New Strategies for the Construction of Highly Functionalized Organic Molecules: Applications to C_{19} Gibberellin Synthesis

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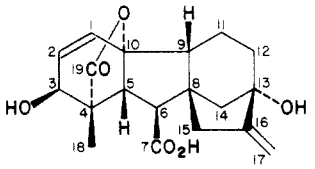
The gibberellins[1] form a group of 60 odd diterpenoid phytohormones, many of which have profound effects on various phases of plant growth, e.g., breaking of dormancy, enzyme synthesis, reversal of dwarfism, induction of stem growth, stimulation of flowering, modification of flower sex expression, parthenocarpic 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., GA_4 (2), GA_{12} (4), GA_{15} (5), and GA_{37} (6),[4] but little progress was made



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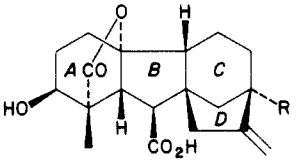
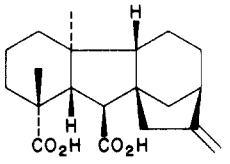


2 R = H
3 R = OH



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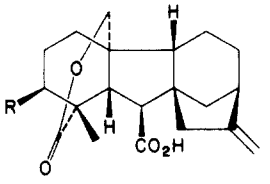
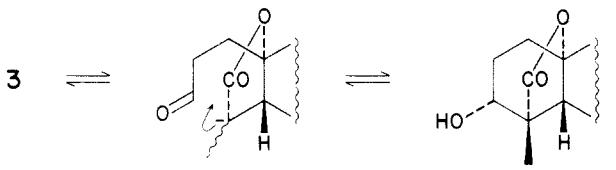


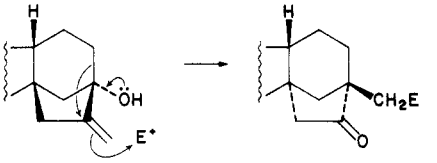
5 R = H
6 R = OH

toward the synthesis of gibberellic acid (GA_3) 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 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.

Scheme I



Scheme II



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Our prime concerns[7] 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-

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(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.

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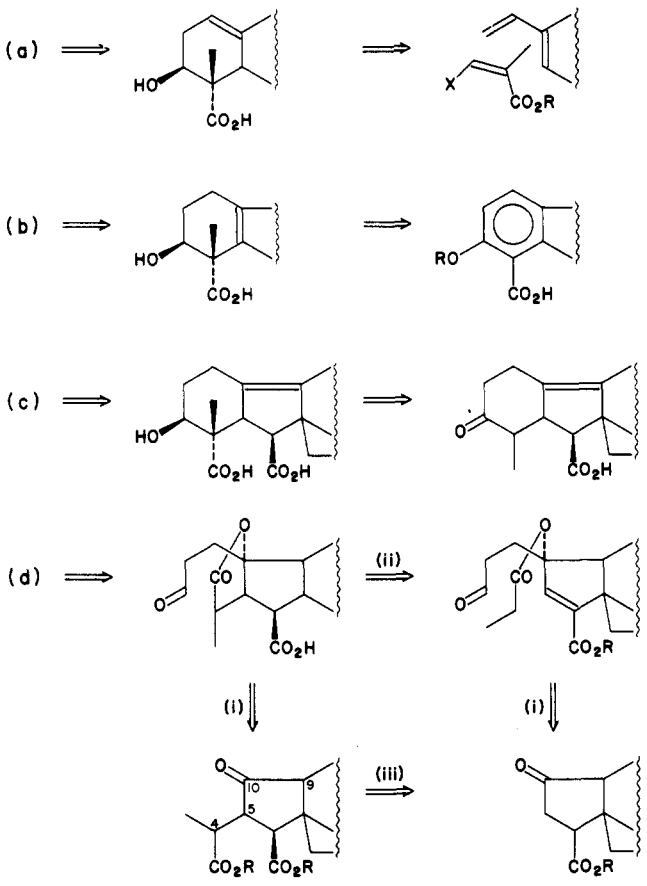
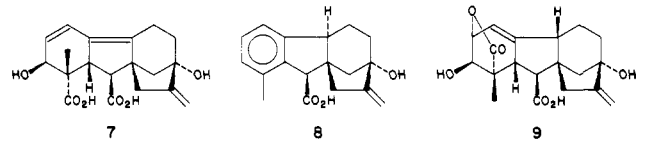
Scheme III



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

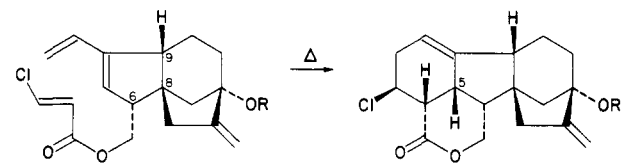
Gibberellic acid (1) undergoes a wide variety of rearrangements, many of which occur under very mild conditions. For example, in unbuffered aqueous solution, GA_3 is autocatalytically transformed into gibberellenic acid (7),[9] while in stronger acid, allogibberic acid



7 8 9

(8) is formed.[10] In cold dilute aqueous alkali, the intriguing rearrangement to isogibberellic acid (9) occurs,[11] whereas the closely related GA_1 (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 rearrangement **10** → **11** (Scheme II) with some ease.[10,13]

Scheme IV

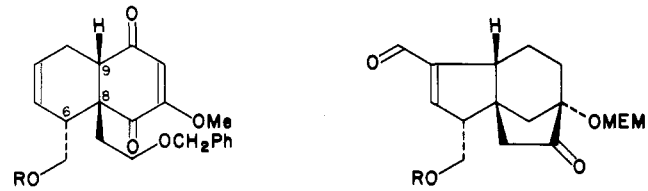


Because of the lability of these various functional arrays and the challenging problems posed by their assembly, the D-ring methylenecyclopentanol moiety and the A-ring region become the natural foci for synthetic plans.

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 C_{19} gibberellins may be conceptually related to a construction sequence based on one of the indicated subsets of bond disconnections.

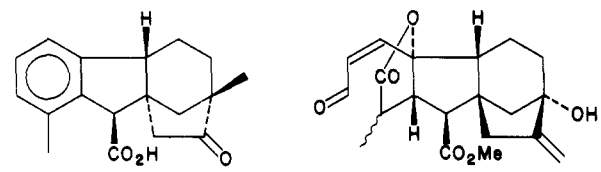
Scheme IIIa became the basis of the strategy employed in the first synthesis of GA_3 (1) by Corey et al.[14] In practice, the elegant intramolecular [4 + 2] cycloaddition was carried out as indicated in Scheme IV; the dienophile component was thus restrained to add to the α face of the molecule, thereby 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



12 13

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

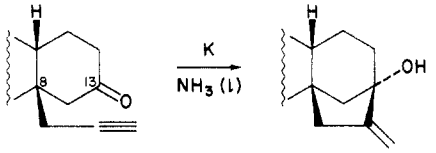
In Scheme III, steps b and c both lead logically to the use of a benzenoid synthon as a precursor to ring A, and a majority of the studies on gibberellin synthesis are based on this premise. The Mori synthesis of GA_4 (2)[15] employed (±)-epigibberic acid (**14**) as a key intermediate, but the complete 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



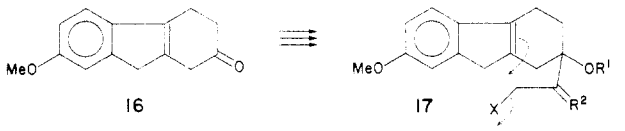
14 15

(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. *J. Chem. Soc. C* **1967**, 740–742.
(13) Bourn, P. M.; Grove, J. F.; Mulholland, T. P. C.; Kidd, B. K.; Klyne, W. *J. Chem. Soc.* **1963**, 154–162.
(14) (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Sinet, P.; Gras, J. 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



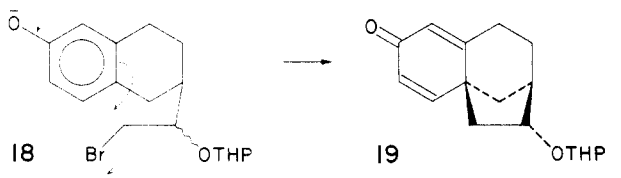
several relays. More sophisticated methodology employing aromatic A rings was pioneered by Loewenthal,[16] developed by House[17] and Baker,[18] but only brought to fruition in our laboratories (vide infra).

In Scheme IIId the aldol-based strategies arise naturally from the chemistry of GA_1 (**3**) (cf. Scheme I). The viability of such an approach was first demonstrated by Dolby et al. in model studies[19] and subsequently refined by Stork and Singh in a stereoselective reconstruction of GA_3 (**1**) methyl ester from aldehyde **15**.[20] The remaining transforms in Scheme IIId afford a considerable conceptual simplification. At first sight there are two attractive possibilities, both requiring the addition of a propionaldehyde synthon[21] 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 GA_3 (**1**).

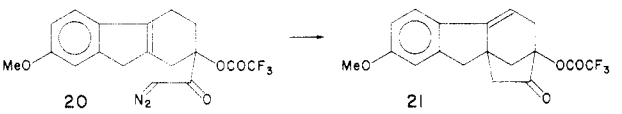
D-Ring Problem

The other focus of any synthetic plan for GA_3 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 invoved 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 GA_3,[14] while a second route followed an aldol-based strategy.[24]

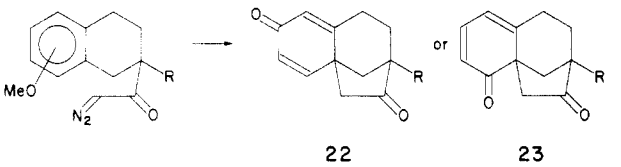
Scheme VII



Scheme VIII



Scheme IX



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Further approaches have been reviewed by Fujita and Node.[4a]

Our own solution to this problem stemmed from a decision to use fluorenone **16**[25] (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 R^2 was sp^2 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

(16) (a) Bachi, M. D.; Epstein, J. W.; Herzberg-Minzly, Y.; Loewenthal, H. J. E. *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 obtained[22] by application of this methodology has been prepared independently and utilized in the second Harvard synthesis of GA_3, however.

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

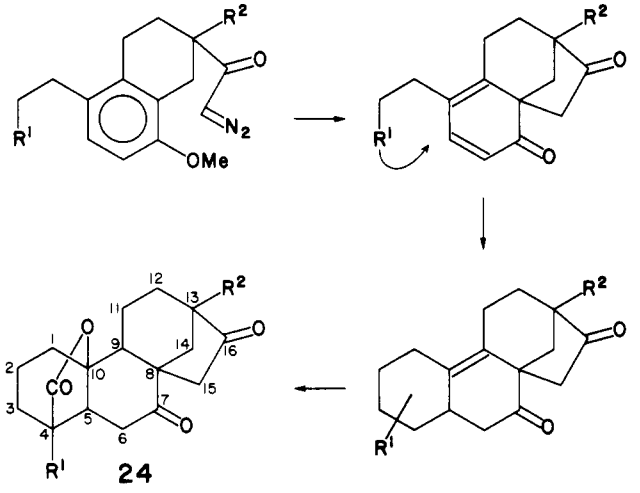
(25) Fried, J.; Abraham, N. A. *Tetrahedron Lett.* **1965**, 3505–3512.

(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.

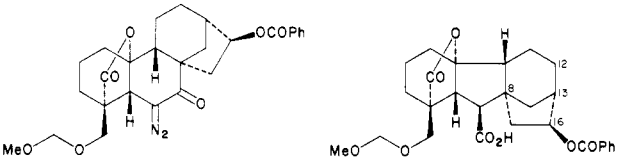
Scheme X



22 and 23 (Scheme IX, R = H, 70–95%; R = Me, 95%; R = $OCOCCl_3$, 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

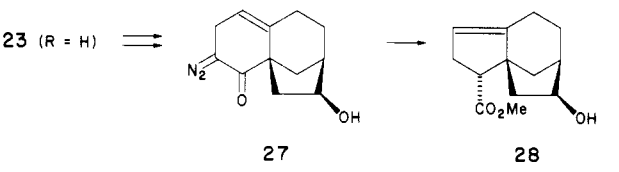
The strategy is outline in Scheme X and is critically dependent on the generalized Michael reaction.[30] The parallel may be drawn with the retrosynthetic sequence in Scheme IIIc. The most successful of the approaches along these lines led to the gibberellin-like molecule **26**[31] that was formed from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



25 26

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

Scheme XI

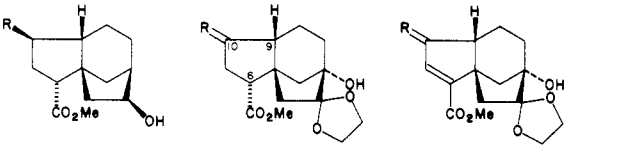


27 28

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** (R^1 = CO_2Me, R^2 = OCH_2OMe),[32] this route for gibberellin synthesis was deferred in favor of the more productive approaches which follow.

Michael–Aldol Approach[33]

The possibility of utilizing dienones **22** or **23** as intermediates in a gibberellin synthesis predicated in Scheme IIId was first demonstrated[34] 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 6α-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]



29 R = H
30 R = OH

31 R = β-OH, α-H
32 R = O

33 R = O
34 R = β-$CH_2CH{=}CH_2$, α-OH

The configuration of the hydroboration product **30** was then deduced from ^{13}C 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 6β-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

(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.

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

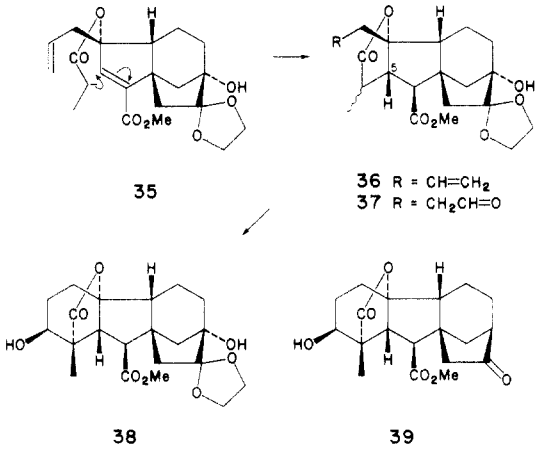
(33) Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626–6628.

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

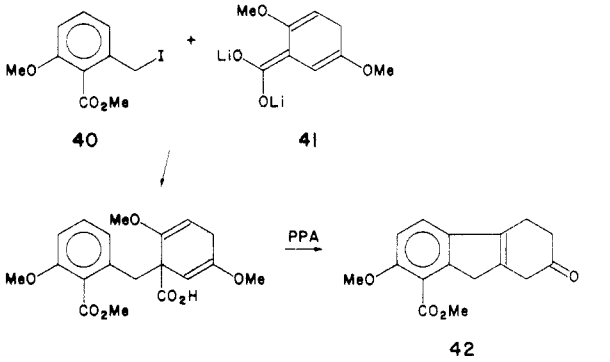
(35) Mander, L. N.; Prager, R. H.; Turner, J. V. *Aust. J. Chem.* **1974**, *27*, 2645–2656. Cossey, A. L.; Mander, L. N.; Pyne, S. G. *Ibid.* **1979**, *32*, 817–822.

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

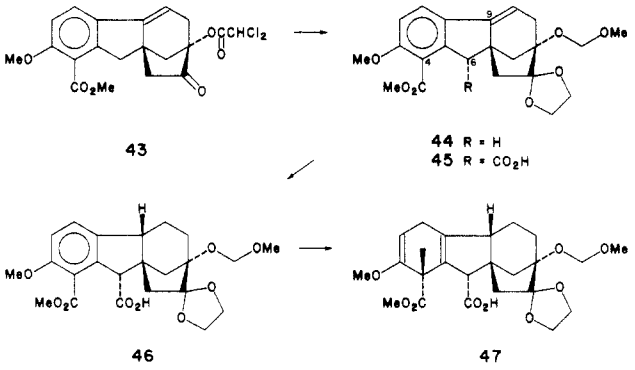
Scheme XII



Scheme XIII



Scheme XIV



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 C_{19} gibberellins had been overcome. The methodology for the transformation of **33** into **38** is also compatible with the preparation off 13-deoxygibberellins, e.g., GA_4 (**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 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.

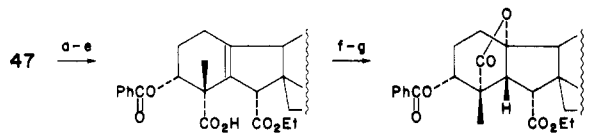
(37) Cossey, A. L.; Lombardo, L.; Mander, L. N. *Tetrahedron Lett.* **1980**, *21*, 4383–4386.

(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: [a]$Hg(II)(NO_3)_2$, MeCN—H_2O; [b]$NaBH_4$; [c]PhCOCl, Py; [d]CH_3CHN_2; [e]*n*-PrSLi, HMPA; [f]$KHCO_3$, KBr_3; [g]$Cr(II)(OAc)_2$, *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 6α-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 GA_3 (**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 4α,10α-carbolactone was in place, the thermodynamically preferred configuration of the ethoxycarbonyl group was 6β[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 A_1 and A_4

With reliable and relatively direct routes to intermediates **38**, 3-epi-**38**, and **39** established, access to the majority of C_{19} gibberellins appeared to be assured. Gibberellin A_4 (**2**) was readily obtained from **39** through Witting methylenation of the derived benzoate [masking of the 3β-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 instantaneous[43]—the substrate is simply titrated with the yellow preformed ylide.

The preparation of GA_1 (**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 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 3α 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 GA_3 (**1**), for which it became necessary to examine the nature of the isomerization.

The synthesis of GA_1 (**3**) was completed by removal of the masking groups, and we were interested to find, as expected, that both the synthetic racemic samples of GA_1 and GA_4 were each half as potent as the respective natural compounds in the barley endosperm bioassay.[45]

Synthesis of Gibberellic Acid (GA_3)

Although GA_3 (**1**) differs from GA_1(**3**) by only the Δ^1 olefinic bond, the increased lability of GA_3, 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 4α-carboxylate group as an internal nucleophile, it was possible to achieve chemoselectivity and the stereochemically controlled introduction of the 3β-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** → **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 GA_1 synthesis must lead ultimately to GA_3.

With the knowledge that hydride reduction of 3-oxogibberellins normally affords mainly 3α-hydroxy derivatives,[47] we elected to proceed via the Δ^2 olefin **48**, which was duly prepared from either **38** or its 3α-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 (±)-**48** 13-chloroformate and (−)-α-phenylethylamine.[14]

(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.

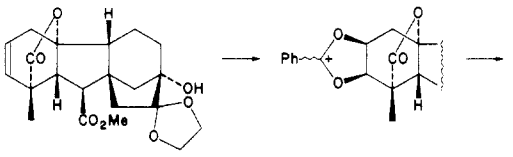
(44) Cf.: Mossetig, E.; Beglinger, U.; Dolder, F.; Lichti, H.; Quitt, P.; Waters, J. A. *J. Am. Chem. Soc.* **1963**, *85*, 2305–2309.

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

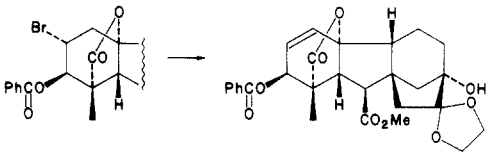
(46) Corey, E. J.; Brennan, T. M.; Carney, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 7316–7317.

(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 3β epimers, however: Bell, R. A.; Turner, J. V. *Tetrahedron Lett.* **1981**, *22*, 4871–4872.

Scheme XVI



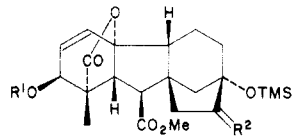
48 49



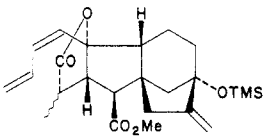
50 51

Stereoelectronically controlled nucleophilic cleavage of a 2β,3β-epoxide could be expected to establish the desired C(3) chirality and to introduce a 2α-substituent which could then be eliminated selectively by an E2 process to introduce the Δ^1 olefinic bond. Unfortunately, epoxidation of **48** was not only very difficult but also gave the 2α,3α isomer as the major product, in spite of lower steric hindrance on the β face of the A ring.[48] An operationally equivalent transformation was achieved, however, by preparation of the 2β,3β-diol and treatment of the derived benzylidene acetal with *N*-bromosuccinimide to furnish bromo benzoate **50** via the presumed 1,3-dioxolan-2-ylium cation **49**;[49] elimination of bromide then furnished allylic benzoate **51** (Scheme XVI).

Hydrolysis of the acetal function was achieved smoothly as expected, but when the silylated ketone **52**



52 R^1 = PhCO, R^2 = O
53 R^1 = $SiMe_3$, R^2 = O
54 R^1 = $SiMe_3$, R^2 = CH_2



55

was treated with Wittig reagent the seco diene mixture **55** was formed—presumably through benzoate cleavage, retro-aldol reaction, and trapping of the transient aldehyde by ylide. Although this problem was resolved subsequently by more careful attention to the reaction conditions, our initial response was to prepare the disilyl ether **53** and submit this to the Wittig methylenation. Epimerization at C(3), which had been a minor irritant with the saturated analogue, now became unavoidable, and a 1:1 mixture of **54** with its 3α epimer was obtained. Apparently, cleavage of the 3-trimethylsilyl group by base had triggered a chain reaction in which the resulting 3-alkoxide, which can undergo inversion at C(3) (cf. Scheme I), may attack a further gibberellin molecule with transfer of the silyl group and liberation of further 3-alkoxide. The solution to the problem was to add (chloroethoxy)trimethylsilane ($(CH_3)_3SiOCH_2CH_2Cl$), which reacts only slowly with the ylide but silylates any alkoxide before it can rearrange.[50] It was also of interest to find that when this reagent was added to the Wittig reaction on benzoate **52**, silyl ether **54** was formed in excellent yield. Completion of the gibberellic acid (1) synthesis was now a formality and was achieved simply by hydrolysis of the silyl groups followed by thiolate-induced demethylation of the ester function.

Conclusion

Little remains to be pursued in the total synthesis of C_{19} gibberellins except the introduction of a (*Z*)-propenal side chain into intermediate **33** (cf. **15**) that would enable even more direct access to GA_3 (**1**); the ease with which **33** enolizes, however, imposes a severe restriction on the choice of possible reagents. Of rather more interest is the adaptation of the aldol–Michael strategy to the total synthesis of C_{20} gibberellins; this has been achieved very recently and will be reported elsewhere.

We believe that the sequences described above provide practical access to the C_{19} gibberellins through total synthesis for the first time. Moreover, the strategies, new methodology, and refinements of standard procedures should be of value to the synthesis of a wide range of complex natural products.

The completion of this study has only been possible through the very considerable conceptual and experimental contributions of my co-workers who are indicated in references, and to whom I gratefully record my considerable debt. I would like to note in particular the skills and ingenuity of Jim Hook and Rudolf Urech who developed the fluorene route, of Luciano Lombardo who singlehandedly established the complete sequence leading to gibberellin A_1, and of John Turner who completed the gibberellic acid synthesis.

(48) Cf.: Corey, E. J.; Noyori, R. *Tetrahedron Lett.* **1970**, 311–313.
(49) Pittman, C. U.; McManus, S. P.; Larson, J. W. *Chem. Rev.* **1974**, 357–438.
(50) Mander, L. N.; Turner, J. V. *Tetrahedron Lett.* **1981**, *22*, 4149–4152.