= 6.5 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 1.17 (s, 3 H), 3.60 (d, J = 7 Hz, 1 H)) in 52% yield from **5b**.

Treatment of the hydroxy ketone **2b** with triphenylmethylenephosphorane in dimethyl sulfoxide (12 h, 55 °C)[10] gave the *exo*-methylene compound **2d**[6] (mp 68.0–69.0 °C (from hexane); NMR δ_{Me_4Si} (CCl_4) 0.74 (d, J = 7 Hz, 3 H), 0.87 (d, J = 7 Hz, 3 H), 0.98 (s, 3 H), 3.60 (d, J = 7.5 Hz, 1 H), 4.63 (br s, 1 H), 4.75 (br s, 1 H)) in 92% yield. Reductive cleavage of **2d** with lithium in ethylamine (1 min, 16 °C) gave a single alcohol, **1b**, in 90% crude yield.[11] There was no evidence that any of the 10β epimer of **1b** (retention of configuration in the ring opening) was obtained in this reaction. Without purification **1b** was converted into the tosylate **1c**[6] (mp 81–82 °C (from hexane); NMR δ_{Me_4Si} (CCl_4) 0.75 (d, J = 6 Hz, 3 H), 0.78 (d, J = 6 Hz, 3 H), 0.86 (d, J = 6 Hz, 3 H), 1.63 (br s, 3 H), 2.45 (s, 3 H), 4.52 (d, J = 8 Hz, 1 H), 5.13 (br s, 1 H), 7.23 (d, J = 8 Hz, 2 H), 7.72 (d, J = 8 Hz, 2 H)) using tosyl chloride in pyridine (96 h, 25 °C) in 60% overall yield from **2d**.

We also carried out the conversion of the model tricyclodecanone **2a** into (+)-spiroaxene (**1d**)[1] in a similar manner. Methylenation of **2a** as above gave **2c** (NMR δ_{Me_4Si} (CCl_4) 0.82 (d, J = 6 Hz, 6 H), 0.97 (s, 3 H), 4.64 (br s, 1 H), 4.47 (br s, 1 H)) which upon reaction with lithium in ethylamine gave **1d**[6] (NMR δ_{Me_4Si} (CCl_4) 0.75 (d, J = 6 Hz, 3 H), 0.83 (d, J = 6 Hz, 6 H), 1.72 (br s, 3 H), 5.28 (br s, 1 H); $[\alpha]^{25}_D$ +11.6° (c 2.0, ether).[11]

Bose, Kistner, and Farber[12] have reported the conversion of menthyl tosylate into neomenthylamine via S_N2 reaction with sodium azide in aqueous dimethylformamide followed by lithium aluminum hydride reduction of the azide. However, attempted conversion of **1c** to the azide **1e** using their procedure led primarily to the formation of elimination products as did the use of potassium azide in acetonitrile containing 18-crown-6. It was clear that it would be necessary to carry out the tosylate displacement under conditions which would be more favorable to an S_N2 reaction. This was accomplished by treating **1c** with 3 equiv of potassium azide in benzene containing 5 equiv of 18-crown-6 (48 h, 80 °C).[13] The azide **1e** showed NMR δ_{Me_4Si} (CCl_4) 0.71 (d, J = 6 Hz, 3 H), 0.93 (d, J = 6 Hz, 3 H), 0.97 (d, J = 6 Hz, 3 H), 1.77 (br s, 3 H), 3.47 (s, 1 H), 5.20 (br s, 1 H); mass spectrum (70 eV), no M^+, m/e 219 ($M - N_2$, weak), 204 ($M - HN_3$, strong). Reduction of **1e** with $LiAlH_4$ in ether at reflux gave the amine **1f** (NMR δ_{Me_4Si} (CCl_4) 0.71 (d, J = 6 Hz, 3 H), 0.87 (d, J = 5 Hz, 6 H), 1.73 (br s, 3 H), 2.63 (br s, 1 H), 5.27 (br s, 1 H)) in 30% overall yield[14] from **1c**.

Using a procedure analogous to that of Hertler and Corey,[15] **1f** was converted into (−)-axisonitrile-3 (**1a**) in 85% overall yield by treatment with a 2:1 mixture of formic acid in acetic anhydride at reflux for 2 h followed by reaction with tosyl chloride in pyridine at 25 °C for 1 h. (The formamide derivative, presumably (+)-axamide-3,[1,16] was isolated as an intermediate in this sequence.) The synthetic material[6] showed mp 97–99 °C (from hexane); NMR δ_{Me_4Si} (CCl_4) 0.75 (d, J = 6.5 Hz, 3 H), 0.93 (br d, J = 6.5 Hz, 6 H), 1.75 (br s, 3 H), 3.52 (br s, 1 H), 5.14 (br s, 1 H); IR (CCl_4) 2120 cm^{-1}; $[\alpha]^{25}_D$ −71° (c 0.35, $CHCl_3$).

These physical properties generally agreed with those reported for (+)-axisonitrile-3,[1] the enantiomer of **1a**, except for the sign of the optical rotation.[1] However, there were small discrepancies between the observed NMR chemical shifts, particularly for the methyl groups of the isopropyl group, and those reported by Sica and co-workers.[1] Therefore, verification of the structure of the synthetic material was desirable. Unfortunately, a direct comparison of the synthetic material with the natural product could not be made since neither a pure authentic sample nor copies of the original spectral data were available to us. In order to confirm the structure of the synthetic compound, a single crystal X-ray study was carried out using a Syntex $P2_1$ four-circle diffractometer. A complete data set was collected; the published coordinates[1] were refined using Sheldrick's SHELX-76 least-squares program. The refinement converged, with a residual of 0.13, using isotropic thermal parameters and without the hydrogen atoms being included. A difference Fourier synthesis showed no peaks of electron density greater than 0.5e/Å^3. This conclusively demonstrated that the synthetic material was in fact (−)-axisonitrile-3 (**1a**).[17]

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(9) (a) For reviews covering the photochemical conversion of bicyclic cross-conjugated dienones into tricyclodecenones, see P. J. Kropp, *Org. Photochem.*, **1**, 1 (1967); K. Schaffner, *Adv. Photochem.*, **4**, 81 (1966). (b) A Hanau NK-20 low-pressure mercury lamp was used as the light source.
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(11) In general, the cyclopropane ring of simple vinylcyclopropanes is not cleaved by metals in liquid ammonia (see S. W. Staley, *Sel. Org. Transform.*, **2**, 97 (1972)). Compound **2c** was found to be stable to excess lithium in liquid ammonia at −33 °C for 2 h. However, **2c** and **2d** were rapidly cleaved by lithium in ethylamine and extreme care had to be exercised to prevent overreduction. To our knowledge the conversions of **2c** and **2d** into **1d** and **1b**, respectively, represent the first examples of reductive cleavages of vinylcyclopropanes with lithium in ethylamine. However, cleavages of strained divinylcyclopropanes such as octamethylsemibullavene with lithium in liquid ammonia have been reported (W. T. Borden, A. Gold, and S. D. Young, *J. Org. Chem.*, **43**, 486 (1978)).
(12) A. J. Bose, J. F. Kishner, and L. Farber, *J. Org. Chem.*, **27**, 2925 (1962).
(13) We are indebted to Professor Charles L. Liotta for discussions on this point and for a gift of 18-crown-6.
(14) The yield of the amine **1f** obtained in the reduction of the azide **1e** with $LiAlH_4$ in ether was surprisingly low. Other methods for accomplishing this conversion are being explored.
(15) W. R. Hertler and E. J. Corey, *J. Org. Chem.*, **23**, 1221 (1958).
(16) Spectral data for (−)-axamide-3 were not reported in ref 1.
(17) We are very grateful to Dr. Donald G. VanDerveer for his assistance in carrying out the X-ray work.

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Stereospecific Total Synthesis of Gibberellic Acid. A Key Tricyclic Intermediate

Sir:

Since the recognition of the central biological role of gibberellic acid (gibberellin A_3, GA_3) (**1**) in the plant kingdom,[1] the clarification of its chemical structure,[2] and commercial production on a large scale from the fungus *Gibberella fujikuroi*, this substance has occupied a major position in the field of natural products.[3] The biosynthesis of gibberellic acid from prenyl units, though long and involved, is known in considerable detail.[1,3,4] Despite extensive efforts (some 150 published papers from about 25 different laboratories), the total chemical synthesis of gibberellic acid has not previously been achieved,[5] largely because the combination of overall molecular complexity, centers of high sensitivity toward many reagents, and

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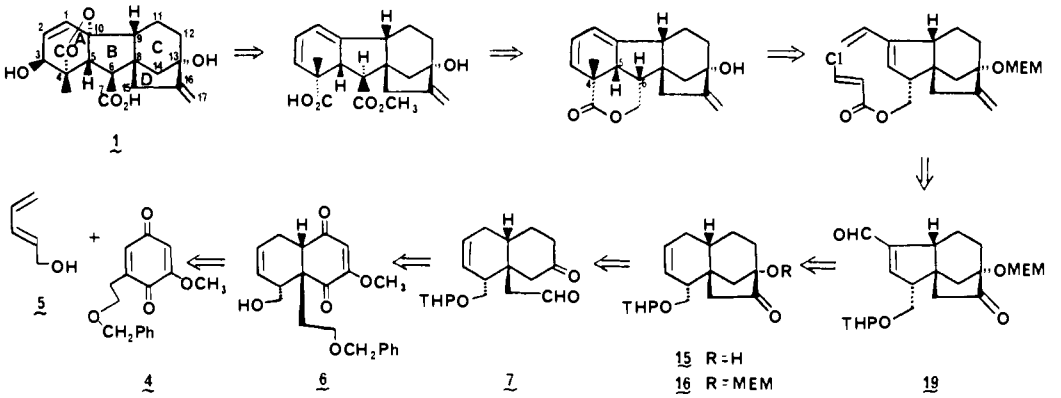
Scheme I

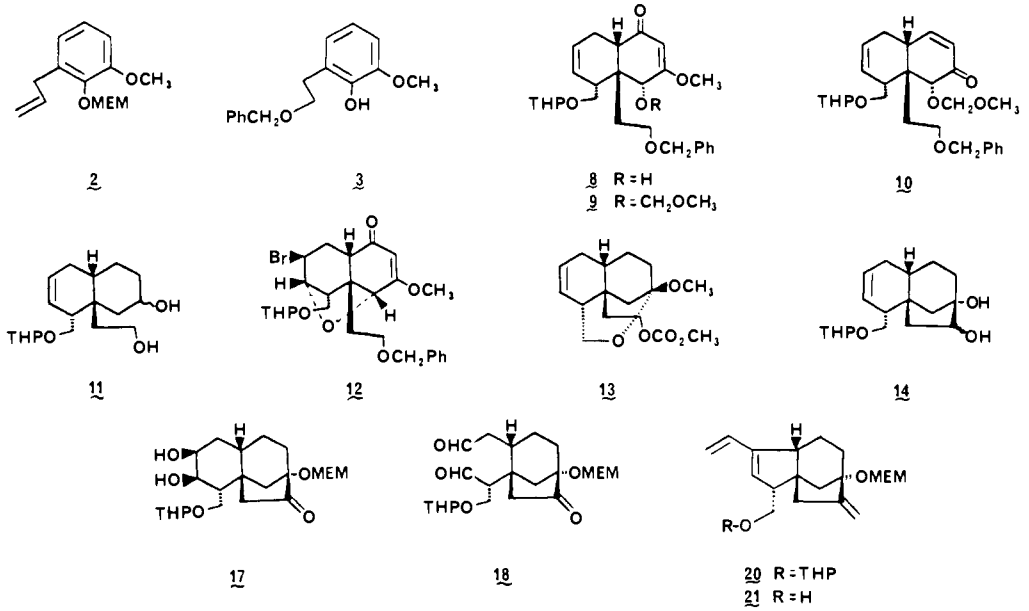


a singularly diabolical placement and density of functionality serves to thwart all but the most sophisticated of approaches.[6] We report in this and the following publication the first total synthesis of gibberellic acid by a route which is structurally unambiguous and stereospecific, and which employs a number of crucial new synthetic methods.[7]

The plan of synthesis, which was derived by extensive antithetic analysis, is outlined briefly in Scheme I.[8] Key features of the approach as revealed in this summary include (mentioned in the order of synthetic execution) (1) the stereospecific generation of the cis-fused B/C ring unit by Diels–Alder addition, (2) formation of the D ring by internal pinacol cyclization, (3) position-specific ring contraction of ring B from six to five members, (4) formation of ring A by internal Diels–Alder reaction and stereospecific methylation to form a pentacyclic lactone with all carbons in place, (5) oxidation and isomerization at C(6) and C(7) of the pentacyclic lactone, and (6) stereospecific elaboration of the complete A/B ring unit of gibberellic acid.[9]

The phenolic ether **2** was prepared in two steps and ~75% overall yield from 2-allyloxyanisole by (1) Claisen rearrangement at 230 °C for 2 h (89% of distilled product, bp 87–97 °C at 0.6 mm, containing 93% ortho-allyllic and 7% para-allylic phenol),[10] followed by (2) etherification of the resulting phenol using sequentially 1.3 equiv of sodium hydride in tetrahydrofuran (THF) at 0 °C and 1.6 equiv of chloromethyl 2-methoxyethyl ether (MEM chloride[11]), first at 0 °C and then at 25 °C for 2 h.[12] Conversion of **2** to the phenol **3** was accomplished by the sequence (1) oxidation of **2** with 3 equiv of sodium periodate and 0.2 mole % of osmium tetroxide in 3:1 THF–H_2O at 0 °C for 0.5 h and 23 °C for 1.5 h, (2) immediate reduction of the noraldehyde so obtained with sodium borohydride in absolute ethanol at 0 °C for 20 min, (3) benzylation of the resulting primary alcohol via the sodium salt (excess NaH in THF) in THF with excess benzyl bromide at reflux for 15 h, and (4) selective cleavage of the MEM group using 1.5 equiv of trifluoroacetic acid in methylene chloride at 23 °C for 18 h. After column chromatography pure phenol **3** was obtained in 74% yield overall from **2** as a colorless oil. Oxidation of the phenol **3** to the yellow quinone **4** (Scheme I), mp 71–72 °C, was effected by stirring in dimethylformamide solution at 23 °C for 4 days with molecular oxygen in the presence of 0.08 equiv of bis(salicylidene)ethylenediiminocobalt(II) (salcomine)[13,14] (>75% yield).

Reaction of the quinone **4** with *trans*-2,4-pentadien-1-ol (**5**)[15] occurred upon heating in benzene solution at reflux for 30 h to afford a *single* crystalline adduct (**6**) in 91% yield.[16] The next phase of the synthesis, transformation of the adduct **6** to the keto aldehyde **7**, was originally attempted using the well-known Woodward procedure.[17a] However, because this direct method failed completely, alternative routes were examined.[17b] The most satisfactory from the standpoint of reproducibility and ease of scale-up consisted of the following sequence: (1) reaction of **6** with 1.1 equiv of dihydropyran and 0.12 mol % *p*-toluenesulfonic acid in methylene chloride (10 mL/g of **6**) at 0 °C for 18 h to form quantitatively the tetrahydropyranyl (THP) ether; (2) reduction of the THP ether with 1 mol equiv of sodium borohydride in absolute ethanol at 0 °C for 100 min to produce the hydroxy enone **8** (100%); (3) conversion of **8** to the α-methoxymethylenoxy ketone **9** by reaction with 8 equiv of *N,N*-diisopropylethylamine and 4 equiv of chloromethyl methyl ether in methylene chloride at



reflux for 9 h (100%); (4) reduction of the keto group in **9** with lithium aluminum hydride in ether at −10 °C for 1 h, isolation, and immediate mesylation of the resulting alcohol at −58 °C in THF with 2 equiv each of methanesulfonyl chloride and triethylamine, followed by slow addition of saturated aqueous potassium bicarbonate and gradual warming to 0 °C over 45 min to effect solvolysis, and finally chromatography of the product on silica gel to give **10** in 77% overall yield from **6**; (5) selective hydrogenation[18] of the enone double bond of **10** using 1.0 equiv of hydrogen and 5% rhodium-on-carbon catalyst at 23 °C in THF; and (6) addition of a solution of the hydrogenation product and *tert*-butyl alcohol (10 equiv) in THF to 12 equiv of lithium in liquid ammonia at −78 °C over 7 min, stirring at reflux for 6 h, quenching with ammonium chloride, and isolation by chromatography on silica gel to yield the THP ether diol **11** in 63% overall yield from **10.** Oxidation of **11** with dipyridinechromium(VI) oxide (Collins reagent) (excess) in methylene chloride at −45 °C for 2 h and −25 °C for 1 h with stirring in the presence of dry, acid-washed Celite gave after treatment with powdered sodium bisulfate monohydrate (stirring at −20 °C for 30 min), dilution with dry ether, filtration, and concentration the sensitive keto aldehyde **7** in 84% yield as a pale yellow oil which was used as such in the next step (intermediate storage at −78 °C for a minimal period).

The persistence of a cis-ring fusion in the various intermediates derived from the Diels–Alder adduct **6** could be demonstrated chemically. Thus, reaction of **8** with *N*-bromosuccinimide in THF at 23 °C afforded quantitatively the bridged bromo ether **12.** Further, reaction of the diol **11** with 1 equiv of methyl chloroformate–pyridine gave selectively the carbonate of the primary alcohol which was oxidized (Collins reagent) to the corresponding cyclohexanone and treated with *p*-toluenesulfonic acid–methanol to produce in high overall yield the bridged ketal **13.**

The pinacol cyclization of the keto aldehyde **7** to the tricyclic intermediate **14** proved to be a more difficult proposition than expected from earlier studies of closely related models.[9a] The most satisfactory and convenient procedure involved preparation of finely powdered metallic titanium under argon by addition of small pieces of potassium to a mixture of titanium trichloride in THF (8.5 equiv of $TiCl_3$ and 24 equiv of K)[9a,19] and then heating cautiously at reflux for 3 h, cooling to 23 °C, and gradual addition of the keto aldehyde **7** in THF. The reaction mixture was stirred at 23 °C for 2.5 h, cooled to 0 °C, and very cautiously treated dropwise with anhydrous methanol, diluted with aqueous K_2CO_3, filtered through Celite, and extracted with 4:1 ether–methylene chloride. After isolation the product (~10-g batch size) was chromatographed on a Waters Associates Model 500 preparative machine which separated the three major components easily and afforded 40% *cis*-**14,** 15% *trans*-**14,** and ~10% diol **11** (which was recycled).[20]

Oxidation of either *cis*- or *trans*-**14** (or a mixture of the two) to form the ketol **15** without appreciable glycol cleavage was readily accomplished via an oxysulfonium intermediate, in accordance with previously published results.[21] The most satisfactory conditions for the oxidation involved addition of pinacol(s) **14** to a suspension of the complex formed from 7 equiv of dimethyl sulfoxide and 3.5 equiv of trichloroacetic anhydride in methylene chloride at −60 °C for 1 h, stirring the mixture of reactants at −50 °C for 45 min, treatment with 3.5 equiv of triethylamine at −50 to +23 °C over 2.5 h, and finally extractive isolation (ether–methylene chloride).[22] The ketol **15** (yield 75–80% if purified chromatographically) was converted directly without purification[23] to the MEM ether derivative **16**[11,24] by treatment with 3 equiv of MEM chloride and 10 equiv of diisopropylethylamine in methylene chloride at reflux for ~16 h (65% yield overall from **14** after chromatographic purification on silica gel).

The next stage of the synthetic approach required the adjustment of size and pattern of functionality of the B ring of the tricyclic intermediate **16,** which was achieved as follows. Treatment of a solution of **16** in acetone–water (2.5:1) with 1.3 equiv of *N*-methylmorpholine *N*-oxide and 0.05 equiv of osmium tetroxide at 23 °C for 80 h furnished a single cis diol (**17**) (89% yield after chromatography)[25] which was cleaved by reaction with 1.03 equiv of lead tetraacetate in benzene at 5 °C for 0.5 h. The sensitive dialdehyde **18,** isolated from the reaction mixture simply by addition of ether, filtration through Celite–anhydrous sodium sulfate, and concentration in vacuo was used directly in the next step without purification (and with minimal delay[26]). Treatment of **18** with 0.2 equiv of dibenzylammonium trifluoroacetate[27] in benzene at 50 °C for 1 h gave after chromatography on silica gel the desired α,β-unsaturated aldehyde **19** in 64% overall yield from the diol **17.** The yield of **17** from the cyclization is actually higher since **19** undergoes partial decomposition on silica gel; in practice, therefore, **19** was used for the next step without purification. Reaction of **19** with 5 equiv of methylenetriphenylphosphorane in THF–hexamethylphosphoramide at reflux for 3.5 h furnished the Wittig product **20** in good yield (44% overall from diol **17;** 80% from purified keto aldehyde **19**). Exposure of **20** to acetic acid–THF–water (3:1:1) at 35 °C for 40 h produced the diene alcohol **21** cleanly without detectible cleavage of the MEM protecting group (32% overall for 5 steps from **16**). The successful production of the critical tricyclic intermediate **21** in quantity set the stage for the completion of the synthesis of gibberellic acid as described in the following communication.[28,29]

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(1) See, H. N. Krishnamurthy, Ed., "Gibberellins and Plant Growth", Wiley, New York, 1975.

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(3) See (a) J. R. Hanson, "The Tetracyclic Diterpenes", Pergamon Press, Oxford, 1968; (b) K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, "Natural Products Chemistry", Vol. 1, Academic Press, New York, 1974, p 265.

(4) See also (a) B. E. Cross in "Progress in Phytochemistry", Vol. 1, Interscience, New York, 1968; (b) B. Dockerill, R. Evans, and J. R. Hanson, *J. Chem. Soc., Chem. Commun.*, 919 (1977), and papers therein cited.

(5) A number of simpler gibberellins and degradation products of gibberellic acid have been synthesized. See (a) K. Mori, M. Shiozaki, N. Itaya, T. Ogawa, M. Matsui, and Y. Sumiki, *Tetrahedron Lett.*, 2183 (1968), and K. Mori, M. Shiozaki, N. Itaya, M. Matsui, and Y. Sumiki, *Tetrahedron*, **25,** 1293 (1969), for a 52-stage synthesis of gibberellin A_4; (b) W. Nagata, T. Wakabayashi, Y. Nayase, M. Narisada, and S. Kamata, *J. Am. Chem. Soc.*, **93,** 5740 (1971), and **92,** 3202 (1970), for a 49-step route to gibberellin A_{15}; (c) H. O. House and D. G. Melillo, *J. Org. Chem.*, **38,** 1398 (1973), and K. Mori, *Tetrahedron*, **27,** 4907 (1971), for syntheses (>30 steps) of epiallogibberic acid.

(6) For a discussion see R. L. Danheiser, Ph.D. Dissertation, Harvard University, 1978.

(7) The problem of the synthesis of gibberellic acid has provided the impetus for the development of many new synthetic methods,[6] for example from the laboratories of Stork (see G. Stork, D. F. Taber, and M. Marx, *Tetrahedron Lett.*, 2445 (1978), and references therein cited), Loewenthal (see H. J. E. Loewenthal and S. Schatzmiller, *J. Chem. Soc., Perkin Trans. 1*, 2149 (1975), and references cited), S. Masamune (see S. Masamune, *J. Am. Chem. Soc.*, **83,** 1009 (1961); **86,** 288 (1964)), Dolby (see L. J. Dolby and R. H. Iwamoto, *J. Org. Chem.*, **30,** 2420 (1965)), Mander (see D. J. Beames, J. A. Halleday, and L. N. Mander, *Aust. J. Chem.*, **25,** 137 (1972)), House (see H. O. House, D. G. Melillo, and F. J. Sauter, *J. Org. Chem.*, **38,** 741 (1973)), and Ziegler (see F. E. Ziegler and J. A. Kloek, *Tetrahedron Lett.*, 315 (1974)).

(8) Much of the work described herein has been disclosed in various lectures, e.g., at the Nichols Award Symposium, Tarrytown, N.Y., March 1977, and at the International Symposium on Organic Synthesis, Oxford, England, 1977.

(9) Certain key stages of this synthetic approach had already been tested and described in previous publications from this laboratory. These include (a) internal pinacol cyclization of a keto aldehyde (E. J. Corey and R. L. Carney, *J. Am. Chem. Soc.*, **93,** 7318 (1971), and E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, **41,** 260 (1976)); (b) internal Diels–Alder approach to the construction of the A/B ring unit (E. J. Corey and R. L. Danheiser, *Tetrahedron Lett.*, 4477 (1973)); (c) stereospecific placement of all A ring ring substituents (E. J. Corey, T. M. Brennan, and R. L. Carney, *J. Am. Chem. Soc.*, **93,** 7316 (1971)).

(10) The mixture was used as such with purification conveniently effected at a subsequent stage.

(11) E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976).
(12) Structural assignments for all stable synthetic intermediates are based upon proton magnetic resonance (^{1}H NMR), infrared, and mass spectra determined using purified, chromatographically homogeneous samples. In addition ultraviolet spectra were determined where appropriate and were also consistent with the formulations shown herein. All reactions involving air- or moisture-sensitive components were carried out in an atmosphere of dry argon.
(13) (a) H. M. Van Dort and H. J. Geursen, *Recl. Trav. Chim. Pays-Bas*, **86**, 520 (1967); (b) L. H. Vogt, Jr., J. G. Wirth, and H. L. Finkbeiner, *J. Org. Chem.*, **34**, 273 (1969).
(14) The quinone **4** could also be obtained in high yield from the phenol **3** by oxidation with 2 equiv of Frémy's salt in aqueous methanol; however, this procedure was less convenient largely because of the labor involved in preparing the reagent. Using the reactions outlined above the quinone **4** can be prepared reproducibly in 100-g lots.
(15) (a) R. G. Glushov and O. Y. Magidson, *Med. Prom. SSSR*, **16**, 27 (1962); (*Chem. Abstr.*, **58**, 4420 (1963)); (b) S. Oida and E. Ohki, *Chem. Pharm. Bull.*, **17**, 1990 (1969).
(16) The structure and stereochemistry of the adduct was anticipated to be that expressed by **6** on the basis of much precedent in the literature, and this expectation is fully confirmed by the data which follow.
(17) (a) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952). (b) For a subsequent application of one of the sequences developed in the course of our investigations, see J.-L. Gras, *Tetrahedron Lett.*, 4117 (1977).
(18) See S. K. Roy and D. M. S. Wheeler, *J. Chem. Soc.*, 2155 (1963).
(19) See J. E. McMurry and M. P. Fleming, *J. Org. Chem.*, **41**, 896 (1976). For a detailed account of the very extensive studies carried out on the cyclization of **7** and related substances with a wide range of reagents, see also ref 6.
(20) The less polar of the isomeric pinacols, mp 97–99 °C, is probably *cis*-**14** and the more polar isomer, mp 87.5–89 °C, *trans*-**14**, based upon previous experience with tricyclic analogues of known configuration (see, for example, ref 9a) and also on chemical data.
(21) See, E. J. Corey and C. U. Kim, *J. Org. Chem.*, **38**, 1233 (1973). The various known chromium(VI) reagents and many other standard oxidizing agents for alcohols afford mainly glycol fission products with substrates such as **14**.
(22) This is a useful modification of the procedure of Swern; see K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41**, 957 (1976), and S. L. Huang, K. Omura, and D. Swern, *ibid.*, **41**, 3329 (1976).
(23) The ketol **15** is prone to 1,2 rearrangement of methylene at the bridgehead to form the stereoisomeric α-ketol upon exposure to base or acid or prolonged chromatography. This allogibberic → gibberic type rearrangement is driven by the relief of strain in going from cis-fused B/C rings (skew-boat C ring) to trans-fused B/C rings (chair C ring). The occurrence of the same rearrangement with 17-nor-17-oxoallogibberic acid represented an inconsistency in the originally assigned stereochemistry of gibberellic acid which led us to propose the X-ray crystallographic study (see ref 2d) that eventually produced the correction of the earlier configurational assignment at C(9).
(24) The β-methoxyethoxymethyl (MEM) protecting group[11] was originally developed for this specific application.
(25) For method see V. Van Rheenen, R. C. Kelly, and D. A. Cha, *Tetrahedron Lett.*, 1973 (1976).
(26) As might be expected the dialdehyde **18** is quite unstable (e.g., to water or silica gel).
(27) The use of this outstanding selective reagent (a crystalline solid) for this very demanding step (see ref 6) was arrived at by systematic experimental variation of secondary amine and acid components based on the idea of activating the methylene group α to the less hindered formyl group as an enamine by means of a not-too-basic, sterically discriminating secondary amine under almost neutral aprotic conditions. Other studies with this reagent will be published separately. Since these investigations one of the undersigned has successfully applied a similar reagent to the direct α methylenation of ketones; see J.-L. Gras, *Tetrahedron Lett.*, 2111 (1978).
(28) This investigation was supported financially by the U.S. National Science Foundation to whom we are deeply grateful.
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Stereospecific Total Synthesis of Gibberellic Acid

Sir:

This communication describes the completion of the stereospecific total synthesis of gibberellic acid (GA_3) (**1**) from a key tricyclic intermediate (**2**) which is readily accessible by the approach detailed in the preceding publication.[1] In addition we disclose a new facet of the chemistry of gibberellic acid which allows access to derivatives in which the C(7) substituent on ring **B** is in the unnatural (and generally less stable[2]) α orientation and which also provided useful direct correlation of GA_3 with a number of advanced synthetic intermediates.

Deprotonation of the hydroxy diene **2** with 1.0 equiv of *n*-butyllithium in tetrahydrofuran (THF) at −40 °C followed by acylation with 1.55 equiv of *trans*-2-chloroacrylyl chloride[3] at −40 °C for 0.5 h afforded the ester **3** in ~80% yield (~62% overall from the THP ether of **2**).[4] When **3** was heated in benzene solution containing ~100 equiv of propylene oxide (as a hydrogen chloride scavenger) in a sealed tube at 160 °C for 45 h under argon the pure crystalline lactone **4**, mp 149–150 °C, could be obtained in 55% yield after recrystallization.[5] The stereochemistry of **4** is assigned from the supposition of concerted, α-face, "endo" internal Diels–Alder addition (there was no evidence for the formation of an appreciable amount of any stereoisomer of **4**); it is supported by ^{1}H NMR data and also by subsequent transformation to GA_3. Treatment of the adduct **4** with 2.2 equiv of lithium isopropylcyclohexylamide and 5 equiv of hexamethylphosphoramide in THF at −78 °C for 50 min followed by reaction with 5 equiv of methyl iodide at −78 to 0 °C over 12 h afforded cleanly the methylated lactone **5** (~75% yield). At this stage the MEM[6] protecting group was removed from **5** by stirring in dry chloroform–ether–nitromethane (15:5:1 by volume) with 25 equiv of finely powdered *anhydrous* zinc bromide at 23 °C for 3 h to yield hydroxy lactone **6** (~70% after chromatography). The IR, ^{1}H NMR, UV, and mass spectra and the TLC mobility of this material were identical with those of a sample of optically active **6** obtained from natural gibberellic acid as described below.

The synthetic (±)-hydroxy lactone **6** was resolved using a novel procedure designed to take advantage of the lone (tertiary bridgehead) hydroxyl in **6**. Exposure of **6** to a large excess of phosgene and 3 equiv of 4-dimethylaminopyridine in dry methylene chloride at 23 °C for 36 h gave, after rapid filtration through dry Celite and concentration in vacuo, crude chloroformate **7**[7] which was directly treated with (−)-α-phenylethylamine ($[\alpha]^{25}_D$ −41.7° in benzene) to provide after isolation a mixture of two diastereomeric urethanes (**8**) (95% total yield) which could be separated cleanly by chromatography on silica gel using 1:1 ethyl acetate–hexane for elution (TLC R_f values in this solvent system, 0.24 and 0.20). The less polar diastereomer, $[\alpha]^{25}_D$ +59° (*c* 0.44, $CHCl_3$), was identical spectroscopically (IR, ^{1}H NMR, mass spectrum) and chromatographically with urethane prepared from hydroxy lactone **6** from natural GA_3 and (−)-α-phenylethylamine which showed $[\alpha]^{25}_D$ +61° (*c* 0.42, $CHCl_3$). Reaction of this less polar synthetic urethane **8** with 5 equiv of triethylamine and 3 equiv of trichlorosilane in dry benzene at 25 °C for 60 h[8] afforded in 95% yield resolved hydroxy lactone **6**, mp 211–212 °C, $[\alpha]^{20}_D$ +162° (*c* 0.58, $CHCl_3$), identical in all respects (IR, ^{1}H NMR, mass spectrum, TLC high pressure liquid chromatography) with the hydroxy lactone **6** derived from natural GA_3 which showed $[\alpha]^{20}_D$ +161° (*c* 0.49, $CHCl_3$).

The optically active lactone **6** was hydrolyzed to the corresponding hydroxy acid salt by heating at reflux with excess 1.0 N aqueous potassium hydroxide for 45 min (argon atmosphere) and the resulting solution was treated at 23 °C with 2.07 equiv of 0.013 M sodium ruthenate[9] in 1 N aqueous sodium hydroxide for 2.5 h. Filtration through Celite, acidification to pH 3 at 0 °C, and extraction afforded upon isolation the diacid **9**, spectroscopically and chromatographically identical with the diacid obtained from GA_3 (see below); the corresponding dimethyl esters (from excess CH_2N_2 in ether) were also identical. The formation of diacid **9** clearly proceeds by way of the intermediate acid aldehyde which undergoes

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