

New Strategies for the Construction of Highly Functionalized Organic Molecules: Applications to C₁₉ Gibberellin Synthesis

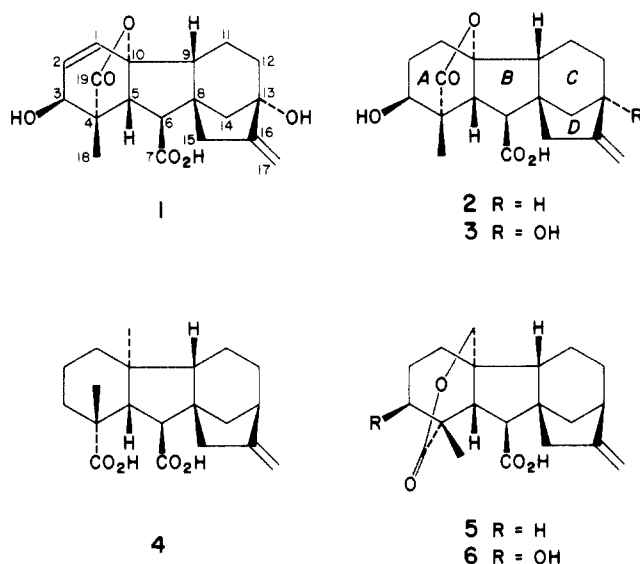
LEWIS N. MANDER

Research School of Chemistry, Australian National University, Canberra, A.C.T. 2600, Australia

Received April 16, 1982 (Revised Manuscript Received October 12, 1982)

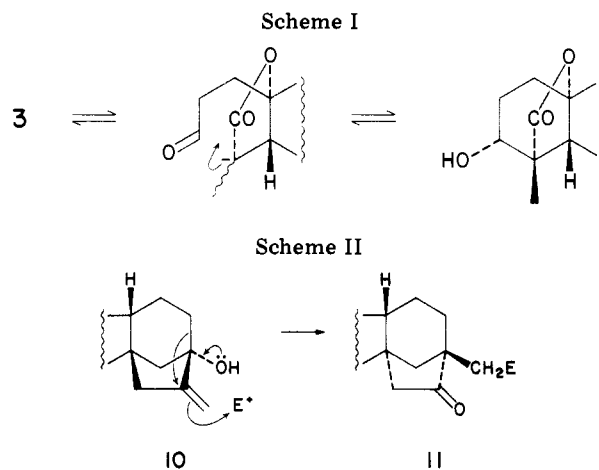
The gibberellins¹ form a group of 60 odd diterpenoid phytohormones, many of which have profound effects on various phases of plant growth, e.g., breaking of dormancy, enzyme synthesis, reversal of dwarfism, induction of stem growth, stimulation of flowering, modification of flower sex expression, parthenocarpic development of fruit, fruit enlargement, and inhibition of senescence. This Account describes a series of studies undertaken in our laboratories with the aim of developing efficient and flexible procedures for the total synthesis of the gibberellins. This research has been pursued within the context of a program concerned with the molecular basis of gibberellin biological activity,² but with the ultimate intent of harnessing the challenge posed by the construction of such molecules, as a vehicle for the development of new synthetic methodology.

Following the structural elucidation of gibberellic acid (1),³ a substantial effort was mounted by several groups toward its synthesis. Several simpler gibberellins were prepared over the next two decades, e.g., GA₄ (2), GA₁₂ (4), GA₁₅ (5), and GA₃₇ (6),⁴ but little progress was made



toward the synthesis of gibberellic acid (GA₃) itself.⁵ Not only is it necessary to cope with its greater complexity, but the high density of functional groups on the strained skeleton renders 1 labile toward a wide range of reagents.⁶ A successful strategy must therefore be based on careful timing and a judicious selection of methods. Because of space limitations, this Account

Lew Mander received his B.Sc. and M. Sc. degrees from the University of Auckland and his Ph.D. from the University of Sydney in 1965. After 2 post-doctoral years spent with Professor R. E. Ireland at the University of Michigan and then the California Institute of Technology, he joined the faculty of the University of Adelaide. He moved to the Australian National University in 1975 where he is now Professor of Chemistry. His research interests include the synthesis of natural products with emphasis on the development of new synthetic strategies and methodology.



focuses on the total synthesis of 1, but the preparations of other gibberellins are described, while the strategies and methodology that have been developed should have applications to other types of molecules.

Our prime concerns⁷ in designing an efficient plan for gibberellin synthesis—and these have general implications for any highly functionalized molecule—were to avoid excessive functionality and to minimize functional group manipulations, e.g., masking procedures, transpositions, and deletions.⁸ The most important consequence of such an approach is that, where possible, the functionality that ultimately forms an integral part of the final structure should be used to activate and control the construction of the carbon framework. A less obvious concomitant is the utilization of intramolecular processes: these ensure regiochemical and ste-

(1) Hedden, P. *ACS Symp. Ser.* 1979, No. 111, 19. Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. "Natural Products Chemistry"; Academic Press: New York, 1974; Vol. 1, p 265 ff.

(2) Mander, L. N.; Turner, J. V.; Twitchin, B. *Tetrahedron Lett.* 1981, 22, 3017-3020. Cossey, A. L.; Mander, L. N.; Turner, J. V. *Aust. J. Chem.* 1980, 33, 2062-2069 and references cited therein.

(3) Cross, B. E.; Grove, J. F.; MacMillan, J.; Moffatt, J. S.; Mulholland, T. P. C.; Seaton, J. C.; Sheppard, N. *Proc. Chem. Soc., London* 1959, 302-303. The complete stereochemical structure was determined subsequently by X-ray diffraction: Hartsuck, J. A.; Lipscomb, W. N. *J. Am. Chem. Soc.* 1963, 85, 3414-3419.

(4) For recent reviews see: (a) Fujita, E.; Node, M. *Heterocycles* 1977, 7, 709-752. (b) Danheiser, R. L. Ph. D. Dissertation, Harvard University, 1978. (c) Urech, R. Ph.D. Dissertation, Australian National University, 1980.

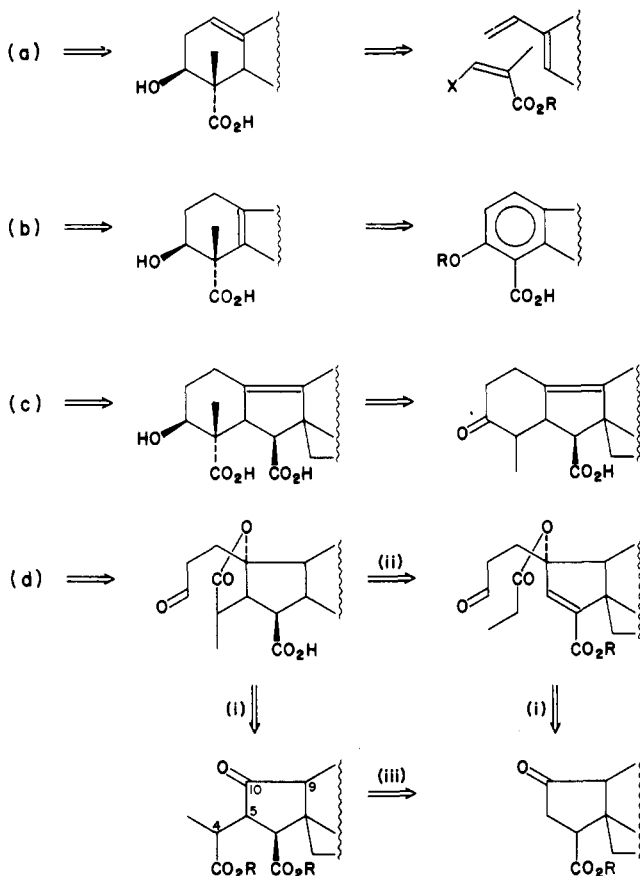
(5) Individual gibberellins are assigned the description GA_n, where n derives from the chronological order of discovery. All natural substances are based on the *ent*-gibberellane skeleton (cf. 4) or its 20-nor derivative (cf. 1), and numbering throughout this article is based on these structures: Rowe, J. R., Ed. "The Common and Systematic Nomenclature of Cyclic Diterpenes", 3rd Rev.; Forest Product Laboratory, U.S. Department of Agriculture: Madison, WI, 1968. Structures may represent single enantiomers or racemates depending on the context.

(6) Hanson, J. R. "The Tetracyclic Diterpenes"; Pergamon Press: Oxford, 1968; p 41 ff.

(7) The normal concerns of convergency, flexibility, efficiency, etc. are assumed. Cf.: Ireland, R. E. "Organic Synthesis"; Prentice Hall: Englewood Cliffs, NJ, 1969.

(8) Cf.: Hendrickson, J. B. *Top. Curr. Chem.* 1976, 62, 49-172.

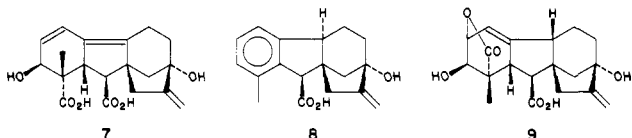
Scheme III



reochemical control, while the relatively favorable entropic changes allow reactions to occur at sites that might otherwise be inaccessible. A design feature of the present work, which could be regarded as a further corollary, but which may be due to predilection, has been the use of benzenoid synthons. These provide stability in the early phases of a synthesis and yet contain a wealth of latent functionality, which may be liberated when required.

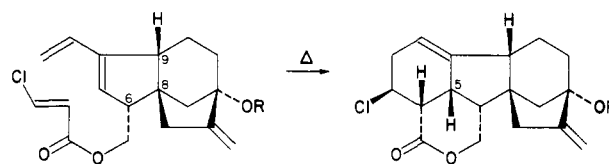
Preliminary Considerations

Gibberellic acid (1) undergoes a wide variety of rearrangements, many of which occur under very mild conditions. For example, in unbuffered aqueous solution, GA₃ is autocatalytically transformed into gibberellenic acid (7),⁹ while in stronger acid, allogibberic acid



(8) is formed.¹⁰ In cold dilute aqueous alkali, the intriguing rearrangement to isogibberellic acid (9) occurs,¹¹ whereas the closely related GA₁ (3) is epimerized at C(3)^{11a} through a retroaldol-aldol sequence (Scheme I).¹² In addition, all 13-hydroxy derivatives undergo the electrophile-initiated Wagner-Meerwein rear-

Scheme IV



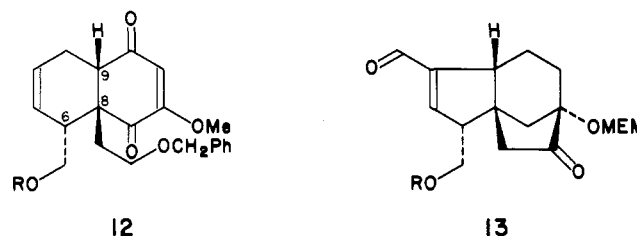
angement 10 → 11 (Scheme II) with some ease.^{10,13}

Because of the lability of these various functional arrays and the challenging problems posed by their assembly, the D-ring methylenecyclopentanol moiety and the A-ring region become the natural foci for synthetic plans.

A-Ring Region

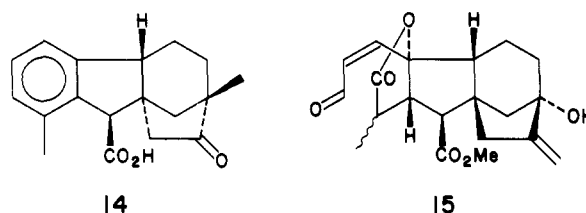
A retrosynthetic analysis of the lactone-A-ring region is outlined in Scheme III, and all published approaches to the synthesis of C₁₉ gibberellins may be conceptually related to a construction sequence based on one of the indicated subsets of bond disconnections.

Scheme IIIa became the basis of the strategy employed in the first synthesis of GA₃ (1) by Corey et al.¹⁴ In practice, the elegant intramolecular [4 + 2] cycloaddition was carried out as indicated in Scheme IV; the dienophile component was thus restrained to add to the α face of the molecule, thereby ensuring the desired chirality at C(5); subsequent control of stereochemistry was then straightforward. The crucial stereochemical relationships between the *pro*-C(6), C(8), and C(9) centers had been established in an earlier Diels-Alder reaction that furnished 12. After elaboration of the



C/D ring system, the required B-ring structure was developed by oxidative cleavage, followed by a delicately controlled aldol condensation to give 13.

In Scheme III, steps b and c both lead logically to the use of a benzenoid synthon as a precursor to ring A, and a majority of the studies on gibberellin synthesis are based on this premise. The Mori synthesis of GA₄ (2)¹⁵ employed (±)-epigibberic acid (14) as a key interme-



diate, but the complete sequence extended over 55 steps, many of them giving very low yields, and it was only feasible to complete the synthesis with the use of

(13) Bourn, P. M.; Grove, J. F.; Mulholland, T. P. C.; Kidd, B. K.; Klyne, W. *J. Chem. Soc.* 1963, 154-162.

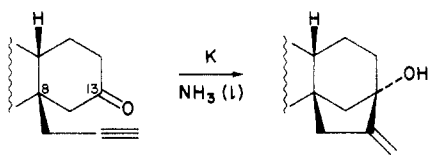
(9) Pryce, R. *J. Phytochemistry* 1973, 12, 507-514.
(10) Cross, B. E. *J. Chem. Soc.* 1954, 4670-4676. Mulholland, T. P. *C. Ibid.* 1958, 2693-2701.

(11) (a) Cross, B. E.; Grove, J. F.; Morrison, A. *J. Chem. Soc.* 1961, 2498-2515. (b) Kirkwood, P. S.; MacMillan, J.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. 1* 1980, 2117-2121.

(12) MacMillan, J.; Pryce, R. *J. Chem. Soc. C* 1967, 740-742.

(14) (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Sinet, P.; Gras, J. *J. Am. Chem. Soc.* 1978, 100, 8034-8036. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J. *L. Ibid.* 1978, 100, 8031-8034.
(15) Mori, K.; Shiozaki, M.; Itaya, N.; Matsui, M.; Sumiki, Y. *Tetrahedron* 1969, 25, 1293-1321.

Scheme V



Scheme VI



several relays. More sophisticated methodology employing aromatic A rings was pioneered by Loewenthal,¹⁶ developed by House¹⁷ and Baker,¹⁸ but only brought to fruition in our laboratories (*vide infra*).

In Scheme III d the aldol-based strategies arise naturally from the chemistry of GA₁ (3) (cf. Scheme I). The viability of such an approach was first demonstrated by Dolby et al. in model studies¹⁹ and subsequently refined by Stork and Singh in a stereoselective reconstruction of GA₃ (1) methyl ester from aldehyde 15.²⁰ The remaining transforms in Scheme III d afford a considerable conceptual simplification. At first sight there are two attractive possibilities, both requiring the addition of a propionaldehyde synthon²¹ to C(10) (transform i) but differing in the construction of the C(4)-C(5) bond. The alkylation route (transform iii) was shown to be feasible in a model system by Dolby,¹⁹ but epimerization at *pro*-C(9) in an actual intermediate would probably be unavoidable. The Michael transform (ii) was accordingly much more attractive and became the basis of a pivotal step in the better of our two successful routes to GA₃ (1).

D-Ring Problem

The other focus of any synthetic plan for GA₃ must be the construction of the D ring with incorporation of the bridgehead-hydroxy and methylene functions. More effort and ingenuity have been expended on this problem than on any other structural feature. Most solutions have involved the bridging of an angular substituent from C(8) to C(13), and undoubtedly the most elegant of these methods is the reductive cyclization of ethynyl ketones devised by Stork (cf. Scheme V)²² although it has not yet been incorporated into a complete synthesis.²³ A related intramolecular pinacol reaction was utilized in the first Harvard synthesis of GA₃,¹⁴ while a second route followed an aldol-based strategy.²⁴

(16) (a) Bachi, M. D.; Epstein, J. W.; Herzberg-Minzly, Y.; Loewenthal, H. J. *J. Org. Chem.* **1969**, *34*, 126-135. (b) Loewenthal, H. J. E.; Schatzmiller, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 944-950.

(17) (a) House, H. O.; Strickland, R. C.; Zaiko, E. J. *J. Org. Chem.* **1976**, *41*, 2401-2408. (b) House, H. O.; Zaiko, E. J. *Ibid.* **1977**, *42*, 3780-3783.

(18) Baker, A. J.; Goudie, A. C. *J. Chem. Soc., Chem. Commun.* **1972**, 951.

(19) Dolby, L. J.; Milligan, R. J. *J. Am. Chem. Soc.* **1966**, *88*, 4536-4537. Dolby, L. J.; Skold, C. N. *Ibid.* **1974**, *96*, 3276-3279.

(20) Stork, G.; Singh, J. *J. Am. Chem. Soc.* **1979**, *101*, 7109-7110.

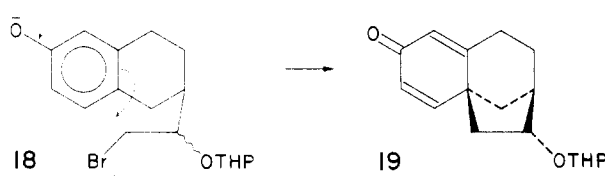
(21) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560-5561. Still, W. C.; Macdonald, T. L. *Ibid.* **1974**, *96*, 5561-5563.

(22) Stork, G.; Boeckmann, R. K.; Taber, D. F.; Still, W. C.; Singh, J. *J. Am. Chem. Soc.* **1979**, *101*, 7107-7109 and references cited therein.

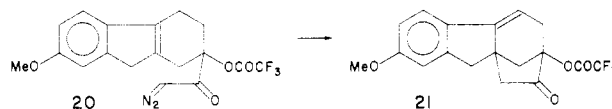
(23) An intermediate obtained²² by application of this methodology has been prepared independently and utilized in the second Harvard synthesis of GA₃, however.

(24) Corey, E. J.; Gorzynski Smith, J. *J. Am. Chem. Soc.* **1979**, *101*, 1038-1039.

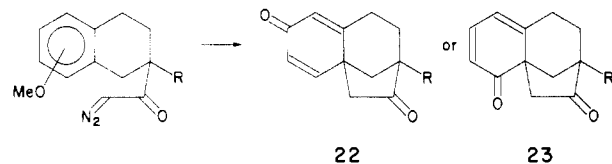
Scheme VII



Scheme VIII



Scheme IX



Further approaches have been reviewed by Fujita and Node.^{4a}

Our own solution to this problem stemmed from a decision to use fluorenone 16²⁵ (or a variant) as a substrate. Nucleophilic addition to the carbonyl group of 16 followed by development of the D-ring elements and then formation of the angular bond through intramolecular alkylation as indicated on structure 17 (Scheme VI) appeared to be an attractive and practical proposition. In refining the concept to a set of possible chemical processes, we were influenced by the intramolecular alkylation 18 → 19 (Scheme VII), a pivotal reaction in the Masamune syntheses of the Garrya diterpene alkaloids.²⁶ Only the diastereomer leading to the *exo* isomer 19 had undergone cyclization, however, and so we therefore concentrated on functional arrays in which the carbon atom in 17 bearing R² was sp² hybridized. The ultimate outcome of those considerations was the acid-catalyzed cyclization of diazo ketone 20 to form 21 (Scheme VIII).²⁷ The trifluoroacetate function was employed to reduce the nucleophilicity of the angular oxy function toward the diazonium intermediate,²⁸ although it was found subsequently that chloroacetate would suffice.

Our fluorenone-based strategy then languished over several years for want of a more satisfactory preparation of fluorenones such as 16. Because of the reliability, efficiency, and potential of the diazo ketone cyclizations, however, we were convinced that this solution to the problem of D-ring construction should be incorporated into whatever alternative route we might devise for gibberellin synthesis. The hyperactivity of the protonated diazoacetyl function allows reactions at sufficiently low temperatures that ipso substitution of anisole synthons can usually be achieved without rearomatization. Thus, a variety of tetrahydronaphthyl diazomethyl ketones were converted in high yields to potentially useful intermediates, e.g., tricyclic ketones

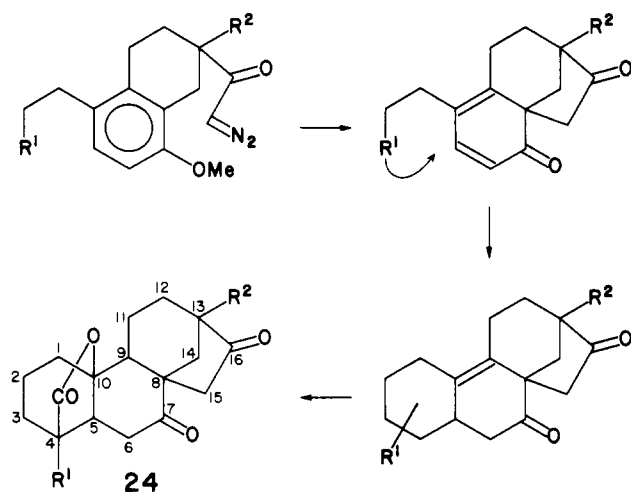
(25) Fried, J.; Abraham, N. A. *Tetrahedron Lett.* **1965**, 3505-3512.

(26) Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 288-289.

(27) Beames, D. J.; Mander, L. N.; Turner, J. V. *Aust. J. Chem.* **1974**, *27*, 1977-1984.

(28) Beames, D. J.; Klose, T. R.; Mander, L. N. *J. Chem. Soc., Chem. Commun.* **1971**, 773-774. Klose, T. K.; Mander, L. N. *Aust. J. Chem.* **1974**, *27*, 1287-1294.

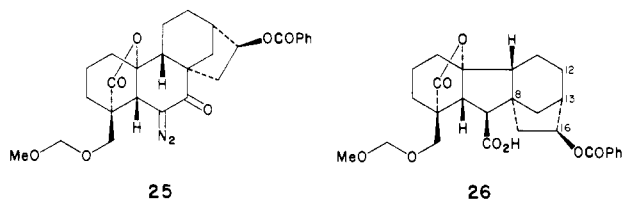
Scheme X



22 and **23** (Scheme IX, R = H, 70–95%; R = Me, 95%; R = OCOCCl₃, 84–88%)²⁹ that provide a wide variety of opportunities for the addition of the A ring and its substituents. Moreover, there is the useful option of attaching substituents to the aromatic B ring of the diazo ketone precursors. Several investigations were mounted, therefore, in order to determine how best these dienone systems might be utilized; the more productive of these are examined in the following sections.

Phenanthrenone Route

The strategy is outlined in Scheme X and is critically dependent on the generalized Michael reaction.³⁰ The parallel may be drawn with the retrosynthetic sequence in Scheme IIIc. The most successful of the approaches along these lines led to the gibberellin-like molecule **26**³¹ that was formed from the photo-Wolff rearrangement of diazo ketone **25**. The overall sequence exhibits



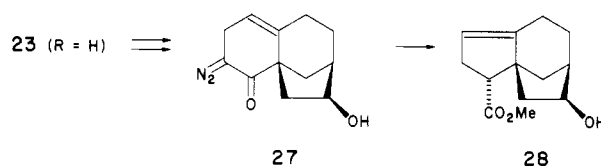
several important design features: the principal carbon-carbon bond forming steps are orchestrated from one functional center C(7), all of the latent functionality in the anisole synthon is utilized, and three new chiral centers, C(4), C(9), and C(10), are established with complete stereoselectivity in a single step. The configuration of the remaining stereocenters at C(8) and C(13) could be corrected if C(12) can be induced to migrate from C(13) to C(16), since it passes through a local symmetry plane, thereby achieving an "inversion" of the D-ring bridge (cf. Scheme II). With this aim in mind, we embarked upon a synthesis of the 13-hydroxy analogue of **26**, for which it was expected that the added

(29) (a) Blair, I. A.; Ellis, A.; Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1978**, *31*, 405–409. (b) Beames, D. J.; Klose, T. R.; Mander, L. N. *Ibid.* **1974**, *27*, 1269–1275. (c) Johnson, D. W.; Mander, L. N. *Ibid.* **1974**, *27*, 1277–1286.

(30) Blair, I. A.; Mander, L. N.; Mundill, P. H. C.; Pyne, S. G. *Aust. J. Chem.* **1981**, *34*, 1887–1898.

(31) Mander, L. N.; Pyne, S. G. *J. Am. Chem. Soc.* **1979**, *101*, 3373–3375. Mander, L. N.; Pyne, S. G. *Aust. J. Chem.* **1981**, *34*, 1899–1911.

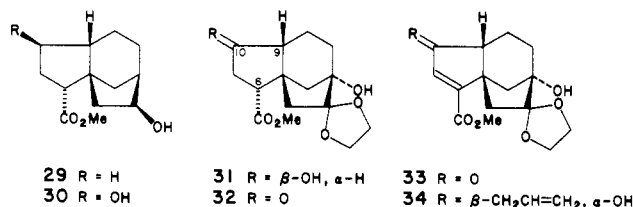
Scheme XI



substituent (which is an integral part of many gibberellins regardless) would assist the desired rearrangement. Although a suitable analogue of **24** was prepared, i.e., **24** (R¹ = CO₂Me, R² = OCH₂OMe),³² this route for gibberellin synthesis was deferred in favor of the more productive approaches which follow.

Michael-Aldol Approach³³

The possibility of utilizing dienones **22** or **23** as intermediates in a gibberellin synthesis predicated in Scheme IIIc was first demonstrated³⁴ with the conversion of **23** (R = H) into ester **28** by a sequence of controlled reductions, followed by photo-Wolff rearrangement of diazo ketone **27** (Scheme XI). Ester **28** and its analogues proved to be crucial intermediates, in that the 6 α -carboxy substituent steers reagents to the β face of the olefinic bond, thereby establishing the required B/C-cis ring fusion. The stereochemical aspects were first established by hydrogenation of **28** to **29** followed by correlation with known compounds.³⁵



The configuration of the hydroboration product **30** was then deduced from ¹³C NMR spectral comparisons with **29**. The more complex derivative **31** was subsequently prepared in an analogous fashion,³³ but we found it to be quite impossible to add to the *pro*-C(10) carbonyl group in **32** any nucleophile that might serve as an acceptable precursor to carbons 1–3 of the A ring; we learned later that the Stork group had encountered the same difficulty with a very similar substrate.³⁶ The problem, which is only too characteristic of hindered cyclopentanones, is compounded by both the presence of the ester function and the risk of epimerization at the adjacent stereocenter C(9). In the hope that enone **33** might be more electrophilic (by virtue of electron withdrawal by the ester function), we attempted its preparation through α -selenenylation of the ester function in **31**. Although most bases, e.g., lithium diisopropylamide, were ineffectual for the removal of the very hindered 6 β -proton, the use of potassium hydride in the presence of diphenyl diselenide resolved the problem efficiently. Selenoxide elimination and then oxidation of the resulting allylic alcohol subsequently

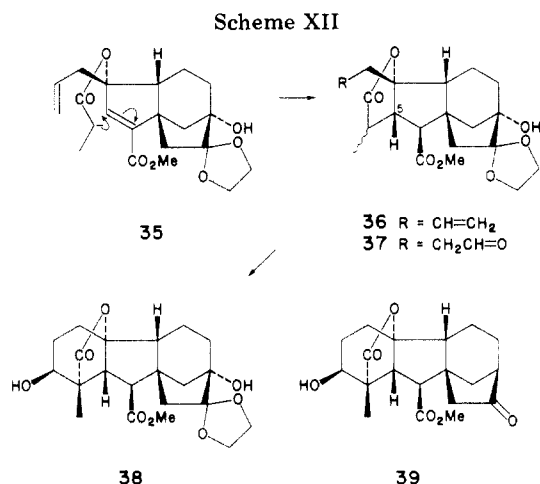
(32) Mander, L. N.; Potter, G. J.; Pyne, S. G.; Woolias, M. *Aust. J. Chem.* **1981**, *34*, 1913–1919.

(33) Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626–6628.

(34) Cossey, A. L.; Mander, L. N. *Tetrahedron Lett.* **1979**, 969–972.

(35) Mander, L. N.; Prager, R. H.; Turner, J. V. *Aust. J. Chem.* **1974**, *27*, 2645–2656. Cossey, A. L.; Mander, L. N.; Pyne, S. G. *Ibid.* **1979**, *32*, 817–822.

(36) Stork, G.; Still, W. C.; Singh, J.; Takei, S. *Tetrahedron Lett.* **1980**, *21*, 4051–4054.



furnished the desired enone **33**, but attempts to add a number of common organometallics were initially no more encouraging than with the saturated analogue **32**.

Progress was finally obtained with a number of unsaturated alanes, the most useful of which was the triallyl derivative. This success presumably stems from an S_E2' mode of addition, in which the electrophilicity of the carbonyl group is enhanced by the Lewis acid properties of the aluminum. Carbinol **34** was thus obtained with 95% stereoselectivity, the general convexity of the β face and approach along the equatorial vector ensuring predominant formation of the desired epimer.

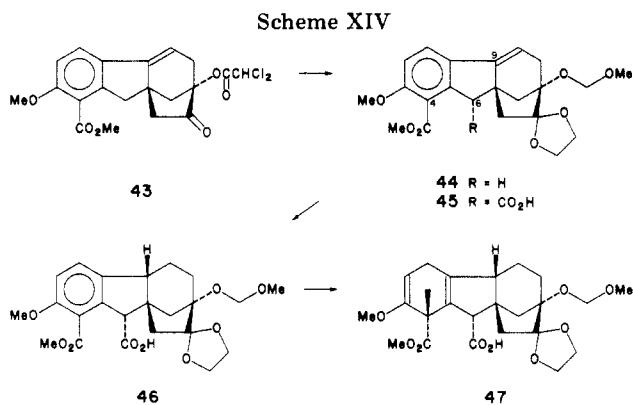
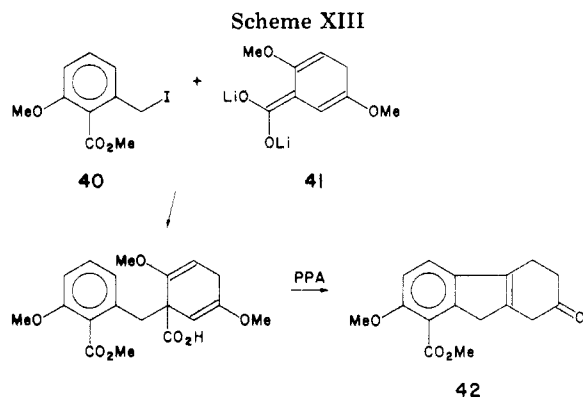
The next phase of the synthetic plan required an intramolecular Michael addition of the enolate anion derived from the propionate residue in **35** to the olefinic ester moiety (Scheme XII). In this way, the nucleophilic residue would be constrained to add to the α face, thereby establishing the correct chirality at C(5). Although it was expected that an auxiliary group would be required for additional stabilization of the ester enolate,³⁶ **35** was converted smoothly and quantitatively into the lactone **36**. Completion of the main skeleton was achieved as originally envisaged, i.e., by the aldol reaction of aldehyde **37** (derived by routine hydroboration and oxidation from **36**), which furnished a 1:1 mixture of alcohol **38** with its 3α epimer. Clearly, with **38** available in only 20 steps from 1,7-dimethoxynaphthalene, the major obstacles to the synthesis of C₁₉ gibberellins had been overcome. The methodology for the transformation of **33** into **38** is also compatible with the preparation off 13-deoxygibberellins, e.g., GA₄ (**2**), which are considerably more active growth promoters for the Curcubitaceae. Thus, ketone **39** was obtained from **30** with equal facility, this time as a 3:1 mixture with its 3α epimer.³⁷

While these studies were being brought to fruition, a crucial advance was made in our fluorenone-based strategy, and the successful development of this approach is described in the following section.

Fluorenone Route

Earlier procedures for the synthesis of the fluorenone **16** (used as a substrate in our original studies on the construction of the D ring) and related compounds were unacceptably protracted or inefficient.²⁷ Moreover, adaptation to the preparation of the more desirable

(37) Cossey, A. L.; Lombardo, L.; Mander, L. N. *Tetrahedron Lett.* **1980**, *21*, 4383-4386.



derivative **42** did not appear to be practicable. The convergent sequence outlined in Scheme XIII,³⁸ however, provided rapid access to **42** and allowed a considerable degree of flexibility. The enediolates, e.g., **41**, derived from Birch reduction of aromatic acids are synthetically equivalent to cyclohexyl β -keto esters but are often more accessible and very much more nucleophilic.³⁹ Thus, iodide **40**, which is very prone to form 6-methoxyphthalide under a variety of reaction conditions, reacts with anion **41** satisfactorily.

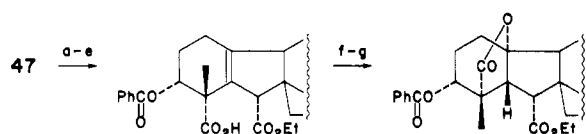
The gibberellin D ring was then added to **42** by adapting the diazo ketone based methodology which had been worked out previously (cf. Scheme VIII). Chloroacetoxy ketone **43**, formed in this way, was hydrolyzed and masked as the acetal **44**, which was then committed to the sequence outline in Scheme XIV. This route, based on the elegant methodology of Loewenthal et al.,^{16b} began with the ester-assisted lithiation of **44** followed by carboxylation to give the key intermediate **45**. Not only is the C(6) carboxyl function an integral part of the gibberellin structure, but it also serves as an essential control element for the subsequent development of chirality at C(4) and C(9). Early studies on the structure of epigibberic acid (**14**) and related compounds had established that hydrogenation of the $\Delta^{9(11)}$ double bond in compounds similar to **45** occurred on the opposite face of the molecule to the 6-carboxy substituent, irrespective of other structural features.⁴⁰ Thus, the desired B/C-cis-fused isomer **46** was obtained with complete stereoselectivity.

(38) Hook, J. M.; Mander, L. N. *J. Org. Chem.* **1980**, *45*, 1722-1724.

(39) (a) Hook, J. M.; Mander, L. N.; Urech, R. *Synthesis* **1979**, 374-376. (b) Mander, L. N.; Hamilton, R. J. *Tetrahedron Lett.* **1981**, *22*, 4115-4118. (c) Hook, J. M.; Mander, L. N.; Woolias, M. *Ibid.* **1982**, *23*, 1095-1098.

(40) Grove, J. F.; MacMillan, J.; Mulholland, T. P. C.; Turner, W. B. *J. Chem. Soc.* **1960**, 3049. Stork, G.; Newman, H. *J. Am. Chem. Soc.* **1959**, *81*, 3168.

Scheme XV



Reagents: ^aHg(II)(NO₃)₂, MeCN-H₂O; ^bNaBH₄; ^cPhCOCl, Py; ^dCH₃CHN₂; ^e*n*-PrSLi, HMPA; ^fKHCO₃, KBr₃; ^gCr(II)(OAc)₂, *n*-PrSH.

Model studies completed by House et al. encouraged us to believe that reductive alkylation at C(4) should occur stereoselectively anti to the 6 α -carboxy function, so we were more concerned over reports of considerable methoxyl loss during Birch reduction,^{17a} and of extremely facile oxidative decarboxylation during isolation of a 13-deoxy C(4) carboxylic acid analogue of 47.¹⁸ The solution to both these problems was the utilization of the C(4) methyl ester, i.e., 46, for the reductive alkylation,⁴¹ which furnished 47 efficiently.⁴² Intermediate 47, which had been obtained in only 13 steps from 2,5-dimethoxybenzoic acid, possessed all the structural features required to complete the synthesis of GA₃ (1), and the remaining stereochemical problems could be expected to be relatively minor. However, the elaboration of the A- and B-ring functionality, while conceptually simple, could only be achieved by the circuitous approach outlined in Scheme XV.

Once the 4 α ,10 α -carbolactone was in place, the thermodynamically preferred configuration of the ethoxycarbonyl group was 6 β ¹⁴ and so the correct stereochemistry of C(6) could be obtained simply by isomerization with base. The identity of the product was confirmed by hydrolysis and then esterification to give 3-*epi*-38.

Synthesis of Gibberellins A₁ and A₄

With reliable and relatively direct routes to intermediates 38, 3-*epi*-38, and 39 established, access to the majority of C₁₉ gibberellins appeared to be assured. Gibberellin A₄ (2) was readily obtained from 39 through Wittig methylenation of the derived benzoate [masking of the 3 β -hydroxyl is essential to avoid base-catalyzed epimerization at C(3)] followed by thiolate-induced demethylation and then careful hydrolysis of the benzoyloxy function at pH 10.³⁷

Wittig reactions on bridged ketones of this type are often slow and difficult to force to completion because of enolate formation. With reagent generated from potassium *tert*-butoxide in *tert*-butyl alcohol, however, the reaction is almost instantaneous⁴³—the substrate is simply titrated with the yellow preformed ylide.

The preparation of GA₁ (3) from 38 was a rather more difficult problem, in that the 13-hydroxy function must also be protected during the Wittig methylenation so as to avoid base-catalyzed rearrangement of the D-ring ketol moiety.⁴⁴ Corey has described the development

(41) We are grateful to Professor Loewenthal for alerting us to this possibility. Cf.: Loewenthal, H. J. E. "Guide for the Perplexed Organic Experimentalist"; Heyden, London, 1978; pp 133-138.

(42) Comparison of ¹H NMR spectral data for 47 and those reported for the model compounds^{17a} was inconclusive, but data obtained from the product of reductive methylation of 6-*epi*-46 were unequivocally consistent with 4,6-*epi*-47. This confirmation of alkylation anti to the C(6) substituent reassured us that equivalent control had been obtained for 46 also and that 47 was indeed the product.

(43) Schlosser, M.; Christman, K. F. *Angew. Chem., Int. Ed. Engl.* 1964, 3, 636.

(44) Cf.: Mossetig, E.; Beglinger, U.; Dolder, F.; Lichti, H.; Quitt, P.; Waters, J. A. *J. Am. Chem. Soc.* 1963, 85, 2305-2309.

of the MEM (methoxyethoxymethyl) protecting group specifically for such a purpose, but also reported that the Wittig reaction on the gibberellin intermediate 13 was carried out over 5 h at 65 °C,¹⁴ conditions which were bound to destroy our more sensitive norgibberellin lactones. We decided, therefore, to employ a trimethylsilyl group, in the hope that the longer bonds to silicon would attenuate steric hindrance and facilitate the Wittig reaction. It was thus possible in the *tert*-butyl alcohol based system to complete the Wittig reaction in only 20 min at 20 °C. It was convenient and efficient to protect the 3-hydroxy group in the same way, but we were surprised to find that a small amount of the 3 α epimer was formed at temperatures above 20 °C. This complication was simply avoided through appropriate temperature control, but became a serious issue in the preparation of GA₃ (1), for which it became necessary to examine the nature of the isomerization.

The synthesis of GA₁ (3) was completed by removal of the masking groups, and we were interested to find, as expected, that both the synthetic racemic samples of GA₁ and GA₄ were each half as potent as the respective natural compounds in the barley endosperm bioassay.⁴⁵

Synthesis of Gibberellic Acid (GA₃)

Although GA₃ (1) differs from GA₁ (3) by only the Δ^1 olefinic bond, the increased lability of GA₃, which stems from this feature, compounds the difficulties of synthesis considerably. The challenging problem of elaborating the A-ring functionality in the presence of the very reactive methylenecyclopentanol moiety contained in the C/D-ring system was solved in the Corey synthesis by means of a sequence of electrophilic lactonizations; i.e., by using the 4 α -carboxylate group as an internal nucleophile, it was possible to achieve chemoselectivity and the stereochemically controlled introduction of the 3 β -hydroxy function.⁴⁶

Before refining our own plans, we established that methyl gibberellate 3-benzoate was stable to the acidic conditions that would be necessary to remove an acetal protecting group from C(16) and that it was possible to hydrolyze the benzoate group without rearrangement of the allylic lactone (cf. 1 \rightarrow 9). Hence, if it was possible to prepare acetal 51 from 38 or an earlier intermediate, we were confident that application of the methodology used in the final stages of the GA₁ synthesis must lead ultimately to GA₃.

With the knowledge that hydride reduction of 3-oxogibberellins normally affords mainly 3 α -hydroxy derivatives,⁴⁷ we elected to proceed via the Δ^2 olefin 48, which was duly prepared from either 38 or its 3 α -epimer by elimination of the derived 3-benzenesulfonate. Before continuing further, however, we took advantage of the low polarity of 48 to undertake an optical resolution through chromatographic resolution of the diastereomeric urethanes obtained from reaction of (\pm)-48 13-chloroformate and (-)- α -phenylethylamine.¹⁴

(45) We are grateful to Dr. B. G. Coombe, Waite Agricultural Research Institute, Aldelaide, South Australia, for these measurements.

(46) Corey, E. J.; Brennan, T. M.; Carney, R. L. *J. Am. Chem. Soc.* 1971, 93, 7316-7317.

(47) Voigt, B.; Adam, G.; Kobrina, N. S.; Serebrayakov, V. F. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Tran.)* 1969, 1668-1671. Procedures have very recently been developed in our laboratories for stereoselective formation of 3 β epimers, however: Bell, R. A.; Turner, J. V. *Tetrahedron Lett.* 1981, 22, 4871-4872.

