# Conversion of Gibberellin $A_7$ into Antheridic Acid, the Antheridium Inducing Factor from the Fern *Anemia phyllitidis*: A New Protocol for Controlled 1,2-Bond Shifts

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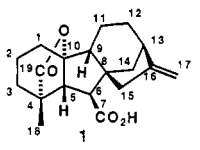
**Abstract:** A general new method for converting compounds based on the standard skeleton of $C_{19}$ gibberellins into fern antheridiogens derived from the antheridane type of structure has been established and illustrated by the transformation of gibberellin $A_7$ (**5**, $R^1$ = H) into antheridic acid (**2**). The key steps involved the formation of the 9,15-cyclogibbane derivative **22** by means of an intramolecular enolate alkylation process and the controlled fragmentation of the C(8)–C(15) bond in **23**. The synthesis of **2** in this way provides the first definitive evidence for the assigned absolute configuration. Attempts to initiate an equivalent 1,2-bond shift in epoxide **14** were unsuccessful, but the preparation of this compound by an intramolecular epoxidation process provided a useful insight into this kind of reaction.

Since the existence of an antheridium inducing factor in gametophytes of the bracken fern, *Pteridium aquilinum*, was first established by Döpp in 1950,[1] several similar substances, for which the term antheridiogen has been coined,[2] have been isolated from various other fern species.[3] Cross-testing of biological activities and chromatographic comparisons have established that several distinct compounds are involved,[4] but detailed structural information has been on the whole very limited. Takahashi et al. determined that the more abundant antheridiogen isolated from *Lygodium japonicum* was the methyl ester of gibberellin $A_9$ (**1**),[5]



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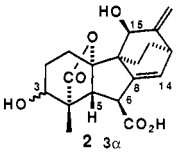
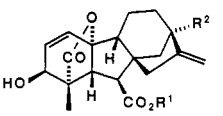


2 3α

3 3β

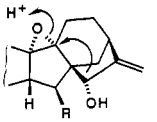
but the most exciting discovery has been the derivation of structure **2** for antheridic acid, the major antheridiogen from *Anemia phyllitidis*.[6] Spectroscopic and degradative studies carried out by Nakanishi et al. led initially to the conclusion that this compound was the 3β-epimer **3**,[7] but the epimeric structure **2** was shown subsequently to be correct, following the total syntheses of *rac*-**2** and the methyl ester of *rac*-**3** by Corey and Myers.[8] It now seems probable that other antheridiogens will resemble **2** or further variants of the parent gibberellin structure.

The likelihood of accumulating sufficient material to enable structural elucidations to be carried out on other members of this intriguing group of phytohormones appears to be remote. The antheridiogen from *P. aquilinum*, for example, occurs in concentrations of 1 μg per L of culture filtrate.[9] The close structural similarities between antheridic acid (**2**) and the fungal gibberellins, gibberellic acid (**4**, $R^1$ = H) and gibberellin $A_7$ (**5**, $R^1$ = H),



4 $R^2$=OH

5 $R^2$=H



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however, not only indicate a general biosynthetic relationship but also raise the prospect of achieving access to **2** and the unknown compounds through a synthetic conversion from readily available materials. Indeed, Nakanishi has speculated on the possibility that the biogenesis of **2** occurs by means of a 1,2-bond shift in a gibberellin derivative and that the process might be initiated by ring-opening of a 9α,10α-epoxide function in an intermediate with the generalized structure **6**.[7]

Although the possibility of achieving a biomimetic conversion appeared to be slight, we nevertheless embarked upon the preparation and a study of the rearrangement of epoxides **14** and **15**. When these endeavors proved to be unproductive, we developed an alternative strategy which effected the desired 1,2-bond shift in a stepwise and fully controlled manner, leading ultimately to the synthesis of antheridic acid (**2**) outlined in Scheme III. This new protocol not only provides the potential for general access to the antheridiogen phytohormones through synthesis but may also prove to be a useful model for similar interconversions in other families of natural products.

A survey of gibberellin degradation products which might serve as precursors to epoxide **14** indicated that gibberellenic acid (**7**) was the most readily accessible. It is formed in aqueous solutions of gibberellic acid (**4**, $R^1$ = H), either by storage at ambient temperatures for several months or by autoclaving at 120 °C.[10] Alternatively, it may be prepared more efficiently by heating **4** ($R^1$ = H) in hydrazine hydrate under reflux.[11] The reported yields are only modest (30–40%) and although we were unable to effect a significant improvement, the availability of **7** and its derivatives in such a direct manner enabled us to proceed quickly to address the more important aspects of the proposed conversion.

If **7** or a simple derivative was to be utilized for this purpose, it was necessary to achieve selective reduction of the 1,2-olefinic bond and then epoxidation of the 9,10-olefinic bond on the ste-

(1) Döpp, W. *Ber. Deut. Bot. Ges.* **1950**, *63*, 139–147.
(2) Näf, U.; Nakanishi, K.; Endo, M. *Bot. Rev.* **1975**, *41*, 315–359.
(3) (a) Pringle, R. B.; Näf, U.; Braun, A. C. *Nature (London)* **1960**, *186*, 1066–1067. (b) Näf, U.; Sullivan, J.; Cummins, M. *Science (Washington, D.C.)* **1969**, *163*, 1357–1358. (c) Näf, U. *Nature (London)* **1959**, *184*, 798–800. (d) Bürcky, K. *Z. Pflanzenphysiol.* **1977**, *84*, 167–172. (e) Zanno, P. R.; Endo, M.; Nakanishi, K.; Näf, U.; Stein, C. *Naturwissenschaften* **1972**, *59*, 512. (f) Näf, U. *Proc. Soc. Exptl. Biol. Med.* **1960**, *105*, 82–86. (g) Bürcky, K.; Gemmrich, A.; Schraudolf, H. *Experientia* **1978**, *34*, 718. (h) Schedlbauer, M. D.; Klekowski, E. J., Jr. *Bot. J. Linn. Soc.* **1972**, *65*, 399. (i) Nester, J. E.; Veysey, S.; Coolbaugh, R. C. *Planta*, in press.
(4) (a) Näf, U. *Plant Cell Physiol.* **1968**, *9*, 27–33. (b) Schedlbauer, M. D. *Plant Physiol.* **1976**, *57*, 666–669.
(5) Yamane, H.; Takahashi, N.; Takeno, K.; Furuya, M. *Planta* **1979**, *47*, 251–256.
(6) Nomenclature and numbering based on the *ent*-gibberellane skeleton: *The Common and Systematic Nomenclature of Cyclic Diterpenes*, 3rd revision; Rowe, J. R., Ed. Forest Product *Laboratory*, U.S. Department of Agriculture: Wisconsin, 1968.
(7) Nakanishi, K.; Endo, M.; Näf, U.; Johnson, L. F. *J. Am. Chem. Soc.* **1971**, *93*, 5579–5581.
(8) (a) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574–5576. (b) Corey, E. J.; Myers, A. G.; Takahashi, N.; Yamane, H.; Schraudolf, H. *Tetrahedron Lett.* **1986**, *27*, 5083–5084.
(9) Pringle, R. B. *Science (Washington, D.C.)* **1961**, *133*, 284.
(10) (a) Moffatt, J. S. *J. Chem. Soc.* **1960**, 3045–3049. (b) Pryce, R. J. *Phytochemistry* **1973**, *12*, 507–514.
(11) Grove, J. F.; Mulholland, T. P. C. *J. Chem. Soc.* **1960**, 3007–3022.

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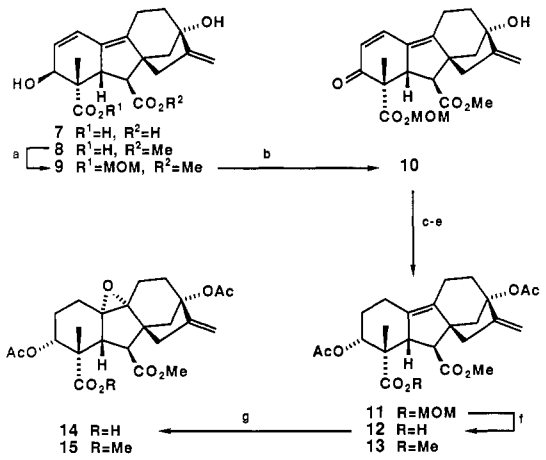
**Scheme I**[a]

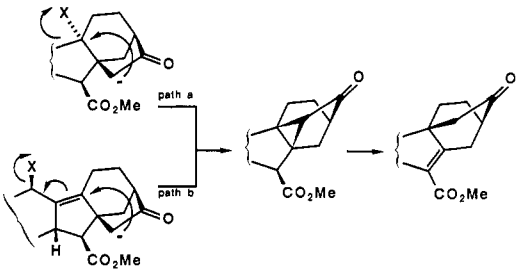



[a] Reagents: (a) *i*-$Pr_2NEt$, $ClCH_2OCH_3$; (b) pyridinium dichromate, 4Å molecular sieves; (c) L-Selectride, *t*-BuOH; (d) $LiAl(OtBu)_3H$; (e) $Ac_2O$, $Et_3N$, DMAP; (f) $Me_2BBr$; (g) $Im_2CO$; 90% $H_2O_2$.

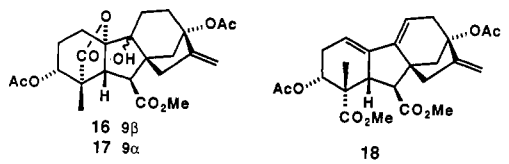
rically less accessible $\alpha$-face. We envisaged that the first task would be readily solved by conjugate addition of hydride to an appropriate 1-en-3-one,[12] but the introduction of the epoxide function was more problematical. In order to ensure subsequent flexibility, we chose to design a sequence which would allow differentiation between the 7- and 19-carboxy functions. Methyl gibberellate (**4**, $R^1$ = Me) was accordingly treated by the hydrazine procedure,[11] affording a 1:1 mixture of **7** with the 7-methyl ester **8**, and the latter compound converted into the diester **9**. The derived trienone **10** was subjected to sequential reduction with L-Selectride (lithium tri-*sec*-butyl borohydride)[13] followed by lithium tri-*tert*-butoxyaluminum hydride,[14] and the resulting 3$\alpha$,13-diol (obtained as an 8:1 mixture with the 3$\beta$-epimer) aceylated to afford diacetate **11**. Finally, the methoxymethyl function was removed by low-temperature treatment with dimethylboron bromide,[15] thereby liberating the desired carboxylic acid **12** (Scheme I).

Although excellent syn stereoselectivity has been obtained in the epoxidation of allylic and homoallylic alcohols, the prognosis for achieving directed epoxidation by a more remote polar group appeared to be poor.[16] We therefore elected to introduce a C(19) peroxycarbonyl function with a view to effecting a direct intramolecular process.[17] When acid **12** was treated with carbonyldiimidazole followed by 90% hydrogen peroxide, a single product was formed within a few minutes at 0 °C. The spectroscopic properties of this compound were consistent with a 9,10-epoxy structure, and given the rate of reaction, it could be assumed that the oxidation stage was indeed intramolecular[18,19]

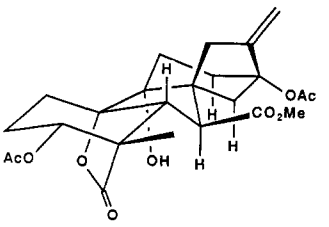
**Scheme II**




and that the desired 9$\alpha$,10$\alpha$-stereochemistry had been obtained. While this conclusion was ultimately confirmed by NMR studies on a derivative (vide infra), it was initially corroborated when the same epoxide was also formed stereoselectively and very much more slowly ($k_{rel}$ <$10^{-2}$) by reaction between **12** and *m*-chloroperoxybenzoic acid. Had reaction occurred on the $\beta$-face, then the strong expectation would have been that hydroxy lactone **16** would have formed instead.[20] It appears, therefore, that in contrast to earlier precedents,[16] the 19-carboxyl assists in the delivery of the reagent to the more hindered face of the olefinic bond. Consistent with this view was the observation that the epoxidation of dimethyl ester **13** afforded a 2:1 mixture of $\alpha$- and $\beta$-9,10-epoxides, respectively.[21]




The reactions of epoxides **14** and **15** with a range of Lewis acids were extremely sensitive to reaction parameters, but no evidence of the desired rearrangement products could be gleaned. Acid **14** could be cleanly converted to a hydroxy lactone by treatment with boron trifluoride etherate, while it appeared that ester **15** afforded mainly triene **18** with a range of catalysts. Extensive NMR experiments based on pyridine-induced chemical shifts (ASIS)[22] combined with 2D $^1H$–$^1H$ COSY[23] and $^1H$–$^{13}C$ COSY (HETCOR)[24] spectra unequivocally demonstrated that the hydroxy lactone should be assigned structure **17** (thereby confirming the 9$\alpha$,10$\alpha$-stereochemistry of the precursor epoxide). In particular, the chemical shifts of the signals arising from H(6), H(14$\alpha$), and H(12$\alpha$) were compatible with deshielding by a 9$\alpha$-hydroxyl (cf. structure I). Moreover, the unusually large magnitude[25] of the vicinal coupling constant $J_{5,6}$ of 12.15 Hz indicated a dihedral angle of ca. 180° between H(5) and H(6)—consistent with the conformation which would be imposed by the 9$\alpha$ stereochemistry on the B-ring.

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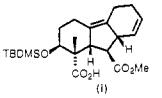
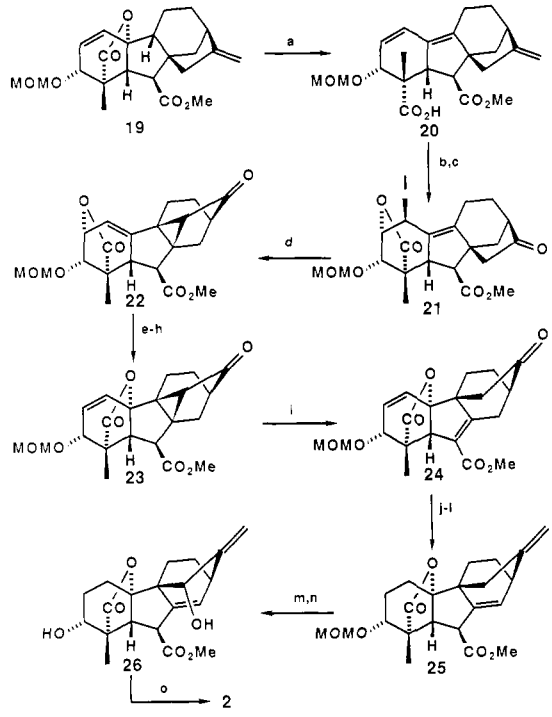
(12) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194–2200.
(13) Aldrich Chemical Co. cf. Lombardo, L.; Mander, L. N.; Turner, J. V. *Aust. J. Chem.* **1981**, *34*, 745–753.
(14) Stepwise reduction in this way was necessary to achieve the desired stereoselection. Complete reduction with L-Selectride afforded a 1:1 mixture of 3-epimers.
(15) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912–3920.
(16) Berti, G. *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley-Interscience: New York, 1973; Vol. 7.
(17) Corey, E. J.; Niwa, H.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 1586–1587.
(18) Although certain substituted peroxycarbamic acids have a high reactivity in epoxidation reactions, the carbonyldiimidazole/hydrogen peroxide combination is reported to be ineffective (Rebek, J.; Wolf, S. W.; Mossman, A. B. *J. Chem. Soc., Chem. Commun.* **1974**, 711.) Premixing of the hydrogen peroxide with carbonyl diimidazole followed by addition of **12** returned the substrate.
(19) A reaction geometry based on the currently accepted mechanism of the peroxycarboxylic acid induced epoxidations of olefinic bonds (Rebek, J. *Heterocycles*, **1981**, *15*, 517–545.) involving the Bartlett "butterfly" conformation (in which the peroxycarbonyl function is internally hydrogen bonded) is clearly not possible for acid **12**. However, it did appear that the requirement for linear overlap between the $\pi$ orbital (HOMO) of the olefinic bond and the $\sigma^*$ orbital (LUMO) of the O–O bond could be met.
(20) A similar argument has been advanced for the analogous substrate (i): Myers, A. G. Ph.D. Dissertation, Harvard University, **1985**, p 45.




(21) Cf. Pearson, A. J.; Hsu, S.-Y. *J. Org. Chem.* **1986**, *51*, 2505–2511.
(22) Hanson, J. R. *J. Chem. Soc.* **1965**, 5036–5040.
(23) Bax, A.; Freeman, R.; Morris, G. *J. Magn. Reson.* **1981**, *42*, 164–168.
(24) Bax, A. J. *Magn. Reson.* **1983**, *53*, 517–520.
(25) The standard value for $C_{19}$ gibberellins is 10.5 Hz.

**Scheme III**




[a] Reagents: (a) $NH_2NH_2$, DMF; (b) $KI_3$, $KHCO_3$; (c) $O_3$, Py, $Me_2S$; (d) KH; (e) LiOH; (f) $KI_3$; (g) $(TFA)_2O$, Py; (h) Zn, KI; (i) DBU; (j) $H_2$, $Rh-Al_2O_3$; (k) $Ph_3PCH_2$; (l) LiCA; $Et_3NH^+Ac^-$; (m) $SeO_2$, *t*-BuOOH; (n) $Me_2BBr$; (o) LiOH.

Clearly, the presence of the 17-methylene group in the D-ring would be expected to reduce the migratory aptitude of C(15), and the proximity of the C(19) substituent in epoxides **14** and **15** may conceivably have interfered with the desired rearrangements. It is also obvious that the choice of these particular compounds is more a consequence of their accessibility than of design. It may be, however, that there is simply an intrinsic preference for cleavage of the C(10)-epoxy bond[26] and that a search for more suitable candidates would have therefore been fruitless. We elected, accordingly, to embark upon a more secure approach which was inspired by some of our very earliest studies in the field of gibberellin synthesis.[27] The initial plan (Scheme II, path a) was to utilize an intramolecular alkylation route based on a 17-nor-16-ketone to afford a 9,15-cyclo derivative and then cleave the C(8)–C(15) bond by means of a retrograde Michael reaction initiated by enolization of the 7-ester function. It was obvious that a suitable substrate could be derived from hydroxy ester **17** or an analogue, but concerns over the difficulties which might be associated with the elaboration and utilization of a suitable 9$\alpha$ leaving group led us to refine the synthetic plan to one based on an intramolecular version of the $S_N2'$ alkylation process involving a $\Delta^9$,1$\beta$-intermediate (path b). The latter variant was especially attractive in view of the possibility of harnessing the 19-carboxy group to assist in the introduction of the 1$\beta$-substituent. The strategy was ultimately translated into the preparation of antheridic acid (**2**) from the 3-*epi*-gibberellin $A_7$ derivative **19** as outlined in Scheme III.

Gibberellin $A_7$ (**5**, $R^1$ = H) is not as readily accessible as gibberellic acid (**5**, $R^1$ = OH) but is clearly a more suitable starting material. It is obtained commercially from fermentation of *Gibberella fujkuroi* also but as a mixture which can only be resolved by HPLC.[28] However, methylation, oxidation to the 3-oxo derivatives, and reduction by sodium borohydride afforded the 3$\alpha$-epimers, which could be separated by conventional chromatography. The methyl ester of 3-*epi*-gibberellin $A_7$[29] obtained in this manner was protected as the 3-methoxymethyl ether **19** and subjected to hydrazine hydrate treatment with a view to obtaining an analogous derivative to methyl gibberellenate (**8**). The desired ester **20** was obtained, but in modest yield—as a consequence yet again of concomitant ester demethylation to the dicarboxylic acid. Fortunately, both compounds could be utilized: as we had anticipated at the planning stage, reaction of the half ester **20** with $KI_3/K_2CO_3$ afforded the 1$\beta$-iodo-19,2-lactone, and the same compound could be obtained from the corresponding dicarboxylic acid following esterification (diazomethane), albeit in lower yield. Selective ozonolysis[30] of the 16,17-olefinic bond to afford ketone **21** was achieved without difficulty, and alkylation was smoothly effected with potassium hydride.[31] The structure of the product was confirmed as **22** from consideration of NMR spectra which, inter alia, displayed a one proton singlet resonance at $\delta$ 2.24 and a doublet $^{13}C$ resonance at $\delta$ 36.99 ($J_{CH}$ = 180 Hz) associated with the cyclopropyl methine group. The 19,10-lactone function was then reassembled by means of a sequence based on the procedure utilized by Corey et al.[32] in the last stage of their synthesis of gibberellic acid. Thus, hydrolysis, iodolactonization, trifluoroacetylation, and then reductive elimination afforded the isomeric lactone **23**.

The desired fragmentation of the C(8)–C(15) bond was carried out by warming with DBU to afford **24**,[33] which was selectively hydrogenated in the A-ring, and the 17-methylene group was then restored by a salt-free Wittig process.[34] The $\alpha,\beta$-unsaturated ester function could be deconjugated by enolization followed by an acidic quench, although this treatment returned predominantly the conjugated isomer. Nevertheless, the diene ester **25** was accumulated in acceptable yield after three cycles. The 6$\beta$-configuration was apparent from the vicinal coupling constant $J_{5,6}$ of 9.75 Hz which was consistent with the value of 9.3 Hz calculated by the MODEL program[35] and distinct from the magnitude (6.8 Hz) estimated for the 6$\alpha$-epimer. Although the $\beta$-face of the dienolate appeared to be more open, better orbital overlap was expected to be maintained in the transition state based on protonation along the axial (6$\alpha$) vector.

Hydroxylation at C(15) was carried out with almost complete stereoselectivity by treatment with selenium dioxide/*tert*-butyl hydroperoxide.[36] This time, it was predicted that the approach of the reagent would be controlled by steric factors and that the removal of steric interactions as a consequence of the $sp^2$ centers in the C-ring should favor formation of the desired 15$\beta$-epimer. This outcome was confirmed when removal of the methoxymethyl masking function revealed a product whose mass spectrum was indistinguishable from one obtained for methyl antheridate (**26**) and whose $^1H$ NMR spectrum corresponded peak for peak with that of the racemate.[37] Antheridic acid (**2**), itself, was obtained after a brief hydrolysis and shown to be identical with natural

(26) Kirk, D. N.; Hartshorn, M. P. *Reaction Mechanisms in Organic Chemistry, Steroid Reaction Mechanisms*; Elsevier: Amsterdam, 1968; Vol. 7, pp 353–370.

(27) Beames, D. J.; Halleday, J. A.; Mander, L. N. *Aust. J. Chem.* **1972**, *25*, 137–147.

(28) We gratefully acknowledge the generosity of Abbott Laboratories in providing the gibberellins utilized in this study.

(29) Beale, M. H.; Gaskin, P.; Kirkwood, P. S.; MacMillan, J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 885–891.

(30) Slomp, G.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915–921.

(31) This reaction did not proceed with some batches of potassium hydride. The material used successfully was obtained from Fluka Chemical Corporation. Cf. MacDonald, T. L.; Natalie, K. J. *J. Org. Chem.* **1986**, *51*, 1124–1126.

(32) Corey, E. J.; Brennan, T. M.; Carney, R. L. *J. Am. Chem. Soc.* **1971**, *53*, 7316–7317.

(33) It was possible to effect fragmentation of the C(8)–C(15) bond in **22** (i.e., prior to reassembling the 19,10-lactone function) but concomitant aromatization of the A ring could not be avoided.

(34) Kirkwood, J. S.; MacMillan, J.; Beale, M. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 699–706.

(35) We are pleased to acknowledge the provision of this computer program by Professor W. C. Still. Calculations were conducted on a Digital Equipment Corporation VAX-11/750 computer.

(36) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528. (b) Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2741–2746.

(37) We express our appreciation to Professor E. J. Corey and Dr. A. G. Myers for helpful discussions, the provision of a comprehensive set of $^1H$ NMR spectra, and a copy of A.G.M.'s Ph.D. dissertation.

material by TLC, bioassay, GCMS comparison of the silylated derivatives, and matching of $^1$H NMR spectra and ORD curves.[38] This last correlation also provides the first definitive evidence for the absolute configuration **2**, which had been in doubt, following the revision[8] of stereochemistry from 3$\beta$ to 3$\alpha$; i.e., if this center had been 3S as originally assigned,[7] then the amended structure should have been antipodal to **2** (and the gibberellins).

## Conclusion

With the present synthesis of **2** and the earlier one of *rac*-**2** there is now an excellent prospect of considerably improved access to the elusive group of antheridiogen phytohormones. The data base of spectroscopic information which has been thus established should allow the fragments of evidence which have been gathered on other members of the class[3] to be translated into tentative assignments of structure. These could then be confirmed by synthesis. The attempts to achieve migration of the C(8)–C(15) bond through the agency of the 9$\alpha$,10$\alpha$-epoxides were viewed from the start as speculative,[26] and although they were not directly productive, the intramolecular route employed in their formation provides a further view of the mechanism of this most basic of reactions.[19] Had the rearrangement succeeded, it could have been considered to furnish circumstantial evidence for the proposed biogenesis. We find the alternative possibility of an intermediate 9,15-cycloderivative to be more attractive, however. Indeed, current investigations in our laboratories and elsewhere indicate that the structures of at least two further antheridiogens are based on such a skeleton.

## Experimental Section

Hydrogen peroxide of ca. 90% concentration was prepared according to a literature procedure.[39] Gibberellins $A_3$ and $A_4/A_7$ mixture (15%:72%) were generously provided by Abbott Laboraties, North Chicago, IL. Chromatography refers either to column chromatography at normal pressure using silica gel (Merck 9385) or to centrifugal chromatography using a Chromatotron Model 7924T with silica $PF_{254}$ (Merck 7749).

***ent*-3$\alpha$,13-Dihydroxy-20-norgibberella-1,9,16-triene-7,19-dioic Acid 7-Methyl Ester (8).** A solution of methyl gibberellate (**4**, $R^1$ = Me) (10 g, 27.8 mmol) in hydrazine monohydrate (25 mL, 0.52 mol) was heated under reflux at 120 °C for 25 min and then cooled in an ice bath. The mixture was poured into ice-water (150 mL), acidified to pH 3 with 6 N HCl, and extracted with EtOAc [the aqueous phase was treated with NaCl to facilitate extraction]. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield 4.51 g of crude product. Chromatography on silica ($CH_2Cl_2$/EtOAc/MeOH, 30:8:5) yielded the desired dihydroxy acid **8** (2.31 g, 23%) as an oil which could be crystallized from acetone as rectangular rods: mp 119–120 °C; $R_f$ 0.50 ($CH_2Cl_2$/EtOAc/MeOH, 17:8:5); $[\alpha]^{26}_D$ −60° (*c* 0.47, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 3600–2400 (m, br, OH), 2960 (m), 1730 (s), 1700 (s) cm$^{-1}$; UV (EtOH) $\lambda_{max}$ 254 nm ($\epsilon$ 19 200 dm$^3$ mol$^{-1}$ cm$^{-1}$); $^1$H NMR (300 MHz, acetone-$d_6$) 6.31 (1 H, d, $J_{1,2}$ = 9.76 Hz, H1), 5.91 (1 H, dd, $J_{2,1}$ = 9.76 Hz, $J_{2,3}$ = 5.47 Hz, H2), 5.12 (1 H, s, br, H17), 4.90 (1 H, s, br, H17), 4.33 (1 H, d, $J_{3,2}$ = 5.47 Hz, H3), 4.0 (1 H, s, br $CO_2H$), 3.73 (1 H, d, $J_{6,5}$ = 8.35 Hz, H6), 3.69 (3 H, s, $CO_2CH_3$), 3.58 (1 H, dd, $J_{5,6}$ = 8.35 Hz, $J_{5,11\beta}$ = 4.25 Hz, H5), 2.60 (1 H, dd, *J* = 16.0 Hz, *J* = 5.6 Hz), 2.27 (1 H, dt, *J* = 16.4 Hz, *J* = 2.8 Hz), 2.17 (1 H, dt, *J* = 2.19 Hz, *J* = 1.9 Hz), 2.13 (1 H, dd, *J* = 10.2 Hz, *J* = 2.4 Hz), 2.05 (2 H, m), 1.8–1.6 (4 H, m), 1.22 (3 H, s, H18); $^{13}$C NMR (50 MHz, acetone-$d_6$) 176.57 (C), 175.40 (C), 155.40 (C), 139.63 (C), 130.20 (CH), 127.95 (C), 124.04 (CH), 105.99 ($CH_2$), 79.16 (C), 69.67 (CH), 56.62 (C), 52.73 ($CH_2$), 51.71 ($CH_3$), 49.84 (2 × C, C and CH), 48.56 (CH), 40.38 ($CH_2$), 39.86 ($CH_2$), 21.05 ($CH_2$), 20.29 ($CH_3$); LRMS 360 ($M^+$, 3%), 297 ($M^+ - CH_3O_3$, 88), 238 ($M^+ - C_3H_6O_5$, 70), 237 ($M^+ - C_3H_7O_5$, 100); HRMS 360.1572, $C_{20}H_{24}O_6$ ($M^+$) requires 360.1573.

***ent*-3$\alpha$,13-Dihydroxy-20-norgibberella-1,9,16-triene-7,19-dioic Acid 19-Methoxymethyl Ester 7-Methyl Ester (9).** To a stirred solution of acid **8** (2.30 g, 6.4 mmol) in dry $CH_2Cl_2$ (25 mL) and Hünig's base (2.23 mL, 12.8 mmol) at −30 °C was added dropwise a solution of chloromethyl methyl ether (0.63 mL, 8.3 mmol) in dry $CH_2Cl_2$ (10 mL). After stirring for 20 min at this temperature, the excess chloromethyl methyl ether was destroyed by addition of saturated aqueous $NaHCO_3$ solution. The mixture was allowed to warm to room temperature and then extracted with EtOAc. The combined organic extracts were washed with 1 N HCl followed by brine and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica ($Et_2O$) yielded the desired MOM ether **9** (2.35 g, 91%) as a colorless oil: $R_f$ 0.35 ($Et_2O$); $[\alpha]^{25}_D$ −123° (*c* 5.53, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 3450 (m, br, OH), 1730 (2 × CO, s), 1670 (m), 1600 (w) cm$^{-1}$; UV $\lambda_{max}$ 254 nm ($\epsilon$ 20040 dm$^3$ mol$^{-1}$ cm$^{-1}$); $^1$H NMR (200 MHz, $CDCl_3$) 6.39 (1 H, d, $J_{1,2}$ = 9.77 Hz, H1), 5.99 (1 H, dd, $J_{2,1}$ = 9.77 Hz, $J_{2,3}$ = 5.86 Hz, H2), 5.20, 5.13, ABd (2 H, *J* = 6.1 Hz, $OCH_2OCH_3$), 5.17 (1 H, t, *J* = 2.4 Hz, H17), 4.99 (1 H, t, *J* = 2 Hz, H17′), 4.38 (1 H, d, $J_{3,2}$ = 5.86 Hz, H3), 3.73 (3 H, s, $CO_2CH_3$), 3.66 (1 H, d, $J_{6,5}$ = 8.79 Hz, H6), 3.52 (1 H, dd, $J_{5,6}$ = 8.79 Hz, $J_{5,11\beta}$ = 4.15 Hz, H5), 3.39 (3 H, s, $CH_2OCH_3$), 2.61 (1 H, dd, *J* = 16.4 Hz, *J* = 5.7 Hz), 2.28 (2 H, m), 2.18 (1 H, dd, *J* = 10.6 Hz, *J* = 2.6 Hz), 2.1 (1 H, m), 2.0–1.4 (5 H, m), 1.29 (3 H, s, H18); $^{13}$C NMR (50 MHz, $CDCl_3$) 174.85 (C), 173.71 (C), 154.14 (C), 140.04 (C), 128.33 (CH), 126.55 (C), 124.51 (CH), 106.11 ($CH_2$), 90.11 ($CH_2$), 78.99 (C), 69.55 (CH), 57.47 ($CH_3$), 56.07 (C), 51.98 ($CH_2$), 51.74 ($CH_3$), 49.64 (C), 49.09 (CH), 47.66 (CH), 39.10 ($CH_2$), 39.01 ($CH_2$), 20.65 ($CH_2$), 19.66 ($CH_3$); LRMS 404 ($M^+$, 9), 359 ($M^+ - CH_2OCH_3$, 31), 315 ($M^+ - CO_2CH_2OCH_3$, 15), 297 ($M^+ - C_3H_7O_4$, 85), 237 ($M^+ - C_5H_{11}O_6$, 100); HRMS 404.1833, $C_{22}H_{28}O_7$ ($M^+$) requires 404.1835.

***ent*-13-Hydroxy-3-oxo-20-norgibberella-1,9,16-triene-7,19-dioic Acid 19-Methoxymethyl Ester 7-Methyl Ester (10).** A solution of diol **9** (2.30 g, 5.7 mmol) in dry $CH_2Cl_2$ (40 mL) was stirred at room temperature with pyridinium dichromate (4.28 g, 11.4 mmol) and powdered 4Å molecular sieves (2 g) for 15 h. The mixture was diluted with $Et_2O$ (400 mL), filtered through Celite, and then washed with 1 N HCl followed by brine. After drying over $MgSO_4$, the solution was concentrated in vacuo and chromatographed on silica ($Et_2O$) to give the desired ketone **10** (1.921 g, 84%) as an oil: $R_f$ 0.39 ($Et_2O$); $[\alpha]^{25}_D$ −184° (*c* 1.09, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 3500 (w, br, OH), 2960 (m), 1735 (s), 1680 (s), 1660 (s) cm$^{-1}$; UV (EtOH) $\lambda_{max}$ 310 nm ($\epsilon$ 23 100 dm$^3$ mol$^{-1}$ cm$^{-1}$); $^1$H NMR (200 MHz, $CDCl_3$) 7.25 (1 H, d, $J_{1,2}$ = 10.05 Hz, H1), 6.04 (1 H, d, $J_{2,1}$ = 10.05 Hz, H2), 5.20, 5.10, ABd (2 H, *J* = 6.0 Hz, $OCH_2OCH_3$), 5.20 (1 H, s, br, H17), 5.02 (1 H, s, br, H17′), 3.74 (3 H, s, $CO_2CH_3$), 3.70 (1 H, dd, $J_{5,6}$ = 8.4 Hz, $J_{5,11\beta}$ = 4.6 Hz, H5), 3.50 (1 H, d, $J_{6,5}$ = 8.4 Hz, H6), 3.36 (3 H, s, $CH_2OCH_3$), 2.71 (1 H, dd, *J* = 16.2 Hz, *J* = 5.6 Hz), 2.5–2.1 (3 H, m), 2.24 (1 H, dd, *J* = 10.5 Hz, *J* = 2.0 Hz), 2.0–1.7 (3 H, m), 1.70 (1 H, s, br, OH), 1.35 (3 H, s, H18); $^{13}$C NMR (50 MHz, $CDCl_3$) 195.75 (C), 173.68 (C), 170.13 (C), 153.31 (C), 147.33 (C), 137.76 (CH), 126.68 (CH), 125.81 (C), 106.74 ($CH_2$), 90.67 ($CH_2$), 77.96 (C), 57.65 ($CH_3$), 57.06 ($CH_3$), 56.84 (C), 53.57 (CH), 51.48 (C), 51.33 ($CH_2$), 49.19 (CH), 38.81 ($CH_2$), 38.63 ($CH_2$), 21.18 ($CH_2$), 18.27 ($CH_3$); LRMS 402 ($M^+$, 20), 313 ($M^+ - CO_2CH_2OCH_3$, 100), 297 (16), 281 (22), 253 (52), 237 (23); HRMS 402.1679, $C_{22}H_{26}O_7$ ($M^+$) requires 402.1679.

***ent*-13-Hydroxy-3-oxo-20-norgibberella-9,16-diene-7,19-dioic Acid 19-Methoxymethyl Ester 7-Methyl Ester.** To a stirred solution of L-Selectride (3 mL, 3 mmol, 1 M/THF) in dry THF (3 mL) at −78 °C was added dropwise a solution of trienone **10** (0.40 g, 1 mmol) in dry THF (5 mL) and *t*-BuOH (0.2 mL). The mixture was stirred at −78 °C for 20 min and then quenched with saturated aqueous $NH_4Cl$ solution. After dilution with $Et_2O$, the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica ($Et_2O$/hexane, 3:1) yielded the desired ketone (0.273 g, 68%) as a colorless oil: $R_f$ 0.43 ($Et_2O$); $[\alpha]^{25}_D$ −113° (*c* 2.08, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 3500 (w, br, OH), 2960 (m), 1730 (3 × CO, s), 1660 (w) cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) 5.20, 5.16, ABd (2 H, *J* = 6.14 Hz, $OCH_2OCH_3$), 5.13 (1 H, s, br, H17), 4.95 (1 H, s, br, H17′), 3.70 (3 H, s, $CO_2CH_3$), 3.40 (3 H, s, $CH_2OCH_3$), 3.40 (1 H, H5, obscured), 3.31 (1 H, d, $J_{6,5}$ = 6.84 Hz, H6), 2.8–1.5 (12 H, m), 1.26 (3 H, s, H18), 0.93 (1 H, m); $^{13}$C NMR (50 MHz, $CDCl_3$) 207.11 (C), 174.15 (C), 170.26 (C), 153.94 (C), 137.41 (C), 125.24 (C), 105.73 ($CH_2$), 90.72 ($CH_2$), 78.87 (C), 60.62 (C), 57.67 ($CH_3$), 57.20 (CH), 55.80 (C), 52.27 ($CH_2$), 51.68 ($CH_3$), 49.76 (CH), 39.13 ($CH_2$), 38.98 ($CH_2$), 37.29 ($CH_2$), 22.40 ($CH_2$), 20.53 ($CH_2$), 18.34 ($CH_3$); LRMS 404 ($M^+$, 3), 315 ($M^+ - CO_2CH_2OCH_3$, 100); HRMS 404.1837, $C_{22}H_{28}O_7$ ($M^+$) requires 404.1835.

***ent*-3$\beta$,13-Dihydroxy-20-norgibberella-9,16-diene-7,19-dioic Acid 19-Methoxymethyl Ester 7-Methyl Ester.** To a stirred solution of the previously prepared ketone (0.26 g, 0.64 mmol) in dry THF (10 mL) at 0 °C was added lithium tri-*tert*-butoxyaluminum hydride (0.213 g, 0.84 mmol). The cooling bath was removed, and the mixture was stirred for 10 min before quenching with saturated aqueous $NH_4Cl$ solution. The solution was diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica ($Et_2O$/hexane, 3:1

(38) The direct comparison, bioassays, and ORD measurements were conducted by Dr. Hisakazu Yamane and Kumiko Nohara in the Department of Agricultural Chemistry, University of Tokyo. We are most grateful for this assistance.

(39) Hurd, C. D.; Puterbaugh, M. P. *J. Am. Chem. Soc.* **1930**, *52*, 950–953.

then $Et_2O$) yielded the desired 3α-alcohol (0.211 g, 81%) as a colorless oil: $R_f$ 0.17 ($Et_2O$); $[\alpha]^{25}_D$ −109° (*c* 4.53, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 3500 (m, br, OH), 2940 (m), 1730 (2 × CO, s), 1660 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 5.34, 5.23, ABd (2 H, *J* = 6.1 Hz, $OCH_2OCH_3$), 5.14 (1 H, t, *J* = 2.5 Hz, H17), 4.96 (1 H, t, *J* = 2 Hz, H17′), 3.73 (3 H, s, $CO_2CH_3$), 3.55 (1 H, dd, $J_{3,2}$ = 12 Hz, $J_{3,2}$ = 4 Hz, H3), 3.48 (3 H, s, $CH_2OCH_3$), 3.10 (1 H, d, $J_{6,5}$ = 6.8 Hz, H6), 3.06 (1 H, dd, $J_{5,6}$ = 6.8 Hz, $J_{5,11\beta}$ = 3.5 Hz, H5), 2.50 (1 H, dd, *J* = 14.8 Hz, *J* = 5.6 Hz), 2.43 (1 H, dd, *J* = 15.78 Hz, *J* = 5.6 Hz), 2.26 (1 H, dt, *J* = 16.6 Hz, *J* = 2.7 Hz), 2.19 (1 H, dq, *J* = 16.4 Hz, *J* = 2.2 Hz), 2.04 (1 H, dd, *J* = 10.15 Hz, *J* = 2.7 Hz), 2.06–1.86 (4 H, m), 1.86–1.62 (5 H, m), 1.32 (3 H, s, H18); $^{13}C$ NMR (50 MHz, $CDCl_3$) 174.90 (C), 173.18 (C), 154.46 (C), 134.84 (C), 127.80 (C), 105.50 ($CH_2$), 90.55 ($CH_2$), 79.22 (C), 76.80 (CH), 57.79 ($CH_3$), 56.65 (CH), 55.65 (C), 53.29 (C), 52.44 ($CH_2$), 51.71 ($CH_3$), 50.57 (CH), 39.42 ($CH_2$), 39.30 ($CH_2$), 30.34 ($CH_2$), 22.72 ($CH_2$), 21.72 ($CH_3$), 20.56 ($CH_2$); LRMS 406 ($M^+$, 3), 388 ($M^+ - H_2O$, 40), 374 ($M^+ - CH_3OH$, 4), 361 ($M^+ - CH_2OCH_3$, 17), 356 ($M^+ - H_2O - CH_3OH$, 28), 343 ($M^+ - H_2O - CH_2OCH_3$, 38), 329 ($M^+ - H_2O - CO_2CH_3$, 100), 312 (58), 299 (73), 283 (71); HRMS 406.1992, $C_{22}H_{30}O_7$ ($M^+$) requires 406.1992. In addition, 23 mg (9%) of the corresponding 3β-isomer was obtained: $R_f$ 0.32 ($Et_2O$); $^1H$ NMR (300 MHz, $CDCl_3$) 5.22, 5.18, ABd (2 H, *J* = 6.15 Hz, $OCH_2OCH_3$), 5.12 (1 H, s, br, H17), 4.94 (1 H, s, br, H17′), 4.11 (1 H, s, br, H3), 3.70 (3 H, s, $CO_2CH_3$), 3.43 (3 H, s, $CH_2OCH_3$), 3.37 (1 H, dd, $J_{5,6}$ = 7.47 Hz, $J_{5,11\beta}$ = 3.9 Hz, H5), 3.31 (1 H, d, $J_{6,5}$ = 7.47 Hz, H6), 2.42 (1 H, dd, *J* = 15.5 Hz, *J* = 5.95 Hz), 2.05 (1 H, dd, *J* = 10.0 Hz, *J* = 2.4 Hz), 2.3–1.5 (12 H, m), 1.24 (3 H, s, H18); $^{13}C$ NMR (75 MHz, $CDCl_3$) 175.46, 173.75, 154.86, 133.49, 127.85, 105.32, 90.12, 79.47, 72.25, 57.62, 55.20, 52.18, 51.92, 51.58, 50.58, 50.05, 39.60, 39.20, 28.75, 20.95, 20.56, 18.67.

***ent*-3β,13-Diacetoxy-20-norgibberella-9,16-diene-7,19-dioic Acid 19-Methoxymethyl Ester 7-Methyl Ester (11).** A solution of the previously prepared diol (0.20 g, 0.5 mmol) in dry $CH_2Cl_2$ (10 mL) and triethylamine (0.5 mL) was treated with acetic anhydride (0.5 mL) and (dimethylamino)pyridine (10 mg), and the mixture was stirred at 4 °C for 72 h. The reaction was quenched with $H_2O$, and after stirring for ca. 10 min, was extracted with $CH_2Cl_2$ and washed with 1 N HCl followed by brine. The solution was dried over $MgSO_4$, concentrated in vacuo, and chromatographed on silica ($Et_2O$/hexane, 2:1) to give the desired diacetate **11** (0.20 g, 83%) as a colorless oil: $R_f$ 0.78 ($Et_2O$); $[\alpha]^{25}_D$ −25° (*c* 1.56, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 2950 (m), 1730 (4 × CO, s), 1660 (w) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) 5.34, 5.25, ABd (2 H, *J* = 6.0 Hz, $OCH_2OCH_3$), 5.03 (1 H, t, *J* = 2.9 Hz, H17), 4.98 (1 H, s, br, H17′), 4.86 (1 H, m, H3), 3.70 (3 H, s, $CO_2CH_3$), 3.48 (3 H, s, $CH_2OCH_3$), 3.13 (1 H, m, H5), 2.71 (1 H, d, $J_{6,5}$ = 7.32 Hz, H6), 2.04 (3 H, s, $OCOCH_3$), 2.03 (3 H, s, $OCOCH_3$), 2.6–1.5 (12 H, m), 1.47 (3 H, s, H18); $^{13}C$ NMR (50 MHz, $CDCl_3$) 173.94 (C), 171.43 (C), 169.88 (C), 169.27 (C), 150.23 (C), 134.43 (C), 127.51 (C), 105.76 ($CH_2$), 90.46 ($CH_2$), 85.56 (C), 77.61 (CH), 57.44 ($CH_3$), 56.21 (CH), 56.07 (C), 51.54 (2 × C, $CH_3$ and C), 50.46 (CH), 47.98 ($CH_2$), 38.63 ($CH_2$), 36.41 ($CH_2$), 26.11 ($CH_2$), 21.90 ($CH_2$), 21.73 ($CH_3$), 21.52 ($CH_3$), 20.71 ($CH_3$), 20.09 ($CH_2$); LRMS 490 ($M^+$, 7), 458 ($M^+ - CH_3OH$, 26), 430 ($M^+ - CH_3CO_2H$, 100), 445 ($M^+ - CH_2OCH_3$, 6), 413 (43), 398 (87), 368 (57), 341 (38), 326 (59), 221 (97); HRMS 490.2205, $C_{26}H_{34}O_9$ ($M^+$) requires 490.2203.

***ent*-3β,13-Diacetoxy-20-norgibberella-9,16-diene-7,19-dioic Acid 7-Methyl Ester (12).** A solution of dimethylboron bromide (0.5 mL) in dry $CH_2Cl_2$ (3 mL) was added dropwise to a stirred solution of MOM ester **11** (0.20 g, 0.408 mmol) in dry $CH_2Cl_2$ (10 mL) at −78 °C until all of the starting material had been consumed according to TLC analysis. The reaction was quenched at −78 °C with THF followed by saturated aqueous $NH_4Cl$ solution, and the product was extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica ($Et_2O$) gave the desired carboxylic acid **12** (0.157 g, 86%) as an oil: $R_f$ 0.50 ($Et_2O$); $[\alpha]^{25}_D$ −21° (*c* 1.82, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 3600–2400 (m, br, $CO_2H$), 2950 (m), 1730 (4 × CO, s), 1660 (w) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) 5.05 (1 H, s, br, H17), 4.99 (1 H, s, br, H17′), 4.87 (1 H, m, H3), 3.71 (3 H, s, $CO_2CH_3$), 3.13 (1 H, m, H5), 2.79 (1 H, d, $J_{6,5}$ = 6.84 Hz, H6), 2.06 (3 H, s, $OCOCH_3$), 2.03 (3 H, s, $OCOCH_3$), 2.6–1.3 (11 H, m), 1.64 (1 H, m), 1.15 (3 H, s, H18); $^{13}C$ NMR (50 MHz, $CDCl_3$) 176.95 (C), 174.12 (C), 170.41 (C), 169.50 (C), 150.26 (C), 134.55 (C), 127.57 (C), 105.82 ($CH_2$),85.82 (C), 77.76 (CH), 56.15 (2 × C, CH and C), 51.68 ($CH_3$), 51.36 (C), 50.72 (CH), 48.30 ($CH_2$), 38.78 ($CH_2$), 36.65 ($CH_2$), 26.05 ($CH_2$), 21.96 ($CH_2$), 21.82 ($CH_3$), 21.64 ($CH_3$), 20.85 ($CH_3$), 20.18 ($CH_2$); LRMS 446 ($M^+$, 21), 428 ($M^+ - H_2O$, 17), 414 ($M^+ - CH_3OH$, 20), 386 ($M^+ - CH_3CO_2H$, 87), 368 ($M^+ - H_2O - CH_3CO_2H$, 18), 354 ($M^+ - CH_3OH - CH_3CO_2H$, 100), 340 (9), 326 (55), 266 (63); HRMS 446.1940, $C_{24}H_{30}O_8$ ($M^+$) requires 446.1941.

**Dimethyl *ent*-3β,13-Diacetoxy-9β,10β-epoxy-20-norgibberell-16-ene-7,19-dioate.** (a) To a stirred solution of acid **12** (0.02 g, 0.045 mmol) in dry $CH_2Cl_2$ (5 mL) was added *N,N′*-carbonyldiimidazole (0.087 g, 0.054 mmol). After having been stirred at room temperature for a period of 30 min, the solution was cooled to 0 °C in an ice/salt bath and treated with concentrated $H_2O_2$ (0.3 mL, ca. 90%). After 5 min at 0 °C, powdered $NaHSO_4$ (1.0 g) was added, and, after an additional 5 min, the solution was diluted with $H_2O$ and extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica gave the desired epoxy acid **14** (0.018 g, 85%) as an oil, which was characterized as the dimethyl ester **15** (obtained by treatment with diazomethane in $Et_2O$ and concentration in vacuo): $R_f$ 0.58 ($Et_2O$); IR ($CHCl_3$) $\nu_{max}$ 1735 (4 × CO, s), 1665 (w), 1250 (s) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) 5.08 (1 H, s, br, H17), 4.99 (1 H, s, br, H17′), 4.80 (1 H, dd, $J_{3,2}$ = 11.3 Hz, $J_{3,2}$ = 4.5 Hz, H3), 3.75 (3 H, s, $CO_2CH_3$), 3.70 (3 H, s, $CO_2CH_3$), 2.67 (1 H, d, *J* = 9.77 Hz), 2.06 (3 H, s, $OCOCH_3$), 2.05 (3 H, s, $OCOCH_3$), 2.9–1.5 (13 H, m), 1.12 (3 H, s, H18); $^{13}C$ NMR (50 MHz, $CDCl_3$) 173.12 (C), 172.45 (C), 170.44 (C), 169.33 (C), 149.21 (C), 106.37 ($CH_2$), 85.58 (C), 77.58 (CH), 70.05 (C), 68.00 (C), 51.92 ($CH_3$), 51.62 ($CH_3$), 50.57 (C), 50.19 (CH), 49.11 (C), 46.08 (CH), 41.90 ($CH_2$), 35.71 ($CH_2$), 34.89 ($CH_2$), 24.99 ($CH_2$), 24.23 ($CH_2$), 22.54 ($CH_3$), 21.99 ($CH_2$), 21.84 ($CH_3$), 20.99 ($CH_3$); LRMS 476 ($M^+$, 11), 475 ($M^+ - H$, 11), 458 ($M^+ - H_2O$, 1), 444 ($M^+ - CH_3OH$, 13), 417 ($M^+ - CO_2CH_3$, 40), 384 ($M^+ - CH_3OH - CH_3CO_2H$, 12), 357 ($M^+ - CH_3CO_2H - CO_2CH_3$, 94), 338 ($M^+ - H_2O - 2 \times CH_3CO_2H$, 16), 297 ($M^+ - 2 \times CH_3CO_2H - CO_2CH_3$, 100); HRMS 476.2047, $C_{25}H_{32}O_9$ ($M^+$) requires 476.2046.

(b) To a stirred solution of acid **12** (3 mg, 6.7 μmol) in dry $CH_2Cl_2$ (1.0 mL) was added *m*-chloroperoxybenzoic acid (MCPBA) (2.0 mg, 11.6 μmol), and the mixture was stirred at room temperature for 20 min. TLC analysis indicated that the reaction was proceeding very slowly, so further MCPBA (2.0 mg) was added, and the solution was heated under reflux for 50 min, after which time, TLC indicated that the reaction was complete. Powdered $NaHSO_3$ (0.10 g) was added, and after having been stirred for 5 min, the mixture was diluted with $CH_2Cl_2$, washed with 1 N HCl and brine, and dried over $MgSO_4$. Concentration and treatment with diazomethane in ether solution afforded a product which was spectroscopically and chromatographically identical with material prepared by procedure (a).

(c) A solution of acid **12** (3.0 mg, 6.7 μmol) in $Et_2O$ was treated with diazomethane at 0 °C, the solution was concentrated to dryness, and the residue was treated as in procedure (b). Spectroscopic and TLC analysis indicated a 2:1 mixture of α- and β-epoxides.

***ent*-3β,13-Diacetoxy-9β,10β-dihydroxy-20-norgibberell-16-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (17).** To a stirred solution of the epoxy acid **14** (0.017 g, 0.037 mmol) in dry $CH_2Cl_2$ (1 mL) at −30 °C was added boron trifluoride etherate (20 μL, 0.16 mmol), and the solution was allowed to warm slowly to 0 °C over 20 min. Saturated aqueous $NH_4Cl$ solution was added, and the product was extracted with $Et_2O$, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica ($Et_2O$/hexane, 3:1) gave hydroxy lactone **17** (0.0154 g, 91%) as a colorless solid, which could be recrystallized from $Et_2O$ as fine needles: mp 237–9 °C; $R_f$ 0.47 ($Et_2O$); $[\alpha]^{25}_D$ +36° (*c* 0.79, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 3450 (w, br, OH), 1790 (s), 1735 (3 × CO, s), 1670 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 5.02 (1 H, t, *J* = 2.5 Hz, H17), 4.97 (1 H, dd, $J_{3,2}$ = 9.9 Hz, $J_{3,2}$ = 6.4 Hz, H3), 4.91 (1 H, s, br, H17′), 3.70 (3 H, s, $CO_2CH_3$), 2.98 (1 H, d, $J_{6,5}$ = 12.15 Hz, H6), 2.94 (1 H, dd, $J_{14\alpha,14\beta}$ = 10.95 Hz, $J_{14\alpha,15\beta}$ = 2.74 Hz, H14α), 2.90 (1 H, s, br, OH), 2.74 (1 H, td, $J_{12\alpha(12\beta,11\beta)}$ = 11.5 Hz, $J_{12\alpha,11\alpha}$ = 6.3 Hz, H12α), 2.49 (1 H, d, $J_{5,6}$ = 12.15 Hz, H5), 2.42–2.30 (2 H, m, H15α and 1 H), 2.20–2.06 (2 H, m, H15β and 1 H), 2.09 (3 H, s, $OCOCH_3$), 2.05 (3 H, s, $OCOCH_3$), 2.02 (1 H, dd, $J_{14\beta,14\alpha}$ = 10.95 Hz, $J_{14\beta,12\beta}$ = 2.2 Hz, H14β), 1.76–1.52 (4 H, m), 1.45 (1 H, m), 1.07 (3 H, s, H18); $^1H$ NMR (300 MHz, $CDCl_3$/pyridine-$d_5$, 2:1) 5.08 (1 H, s, br, H17), 5.05 (1 H, m, H3), 5.04 (1 H, s, br, H17′), 4.4 (1 H, s, br, OH), 3.62 (3 H, s, $CO_2CH_3$), 3.24 (1 H, d, $J_{6,5}$ = 12.15 Hz, H6), 3.21 (1 H, d, br, $J_{14\alpha,14\beta}$ = 10.95 Hz, H14α), 2.96 (1 H, m, H12α), 2.54 (1 H, d, $J_{5,6}$ = 12.15 Hz, H5), 2.43 (1 H, d, br, $J_{15\alpha,15\beta}$ = 17.6 Hz, H15α), 2.29 (1 H, m), 2.20 (1 H, d, br, $J_{15\beta,15\alpha}$ = 17.6 Hz, H15β), 2.13 (1 H, d, br, $J_{14\beta,14\alpha}$ = 10.95 Hz, H14β), 2.02 (4 H, s, $OCOCH_3$ and 1 H), 2.01 (3 H, s, $OCOCH_3$), 1.8–1.55 (4 H, m), 1.50 (1 H, m), 1.12 (3 H, s, H18); $^{13}C$ NMR (75 MHz, $CDCl_3$) 174.27 (C), 171.41 (C), 170.31 (C), 169.45 (C), 147.89 (C, C-16), 105.01 ($CH_2$, C-17), 88.76 (C, C-10), 85.62 (C, C-13), 78.52 (C, C-9), 74.01 (CH, C-3), 57.19 (C, C-4), 56.84 (CH, C-5), 52.21 ($CH_3$), 50.83 (C, C-8), 45.69 (CH, C-6), 37.25 ($CH_2$, C-14), 34.81 ($CH_2$, C-15), 33.05 ($CH_2$, C-12), 29.98 ($CH_2$), 28.34 ($CH_2$), 26.43 ($CH_2$), 22.00 ($CH_3$), 20.85 ($CH_3$), 12.56 ($CH_3$); LRMS 444 ($M^+ - H_2O$, 3); 420 (41), 342 ($M^+ - CH_3CO_2 - CO_2 - OH$, 79), 91 (100); HRMS 444.1783, $C_{24}H_{28}O_8$ ($M^+ - H_2O$) requires 444.1784.

**Dimethyl *ent*-3β,13-Diacetoxy-20-norgibberella-1(10),9,16-triene-7,19-dioate (18).** To a stirred solution of epoxide **15** (0.015 g, 0.032 mmol) in dry $CH_2Cl_2$ (3 mL) was added ca. 1.0 equiv of a Lewis acid ($BF_3$·$Et_2O$, $SnCl_4$, $Me_2BBr$, or *t*-$BuMe_2SiOTf$) at 0 °C. The stirred mixture was allowed to warm to room temperature, quenched with $H_2O$ when TLC analysis indicated the reaction was complete (e.g., $BF_3$·$Et_2O$ ca. 10 min), and then extracted with $CH_2Cl_2$. In each case a single product was indicated by TLC analysis. $^1H$ NMR spectroscopy showed this to be the diene **18**: UV $\lambda_{max}$ 265 nm ($\epsilon$ 12 100 $dm^3$ $mol^{-1}$ $cm^{-1}$); $^1H$ NMR (200 MHz, $CDCl_3$) 5.91 (1 H, m, H11), 5.73 (1 H, m, H1), 5.13–5.0 (3 H, m), 3.74 (3 H, s, $CO_2CH_3$), 3.68 (3 H, s, $CO_2CH_3$), 3.10 (1 H, m, H5), 2.77 (1 H, d, $J_{6,5}$ = 11.72 Hz, H6), 2.08 (3 H, s, $OCOCH_3$), 2.06 (3 H, s, $CO_2CH_3$), 2.65–1.4 (8 H, m), 1.22 (3 H, s, H18).

***ent*-3β-(Methoxymethoxy)-20-norgibberella-1,9,16-triene-7,19-dioic Acid 7-Methyl Ester (20).** To a stirred solution of 3-*epi*-gibberellin $A_7$ methyl ester (5.90 g, 17.2 mmol) in dry $CH_2Cl_2$ (250 mL) and Hünig's base (14.7 mL, 85 mmol) at 0 °C was added dropwise a solution of chloromethyl methyl ether (6.7 mL, 85 mmol) in dry $CH_2Cl_2$ (20 mL). (Dimethylamino)pyridine (0.1 g, 0.8 mmol) was added, and the mixture was stirred at room temperature for 15 h. The excess chloromethyl methyl ether was destroyed by treatment with saturated aqueous $NaHCO_3$ solution, and the product was extracted with $CH_2Cl_2$, washed with brine, and dried over $MgSO_4$. Concentration in vacuo gave 3-*epi*-gibberellin $A_7$ MOM ether methyl ester **19** (6.1 g, 92%) as an oil, which was used without further purification. A stirred solution of MOM ether **19** (6.1 g, 15.72 mmol) in DMF (15 mL) and hydrazine monohydrate (15 mL) was heated at 120 °C for 1 h under $N_2$. A second portion of hydrazine hydrate (10 mL) was added, and the mixture was refluxed for a further 1 h. The solution was cooled in an ice bath, then poured into $H_2O$ (100 mL), and carefully acidified to pH 3 with 6 N HCl. The heterogeneous mixture was extracted with EtOAc, and the organic extracts were washed with brine and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica ($CH_2Cl_2$/hexane/EtOAc/MeOH, 17:30:8:5) yielded 1.1539 g (19%) of the desired monoacid **20**: $R_f$ 0.56 ($CH_2Cl_2$/hexane/EtOAc/MeOH, 17:20:8:5); IR ($CHCl_3$) $\nu_{max}$ 3500–2400 (w, br, OH), 2940 (m), 1740 (s), 1700 (s), 1660 (w) $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 255 nm ($\epsilon$ 14 970 $dm^3$ $mol^{-1}$ $cm^{-1}$); $^1H$ NMR (200 MHz, $CDCl_3$) 6.31 (1 H, d, *J* = 10 Hz, H1), 5.69 (1 H, d, *J* = 10 Hz, H2), 4.92 (1 H, s, br, H17), 4.88 (1 H, s, br, H17′), 4.87, 4.75, ABd (2 H, d, *J* = 6.9 Hz, $OCH_2OCH_3$), 4.38 (1 H, s, br, H3), 3.71 (3 H, s, $CO_2CH_3$), 3.57 (1 H, m, H5), 3.44 (3 H, s, $CH_2OCH_3$), 3.39 (1 H, m, H6), 2.74 (1 H, s, br, H13), 2.44 (1 H, dd *J* = 16.8 Hz, *J* = 5 Hz), 2.18 (1 H, d, *J* = 16.8 Hz), 2.1–1.5 (6 H, m), 1.29 (3 H, s, H18); $^{13}C$ NMR (50 MHz, $CDCl_3$) 175.99, 174.82, 153.12, 140.80, 128.99, 125.21, 122.81, 106.08, 96.74, 81.41, 58.66, 56.07, 53.41, 51.60, 49.82, 49.47, 46.05, 42.02, 40.30, 33.00, 21.23, 20.04; LRMS 388 ($M^+$, 33), 343 ($M^+$ – $HCO_2$, 25), 281 ($M^+$ – $C_3H_7O_4$, 100), 221 ($M^+$ – $C_5H_{11}O_6$, 72); HRMS 388.1884, $C_{22}H_{28}O_6$ ($M^+$) requires = 388.1886.

The corresponding diacid (1.1613 g 20%), resulting from competitive ester cleavage, was also obtained.

***ent*-2β-Hydroxy-1α-iodo-3β-(methoxymethoxy)-20-norgibberella-9,16-diene-7,19-dioic Acid 7-Methyl Ester 19,2-Lactone.** A stirred solution of the monoacid **20** (1.1539 g, 2.97 mmol) in THF (50 mL) was treated with 1 M aqueous $K_2CO_3$ solution (20 mL) at room temperature. A 1 M solution of $KI_3$ in 1:1 THF/$H_2O$ was added dropwise until all of the acid **20** had been consumed according to TLC analysis. The mixture was diluted with $Et_2O$, washed with saturated aqueous $NH_4Cl$ solution and then brine, and finally dried over $MgSO_4$. In similar manner, the corresponding diacid was taken up in THF (50 mL) and treated with 1 M aqueous $K_2CO_3$ and 1 M aqueous $KI_3$ solutions. The mixture was acidified to pH 3 with 1 N HCl, and the product was extracted with EtOAc. After drying over $MgSO_4$ and concentration in vacuo, the product was dissolved in a small quantity of $Et_2O$ and treated with diazomethane to give the desired methyl ester plus several other unidentified products according to TLC analysis.

Combination of the two crude products followed by chromatography on silica ($Et_2O$/hexane, 2:1) yielded the desired iodolactone (1.5911 g). The product crystallized from the collection tubes as colorless rectangular rods: mp 132–3 °C dec; $R_f$ 0.68 ($Et_2O$/hexane, 2:1); $[\alpha]^{26}_D$ –359° (*c*, 4.71, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 2940 (m), 1780 (s), 1730 (s), 1670 (w), 1660 (w) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) 5.15 (1 H, d, $J_{1,2}$ = 3.9 Hz, H1), 4.96 (1 H, s, br, H17), 4.91 (1 H, s, br, H17′), 4.81, 4.73 ABd (2 H, *J* = 7.0 Hz, $OCH_2OCH_3$), 4.72 (1 H, s, br, H3), 4.69 (1 H, d, $J_{2,1}$ = 3.9 Hz, H2), 3.74 (3 H, s, $CO_2CH_3$), 3.59 (1 H, dd, $J_{5,6}$ = 8.8 Hz, $J_{5,11}$ = 4.1 Hz, H5), 3.42 (3 H, s, $CH_2OCH_3$), 3.02 (1 H, d, $J_{6,5}$ = 8.8 Hz, H6), 2.74 (1 H, m, H13), 2.34 (1 H, m), 2.2–1.5 (6 H, m), 1.37 (1 H, dd, *J* = 11 Hz, *J* = 2.2 Hz), 1.15 (3 H, s, H18); $^{13}C$ NMR (50 MHz, $CDCl_3$) 177.05, 173.17, 151.92, 149.68, 124.36, 107.05, 95.71, 82.89, 80.96, 57.82, 55.74, 51.86, 50.71, 50.55, 49.23, 44.74, 41.22, 38.73, 31.73, 20.22, 19.42, 11.87; LRMS 483 ($M^+$ – $OCH_3$, 3), 387 ($M^+$ – I, 29), 343 ($M^+$ – I – $CO_2$, 4), 281 ($M^+$ – $C_3H_6O_4I$, 95), 221 ($M^+$ – $C_kH_{10}O_6I$, 100); HRMS 483.0668, $C_{21}H_{24}O_5I$ ($M^+$ – $OCH_3$) requires 483.0669.

***ent*-2β-Hydroxy-1α-iodo-3β-(methoxymethoxy)-16-oxo-17,20-dinorgibberell-9-ene-7,19-dioic Acid 7-Methyl Ester 19,2-Lactone (21).** A solution of the previously prepared iodolactone (1.59 g, 3.1 mmol) in dry $CH_2Cl_2$ (25 mL) and pyridine (5 mL) was added in 1 portion to a saturated solution of ozone in dry $CH_2Cl_2$ (400 mL) at –78 °C. The mixture was stirred vigorously for ca. 5 s, and the reaction was then quenched with $Me_2S$ (5 mL). The solution was concentrated in vacuo on a warm water bath, and the residue was chromatographed on silica ($Et_2O$/hexane, 2:1) to yield the desired ketone **21** (1.059 g, 66%) as an oil which could be crystallized from $Et_2O$/hexane as colorless needles: mp 158–9 °C; $R_f$ 0.54 ($Et_2O$); $[\alpha]^{26}_D$ –332° (*c* 3.55, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 2955 (m), 1780 (s), 1740 (2 × CO, s), 1675 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 5.12 (1 H, d, $J_{1,2}$ = 3.71 Hz, H1), 4.83, 4.76 ABd (2 H, *J* = 7.07 Hz, $OCH_2OCH_3$), 4.74 (1 H, s, H3), 4.74 (1 H, d, $J_{2,1}$ = 3.71 Hz, H2), 3.79 (3 H, s, $CO_2CH_3$), 3.66 (1 H, dd, $J_{5,6}$ = 8.8 Hz, $J_{5,11}$ = 4.3 Hz, H5), 3.45 (3 H, s, $CH_2OCH_3$), 3.09 (1 H, d, $J_{6,5}$ = 8.8 Hz, H6), 2.57 (1 H, m, H13), 2.53 (1 H, dd, *J* = 16.4 Hz, *J* = 5.1 Hz), 2.36 (1 H, ddd, *J* = 12.2 Hz, *J* = 4.3 Hz, *J* = 1 Hz), 2.03 (1 H, dd, *J* = 17.77 Hz, *J* = 3.2 Hz), 2.03 (1 H, m), 1.94 (1 H, dd, *J* = 17.77 Hz, *J* = 1 Hz), 1.88–1.64 (2 H, m), 1.69 (1 H, dd *J* = 12.2 Hz, *J* = 3.2 Hz), 1.19 (3 H, s, H18); $^{13}C$ NMR (75 MHz, $CDCl_3$) 217.58, 176.91, 172.51, 146.48, 126.59, 95.75, 82.85, 81.01, 56.05, 52.32, 50.69, 50.59, 49.98, 46.70, 45.57, 42.59, 30.95, 27.70, 20.29, 17.71, 11.88; LRMS 485 ($M^+$ – $OCH_3$, 5), 389 ($M^+$ – I, 100), 345 ($M^+$ – I –$CO_2$, 4), 283 ($M^+$ – $C_3H_6O_4I$, 85); HRMS 485.0460, $C_{20}H_{22}O_6I$ ($M^+$ – $OCH_3$) requires 485.0461.

***ent*-2β-Hydroxy-3β-(methoxymethoxy)-16-oxo-17,20-dinor-9α,15α-cyclogibberell-1(10)-ene-7,19-dioic Acid 7-Methyl Ester 19,2-Lactone (22).** A solution of iodo ketone **21** (1.059 g, 2.05 mmol) in dry THF (5 mL) was added slowly to a stirred suspension of KH (washed with hexane, 2 g) in dry THF (100 mL) at 0 °C. Reaction was judged to be complete by TLC analysis after 10 min. The reaction mixture was diluted with $Et_2O$ and filtered through Celite. Concentration in vacuo and chromatography on silica yielded the desired cyclopropyl ketone **22** (0.6016 g, 80%), which crystallized from the collection tubes as colorless needles: mp 203–5 °C; $R_f$ 0.23 ($Et_2O$); $[\alpha]^{25}_D$ –192° (*c* 2.48, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 2950 (m), 1770 (s), 1730 (2 × CO, s), 1665 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 5.94 (1 H, dd, $J_{1,2}$ = 5.7 Hz, $J_{1,5}$ = 2.5 Hz, H1), 4.81 (1 H, d, $J_{2,1}$ = 5.7 Hz, H2), 4.77, 4.71, ABd (2 H, *J* = 7.2 Hz, $OCH_2OCH_3$), 4.09 (1 H, s, H3), 3.78 (3 H, s, $CO_2CH_3$), 3.41 (3 H, s, $CH_2OCH_3$), 3.03 (1 H, d, $J_{6,5}$ = 9.5 Hz, H6), 2.88 (1 H, dd, $J_{5,6}$ = 9.5 Hz, $J_{5,1}$ = 2.5 Hz, H5), 2.35 (1 H, ddd, *J* = 11.7 Hz, *J* = 5.8 Hz, *J* = 1.2 Hz), 2.24 (1 H, s, H15), 2.29–2.18 (2 H, m), 2.05 (1 H, m), 1.91–1.81 (3 H, m), 1.21 (3 H, s, H18); $^{13}C$ NMR (75 MHz, $CDCl_3$) 211.68, 176.86, 172.25, 148.40, 118.83, 95.90, 83.50, 75.85, 55.88, 52.49, 51.43, 48.20, 47.17, 45.45, 45.03, 42.19, 36.99, 30.54, 26.03, 17.73, 13.74; LRMS 388 ($M^+$, 33), 343 $M^+$ – $HCO_2$, 14), 282 ($M^+$ – $C_3H_6O_4$, 100); HRMS 388.1523, $C_{21}H_{24}O_7$ ($M^+$) requires 388.1522.

***ent*-2β,10β-Dihydroxy-1α-iodo-3β-(methoxymethoxy)-16-oxo-17,20-dinor-9α,15α-cyclogibberellane-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone.** To a stirred solution of lactone **22** (0.26 g, 0.67 mmol) in EtOH (25 mL) and THF (5 mL, to solubilize) was added a solution of 2 M aqueous LiOH (8 mL). After stirring for 2 h at room temperature followed by 20 min on a warm water bath, the reaction mixture was cooled to 0 °C and treated with 1 M aqueous KI solution (5 mL) and $I_2$ (0.5 g). The mixture was stirred for 10 min, then diluted with $Et_2O$, and washed with saturated aqueous sodium thiosulfate solution followed by brine. The organic phase was dried over $MgSO_4$, concentrated in vacuo, and chromatographed on silica ($Et_2O$/hexane, 2:1) to give the desired iodolactone (0.354 g, 47%) as a colorless oil: $R_f$ 0.19 ($Et_2O$); $[\alpha]^{25}_D$ +26° (*c* 1.21, $CH_2Cl_2$) IR ($CHCl_3$) $\nu_{max}$ 3500 (w, br, OH), 2960 (m), 1785 (s), 1735 (2 × CO, s) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) 4.76, 4.69, ABd (2 H, *J* = 7 Hz, $OCH_2OCH_3$), 4.67 (1 H, s, H3), 4.53 (1 H, d, $J_{1,2}$ = 4.15 Hz, H1), 4.01 (1 H, d, $J_{2,1}$ = 4.15 Hz, H2), 3.76 (3 H, s, $CO_2CH_3$), 3.42 (3 H, s, $CH_2OCH_3$), 2.96 (1 H, d, $J_{6,5}$ = 8.3 Hz, H6), 2.95 (1 H, s, OH), 2.82 (1 H, d, $J_{5,6}$ = 8.3 Hz, H5), 2.62 (1 H, s, br, H15), 2.5–1.7 (7 H, m), 1.21 (3 H, s, H18); $^{13}C$ NMR (50 MHz, $CDCl_3$) 210.73, 175.61, 170.90, 97.24, 92.01, 78.93, 75.99, 56.62, 52.65, 50.98, 49.82, 47.42, 46.52, 43.80, 42.78, 37.61, 30.58, 25.93, 21.18, 15.34, 13.06; LRMS 532 ($M^+$, 14), 405 ($M^+$ – I, 100); HRMS 532.0593, $C_{21}H_{15}O_8I$ ($M^+$) requires 532.0594.

***ent*-10β-Hydroxy-3β-(methoxymethoxy)-16-oxo-17,20-dinor-9α,15α-cyclogibberell-1-ene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (23).** To a stirred solution of the previously prepared hydroxy iodolactone (0.35 g, 0.66 mmol) in dry THF (15 mL) and dry pyridine (2 mL) at 0 °C was added trifluoroacetic anhydride (0.28 mL, 2 mmol). After having been stirred at 0 °C for 1 h, the solution was treated with KI (0.22 g, 1.3

mmol) and activated zinc dust (0.3 g, 4.6 mmol). The mixture was stirred at 0 °C, allowed to warm to room temperature over 2 h, and then treated with saturated aqueous $NaHCO_3$ solution to destroy the excess anhydride. The mixture was diluted with $Et_2O$, then washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica ($Et_2O$/hexane, 1:1) yielded the desired olefinic lactone **23** (0.211 g, 82%) as a pale yellow oil: $R_f$ 0.30 ($Et_2O$); $[\alpha]^{26}_D$ −118 ° (*c*, 1.90, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 2950 (m), 1780 (s), 1735 (2 × CO, s) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) 6.41 (1 H, d, br, $J_{1,2}$ = 9.5 Hz, H1), 5.96 (1 H, dd, $J_{2,1}$ = 9.5 Hz, $J_{2,3}$ = 2.5 Hz, H2), 4.78, 4.69, ABd (2 H, *J* = 7.0 Hz, $OCH_2OCH_3$), 4.16 (1 H, d, br, $J_{3,2}$ = 2.5 Hz, H3), 3.74 (3 H, s, $CO_2CH_3$), 3.39 (3 H, s, $CH_2OCH_3$), 3.00 (1 H, d, $J_{6,5}$ = 9.1 Hz, H6), 2.39 (1 H, d, $J_{5,6}$ = 9.1 Hz, H5), 2.17 (1 H, s, H15), 2.5–1.8 (7 H, m), 1.31 (3 H, s, H18); $^{13}C$ NMR (50 MHz, $CDCl_3$) 211.36, 174.72, 170.89, 132.70, 127.95, 96.89, 88.73, 79.34, 55.83, 55.07, 52.44, 52.30, 46.49, 45.39, 44.40, 42.60, 33.88, 30.31, 26.66, 15.41, 14.19; LRMS 388 ($M^+$, 51), 343 ($M^+ - HCO_2$, 88), 283 ($M^+ - C_3H_5O_4$, 100), 282 ($M^+ - C_3H_6O_4$, 73); HRMS 388.1523, $C_{21}H_{24}O_7$ ($M^+$) requires 388.1522.

**10α-Hydroxy-3α-(methoxymethoxy)-16-oxo-17-norantherida-1,6-(8)-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (24).** A solution of cyclopropyl ketone **23** (0.10 g, 0.26 mmol) in dry DMF (5 mL) and DBU (1 mL) was heated under $N_2$ at 70 °C for 1 h. The mixture was cooled, diluted with $Et_2O$, and then washed with 1 N HCl followed by brine. After having been dried over $MgSO_4$, the solution was concentrated in vacuo, and the product was chromatographed on silica ($Et_2O$) to give the desired α,β-unsaturated ester **24** (0.093 g, 93%) as a colorless oil: $R_f$ 0.45 ($Et_2O$/MeOH, 19:1); $[\alpha]^{25}_D$ −65° (*c* 0.89, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 2950 (m), 1780 (s), 1730 (s), 1710 (s), 1640 (m) $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 228 nm ($\epsilon$ 12 200 $dm^3$ $mol^{-1}$ $cm^{-1}$); $^1H$ NMR (300 MHz, $CDCl_3$) 6.31 (1 H, dd, $J_{1,2}$ = 9.34 Hz, $J_{1,3}$ = 1.78 Hz, H1), 5.99 (1 H, dd, $J_{2,1}$ = 9.34 Hz, $J_{2,3}$ = 2.5 Hz, H2), 4.80, 4.71, ABd (2 H, *J* = 7.0 Hz, $OCH_2OCH_3$), 4.26 (1 H, dd, $J_{3,2}$ = 2.5 Hz, $J_{3,1}$ = 1.78 Hz, H3), 3.72 (3 H, s, $CO_2CH_3$), 3.47 (1 H, dd, $J_{5,14}$ = 3.87 Hz, $J_{5,14'}$ = 1.93 Hz, H5), 3.40 (3 H, s, $CH_2OCH_3$), 3.0 (1 H, ddt, $J_{14,14'}$ = 19.4 Hz, $J_{14,5}$ = 3.87 Hz, *J* = 1.7 Hz, H14), 2.71 (1 H, d, br, $J_{14',14}$ = 19.4 Hz, H14′), 2.55 (1 H, m), 2.40 (1 H, d, *J* = 18.0 Hz), 2.30 (1 H, m), 2.1–1.8 (4 H, m), 1.40 (3 H, s, H18); $^{13}C$ NMR (75 MHz, $CDCl_3$) 211.21, 174.64, 164.85, 162.33, 133.67, 127.05, 122.90, 97.16, 86.16, 79.90, 62.58 (2 × C), 55.91, 53.93, 51.95, 51.50, 43.30, 43.20, 30.71, 21.32, 15.65; LRMS 388 ($M^+$, 22), 357 ($M^+ - OCH_3$, 37), 343 ($M^+ - HCO_2$, 87), 332 (100), 299 (70), 283 (23), 271 (89); HRMS 388.1523, $C_{21}H_{24}O_7$ ($M^+$) requires 388.1522.

**10α-Hydroxy-3α-(methoxymethoxy)antherida-6(8),16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone.** To a solution of diene **24** (0.0825 g, 0.21 mmol) in EtOAc (10 mL) was added 5% Rh on alumina (17 mg), and the mixture was stirred under an atmosphere of $H_2$ for 20 h. The solution was diluted with EtOAc, filtered (Whatman GF/A), and concentrated in vacuo. The crude product was dissolved in dry THF (10 mL) and treated dropwise with a solution of methylidenetriphenylphosphorane (salt free in THF) until all the starting material had been consumed according to TLC analysis. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution, then extracted with $Et_2O$, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica ($Et_2O$/hexane, 1:1 then 2:1) yielded the desired product (0.066 g, 80%) as a colorless oil: $R_f$ 0.52 ($Et_2O$); $[\alpha]^{25}_D$ −4° (*c* 0.51, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 2950 (m), 1770 (s), 1710 (s), 1640 (m) $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 230 nm ($\epsilon$ 13 100 $dm^3$ $mol^{-1}$ $cm^{-1}$); $^1H$ NMR (300 MHz, $CDCl_3$) 4.88 (1 H, s, br, H17), 4.74, 4.66, ABd (2 H, *J* = 7.0 Hz, $OCH_2OCH_3$), 4.67 (1 H, s, br, H17′), 3.73 (3 H, s, $CO_2CH_3$), 3.66 (1 H, dd, $J_{3,2}$ = 10.0 Hz, $J_{3,2}$ = 6.0 Hz, H3), 3.40 (3 H, s, $CH_2OCH_3$), 3.04 (1 H, s, br, H5), 2.73 (1 H, ddt, $J_{14,14'}$ = 19.1 Hz, *J* = 4 Hz, *J* = ca. 2 Hz, H14), 2.54 (1 H, d, br, $J_{14',14}$ = 19.1 Hz, H14′), 2.50 (1 H, m), 2.4–2.25 (2 H, m), 2.25–1.94 (3 H, m), 1.9–1.56 (5 H, m), 1.29 (3 H, s, H18); $^{13}C$ NMR (75 MHz, $CDCl_3$) 176.37, 166.41, 165.81, 147.78, 120.96, 108.18, 96.13, 90.10, 78.52, 60.76, 55.76, 53.11, 51.88, 51.19, 36.83, 35.98, 34.60, 27.11, 25.11, 25.02, 22.07, 14.36; LRMS 388 ($M^+$, 31), 360 (78), 357 ($M^+ - OCH_3$, 50), 298 (100), 283 (82), 270 (58); HRMS 388.1884, $C_{22}H_{28}O_6$ ($M^+$) requires 388.1886.

**10α-Hydroxy-3α-(methoxymethoxy)antherida-8(14),16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (25).** A solution of the previously prepared α,β-unsaturated ester (0.04 g, 0.1 mmol) in dry THF (1 mL) was added dropwise to a stirred solution of LICA [prepared from dry *N*-isopropylcyclohexylamine (0.1 mL, 0.6 mmol) and *n*-BuLi (1.5 M, 0.27 mL, 0.4 mmol) in dry THF (5 mL)] at −78 °C. The solution was slowly allowed to warm to −20 °C over 30 min, then recooled to −78 °C, and quenched with $Et_3NH^+Cl^-$ (0.1 g) followed, after ca. 10 min, by saturated aqueous $NH_4Cl$ solution. The mixture was diluted with $Et_2O$, washed with 1 N HCl, solution and then brine, and finally dried over $MgSO_4$. Concentration in vacuo and chromatography on silica ($Et_2O$/hexane, 1:1) yielded the desired β,γ-unsaturated ester **25** along with recovered α,β-unsaturated ester in a ca. 1:3 ratio. By repeating the deprotonation/reprotonation sequence, 22.5 mg of ester **25** could be obtained after 3 cycles [74% based on recovered starting material]. Recrystallization from $Et_2O$/hexane gave colorless needles: mp 159–160 °C; $R_f$ 0.55 ($Et_2O$); $[\alpha]^{26}_D$ +84° (*c* 0.96, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 2960 (m), 1775 (s), 1735 (s), 1650 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 6.14 (1 H, dd, $J_{14,13}$ = 6.40 Hz, $J_{14,6}$ = 2.70 Hz, H14), 4.82 (1 H, s, br, H17), 4.74, 4.64, ABd (2 H, *J* = 7.0 Hz, $OCH_2OCH_3$), 4.62 (1 H, s, br, H17′), 3.76 (3 H, s, $CO_2CH_3$), 3.66 (1 H, m, H3), 3.45 (1 H, dd, $J_{6,5}$ = 9.75 Hz, $J_{6,14}$ = 2.70 Hz, H6), 3.38 (3 H, s, $CH_2OCH_3$), 3.07 (1 H, dt, $J_{13,14}$ = 6.40 Hz, $J_{13,12}$ = 2.78 Hz, H13), 2.76 (1 H, d, $J_{5,6}$ = 9.75 Hz, H5), 2.4–2.0 (3 H, m), 1.9–1.4 (7 H, m), 1.22 (3 H, s, H18); $^{13}C$ NMR (50 MHz, $CDCl_3$) 176.69, 171.49, 147.37, 146.14, 125.32, 105.62, 95.98, 91.98, 77.73, 58.08, 55.74, 53.32, 52.33, 50.69, 47.39, 41.90, 36.65, 27.51, 26.81, 26.14, 24.15, 13.41; LRMS 388 ($M^+$, 90), 360 (100), 326 (37), 312 (53), 300 (66); HRMS 388.1884, $C_{22}H_{28}O_6$ ($M^+$) requires 388.1886.

**10α,15α-Dihydroxy-3α-(methoxymethoxy)antherida-6(8),16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone.** A solution of diene **25** (0.022 g, 0.057 mmol) in $CH_2Cl_2$ (5 mL) was treated with selenium dioxide (0.04 g, 0.36 mmol) and *tert*-butyl hydroperoxide (0.3 mL, 80% aqueous solution), and the mixture was stirred at room temperature for 20 h. The mixture was diluted with $CH_2Cl_2$ and washed twice with $H_2O$ and then brine. After having been dried over $MgSO_4$, the product was concentrated in vacuo and chromatographed on silica ($Et_2O$) to give the desired 15α-carbinol (19.5 mg, 85%) as a colorless oil: $R_f$ 0.37 ($Et_2O$); $[\alpha]^{26}_D$ +61° (*c* 0.69, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 3550 (w, br, OH), 2960 (m), 1775 (s), 1735 (s), 1650 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 6.25 (1 H, dd, $J_{14,13}$ = 6.64 Hz, $J_{14,6}$ = 2.73 Hz, H14), 5.08 (1 H, s, H17), 5.02 (1 H, s, H17′), 4.73, 4.62, ABd (2 H, *J* = 7.0 Hz, $OCH_2OCH_3$), 4.07 (1 H, d, $J_{15,OH}$ = 9.3 Hz, H15), 3.76 (3 H, s, $CO_2CH_3$), 3.68 (1 H, dd, $J_{3,2}$ = 10.9 Hz, $J_{3,2'}$ = 5.9 Hz, H3), 3.42 (1 H, dd, $J_{6,5}$ = 9.37 Hz, $J_{6,14}$ = 2.73 Hz, H6), 3.37 (3 H, s, $CH_2OCH_3$), 3.13 (1 H, ddd, $J_{13,14}$ = 6.64 Hz, $J_{13,12}$ = 3.1 Hz, $J_{13,12'}$ = 2.1 Hz, H13), 2.90 (1 H, d, $J_{5,6}$ = 9.37 Hz, H5), 2.4–2.2 (2 H, m), 2.10 (1 H, m), 1.84–1.2 (6 H, m), 1.23 (3 H, s, H18); $^{13}C$ NMR (75 MHz, $CDCl_3$) 176.38, 172.36, 152.75, 143.57, 126.47, 109.99, 95.54, 92.43, 77.50, 72.47, 59.76, 55.56, 55.38, 52.79, 52.13, 47.10, 40.83, 26.31 (2 × C), 24.43, 20.15, 13.07; LRMS 404 ($M^+$, 23), 372 ($M^+ - CH_3OH$, 29), 360 ($M^+ - CO_2$, 11), 342 (76), 327 (43), 315 (86), 298 (99), 283 (100), 255 (72), 237 (73), 213 (67); HRMS 404.1837, $C_{22}H_{28}O_7$ ($M^+$) requires 404.1835.

**3α,10α,15α-Trihydroxyantherida-6(8),16-diene-7,19-dioic Acid 7-Methyl Ester 19,10-Lactone (26). [Methyl Antheridate].** A solution of dimethylboron bromide (0.1 mL) in dry $CH_2Cl_2$ (2 mL) was added dropwise to a stirred solution of the previously prepared MOM lactone (0.019 g, 0.047 mmol) in dry $CH_2Cl_2$ (3 mL) at −90 °C, until all of the starting material had been consumed according to TLC analysis. THF (0.2 mL), followed by saturated aqueous $NH_4Cl$ solution, was added, and the product was extracted with $Et_2O$. The organic extracts were washed with brine, then dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica ($Et_2O$) yielded methyl antheridate (**26**) (13.3 mg, 79%) as a colorless oil. Spectroscopic data were identical with those of authentic material:[8,37] $R_f$ 0.54 ($Et_2O$/MeOH, 9:1); $[\alpha]^{26}_D$ +38° (*c* 0.87, $CH_2Cl_2$); IR ($CHCl_3$) $\nu_{max}$ 3500 (w, br, OH), 2960 (m), 1770 (s), 1730 (s), 1650 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 6.27 (1 H, dd, $J_{14,13}$ = 6.69 Hz, $J_{14,6}$ = 2.74 Hz, H14), 5.09 (1 H, s, H17), 5.04 (1 H, s, H17′), 4.08 (1 H, s, br, H15), 3.77 (3 H, s, $CO_2CH_3$), 3.74 (1 H, dd, $J_{3,2}$ = 11 Hz, $J_{3,2'}$ = 5.5 Hz, H3), 3.43 (1 H, dd, $J_{6,5}$ = 9.42 Hz, $J_{6,14}$ = 2.74 Hz, H6), 3.15 (1 H, ddd, $J_{13,14}$ = 6.69 Hz, $J_{13,12}$ = 3.4 Hz, $J_{13,12'}$ = 2.4 Hz, H13), 2.88 (1 H, d, $J_{5,6}$ = 9.42 Hz, H5), 2.30 (2 H, m), 2.12 (1 H, m), 1.78 (1 H, m), 1.64 (1 H, s, br, O*H*), 1.62–1.46 (3 H, m), 1.46–1.24 (2 H, m), 1.25 (3 H, s, H18); $^{13}C$ NMR (75 MHz, $CDCl_3$) 176.92, 172.82, 153.00, 144.05, 127.02, 110.49, 93.36, 73.18, 72.84, 59.87, 55.91, 54.12, 52.54, 47.49, 41.19, 29.39, 26.64, 25.17, 20.56, 13.07; LRMS 360 ($M^+$, 68), 342 ($M^+ - H_2O$, 49), 328 ($M^+ - CH_3OH$, 83), 316 ($M^+ - CO_2$, 99.7), 298 ($M^+ - H_2O - CO_2$, 89), 283 (75), 256 (90), 213 (100); HRMS 360.1575, $C_{20}H_{24}O_6$ ($M^+$) requires 360.1573.

**3α,10α,15α-Trihydroxyantherida-6(8),16-diene-7,19-dioic Acid 19,10-Lactone (2). [Antheridic Acid or Antheridiogen $A_n$].** A solution of the methyl ester **26** (7 mg) was stirred for 30 min at 0 °C with 1:1 DME/1 M aqueous LiOH solution (4 mL). The product was acidified to pH 3 with 1 N HCl solution, extracted with EtOAc, dried over $MgSO_4$, and concentrated in vacuo to yield antheridic acid (5.8 mg). This material was identical both spectroscopically[37] and chromatographically with authentic material: co-elution of synthetic and natural materials for **1** $R_f$ 0.37 (EtOAc/$CHCl_3$/$CH_3CO_2H$, 15:5:1) and **2** $R_f$ 0.56 ($CH_2Cl_2$/MeOH/$Et_3N$, 16:3:1); $[\alpha]^{25}_D$ +32° (*c* 0.26, EtOAc); synthetic antheridic acid ORD (*c* 1.56 × $10^{-4}$, $CH_3OH$), positive plain ORD curve ($[\Phi]^{25}_{230}$ +3.30 × $10^3$), natural antheridic acid ORD (*c* 2.48 × $10^{-4}$, $CH_3OH$), positive plain ORD curve ($[\Phi]^{25}_{230}$ +3.27 × $10^3$); $^1H$ NMR (300 MHz, acetone-$d_6$) 6.36 (1 H, dd, $J_{14,13}$ = 6.41 Hz, $J_{14,6}$ = 2.74 Hz, H14), 5.00 (2 H, s, br, H17, H17′), 4.13 (1 H, s, H15), 3.73

**Table I**

| concntrn (ppm) | synthetic antheridic acid[a] | natural antheridic acid[a] |
|---|---|---|
| 0.5 | 95.8 ± 1.4 | 95.7 ± 1.1 |
| 0.05 | 83.4 ± 3.7 | 87.8 ± 1.9 |
| 0.005 | 4.9 ± 1.1 | 5.6 ± 1.2 |
| 0.0005 | 0 | 0 |
| 0 (blank) | 0 | |

[a] Each value is the average percent germination from four replicates.

(1 H, dd, $J_{3,2}$ = 11.16 Hz, $J_{3,2'}$ = 5.19 Hz, H3), 3.31 (1 H, dd, $J_{6,5}$ = 9.38 Hz, $J_{6,14}$ = 2.74 Hz, H6), 3.16 (1 H, dt, $J_{13,14}$ = 6.41 Hz, $J_{13,12}$ = ca. 3 Hz), 3.5-3.0 (1 H, s, br, $CO_2H$), 2.85 (1 H, d, $J_{5,6}$ = 9.38 Hz, H5), 2.4-2.0 (4 H, m), 1.74-1.26 (6 H, m), 1.19 (3 H, s, H18); $^{13}C$ NMR (75 MHz, acetone-$d_6$) 176.39, 173.65, 155.25, 146.01, 127.24, 110.21, 93.66, 74.25, 73.91, 61.17, 57.00, 55.37, 49.00, 42.73,[40] 28.45, 26.38, 21.83, 14.44; capillary GC-LRMS [tri-TMS derivative] 562 ($M^+$), 547, 534, 416, 400, 367, 129; HRMS 562.2606, $C_{28}H_{46}O_6Si_3$ ($M^+$) requires 562.2602.

**Bioassay (induction of dark germination)**: Approximately 150 *Anemia phyllitidis* spores, sterilized by soaking in 0.5% NaOCl solution for 1 min, were innoculated on the surface of 0.2 mL of solidified growth medium ($MgSO_4$, 0.25 g; $Ca(NO_3)_2$, 1.0 g; $KNO_3$, 0.12 g; $KH_2PO_4$, 0.25 g; ferric citrate, 5 mg; agar, 9 g; and $H_2O$, 1 L) containing the sample to be tested. The samples were incubated in the dark in small round glass vessels (8 mm i.d., 7 mm depth) for 10 days at 25 °C, and the percentage of germinated spores in each vessel was determined under a microscope at 60-fold magnification.[38]

(40) One $^{13}C$ resonance is obscured by the acetone-$d_6$ solvent peaks.

# 2-(Phenylsulfonyl)-1,3-dienes as Versatile Synthons in Organic Transformations. Multicoupling Reagents and Diels-Alder Dienes with a Dual Electron Demand

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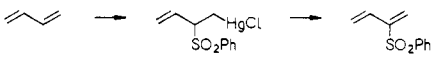
**Abstract:** 2-(Phenylsulfonyl)-1,3-dienes were stereo- and regioselectively functionalized via Michael addition of nucleophiles and subsequent addition of nucleophiles and/or electrophiles to the resulting allylic sulfones. The second nucleophile is introduced via a palladium-catalyzed or a cuprate-promoted nucleophilic substitution of the allylic sulfone. The strategy was applied to the synthesis of a Monarch butterfly pheromone. The sulfonyldienes were shown to undergo [4 + 2] cycloadditions with both electron-rich and electron-deficient dienophiles. Enamines and enol ethers gave highly regioselective reactions, whereas the regioselectivity in the reaction with methyl acrylate depends on the structure of the sulfonyldiene. The sulfonyl group in the cycloaddition products allows further useful transformations, which was demonstrated in a few cases.

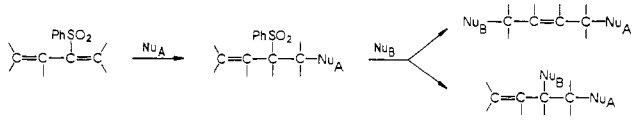
We recently reported a procedure for the synthesis of 2-(phenylsulfonyl)-1,3-dienes from conjugated dienes.[2] The method is based upon a sulfonylmercuration-elimination sequence and allows a one-pot synthesis of the sulfonyldiene (eq 1). The



(1)

reaction is highly regioselective for a number of dienes. The sulfonyldienes obtained are useful building blocks for further functionalization,[2] and furthermore, they are potentially interesting Diels-Alder dienes.[3,4] In view of these aspects and the general synthetic potential of unsaturated sulfones[5-9] we decided to explore the synthetic utility of the readily available 2-(phenylsulfonyl)-1,3-dienes. In this paper we report (i) that they can be regio- and stereoselectively functionalized via sequential nucleophilic addition of carbon and nitrogen nucleophiles and (ii) that they show a duality in their Diels-Alder cycloadditions and give [4 + 2] adducts with *both* electron-deficient and electron-rich olefins.

**Scheme I**




## Results and Discussion

**Stereo- and Regioselective Additions of Nucleophiles.** The principle for the sequential nucleophilic additions to 2-(phenylsulfonyl)-1,3-dienes is shown in Scheme I. After a Michael-type addition of the first nucleophile, the second nucleophile can substitute the allylic sulfonyl group in a copper-[6] or palladium-catalyzed[7] reaction. A variety of different nucleophiles can be used in the first addition, and a few representative examples for the preparation of allylic sulfones are shown in Table I.

The Michael addition to sulfonyldiene **1** was found to be diastereoselective for all nucleophiles tried, leading preferentially to the trans isomer (entries 1-5, Table I). For the addition of dimethyl malonate and dimethylamine, the selectivity for the trans isomer was >95%, whereas for the cuprate addition (or copper-assisted alkyllithium addition), the trans:cis ratio was 90:10. In the latter case, however, treatment of the crude product with

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