Demethylation (*n*-PrSLi, DMF, 20 °C, 2 h)[38] and desilylation (acidic workup) finally furnished (±)-gibberellin A_1, mp 251–254 °C, then 271–274 °C (>80% overall yield from **23**), with IR, ^1H NMR, and mass spectra indistinguishable from those of the (+) enantiomer (**2**).[8]

The elaboration of the gibberellic acid (A_3) structure (**1**), however, poses a rather more formidable challenge. The allylic lactone moiety is labile toward weak bases[39] and acids (even autocatalysis),[40] while Wagner–Meerwein rearrangement of the C/D-ring system is readily initiated by electrophiles.[41] Consequently, assembly of the complete A_3 structure requires delicate timing, as well as a judicious selection of reagents and conditions.

It appeared that Δ^1-3β-ol functionality of A_3 could most readily be introduced from a Δ^2-olefin,[42] so **25** was converted into phenylsulfonate **26**, mp 212–214 °C ($PhSO_2Cl$, C_5H_5N, 25 °C, 4 h, 95%), and thence (±)-**29**, mp 244–248 °C, by treatment with a mixture of tetra-*n*-butylammonium bromide (5 equiv) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)(5 equiv) in dimethylformamide (DMF) at 90 °C for 21 h (82% yield).[43] An optical resolution of (±)-**29** was effected through chromatographic separation of the derived diastereomeric urethanes **30** [phosgene, pyridine, DMAP, 25 °C, 6 h; (−)-α-phenylethylamine].[44,45] Reaction of the more polar urethane with tetrachlorosilane (10 equiv) and triethylamine (20 equiv) in dichloromethane (25 °C, 48 h)[46] afforded (−)-**29**, identical in all respects (mp, TLC ^1H NMR, IR and mass spectra) with an authentic sample [mp 263–264 °C, $[\alpha]^{27}_D$ −88° (*c* 0.56, $CHCl_3$)] prepared from the 3α-phenylsulfonate, mp 186–188 °C, of (−)-ketal **25**, which had been obtained from natural A_3.[33]

Hydroxylation[47] [OsO_4, *N*-methylmorpholine *N*-oxide, acetone/H_2O (3:1), 5 °C, 90 h] of **29** furnished triol **27** [mp 256–258 °C, $[\alpha]^{27}_D$ + 17° (*c* 0.54, EtOH)] in 98% yield, and the derived benzylidene acetal (diastereomeric mixture) [PhCHO, $(CH_2Cl)_2$, *p*-toluenesulfonic acid, 4 A sieves, reflux 16 h] was treated with *N*-bromosuccinimide [CCl_4, reflux 1 min; 250-W tungsten lamp, 0.9 m, 35 °C, 1.25 h]. Stereoelectronically controlled fission of the 1,3-dioxolan-2-ylium cation[48] generated in this way ensured specific formation of the 2α-bromide **28**, mp 186–189 °C (95% yield), which was converted [DBN (5 equiv), THF/DMF (1:1), 65 °C, 1 h, 90% yield] into allylic benzoate **31** [mp 243–246 °C, $[\alpha]^{28}_D$ + 190° (*c* 0.79, $CHCl_3$)] and then ketol **32** [mp 231–234 °C, $[\alpha]^{30}_D$ +197° (*c* 0.8, $CHCl_3$)] by treatment with dilute acid [3 M HCl/THF (1:2), 30 °C, 6 h, ~100% yield]. The A_3 structure was then completed in ~75% overall yield in essentially the same manner as in the A_1 synthesis, i.e., silylation, Wittig methylenation,[49] and desilylation to give **33**; mp 169–170 °C, $[\alpha]^{25}_D$ +214° (*c* 1.0, $CHCl_3$). Finally, hydrolysis at pH 10 [$K_2CO_3/KHCO_3$, MeOH/THF/H_2O (4:1:1), 25 °C, 1 h] furnished methyl gibberellate, which was demethylated, as reported,[50] to gibberellic acid **1**. Spectra (^1H NMR, IR, mass spectra), mp, and TLC mobility of **1** and its methyl ester were indistinguishable from those of authentic samples.[51]

While the focus of this work has been the preparation of A_3 (**1**), it is clear that all the most common C_{19} gibberellins are accessible through applications of the present strategy.[52] Moreover, many of the procedures are highly suited to the manipulation of natural gibberellins and the preparation of analogues for biological investigations.

(38) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459–4462. The rate of the present reaction is similar to that in the carcinogenic solvent hexamethylphosphoric triamide.

(39) Cross, B. E.; Grove, J. F.; Morrison, A. *J. Chem. Soc.* **1961**, 2498–2515.

(40) (a) Cross, J. *J. Chem. Soc.* **1954**, 4670–4676. (b) Pryce, R. J. *Phytochemistry* **1973**, *12*, 507–514, and references cited therein.

(41) Hanson, J. R. "The Tetracyclic Diterpenes", Pergamon Press: Oxford, 1968; pp 41–59.

(42) Approaches based on a 3-oxo derivative are unattractive since hydride reduction at C(3) favors the formation of 3α-alcohols: Voigt, B.; Adam, G.; Kobrina, N. S.; Serebrayakov, E. P. *Z. Chem.* **1977**, *17*, 372–374. Gurvich, I. A.; Kobrina, N. S.; Kucherov, V. F. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1969**, 1668–1671.

(43) Lower concentrations of bromide ion or DBN resulted in an accumulation of the 3α-bromide (double inversion), which does not undergo elimination at this temperature. The excess of bromide ion increases the rate of formation of 3β-bromide, which is then eliminated by the nitrogen base. The 3β-epimer of **26** afforded olefin **29** in 90% yield after only 4.5 h under equivalent conditions.

(44) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 1839–1844. Cf. ref 3b.

(45) Three 15-min developments in ether/pentane (3:2) on Merck DC-Alufolien Kieselgel 60 (0.2 mm) cleanly separated the two diastereomers (R_f 0.53 and 0.58). The more polar isomer, $[\alpha]^{25}_D$ −48° (*c* 0.22, $CHCl_3$), was spectroscopically (^1H NMR, IR) and chromatographically identical with an authentic sample, $[\alpha]^{25}_D$ −48.7° (derived from natural A_3). The less polar isomer was chromatographically and spectroscopically (^1H NMR, IR) indistinguishable from the enantiomeric urethane derived from (−)-**29** and (+)-α-phenylethylamine.

(46) Cf.: Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2781–2782.

(47) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976.

(48) Pittman, C. U.; McManus, S. P.; Larson, J. W. *Chem. Rev.* **1972**, 357–438.

(49) Greater care was required than in the A_1 preparation. The KO-*t*-Bu was prepared from potassium metal; traces of moisture or the use of commercially obtained KO-*t*-Bu, even after resublimation, led to cleavage of the benzoate group with a consequent retroaldol reaction and methylenation of the seco aldehyde.

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

(51) We are indebted to A. Cossey for technical assistance and to G. W. Elson, I.C.I. Plant Protection, for gifts of gibberellins.

(52) The obvious conversions of **27** and **29** into gibberellins A_8 and A_5, respectively, have been completed. The adoption of the general strategy to the preparation of 13-deoxy C_{19} gibberellins, culminating in the synthesis of (±)-A_4 (**3**), mp 220–222 °C, has also been carried out. Applications to further gibberellins, including C_{20} derivatives, are well advanced.

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Total Synthesis of Gibberellic Acid. The Hydrofluorene Route

Sir:

A recurring theme in a broad spectrum of proposals[1] for the synthesis of the C_{19} gibberellin phytohormones[2] has been the utilization of a benzenoid synthon as a precursor to the A-ring/lactone moiety in these compounds. The pioneering studies undertaken by Loewenthal,[3] in particular, appeared to hold considerable promise for this strategy,[4] which dovetails efficiently with the construction of the remainder of the molecule through the application of our diazo ketone based methodology.[5] We now report the application of these concepts to the transformation of fluorenone **1**[6] into the tetracyclic lactone **2**, an advanced intermediate in our recently completed total synthesis of gibberellic acid.[7]

Our first objective was the development of an efficient preparation of tetracyclic ketone **8**. This was achieved through the use of reported procedures,[5c] but with several important refine-

(1) For reviews, see: Fujita, E.; Node, M. *Heterocycles* **1977**, *7*, 709–752. Danheiser, R. L. Ph.D. Dissertation, Harvard University, 1978.

(2) Hanson, J. R. "The Tetracyclic Diterpenes"; Pergamon Press: Oxford, 1968; pp 41–59.

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

(4) See also: (a) House, H. O.; Strickland, R. C.; Zaiko, E. J. *J. Org. Chem.* **1976**, *41*, 2401–2408. (b) House, H. O.; Zaiko, E. J. *Ibid.* **1977**, *42*, 3780–3783. (c) Baker, A. J.; Goudie, A. C. *J. Chem. Soc., Chem. Commun.* **1972**, 951.

(5) (a) Beames, D. J.; Klose, T. R.; Mander, L. N. *J. Chem. Soc., Chem. Commun.* **1971**, 773–774. (b) Klose, T. R.; Mander, L. N. *Aust. J. Chem.* **1974**, *27*, 1287–1294. (c) Beames, D. J.; Turner, J. V.; Mander, L. N. *Ibid.* **1974**, *27*, 1977–1984.

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

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

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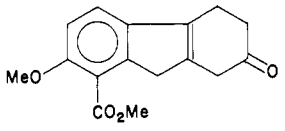
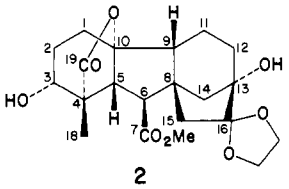
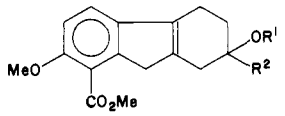


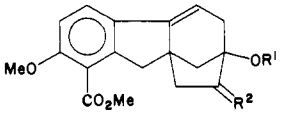
1



2

ments. Thus, the cyanohydrin, mp 165–169 °C,[8] derived from **1**[6,9] was subjected to methanolysis[10] (HCl, MeOH, saturated, 0 °C then 25 °C, 16 h; H_2O), and the resulting dimethyl ester, mp 118–120 °C, was selectively hydrolyzed by KOH (2 equiv, 25 °C, 2 h) to acid **3**, mp 230–232 °C (60% overall yield from **1**). The

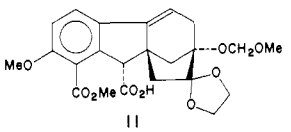




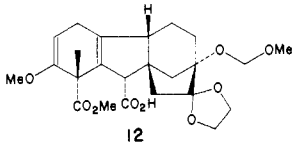
3 R^1 = H, R^2 = CO_2H
4 R^1 = $COCH_2Cl$, R^2 = CO_2H
5 R^1 = $COCH_2Cl$, R^2 = COCl
6 R^1 = $COCH_2Cl$, R^2 = $COCHN_2$
7 R^1 = $COCH_2Cl$, R^2 = O
8 R^1 = H, R^2 = O
9 R^1 = H, R^2 = OCH_2CH_2O
10 R^1 = CH_2OMe, R^2 = OCH_2CH_2O

derived chloro acetate **4**, mp 183–185 °C [$ClCH_2(CO)_2O$, $(CH_2Cl)_2$, reflux, 3 h, 90% yield], was transformed to diazo ketone **6**, mp 147–150 °C (71% yield), in the usual way by treatment of acyl chloride **5** with an excess of ethereal diazomethane at −20 °C,[11] but a satisfactory procedure for the formation of **5** [**4** + oxalyl chloride (3 equiv), CH_2Cl_2 (10 mL/mmol), 0 °C, 2 h then 25 °C, 3 h; addition of DMF (1.5 μL/mmol **4**) at 2-h intervals] was obtained only after extensive experimentation. Cyclization of **6** [trifluoroacetic acid/CH_2Cl_2 (2:1), −20 °C, 10 min] proceeded smoothly, however, to give **7**, mp 133–135 °C, which was readily hydrolyzed [K_2CO_3, MeOH/THF/H_2O (8:1), 24 °C, 1.5 h] to the target ketol **8**, mp 150–152 °C, in 89% overall yield from **6**.

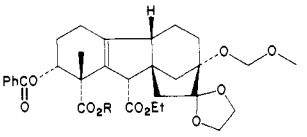
In the next phase of the synthesis, substituents were introduced at C(4) and C(6) and the correct stereochemistry established at C(4) and C(9) relative to C(8). Ketal **9**, mp 162–165 °C, was prepared [$(CH_2OH)_2$ (10 equiv), *p*-toluenesulfonic acid, $(CH_2Cl)_2$, reflux, 16 h, 95% yield], protected further as the methoxymethyl ether **10**, mp 122–125 °C [$ClCH_2OMe$ (20 equiv), *i*-Pr_2NEt/CH_2Cl_2 (3:1), 25 °C, 16 h, 98% yield], and carboxylated at C(6) [lithium *N*-*tert*-butyl-*N*-cyclohexylamide (1.5 equiv), THF, HMPA (1.1 equiv), −20 °C, 5 min; excess CO_2, −78 → 25 °C] to give acid **11**, mp 173–175 °C, in 89% yield The close correspondence between the ^1H NMR data obtained for the dimethyl ester from **11** and those reported for the 13-deoxy analogue[3b] provided confirmation of the expected 6α stereochemistry, which was so vital for the subsequent development of the correct chirality at C(9)[3b] and C(4).[4a] Thus, hydrogenation of **11** over a minimal quantity of catalyst [10% Pd–C (1% w/w), MeOH/EtOAc (1:1), 25 °C, 16 h, 91% yield], followed by reductive methylation[12] [*t*-BuOK (1 equiv),[13] THF, 24 °C, 15 min; K (2.5 equiv), liquid NH_3/THF (10:1), −78 °C, 20 min; MeI (10 equiv), −78 → −33 °C; excess NH_4Cl], furnished **12**, mp 170–172 °C, with complete stereoselectivity in 84% yield.



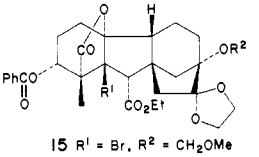
11



12



13 R = Me
14 R = H



15 R^1 = Br, R^2 = CH_2OMe
16 R^1, R^2 = H

Finally, the conversion of acid **12** to lactone **2** was essentially a matter of refunctionalization. Although direct lactonization of model compounds analogous to **12** has been achieved,[3a,4b] this appeared to be impractical on a substrate as complex as **12**. It was accordingly modified to **14** before attempting such a transformation. Selective acid-catalyzed hydrolysis of the enol ether function of **12** could not be achieved,[12] but with mercury(II) nitrate catalysis[14] [0.33 equiv, $MeCN/H_2O$ (5:1), 24 °C, 18 h] the corresponding ketone, mp 129–131 °C (77% yield), was obtained and reduced ($NaBH_4$, EtOH, 0 °C, 1.5 h) to the 3α-alcohol,[15] mp 129–132 °C (90%), followed by ethylation ($MeCH{=}N_2$) and benzoylation to give **13**, mp 133–135 °C (79%). Protection of the 6α-carboxyl function as the ethyl ester allowed the 4α-carboxyl function to be liberated selectively,[16] furnishing acid **14**, mp 178–182 °C (77%), which was then converted ($KHCO_3$, KBr_3, 0 °C, 1.5 h) into the unstable bromo lactone **15** [IR (CH_2Cl_2) 1790, 1740, 1720 cm^{-1}]. Removal of the bromine substituent with *n*-Bu_3SnH[4b] gave a complex mixture of products, but treatment with a large excess of chromium(II) diacetate in the presence of *n*-PrSH[17] removed both the halogen and the methoxymethyl protecting group to give lactone **16**, mp 209–212 °C (50% from **14**). Finally, the C(6) ester group was isomerized [DBU (5 equiv), DMF, 90 °C, 17 h] to the more stable β configuration and the resulting product, mp 215–218 °C (86%) hydrolyzed [0.25 M NaOH, MeOH/H_2O (4:1), 28 °C, 40 h] and methylated (CH_2N_2) to give **2**, mp 272–274 °C, which was chromatographically and spectroscopically indistinguishable (^1H NMR, IR, mass spectrum) from an authentic sample.[7]

This preparation of **2** translates into a ~34-step sequence to gibberellic acid.[18,19] Although somewhat more lengthy than our earlier approach,[7] the present synthesis is completely stereoselective, and the scope for refinements to more efficient routes is considerable.

(8) All compounds gave ^1H NMR, IR, and mass spectral data as well as C and H microanalyses (±<0.4%) which were consistent with structural assignments. Reactions were carried out, where appropriate, under an atmosphere of purified nitrogen, and yields are given for homogeneous, crystalline products. Numbering of structures **2** and **11–16** is according to; Rowe, J. R., (Ed. "The Common and Systematic Nomenclature of Cyclic Diterpenes", 3rd Rev.; Forest Product Laboratory, U.S. Department of Agriculture: Wisconsin, 1968. Structural formulas **2–16** represent racemic compounds.

(9) Fluorenone **1** was obtained[6] as a 4:1 mixture with its $\Delta^{1(9a)}$ isomer. Since considerable losses were incurred during chromatography of these air-sensitive compounds, the mixture was used directly in the hydrocyanation process. The α,β-unsaturated ketone does not add HCN but isomerized slowly to **1** during the course of the reaction.

(10) Birch, A. J.; Macdonald, P. L.; Powell, V. H. *J. Chem. Soc. C* **1970**, 1469–1476.

(11) Blair, I. A.; Ellis A.; Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1978**, *31*, 405–409.

(12) Loewenthal, H. J. E. "Guide for the Perplexed Organic Experimentalist"; Heyden: London, 1978; pp 133–138. We are grateful to Professor Loewenthal for helpful correspondence on this procedure.

(13) Brown, J. M.; Cresp, T. M.; Mander, L. N. *J. Org. Chem.* **1977**, *42*, 3984–3986.

(14) de Oliveira Baptista, M. J. V.; Barrett, A. G. M.; Barton, D. H. R.; Girijavallabhan, M.; Jennings, R. C.; Kelly, J.; Papadimitriou, V. J.; Turner, J. V.; Usher, N. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1477–1550. We are grateful to Dr. J. V. Turner for drawing our attention to the use of mercury(II) nitrate; the acetate was unsatisfactory.

(15) The stereochemistry at C(3) was assumed on the basis of ref 3a and confirmed subsequently by the observation of deshielding of the C(3) proton in the ^1H NMR spectra when bromine was introduced at C(5) to give lactone **15**.

(16) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459–4462.

(17) Barton, D. H. R.; Basu, N. K.; Hesse, R. H.; Morehouse, F. S.; Pechet, M. M. *J. Am. Chem. Soc.* **1966**, *88*, 3016–3021.

(18) Cf.: Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031–8034. Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *Ibid.* **1978**, *100*, 8034–8036.

(19) We are indebted to A. L. Cossey for technical assistance and to Dr. A. J. Baker for helpful correspondence.

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