The first event in the diagenesis of proteins in fossils is likely the cleavage of labile peptide bonds,[14] i.e., those involving sterically unhindered residues, and hydroxy and acidic amino acid residues. After these initial cleavages, peptide decomposition should proceed largely by successive formation of diketopiperazines according to eq 1. The liberated diketopiperazines then undergo hydrolysis to dipeptides, which are in turn hydrolyzed to free amino acids. Rapid racemization occurs in the diketopiperazine intermediate.[3] The subsequent hydrolysis of the diketopiperazines into dipeptides and eventually free amino acids would thus yield the highly racemized low molecular weight peptides and free amino acids that are observed in calcareous fossils.[2,13,15]

In addition to the geochemical implications, the diketopiperazine hydrolysis mechanism for peptides may also have implications for the thermal processing of food proteins, where the rapid rate of racemization accompanying diketopiperazine formation could produce significant amounts of D-amino acids. Several diketopiperazines have been identified in aged and heated foods and in protein hydrolysates.[16] The presence of D-amino acids in foods has important nutritional consequences.[17]

**Acknowledgment.** This work was supported in part by a grant from the Alfred P. Sloan Foundation. We thank R. Doolittle for synthesizing the hexapeptide.

**Registry No.** Leu-Gly-Gly, 1187-50-4; Gly-Leu-Gly, 2576-67-2; Phe-Gly-Leu-Gly-Val-Gly, 85864-65-9; c-(-Leu-Gly-), 5845-67-0; c-(-Gly-Gly-), 106-57-0; c-(-Phe-Gly-), 10125-07-2; c-(-Val-Gly-), 16944-60-8.

(13) Wehmiller, J. F.; Hare, P. E. *Science (Washington, D.C.)* **1971**, *173*, 907. Bada, J. L.; Schroeder, R. A. *Earth Planet. Sci. Lett.* **1972**, *15*, 1. Schroeder, R. A.; Bada, J. L. *Earth-Sci. Rev.* **1976**, *12*, 347.
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(17) Masters, P. M.; Friedman, M. *Agr. Food Chem.* **1979**, *27*, 507.

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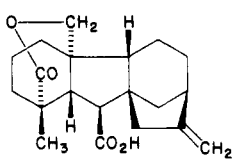
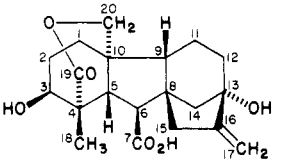
## A New Strategy for $C_{20}$ Gibberellin Synthesis: Total Synthesis of (±)-Gibberellin $A_{38}$ Methyl Ester[†,1]

*Summary:* The extension of the strategy used for $C_{19}$ gibberellin synthesis to include the $C_{20}$ gibberellins has been realized through elaboration of the common intermediate **7** to give aldehyde **10** and then a novel intramolecular conjugate addition of an anionic ester species via a six-membered transition state, **3** → **4**, followed by the intramolecular aldol cyclization, **5** → **6**.

*Sir:* The molecular basis for the biological activity of the gibberellin phytohormones has yet to be established, while many questions relating to their biosynthesis also remain unanswered.[3] Reasonably practical access to the gibberellins through total synthesis has recently been established[4] for the $C_{19}$ compounds, e.g., gibberellic acid, but only one of the simplest $C_{20}$ gibberellins, (±)-$GA_{15}$ (1), has



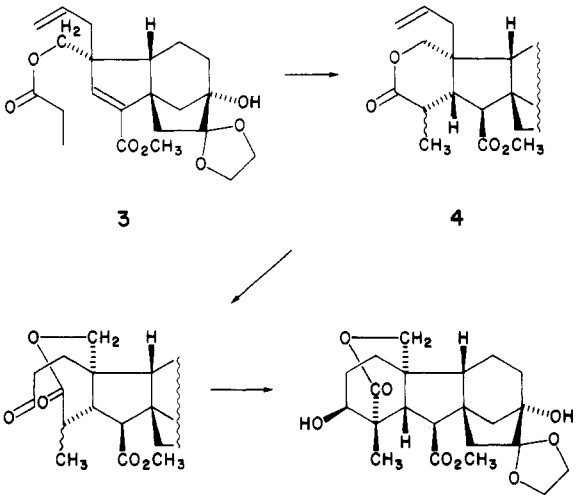
1



2

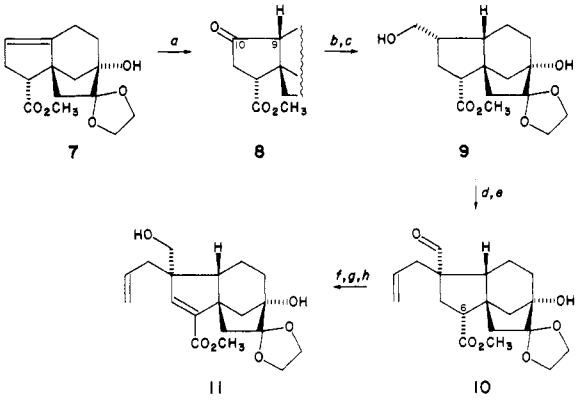
been prepared by total synthesis, and then from an arduous 45-step sequence.[5]

Chart I



3 4 5 6

Chart II



7 8 9 11 10

Reagents: [a] $BH_3$.DMS; $CrO_3$.2Py. [b] Zn, $TiCl_4$, $CH_2Br_2$. [c] Thexylborane; $H_2O_2$, $Na_2HPO_4$. [d] $CrO_3$.2Py. [e] LDA; $CH_2$=$CHCH_2Br$, HMPA. [f] KH, $Ph_2Se_2$. [g] $NaBH_4$. [h] $H_2O_2$, 2,6-lutidine.

(3) Hedden, P.; Phinney, B. O. *ACS Symp. Ser. No. 3*, **1979**, 19, 57.
(4) (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8034-8036. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Sinet, P.; Keck, G. E.; Gras, J. L. *Ibid.* **1978**, *100*, 8031-8034. (c) Lombardo, L.; Mander, L. N.; Turner, J. V. *Ibid.* **1980**, *102*, 6626-6628. (d) Cossey, A. L.; Lombardo, L.; Mander, L. N. *Tetrahedron Lett.* **1980**, *21*, 4383-4386. (e) Hook, J. M.; Mander, L. N., Urech, R. *J. Am. Chem. Soc.* **1980**, *102*, 6628-6629.
(5) (a) Nagata, W.; Wakabayashi, T.; Narisada, M.; Hayase, Y.; Kamate, S. *J. Am. Chem. Soc.* **1971**, *93*, 5740-5758. Totally synthetic routes via relays, but lacking optical resolutions, have been established for other $C_{20}$ gibberellins including (b) gibberellins $A_{15}$ and $A_{37}$ (~46 steps) [Fujita, E.; Node, M.; Hori, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 611-621] and (c) gibberellin $A_{12}$ (~35 steps) [Mori, K.; Takemoto, I.; Matsui, M. *Tetrahedron* **1976**, *32*, 1497-1502].

(1) This work was described at the Seventh National Convention of the R.A.C.I., Canberra, Australia, Aug 1982.
(2) Queen Elizabeth II Fellow.

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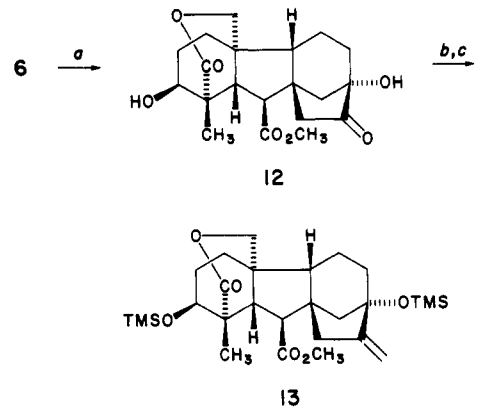
In this communication we report the development of a much more efficient approach to $C_{20}$ gibberellin total synthesis based on an adaptation of our earlier strategy[4c,d] for the preparation of the $C_{19}$ analogues. The success of this present study, which was focused on the construction of the challenging $GA_{38}$ structure **2**,[6] depended critically on the intramolecular Michael and aldol reactions (**3** → **4** and **5** → **6**, respectively) outlined in Chart I. The most difficult stage of the synthesis, however, proved to be the elaboration of the quaternary center at *pro*-C(10)[7] (Chart II).

Olefinic ester **7**[4c] was converted smoothly ($BH_3$·$Me_2S$; $CrO_3$·2py,[8] 0 °C, 70% yield)[9] into ketone **8**, mp 149–151 °C,[10] but homologation of the new carbonyl function proved to be difficult. All standard reagents examined either failed to add to **8** or led to loss of stereochemical integrity at *pro*-C(9) because of enolization processes. A modification[11] of the Oshima methylenation procedure (Zn, $TiCl_4$, $CH_2Br_2$), however, furnished a 90% yield of the methylene derivative from which the 10α-hydroxymethyl derivative **9**, mp 180–182 °C, was obtained by hydroboration (thexylborane,[12] ether, 0 °C, 2 h; $Na_2HPO_4$, $H_2O_2$, 35 °C, 3 h, 81% yield). Further oxidation ($CrO_3$·2py, $CH_2Cl_2$, 8 °C, 91% yield) to the aldehyde, mp 115–117 °C, followed by deprotonation (lithium diisopropylamide, THF, −90 °C, 5 min), and stereoselective alkylation on the more exposed β-face with allyl bromide (HMPA, 18 °C, 5 h, 85% yield[13]) provided the adduct **10** as a homogeneous gum. This stage of the synthesis was completed by means of selenenylation[14] of **10** (KH, THF, $Ph_2Se_2$, 20 °C, 1.5 h)[4c,d] at *pro*-C(6), followed by reduction of the formyl group ($NaBH_4$, EtOH, 0 °C, 15 min) and selenoxide elimination ($H_2O_2$, ether, 2,6-lutidine, 20 °C) to afford the olefinic ester **11**, mp 102–103 °C, in 85% overall yield.

The lactone and A-ring moieties were then assembled smoothly as outlined in Chart I, although the annulation processes were not as facile as in the $C_{19}$ series. Thus, ester **11** was converted to the propionate **3** [$(EtCO)_2O$, $Et_3N$, 4-(dimethylamino)pyridine, room temperature, 1 h, 95% yield], which was cyclized [KH, DMF, 2 h, −20 °C] under kinetic control,[15] and the resultant anion was quenched [$Et_3NH^+OAc^-$, −40 °C] to give an ~4:1 mixture of δ-lactones **4** (100% crude yield), major isomer[16] crystallized, mp 175–177 °C. The olefin side chain was oxidized [thexylborane,[12] ether, 0 °C; $Na_2HPO_4$, $H_2O_2$, 35 °C, 3 h; pyridinium dichromate,[17] $CH_2Cl_2$] to the aldehyde **5**, and aldol cyclization ($K_2CO_3$, MeOH, 25 °C, 12 h) completed the basic gibberellin skeleton in 90% crude overall yield from **4** to give a 1:4 mixture of the 3β-alcohol **6**, mp 203–206 °C, with its 3α-epimer, mp 245–246 °C. The alcohols were separated, and the undesired 3α-isomer converted into the 3β-epimer by oxidation (pyridinium dichromate, $CH_2Cl_2$, 25 °C) to the 3-ketone, mp 262–264 °C, followed by Meerwein–Pondorf reduction[18,5b] with aluminum isopropoxide to give **6** (61% yield)[19] plus its 3α-epimer (29%).

Chart III




Reagents: [a] HCl, THF. [b] $Me_3SiCl$, $^iPr_2NEt$. [c] $Ph_3P{=}CH_2$.

The completion of the gibberellin $A_{38}$ structure (Chart III) now simply required the addition of the C(17) methylene group, and, to this end, the acetal function was removed from **6** (3 M HCl, THF, 1:1, 25 °C, 6 h) to give ketone **12**, mp 221–224 °C, and the hydroxy functions were silylated ($Me_3SiCl$, *i*-$Pr_2NEt$) to prevent base-catalyzed isomerization[6] at C(3) or C(13); Wittig methylenation was then carried out on the disilyl ether, mp 187–189 °C, with "salt-free" reagent ($Ph_3P^+MeBr^-$, *n*-BuLi, PhH–hexane, 25 °C, 4 h). The product olefin **13** furnished a mass spectrum that was indistinguishable from that of an authentic sample[20] derived from (+)-$GA_{38}$, while removal of the silyl groups (4% HCl, THF (1:10), 25 °C, 20 min) yielded (±)-$GA_{38}$ methyl ester, mp 244–247 °C (81% overall yield from **6**), NMR and IR spectra of which, as well as TLC mobility, corresponded exactly with those reported[6,21] for the (+)-enantiomer.[22]

Thus, we have now demonstrated the general applicability of the Michael/aldol-based approach to the construction of both $C_{19}$ and $C_{20}$ gibberellins. Moreover, it is possible to utilize a common tricyclic intermediate for both series. It should now be possible to prepare efficiently almost all the sixty-odd known gibberellins by a single strategy.[23] There is also the prospect of utilizing aspects

(6) Hiraga, K.; Yokota, T.; Murofushi, N.; Takahashi, N. *Agr. Biol. Chem.* **1972**, *36*(2), 345–347.

(7) The atoms of all the structures presented have been numbered on the basis of the full gibberellin skeleton: Rowe, J. R., Ed. "The Common and Systematic Nomenclature of Cyclic Diterpenes", 3rd rev.; Forest Product Laboratory, U.S. Dept. of Agriculture: Wisconsin, 1968.

(8) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363–3366.

(9) This direct procedure was adapted from Gundu Rao et al. [Gundu Rao, C.; Kulparni, S. U.; Brown, H. C. *J. Organomet. Chem.* **1979**, *172*, C20–C22]; it was found that Collins reagent at 0 °C oxidized the intermediate borane to the carbonyl compound. However, a higher overall yield (82%) was obtained from the stepwise procedure via the carbinol.

(10) The structures of all new compounds are fully consistent with their NMR, IR, and mass spectral data. Satisfactory microanalyses (± <0.3%) were obtained for all crystalline compounds. All reactions where appropriate were carried out under a nitrogen atmosphere, and the yields reported are for analytically pure products.

(11) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293–4296.

(12) Zweifel, G.; Brown, H. C. *Org. React. (N.Y.)* **1963**, *13*, 1–54.

(13) The aldehyde was prepared more directly by oxidation [$CrO_3$·$py_2$, 0 °C] of the intermediate borane [$BH_3$·$Me_2S$], but somewhat lower yields of **10** were obtained from this material.

(14) Cf.: Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.

(15) Under these conditions the rate of cyclization via the six-membered transition state was much slower than the corresponding five-membered transition-state cyclization used to construct the $C_{19}$ gibberellins.[4c] This retardation can often lead to side reactions, see: MacDonald, T. L.; Mahalingam, S. *J. Am. Chem. Soc.* **1980**, *102*, 2113–2115. Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 369–379.

(16) The $^{13}C$ NMR spectrum of this compound ($\delta_{14,15}$ 47.1, 48.4) was consistent with the 6β stereochemistry; cf. footnote 29 in ref 4c.

(17) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.

(18) Bowen, D. H.; Cloke, C.; Harrison, D. M.; MacMillan, J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 83–88.

(19) The total isolated yield of **6** ater the recycling procedure becomes 37% from **4** and its 3α-epimer, 13%.

(20) We thank Dr. Jake MacMillan, University of Bristol, for providing us with mass spectral data.

(21) Koshimizu, K.; Fukui, H.; Inui, M.; Ogawa, Y.; Mitsui, T. *Tetrahedron Lett.* **1968**, *9*, 1143–1147.

(22) Attempts to convert the ester into the parent acid **2** have been hampered by the limited availability of material. Procedures that we and others[4,5b] have employed successfully on other gibberellin methyl esters have not been successful to date. We expect to resolve this problem and will report the details in the full paper describing this work.

of the present methodology for the preparation of $C_{20}$ gibberellins from the more readily available $C_{19}$ analogues.

**Acknowledgment.** We thank the Queen Elizabeth II Fellowship Committee for financial assistance.

**Registry No.** (±)-2 methyl ester, 86064-48-4; (±)-3, 86047-03-2; (±)-4 (isomer 1), 86047-04-3; (±)-4 (isomer 2), 86117-00-2; 5, 86047-05-4; (±)-6 (isomer 1), 86047-06-5; (±)-6 (isomer 2), 86047-07-6; (±)-7, 75801-07-9; (±)-8, 84693-19-6; (±)-9, 86047-08-7; (±)-10, 86047-09-8; (±)-11, 86047-10-1; (±)-12, 86047-11-2; (±)-12·2-TMS, 86047-12-3; (±)-13, 86047-13-4; allyl bromide, 106-95-6.

† Dedicated to the memory of the late Franz Sondheimer.

(23) $C_{19}$ gibberellins have been prepared in 22,[4d] 24,[4c] and 29[4c] steps from commercially available naphthalene derivatives, while the present synthesis extends over 27 steps.

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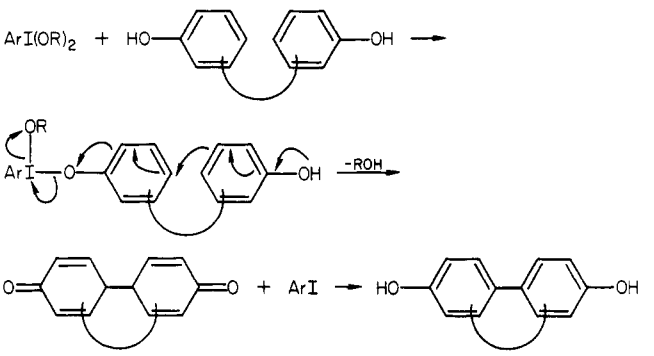
## Phenolic Oxidative Coupling with Hypervalent Iodine. A Synthesis of 6a-Epipretazettine

*Summary:* 6a-Epipretazettine was synthesized in seven steps from piperonal and synephrine. Intramolecular, monophenolic, oxidative coupling of a functionalized benzylic acetal, employing [bis(trifluoroacetoxy)iodo]-benzene as oxidant, gave a spirodienone in 13% yield. Subsequent deprotection of the secondary amine was followed by spontaneous closure to a tetracyclic pyrrolidine possessing an all-cis ring fusion. This substance was reduced with diisobutylaluminum hydride, and the resulting alcohol was transformed, via methanolysis of the corresponding mesylate, to *O*-methyl-6a-epipretazettine. Acidic hydrolysis of the latter yielded 6a-epipretazettine, identical with material previously obtained by Danishefsky.

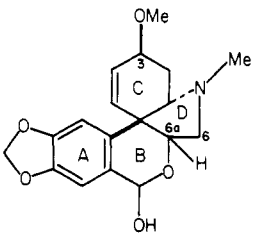
*Sir:* Intramolecular, oxidative coupling of phenols is a ubiquitous process in secondary metabolism.[1] Its central role in the biosynthesis of alkaloids of the Amaryllidaceae family[2] has prompted numerous attempts to simulate the natural pathway in vitro.[3] Conventional methodology for effecting oxidative, phenolic coupling has been based upon metallic reagents, many of which appear to function as homolytic (one-electron) oxidants. In a departure from this protocol, we have investigated hypervalent iodine(III) species[4] as potential reagents for phenolic coupling[5] via a heterolytic mechanism, as expressed in Scheme I.

The efficacy of this approach was recently demonstrated with a total synthesis of (−)-codeine.[6] We now report a synthesis of 6a-epipretazettine (**2**), in which the focal step

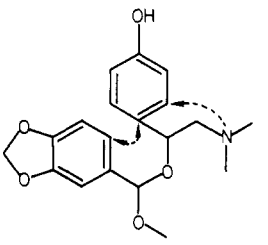
Scheme I



also entails an iodine(III)-mediated linkage of two aryl rings.



1, $\beta 6_aH$
2, $\alpha 6_aH$



3

Pretazettine (**7**) and its 6a epimer (**8**) were first described by Wildman,[7] who also prepared **1** from the related alkaloid haemanthidine.[8] Recently, Danishefsky, in a thwarted endeavor to achieve a de novo synthesis of **1**, acquired **2** by an elegant variation of a strategy previously employed for the structurally simpler mesembrine group.[9] By contrast, our plan envisaged construction of the spirocyclic portion of the tazettine skeleton via a biomimetic, oxidative coupling of a fully functionalized dibenzylic ether **3**, with closure of the pyrrolidine D ring[10] at a late stage.

To this end, piperonal (**4**) and *dl*-synephrine (**5**) (Scheme II) were condensed (MeOH, 25 °C, 10 h) to give the crystalline oxazolidine **6** in quantitative yield.[11] Treatment of **6** with 2,2,2-trichloroethyl chloroformate in MeOH–$CHCl_3$ (1:1, 25 °C, 12 h) afforded urethane **8** in 53% yield via the oxazolidinium salt **7**. After considerable experimentation, it was found that the labile acetal **8** could be converted to the oxidative coupling product **9** with [bis-(trifluoroacetoxy)iodo]benzene[12] (2 equiv, $CH_2Cl_2$, −10 °C, 0.5 h) in the presence of propylene oxide (10 equiv) in 13% yield.[13]

A parallel sequence employing methyl chloroformate led from **6** (via **10**) to the urethane **11** and then to the dienone **12** in analogous fashion. However, hydrolytic attempts to remove the urethane substituent in this case were unrewarding, while nucleophiles (e.g., trimethylsilyl iodide) effected an exceptionally clean conversion of **12** to the biphenyl derivative **13**, presumably via a retroaldol fragmentation originating from the derived hemiacetal.

In contrast, exposure of **9** (Scheme III) to zinc (THF with 10% 1 M $NH_4OAc$, 25 °C, 40 h)[14] resulted in smooth

(1) Dhingra, O. P. "Oxidation in Organic Chemistry"; Trahanovsky, W. S., Ed.; Academic Press: New York, 1982; Vol. 5-D, p 207.
(2) Barton, D. H. R.; Cohen, T. *Festschr. Prof. Dr. Arthur Stoll Siebzigsten Geburtstag 1957* **1957**, 129.
(3) Herbert, R. B. "Comprehensive Organic Chemistry"; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford England, 1979; Vol. 5, p 1076.
(4) Balaban, A. T. *Rev. Roum. Chim.* **1969**, *14*, 1281.
(5) Szantay, C.; Blaskó, G.; Barczai-Beke, M.; Pêchy, P.; Dörnyei, G. *Tetrahedron Lett.* **1980**, *21*, 3509.
(6) White, J. D.; Caravatti, G.; Kline, T. B.; Edstrom, E.; Rice, K. C.; Brossi, A. *Tetrahedron*, in press.
(7) Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1968**, *33*, 3749.
(8) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150.
(9) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591.
(10) This designation adheres to the system used originally by Wildman (ref 8).
(11) Satisfactory spectroscopic and analytical data were obtained for all new compounds.
(12) Spyroudis, S.; Varvoglis, A. *Synthesis* **1975**, 445.
(13) The major product from this reaction is piperonal, which is formed even under rigorously anhydrous conditions.

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