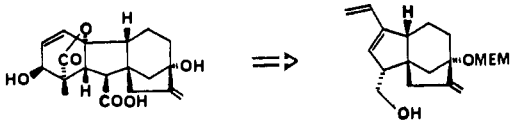
Total Synthesis of Gibberellic Acid. A New and Effective Route to a Key Tricyclic Intermediate

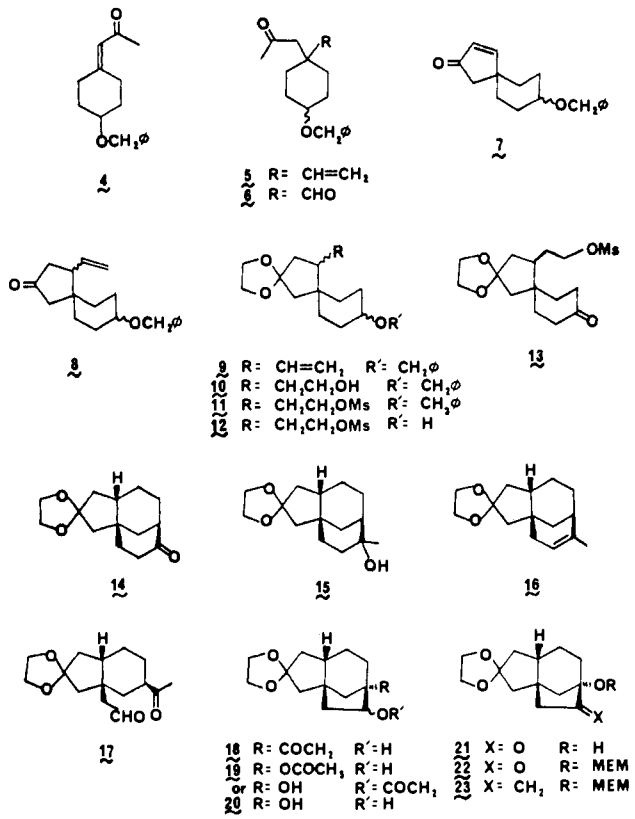
Sir:

A stereospecific total synthesis of gibberellic acid (GA_3, **1**), the first to be realized, has recently been reported.[1] A crucial part of this effort was the construction of the tricyclic diene **2**, a substance whose synthesis is considerably more challenging than might be expected for a molecule of its size. The problem of developing effective approaches to the tricyclic bridged structure **2** is of interest not only in connection with the synthesis of GA_3, but because it exposes some major gaps in current synthetic methodology. This communication outlines another approach to the synthesis of **2** which has emerged from our program.



1 ⇒ **2**

The new route to the dienol **2** begins with the conversion of 4-benzyloxycyclohexanone (**3**)[2] to enone **7** by a four-step spiroannulation sequence which is readily performed regardless of scale. Treatment of **3** with 1.5 equiv each of diethyl 2-oxopropylphosphonate[3] and potassium hydroxide in 4:1 ethanol–water at 5 °C for 28 h afforded enone **4** quantitatively after filtration through a column of silica gel.[4] Conjugate addition of the vinyl Gilman reagent (1.2 equiv; prepared from cuprous iodide and 2 equiv of vinyl magnesium bromide) in ether at −50 °C for 30 min afforded vinyl ketones **5a** and **5b** (3:1 mixture of isomers by ^1H NMR analysis; 93% yield).[5,6] Lemieux–Johnson oxidation of keto olefin **5** using osmium tetroxide (0.07 equiv), sodium metaperiodate (3 equiv), and pyridine (3 equiv) in 2:1 *tert*-butyl alcohol–water at 0 °C for 38 h gave keto aldehyde **6** (73%). Treatment of **6** with 0.11 equiv of ethanolic sodium hydroxide at 25 °C for 9 h yielded spiro enone **7** (87–100% after chromatography on silica gel).



Elaboration of spiro enone **7** to tricyclic ketone **14** was then accomplished as follows. Treatment of **7** with 2 equiv of divinyl cuprate (prepared from cuprous iodide and 2 equiv of vinyl magnesium bromide) in tetrahydrofuran (THF) at −50 °C for 15 min afforded keto olefin **8** in 63% yield after chromatography on silica gel.[7,8] Conversion of **8** to mesylate **11** was accomplished by the sequence (1) ketalization of **8** using 6:1 ethylene glycol–triethyl orthoformate and *p*-toluenesulfonic acid (~0.075 equiv) at 59 °C for 1.5 h;[9] (2) hydroboration of **9** with 3 equiv of disiamylborane in THF at 25 °C for 17 h, followed by oxidation with basic hydrogen peroxide; and (3) mesylation of **10** with methanesulfonyl chloride (1.3 equiv) and triethylamine (2 equiv) in methylene chloride at 0 °C for 1 h[10] (92% yield overall from **8**). Debenzylation of crude mesylate **11** to the desired alcohol **12** was cleanly accomplished only after pretreatment of crude mesylate **11** in THF with anhydrous sodium carbonate (0.4 equiv) and 10% palladium/carbon (0.12 wt equiv) at 25 °C under hydrogen (1 atm) until ^1H NMR analysis indicated complete removal of a sulfur-containing contaminant carried over from the previous step (5–24 h).[11] Subsequently, treated mesylate was submitted to hydrogenolysis in THF using ~10% by weight of 10% palladium/carbon under hydrogen at 25 °C for 4–24 h to afford **12** quantitatively. Oxidation of alcohol **12** to keto mesylate **13** was effected in 98% yield with pyridinium chlorochromate (2 equiv) in the presence of sodium acetate (0.4 equiv) in methylene chloride at 25 °C for 2.5 h.[12] Keto mesylate **13** was cleanly cyclized to a single tricyclic ketone **14** in 93% yield using potassium *tert*-butoxide (1.05 equiv) in 1:6 *tert*-butyl alcohol–benzene at 25 °C for 10 min. The stereochemistry of the cyclization product, which was expected to be as indicated by **14** from much literature precedent,[13] was subsequently confirmed by the successful conversion to the known synthetic target **2**.

Conversion of the bicyclo[3.3.1]nonane system in **14** to the hydroxylated bicyclo[3.2.1]octane skeleton in **24** was accomplished as follows. Addition of 1.4 equiv of methyllithium to an ethereal solution of **14** followed by quenching with 1.4 equiv of methanol (procedure repeated at 0 °C three times) afforded the tertiary alcohol **15** in 90% yield. Dehydration to the desired endocyclic olefin **16** was best carried out by heating **15** in 6:1 ethylene glycol–triethyl orthoformate containing *p*-toluenesulfonic acid (~0.085 equiv) at 57 °C for 6 h (58–63% yield after chromatography on Florisil), uncontaminated by any exocyclic isomer. Other methods of dehydration (thionyl chloride in pyridine, methanesulfonyl chloride and triethylamine in methylene chloride, phosphorus oxychloride in pyridine) afforded mixtures of exo- and endocyclic olefin. Ozonolysis of **16** (ozone at −78 °C in methanol, followed by addition of excess dimethyl sulfide, warming to 0 °C over 3 h, and stirring at 0 °C for 16 h) afforded the labile keto aldehyde **17**, which was immediately cyclized to the desired aldol product **18** (2:1 mixture of isomers; 82% yield overall from **16**) by treatment with 20 equiv of sodium hydroxide in ethanol at 0 °C for 2.5 h.

Introduction of the required bridgehead oxygen function was accomplished by Baeyer–Villiger reaction of **18**[14a] using 3,5-dinitroperoxybenzoic acid[14b] (5 equiv) and sodium carbonate (10 equiv) in 1,2-dichloroethane at 54 °C for 1.5 h in the presence of 4,4′-thiobis(6-*tert*-butyl-3-methylphenol) as radical scavenger[14,15] (0.01 equiv) to afford acetates **19** (2:1 mixture of isomers; 71% yield after chromatography on activity III basic Woelm alumina). Acetate cleavage was effected by treatment of **19** with 4 equiv of sodium hydroxide in methanol at 0 °C for 0.5 h to afford diols **20** in 92% yield. Oxidation of diols **20** and protection of the resulting ketol **21** as a β-methoxyethoxymethyl (MEM) ether[16] was accomplished as

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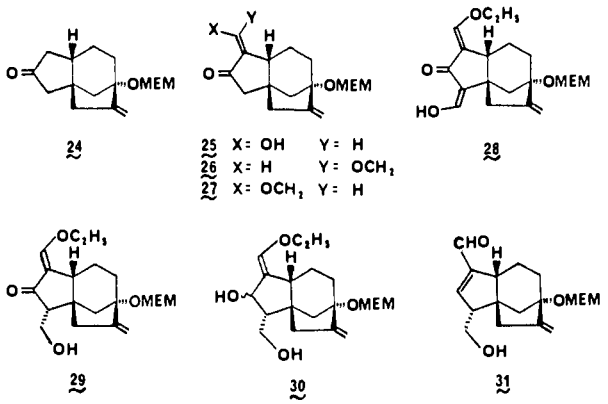
previously described[1a] to afford the keto MEM ether **22** in 53% overall yield from **20** (after chromatography on activity III basic Woelm alumina). Wittig methylenation was accomplished with 5 equiv of methylenetriphenylphosphorane in 2.5:1 THF-HMPA for 1.8 h at reflux to yield the desired olefin **23** (71% yield after chromatography on silica gel). Deketalization using 3:1 acetic acid-water for 1 h at 25 °C gave tricyclic ketone **24** quantitatively.



Conversion of tricyclic ketone **24** to target dienol **2** was accomplished by a seven-step sequence.[17] Selective formylation at the less shielded methylene α to the carbonyl in **24** was achieved in 88% yield by reaction with sodium hydride (6 equiv), ethyl formate (~30 equiv), and a trace of ethanol in 1,2-dimethoxyethane (DME) for 1 h at 0–25 °C.[18] The crude ketone **25** was immediately methylated using potassium *tert*-butoxide (2 equiv) and methyl iodide (18 equiv) in 10:1 THF-HMPA at 25 °C for 2 h to afford **26** and **27** (6:1 ratio; 60% yield overall from **24** after chromatography on silica gel). The assignment of structure is supported by ^{1}H NMR data and by the subsequent conversion of **26** and **27** to the known dienol **2.** Treatment of the mixture of **26** and **27** with sodium hydride (6 equiv), ethyl formate (~30 equiv), and a trace of ethanol in DME at 30 °C for 15–30 min afforded **28.** The β-dicarbonyl system was immediately reduced by conversion to the sodium enolate with sodium hydride (5 equiv) in THF at 25 °C, treatment with sodium bis(2-methoxyethoxy)aluminium hydride (5 equiv) at −20 to 0 °C for 50 min, and quenching with ammonium chloride at 0 °C to give after column chromatography a single stereoisomer **29.**[18,19] The stereochemistry of **29** was predicted from the consideration that the enolate protonation step which determines the stereochemistry of the final product should involve attack from the less shielded β face. Addition of **29** to a toluene solution containing sodium bis(2-methoxyethoxy)aluminum hydride (5 equiv) and 1,4-diazabicyclo[2.2.2]octane (5 equiv) at −20 °C followed by stirring at −20 °C for 0.5 h afforded diols **30** quantitatively.[20] An ethereal solution of the labile diols was immediately treated with a solution of aqueous oxalic acid (pH 3) at 0 °C for 2 h to afford α,β-unsaturated aldehyde **31** (60%). Treatment of **31** with 10 equiv of methylenetriphenylphosphorane in THF at 0 °C for 10 min afforded dienol **2** (65% yield after chromatography on silica gel). The spectra (IR, ^{1}H NMR, mass) and chromatographic behavior (TLC and high-pressure liquid chromatography) of this product were all identical with those found for a pure sample of **2** prepared by the previously described route.[1a] Further, the corresponding acetate esters were likewise demonstrated to be identical.

The synthesis of **2** reported herein demonstrates a completely different synthetic strategy from that previously utilized.[1a] In addition it illustrates a number of interesting situations in which high positional and stereoselectivity could be achieved by taking advantage of rather modest geometrical differences.[21]

References and Notes

(1) (a) E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, **100**, 8031 (1978); (b) E. J. Corey, R. L. Danheiser, S. Chandrasekaran, G. E. Keck, B. Gopalan, S. D. Larsen, P. Siret, and J.-L. Gras, *ibid.*, **100**, 8034 (1978).
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(3) Diethyl 2-oxopropylphosphonate is commercially available from Aldrich Chemical Co.; alternatively, this reagent (or the corresponding dimethyl phosphonate ester) may be prepared as previously described, (a) from iodoacetone and triethyl phosphite, H. I. Jacobson, M. J. Griffin, S. Preis, and E. V. Jensen, *J. Am. Chem. Soc.*, **79**, 2608 (1957); (b) from the cuprous salt of dimethyl methyl phosphonate and acetyl chlorlde, P. Savignac and F. Mathey, *Tetrahedron Lett.*, 2829 (1976).
(4) Satisfactory infrared, proton magnetic resonance, and high resolution mass spectral data were obtained on purified, chromatographically homogeneous samples of all synthetic intermediates described herein. All reactions involving air- or moisture-sensitive species were carried out in an atmosphere of dry argon.
(5) For a similar reaction of lithium dimethylcuprate with an exocyclic enone, see H. O. House, W. L. Respress, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).
(6) Intermediates **5–12** were carried through the synthetic scheme as a mixture of diastereomers.
(7) The addition of cuprates to cyclopentenones is often complicated by competing side reactions. See, for example, (a) G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973); (b) A. F. Kluge, K. G. Untch, and J. H. Fried, *ibid.*, **94**, 7827 (1972).
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(11) Some deketalization of the rather labile ketal occurred if the indicated two-step procedure was not employed.
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(19) We could only detect a single isomer of intermediates **29, 31,** and **2** by ^{1}H NMR and multiple development TLC analysis.
(20) We were unable to effect this type of carbonyl reduction in a similarly functionalized model system with a variety of other reducing agents including basic $NaBH_4$, $LiBH_4$, L-selectride, or 9-BBN.

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Stereochemistry of the Reaction of Chlorine(I) Trifluoromethanesulfonate with Alkenes and Alkyl Halides

Sir:

Trifluoromethanesulfonate derivatives (triflates) are important intermediates in organic chemistry. There are many methods for the synthesis of these compounds,[1] but few are applicable to the preparation of highly halogenated esters and only one perfluoro ester, $CF_3SO_3CF_3$, has been reported.[2,3] With the discovery of CF_3SO_3Cl,[4] a variety of new halogenated esters can be obtained by the addition of CF_3SO_3Cl to alkenes and by the novel halogen displacement reaction shown in the following equation.

$$CF_3SO_3Cl + R\text{-}X \rightarrow XCl + CF_3SO_3R$$

$$X = Cl, Br; R = \text{alkyl and haloalkyl}$$

Our interest has been in the synthesis of highly fluorinated esters and in the mechanisms of the addition and displacement

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