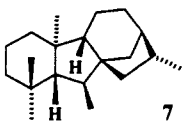
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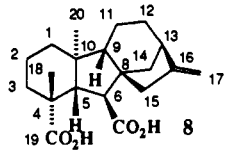
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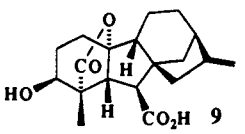
Most of the remaining GAs possess the full 20-carbon *ent*-gibberellane skeleton (7),[15] in which the C(20) substituent ranges from methyl through to carboxyl and are 7,19-dicarboxylic acids, except for a number of 19,20-δ-lactones. The parent compound is GA_{12} (8), and for the most part, further variations in structure for this group of C-20 GAs stem from the addition of one or two hydroxy groups as summarized in Figure 4. Only one trihydroxy C-20 GA has been isolated, namely GA_{52}.[16,17]

The homogeneity in the basic structures of these GAs is striking, but two naturally occurring antheridium-inducing substances obtained from fern gametophytes are based on a 20-nor-9β,15β-cyclogibberellane skeleton and a rearranged norgibberellane skeleton respectively (cf. section VII.G).

II. History

The history of gibberellin research[18] began in the early part of the 19th century with reports in 1828 of a disease of rice plants.[19] Hori described in 1898 how the disease could be induced in healthy plants by inoculation with the "bakanae fungus", *Gibberella fujikuroi*, the "perfect", i.e. sexual, stage of *Fusarium moniliforme*. The infected rice plants were variously described as "thin noodle seedling", "foolish seedling", and "stupid rice crop". In more recent times the term "bakanae disease" has become the accepted description of seedling elongation associated with lack of fruit, resulting from infection by the fungus. Damage to the rice crop has often been extensive, resulting in up to 40% reduction in yields.

The first indication that a substance produced by the fungus was responsible for the effect was provided in a paper published in 1912 by Sawada, a plant pathologist working in Taipei.[20] Firm evidence for the formation of a discrete toxin was adduced by Kurosawa and reported in 1926.[21] Following this disclosure, 50 publications by plant pathologists appeared on the subject during the period 1927–1940. The turning point came with the isolation of a crystalline fraction in 1938 by Yabuta and Sumiki.[22] Progress was disrupted during the war and its aftermath, but in 1950, *Chemical Abstracts* published a collection of reports on the Japanese studies which were noted by W. A. Sexton, Research Director of I.C.I.s Pharmaceutical division, who brought them to the attention of P. W. Brian, a mycologist in charge of basic research at the I.C.I. Akers Laboratories in Welwyn. A screening program was set up to search for the best gibberellin-producing strain of the *Fusarium* fungus. The strain selected for fermentation studies produced mainly one gibberellin, GA_3 (1), which may be obtained simply by crystallization from an ethyl acetate extract of the acidified broth. By modifying the culture conditions the fungus may be induced to produce a mixture of GA_4 (9) and GA_7 (10), containing a small amount of GA_9 (2), although rather less efficiently than for GA_3.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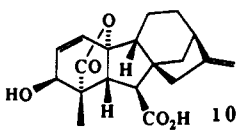

10

With the availability of reasonable quantities of GA_3, there was a virtual explosion in the number of studies on plant responses to the application of GAs. There were also reports of the isolation of GAs from higher plants,[23,24] in which (as we now know) they are essential for growth and development. The stage has now been reached where the structures of 86 naturally occurring GAs have been established and the rate of discovery continues unabated. Sixty-six have been found exclusively in plants (including angiosperms, gymnosperms,

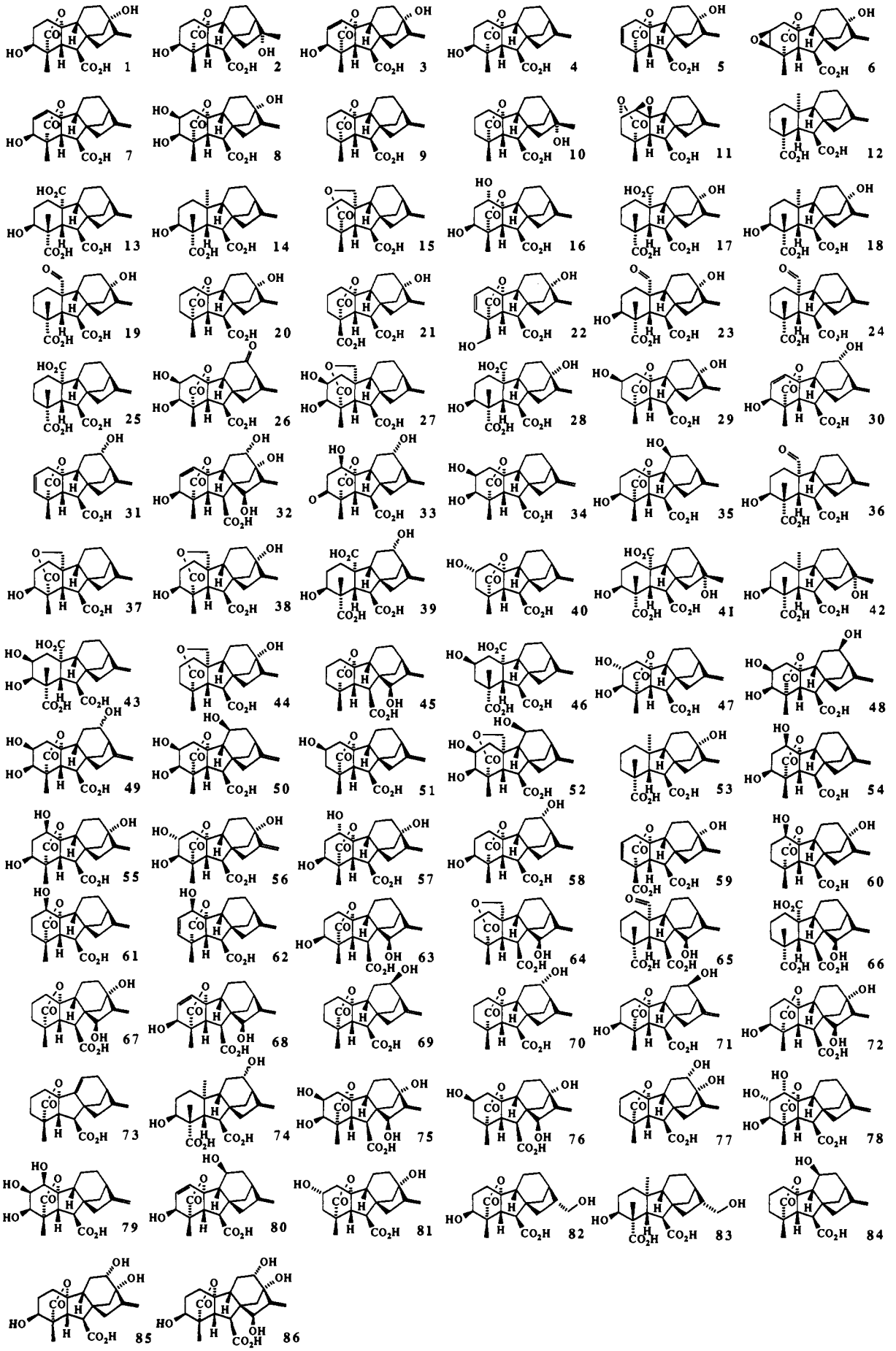


Figure 1. Complete set of gibberellin structures in order of discovery. Structure numbers correspond to n in GA_n.

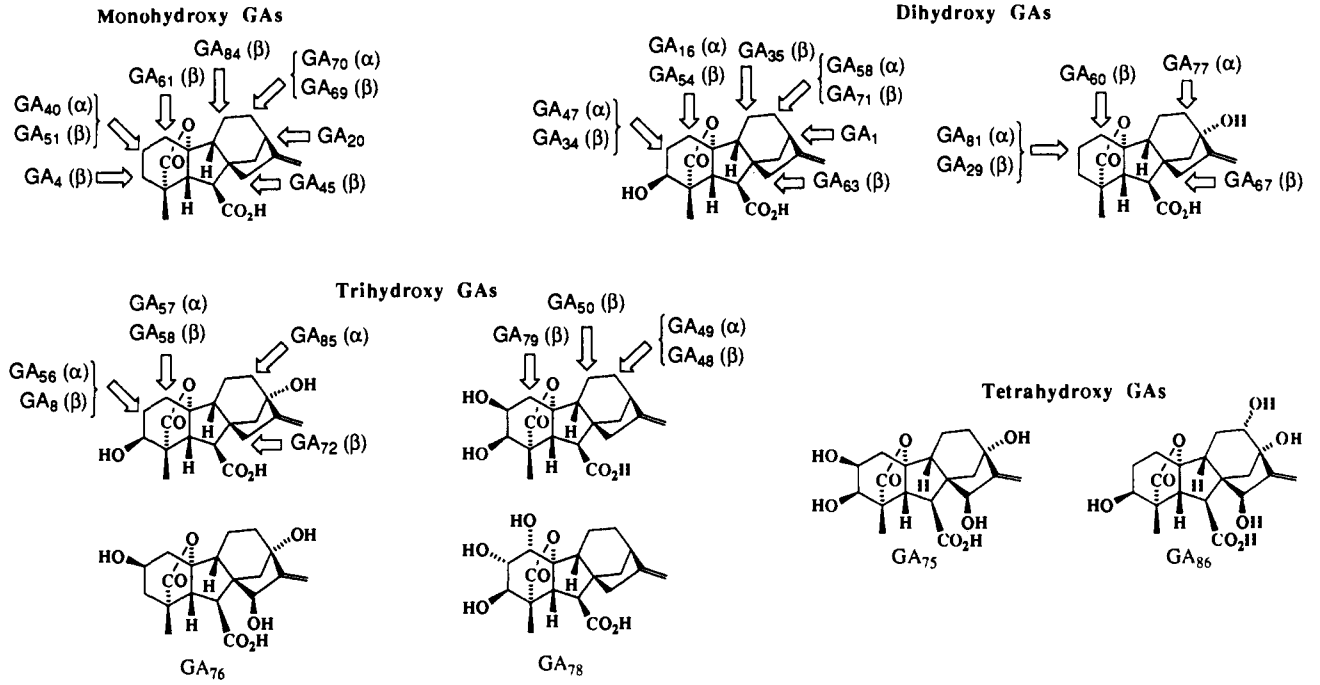


Figure 2. Simple hydroxylated C-19 gibberellins (⇒ indicates hydroxylation site).

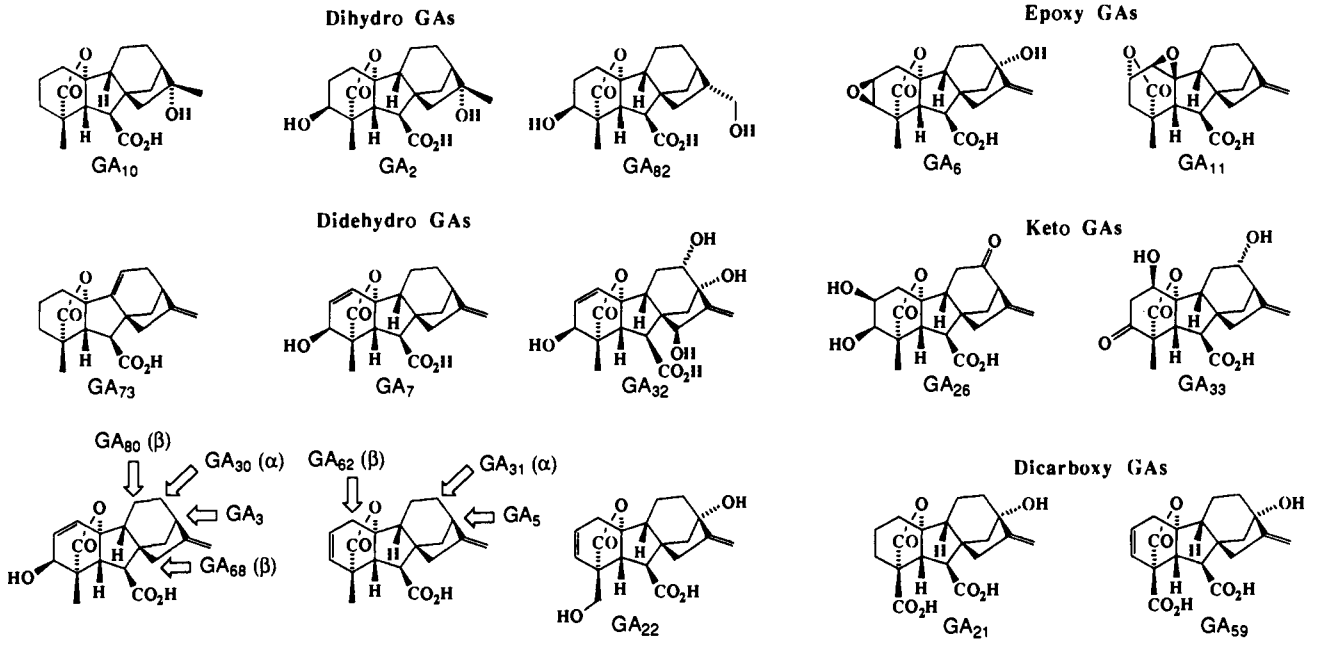


Figure 3. Dihydro and dehydro C-19 gibberellins (⇒ indicates hydroxylation sites).

and ferns), 11 in the fungus only, and the rest from both sources. A summary of structural information, source(s), and structure determination (often by partial synthesis) is provided in Table I. A number of putative GAs have been detected and structures assigned by gas chromatography–mass spectrometry (GC–MS), but rigorous identification with authentic synthetic samples has not yet been carried out. These compounds are listed in Table II.

III. Bioactivity and Applications

GAs affect almost every aspect of plant growth and development,[3] but their most typical (and spectacular) property is the enhancement of stem growth. The phenomenon of bolting in rosette plants (i.e. the explosive growth which precedes flowering in plants like spinach) is caused naturally by endogenous GAs,[93] while dwarf plants in which there are single gene lesions for the biosynthesis of GAs respond to the exogenous application of GAs with normal growth. The vigorous shoot growth obtained with maize hybrids has been shown to be due to the production of higher than normal levels of GAs.[94] Flowering is also stimulated by GAs which may also modify the sex expression of flowers, induce the parthenocarpic development of fruit, and delay senescence. They obviate the requirement for exposure to red light in the germination of seeds and spores and the need for vernalization (winter chilling) in the growth of bulbs and tubers. They are associated with the breaking of winter dormancy and stimulate the formation of hydrolytic enzymes in germinating cereal

TABLE I. Functionality Patterns for Naturally Occurring Gibberellins (GA_n)[a]

n	C-1	C-2	C-3	C-11	C-12	C-13	C-15	C-16	C-17	C-18	C-19	C-20	Δ	Original Source	Reference
1	-	-	β	-	-	√	-	-	-	-	-	-	-	*G. fujikuroi*	25
2	-	-	β	-	-	-	-	α	-	-	-	-	-	*G. fujikuroi*	25
3	-	-	β	-	-	√	-	-	-	-	-	-	1	*G. fujikuroi*	26
4	-	-	β	-	-	-	-	-	-	-	-	-	-	*G. fujikuroi*	27
5	-	-	-	-	-	√	-	-	-	-	-	-	2	*Phaseolus vulgaris*	28
6	-	2β,3β-epoxy		-	-	√	-	-	-	-	-	-	-	*Phaseolus coccineus*	29
7	-	-	β	-	-	-	-	-	-	-	-	-	1	*G. fujikuroi*	30
8	-	β	β	-	-	√	-	-	-	-	-	-	-	*Phaseolus coccineus*	29
9	-	-	-	-	-	-	-	-	-	-	-	-	-	*G. fujikuroi*	30
10	-	-	-	-	-	-	-	α	-	-	-	-	-	*G. fujikuroi*	31
11	1β,10β-epoxy		-	-	-	-	-	-	-	-	-	-	-	*G. fujikuroi*	32
12	-	-	-	-	-	-	-	-	-	-	CO_2H	Me	-	*G. fujikuroi*	33
13	-	-	β	-	-	-	-	-	-	-	CO_2H	CO_2H	-	*G. fujikuroi*	34
14	-	-	β	-	-	-	-	-	-	-	CO_2H	Me	-	*G. fujikuroi*	35
15	-	-	-	-	-	-	-	-	-	-	CO—OCH_2		-	*G. fujikuroi*	36
16	α	-	β	-	-	-	-	-	-	-	-	-	-	*G. fujikuroi*	37
17	-	-	-	-	-	√	-	-	-	-	CO_2H	CO_2H	-	*Phaseolus coccineus*	38
18	-	-	β	-	-	√	-	-	-	-	CO_2H	Me	-	*Lupinus luteus*	39, 40
19	-	-	-	-	-	√	-	-	-	-	CO_2H	CH=O	-	*Phyllostachys edulis*	41, 42
20	-	-	-	-	-	√	-	-	-	-	-	-	-	*Pharbitis nil*	43
21	-	-	-	-	-	√	-	-	-	CO_2H	-	-	-	*Canavalia gladiata*	44
22	-	-	-	-	-	√	-	-	-	√	-	-	2	*Canavalia gladiata*	45
23	-	-	β	-	-	√	-	-	-	-	CO_2H	CH=O	-	*Lupinus luteus*	46
24	-	-	-	-	-	-	-	-	-	-	CO_2H	CH=O	-	*G. fujikuroi*	47
25	-	-	-	-	-	-	-	-	-	-	CO_2H	CO_2H	-	*G. fujikuroi*	48
26	-	β	β	-	=O	-	-	-	-	-	-	-	-	*Pharbitis nil*	49
27	-	β	β	-	-	-	-	-	-	-	CO—OCH_2		-	*Pharbitis nil*	50
28	-	-	β	-	-	√	-	-	-	-	CO_2H	CO_2H	-	*Lupinus luteus*	51
29	-	β	-	-	-	√	-	-	-	-	-	-	-	*Pharbitis nil*	52
30	-	-	β	-	α	-	-	-	-	-	-	-	1	*Calonyction aculeatum*	53
31	-	-	-	-	α	-	-	-	-	-	-	-	2	*Calonyction aculeatum*	53
32	-	-	β	-	α	√	β	-	-	-	-	-	1	*Prunus armenica, P. persica*	54, 55
33	β	-	=O	-	-	-	-	-	-	-	-	-	-	*Calonyction aculeatum*	53
34	-	β	β	-	-	-	-	-	-	-	-	-	-	*Calonyction aculeatum*	53
35	-	-	β	β	-	-	-	-	-	-	-	-	-	*Cytisus scoparius*	56
36	-	-	β	-	-	-	-	-	-	-	CO_2H	CH=O	-	*G. fujikuroi*	57
37	-	-	β	-	-	-	-	-	-	-	CO—OCH_2		-	*Phaseolus vulgaris*	58
38	-	-	β	-	-	√	-	-	-	-	CO—OCH_2		-	*Phaseolus vulgaris*	58
39	-	-	β	-	α	-	-	-	-	-	CO_2H	CO_2H	-	*Cucurbita pepo*	59
40	-	α	-	-	-	-	-	-	-	-	-	-	-	*G. fujikuroi*	60
41	-	-	-	-	-	-	-	α	-	-	CO_2H	CO_2H	-	*G. fujikuroi*	61
42	-	-	-	-	-	-	-	α	-	-	CO_2H	Me	-	*G. fujikuroi*	61
43	-	β	β	-	-	-	-	-	-	-	CO_2H	CO_2H	-	*Cucurbita maxima*	62
44	-	-	-	-	-	√	-	-	-	-	COO—CH_2		-	*Pisum sativum*	63
45	-	-	-	-	-	-	β	-	-	-	-	-	-	*Pyrus communis*	64
46	-	β	-	-	-	-	-	-	-	-	CO_2H	CO_2H	-	*Marah macrocarpus*	62, 65
47	-	α	β	-	-	-	-	-	-	-	-	-	-	*G. fujikuroi*	65, 66
48	-	β	β	-	β	-	-	-	-	-	-	-	-	*Cucurbita pepo*	59
49	-	β	β	-	α	-	-	-	-	-	-	-	-	*Cucurbita pepo*	59
50	-	β	β	β	-	-	-	-	-	-	-	-	-	*Lagenaria leucantha*	16
51	-	β	-	-	-	-	-	-	-	-	-	-	-	*Pisum sativum*	67
52	-	β	β	β	-	-	-	-	-	-	CO—OCH_2		-	*Lagenaria leucantha*	16
53	-	-	-	-	-	√	-	-	-	-	CO_2H	Me	-	*Vivia faba*	68
54	β	-	β	-	-	-	-	-	-	-	-	-	-	*G. fujikuroi*	69, 70
55	β	-	β	-	-	√	-	-	-	-	-	-	-	*G. fujikuroi*	70, 71
56	-	α	β	-	-	√	-	-	-	-	-	-	-	*G. fujikuroi*	69
57	α	-	β	-	-	√	-	-	-	-	-	-	-	*G. fujikuroi*	71
58	-	-	β	-	α	-	-	-	-	-	-	-	-	*Cucurbita maxima*	72
59	-	-	-	-	-	-	-	-	-	CO_2H	-	-	2	*Canavalia gladiata*	73
60	β	-	-	-	-	√	-	-	-	-	-	-	-	*Triticum aestivum*	74
61	β	-	-	-	-	-	-	-	-	-	-	-	-	*Triticum aestivum*	74
62	β	-	-	-	-	-	-	-	-	-	-	-	2	*Triticum aestivum*	74
63	-	-	β	-	-	-	β	-	-	-	-	-	-	*Pyrus communis*	75
64	-	-	-	-	-	-	β	-	-	-	CO—OCH_2		-	*Helianthus annuus*	76
65	-	-	-	-	-	-	β	-	-	-	CO_2H	CH=O	-	*Helianthus annuus*	76
66	-	-	-	-	-	-	β	-	-	-	CO_2H	CO_2H	-	*Helianthus annuus*	76
67	-	-	-	-	-	√	β	-	-	-	-	-	-	*Helianthus annuus*	76
68	-	-	β	-	-	-	β	-	-	-	-	-	1	*Malus sylvestris*	77
69	-	-	-	-	β	-	-	-	-	-	-	-	-	*Hordeum vulgare*	78
70	-	-	-	-	α	-	-	-	-	-	-	-	-	*Cyathea australis*	79
71	-	-	β	-	β	-	-	-	-	-	-	-	-	*Cyathea australis*	79
72	-	-	β	-	-	√	β	-	-	-	-	-	-	*Helianthus annuus*	76
73	-	-	-	-	-	-	-	-	-	-	-	-	9(11)	*Lygodium japonicum*	12
74	-	-	β	-	α	-	-	-	-	-	CO_2H	Me	-	*Cucurbita maxima*	80
75	-	β	β	-	-	√	β	-	-	-	-	-	-	*Helianthus annuus*	81
76	-	β	-	-	-	√	β	-	-	-	-	-	-	*Helianthus annuus*	81
77	-	-	-	-	α	√	-	-	-	-	-	-	-	*Raphanus sativus*	82
78	α	α	β	-	-	-	-	-	-	-	-	-	-	*G. fujikuroi*	29, 83
79	β	β	β	-	-	-	-	-	-	-	-	-	-	*Triticum aestivum*	74, 83
80	-	-	β	β	-	-	-	-	-	-	-	-	1	*Eriobotrya japonica*	84
81	-	α	-	-	-	√	-	-	-	-	-	-	-	*Pisum sativum*	85
82	-	-	β	-	-	-	-	-	√	-	-	-	-	*Lupinus alba*	86
83	-	-	β	-	-		-	-	√	-	CO_2H	Me	-	*Lupinus alba*	86
84	-	-	-	β	-	-	-	-	-	-	-	-	-	*Eriobotrya japonica*	84
85	-	-	β	-	α	√	-	-	-	-	-	-	-	*Brassica campestris*	87
86	-	-	β	-	α	√	β	-	-	-	-	-	-	*Prunus persica*	88

[a] Δ denotes location of double bond; √ denotes location of hydroxyl; α denotes location of hydroxyl with α-configuration; β denotes location of hydroxyl with β-configuration; 20-norgibberellins all possess a 19,10-γ-lactone function (cf. GA_9, structure **2**) except for GA_{11} which has a 19,2-γ-lactone function.

grain. The biologically most potent gibberellins possess a free 7-carboxyl, the 19,10-γ-lactone function, and a 3β-hydroxyl;[95-97] the presence or absence of a 13-hydroxyl may also have a major influence on bioactivity, but this is species dependent. The observed activity of GAs without these features may be due to in situ metabolism which establishes these features.[98] Practical applications, however, have been confined to the fungal gibberellins, GA_3 (**1**), GA_4 (**9**), and GA_7 (**10**).

It is sometimes difficult to distinguish between actual applications in agriculture and wishful thinking.[99,100] In many cases the utility is limited by economics (cost-benefits). Nevertheless, there are several commercially valuable applications, including

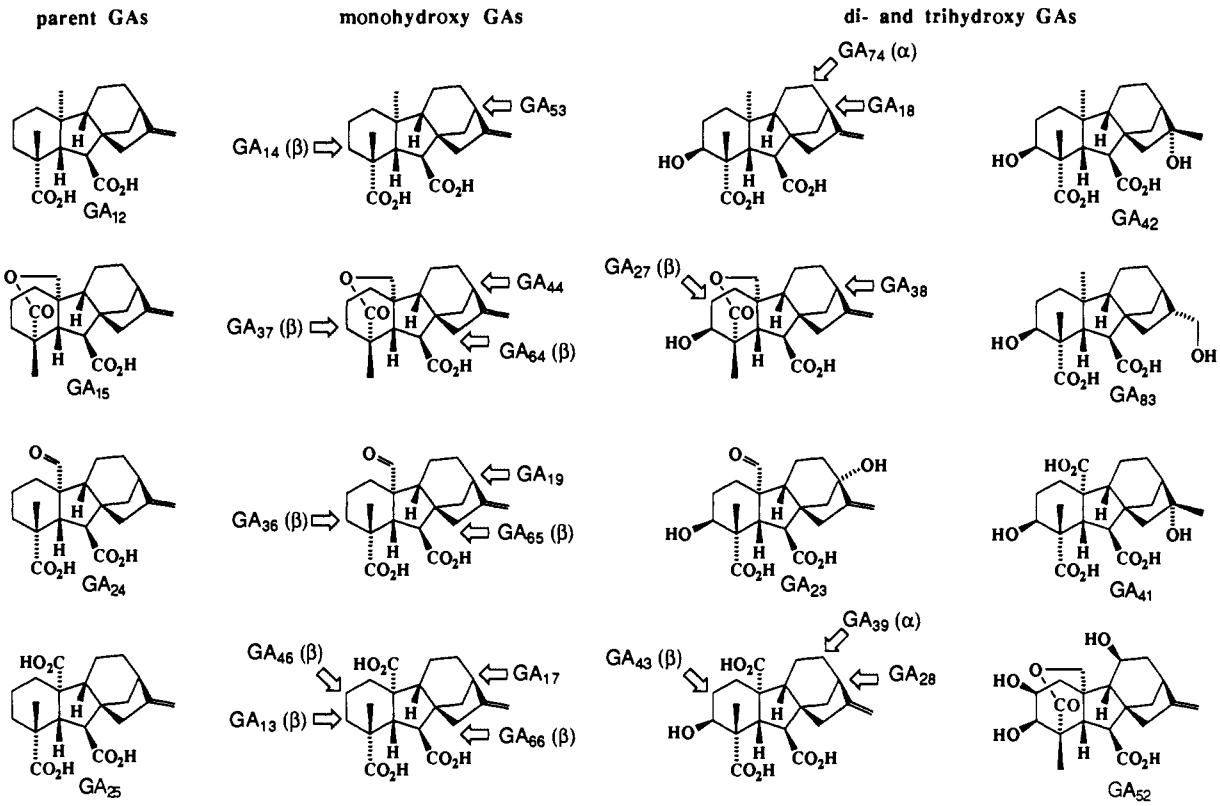


Figure 4. C-20 gibberellins (⇒ indicates hydroxylation site).

TABLE II. Recently Detected Gibberellins (Tentative Identifications)[a]

entry	C-1	C-2	C-3	C-11	C-12	C-13	C-15	C-18	C-19	C-20	Δ	Source	Ref
1	-	β	-	-	-	√	-	-	CO_2H	Me	-	*Silene armeria*	89
2	-	β	-	-	β	-	-	-	-	-	-	*Hordeum vulgare*	78
3	-	β	β	-	-	-	-	√	-	-	-	*Hordeum vulgare*	78
4	-	β	β	-	β	-	-	√	-	-	-	*Hordeum vulgare*	78
5	-	α	β	-	-	-	-	√	-	-	-	*Hordeum vulgare*	78
6	-	-	β	-	-	-	-	√	-	-	-	*Hordeum vulgare*	78
7	-	-	β	-	-	-	-	-	-	-	9(11)	*Malus domestica*	90
8	-	-	β	-	α	-	-	-	CO—OCH_2		-	*Cucurbita maxima*	91
9	-	-	-	α	-	-	-	-	CO_2H	Me	-	*Cibotium glaucum*	92
10	-	-	-	-	β	-	-	-	CO_2H	Me	-	*Cibotium glaucum, Dicksonia antarctica*	92
11	-	-	-	-	β	-	-	-	CO_2H	CH=O	-	*Raphanus sativus*	82
12	-	-	-	-	α	-	-	-	CO_2H	Me	-	*Cucurbita maxima, C. glaucum, D. antarctica*	91, 92
13	-	-	-	-	α	-	-	-	CO_2H	CO_2H	-	*Cibotium glaucum*	92
14	-	-	-	-	-	√	β	-	CO_2H	Me	-	*Helianthus annuus*	76
15	-	-	-	-	-	√	β	-	CO—OCH_2		-	*Helianthus annuus*	76
16	-	-	-	-	-	√	β	-	CO_2H	CH=O	-	*Helianthus annuus*	76
17	-	-	-	-	-	√	β	-	CO_2H	CO_2H	-	*Helianthus annuus*	76

[a] Δ denotes location of double bond; √ denotes location of hydroxyl; α denotes location of hydroxyl with α-configuration; β denotes location of hydroxyl with β-configuration; 20-norgibberellins all possess a 19,10-γ-lactone function [cf. GA_9 (2)].

(a) Thinning of grape flowers linked with increased berry size in seedless table grapes. As well as the greater customer appeal, the improvement in microclimate (better circulation of air around the berries) assists management of fungal infections.

(b) Applications to citrus fruit, e.g. the rind of navel oranges typically softens at maturity and is subject to injury by pests and environmental factors which adversely affect the appearance of otherwise marketable fruit. By inhibiting senescence, GAs maintain the rind in better condition. Lemons are harvested with intact stems and are kept in cold storage for long periods. If the stem senesces and is abscised, the fruit become prone to infection by *Alternaria* fungi. Abscission may be delayed and storage life thereby prolonged through the use of GAs. Harvesting of lemons and grapefruit may also be delayed by GA application.

(c) Control of russet, a scablike skin disorder in apples, (especially in "golden delicious") may be achieved by the application of the mixture of GA_4 (**9**) and GA_7 (**10**) obtained from *G. fujikuroi* (vide supra), although the GA_7 in the mixture unfortunately tends to inhibit flowering in the following season and is not readily separated from the GA_4.

(d) Malt production in the brewing of beer. This is a costly, time-consuming step, requiring 8–10 days for ale malts (somewhat less for lager malts). Two or three days may be saved by the addition of 25–500 μg of GA_3 for each kilogram of barley.

(e) flowering applications. A variety of ornamental plants can be induced to flower either earlier than usual, or in off-seasons, e.g. camellias and azaleas. Sporadic flowering in some plants is often a problem for plant breeders, but may be ameliorated with GA applications.

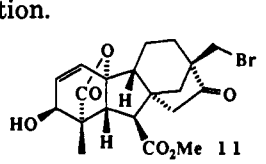
A further important use is in the breeding of cucumbers for which GA_4/GA_7 applications induce male flower formation in monoecious and gynoecious varieties.

Less common applications of GAs, include increased fruit set (tangerine hybrids and blueberries), increased vegetative growth (sugar cane, spinach, and hops), induced sprouting of potatoes (obviating the need for a long rest period), and control of bolting and flowering in artichokes, seed production in tight headed lettuce, petiole elongation in celery, and parthenocarpic development of fruit where late frosts have damaged blossom and prevented fertilization. Martin has provided a comprehensive summary of these treatments and others for which commercial utility has not yet been established.[99]

One of the ironies of gibberellin research is that there has been more commercial success with GA antagonists and inhibitors of GA biosynthesis. These have been used for "chemical pruning", i.e. dwarfing of fruit and ornamental street trees, and for yield enhancement in intensive cereal cultivation.[101]

IV. Structure Elucidation and Spectroscopy of GAs

A complex chemistry and numerous rearrangements made the structure determination of GA_3 (1) difficult and tortuous.[102] The correct structure, except for an assignment of stereochemistry as C(9α) instead of the actual C(9β) configuration, was proposed in 1959,[103] and this last feature was elucidated in 1962 when an X-ray crystallographic study was completed on the bromo ketone derivative 11.[104] This had been obtained by treatment of 1 methyl ester with pyridinium perbromide and involves a Wagner–Meerwein rearrangement of C(12) from C(13) to C(16). A further structure was completed on the 3,13-di-*p*-bromo benzoate of 1[105] in the following year, and then in 1983 of 1 itself.[106] Further X-ray structures on other GAs have been obtained[107] and have provided, inter alia, important data on spatial relationships and the shape of the molecule, including the valuable information that the C-ring possesses a boat rather than the normally preferred chair conformation.



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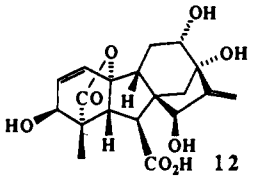
The availability of the GA_3 structure has provided the linchpin for the elucidation of further GA structures, initially by interconversions,[108] but increasingly by spectroscopic means.[4,5] If sufficient material is available, then a combination of NMR spectroscopy and mass spectrometry can be expected to lead readily to a putative structure, but concentrations of GAs in plant material of the order of micrograms per kilogram ranging down to nanograms per kilogram are common. The effort to obtain sufficient material may therefore be considerable, e.g. 38 mg of GA_{32} (12) was accumulated from the immature seeds obtained from 1 ton of unripe peaches,[55] while 14 mg of GA_{19} (13) was obtained from the aqueous washings of 44 ton of bamboo shoots.[41] In many cases it has only been practical to obtain nanogram quantities, and after making an educated guess on the basis of mass spectrometry and chromatographic behavior, it is then necessary to seek confirmation by a partial synthesis.



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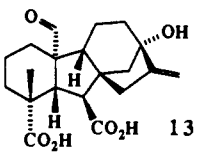

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A. ^{1}H NMR Spectra of GAs

Because of problems with solubility and line broadening with the free acids, NMR spectra of GAs are normally measured on the methyl esters. These display the expected resonances associated with (a) the 17-methylene protons (e.g. δ 4.75–4.99 for GAs lacking hydroxy groups in the C- and D-rings; δ 4.99–5.10 for 12α-hydroxy GAs; δ 5.10–5.17 for 12β-hydroxy GAs; δ 4.95–5.26 for 13-hydroxy GAs; δ 5.00–5.14 for 15β-hydroxy GAs) and (b) the 18-methyl group (e.g. δ 1.08–1.18 for C-19 GAs with saturated A-rings, regardless of hydroxylation; δ 1.18–1.28 for C-20 GAs hydroxylated in the A-ring and Δ^1- or Δ^2-didehydro C-19 GA derivatives, with or without hydroxylation) as appropriate (data are given for $CDCl_3$ solutions of methyl esters).

The most diagnostic feature of GA spectra, however, is the pair of AB doublets (J = ~10 Hz in C-19 GAs and ~12 Hz in C-20 GAs) arising from the 5β and 6α protons. For C-19 GAs, the chemical shift of the resonance arising from the 6α-H falls in a narrow range, δ 2.70 ± 0.10, but values for the 5β-H vary considerably. The "base" shift occurs at a relatively low field because of the effect of the electronegative 10α-oxygen atom [δ 2.49 for GA_9 (2)] and may be further deshielded by 1β- and/or 3β-hydroxyls. Thus, the signal from the 5β-H in GA_4 (9) (3β-OH) is observed at δ 3.22, in GA_{61} (1β-OH) at δ 3.15, and in GA_{54} [1β,3β-(OH)$_2$] at δ 3.56. In C-20 GAs, the 6α-H experiences a wider range of environments because of greater variations in the nature of the C(19) and C(20) substituents. In the δ-lactones like GA_{15}, a value of δ 2.78 ± 0.03 is observed, similar to that found for the C-19 GA γ-lactones, but when the 19-substituent is free to rotate, as in the 20-methyl derivatives, a lower range of δ 3.30 ± 0.08 for H-6 is observed, while an even lower set of shifts (δ 3.72–3.96) is found for 20-formyl and 20-carboxy derivatives. In the absence of the electronegative 10α-oxygen substituent of the C-19 derivatives, the 5β-H resonance is found at higher field in C-20 GAs, e.g. δ 1.82 in GA_{12} (8) dimethyl ester. A modest shift of 0.15–0.30 ppm to lower field occurs when C(20) is oxygenated and the expected greater shift of ca. 0.50 ppm when a 3β-hydroxyl is present. A fairly comprehensive set of GA NMR data has been provided in earlier reviews,[4,5] while a full analysis of the spectrum of GA_3 (1) and its 3,13-diacetate based on 2D J-resolved and ^{1}H–^{1}H COSY spectra as well as ASIS, has been reported by Preiss et al.[109]

B. ^{13}C NMR Spectroscopy of GAs

Because of scarce supplies of material, ^{13}C NMR spectroscopy has found limited use in the structure determination of naturally occurring GAs, although it played an important role in the elucidation of the

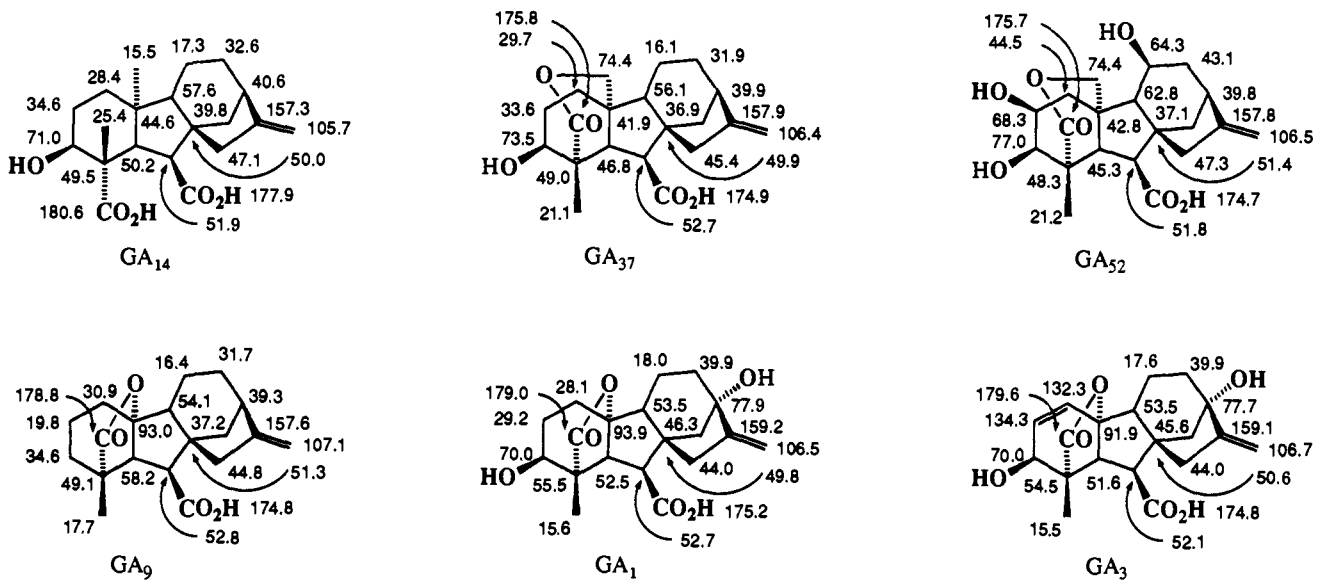


Figure 5. Selected examples of ^{13}C NMR chemical shift data.

structures of GA_{40}[60] and GA_{52}.[16] It has been of inestimable value for monitoring synthetic interconversions, however. Figure 5 displays assignments for a range of characteristic GA structures, including the data for GA_{52} and GA_{37} which allowed the assignment of structure to the former compound. Further sets of chemical shifts have been reported elsewhere.[110] The data are on the whole unexceptional and require no comment. Nevertheless, it is worth noting the unusually high chemical shift of C(11), a consequence of its location in the bay region of the hydrofluorene skeleton and the prow interaction with C(14). The shielding of carbons in a γ-relationship to the 3-hydroxyl is also notable, especially for C(5).

C. Mass Spectrometry of GAs

For very small amounts of unknown GAs, gas chromatography–mass spectrometry (GC–MS), usually measured on the trimethylsilylated derivatives of the methyl esters ("Me–TMSi"), is an essential technique.[111] The analysis of GAs has been considerably simplified by the structural homogeneity of these substances, which possess one of two readily distinguished carbon skeletons (either C-19 or C-20), although the discovery of the two novel skeletal types in fern gametophytes could complicate future studies. There are a number of characteristic ions or mass losses which are associated with certain isolated molecular features, but combinations of these in the one molecule frequently lead to the suppression of an otherwise diagnostic fragmentation.

Methyl esters of C-20 GAs possessing 2 or 3 methoxycarbonyl groups show intense peaks associated with cleavage or part cleavage of these functions: $M^+ - 91/92$ ($MeCO_2/MeCO_2H$ + MeOH) and $M^+ - 119/120$ ($MeCO_2/MeCO_2H + MeCO_2$). 20-Aldehydes would be expected to show a prominent $M^+ - 28$ (CO). While this is the base peak for the MeTMSi derivatives of the 13-hydroxy GAs, GA_{19} (**13**), and GA_{23}, it is relatively weak in other derivatives.

For C-19 GA methyl esters, losses of 18 (H_2O), 31/32 (MeO/MeOH), 44 (CO_2), 46 (HCO_2H), 50 (MeOH + H_2O), 59/60 ($MeCO_2/MeCO_2H$), 78 ($MeCO_2H + H_2O$), 104 ($MeCO_2H + CO_2$), 106 ($MeCO_2H + HCO_2H$), and 122 ($MeCO_2H + CO_2 + H_2O$) are generally observed, but are not diagnostic for individual GAs. Double bonds in the A-ring promote the loss of CO_2 (prominent $M^+ - 44$), while 3-hydroxylated GAs display strong peaks at $M^+ - 62$ ($M^+ - H_2O + CO_2$). Δ^1-En-3-ols give rise to intense peaks at $M^+ - 62$ ($M^+ - H_2O + CO_2$ + H) and are considered to be associated with aromatization of the A-ring.

For Me–TMSi derivatives, ions at m/z = 207/208 and 193 (arising from a C/D-ring fragment) indicate a 13-hydroxylated GA, while 15β-hydroxy GAs without further hydroxylation on the C- or D-rings afford a prominent ion at m/z = 156. A strong peak with m/z = 129 signals an A-ring containing one trimethylsilyloxy group (Me_3SiO) at C-3 and corresponds to a C(1)–C(2)–C(3)–$OSiMe_3$ fragment. The same peak may be observed with 1- and 2-$OSiMe_3$ derivatives, but is not as prominent. A diagnostic peak for the former substitution pattern is m/z = 116 due to the C(2)–C(1)–$OSiMe_3$ fragment. A prominent loss of m/z = 103 (CH_2OTMSi) occurs with Δ^2-en-18-ols (but not with all 18-hydroxy GAs) and 12,13-dihydroxy GAs, except in GA_{32} (**12**) and its 1,2-dihydro derivative, GA_{86}, for which a relatively weak peak is observed. Several reviews with more detailed analyses are available[4,5,112,113] while a comprehensive treatment of the subject has just been completed.[114]

V. Biosynthesis

The biosynthesis of GAs lies outside the main focus of this article and has already been reviewed extensively.[115–118] It has provided an important raison d'etre for much of the synthetic work, however, and establishes a useful framework for correlating the observed structural variations. A brief summary is therefore provided below.

A. Biosynthesis of GAs

The basic pathway for the biogenesis of GAs is outlined in Figure 6. GAs are derived from *ent*-kauren-19-oic acid (**14**) by hydroxylation at C(7) followed by abstraction of the 6β-H and migration of C(8) to C(6)

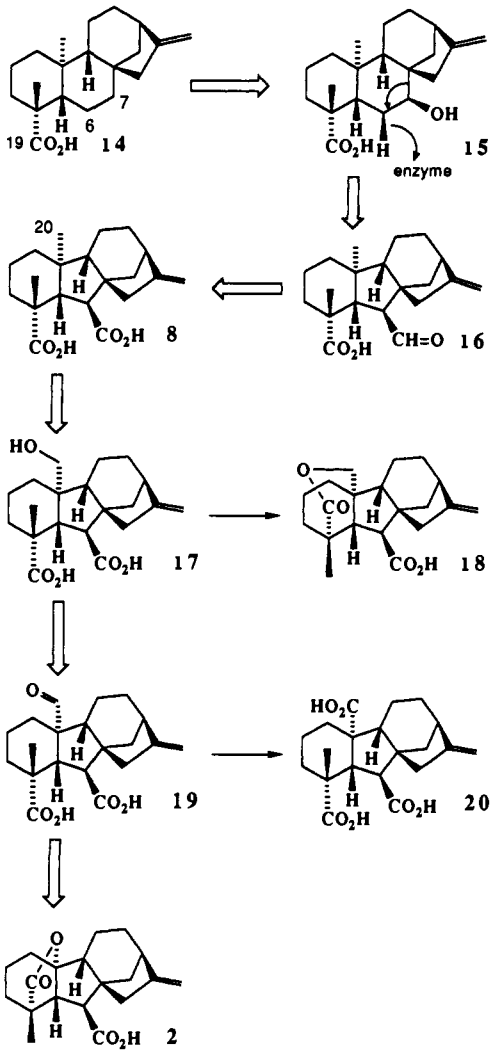


Figure 6. Basic pathway for the biosynthesis of gibberellins.

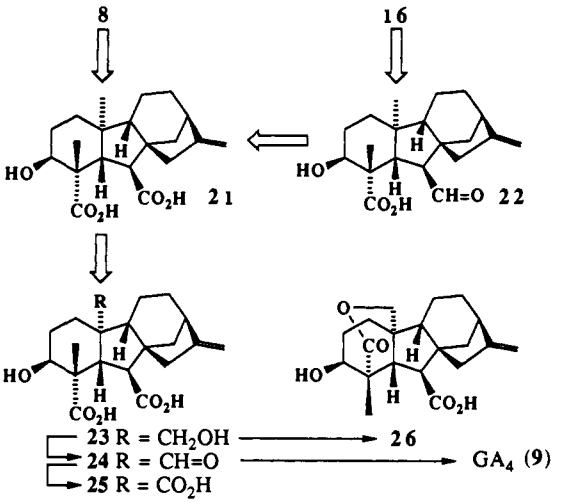


Figure 7. Early 3-hydroxylation biosynthetic pathway in GAs.

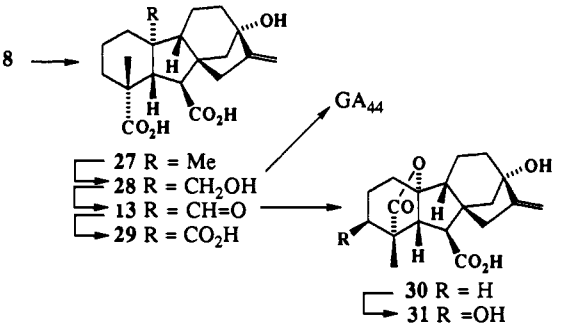


Figure 8. Early 13-hydroxylation biosynthetic pathway in GAs.

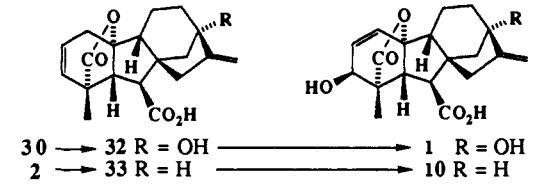


Figure 9. Biosynthesis of GA_3 and GA_7 in higher plants.

with extrusion of C(7), affording the gibberellin prototype, GA_{12} aldehyde (**16**).[119,120] After oxidation to the dicarboxylic acid, GA_{12} (**8**), C(20) is progressively oxidized following the sequence **8** → **17** → **19** and is ultimately lost as CO_2 with the formation of the C-19 gibberellin GA_9 (**2**).[121] Although the tricarboxylic acid GA_{25} (**20**) is also produced, it is not a precursor to **2**. The intermediacy of hydroxy acid **17** may be inferred from the isolation of the lactone GA_{15} (**18**). It is usually necessary to hydrolyze **18** to **17** before it can be incorporated into GA_{24} (**19**)[122] and this is generally the case for other lactones of this type.[123,124] However, a cell-free preparation from spinach leaves can be used directly on the lactones,[125] possibly because this system contains an enzyme which can effect the hydrolysis. The two oxygen atoms of the 19,10-γ-lactone function in GA_9 (**2**) have been shown to arise from the 19-carboxyl.[126]

The biosynthetic sequence outlined above is, at best, a minor pathway. The major routes involve early hydroxylation at either C(3) (Figure 7) or C(13) (Figure 8). In *G. fujikuroi*, it has been established by feeding studies with the B1-41a mutant (in which the endogenous GA biosynthesis is 97.5% blocked at the *ent*-kauren-19-al → *ent*-kauren-19-oic acid stage),[127] that 3β-hydroxylation occurs on both **8** and **16** to form GA_{14} **21** and its 7-aldehyde **22**, respectively, and that these products are then converted into GA_4 (**9**) via GA_{36} (**24**).[122] The intermediacy of **23** can be inferred from the production of GA_{37} (**26**). This early 3β-hydroxylation pathway has also been mapped out in *Cucurbita maxima*.[128,129]

An early 13-hydroxylation pathway (Figure 8) leading from GA_{12} (**8**) via GA_{53} (**27**), **28**, GA_{19} (**13**) and GA_{20} (**30**) to GA_1 (**31**) (the gibberellin which has been shown to be responsible for stem elongation in maize[130] and pea[131]) has been established by using single gene dwarf mutants and a combination of bioassay, quantitative analysis, and feeding studies for maize shoots[132] and with a cell-free system from pea seeds.[124] There is evidence that it also occurs in the shoots of many other plant species.[117]

GA_1 (**31**) is not a biosynthetic precursor to GA_3 (**1**). In *G. fujikuroi*, the biosynthetic route to GA_3 (**1**) proceeds via GA_4 (**9**) and GA_7 (**10**),[122] whereas in higher plants, the sequence is GA_{20} (**30**) → GA_5 (**32**) → **1** (Figure 9)[132] as shown with maize and a cell-free enzyme preparation from the seeds of *Marah macrocarpus*.[133] The latter also effects the parallel transformation of GA_9 (**2**) and of 2,3-didehydro-GA_9 (**33**) into GA_7 (**10**). Although **33** has not been detected as an endogenous GA in these or any other species, it seems not unrea-

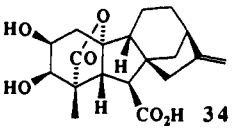
TABLE III. Metabolites from the Incubation of Substituted Kauren-19-oic Acids and Related Kaurenolds with *Gibberella fujikuroi*

Kaurenoic acid derivative or analogue ↓	Gibberellin product with equivalent substitution pattern (GA_n)[a] → n = 1	3	4	7	9	12	13	14	15	24	25	36	37	other GAs	Ref.
2-ene[b,c]	-	-	-	-	2.7	6	-	-	-	0.6	1.0	-	-	various 2β,3β-epoxides	138
2α-OH[d,e]	-	-	-	-	-	-	-	+	-	-	-	-	-	GA_3	139
2β-OH[d,e]	-	-	+	-	+	-	+	-	-	-	-	-	-		139
3β-OH[f]	-	-	-	-	-	-	-	-	-	-	-	-	-	GA_1, GA_3, GA_{13}	139
2β,3β-$(OH)_2$[f]	-	-	-	-	+	+	-	-	-	-	-	-	-		139
11α-OH[f]	-	-	-	-	-	+	-	+	-	-	-	-	-		140
11-oxo[f]	-	-	-	-	-	-	+		+	-	-	-	-		140
12α-OH[f]	-	-	+	-	-	+	+	+	-	-	-	?	?		140
12α-OH[e]	-	-	-	-	-	+	-	-	-	-	+	-	-		141
12β-OH[f]	-	-	+	-	+	+	-	+	+	+	-	+	-		140
12-oxo[f]	-	-	+	-	+	+	+	+	-	-	+	-	-		140
13-OH[f]	-	-	180	-	+	18	+	61	-	12	-	-	-		142
13-OH[e]	-	-	150	-	-	45	-	40	-	20	-	-	-		143
13-OAc[f]	-	-	-	-	200	-	-	-	-	-	40	-	-	GA_{81} -13-acetate	144
13-OAc[e]	-	-	-	-	45	-	-	-	-	-	40	-	-		143
15-ene[e,g]	-	67	-	-	-	-	-	-	-	-	-	-	-	16,17-dihydro-GA_{16}-15-ene (73)	145
15-en-7β-ol[e,h]	-	-	-	83	-	-	73	-	-	-	-	-	-		145
15α-OH[e,f]	-	-	-	-	-	-	-	-	12	(7,15-lactone)		-	-		140,146
15β-OH[f]	-	-	+	-	+	-	-	-	-	+	+	-	-		147,148
15β-OH[e]	-	-	-	+	-	+	-	-	-	-	+	-	-		141
15α-F[e]	-	-	+	-	-	-	-	38	-	-	-	-	-	15α-hydroxy-GA_{14} 7,15-lactone (97)	149
17-nor-16-oxo[e]	-	-	-	-	-	-	51	-	12	-	-	-	-		141
15-en-17-OH[e]	-	-	9	9	-	76	-	6	11	22	-	-	-		141

[a] Yields of GA derivative corresponding to kaurenoic acid derivative indicated in μg/mg of substrate; + indicates positive detection of GA, but yield not measured; ? indicates tentative identification. [b] 19-ol 19-hemisuccinate; 19-ol metabolized to the same range of products, but more slowly. [c] *G. fujikuroi* wild strain. [d] 19-ol. [e] *G. fujikuroi* plus inhibitor. [f] *G. fujikuroi* B1-41a mutant. [g] *ent*-Kaur-15-ene. [h] *ent*-Kaur-15-en-7α-ol.

sonable to assume that its absence is due to rapid metabolism to GA_7.

These conversions occur with loss of the 1β and 2β hydrogens, a result that was predicted by MacMillan in the light of the propensity for β-hydroxylation at C(1) and C(2) in higher plants, thereby underlining the differences between the enzymes in these species and those of the fungus.[134] When GA_4 was the substrate, only GA_{34} (**34**) was formed and GA_7 could not be detected.



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Hydroxylation at C(2) in C-20 GAs is rare, but is common in the higher plant C-19 GAs for both unsubstituted and 3β-hydroxylated A-rings. Thus, GA_9 (**2**) is converted into GA_{51} (**35**) by *P. sativum*, GA_{20} (**30**) into GA_{29} (**36**) by *P. sativum*[67,135] and several other legumes, and GA_1 (**31**) into GA_8 (**38**) by numerous species. 2β-Hydroxylation removes biological activity and has been shown to precede degradation of the GA molecule, as in the formation in *P. sativum* of the catabolites **37** and **39** from **36** and **38**, respectively (Figure 10).[68,136,137] Glycosylated GAs, particularly of 2β-hydroxy GAs, have been shown to accumulate in the mature seeds of numerous species.[7] Their formation has been shown to be reversible, but their function is not known.

B. Metabolic Transformations of GAs and Related Compounds

The enzymes of the fungus *Gibberella fujikuroi* are not substrate specific and so it has been possible to gain access to the rarer GAs and numerous unnatural analogues by treating a wide range of *ent*-kaurene derivatives as well as a number of skeletal variants. Most

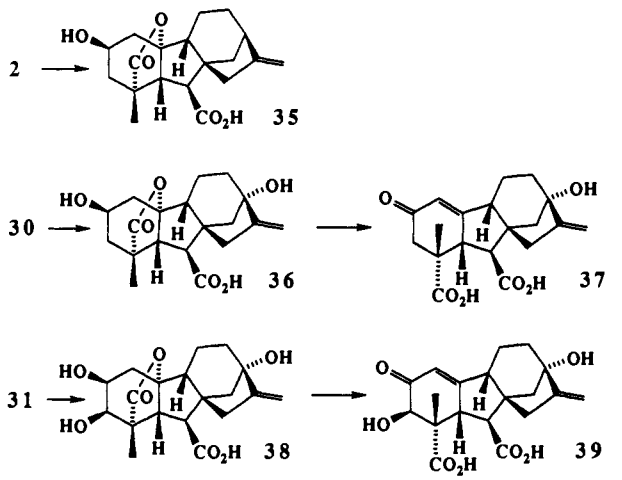


Figure 10. Later stages of GA biosynthesis in higher plants.

experiments have been carried out with resuspended mycelia of the B1-41a mutant in which the normal biosynthesis of GAs is 97.5% blocked,[127] or in the presence of an enzyme inhibitor which achieves a similar end.[150] Examples of *ent*-kaurene derivatives are summarized in Table III, while Figure 11 provides an outline of results obtained with the related skeletal types.

It should be noted that variable amounts of *ent*-kaurene derivatives are also formed and that the yields in Table III are only indicative, since they vary considerably with, inter alia, time and pH. The enzymes are especially tolerant of substitution in the C- and D-rings, and even significant skeletal variations, but conversions of C-20 analogues to C-19 derivatives may be blocked. A 3α-hydroxy group exerts an inhibitory effect on the oxidation of C(19),[151] while an 18-hydroxyl appears to interfere with oxidation at C(6),[152] and so kaurenoids of either type are not converted to GAs, but to more complex kaurenoids.

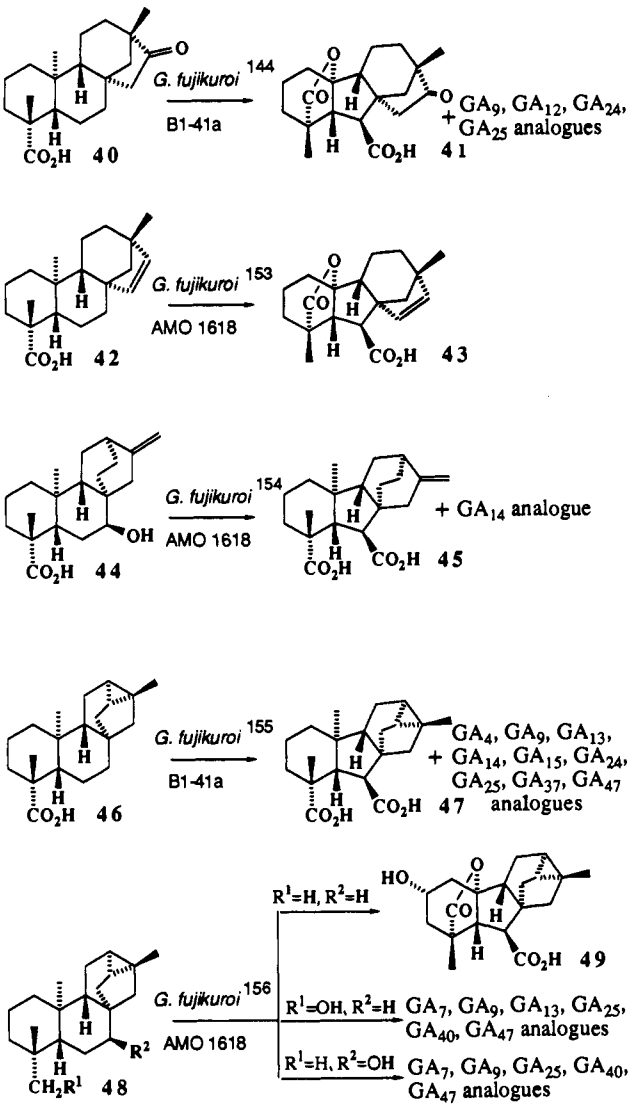
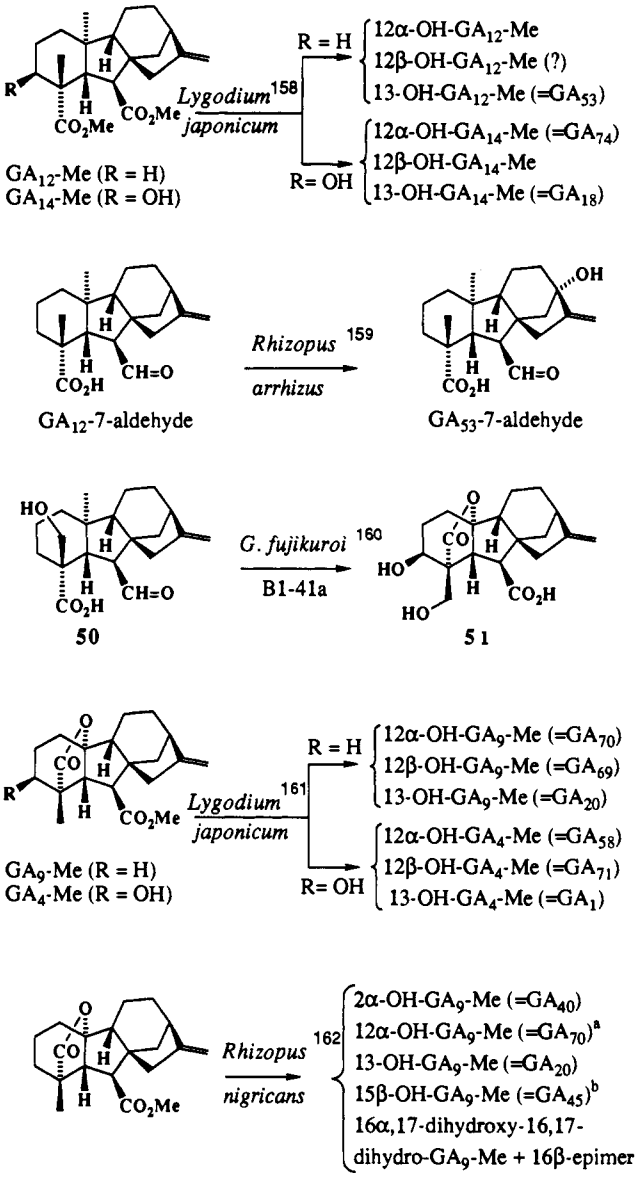


Figure 11. Metabolic conversion of non-kaurenoid substrates by *Gibberella fujikuroi* to GA analogues.

Obtaining GAs from kaurenoids in this way has been of considerable value for structure determination, as in the case of the conversion of 15β-hydroxykauren-19-oic acid to GA_{45}.[147] Metabolism of GAs themselves (often by organisms other than *G. fujikuroi*) has also been useful within this context, and a range of examples is provided in Figure 12. A combination of synthetic and metabolic procedures has been especially useful. Thus, 7β-hydroxykaurenolide (see section VII.F) may be obtained in gram quantities from the neutral fraction of *G. fujikuroi* fermentations and can be readily converted by chemical means into GA_{12}-7-aldehyde (**16**).[157] Hydroxylation by *Rhizopus* spp. then affords access to the biosynthetically important, but difficultly obtained, GA_{53} (**27**) and its 7-aldehyde.[159] This approach is considerably superior to the more direct route from the metabolism of 13-hydroxykaurenoic acid (steviol) which affords GA_{53} in ca. 2% yield.[142,143] 7β,18-Dihydroxykaurenolide is also available from *G. fujikuroi*, but as noted above, 18-hydroxykaurenoids cannot be transformed enzymatically into GAs. Fortunately, this conversion can be achieved synthetically,[157] giving access to 18-hydroxy GA_{12} (**50**) which can then be transformed to 18-hydroxy C-19 GAs, e.g. 18-hydroxy-GA_4 (**51**),[160] a putative GA from germinating barley grain.[59]



(a only Z14a strain; b only DP1563 strain)

Figure 12. Metabolic conversions of gibberellins into rare derivatives.

VI. Characteristic Reactions of GAs

The density of functionality on the highly strained skeleton possessed by gibberellins has ensured a rich and fascinating variety of chemistry. In particular, gibberellic acid (1) has enjoyed a significant notoriety for instability and rearrangement. While this impression may have been valid initially, general advances in synthetic methodology and the accumulation of several decades of experience with this compound now make this early view appear to be exaggerated. The chemistry of GAs has been thoroughly reviewed recently,[163] so this section contains only a summary of the more important and useful aspects. The emphasis is on material which provides a background to the synthetic endeavors described in the following parts of this review.

A. A-Ring Region

GA_3 (1) is rapidly isomerized by 0.01 M NaOH to lactone **53**,[164] a process which has been rationalized in terms of the participation of the 3β-hydroxyl to form

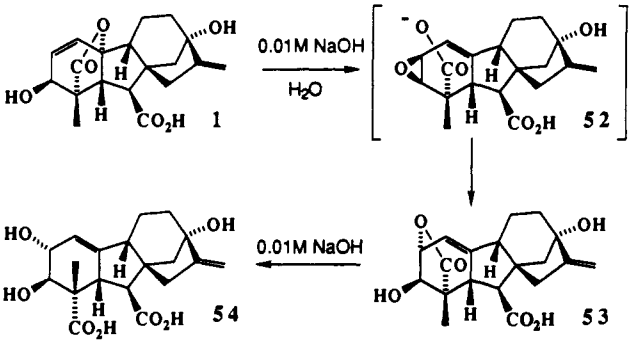


Figure 13. Lactone rearrangement in GA_3.

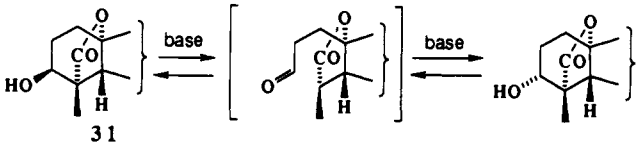


Figure 14. Epimerization of 3-hydroxygibberellins.

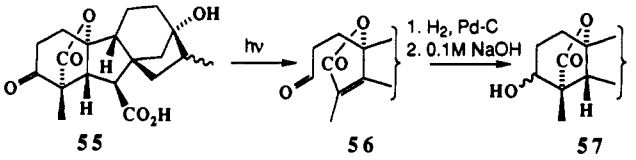


Figure 15. Norrish type I cleavage of a 3-oxo GA.

the 2β,3β-epoxy 19-carboxylate **52**, which recyclizes to form **53** (Figure 13).[165] Lactone **53** is hydrolyzed to the corresponding hydroxy acid **54** on further treatment with base. Equivalent processes have also been observed for GA_7 (**10**). The isomerization may also be effected by palladium acetate and Pd(0) complexes,[166] or weak Lewis acids, e.g. ferric chloride[167] and zinc bromide (see section VII.G).

Under similar conditions for the isomerization of the allylic lactone function in **1**, the dihydro derivatives GA_4 (**9**) and GA_1 (**31**) undergo inversion at C(3) by means of a retrograde aldol/aldol process (Figure 14).[168] Epimerization at C(3) in Δ^1-en-3β-ols may be effected with alkoxide bases,[169,170] and has even been observed on 3-trimethylsilyl derivatives of both of these systems under such conditions.[171]

The 3-oxo analogues (with or without a Δ^1-olefinic bond) are even more reactive toward nucleophilic bases and undergo a retrograde Claisen reaction to form seco-A-ring acids.[172-174] Alternatively, photolysis of 3-oxo GAs induces a Norrish type I cleavage, e.g. **55** afforded the seco aldehyde **56** (Figure 15), thereby providing an opportunity to test the veracity of the retro-aldol mechanism outlined in Figure 14.[175] Thus, hydrogenation of **56** followed by treatment with base afforded the epimeric mixture **57**.

Because GA_3 (**1**) has been such a major source of semisynthetic gibberellins, there has been a considerable effort invested into reactions which discriminate between the two olefinic bonds in this molecule, especially those concerned with the selective reduction of the Δ^1-olefinic bond. Selective hydrogenation of the A-ring double bond in GA_3 derivatives employing special palladium catalysts has been reported,[176] but has been difficult to reproduce. The Δ^{16}-ene is most effectively preserved by including an amine base in the reaction medium, but then diene acid **58** is the major product. The GA_1 system may be readily reconstituted from **58**, however, by iodolactonization to form **59** followed by removal of the halogen (Figure 16).[177]

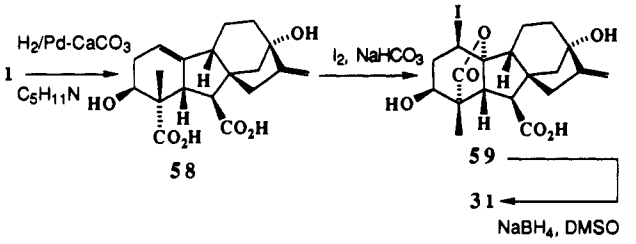


Figure 16. Hydrogenolysis of the A-ring allylic lactone function (synthesis of GA_1).

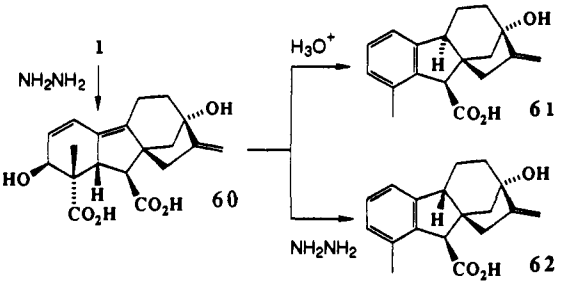


Figure 17. Aromatic A-ring degradation products of GA_3.

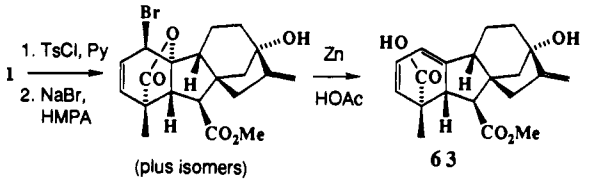


Figure 18. Reductive cleavage of the lactone function in GA_3.

Treatment of GA_3 (**1**) with acid leads initially to mixtures of diene acids, predominantly gibberellenic acid (**60**).[178] Under more vigorous conditions, these undergo decarboxylative elimination with aromatization of the A-ring and epimerization at C(9) to afford mainly allogibberic acid (**61**) (Figure 17).[179,180] Gibberellenic acid (**60**), which is a useful intermediate for further elaboration to some unusual GA derivatives (see section VII.G), is most conveniently derived from **1** by heating in hydrazine hydrate. Prolonged reflux causes aromatization, as in the formation of **61**, but this time, a B/C-cis ring-fusion is obtained to give epiallogibberic acid (**62**).[181,182] Since the cis ring fusion is thermodynamically less stable than the trans, it appears that there may be a concerted 1,3-suprafacial shift of H(5β) to C(9).

The A-ring functionality may also be dismantled by reduction with dissolving metals. This was originally carried out as outlined in Figure 18 within the context of devising a sequence for the "end game" in the first total synthesis of GA_3 (**1**) (section VIII.C). Thus, GA_3 methyl ester 3-tosylate was treated with NaBr in HMPA and the resulting mixture of allylic bromides reduced in acetic acid by Zn metal to afford the triene acid **63**.[183] Later, it was shown that reduction to **63** could be achieved more directly by Zn/acetonitrile reduction of the 3-acetate of GA_3 methyl ester.[184] GA_3 derivatives have also been reduced by lithium/ammonia

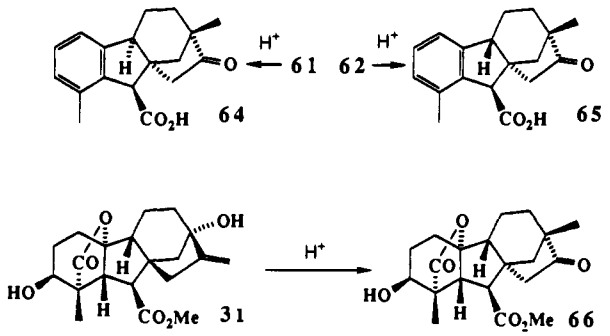


Figure 19. C/D-ring rearrangements of 13-hydroxy GAs.

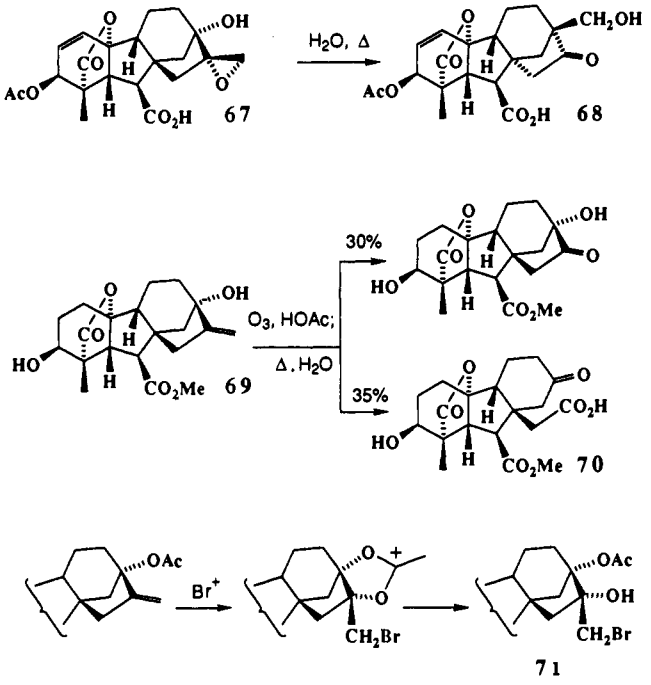


Figure 20. Chemistry of the D-ring in GAs.

solutions as part of a conversion of GA_3 into C-20 GAs (section VII.E).[185]

B. C/D-Ring Region

More vigorous treatment of **61** (or **1**) with strong acid induces a Wagner–Meerwein rearrangement (promoted by the stabilization of the incipient C(13)-carbocation by the attached hydroxyl) to gibberic acid (**64**),[186] while **62** rearranges to epigibberic acid (**65**).[187] GA_1 (**31**) is converted into "gibberellin C" (**66**) (Figure 19).[188,189] The equivalent rearrangement is effected even more readily with softer electrophiles, such as the halogens,[188,190,191] e.g. **1** → **11** (section IV).

The 13-hydroxyl also promotes rearrangement of 16,17-epoxides (e.g. **67** → **68**) (Figure 20)[192] and oxidative cleavage of the C(13)–C(16) bond may be a problem during ozonolysis of the 17-methylene group (e.g. **69** → **70**).[193] To avoid such processes it may be necessary to protect the 13-hydroxyl, preferably by acylation, although the acyloxy group may participate in the electrophilic process as in the formation of bromohydrin **71**.[191] It should be noted that the double bond in the A-ring in these substrates is significantly deactivated toward electrophilic reagents by the neighboring electronegative substituents. The 17-methylene group in GAs lacking a 13-hydroxyl is even more reactive toward

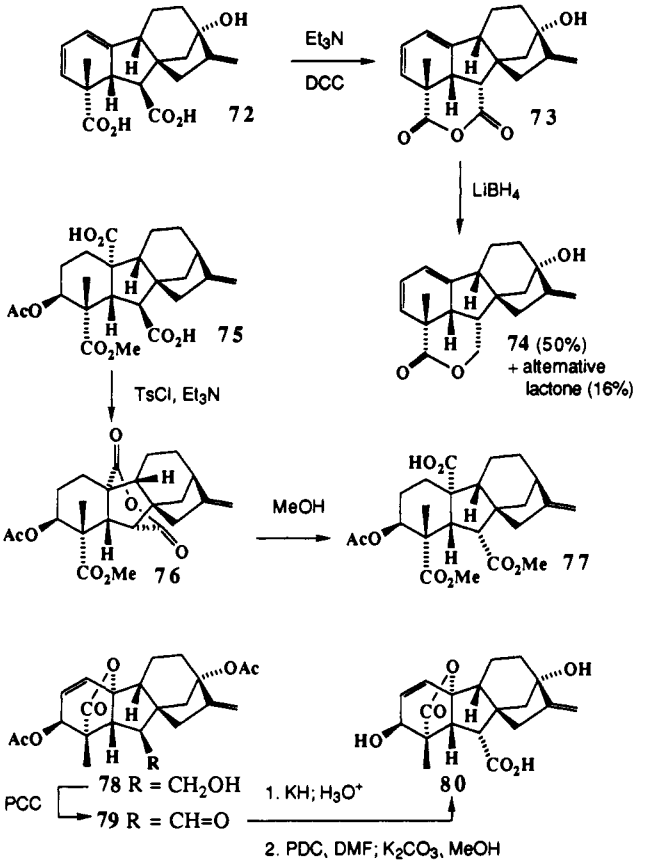


Figure 21. Preparation of 6-*epi*-GAs.

acids. It readily migrates into the ring with Lewis acids and is rapidly hydrated by aqueous acids, giving 17-methyl-16-carbinols.[194]

C. B-Ring Region

The chemistry of the B-ring is largely centered on the 7-carboxy function. The 6β-stereochemistry is thermodynamically preferred to 6α, but the latter geometry is fairly readily accessible. 6α-Epimers have been obtained (Figure 21) by "capture" of the 6-carboxy function by neighboring groups. For example, lactone **74**, an important intermediate in the Corey total synthesis of GA_3, was obtained by reduction of anhydride **73** which is formed from treatment of the diacid **72** with dicyclohexylcarbodiimide and triethylamine.[195] In the C-20 group of GAs, treatment of the GA_{13} derivative **75** with tosyl chloride and triethylamine furnished anhydride **76**, which was selectively methanolyzed to dimethyl ester **77**.[196] A more general procedure for inverting the C(6) stereochemistry has been based on enolization of aldehyde **79**, followed by quenching under kinetic control, thereby affording a 2:3 mixture of 6β- and 6α-epimers, respectively.[197,198] The latter was oxidized to the acid and, after removal of the acetate functions, 6-*epi*-GA_3 (**80**) was obtained. Aldehyde **79** was obtained by activation of GA_3 3,13-diacetate as the symmetrical anhydride followed by reduction to the hydroxymethyl derivative **78**, and then oxidation.

As a part of studies to determine the impact of structural changes on bioactivity, GA_3 diacetate was treated with lead tetraacetate to give the 7-nor-6β-acetate **81**, from which the 6β-ol **82** and 6-one **83** were easily prepared (Figure 22).[199,200] Deoxygenation of carbinol **78** to give the 6β-methyl derivative **84** was also

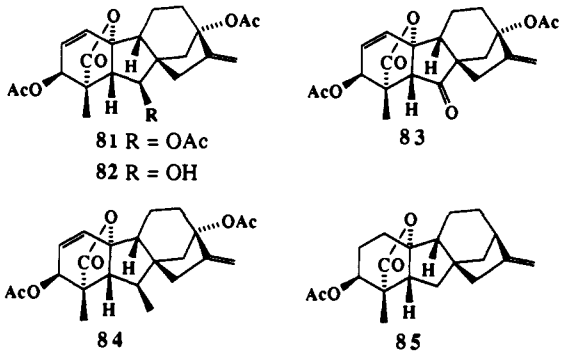


Figure 22. Modified GAs.

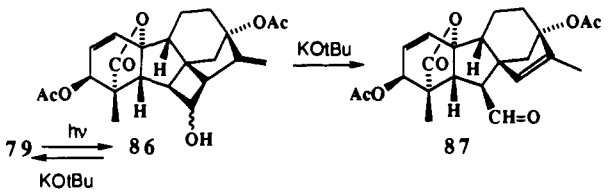


Figure 23. Preparation and fragmentation of a 7,15-cyclo-GA.

effected,[201] while in the GA_4 series, complete removal of the 7-substituent was achieved by lead tetraacetate/I_2 treatment followed by dehalogenation with tri-*n*-butylstannane to give **85**.[202]

The aldehyde **79** is also a convenient intermediate for the introduction of deuterium or tritium at C(6) or C(15). Replacement of H(6) is easily effected by base-catalyzed exchange,[203] while to incorporate the isotopic label at C(15), **79** was photolyzed to form the cyclobutanol **86** which undergoes fragmentation with tritiation at C(15) or C(17) when treated with KOt-Bu/^3H_2O to form a mixture of 15-^{3}H labeled **79** and the isomeric 17-^{3}H-labeled Δ^{15}-ene **87** (Figure 23).[204]

VII. Partial Syntheses of GAs

A. General Procedures for Functional Group Manipulation and Removal

In order to facilitate manipulations and isolation procedures and to improve solubility, most reactions of gibberellins have been conducted on the 7-esters (usually methyl esters), but in many cases the final reconstitution of the carboxylic acid is not straightforward. Hydrolysis with hydroxide is very slow as a consequence of steric hindrance and prior hydrolysis of the lactone function (in C-19 gibberellins), which could be presumed to give rise to Coulombic repulsion by the 19-carboxylate anion. It is nevertheless satisfactory for the simpler analogues, e.g. GA_9 (**2**), GA_{20} (**30**), and GA_5 (**32**). However, it is essential to mask any 3-hydroxyl to avoid epimerization at C(3) or in the case of Δ^1-ene-3β-ol derivatives to prevent isolactone formation (as described earlier). Otherwise, hydrolysis by means of O-alkyl cleavage should be considered and has been achieved by iodide ion[205] or preferably by lithium propanethiolate in hexamethyl phosphoric triamide.[206,207] The latter method has been effective even for the very labile GA_3 (**1**) molecule.[183] Phenacyl esters (removed by zinc/acetic acid)[75] have been used to good effect as well as cyanomethyl esters (removed with aqueous sodium sulfide),[208] tri-*n*-butylstannyl esters (removed with aqueous acetic acid),[209] *p*-methoxyphenacyl esters (photolabile),[210] and methoxymethyl esters (removed by trimethylsilyl chloride/methanol).[211]

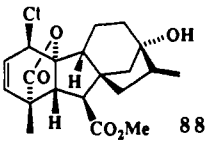
Conjugate reduction of Δ^1-en-3-ones by various borohydride derivatives provides a useful alternative to hydrogenation for the selective removal of an A-ring double bond,[212-216] although hydride reduction of 3-ketones normally affords predominantly the unnatural, 3α-hydroxy epimers (cf. section VII.B). The 17-methylene group may be "preserved" by selective epoxidation and reestablished by subsequent deoxygenation.[217,218] Alternatively, this group may be cleaved by ozonolysis or osmium tetraoxide/periodate to afford the 16-norketone and reintroduced subsequently by means of the Wittig reaction with methylene triphenylphosphorane—a reaction which has been used extensively for the introduction of isotopic labels.[144,219] The Lombardo modification[220] of the nonbasic Nozaki–Oshima reaction (dibromo- or diiodomethane/titanium chloride/zinc metal)[221] may offer advantages over the Wittig reaction.

The remaining general requirement for modification of the gibberellin molecule is a deoxygenation process which is compatible with the 7-ester and 19,10-lactone functionalities, and preferably with the 17-methylene group as well. This is best satisfied by stannane reduction of halides,[222] thioesters,[223] thioamides,[224] mesylates,[225] or methyl oxalyl esters.[226] The last procedure is especially useful with hindered alcohols which are unreactive toward the thiocarbonyl reagents and is the preferred method for removing the 13-hydroxyl from intermediates based on GA_3 (**1**).

B. Interconversions of C-19 GAs

1. Desoxy-A-Ring GAs

Apart from GA_5 (**32**), Δ^2-gibberellins are relatively rare, but this structural feature is especially useful for the preparation of a wide range of A-ring derivatives, and as a consequence, several methods have been developed for its introduction. Hydrogenolysis of GA_3 methyl ester 3β-mesylate or tosylate (H_2,Pd-$CaCO_3$-Py) leads directly to Δ^2-olefins,[227] but the reaction can be difficult to control and may give a number of byproducts. Better yields have been obtained from the treatment of the parent alcohol with thionyl chloride to afford the Δ^2-1β-chloride (**88**) followed by reduction with tri-*n*-butyl stannane.[228] The most reliable method is based on the elimination of the 3-sulfonates of GA_1 and GA_4 derivatives.[229,230] As expected, the 3β-derivatives in which the leaving group is axial are more reactive, but good yields were also obtained from the 3α-derivatives when tetra-*n*-butyl ammonium bromide was added to the reaction mixture (this was presumed to generate a small equilibrium concentration of the 3β-bromide).[216]

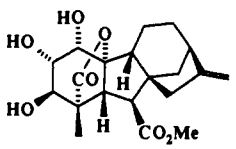


Hydrogenation of the Δ^2-olefins to saturated A-ring gibberellin derivatives, e.g. GA_9 (**2**) and GA_{20} (**30**) can only be achieved satisfactorily if the 17-methylene group is masked (e.g. epoxide) or temporarily removed (to form 17-nor-16-ones). Access to these gibberellins may

therefore be achieved more satisfactorily by stannane reduction of halides or thiocarbonyl derivatives (vide supra).

2. 1-Hydroxy-, 1,3-Dihydroxy-, and 1,2,3-Trihydroxy GAs

Ten of the known natural gibberellins are hydroxylated at the C(1) position. The methyl ester of the 1α,2α,3β-trihydroxy derivative GA_{78} (**89**) was obtained with complete stereoselectivity from GA_7 (**10**) after temporarily masking the Δ^{16}-ene group as the epoxide, treating with osmium tetraoxide, and reconstituting the D-ring alkene.[83] The π-facial selectivity of this reaction is apparently controlled by the 3β-hydroxyl,[231] since the corresponding 3α-hydroxy and 3-desoxy analogues gave only 1β,2β-dihydroxylation. To obtain the 1β,2β,3β-trihydroxy isomer, GA_{79} (**90**), it was necessary to take an indirect route.



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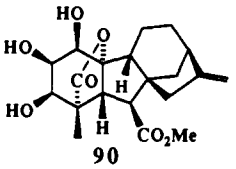

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Hydration of 1-en-3-one derivatives occurs under acidic conditions to afford a 2:3 mixture of 1α- and 1β-products.[70,232] These have been utilized in the synthesis of GA_{60} (**91**) and GA_{61} (**92**) as outlined in Figure 24.[74]

An alternative method has been based on the addition of hydrazoic acid and photolysis of the adducts to form the 1-imines which are hydrolyzed in situ to the 1-ones. These, in turn, undergo facile elimination to furnish 2-en-1-one derivatives which are reduced by sodium borohydride to a ~2:1 mixture of 1α- and 1β-epimers.[233,234] The 1β-epimers are formed with complete stereochemical control by peroxycarboxylic acid induced hydroxylactonization of 1(10)-ene-19-carboxylic acids, but the reported yields are modest.[69] The most direct method for making 1β-alcohols is through solvolysis of a 1-ene-3β-mesylate in buffered aqueous acetone, which affords roughly equal amounts of S_N2 and syn-S_N2' products (i.e. 1-en-3α-ol and 2-en-1β-ol, respectively), contaminated with a small amount of the anti-S_N2' product, i.e. 2-en-1α-ol (Figure 25).[235] Formation of this last isomer can be suppressed by utilizing a dipolar aprotic medium, however (cf. section VII.G), while the 1-en-3α-ol may be recycled via the 3α-tosylate back to the 1-en-3β-ol. Because there is no overlap between the σ-bond of the equatorial 3α-substituent and the 1,2-π-bond, no S_N2' products are obtained.[235]

3. 2-Hydroxy- and 2,3-Dihydroxy GAs

Hydrolysis of GA_3 in dilute aqueous alkali affords direct access to 2α-hydroxy acids, e.g. **54**, as noted in section VI.A, and so it has been a relatively simple matter to prepare the 2α,3β,13-trihydroxy gibberellin GA_{56} (**94**) by means of an iodolactonization of **54** to give **93**, followed by dehalogenation (Figure 26).[69]

A more common approach to functionalization of the C(2) position, however, has been via Δ^2-olefins. The 2β,3β-dihydroxylation pattern is on the major catabolic biosynthetic pathway and is found in 10 gibberellin derivatives, e.g. GA_{34} (**34**) and GA_8 (**38**). These are

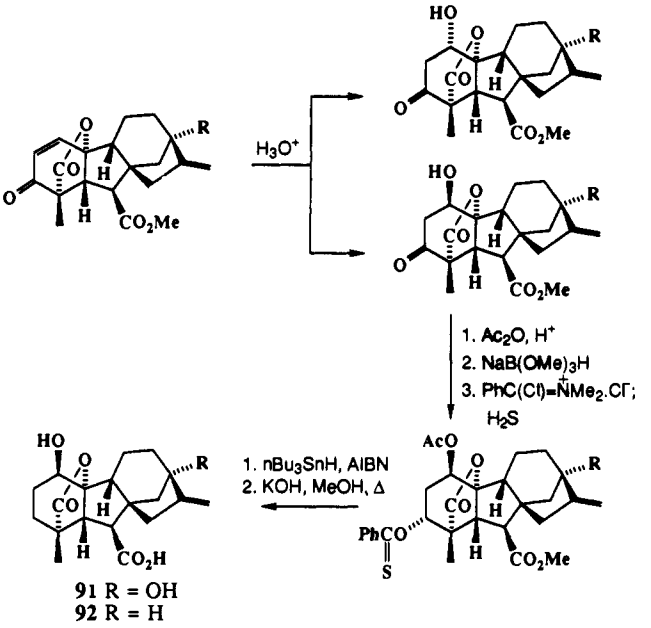


Figure 24. Preparation of 1-hydroxy GAs.

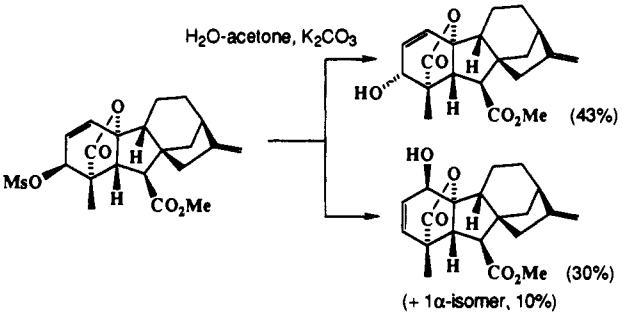


Figure 25. Solvolysis of GA 1-ene-3-mesylates.

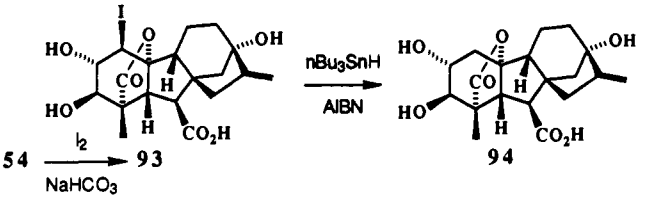


Figure 26. Preparation of the 2α-hydroxylated gibberellin, GA_{56}.

readily prepared by osmium tetroxide oxidation of Δ^2-olefins (stereoselectivity appears to be complete and it is even possible to achieve moderate chemoselectivity in the presence of the 17-methylene group).[236] On the other hand, acetoxybromination (of the 17-nor-16-one derivatives) (Figure 27) has been employed in the elaboration of 2α,3β-dihydroxy derivatives, as in the preparation of GA_{47} methyl ester (**98**) via epoxide **96**. The simple 2α-hydroxy analogue, GA_{40} methyl ester (**97**), was prepared by stannane reduction of the 3β-bromo intermediate **95**.[237] The 2β-epimers, e.g. GA_{51} (**35**), have been prepared by borohydride reduction of the 2-ketones (1:1 mixture with the 2α-epimers),[238,239] but the conversion is more efficiently and reliably carried out by S_N2 displacement of 2α-mesylates with cesium acetate/18-crown-6.[240]

4. 3-Hydroxy GAs

Because the most readily obtained gibberellins all possess a 3β-hydroxy group, the introduction of such

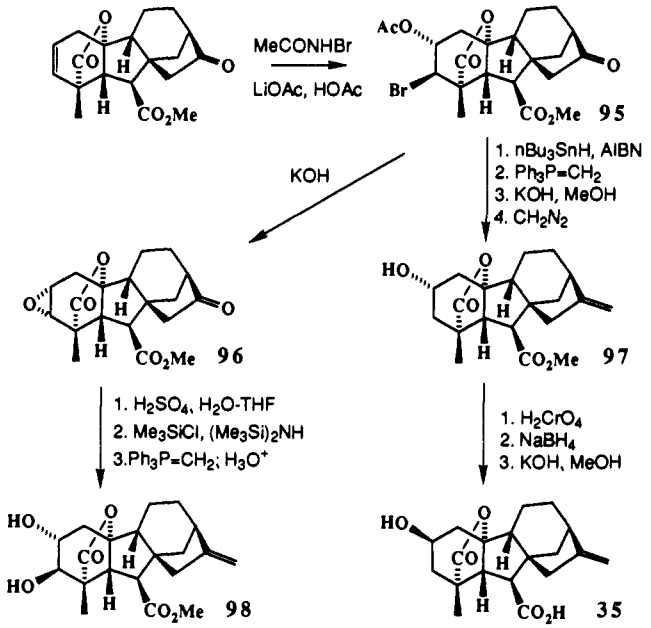


Figure 27. Preparation of 2-hydroxy GAs from Δ^2-alkenes.

a function is not normally an issue, but reestablishment of the 3β-stereochemistry may be necessary following manipulations which disturb this part of the molecule. Hydride reductions of 3-oxo gibberellin esters afford mainly the 3α-alcohols, and although the 3α- and 3β-epimers are formed in equal amounts from Meerwein–Ponndorf–Verley reductions of 3-oxo C-20 gibberellins,[241] this method gave a poor yield in the case of a C-19 analogue.[214] K-Selectride reduction of 3-oxo-7-carboxylic acids derived from GA_1 and GA_4, however, affords predominantly the 3β-epimers. This outcome has been rationalized in terms of steric and Coulombic inhibition to approach of the reagent to the upper face of the substrate by the 7β-carboxylate boronate complex.[242] S_N2 displacement of 3α-mesylates with cesium acetate/18-crown-6 followed by careful hydrolysis is also moderately effective.[240]

5. GA $\Delta^{9(11)}$-Enes

The first natural GA to possess a $\Delta^{9(11)}$-ene function was the methyl ester **6** of 9,11-didehydro-GA_9 (GA_{73}), discovered in cultured gametophytes of the fern *Lygodium japonicum* in which it serves as a potent antheridiogen.[14] Only one other GA of this type has been detected to date: 9,11-didehydro-GA_4 from apple seeds (Table II).[90] Because of the very limited amount of isolated natural material (35 ng), the synthesis of GA_{73}-Me (**6**) (Figure 28)[13] was an essential contribution to the structure determination. Two routes were followed, but both had in common the key sequence involving iodolactonization of a Δ^9-ene 19-oic acid to form a 9β-iodo-19,10-lactone followed by DBU induced elimination of HI. The preferred route to **6** involved early removal of the 3β-hydroxyl.

6. 11-Hydroxy GAs

The availability of $\Delta^{9(11)}$-dehydro GAs opened up a route to the stereocontrolled synthesis of 11β-hydroxy GAs.[243] Stereochemical control is probably important, since inversion at the crowded C(11) site may be impractical, while an oxidation/reduction cycle via an

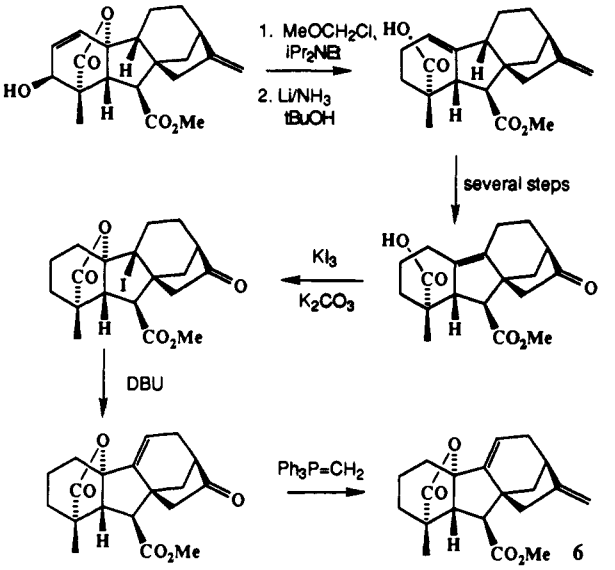


Figure 28. Preparation of the fern antheridiogen GA_{73} methyl ester.

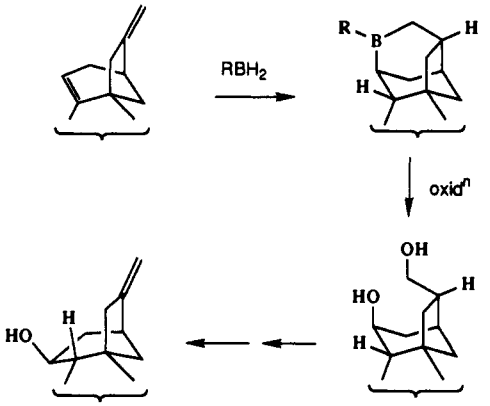


Figure 29. Strategy for the synthesis of 11-hydroxy GAs.

11-one function is likely to engender β-elimination of the strained 19,10-lactone group.[56] The essential part of the synthesis strategy (Figure 29) was based on the hydroboration of a suitable 9(11),16-diene, in the expectation that the initial addition of the borane to the exo-face of the more accessible Δ^{16}-ene function would occur first and be followed by intramolecular addition to the upper face of the $\Delta^{9(11)}$ double bond, reestablishing the crucial 9β configuration; oxidation in the usual way would then afford an 11β,17-diol from which it appeared that the target compounds could be obtained.[244]

The plan was tested initially by undertaking the synthesis of the methyl ester (**103**) of the known gibberellin, GA_{35} (Figure 30), beginning with intermediate **99** employed in one of the syntheses of GA_{73} methyl ester referred to above. In the event, hydroboration of the diene, which could be readily prepared by Wittig methylenation of **99**, afforded the expected diol **100**. This was protected as the 17-*tert*-butyldimethylsilyl ether **101** so as to allow selective acetylation of the 11β-hydroxyl, a necessary prelude to restoring the 17-methylene function. Otherwise, an 11β,17-cyclic ether is likely to be formed by displacement of any leaving group attached to C(17) by the free 11β-hydroxyl. Alkene formation was best achieved by DBU-induced elimination of HI from iodide **102** which was formed

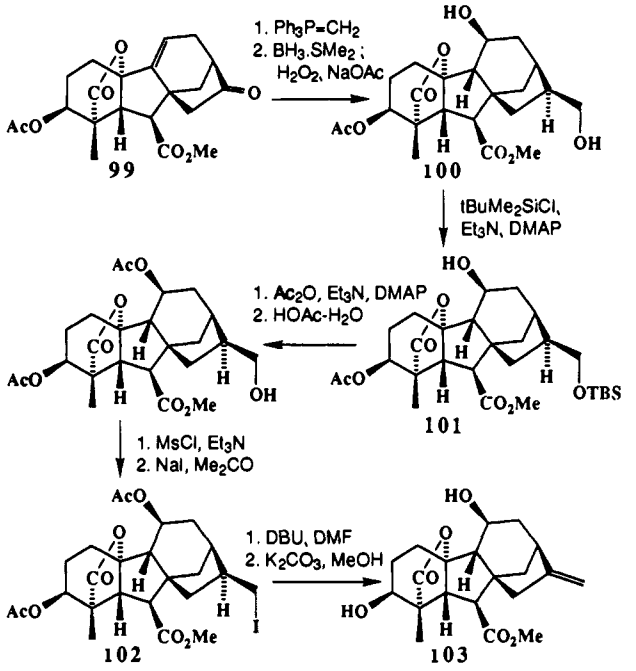


Figure 30. Synthesis of GA_{35}.

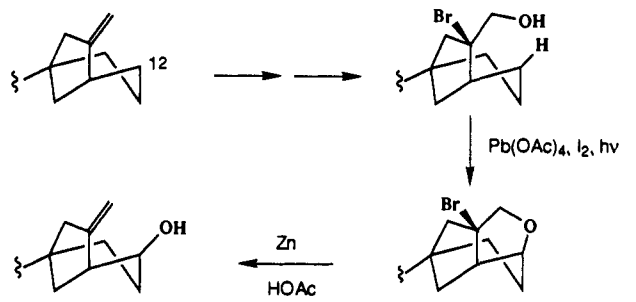
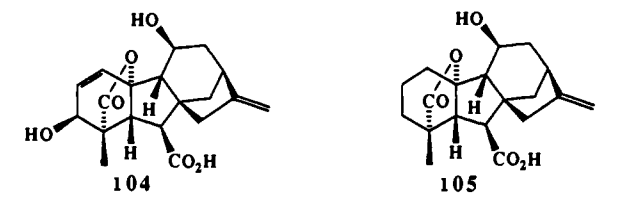


Figure 31. Introduction of a 12β-OH group by transannular oxidation.

from **101** via the mesylate as indicated.

This synthesis was then adapted to the preparation of two new GAs from loquat fruit, GA_{80} (**104**) and GA_{84} (**105**),[84] thereby confirming tentative assignments of structure and bringing to five the total number of naturally occurring 11-hydroxy GAs.



7. 12-Hydroxy GAs

12-Hydroxy gibberellins, e.g. GA_{32} (**12**), appear to have considerable potential for biological activity, but are among the least accessible of the natural gibberellins, both in terms of isolation and synthesis. Until recently, the only means of gaining access to such compounds (of which there are >16 known variants) had been from microbiological transformations.[140,245] However, transannular oxidation of 16α-bromo-17-hydroxy derivatives has now made this type of gibberellin freely available (Figure 31).[246]

The pivotal lead tetraacetate/iodine oxidation to form the 12β,17-ether depends in part for its success

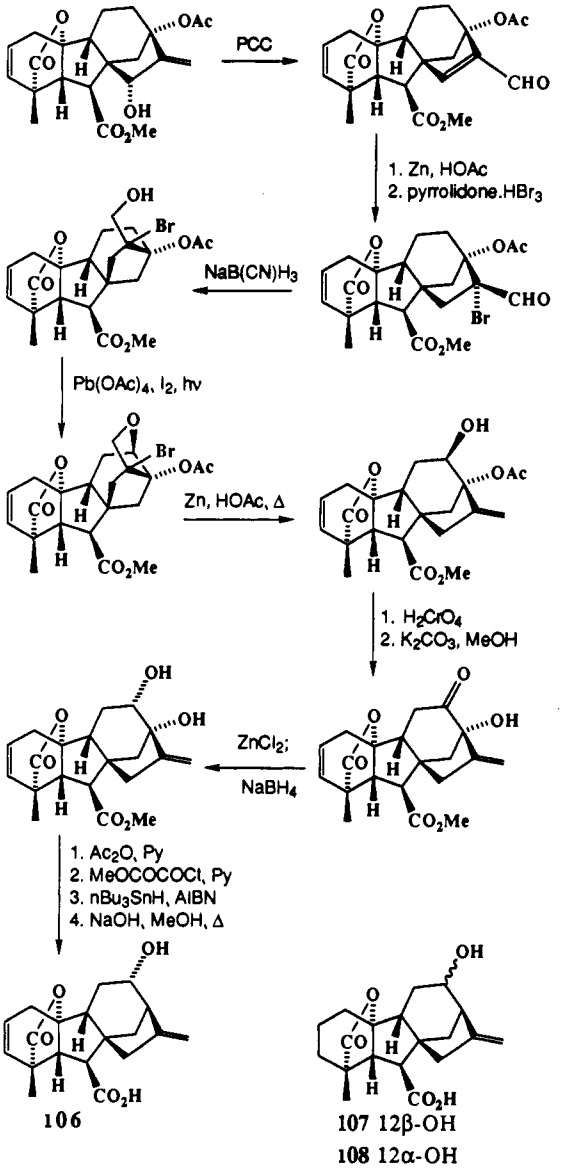
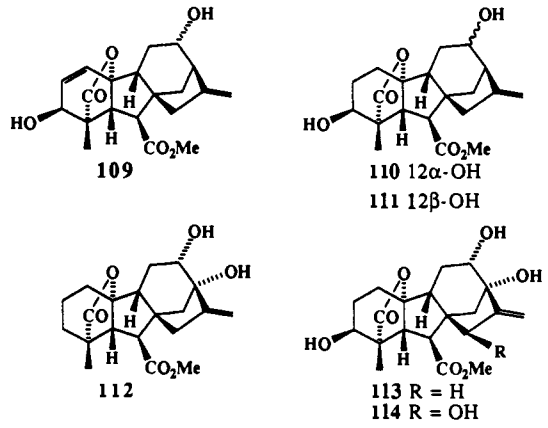


Figure 32. Synthesis of 12-hydroxy GAs.

on the boat conformation of the C-ring, while the incorporation of the bromo substituent allows opening of the ether ring under conditions which are sufficiently mild not to disturb any sensitive A-ring functionality which may be present. Reductive cleavage leads to 12β-carbinols which may be converted into the 12α-epimers by means of an oxidation/reduction cycle via the zinc-chelated 13-hydroxy-12-ones. Chelation flattens the C-ring, opening up the upper face to attack by borohydride; otherwise, the 12β-isomers are reformed.

The synthesis of 12-hydroxy GAs was initially demonstrated with the preparation of the simpler derivatives, GA_{31} (**106**), GA_{69} (**107**), and GA_{70} (**108**) (Figure 32),[247] but the methodology was then extended to methyl esters of the more complex analogues, GA_{30} (**109**),[247] GA_{32} (**12**),[248] GA_{58} (**110**), and GA_{72} (**111**).[247] More recently, it has allowed the structures of three new metabolites, GA_{77},[82] GA_{85}, and GA_{86}[88] to be established by preparation of their corresponding methyl esters, **112**, **113**, and **114**, respectively.

Several important modifications to the methodology were introduced in later work. Although it is possible to introduce oxygen efficiently at C(17) in GAs lacking a 13-hydroxyl through hydroboration or by treatment



of epoxides with sulfuryl chloride,[249] it was initially found to be necessary to take an indirect route when a 13-substituent was involved, e.g. the PCC oxidation of 15-carbinols (Figure 32). The discovery that $Cp_2Ti(III)Cl$ reacts with epoxide **115** to form the 17-carboxaldehyde provided a useful advance.[250] This process was assumed to proceed via stepwise reduction[251] and then a β-hydride elimination to afford the titanium enolate of the 17-carboxaldehyde (Figure 33) which could be brominated in situ if desired, affording **116** directly. The reductive opening of the epoxide avoids the probability of a Wagner Meerwein rearrangement which is likely to accompany a Lewis acid catalyzed opening of the epoxide (cf. **69** → **70**).

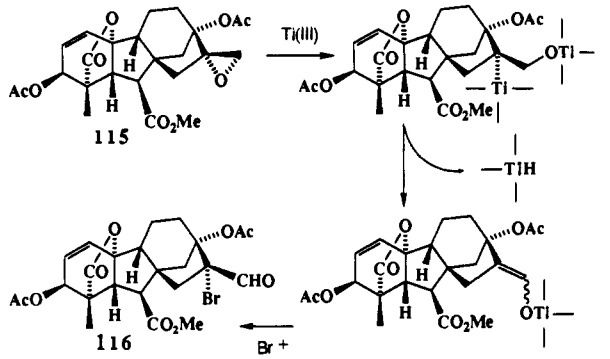


Figure 33. Epoxide route to GA 17-carboxaldehydes.

8. 14-Hydroxy GAs

14-Hydroxy GAs have not yet been isolated from natural sources, and so the task of introducing a hydroxyl into this rather inaccessible part of the molecule has been addressed only recently.[252] It was achieved by means of sequential rearrangements of the C- and D-rings as outlined in Figure 34. Thus, GA_3 (**1**) was converted into ketone **117** and then epoxide **118** which, when treated with $Cl_2Ti(iPrNC_6H_{11})_2$, gave a 1.4:1 mixture of the 14-hydroxy GA_7 derivative **119** and its Δ^{15}-ene isomer. The choice of this particular titanium(IV) reagent was made after a systematic examination of other ligand combinations which either led to a higher proportion of the Δ^{15}-ene or were unreactive.

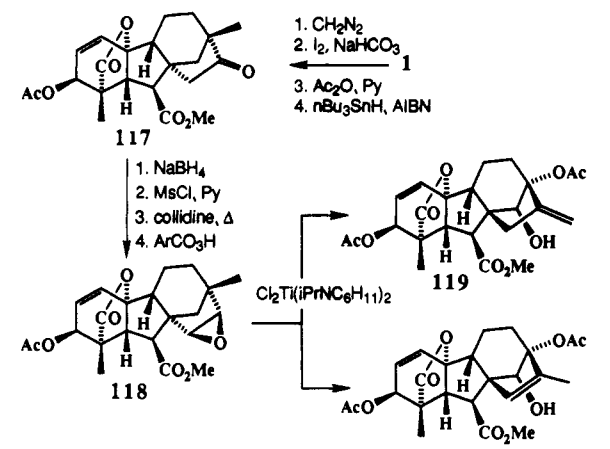


Figure 34. Preparation of 14-hydroxy GAs.

9. 15-Hydroxy GAs

Oxidation of gibberellins by selenium dioxide/*tert*-butyl hydroperoxide[253] affords excellent yields of the 15α-hydroxy derivatives, and although these are prone to undergo lactonization with the 7-methoxycarbonyl group, they may be manipulated satisfactorily with due care. For the synthesis of GA_{32}, it was necessary to use ultrasound to achieve the introduction of the 15α-hydroxyl because of apparent deactivation of the substrate by the 12α-acetoxyl. All natural 15-hydroxy gibberellins (12 in number) have the 15β-configuration, e.g. GA_{63} (**120**), and several have been obtained (Figure 35) by Swern oxidation followed by zinc/acetic acid reduction, the latter procedure proving to be superior to the more obvious hydride/lanthanide reagents which are normally selected in order to minimize 1,4-reduction.[75,77]

Unfortunately, the yields from this sequence deteriorate with 13-oxygenated GAs and, for no obvious reason, have been quite low (20–25%) when applied to

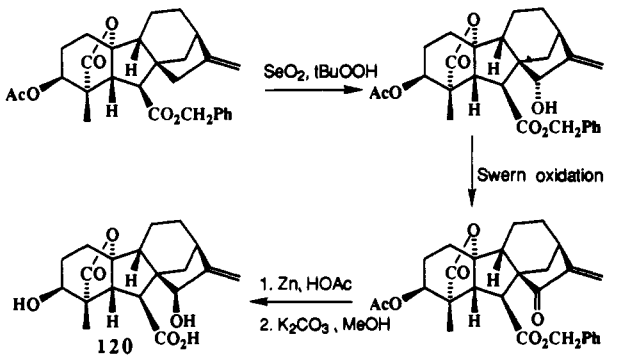
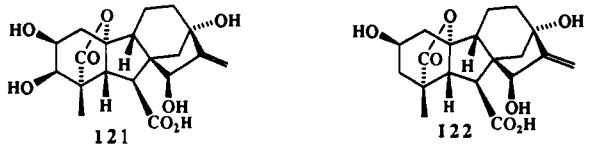


Figure 35. Preparation of the 15-hydroxy gibberellin, GA_{63}.

the preparation of the polyhydroxylated GAs, GA_{32} (**12**), GA_{75} (**121**), and GA_{76} (**122**).[81]



After an extensive search for a solution to this problem two promising approaches were discovered. It was found that masking of the Δ^{16}-ene group as the 16α,17-epoxide in the GA_3 derived enone **123** (R = Me), followed by borohydride reduction, acetylation, and then reduction of the epoxy function in the product **124** with the seleno reagent **125** afforded a reliable and high yielding procedure (71% over three steps) as outlined in Figure 36. More than a dozen other reagents were tested, but all failed to reduce **124** satisfactorily. In a more direct approach, it was found that the 15-oxo acid

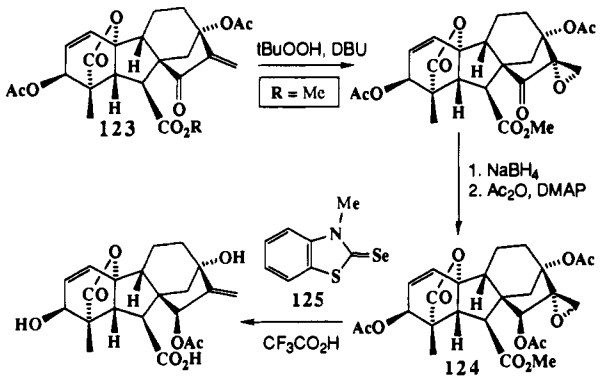


Figure 36. Improved methods for the preparation of 15-hydroxy GAs.

123 (R = H) could be reduced directly with sodium triacetoxyborohydride to the desired 15β-hydroxy acid in 65% yield.[250]

C. Interconversions of C-20 GAs

Relatively few interconversions of C-20 gibberellins have been carried out, essentially as a consequence of the limited availability of substrates. GA_{13} (**25**) is the only compound which can be readily obtained in gram quantities and this has been transformed into the methyl esters of GA_{43} (**126**) and GA_{46} (**127**) by the same methods employed for the C-19 analogues.[62,65] GA_{13} has also been converted into GA_{37} (**26**) (Figure 37).[241] The inaccessibility of the C(20) carboxyl function makes reduction of this group difficult, and this was only achieved by harnessing a 3α-hydroxyl in the formation of the 3α,20-lactone **128** which could then be reduced by $LiBH_4$ to give 3-*epi*-GA_{37} (**129**). The stereochemistry at C(3) was then corrected by oxidation followed by Meerwein–Ponndorf–Verley reduction, which afforded a 1:1 mixture of **26** and **129**.

As well as steric problems, manipulations of C(20) are complicated by the ease with which lactonization occurs with the C(19) carboxyl, so synthetic access to 20-methyl gibberellins such as GA_{12} (**8**) is most satisfactorily effected by ring contraction in kaurenolides (section VII.F), while 20-oxo GAs, e.g. GA_{19} (**13**), may be efficiently obtained from C-19 gibberellins (section VII.E).

D. Conversions of C-20 into C-19 GAs

GA_{13} (**25**) has been converted into GA_4 (**9**) by two closely related approaches in which the key step is the oxidative decarboxylation of the C(20) carboxyl by lead tetraacetate (Figure 38).[254] In one case the γ-lactone function was obtained directly, while in the other, it was formed by means of an iodolactonization on **131** followed by dehalogenation. Given the more plentiful supplies of C-19 GAs, such conversions are of primarily academic interest, although the isomeric lactone **130** provides an interesting structure–bioactivity probe.

E. Conversions of C-19 GAs into C-20 GAs

Of very much greater utility than the C-20 → C-19 GA conversion outlined above, is the reverse type of transformation illustrated in Figures 39 and 40, i.e. of GA_3 (**1**) into GA_{19} (**13**)[255] and into the methyl esters of GA_{36} (**24**) and GA_{37} (**26**).[256] These syntheses, for their success, depend on an unusual oxidative cleavage me-

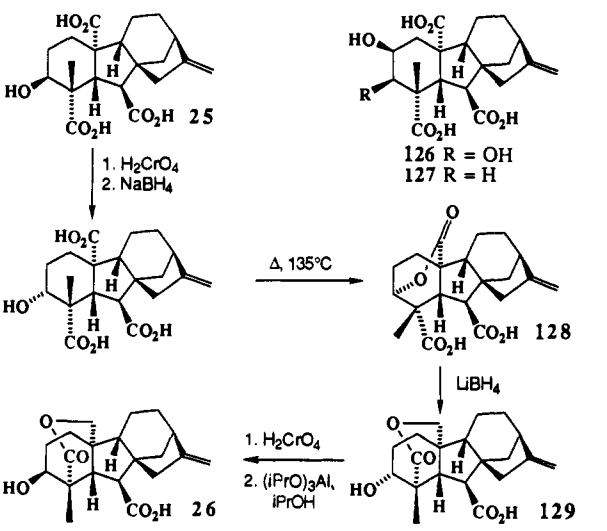


Figure 37. Synthesis of GA_{37} from GA_{13}.

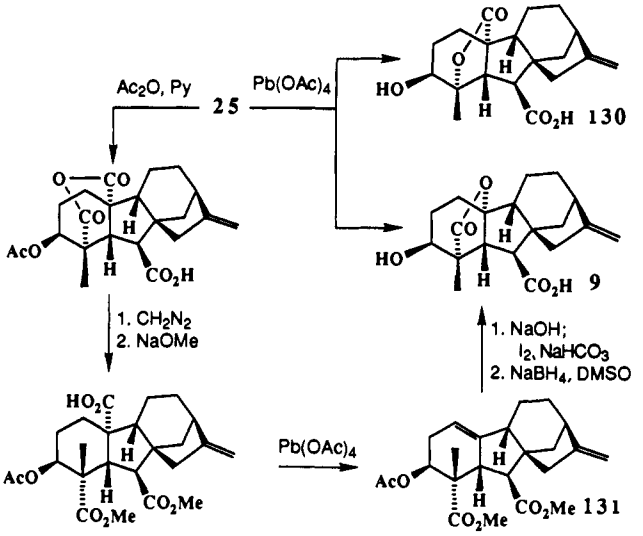


Figure 38. Synthesis of GA_4 from GA_{13}.

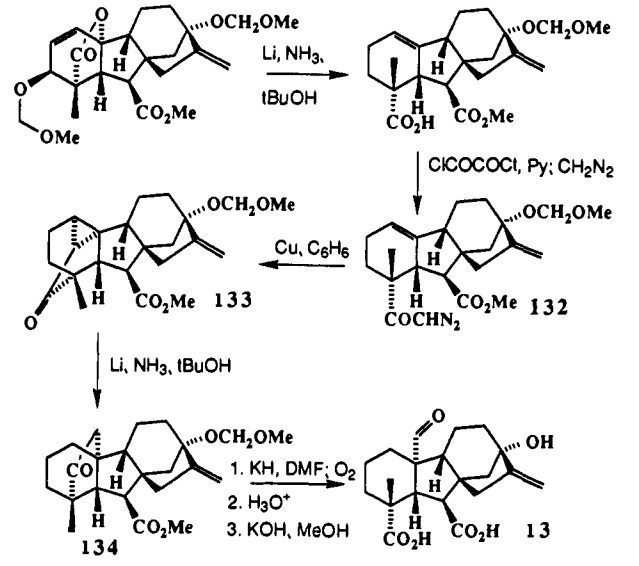


Figure 39. Synthesis of GA_{19} from GA_3.

diated by O_2 gas on the potassium enolates derived from the cyclopentanone moieties in intermediates like **134**. This was formed in a regioselective lithium/ammonia reduction of the cyclopropyl ketone **133**, obtained from

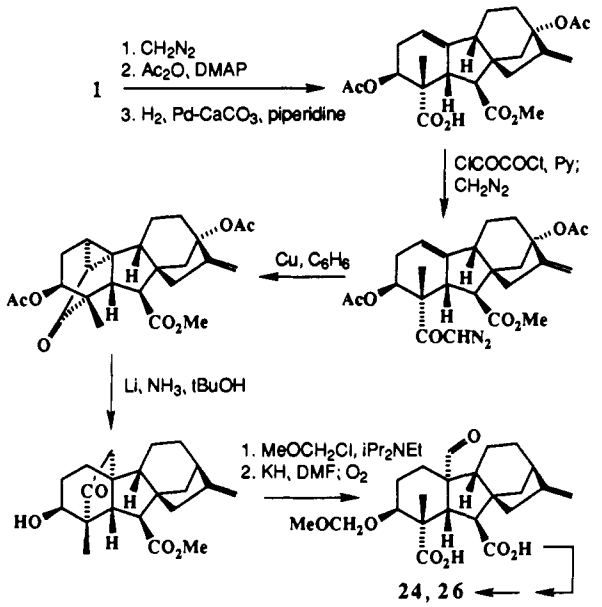


Figure 40. Synthesis of GA_{36} and GA_{37} from GA_3.

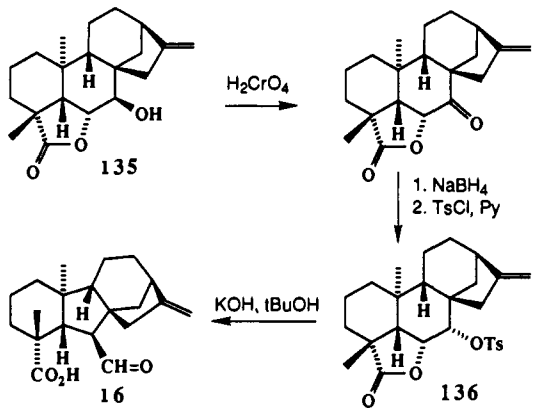


Figure 41. Synthesis of GA_{12} aldehyde from 7β-hydroxykaurenolide.

an intramolecular cyclopropanation reaction of the $\Delta^{1(10)}$-ene 19-diazo ketone **132**.

The hydrogenolysis of the 3β-methoxymethyl group in the synthesis of GA_{19} and of the bridgehead 13-acetate substituent in the preparation of GA_{36} and GA_{37} by the reducing metal system is of interest. In the latter syntheses, the 16-ene function is prone to migrate into the D-ring under acidic conditions, so it was essential to remove the protecting 3-methoxymethyl group with great care. This was achieved by brief exposure to dimethylbromoborane[257] at −70 °C.

F. Conversions of Kaurenoids into C-20 GAs

1. Conversions Based on Kaurenolides

The first synthesis of a natural gibberellin[258] was that of GA_{12} aldehyde (**16**) from 7β-hydroxykaurenolide (**135**), which may be fairly easily isolated from the neutral fraction obtained from the fermentation of *Gibberella fujikuroi*. This transformation (Figure 41) continues to provide the best access to this important gibberellin and its isotopically labeled derivatives. The pivotal step in this sequence is the pinacol-like B-ring contraction **136** → **16**, which is best effected by potassium hydroxide in aqueous tertiary butyl alcohol[157] and for which it is essential that the nucleofugal tosylate

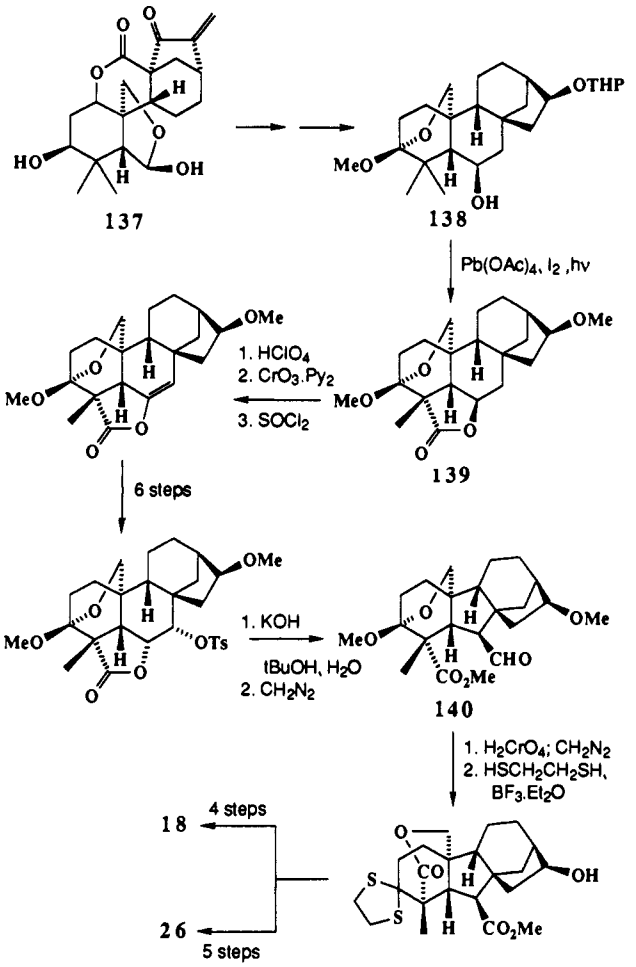


Figure 42. Synthesis of GA_{15} and GA_{37} from a degradation product of the diterpene enmein.

function is aligned antiperiplanar with the migrating C(6)–C(7) bond. Thus, it was necessary first to invert the stereochemistry at C(7) in the natural kaurenolide **135** by oxidation followed by borohydride reduction. The parent GA_{12} (**8**) is readily formed by Jones' oxidation and the methodology has been extended to the synthesis of GA_{14} aldehyde (**22**) from 3β,7β-dihydroxykaurenolide,[259] as well as GA_{15} (**18**).[260] The latter sequence involves an inefficient (18% yield) transannular functionalization of the 20-methyl group, and so access to **18** and its analogues is therefore best effected from GA_{13} (**25**) via GA_{37} (**26**), or from GA_3 (**1**) via GA_{19} (**13**) or GA_{36} (**24**) (cf. previous sections).

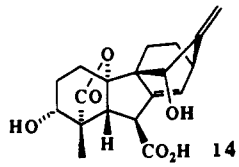
2. Conversions Based on Enmein

Gibberellins A_{15} (**18**) and A_{37} (**26**) have been prepared from degradation products of the diterpenoid, enmein (**137**) for which it was necessary to carry out a transannular oxidation to functionalize C(19). In one sequence this was effected by photolysis of a nitrone,[261] while in a second approach (Figure 42), carbinol **138** was oxidized by lead tetraacetate/iodine to lactone **139**. Following oxidation at C(7) it was possible to adapt the kaurenolide based methodology (vide supra) in the formation of the ring-contracted aldehyde **140**, from which GA_{15} and GA_{37} were readily prepared.[262] (±)-**138** was also prepared by total synthesis[263] which would have established a formal total synthesis of these gibberellins except for the required optical resolution.

G. Fern Antheridiogens

Following the pioneering studies of Döpp on the bracken fern, *Pteridium aquilinum*,[264] it was shown that a significant number of distinct growth substances were produced by developing gametophytes of the Pteridophyta (ferns).[265] These compounds, which are biologically active at subpicomolar concentrations, promote the formation of antheridia on prothallia and have therefore been termed antheridiogens. They also promote spore germination and, in at least one species, inhibit the growth of archegonia.[14] One of the first clues to the structures of these compounds was the discovery that some had gibberellin-like properties[266] and, conversely, that gibberellins could induce the same changes in fern gametophytes as the antheridiogens,[267] although not as well. These correlations have thus far been limited to members of the Schizaeaceae, one of the more primitive families.

The most important breakthrough in the chemistry of these growth substances was the determination of the structure **141** for the major antheridiogen isolated from *Anemia phyllitidis*. The stereochemistry at C(3) was originally determined to be 3β,[268] but after completing the total synthesis of the racemate of the corresponding methyl ester and finding that it was different, Corey and Myers concluded that the correct structure should be the 3α-epimer **141**, confirmed this by synthesis,[269] and coined the name "antheridic acid".[270] Nester et al. reported the discovery of another antheridiogen in 1987, this time from *Anemia mexicana*.[271] The new compound was assigned structure **142** following spectroscopic and synthetic studies.[272]



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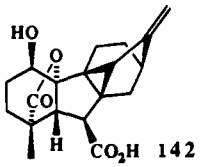


142

1. Fern Antheridiogens from GA_7

Nakanishi et al., had suggested that antheridic acid could well have been formed biogenetically by rearrangement of a 9,10-epoxide.[268] Irrespective of whether this hypothesis had any foundation, the equivalent chemical transformation appeared to be an attractive prospect for gaining access to these rare compounds and the model epoxide **145** was prepared by an intramolecular transfer of oxygen from a 4α-peroxycarbonyl function to the more hindered face of the Δ^9-olefinic bond in **144**, which had been obtained from the 7-methyl ester **143** of gibberellenic acid (**60**). However, treatment with Lewis acids afforded predominantly lactone **146**, while the derived dimethyl ester was converted into diene **147** (Figure 43).[273]

Given the speculative nature of the epoxide initiated rearrangement and the highly functionalized nature of the substrate, this outcome was hardly surprising. An alternative strategy based on an intramolecular alkylation to form a 9,15-cyclogibberellin followed by fragmentation of the C(8)–C(15) bond (Figure 44) was therefore explored.

The successful sequence, beginning with GA_7 (**10**) and culminating with **152**, proceeded smoothly as summarized in Figure 45.[273] The stereochemistry at C(3) was

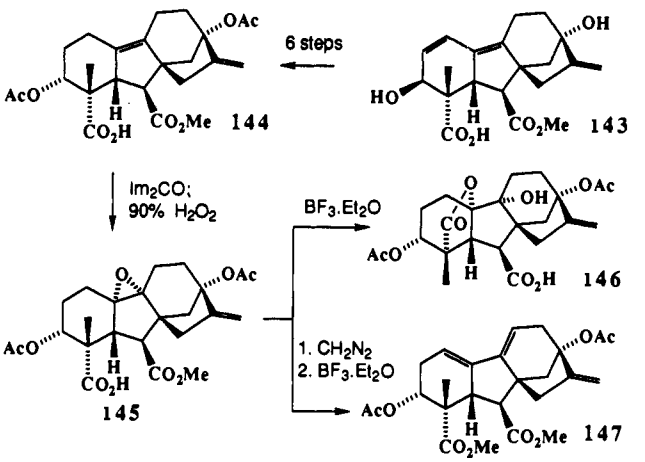


Figure 43. Model study on the attempted rearrangement of a GA epoxide to the antheridane system.

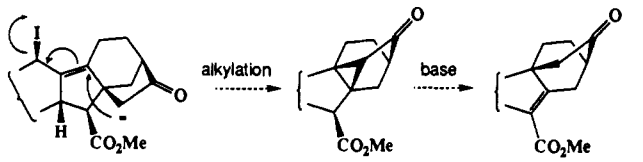


Figure 44. Strategy for the conversion of the GA skeleton into the antheridane system.

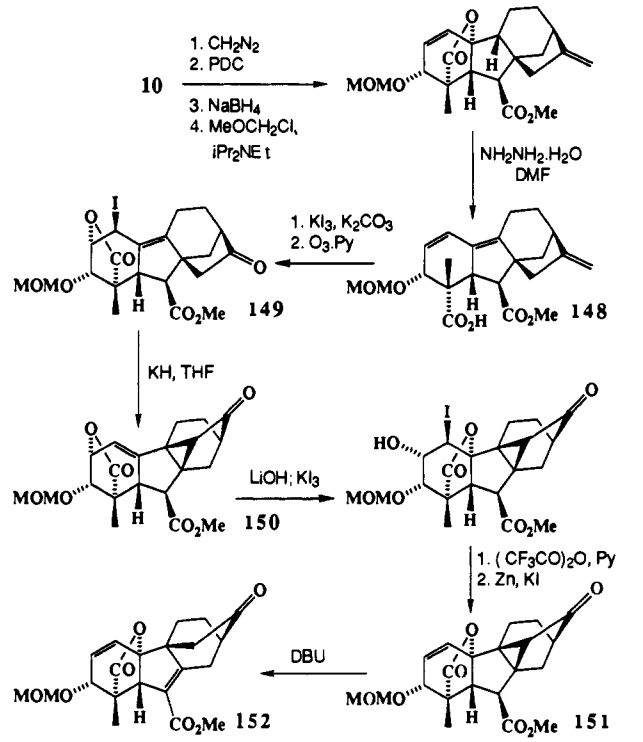


Figure 45. Synthesis of antheridic acid from GA_7: first stage.

inverted by means of an oxidation/reduction cycle, and then, after protection of the 3-hydroxyl, the triene acid **148** was formed by treatment with hydrazine in an analogous way to gibberellenic acid (**60**). Iodolactonization followed by ozonolysis of the 17-methylene group afforded the desired substrate **149** for the intramolecular alkylation to **150**, which was effected with potassium hydride. After reconstruction of the 19,10-lactone function the 17-norantheridane skeleton was obtained by heating ester **151** with DBU.

The latter stages of the antheridic acid (**141**) synthesis are outlined in Figure 46. After selective hydrogenation

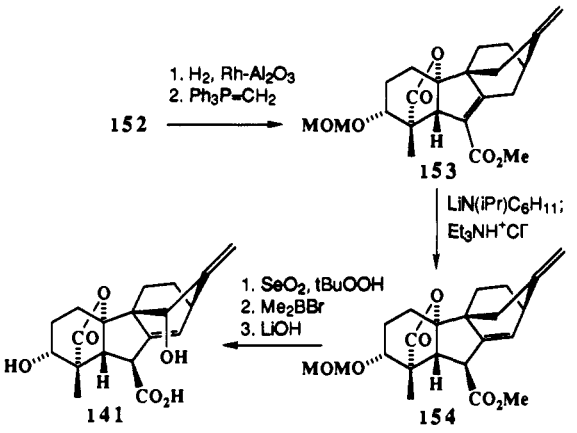


Figure 46. Synthesis of antheridic acid from GA_7: final stages.

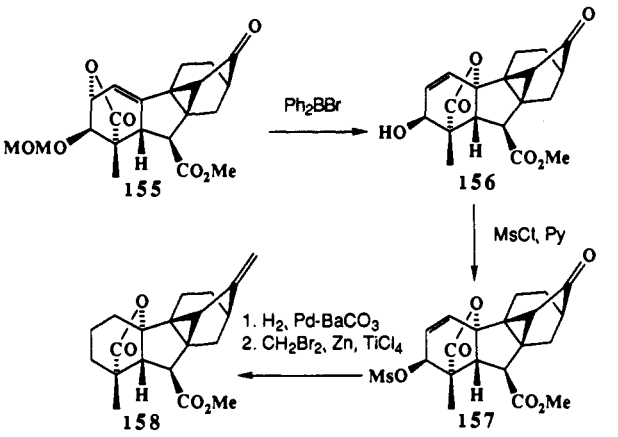


Figure 47. Synthesis of 9,15-cyclo-GA_9.

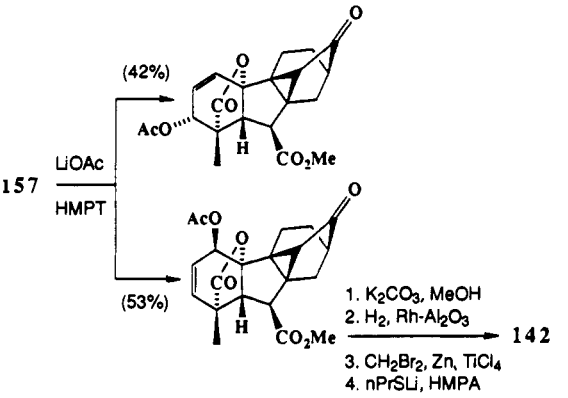


Figure 48. Synthesis of the major antheridiogen from *Anemia mexicana*.

of the A-ring double bond in **152**, the 17-methylene group was restored by a Wittig reaction and then deconjugation of the $\Delta^{6(8)}$-alkene bond by kinetically controlled protonation of the derived ester enolate was examined. Formation of the correct stereochemistry at C(6) appears at first to be problematical, since inspection of models reveals that the upper face of this molecule is the more accessible one, i.e. the 6α-epimer might well be formed. However, stereoelectronic control could be expected to favor protonation along an axiallike trajectory and afford the desired 6β-isomer. In the event only the desired diastereomer **154** was formed, along with recovered **153** (which was separated and recycled). The remaining stereochemical issue of concern in the sequence centered on allylic hydroxylation at C(15), but reaction on the more accessible face of the system was expected, and selenium dioxide/*tert*-butyl hydroperoxide treatment afforded the desired 15β-diastereomer as a 9:1 mixture with its 15α-epimer. Hydrolysis of the methyl ester occurs very much more readily than in most GAs and may be assumed to be assisted by the 15β-hydroxyl.

2. Structure and Synthesis of the Major Fern Antheridiogen from Anemia mexicana

A further antheridiogen isolated by Nester from the related species, *Anemia mexicana* was found from mass spectra to be gibberellin-like and isomeric with GA_7 (**10**).[271] However, the ^{1}H NMR spectrum measured on a ca. 20-μg sample displayed no olefinic resonances apart from those arising from a presumed 17-methylene group. It appeared, therefore, that the degree of unsaturation over and above the standard gibberellin skeleton [as represented by GA_4 (**9**)] might be accounted for by an extra ring, rather than a further olefinic bond, and after taking biosynthetic considerations into account, Takahashi and Yamane concluded that the antheridiogen might be based on a 9,15-cyclogibberellin structure (cf. **142**), tentatively locating the hydroxyl as 2α. However, it was noted that the mass spectrum of the trimethylsilyl methyl ester derivative of the new compound showed a peak at m/z 116 and was therefore more consistent with a 1-hydroxylation pattern (cf. section IV.C). Given this uncertainty, the parent system **158** was prepared (Figure 47) with a view to determining the location of the hydroxyl before proceeding with the synthesis of the new antheridiogen itself.[272] The preparation of **158** was effected by a route which paralleled the preparation of **151**, initially differing only in the stereochemistry at C(3), but during the removal of the methoxymethyl ether protecting group from **155** with diphenylboron bromide,[257] an unexpected rearrangement of the $\Delta^{1(10)}$-19,2-allylic lactone system took place to afford **156** (thereby obviating the need for an additional four steps). This contrathermodynamic process was completely unexpected, but appears to be general for GA derivatives of this type. Functionality was removed from the A-ring and then the usual Wittig reaction to reintroduce the 17-methylene group carried out. When this gave mainly water-soluble material, the Lombardo methylenation which utilizes a complex preformed from a mixture of Zn, CH_2Br_2, and $TiCl_4$ was used instead.[220]

^{1}H NMR comparisons with the natural product indicated that both H(5) and H(15) were deshielded relative to the parent system **158**. It was therefore concluded that the hydroxyl should be located in the 1β-position, i.e. that the new antheridiogen should be formulated as **142**. This was confirmed by the synthesis outlined in Figure 48, beginning with the previous intermediate **157**. The oxygen substituent was introduced into the C(1) position with the desired stereochemistry by means of a syn S_N2' substitution reaction with lithium acetate in HMPA (cf. Figure 25). The synthesis was then completed by hydrolysis, hydrogenation, methylenation, and finally demethylation of the ester function with lithium propanethiolate.[272]

3. Second Generation Syntheses of Fern Antheridiogens from GA_7

A serious deficiency in the preparations outlined above stems from the low yields of the triene acid **148**

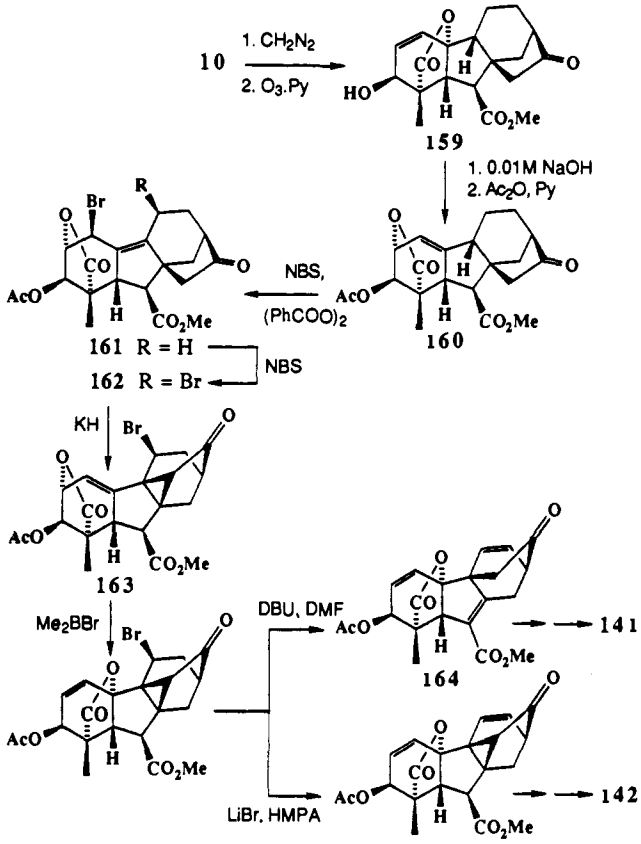


Figure 49. Second generation syntheses of the antheridiogens from *Anemia* spp.

and its analogues. In an attempt to bypass these intermediates, lactone **160** (which may be obtained in 70% yield by treatment of 17-nor-GA_7-16-one methyl ester **159** with 0.01 M NaOH followed by acetylation) was examined as an alternative substrate. It was envisaged that allylic bromination of this substrate with NBS would take place with rearrangement of the olefinic bond to afford the 1-bromo-9-ene **161** which could then serve as an alternative substrate to **149** or its 3-epimer. In any event, it was difficult to prevent further bromination to the 1,11-dibromide **162** and it was more efficient to carry out the intramolecular alkylation on this intermediate (giving **163**) and then to remove the 11-bromo substituent at a later stage by base-induced elimination of HBr, followed by hydrogenation. The resulting sequence (Figure 49) afforded access to both **141** and **142**. When the loss of HBr was effected with DBU, fragmentation of the C(8)–C(15) bond also occurred to yield **164**, which was utilized for the preparation of antheridic acid (**141**). By utilizing bromide ion as the base, however, the cyclopropyl ring could be preserved, opening up an alternative route to the *A. mexicana* antheridiogen **142** as well.[274]

4. Biosynthesis of Antheridic Acid

With the discovery of the antheridiogen **142**[271] it appeared possible that the biogenetic precursor to **141** might be based on the same cyclogibberellin skeleton. Abstraction of a hydrogen atom from C(14) could be expected to result in rearrangement of the resulting cyclopropyl carbinyl radical to a homoallylic system with further oxidation and capture of the C(15) cation by water or some equivalent nucleophile (Figure 50). Strong support for the hypothesis was obtained when

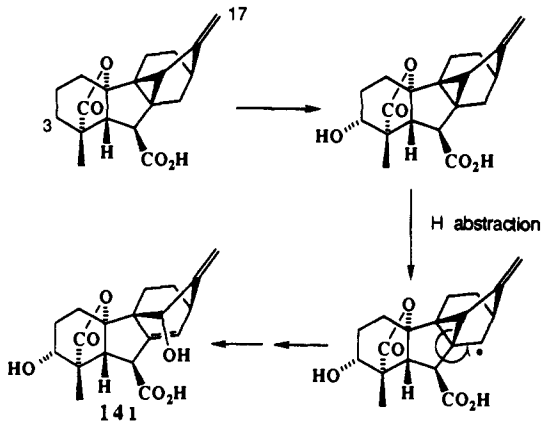


Figure 50. Proposed biosynthesis of antheridic acid.

the 17,17-D_2-acid corresponding to **158** was converted by gametophytes of the fern *Anemia phyllitidis* into the 3α-hydroxy derivative and thence 17,17-D_2-antheridic acid.[276]

VIII. Total Syntheses of GAs

The total synthesis of gibberellins has attracted the attention of numerous research groups and has generated a great deal of creative endeavor.[277,278] Not surprisingly, many approaches have evolved out of earlier work on kaurenoids, especially for the C-20 group of GAs. The first synthesis of a C-19 GA was that of GA_4 (**9**), but this was more a reassembly process using epigibberic acid (**65**) as a relay intermediate.[279] The main interest in the synthesis of the C-19 types has been addressed to GA_3 (**1**) which, because of its highly functionalized nature and propensity for rearrangement, has posed an appealing, but formidable synthetic challenge. It was first synthesized by Corey et al. after some 15 years of sustained effort[195,280] and an interesting account of this work has been provided by Danheiser.[281] Shortly after the disclosure of this major accomplishment in 1978, further successful approaches were reported by Corey[282,283] and by the author.[170,284] The next significant milestone was the preparation of (±)-GA_5 (**32**),[285] while a synthesis of (±)-GA_3 commencing with an intermediate first prepared in the 1960s[286] was completed recently by Yamada et al.[287] There have also been several other syntheses of the same advanced intermediate as that employed by Corey in his latter approaches to GA_3.[288,289]

A. Strategies and Methods

The more popular strategies for the total synthesis of kaurenoids have been based on the addition of the D-ring to a hydrophenanthrene intermediate. The equivalent hydrofluorene based approach to gibberellins is an attractive proposition and has also been widely pursued, but apart from the preparation of several GA degradation products, only four syntheses of this type have been brought to fruition, those of GA_{12} (**8**),[290] (±)-GA_{15} (**18**),[291] and two of GA_3 (**1**).[284,287] In the last two cases the carbon skeleton was assembled in a moderate number of steps, but it was difficult to contain the number of subsequent refunctionalization processes (cf. Figures 61 and 69). More efficient strategies have employed either BCD-tricyclic intermediates[170,280] or, in one case, a CD-bicyclic.[285] It appears that a more

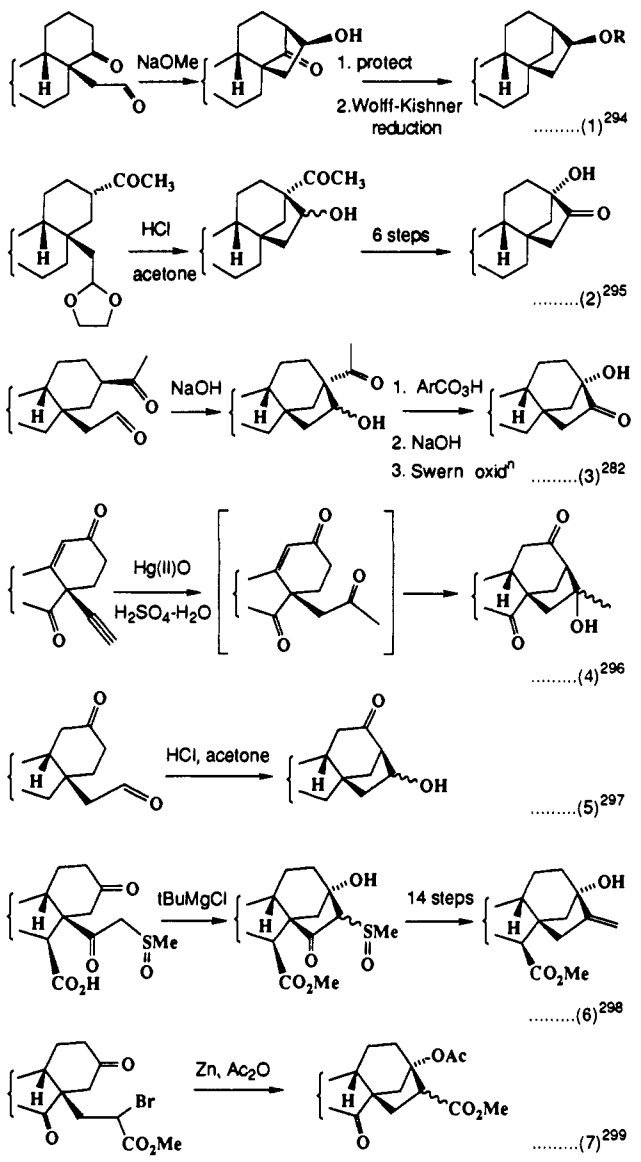


Figure 51. Aldol-based strategies for the construction of the D-ring.

linear approach is more suitable for the assembly of the highly functionalized A-ring in GA_3 (1). The five-membered B-ring has been constructed either directly, or by ring contraction of a cyclohexanoid intermediate with the extruded carbon atom becoming the C(7) carboxyl. The pinacol type of rearrangement described earlier (Figure 42) is one such example of the latter approach,[36] while other methods have been based on a benzilic acid rearrangement,[290,291] the oxidative cleavage of cyclohexene moieties followed by intramolecular aldol condensations,[280,292] and the Wolff rearrangement of α-diazoketones[170,293] (vide infra).

1. Construction of the D-Ring

The main focus for the total synthesis of gibberellins has been the construction of the D-ring with incorporation (as appropriate) of the bridgehead 13-hydroxyl, although in many cases the approaches have not been brought to full fruition. The most popular methods have been based on the intramolecular aldol reaction and a summary is provided in Figure 51 (including some routes which have been developed for the synthesis of the structurally related kaurenoids).

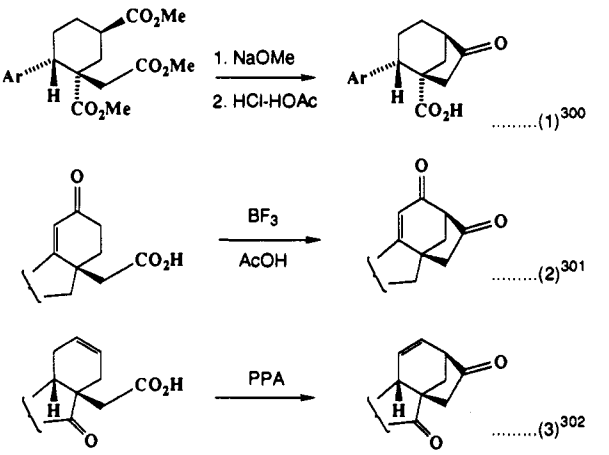
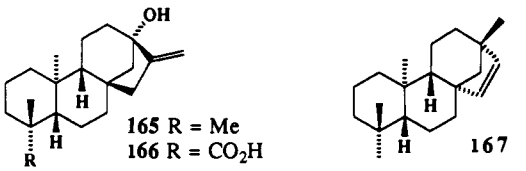


Figure 52. Acylation-based strategies for the construction of the D-ring.

The sequence indicated in entry 1 was originally developed by Ireland et al. for the synthesis of kaurenes[294] and then applied by Fujita to enmein (**137**).[263] The variant on entry 2 was also established by the Ireland group and applied to the preparation of **165**, a model for the synthesis of steviol (**166**) and an intermediate en route to (±)-stachene (**167**).[295] Some difficulty was experienced in cutting back the bridgehead acetyl group, but this was effected efficiently by means of a Beckmann rearrangement of the oxime to the corresponding acetamide followed by rearrangement of the *N*-nitroso derivative to the bridgehead acetate (loss of nitrogen). The equivalent process was accomplished more directly in the Corey–Smith synthesis of GA_3 (1) with a Baeyer–Villiger oxidation.[282]



Entries 4 and 5 indicate methods employed by Takano et al. in the only enantioselective approaches thus far reported for approaches to GA synthesis,[296,297] but the described sequences fall considerably short of the final objective. The conversion indicated in entry 6 has been applied successfully by House et al. to the preparation of (±)-epiallogibberic acid (**62**),[298] while an intramolecular Reformatsky reaction has been reported for a model system by Ziegler.[299] Closely related to these aldol processes have been the acylations summarized in Figure 52,[300-302] but none have been incorporated into a complete synthesis.

More success has been achieved with the alkylation-based methods summarized in Figure 53. The utilization of a bromo ether (entry 1) in a synthesis of GA_{12} (8) is reminiscent of a pivotal conversion in the Masamune syntheses of diterpene alkaloids,[303] while the conversion indicated in entry 2 was an important step in the synthesis of (±)-GA_{15} (18) by Nagata et al.[292] Of the remaining sequences, variants of the diazoketones employed in entries 4 and 5[305,306] were utilized in several completed syntheses of GAs, descriptions of which are provided in section VIII.B and C, while the second of the Pummerer-based cyclizations (entries 6[307] and 7[308]) has provided alternative access to an advanced tricyclic

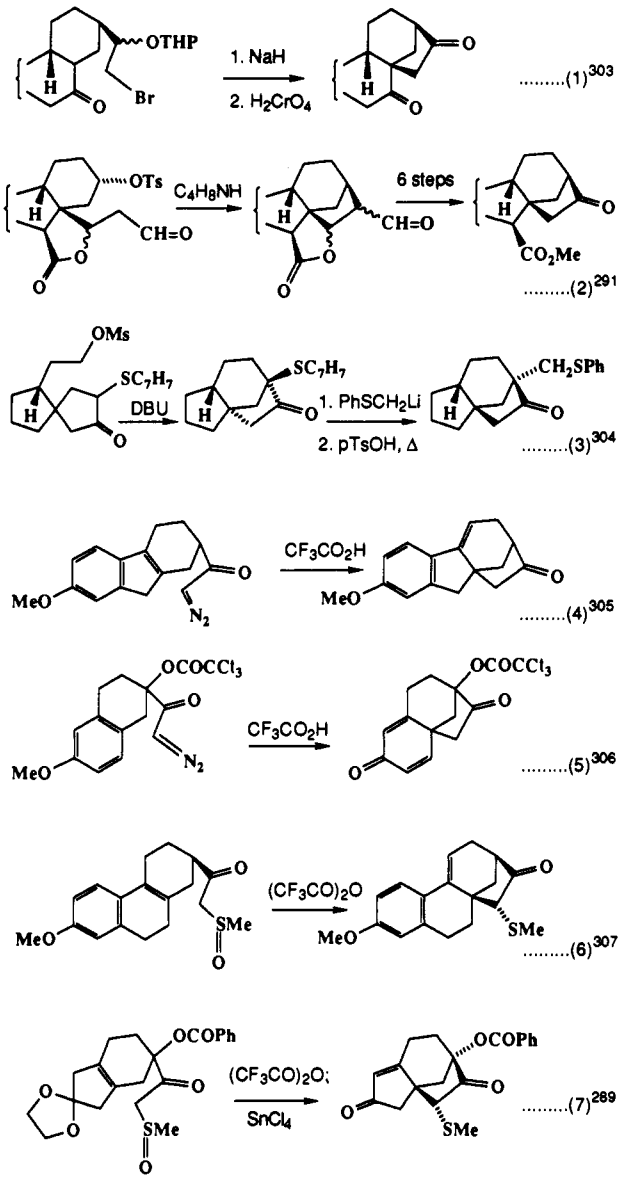


Figure 53. Alkylation-based strategies for the construction of the D-ring.

intermediate which had already been converted to GA_3 (1).[282]

Some of the more direct methods for the preparation of 13-hydroxylated GAs involved the reductive cyclization procedures outlined in Figure 54. Indeed, the very first preparation of the D-ring methylene pentanol moiety which is characteristic of many GAs, is the transformation indicated in entry 1.[308] This remains the most elegant solution to this challenging problem, but has been incorporated into an actual GA synthesis in only a formal sense.[288] The intramolecular acyloin condensation (entry 2) was first applied successfully to the synthesis of steviol (**166**)[309] and then later to the only synthesis of (±)-GA_3,[287] while the related pinacol reaction (entry 3)[310] was used in the first synthesis of GA_3 (1) by Corey et al.[195] The cyclization of a bromoalkene (entry 4)[311] allowed a much more direct approach by the same group,[283] however, and was also employed by De Clercq in a synthesis of GA_5 (**32**).[285] Marinovic used the same functionality in a hydronaphthalene system to initiate a free radical cyclization in a model study (entry 5).[312]

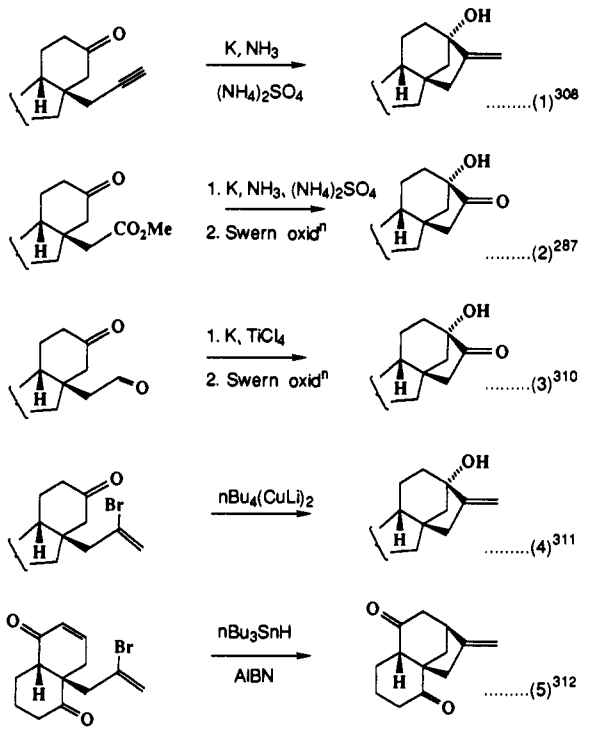


Figure 54. Redox-based strategies for the construction of the D-ring.

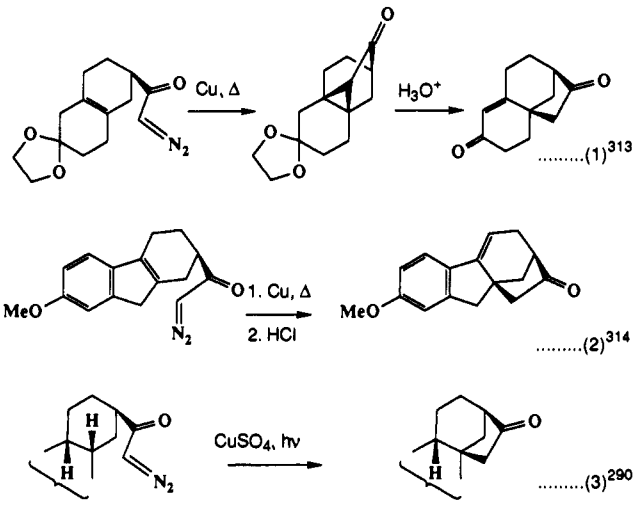


Figure 55. Carbenoid-based strategies for the construction of the D-ring.

Carbenoids derived from diazoketones have been used to cyclopropanate cyclohexene bonds, and then one of the newly formed bonds are selectively cleaved to afford a bicyclo[3.2.1]octanyl skeleton (Figure 55, entries 1[313] and 2[314]), but this approach was quickly superseded by the more direct acid catalyzed approach typified by entry 4 in Figure 53.[305] The CH insertion indicated in entry 3, however, was a crucial step in a synthesis of GA_{12} (**8**).[290]

Several other approaches to the bicyclo[3.2.1]octanyl skeleton involving Wagner–Meerwein rearrangements are summarized in Figure 56. They include the rearrangement of an isomeric [3.2.1] system (entry 1),[186] a bicyclo[3.2.0]heptane-derived intermediate (entry 2),[315] and several bicyclo[2.2.2]octanyl derivatives (entries 3–5).[316-318] The last of these involved reduction of a 1,3-diketone to a dihydroxy cyclopropane followed by fragmentation to the desired ketol as part of a synthesis

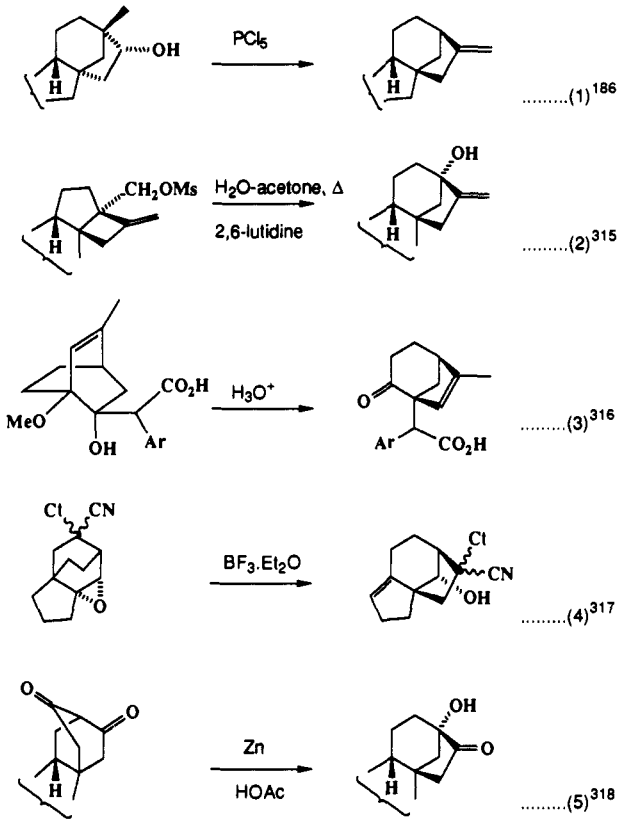


Figure 56. Strategies for the construction of the D-ring based on rearrangements.

of (±)-epiallogibberic acid (**62**). The stereochemical outcome is somewhat surprising, given that the isomeric trans-fused product would be energetically favored.

2. Construction of the A-Ring and Lactone Moiety

Methods for the construction of the A-ring and, as appropriate, the associated lactone function may be conveniently grouped into four distinct types: those involving aromatic A-rings, [4+2] cycloadditions, intramolecular aldol reactions, and intramolecular Michael reactions. The first kind of approach (Figure 57) has had a strong appeal, possibly because of the considerable number of GA degradation products possessing this structural feature. Indeed, much early effort was directed toward the preparation of these products and it is probably no coincidence that the first formal synthesis of a GA utilized epigibberic acid (**65**) as a relay intermediate. A very brief indication of the extensive number of reactions involved is indicated in entry 1.[279] The introduction of a carboxy group into the C(4) position of the A-ring either midway (entry 2)[319] or at an early stage (entry 3)[320] greatly facilitates the elaboration of this part of the molecule, using the Birch reduction with in situ alkylation as a key step; stereochemical control may be exerted by the second carboxy substituent at C(6).[321] The final example in this category (entry 4)[268] was part of the synthesis of (±)-antheridic acid (**141**).

The Diels–Alder reaction (Figure 58) inevitably features in some of the more efficient approaches to the synthesis of GAs. Intramolecular variants are especially effective for the control of stereochemistry and the first synthesis of GA_3 (**1**) employed such an approach (entry 1).[280] The furan-based sequence illustrated in entry 2[285] has been applied with considerable success to both fluorene[285] and phenanthrene[322] derived intermediates. Intermolecular versions have also been pursued (entries 3[323] and 4[287]).

The facile epimerization of the hydroxy function in 3-hydroxy GAs (Figure 15) was rationalized as a retro-aldol/aldol process[168] and inspired the use of the aldol reaction to complete the A-ring in GAs (Figure 59). It was demonstrated by Dolby et al. in the model systems outlined in entries 1[324] and 2,[325] and by Stork for a degradation product of GA_3 (**1**) (entry 3).[172] The 3β-epimer is kinetically favored, but is rapidly isomerized under the reaction conditions to the more stable equatorial 3α-epimer. The aldol approach was subsequently employed in the author's laboratories for the synthesis of several C-19 GAs[170,326] and a C-20 GA as well (entry 4).[327]

The 1,5-relationship between the carbonyl groups at C(4) and C(7) in GAs raises the prospect of a Michael

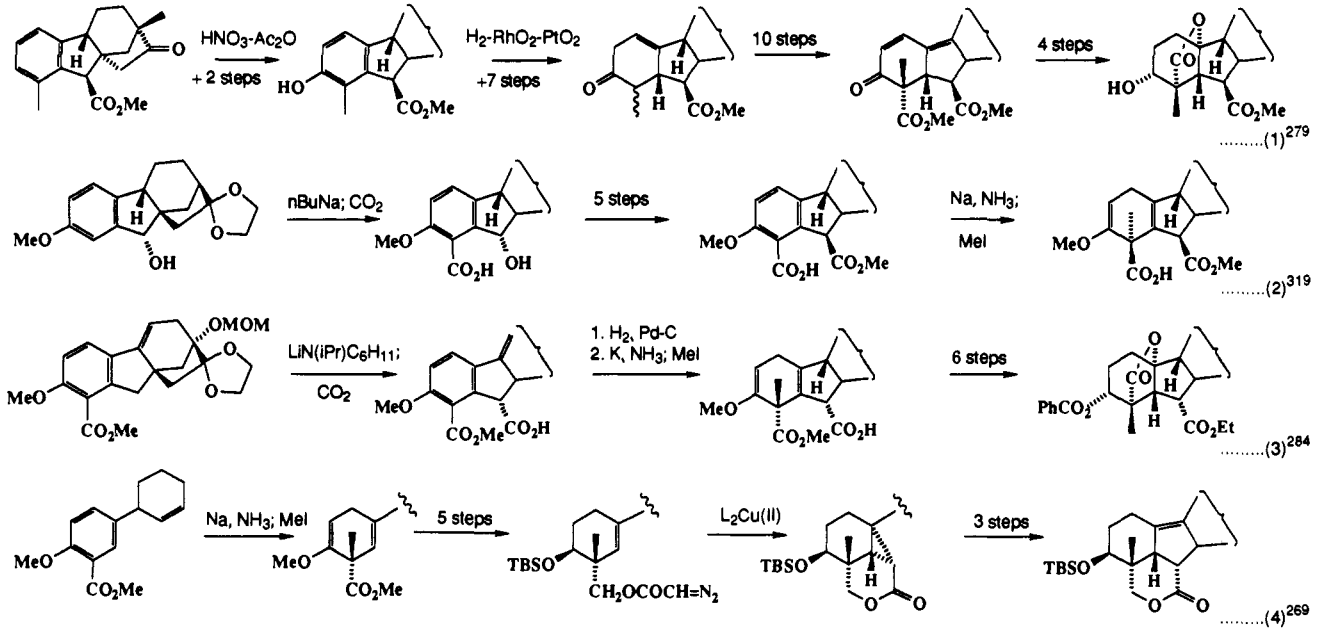


Figure 57. Strategies for the construction of the A-ring based on aryl precursors.

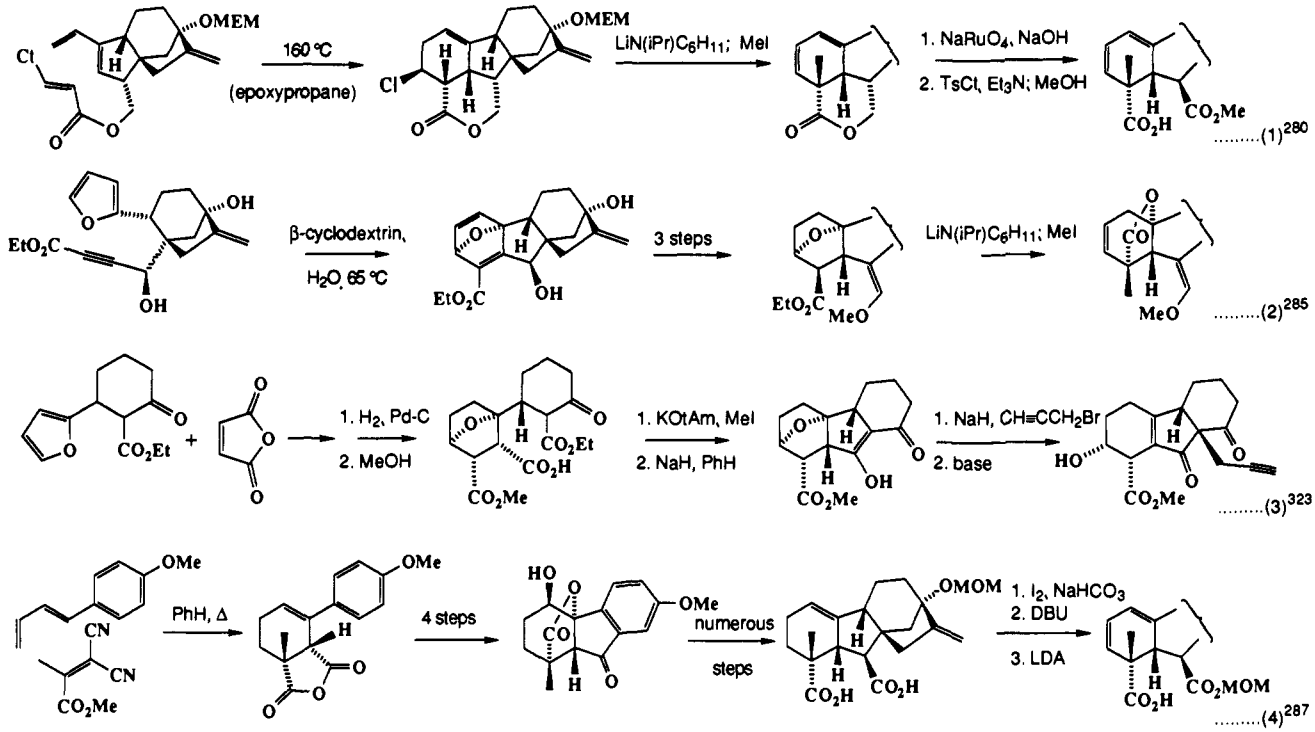


Figure 58. Strategies for the construction of the A-ring based on [4+2] cycloadditions.

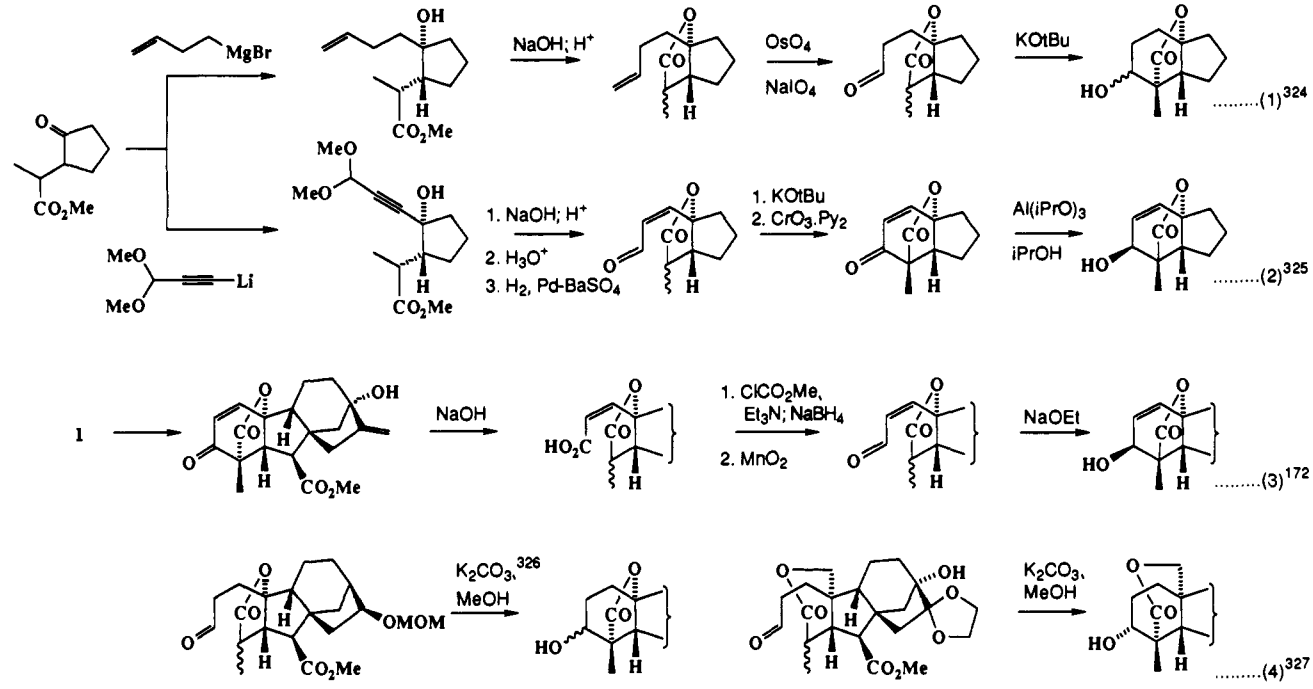


Figure 59. Strategies for the construction of the A-ring based on an intramolecular aldol reaction.

reaction for the construction of either the C(4)–C(5) or C(5)–C(6) bond. No example of the latter conversion has been reported, but the former process has been pursued independently by two groups as illustrated in Figure 60, the sequences in entries 1[328] and 2[326] leading naturally to the aldol step described above. An attempt to utilize a dienone moiety generated from the ipso alkylation of an aromatic B-ring precursor as the Michael acceptor (entry 3) led to an 8,13-*epi*-GA.[329]

B. Total Syntheses of C-19 GAs

The absence of the 20th carbon has encouraged the use of intermediates with aromatic A-rings in the synthesis of C-19 gibberellins, but only two routes based on such intermediates have been brought to a fruitful conclusion. Designs which involve the addition of the A-ring and lactone functions at a late stage have proven to be more effective.

1. Aromatic A-Ring-Based Routes to Gibberellin Synthesis

The first synthesis of a C-19 GA, namely GA_4 (9) was completed in a formal sense by Mori et al.[279] by utilizing epigibberic acid (65) as a starting material. This compound had been made as the racemate by the same group, but no optical resolution was reported.[330] The

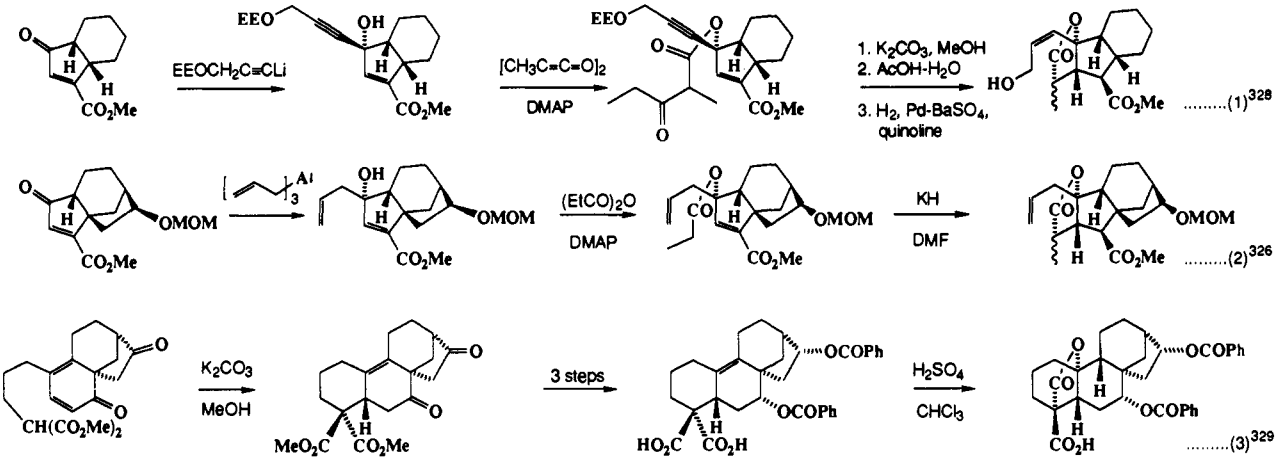


Figure 60. Strategies for the construction of the A-ring based on an intramolecular Michael reaction.

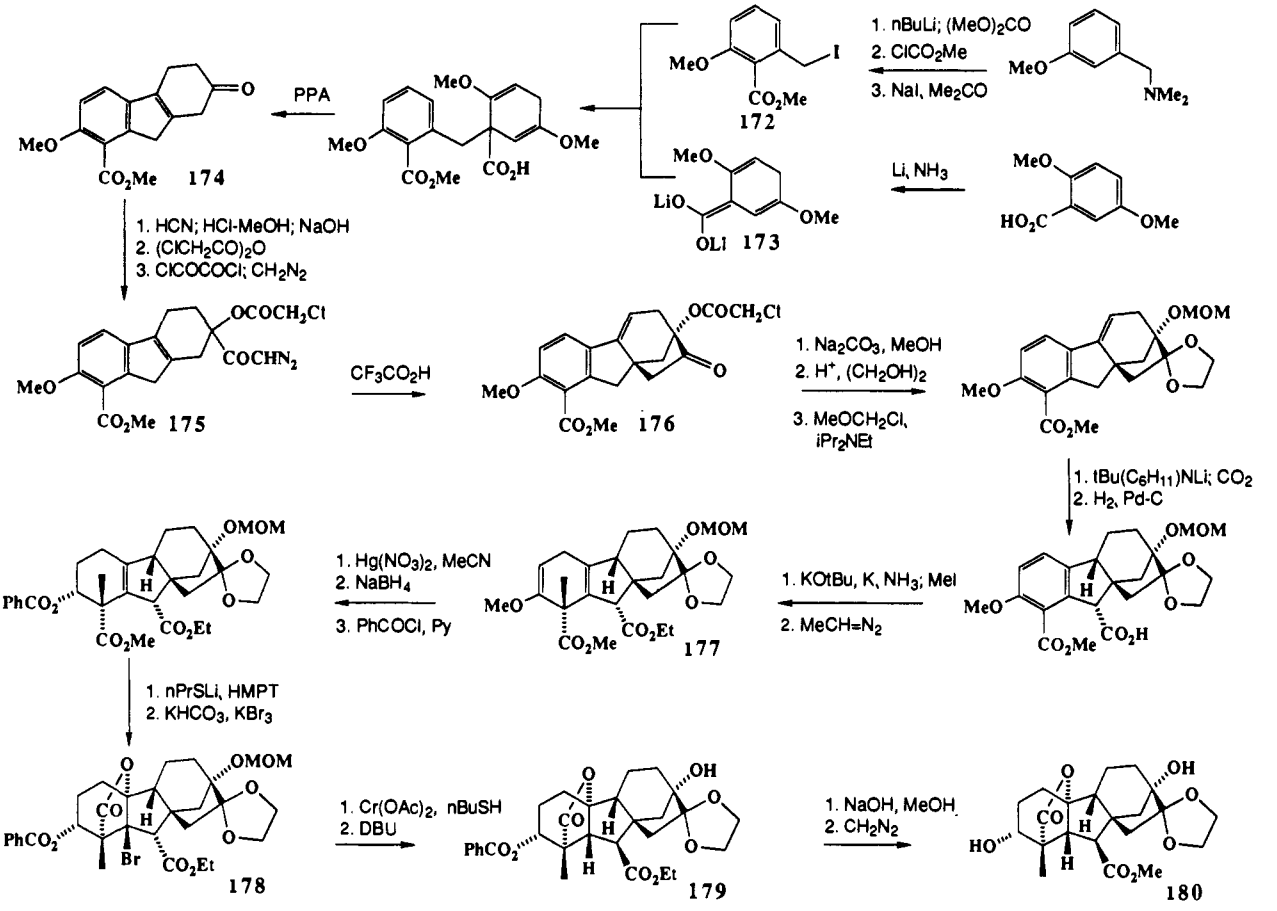


Figure 61. Fluorene-based route to GA synthesis.

synthesis began with hydroxylation of the A-ring at the C(3) position followed by catalytic hydrogenation and then an extensive series of elaborations to various enone intermediates, carboxylation at C(4) and then further manipulation. More efficient strategies were based on the incorporation of the 4-carboxyl into the A-ring at the aromatic stage, however.

After establishing the utility of Birch reductive alkylations on 1-naphthoic acids to form intermediates which could be readily converted into the A-ring/γ-lactone moiety present in almost all naturally occurring C-19 gibberellins,[331] Loewenthal et al. prepared the advanced intermediate **168**[301] and carried out a reductive methylation.[332] Although the work was never completed, some of the methodology developed for the preparation of **168** was incorporated into the successful synthesis of GA_3 outlined in Figure 61. In an independent study, Baker and Goudie arrived at a similar intermediate, namely **169**, but found the product of the reductive alkylation, **170**, to be very unstable, undergoing oxidative decarboxylation to the toluene derivative **171**.[319] Apart from these difficulties, however, it seems unlikely that either of these intermediates would have led to a natural GA, since House et al. established in model substrates that, in order to achieve the desired stereochemistry at C(4), it would probably be necessary to carry out the reductive alkylation on the 6α-epimers.[321] Indeed, this expectation was confirmed

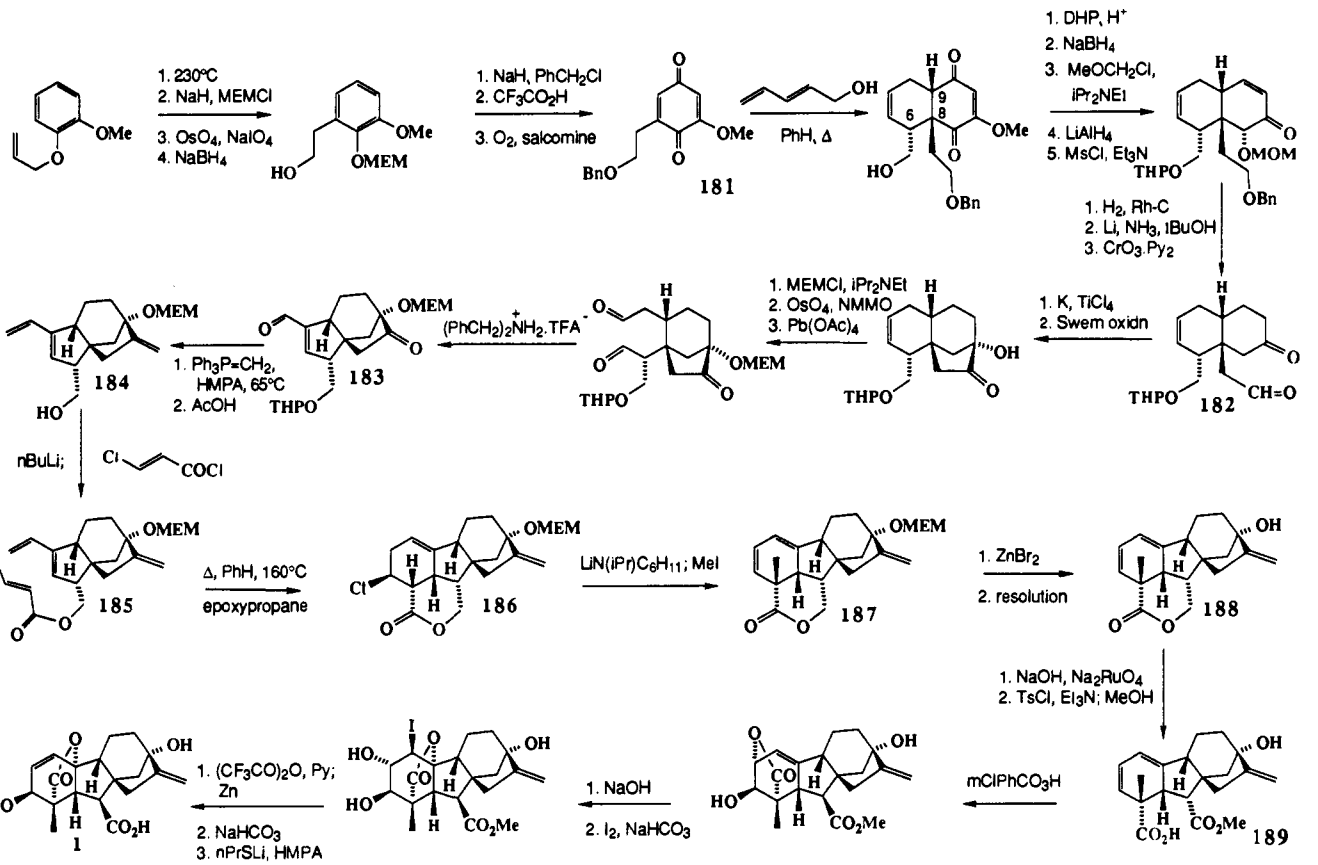
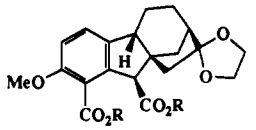
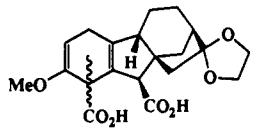


Figure 62. Intramolecular Diels–Alder Route to the synthesis of gibberellic acid GA_3.

when a formal total synthesis of GA_3 (1) along these general lines was brought to completion.



168 R = Me
169 R = H



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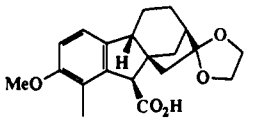

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In this synthesis (Figure 61),[284] the assembly of a suitable hydrofluorene precursor began with the reduction of 2,5-methoxybenzoic acid followed by alkylation with the benzylic iodide **172**, the adduct from which smoothly cyclized in polyphosphoric acid with concomitant decarboxylation to form **174**. Iodide **172** readily cyclizes to a phthalide, so the use of the highly nucleophilic enediolate **173** as a more reactive synthetic equivalent of a ketone enolate was crucial. Building on earlier studies, **174** was converted into diazoketone **175** which underwent acid-catalyzed cyclization to the tetracyclic ketone **176**. After protection of the D-ring functionality the C(6) benzylic position was carboxylated using the Loewenthal methodology,[301] the $\Delta^{9(11)}$-olefinic bond reduced, and the Birch reductive alkylation at C(4) executed with complete diastereoselectivity to afford **177**. The 6α stereochemistry from the carboxylation step ensured that both hydrogenation of the $\Delta^{9(11)}$-ene bond and alkylation at C(4) occurred on the upper face as desired. Protection of the B-ring carboxyl as the ethyl ester allowed selective cleavage of the A-ring methyl ester with thiolate[206] and hence elaboration of the lactone function. Once this was in place, it was possible to correct the stereochemistry at C(6) by equilibration to the thermodynamically more stable 6β-epimer **179**. Hydrolysis and reesterification then afforded **180** which had already been converted into GA_3 (1) (cf. Figure 67).[170]

2. BCD + A-Ring Approaches

a. Intramolecular Diels–Alder Route to the Synthesis of GA_3 (1). The first synthesis of gibberellic acid, GA_3 (1), was completed by Corey and co-workers and is outlined in Figure 62.[195,280] A pivotal step in this synthesis was the addition of the A-ring by means of the intramolecular Diels–Alder reaction **185** → **186**. The synthesis of the precursor vinyl carbinol **184** was carried out by means of a 23-step sequence from anisole, one of the more important steps of which was the Diels–Alder reaction between the quinone **181** and (*E*)-2,4-pentadien-1-ol, thereby establishing the correct relative stereochemistry between pro-C(6), C(8), and C(9). It also established a double bond in the B-ring where it could be subsequently cleaved at a later stage and then reclosed by means of a carefully controlled aldol condensation to furnish the α,β-unsaturated aldehyde **183**. This was subjected to a double Wittig methylenation and the product hydrolyzed to give the target carbinol **184**. A further feature of this synthesis was the pinacol reduction of the keto aldehyde **182** to form the D-ring with incorporation of the bridgehead hydroxyl.[310]

Carbinol **184** was converted into the β-chloroacrylic ester **185** and thence the pentacyclic lactone **186** by

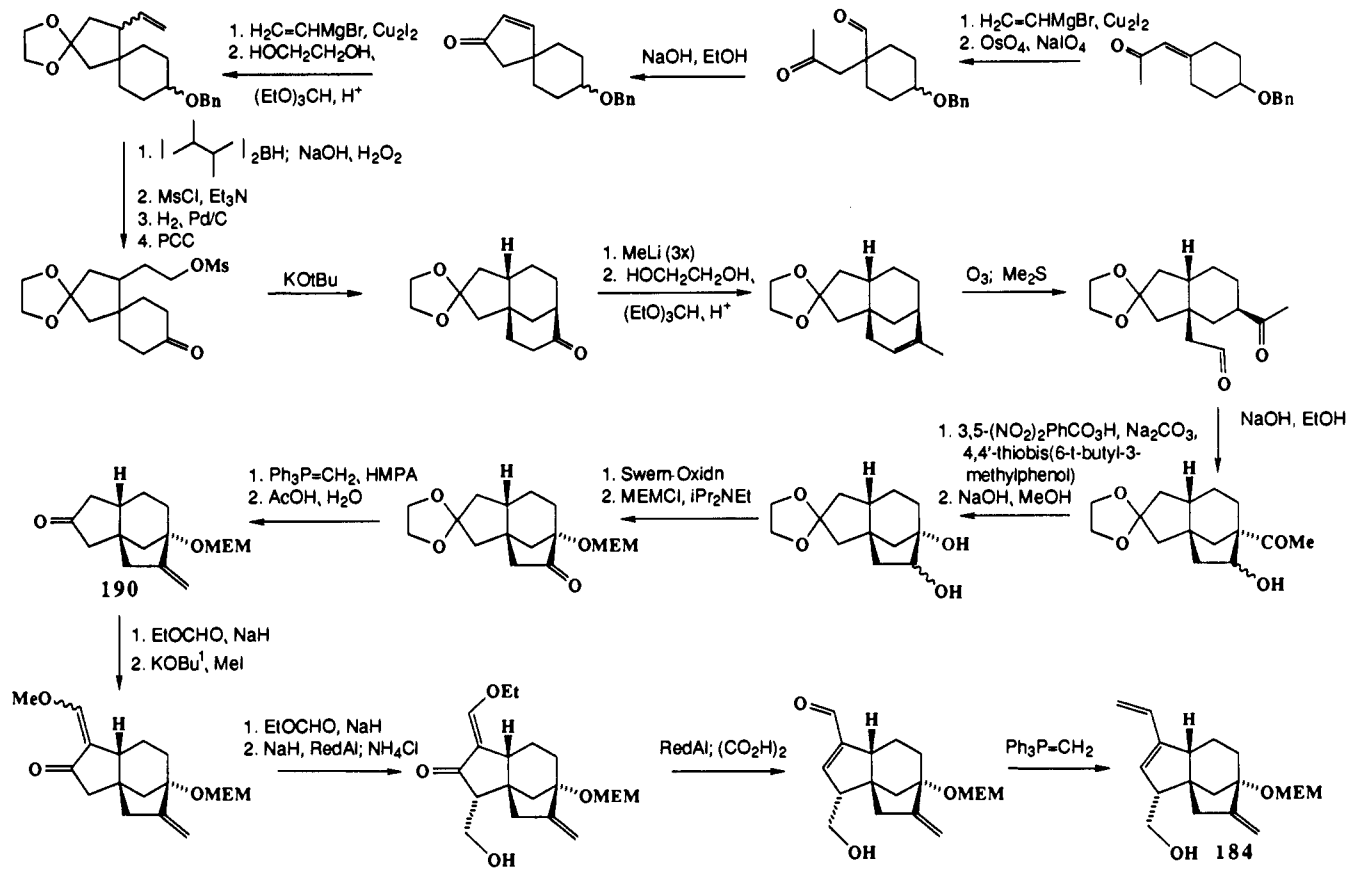

Figure 63. Alternative route to a key intermediate for the synthesis of GA_3.

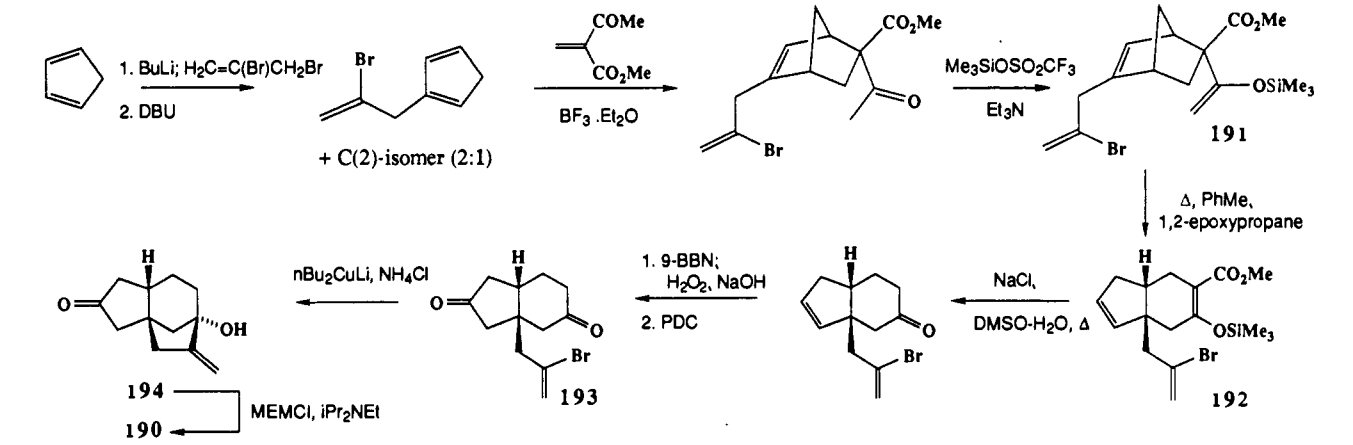

Figure 64. An improved synthesis of the key intermediate **192**.

heating to 160 °C in benzene with propylene oxide as an acid scavenger. The intramolecular nature of the process guaranteed the development of the correct relative stereochemistry at C(5) and, because of the convexity this imposed on the upper face of the enolate anion derived from the lactone function, ensured that C-methylation at C(4) would subsequently take place in the desired stereochemical sense to furnish **187**. The MEM protecting group was removed from this material to allow derivatization with (−)-α-phenethylamine, furnishing a mixture of diastereomeric carbamates which could be separated chromatographically,[333] ultimately effecting an optical resolution of (±)-carbinol **188** once the carbamate function had been removed. The (+)-enantiomer was then converted into the half-ester **189**, thereby completing the formal total synthesis of GA_3 (**1**), since **189** had been previously obtained as a degradation product from GA_3 and reconstituted[183] as outlined above.

In an attempt to improve upon the preparation of **184**, further syntheses were undertaken by Corey and his co-workers. The first of these is outlined in Figure 63,[282] and although it proved to be more protracted than the previous one, the elaboration of the tricyclic skeleton from a spirocyclohexane precursor is an interesting departure from more traditional routes. A similar strategy had also been pursued earlier by Trost and Latimer.[304] A subsequent approach (Figure 64) to **184** via the same intermediate ketone **190**, however, proved to be very much more direct, saving nine steps over the original synthesis.[283] The pivotal step in this new route was the oxy-Cope rearrangement of the norbornene derivative **191** to afford the cis-fused indene **192**, from which dione **193** was obtained by a regioselective hy-

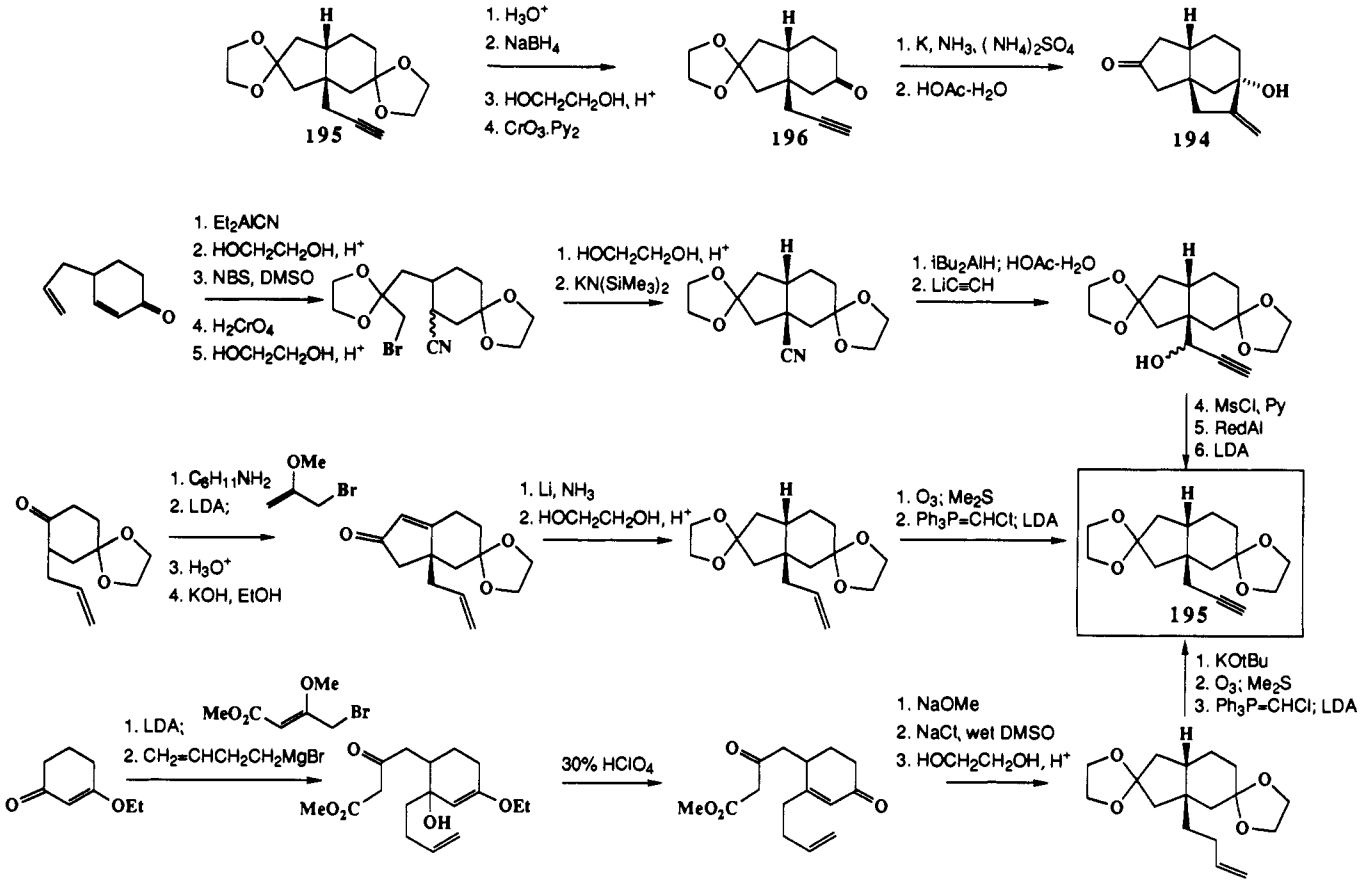

Figure 65. Further preparations of the tricyclic ketone **196**.

droboration followed by oxidation. A selective intramolecular cyclization to the desired ethanoindene **194** (a result which had been predicted from molecular mechanics calculations to be 2 Kcal/mol more favorable than the alternative cyclization onto the cyclopentanone carbonyl group) followed by protection afforded **190**. The tricyclic ketone **194** had also been prepared previously by Stork et al. by several different approaches[288] converging on the reductive cyclization of the acetylenic ketone **196** to **194** (Figure 65) and more recently by Barco et al.[289]

b. Intramolecular Michael/Aldol Based Approach to the Synthesis of (±)-GA_1 (*31*) *and* GA_3 (*1*). Model studies by Dolby et al. had established the feasibility of completing the A-rings of GA_3 (**1**) and GA_1 (**31**) by forming the C(3)–C(4) bond by an aldol reaction.[324,325] Stork and Singh had also achieved this conversion on a degradation product of GA_3 (**1**) (cf. Figure 59).[172] The 1,5-relationship between the carbonyls of the lactone and 7-carboxy functions in these seco-aldehydes led naturally to the possibility of using a Michael reaction for forming the C(4)–C(5) bond (cf. entries 1 and 2, Figure 60), and once it had been established that the D-ring could be added very efficiently to a hydronaphthalene intermediate by means of an intramolecular ipso-alkylation with a protonated diazoacetyl function (cf. entry 5, Figure 53), a powerful strategy for the synthesis of C-19 GAs began to take shape. This was carried out as outlined in Figure 66, culminating in the synthesis of (±)-GA_1 (**31**).[170] The racemate of GA_4 (**9**) was prepared in an analogous way,[326] and the methodology extended to the synthesis of C-20 GAs as well (vide infra). Noteworthy features of the sequence are the initial diazoketone cyclization, the direct method for formation of the α-diazocyclohexanone moiety[334] as a prelude to the Wolff ring contraction, and the unusual ester-based intramolecular Michael reaction. The crucial cis B–C-ring fusion was established at the hydroboration step and then the convexity of the upper face of the product ensured addition of the allyl fragment in the desired stereochemical sense. The intramolecular nature of the ensuing steps guaranteed that the correct stereochemistry was also obtained at C(5) and C(4). Ironically, the more speculative steps in the synthesis proceeded smoothly, while most difficulty was experienced with the addition of nucleophiles to the cyclopentenone function in **197**. The carbonyl function was especially prone to enolization, severely limiting the choice of a suitable precursor synthon for addition of the C(1)–C(3) fragment. However, the problem was solved with the addition of triallylalane, the success of which might be attributable to the S_E2' mode of addition.

For the purpose of synthesizing GA_3 (**1**) (Figure 67), the aldol product **180** and its 3β-epimer were both converted into the Δ^2-olefinic ketal **198** by elimination of a 3-phenylsulfonate function. **198** was subjected to a Pirkle resolution[333] as in the Corey synthesis and converted into diol **199** and then bromobenzoate **201** by treatment of the benzyl acetal **200** with NBS. Elimination of the bromide group with DBU proceeded smoothly, as did liberation of the 16-carbonyl group, but the Wittig reaction on allylic benzoate **202** to form **204** was complicated by the formation of triene **203** as a consequence of the intervention of the retro-aldol reaction which had been well known for GA_1 (**31**), but not

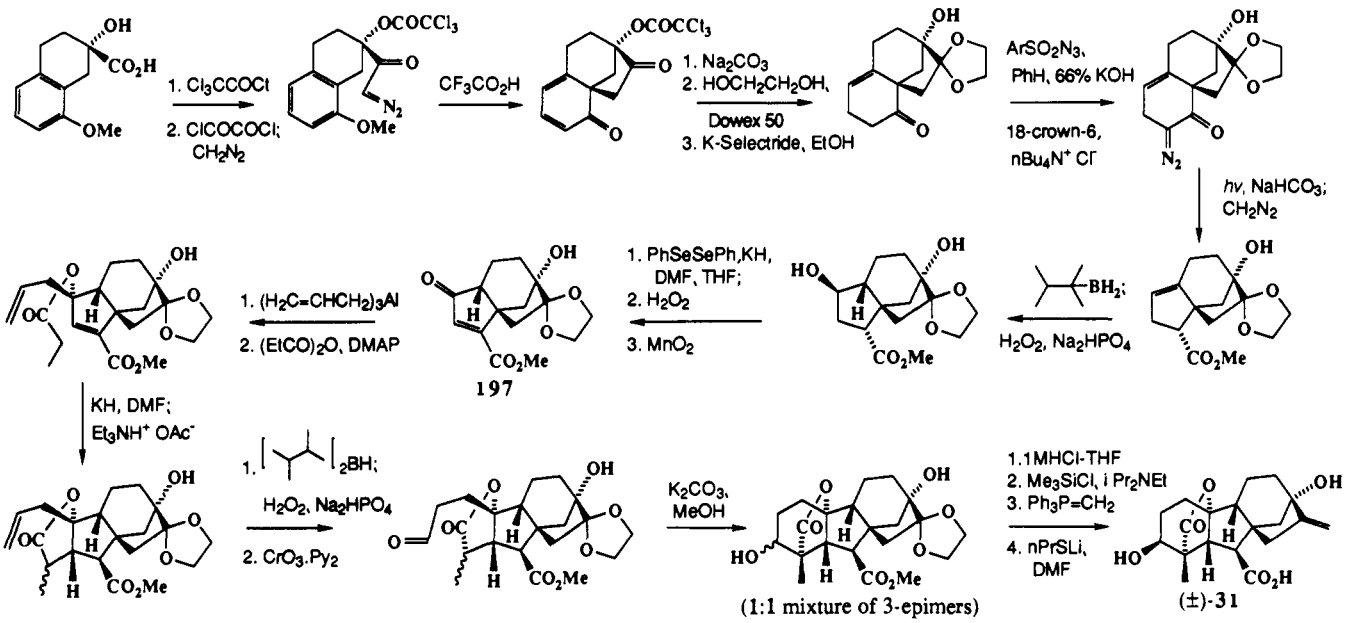

Figure 66. Michael/aldol route to the synthesis of (±)-GA_1.

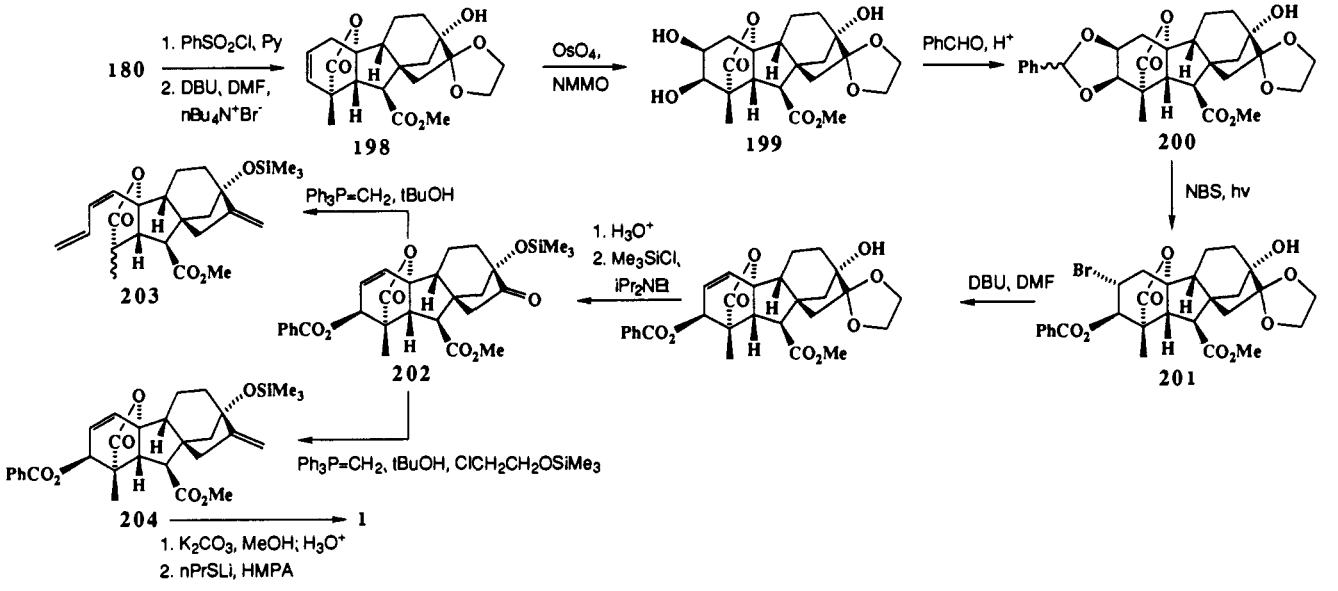

Figure 67. Synthesis of GA_3 (1) from a gibberellin Δ^2-ene intermediate.

for Δ^2-ene derivatives. The problem was most effectively solved by the addition of (2-chloroethyl)trimethylsilane which served as a "buffer" toward the *tert*-butoxide base in equilibrium with the phosphonium ylide.[171]

3. A Further Intramolecular Diels–Alder-Based Approach to the Synthesis of GAs: Synthesis of (±)-GA_5 (32)

De Clercq and his co-workers have made especially effective use of intramolecular Diels–Alder reactions of furans in the construction of several natural products,[335] a strategy which has afforded an especially direct approach to the total synthesis of C-19 gibberellins. The preparation of (±)-GA_5 (**32**) from 3-methoxybenzoic acid outlined in Figure 68[285] hinged on the cycloaddition of **205**. The kinetic product **206** tended to isomerize to the 3β,10β-epimer **207** in boiling benzene, but this could be avoided by conducting the reaction at 65 °C in an aqueous medium in the presence of β-cyclodextrin. A second synthesis of (±)-GA_5 **32** has also been achieved recently by the same group using this Diels–Alder methodology, but via an analogous ethanophenanthrene intermediate, the conversion to the gibberellin framework being effected by means of a Wolff rearrangement of a B-ring α-diazo ketone.[293]

4. An Intermolecular Diels–Alder-Based Approach to the Synthesis of (±)-GA_3 (1)

This final example of a total synthesis of a C-19 GA (Figure 69)[287] also utilizes a Diels–Alder reaction, but of the normal intermolecular variety. It was used in the assembly of a hydrofluorene intermediate to which was added the elements of the D-ring by means of a [2+2] cycloaddition of allene to the C-ring cyclohexenone moiety, following the work of Wiesner et al.[336] The D-ring was closed by means of an intramolecular acyloin condensation and then after a series of functional group

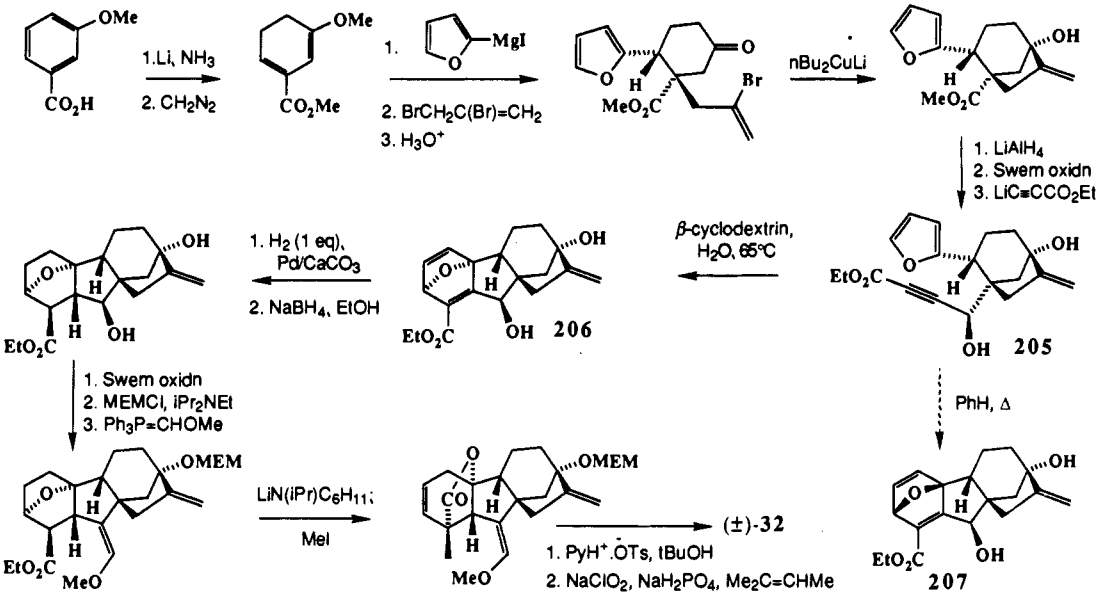

Figure 68. A highly efficient synthesis of (±)-GA_5 (32).

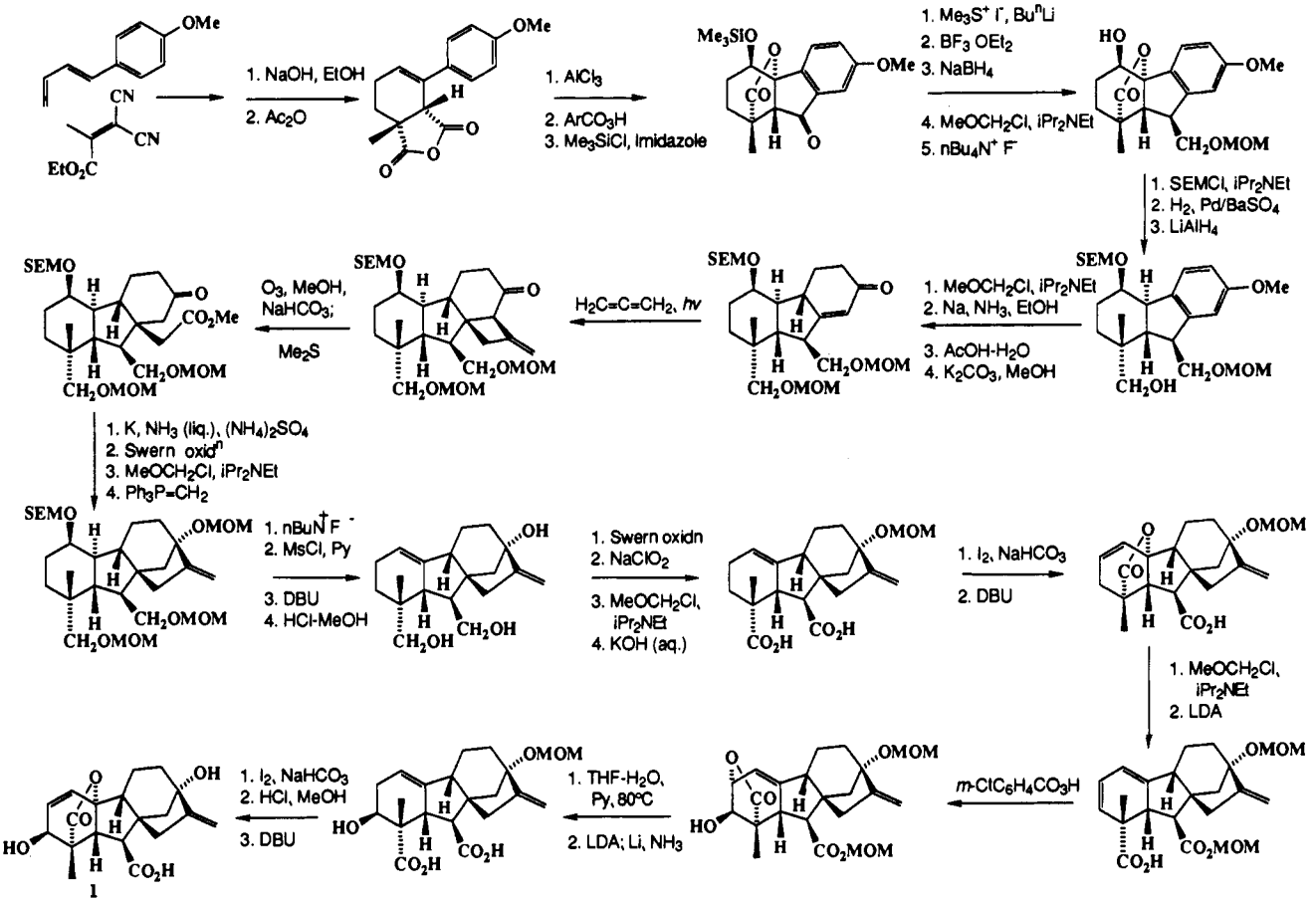

Figure 69. Synthesis of (±)-GA_3 (1).

modifications, the sequence was completed in a similar fashion to the approach used by Corey.

C. Total Syntheses of C-20 GAs

All but one of the total syntheses of C-20 GAs have been based on a tricyclic intermediate with an aromatic C-ring. The exception is the translation of the Michael/aldol strategy which had been so effective in the synthesis of C-19 GAs (Figure 66).[327]

1. Syntheses of Gibberellin A_{12} (8)

Gibberellin A_{12} (8) is the simplest of all gibberellins and the biosynthetic prototype. By utilizing the phenanthrene ester (208) which had been an intermediate in an earlier synthesis of (±)-kaurenoic acid (14),[337] Mori et al. were able to prepare the racemate[303] of the dioxo ester (209) which had been converted by Galt and Hanson into the norkaurenolide 210 (Figure 70).[258] The conversion of the kaurenolide into gibberellin A_{12}

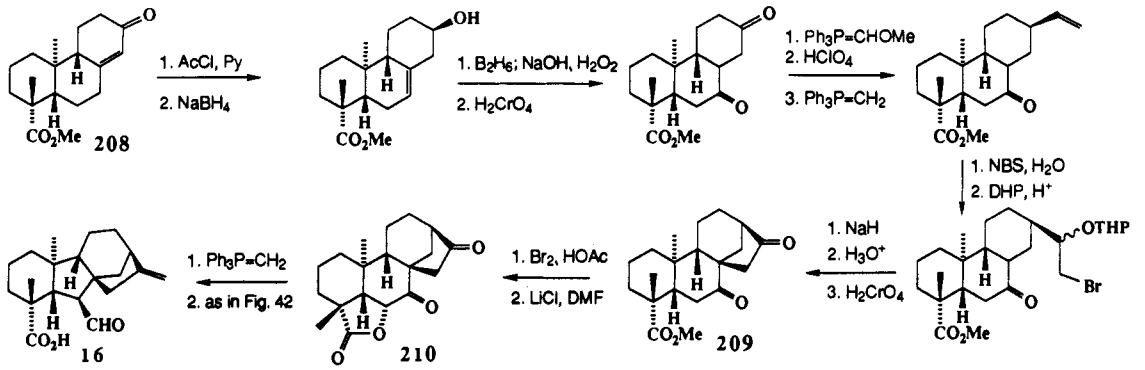

Figure 70. A formal total synthesis of GA_{12} aldehyde (17).

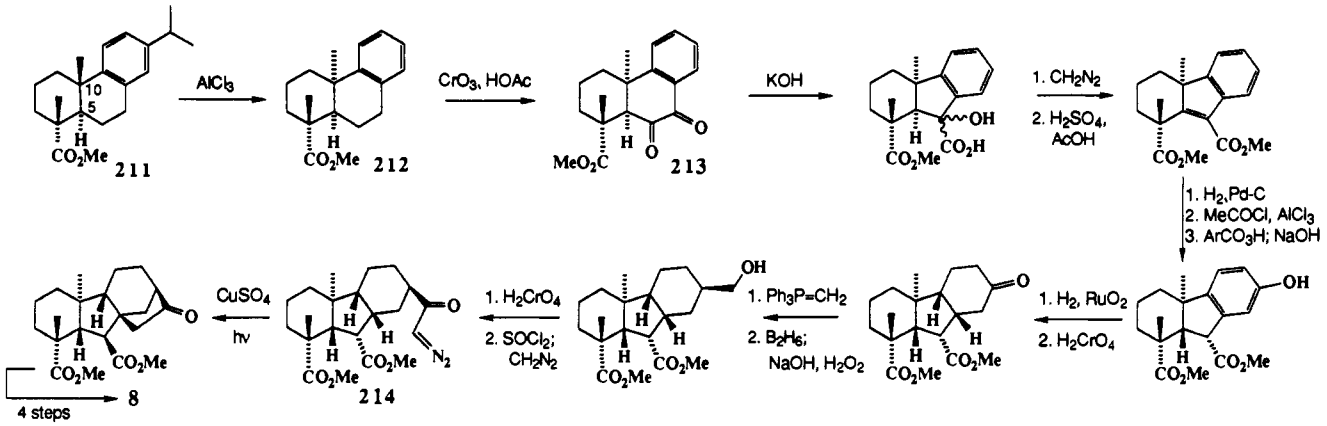

Figure 71. The synthesis of GA_{12} (8) from dehydroabietic acid.

aldehyde (16) has been described earlier (Figure 42).

Methyl dehydroabietate (211) is antipodal to the gibberellins at C(5) and C(10), but during a retro-grade-Friedel–Crafts removal of the isopropyl group, inversion occurs at C(10) to afford ester (212), which thus becomes a feasible, enantiomerically pure substrate for the preparation of GA_{12} (8). The synthesis was completed by Ohtsuka and Tahara as outlined in Figure 71.[290] The important features of this synthesis are the benzilic acid type of rearrangement on diketone (213) and the carbenoid insertion into the C-8βH bond in (214).

2. Total Synthesis of (±)-GA_{15} (19)

The synthesis of (±)-GA_{15} (19) by Nagata et al. (Figure 72)[205] was the first genuine total synthesis of a gibberellin and established a significant milestone in the field. It extended over 35 steps from the tetracyclic amine 215 which had been utilized in earlier studies on the total synthesis of diterpene alkaloids. Unfortunately, the choice of 215 as a starting material led to a major inefficiency at a late stage in the synthesis: although model studies promised a more encouraging outcome, transformation of the piperidine ring into the δ-lactone function of the target molecule proceeded without regiochemical control and in only 5% yield. In the early stages of the synthesis, standard procedures led to the B-ring olefin 216 which was subjected to ozonolysis followed by a careful aldol reaction to afford the hydrofluorenone 217. After transformation to the enone 218, elaboration of the D-ring was carried out on the basis of methodology developed earlier by the same group, i.e. 1,4-addition of HCN through the agency of diethylaluminum cyanide,[338] and homologation of aldehyde 219 with diethyl [(cyclohexylamino)vinyl]-phosphonate anion,[339] to afford enal 220. This was further elaborated to 221 and then Wolff–Kishner reduction proceeded with migration of the olefinic bond to furnish the methylene derivative 222. The last stages were based on a procedure developed by ApSimon[340] and afforded the isomeric lactones 223 and 224. Demethylation was effected by lithium iodide in collidine and it was of considerable interest to find that (±)-GA_{15} (18) had half of the biological activity of the natural material in the Tanginbozu rice growth bioassay. The isomeric lactone acid derived from 223 was inactive.

3. Total Synthesis of (±)-GA_{38} Methyl Ester (232)

This synthesis (Figure 73)[327] was based on procedures developed from methodology originally conceived for the construction of C-19 gibberellins. It also utilized a common intermediate from this earlier work. Two of the more important steps were the Michael reaction 228 → 229 and the aldol reaction 230 → 231, homologous variants of processes which had proved to be so effective in the total synthesis of (±)-GA_1 (cf. Figure 66). These conversions were just as effective as before, although the aldol reaction was much slower, presumably a consequence of the lower acidity of H(4) in the δ-lactone function. As expected from the C-19 GA syntheses, the introduction of C(20) into ketone 225 proved to be the most troublesome transformation. Most organometallic reagents led to enolization rather than addition, while less basic reagents, e.g. phosphoranes and sulfuranes led to proton exchange and epimerization at pro-C(9). The problem was solved by a modification of the Nozaki–Oshima methylenation,[220] following which, hydroboration and oxidation afforded aldehyde 226. The

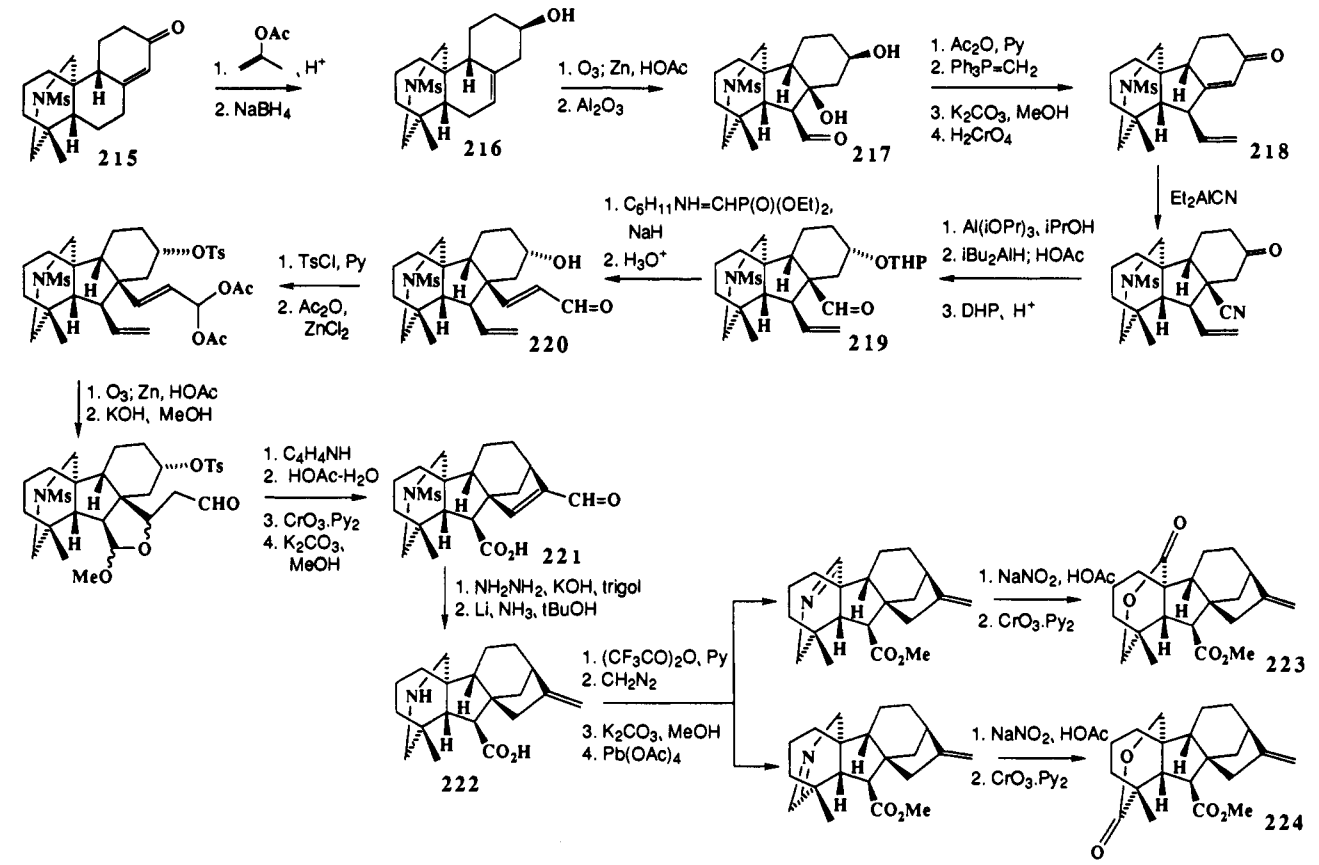

Figure 72. Total synthesis of (±)-GA_{15} (19).

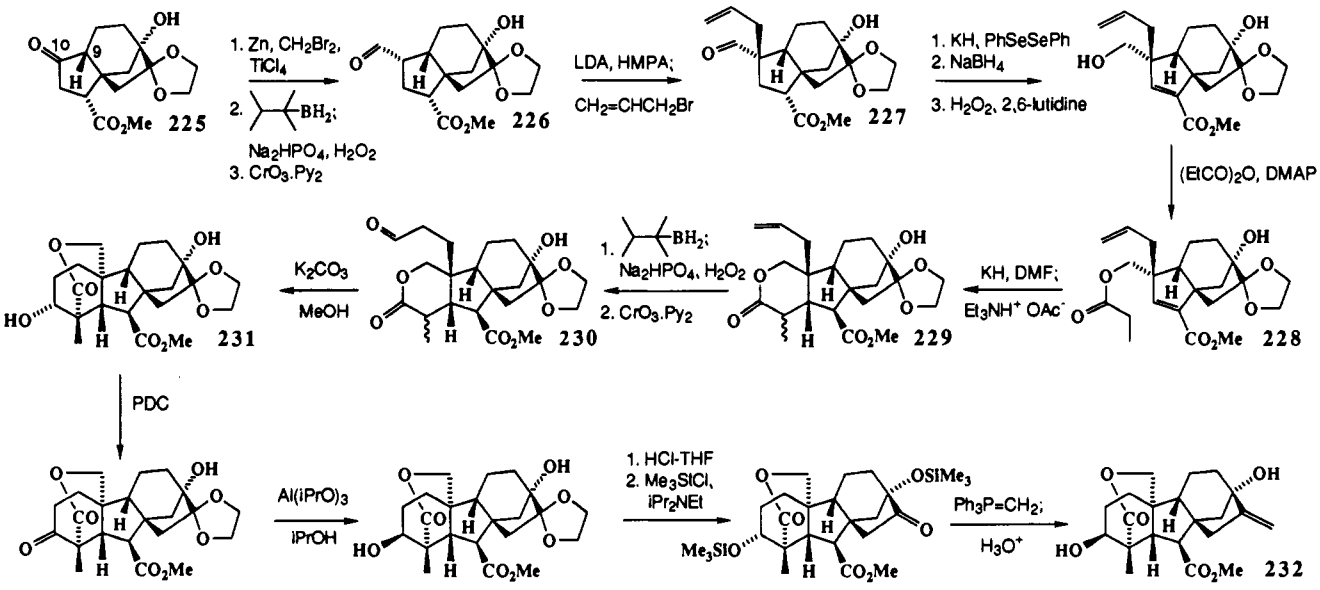

Figure 73. Total synthesis of (±)-GA_{38} methyl ester (232).

convex upper face of 226 ensured that alkylation of the derived enolate anion took place in the desired way to afford only aldehyde 227 with the correct relative configuration at pro-C(10).

D. Fern Antheridiogens

Only one total synthesis of this group of gibberellins has been reported, that of (±)-antheridic acid (141) and its 3β-epimer.[269] The latter structure had been deduced from degradative studies[268] and was the first objective of this study. When it was compared with the natural substance, however, it became apparent that the structure should be 141. This was then prepared and shown to be correct. The sequence (Figure 74) began with a coupling of (η^3-cyclohexenyl)nickel bromide to the methyl ether of methyl 4-iodosalicylate and then the beginnings of the A-ring functionality elaborated by means of a Birch reduction. Following the intramolecular cyclopropanation 233 → 234, the B-ring was formed by a Lewis acid-catalyzed vinylcyclopropane → cyclopentene rearrangement, i.e. 235 → 236, and then the bicyclo[2.2.2]octenyl ring system in the rest of the molecule was constructed by yet another Diels–Alder

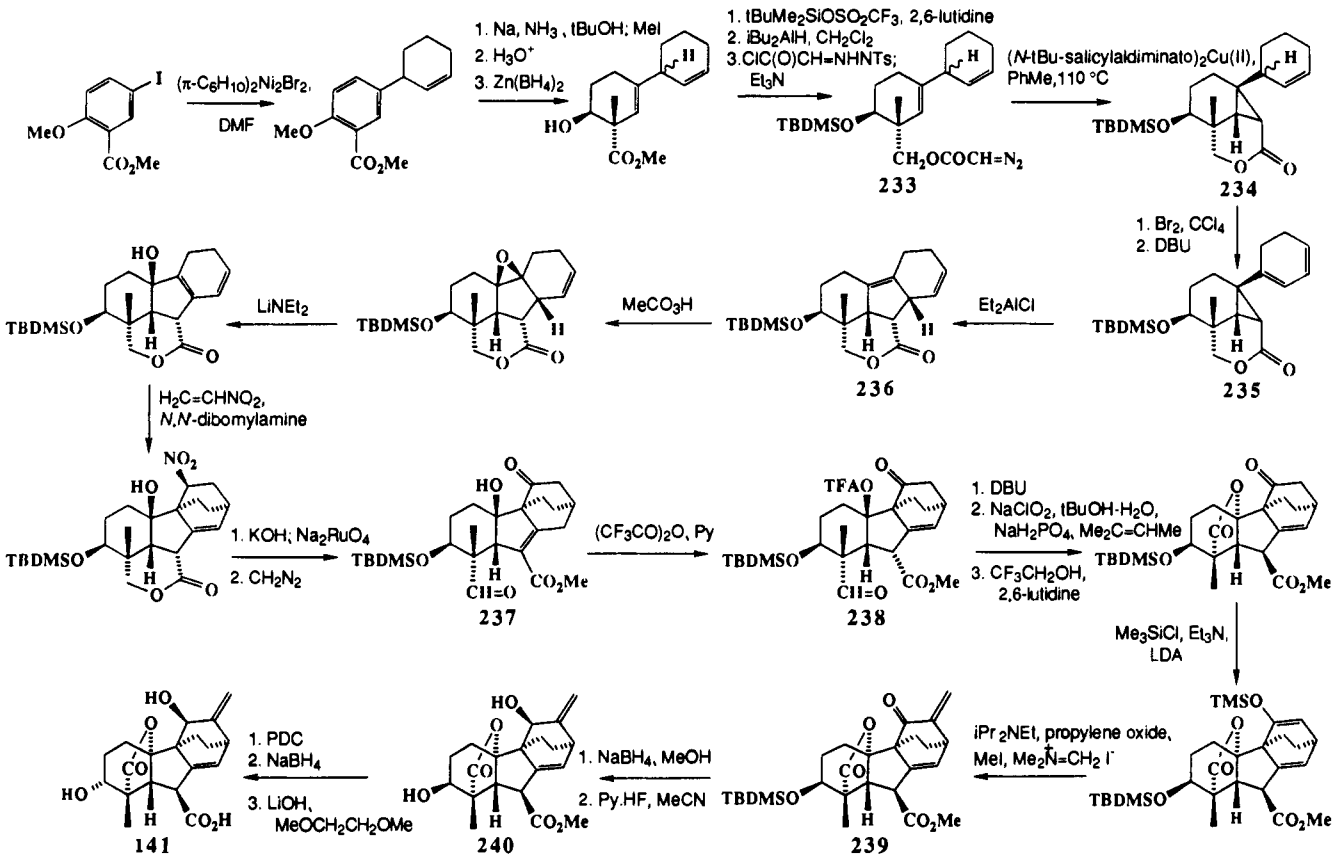

Figure 74. Total synthesis of antheridic acid.

reaction. As a prelude to the formation of the lactone ring, **237** was trifluoroacetylated and, in what must have been a pleasant surprise, it was discovered that the double bond had migrated into the desired $\Delta^{8(14)}$ location. The desired 7β-stereochemistry was obtained by DBU-catalyzed equilibration and the final part of the skeleton introduced in a one-pot process involving a Mannich reaction followed by in situ elimination. The resulting enone **239** was then reduced with sodium borohydride reduction to mainly the desired 15β-epimer, with no evidence of 1,4-reduction, the normal pathway in the GA molecule (cf. the synthesis of GA_{63}, Figure 35). Removal of the TBS group revealed that the product, **240**, was different from methyl antheridate, and so the stereochemistry at C(3) was inverted by an oxidation/reduction cycle. Hydrolysis of the product, a process which was apparently assisted by the neighboring 15β-hydroxyl, then afforded (±)-antheridic acid (**141**).

An enantioselective approach to the synthesis of **141** based on the same intramolecular cyclopropanation strategy and culminating in the preparation of the (+)-3α-epimer of **236** has also been described.[341]

IX. Concluding Remarks

The chemistry of gibberellins is rich and diverse. Early work was plagued by unexpected and unwanted rearrangements, but we are now in a position to manipulate these complex structures in a controlled fashion. Total syntheses of complex natural products rarely provide more than a few milligrams of the target compounds when more than 20–25 steps are involved, and the preparation of gibberellins by this mode is no exception. On the whole, the major benefits of this kind of activity have been the development of general concepts, strategies, and methodology. The synthetic conversions of the fungal GAs into the rarer plant derivatives have undoubtedly been of greater value to the GA field and there is a continuing need to synthesize further GAs in order to confirm tentative structure assignments as well as providing sufficient material for more extensive biological investigations.

The most exciting prospects for the discovery of novel structures appear to be among the lower plants, where only a tiny selection of species has been examined to date. The greater skeletal diversity encountered among the fern antheridiogens injects considerable interest from both a biosynthetic and evolutionary perspective, but it has also made the task of elucidating new structures more complicated. It is therefore inevitable that synthesis will continue to play a crucial role in further developments.

X. References

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