SYNTHETIC STUDIES ON GIBBERELLINS

A THESIS

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by

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DECLARATION

This thesis contains no material previously submitted for a degree in any other University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

W. L. A. CHU
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ABSTRACT

This thesis describes the first chemical synthesis of derivatives of the less abundant naturally occurring 12-hydroxy gibberellins from the freely available fungal gibberellin, gibberellic acid. The key steps in these conversions are the lead tetra-acetate transannular oxidation of the 16α-bromo-17-carbinol and the reductive fission of the resulting 12β,17-cyclic ether.

Chapter 1 contains a brief survey of research into gibberellins, one of the most important groups of plant growth hormones.

Chapter 2 details the methodology for the introduction of oxygen functionality at the exocyclic C-17 position involving the oxidative 1,3-transposition of functionality, thereby converting a 16-ene-15α-carbinol to a Δ15-ene-17-carboxaldehyde. Subsequent adjustment of the oxidation level of the resulting product gives the 17-carbinol required for the crucial transannular oxidation studies.

Chapter 3 describes the preparation of 12-hydroxy-GA$_1$ and -GA$_3$ derivatives. Transannular oxidation of the 17-carbinol affords the 12β,17-ether, reductive ring opening of which, followed by oxidation furnishes the 12-oxo-gibberellins. Reduction of the 12-oxo-13-hydroxy gibberellin derivatives with zinc borohydride gives a mixture of the 12α, and 12β-carbinols.

Chapter 4 deals with the elaboration of the remaining 15β-allylic alcohol fragment in one of the targeted 12-hydroxy gibberellins, GA$_{32}$, and 1,2-dihydro GA$_{32}$, a suspected new gibberellin.
Chapter 5 describes the extension of the GA32 methodology to the synthesis of derivatives of most of the naturally occurring 12-hydroxy C-19 gibberellins, including: GA30, GA31, GA58, GA69, GA70 and GA71.

Chapter 6 outlines complementary methods for preparing deuterium labelled gibberellins, each of which utilised intermediates derived from the C(12) functionalisation studies. These methods are found to be more efficient and versatile compared to most of the existing procedures, and can be easily extended to the preparation of tritium labelled GAs.
ABBREVIATIONS

Ac acetyl
AIBN \(\alpha,\alpha'\)azobis(isobutyronitrile)
Bu butyl
Bz benzoyl
CIMS chemical ionisation mass spectroscopy
m-CPBA meta-chloroperoxybenzoic acid
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H diisobutylaluminum hydride
DMAP 4-(dimethylamino)pyridine
DME 1,2-dimethoxyethane
DMF dimethylformamide
GA gibberellin
GC gas chromatography
GC-MS gas chromatography-mass spectroscopy
HMPA hexamethylphosphoric triamide
HRMS high resolution mass spectroscopy
IR infra red spectroscopy
J coupling constant
LTA lead tetra-acetate
Me methyl
MOM methoxymethyl
mp melting point
MPLC medium pressure liquid chromatography
MS mass spectroscopy
Ms methanesulfonyl
NMR nuclear magnetic resonance spectroscopy
OTf trifluoromethanesulfonate
<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PNPBA</td>
<td>para-nitroperoxybenzoic acid</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultra violet</td>
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Chapter 1

1. Introduction

Chemical research has played an important role during the agriculture revolution. The use of chemical substances - fertilisers, pesticides and herbicides - to manipulate crop production processes can be regarded as one of the most important advances in modern agriculture. Parallel to the introduction of these materials in commercial applications, a new class of naturally occurring chemical substances, collectively known as plant growth regulators, has been added to the field of agricultural chemical research. When applied in low concentrations, this group of compounds [abscisic acids, e.g. (1), auxins, e.g. (2), brassinolides, e.g. (3), cytokinins, e.g. (4), ethylene, e.g. (5) and gibberellins, e.g. (6)] can alter the normal physiological processes of growth and development in plants.1
The first clear indication that plant growth regulators occur naturally in plants was the demonstration by Went in 1926 that oat seedlings contained a diffusible substance that would promote their growth.\(^2\) A later discovery by Kögl that indoleacetic acid (IAA) \(^2\) was capable of promoting the elongation of plant cells, focussed considerable attention on this compound, which is now recognised as the most important member of the auxin family.\(^3\)

The smoke from an accidental fire in a greenhouse caused pineapple plants to burst into flower instead of being damaged. This astonishing effect was later found to have been induced by the smoke’s content of unsaturated gases, such as ethylene \(^5\) and acetylene, which led to the first practical uses of ethylene plant growth regulators in stimulating root formation and promoting flowering in pineapple plants.\(^4\) The importance of these ethylene compounds in agriculture has steadily increased. The commercially available ethylene releasing compound, 2-chloroethyl phosphonic acid (Ethephon), is now being utilised in commercial agricultural production and was registered in 1981 for use on more than 20 different crops.\(^5\)

1.1 Discovery and History of Gibberellins.

The 'foolish seedling' effect in rice, a pathological disorder, has been known for many decades. The symptoms of this disease include excessive elongation of the seedlings with the result that the mature plant dies before reaching the stage of fruition. At the turn of the century, this disease was widespread in the paddy fields of Southeast Asia, causing extensive damage to rice plants, with disastrous yields of rice often being recorded. Such devastating effects motivated Japanese researchers to initiate a program of studies, not only to find a means of combating the disease, but also with the hope of turning this unwanted phenomenon to their advantage, i.e. the raising of larger rice plants with increased crop yields. After working actively on methods for controlling the disease,
Kurosawa, in 1926 provided the first evidence for the disease being caused by infection with the fungus *Gibberella fujikuroi*, demonstrating that the infected plants grew much faster than uninfected ones. It was not until 1938, however, that a metabolite of this fungus was isolated and shown to be the causative agent of the disease. The isolation, crystallisation, and structural determination of this material by Yabuta and Sumiki heralded the discovery of a new class of plant growth hormones, the gibberellins. Due to lack of communication between Japan and the Western world during World War II, the early research on gibberellins was carried out almost exclusively in Japan. After this work had been announced to the Western world in the mid-1950's, an explosion in gibberellin research occurred.

Fermentation of the fungus *G. fujikuroi* was subjected to extensive investigation, resulting in the isolation of several physiologically active gibberellins from the culture broth; these compounds were later named GA₁ *(7), GA₂ (8)* and gibberellic acid GA₃ (6). GA₃ (6) is the major metabolite from the culture and the first patents for its commercial production were granted to Imperial Chemical Industries in Britain. Production of GA₃ (6) by fungal fermentation of *G. fujikuroi* for agricultural consumption in the western world alone has now reached 12-15 tons annually.

*The trivial nomenclature based on the chronological order of discovery has been adopted. As further GAs are characterised, they are allocated numbers sequentially.*

\[ \text{GA}_1 \] (7)

\[ \text{GA}_2 \] (8)
The next major advance in gibberellin research was the discovery that extracts from the higher plants contained material which could induce biological responses identical to those elicited by the fungal gibberellins. This pioneering work was immediately followed by the isolation and identification of gibberellins from such sources. In 1958, MacMillan reported the first isolation of gibberellins from higher plants, i.e., the identification of gibberellin A_1 (7) from the immature seed of scarlet runner bean. There are currently more than 70 gibberellins that have been characterised and isolated from various sources within the plant kingdom. Each of these gibberellins can be placed in one of two distinct groups, the C-19 or C-20 gibberellins, but they are all based on the same diterpenoid ent-gibberellane skeleton, differing from each other only in the level of oxidation and various substitution patterns.

### 1.2 Plant Growth Regulating Properties of Gibberellins

Many gibberellins have profound effects on various phases of plant growth, such as seed germination, the breaking of dormancy, enzyme synthesis, reversal of dwarfism, induction of stem growth, stimulation of flowering, modification of flower sex expression, parthenocarpic development of fruit, fruit enlargement, and inhibition of senescence. These responses are normally rapid, easily observed and striking, compared to untreated plants. Many of these spectacular physiological phenomena have been exploited commercially in agricultural practices and have proven to be of great economic value.
1.3 Biosynthesis of Gibberellins

The biological importance of the gibberellins and their isolation from various plant sources has stimulated vigorous biogenetic studies involving the feeding of radioactively labelled precursors to fungal cultures or cell free extracts from higher plants, and sometimes its extension to intact plant tissues. A thorough understanding of the biosynthesis and biometabolism of gibberellins should provide vital information for the design of selective inhibitors or activators for the metabolic conversion of the gibberellins. Such designed inhibitors or activators could allow a specific modification of plant growth and development in the desired direction and to the desired degree, which could ultimately be exploited commercially.

Birch first defined the terpenoid nature of gibberellins by feeding radioactively labelled 2-¹⁴C acetic acid and 2-¹⁴C-mevalonate to the culture media of G. fujikuroi, which resulted in radioactive incorporation into gibberellin A₃. Subsequent progress in the study of biosynthesis and metabolism of GAs was rapid, and a wealth of information has been obtained on the nature of the biosynthetic pathways to gibberellins, from both a structural and mechanistic point of view.

The biosynthetic pathways to GAs are basically the same for both fungi and higher plants. However, more structural variety is observed for plant GAs than for fungal GAs. The variety of positions and stages in biosynthesis at which hydroxy groups and olefinic linkages are introduced, provides a wider variety of gibberellins in higher plants. The gibberellin biosynthetic pathways can now be divided roughly into three distinct stages (scheme1.1): i. conversion of mevalonic acid (MVA) (9) to ent-kaurene (10), ii. conversion of ent-kaurene (10) to GA₁₂-7-aldehyde (11), iii. conversion of
GA\textsubscript{12}-7-aldehyde (11) to C-20 GAs, C-19 GAs and the conversion of GAs.

![Scheme 1.1: General pathway of gibberellin biosynthesis](image)

Although many aspects of biosynthesis have been determined, the detailed mechanism by which the twentieth carbon is lost is not yet fully understood\cite{16}. This point is of considerable interest within the context of a search for selective inhibitors of the conversion of C-20 gibberellins to C-19 gibberellins. Since most of the C-20 gibberellins are biologically inactive\cite{17}, an inhibitor of this kind would result in retardation of certain aspects of plant growth. For example, reduced stem growth could make plants less prone to storm damage.

With the objective of preparing radioactively labelled C-20 gibberellin derivatives to unravel this mystery in the biosynthesis of gibberellins, two methods were established for preparing deuterated gibberellins which will be discussed in Chapter 6.
1.4 Gibberellin Structural Determination.

Soon after pure gibberellins were obtained from the fermentation of *G. fujikuroi*, extensive structural elucidation studies were undertaken. After extensive degradation studies on gibberellic acid, a tetracyclic lactone structure with a molecular formula of \( \text{C}_{19}\text{H}_{22}\text{O}_6 \) was proposed by Cross\(^{18} \) and later confirmed by McCapra\(^{19} \) through X-ray analysis using a single crystal of methyl bromogibberellate. The complete stereochemical structure was determined subsequently by an X-ray diffraction study of a di-\( p \)-bromobenzoate of GA\(_3\)\(^{20} \). More recently Adam\(^{21} \) has reported the full set of data from X-ray analysis on GA\(_3\) itself. To date, more than 73 gibberellins have been isolated and fully characterised as C-19 and C-20 tetracyclic diterpenoids with a common *ent*-gibberellane skeleton (scheme 1.2), but with a variety of substitution patterns.\(^{10} \)

![Scheme 1.2 ent-gibberellane skeleton](image)

1.5 General Chemistry of Gibberellins

Many of the gibberellins contain a high density of labile functional groups, rendering them susceptible to rearrangement and degradation.\(^{22} \) All 13-hydroxylated gibberellins can undergo an electrophile-induced Wagner-Meerwein rearrangement with inversion of the C/D-ring configuration (reaction a). Whereas the exocyclic olefin in all 13-desoxy gibberellins not only reacts readily with water to give the tertiary alcohol (reaction b) but also isomerises to the endocyclic position with great ease (reaction c).
Gibberellic acid (6) undergoes a wide variety of rearrangements, many of which occur under very mild conditions. For example, in unbuffered aqueous solution, GA₃ (6) is autocatalytically transformed into gibberellenic acid (12) (reaction d), while in stronger acid, allogibberic acid (13) is formed (reaction e). In cold dilute aqueous alkali, the intriguing rearrangement to isogibberellic acid (14) occurs (reaction f), whereas the closely related GA₁ (7) is epimerised at C(3) through a retroaldol-aldol like sequence (reaction g) (scheme 1.3).

Scheme 1.3 : General Chemistry of Gibberellins
Gibberellic acid (6) represents one of the most highly functionalised gibberellins. The great structural complexity of this molecule, which bears eight asymmetric centers and a cluster of labile functional groups on a strained carbocyclic skeleton, poses a difficult challenge to synthetic chemists. Substantial efforts were mounted by several research groups towards a total synthesis. However, after the complete structural elucidation was reported, little progress was made over the next two decades. Only several simpler gibberellins were prepared, and even then, through very lengthy sequences with the repeated use of relay intermediates.23

It was not until 1978 that the first stereoselective total synthesis of gibberellic acid was announced by Corey et al.24 The key features of this synthesis (scheme 1.4) include, a). an intramolecular pinacol cyclisation of the keto-aldehyde (15) with titanium to construct the strained bicyclo [3.2.1] octane system, followed by oxidation of the diol under Swern-type conditions to give the α-ketol (16) - later used to assemble the sensitive D-ring methylenecyclopentanol moiety; b). an intramolecular [4+2] cycloaddition for the construction of the A-ring with the desired stereochemistry at C5; c). stereoselective methylation at C4 with methyl iodide to give the diene (17); d). conversion of diene (17) into the corresponding diene acid (18) which was subsequently used to construct the A-ring functionalities through repeated lactonisations.
Corey and Munroe later reported a more efficient sequence, saving 9 steps on the original synthesis, for elaboration of the key tricyclic intermediate (21). The crucial steps in this new synthesis include, a). a Cope rearrangement of the norbornene derivative (19) to afford the cis-fused indene (20) and, b). selective intramolecular cyclisation to give the desired ethanoindene (21) (scheme 1.5).
The same key tricyclic ketone (21) can also be obtained efficiently by three different approaches devised independently by Stork, all of which employ the elegant method of reductive cyclisation of an ethynyl ketone (22) to give the D-ring methylene carbinol moiety (scheme 1.6).

Shortly after the first total synthesis of GA₃ (6) was published, Mander et al. reported a comparatively shorter and more efficient route to the target molecule (scheme 1.7). The synthesis featured a considerable amount of new synthetic methodology including: a). construction of the strained C/D ring bicyclo-[3.2.1]-octane skeleton by means of a diazoketone cyclisation reaction; b). stereoselective functionalisation of the C(10) carbonyl group by nucleophilic addition of triallylalane, which fulfilled three essential requirements: it did not attack the ester function, the Lewis acid character of the reagent enhanced the reactivity of the conjugated carbonyl group and also added stereoselectively to give the desired C(10) sterochemistry; c). formation of the γ-lactone functionality by an intramolecular Michael addition of a propionate enolate anion to the olefinic ester moiety, which took place from the α-face of the molecule, thereby establishing the correct stereochemistry at C(5); d). formation of the A-ring with introduction of the desired 3β-hydroxy group was achieved through a kinetically controlled
aldol condensation. Some of these methods were later extended to the preparation of 13-deoxy and C-20 gibberellins, such as GA\textsubscript{4} \textsuperscript{28} and GA\textsubscript{38} \textsuperscript{29}.

Mander also published a second total synthesis of GA\textsubscript{3} using an alternative fluorenone based approach,\textsuperscript{30} which afforded a more convergent route to the target molecule. Reductive alkylation of the aromatic acid (23) with iodide (24) provided rapid access to the fluorenone which was then utilised for incorporation of the D-ring by the diazoketone cyclisation methodology. Lithiation of (25) followed by carboxylation afforded a carboxylic acid, which was subsequently hydrogenated to furnish the desired B/C-cis-fused tetracyclic compound (26). Reductive alkylation of (26) at C(4) occurred stereoselectively anti to the 6α-carboxyl function to give the dihydro compound which possessed all the structural features required to complete the synthesis of GA\textsubscript{3} (6) (scheme 1.8).
It is now possible to achieve the total synthesis of almost any member of the gibberellin class of phytohormone by means of these efficient strategies.

1.7 Partial Synthesis of Less Readily Available Gibberellins

Gibberellins are required as standards for various obvious reasons: qualitative and quantative analysis, as substrates for metabolism studies, for identification of putative gibberellins and more importantly, for biological assays. The isolation of significant quantities of many of the less accessible GAs from plant tissues is usually impractical. Total chemical synthesis is also not a feasible method for preparing useful quantities of GAs. However, preparatively useful chemical methods have been developed for the partial synthesis of some less readily available GAs from more abundant precursors such as the fungal gibberellin, gibberellic acid. A repository of methodology for the preparation of many of these gibberellins has been reviewed by Takahashi et al.,31 and more recently, an extensive survey on both aspects of partial and total synthesis of gibberellins has also been compiled by Mander.32
MacMillan and his coworkers have made major contributions throughout the entire history of gibberellin chemistry, many of the less abundant gibberellins being prepared in his laboratory. Some of his more recent achievements include the development of an efficient method for the conversion of the most abundant fungal gibberellin A3 (6) to the less accessible GA7 (28) via the deoxygenation of the GA3-13-methyl oxalate (27) with tri-n-butyl tin hydride (scheme 1.9), and the partial syntheses of a range of 15β-hydroxylated gibberellin derivatives (scheme 1.10), thereby confirming the identities of several new gibberellins isolated from the extracts of pear and apple seeds which were assigned: GA45 (29), GA63 (30), GA67 (31) and GA68 (32).

Scheme 1.9: Deoxygenation of 13-methyl oxalate

![Scheme 1.9: Deoxygenation of 13-methyl oxalate](image)

Scheme 1.10: Partial synthesis of 15β-hydroxy gibberellins

![Scheme 1.10: Partial synthesis of 15β-hydroxy gibberellins](image)
Mander's stereoselective partial synthesis of 13-hydroxylated C-20 gibberellins from the freely available GA3 (6), represents an important breakthrough in this area. Stereoselective introduction of the Cl unit at C(10) was achieved through an intramolecular cyclopropanation reaction. Decomposition of the diazoketone (33) with copper afforded the carbene intermediate which cyclised onto the Δ\textsubscript{1,10}-olefin to form the cyclopropyl ketone (34). Reductive ring-opening of the cyclopropane ring took place regioselectively between C(1) and C(20) to give the cyclopentanone (35), and subsequent oxidative cleavage of the C(19) and C(20) bond furnished the desired C-20 gibberellin skeleton (scheme 1.11).

C-20 GAs have been strongly implicated as key intermediates in the biosynthesis of C-19 GAs, but investigation into such aspects has, until now, been severely hampered by the lack of suitable substrates. Success in the preparation of these compounds has provided valuable materials for biosynthetic studies.
Flowering is one of the most crucial events in the life cycle of plants which is the end product of the cumulative effect of many subtle metabolic changes resulting in the initiation of flower buds. It also marks an important morphological transition from vegetative growth to reproductive development. Certain environmental factors such as day-length and temperature can affect dramatically the formation of flowers in plants. Many plants show a peculiar sensitivity to light such that flower buds will be initiated in such plants only under certain day lengths and some other plant species require exposure to cold temperature before they can start to flower. The control of flower bud initiation by day-length is called photoperiodism. There are roughly three distinct classes of day-length responsive plant types which include long day plants (LDP), short day plants (SDP) and day neutral plants. LDP can only flower if exposed to certain photoperiods longer than the critical one, whereas SDP require a maximum of darkness for flowering, while day neutral plants can flower irrespective of day-length.

One hypothesis which has been put forward to explain the mechanism for induction of flowering in plants is based on the hormonal concept that certain environmental factors such as photoperiod and temperature are responsible for the production of flowering inducing substances, the "florigen". By means of transplantation experiments, Chailakhyan showed that the flowering of LDP species can be induced under non-inductive conditions by their grafting onto the flowering short day plant species, and on the other hand, the flowering of SDP under long-day conditions can also be induced by their grafting onto the flowering plants of long-day species. Similar results were obtained from intergeneric grafting experiments, suggesting that the hormonal systems present in the species being investigated are very similar, and perhaps the same, all containing a non-specific and transmissible floral promoter. Subsequent experiments with extracts from the leaves of flowering plants further support the florigen hypothesis. Induction of
flowering can also be observed with SDP seedlings under non-inductive conditions when treated with ethanol extracts from the leaves of flowering SDP.\textsuperscript{42} It is now widely believed that light perceptive organs as well as sites for the production of floral stimuli are both located in the leaf. The photoperiodic receptors can be activated in response to certain light requirements and once activated, the biological system responsible for synthesis of the floral inducing substances can then be switched on for production. The floral stimuli being produced are then discharged from the leaf and transmitted to the shoot apex for flower initiation. In spite of such evidence that a transmissable stimulus is being produced and discharged from the leaves during the photoperiodic response, attempts to isolate this(these) elusive compound(s) have so far been unsuccessful, there being no unequivocal indication of its nature, nor of the precise functions of these endogenous stimuli.

Although the mechanism of flowering initiation is still largely not understood by plant physiologists, control of flowering remains one of the most practically useful aspects of horticulture and agriculture.\textsuperscript{43} With many horticultural crops, the key to financial success is the capability to induce flowering and more importantly, to induce it on command in order to meet certain major market and festival dates; considerable market advantage may be gained if greenhouse plants could be induced to flower earlier or flower over a longer period. Conversely, the ability to prevent flowering is extremely important in agricultural crops when flowering causes a decrease in economic benefit; for example, flowering in sugarcane plantations often leads to reduction in sugar yields. Delaying the onset of flowering in certain plants may be useful to avoid adverse weather conditions such as extremes in temperature and moisture.

Several kinds of evidence implicate plant growth regulators as playing an important role in the initiation of flowering.\textsuperscript{44} In particular, gibberellins are the first examples of PGRs that can induce flower formation under non-inductive conditions\textsuperscript{45} and have now enjoyed a very reputable place in commercial agriculture. Of considerable
economic importance, commercial forest trees have a poor natural regeneration because of the infrequency of good seed years; thus there is a need for reliable methods for increasing seed production. Application of gibberellins has been shown to cause an increase of flowering in several Conifer species, including Cupressaceae, Taxodiaceae and Pinaceae. The promotive effect of GAs in flowering also leads to an increase in production of viable seeds. Such an increase would enable breeding programs to be carried out more efficiently, providing a better prospect for forest conservation. If we ever wish to achieve the ability to manipulate flowering with precision, the physiology of flowering needs to be investigated in more detail.

In a continuing search of the role played by gibberellins in determination of plant developments, Pharis recently published results from the study of endogenous and applied gibberellins in relation to flower induction in the Long-Day Plant Lolium temulentum. Exposure of the plant to a single LD causes floral initiation with virtually no effect on stem length. Examination of the endogenous GA-like substances in the shoot apices, on and after LD induction, reveals remarkable changes in the level of GA-like substances. The level of GA-like substances remains low throughout the non-inductive period, but starts to increase by several-fold on the day after the long day induction, and then declines. A similar trend is observed in the leaf from these experiments. Among all these GA-like substances present, one particular fraction of compounds from HPLC elution displays a striking pattern in their changes. The content of this fraction increases sharply by 3- to 5-fold after a single LD induction and subsides quickly to a lower level when returning to SD conditions. Bioassay studies shows the GA-like substances present in this fraction constitute up to 30% of the total GA bioactivity in day II shoot apices. The rapid appearance of these compounds appears to be consistent with the overall increase in the total GA-like substances, thereby, suggesting rapid GA turnover is associated with the LD induction. This result and several others aroused general speculation that photoperiodic induction may actually trigger off the mechanism responsible for a rapid GA metabolism,
thereby, causing an accumulation of the plausible floral initiation GA. Very limited information is available to support this assumption, however.

Based on the HPLC elution profile, this particular fraction seems to represent a group of several polar poly-hydroxylated gibberellins which exhibit retention times between those of GA₂₈ (39) (three hydroxyls) and GA₃₂ (36) (four hydroxyls). Tentative structural assignment of these putative poly-hydroxylated gibberellins is extremely important and although it is currently under continuing investigation, progress is severely hampered by the small quantity of material available by isolation from natural sources and the lack of suitable reference materials for comparsion. It is estimated that each apex contains about 20 picograms of GA-like substances (or 6-15 µg per g of dry weight). Since each apex weighs only 2-3 µg, in order to obtain 1-2 mg fresh weight of shoot apices, it therefore requires 4 man-days to harvest sufficient apices (600) for mass spectrometric analysis. Extraction of the whole sample will only provide 30 nanograms of the GA-like fraction.⁴⁹

Parallel to monitoring the level of endogenous GAs on and after photoperiodic induction, the effect of exogenously applied GA on flowering initiation was also investigated by the same authors. When various gibberellins were applied to plants under non-inductive conditions, flower initiation was induced by several gibberellins; most notably by GA₃₂ (36), GA₅ (37), 2,2-dimethyl GA₄ (38), GA₃ (6) and GA₇ (28). GA₃₂ (36) is found to be the most potent in eliciting flower formation (figure 1.1), (scheme 1.12).⁵₀ It does not cause any appreciable shoot elongation and its effect is similar to a single LD treatment. Lona also demonstrated that extracts from peach seeds, presumably containing GA₃₂, can induce flowering in SDP species under non-inductive conditions.⁵¹ On the other hand, GA₁ (7), differs from GA₃₂ (36) in lacking the A-ring double bond and the two hydroxy groups at C(12) and C(15), and is found to exhibit effects opposite to those of GA₃₂ (36). It does not show any significant effect in flowering induction but
causes a dramatic increase in stem length. The pronounced differences between the various GAs in their relative effects on shoot elongation and flowering induction suggests that structural requirements for reproductive developments are quite different from those for vegetative growth. This premise offers excellent potential for commercial exploitation, that is to say, by choosing the correct GA structure, one can achieve the capability to manipulate the two distinct phases of plant growth with more precision.

Figure 1.1
Based on these results, the presence of the double bond in the A-ring is seen to be necessary for high induction of flowering, while the absence of this A-ring unsaturation leads to an increase in vegetative growth with negligible effect on flower induction. The differences in relative effects on stem elongation and florigenic activity between gibberellins that possess differing degrees of A-ring saturation could be accounted for by their respective fates in metabolism. It has been well established from metabolic studies that GA$_1$ (7), with a saturated A-ring structure, is readily hydroxylated at the C(2) position to give GAg (39). Since GAg (39) is found to be inactive in most bioassays, transformation of GA$_1$ (7) to GAg (39) could be the cause of the reduction in activity of GA$_1$, whereas the presence of the A-ring double bond in some gibberellins, such as GA$_3$, GA$_5$ and GA$_{32}$, prevents C(2) hydroxylation, thereby retaining their biological activities. 2,2-dimethyl GA$_4$ (38) with no A-ring unsaturation, is also highly active in florigenic activity. Obviously, in this case, C(2) hydroxylation is blocked by the quaternary nature of C(2).
The high florigenic activity of GA32 (36) correlates nicely with the transient increase in the level of endogenous poly-hydroxylated GAs after the single LD induction. The relationship between hydroxylation at C(12) and C(15) and the effectiveness in flowering induction in *Lolium* is not clear, however. Attempts to investigate the role played by these hydroxyl groups in florigenic activity have been severely proscribed by the unavailability of materials.

Only with procedures for the partial synthesis of 15β-hydroxylated gibberellins published recently by MacMillan,34 has investigation into the structure-activity relationships of the 15β-hydroxylated gibberellins in flowering initiation become possible. The bioassay results indicate that hydroxylation at C(15) is important for promotion of flowering, and that 15β-hydroxylated gibberellins are generally more active in promoting floral initiation than the corresponding 15-desoxy analogues (figure 1.2).54

![Figure 1.2](image-url)
Although there are more than 15 naturally occurring GAs (constituting almost 25% of all known GAs) that bear an oxygen function at the C(12) position, evaluation of the relationship between the 12-hydroxyl group and the effectiveness in flower induction has not been realised, so far. This family of compounds represents one of the least accessible class of natural gibberellins, both in terms of isolation and synthesis. Most of these compounds are isolated in minute quantities from large volumes of tissue extracts,\textsuperscript{55} e.g. only 30mg of 12α-hydroxylated GA7 [GA30 (176)] and 10mg of GA31 (177) were obtained from 11kg of immature seeds of evening glory (*Calonyction aculeatum*). These compounds bear an oxygen function at the relatively inaccessible C(12) position, posing an extremely difficult challenge with respect to chemical synthesis, such that none of these compounds have previously been prepared by chemical means. Until recently, small quantities of these compounds could be obtained via microbiological conversion of the 12-oxygenated kaurenoic acids.\textsuperscript{56} Further amounts of these 12-oxygenated compounds are nevertheless very much in demand for biological and related studies.

Among this class of 12-oxygenated gibberellins, GA32 is by far the most active\textsuperscript{57} and highly functionalised gibberellin that has ever been isolated from natural sources.\textsuperscript{58} Because of the pronounced biological activity and the unique oxygenation pattern, we undertook chemical studies towards it synthesis. From the total synthesis point of view, GA32 clearly poses a much more difficult synthetic problem, compared to GA3. It is necessary to grapple with the higher degree of oxygenation in addition to the chemically sensitive functional systems inherited from GA3. The close structural similarities between GA32 and the fungal gibberellin, gibberellic acid, however, not only indicate a potential biosynthetic relationship, but also raise the prospect of achieving access to GA32 and other 12-oxygenated GAs by synthetic means. With regard to the conversion of GA3 into GA32, the most difficult task in this endeavour is functionalisation of the non-activated and inaccessible C(12) position. While functionalisation of the gibberellin C-ring has not been
reported in the literature, a method for the elaboration of the D-ring allylic carbinol fragment has recently been published by MacMillan as noted above.\textsuperscript{34}

Although the possibility of achieving functionisation of the gibberellin C-ring appeared to be remote, we nevertheless embarked upon the synthesis and a study of the transannular oxidation of the 17-hydroxylated GA derivatives. We met with severe problems initially, but this strategy was shown to be viable for C(12) hydroxylation and ultimately translated into the preparation of GA\textsubscript{32} derivatives and their 1,2-dihydro-analogues.

Even though, we focussed initially on GA\textsubscript{32} as our prime target, the successful outcome of this investigation serves as a model for the preparation of the whole range of the naturally occurring 12-oxygenated gibberellins. The strategy was subsequently extended, with slight modification, to the preparation of most of the known 12-oxygenated C-19 gibberellin derivatives.

During the course of this investigation, a large number of unnatural 12-hydroxylated GA intermediates, with various substitution patterns in the A-ring, has been accumulated. Certainly, these compounds will prove to be extremely useful not only in structure-bioactivity relationship studies, but possibly for structural assignments to undiscovered gibberellins as well.
CHAPTER 2
Chapter 2.


2.1 General Considerations for C(12) Functionalisation.

Conceptually, several broad strategies for introduction of oxygen functionalities at C(12) appear possible. One approach is to transpose functionalities from the A-ring into the C-ring in order to achieve chemical activation at the C(12) position (scheme 2.1). Gibberellenic acid (12), readily available from GA₃ (6) through hydrazine degradation,⁵⁹ was considered as a key intermediate for effecting such a transposition. Oxidation of the allylic alcohol (12) to the trienone could be achieved with one of the many available chromium reagents and subsequent 1,4-addition of a suitable hydride reagent to the trienone would give the diene acid (40). Iodo-lactonisation followed by β-elimination could introduce the Δ⁹,₁¹- olefinic bond into the C-ring appropriately*.⁶⁰

* This strategy has very recently been successfully employed by Dr. M. Furber of this laboratory for the synthesis of Δ⁹,₁¹-didehydroGA₉ methyl ester (i), a new gibberellin isolated from prothallia of the fern Lygodium japonicum, assigned as GA₇₃ methyl ester.
This diene (41) closely resembles grandiflorenic acid (42), a substrate used by MacMillan as starting material for the synthesis of 12-hydroxylated kaurenoic acid (43) (scheme 2.2). The C(12) position would now be activated by the \( \Delta^{9,11} \)-olefin and allylic oxidation could be performed to give the dienone (44). Selective reduction of the \( \Delta^{9,11} \)-olefin followed by reduction of the 12-ketone (45) would give access to the desired 12-hydroxylated gibberellin series. Unfortunately, the yield for the conversion of GA\(_3\) (6) to gibberellic acid (12) is low and re-establishment of the correct stereochemistry at C(9) did not appear to be straightforward, so this approach was not pursued.
The second approach considered was to employ the 13-hydroxy group as an anchor for the attachment of an activated functional group, such as a diazoacetate (46) or oxycarbonyl azide (47) (scheme 2.3 and 2.4). These methods have been widely used to prepare photoaffinity labels to probe receptor sites. Decomposition of these compounds, either chemically or photolytically, would generate a highly reactive carbene or nitrene intermediate. In principle, any group in close proximity could react with such an intermediate, but it was hoped that the carbene or the nitrene would insert into the 12α-CH bond to give the cyclic lactone (48) or carbamate (49). Further manipulation of these insertion products might afford the desired 12-oxygenated GA derivatives. Treatment of the carbamate (49) with nitrous acid could afford the cyclic carbonate (50) and sequential oxidative cleavages of the enol derivatives of lactone (48) could furnish the 12-hydroxylated derivatives. The carbene or nitrene insertion reactions are expected to be non-selective processes, however, and the proximal C(14) and 16,17-exocyclic double bond are potential reaction sites.
Subsequent model studies revealed that alignment of the 13-oxygen functional group did not favour the insertion into the 12α-CH bond. This approach was therefore discarded. The Breslow procedure for remote functionalisation of non-activated carbon atom was also considered briefly but was abandoned on similar grounds.
A more realistic approach appeared to be the utilisation of a transannular oxidation of an endo-17-hydroxylated GA derivative to provide an 11,17- or 12,17-cyclic ether\(^\text{66}\) with subsequent ring-cleavage of the ether to introduce oxygen functionalities at C(12) (scheme 2.5).

\[
\begin{align*}
\text{HO} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad
\end{align*}
\]

Scheme 2.5
McCrindle reported functionalisation of the C-ring of kauranes by employing the hypoiodite reaction on the corresponding 17-hydroxylated kaurane derivative (51)\(^{67}\) (scheme 2.6).

In actuality, Fuji subsequently applied this procedure to prepare 12α-hydroxylated kaurene (54)\(^{68}\). The cyclic ether (52) was cleaved by reaction with a large excess (20 equivalents) of aluminum chloride and sodium iodide in acetonitrile to give the corresponding iodo-olefin (53) via the elimination of the iodo-alcohol intermediate. Hydroboration of the iodo-olefin followed by β-elimination of hydrogen iodide gave the desired 12α-hydroxylated kaurene (54) (scheme 2.7).
Examination of a Dreiding model of (51) (diagram 2A) indicates that the derived oxygen radical should be able to abstract a β-hydrogen from either C(11) or C(12) positions. Based on the expectation that the rate of hydrogen abstraction reaches a maximum if the internuclear distance between oxygen atom and the carbon atom from which hydrogen is abstracted lies in the range 2.5-2.7 Å, however, it would appear that attack at C(11) should occur more readily than attack at C(12). This is confirmed by experimental results obtained from hypoiodite reaction on (51), from which the principal products are indeed derived from abstraction of 11β-H.

X-ray crystallographic data for gibberellic acid (6) indicate that the C-ring is confined to a boat conformation. On the basis of this information and distances measured on the Dreiding model of GA3, it appeared that hydrogen abstraction should take place predominantly at the C(12) position to form a 12β,17-ether (diagram 2B), assuming that the transition state is based on the ground state conformation.
In the event of the $12\beta,17$-ether being too sterically hindered for a ring-opening process, we envisaged that replacement of the $16\alpha$-hydrogen with a bromine atom would facilitate the ring-opening process as well as regeneration of the exocyclic methylene unit. Thus, reductive ring-opening of the bromo-ether by reaction with zinc could, in principle, afford the 12-hydroxylated gibberellin derivative (scheme 2.8).
2.2 Approaches to Preparation of 17-Hydroxylated Gibberellin Derivatives

The preparation of a 17-oxygenated GA derivative turned out to be a non-trivial task. We had originally explored this chemistry within the context of another problem associated with C-20 GAs,* but we were able in due course to transfer the technology to the task in hand.

2.2.1 Attempted Hydroboration on \( \Delta^{16}\)-Ene (55)

Hydroboration followed by oxidation with basic hydrogen peroxide could be expected to provide a convenient method of transforming a terminal alkene to the corresponding primary alcohol 71 (scheme 2.9).

\[
\begin{align*}
\text{OTBDMS} & \quad \text{OMOM} \\
\text{MeO} & \quad \text{OH} \\
\text{CO}_{2}\text{Me} & \quad \text{CO}_{2}\text{Me}
\end{align*}
\]

Scheme 2.9

* At the start of this work, one of our objectives was the development of methodology for the preparation of the 17-carboxy C-20 gibberellins, to supply plant biologists with C-20 gibberellin substrates for antibody synthesis which would be used for radioimmunoassay studies. The aim was to provide substrates with an alternative site, other than the conventional C-7 carboxy group, with which to couple with protein macromolecules for antibody synthesis, thereby increasing the range of available antisera, hopefully with a more desirable set of characteristics. In particular, GA\(_{19}\) dimethyl ester 17-carboxylic acid (ii), was chosen as the initial target. Since this project is currently under continuing investigation, the detailed results will not be included in this thesis, but the successful outcome will be reported in due course. However, some of the results based on the C-20 gibberellin derivatives, such as (55), will be presented, in order to illustrate problems associated with the introduction of oxygen functionalities at the C(17) position.
Although McCrindle had successful employed hydroboration to prepare 17-hydroxylated kaurane derivative from the corresponding kaurene\(^6\), when olefin (55) was treated with several borane reagents, unsatisfactory results were obtained. Diborane-THF complex caused destruction of the molecule, since it contained functional groups which are potentially reactive towards diborane, while more hindered borane derivatives, such as thexylborane\(^7\) and disiamylborane\(^8\) gave no reaction with the olefin, leading to recovery of the starting material.

### 2.2.2 Attempted One-Carbon Homologation of the 17-Norketone (56)

Attention was then directed towards a one-carbon homologation of the 17-norketone with a hetero-atom substituted Wittig-type reagent to give an enol ether derivative\(^9\); it was hoped that subsequent demasking of the enol ether and reduction of the resulting aldehyde would give the desired 17-carbinol (scheme 2.10).

![Scheme 2.10](image)

Treatment of olefin (55) with ozone in dichloromethane at -78°C, followed by reductive work-up with dimethyl sulfide\(^10\) gave a mixture of two products. Chromatography of the crude product mixture first afforded the ketone (56) in 40% yield, followed by an unknown compound in 30% yield which was later found to be the lactone (57)\(^11\) by NMR studies. The combination of osmium tetroxide and sodium periodiate provides an alternative procedure for the oxidative cleavage of olefinic compounds to
carbonyl compounds. When the olefin was treated with sodium periodate and catalytic amounts of osmium tetroxide in acetone overnight, the norketone was obtained in 50% yield. By addition of small amounts of pyridine (10%) to the ozonolysis reaction mixture, however, the side reaction could be reduced and the desired norketone (56) could be obtained in 75% yield.

Although Wittig reactions with methylene triphenylphosphorane are frequently used for regeneration of the \( \Delta^{16} \)-olefin from the corresponding norketone, when norketone (56) was allowed to react with several more complex Wittig-type reagents, such as methoxymethylene triphenylphosphorane, methoxymethyl diphenylphosphine oxide and 1,3-dithiane diethylphosphonate, unsatisfactory results were obtained. No heteroatom - substituted alkene could be detected from these reactions, presumably due to rapid enolisation of this sterically hindered ketone.

In a total synthesis of aphidicolin, Corey reported a procedure for overcoming the problem of enolisation of sterically hindered ketones involving the following sequence (scheme 2.11): a). treatment of the carbonyl compound with trimethylsilyl cyanide and a catalytic amount of zinc iodide to give the O-trimethylsilyl cyanohydrin; b). reduction of the cyano group with di-isobutylaluminum hydride to afford the formyl compound; c). addition of trimethylsilyl-lithium to the formyl compound to furnish the bistrimethylsilyl adduct; d). treatment with lithium diisopropylamide followed by acidic work-up to give the desired aldehyde. Unfortunately, the reagents employed
seemed incompatible with the functionalities already present in the gibberellin molecules that we were working with, and so this approach was not attempted.

In pursuing the preparation of gibberellin photoaffinity ligands, MacMillan has successfully used a modified version of the Peterson reaction to introduce a carboxyl functionality at the C(17) position of 13-desoxy-gibberellins\textsuperscript{83} (scheme 2.12), such as GA\textsubscript{4}. Unfortunately, this reaction is found to be inapplicable to 13-hydroxylated GAs.

![Scheme 2.11](image)

![Scheme 2.12](image)
2.2.3 Attempted Epoxide to Allylic Alcohol Isomerisation

The olefin (55) was converted to the epoxide (58) in 90\% yield by reaction with MCPBA in dichloromethane with powdered sodium bicarbonate as a buffer.\(^8^4\) It was hoped that an isomerisation of the epoxide (58) to the allylic alcohol (59) could be achieved with one of the standard literature reagents (scheme 2.13).\(^8^5\) The non-nucelophilic and bulky diethyl aluminium 2,2,6,6-tetramethyl piperidine\(^8^6\) gave no reaction, nor did trimethylsilyl triflate,\(^8^7\) while trimethylsilyl iodide\(^8^8\) caused destruction of the molecule.

\[ \text{Scheme 2.13} \]

2.2.4 Attempted Epoxide to Aldehyde Isomerisation

The rearrangement of epoxides to carbonyl compounds by aprotic acids or Lewis acids has been known for some time.\(^8^9\) However, the choice of reagents for such an isomerisation is severely limited by the fact that C(13) hydroxylated gibberellin derivatives tend to undergo electrophile-initiated Wagner-Meerwein rearrangement.\(^9^0\) When the epoxide (58) was treated with boron-trifluoride etherate solution in benzene,\(^9^1\) the
rearranged ketone (60) was indeed obtained exclusively.

![Chemical structure of rearranged ketone (60)](image)

Rearrangement of epoxides to carbonyl functions has been reported to occur with lithium bromide in hexamethylphosphoric triamide and benzene. It was hoped that the mild Lewis acid character of this reagent might avoid the Wagner-Meerwein type of rearrangement. When the epoxide (58) was treated with an excess of anhydrous lithium bromide in benzene and hexamethylphosphoric triamide at room temperature for 3 days, a single product was obtained in quantitative yield. Spectroscopic details for this product suggested the absence of the expected aldehydic group, the product eventually being identified by $^1$H NMR and $^{13}$C NMR studies as the bromohydrin (61) with the oxygen atom attached to the tertiary C(16) carbon atom.

![Chemical structure of rearrangement reaction](image)
It has been proposed that the mechanism for lithium bromide catalyzed epoxide-carbonyl rearrangement involves the lithium salt of the bromohydrin as an intermediate (pathway a). In our gibberellin case, backside attack by the bromide ion on the C(16) carbon atom was presumably prevented by steric hindrance; substitution then took place at the less hindered C(17) carbon atom to give the regioisomeric bromohydrin (pathway b) (scheme 2.14).

2.2.5 Electrophilic Addition of Hypobromous Acid to Δ^16-Ene Derivatives

Following the same stereoelectronic argument, the regiochemistry should be reversed if the bromohydrin were to be prepared directly (scheme 2.15). It was hoped that electrophilic attack on the double bond by hypobromous acid would take place from the exo-face of the molecule to generate an intermediate bromonium ion (62)^93 which could subsequently react with water as the nucleophile at the more exposed C(17) position to furnish the bromohydrin (63) with the oxygen attached at the C(17) position.
Success in this approach would offer direct access to the bromohydrin intermediate with the correct regio- and stereo-chemistry required for investigation of the crucial transannular oxidation.

When olefin (55) was treated with N-bromosuccinimide in aqueous acetone, the electrophile-initiated Wagner-Meerwein rearrangement was again unavoidable, giving the rearranged ketone (64) as the predominant product. The Prevost method and its modification using thallium salts were attempted on the olefin (55), but afforded a similar rearranged product, as did N-iodosuccinimide.

The methoxymethyl ether was later replaced with an acetate protecting group in the hope that the electron-withdrawing property of the acetate group might diminish the availability of the lone pair of electrons on the 13-oxygen atom for participation in the Wagner-Meerwein rearrangement. The readily available GA1-13-acetate derivative (65) was used as a model substrate to assess the behaviour of the allylic acetate towards the electrophilic addition reaction. Upon treatment with N-bromosuccinimide in aqueous acetone for 15 min, the olefin afforded a single product in quantitative yield. $^1$H NMR and $^{13}$C NMR studies showed the product to be a single bromohydrin regioisomer with no evidence for rearrangement having occurred. Based on the aforementioned stereoelectronic argument and INEPT-$^{13}$C NMR spectroscopic data (which were later found to be
misleading), the bromohydrin was assigned the primary alcohol structure (66). Subsequent chemical studies revealed this initial assignment to be incorrect.

When a mixture of the presumed bromohydrin (66), LTA, iodine and calcium carbonate in cyclohexane was heated to reflux with irradiation by a 250W tungsten lamp for 1 h.,96 a compound was obtained in good yield and was later found to be the bromo-diketone (68).

This result was attributed to fragmentation of the carbon-carbon bond between C(13) and C(16) initiated by the oxygen radical derived from reaction between the 16-hydroxyl group and LTA97(scheme 2.16).
This result led us to believe that the bromohydrin was indeed regioisomeric to the one required for the studies on the transannular oxidation. It is now clear that the neighbouring acetate group participates as an internal nucleophile by reaction with the bromonium cation (69) to give the intermediate cation (70), which then reacts with water to give an unstable ortho-acid intermediate (71). Upon hydrolysis during work-up, the orthoacid (71) presumably gives the bromohydrin (67) (scheme 2.17).

![Scheme 2.17](image-url)
2.2.6 1,3-Oxygen Transposition

When these endeavours proved to be unsuccessful, we set out to investigate an alternative protocol which led ultimately to the synthesis of the desired bromohydrin in a controlled manner.

When the $\Delta^{16}$-olefin (72) was treated with selenium dioxide and t-butyl hydroperoxide according to MacMillan's procedure, the allylic alcohol (73) was obtained in 90% yield. It was expected that a 1,3-transposition of the allylic oxygen functionality would achieve the task of introducing an oxygen function at the primary C(17) position (scheme 2.18).

![Scheme 2.18](image)

Although the allylic alcohol (73) can be obtained efficiently, it was found to undergo cyclisation readily with the nearby methyl ester function to form the cyclic lactone, thereby limiting the choice of reagents. $S_N2'$ substitution was attempted on the allylic alcohol but proved to be unsuccessful. Thus, when the alcohol was treated with freshly distilled thionyl chloride in ether at 0°C, a mixture of several products was obtained. Derivatisation of the allylic alcohol as the mesylate was also found to be fruitless.

In the synthesis of 15β-hydroxylated gibberellins (scheme 1.10), MacMillan employed an oxidation and reduction approach on the 15-exo-alcohol, although oxidation of the 15α-carbinol to the desired enone was not straightforward. Swern's activated dimethyl sulfoxide procedure was chosen in order to avoid oxidation of
the adjacent double bond which occurs with most chromium reagents.

Oxidation of tertiary and certain secondary allylic alcohols with chromium based oxidants has frequently been reported to result in 1,3-oxidative rearrangement to \(\alpha,\beta\)-unsaturated carbonyl compounds as depicted in scheme 2.19.\(^{100}\)

\[
\text{HO}_\text{R} \quad \rightarrow \quad \text{R} \quad \rightarrow \quad \text{R} \quad \rightarrow \quad \text{R} \\
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{Cl-\text{CrO}_3} \\
\end{array} \\
\end{array} \quad \text{H} \\
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{Cl-\text{CrO}_3} \\
\end{array} \\
\end{array} \\
\end{array}
\]

\text{Scheme 2.19}

Success in the case of certain secondary allylic alcohols seems to be due to the difficulty encountered by the reagent in abstracting a hydrogen atom from the carbon atom bearing the hydroxy group. In particular, the efficient procedure of using pyridinium chlorochromate developed independently by Herz\(^{101}\) and Dauben\(^{102}\) was appealing for the purpose of effecting the transposition of oxygen functionalities from C(15) to C(17).

Upon treatment of the alcohol (73) with 5 equivalents of pyridinium chlorochromate in dichloromethane, thin layer chromatography analysis indicated that the starting material had been completely consumed after 3 h. Subsequent chromatography of the crude product mixture first afforded the desired \(\alpha,\beta\)-unsaturated aldehyde (74) in 25\% yield, followed by a more polar product in 50\% yield. Based on \(^1\)H NMR and \(^{13}\)C NMR spectroscopic data, we believed that the more polar material was the epoxyalcohol (75). When the duration of the pyridinium chlorochromate reaction was extended from 3 h. to 16 h., a ca 1:2 mixture of the enal (74) and the epoxyaldehyde (76) was obtained in an overall 75\% yield. Separation of the crude product on MPLC gave the enal (74) in 21\% yield,
followed by the epoxyaldehyde (76) in 42% yield.

The epoxyalcohol (75) could be derived from the mechanism shown in scheme 2.20 and when subjected to further oxidation could afford the epoxyaldehyde (76).101

The epoxyaldehyde (76) could be converted efficiently to the desired enal (74), however. Thus, exposure of the epoxyaldehyde (76) to aqueous chromous chloride solution in acetone under a carbon dioxide atmosphere, gave the desired enal (74) in 80% yield.103
Presumably, reduction of the epoxy carbonyl compound with chromous chloride first affords the radical anion which is protonated and reduced further to give the β-hydroxy aldehyde and subsequent β-elimination under acidic conditions furnishes the desired α,β-unsaturated carbonyl compound* (scheme 2.21).

* Subsequent to our work, an alternative approach to the 13-desoxy gibberellin Δ⁵-enal based on the isomerisation of the gibberellin 16,17-epoxide was reported (Scheme 2F.1). Upon treatment with sulfuryl chloride, the 16,17-epoxy GA₄ derivative (iii) gave the Δ⁵-enal (iv) in good yield. Unfortunately, this method was again found to be inapplicable to the 13-hydroxylated gibberellin derivatives. Reaction of the corresponding 16,17-epoxy GA₇ derivative(v) with sulfuryl chloride led to the isolation of ketone (vi), presumably derived from the Wagner-Meerwein type of rearrangement of the C/D-ring.
Hydrogenation of enal (74) over palladium on carbon in ethyl acetate, gave a mixture of the epimeric aldehydes (77) and (78) in fair to good yield. The use of palladium as catalyst always resulted, to a certain extent, in hydrogenolysis of the allylic lactone moiety in the A-ring;\(^{105}\) the yield of the resulting ene-acids (79) and (80) varied considerably and sometimes reached as high as 40%.

The customary choice of using palladium as a catalyst is not always appropriate, since palladium is recognised for its ability to promote hydrogenolysis of allylic oxygen functionalities.\(^ {106}\) In view of this fact, we examined alternative catalyst systems. When palladium was replaced by rhodium on alumina, the problem of hydrogenolysis was eliminated, but unfortunately, rhodium did not effect enal hydrogenation. This problem was overcome by hydrogenation of the enal in two separate stages, first over rhodium, then over palladium, giving a ca 6:4 mixture of the endo and exo-aldehydes (77) and (78) in 75% overall yield. When hydrogenation of the enal functionality was carried out in the presence of powdered sodium bicarbonate as a buffer, the endo-aldehyde (79) was obtained in 75% yield.

At this juncture, the task of introducing an oxygen function at C(17) had been achieved; preparation of 17-hydroxylated gibberellin derivatives and 16\(\alpha\)-bromo-17-hydroxylated gibberellin derivatives now became straightforward. A portion of the
aldehyde (77) was reduced by reaction with sodium borohydride in methanol to give the endo-17-carbinol (81) in 80% yield. This alcohol was subsequently employed as a model for the transannular oxidation studies.

Alternatively, when the mixture of aldehydes was treated with pyrrolidone hydrotribromide in dichloromethane, the α-bromoaldehyde (83) was obtained in 70% yield.

The reduction of α-bromo carbonyl compounds can lead to the formation of epoxides if a basic reducing agent is used. In order to avoid the problem of epoxide formation, sodium cyanoborohydride was chosen by virtue of its reducing properties in low pH media. When the bromoaldehyde (83) was allowed to react with sodium cyanoborohydride in methanol at pH 3, the bromohydrin (66) was obtained in 65% yield. Sodium borohydride in dimethoxyethane was found to be equally effective, however, and the yield was found to be slightly improved.
The objective of preparing the required intermediates for the study of the crucial transannular oxidation had been achieved and the outcome of the investigation will be presented in the next chapter.
CHAPTER 3

Propagation of 137-labeled Nucleoside Derivatives

Propagation of 137-Hydroxyflouridine Derivatives

Preparation of the 12,17-Ether (85)

With the methylated DPN at hand, we attempted the desired immunoanalysis. Unfortunately, when the mixture of immunosorbent (86) was applied with 137-hydroxyflouridine (12,17) in aqueous solution, the desired reaction did not occur and individual measurement using ISOM (85) for DPN" 137 in complex mixture of 137-hydroxyflouridine was obtained where part of the actual results matched with the results obtained by methods based on the immunosorbent in the present work and improvement of the reaction by different concentration of immobilized antibodies.
Chapter 3

3. Preparation of 12-Oxygenated Gibberellin Derivatives

3.1 Preparation of 12β-Hydroxylated-GA\textsubscript{1} Derivatives

3.1.1 Preparation of the 12β,17-Ether (85)

With the bromohydrin (66) in hand, we attempted the crucial transannular oxidation on this intermediate. Unfortunately, when the mixture of bromohydrin (66), 4 equivalents of LTA, calcium carbonate and one equivalent of iodine in cyclohexane was heated to reflux and irradiated with a tungsten lamp (250W) for 1 h,\textsuperscript{96} a complex mixture of products was obtained. NMR spectral data showed the absence of any of the desired ether. Further attempts to form the desired ether by methods based on N-iodo-succinimidell\textsuperscript{10} or cerium ammonium nitrate\textsuperscript{111} also proved fruitless.

These results were somewhat disappointing, but were not too surprising. We had expected that the substrate might be functionally too complex for such drastic conditions. Not only is the bromohydrin susceptible to epoxide formation, but in addition, oxidation and rearrangement - fragmentation of this highly strained system could compete with ether formation. In view of these setbacks, we opted to use the simpler endo-17-carbinol (81) to examine the possibilities for remote functionalisation at the C(12) position.

When the alcohol (81) was subjected to the LTA reaction described earlier, a mixture of two products (inseparable by flash chromatography or MPLC) was obtained. The $^1$H NMR spectrum suggested a mixture of the 11β,17-ether (84) and 12β,17-ether (85) (scheme 3.1). Further characterisation by $^{13}$C NMR studies proved that our initial analysis was incorrect, however, and spectroscopic data were ultimately judged to be
inconsistent with either of these ethers.

Scheme 3.1

The original version of the Barton reaction,\textsuperscript{112} with decomposition of the intermediate nitrite, was also attempted, but when the alcohol (81) was treated with nitrosyl chloride in pyridine for 1h and later irradiated with a medium pressure mercury lamp, a mixture of several unidentified products was obtained.

On the verge of abandoning this approach, our hope was renewed on reading a review by Heusler and Kalvoda on remote functionalisation of non-activated carbon.\textsuperscript{113} These authors wrote: 'the disadvantages of the thermal LTA oxidation can easily be overcome by photo-decomposition of lead alkoxides. Irradiation of lead alkoxides with light at wavelengths above 300 nm induces a very clean one electron transfer from oxygen to lead. Since photolysis could be performed at room temperature where the rate of the base-catalysed two electron transfer (oxidation of alcohol to carbonyl) is very low, the specific excitation of the radical process by light also increases the selectivity of the reaction. Therefore ketals, ketones, double bonds etc., which are susceptible to attack by LTA at higher temperatures, remain unaffected. Although very few applications of the photolytic LTA reaction have been reported thus far, it appears to be an extremely efficient, mild and simple procedure for intramolecular functionalisation.'

When a mixture of the alcohol (81) and 4 equivalents of LTA in benzene, under a nitrogen atmosphere, was irradiated with a medium pressure mercury lamp (250W)
at room temperature, no reaction was observed after 1 h. 0.5 Equivalents of iodine were then added and after irradiation for a further 30 min, thin layer chromatographic analysis indicated that all of the starting material had been consumed. To our delight, the desired cyclic ether (85) was obtained as the major product in 70% yield along with the minor product (86), isolated in 15% yield after chromatography.

Based on $^{13}$C NMR spectroscopic data* and subsequent chemical studies, the major product was assigned the 12β,17-ether (85) structure and not the regioisomeric 11β,17-ether (84) (scheme 3.2).

**Scheme 3.2**

*Insertion of oxygen atom onto C(12) caused a deshielding effect on the adjacent C(11) and C(13) by 10 ppm and 7 ppm respectively, had the insertion taken place at C(11), we would expect a similar change in chemical shifts for the adjacent C(9) and C(12) atom but no effect on C(13).
3.1.2 Attempted Ring-Opening of the 12β,17-Ether (85)

With the structure of the ether assured, we set out to assess its response to various Lewis acid reagents in the hope of effecting the ring-opening reaction. Hindered cyclic ethers are notorious for their resistance towards ring-opening. In our case, the ether (85) did not seem to undergo ring-opening with great ease. Treatment of the ether (85) with a large excess of dimethyl boron bromide in dichloromethane over an extended period afforded a mixture of products in poor yield. \(^1\)H NMR evidence was interpreted in terms of the diols (87) and (88) (Scheme 3.3), but the inefficiency of this process precluded any further studies.

Exposure of the ether (85) to stronger Lewis acid reagents, such as boron trifluoride or boron tribromide caused destruction of the molecule.

The minor product from the LTA reaction was later identified as the 11α-iodo-12β,17-ether (86) by NMR and chemical studies. McCrindle reported the isolation of a similar compound in the LTA oxidation of a 17-kauranol derivative. The
iodoether (86) could be derived according to the following mechanism: oxidation of the C(12) radical (89) to a carbonium ion (90) followed by proton elimination to give the intermediate $\Delta^{11}$-olefin (91) and subsequent electrophilic addition by iodine to afford the cyclised iodoether (86) (scheme 3.4).

![Scheme 3.4](image)

Upon treatment with zinc in acetic acid, the iodoether (86) gave the ene-alcohol (92) in good yield. With the introduction of the olefin in the C-ring between C(11) and C(12), the prospect of utilising this intermediate to elaborate the required 12$\alpha$-alcohol seemed to be promising. It was hoped that electrophilic addition of hypobromous acid to the $\Delta^{11}$-olefin (93) would generate an intermediate bromonium cation (94), and neighbouring group participation by 13-acetate group would afford the bromohydrin (95). Reductive debromination$^{119}$ would furnish the 12$\alpha$-hydroxylated derivative (96) and subsequent elimination of a suitable 17-substituent would give a 12$\alpha$-hydroxylated gibberellin derivative (scheme 3.5).
The ene-alcohol (92) was first protected as the t-butyldimethylsilyl ether (93), by reaction with t-butyldimethylsilyl triflate and triethylamine in dichloromethane, in order to prevent recyclisation back to the bromo-ether. When the ether (93) was treated with N-bromoacetamide in aqueous acetone for 3 h, however, no reaction was observed.

Although the cyclic ether (85) was accessible and could in principle be elaborated via the sequence of ether ring-opening, selective hydroxyl protection and regeneration of the exocyclic olefin to give the 12-hydroxylated derivatives, the inefficiency of the ring-opening procedure rendered this route unattractive. The difficulties encountered prompted re-investigation of the original approach of using the bromo-ether to facilitate the ring-opening as well as regeneration of the $\Delta^{16}$-olefin.
3.1.3 Preparation of 16α-Bromo-12β,17-ether (97)

When the bromohydrin (66) was allowed to react with LTA in the same manner as described previously, the cyclic bromo-ether (97) was obtained in good yield. The reaction was found to be much slower than for the corresponding 17-alcohol, but addition of 2 extra equivalents of LTA, shortened the reaction time and improved the efficiency of the reaction. The bromo-ether (97) was consistently obtained in 75% yield, while the corresponding iodoether was never detected.

3.1.4 Reductive Ring-opening of the 16α-Bromo-12β,17-ether (97)

At this juncture, our synthetic strategy called for reductive ring-opening of the bromo-ether. This was conveniently accomplished by treatment of the bromo-ether (97) with zinc in acetic acid at reflux to give the 12β-hydroxylated GA₁ derivative (98) in 70% yield. The overall procedure thus proved viable for the introduction of oxygen functionalities at C(12).
3.2 Preparation of 12α-hydroxylated GA₁ Derivatives

3.2.1 Attempted SN₂ Displacement on the 12β-hydroxy GA Derivatives

Our next task was to invert the stereochemistry at C(12) to give the required 12α-configuratiom of the target GA₃₂ molecule. Our initial approach was based on an attempt to displace the 12β-hydroxy group or a derivative by a SN₂ process. The well-documented Mitsunobu procedure\(^1\) was an obvious choice, but when the 12β-alcohol (98) was treated with diethyl azodicarboxylate, triphenylphosphine and formic acid in benzene overnight, only the starting material was recovered.

The 12β-alcohol (98) was then derivatised as the methanesulfonate (99) by reaction of the alcohol (98) with methanesulfonyl chloride in pyridine. When the methanesulfonate (99) was treated with either tetra-n-butyl-ammonium formate\(^1\) or tetra-n-butyl-ammonium bromide\(^2\) in boiling acetone overnight, no reaction was observed. Presumably, the neopentyl nature of the 12β-alcohol is the cause of this problem, preventing efficient SN₂ type displacement.
In a synthesis of epiallogibberic acid, House observed the displacement of a methanesulfonate moiety by a neighbouring acetate group in one intermediate\textsuperscript{124} (scheme 3.6). We felt that the situation was very similar to the case in hand, but, when the methanesulfonate (99) was heated with either DBU or aqueous DMF\textsuperscript{125}, an intractable mixture of products was obtained.

\begin{center}
\textbf{Scheme 3.6}
\end{center}

3.2.2 Hydride Reduction of 12-Oxo Gibberellin Derivatives

Reduction of the 12-oxo derivative is an obvious alternative approach, although precedents suggested that reduction would return the 12\(\beta\)-alcohol\textsuperscript{126}. The 12-oxo compound (100) was obtained in excellent yield by reaction of the 12\(\beta\)-alcohol (98) with Jones' reagent, but reduction of the ketone (100) by reaction with sodium borohydride in methanol, indeed gave exclusively the 12\(\beta\)-alcohol (98).
It is well established that diastereofacial preference for hydride addition to the 12-carbonyl group is largely controlled by the steric environment of the C/D-ring system; hydride approach from the top face of molecule is blocked by the congested nature of the endo-face of the C/D-ring system. Therefore, hydride reduction of 12-oxo-gibberellin derivatives normally returned the axial 12β-alcohol as the only product as a result of hydride delivery to the less hindered exo-face of the molecule (diagram 3A).

Several other reducing systems were attempted but without any success. These systems included: a. sodium cyanoborohydride in methanol at pH 3, b. aluminum isopropoxide in isopropyl alcohol at reflux and c. samarium iodide in aqueous THF.

During the course of investigation of the Meerwein-Ponndorf-Verley reduction of the ketone (100), we felt that the diacetate was not an ideal candidate because the system could be sufficiently basic to remove the acetate groups to give the α-ketol (101). The α-ketol (101) can easily undergo a facile 1,2-isomerisation under basic conditions, to give the less strained bicyclo-[2.2.2]-octane skeleton (102) (scheme 3.7).
It was then decided to change the acetate group to the base-stable methoxymethyl ether protecting group. When the diacetate (100) was treated with potassium carbonate in methanol for 3 hrs, the diol (101) was obtained in 80% yield. Treatment of the diol with chloromethylmethoxy ether, Hünig's base and a catalytic amount of DMAP in dichloromethane gave the bis-methoxymethylether in 85% yield, but when the ether was allowed to react with aluminum isopropoxide in boiling 2-propanol, an intractable mixture was obtained.

Comparison between the respective $^1$H NMR spectra from the diacetate (100) and the ketol (101) showed that the magnitude of the vicinal coupling constant $J_{1\alpha,9\beta}$ diminished by 2Hz while the magnitude of the vicinal coupling constant $J_{1\beta,9\beta}$ was increased by 1.5Hz, which suggested that the conformation of C-ring of the ketol was changing from a boat to a half-chair conformation. The preference for a half-chair conformation of the C-ring in the ketol over the preferred boat conformation in the acetate is presumably due to the extra-stabilisation gained through hydrogen bonding between the 12-oxo function and the 13-hydroxy group. It is possible for intramolecular hydrogen bonds to introduce sufficiently powerful attractive forces to modify or reverse normal conformational preferences. Thus, with the case in hand, intramolecular hydrogen-bonding formation requires C(12), C(13), the oxygen atom of the 12-oxo function and the 13-hydroxy group to lie in the same plane. This coplanar nature between 12- and 13-substituents in turn forces the C-ring to adopt a half-chair conformation.
It was hoped that chelation between these groups and a suitable cation would also favour this particular conformation and allow less encumbered approach by the hydride nucleophile to the upper face of the 12-oxo group to give the required equatorial alcohol (Diagram 3C).

Zinc borohydride\textsuperscript{131} was chosen, not only by virtue of its neutral properties (in order to avoid the facile base-induced 1,2-ketol rearrangement), but also because of its well-defined chelating abilities during reduction processes.\textsuperscript{132} Indeed, when the ketol (101) was treated with dropwise addition of zinc borohydride in ether at 0°C, we
were strongly encouraged to find that a *ca* 3:7 mixture of the $12\alpha$- and $12\beta$- alcohols (103) and (104) was obtained in 80% overall yield.

The $12\beta$-alcohol (104) was shown to be identical with the product from the direct hydrolysis of the $12\beta$-hydroxylated-GA-diacetate (98). In an attempt to aid assignment, the $12\alpha$-alcohol (103) was first derivatised as the triacetate (105), but spectroscopic data remained inconclusive. Confirmation of the $12\alpha$-stereochemistry was provided by treatment of the triol (103) with phosgene and triethylamine\textsuperscript{133} in dichloromethane, giving the $12\alpha,13$-carbonate (106).

When scaling-up the reaction, solubility of the ketol (101) in ether became a
problem and addition of DMF was required to homogenise the solution mixture. Surprisingly, when the reaction was performed in a 1:1 mixture of ether and DMF at -30°C, a ca. 3:2 mixture of the 12α-hydroxylated GA\textsubscript{1} derivative (103) and 12β-hydroxylated GA\textsubscript{1} derivative (104) was obtained in 70% overall yield.

The present methodology has demonstrated the possibility of chemical synthesis of 12-oxygenated GA derivatives and indeed it is the first of its kind in chemical functionalisation of the C-ring of GAs. The regioselective functionalisation of C(12) is a consequence of a strong preference for the boat conformation of the C-ring in the gibberellin molecule\textsuperscript{21} and provides a sharp contrast to results obtained in similar experiments with kaurene types of substrate which have been reported to afford products derived from the abstraction of H(11β).\textsuperscript{67,68}
3.3 Preparation of 12-hydroxylated GA₃ Derivatives

3.3.1 Preservation of the A-ring Double Bond

Having succeeded in introducing an oxygen functionality at the C(12) position in a GA₃ derivative, we turned our attention towards preservation of the A-ring Δ¹-olefinic bond. We were well aware of the fact that this olefin could react with LTA, thereby complicating the radical cyclisation reaction. The possibility of such a complication appeared to necessitate protection of the olefin to permit the required operation for the formation of the cyclic ether.

We first conceived that the bromolactone derivative (109) could be employed as a masking unit for the A-ring olefin and access gained to the key intermediate (110) along the lines indicated in scheme 3.8. Regeneration of the allylic lactone moiety would, in principle, be accomplished by E2-elimination of the bromide (109) by DBU at reflux.

The bromo-aldehyde (107) was obtained by reaction of olefinic acids (79) and (80) with pyrrolidone hydrotribromide in dichloromethane. The mixture of Δ¹,₁₀-ene acids (79) and (80) was produced by hydrogenolysis of the enal (74) in the presence of an amine base; the simple hydrogenation products (77) and (78) were also obtained. When the crude product mixture from the hydrogenation was exposed to pyrrolidone hydrotribromide in dichloromethane, a mixture of the bromo-aldehyde (107) and the corresponding GA₁-bromo-aldehyde (83) (p48, Chapter 2) was obtained. Separation of the two products was possible by means of MPLC.
The bromo-aldehyde (107) was found to behave very much the same as the GA₁ derivatives, and the bromo-ether (109) was obtained in good yield. This bromo-ether (109) offered a flexible intermediate for the construction of both the GA₁ and GA₃ derivatives. Thus, reductive debromination of the bromolactone (109), under conditions which would avoid reductive elimination of the lactone function, could afford the GA₁ derivatives (97). Alternatively, the GA₃ derivative (110) could be obtained from (109) by β-elimination.

Although the synthesis of this flexible intermediate was quite efficient, the inconsistent results obtained from the hydrogenolysis of the A-ring allylic lactone moiety and tedious separation of (107) and the GA₁ derivative (83) precluded further investigation of this sequence.
In the interest of flexibility and generality, we chose to investigate the possibility of retaining the $\Delta^1$-olefinic bond throughout the entire transformation sequence. Although we originally expected that this would not be possible, preliminary studies demonstrated that the $\Delta^1$-ene was stable towards LTA under mild conditions. Thus, when 3,13-diacetoxyl GA$_3$ methyl ester (72) was treated with an excess of LTA in benzene at 50°C for 1 hour, the starting material was recovered in good yield. Prolonged heating caused the destruction of the molecule. These results suggested that the A-ring double bond might indeed be stable towards the hypoiodite reaction.

We now encountered the problem of selectively reducing the $\Delta^{15}$-olefinic bond in the presence of the $\Delta^1$-ene. This task was achieved by reduction of the enal (74) with zinc in acetic acid at room temperature for 1 hour, whereby the aldehyde (111) was obtained in 75% yield and competitive 1,2-reduction did not seem to be a serious problem. The aldehyde (111) behaved in exactly the same way as its 1,2-dihydro-analogues for the next few reaction steps. The bromohydrin (113) was formed efficiently and when this bromohydrin (113) was subjected to the transannular oxidation reaction, the bromo-ether (110) was obtained in 65% yield.

Scheme 3.9: i. Zn, AcOH ii. Pyrrolidine.HBr$_3$ iii. NaBH$_4$ iv. Pb(OAc)$_4$, I$_2$, hv v. Zn, AcOH, $\Delta$
3.3.2 Reductive Ring-Opening of (110)

At this stage, it seemed that the task of retaining the A-ring double bond had been achieved, but in fact, it turned out to be the beginning of yet another problem. When the bromo-ether (110) was treated with zinc in boiling acetic acid, a very polar material was obtained. $^1$H NMR and $^{13}$C NMR studies revealed the product to be the diene-acid (114), probably derived from the reductive elimination of the A-ring acetoxy-allylic lactone moiety* (scheme 3.9).

Hanson reported the isolation of a very unusual ketal product (115) from the reaction of GA3 derivative (72) with zinc in boiling acetic anhydride.‡ They proposed that formation of the ketal occurred via a [4+2] cyclo-addition reaction between the diene moiety and the carbonyl group of the mixed anhydride. They prepared the diene-acid intermediate by an alternative route based on treatment of GA3 (72) with zinc in boiling acetonitrile, and proved that the diene-acid was an intermediate in the formation of the ketal (115) (scheme 3.10).

---

* Barton‡ has reported that acetates of vicinal diols undergo reductive elimination upon treatment with metal-ammonia. Formation of olefin is most significant when one of the esters is tertiary and the geometrical arrangement is trans-diaxial.
The diene-acid (114) could, in principle, be used for elaboration of the A-ring functionalities. In fact, a similar diene-acid (18) was utilised to construct the A-ring functional system by Corey et al in the final stage of their synthesis of gibberellic acid.24

The diene-acid (18) was obtained as a relay intermediate from degradation of GA3 (6) and the A-ring allylic lactone was reassembled by means of the following sequence: epoxidation, hydrolysis, iodolactonisation, trifluoroacetylation, and reductive elimination (scheme 3.11).139

Although it is possible to reconstruct the A-ring functionality from the diene-acid (114), the inefficiency of the whole process rendered this route unattractive and prompted investigation of alternative procedures for the reductive ring-opening of the bromo-ether (110).

A chromium (II) amine complex in DMF was reported by Kochi to effect reductive elimination of bromohydrins to form olefins.140 However, when the bromo-ether (110) was treated with this reagent under a nitrogen atmosphere, the
debrominated ether (116) was obtained exclusively.

\[
\text{Cr(II)(en)}_2\text{Cl}_2 \rightarrow \text{OAc} \quad \text{OAc}
\]

In attempts to suppress reductive elimination of the A-ring acetoxy-allylic-lactone, the bromo-ether (110) was treated with freshly activated zinc dust in acetic acid at room temperature overnight, but no reaction was detected. The reaction mixture was then warmed slowly to 60°C for 2 h; again, no reaction was observed. The reaction was later heated to 100°C and, after stirring for 1 hr, thin layer chromatographic analysis indicated that the starting material was completely consumed and replaced by a more polar product. \(^1\)H NMR and \(^{13}\)C NMR studies revealed that the single spot on TLC contained a ca 1:1 mixture of the 12\(\beta\)-hydroxylated GA3 (117) and the 12\(\beta\)-hydroxylated iso-GA3 derivatives (118). Further attempts to resolve the two products by means of MPLC failed.

\[
\text{CH}_2\cdots\text{OAc} \quad \text{OAc}
\]

A-ring 1,2-double bond isomerisation is well documented, but normally occurs under basic conditions.\(^{141}\) Takahashi has, however, reported the isolation of an isogibberellic acid derivative from the reaction of GA3 with selenium dioxide in boiling ethanol.\(^{55}\) We believe that the rearrangement is catalyzed either by zinc or by zinc acetate.

Identification of this iso-gibberellic acid derivative (118) from the zinc/acetic acid reaction raised the possibility that the previously mentioned reductive elimination of an acetoxy-allylic lactone moiety might also proceed via an isogibberellic acid intermediate of this type.
Despite the fact that a mixture of GA₃ derivative (117) and iso-GA₃ derivative (118) was obtained, the result indicated that we were indeed on the right track. Conia⁴² reported that silver-activated zinc dust was found to effect reductive elimination reactions more efficiently than any other zinc related reagents. When (110) was treated with an excess of zinc-silver couple in acetic acid at room temperature for 2 h, the desired 12β-hydroxylated GA₃ derivative (117) was obtained in 70% yield, along with the reductively debrominated ether (116) (10% yield). When alcohol (117) was subjected to the sequence described for the preparation of 12-hydroxylated GA₁ derivatives (p62), essentially identical results were obtained (scheme 3.12).

![Scheme 3.12](image)

Scheme 3.12: i. CrO₃, ii. K₂CO₃, MeOH, iii. Zn(BH₄)₂

Success in preserving the A-ring olefin throughout this approach, not only provides access to the 12-oxygenated GA₃ derivatives, but also permits a high degree of flexibility in planning the A-ring oxidation level. Although these 12,13-dihydroxylated gibberellin derivatives are not known compounds, they can serve as reference materials for the future identification of new gibberellins. More importantly, these synthetic samples will prove to be extremely valuable materials for structure-activity relationship studies.

The present methodology has demonstrated not only the feasibility of chemical synthesis of 12-oxygenated GAs, but also the possibility for extensions to further chemical manipulations of the C-ring such as C(11) hydroxylation and preparation of Δ⁹,₁₁-olefins (see p25).
CHAPTER 4

Attemped Alkylation and Hydroxylation on 11-Oxygenated Cholesterol
Chapter 4.

4. Approaches to the Preparation of GA$_{32}$ (36) and its 1,2-Dihydro-Analogue (123)*

4.1 Attempted Allylic Hydroxylation on 12-Oxygenated Gibberellins

We were now confronted with the final phase in the partial synthesis of Gibberellin A$_{32}$ (36): elaboration of the D-ring allylic carbinol array. Since the most difficult aspect of this transformation had been achieved, namely the functionalisation of the non-activated C(12) position, and methodology for the introduction of the remaining hydroxyl group at C(15) had been worked out, the prognosis for access to GA$_{32}$ (36) and its 1,2-dihydro-analogue (123) through synthesis appeared to be excellent.

4.1.1 12$\alpha$-Hydroxylated Derivatives

The derivatives (105) and (106) appeared to be the most suitable intermediates with which to complete the sequence even though, the parent 12$\alpha$-hydroxy GA$_1$ methyl ester was obtained in less than 40% yield from zinc borohydride reduction of the $\alpha$-ketol (see p 62).

*Both GA$_1$ and GA$_3$ derivatives have been indiscriminately used as substrates for this investigation and identical results were obtained in most cases.
Unfortunately, initial attempts to perform an allylic oxidation on these compounds with selenium dioxide proved to be unrewarding. When these compounds were treated individually with 2 equivalents of selenium dioxide and t-butyl hydroperoxide in a ca 1:1 mixture of dichloromethane and acetic acid over extended periods, only starting materials were recovered in both cases. The reason for the perturbation caused by the 12α-hydroxy substituent on the reactivity of the Δ^{16}-ene towards selenium dioxide was not obvious.

4.1.2 12β-Hydroxylated Derivatives

Due to limited substrate availability and difficulties encountered in the attempted allylic oxidation of these 12α-hydroxy derivatives, we embarked upon a study of the possibility of using the 12β-derivatives. No reaction was observed when the 12β-TBDMS ether (124) was subjected to a similar reaction with selenium dioxide, however.

The failure of (124) to react with selenium dioxide could conceivably be explained in terms of steric congestion between the D-ring bridge and the 12β-substituent.
There is good evidence that the mechanism for the reaction between selenium dioxide and olefins, in general, involves sequential pericyclic steps.\textsuperscript{143} With the case in hand, the transition state for the first pericyclic reaction requires the tilting of the 17-carbon atom towards the C(9)-C(11)-C(12) portion of the C-ring, but steric repulsion exerted by the bulky 12\beta-axial substituent might well disfavour this process (scheme 4.1).

\begin{center}
\includegraphics[scale=0.5]{scheme41.png}
\end{center}

Scheme 4.1

When the 12\beta-hydroxy GA\textsubscript{1} derivative (98) was allowed to react with selenium dioxide and tert-butyl hydroperoxide in dichloromethane for 10 minutes, a \textit{ca} 4:1 mixture of two products was obtained, which could be separated by chromatography.

\begin{center}
\includegraphics[scale=0.5]{product98.png}
\end{center}

On the basis of \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopic data and by comparison with compound (67), we deduced that the major compound was the seleno-compound (125)\textsuperscript{*} which could be derived from an initial reaction between the 12\beta-hydroxy group and selenium dioxide to give the seleninic acid; subsequent electrophilic addition to the \Delta^{16}-olefin followed by neighbouring group participation by the 13-acetate to form an ortho-acid intermediate with eventual collapse would then deliver the product (125) (scheme 4.2).

\*Similar selenium-containing compounds had been reported by Sharpless and co-workers.\textsuperscript{144}
4.1.3 12-Oxo Derivatives

In contrast to these disappointing results, conversion of the 12-oxo compounds (100) and (119) to the allylic alcohols (126) and (127) proceeded smoothly, if rather slowly. Exposure of (100) and (119) individually to 2 equivalents of selenium dioxide and an excess of tert-butyl hydroperoxide in a 1:1 mixture of dichloromethane and acetic acid for 3 days, provided the required allylic alcohols (126) and (127) in 80% yield respectively.
4.2. Attempted Preparation of 15β-Hydroxy-12-One (129)

The failure of 12α-hydroxy derivatives to react with selenium dioxide necessitated modification of our initial plan for the synthesis of GA32. MacMillan employed an oxidation/reduction strategy for introduction of the 15β-hydroxy group into several gibberellin molecules. We hoped that this methodology would be equally effective for elaboration of the 15β-alcohol in the closely related 12-oxo derivatives (128). The 15β-hydroxy group of (129) might possibly be utilised, in the subsequent reduction of the 12-carbonyl group to direct the hydride delivery to the more hindered endo-face of the 12-oxo function to give the desired 12α-carbinol (130) (diagram 4A, scheme 4.3).
4.2.1 Reduction of 12,15-Dione (128)

In practice, this strategy proved to be unsuccessful. Treatment of the enone (128) (obtained in 75% yield from Swern oxidation of the allylic alcohol) with activated zinc dust in glacial acetic acid gave the dioxo-compound (131) resulting from 1,4-conjugate reduction. Similarly, reduction with: a). sodium borohydride in methanol, b). sodium borohydride with cerium trichloride in methanol and c). DIBAL in THF at -78°C failed to give any of the desired 15β-allylic alcohol (129).

4.2.2 Attempted Preparation of 17-Bromo-15β,16β-epoxy-12-One (136)

In view of these difficulties, an alternative, albeit more lengthy approach was considered involving the following steps: a). derivatisation of the allylic alcohol (127) as the methanesulfonate ester (132), b). SN2' displacement of the methanesulfonate by reaction with lithium bromide to give the allylic bromide (133), c). metal hydride reduction of the 12-oxo derivative (133) to return the 12β-hydroxy derivative (134), d). selective epoxidation of the Δ15-ene under the directing influence of the 12β-hydroxy group to deliver the 15β,16β-epoxide (135), e). oxidation of the 12β-alcohol (135) to afford the 12-oxo derivative (136), f). reductive elimination of the bromo-epoxide (136) to give the desired 15β-allylic alcohol (129) (scheme 4.4).

The requisite methanesulfonate ester (132) was obtained by reaction of the alcohol (127) with an excess of methanesulfonyl chloride in pyridine at -20°C, although, its formation was accompanied by a significant amount of the undesired allylic chloride (137).

In an attempt to prepare the allylic bromide (133) directly, the allylic alcohol (127) was exposed to phosphorous oxybromide in pyridine in the hope that this reagent would lead to the formation of a phosphate intermediate; subsequent allylic displacement by
bromide anion at the more exposed C(17) should then give the desired allylic bromide (133). The action of phosphorous oxybromide on the allylic alcohol (127) resulted in the formation of a product whose spectroscopic properties were consistent with the secondary allylic bromide (138), however, indicating that displacement had surprisingly occurred on the neopentyllic C(15) from the congested β-face of the molecule rather than at the more exposed C(17) atom.

Model studies were later made on (73) in order to examine alternative procedures for effecting an efficient conversion of the allylic alcohol to the allylic bromide, but these proved to be fruitless. Treatment of the allylic alcohol (73) with triphenylphosphine/carbon tetrabromide in dichloromethane\(^{147}\) or DEAD/lithium bromide/triphenylphosphine in benzene\(^{121}\) overnight, led to recovery of starting material in both cases. Fortunately, the proportion of the allylic chloride (137) during the methanesulfonylation reaction could be reduced by shortening the reaction time and destroying the excess of methanesulfonyl chloride by very slow addition of aqueous acetone before work-up. The methanesulfonate ester (132) was then obtained in 70% yield.
4.2.2.1 Reduction of the Allylic Bromide (133)

Treatment of the methanesulfonate ester (132) with anhydrous lithium bromide in dimethyl formamide overnight, gave the allylic bromide (133) in 90% yield. However, reduction of this product with sodium borohydride in methanol gave a mixture of two alcohols (134) and (140) in 20% and 60% yield, respectively.

The $^1$H NMR spectrum of the major product (140) showed a new triplet resonance signal at 5.0 ppm which was too far downfield to be consistent with the methine proton of the newly created carbinol centre. This result, presumably a consequence of migration of the neighbouring 13-acetate group to the 12-alcohol function, piqued our curiosity and caused us to speculate that we had obtained the 12α-acetoxy GA₃ derivative (140) from sodium borohydride reduction of the 12-oxo compound (133). Comparison of Dreiding models of the 12-oxo-allylic bromide (133) and the 12-oxo GA derivative (100) revealed that in the latter, the 15β-hydrogen atom blocked approach of the reducing reagent to the more hindered endo-face of the molecule. Removal of this hydrogen atom, by introduction of the $\Delta^{15}$-olefinic bond, made hydride delivery to the β-face (to give the
12α-carbinol) more favourable. The cis-relationship between the 12α-hydroxy group and the 13-acetate group permitted migration of the acetate group to the less hindered C(12) to give the thermodynamically more favoured 12α-acetate via an ortho-acid intermediate (139) (scheme 4.5).

Neighbouring group rearrangements of this class are frequently observed in carbohydrate chemistry and generally occur quite readily between vicinal gauche hydroxy groups bearing a cis relationship. The minor product from the sodium borohydride reduction was identified as the 12β-hydroxy derivative (134) by comparison with (98).
4.2.2.2 Epoxidation of (141)

It seemed that the stereochemical problem of the reduction of the 12-carbonyl group had been solved and that the remaining task was elaboration of the 15β-carbinol fragment from the allylic bromide. Our modified scheme for redeploying an oxygen function at C(15) envisioned epoxidation of the Δ^15-ene, followed by reductive elimination of the bromo epoxide to furnish the allylic alcohol. The allylic bromide (140) was first derivatised as an acetate (141), then treated with p-nitroperbenzoic acid in dichloromethane for 2 days to afford a single product (142 or 143) in 70% yield. H NMR studies suggested that the epoxide was a single diastereomer.

Comparison of the spectra of the starting material (141) and the product from epoxidation revealed that the signal due to the 12β-proton was shifted downfield by 0.3 ppm. The downfield shift could be explained either by the anisotropic deshielding effect exerted by the oxygen atom of the endo-epoxide (142) or by the steric deshielding effect caused by the tilting of the 17-methylene group in the exo-epoxide (143) towards the 12β-proton (diagram 4B). At this stage, we were not sure which isomer was obtained, but, on the basis of steric considerations derived from examination of Dreiding models, we
assumed this epoxide to be the exo-epoxide (143).

\[ \text{Diagram 4B} \]

Model studies with a GA3 derivative were also pursued, the allylic bromide (144) again giving a single diastereomer (145) upon treatment with p-nitroperbenzoic acid. This epoxide (145) was subsequently allowed to react with silver-zinc couple in acetic acid at room temperature for 5 minutes to regenerate the starting 15α-alcohol (73). This result indicated that epoxidation must have taken place on the less hindered α-face of the D-ring to give the exo-epoxide (145).
4.2.2.3 Attempted Reduction of (143).

Unfortunately, although the allylic bromide (141) reacted smoothly with $p$-nitroperbenzoic acid to give a single epoxide (143), treatment of the epoxide (143) with zinc in boiling acetic acid resulted in the recovery of starting material. The stability of this epoxide towards zinc reduction was somewhat puzzling, given the known propensity of bromoepoxides towards reductive ring opening. Whether this was due to the presence of the 12α-acetoxy substituent diminishing the reactivity of the bromo-oxirane towards reductive elimination, or to some other factor, was not known. The quite unexpected failure of this epoxide to undergo reductive elimination with most zinc reagents foiled the intended transformation of allylic bromide (141) to the 15-hydroxy derivatives.

4.2.2.4 Preparation of 12β-Hydroxy-15-ene-17-bromide (134)

The difficulties encountered with re-introduction of the 15-allylic oxygen function to the allylic bromide (141) prompted us to re-examine the original plan of using the 12β-hydroxy group to direct the epoxidation on the Δ15-ene to give the required 15β,16β-epoxide. Since reduction of the Δ15-ene-12-oxo compounds gave the 12β-alcohol as a minor product, we attempted the hydride reduction step on the 15-methanesulfonate ester derivative before executing the displacement of the methanesulfonate ester with bromide anion in the hope that the presence of the 15β-hydrogen atom could, to a certain degree, prevent the approach of the reducing agent to the hindered top-face thereby affording the 12β-alcohol more selectively. In actual fact,
the hindered top-face thereby affording the 12β-alcohol more selectively. In actual fact, when the methanesulfonate ester (132) was subjected to reaction with sodium borohydride in methanol, a ca 2:3 mixture of (146) and (147) was obtained.

Examination of a Dreiding model of (132) suggested that steric repulsion between the bulky 15α-methanesulfonate ester substituent and the 7-methyl ester group could cause twisting of the C/D-ring in order to adopt a more stable conformation, effectively moving the 15β-hydrogen atom away from the trajectory for approach of reagent to the upper face of the 12-carbonyl group (diagram 4C).
4.2.2.5 Epoxidation of (134)

The mixture of (146) and (147) was readily separated by flash chromatography and the 12β-alcohol (147) was obtained in 50% yield. Upon treatment with anhydrous lithium bromide in dimethylformamide overnight, the allylic methanesulfonate (147) gave the allylic bromide (134) in 80% yield. This bromide was subjected to epoxidation with p-nitroperbenzoic acid overnight to afford the bromoepoxide (135) in good yield. $^1$H NMR studies revealed the product to be a single diastereomer, but we were again unable to assign the stereochemistry at this stage. Upon treatment with Jones' reagent, the 12β-alcohol (135) gave the corresponding ketone (136) in 95% yield.

4.2.2.6 Attempted Reductive Elimination of (136)

Although epoxide (136) was obtained from a different sequence of reactions with the epoxidation taking place in the presence of the 12β-alcohol, we were unable to assign the stereochemistry of the oxirane because of the inadequacy of $^1$H NMR data. Disappointingly, the bromoepoxide (136) was also found to be unreactive towards
reductive elimination with zinc-silver couple in acetic acid even at elevated temperatures for 3 hours.

4.3 Protection of the Exocyclic Olefin

In view of the highly unexpected stability of these bromo-oxirane compounds, we turned our attention towards the approach of protecting the exocyclic olefin during the hydride reduction of the 15-ketone.

4.3.1 Attempted Preparation of 15-Oxo-17-phenylselenenyl Derivatives

The $\beta$-phenylseleno silylenol ether (148) was considered to be an ideal intermediate for accomplishing the required operation in several aspects. Our previous investigation of the hydride reduction of allylic bromide (133) provided evidence that introduction of an sp$^2$ centre at C(15) favoured approach of the reducing reagent along the upper face of the molecule to give predominantly the 12$\alpha$-alcohol; therefore, hydride reduction of the silyl enol ether (148) was expected to give the required 12$\alpha$-alcohol (149) (Diagram 4D).

\[
\begin{array}{c}
\text{Me}_3\text{Si} \quad \text{PhSe} \\
\text{O} \\
\end{array}
\]

Diagram 4D

Hydrolysis of the silyl enol ether would regenerate the keto functionality at C(15) to give (150) which, upon hydride reduction would be expected, to afford the
15β-alcohol (151). Subsequent oxidation of the 17-phenylselenide to the selenoxide, followed by elimination would elaborate the required 15β-allylic alcohol (152) (scheme 4.6).

Unfortunately, model studies based on the more readily available GA3 enone derivative (153) proved to be disappointing. A number of attempts to convert (153) to the β-phenylselenosilylenol ether (154) or the β-phenylseleno ketone (155) by literature procedures failed completely.
4.3.2 Preparation of Epoxyketone

Epoxyketones, which can be easily prepared from the corresponding enone by treatment with basic hydrogen peroxide\(^{152}\), have been frequently used as a masked form of the enone functionality.\(^{153}\)

![Diagram showing the preparation of epoxyketones](image)

When enone (153) was subjected to several standard basic hydrogen peroxide epoxidation conditions, unsatisfactory results were obtained. Presumably, the base sensitive functional groups present in the substrate were the cause of the trouble.

An alternative procedure was sought for preparation of the epoxyketone. Epoxidation of the \(\Delta^{16}\)-double bond in compound (126) was again realised with an excess of \(p\)-nitroperbenzoic acid to give a ca 1:1 mixture of the diastereomeric epoxides (156) and (157), which could be resolved upon chromatography. On the basis of their polarity profile on TLC analysis, the first compound eluted from the column was assumed to be the endo-epoxide (156) while the more polar compound was assigned as the exo-epoxide (157). Considerable difficulties were encountered in attempting to oxidise the individual epoxyalcohols to the corresponding epoxyketones. Oxidation of the exo-epoxyalcohol (156) with Jones' reagent was found to be extremely sluggish, requiring prolonged reaction times and a large excess of oxidant to give the epoxyketone (158) in 75% yield. The endo-epoxyalcohol (157) was found to be unreactive under similar reaction conditions.
4.3.3 Reduction of Epoxyketone (158)

With the availability of the epoxyketone (158), we addressed the problem of reduction of this di-oxo-compound. Initial studies with sodium borohydride in methanol resulted in a complex mixture of several polar compounds; attempts to acetylate the mixture of products in order to aid product identification proved to be unrewarding. A less basic reducing system, zinc borohydride in ether, was later chosen to re-investigate the behaviour of this di-oxo-compound (158) towards hydride reduction. When the epoxyketone (158) was treated with an excess of zinc borohydride in ether at 0°C, TLC analysis showed two spots which were separated by silica gel chromatography. $^1$H NMR data on these products suggested that each of these two spots in fact represented a mixture of two compounds and were interpreted in terms of the four alcohols (159), (160), (161) and (162). In subsequent experiments, formation of the mixture of more polar products (161) and (162) could be suppressed by using smaller quantities of the zinc borohydride reagent to give a ca 4:1 mixture of the alcohols (159) and (160) in 70% yield (inseparable by flash
The differences in relative reactivities between the 12- and 15-oxo groups towards zinc borohydride reduction can be accounted for by the fact that the oxygen atom of the oxirane ring is capable of forming a co-ordinated complex with the zinc reagent rendering the neighbouring 15-carbonyl group more susceptible towards hydride reduction (Diagram 4E).\textsuperscript{154}
At this juncture, two concurrent studies were pursued for the synthesis of the target molecule. a). Deoxygenation of the oxirane functionality in the epoxyalcohol (159) would effectively furnish the crucial 15β-allylic alcohol intermediate (129), but regeneration of the Δ16-ene from the epoxide could not be effected by using any of the standard conditions. For example, treatment of the epoxide (144) with either the chromium (II) ethanediamine complex in DMF or sodium iodide and zinc dust in acetic acid gave a mixture of several products.

b). The epoxyalcohol (159) was subjected to further reduction in order to assess the possibility of using the 15β-hydroxy group to direct the delivery of hydride along the more hindered β-face during reduction of the 12-carbonyl group to give the required 12α-alcohol (162) (Diagram 4F).
Unfortunately, the epoxyalcohol (159) was found to be unreactive towards sodium triacetoxyborohydride\textsuperscript{157} and upon treatment with zinc borohydride in ether, the epoxyalcohol gave the 12\(\beta\)-alcohol.*

*Reduction of 15\(\beta\)-hydroxy-12-oxo-songorine with lithium aluminum hydride gives predominantly the 12\(\alpha\)-carbinol (scheme 4 F1).\textsuperscript{145} Although this result contrasts with the 12\(\beta\)-carbinol formed by reduction of the epoxyalcohol (159) with zinc borohydride, it is possible that borohydride reagent could also form complexes with the 15-hydroxy group, the shorter bond distance between the boron atom and the hydrogen atom rendering the boron reagent incapable of reaching the 12-carbonyl group to deliver the hydride to the top-face of the 12-carbonyl group. Further investigation into this aspect has not been carried out, however.
4.4 Re-examination of Allylic Oxidation of 12α-Hydroxy GA Derivatives

4.4.1 Preparation of Diol (164).

Because of the difficulties encountered with the hydride reduction of the 12-carbonyl group, we returned to an earlier approach of employing the 12α-hydroxy GA₃ derivatives to achieve the goal of synthesising GA₃₂. Based upon our previous experience with the allylic oxidation of various gibberellins with selenium dioxide (summarised in scheme 4.7), we reasoned that the failure of compound (120) to react with selenium dioxide could be due to steric hindrance exerted by the 13-substituent which is forced by any 12α-substituent to take up a preferred set of conformations which hinder the exo-face of the D-ring.

Indeed, when compound (163), with the acetate group replaced by a hydroxyl function, was allowed to react with an excess of selenium dioxide and t-butyl...
(164) was obtained in 60% yield along with recovered starting material in 30% yield. Unfortunately, our attempts to oxidise the diol (164) selectively to the enone proved to be unsuccessful, even though MacMillan et al.\textsuperscript{34b} were able to oxidise a similar diol to the required enone without any apparent major difficulties. When the diol (164) was subjected to Swern oxidation, a mixture of several products was obtained.

4.4.2 Preparation of GA32 Methyl Ester 3,12,13-Triacetate (169)

In view of the difficulties encountered during the transformation of the diol (164) to the required enone, we re-examined the allylic oxidation of the triacetate (165) and were gratified to find that the allylic alcohol (166) could be obtained in 70% yield after prolonged reaction of the triacetate (165) with a very large excess of selenium dioxide and tert-butyl hydroperoxide in glacial acetic acid for 72 hrs.

The allylic alcohol (166) was oxidised to the corresponding enone (167) in
80% yield by using Swern's conditions and subsequent reduction with activated zinc dust in glacial acetic acid for 30 minutes gave, after chromatographic purification, the saturated ketone (168) and the desired 15β-allylic alcohol (169), in 50% yield respectively. It is expected that treatment of (169) with potassium carbonate in methanol should give the tetrahydroxy gibberellin derivative (170), thereby providing the prospect of the synthesis of the GA32 methyl ester.
Two groups have speculated that they have isolated the 1,2-dihydro analogue of GA$_32$ from *Prunus persica*. However, due to the lack of an authentic sample for comparison, its identity remains unconfirmed. With the success in the partial synthesis of a GA$_32$ derivative, preparation of its 1,2-dihydro analogue (123) now became a trivial problem. Reduction of the A-ring $\Delta^1$-olefin was conveniently achieved by catalytic hydrogenation of the bromoether (110) over rhodium to give the saturated analogue (97), which was then subjected to the aforementioned sequence of reactions for the preparation of GA$_32$ derivative (169) to give (174). Hydrolysis of the tri-acetate (174) with potassium carbonate in methanol is expected to give the tetra-hydroxy GA$_1$ methyl ester (175) which could be used for direct comparison with the putative new gibberellin from *Prunus persica*. 

\[
\begin{align*}
\text{i. Zn/AcOH} & \quad \text{ii. CrO}_3 \\
\text{iii. K}_2\text{CO}_3 & \quad \text{iv. Zn(BH}_4\text{)}_2 \\
\text{v. Ac}_2\text{O} & \quad \text{SeO}_2 \\
\end{align*}
\]
Preparation of 12-Oxygenated-13-Deoxy Gibberellane

In the preceding chapter, we focused on the partial synthesis of GA32 (G3) from GA3 (G3), but this is the only member of the known 12-oxygenated GA series which bears a 13-hydroxy substituent. The rest of these 12-oxygenated GAs all belong to the family of 13-deoxy-11-oxo-gibberellanes (Section 5.1).
Chapter 5.

Preparation of 12-Oxygenated-13-Desoxy Gibberellins

In the preceding chapter, we focussed on the partial synthesis $\text{GA}_{32}$ (36) from $\text{GA}_3$ (6), but this is the only member of the known 12-oxygenated GA series which bears a 13-hydroxy substituent. The rest of these 12-oxygenated GAs all belong to the family of 13-desoxy-analogues (Scheme 5.1).

Scheme 5.1 : Structures of some 12-hydroxy C-19 gibberellins
Since we had successfully employed the transannular oxidation route to gain access to 12-hydroxy GA₃ derivatives, the objectives of the present study were to extend the GA₃₂ methodology to the preparation of all of these 12-oxygenated GAs.

5.1 Partial Synthesis of 12β-Hydroxy GA₇ Methyl Ester (193)

Pharis and co-workers have speculated they have isolated 12β-hydroxy GA₇ from *Lolium* species. Our first approach was based on the expectation that the synthesis of these compounds could be completed with the same methodology, by changing the starting material from GA₃ (6) to GA₇ (28).

GA₇ (28) can also be produced by fermentation of *Gibberella fujikuroi*, but unlike GA₃ (6), it is obtained as a mixture with GA₄ (183). Separation of GA₇ from GA₄ is possible only through tedious HPLC procedures. Several chemical syntheses of GA₇ from GA₃ have been reported, but, because of the structural complexities of these molecules, the yields are generally far from ideal. We chose, therefore, to begin our investigation with a GA₇ rich mixture of GA₄ (183) and GA₇ (28).

Unfortunately, these compounds were found to behave quite differently.
from their 13-oxygenated counterparts. The enal (185) was obtained by standard methods in 60% yield, and reduction of this compound (185) with zinc in acetic acid gave a ca 1:1 mixture of the aldehyde (186) and the allylic alcohol (187) in 75% overall yield. The allylic alcohol (187) could be recycled by oxidation with pyridinium chlorochromate to regenerate the enal (185), however. Treatment of the aldehyde (186) with pyrrolidone hydrotribromide surprisingly gave a ca 3:1 mixture of the bromo aldehydes (188) and (189) (inseparable by flash chromatography). Reduction of the mixture of bromo aldehydes (188) and (189) with either sodium cyanoborohydride in methanol or sodium borohydride in dimethoxyethane, gave a complex mixture of products and the bromohydrin (190) was obtained in only 35% yield after extensive chromatography. When (190) was subjected to the lead tetra-acetate reaction, the bromoether (191) was obtained in 60% yield. Reductive elimination of this product with zinc-silver couple gave the 12β-hydroxy GA7 derivative (192), but although the 12β-hydroxy compounds were accessible by this route, the overall yield was found to be unacceptably low compared to the sequence using the 13-oxygenated analogues.
Pure GA7 methyl ester derivative (supplied by Bruce Twitchin), prepared from GA3 through deoxygenation of the 13-methyl oxalate according to the MacMillan procedure, was used to re-examine the sequence of reactions in the hope of optimizing the yields of some of these reactions. Regrettably, these still proved to be unrewarding and the 12β-hydroxy GA7 derivative was obtained in less than satisfactory overall yield. The 3-acetate was removed by treatment with aqueous potassium carbonate in methanol to give the 12β-hydroxy GA7 methyl ester (193). The mass spectrum of the synthetic sample was very similar to one of the putative GAs isolated from *Lolium* species, but the two compounds exhibited different Kovat's Retention Indices. It is therefore likely that the *Lolium* compound is an 11-hydroxy derivative of GA7.159

5.2 Preparation of 12α-Hydroxy GA7 Methyl Ester (GA30)

We now wished to direct our attention to the synthesis of GA31 (176) and were not only confronted with the persistent problem of overall low yield, but also the task of inverting the 12β-configuration to give the 12α-carbinol in the target molecule. In principle, the 13-hydroxy group could be removed from a suitable GA3 derivative at any stage of the sequence, but the abnormal behaviour of the 13-deoxygenated compounds led us to consider the postponement of the deoxygenation step to a late stage of the synthesis. The 12-ketone (119) was considered as an ideal intermediate for the execution of the deoxygenation step, and it was hoped that the activation caused by the 12-carbonyl group would enable the selective hydrolysis of the neighbouring 13-acetate160 and conceivably facilitate the reductive removal of the 13-methyl oxalate function (scheme 5.2 ).
Attempts to effect the selective removable of the 13-acetate proved to be fruitless. When the diacetate (119) was treated with aqueous potassium carbonate in tetrahydrofuran overnight,\textsuperscript{160} the starting material was recovered unchanged, while treatment of the diacetate with aqueous potassium carbonate in methanol, gave the diol (120) in 80\% yield.

Julia reported that reduction of a halohydrin ester with tri-n-butyltin hydride led to a stereospecific 1,2-migration of the acetoxy group from a tertiary carbon to a secondary carbon atom (scheme 5.3).\textsuperscript{161}
The 12β-methyl oxalate (197) was prepared in order to examine the possibility of applying the procedure to effect the removal of the 13-oxygen function as well as inversion of the stereochemistry of the 12β-carbinol. It was hoped that treatment of the 12β-methyl oxalate (197) with tin hydride could generate the radical at C(12) (198). Subsequent migration of the acetoxy group and hydrogen transfer could lead to the desired 12α-acetoxy GA7 derivative (199) (scheme 5.4).

Scheme 5.4

Unfortunately, when the 12β-methyl oxalate (197) was treated with tri-n-butyltin hydride and AIBN in boiling toluene, the 12β-alcohol (118) was obtained as the sole product.査

*The mechanism for acyloxy migration has not been established. It could involve formation of a \( \pi \)-bond between the participating carbon atoms, in which case migration would not be possible in these GA derivatives. The formation of the 12-carbinol, however, indicates that the problem lies with the formation of the C(12) free radical.
Compound (140), an advanced intermediate in our attempts to synthesise GA32, was considered as a potential intermediate for elaboration of the 12α-hydroxy GA7 derivative (204) via the following scheme: a) displacement of the bromide (139) with hydrazine, oxidation of the hydrazide (200) to the azine (201) followed by 1,5-sigmatropic rearrangement and loss of nitrogen to generate the Δ16-olefin (202), derivatisation of the 13-alcohol (202) as the methyl oxalate (203) and finally reduction of the 13-methyl oxalate function with tri-n-butyltin hydride (scheme 5.5). The idea was reserved due to lack of material at that stage, however.
of the triols (121) and (122) in 48% and 32% yields respectively. Selective protection of alcohol functions in (121) was contemplated by virtue of the differences in steric hindrance among these hydroxy groups.

When (121) was treated with an excess of acetic anhydride and triethylamine in dichloromethane, the diacetate (163) was obtained in 95% yield, thereby, affording the prospect of selectively derivatising the 13-hydroxy group as the methyl oxalate. When (163) was treated with methyl oxalylchloride, triethylamine and a catalytic amount of DMAP in dichloromethane, the 13-methyl oxalate ester (203) was obtained in 80% yield. Upon treatment of (203) with tri-n-butyltin hydride and a catalytic amount of AIBN in boiling toluene, the corresponding 13-deoxygenated product (204) was obtained in 70% yield. Subsequent hydrolysis of the 3-acetate group with potassium carbonate gave the 12α-hydroxy GA7 methyl ester (GA30 methyl ester) (205).
12α-Hydroxy GA7 has been isolated from *Calonyction aculeatum* and assigned as GA30 (176), but identification of 12β-hydroxy GA7 from natural sources has not yet been reported. Success in the partial synthesis of 12-hydroxy GA7 derivatives from GA3 not only demonstrated the generality of the sequence but also provided access to the whole range of 12-hydroxy GAs.
5.3 Preparation of GA₅₈ and GA₇₁ Derivatives from GA₃

With the success in the synthesis of 12-hydroxylated GA₇ derivatives, preparation of 12-hydroxy GA₄ derivatives (208) and (212) now became straightforward. When ketol (101) was subjected to the aforementioned sequence of reactions for the synthesis of (205), GA₅₈ and GA₇₁ derivatives (208) and (212) were obtained in good overall yields (scheme 5.6). Treatment of (208) with potassium carbonate in methanol gave 12α-hydroxy GA₄ methyl ester (GA₅₈ methyl ester) (209). Hydrolysis of (212) to GA₇₁ methyl ester (213) has not been fully investigated because of lack of material, however.
5.4 Synthesis of GA₃₁, GA₆₉ and GA₇₀ Methyl Esters

In order to extend the strategy further, we turned our attention towards the synthesis of the remaining 12-hydroxylated C-19 gibberellins. GA₅ (37) has been shown to be a versatile intermediate for access to a wide range of gibberellins with various A-ring substitution patterns.³¹ We therefore envisaged that the corresponding bromoether (218) might be an ideal intermediate for the synthesis of the remaining 12-oxygenated C₁₉ gibberellins. The cyclic bromoether (218) moiety not only serves as a precursor for the 12-hydroxy gibberellins, but also offers chemical protection for the incipient Δ¹⁶-olefin. Chemical manipulations of the Δ²-olefin could now be performed without restrictions imposed by the presence of the Δ₁⁶-olefin; hydrogenation of the Δ²-olefin could provide access to the saturated A-ring analogues, GA₆₉ (180) and GA₇₀ (181), while hydroxylation with osmium tetroxide could afford the 2,3-dihydroxylated A-ring structure, such as GA₄₈ (178).

The starting GA₅ derivative (214) (supplied by Bruce Twitchin) was conveniently prepared from the readily available GA₃ (6) via the following sequence: a). oxidation of the allylic alcohol to give the Δ¹-enone, b). reduction of the enone to afford the saturated alcohol, c. derivatisation of the alcohol as the tosylate ester, and d), elimination of the tosylate to furnish the Δ²-ene (scheme 5.7).
Scheme 5.8
As shown in scheme 5.8, conversion of (214) to the corresponding GA₅-bromoether (218) followed closely the methodology for the preparation of the GA₃ bromoether (110). GA₃₁ methyl ester (227) was prepared from (218) in an analogous manner to the synthesis of 12α-hydroxy GA₇ methyl ester (GA₃₀) (205), while hydrogenation of the bromoether (218) provided the starting material with the saturated A-ring structure for the preparation of GA₆₉ and GA₇₀ methyl esters (237) and (241).

12β-hydroxy GA₉, 12α-hydroxy GA₉ and 12β-hydroxy GA₄ have recently been isolated from the sporophytes of the tree fern (*Cyathea australis*) and were assigned GA₆₉ (180), GA₇₀ (181) and GA₇₁ (182).¹⁶⁴

We have thus extended the lead tetra-acetate transannular oxidation strategy to the synthesis of most of the naturally occurring 12-oxygenated C-19 gibberellins and opened a direct avenue to the series of 12-hydroxy GAs stereoisomeric at C(12) which are likely to be discovered in other plant species.
Although many of the physiological responses elicited by exogenous application of gibberellins have been successfully exploited experimentally in agriculture, an understanding of the mode of action of these compounds at the molecular level still remains in its infancy. The question of whether gibberellins exert their biological effects through interactions with specific receptors themselves, or through systemic conversion into other biologically active compounds remains as unsolved as ever. For this reason, a thorough understanding of gibberellic metabolism is required to enable us to allow the design of more effective plant growth regulators that allow a beneficial and predictable modification of plant growth and development.

CHAPTER 6

Lamberts recently reported that a modification of the Ochiai (treated) identification procedure can be applied successfully to the gibberellin 17-glucosidase system. The procedure was found to be sensitive and applicable to more gibberellic structures. With this modification it is possible to use the new method to the preparation of deuterium-labelled gibberellins. Previously, a whole range of 17-deuterium-labelled gibberellic analogues have been prepared by this method. A stock of these deuterium-labelled gibberellins is maintained by our group.
Preparation of Isotopically Labelled Gibberellins

Although many of the physiological responses elicited by exogenous application of gibberellins have been successfully exploited commercially in agriculture, an understanding of the mode of action of these compounds at the molecular level still remains in its infancy. The question of whether gibberellins exert their biological effects through interactions with specific receptors themselves, or through enzymic conversion into other biologically active compounds remains an unresolved issue. For this reason, a thorough understanding of gibberellin metabolism is required in order to allow the design of more efficacious plant growth regulators that allow a beneficial and predictable modification of plant growth and development.

For the past three decades, biosynthetic studies of gibberellins have relied heavily on the availability of isotopically labelled substrates as tracers. A tremendous effort has been devoted to chemical studies on this group of natural products, leading to the build-up of a wealth of methodologies for efficient chemical conversions of the more readily available gibberellins to the less accessible ones. Many of these procedures have been extended to the preparation of radioactive isotopically labelled gibberellins.

Lombardo recently reported that a modification of the Oshima-Nozaki methylenation procedure can be applied successfully to the gibberellin 17-norketone system. The procedure was found to be versatile and applicable to most gibberellin structures. When dibromomethane is replaced by the deuterated dibromomethane reagent, the method can be extended to the preparation of deuterium labelled gibberellins (scheme 6.1), a whole range of 17-dideuterated gibberellin analogues have been prepared by this method. A stock of these deuterium labelled gibberellins is maintained by our group.
enabling us to supply researchers all over the world. Deuterium labelled gibberellins make excellent internal standards in quantitation of native GAs, but used on their own are of limited utility in metabolic studies. Unfortunately, the Lombardo methylenation method can not be satisfactorily extended to the preparation of radioactive labelled gibberellins because it requires a large excess of reagent.

Following success in the stereoselective partial synthesis of C-20 gibberellins in this laboratory from the freely available GA3, our attention was directed towards the development of methodology for the preparation of radioactively labelled C-20 gibberellin derivatives as tracers for gibberellin biosynthesis studies, with the hope of unravelling the pathway by which the twentieth carbon atom is lost in gibberellin biosynthesis.

6.1 Attempted Ring-opening Reaction on the Cyclopropyl Ketone

Our initial plan focussed on a sequence for the stereoselective partial synthesis of GA19 from GA3 (scheme 1.11), with the hope that a flexible intermediate could be employed for the incorporation of radioactive labels. The cyclopropyl ketone (34) seemed to be a potential candidate since an electrophile induced ring-opening of the 3-membered ring could be expected to afford the unsaturated ketone (242).\textsuperscript{167} The presence of the double bond in the A-ring offers an opportunity for isotope incorporation by catalytic tritiation (scheme 6.2).
Unfortunately, when the cyclopropyl ketone (34) was treated with 1.1 equivalents of trimethylsilyl triflate in dichloromethane at -10°C, a mixture of several products was obtained. Attempts to find suitable conditions to effect the conversion proved to be fruitless. The approach was therefore abandoned.

### 6.2 Attempted Hydrogenolysis on the 15α- Allylic Oxygen Function

During the course of investigation into functionalization of the gibberellin C-ring, several intermediates appealed to us as potential substrates for incorporation of isotopical labels. Attention was first directed towards the hydrogenolysis of readily available 15α-allylic oxygen compounds such as alcohol (73) or lactone (243) (scheme 6.3).
A variety of hydrogenation procedures were examined with these compounds, including those based on: a). palladium-on-carbon in ethyl acetate, b). palladium-on-carbon in ethyl acetate and pyridine (10%), c). palladium-on-barium carbonate in pyridine. Regrettably, none of them provided any promising results. This approach was therefore discarded.

6.3 Preparation of 17-d\textsubscript{1}-GA\textsubscript{1}

We next examined the possibility of utilizing the enal (74) as a substrate for the labelling studies. This polyfunctional compound offers two opportunities for isotope incorporation. The enal can be reduced to the saturated alcohol, with radioactive isotope incorporation being, in principle, performed at either of the two stages: a). catalytic tritiation and/ or b). reduction of the aldehyde with tritiated hydride reagents. Subsequent regeneration of the exocyclic methylene unit from the 17-carbinol could be achieved by one of the standard procedures reported in the literature (scheme 6.4).

![Scheme 6.4](image_url)

Coincidentally, at the start of our work, a method employing a similar approach for the preparation of tritiated Cembrene-A was reported by Prestwich, which
employed Grieco's selenoxide elimination procedure for the regeneration of the exocyclic methylene unit from the primary alcohol \(168\) (scheme 6.5).

\[
\begin{align*}
\text{Cembrene-A} & \xrightarrow{9\text{-}BBN} \text{OH} \xrightarrow{PCC} \text{H} & \text{KOH} & \text{H/HT} & \text{H}_{2}O_{2} & \text{H/HT} & \text{OH} \\
\end{align*}
\]

Scheme 6.5

6.3.1 Reduction of Bromo-aldehyde with Sodium Cyanoborodeuteride

While the approach of utilizing enal (74) as an intermediate for labelling studies seemed encouraging, it was subsequently felt that bromo-aldehyde (83), an intermediate in the sequence for the preparation of 12-oxygenated gibberellins, looked even more appealing. Reduction of the bromo-aldehyde with tritiated hydride reagent could afford the radioactively labelled bromohydrin. The bromohydrin offers an advantage over the 17-carbinol with respect to elaboration of the exocyclic \(\Delta^{16}\)-olefin. Treatment of the bromohydrin with zinc should lead to the formation of the desired exocyclic methylene derivative (scheme 6.6).

\[
\begin{align*}
\text{Scheme 6.6} \\
\end{align*}
\]

Sodium cyanoborohydride was used in our original procedure for the reduction of the bromo-aldehyde to the bromohydrin. Literature reports suggested that the
hydrogen atoms of the cyanoborohydride anion could be readily exchanged for either deuterium or tritium under acidic conditions,\textsuperscript{109,169} thus permitting direct syntheses of sodium cyanoborodeuteride and tritiated sodium cyanoborohydride. This interesting reaction made the approach even more appealing.

To investigate the feasibility of applying this approach to the preparation of radioactively labelled C-20 gibberellins, the readily available GA\textsubscript{1} bromo-aldehyde (83) was used as a model rather than one of the available C-20 gibberellins. Sodium cyanoborodeuteride, prepared by the literature procedure,\textsuperscript{109} was used initially to avoid unnecessary handling of radioactive material during the trial stage. When the bromo-aldehyde (83) was allowed to react with the deuterated cyanoborohydride and bromocresol green in tetrahydrofuran, with the acidity of the reaction maintained at pH 3 by occasional addition of a solution of acetyl chloride in deuterium oxide,\textsuperscript{109} the deuterated bromohydrin (244) was obtained in 70\% yield with excellent deuterium incorporation. Subsequent treatment of the deuterated bromohydrin with zinc in boiling acetic acid, afforded a mixture of E/Z-17-d\textsubscript{1}-gibberellin A\textsubscript{1} derivatives (245) with 93\% deuterium incorporation, in 80\% yield.

\begin{center}
\includegraphics[width=\textwidth]{diagram.png}
\end{center}

The same procedure was extended to the preparation of deuterium labelled GA\textsubscript{3} by changing the starting material from GA\textsubscript{1} bromo-aldehyde (83) to GA\textsubscript{3} bromo-aldehyde (112). In order to aid the regeneration of the exocyclic olefin, the deuterated bromohydrin (246) was first acetylated to give the corresponding bromo-acetate...
(247); subsequent treatment of (247) with zinc-silver couple at room temperature for 10 minutes afforded the deuterated GA$_3$ derivatives (248).

6.4 Preparation of 15-d$_1$-17-d$_1$-GA$_3$ Derivative

The overall transformation of enal to the $\Delta^{16}$-ene can be viewed as a single process of deoxygenation accompanied by the migration of the double bond to the exocyclic position. Hutchins has reported that reduction of tosylhydrazones with cyanoborohydride in acidic media can afford the corresponding hydrocarbon in good yield. With $\alpha,\beta$-unsaturated derivatives, alkenes are normally furnished in which the double bond migrates to the position formerly occupied by the carbonyl group even when such movement produces less thermodynamically stable positional isomers.$^{170}$ This procedure not only provides a mild and selective alternative to the standard Wolff-Kishner deoxygenation, but also offers a convenient pathway to exocyclic olefins. It was then decided to examine the possibility of applying this method to prepare isotopically labelled gibberellins.

The $\alpha, \beta$-unsaturated tosylhydrazone was prepared by reaction of the enal (74) with 1.1 equivalents of tosylhydrazine in ethanol at room temperature for 30 minutes. Evaporation of the ethanol gave the tosylhydrazone (249) in almost quantitative yield. Without further purification, the crude product was dissolved in a 1:1 mixture of dimethylformamide and sulfolane. Sodium cyanoborodeuteride and a trace of bromocresol green were added to the reaction mixture with the acidity of the solution
maintained at pH3 by addition of a mixture obtained from the addition of acetyl chloride to deuterium oxide. After heating at 110°C for 1h, the di-deuterio-GA3 derivative (250) was obtained in 65% yield. 1H NMR, 2H NMR and 13C NMR studies revealed that each molecule of GA3 was doubly labelled, deuterium atoms being located both at C(15) and C(17).

Hutchins originally proposed that double bond migration in the acid catalysed reduction of α,β-unsaturated tosylhydrazones with sodium cyanoborohydride proceeds through an initial attack by the cyanoborohydride in a Michael fashion to give the rearranged tosylhydrazine intermediate (252), which subsequently decomposes to the product. (scheme 6.7)

Djerassi undertook detailed studies on the mechanism of the sodium cyanoborohydride reduction of several steroidal α,β-unsaturated tosylhydrazones and suggested a more plausible mechanism. The proposed reaction pathway involves an initial sodium cyanoborohydride reduction of an imminium ion (251) formed by
protonation of the tosylhydrazone (249), to give an intermediate hydrazide (253); 1,2-elimination of toluenesulfinic acid from the resulting intermediate would then afford an intermediate alkylidiazene (254) and a 1,5-sigmatropic rearrangement with loss of nitrogen could lead to formation of the alkene (scheme 6.8).

In the stereospecific total synthesis of (+)-cafestol,\textsuperscript{162} Corey employed an allylic hydrazide intermediate for the elaboration of the exocyclic methylene unit. Oxidation of the allylic hydrazide gave the diazene which underwent a 1,5-sigmatropic hydrogen transfer, followed by expulsion of nitrogen to give the desired alkene (scheme 6.9). This result further supported the 1,5-sigmatropic rearrangement mechanism proposed for the hydride reduction of the $\alpha,\beta$-unsaturated tosylhydrazone.
In conclusion, we have established two versatile and efficient methods for preparing isotopically labelled gibberellins which should be extendable to the preparation of tritiated gibberellins. Radioactively labelled gibberellins are constantly required by plant physiologists, not only to follow the biosynthesis and metabolism of gibberellins in plants, but also for transport, localization, radioimmunoassay and photoaffinity labelling studies.
CONCLUSION

Success in the introduction of oxygen functionalities at the C(13) position not only fulfills our objectives of preparing 13-carboxyl intermediates essential for CO(2) functionalization, but also provides a new range of amenable for monoclonal antibody systems which will be used for radioimmunoassay studies. Since these substrates provide an alternative site, other than the conventional C-7 carboxyl group, with which to couple with protein molecules, the antibodies raised are expected to possess a different, and hopefully more desirable range of characteristics. In addition to being utilized in radioligand assay, antibodies raised against gibberellins can also be used for immunoblotting. Chromatography columns containing carbohydrates would act as selective filters, passing all of the unwanted biochemical material while retaining the compound of interest. In this role they offer the opportunity of rapid and effective purification of carboxylic acid and other analytes. Immunoadsorption columns have been successfully used for the purification of GA-3.\\n
13-Oxogenerated gibberellins could also be utilized in the preparation of affinity columns to aid isolation of GA-receptor macromolecules or enzymes responsible for gibberellin inactivation, and for the synthesis of affinity labels. Several photosensitive gibberellin derivatives were prepared and investigated by Machin and associates with the hope of isolating the supposedly bound bound ligand-receptor macromolecular complex which could eventually reveal additional information regarding the physiological hormone-receptor contact hypothesis for the development of observed physiological response.

Most of the synthetic 12-hydroxy gibberellins reported in this theme are the methyl ether derivatives, but not the natural free acids. Although these compounds can be used for direct comparison in confirming potential unmasking of recognition of natural gibberellins, they cannot be used directly for biological testing. Future work therefore needs to address the conversion of the methyl ether to the corresponding free acids. We consider that the method of using lithium fluoride to desilylate phosphonic esters is
Conclusion

Success in the introduction of oxygen functionalities at the C(17) position not only fulfills our objective of preparing 17-carbinol intermediates required for C(12) functionalisation, but also provides a new range of substrates for monoclonal antibody synthesis which will be used for radioimmunoassay studies. Since these substrates provide an alternative site, other than the conventional C-7 carboxy group, with which to couple with protein macromolecules, the antibodies raised are expected to possess a different, and hopefully more desirable range of characteristics.\textsuperscript{175} In addition to being utilized in immunoassays, antibodies raised against gibberellins can also be used for immunoaffinity chromatography.\textsuperscript{176} Chromatography columns containing immobilized antibodies would act as selective filters, passing all of the unwanted biochemical 'noise', while retaining the compound of interest. In this role they offer the possibility of rapid and effective purification of extracts prior to quantitative analysis. Immunoaffinity columns have been successfully used for the purification of GA\textsubscript{3}.\textsuperscript{176}

17-Oxygenated gibberellins could also be utilised in the preparation of affinity columns to aid isolation of GA-receptor macromolecules or enzymes responsible for gibberellin biometabolism, and for the synthesis of affinity labels. Several photoaffinity gibberellin ligands were prepared and investigated by MacMillan \textit{et al} \textsuperscript{83} with the hope of isolating the covalently bound ligand-receptor macromolecule complex which could eventually reveal additional information relating to the postulated hormone-receptor contact hypothesis for the development of observed physiological responses.

Most of the synthetic 12-hydroxy gibberellins reported in this thesis are the 7-methyl ester derivatives, but not the natural free acids. Although these compounds can be used for direct comparison in confirming tentative structural assignments of natural gibberellins, they cannot be used directly for biological testing. Future work therefore, needs to address the conversion of the methyl esters to the corresponding free acids. We consider that the method of using lithium thiolate in hexamethyl phosphoric triamide\textsuperscript{177}
consider that the method of using lithium thiolate in hexamethyl phosphoric triamide \(^{177}\) should provide an effective means for the reconstitution of the carboxylic acid, even with some of the base-sensitive substrates, such as GA\(_5\) and GA\(_{71}\).

The sequence of reactions employed in elaboration of 12-hydroxy gibberellins provides several opportunities for deuterium incorporation. Efforts directed towards the preparation of labelled C12-hydroxy gibberellins for quantitative studies are already in progress. The possibility of extending the C(12) functionalisation methodology to the preparation of C11-hydroxy gibberellins is also being examined.

The conversion of GA\(_3\) to GA\(_{32}\) derivative was achieved through a lengthy sequence of reactions but with a fair overall yield. We envisage that transannular oxidation of a 16\(\alpha\)-bromo-15,17-diol derivative could provide a shorter and a more efficient route to the target molecule (scheme C1).

With the development of sodium cyanoborohydride methodology for preparing isotopically labelled gibberellins, attention in the future will be directed towards the preparation of tritiated GA\(_3\), GA\(_7\) and the C-20 GA\(_{19}\).
understanding of the principles of their chemistry, biochemistry and physiology. With these recent developments in new methodologies for preparing some of the less abundant gibberellins, it is now technically possibly to prepare almost any one of the known gibberellins. As a result, a variety of gibberellins with a whole array of substitution patterns are potentially available to plant biologists for investigation and hopefully a clearer picture of the mechanism of the biological action of gibberellins will emerge.
EXPERIMENTAL

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**General Topics**

i. Melting points were determined with a Reichert hot stage apparatus. Melting points and boiling points are uncorrected.

ii. Infrared spectra (IR) were recorded on a Perkin-Elmer 683 Infrared Spectrophotometer in chloroform solution (0.25mm cells) unless otherwise stated.

iii. $^1$H NMR spectra were recorded on several instruments operating at the following frequencies: (a) 200MHz (JEOL JNM FX 200), (b) 200MHz (Varian XL200E) (c) 300MHz (Varian XL300). $^1$H NMR data in the experimental section refer to spectra recorded at 200MHz using instrument (a) unless otherwise stated. Samples were run in deuterochloroform (99.8% D), unless indicated otherwise, using tetramethylsilane as an internal standard ($\delta$ 0.00ppm). Data are presented in the following order: chemical shift (ppm) relative to tetramethylsilane; multiplicity; coupling constant-$J$ (Hz); intensity as the number of protons; assignment (if appropriate). The following abbreviations are adopted: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets); dt (doublet of triplets); bd (broad doublet); bs (broad singlet); bt (broad triplet). First order analyses of spectra were attempted when possible and, consequently, chemical shifts and coupling constants for multiplets may only be approximate. Most homonuclear decoupling experiments were performed on instrument (a).

iv. $^2$H NMR were recorded on a Bruker CXP200 instrument.

v. Most $^{13}$C NMR spectra were recorded on instrument (a) operating at 50.10MHz and $^{13}$C NMR data in the Experimental refer to spectra recorded on this instrument unless otherwise stated. Samples were run in deuterochloroform (99.8% D), unless indicated otherwise, using tetramethylsilane as an internal standard ($\delta$ 0.00ppm). Chemical shift (ppm) are reported relative to tetramethylsilane; assignments are based on the multiplicity and correlations of chemical shifts with closely related compounds.$^{172}$ Multiplicities were
determined from their broad band decoupled refocussed 'INEPT' spectra. The Insensitive Nuclei Enhanced by Polarization transfer (INEPT) pulse sequence uses a predelay time of 5.5ms to give methine and methyl signals in phase (in), methylene carbon signals 180° out of phase (out), and quaternary carbon signal suppressed (sup.).

vi. Low resolution electron impact mass spectra (MS) were recorded at 70 e.v. on either (a) AEI MS 902 or (b) VG-Micromass 7070E double focussing mass spectrometers. Data are presented in the following order: m/z value; relative intensity as a percentage of the base peak. Chemical ionization mass spectra (CIMS) were run with ammonia as the reagent gas, unless stated otherwise, and recorded on instrument (b). High resolution mass spectrum (HRMS) were recorded on either (a) or (b) using heptacosfluorotributylamine or perfluorokerosene as a reference.

vii. Microanalyses were performed by the Australian National University Analytical Services Unit, Canberra.

viii. Column chromatography was carried out using Merck Kieselgel 60 as the absorbent. Preparative thick layer chromatography (plc) was carried out on glass-backed plates (20x20cm, 20x40cm; 0.5mm-2mm thick) coated with Merck Kieselgel KG254. Analytical t.l.c. was performed on micro-slides coated with Merck Kieselgel KG254. The microslides were visualized using first ultra-violet light and then by spraying with a solution of 5% (w/v) vanillin in concentrated sulfuric acid and heated at 180°C. MPLC was carried out using Lobar LiChroprep Si 60 (40-63µm) prepacked columns, sizes A (for 50-200mg quantities) and B (for 100mg-1g quantities).

ix. Reactions were run under an atmosphere of nitrogen and the solvents used were dried over molecular sieves. In particular, THF and diethyl ether were distilled from the ketyl formed by the reaction of sodium with benzophenone.

x. Reaction mixtures were magnetically stirred, unless otherwise stated. Reaction temperatures refer to external bath temperatures, unless indicated otherwise.

xi. Organic solvents were dried over anhydrous sodium sulfate unless otherwise
stated. After filtration, the bulk of the solvent was evaporated on a Büchi rotary evaporator (water aspirator pressure). The last traces of solvent were removed under high vacuum.

xii. All 15α-hydroxy gibberellins were prepared according to the procedure published by MacMillan.34a

xiii. 13-Acetoxy GA5 methyl ester was kindly provided by B. Twitchin.

xiv. Aqueous chromous chloride solution was prepared according to the procedure published in 'Reagents for Organic Synthesis' Vol I, pp149-150.104

xv. Pyrrolidone hydrotribromide was prepared according to the procedure of Daniels.107

xvi. Lead tetra-acetate was purchased from Aldrich Chemical Company and used without purification.

xvii. Thorn's "Compact source" Mercury Discharge Lamp (250V,250W) was used as the irradiation source in all the lead tetra-acetate reaction.

xviii. Sodium cyanoborodeuteride was prepared by exchanging the hydrogens of sodium cyanoborohydride for deuterium using the procedure of Borch.109

Notes on Nomenclature

Compounds described in the Experimental have been named as derivatives of ent-gibberellane.11
CHAPTER 2

ent-20\(\xi\)-(1,1-Dimethylethyl)dimethylsiloxo-20\(\xi\)-hydroxy-13-methoxy-methyloxy-gibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (55).

\[
\text{CHO} \quad \text{OMOM} \quad \text{OTBDMS} \quad \text{OMOM}
\]

tert-Butyl dimethylsilyl triflate (70µl, 0.3mmol) was added dropwise to a stirred solution of the acid-aldehyde* (100mg, 0.24mmol) and triethylamine (45µl, 0.33mmol) in dichloromethane (5ml) at -20°C. After stirring at the same temperature for 0.5h., saturated sodium bicarbonate solution was added. The resulting reaction mixture was extracted with dichloromethane (2x10ml) and the combined organic extract was washed with water, then brine and dried over sodium sulfate. Concentration \textit{in vacuo} and chromatography on silica gel (ethyl acetate:hexane, 1:3) gave (55) (110mg, 94%) as solids. Recrystallisation with ether afforded colourless crystals (110mg).

\[ R_f : \quad 0.85 \text{ (ethyl acetate:hexane, 1:1)} \]

\[ \text{m.p.} \quad 234-242^\circ \text{C} \]

\[ \text{^1H NMR} : \quad 0.21 \text{ (s, 3H, SiMe)} \quad 0.25 \text{ (s, 3H, SiMe)} \quad 0.91 \text{ (s, 9H, Si^Bu)} \quad 1.08 \text{ (s, 3H, 4Me)} \quad 2.21 \text{ (m, 2H, H6+H15, overlapped)} \quad 2.40 \text{ (m, 1H, H15'')} \quad 2.75 \text{ (d, J=13.0Hz, 1H, H5)} \quad 3.35 \text{ (s, 3H, OCH}_2\text{OMe)} \quad 3.78 \text{ (s, 3H, OMe)} \quad 4.53, 4.72 \text{ (ABd, J=8.0Hz, 2H, MOM)} \quad 4.95 \text{ (bs, 1H, H17)} \quad 5.10 \text{ (bs, 1H, H17'')} \quad 5.55 \text{ (s, 1H, H2O)}.
\]

\[ \text{MS} : \quad 534 (M^+, 2%) \quad 519 (1) \quad 503 (1) \quad 489 (3) \quad 477 (5) \quad 445 (12) \quad 433 (10) \quad 403 (3) \quad 387 (2) \quad 357 (3) \quad 340 (3) \quad 314 (3) \quad 284 (10) \quad 265 (5) \quad 253 (3) \quad 237 (6) \quad 211 (3) \quad 198 (9) \quad 185 (4) \quad 157 (4) \quad 143 (9) \quad 121 (5) \quad 105 (6) \quad 89 (9) \quad 73 (40) \quad 45 (100).
\]

\[ \text{HRMS} : \quad \text{C}_{29}\text{H}_{46}\text{O}_7\text{Si} (M^+): \text{ requires } 534.3013, \text{ found } 534.3015.
\]

*The starting acid-aldehyde was prepared according to the published sequence (scheme 1.1, pg15).
Ozone was bubbled through a stirred solution of (55) (20mg, 27µmol) and pyridine (0.5ml) in dichloromethane (5ml) at -78°C. After bubbling for 5 min, dimethyl sulfide (100µl) was added and the resulting mixture was allowed to warm to ambient temperature. Evaporation to dryness and chromatography on silica gel (ethyl acetate:hexane, 1:2) afforded (56) (15mg, 75%) as a colourless oil.

**Rf:** 0.60 (ethyl acetate:hexane, 1:1).

**1H NMR:**
- 0.21 (s, 3H, SiMe) 0.26 (s, 3H, SiMe) 0.91 (s, 9H, Si^t^Bu) 1.11 (s, 3H, 4Me) 2.45 (m, 1H, Hl5) 2.83 (d, J=13.0Hz, 1H, H5) 3.35 (s, 3H, OCH2OMe) 3.71 (s, 3H, OMe) 4.63, 4.78 (ABd, J=7.4Hz, 2H, MOM) 5.55 (s, 1H, H20).

**13C NMR:**
- -5.3 (SiMe) -3.6 (SiMe) 18.7 (C18) 20.8 (-CH2-) 22.8 (-CH2-) 25.6 (Si^t^Bu) 32.1 (-CH2-) 33.1 (-CH2-) 37.5 (-CH2-) 40.6 (-CH2-) 42.7 (q) 46.5 (-CH2-) 48.7 (q) 51.2 (-CH-) 52.3 (OMe) 52.4 (-CH-) 53.0 (OMe) 54.0 (q) 56.2 (-CH-) 83.1 (C13) 92.5 (MOM) 98.0 (C20) 173.0 (C7) 174.1 (C19) 215.6 (C16).

**ent-20ζ-(1,1-Dimethylethyl)dimethylsiloxy-20ζ-hydroxy-13-methoxy-16-oxo-17-norgiberellane-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (56).**

MCPBA (10mg, 58µmol) was added to a stirred solution of (55) (20mg, 27µmol) and sodium bicarbonate (5mg) in dichloromethane (5ml). After stirring at room temperature for 6 h., the reaction mixture was diluted with dichloromethane (10ml) and washed with saturated sodium bicarbonate solution, water then brine and dried over sodium sulfate. Concentration
in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) gave the epoxide (58) (18mg, 90%) as a foam.

Rf : 0.55 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 0.19 (s, 3H, SiMe) 0.24 (s, 3H, SiMe) 0.91 (s, 9H, Si$^t$Bu) 1.12 (s, 3H, 4Me) 2.77 (s, 2H, H17+H17') 2.81 (d, J=12.0Hz, 1H, H5) 3.34 (s, 3H, OCH$_2$OMe) 3.73 (s, 3H, OMe) 4.60,4.72 (ABd, J=7.4Hz, 2H, MOM) 5.55 (s, 1H, H20).

$^{13}$C NMR : -5.3 (SiMe) -3.6 (SiMe) 18.7 (C18) 20.8 (-CH$_2$-) 21.8 (-CH$_2$-) 25.6 (Si$^t$Bu) 32.1 (-CH$_2$-) 34.3 (-CH$_2$-) 39.5 (-CH$_2$-) 40.2 (-CH$_2$-) 42.7 (q) 44.5 (-CH$_2$-) 46.2 (q) 47.2 (q) 49.2 (-CH-) 51.2 (-CH-) 52.3 (OMe) 53.1 (OMe) 53.7 (-CH-) 54.0 (q) 58.1 (C17) 63.2 (C16) 78.0 (C13) 92.5 (MOM) 98.0 (C20) 172.9 (C7) 174.2 (C19).

ent-17-Bromo-20$\xi$-(1,1-dimethylethyl)dimethylsiloxo-16β,20$\xi$-dihydroxy-13-methoxymethyloxy-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (61).

Anhydrous lithium bromide (3.5mg, 40µmol) was added to a solution of (58) (15mg, 27µmol) in benzene (1ml) and HMPA (1ml). After stirring at room temperature for 48 h., the reaction was diluted with ethyl acetate (10ml), washed with dilute hydrochloric acid (2M), water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane ; 1:2) gave the bromohydrin (61) (16mg, 93%).

Rf : 0.55 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 0.19 (s, 3H, SiMe) 0.24 (s, 3H, SiMe) 0.91 (s, 9H, Si$^t$Bu) 1.10 (s, 3H, 4Me) 2.16 (d, J=13.0Hz, 1H, H6) 2.32 (d, J=11.0Hz, 1H, H14) 2.73 (d, J=13.0Hz, 1H, H5) 3.33 (bs, 1H, OH) 3.40 (s, 3H, OCH$_2$OMe) 3.55 (ABd, J=11.0Hz, 2H, H17+H17') 3.72 (s, 3H, OMe) 4.75 (s, 2H, MOM) 5.55 (s, 1H, H20).
ent-17-Bromo-20ξ-(1,1-dimethylethyl)silyloxy-20ξ-hydroxy-13-oxo-12(13→16β)-abeo-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,20-Lactone (64).

N-Bromo-acetamide (3mg, 22µmmol) was added to a solution of (55) (10mg, 18.5µmol) and water (0.05ml) in acetone (5ml). After stirring at room temperature for 30min, the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10ml), washed with water, then brine and dried over sodium sulfate. Concentration in vacuo and filtration through a plug of silica gel gave ketone (64) (10mg, 96%).

Rf : 0.80 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 0.14 (s, 3H, SiMe) 0.22 (s, 3H, SiMe) 0.88 (s, 9H, SiBu) 1.09 (s, 3H, 4Me) 2.33 (d, J=12.0Hz, 1H, H14) 2.51 (s, 2H, H15+H15’) 2.16 (d, J=13.0Hz, 1H, H6) 2.71 (d, J=12.0Hz, 1H, H5) 3.41 (ABd, J=11.0Hz, 2H, H17+H17’) 3.74 (s, 3H, OMe) 5.55 (s, 1H, H20).

$^{13}$C NMR : -5.3 (SiMe) -3.6 (SiMe) 20.6 (C18) 20.8 (-CH₂-) 22.2 (-CH₂-) 25.6 (SiBu) 32.1 (-CH₂-) 34.3 (-CH₂-) 35.4 (-CH₂-) 40.6 (-CH₂-) 42.7 (sup) 46.5 (-CH₂-) 46.6 (sup) 47.2 (sup) 50.6 (-CH-) 51.5 (-CH₂-) 52.2 (OMe) 56.0 (-CH-) 56.5 (-CH-) 58.2 (-CH-) 98.0 (C20) 173.2 (C7) 174.1 (C19) 213.1 (C13).

M.S. : 537 (M⁺-31, 1%) 511 (5) 483 (6) 467 (15) 423 (5) 391 (6) 359 (6) 331 (17) 320 (9) 287 (5) 259 (6) 241 (7) 211 (10) 198 (16) 171 (8) 143 (22) 129 (16) 105 (23) 91 (32) 73 (100).
ent-17-Bromo-3α,13-diacetoxy-10β,16β-dihydroxy-20-norgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (67).

\[
\begin{align*}
\text{AcO} & \quad \text{CO}_2\text{Me (65)} \\
\text{OAc} & \quad \text{AcO}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{Br} \\
\text{OAc} & \quad \text{AcO}
\end{align*}
\]

N-Bromo-acetamide (45mg, 0.33mmol) was added to a stirred solution of (65) (100mg, 0.224mmol) and water (0.1ml) in acetone (10ml). After stirring at room temperature for 15 min, acetone was removed under reduced pressure and the residue was dissolved in ethyl acetate (10ml), washed with water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) gave (67) (115mg, 96%) as a yellow foam.

\[\text{Rf} = 0.60 \text{ (ethyl acetate:hexane, 1:1)}.\]

\[\text{\textsuperscript{1}H NMR:} \quad 0.99 \text{ (s, 3H, 4Me)} \quad 2.02 \text{ (s, 3H, OAc)} \quad 2.08 \text{ (s, 3H, OAc)} \quad 2.63 \text{ (d, J=11.0Hz, 1H, H6)} \quad 2.69 \text{ (s, J=12.2Hz, 1H, H14)} \quad 2.95 \text{ (bs, 1H, OH)} \quad 3.11 \text{ (d, J=11.0Hz, 1H, H5)} \quad 3.63 \text{ (ABd, J=19.8Hz, 2H, H17+H17')} \quad 3.72 \text{ (s, 3H, OMe)} \quad 4.91 \text{ (bs, 1H, H3)}.\]

\[\text{\textsuperscript{13}C NMR:} \quad 14.5 \text{ (C18)} \quad 16.9 \text{ (C11)} \quad 21.1 \text{ (OAc)} \quad 21.9 \text{ (OAc)} \quad 25.4 \text{ (C2)} \quad 27.5 \text{ (C1+C17, overlapped)} \quad 39.1 \text{ (C14)} \quad 40.0 \text{ (C15)} \quad 48.5 \text{ (C8)} \quad 50.2 \text{ (C9)} \quad 52.3 \text{ (OMe)} \quad 53.3 \text{ (C6)} \quad 55.6 \text{ (C4)} \quad 55.5 \text{ (C5)} \quad 71.3 \text{ (C3)} \quad 79.5 \text{ (C16)} \quad 85.6 \text{ (C13)} \quad 92.6 \text{ (C10)} \quad 169.2 \text{ (OAc)} \quad 170.1 \text{ (OAc)} \quad 172.5 \text{ (C7)} \quad 176.4 \text{ (C19)}.\]

\[\text{M.S.:} \quad 511 \text{ (M\textsuperscript{+}-31, 1\%)} \quad 444 \text{ (100)} \quad 403 \text{ (57)} \quad 385 \text{ (17)} \quad 371 \text{ (30)} \quad 363 \text{ (16)} \quad 341 \text{ (44)} \quad 311 \text{ (16)} \quad 297 \text{ (22)} \quad 281 \text{ (55)} \quad 267 \text{ (31)} \quad 239 \text{ (33)} \quad 221 \text{ (17)} \quad 211 \text{ (14)} \quad 197 \text{ (13)} \quad 169 \text{ (12)} \quad 155 \text{ (15)} \quad 129 \text{ (18)} \quad 117 \text{ (11)} \quad 91 \text{ (23)}.\]

\[\text{HRMS:} \quad \text{C}_{23}\text{H}_{28}\text{O}_{8}^{79}\text{Br} \text{ (M\textsuperscript{+}-31) requires 511.0967, found 511.0959}.\]
ent-3α-Acetoxy-17-bromo-13,16-dioxo-10β-hydroxy-20-nor-(13,16)-seco-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (68).

LTA (160mg, 0.37mmol) was added to a solution containing (67) (50mg, 0.092mmol), iodine (46mg, 0.18mmol) and calcium carbonate (20mg) in cyclohexane (10ml). The purple reaction mixture was heated to boiling with irradiation from a tungsten lamp (250W) placed about 2" from the reaction vessel. After stirring at reflux temperature for 1h, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (50ml). The resulting mixture was filtered through celite and washed with saturated sodium thiosulfate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) gave the diketone (68) (29mg, 66%).

R_f : 0.65 (ethyl acetate:hexane, 1:1)

^1H NMR : 1.10 (s, 3H, 4Me) 2.56 (d, J=18.0Hz, 1H, H14) 2.61 (d, J=10.0Hz, 1H, H6) 2.70 (s, 2H, H15+H15') 2.92 (d, J=18.0Hz, 1H, H14') 3.31 (d, J=10.0Hz, 1H, H5) 3.72 (s, 3H, OMe) 3.95 (s, 2H, H17+H17') 4.96 (bs, 1H, H3).

^13C NMR : 14.8 (C18) 20.0 (C11) 20.5 (OAc) 25.6 (C1) 28.0 (C2) 35.3 (C17) 36.2 (C12) 46.9 (C14) 47.9 (C8) 48.1 (C9) 50.4 (C6) 52.5 (OMe) 53.4 (C4) 55.7 (C5) 71.1 (C3) 93.8 (C10) 169.5 (OAc) 171.5 (C7) 176.3 (C19) 199.9 (C16) 209.0 (C13).

M.S. : 419 (M^-79, 5%) 386 (17) 358 (30) 363 (16) 311 (22) 297 (20) 281 (45) 239 (33) 221 (17) 211 (16) 197 (15) 169 (11) 155 (15) 129 (18) 105 (100) 91 (23).

HRMS : C_{22}H_{27}O_{8} (M^-79) requires 419.1698, found 419.1703.
Preparation of (74) and (76).

To a stirred solution of the allylic alcohol (73)* (5g, 11mmol) in dichloromethane (200ml) at room temperature was added pyridinium chlorochromate (12g, 55mmol). After stirring at room temperature for 16 h., the solution was diluted with ether (500ml) and filtered through silica gel. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) yielded a ca 1:2 mixture of (74) and (76) (3.5g, 75%).

Further chromatography with a portion of the mixture (1g) on MPLC (ethyl acetate:hexane, 1:1) first afforded (76) (0.6g, 60%), followed by (74) (0.32g, 32%).

Aqueous chromous chloride-hydrochloric acid solution\textsuperscript{104} was added to a stirred solution of the mixture (74) and (76) (3.0g) in acetone (100ml) under a carbon dioxide atmosphere. Addition ceased when the solution remained blue in colour. After concentration in vacuo, the residue was diluted with ethyl acetate (250ml) and washed with water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) gave (74) (2.5g, 83%). Recrystallisation from ether afforded colourless crystals (2.3g).

\textit{ent-3a,13-Diacetoxy-10\beta-hydroxy-17-o xo-20-norgibberella-1,15-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (74).}

R\textsubscript{f} : 0.43 (ethyl acetate:hexane, 1:1)

m. p. : 183-188°C

I.R. : 1755, 1725, 1700, 1590 cm\textsuperscript{-1}

\textsuperscript{1}H NMR : 1.21 (s, 3H, 4Me) 2.03 (s, 3H, OAc) 2.11 (s, 3H, OAc) 2.80 (d, J=14.0Hz, 1H, H14) 2.83 (d, J=10.0Hz, 1H, H6) 3.33 (d, J=10.0Hz, 1H, H5) 3.78 (s, 3H, OMe) 5.39 (d, J=4.0Hz, 1H, H3) 5.88 (dd, J=4.0Hz, 10.0Hz, 1H, H2) 6.29 (d, J=10.0Hz, 1H, H1) 6.78 (s, 1H, H15) 9.61 (s, 1H, CHO).
\( ^{13} \text{C NMR:} \) 14.3 (C18) 18.2 (C11) 20.8 (OAc) 21.5 (OAc) 26.1 (C12) 43.7 (C14) 52.3 (C9) 52.6 (C8) 53.9 (C6) 54.1 (C4) 55.3 (OMe) 55.9 (C5) 70.3 (C3) 83.7 (C13) 89.6 (C10) 129.8 (C2) 133.0 (C1) 151.1 (C16) 152.9 (C15) 169.9 (OAc) 171.9 (OAc) 172.0 (C7) 176.2 (C19) 187.3 (C17).

\( \text{MS:} \) 458 (M\(^+\), <1%) 427 (7) 416 (5) 398 (79) 311 (24) 253 (47) 235 (55) 223 (47) 207 (29) 195 (18) 181 (15) 165 (15) 149 (22) 132 (14) 105 (10) 91 (14) 43 (100).

\( \text{HRMS:} \) C\(_{24}\)H\(_{26}\)O\(_9\) (M\(^+\)); requires 458.1577, found 458.1580.

\( \text{ent-3\(\alpha\),13-Diacetoxy-15\(\beta\),16\(\beta\)-epoxy-10\(\beta\)-hydroxy-17-oxo-20-norgibberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (76).} \)

\( \text{Rf:} \) 0.45 (ethyl acetate:hexane, 1:1)

\( ^{1} \text{H NMR:} \) 1.22 (s, 3H, 4Me) 2.04 (s, 3H, OAc) 2.13 (s, 3H, OAc) 2.45 (d, J=11.4Hz, 1H, H14) 2.64 (d, J=10.6Hz, 1H, H6) 3.31 (d, J=10.6Hz, 1H, H5) 3.62 (s, 1H, H15) 3.78 (s, 3H, OMe) 5.32 (d, J=4.0Hz, 1H, H3) 5.88 (dd, J=4.0Hz, 10.0Hz, 1H, H2) 6.36 (d, J=10.0Hz, 1H, H1) 9.31 (s, 1H, CHO).

\( ^{13} \text{C NMR:} \) 14.3 (C18) 16.3 (C11) 20.8 (OAc) 21.5 (OAc) 26.3 (C12) 32.1 (C14) 45.9 (C9) 49.1 (C6) 52.2 (C8) 52.8 (C4) 53.5 (C5) 54.4 (OMe) 61.6 (C15) 66.2 (C16) 70.1 (C3) 82.5 (C13) 89.6 (C10) 129.8 (C2) 133.0 (C1) 169.8 (OAc) 169.9 (OAc) 172.2 (C7) 176.4 (C19) 192.6 (C17).

\( \text{MS:} \) 474 (M\(^+\), <1%) 443 (13) 432 (5) 403 (8) 299 (100) 267 (38) 251 (33) 239 (46) 223 (40) 211 (93) 195 (52) 179 (30) 169 (39) 155 (43) 141 (23) 128 (23) 115 (23) 91 (37).

\( \text{HRMS:} \) C\(_{24}\)H\(_{26}\)O\(_{10}\) (M\(^+\)) requires 474.1526, found 474.1530.

\(^{(73)}\) was prepared according to the published procedure.\(^{34b}\)
To a solution of (74) (2.8g, 6.1mmol) in ethyl acetate (50ml) was added rhodium on alumina (5%, 200mg). After stirring at room temperature under an hydrogen atmosphere for 16 h., the reaction mixture was diluted with ethyl acetate (100ml), filtered through celite and concentrated *in vacuo* to afford the 1,2-dihydro-enal. The crude product mixture was dissolved in ethyl acetate (50ml), palladium-on-carbon (10%, 200mg) and sodium bicarbonate (50mg) were added. The reaction mixture was again stirred under an atmosphere of hydrogen. After 3 h. at room temperature, the solution was diluted with ethyl acetate (100ml), filtered through celite and concentrated *in vacuo*. Chromatography on silica gel (ethyl acetate:hexane, 1:2) afforded (77) (2.1g, 75%). Recrystallisation from ether and hexane gave colourless crystals (2.0g).

R<sub>f</sub> : 0.5 (ethyl acetate:hexane, 1:1)

m.p. : 171-173°C

I.R. : 1755, 1728 cm<sup>-1</sup>

<sup>1</sup>H NMR : 1.04 (s, 3H, 4Me) 1.40-2.00 (m, 5H) 2.12 (s, 3H, OAc) 2.15 (s, 3H, OAc) 2.68 (d, J=11.2Hz, 1H, H<sub>6</sub>) 3.20 (m, 2H, H<sub>5</sub>+H<sub>14</sub>) 3.74 (s, 3H, OMe) 4.97 (bs, 1H, H<sub>3</sub>) 10.1 (s, 1H, CHO).

<sup>13</sup>C NMR : 14.6 (C18) 16.7 (C11) 21.2 (OAc) 21.7 (OAc) 25.5 (C1) 27.6 (C2) 29.9 (C12) 34.8 (C14) 43.9 (C15) 50.2 (C8) 51.6 (C9) 52.1 (C6+OMe, overlapped) 53.3 (C4) 57.8 (C5) 57.8 (C16) 71.4 (C3) 85.5 (C13) 93.0 (C10) 170 (OAc) 170.5 (OAc) 172.3 (C7) 176.6 (C19) 200.3 (C17).

MS : 462 (M<sup>+</sup>, <1%) 431 (11) 420 (19) 402 (28) 374 (29) 363 (35) 342 (40) 314 (40) 298 (97) 270 (100) 257 (29) 239 (29) 227 (14) 211 (59) 199 (23) 183 (21) 171 (16) 143 (27) 129 (21) 119 (16) 105 (28) 91 (29) 79 (18).

HRMS. : C<sub>23</sub>H<sub>27</sub>O<sub>8</sub> (M<sup>+</sup>-31); requires 431.1706, found 431.1707.

Calcd. for C<sub>24</sub>H<sub>30</sub>O<sub>8</sub> : C 62.33; H 6.54
found : C 62.10; H 6.32.
ent-3α,13-Diacetoxy-10β,17-dihydroxy-20-norgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (81).

Sodium borohydride (20mg, 0.53mmol) was added to a solution of (77) (200mg, 0.43mmol) in methanol (10ml) at 0°C. After stirring at the same temperature for 15min, dilute hydrochloric acid (2M, 0.1ml) was added dropwise to quench the excess of reagent. The resulting reaction mixture was diluted with water (10ml) and extracted with ethyl acetate (3x10ml). The combined extract was washed with water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:1) gave (81) (170mg, 85%).

Rf : 0.1 (ethyl acetate:hexane, 1:1).

\[ \begin{align*} \text{H NMR :} & \quad 1.01 (s, 3H, 4\text{Me}) \quad 1.95 (s, 3H, \text{OAc}) \quad 2.10 (s, 3H, \text{OAc}) \quad 2.69 (d, J=10.0Hz, 1H, H6) \quad 3.15 (d, J=10.0Hz, 1H, H5) \quad 3.60 (dd, J=8.0Hz, 10.0Hz, 1H, H17) \quad 3.75 (s, 3H, \text{OMe}) \quad 3.80 (dd, J=6.0Hz, 10.0Hz, 1H, H17') \quad 4.95 (bs, 1H, H3). \\
\text{C NMR :} & \quad 14.5 (C18) \quad 16.8 (C11) \quad 21.8 (OAc) \quad 21.9 (OAc) \quad 25.4 (C1) \quad 27.1 (C2) \quad 27.6 (C12) \quad 38.5 (C14) \quad 43.4 (C15) \quad 48.3 (C16) \quad 50.1 (C8) \quad 52.1 (C6,C9+OMe, overlapped) \quad 53.25 (C4) \quad 55.0 (C5) \quad 63.0 (C17) \quad 71.3 (C3) \quad 85.9 (C13) \quad 92.8 (C10) \quad 170.0 (OAc) \quad 170.7 (OAc) \quad 172.5 (C7) \quad 176.5 (C19). \\
\text{M.S. :} & \quad 464 (M^+, <1\%) \quad 404 (10) \quad 363 (10) \quad 344 (5) \quad 331 (4) \quad 300 (16) \quad 285 (9) \quad 271 (13) \quad 241 (18) \quad 223 (8) \quad 209 (11) \quad 183 (9) \quad 157 (12) \quad 143 (10) \quad 119 (6) \quad 105 (10) \quad 91 (8) \quad 43 (100). \\
\text{HRMS :} & \quad C_{24}H_{32}O_{9} (M^+) \text{ requires 464.1922, found 464.1919.} \end{align*} \]
ent-16β-Bromo-3α,13-diacetoxy-10β-hydroxy-17-oxo-20-norgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (83).

To a solution of (77) (1.5g, 3.2mmol) in dichloromethane (50ml) was added pyrrolidone hydrotribromide (2.5g, 5.0mmol). After stirring at room temperature for 16 h., the solution was diluted with dichloromethane (100ml), washed with saturated sodium thiosulfate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) afforded (83) (1.3g, 74%).

Rf : 0.8 (ethyl acetate:hexane, 1:1).

1H NMR : 1.04 (s, 3H, 4Me) 2.08 (s, 6H, 2xOAc) 2.15 (d, J=11.4Hz, 1H, H15) 2.50 (d, J=11.4Hz, 1H, H15') 2.69 (d, J=11.4Hz, 1H, H6) 3.14 (d, J=11.4Hz, 1H, H5) 3.80 (s, 3H, OMe) 4.95 (bs, 1H, H3) 9.57 (s, 1H, CHO).

ent-16β-Bromo-3α,13-diacetoxy-10β,17-dihydroxy-20-norgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (66).

Sodium cyanoborohydride (0.48g, 7.4mmol) was added to a stirred solution of (83) (1g, 1.85mmol) and bromocresol green (5mg) in methanol (25ml). Methanolic hydrochloric acid (2M) was added dropwise to the blue solution until the colour changed to yellow. The mixture was allowed to stir at room temperature for 1 h., methanolic hydrochloric acid (2M) was added occasionally to maintain the yellow colour. Methanol was removed under reduced pressure and the crude product mixture was diluted with ethyl acetate (100ml), washed with dilute hydrochloric acid (2M), water, then brine and dried with sodium sulfate. Concentration in vacuo and chromatography on silica gel gave (66) (0.73g, 73%).

Rf : 0.1 (ethyl acetate:hexane, 1:1).
$^1$H NMR: 1.04 (s, 3H, 4Me) 2.08 (s, 3H, OAc) 2.14 (s, 3H, OAc) 2.69 (d, J=10.8Hz, 1H, H6) 3.14 (d, J=10.8Hz, 1H, H5) 3.19 (bs, 1H, OH) 3.78 (s, 3H, OMe) 3.82, 4.08 (ABd, J=13.0Hz, 2H, H17+H17') 4.95 (bs, 1H, H3).

$^{13}$C NMR: 14.5 (C18) 16.6 (C11) 21.5 (OAc) 21.7 (OAc) 25.3 (C1) 27.3 (C2) 28.4 (C12) 41.4 (C14) 48.1 (C15) 51.8 (C8) 51.9 (C9) 52.1 (OMe) 52.4 (C6) 53.2 (C4) 55.6 (C5) 68.7 (C17) 71.2 (C3) 81.4 (C16) 85.9 (C13) 92.7 (C10) 170.0 (OAc) 170.4 (OAc) 172.2 (C7) 176.4 (C19).

M.S.: 445 (M+-97, <1%) 403 (8) 383 (4) 374 (3) 343 (5) 311 (6) 298 (11) 255 (7) 239 (13) 221 (10) 197 (7) 169 (6) 143 (6) 129 (8) 105 (6) 91 (10) 43 (100).

CIMS: 560 (M^+18, 3%) 542 (10) 480 (100) 464 (15) 438 (7) 420 (12) 403 (6) 378 (9).

HRMS: $\text{C}_{24}\text{H}_{29}\text{O}_8$ (M^+97) requires 445.1862, found 445.1861.
CHAPTER 3

Preparation of Ethers (85) and (86).

LTA (380mg, 0.85mmol) was added to a pyrex test tube equipped with a nitrogen outlet and a cold-finger condenser containing (81) (100mg, 0.22mmol) in benzene (10ml). After irradiating with a medium pressure mercury lamp (250W) (held 2” away from the reaction vessel) for 30 min, iodine (54mg, 0.22mmol) was added and irradiation was continued for a further 30 min. The reaction mixture was diluted with ethyl acetate (50ml), washed with saturated sodium thiosulfate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) first gave (86) (20mg, 15%), followed by (85) (70mg, 70%).

ent-3α,13-Diacetoxyl-12α,17-epoxy-10β-hydroxy-20-norgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (85).

Rf : 0.65 (ethyl acetate:hexane, 1:1)

$^1$H NMR: 1.03 (s, 3H, 4Me) 2.02 (s, 3H, OAc) 2.12 (s, 3H, OAc) 2.64 (d, J=10.0Hz, 1H, H6) 3.16 (d, J=10.0Hz, 1H, H5) 3.69 (d, J=9.0Hz, 1H, H17) 3.91 (s, 3H, OMe) 3.91 (dd, J=8.5Hz, 9.0Hz, 1H, H17') 4.46 (bs, 1H, H3) 4.95 (bs, 1H, H3).

$^{13}$C NMR: 14.5 (C18) 21.2 (OAc) 21.5 (OAc) 25.0 (C11) 25.4 (C2) 27.6 (C1) 40.1 (C14) 41.2 (C15) 50.8 (C16) 50.1 (C8) 52.1 (C9+C8, overlapped) 52.4 (OMe) 52.6 (C6) 53.5 (C4) 55.0 (C5) 71.3 (C3) 72.3 (C17) 82.8 (C12) 92.8 (C13) 93.4 (C10) 170.0 (OAc) 170.2 (OAc) 172.5 (C7) 176.5 (C19).

MS: 462 (M+, <1%) 461(10) 446 (10) 431 (5) 402 (5) 342 (12) 298 (25) 269 (9) 253 (8) 239 (15) 207 (32) 183 (12) 169 (8) 143 (13) 133 (41) 119 (7) 105 (14) 95 (28) 43 (100).

HRMS: C$_{24}$H$_{30}$O$_9$ (M⁺) requires 462.1881, found 462.1879.
ent-3α,13-Diacetoxy-12α,17-epoxy-10β-hydroxy-11β-iodo-20-norgiberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (86).

Rf : 0.75 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 1.05 (s, 3H, 4Me) 2.10 (s, 3H, OAc) 2.19 (s, 3H, OAc) 2.60 (d, J=10.0Hz, 1H, H6) 3.20 (d, J=10.0Hz, 1H, H5) 3.50-3.70 (m, overlapping, 5H, H17, H17'+OMe) 4.46 (bs, 1H, H3) 4.65 (dd, J=3.0Hz, 9.0Hz, 1H, H11) 4.95 (bs, 1H, H3).

ent-3α,13-Diacetoxy-10β,17-dihydroxy-20-norgiberell-11-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (92).

Zinc dust (5mg) was added to a solution of (86) (15mg, 0.025mmol) in acetic acid (5ml). After stirring at room temperature for 30min the reaction was diluted with dichloromethane (10ml) and filtered through celite. The filtrate was washed with water (2x10ml), saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and filtration through a plug of silica gel gave (92) (12mg, 82%).

Rf : 0.15 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 1.05 (s, 3H, 4Me) 2.02 (s, 3H, OAc) 2.12 (s, 3H, OAc) 2.5-2.7 (m, 2H, H6+H14, overlapped) 3.20 (d, J=9.0Hz, 1H, H5) 3.40-3.80 (m, 5H, H17, H17'+OMe, overlapped) 4.94 (bs, 1H, H3) 5.66 (dd, J=2.7Hz, 9.6Hz, 1H, H11) 6.03 (d, J=9.6Hz, 1H, H12).

ent-3α,13-Diacetoxy-17-(1,1-dimethylethyl)dimethylsilyloxy-10β-hydroxy-20-norgiberell-11-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (93).

tert-Butyl dimethylsilyl triflate (10µ1, 40µmol) was added dropwise to a stirred solution of (92) (10mg, 21.3µmol) and triethylamine (6ul, 44µmol) in dichloromethane (5ml) at -20°C.
After stirring at the same temperature for 30 min, saturated sodium bicarbonate solution was added. The resulting reaction mixture was extracted with dichloromethane (2x10ml) and the combined extract was washed with saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) afforded (93) (11mg, 90%).

\[ R_f : \quad 0.8 \text{ (ethyl acetate:hexane, 1:1).} \]

\[
\begin{align*}
{^1H\text{NMR}} & : \quad 0.30 \text{ (s, 6H, SiMe}_2\text{)} \quad 0.91 \text{ (s, 9H, Si}^4\text{Bu)} \quad 1.06 \text{ (s, 3H, 4Me)} \quad 2.03 \text{ (s, 3H, OAc)} \quad 2.12 \text{ (s, 3H, OAc)} \quad 2.50-2.70 \text{ (m, 2H, H6+H14, overlapped)} \quad 3.21 \text{ (d, J=9.0Hz, 1H, H5)} \quad 3.40-3.60 \text{ (m, 2H, H17+H17', overlapped)} \quad 3.74 \text{ (s, 3H, OMe)} \quad 4.94 \text{ (bs, 1H, H3)} \quad 5.66 \text{ (dd, J=2.7Hz, 9.6Hz, 1H, H11)} \quad 6.03 \text{ (d, J=9.6Hz, 1H, H12)}.
\end{align*}
\]

\[
\text{ent-16β-Bromo-3α,13-diacetoxy-12α,17-epoxy-10β-hydroxy-20-norgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (97).}
\]

To a round bottom pyrex flask under a nitrogen atmosphere, equipped with a cold finger condenser, was added (66) (0.7g, 1.3mmol) in benzene (50ml), LTA (3.5g, 8.0mmol) and iodine (0.165g, 0.65mmol). The reaction mixture was irradiated with a medium pressure mercury lamp (250W) held 2" from the reaction vessel for 1 h. and the temperature was maintained at ca 30°C. The reaction mixture was diluted with ethyl acetate (50ml), washed with saturated sodium thiosulfate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) afforded (97) (0.52g, 74%).

\[ R_f : \quad 0.8 \text{ (ethyl acetate:hexane, 1:1).} \]

\[
{^1H\text{NMR}} : \quad 1.04 \text{ (s, 3H, 4Me)} \quad 2.11 \text{ (s, 3H, OAc)} \quad 2.13 \text{ (s, 3H, OAc)} \quad 2.38 \text{ (d, J=14.4Hz, 1H, H15)} \quad 2.65 \text{ (d, J=14.4Hz, 1H, H15')} \quad 2.66 \text{ (d, J=10.0Hz, 1H, H6)} \quad 3.14 \text{ (d, J=10.0Hz, 1H, H5)} \quad 3.77 \text{ (s, 3H, OMe)} \quad 3.88 \text{ (bs, 2H, H17+H17')} \quad 4.45 \text{ (bs, 1H, H12)} \quad 4.95 \text{ (bs, 1H, H3)}.
\]

\[
{^{13}C\text{NMR}} : \quad 14.4 \text{ (C18)} \quad 21.2 \text{ (OAc)} \quad 21.3 \text{ (OAc)} \quad 24.1 \text{ (C11)} \quad 25.3 \text{ (C1)} \quad 27.0 \text{ (C2)} \quad 38.4 \text{ (C14)} \quad 49.3 \text{ (C8)} \quad 50.1 \text{ (C9)} \quad 52.2 \text{ (C6)} \quad 52.5 \text{ (OMe)} \quad 52.8 \text{ (C5)} \quad 53.4 \text{ (C15)} \quad 65.2 \text{ (C16)} \quad 71.3 \text{ (C3)} \quad 75.8 \text{ (C17)} \quad 82.6 \text{ (C12)} \quad 87.7 \text{ (C13)} \quad 92.9 \text{ (C10)} \quad 169.9
\]
Freshly activated zinc dust (0.1g) was added to a solution of (97) (0.4g, 0.74mmol) in acetic acid (10ml), and the mixture was heated at reflux temperature for 10 min. The cooled mixture was diluted with dichloromethane (50ml) and washed successively with water, saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:1) yielded (98) (0.27g, 80%).

**Rf:** 0.25 (ethyl acetate:hexane, 1:1).

**1H NMR:**
- 1.05 (s, 3H, 4Me) 2.07 (s, 3H, OAc) 2.12 (s, 3H, OAc) 2.26 (m, 2H, H14+H15, overlapped) 2.38 (d, J=11.8Hz, 1H, H15') 2.66 (d, J=10.0Hz, 1H, H6) 2.87 (d, J=5.4Hz, 1H, OH) 3.17 (d, J=10.0Hz, 1H, HS) 3.73 (s, 3H, OMe) 4.34 (bs, 1H, H12) 4.96 (bs, 1H, H3) 5.12 (bs, 1H, H17) 5.23 (bs, 1H, H17').

**13C NMR:**
- 14.5 (C18) 21.2 (OAc) 22.0 (OAc) 25.5 (C1) 27.5 (C2) 27.7 (C11) 42.0 (C14) 43.0 (C15) 49.9 (C8) 50.7 (C9) 50.9 (C6) 52.2 (C5) 52.9 (OMe) 53.3 (C4) 71.4 (C3) 72.0 (C12) 88.8 (C13) 93.0 (C10) 112.5 (C17) 144.9 (C16) 170.1 (OAc) 170.7 (OAc) 172.6 (C7) 176.5 (C19).

**MS:**
- 462 (M, 2%) 420 (20) 402 (22) 360 (12) 342 (33) 327 (10) 314 (23) 298 (37) 282 (31) 271 (15) 255 (23) 227 (16) 211 (32) 197 (15) 183 (13) 157 (14) 143 (14) 133 (22) 121 (14) 105 (21) 85 (12) 69 (21) 43 (100).

**HRMS:**
- C_{24}H_{30}O_{9}(M^+ ) requires 462.1890, found 462.1893.
ent-3α,13-Diacetoxy-10β-hydroxy-12-oxo-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (100).

Jones' reagent was added dropwise to a stirred solution of (98) (0.2g, 0.43mmol) in acetone (10ml) at 0°C. Addition was ceased when the orange colour persisted. Propan-2-ol was added dropwise to destroy the excess of reagent. The green reaction mixture was diluted with ethyl acetate (50ml), washed with water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) afforded (100) (0.18g, 95%).

Rf : 0.6 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 1.02 (s, 3H, 4Me) 2.06 (s, 3H, OAc) 2.09 (s, 3H, OAc) 2.25 (m, 2H, H14 +H15, overlapped) 2.38 (d, J=11.8Hz, 1H, H15') 2.48 (dd, J=6.6Hz, 17.1Hz, 1H, H11) 2.75 (d, J=10.5Hz, 1H, H6) 2.93 (bd, J=12Hz, 1H, H14) 3.02 (dd, J=12Hz, 17.1Hz, 1H, H11') 3.24 (d, J=10.5Hz, 1H, H5) 3.73 (s, 3H, OMe) 4.94 (bs, 1H, H3) 5.2 (bs, 1H, H17) 5.34 (bs, 1H, H17').

$^{13}$C NMR : 14.4 (C18) 20.6 (OAc) 21.0 (OAc) 25.3 (C1) 27.3 (C2) 35.4 (C11) 41.9 (C14) 42.3 (C15) 49.8 (C9) 49.9 (C8) 51.3 (C6) 52.2 (OMe) 52.9 (C5) 53.8 (C4) 71.0 (C3) 86.2 (C13) 92.3 (C10) 114.4 (C17) 142.3 (C16) 169.9 (OAc) 170.0 (OAc) 172.0 (C7) 175.7 (C19) 201.1 (C12).

MS : 460 (M+, 21%) 432 (34) 418 (100) 402 (64) 400 (41) 390 (35) 376 (15) 358 (61) 340 (60) 330 (40) 314 (50) 284 (48) 270 (60) 262 (29) 255 (41) 237 (25) 227 (37) 211 (38) 197 (26) 183 (26) 171 (26) 157 (32) 149 (28) 143 (36) 133 (47) 121 (42) 115 (26) 105 (47) 91 (59).

HRMS : $\text{C}_{24}\text{H}_{28}\text{O}_9(M^+)$ requires 460.1733, found 460.1733.
ent-12-Oxo-3α,10β,13-trihydroxy-20-norgiberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (101).

Anhydrous potassium carbonate (30mg) was added to a stirred solution of (100) (150mg, 0.33mmol) in methanol (5ml). After stirring at room temperature for 4 h., the reaction mixture was diluted with ethyl acetate (25ml), washed successively with dilute hydrochloric acid (2M), saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:1) afforded (101) (0.09g, 75%).

$\text{R}_f$ : 0.3 (ethyl acetate:hexane, 2:1).

$^1$H NMR : 1.02 (s, 3H, 4Me) 2.44 (bd, $J=16.0\text{Hz}$, 1H, H15) 2.62 (dd, $J=8.1\text{Hz}$, 19.0Hz, 1H, H11') 2.78 (d, $J=10.0\text{Hz}$, 1H, H6) 2.85 (dd, $J=9.8\text{Hz}$, 19.0Hz, 1H, H11') 3.32 (d, $J=10.0\text{Hz}$, 1H, H5) 3.75 (s, 3H, OMe) 3.86 (bs, 1H, H3) 4.13 (bs, 1H, OH) 5.2 (bs, 2H, H17+H17').

$^{13}$C NMR : 14.4 (C18) 26.6 (C1) 27.0 (C2) 33.2 (C11) 43.2 (C14) 43.3 (C15) 49.1 (C9) 49.6 (C8) 51.0 (C6) 51.7 (OMe) 52.2 (C4) 55.1 (C5) 69.5 (C3) 83.0 (C13) 93.3 (C10) 112.8 (C17) 146.3 (C16) 172.6 (C7) 176.7 (C19) 207.1 (C12).

MS : 376 (M$^+$, 33%) 358 (13) 348 (30) 330 (20) 316 (67) 307 (100) 298 (36) 289 (31) 270 (43) 255 (25) 243 (32) 229 (49) 217 (19) 211 (30) 201 (23) 185 (26) 171 (24) 149 (27) 129 (24) 121 (48) 105 (31) 91 (58).

HRMS : C$_{20}$H$_{24}$O$_7$(M$^+$) requires 376.1522, found 376.1521.

Reduction of Ketol (101) with Zinc Borohydride
Zinc borohydride in ether (0.1ml, 1.2M) was added dropwise to a stirred solution of (101) (100mg, 0.27mmol) in a mixture of anhydrous ether (5ml) and DMF (5ml) at -30°C. After stirring at the same temperature for 15min, dilute hydrochloric acid (2M) was added dropwise to destroy the excess of reagent. The resulting solution was diluted with ethyl acetate, washed with water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) first gave (103) (48mg, 48%), followed by (104) (32mg, 32%).

**ent-3α,10β,12β,13-Tetrahydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (103).**

\[ R_f : \ 0.4 \ (\text{ethyl acetate:hexane, 3:1}). \]

\[ ^1H \text{ NMR :} \ 1.21 \ (s, \ 3H, \ 4\text{Me}) \ 2.70 \ (d, \ J=10.5Hz, \ 1H, \ H6) \ 3.20 \ (d, \ J=10.5Hz, \ 1H, \ H5) \ 3.65-3.72 \ (m, \ 5H, \ H12+O\text{Me}, \ overlapped) \ 3.85 \ (bs, \ 1H, \ H3) \ 5.11 \ (bs, \ 1H, \ H17) \ 5.30 \ (bs, \ 1H, \ H17'). \]

**ent-3α,10β,12α,13-Tetrahydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (104).**

\[ R_f : \ 0.35 \ (\text{ethyl acetate:hexane, 3:1}). \]

\[ ^1H \text{ NMR :} \ 1.2 \ (s, \ 3H, \ 4\text{Me}) \ 2.62 \ (d, \ J=10.0Hz, \ 1H, \ H6) \ 3.15 \ (d, \ J=10.0Hz, \ 1H, \ H5) \ 3.71 \ (s, \ 3H, \ O\text{Me}) \ 3.84 \ (bs, \ 1H, \ H3) \ 3.99 \ (t, \ J=7.0Hz, \ 1H, \ H12) \ 5.20 \ (bs, \ 2H, \ H17+H17'). \]

\[ ^{13}C \text{ NMR :} \ 14.5 \ (C18) \ 26.7 \ (C1) \ 27.8 \ (C2) \ 28.1 \ (C11) \ 42.4 \ (C14) \ 47.0 \ (C15) \ 50.3 \ (C9) \ 50.4 \ (C8) \ 51.2 \ (O\text{Me}) \ 51.2 \ (C4) \ 52.6 \ (C6) \ 54.3 \ (C5) \ 70.4 \ (C3) \ 74.4 \ (C12) \ 80.6 \ (C13) \ 93.7 \ (C10) \ 110.8 \ (C17) \ 149.1 \ (C17) \ 173.6 \ (C7) \ 178.2 \ (C19). \]

\[ \text{MS :} \ 378 \ (M^+, \ 30\%) \ 360 \ (86) \ 346 \ (34) \ 328 \ (68) \ 318 \ (57) \ 300 \ (98) \ 291 \ (23) \ 282 \ (48) \ 275 \ (41) \ 255 \ (60) \ 229 \ (85) \ 211 \ (69) \ 197 \ (40) \ 185 \ (40) \ 167 \ (18) \ 159 \ (36) \ 143 \ (33) \ 135 \ (55) \ 129 \ (31) \ 121 \ (54) \ 115 \ (28) \ 105 \ (40) \ 91 \ (48). \]

\[ \text{HRMS :} \ C_{20}H_{26}O_{7}(M^+) \text{ requires 378.1679, found 378.1678.} \]
ent-10β-Hydroxy-3α,12β,13-triacetoxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (105).

Acetic anhydride (0.05ml, 0.53mmol) was added to a stirred solution of (103) (30mg, 79µmol), triethylamine (0.1ml, 0.72mmol) and a crystal of DMAP in dichloromethane (5ml) at 0°C. After stirring at room temperature for 16 h., ice cooled water was added dropwise and the reaction mixture was allowed to stir for a further 30 min. The solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (10ml), washed successively with dilute hydrochloric acid (2M), saturated sodium bicarbonate, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) gave (105) (38mg, 95%).

Rf : 0.8 (ethyl acetate:hexane, 1:1).

1H NMR : 1.05 (s, 3H, 4Me) 1.97 (s, 3H, OAc) 2.09 (s, 3H, OAc) 2.12 (s, 3H, OAc) 2.62 (d, J=11.3Hz, 1H, H14) 2.69 (d, J=10.5Hz, 1H, H6) 3.17 (d, J=10.5Hz, 1H, H5) 3.74 (s, 3H, OMe) 4.96 (bs, 1H, H3) 5.01 (t, J=7.5Hz, 1H, H12) 5.15 (bs, 1H, H17) 5.19 (bs, 1H, H17').

MS : 504 (M+, 10%) 473 (10) 462 (70) 444 (30) 434 (23) 402 (58) 384 (36) 360 (25) 342 (76) 324 (24) 314 (40) 298 (91) 282 (67) 270 (36) 255 (60) 237 (75) 221 (33) 211 (65) 195 (57) 183 (32) 155 (34) 143 (46) 129 (46) 121 (36) 105 (77) 91 (82) 85 (40) 69 (61) 55 (100).

HRMS : C26H32O10(M+) requires 504.1995, found 504.1995.

ent-3α,10β,12β,13-Tetrahydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone 12,13-Carbonate (106).

Phosgene in toluene (50µl, 1.6M) was added dropwise to a stirred solution of (103) (10mg, 26µmol), triethylamine (50µl) and a crystal of DMAP in dichloromethane (5ml) at 0°C. The
mixture was stirred for 4 h. at room temperature. Ice was added and after 0.5 h., the mixture was diluted with ethyl acetate (10 ml) and washed successively with dilute hydrochloric acid (2M), saturated sodium bicarbonate solution, water and brine. The organic extract was dried over sodium sulfate, filtered through silica gel and concentrated in vacuo to afford the carbonate (106) (9 mg, 86%).

Rf : 0.6 (ethyl acetate:hexane, 1:1).

$^1$H NMR: 1.2 (s, 3H, 4Me) 2.74 (d, J=11 Hz, 1H, H6) 3.28 (d, J=11 Hz, 1H, H5) 3.72 (s, 3H, OMe) 3.86 (bs, 1H, H3) 4.36 (t, J=8.0 Hz, 1H, H12) 5.16 (bs, 1H, H17) 5.40 (bs, 1H, H17').

MS: 386 (M$^+$-18, <1%) 373 (7) 372 (8) 360 (6) 342 (100) 283 (32) 254 (6) 239 (100) 216 (10) 195 (8) 183 (8) 169 (8) 157 (12) 143 (10) 129 (11) 115 (13) 101 (19) 91 (23).

HRMS: C$_{20}$H$_{21}$O$_7$(M$^+$-31); requires 373.1287, found 373.1289.

$\textit{ent-3}$$\alpha$,13-Diacetoxy-1$\alpha$,16$\beta$-dibromo-10$\beta$-hydroxy-17-oxo-20-norgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (107).

To a solution of (74) (200 mg, 0.43 mmol) and pipiderine (1 ml) in ethyl acetate (10 ml) was added palladium on carbon (10%, 20 mg). After stirring under an atmosphere of hydrogen at room temperature for 16 h., the reaction was filtered through celite and concentrated in vacuo to afford a foam.

The crude product mixture was dissolved in dichloromethane (10 ml) and pyrrolidone hydrotribromide (0.45 g, 0.9 mmol) was then added. After stirring at room temperature for 16 h., the reaction mixture was diluted dichloromethane (50 ml) and washed with saturated sodium thiosulfate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and MPLC chromatography (ethyl acetate:hexane, 1:1) first gave (107) (140 mg, 53%), followed by (83) (60 mg, 26%) (see p. 135).

Rf : 0.85 (ethyl acetate:hexane, 1:1).
When (107) (130mg, 0.24mmol) was allowed to react with sodium cyanoborohydride (60mg, 0.94mmol) in methanol (10ml) according to the procedure for conversion of (83) to (66), (108) (90mg, 71%) was obtained.

R<sub>f</sub> : 0.20 (ethyl acetate:hexane, 1:1).

**1H NMR**: 1.08 (s, 3H, 4Me) 2.06 (s, 3H, OAc) 2.14 (s, 3H, OAc) 2.68 (d, J=10.0Hz, 1H, H6) 3.70-3.83 (m, 5H, H5,H17+OMe, overlapped) 4.06 (d, J=11.0Hz, 1H, H17') 4.24 (bs, 1H, H1) 4.87 (bs, 1H, H3).

**13C NMR**: 14.4 (C18) 16.3 (C11) 21.2 (OAc) 21.7 (OAc) 28.3 (C12) 33.9 (C2) 41.3 (C14) 42.7 (C15) 47.4 (C1, C8+C9, overlapped) 51.9 (OMe) 52.1 (C6) 52.3 (C5) 53.2 (C4) 68.8 (C17) 70.7 (C3) 81.6 (C16) 85.4 (C13) 94.1 (C10) 170.2 (OAc) 170.3 (OAc) 171.7 (C7) 175.6 (C19).
When (108) (30mg, 48µmol) was subjected to reaction with LTA (130mg, 0.29mmol) and iodine (6mg, 0.24mmol) in benzene (10ml) according to the procedure for conversion of (66) to (97), (109) (19mg, 64%) was obtained.

$R_f : 0.80$ (ethyl acetate:hexane, 1:1).

$^1H$ NMR: 1.10 (s, 3H, 4Me) 2.07 (s, 3H, OAc) 2.14 (s, 3H, OAc) 2.30-2.80 (m, 4H, overlapped) 3.70-3.83 (m, 4H, H5+OMe, overlapped) 3.88 (s, 2H, H17+H17') 4.27 (bs, 1H, H1) 4.42 (bs, 1H, H12) 4.88 (bs, 1H, H3).

Activated zinc dust (0.5g) was added to a stirred solution of (74) (3g, 6.5mmol) in glacial acetic acid (50ml). After stirring at room temperature for 1 h., the reaction was diluted with dichloromethane (200ml) and filtered through celite. The filtrate was washed with water (2x50ml), saturated sodium bicarbonate solution, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) afforded (111) (2.3g, 75%).

$R_f : 0.5$ (ethyl acetate:hexane, 1:1)
\(^1\)H NMR: 1.13 (s, 3H, 4Me) 2.11 (s, 6H, 2xOAc) 2.8 (d, J=10.0Hz, H6) 3.05 (m, 1H, H6) 3.31 (d, J=10.0Hz, 1H, H5) 3.73 (s, 3H, OMe) 5.32 (d, J=4.0Hz, 1H, H3) 5.82 (dd, J=4.0Hz, 9.3Hz, 1H, H2) 6.36 (d, J=9.3Hz, 1H, H1) 9.78 (s, 1H, CHO).

ent-16β-Bromo-3α,13-diacetoxy-10β-hydroxy-17-oxo-20-norgiberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (112).

When (111) (6.5g, 13.5mmol) was subjected to reaction with pyrrolidone hydrotribromide (10g, 20mmol) in dichloromethane (100ml) according to procedure for conversion of (77) to (83), (112) (5.3g, 72%) was obtained. Recrystallisation from ether and hexane gave pale yellow crystals (5.1g).

Rf : 0.8 (ethyl acetate:hexane, 1:1).

m.p. : 168-170°C

I.R. : 1752, 1728, 1695 cm\(^{-1}\).

\(^1\)H NMR : 1.14 (s, 3H, 4Me) 2.12 (s, 6H, 2xOAc) 2.28 (d, J=11.4Hz, 1H, H15) 2.52 (d, J=11.4Hz, 1H, H15') 2.81 (d, J=11.4Hz, 1H, H6) 2.93 (d, J=16Hz, 1H, H14) 3.31 (d, J=11.4Hz, 1H, H5) 3.80 (s, 3H, OMe) 5.33 (d, J=4.0Hz, 1H, H3) 5.89 (dd, J=4.0Hz, 9.5Hz, 1H, H2) 6.40 (d, J=9.5Hz, 1H, H1) 9.57 (s, 1H, CHO).

\(^{13}\)C NMR : 14.3 (C18) 16.4 (C11) 20.7 (OAc) 21.3 (OAc) 29.7 (C12) 41.3 (C14) 48.8 (C9) 49.3 (C15) 51.5 (C6) 52.2 (OMe) 52.4 (C8) 52.9 (C5) 70.0 (C3) 78.8 (C16) 83.7 (C13) 89.7 (C10) 129.4 (C1) 133.7 (C2) 169.8 (OAc) 170.3 (OAc) 171.7 (C7) 176.7 (C19) 193.9 (C17).

MS : 507 (M\(^+\)-31, 8%) 496 (4) 450 (8) 430 (9) 399 (23) 388 (8) 375 (10) 355 (14) 339 (9) 313 (38) 295 (78) 283 (42) 267 (58) 253 (44) 143 (34) 128 (32) 115 (37) 105 (28) 91 (48).
HRMS: \( \text{C}_{23}\text{H}_{24}\text{O}_{8}^{79}\text{Br} \) (M\(^+\)-31) requires 507.0655, found 507.0656.

Calcd. for \( \text{C}_{24}\text{H}_{27}\text{O}_{9}\text{Br} \): C 53.44; H 5.05; Br 14.81.

Found: C 53.39; H 5.19; Br 14.77.

\textit{ent-16\textbeta-}Bromo-3\textalpha,13-diacetoxy-10\textbeta,17-dihydroxy-20-norgibberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (113).

\[
\begin{align*}
\text{AcO} & \quad \text{Br} \\
\text{CO}_2\text{Me} & \quad \text{AcO}
\end{align*}
\]

Sodium borohydride (0.5g, 13.2 mmol) was added to a stirred solution of (112) (5g, 9.3mmol) in DME (100ml). After stirring at room temperature for 30 min, the reaction was diluted with ethyl acetate (250ml) and dilute hydrochloric acid (2M, 10ml) was added dropwise over 15 min. The resulting mixture was washed with water (100ml), then brine and dried over sodium sulfate. Concentration \textit{in vacuo} and chromatography on silica gel (ethyl acetate:hexane, 1:1) afforded (112) (3.6g, 72%) as a pale yellow foam.

\( \text{R}_f : 0.15 \) (ethyl acetate:hexane, 1:1).

\textit{\textbf{\textit{1}}H NMR:} 1.04 (s, 3H, 4Me) 2.08 (s, 6H, OAc) 2.14 (s, 3H, OAc) 2.69 (d, \( J=10.8\text{Hz} \), 1H, H6) 3.21 (d, \( J=10.8\text{Hz} \), 1H, H5) 3.78 (s, 3H, OMe) 4.08 (d, \( J=13.0\text{Hz} \), 1H, H17) 4.08 (d, \( J=13.0\text{Hz} \), 1H, H17') 5.33 (d, \( J=4.0\text{Hz} \), 1H, H3) 5.89 (dd, \( J=4.0\text{Hz} \), 9.5Hz, 1H, H2) 6.37 (d, \( J=9.5\text{Hz} \), 1H, H1).

\textit{\textbf{\textit{13}}C NMR:} 14.1 (C18) 16.4 (C11) 21.6 (OAc) 21.6 (OAc) 28.3 (C12) 41.1 (C14) 48.9 (C9) 51.5 (C6) 51.8 (C8) 52.0 (OMe) 52.1 (C4) 53.2 (C5) 68.4 (C17) 69.9 (C3) 81.1 (C16) 85.2 (C13) 89.6 (C10) 129.2 (C1) 133.7 (C2) 169.7 (OAc) 170.1 (OAc) 171.8 (C7) 176.5 (C19).

\textit{\textbf{\textit{MS:}}} 540 (M\(^+\), 1\%) 480 (2) 445 (4) 400 (5) 368 (4) 356 (11) 339 (7) 312 (12) 297 (33) 281 (11) 268 (22) 254 (42) 238 (36) 221 (23) 209 (49) 193 (100) 179 (70) 165 (52) 141 (32) 128 (23) 115 (26) 105 (8) 91 (13) 43 (100).

\textit{\textbf{\textit{CIMS:}}} 558 (M\(^+\)+18, 2\%) 540 (2) 496 (3) 480 (16) 478 (20) 401 (16) 374 (78) 357 (56) 339 (57) 314 (43) 297 (100) 281 (23) 269 (14).

HRMS: \( \text{C}_{24}\text{H}_{29}\text{O}_{9}^{79}\text{Br} \) (M\(^+\)) requires 540.0995, found 540.0993.
ent-16β-Bromo-3α,13-diacetoxy-12α,17-epoxy-10β-hydroxy-20-norgibberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (110).

When (113) (1g, 1.85mmol) was subjected to reaction with LTA (5g, 11mmol) and iodine (0.24g, 0.95mmol) in benzene (50ml) according to the procedure for conversion of (66) to (97), (110) (0.68g, 68%) was obtained.

Rf : 0.8 (ethyl acetate:hexane, 1:1).

1H NMR : 1.12 (s, 3H, 4Me) 2.09 (s, 6H, 2xOAc) 2.62 (d, J=11.0Hz, 1H, H14) 2.72 (d, J=11.0Hz, 1H, H6) 3.27 (d, J=11.0Hz, 1H, H5) 3.77 (s, 3H, OMe) 3.87 (bs, 2H, H17+H17') 4.43 (bs, 1H, H12) 5.5 (d, J=4.0Hz, 1H, H3) 5.87 (dd, J=4.0Hz, 9.3Hz, 1H, H2) 6.37 (d, J=9.3Hz, 1H, H1).

13C NMR : 14.2 (C18) 20.8 (OAc) 21.3 (OAc) 24.0 (C11) 38.0 (C14) 48.9 (C9) 50.3 (C8) 51.2 (C6) 52.3 (OMe) 53.3 (C5) 53.5 (C4) 53.8 (C15) 65.2 (C16) 70.3 (C3) 75.9 (C17) 82.6 (C12) 87.7 (C13) 90.1 (C10) 129.4 (C1) 133.1 (C2) 169.9 (OAc) 170.1 (OAc) 172.1 (C7) 176.8 (C19).

MS : 478 (M+60, 11%) 459 (6) 435 (6) 399 (20) 391 (10) 375 (40) 327 (10) 311 (23) 295 (84) 277 (22) 267 (32) 253 (38) 235 (100) 223 (33) 209 (61) 192 (69) 179 (61) 155 (48) 143 (54) 128 (32) 115 (35) 105 (24) 91 (39).

CIMS : 556 (M+18, 85%) 452 (31) 435 (85) 372 (33) 355 (26) 295 (45) 235 (15).

HRMS : C24H29O9Br (M+60) requires 478.0627, found 478.0629.
ent-13-Acetoxy-12α-hydroxy-20-norgibberella-1(10),2,16-triene-7,19-dioic Acid 7-Methyl Ester (114).

A stirred solution containing (110) (20mg, 37µmol) and zinc dust (5mg) in acetic acid (5ml) was heated to boiling. After stirring at reflux temperature for 15 min, the reaction mixture was allowed to cool. The cooled mixture was diluted with ethyl acetate (25ml) and filtered through celite. The filtrate was washed with water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 2:1) gave (114) (7mg, 49%).

Rf : 0.2 (ethyl acetate:hexane, 2:1).

1H NMR : 1.42 (s, 3H, 4Me) 2.51 (d, J=10.8Hz, 1H, H6) 3.35 (m, 1H, H5) 3.76 (s, 3H, OMe) 4.35 (bs, 1H, H12) 5.25 (bs, 2H, H17+H17') 5.83 (d, J=9.3Hz, 1H, H3) 6.25 (dd, J=5.4Hz, 9.3Hz, 1H, H12) 6.59 (d, J=5.4Hz, 1H, H1).

13C NMR : 21.5 (OAc) 24.1 (C18) 27.5 (C11) 37.1 (C14) 42.9 (C15) 45.6 (C8) 48.5 (C9) 49.5 (C5) 49.9 (OMe) 52.2 (C4) 70.8 (C12) 86.8 (C13) 111.2 (C1) 112.9 (C17) 122.9 (C2) 137.7 (C10) 146.0 (C17) 170.7 (OAc) 176.5 (C7) 178.4 (C19).

ent-3α,13-Diacetoxy-10β,17-dihydroxy-20-norgibberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (116).

Freshly prepared aqueous chromous chloride solution (5ml) was added to a stirred solution of ethylenediamine (5ml) and DMF (10ml) under an argon atmosphere. The resulting purple solution (0.1ml) was transferred to a solution of (110) (10mg, 18.6µmol) in DMF (5ml) under argon. After stirring at room temperature for 30 min, the solution was diluted with ethyl acetate (20ml), washed with dilute hydrochloric acid (2M), saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and filtration through a plug of silica gel afforded the ether (116) (7.5mg, 87%).
Rf : 0.55 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 1.03 (s, 3H, 4Me) 2.03 (s, 3H, OAc) 2.10 (s, 3H, OAc) 2.68 (d, J=10.0Hz, 1H, H6) 3.31 (d, J=10.0Hz, 1H, H5) 3.67 (d, J=9.0Hz, 1H, H17) 3.73 (s, 3H, OMe) 3.91 (dd, J=9.0Hz, 1H, H17') 4.46 (bs, 1H, H12) 5.30 (d, J=4.0Hz, 1H, H3) 5.87 (dd, J=4.0Hz, 9.3Hz, 1H, H2) 6.37 (d, J=9.3Hz, 1H, H1).

ent-16β-Bromo-3α,13-diacetoxy-10β,17-dihydroxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (117).

Silver activated zinc dust$^{142}$ (0.1g) was added to a stirred solution of (110) (0.25g, 0.46mmol) in glacial acetic acid (10ml). After stirring at room temperature for 1h, the reaction mixture was diluted with dichloromethane (50ml) and filtered through celite. The filtrate was washed twice with water, saturated sodium bicarbonate solution, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:1) first gave (116) (20mg, 9.5%), followed by (117) (0.15g, 67%) as a gum.

Rf : 0.25 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 1.13 (s, 3H, 4Me) 2.06 (s, 3H, OAc) 2.11 (s, 3H, OAc) 2.37 (d, 2H, H14+H15, overlapped) 2.38 (d, J=11.8Hz, 1H, H15') 2.66 (d, J=11.3Hz, 1H, H14) 2.75 (d, J=11Hz, 1H, H6) 2.9 (bs, 1H, OH) 3.32 (d, J=11Hz, 1H, H5) 3.74 (s, 3H, OMe) 4.39 (bs, 1H, H12) 5.20 (bs, 2H, H17+H17') 5.33 (d, J=4.0Hz, 1H, H3) 5.86 (dd, J=4.0Hz, 9.3Hz, 1H, H2) 6.37 (d, J=9.3Hz, 1H, H1).

$^{13}$C NMR : 14.3 (C18) 20.8 (OAc) 21.9 (OAc) 27.5 (C11) 41.8 (C14) 42.9 (C15) 48.5 (C9) 50.3 (OMe) 50.6 (C8) 52.2 (C4) 52.3 (C6) 53.8 (C5) 70.2 (C3) 71.8 (C12) 88.8 (C13) 90.1 (C10) 112.9 (C17) 129.3 (C1) 133.9 (C2) 144.7 (C17) 169.9 (OAc) 170.7 (OAc) 172.1 (C7) 176.8 (C19).

MS : 429 (M$^+$-31, 8%) 418 (20) 400 (11) 358 (10) 296 (58) 269 (51) 254 (42) 237 (78) 209 (100) 181 (30) 167 (69).

HRMS : C$_{24}$H$_{28}$O$_9$ (M$^+$) requires 460.1733, found 460.1733.
ent-3α,13-Diacetoxy-10β-hydroxy-12-oxo-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (119).

When (117) (0.5g, 1.1mmol) was subjected to reaction with Jones' reagent (0.3ml) in acetone (10ml) according to the procedure for conversion of (98) to (100), (119) (0.49g, 98%) was obtained.

\[ R_f : 0.6 \text{ (ethyl acetate:hexane, 1:1).} \]

\[ {^1}H \text{ NMR : 1.14 (s, 3H, 4Me) 2.09 (s, 6H, 2xOAc) 2.09 (s, 3H, OAc) 2.25 (m, 2H, H14+H15) 2.48 (dd, J=6.6Hz, 17.1Hz, 1H, H11) 2.75 (d, J=10.5Hz, 1H, H6) 2.93 (bd, J=12Hz, 1H, H14) 3.02 (dd, J=12.0Hz, 17.1Hz, 1H, H11') 3.4 (d, J=10.5Hz, 1H, H5) 3.75 (s, 3H, OMe) 5.24 (bs, 1H, H17) 5.33 (d, J=4.0Hz, 1H, H3) 5.42 (bs, 1H, H17') 5.86 (dd, J=4.0Hz, 9.3Hz, 1H, H2) 6.37 (d, J=9.3Hz, 1H, H1).} \]

\[ {^{13}C \text{ NMR : 14.2 (C18) 20.6 (OAc) 21.7 (OAc) 35.4 (C11) 41.9 (C14) 42.3 (C15) 47.7 (C9) 50.5 (C6) 51.0 (C8) 52.4 (OMe) 52.6 (C4) 53.8 (C5) 69.9 (C3) 86.1 (C13) 89.5 (C10) 114.4 (C17) 129.8 (C1) 133.0 (C2) 142.1 (C16) 169.9 (OAc) 170.0 (OAc) 172.0 (C7) 175.7 (C19) 201.1 (C12).} \]

\[ MS : 427 (M^+·31, 6%) 416 (12) 356 (13) 313 (22) 296 (53) 282 (84) 268 (45) 252 (37) 223 (70) 209 (100) 195 (34) 181 (30) 155 (30) 141 (24) 128 (20) 115 (22) 91 (26) 77 (17). \]

\[ HRMS : C_{23}H_{23}O_{8}(M^+·31) \text{ requires 427.1471, found 427.1471.} \]

ent-3α,10β,13-Trihydroxy-12-oxo-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (120).
When (119) (0.45g, 0.98mmol) was treated with potassium carbonate (10mg) in methanol (5ml) according to the procedure for conversion of (100) to (101), (120) (0.28g, 78%) was obtained.

$$R_f : \quad 0.3 \text{ (ethyl acetate:hexane, 2:1).}$$

$$^1H\text{ NMR : 1.02 (s, 3H, 4Me) 2.44 (bd, J=16.0Hz, 1H, H15) 2.62 (dd, J=8.1Hz, 19.1Hz, 1H, H11') 2.75 (d, J=10.0Hz, 1H, H6) 2.85 (dd, J=9.8Hz, 19.1Hz, 1H, H11') 3.41 (d, J=10.0Hz, 1H, H5) 3.75 (s, 3H, OMe) 4.00 (bs, 1H, OH) 4.14 (bs, 1H, H3) 5.22 (bs, 2H, H17+H17') 5.33 (d, J=4.0Hz, 1H, H3) 5.86 (dd, J=4.0Hz, 9.3Hz, 1H, H2) 6.37 (d, J=9.3Hz, 1H, H1).$$

$$^{13}C\text{ NMR : 14.2 (C18) 33.4 (C11) 42.0 (C14) 43.1 (C15) 47.7 (C9) 50.5 (C6) 51.0 (C8) 52.4 (OMe) 52.6 (C4) 53.8 (C5) 69.1 (C3) 83.4 (C13) 93.3 (C10) 114.8 (C17) 129.8 (C1) 133.0 (C2) 146.1 (C16) 172.6 (C7) 177.7 (C19) 206.5 (C12).}$$

$$MS : \quad 374 (M^+, 25\%) 356 (12) 328 (15) 314 (35) 298 (36) 282 (56) 268 (45) 252 (42) 223 (56) 209 (100) 195 (34) 181 (30) 115 (22) 91 (26).$$

$$HRMS : \quad C_{20}H_{22}O_7(M^+) \text{ requires 374.1363, found 374.1361.}$$

Reduction of Ketol (120) with Zinc Borohydride.

When (120) (250mg, 0.67mmol) in a mixture of ether (5ml) and DMF (5ml) was treated with zinc borohydride in ether (1.2M, 0.3ml) according to the procedure for conversion of (101) to (103) and (104), (121) (115mg) and (122) (75mg) were obtained in 46% and 30% yields respectively.

$$ent-3\alpha,10\beta,12\beta,13\text{-Tetrahydroxy-20-norgiberella-1,16-diene-7,19-dioic Acid 7- Methyl Ester 19,10-Lactone (121).}$$

$$R_f : \quad 0.4 \text{ (ethyl acetate:hexane, 3:1).}$$

$$^1H\text{ NMR : 1.14 (s, 3H, 4Me) 2.69 (d, J=10.3Hz, 1H, H6) 3.32 (d, J=10.3Hz, 1H, H5) 3.70-3.75 (m, 4H, H12+OMe, overlapped) 4.15 (bs, 1H, H3) 5.14}$$
ent-3α,10β,12α,13-Tetrahydroxy-20-norgiberella-1,16-diene-7,19-dioic Acid 7- Methyl Ester 19,10-Lactone (122).

Rf : 0.35 (ethyl acetate:hexane, 3:1).

$^1$H NMR : 1.15 (s, 3H, 4Me) 2.67 (d, J=10.0Hz, 1H, H6) 3.34 (d, J=10.0Hz, 1H, H5) 3.71 (s, 3H, OMe) 4.02 (t, J=7.0Hz, 1H, H12) 4.13 (d, J=3.7Hz, 1H, H12) 5.23 (bs, 2H, H17+H17') 5.79 (dd, J=3.7Hz, 9.3Hz, 1H, H2) 6.26 (d, J=9.3Hz, 1H, H1).
Selenium dioxide (5mg) was added to a stirred solution of (98) (10mg, 21.6µmol) and tert-butyl hydroperoxide (10µl) in dichloromethane (5ml). After stirring at room temperature for 15 min, the reaction was diluted with dichloromethane (10ml), washed successively with dilute hydrochloric acid (2M, 5ml), water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate : hexane; 1:2) afforded (125) (7mg, 57%).

ent-3α,13-Diacetoxy-10β,12α-dihydroxy-20-norgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone 12,17-Seleniolactone (128).

Rf : 0.5 (ethyl acetate:hexane, 1:1).

1H NMR : 1.05 (s, 3H, 4Me) 2.09 (s, 3H, OAc) 2.14 (s, 3H, OAc) 2.48-2.76 (m, 3H, H6 ., H14+H15, overlapped) 3.24 (d, J=10.4Hz, 1H, H5) 3.36, 3.57 (ABd, J=10.5Hz, 2H, H17+H17') 3.76 (s, 3H, OMe) 4.75 (bs, 1H, H12) 4.99 (bs, 1H, H3).

13C NMR : 8.14 (C17) 14.5 (C18) 20.9 (OAc) 21.2 (OAc) 24.4 (C11) 25.4 (C1) 26.7 (C2) 40.1 (C14) 47.5 (C9) 48.1 (C15) 49.9 (C8) 51.9 (C6) 52.3 (OMe) 52.9 (C5) 53.6 (C4) 71.5 (C3) 81.1 (C12) 82.9 (C16) 90.1 (C13) 93.4 (C10) 169.4 (OAc) 170.1 (OAc) 172.5 (C7) 176.6 (OAc).

ent-3α,13-Diacetoxy-10β,15β-dihydroxy-12-oxo-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (126).

To a stirred solution of (100) (100mg, 0.22mmol) in dichloromethane (5ml) and acetic acid (5ml), was added selenium dioxide (100mg) and tert-butyl hydroperoxide (0.1ml). After stirring at room temperature for 3 days, the reaction mixture was diluted with
dichloromethane (20ml), washed with dilute hydrochloric acid (2M), water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:1) gave (126) (84mg, 81%).

\[ R_f : 0.1 \text{ (ethyl acetate:hexane, 1:1)} \]

\[ ^1H \text{ NMR} : 1.07 \text{ (s, 3H, 4Me)} \quad 2.11 \text{ (s, 3H, OAc)} \quad 2.12 \text{ (s, 3H, OAc)} \quad 2.52 \text{ (dd, J=7.1Hz, 18.1Hz, 1H, H11)} \quad 2.58 \text{ (d, J=12.5Hz, 1H, H14)} \quad 2.66 \text{ (d, J=10.0Hz, 1H, H6)} \quad 2.82 \text{ (d, J=12.5Hz, 1H, H14')} \quad 2.99 \text{ (dd, J=11.0Hz, 18.1Hz, 1H, H11')} \quad 3.24 \text{ (d, J=10.0Hz, 1H, H5)} \]

\[ ^1C \text{ NMR} : 14.3 \text{ (C18)} \quad 21.1 \text{ (OAc)} \quad 21.2 \text{ (OAc)} \quad 25.4 \text{ (C1)} \quad 27.4 \text{ (C2)} \quad 34.4 \text{ (C11)} \]

When (119) (250mg, 0.55mmol) was subjected to reaction with selenium dioxide (200mg) and tert-butyl hydroperoxide (0.5ml) in a mixture of acetic acid (10ml) and dichloromethane (10ml) according to the procedure for conversion of (100) to (126), (127) (200mg, 77%) was obtained.

\[ R_f : 0.1 \text{ (ethyl acetate:hexane, 1:1)} \]

\[ ^1H \text{ NMR} : 1.17 \text{ (s, 3H, 4Me)} \quad 2.11 \text{ (s, 3H, OAc)} \quad 2.13 \text{ (s, 3H, OAc)} \quad 2.50-2.64 \text{ (m, overlapped, 2H, H14+H11)} \quad 2.75 \text{ (d, J=10.5Hz, 1H, H6)} \quad 2.85 \text{ (d, J=12.0Hz, 1H, H14)} \quad 3.02 \text{ (dd, J=11.3Hz, 18.0Hz, 1H, H11')} \quad 3.41 \text{ (d, J=10.5Hz, 1H, H5)} \]

HRMS: \[ C_{24}H_{28}O_{10} \text{ (M+)} ; \text{ requires 476.1682, found 476.1680.} \]

ent-3α,13-Diacetoxy-10β,15β-dihydroxy-12-oxo-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (127).
ent-3α,13-Diacetoxy-12,15-dioxo-10β-hydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (128).

Oxalyl chloride (50 µl) was added to dry dichloromethane (5ml) in a flask under nitrogen at -78 °C. After stirring at that temperature for 5 min, dimethyl sulfoxide (0.2 ml) was added slowly and the mixture was allowed to react for 10 min. A solution of (126) (50 mg, 0.1 mmol) in dry dichloromethane (5 ml) was then added dropwise to the reaction mixture at -78 °C. After stirring at -78 °C for 1 h, triethylamine (0.5 ml) was added dropwise and the resulting mixture was warmed to ambient temperature over 30 min. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate: hexane, 2:1) to give (128) (37 mg, 74%).

Rf : 0.55 (ethyl acetate:hexane, 1:1)

1H NMR : 1.13 (s, 3H, 4Me) 2.16 (s, 3H, OAc) 2.17 (s, 3H, OAc) 2.38 (d, J=12.0 Hz, 1H, H14) 2.62 (dd, J=6.6 Hz, 16.4 Hz, 1H, H11) 2.73 (d, J=10.3 Hz, 1H, H6) 3.33 (dd, J=12.2 Hz, 16.4 Hz, 1H, H11') 3.43 (d, J=12.0 Hz, 1H, H14') 3.45 (d, J=10.3 Hz, 1H, H5) 3.66 (s, 3H, OMe) 5.02 (bs, 1H, H3) 5.88 (s, 1H, H17) 6.32 (s, 1H, H17').

13C NMR : 14.9 (C18) 20.6 (OAc) 21.2 (OAc) 25.4 (C1) 27.2 (C2) 34.7 (C11) 37.8 (C14) 46.1 (C9) 48.9 (C6) 52.0 (OMe) 52.3 (C5) 54.3 (C4) 60.4 (C8) 71.0 (C3) 84.3 (C13) 92.2 (C10) 123.9 (C16) 140.2 (C17) 167.2 (OAc) 169.6 (OAc) 173.6 (C7) 175.5 (C19) 199.1 (C12) 200.4 (C15).

MS : 474 (M+, 2%) 464 (3) 443 (8) 432 (11) 415 (4) 404 (10) 386 (3) 362 (10) 344 (11) 326 (9) 311 (7) 298 (100) 284 (28) 239 (8) 224 (15) 211 (4) 197 (3) 183 (7) 169 (6) 157 (9) 143 (9) 129 (8) 105 (7) 43 (100).

HRMS : C24H26O10 (M+); requires 474.1526, found 474.1525.
ent-3α,13-Diacetoxy-12,15-dioxo-10β-hydroxy-20-nor-16ξ-gibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (131).

Zinc dust (5mg) was added to a solution of (128) (10mg, 21µmol) in acetic acid (5ml). After stirring for 30 min, the reaction mixture was diluted with dichloromethane (25ml) and filtered through celite. The filtrate was washed successively with water (3x10ml), saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration *in vacuo* and filtration through a plug of silica gel gave (131) (8.2mg, 83%).

Rf : 0.55 (ethyl acetate:hexane, 1:1)

1H NMR : 1.05 (d, J=7.0Hz, 3H, 16Me) 1.13 (s, 3H, 4Me) 2.12 (s, 3H, OAc) 2.15 (s, 3H, OAc) 2.39 (d, J=12.0Hz, 1H, H14) 2.55 (dd, J=6.6Hz, 16.5Hz, 1H, H11) 2.74 (d, J=10.0Hz, 1H, H6) 3.25 (dd, J=12.0Hz, 16.5Hz, 1H, H11') 3.42 (d, J=12.0Hz, 1H, H14') 3.46 (d, J=10.0Hz, 1H, H5) 3.66 (s, 3H, OMe) 5.01 (bs, 1H, H3).

ent-3α,13-Diacetoxy-10β-hydroxy-15β-methanesulfonyloxy-12-oxo-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (132).

Methanesulfonyl chloride (10µl) was added dropwise to a solution of (127) (70mg, 0.105mmol) in dry pyridine (2ml) at -10°C under nitrogen. After stirring at the same temperature for 1 h., ice cooled aqueous acetone solution (10%, 2ml) was added slowly to the reaction mixture and the mixture was warmed to ambient temperature over 30 min. The solution was diluted with ethyl acetate (25ml), washed with dilute hydrochloric acid (2M), saturated sodium bicarbonate solution, then brine and dried over sodium sulfate. Concentration *in vacuo* and chromatography on silica gel (ethyl acetate:hexane, 2:1) gave (132) (60mg, 73%).
Rf : 0.45 (ethyl acetate:hexane, 1:1)

**1H NMR**: 1.17 (s, 3H, 4Me)  2.10 (s, 3H, OAc)  2.12 (s, 3H, OAc)  2.59 (bd, J=13.0Hz, 1H, H14)  2.62 (dd, J=7.1Hz, 17.0Hz, 1H, H11)  2.84 (d, J=11.0Hz, 1H, H6)  2.98 (s, 3H, SO3Me)  3.07 (dd, J=11.0Hz, 17.0Hz, 1H, H11)  3.45 (d, J=3.5Hz, 1H, H3)  5.21 (s, 1H, H15)  5.33 (d, J=3.5Hz, 1H, H3)  5.85 (s, 1H, H17)  5.92 (dd, J=3.5Hz, 9.3Hz, 1H, H2)  6.06 (s, 1H, H17')  6.30 (d, J=9.3Hz, 1H, H1).

**MS** : 552 (M+, <1%)  521 (4)  457 (5)  416 (20)  388 (14)  326 (10)  296 (10)  268 (23)  251 (20)  223 (62)  209 (40)  175 (100)  167 (32)  135 (45)  118 (62).

**HRMS** : C25H23O12S (M+); requires 552.1301, found 552.1301.

**ent-15α-Bromo-3α,13-diacetoxy-10β-hydroxy-12-oxo-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (138).**

Phosphorus oxybromide (9mg, 31.6µmol) was added to a stirred solution of (127) (10mg, 21.1µmol) in pyridine (5ml) at 0°C. After stirring at the same temperature for 1 h., saturated sodium bicarbonate solution (5ml) was added to quench the reaction. The resulting reaction mixture was diluted with ethyl acetate (20ml), washed with dilute hydrochloric acid (2M, 10ml), saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration *in vacuo* and chromatography on silica gel (ethyl acetate:hexane; 1:2) afforded (138) (7mg, 62%).

Rf : 0.55 (ethyl acetate:hexane; 1:1)

**1H NMR** : 1.15 (s, 3H, 4Me)  2.08 (s, 3H, OAc)  2.11 (s, 3H, OAc)  2.30 (d, J=12.0Hz, 1H, H14)  2.60 (dd, J=7.0Hz, 17.0Hz, 1H, H11)  2.87 (d, J=10.0Hz, 1H, H6)  3.00-3.20 (m, 2H, H11+H14, overlapped)  3.48 (d, J=11.0Hz, 1H, H5)  3.83 (s, 3H, OMe)  5.08 (t, J=2.7Hz, 1H, H15)  5.37 (d, J=3.5Hz, 1H, H3)  5.62 (d, J=2.7Hz, 1H, H17)  5.70 (d, J=2.7Hz, 1H, H17')  5.93 (dd, J=3.5Hz, 9.3Hz, 1H, H2)  6.39 (d, J=9.3Hz, 1H, H1).
ent-17-Bromo-3α,13-diacetoxy-10β-hydroxy-12-oxo-20-norgibberella-1,15-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (133).

A solution of (132) (40mg, 0.073mmol) in DMF (2ml) was added dropwise to a solution of anhydrous lithium bromide (50mg) in DMF (2ml) under nitrogen. After stirring at room temperature for 16 h., the reaction mixture was diluted with ethyl acetate (20ml), washed with saturated sodium thiosulfate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) afforded (133) (35mg, 90%).

Rf : 0.65 (ethyl acetate:hexane, 1:1)

$^1$H NMR : 1.20 (s, 3H, 4Me) 2.10 (s, 3H, OAc) 2.11 (s, 3H, OAc) 2.38 (d, J=11.0Hz, 1H, H14) 2.43 (dd, J=7.0Hz, 10.0Hz, 1H, H9) 2.65-2.85 (m, 2H, H6+H11, overlapped) 3.30 (dd, J=10.0Hz, 16.4Hz, 1H, H11') 3.40 (d, J=9.8Hz, 1H, H5) 3.48 (d, J=11.0Hz, 1H, H14) 3.77 (s, 3H, OMe) 3.93, 3.80 (ABd, J=13.0Hz, 2H, H17+H17') 5.35 (d, J=4.0Hz, 1H, H3) 5.91 (dd, J=4.0Hz, 9.0Hz, 1H, H2) 6.17 (bs, 1H, H15) 6.3 (d, J=9.0Hz, 1H, H1).

$^{13}$C NMR : 14.1 (C18) 20.4 (OAc) 20.7 (OAc) 23.7 (C11) 36.2 (C14) 47.0 (C17) 49.5 (C9) 50.2 (C6) 52.4 (OMe) 52.5 (C5) 54.5 (C8) 55.2 (C4) 70.0 (C3) 87.0 (C13) 90.1 (C10) 130.2 (C2) 132.1 (C1) 138.9 (C15) 140.6 (C16) 169.1 (OAc) 169.9 (OAc) 171.6 (C7) 176.3 (C19) 196.9 (C12).

M. S. : 505 (M$^+$/31, 3%) 457(10) 415 (5) 309 (11) 279 (7) 268 (16) 251 (9) 223 (18) 209 (14) 175 (20) 165 (11) 135 (9) 118 (20) 43 (100).

CIMS : 554 (M$^+$/18, 98%) 534 (10) 510 (43) 476 (43) 372 (26).

HRMS : C$_{23}$H$_{22}$O$_8$,$^{79}$Br (M$^+$/31); requires 505.0498, found 505.0499.
Reduction of (133) with sodium borohydride

To a solution of (133) (30mg, 55µmol) in methanol (3ml) at 0°C was added sodium borohydride (5mg, 0.13mmol). After stirring at the same temperature for 10 min, the reaction was quenched with dilute hydrochloric acid (2M, 1ml) and diluted with ethyl acetate (10ml), washed successively with dilute hydrochloric acid (2M, 5ml), saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) first gave (140) (19mg, 63%), followed by (134) (5mg, 17%).

ent-17-Bromo-3α,13-diacetoxy-10β,12α-dihydroxy-20-norgibberella-1,15-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (134).

Rf : 0.35 (ethyl acetate:hexane, 1:1)

1H NMR : 1.08 (s, 3H, 4Me) 2.14 (s, 6H, 2xOAc) 2.30 (d, J=11.0Hz, 1H, H14) 2.55 (d, J=11.0Hz, 1H, H14) 2.60 (d, J=10.3Hz, 1H, H6) 3.21 (d, J=10.3Hz, 1H, H5) 3.73 (s, 3H, OMe) 4.12, 4.25 (ABd, J=13.0Hz, 2H, H17+H17') 4.29 (bs, 1H, H12) 5.32 (d, J=4.0Hz, 1H, H3) 5.53 (dd, J=4.0Hz, 9.0Hz, 1H, H2) 6.07 (s, 1H, H15) 6.30 (d, J=9.0Hz, 1H, H1).

ent-17-Bromo-3α,12β-diacetoxy-10β,13-dihydroxy-20-norgibberella-1,15-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (140).

Rf : 0.45 (ethyl acetate:hexane, 1:1)

1H NMR : 1.20 (s, 3H, 4Me) 2.10 (s, 3H, OAc) 2.11 (s, 3H, OAc) 2.60 (d, J=12.3Hz, 1H, H14) 2.68 (d, J=10.0Hz, 1H, H6) 3.31 (d, J=10.0Hz, 1H, H5) 3.72 (s, 3H, OMe) 4.02 (s, 2H, H17+H17') 4.96 (t, J=7.0Hz, 1H, H12) 5.32 (d, J=4.0Hz, 1H, H3) 5.53 (dd, J=4.0Hz, 9.0Hz, 1H, H2) 6.02 (s, 1H, H15) 6.30 (d, J=9.0Hz, 1H, H1).
ent-17-Bromo-10β-hydroxy-3α,12β,13-triacetoxy-20-norgibberella-1,15-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (141).

Acetic anhydride (20µl, 0.21mmol) was added to a stirred solution of (140) (15mg, 28µmol), triethylamine (30µl, 0.21mmol) and a crystal of DMAP in dichloromethane (5ml) at room temperature. After stirring for 16 h., water (0.1ml) was added and the solvent was removed in vacuo. The residue was diluted with ethyl acetate (10ml), washed with saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) gave (141) (15mg, 92%).

Rf : 0.7 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 1.12 (s, 3H, 4Me) 2.03 (s, 3H, OAc) 2.04 (s, 3H, OAc) 2.13 (s, 3H, OAc) 2.46 (d, J=11.0Hz, 1H, H14) 2.62 (d, J=9.8Hz, 1H, H6) 2.99 (d, J=11Hz, 1H, H14') 3.31 (d, J=9.8Hz, 1H, H5) 3.72 (s, 3H, OMe) 4.13 (bs, 2H; H17+H17') 5.13 (t, J=7.5Hz, 1H, H12) 5.3 (d, J=4.0Hz, 1H, H3) 5.48 (dd, J=4.0Hz, 9.0Hz, 1H, H2) 6.06 (s, 1H, H15) 6.31 (d, J=9.0Hz, 1H, H1).

$^{13}$C NMR : 14.1 (C18) 20.9 (OAc) 21.2 (OAc) 21.4 (OAc) 22.7 (C11) 39.2 (C14) 43.7 (C17) 47.8 (C9) 50.9 (C8) 52.1 (C6) 52.5 (OMe) 53.5 (C4) 54.2 (C5) 65.11 (C12) 70.0 (C3) 87.0 (C13) 130.2 (C2) 132.1 (C1) 137.5 (C15) 145.0 (C16) 169.1 (OAc) 169.5 (OAc) 169.9 (OAc) 171.6 (C7) 176.3 (C19).

ent-17-Bromo-15ξ,16ξ-epoxy-10β-hydroxy-3α,12β,13-triacetoxy-20-norgibberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (142).

PNPBA (10mg, 55µmol) was added to a stirred solution of (141) (15mg, 26µmol) in dichloromethane (5ml). After stirring at room temperature for 40 h., dichloromethane was
removed under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate:hexane, 1:2) to give the epoxide (11mg, 71%).

R\text{f} : 0.45 (ethyl acetate:hexane, 1:1)

\text{H NMR} : 1.12 (s, 3H, 4Me) 2.04 (s, 6H, 2xOAc) 2.13 (s, 3H, OAc) 2.62 (d, J=9.8Hz, 1H, H6) 3.35 (d, J=9.8Hz, 1H, H5) 3.55 (bs, 1H, H15) 3.69 (s, 3H, OMe) 3.91, 4.32 (ABd, J=13.0Hz, 2H, H17+H17') 5.3 (d, J=4.0Hz, 1H, H3) 5.46 (t, J=7.5Hz, 1H, H12) 5.62 (dd, J=9.0Hz, 9.0Hz, 1H, H2) 6.35 (d, J=9.0Hz, 1H, H1).

\text{Preparation of (144).}

Methanesulfonyl chloride (0.12ml, 1.56mmol) was added dropwise to a stirred solution of (73) (0.5g, 1.04mmol) in pyridine (25ml) at 0°C. After stirring at the same temperature for 4 h., saturated sodium bicarbonate solution (10ml) was added dropwise over 15 min. The resulting mixture was diluted with ethyl acetate (50ml), washed successively with water, dilute hydrochloric acid (2M, 10ml), saturated sodium bicarbonate solution, then brine and dried over sodium sulfate. Concentration \textit{in vacuo} and chromatography on silica gel (ethyl acetate:hexane; 1:2) gave the mesylate (0.5g, 86%) as a foam.

\textit{ent-3α,13-Diacetoxy-10β-hydroxy-15α-methanesulfonyloxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone.}

R\text{f} : 0.35 (ethyl acetate:hexane: 1:1)

\text{H NMR} : 1.15 (s, 3H, 4Me) 1.98 (s, 3H, OAc) 2.08 (s, 3H, OAc) 2.73 (d, J=10.0Hz, 1H, H6) 2.85 (d, J=11.0Hz, 1H, H14) 2.96 (s, 3H, SO\textsubscript{3}Me) 3.24 (d, J=10.0Hz, 1H, H5) 3.78 (s, 3H, OMe) 5.19 (bs, 1H, H15) 5.30 (d, J=4.0Hz, 1H, H3) 5.59 (bs, 1H, H17) 5.81-5.88 (m, 2H, H2+H17', overlapped) 6.36 (d, J=9.3Hz, 1H, H1).

\text{MS} : 538 (M\textsuperscript{+}, 5%) 496 (5) 478 (5) 443 (9) 400 (25) 340 (16) 312 (10) 296 (48) 267 (44) 253 (54) 237 (100) 209 (76) 195 (45) 179 (47) 155 (37) 128 (29) 105 (24).

\text{HRMS} : C\textsubscript{23}H\textsubscript{30}O\textsubscript{11}S (M\textsuperscript{+}) requires 478.1297; found 478.1297.
ent-17-Bromo-3α,13-diacetoxy-10β-hydroxy-20-norgibberella-1,15-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (144).

Lithium bromide (250mg) was added to a stirred solution of the mesylate (0.45g, 0.81mmol) in DMF (25ml). After stirring at room temperature for 16 h., the reaction was diluted with ethyl acetate (100ml), washed with water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane; 1:2) gave (144) (0.35g, 83%).

\[ \text{Rf: 0.65 (ethyl acetate:hexane; 1:1).} \]

\[ \text{\( ^{1}H\)NMR: 1.12 (s, 3H, 4Me) 1.99 (s, 3H, OAc) 2.10 (s, 3H, OAc) 2.68 (d, J=10.5Hz, 1H, H6) 3.04 (d, J=12.0Hz, 1H, H14) 3.29 (d, J=10.5Hz, 1H, H5) 3.70 (s, 3H, OMe) 3.98 (s, 2H, H17+H1') 5.32 (d, J=4.0Hz, 1H, H3) 5.90 (dd, J=4.0Hz, 9.5Hz, 1H, H2) 6.29 (d, J=9.5Hz, 1H, H1).} \]

\[ \text{\( ^{13}C\)NMR: 14.3 (C18) 18.4 (C11) 20.9 (OAc) 21.8 (OAc) 25.2 (C12) 25.4 (C17) 43.6 (C14) 46.2 (C9) 50.5 (C8) 52.2 (C6+OMe, overlapped) 53.3 (C5) 55.3 (C4) 70.3 (C3) 86.0 (C13) 89.6 (C10) 129.5 (C1) 133.3 (C2) 137.4 (C15) 147.7 (C16) 169.9 (2xOAc) 172.1 (C7) 177.1 (C19).} \]


PNPBA (0.15g, 0.82mmol) was added to a stirred solution of (144) (0.3g, 0.57mmol) in dichloromethane (50ml). After stirring at room temperature for 16h., the reaction mixture was diluted with dichloromethane (100ml), washed with saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane; 1:2) gave (146) (0.25g, 81%) as a foam.

\[ \text{Rf: 0.5 (ethyl acetate:hexane; 1:1).} \]

\[ \text{\( ^{1}H\)NMR: 1.10 (s, 3H, 4Me) 2.00 (s, 3H, OAc) 2.10 (s, 3H, OAc) 2.52 (d, J=11.5Hz, 1H, H14) 2.67 (d, J=10.8Hz, 1H, H6) 3.33 (d, J=10.8Hz, 1H, H5) 3.47 (bs, 1H, H15) 3.80 (s, 3H, OMe) 3.74, 3.88 (ABd, J=12.0Hz,} \]
2H, H17+H17') 5.30 (d, J=4.0Hz, 1H, H3) 5.92 (dd, J=4.0Hz, 9.5Hz, 1H, H2) 6.30 (d, J=9.5Hz, 1H, H1).

$^{13}$C NMR: 14.5 (C18) 17.2 (C11) 20.1 (OAc) 21.5 (OAc) 25.5 (C12) 27.3 (C17) 33.7 (C14) 41.8 (C9) 50.1 (C6) 52.6 (C8) 53.2 (C5) 53.8 (C4) 54.6 (OMe) 64.5 (C15) 65.1 (C16) 71.2 (C3) 77.5 (C13) 89.9 (C10) 129.7 (C1) 133.4 (C2) 169.8 (OAc) 170.2 (OAc) 173.5 (C7) 176.3 (C19).

ent-3α,13-Diacetoxy-10β,15β-dihydroxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (73).

Silver activated zinc dust (25mg) was added to a stirred solution of (145) (50mg, 93µmol) in acetic acid (10ml). After stirring at room temperature for 15 min, the reaction mixture was diluted with dichloromethane (50ml), filtered through celite. The filtrate was washed with water (2x20ml), saturated sodium bicarbonate solution, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate: hexane; 1:2) gave (73) (40mg, 93%).

Rf : 0.3 (ethyl acetate:hexane; 1:1)

$^1$H NMR : 1.05 (s, 3H, 4Me) 2.01 (s, 3H, OAc) 2.10 (s, 3H, OAc) 2.63 (d, J=10.5Hz, 1H, H6) 2.90 (d, J=12.0Hz, 1H, H14) 3.31 (d, J=10.5Hz, 1H, H5) 3.70 (s, 3H, OMe) 4.05 (bs, 1H, H15) 5.20 (bs, 1H, H17) 5.33 (d, J=4.0Hz, 1H, H3) 5.41 (bs, 1H, H17') 5.92 (dd, J=4.0Hz, 9.5Hz, 1H, H2) 6.30 (d, J=9.5Hz, 1H, H1).

Reduction of (132) with sodium borohydride

Sodium borohydride (5mg, 0.13mmol) was added to a stirred solution of (132) (50mg, 90.6µmol) in methanol (5ml) at 0°C. After stirring at the same temperature for 15 min, dilute hydrochloric acid (2M, 1ml) was added dropwise to destroy the excess of reagent. The resulting reaction mixture was diluted with ethyl acetate (20ml), washed successively
with dilute hydrochloric acid (2M, 10ml), saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane; 1:1) first gave (146) (14mg, 28%), followed by (147) (20mg, 39%).

**ent-3α,12β-Diacetoxy-10β,13-dihydroxy-15β-methanesulfonyloxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (146).**

$R_f$: 0.25 (ethyl acetate:hexane: 1:1)

$^1$H NMR: 1.19 (s, 3H, 4Me) 2.10 (s, 3H, OAc) 2.12 (s, 3H, OAc) 2.90 (s, 3H, SO$_3$Me) 3.31 (d, J=10.5Hz, 1H, H5) 3.78 (s, 3H, OMe) 4.74 (t, J=7.0Hz, 1H, H12) 5.33 (d, J=3.5Hz, 1H, H3) 5.40 (bs, 1H, H15) 5.65 (s, 1H, H17) 5.92 (dd, J=3.5Hz, 9.3Hz, 1H, H2) 6.00 (bs, 1H, H17') 6.30 (d, J=9.3Hz, 1H, H1).

**ent-3α,13-Diacetoxy-10α,12α-dihydroxy-15α-methanesulfonyloxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (147).**

$R_f$: 0.1 (ethyl acetate:hexane; 1:1)

$^1$H NMR: 1.19 (s, 3H, 4Me) 2.09 (s, 3H, OAc) 2.11 (s, 3H, OAc) 2.65 (d, J=7.0Hz, 1H, H6) 2.85 (d, J=7.0Hz, 1H, H5) 3.00 (s, 3H, SO$_3$Me) 3.80 (s, 3H, OMe) 4.19 (m, 1H, H12) 5.33 (d, J=3.5Hz, 1H, H3) 5.38 (bs, 1H, H15) 5.58 (s, 1H, H17) 5.92 (m, overlapped, 2H, H2+H17') 6.30 (d, J=9.3Hz, 1H, H1).

**ent-17-Bromo-3α,13-diacetoxy-10β,12α-dihydroxy-20-norgibberella-1,15-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (134).**

Lithium bromide (25mg) was added to a stirred solution of (147) (20mg, 36µmol) in DMF (5ml) under a nitrogen atmosphere. After stirring at room temperature for 16 h., the reaction mixture was diluted with ethyl acetate (25ml), washed with sodium thiosulfate, water, then brine and dried over sodium sulfate. Concentration in vacuo and
chromatography on silica gel (ethyl acetate:hexane; 1:1) gave (134) (15mg, 77%) (see pg.163).

**ent-17-Bromo-3α,13-diacetoxy-10β,12α-dihydroxy-15ξ,16ξ-epoxy-20-norgibberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (135).**

![Diagram of ent-17-Bromo-3α,13-diacetoxy-10β,12α-dihydroxy-15ξ,16ξ-epoxy-20-norgibberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (135).]

PNPBA (10mg, 55μmol) was added to a stirred solution of (134) (15mg, 28μmol) in dichloromethane (5ml). After stirring at room temperature for 16 h., the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate:hexane; 2:1) to give (135) (13mg, 82%).

Rf : 0.4 (ethyl acetate:hexane, 2:1)

**1H NMR:** 1.18 (s, 3H, 4Me) 2.20 (s, 6H, 2xOAc) 2.58 (d, J=9.0Hz, 1H, H6) 3.31 (d, J=9.0Hz, 1H, H5) 3.54 (s, 1H, H15) 3.80 (s, 3H, OMe) 4.12 (s, 2H, H17+H17') 4.5 (bs, 1H, H12) 5.30 (d, J=3.5Hz, 1H, H3) 5.90 (dd, J=3.5Hz, 9.3Hz, 1H, H2) 6.29 (d, J=9.3Hz, 1H, H1).

**ent-17-Bromo-3α,13-diacetoxy-15ξ,16ξ-epoxy-10β-hydroxy-12-oxo-20-norgibberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (136).**

Jones' reagent (0.1ml) was added dropwise to a stirred solution of (135) (10mg, 18μmol) in acetone (5ml) at 0°C. After stirring at the same temperature for 1h., propan-2-ol was added to destroy the excess of reagent. The resulting green solution was diluted with ethyl acetate (20ml), washed with water (2x10ml), then brine and dried over sodium sulfate. Concentration in vacuo and filtration through a plug of silica gel gave (135) (8mg, 80%).

Rf : 0.4 (ethyl acetate:hexane; 1:1).

**1H NMR:** 1.15 (s, 3H, 4Me) 2.09 (s, 3H, OAc) 2.11 (s, 3H, OAc) 2.60 (dd, J=7.0Hz, 17.0Hz, 1H, H11) 2.72 (d, J=11.0Hz, 1H, H6) 3.00 (dd, J=11.0Hz, 17.0Hz, 1H, H11') 3.35 (d, J=11.0Hz, 1H, H5) 3.55 (bs, 1H,
H15) 3.80 (s, 3H, OMe) 3.90, 4.10 (ABd, J=15.0Hz, 2H, H17+H17')
5.33 (d, J=3.5Hz, 1H, H3) 5.92 (dd, J=3.5Hz, 9.3Hz, 1H, H2) 6.30 (d,
J=9.3Hz, 1H, H1).

Preparation of Epoxyalcohols (156) and (157).

\[
\begin{align*}
\text{PNPBA (100mg, 0.55mmol) was added to a solution of (126) (50mg, 0.105mmol) in} \\
\text{dichloromethane (5ml). After stirring at room temperature for 3 days, the solvent was} \\
\text{removed in vacuo and the residue was chromatographed on silica gel (ethyl acetate:hexane;} \\
\text{2:1) to give (156) (15mg, 30%) and (157) (20mg, 40%).}
\end{align*}
\]

**ent-3α,13-Diacetoxy-10β,15β-dihydroxy-16α,17-epoxy-12-oxo-20-nor-

gibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (156).**

Rf : 0.3 (ethyl acetate:hexane, 2:1)

\[
\begin{align*}
\text{H NMR :} & \quad 1.15 (s, 3H, 4Me) 2.11 (s, 6H, OAc, OAc') 2.67 (dd, J=6.8Hz, 18.0Hz, \\
& \quad 1H, H11) 2.82 (d, J=11.0Hz, 1H, H6) 2.93 (d, J=12.2Hz, 1H, H14) \\
& \quad 2.95, 3.05 (ABd, J=11.5Hz, 2H, H17+H17') 3.17 (dd, J=12.0Hz, 18.0Hz, \\
& \quad 1H, H11') 3.40 (d, J=11.0Hz, 1H, H5) 3.72 (s, 3H, OMe) 3.77 (s, 1H, \\
& \quad H15) 4.96 (bs, 1H, H3).
\end{align*}
\]

\[
\begin{align*}
\text{C NMR :} & \quad 14.1 (C18) 20.7 (OAc) 20.8 (OAc) 25.4 (C1) 27.4 (C2) 34.7 (C11) \\
& \quad 44.4 (C14) 49.3 (C9) 52.1 (C6+OMe, overlapped) 52.6 (C4) 52.8 (C8) \\
& \quad 54.9 (C5) 55.9 (C17) 63.4 (C16) 71.0 (C3) 76.0 (C15) 79.8 (C13) 92.2 \\
& \quad (C10) 169.7 (OAc) 169.9 (OAc) 172.7 (C7) 175.9 (C19) 202.4 (C12).
\end{align*}
\]

\[
\begin{align*}
\text{MS :} & \quad 492 (M^+, 5%) 478 (3) 450 (2) 432 (70) 404 (15) 390 (31) 372 (18) \\
& \quad 344 (19) 330 (27) 312 (34) 298 (18) 269 (24) 257 (22) 241 (30) 223 \\
& \quad (22) 211 (24) 202 (19) 185 (20) 167 (18) 157 (30) 149 (36) 129 (25) \\
& \quad 117 (24) 105 (30) 91 (34) 60 (100).
\end{align*}
\]

\[
\begin{align*}
\text{HRMS :} & \quad \text{C}_{24}\text{H}_{28}\text{O}_{11} (M^+) \text{; requires 492.1632, found 492.1633.}
\end{align*}
\]
ent-3α, 13-Diacetoxy-10β, 15β-dihydroxy-16β, 17-epoxy-12-oxo-20-norgibberellane-7, 19-dioic Acid 7-Methyl Ester 19, 10-Lactone (157).

Rₖ : 0.25 (ethyl acetate: hexane, 2:1)

1H NMR : 1.15 (s, 3H, 4Me) 2.11 (s, 6H, 2xOAc) 2.41 (dd J=6.4Hz, 12.0Hz, 1H, H9) 2.70 (dd, J=6.8Hz, 17.0Hz, 1H, H11) 2.82 (d, J=11.0Hz, 1H, H6) 2.93 (d, J=12.2Hz, 1H, H14) 2.95, 3.05 (ABd, J=11.5Hz, 2H, H17+H17') 3.18 (dd, J=12.0Hz, 17.0Hz, 1H, H11') 3.12 (d, J=11.0Hz, 1H, H5) 3.71 (s, 1H, H15) 3.72 (s, 3H, OMe) 4.96 (bs, 1H, H3).

13C NMR : 14.1 (C18) 20.7 (OAc) 20.8 (OAc) 25.4 (C1) 27.2 (C2) 34.6 (C11) 44.4 (C14) 49.3 (C9) 52.1 (C6+OMe, overlapped) 52.6 (C8) 52.8 (C4) 54.9 (C5) 56.3 (C17) 64.3 (C16) 70.0 (C3) 75.9 (C15) 81.2 (C13) 92.2 (C10) 169.7 (OAc) 169.9 (OAc) 172.7 (C7) 175.9 (C19) 201.4 (C12).

MS : 492 (M+, 10%) 478 (5) 450 (2) 432 (71) 404 (18) 390 (31) 372 (18) 344 (19) 330 (27) 312 (34) 298 (18) 269 (24) 257 (22) 241 (30) 223 (22) 211 (24) 202 (19) 185 (20) 167 (18) 157 (30) 149 (36) 129 (25) 117 (24) 105 (30) 91 (34) 60 (100).

HRMS : C₂₄H₂₃O₁₁ (M⁺); requires 492.1632, found 492.1635.

ent-3α, 13-Diacetoxy-12, 15-dioxo-16β, 17-epoxy-10β-hydroxy-20-norgibberellane-7, 19-dioic Acid 7-Methyl Ester 19, 10-Lactone (158).

To a stirred solution of (157) (20mg, 0.04mmol) in acetone (2ml), was added Jones' reagent (0.25ml). After stirring at room temperature for 3 h., propan-2-ol was added to destroy the excess of reagent. The resulting green solution was diluted with ethyl acetate (10ml), washed with water, then brine and dried over sodium sulphate. Concentration in vacuo and filtration through a short column of silica gel gave (158) (15mg, 75%).

Rₖ : 0.7 (ethyl acetate:hexane, 1:1)
**1H NMR:**  1.15 (s, 3H, 4Me)  2.12 (s, 3H, OAc)  2.13 (s, 3H, OAc)  2.24 (dd, J=6.4Hz, 12.0Hz, 1H, H9)  2.69 (dd, J=6.4Hz, 16.0Hz, 1H, H11)  2.74 (d, J=12.0Hz, 1H, H14)  2.82 (d, J=10.3Hz, 1H, H6)  3.15 (bs, 2H, H17+H17')  3.40 (dd, J=10.3Hz, 16.0Hz, 1H, H11')  3.45 (d, J=10.3Hz, 1H, H5)  3.53 (d, J=12.0Hz, 1H, H14')  3.62 (s, 3H, OMe)  5.00 (bs, 1H, H3).

**13C NMR:**  14.1 (Cl8)  20.4 (OAc)  20.7 (OAc)  25.4 (C1)  27.2 (C2)  34.9 (C11)  43.9 (C14)  48.5 (C9)  48.6 (C6)  52.5 (C4)  53.1 (C5)  53.2 (OMe)  59.5 (C8)  60.5 (C17)  68.4 (C16)  70.0 (C3)  78.5 (C13)  92.2 (C10)  169.6 (OAc)  169.9 (OAc)  170.0 (C7)  175.8 (C19)  202.4 (C12)  207.6 (C15).

**MS:**  490 (M+, 5%)  460 (14)  459 (50)  420 (20)  377 (20)  360 (82)  328 (21)  314 (88)  300 (100)  283 (39)  271 (20)  255 (34)  239 (52)  227 (22)  201 (22)  175 (23)  157 (35)  129 (25)  119 (19)  91 (26)  69 (30).

**HRMS:**  C_{24}H_{26}O_{11} (M+); requires 490.1475, found 490.1480.

**ent-3α,13-Diacetoxy-10β,15α-dihydroxy-16β,17-epoxy-12-oxo-20-norgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (159).**

Zinc borohydride in ether (50 µl, 1.2M) was added dropwise to a solution of the epoxyketone (158) (20 mg, 0.04 mmol) in ether (5 ml) at -30°C. After stirring at the same temperature for 10 min, the reaction was quenched with dilute hydrochloric acid (2M, 1 ml). The resulting mixture was diluted with ethyl acetate (10 ml), washed successively with saturated sodium bicarbonate, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:1) afforded (159) (12 mg, 61%).

**Rf:**  0.45 (ethyl acetate:hexane, 1:1)

**1H NMR:**  1.12 (s, 3H, 4Me)  2.11 (s, 3H, OAc)  2.12 (s, 3H, OAc)  2.59 (dd, J=6.0Hz, 16.0 Hz, 1H, H11)  2.72 (d, J=10.5Hz, 1H, H6)  2.8 (m, 1H, OH)  2.94 (d, J=11.0Hz, 1H, H14)  2.92-3.11 (m, 3H, H11', H17+H17', overlapped)  3.10 (d, J=10.5Hz, 1H, H5)  3.72 (s, 3H, OMe)  3.98 (d, J=4.0Hz, 1H, H15)  4.96 (bs, 1H, H3).
**13C NMR**: 14.1 (C18) 20.6 (OAc) 20.8 (OAc) 25.4 (C1) 27.2 (C2) 34.2 (C11) 36.9 (C14) 47.3 (C9) 51.5 (OMe) 52.8 (C6) 53.1 (C4) 53.2 (C5) 54.7 (C8) 55.7 (C17) 63.9 (C16) 70.0 (C3) 75.2 (C15) 79.9 (C13) 92.2 (C10) 169.6 (OAc) 169.8 (OAc) 174.1 (C7) 175.9 (C19) 202.5 (C12).

**MS**: 492 (M+, 3%) 450 (2) 432 (69) 404 (18) 390 (31) 372 (18) 344 (19) 330 (27) 312 (24) 298 (15) 269 (24) 257 (20) 241 (32) 223 (22) 211 (24) 202 (19) 185 (20) 167 (18) 157 (30) 149 (36) 129 (20) 117 (24) 105 (30) 91 (34) 60 (100).

**HRMS**: C_{26}H_{30}O_{11} (M+) requires 502.1836, found 502.1840.

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**ent-10β-Hydroxy-3α,12β,13-triacetoxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (165).**

When (121) (50mg, 0.135mmol) was subjected to reaction with acetic anhydride (0.1ml, 1mmol), triethylamine (0.2ml, 1.4mmol) and DMAP (5mg) in dichloromethane (10ml) according to the procedure for conversion of (103) to (105), (165) (64mg, 95%) was obtained.

**Rf**: 0.8 (ethyl acetate:hexane, 1:1).

**1H NMR**: 1.15 (s, 3H, 4Me) 2.01 (s, 3H, OAc) 2.02 (s, 3H, OAc) 2.12 (s, 3H, OAc) 2.60 (m, 1H, H14) 2.68 (d, J=10.0Hz, 1H, H6) 3.31 (d, J=10.0Hz, 1H, H5) 3.75 (s, 3H, OMe) 5.03 (t, J=7.0Hz, 1H, H12) 5.10 (bs, 1H, H17) 5.15 (bs, 1H, H17') 5.30 (d, J=4.0Hz, 1H, H3) 5.88 (dd, J=4.0Hz,9.3Hz, 1H, H2) 6.31 (d, J=9.3Hz, 1H, H1).

**MS**: 502 (M+, 1%) 471(5) 462 (2) 444 (6) 402 (30) 384 (16) 352 (35) 342 (40) 324 (14) 280 (40) 238 (35) 221 (70) 209 (25) 195 (23) 178 (45) 155 (27) 129 (64) 105 (100).

**HRMS**: C_{26}H_{30}O_{10} (M+) requires 502.1836, found 502.1840.
ent-10β,15β-Dihydroxy-3α,12β,13-triacetoxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (166).

To a stirred solution of (165) (60mg, 0.12mmol) in acetic acid (5ml), was added selenium dioxide (100mg) and tert-butyl hydroperoxide (0.1ml). After stirring at room temperature for 2 days, the reaction mixture was diluted with dichloromethane (20ml), washed with dilute hydrochloric acid (2M, 10ml), water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:1), gave (166) (48mg, 78%).

Rf : 0.2 (ethyl acetate:hexane, 1:1)

1H NMR: 1.14 (s, 3H, 4Me) 2.00 (s, 3H, OAc) 2.09 (s, 6H, OAc, OAc') 2.64 (d, J=10.8Hz, 1H, H6) 2.83 (d, J=11.8Hz, 1H, H14) 3.32 (d, J=10.8Hz, 1H, H5) 3.70 (s, 3H, OMe) 4.04 (bs, 1H, H15) 5.08 (t, J=8.0Hz, 1H, H12) 5.29 (d, J=4.0Hz, 1H, H3) 5.39 (s, 1H, H17) 5.56 (s, 1H, H17') 5.85 (dd, J=4.0Hz, 9.3Hz, 1H, H2) 6.29 (d, J=9.3Hz, 1H, H1).

13C NMR: 14.0 (C18) 20.8 (OAc) 21.1 (OAc) 22.0 (OAc) 24.5 (C11) 32.0 (C14) 44.9 (C9) 48.3 (C6) 52.4 (C8) 52.5 (OMe) 54.1 (C5) 57.8 (C4) 70.1 (C3) 74.4 (C12) 77.7 (C15) 82.1 (C13) 89.9 (C10) 116.4 (C17) 129.7 (C2) 133.4 (C1) 151.2 (C16) 169.9 (OAc) 170.5 (OAc) 170.6 (OAc) 172.8 (C7) 176.7 (C19).

MS: 518 (M+, 5%) 476 (5) 458 (10) 444 (8) 416 (14) 398 (28) 356 (11) 338 (32) 324 (18) 310 (22) 294 (52) 268 (48) 251 (93) 235 (100) 223 (72) 208 (95) 193 (53) 179 (55) 165 (48) 157 (52) 149 (76) 129 (79) 115 (41) 94 (21) 71 (24).

HRMS: C26H30O11 (M+); requires 518.1788, found 518.1788.

When (166) (40mg, 77µmol) was subjected to oxidation with oxalyl chloride (50µl) and dimethyl sulfoxide (0.2ml) in dichloromethane (5ml) according to the procedure for conversion of (126) to (128), (167) (31mg, 78%) was obtained.

\[ \text{Rf : 0.55 (ethyl acetate:hexane, 1:1)} \]

\[ \begin{align*}
1H \text{ NMR : 1.23} & \text{ (s, 3H, OAc)} \quad 2.09 \text{ (s, 6H, 2xOAc)} \quad 2.13 \text{ (s, 3H, OAc)} \quad 2.68 \text{ (d, J=10.0Hz, 1H, H6)} \quad 2.74 \text{ (d, J=12.0Hz, 1H, H14)} \quad 2.84 \text{ (d, J=12.0Hz, 1H, H14')} \quad 3.47 \text{ (d, J=10.0Hz, 1H, H5)} \quad 3.67 \text{ (s, 3H, OMe)} \quad 5.19 \text{ (t, J=8.0Hz, 1H, H12)} \quad 5.35 \text{ (d, J=4.0Hz, 1H, H3)} \quad 5.89 \text{ (s, 1H, H17)} \quad 5.90 \text{ (dd, partially overlapped with H17, J=4.0Hz, 9.3Hz, 1H, H2)} \quad 6.28 \text{ (d, J=9.3Hz, 1H, H1)} \quad 6.31 \text{ (s, 1H, H17')} 
\end{align*} \]

Reduction of (167) with zinc in acetic acid.

To a solution of (167) (10mg, 0.2mmol) in acetic acid (2ml) was added freshly activated zinc dust (5mg). After stirring at room temperature for 20 min, the solution was diluted with dichloromethane (10ml), washed with water (2x10ml), saturated sodium bicarbonate solution, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane 1:2) first afforded (168) (4mg, 40%), followed by (169) (4mg, 40%).


\[ \text{Rf : 0.55 (ethyl acetate:hexane, 1:1)} \]

\[ \begin{align*}
1H \text{ NMR : 1.21} & \text{ (s, 3H, 4Me)} \quad 1.35 \text{ (d, J=7.3Hz, 3H, 16Me)} \quad 2.05 \text{ (s, 3H, OAc)} \quad 2.06 \text{ (s, 3H, OAc)} \quad 2.13 \text{ (s, 3H, OAc)} \quad 2.75 \text{ (m, 2H, H6+H14, overlapped)}
\end{align*} \]
3.03 (d, J=12.0Hz, H14') 3.42 (d, J=10.7Hz, 1H, H5) 3.65 (s, 3H, OMe) 5.32 (t, J=8.0Hz, 1H, H12) 5.34 (d, J=4.0Hz, 1H, H3, partially overlapped with H12) 5.90 (dd, J=4.0Hz, 9.5Hz, 1H, H2) 6.30 (d, J=9.5Hz, 1H, H1).

**ent-10β,15α-Di hydroxy-3α,12β,13-triacetoxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (169).**

**Rf** : 0.4 (ethyl acetate:hexane, 1:1)

**1H NMR** : 1.14 (s, 3H, 4Me) 1.95 (s, 3H, OAc) 2.10 (s, 3H, OAc) 2.15 (s, 3H, OAc) 2.58 (dd, J=6.6Hz, 12.5Hz, 1H, H9) 2.81 (d, J=11.0Hz, 1H, H6) 3.17 (d, J=11.0Hz, 1H, H5) 3.82 (s, 3H, OMe) 4.42 (bs, 1H, H15) 5.06 (t, J=7.5Hz, 1H, H12) 5.32 (d, J=4.0Hz, 1H, H3) 5.38 (d, J=2.5Hz, 1H, H17) 5.40 (d, J=3Hz, 1H, H17') 5.86 (dd, J=4.0Hz, 9.3Hz, 1H, H2) 6.37 (d, J=9.3Hz, 1H, H1).

**13C NMR** : 14.9 (C18) 21.6 (OAc) 22.2 (OAc) 22.8 (OAc) 24.7 (C11) 38.3 (C14) 51.0 (C9) 51.1 (C6) 52.3 (C8) 52.5 (OMe) 54.3 (C5) 56.1 (C4) 71.2 (C3) 74.1 (C12) 75.5 (C15) 81.2 (C13) 90.4 (C10) 112.3 (C16) 129.3 (C2) 133.8 (C1) 150.4 (16) 167.2 (OAc) 169.6 (OAc) 170.5 (OAc) 172.6 (C7) 175.5 (C19).

**MS** : 518 (M+, 5%) 476 (10) 458 (10) 416 (22) 398 (10) 372 (10) 356 (14) 338 (20) 312 (47) 294 (61) 282 (33) 267 (50) 251 (100) 235 (72) 223 (66) 209 (51) 195 (34) 179 (21) 165 (30) 143 (44) 115 (32) 105 (24) 83 (38) 55 (93).

**HRMS** : C_{26}H_{30}O_{11} (M+); requires 518.1788, found 518.1789.

**ent-10β,15β-Di hydroxy-3α,12β,13-triacetoxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (171).**
When (105) (75mg, 0.15mmol) was subjected to reaction with selenium dioxide (50mg) and tert-butyl hydroperoxide (0.1ml) in acetic acid (5ml) according to the procedure for conversion of (119) to (166), (171) (60mg, 76%) was obtained.

**Rf :** 0.2 (ethyl acetate:hexane, 1:1)

**1H NMR :** 1.07 (s, 3H, 4Me) 2.01 (s, 3H, OAc) 2.11 (s, 6H, 2xOAc) 2.57 (d, J=10.3Hz, 1H, H6) 2.82 (dd, J=2.0Hz, 12.0Hz, 1H, H14) 3.17 (d, J=10.3Hz, 1H, H5) 3.69 (s, 3H, OMe) 4.03 (bs, 1H, H15) 4.93 (bs, 1H, H3) 5.07 (dt, J=2Hz, 7Hz, 1H, H12) 5.38 (s, 1H, H17) 5.55 (s, 1H, H17').

**13C NMR :** 14.2 (C18) 21.1 (OAc) 21.2 (OAc) 24.7 (C11) 25.4 (C1) 27.4 (C2) 32.2 (C14) 47.0 (C9) 49.0 (C4) 52.4 (C8) 53.1 (OMe) 53.6 (C4) 56.9 (C5) 71.1 (C3) 73.5 (C15) 77.7 (C12) 82.2 (C13) 92.7 (C10) 116.4 (C16) 151.3 (C17) 170.5 (OAc) 170.1 (OAc) 173.3 (C7) 176.4 (C19).

**MS :** 520 (M+, 5%) 478 (10) 460 (10) 420 (10) 418 (36) 400 (64) 386 (19) 385 (20) 368 (13) 358 (20) 340 (11) 326 (11) 308 (48) 296 (82) 280 (58) 269 (21) 236 (73) 209 (100) 194 (27) 169 (24) 155 (26) 143 (40) 129 (38) 115 (28) 105 (55) 91 (69) 82 (54) 55 (100).

**HRMS :** C_{26}H_{32}O_{11} (M+); requires 520.1945, found 520.1946.

**ent-10β-Hydroxy-15-oxo-3α,12β,13-triacetoxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (172).**

When (171) (40mg, 77µmol) was subjected to oxidation with oxalyl chloride (50µl) and dimethyl sulfoxide (0.2ml) in dichloromethane (5ml) according to the procedure for conversion of (126) to (128), (167) (29mg, 78%) was obtained.

**Rf :** 0.6 (ethyl acetate:hexane, 1:1)

**1H NMR :** 1.12 (s, 3H, OAc) 2.08 (s, 3H, OAc) 2.09 (s, 3H, OAc) 2.15 (s, 3H, OAc) 2.64 (d, J=10.0Hz, 1H, H6) 2.65 (bd, J=12.0Hz, 1H, H14) 2.84 (bd, J=12.0Hz, 1H, H14') 3.34 (d, J=10.0Hz, 1H, H5) 3.65 (s, 3H, OMe)
4.99 (bs, 1H, H3)  5.17 (t, J=8.0Hz, 1H, H12)  5.87 (s, 1H, H17)  6.30 (s, 1H, H17').

\[ ^{13}C\text{NMR} : 14.9 \text{ (C18)} \quad 20.6 \text{ (OAc)} \quad 21.2 \text{ (OAc)} \quad 25.0 \text{ (C11)} \quad 25.4 \text{ (C1)} \quad 27.2 \text{ (C2)} \quad 34.7 \text{ (C14)} \quad 47.1 \text{ (C9)} \quad 48.5 \text{ (C6)} \quad 52.0 \text{ (OMe)} \quad 52.3 \text{ (C5)} \quad 54.3 \text{ (C4)} \quad 60.2 \text{ (C8)} \quad 71.0 \text{ (C3)} \quad 72.5 \text{ (C12)} \quad 81.3 \text{ (C13)} \quad 92.2 \text{ (C10)} \quad 123.9 \text{ (C16)} \quad 145.2 \text{ (C17)} \quad 167.2 \text{ (OAc)} \quad 169.6 \text{ (OAc)} \quad 173.6 \text{ (C7)} \quad 175.5 \text{ (C19)} \quad 200.4 \text{ (C15)}. \]

MS : 518 (M+, <1%)  500 (16)  476 (16)  458 (16)  448 (48)  434 (100)  416 (48)  402 (16)  385 (32)  374 (64)  356 (16)  342 (16)  328 (30)  312 (20)  284 (27)  268 (43)  253 (38)  241 (25)  225 (53)  211 (23)  197 (22)  181 (20)  167 (22)  157 (26)  143 (44)  129 (33)  115 (26)  91 (50)  85 (38)  77 (33)  71 (64).

HRMS :  C\text{24H26O8} \text{ (M+-60)}; \text{ requires 458.1577, found 458.1577.}

Reduction of (172) with zinc in acetic acid.

When (172) (10mg, 19.3µmol) was subjected to reduction with zinc dust (5mg) in acetic acid (5ml) according to the procedure for reduction of (167), 4mg of (173) and 3mg of (174) were obtained (40% and 30% yield respectively).


Rf :  0.55 (ethyl acetate:hexane, 1:1).

\[ ^{1}H\text{NMR} : 1.04 \text{ (s, 3H, 4Me)} \quad 1.25 \text{ (d, J=7.5Hz, 3H, 16Me)} \quad 2.06 \text{ (s, 3H, OAc)} \quad 2.07 \text{ (s, 3H, OAc)} \quad 2.12 \text{ (s, 3H, OAc)} \quad 2.30-2.60 \text{ (m, overlapped, 2H, H6+H14)} \quad 2.73 \text{ (d, J=12.0Hz, 1H, H14')} \quad 3.00 \text{ (d, J=10.8Hz, 1H, H5)} \quad 3.66 \text{ (s, 3H, OMe)} \quad 4.95 \text{ (bs, 1H, H3)} \quad 5.45 \text{ (t, J=9.0Hz, 1H, H12)}. \]
ent-10β,15α-Dihydroxy-3α,12β,13-triacetoxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (174).

Rf : 0.4 (ethyl acetate:hexane, 1:1)

1H NMR : 1.07 (s, 3H, 4Me) 1.97 (s, 3H, OAc) 2.09 (s, 3H, OAc) 2.12 (s, 3H, OAc) 2.55 (dd, J=6.6Hz, 12.5Hz, 1H, H9) 2.73 (d, J=11.0Hz, 1H, H6) 3.02 (d, J=11.0Hz, 1H, H5) 3.81 (s, 3H, OMe) 4.40 (bs, 1H, H15) 4.95 (bs, 1H, H3) 5.05 (t, J=7.5Hz, 1H, H12) 5.37 (d, J=2.5Hz, 1H, H17) 5.39 (d, J=3Hz, 1H, H17')

MS : 520 (M+, 5%) 504 (2) 489 (2) 478 (18) 446 (20) 418 (33) 400 (25) 386 (53) 358 (37) 340 (46) 326 (34) 298 (43) 280 (35) 269 (25) 253 (56) 225 (34) 183 (28) 149 (100) 129 (59) 121 (92) 111 (74) 97 (100) 71 (100).

HRMS : C26H32O11 (M+); requires 520.1945, found 520.1946.
ent-3α-Acetoxy-10β-hydroxy-17-oxo-20-norgiberella-1,15-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (185).

Pyridinium chlorochromate (7.5g, 34.4mmol) was added to a stirred solution of the allylic alcohol (184)* (2.8g, 6.8mmol) in dichloromethane (250ml). After stirring at room temperature for 16 h., the reaction mixture was diluted with ether (500ml) and filtered through silica gel (50g). Concentration \textit{in vacuo} gave the crude product mixture (2.2g, 78%) as a white foam. The crude mixture was dissolved in acetone (50ml) under a carbon dioxide atmosphere and aqueous chromous chloride (50ml) was then added. After stirring at room temperature for 10 min, the reaction mixture was diluted with ethyl acetate (100ml), washed with water (2x50ml), then brine and dried over sodium sulfate. Concentration \textit{in vacuo} and chromatography on silica gel (ethyl acetate:hexane, 1:2) afforded (185) (1.7g, 58% yield from 184) as pale yellow solids. Recrystallisation from ether and hexane gave colourless crystals (1.6g).

\begin{itemize}
\item \textbf{R}_f : \quad 0.6 \text{ (ethyl acetate:hexane, 1:1).}
\item \textbf{m.p.} : \quad 169-174°C.
\end{itemize}
**1H NMR**: 1.11 (s, 3H, 4Me) 2.06 (s, 3H, OAc) 2.71 (d, J=10.3Hz, 1H, H6) 2.92 (m, 1H, H13) 3.24 (d, J=10.3Hz, 1H, H5) 3.68 (s, 3H, OMe) 5.28 (d, J=3.7Hz, 1H, H3) 5.83 (dd, J=3.7Hz, 9.5Hz, 1H, H2) 6.30 (d, J=9.5Hz, 1H, H1) 6.84 (s, 1H, H15) 9.60 (s, 1H, CHO).

**13C NMR**: 14.2 (C18) 18.2 (C11) 20.6 (OAc) 22.3 (C12) 39.6 (C13) 44.4 (C14) 50.3 (C8+C9, overlapped) 52.2 (C4) 52.3 (C6) 53.3 (OMe) 57.4 (C5) 70.2 (C3) 90.2 (C10) 129.5 (C1) 133.1 (C2) 154.3 (C16) 156.5 (C15) 169.8 (OAc) 172.3 (C7) 176.9 (C19) 188.4 (C17).

**MS**: 400 (M+, 7%) 369 (10) 358 (4) 340 (7) 322 (3) 308 (7) 296 (31) 278 (6) 267 (13) 237 (78) 209 (20) 195 (15) 179 (49) 165 (22) 155 (37) 129 (11) 119 (100) 105 (13) 91 (27).

**HRMS**: C_{22}H_{24}O_{7} (M+) requires 400.1522, found 400.1522.

*Allylic alcohol (184) was prepared according to the procedure published by MacMillan, while the precursor to (184) was supplied by Bruce Twitchin.*

**Preparation of (186) and (187).**

Zinc dust (0.5g) was added to a stirred solution of (185) (1.6g, 3.7mmol) in acetic acid (50ml). After stirring at room temperature for 1 h., the reaction mixture was diluted with dichloromethane (150ml) and filtered through celite. The filtrate was washed with water (2x50ml), saturated sodium bicarbonate solution, then brine and dried over sodium sulfate. Concentration *in vacuo* and chromatography on silica gel (ethyl acetate:hexane, 1:2) first gave (186) (0.67g, 42%), followed by (187) (0.56g, 35%).

**ent-3α-Acetoxy-10β-hydroxy-17-oxo-20-norgiberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (186).**

R\_f : 0.65 (ethyl acetate:hexane, 1:1)

**1H NMR**: 1.04 (s, 3H, 4Me) 2.04 (s, 3H, OAc) 2.67 (d, J=11.0Hz, 1H, H6) 2.95 (m, 1H, H13) 3.10 (m, 1H, H16) 3.24 (d, J=11.0Hz, 1H, H5) 3.65 (s, 3H, OMe) 5.24 (d, J=3.7Hz, 1H, H3) 5.78 (dd, J=3.7Hz, 9.5Hz, 1H, H2) 6.31 (d, J=9.5Hz, 1H, H1) 9.71 (CHO).
ent-3α-Acetoxy-10β, 17-dihydroxy-20-norgibberella-1, 15-diene-7, 19-dioic Acid 7-Methyl Ester 19, 10-Lactone (187).

Rf : 0.2 (ethyl acetate:hexane, 1:1)

$^1$H NMR : 1.10 (s, 3H, 4Me) 2.06 (s, 3H, OAc) 2.21 (d, J=11.0Hz, 1H, H14) 2.24 (m, 1H, H13) 2.62 (d, J=10.3Hz, 1H, H6) 3.20 (d, J=10.3Hz, 1H, H5) 3.65 (s, 3H, OMe) 4.12 (s, 2H, H17+H17') 5.28 (d, J=3.7Hz, 1H, H3) 5.63 (s, 1H, H15) 5.78 (dd, J=3.7Hz, 9.5Hz, 1H, H2) 6.31 (d, J=9.5Hz, 1H, H1).

$^{13}$C NMR : 14.5 (C18) 18.4 (C11) 20.8 (OAc) 22.3 (C12) 40.6 (C13) 45.6 (C14) 50.3 (C8+C9, overlapped) 52.2 (C4) 52.3 (C6) 53.3 (OMe) 57.4 (C5) 60.5 (C17) 70.4 (C3) 90.3 (C10) 129.1 (C1) 131.1 (C2) 133.6 (C15) 156.5 (C15) 169.8 (OAc) 172.3 (C7) 176.9 (C19).

MS : 402 (M+, 12%) 371 (10) 300 (22) 280 (32) 267 (17) 238 (100) 221 (83) 215 (28) 209 (37) 193 (43) 179 (66) 165 (35) 155 (76) 143 (30) 131 (29) 115 (28) 105 (36) 91 (56) 79 (35).

HRMS : C$_{22}$H$_{26}$O$_7$ (M+) requires 402.1679, found 402.1678.

Preparation of (188) and (189).

When (186) (0.65g, 1.5mmol) was allowed to react with pyrrolidone hydrotribromide (1g, 2mmol) in dichloromethane (20ml) according to the procedure for conversion of (77) to (83), a ca 3:1 mixture of (188) and (189) (0.53g, 73%) was obtained after chromatography. Further attempts to resolve the mixture on MPLC failed.

Rf : 0.8 (ethyl acetate:hexane, 1:1)

$^1$H NMR : 9.53 (s, 0.75H, CHO) (188) and 9.28 (s, 0.25H, CHO) (189) (mixture of two isomers).

ent-3α-Acetoxy-16β-bromo-10β, 17-dihydroxy-20-norgibberell-1-ene-7, 19-dioic Acid 7-Methyl Ester 19, 10-Lactone (190).

The mixture of (188) and (189) (0.5g, 1.04mmol) was subjected to reaction with sodium borohydride (50mg, 1.3mmol) in DME (10ml) according to the procedure for conversion of (112) to (113), (190)* (0.17g, 35%) was obtained as a thick oil after chromatography on
MPLC (ethyl acetate:hexane; 1:1). The rest of the material was obtained as a mixture of several products which could not be properly identified.

\[ R_f : 0.25 \] (ethyl acetate:hexane, 1:1).

**1H NMR:**
- 1.10 (s, 3H, 4Me) 2.05 (s, 3H, OAc) 2.20-2.40 (m, 2H, H6+H13, overlapped) 2.70 (d, J=10.5Hz, 1H, H5) 3.40-3.80 (m, 5H, OMe, H17 + H17', overlapped) 5.28 (d, J=3.7Hz, 1H, H3) 5.78 (dd, J=3.7Hz, 9.5Hz, 1H, H2) 6.31 (d, J=9.5Hz, 1H, H1).

**13C NMR:**
- 14.4 (C18) 15.4 (C11) 20.8 (OAc) 22.6 (C12) 36.2 (C13) 46.8 (C14) 51.7 (C15) 52.2 (C6+C8, overlapped) 52.8 (OMe) 53.3 (C4) 54.2 (C5) 69.3 (C17) 70.3 (C3) 83.7 (C16) 90.5 (C10) 129.4 (C1) 134.0 (C2) 169.9 (OAc) 172.5 (C19) 176.3 (C7).

* A sample of compound (190) was found to decompose when stored under nitrogen overnight.

**ent-3α-Acetoxy-16β-bromo-12α,17-epoxy-10β-hydroxy-20-norgiberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (191).**

When (190) (30mg, 62.5µmol) was subjected to reaction with LTA (0.17g, 375µmol) and iodine (8mg, 31.5µmol) in benzene (5ml) according to the procedure for conversion of (66) to (87), (191) (20mg, 68%) was obtained as a foam.

\[ R_f : 0.85 \] (ethyl acetate:hexane, 1:1).

**1H NMR:**
- 1.4 (s, 3H, 4Me) 2.11 (s, 3H, OAc) 2.29 (d, J=14.0Hz, 1H, H14) 2.70-2.80 (m, 2H, H6+H13) 3.25 (d, J=10.5Hz, 1H, H5) 3.78 (s, 3H, OMe) 3.96 (s, 2H, H17+H17') 4.49 (dt, J=2.0Hz, 9.5Hz, 1H, H12) 5.33 (d, J=3.7Hz, 1H, H3) 5.88 (dd, J=3.7Hz, 9.5Hz, 1H, H2) 6.35 (d, J=9.5Hz, 1H, H1).

**13C NMR:**
- 14.3 (C18) 20.8 (OAc) 24.1 (C11) 35.1 (C14) 49.0 (C9) 51.9 (C13) 52.2 (C6) 52.4 (C8) 53.1 (C4) 53.4 (OMe) 53.4 (C15) 55.7 (C5) 64.2 (C16) 70.3 (C3) 77.3 (C17) 78.6 (C12) 90.8 (C10) 129.4 (C1) 133.5 (C2) 170.0 (OAc) 172.6 (C19) 176.8 (C7).

**ent-3α-Acetoxy-10β,12-dihydroxy-20-norgiberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (192).**

When (191) (15mg, 31.25µmol) was treated with silver-zinc couple (5mg) in acetic acid (1ml) according to the procedure for conversion of (110) to (117), (192) (8mg, 64%) was
obtained as a gum.

Rf : 0.3 (ethyl acetate:hexane, 1:1).

\(^1\)H NMR : 1.13 (s, 3H, 4Me) 2.05 (s, 3H, OAc) 2.75 (d, J=10.5Hz, 1H, H6) 2.90 (m, 1H, H13) 3.30 (d, J=10.5Hz, 1H, H5) 3.75 (s, 3H, OMe) 4.15 (bs, 1H, H12) 5.15 (bs, 1H, H17) 5.20 (bs, 1H, H17') 5.30 (d, J=3.7Hz, 1H, H3) 5.85 (dd, J=3.7Hz, 9.5Hz, 1H, H2) 6.35 (d, J=9.5Hz, 1H, H1).

MS : 371 (M+-31, 1%) 358 (5) 342 (5) 326 (7) 313 (12) 297 (16) 280 (14) 267 (13) 252 (60) 240 (71) 221 (32) 209 (50) 193 (100) 179 (65) 165 (31) 155 (43) 143 (29) 129 (29) 119 (40) 105 (36) 91 (100).

HRMS : C\(_{22}\)H\(_{26}\)O\(_7\) (M\(^+\)) requires 402.1679, found 402.1677.

\(\textit{ent-3α,10β,12α-Trihydroxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (193).}\)

Anhydrous potassium carbonate (1mg) was added to a stirred solution of (192) (7mg, 17µmol) in methanol (2ml). After stirring at room temperature for 1 h., the reaction mixture was diluted with ethyl acetate (10ml), washed with dilute hydrochloric acid (2M, 3ml), saturated sodium bicarbonate, water, then brine and dried over sodium sulfate. Concentration \textit{in vacuo} and chromatography on silica gel (ethyl acetate:hexane, 1:1) gave (193) (5mg, 82% yield).

Rf : 0.1 (ethyl acetate:hexane, 1:1).

\(^1\)H NMR : 1.13 (s, 3H, 4Me) 2.05 (s, 3H, OAc) 2.75 (d, J=10.5Hz, 1H, H6) 3.01 (m, 1H, H13) 3.30 (d, J=10.5Hz, 1H, H5) 3.75 (s, 3H, OMe) 4.10-4.15 (m, overlapped, 2H, H3+H12) 5.15 (bs, 1H, H17) 5.20 (bs, 1H, H17') 5.88 (dd, J=3.7Hz, 9.5Hz, 1H, H2) 6.35 (d, J=9.5Hz, 1H, H1).

MS(TMS-ether) : 504 (12) 488 (3) 460 (2) 444 (5) 432 (7) 414 (8) 369 (24) 342 (4) 279 (21) 253 (8) 239 (10) 221 (33) 207 (9) 193 (19) 167 (10) 149 (22) 117 (9) 91 (12) 73 (100).
ent-3α,12β-Diacetoxy-10β,13-dihydroxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (163).

Acetic anhydride (66µl, 0.69mmol) was added to a stirred solution of (121) (50mg, 0.14mmol) and triethylamine (100µl, 0.69mmol) in dry dichloromethane (5ml) at room temperature. After stirring at room temperature for 16h., water (0.1ml) was added dropwise over 15 min. and the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate (10ml), washed successively with dilute hydrochloric acid (2M, 5ml), saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) gave (163) (58mg, 91%) as a foam.

Rf : 0.4 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 1.14 (s, 3H, 4Me) 2.11 (s, 3H, OAc) 2.13 (s, 3H, OAc') 2.78 (d, J=10.8Hz, 1H, H6) 3.33 (d, J=10.8Hz, 1H, H5) 3.74 (s, 3H, OMe) 4.75 (t, J=7.5Hz, 1H, H12) 5.23 (s, 1H, H17) 5.33 (d, J=4.0Hz, 1H, H3) 5.41 (s, 1H, H17') 5.89 (dd, J=4.0Hz, 9.0Hz, 1H, H2) 6.35 (d, J=9.0Hz, 1H, H1).

MS : 460 (M+, <1%) 418 (1%) 400 (6) 340 (12) 326 (29) 308 (14) 295 (30) 280 (14) 267 (15) 252 (33) 237 (50) 223 (16) 209 (73) 192 (100) 179 (43) 167 (30) 155 (28) 141 (27) 128 (26) 121 (20) 105 (25) 91 (43) 77 (31) 55 (34).

HRMS : C$_{22}$H$_{24}$O$_7$ (M+-60): requires 400.1522, found 400.1522.
ent-3α,12β-Diacetoxy-10β-hydroxy-13-methyloxyloxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (203).

Methyl oxalyl chloride (0.015ml, 0.167mmol) was added to a stirred solution of (163) (50mg, 0.1mmol), triethylamine (0.025ml, 0.18mmol) and a crystal of DMAP in dry dichloromethane (5ml). After stirring at room temperature for 2 h., the reaction mixture was diluted with ethyl acetate (10ml), washed successively with dilute hydrochloric acid (2M, 2ml), saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration *in vacuo* and chromatography on silica gel (ethyl acetate:hexane, 1:2) afforded (203) (50mg, 63%).

**Rf**: 0.5 (ethyl acetate:hexane, 1:1).

**1H NMR**: 1.16 (s, 3H, 4Me) 2.11 (s, 3H, OAc) 2.12 (s, 3H, OAc) 2.64 (dd, J=1.5Hz, 11.3Hz, 1H, H14) 2.81 (d, J=10.8Hz, 1H, H6) 3.34 (d, J=10.8Hz, 1H, H5) 3.77 (s, 3H, OMe) 3.87 (s, 3H, OCOCO2Me) 5.18 (t, J=7.0Hz, 1H, H12) 5.25 (bs, 1H, H17) 5.33 (d, J=3.7Hz, 1H, H3) 5.39 (bs, 1H, H17’) 5.89 (dd, J=3.7Hz, 9.6Hz, 1H, H2) 6.33 (d, J=9.6Hz, 1H, H1).

**MS**: 426 (M+-120, 3%) 398 (7) 382 (10) 355 (7) 339 (3) 295 (35) 278 (14) 267 (28) 251 (31) 223 (29) 209 (50) 193 (35) 181 (25) 167 (13) 155 (16) 143 (14) 129 (15) 115 (15) 105 (22) 91 (31) 77 (19) 59 (100).

**HRMS**: C_{24}H_{26}O_{7} (M+-120) requires 426.1679, found 426.1679.

ent-3α,12β-Diacetoxy-10β-hydroxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (204).

Tri-n-butyltin hydride (30µl, 0.11mmol) was added to a solution of (203) (20mg, 36µmol) and AIBN (2mg) in boiling toluene (10ml). After stirring at reflux temperature for 15 min, the reaction mixture was cooled to room temperature and toluene was removed under reduced pressure. Chromatography on silica gel (first with hexane, followed by ethyl acetate:hexane, 1:2) gave (204) (9mg, 56%).

**Rf**: 0.75 (ethyl acetate:hexane, 1:1).

**1H NMR**: 1.16 (s, 3H, 4Me) 2.05 (s, 3H, OAc) 2.11 (OAc) 2.69 (bs, 1H, H13) 2.80 (d, J=10.5Hz, 1H, H6) 3.35 (d, J=10.5Hz, 1H, H5) 3.74 (s, 3H, OMe) 4.69 (t, J=7.0Hz, 1H, H12) 5.08 (bs, 1H, H17) 5.25 (bs, 1H, H17’) 5.34
ent-3α,10β,12β-Trihydroxy-20-norgiberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (205).

When (204) (9mg, 15.8µmol) was treated with potassium carbonate (2mg) in methanol (3ml) according to the procedure for conversion of (192) to (193), (205) (4.7mg, 83%) was obtained.

\[ \text{Rf : 0.15 (ethyl acetate:hexane, 1:1)} \]

\[ ^1\text{H NMR} : \]

\[
\begin{align*}
&1.12 (s, 3H, \text{H4}) \\
&2.64 (bs, 1H, \text{H13}) \\
&2.76 (d, J=10.3Hz, 1H, \text{H6}) \\
&3.31 (d, J=10.3Hz, 1H, \text{H5}) \\
&3.70-3.80 (m, 4H, \text{H12+OMe, overlapped}) \\
&4.14 (d, J=3.7Hz, 1H, \text{H3}) \\
&4.99 (bs, 1H, \text{H17}) \\
&5.10 (bs, 1H, \text{H17'}) \\
&5.75 (dd, J=3.7Hz, 9.6Hz, 1H, \text{H2}) \\
&6.30 (d, J=9.6Hz, 1H, \text{H1})
\end{align*}
\]

\[ \text{MS (TMS-ether)}: 504 (M^+, 12%) 488 (3) 473 (5) 460 (2) 444 (5) 429 (3) 414 (8) 369 (24) 355 (4) 343 (3) 311 (8) 279 (21) 265 (10) 253 (8) 239 (10) 221 (33) 207 (9) 193 (19) 197 (10) 157 (5) 117 (9) 103 (20) 91 (12) 73 (100). \]

ent-3α,12β-Diacetoxy-10β,13-dihydroxy-20-norgiberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (206).

When (103) (60mg, 0.16mmol) was treated with acetic anhydride (70µl, 0.73mmol) and triethylamine (115µl, 0.8mmol) in dichloromethane (5ml) according to the procedure for conversion of (121) to (163), (206) (70mg, 95%) was obtained.

\[ \text{Rf : 0.4 (ethyl acetate:hexane, 1:1)} \]
ent-3α,12β-Diacetoxy-10β-hydroxy-13-methylxaloxyloxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (207).

When (206) (40mg, 86.6µmol) was allowed to react with methyl oxalyl chloride (12µl, 0.13mmol), triethylamine (20µl, 0.144mmol) and a crystal of DMAP in dichloromethane (5ml) according to the procedure for conversion of (163) to (203), (207) (37mg, 81%) was obtained.

Rf : 0.55 (ethyl acetate:hexane, 1:1).

ent-3α,12β-Diacetoxy-10β-hydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (208).

When (207) (30mg, 55µmol) was subjected to reaction with tin hydride (45µl, 0.17mmol) and AIBN (3mg) according to procedure for conversion of (203) to (204), (208) (15mg, 64%) was obtained.
Rf : 0.75 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 1.06 (s, 3H, 4Me) 2.12 (s, 3H, OAc) 2.13 (OAc) 2.69 (bs, 1H, H13) 2.80 (d, J=10.5Hz, 1H, H6) 3.28 (d, J=10.5Hz, 1H, H5) 3.74 (s, 3H, OMe) 4.69 (t, J=7.0Hz, 1H, H12) 4.95 (bs, 1H, H3) 5.08 (bs, 1H, H17) 5.25 (bs, 1H, H17').

MS : 446 (M+, <1%) 428 (1) 415 (5) 404 (7) 386 (8) 342 (10) 326 (17) 298 (10) 282 (75) 231 (5) 223 (30) 208 (15) 195 (18) 183 (25) 168 (100) 153 (45) 142 (65) 127 (78).

HRMS : C$_{24}$H$_{30}$O$_8$ (M+) requires 446.1938, found 446.1938.

ent-3α,12β,10β-Trihydroxy-20-norgiberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (GA58 Methyl Ester) (209).

When (208) (12mg, 27µmol) was allowed to react with potassium carbonate (2mg) in methanol (3ml) according to procedure for conversion of (192) to (193), (209) (7mg, 72%) was obtained.

Rf : 0.2 (ethyl acetate:hexane, 1:1)

$^1$H NMR : 1.15 (s, 3H, 4Me) 2.63 (bs, 1H, H13) 2.72 (d, J=11.0Hz, 1H, H6) 3.22 (d, J=11.0Hz, 1H, H5) 3.71 (s, 3H, OMe) 3.76 (t, J=8.0Hz, 1H, H12) 3.85 (bs, 1H, H3) 5.00 (bs, 1H, H17) 5.10 (bs, 1H, H17').

MS (TMS-ether) 506 (M+, 31%) 491 (9) 475 (5) 451 (5) 433 (5) 416 (43) 398 (9.5) 384 (37) 370 (19) 356 (40) 339 (10) 317 (18) 294 (19) 282 (38) 267 (33) 253 (16) 239 (16) 223 (62) 195 (27) 181 (29) 167 (27) 149 (49) 129 (100) 117 (38) 91 (48).
ent-3α,12α-Diacetoxy-10β,13-dihydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19, 10-Lactone (210).

When (104) (55mg, 0.15mmol) was treated with acetic anhydride (64µl, 0.67mmol) and triethylamine (105µl, 73mmol) in dichloromethane (5ml) according to procedure for conversion of (121) to (163), (210) (64mg, 87%) was obtained.

Rf : 0.4 (ethyl acetate:hexane, 1:1)

1H NMR: 1.04 (s, 3H, 4Me) 2.05 (s, 3H, OAc) 2.13 (s, 3H, OAc) 2.66 (d, J=10.5Hz, 1H, H6) 3.20 (d, J=10.5Hz, 1H, H5) 3.70 (s, 3H, OMe) 4.95 (bs, 1H, H3) 4.99-5.10 (m, 3H, H12, H17+H17')

MS : 462 (M+, 5%) 431 (6) 444 (12) 402 (20) 370 (15) 342 (40) 314 (20) 298 (75) 282 (40) 270 (30) 239 (50) 225 (20) 211 (55) 195 (70) 181 (25) 169 (32) 155 (40) 143 (40) 129 (47) 115 (34) 105 (65) 91 (85) 77 (55) 69 (45) 55 (100).

HRMS: C_{24}H_{30}O_{9} (M+); requires 462.1890, found 462.1887.

ent-3α,12α-Diacetoxy-10β-hydroxy-13-methyloxalyloxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (211).

When (211) (40mg, 86.6µm) was allowed to react with methyl oxalyl chloride (12µl, 0.13mmol), triethylamine (20µl, 0.144mmol) and a crystal of DMAP in dichloromethane (5ml) according to the procedure for conversion of (163) to (203), (207) (37mg, 81%) was obtained.

Rf : 0.50 (ethyl acetate:hexane, 1:1).
\(^1\)H NMR: 1.04 (s, 3H, 4Me) 2.06 (s, 3H, OAc) 2.12 (s, 3H, OAc) 2.67 (d, J=10.3Hz, 1H, H6) 3.17 (d, J=10.3Hz, 1H, H5) 3.75 (s, 3H, OMe) 3.88 (s, 3H, OMe) 4.95 (bs, 1H, H3) 5.26 (bs, 2H, H17+H17') 5.72 (dd, J=2.2Hz, 7.0Hz, 1H, H12).

MS: 517 (M\(^+\)-31, <1%) 488 (1) 461 (40) 443 (15) 428 (15) 400 (10) 384 (20) 342 (15) 325 (16) 313 (12) 297 (40) 269 (13) 253 (14) 237 (41) 221 (30) 209 (20) 195 (22) 181 (18) 169 (12) 155 (11) 143 (19) 129 (18) 105 (34) 91 (40) 59 (100).

HRMS: C\(_{24}\)H\(_{29}\)O\(_9\) (M\(^+\) - 87); requires 461.1812, found 461.1813.

\textit{ent}-3\(\alpha\),12\(\alpha\)-Diacetoxy-10\(\beta\)-hydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (212).

When (211) (20mg, 36\(\mu\)mol) was subjected to reaction with tin hydride (25\(\mu\)l, 0.1mmol) and AIBN (5mg), according to the procedure for conversion of (203) to (204), (212) (9mg, 58\%) was obtained.

R\(_f\): 0.7 (ethyl acetate:hexane, 1:1).

\(^1\)H NMR: 1.06 (s, 3H, 4Me) 2.09 (s, 3H, OAc) 2.12 (s, 3H, OAc) 2.75 (d, J=10.5Hz, 1H, H6) 3.05 (bs, 1H, H13) 3.2 (d, J=10.5Hz, 1H, H5) 3.72 (s, 3H, OMe) 4.90-5.20 (m, overlapped, 4H, H3, H12, H17+H17').

MS: 446 (M\(^+\), 1\%) 428 (2) 415 (4) 404 (5) 386 (8) 354 (5) 342 (10) 326 (17) 282 (73) 255 (5) 223 (31) 208 (12) 195 (18) 183 (26) 168 (100) 153 (54) 142 (70) 127 (80) 105 (9).

HRMS: C\(_{24}\)H\(_{30}\)O\(_8\) (M\(^+\)) requires 446.1938, found 446.1940.
ent-3α-Acetoxy-10β,15β-dihydroxy-20-norgiberella-2,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (215).

When 13-acetoxy Ga5 methyl ester (214)* (10g, 25mmol) was subject to reaction with selenium dioxide (500mg) and tert-butyl hydroperoxide (1ml) in dichloromethane (100ml) according to the procedure published by MacMillan,34 (215) (9.6g, 92%) was obtained as a foam.

R<sub>f</sub> : 0.3 (ethyl acetate:hexane, 1:1)

<sup>1</sup>H NMR : 1.22 (s, 3H, 4Me) 2.12 (s, 3H, OAc) 2.68 (d, J=10.5Hz, 1H, H6) 2.79 (d, J=10.5Hz, 1H, H5) 2.90 (d, J=12.0Hz, 1H, H14) 3.76 (s, 3H, OMe) 4.08 (bs, 1H, H15) 5.22 (s, 1H, H17) 5.41 (s, 1H, H17') 5.63 (dt, J=2.0Hz, 9.0Hz, 1H, H3) 5.78 (dt, J=3.0Hz, 9.0Hz, 1H, H2).

MS : 402 (M<sup>+</sup>, 1%) 385 (8) 371 (10) 358 (5) 342 (11) 310 (15) 298 (5) 280 (17) 237 (35) 221 (27) 209 (12) 195 (16) 181 (11) 143 (13) 105 (100).

HRMS : C<sub>22</sub>H<sub>26</sub>O<sub>6</sub> (M<sup>+</sup>) requires 402.1676, found 402.1678.

*Prepared by adaptation of the method of Lombardo et al.160 and supplied by Bruce Twitchin.

ent-3α-Acetoxy-16β-bromo-10β-hydroxy-17-oxo-20-norgiberell-2-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (216).

Pyridinium chlorochromate (26g, 120mmol) was added to a stirred solution of (215) (9.5g, 23.6mmol) in dichloromethane (500ml). After stirring at room temperature for 16 h., the reaction mixture was diluted with ether (1l) and filtered through silica gel (100g). Concentration <i>in vacuo</i> gave the crude mixture of the epoxyaldehyde and enal (7.8g).

The crude mixture was dissolved in acetone (250ml) under a carbon dioxide atmosphere,
aqueous chromous chloride (100ml) was then added. After stirring at room temperature for 10min, the reaction mixture was diluted with ethyl acetate (250ml), washed with water (2x100ml), then brine and dried over sodium sulfate. Concentration in vacuo gave the crude \( \alpha,\beta \)-unsaturated aldehyde (7g).

Zinc dust (1g) was added to the solution of the \( \alpha,\beta \)-unsaturated aldehyde (7g) in acetic acid (100ml) at room temperature. After stirring for 1 h., the reaction mixture was diluted with dichloromethane (500ml) and filtered through celite. The filtrate was washed with water (3x100ml), saturated sodium bicarbonate solution, then brine and dried over sodium sulfate. Concentration in vacuo afforded the crude saturated aldehyde (6.5g).

Pyrrolidone hydrotribromide (12g, 24mmol) was added to the solution of the crude aldehyde (6.5g) in dichloromethane (250ml). After stirring at room temperature for 16 h., the reaction mixture was diluted with dichloromethane (250ml), washed with saturated sodium thiosulfate, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:3) afforded (216) (4.3g, 38% yield from 215). Recrystallisation from ether and hexane gave a colourless crystalline solid (4.2g).

\[ R_f = 0.9 \text{ (ethyl acetate:hexane, 1:1)} \]

m. p. : 179-185 °C.

\[ ^1H \text{ NMR} : \]

\[
1.22 \text{ (s, 3H, 4Me)} \quad 2.11 \text{ (s, 3H, OAc)} \quad 2.68 \text{ (d, J=10.5Hz, 1H, H6)} \quad 2.79 \\
\text{ (d, J=10.5Hz, 1H, H5)} \quad 3.76 \text{ (s, 3H, OMe)} \quad 5.63 \text{ (dt, J=2.0Hz, 9.0Hz, 1H, H3)} \\
5.78 \text{ (dt, J=3.0Hz, 9.0Hz, 1H, H2)} \quad 9.57 \text{ (CHO)}.
\]

\[ \text{MS} : \]

449 (M\(^+\)-31, 2%) 394 (2) 376 (6) 357 (3) 341 (5) 315 (4) 297 (16) 281 (4) 271 (6) 255 (5) 237 (31) 219 (4) 209 (14) 199 (8) 181 (8) 169 (6) 155 (9) 143 (11) 129 (9) 118 (12) 105 (19) 91 (30) 77 (12) 55 (19) 43 (100).

Calcd. for C\(_{22}\)H\(_{25}\)O\(_7\)Br : C 54.90; H5.54.

Found : C 54.58; H5.54.

\textit{ent-13-Acetoxy-16β-bromo-10β,17-dihydroxy-20-norgiberell-2-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (217).}

When (216) (4.2g, 8.8mmol) was subjected to reaction with sodium borohydride (500mg, 13.2mmol) in DME (50ml) according to the procedure for conversion of (112) to (113), (217) (3.2g, 76%) was obtained.
Rf : 0.4 (ethyl acetate:hexane, 1:1)

**1H NMR:** 1.18 (s, 3H, 4Me) 2.05 (s, 3H, OAc) 2.64 (d, J=10.3Hz, 1H, H6) 2.73 (d, J=10.3Hz, 1H, H5) 3.75 (s, 3H, OMe) 3.75 (d, J=12.0Hz, 1H, H17) 4.04 (d, J=12.0Hz, 1H, H17) 5.63 (dt, J=2.0Hz, 9.0Hz, 1H, H3) 5.78 (dt, J=3.0Hz, 9.0Hz, 1H, H2).

**13C NMR:** 15.3 (C18) 16.7 (C11) 21.8 (OAc) 28.6 (C12) 37.1 (C1) 41.8 (C14) 48.2 (C8) 52.3 (C9) 52.4 (OMe) 55.0 (C6) 56.2 (C6) 68.9 (C17) 81.6 (C16) 85.6 (C13) 91.2 (C10) 127.6 (C2) 132.1 (C3) 170.5 (OAc) 172.4 (C7) 177.2 (C19).

**MS:** 402 (M+-80, <1%) 371 (10) 360 (10) 342 (15) 310 (13) 298 (16) 281 (15) 266 (10) 255 (10) 239 (33) 221 (30) 209 (37) 123 (100).

**HRMS:** C_{22}H_{26}O_{7} (M+-80); requires 402.1679, found 402.1678.

*ent-13-Acetoxy-16β-bromo-12α,17-epoxy-10β-hydroxy-20-norgibberell-2-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (218).*

When (217) (3.2g, 6.6mmol) was subjected to reaction with LTA (17.5g, 39mmol) and iodine (0.84g, 3.3mmol) in benzene (100ml) according to the procedure for conversion of (66) to (97), (218) (2.1g, 66%) was obtained. Recrystallisation from ether and hexane gave the ether as pale yellow crystals (1.9g).

Rf : 0.85 (ethyl acetate:hexane, 1:1)

m.p. : 158-162 (decompose).

**1H NMR:** 1.19 (s, 3H, 4Me) 2.08 (s, 3H, OAc) 2.63 (d, J=11.1Hz, 1H, H6) 2.78 (d, J=11.1Hz, 1H, H5) 3.74 (s, 3H, OMe) 3.85 (bs, 2H, H17) 4.43 (bs, 1H, H12) 5.63 (dt, J=2.0Hz, 9.0Hz, 1H, H3) 5.78 (dt, J=3.0Hz, 9.0Hz, 1H, H2).

**13C NMR:** 15.3 (C18) 21.3 (OAc) 24.3 (C11) 34.7 (C1) 38.1 (C14) 48.3 (C8) 50.2 (C4) 51.7 (C9) 52.2 (C6) 52.7 (OMe) 53.8 (C15) 55.4 (C5) 65.3 (C16) 75.8 (C17) 82.7 (C12) 87.8 (C13) 91.5 (C10) 127.7 (C2) 132.0 (C3) 170.0 (OAc) 172.6 (C7).

**MS:** 449 (M+-31, 2%) 436 (2) 420 (2) 376 (17) 297 (21) 237 (37) 209 (12)
ent-13-Acetoxy-12α,10β-dihydroxy-20-norgibberella-2,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (219).

When (218) (0.5 g, 1.04 mmol) was subjected to reduction with zinc dust (0.1 g) in boiling acetic acid (10 ml) according to the procedure for conversion of (97) to (98), (219) (0.32 g, 77%) was obtained.

Rf : 0.35 (ethyl acetate:hexane, 1:1)

$^{1}$H NMR : 1.22 (s, 3H, 4Me) 2.05 (s, 3H, OAc) 2.63 (d, J=11.0 Hz, 1H, H6) 2.78 (d, J=11.0 Hz, 1H, H5) 3.72 (s, 3H, OMe) 4.32 (bs, 1H, H12) 5.12 (bs, 1H, H17) 5.18 (bs, 1H, H17') 5.63 (dt, J=2.0 Hz, 9.0 Hz, 1H, H3) 5.78 (dt, J=3.0 Hz, 9.0 Hz, 1H, H2).

$^{13}$C NMR : 15.1 (C18) 21.2 (OAc) 27.6 (C11) 35.2 (C1) 42.3 (C14) 42.8 (C15) 48.2 (C8) 50.6 (C9) 51.2 (C4) 51.2 (C6) 52.5 (OMe) 56.2 (C5) 72.2 (C12) 88.4 (C13) 91.0 (C10) 111.7 (C17) 127.8 (C2) 132.6 (C3) 144.7 (C16) 170.4 (C7) 172.9 (C19).

MS : 402 (M$^{+}$, 1%) 360 (65) 342 (58) 328 (15) 310 (22) 298 (93) 282 (43) 272 (25) 237 (64) 223 (31) 211 (75) 202 (24) 195 (57) 180 (41) 167 (75) 155 (42) 143 (79) 135 (42) 129 (54) 121 (64) 105 (100) 95 (44) 91 (77) 77 (46).

HRMS : $^{195}$C$_{21}$H$_{22}$O$_{679}$Br (M$^{+}$-31), requires 449.0600, found 449.0598.
ent-13-Acetoxy-10β-hydroxy-12-oxo-20-norgibberella-2,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (220).

When (219) (0.3g, 0.75mmol) was allowed to react with Jones' reagent (0.2ml) in acetone (10ml) according to the procedure for conversion of (98) to (100), (220) (0.29g, 95%) was obtained.

\[ R_f : 0.7 \] (ethyl acetate: hexane, 1:1)

\[ ^1H\text{ NMR} : 1.23 \text{ (s, 3H, 4Me)} \quad 2.10 \text{ (s, 3H, OAc)} \quad 2.54 \text{ (dd, J=6.6Hz,17.0Hz, 1H, H11)} \]
\[ 2.77 \text{ (d, J=10.0Hz, 1H, H6)} \quad 2.91 \text{ (d, J=10.0Hz, 1H, H5)} \quad 3.01 \text{ (dd, J=2.0Hz, 11.6Hz, 1H, H14)} \]
\[ 3.16 \text{ (dd, J=12.0Hz,17.0Hz, 1H, H11')} \quad 3.75 \text{ (s, 3H, OMe)} \quad 5.23 \text{ (bs, 1H, H17)} \quad 5.42 \text{ (bt, J=1.7Hz, 1H, H17')} \quad 5.63 \text{ (dt, J=2.0Hz, 9.0Hz, 1H, H3)} \]

\[ MS : 369 (M^{+}-31, 2%) \quad 340 (3) \quad 330 (2) \quad 312 (10) \quad 298 (13) \quad 284 (5) \quad 270 (10) \quad 237 (7) \quad 225 (8) \quad 209 (15) \quad 193 (6) \quad 181 (5) \quad 167 (13) \quad 155 (6) \quad 143 (9) \quad 135 (5) \]
\[ 129 (7) \quad 121 (11) \quad 105 (17) \quad 91 (15) \quad 77 (13) \quad 42 (100). \]

\[ HRMS : C_{21}H_{21}O_{6} (M^{+}-31) \text{ requires 369.1338, found 369.1338}. \]

ent-10β,13-Dihydroxy-12-oxo-20-norgibberella-2,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (221).

When (220) (0.28g, 0.7mmol) was subjected to reaction with potassium carbonate (50mg) in methanol (10ml) according to procedure for conversion of (100) to (101), (221) (0.21g, 84%) was obtained.

\[ R_f : 0.37 \] (ethyl acetate:hexane, 1:1)

\[ ^1N\text{ NMR} : 1.23 \text{ (s, 3H, 4Me)} \quad 2.65 \text{ (dd, J=8.0Hz, 19.0Hz, 1H, H11)} \]
\[ 2.78 \text{ (d, J=10.0Hz, 1H, H6)} \quad 2.84 \text{ (dd, J=9.7Hz, 19.0Hz, 1H, H11')} \quad 2.91 \text{ (d, J=10.0Hz, 1H, H5)} \]
\[ 3.01 \text{ (dd, J=1.8Hz,11.6Hz, 1H, H14)} \quad 3.75 \text{ (s, 3H, OMe)} \quad 5.23 \text{ (bs, 1H, H17)} \quad 5.42 \text{ (bt, J=1.7Hz, 1H, H17')} \quad 5.63 \text{ (dt, J=2.0Hz, 9.0Hz, 1H, H3)} \]

\[ MS : 358 (M^{+}, 30\%) \quad 340 (2) \quad 330 (2) \quad 312 (11) \quad 298 (45) \quad 284 (25) \quad 237 (35) \quad 225 (43) \quad 209 (70) \quad 193 (36) \quad 167 (65) \quad 155 (31) \quad 143 (40) \quad 135 (25) \quad 121 (55) \]
\[ 105 (100). \]

\[ HRMS : C_{20}H_{22}O_{6} (M^{+}) \text{ requires 358.1414, found 358.1415}. \]
Reduction of ketol (221) with Zinc borohydride

When (221) (200mg, 0.56mmol) was subjected to reduction with zinc borohydride in ether (0.2ml, 1.2M) in a mixture of ether (5ml) and DMF (5ml) at -30°C according to the procedure for conversion of (101) to (103) and (104), (222) (58mg) and (223) (93mg) were obtained (46% and 29% yield respectively).

\[ \text{ent-10β,12α,13-Trihydroxy-20-norgibberella-2,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (222).} \]

\[ \text{Rf: 0.15 (ethyl acetate:hexane, 1:1).} \]

\[ \text{\textsuperscript{1}H NMR: 1.23 (s, 3H, 4Me) 2.75 (d, \textit{J}=10Hz, 1H, H6) 2.90 (d, \textit{J}=10Hz, 1H, H5) 3.75 (s, 3H, OMe) 3.99 (t, \textit{J}=7.0Hz, 1H, H12) 5.20 (bs, 2H, H17+H17') 5.62 (dt, \textit{J}=2Hz, 9.06Hz, 1H, H3) 5.78 (dt, \textit{J}=3Hz, 9Hz, 1H, H2).} \]

\[ \text{ent-10β,12β,13-Trihydroxy-20-norgibberella-2,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (223).} \]

\[ \text{Rf: 0.2 (ethyl acetate:hexane, 1:1).} \]

\[ \text{\textsuperscript{1}H NMR: 1.23 (s, 3H, 4Me) 2.75 (d, \textit{J}=10.0Hz, 1H, H6) 2.89 (d, \textit{J}=10.0Hz, 1H, H5) 3.70-3.75 (m, overlapped, 4H, H12+OMe) 5.14 (bs, 1H, H17) 5.38 (bs, 1H, H17').} \]

\[ \text{ent-12β-Acetoxy-10β,13-dihydroxy-20-norgibberella-2,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (224).} \]

When (223) (55mg, 0.15mmol) was treated with acetic anhydride (35µl, 0.36mmol) and
triethylamine (60µl, 0.41mmol) in dichloromethane (5ml) according to the procedure for conversion of (121) to (163), (224) (55mg, 93%) was obtained.

**R<sub>f</sub>** : 0.45 (ethyl acetate:hexane, 1:1)

**<sup>1</sup>H NMR** :
1.21 (s, 3H, 4Me) 2.12 (s, 3H, OAc) 2.53 (J=12.0Hz, 1H, H14) 2.65 (d, J=10.0Hz, 1H, H6) 2.80 (d, J=10.0Hz, 1H, H5) 3.72 (s, 3H, OMe) 4.73 (t, J=7.0Hz, 1H, H12) 5.19 (bs, 1H, H17) 5.38 (bs, 1H, H17') 5.63 (dt, J=2.0Hz, 9.0Hz, 1H, H3) 5.78 (dt, J=3.0Hz, 9.0Hz, 1H, H2).

**MS** : 402 (M<sup>+</sup>, 10%) 384 (5) 370 (10) 342 (15) 324 (28) 310 (54) 298 (73) 282 (20) 267 (20) 237 (51) 223 (32) 209 (55) 195 (100) 180 (95) 167 (44) 155 (34) 149 (32) 134 (60) 129 (65) 105 (91).

**HRMS** : C<sub>22</sub>H<sub>26</sub>O<sub>7</sub> (M<sup>+</sup>); requires 402.1679, found 404.1678.

**ent-12β-Acetoxy-10β-hydroxy-13-methyloxalylloxy-20-norgibberella-2,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (225).**

When (224) (25mg, 62.2µm) was allowed to react with methyl oxalyl chloride (10µl, 0.11mmol), triethylamine (15µl, 0.11mmol) and a crystal of DMAP in dichloromethane (5ml) according to procedure for conversion of (163) to (203), (225) (23mg, 80%) was obtained.

**R<sub>f</sub>** : 0.6 (ethyl acetate:hexane, 1:1).

**<sup>1</sup>HNMR** :
1.24 (s, 3H, 4Me) 2.12 (s, 3H, OAc) 2.47 (bd, J=17.4Hz, 1H, H1) 2.59 (bd, J=10.0Hz, 1H, H14) 2.70 (d, J=10.1Hz, 1H, H6) 2.82 (d, J=10.1Hz, 1H, H5) 3.75 (s, 3H, OMe) 3.87 (s, 3H, OCOCO<sub>2</sub>Me) 5.15 (t, J=8.0Hz, 1H, H12) 5.23 (bs, 1H, H17) 5.34 (bd, J=2.9 Hz, 1H,H17').

**MS** : 488 (M<sup>+</sup>, <1%) 457 (1) 429 (1) 401 (10) 384 (2) 297 (13) 283 (6) 253 (4) 237 (31) 220 (21) 209 (10) 195 (10) 181 (6) 155 (5) 143 (7) 119 (6) 105 (16) 91 (15) 77 (10) 59 (31) 43 (100).

**HRMS** : C<sub>22</sub>H<sub>25</sub>O<sub>7</sub> (M<sup>+</sup> - 87) requires 401.1600, found 401.1602.
ent-12β-Acetoxy-10β-hydroxy-20-norgibberella-2,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (226).

When (225) (15mg, 31µmol) was subjected to reaction with tin hydride (25µl, 96µmol) and AIBN (3mg), according to the procedure for conversion of (203) to (204), (226) (8mg, 65%) was obtained.

\[ \text{RF} : 0.8 \text{ (ethyl acetate:hexane, 1:1)} \]

\[ \text{1H NMR: } 1.22 \text{ (s, 3H, 4Me) } 2.05 \text{ (s, 3H, OAc) } 2.32 \text{ (dt, } J=2.4\text{Hz, } 18.8\text{Hz, 1H, H1)} \ 2.58 \text{ (bd, } J=18.8\text{Hz, 1H, H1') } 2.69 \text{ (bd, } J=6.0\text{Hz, 1H, H12)} \ 2.70 \text{ (d, } J=10.5\text{Hz, 1H, H6)} \ 2.84 \text{ (d, } J=10.5\text{Hz, 1H, H5)} \ 3.72 \text{ (s, 3H, OMe) } 4.68 \text{ (t, } J=8.0\text{Hz, 1H, H12)} \ 5.05 \text{ (bs, 1H, H17)} \ 5.23 \text{ (bs, 1H, H17') } 5.66 \text{ (dt, } J=2.4\text{Hz, 9.0Hz, 1H, H3)} \ 5.78 \text{ (dt, } J=3\text{Hz, 9.0Hz, 1H, H2)} \]

\[ \text{MS: } 355 \text{ (M+ - 31, 4%) } 326 \text{ (1) } 282 \text{ (46) } 239 \text{ (7) } 222 \text{ (100) } 207 \text{ (29) } 201 \text{ (20) } 195 \text{ (29) } 181 \text{ (36) } 167 \text{ (15) } 155 \text{ (23) } 143 \text{ (30) } 131 \text{ (36) } 119 \text{ (34) } 105 \text{ (47) } 91 \text{ (54) } 79 \text{ (30) } 65 \text{ (14) } 54 \text{ (22)} \]

HRMS: \[ C_{21}H_{23}O_5 \text{ (M+ - 31) requires 355.1545, found 355.1547.} \]

ent-3α,12β,10β-Trihydroxy-20-norgibberella-2,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (GA31 Methyl Ester) (227).

When (226) (7mg, 18µmol) was allowed to react with potassium carbonate (2mg) in methanol (3ml) according to the procedure for conversion of (192) to (193), (227) (5mg, 83%) was obtained.

\[ \text{RF} : 0.4 \text{ (ethyl acetate:hexane, 1:1).} \]

\[ \text{1H NMR: } 1.23 \text{ (s, 3H, 4Me) } 2.55 \text{ (bs, 1H, H13)} \ 2.69 \text{ (d, } J=11.0\text{Hz, 1H, H6)} \ 2.82 \text{ (d, } J=11.0\text{Hz, 1H, H5)} \ 3.72 \text{ (s, 3H, OMe)} \ 3.76 \text{ (t, } J=7.5\text{Hz, 1H, H12)} \ 4.99 \text{ (bs, 1H, H17)} \ 5.10 \text{ (bs, 1H, H17')} \ 5.67 \text{ (dt, } J=2.4\text{Hz, 9.0Hz, 1H, H3)} \ 5.78 \text{ (dt, } J=3.0\text{Hz, 9.0Hz, 1H, H2)} \]

\[ \text{MS(TMS-ether): } 416 \text{ (M+, 3%) } 401 \text{ (1) } 385 \text{ (3) } 369 \text{ (3) } 361 \text{ (2) } 299 \text{ (5) } 282 \text{ (17) } 266 \text{ (9) } 222 \text{ (36) } 207 \text{ (12) } 181 \text{ (13) } 155 \text{ (10) } 129 \text{ (16) } 119 \text{ (21) } 91 \text{ (23) } 73 \text{ (100).} \]
ent-13-Acetoxy-16\(\beta\)-bromo-12\(\alpha\),17-epoxy-10\(\beta\)-hydroxy-20-norgibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (228).

To a solution of (218) (0.5g, 8.3mmol) in ethyl acetate (50ml) was added rhodium on alumina (5\%, 50mg) and the mixture was stirred under an atmosphere of hydrogen. After 16 h. at room temperature, the solution was diluted with ethyl acetate (100ml) and filtered through celite. Concentration in vacuo and filtration through a short plug of silica gel afforded (228) (0.48g, 96\%).

R\(f\) : 0.85 (ethyl acetate:hexane, 1:1)

m.p. : 138-140\(^\circ\)C (decomp.)

\(^1\)H NMR : 1.04 (s, 3H, 4Me) 2.06 (s, 3H, OAc) 2.33 (bd, J=14.7Hz, 1H, H14) 2.49 (d, J=10.0Hz, 1H, H6) 2.61 (bd, J=14.7Hz, 1H, H14') 2.65 (d, J=10.0Hz, 1H, H5) 3.72 (s, 3H, OMe) 3.84 (bs, 2H, H17) 4.40 (bs, 1H, H12)

\(^{13}\)C NMR: 17.1 (C18) 19.5 (C2) 21.1 (OAc) 24.2 (C11) 30.0 (C1) 34.3 (C3) 37.9 (C14) 49.2 (C9) 51.3 (OMe) 52.1 (C8) 53.2 (C6) 53.8 (C15) 58.4 (C5) 65.4 (C16) 75.7 (C17) 82.7 (C12) 87.7 (C13) 92.6 (C10) 169.9 (OAc) 172.8 (C7) 178.7 (C19).

MS : 451 (M\(^+\)-31, 7\%) 422 (49) 403 (7) 390 (8) 376 (17) 362 (19) 343 (36) 299 (66) 283 (36) 262 (23) 255 (20) 239 (63) 237 (39) 211 (43) 197 (17) 183 (21) 159 (22) 145 (35) 129 (27) 115 (35) 105 (35) 91 (100)

HRMS : C\(_{21}\)H\(_{24}\)O\(_6\)\(^{79}\)Br (M\(^+\) - 31), requires 451.0756, found, 451.0758.
ent-13-Acetoxy-12α,10β-dihydroxy-20-norgiberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (229).

When (228) (0.45g, 0.93mmol) was subjected to reduction with zinc dust (100mg) in boiling acetic acid (10ml) according to the procedure for conversion of (97) to (98), (229) (315mg, 83%) was obtained.

Rf : 0.35 (ethyl acetate:hexane, 1:1)

\[ \begin{align*}
\text{H NMR :} & \\
& 1.02 (s, 3H, 4Me) 2.01 (s, 3H, OAc) 2.50 (d, J=9.5Hz, 1H, H6) 2.62 (d, J=9.5Hz, 1H, H5) 3.66 (s, 3H, OMe) 4.31 (dd, J=3.7Hz, 5.26Hz, H12) 5.15 (bs, 2H, H17+H17'). \\
\text{C NMR :} & \\
& 17.0 (C18) 19.1 (C2) 21.8 (OAc) 27.4 (C11) 30.2 (C1) 34.5 (C3) 41.9 (C14) 42.6 (C15) 48.4 (C9) 49.9 (C8) 50.6 (C6) 50.9 (C4) 52.0 (OMe) 58.9 (C5) 72.0 (C12) 88.4 (C13) 92.9 (C10) 112.1 (C17) 144.6 (C16) 170.6 (OAc) 172.8 (C7) 179.8 (C19). \\
\text{MS :} & \\
& 404 (M+, 6%) 373 (14) 362 (34) 344 (100) 30 (11) 312 (36) 298 (49) 284 (74) 266 (12) 257 (25) 239 (33) 229 (11) 213 (26) 197 (18) 190 (8) 185 (14) 159 (21) 133 (42) 121 (19) 105 (29) 95 (41) 91 (33). \\
\text{HRMS :} & \\
& C_{22}H_{23}O_7 (M+) \text{ requires 404.1835, found } 404.1834. \\
\end{align*} \]


When (229) (300mg, 0.74mmol) was allowed to react with Jones' reagent (0.5ml) in acetone (10ml) according to the procedure for conversion of (98) to (100), (230) (0.29g, 97%) was obtained.

Rf : 0.7 (ethyl acetate: hexane, 1:1)

\[ \begin{align*}
\text{H NMR :} & \\
& 1.03 (s, 3H, 4Me) 2.04 (s, 3H, OAc) 2.44 (dd, J=6.6Hz, 17.0Hz, 1H, H11) 2.62 (d, J=10.3Hz, 1H, H6) 2.75 (d, J=10.3Hz, 1H, H5) 2.90 (d, J=10.0Hz, 1H, H14) 3.00 (dd, J=12.0Hz,17.0Hz, 1H, H11') 3.68 (s, 3H, OMe) 5.17 (bs, 1H, H17) 5.35 (bs, 1H, H17'). \\
\text{C NMR :} & \\
& 17.8 (C18) 19.0 (C2) 20.5 (OAc) 30.2 (C1) 34.0 (C3) 35.4 (C11) 41.9 (C14) 42.3 (C15) 49.6 (C9) 49.8 (C8) 50.0 (C6) 51.7 (C4) 52.1 (OMe). \\
\end{align*} \]
58.6 (C5) 86.2 (C13) 92.0 (C10) 114.1 (C17) 142.5 (C16) 169.5 (OAc) 172.2 (C7) 178.0 (C19) 201.3 (C12).

MS : 374 (M⁺ - 28, 7%) 371 (4) 360 (15) 342 (5) 332 (18) 314 (22) 300 (17) 286 (16) 272 (23) 262 (25) 244 (9) 227 (16) 213 (12.90) 199 (7) 185 (9) 159 (9) 141 (17) 121 (14) 105 (14) 91 (100) 77 (27).

HRMS : C₂₁H₂₃O₆ (M⁺ - 31), requires 371.1495, found 371.1493.

ent-10β,13-Dihydroxy-12-oxo-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (231).

When (230) (0.28g, 0.7mmol) was subjected to reaction with potassium carbonate (50mg) in methanol (10ml) according to the procedure for conversion of (100) to (101), (231) (0.22g, 88%) was obtained.

Rf : 0.35 (ethyl acetate:hexane, 1:1)

¹H NMR : 1.03 (s, 3H, 4Me) 2.65 (dd, J=8.0Hz, 19.0Hz, 1H, H₁₁) 2.60 (d, J=10.0Hz, 1H, H₆) 2.84 (dd, J=9.7Hz, 19.0Hz, 1H, H₁₁') 2.70 (d, J=10.0Hz, 1H, H₅) 3.01 (dd, J=1.8Hz,11.6Hz, 1H, H₁₄) 3.68 (s, 3H, OMe) 5.23 (bs, 1H, H₁₇) 5.42 (bs, 1H, H₁₇').

MS : 360 (M⁺, 10%) 342 (3) 332 (2) 314 (6) 272 (23) 262 (25) 244 (9) 227 (16) 213 (14) 199 (7) 185 (9) 159 (9) 141 (17) 105 (14) 91 (100)

HRMS : C₂₀H₂₄O₆ (M⁺) requires 360.1571, found 360.1571.

Reduction of ketol (231) with Zinc borohydride

When ketol (231) (210mg, 0.58mmol) was subjected to reduction with zinc borohydride in ether (0.25ml, 1.2M) in a ca 1:1 mixture of ether and DMF (5ml) at -30°C according to the procedure for conversion of (101) to (103) and (104), (232) (65mg, 31% yield) and (233) (90mg, 43% yield) were obtained.

ent-10β,12α,13-Trihydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (232).

Rf : 0.17 (ethyl acetate:hexane, 1:1).
1H NMR : 1.07 (s, 3H, 4Me) 2.55 (d, J=10.0Hz, 1H, H6) 2.70 (d, J=10.0Hz, 1H, H5) 3.71 (s, 3H, OMe) 4.01 (t, J=7.0Hz, 1H, H12) 5.21 (bs, 2H, H17+H17')

etn-10β,12β,13-Trihydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (233).

Rf : 0.2 (ethyl acetate:hexane, 1:1).

1H NMR : 1.07 (s, 3H, 4Me) 2.57 (d, J=10.0Hz, 1H, H6) 2.72 (d, J=10.0Hz, 1H, H5) 3.70-3.75 (m, overlapped, 4H, H12+OMe) 5.12 (bs, 1H, H17) 5.30 (bs, 1H, H17')

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ent-12α-Acetoxy-10β,13-dihydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (234).

When (232) (60mg, 0.165mmol) was treated with acetic anhydride (30µl, 0.31mmol) and triethylamine (50µl, 0.35mmol) in dichloromethane (5ml) according to the procedure for conversion of (121) to (163), (234) (62mg, 93%) was obtained.

Rf : 0.5 (ethyl acetate:hexane, 1:1)

1H NMR : 1.07 (s, 3H, 4Me) 2.11 (s, 3H, OAc) 2.55 (d, J=10.3Hz, 1H, H6) 2.71 (d, J=10.3Hz, 1H, H5) 3.71 (s, 3H, OMe) 4.99-5.10 (m, 3H, H12, H17+H17')

MS : 404 (M+, 25%) 386 (5) 372 (24) 362 (12) 344 (74) 326 (20) 312 (54) 298 (73) 284 (100) 257 (48) 239 (51) 227 (20) 213 (43) 197 (32) 185 (20) 171 (25) 159 (22) 135 (30) 121 (30) 105 (40).

HRMS : C_{22}H_{28}O_{7} (M+); requires 404.1835, found 404.1834.

When (234) (50mg, 0.123mmol) was allowed to react with methyl oxalyl chloride (20µl, 0.22mmol), triethylamine (30µl, 0.23mmol) and a crystal of DMAP in dichloromethane (5ml) according to the procedure for conversion of (163) to (203), (235) (49mg, 81%) was obtained.

Rf : 0.65 (ethyl acetate:hexane, 1:1).

1H NMR : 1.07 (s, 3H, 4Me) 2.11 (s, 3H, OAc) 2.57 (d, J=10.3Hz, 1H, H6) 2.70 (d, J=10.3Hz, 1H, H5) 3.71 (s, 3H, OMe) 3.88 (s, 3H, OMe) 5.27 (bs, 2H, H17+H17') 5.75 (dd, J=2.0Hz, 7.0Hz, 1H, H12).

MS : 459 (M+ -31, <1%) 430 (1) 403 (20) 385 (10) 344 (4) 325 (15) 283 (10) 239 (12) 223 (4) 211 (5) 197 (6) 183 (2) 164 (13) 155 (3) 129 (6) 115 (4) 105 (9) 91 (17) 79 (8) 59 (23) 43 (100).

HRMS : C22H27O7 (M+) requires 403.1757, found 403.1760.

ent-12α-Acetoxy-10β-hydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (236).

When (235) (40mg, 82µmol) was subjected to reaction with tin hydride (52µl, 0.20mmol) and AIBN (5mg), according to the procedure for conversion of (203) to (204), (236) (20mg, 63%) was obtained.

Rf : 0.7 (ethyl acetate:hexane, 1:1).

1H NMR : 1.07 (s, 3H, 4Me) 2.11 (s, 3H, OAc) 2.53 (d, J=10.0Hz, 1H, H6) 2.68 (d, J=10.0Hz, 1H, H5) 3.03 (bs, 1H, H13) 3.72 (s, 3H, OMe) 5.00-5.20 (m, overlapped, 3H, H12, H17+H17').

MS : 388 (M+, 12%) 357 (10) 328 (70) 310 (15) 300 (59) 282 (55) 268 (56) 256 (20) 241 (45) 223 (66) 211 (22) 197 (74) 183 (43) 155 (33) 143 (36) 129 (40) 105 (60) 91 (100).

HRMS : C22H28O6 (M+) requires 388.1886, found 388.1883.
ent-12α,10β-Dihydroxy-20-norgiberrell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (GA69 Methyl Ester) (237).

When (236) (15mg, 38.7µmol) was allowed to react with potassium carbonate (10mg) in methanol (3ml) according to the procedure for conversion of (192) to (193), (237) (11mg, 81%) was obtained.

\[ \text{Rf} : 0.35 \text{ (ethyl acetate:hexane, 1:1).} \]

\[ \text{\textsuperscript{1}H NMR} : 1.10 \text{ (s, 3H, 4Me)} 2.55 \text{ (d, J=9.5Hz, 1H, H6)} 2.69 \text{ (d, J=9.5Hz, 1H, H5)} 2.82 \text{ (bs, 1H, H13)} 3.72 \text{ (s, 3H, OMe)} 4.10 \text{ (m, 1H, H12)} 5.11 \text{ (bs, 1H, H17)} 5.16 \text{ (bs, 1H, H17').} \]

\[ \text{\textsuperscript{1}H NMR (D5-Pyridine)} : 1.01 \text{ (s, 3H, 4Me)} 2.46 \text{ (d, J=9.3Hz, 1H, H6)} 2.60 \text{ (d, J=9.3Hz, 1H, H5)} 2.70 \text{ (d, J=9.3Hz, 1H, H5)} 3.61 \text{ (s, 3H, OMe)} 4.02 \text{ (m, 1H, H12)} 5.04 \text{ (bs, 2H, H17+H17').} \]

\[ \text{MS (TMS-ether)} : 418 \text{ (M+, 12)} 403 \text{ (14)} 386 \text{ (8)} 372 \text{ (10)} 358 \text{ (10)} 343 \text{ (6)} 328 \text{ (20)} 311 \text{ (6)} 296 \text{ (39)} 282 \text{ (26)} 268 \text{ (54)} 241 \text{ (13)} 223 \text{ (51)} 109 \text{ (10)} 197 \text{ (21)} 183 \text{ (16)} 169 \text{ (13)} 155 \text{ (12)} 143 \text{ (16)} 129 \text{ (19)} 117 \text{ (14)} 105 \text{ (18)} 91 \text{ (23)} 73 \text{ (100).} \]

\[ \text{ent-12β-Acetoxy-10β,13-dihydroxy-20-norgiberrell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (238).} \]

When (233) (40mg, 0.11mmol) was treated with acetic anhydride (20µl, 0.21mmol) and triethylamine (35µl, 0.25mmol) in dichloromethane (5ml) according to the procedure for conversion of (121) to (163), (238) (43mg, 95%) was obtained.
Rf : 0.5 (ethyl acetate: hexane, 1:1)

$^1$HNMR : 1.07 (s, 3H, 4Me) 2.11 (s, 3H, OAc) 2.55 (d, J=10.3Hz, 1H, H6) 2.71 (d, J=10.3Hz, 1H, H5) 3.71 (s, 3H, OMe) 4.72 (t, J=7.0Hz, 1H, H12) 5.18 (bs, 1H, H17) 5.36 (bs, 1H, H17').

MS : 404 (M+, 21%) 373 (21) 372 (24) 362 (17) 344 (74) 326 (19) 312 (52) 298 (69) 284 (100) 257 (54) 239 (51) 227 (19) 213 (47) 197 (39) 185 (21) 157 (23) 145 (32) 135 (28) 121 (29) 105 (40) 91 (48) 79 (32)

HRMS : C$_{22}$H$_{23}$O$_7$ (M+) requires 404.1835, found 404.1832.


When (238) (30mg, 98µmol) was allowed to react with methyl oxalyl chloride (10µl, 0.11mmol), triethylamine (15µl, 0.12mmol) and a crystal of DMAP in dichloromethane (5ml) according to procedure for conversion of (163) to (203), (239) (30mg, 85%) was obtained.

Rf : 0.6 (ethyl acetate:hexane, 1:1)

$^1$HNMR : 1.09 (s, 3H, 4Me) 2.10 (s, 3H, OAc) 2.57 (m, 2H, H6+H14) 2.74 (d, J=10.0Hz, 1H, H5) 3.74 (s, 3H, OCOCO$_2$Me) 3.88 (s, 3H, OMe) 5.18 (t, J=8.0Hz, 1H, H12) 5.21 (bs, 1H, H17') 5.34 (bs, 1H, H17').

MS : 459 (M+ - 31, 1%) 430 (1) 403 (25) 385 (9) 344 (5) 325 (11) 299 (13) 283 (10) 239 (12) 223 (4) 211 (5) 197 (6) 183 (2) 164 (13) 155 (3) 129 (6) 115 (4) 105 (9) 91 (17) 79 (8) 59 (23) 43 (100).

HRMS : C$_{22}$H$_{27}$O$_7$ (M+ - 87) requires 403.1757, found 403.1758.

ent-12β-Acetoxy-10β-hydroxy-20-norgibbonell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (240).

When (239) (25mg, 51µmol) was subjected to reaction with tin hydride (25µl, 0.11mmol) and AIBN (5mg), according to the procedure for conversion of (203) to (204), (240) (12mg, 64%) was obtained.
Rf : 0.8 (ethyl acetate:hexane, 1:1)

$^1$H NMR : 1.04 (s, 3H, 4Me) 2.04 (s, 3H, OAc) 2.58 (d, J=10.5Hz, 1H, H6) 2.67 (bd, J=5.0Hz, 1H, H13) 2.74 (d, J=10.5Hz, 1H, H5) 3.71 (s, 3H, OMe) 4.67 (t, J=8.0Hz, 1H, H12) 5.05 (bs, 1H, H17) 5.23 (bs, 1H, H17').

MS : 388 (M+, 12%) 357 (11) 356 (16) 328 (75) 310 (21) 300 (55) 282 (55) 268 (97) 256 (22) 241 (57) 233 (23) 223 (66) 211 (22) 197 (74) 183 (43) 169 (38) 155 (33) 143 (36) 129 (42) 115 (33) 105 (62) 91 (100) 79 (70) 66 (36) 54 (93).

HRMS : C$_{22}$H$_{28}$O$_6$ (M+) requires 388.1886, found 388.1886.

ent-12$\beta$,10$\beta$-Dihydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (GA$_{70}$ Methyl Ester) (241).

When (240) (10mg, 26$\mu$mol) was allowed to react with potassium carbonate (5mg) in methanol (3ml) according to the procedure for conversion of (192) to (193), (241) (7mg, 81%) was obtained.

Rf : 0.3 (ethyl acetate:hexane, 1:1).

$^1$H NMR : 1.08 (s, 3H, 4Me) 2.56 (d, J=10.3Hz, 1H, H6) 2.61 (m, 1H, H13) 2.73 (d, J=10.3Hz, 1H, H5) 3.70 (s, 3H, OMe) 3.74 (t, J=7.5Hz, 1H, H12) 4.98 (bs, 1H, H17) 5.09 (bs, 1H, H17').

MS (TMS-ether) : 418 (M+, 20) 403 (10) 386 (13) 372 (17) 358 (16) 343 (8) 328 (43) 311 (15) 296 (69) 283 (53) 268 (100) 241 (38) 223 (97) 209 (21) 197 (59) 183 (34) 169 (32) 155 (32) 143 (43) 129 (50) 117 (36) 105 (57) 91 (92).
ent-3α,13-Diacetoxy-17-δ-deuterio-10β-hydroxy-20-norgibberell-16-ene-7, 19-dioic Acid 7-Methyl Ester 19,10-Lactone (245).

Sodium cyanoborodeuteride (24mg, 0.36mmol) was added to a stirred solution of (83) (50 mg, 0.093 mmol) and bromoresol green (1mg) in anhydrous THF (5ml). A solution of DCl-DOAc in THF [prepared by the addition of D2O (0.3ml) to acetyl chloride (0.3ml) in THF (2ml)] was added dropwise to the blue solution until the colour changed to yellow. The mixture was allowed to stir at room temperature for 1 h., while the solution of DCl-DOAc in THF was added dropwise occasionally to maintain the yellow colour. The solvent was removed under reduced pressure and the crude product mixture was diluted with ethyl acetate (10ml), washed with dilute hydrochloric acid (2M), water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:1) gave (244) (35mg, 70%).

Freshly activated zinc dust (10mg) was added to the solution of (244) (35mg, 0.065mmol) in boiling acetic acid (5ml). After stirring at reflux temperature for 10 min, the cooled reaction mixture was diluted with dichloromethane (10ml) and filtered through celite. The filtrate was washed twice with water, saturated sodium bicarbonate solution, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) gave a mixture of E/Z 17-deuterated GA1-3,13-diacetate methyl ester (245) (24mg, 80%).

1H HMR : 5.13 (bs, 0.5H, H17) 4.97 (bs, 1.5H, H3 + H17’)

2H NMR : 5.15 (bs, 17D)

13C NMR : 107 ppm (suppressed, C17)

MS : 447 (M⁺, C24H29O8D1) (DÎ=93%)
Preparation of (246).

When (112) (50mg, 93µmol) was subjected to reduction with sodium cyanoborodeuteride (25mg, 0.38mmol) in THF (5ml) according to the procedure for preparation of (244), (246) (34mg, 68%) was obtained.

Acetic anhydride (10µl, 0.1mmol) was added to a stirred solution of (246) (30mg, 55µmol) and triethylamine (15µmol, 0.11mmol) in dichloromethane (5ml). After stirring at room temperature for 1 h., the reaction was concentrated in vacuo and chromatographed on silica gel (ethyl acetate:hexane, 1:3) to give the acetate (247) (30mg, 93%).

ent-16β-Bromo-17ξ-deuterio-10β-hydroxy-3α,13,17-triacetoxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (247).

R_f : 0.9 (ethyl acetate:hexane, 1:1)

^1H NMR : 1.05 (s, 3H, 18Me) 2.09 (s, 6H, 2xOAc) 2.12 (s, 3H, OAc) 2.70 (d, J=10.0Hz, 1H, H6) 3.2 (d, J=10.0Hz, 1H, H5) 3.75 (s, 3H, OMe) 4.65 (bs, 1.1H, H17) 5.33 (d, J=4.0Hz, 1H, H3) 5.87 (dd, J=4.0Hz, 9.6Hz, 1H, H1) 6.32 (d, J=9.6Hz, 1H, H1).

MS : 552 (M+−31, 3%) 523 (5) 504 (5) 444 (8) 402 (16) 384 (12) 339 (11) 298 (38) 280 (100) 256 (26) 238 (48) 220 (24) 197 (28) 179 (15) 169 (19) 155 (23) 143 (14) 118 (12).

HRMS : C_{25}H_{27}DO_{9}^{79}Br (M+−31) requires 552.0979, found 552.0981.

ent-3α,13-Diacetoxy-17ξ-deuterio-10β-hydroxy-20-norgibberella-1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (248).

Silver-activated zinc dust (10mg) was added to a stirred solution of (247) (25mg, 43µmol) in acetic acid (5ml). After stirring at room temperature for 15min, the reaction mixture was diluted with dichloromethane (20ml), filtered through celite. The filtrate was washed with water (2x10ml), saturated sodium bicarbonate solution, then brine and dried.
over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) gave the deuterated GA3 derivative (248) (15mg, 78%).

$^1$H NMR :  5.01 (bs, 0.55H, H17)  5.15 (bs, 0.55H, H17')

$^{13}$C NMR :  107 ppm (suppressed, C17)

MS :  445 (M+, C$_{24}$H$_{27}$O$_8$D$_1$) (D$_1$=90%)

$\textit{ent-3a,13-Diacetoxy-15\beta,17\epsilon$-dideuterio-10\beta$-hydroxy-20-norgibberella}$
$\textit{1,16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (250).}$

To a stirred solution of (74) (50mg, 0.11mmol) in absolute ethanol (5ml) was added $p$-toluenesulfonylhydrazine (22mg, 0.12mmol). After stirring at room temperature for 10 min, ethanol was removed under reduced pressure to give the crude GA3 hydrazone derivative (249) as colourless solids (70mg).

Sodium cyanoborodeuteride (28mg, 0.44mmol) was added to a solution of the crude hydrazone (249) (70mg, 0.11mmol) and a trace of bromocresol green in a mixture of DMF (2ml) and sulfolane (2ml). A solution of DCl-DOAc in THF [prepared by the addition of D$_2$O (0.3ml) to acetyl chloride (0.3ml) in THF (2ml)] was added dropwise to the blue solution until the colour changed to yellow. After heating at 110$^\circ$C for 2 h., the cooled reaction mixture was diluted with ethyl acetate (20ml) and washed successively with hydrochloric acid solution (2M), saturated sodium bicarbonate solution, water, then brine and dried over sodium sulfate. Concentration in vacuo and chromatography on silica gel (ethyl acetate:hexane, 1:2) gave (250) (32mg, 64%) as a foam.

$^1$H NMR :  4.99 (bs, 0.6H, H17)  5.16 (bs, 0.6H, H17').

$^2$H NMR :  2.25 (bs, D15)  5.22 (bs, D17).

$^{13}$CNMR :  42.7 (suppressed, C15)  108.2 (suppressed, C17).

M.S. :  446 (M+, C$_{24}$H$_{26}$O$_8$D$_2$) (D$_2$=80%) (D$_1$=9%).
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