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Stereoselective Total Synthesis of Racemic Acorone

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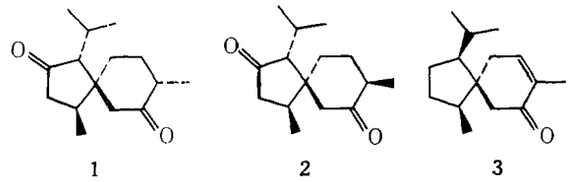
An efficient, stereoselective total synthesis of the acorane sesquiterpenes, (±)-acorone (1) and (±)-isoacorone (2), has been achieved. The synthetic approach, which utilizes a newly developed procedure for the spiroannulation of a cyclopentenone ring, commences with the alkylation of the pyrrolidine enamine (10) of 4-methyl-3-cyclohexene-1-carboxaldehyde with 3-iodo-2-chloropropene. Mercuric ion promoted hydrolysis of the vinyl halide 13 thus produced gave the γ-keto aldehyde 14, which underwent smooth, base-catalyzed cyclization to give the key intermediate, 8-methylspiro[4.5]deca-1,7-dien-3-one (15). Condensation of the enolate generated from compound 15 with acetaldehyde followed by the acid-catalyzed dehydration of the aldols gave a 47:53 mixture of (*E*)- and (*Z*)-1-ethylidene-8-methylspiro[4.5]deca-3,7-dien-2-one (17a and 17b, respectively). After the introduction of the two remaining methyl groups by a facile, one-pot procedure involving two successive treatments of 17a and 17b with lithium dimethylcuprate, followed by hydroboration and direct oxidation, a mixture consisting primarily of (±)-acorone (1) and (±)-isoacorone (2) was obtained. Separation of this mixture by preparative high-pressure liquid chromatography afforded the pure racemic natural products.

The greatest obstacle to the synthesis of the acorane sesquiterpenes such as acorone (1), isoacorone (2), and acorenone B (3) is the stereocontrolled construction of the spirocyclic carbon skeleton. A successful synthesis of these spiro sesquiterpenes depends critically, therefore, upon the generation of a quaternary carbon center which is suitably substituted for the direct annulation to a functionalized spiro[4.5]decane that may be subsequently elaborated to the target natural product. Although several syntheses of acorone (1) and isoacorone (2) have been reported,[1] the primary synthetic interest has been in acorenone B (3).[2] We now wish to report a highly stereoselective synthesis of racemic acorone and racemic isoacorone using a new approach for the spiroannulation of a cyclopentenone ring.[3]



1 2 3

As part of a general synthetic program, we have been interested in developing new synthetic methods for the construction of quaternary carbon atoms which bear dissimilarly functionalized alkyl appendages. We have recently discovered one particularly attractive procedure for the geminal alkylation at a carbonyl carbon atom that involves the direct conversion of ketones into the enamines of the homologous aldehydes.[4] These enamines are useful synthetic intermediates and may be employed without purification in subsequent reactions with electrophiles. For example, by the appropriate choice of electrophiles, this general synthetic procedure, which is depicted in eq 1, may be exploited for the preparation of α-allyldialkyl aldehydes,[4a] 4,4-disubstituted cyclohexenones,[4b] and 4,4-disubstituted cyclopentenones.[4c] When the starting ketone is cyclic, the latter two methods allow for the facile spiroannulation of cyclohexenones and cyclopentenones.

Our initial approach to the synthesis of acorone (1), shown in Scheme I, was based upon our new method for the spiroannulation of cyclopentenones and began with the ethylene glycol monoketal of cyclohexane-1,4-dione 4.[5] Thus, reaction

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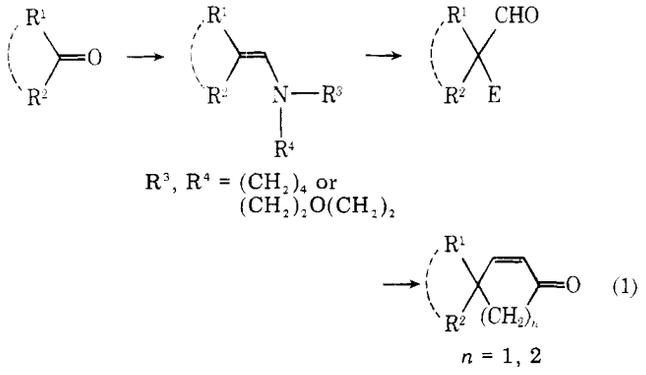


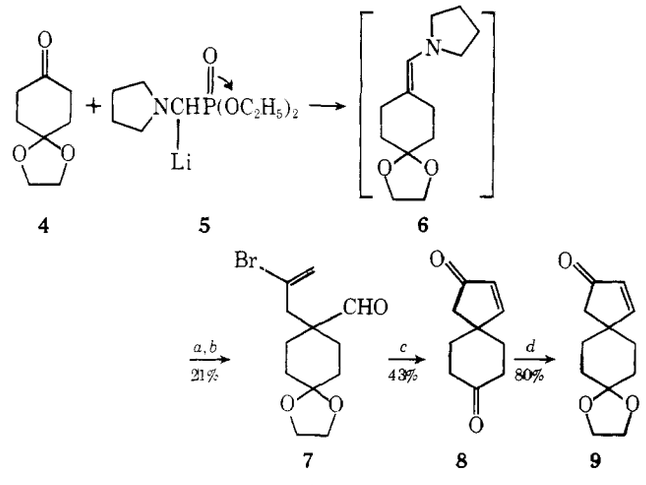
(1)

of **4** with diethyl lithiopyrrolidinomethylphosphonate (**5**), followed by the direct alkylation of the enamine **6**, produced the aldehyde **7**, albeit in only 21% overall yield. When this 2-(2-bromo-2-propenyl) aldehyde **7** was treated with concentrated sulfuric acid at 0 °C, cyclization to the cyclopentenone ring proceeded as anticipated, but unavoidable hydrolysis of the ketal also occurred concomitantly to give the spiro enedione **8** in 43% yield. Despite this difficulty, selective ketalization of the saturated carbonyl function was readily achieved producing the monoprotected enedione **9** in 80% yield. Owing to the low yield at the outset of this synthetic sequence, coupled with the problem of ketal hydrolysis in the subsequent cyclization step, an alternate approach to the synthesis of acorone was examined (Scheme II).

Another attractive enamine precursor to a suitably functionalized spiro[4.5]decane ring system is the enamine **10**. Unfortunately, all attempts to generate **10** in situ by the reaction of diethyl lithiopyrrolidinomethylphosphonate (**5**) with 4-methyl-3-cyclohexenone (**11**)[6] were unsuccessful. However, the reaction of the readily available 4-methyl-3-cyclohexene-1-carboxaldehyde (**12**)[7] with pyrrolidine in refluxing benzene containing a catalytic amount of *p*-toluenesulfonic acid cleanly provided the desired enamine **10** in 94% yield. When the enamine **10** was treated with 2-chloro-3-iodopropene, followed by aqueous hydrolysis, the alkylated aldehyde **13** was produced in 74% yield.

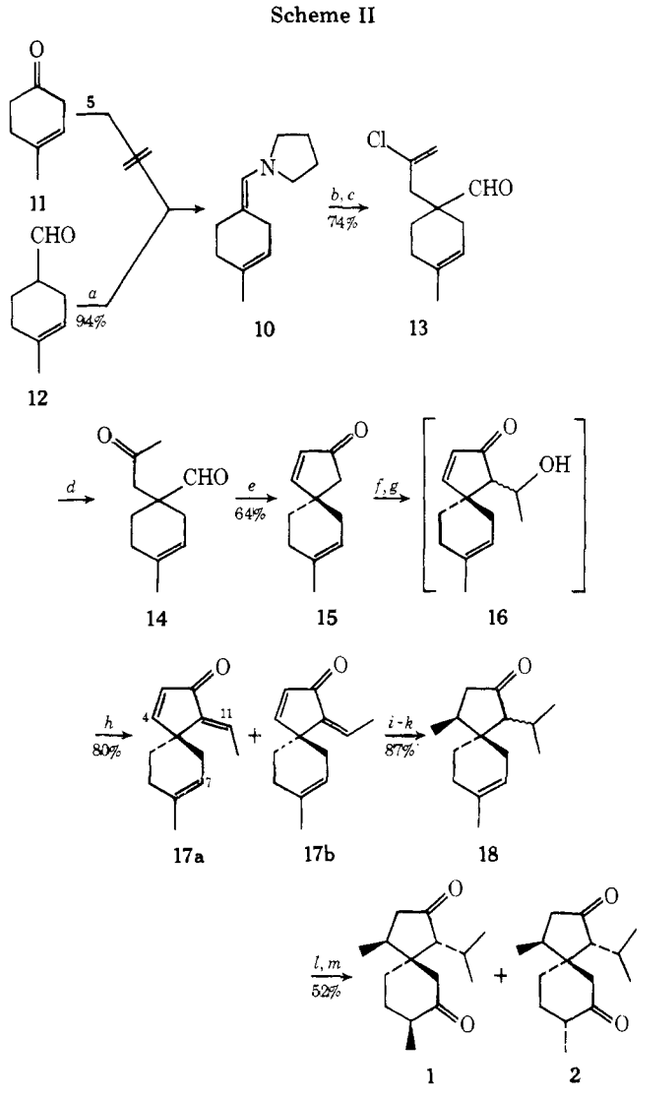
Efforts to promote the cyclization of the vinylchloro aldehyde **13** with concentrated sulfuric acid were rather unsatisfactory because they resulted in the formation of several products, only one of which was the desired spiro[4.5]decadienone **15**. Moreover, several other known methods for the hydrolysis of vinyl chlorides[8] proved equally fruitless. We have recently discovered, however, that vinyl chlorides may be

Scheme I



[a] $BrCH_2CHBr{=}CH_2/THF/\Delta$. [b] H_2O. [c] 98% $H_2SO_4/CH_2Cl_2/0$ °C. [d] $HOCH_2CH_2OH/TosOH/C_6H_6/\Delta$.

Scheme II



[a] $(CH_2)_4NH/TosOH/C_6H_6/\Delta$. [b] $ICH_2CHCl{=}CH_2/CH_3CN/\Delta$. [c] H_2O. [d] $Hg(OAc)_2/BF_3{\cdot}Et_2O/HOAc$. [e] 10% KOH/CH_3OH. [f] LDA/THF/−30 °C. [g] $CH_3CHO/THF/-78$ °C. [h] $TosOH/C_6H_6/\Delta$. [i] $(CH_3)_2CuLi/Et_2O/0$ °C. [j] HOAc. [k] $(CH_3)_2CuLi/Et_2O/0$ °C. [l] $B_2H_6/THF/25$ °C. [m] $Na_2Cr_2O_7/H_2SO_4/H_2O$.

conveniently converted into ketones under very mild conditions using mercuric acetate in the presence of boron trifluoride etherate.[9] For example, hydrolysis of the vinyl chloride **13** to the γ-keto aldehyde **14** was readily achieved with mercuric acetate and boron trifluoride etherate in glacial acetic acid at room temperature. When crude **14** was treated with 10% aqueous potassium hydroxide in methanol, cycloaldolization and dehydration proceeded smoothly to give the key intermediate spiro[4.5]decadienone **15** in 64% overall yield from compound **13**.

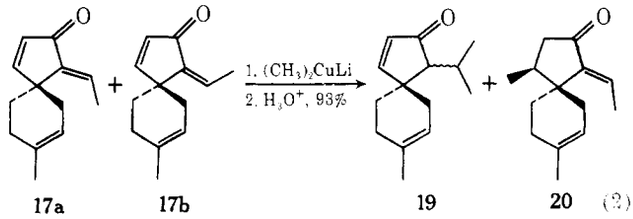
Completion of the construction of the carbon skeleton entailed the stereocontrolled introduction of an isopropyl group at C-1 and a methyl group at C-4. Since we anticipated that the direct isopropylation at C-1 might be attended with considerable difficulty, we elected instead to introduce the isopropyl group by an indirect method. Thus, the reaction of the enolate generated from the ketone **15** with acetaldehyde[10] produced a mixture of uncharacterized compounds presumed to be the directed aldols **16**. The subsequent *p*-toluenesulfonic acid catalyzed dehydration proceeded without incident to give an 80% overall yield of a mixture of the diastereomeric *E* and *Z* trienones **17a** and **17b** in the ratio of 47:53, respectively. This stereochemical assignment was based upon the downfield position of the C-11 vinyl proton of the *E* isomer **17a** [δ 6.57

(dq, J = 7.5, 0.8 Hz)] in relation to the C-11 vinyl proton of the Z isomer **17b** [δ 6.03 (q, J = 7.5 Hz)]. Moreover, the C-12 methyl group of **17a** has a high field position [δ 1.90 (d, J = 7.5 Hz)] with respect to the C-12 methyl group of **17b** [δ 2.19 (d, J = 7.5 Hz)]. In agreement with this assignment, the $Eu(fod)_3$ induced shifts of the vinyl proton at C-11 of **17a** are larger (0.11–0.41 ppm) than the corresponding shifts of the C-11 proton of **17b** (0.04–0.13 ppm). The comparison of the relative magnitudes of these shifts implies that the C-11 hydrogen in **17a** is syn to the carbonyl group. A similar comparison of the $Eu(fod)_3$ induced shifts of the C-12 methyl groups in **17a** and **17b** lends further support to this stereochemical assignment.

The next stage of the synthesis required the introduction of the two remaining methyl groups at C-4 and C-11, thereby completing the construction of the carbon skeleton of acorone. We anticipated that this task could be easily accomplished by the sequential addition of lithium dimethylcuprate to both the exo- and endocyclic enone systems of **17a,b**,[11] and a one-pot procedure was especially attractive. Following the addition of the E and Z trienones **17a** and **17b** to a slight excess of lithium dimethylcuprate, an equivalent of glacial acetic acid was added to quench the reaction. When the reaction mixture thus obtained was added directly to an excess of lithium dimethylcuprate, a product mixture consisting primarily (>95%) of the diastereomeric ketones **18**, which were epimeric at C-1, was obtained in 87% yield. Integration of the ^{13}C nmr signals for C-2 at δ 219.03 and 217.67 indicated **18** to be an approximately 1:1 mixture of C-1 epimers. Moreover, careful examination of the ^{13}C NMR spectrum revealed the presence of only one other carbonyl carbon (δ 219.75), albeit in less than 5% of the total products, which might be due to the presence of a C-4 epimer. Although unnecessary for the actual synthesis of acorone, base-catalyzed (methanolic sodium methoxide) epimerization at C-1 of **18** afforded an apparent equilibrium mixture that contained, on the basis of ^{13}C NMR, an 8:1 mixture of C-1 epimers.

This important reaction sequence generates two chiral centers and merits further comment. On the basis of previous reports,[12] the required configuration at the epimerizable center C-1 was known to be greatly favored thermodynamically and presented, therefore, no difficulty. The creation of the other new chiral center at C-4 was less predictable, but a careful examination of Dreiding molecular models suggested that the dimethylcuprate reagent should approach past the Δ^7 double bond, thus adding selectively to the endocyclic enone system from the sterically less hindered direction to give the desired configuration at C-4. The subsequent conversion of **18** into acorone and isoacorone (vide infra) verifies that the introduction of the methyl group at C-4 did indeed proceed with the anticipated stereoselectivity. A similar high degree of stereochemical control in a closely related cuprate addition has also been recently reported by Dolby.[1a]

While it was not crucial to the total synthesis of acorone, we were interested in determining whether there was any regioselectivity in the addition of the first equivalent of lithium dimethylcuprate to the trienones **17a** and **17b**. Consequently, treatment of a 47:53 mixture of the E and Z trienones **17a** and **17b** with a slight excess of lithium dimethylcuprate at 0 °C,[13] followed by quenching the reaction with aqueous acid, gave a mixture of the monoadducts **19** and **20** as the major products in 93% yield (eq 2). Integration of the signals for the protons at C-4 of **19** [δ 7.67 and 7.56 (overlapping d, J = 6 Hz)] and at C-11 of **20** [δ 6.71 (q, J = 7.5 Hz)] clearly showed that **19** and **20** were formed in approximately equal amounts. The stereochemical assignment of the E configuration for the enone **20** was based upon a comparison of the chemical shifts of the vinyl proton at C-11 (δ 6.71) and the C-12 methyl group (δ 1.82) with those observed for compound **17a**. Not only is this



17a **17b** **19** **20** (2)

assignment supported by the $Eu(fod)_3$ induced shifts of the vinyl and methyl protons, but it is also consistent with the NMR data previously reported for this compound.[1a] Apparently, lithium dimethylcuprate adds preferentially to the endocyclic double bond of the E isomer **17a**, but it adds selectively to the exo double bond of the Z isomer **17b**.

Returning to the synthetic task at hand, attention was directed to the conversion of the diastereomeric ketones **18** into acorone. After treating **18** with excess diborane in tetrahydrofuran, followed by oxidation of the intermediate boranes with chromic acid,[14] a mixture of (±)-acorone (**1**) and (±)-isoacorone (**2**), together with several minor unidentified products, was obtained. Separation of the components of the reaction mixture by preparative high-pressure liquid chromatography afforded pure (±)-acorone (**1**) [mp 101.5–102 °C (lit.[1a] 101.5–103.5 °C)] in 25% yield and pure (±)-isoacorone (**2**) (mp 66–67 °C) in 27% yield. Comparison of the IR, NMR, and mass spectra, as well as the GLC and TLC of synthetic racemic acorone and isoacorone, with those of authentic samples[15] confirmed their identity.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All boiling points are uncorrected. ^1H NMR spectra were determined on a Varian A-60A or HA-100 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield from the internal reference, tetramethylsilane (Me_4Si). The ^{13}C NMR spectra were determined on a Bruker WH-90 FT spectrometer, and the chemical shifts are reported in δ units downfield from internal Me_4Si. The infrared spectra (IR) were recorded on a Beckman IR-5A spectrophotometer using chloroform as solvent. Low-resolution mass spectra were obtained on a Du Pont (CEC) 21-491 instrument, and the high-resolution mass spectra were obtained on a Du Pont (CEC) 21-110 instrument. GLC analyses were performed on a Varian Aerograph 2720 equipped with a thermal conductivity detector and a 5 ft × 0.25 in. 1.5% OV-101, Chromosorb HP column unless otherwise noted. Glassware was oven dried prior to use, and all reactions were executed under dry nitrogen. The tetrahydrofuran (THF) was freshly distilled from potassium–benzophenone, and the ether was freshly distilled from sodium–benzophenone. The n-butyllithium–hexane and the methyllithium–ether were purchased from Alfa Inorganics, Danvers, Mass., and titrated prior to use. 2-Chloro-3-iodopropene was prepared in 65% yield by the procedure of Letsinger and Traynham.[16] Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

8-(2-Bromo-2-propenyl)-8-formyl-1,4-dioxaspiro[4.5]decane (7). To a well-stirred solution of diethyl pyrrolidinomethylphosphonate (4.0 g, 18.0 mmol) in anhydrous THF (60 mL) at −78 °C was slowly added n-butyllithium–hexane (18.0 mmol). After being stirred at −78 °C for 1 h, a solution of 1,4-dioxaspiro[4.5]decanone (**4**)[5] (2.3 g, 15.0 mmol) in anhydrous THF (5 mL) was added, and the stirring was continued at −78 °C for 4 h and then at room temperature overnight to give a solution of the enamine **6**. 2,3-Dibromopropene (15.0 g, 75.0 mmol) was added, and the mixture was heated at reflux for 48 h. Upon cooling to room temperature, H_2O (30 mL) was added, and the resulting reaction mixture was stirred vigorously at room temperature for 4 h. Saturated brine (50 mL) was then added, and the layers were separated. The aqueous layer was extracted with ether (3 × 75 mL), and the combined organic layers were washed with 1 N HCl and saturated $NaHCO_3$ and dried ($MgSO_4$). After removal of the excess solvent under reduced pressure, vacuum distillation gave 0.91 g (21%) of **7**: bp 128–130 °C (0.05 mm); IR 1625, 1715, 2705 cm^{-1}; NMR δ 9.69 (s, 1 H), 5.56 (m, 2 H), 3.91 (s, 4 H), 2.75 (s, 2 H), 1.50–2.20 (complex, 8 H); mass spectrum m/e 290, 288, 209 (base), 165, 99. The alkylated aldehyde **7** thus obtained was used in the next step without further purification.

Spiro[4.5]dec-1-ene-3,8-dione (8). While a rapid stream of dry

nitrogen was bubbled through concentrated sulfuric acid (3 mL) cooled to 0 °C, compound **7** (0.91 g, 3.15 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise. After completion of the addition, the dark reaction mixture was stirred at 0 °C for 2 h, whereupon it was poured slowly onto crushed ice. The aqueous mixture was extracted with methylene chloride (3 × 70 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of the excess solvent under reduced pressure, followed by flash distillation [oil bath at 200 °C (0.05 mm)] of the crude material thus obtained, afforded 0.24 g (43%) of **8**: >90% pure by GLC. Preparative GLC (5% Carbowax 20M, firebrick) provided an analytical sample: IR 1595 and 1715 cm^{-1}; NMR δ 7.67 (d, 1 H, J = 6 Hz), 6.16 (d, 1 H, J = 6 Hz), 2.47 (s, 2 H), 1.75–2.70 (complex, 8 H); mass spectrum m/e 164 (base), 94, 79, 66, 55; exact mass (calcd for $C_{10}H_{12}O_2$) 164.0837, found 164.0836.

1,4-Dioxadispiro[4.2.4.2]tetradec-9-en-11-one (9). A mixture of compound **8** (0.12 g, 0.8 mmol) and ethylene glycol (0.15 g, 2.4 mmol) in anhydrous benzene (2 mL) containing a catalytic amount of p-toluenesulfonic acid was heated at reflux for 12 h in the presence of Linde 4A molecular sieves (0.5 g). After cooling to room temperature, saturated brine (10 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (3 × 25 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). The excess solvent was evaporated under reduced pressure and the residue flash distilled [oil bath at 200 °C (0.05 mm)] to give 0.13 g (80%) of **9**: >90% pure by GLC; IR 1590 and 1705 cm^{-1}; NMR δ 7.59 (d, 1 H, J = 6 Hz), 6.08 (d, 1 H, J = 6 Hz), 3.97 (s, 4 H), 2.29 (s, 2 H), 1.62–1.90 (complex, 8 H); mass spectrum m/e 208, 164, 99, 86, 55; exact mass (calcd for $C_{12}H_{16}O_3$) 208.1099, found 208.1093.

1-(4-Methyl-3-cyclohexenylidenemethyl)pyrrolidine (10). A solution of 4-methyl-3-cyclohexene-1-carboxaldehyde[7] (**12**) (10.0 g, 0.08 mol) and pyrrolidine (7.2 g, 0.10 mol) in anhydrous benzene (60 mL) containing a catalytic amount of p-toluenesulfonic acid was heated at reflux for 8 h with continuous removal of water (Dean-Stark trap). The excess solvent was then evaporated under reduced pressure, and the crude enamine was distilled to give 13.3 g (94%) of **10**: >95% pure by GLC; bp 84–85 °C (0.7 mm); IR 1660 cm^{-1}; NMR δ 5.67 (br s, 1 H), 5.33 (br s, 1 H), 1.50–3.10 (complex, 17 H); mass spectrum m/e 177, 162, 91 (base), 70; exact mass (calcd for $C_{12}H_{19}N$) 177.1517, found 177.1517.

1-(2-Chloro-2-propenyl)-4-methyl-3-cyclohexene-1-carboxaldehyde (13). To a solution of the enamine **10** (8.0 g, 0.045 mol) in anhydrous acetonitrile (100 mL) was added 2-chloro-3-iodopropene (25.0 g, 0.125 mol), and the resulting solution was heated at reflux for 48 h. After evaporation of the excess solvent under reduced pressure, aqueous THF (100 mL, 1:1) was added, and the resulting mixture was stirred vigorously at room temperature for 5 h. Saturated brine (100 mL) was then added, and the layers were separated. The aqueous layer was extracted with ether (5 × 80 mL), and the combined organic layers were washed with 1 N HCl, 5% $Na_2S_2O_3$, and saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of the excess solvent under reduced pressure followed by distillation afforded 6.7 g (74%) of the alkylated aldehyde **13**: bp 74–75 °C (0.2 mm); IR 1640, 1725, 2735 cm^{-1}; NMR δ 9.57 (s, 1 H), 5.37 (br s, 1 H), 5.19 (m, 2 H), 1.50–2.70 (complex, 6 H), 2.60 (m, 2 H), 1.63 (br s, 3 H); mass spectrum m/e 200, 198, 123 (base), 122, 95, 93; exact mass (calcd for $C_{11}H_{15}ClO$) 198.0811, found 198.0805.

1-(2-Oxopropyl)-4-methyl-3-cyclohexene-1-carboxaldehyde (14). To a well-stirred solution of mercuric acetate (4.50 g, 14.0 mmol) and the vinyl halide **13** (1.86 g, 9.3 mmol) in glacial acetic acid (90 mL) was added freshly distilled boron trifluoride etherate (2.60 g, 18.0 mmol). Stirring was continued at room temperature for 12 h, during which time a white precipitate formed. After filtration of the reaction mixture and evaporation of the acetic acid in vacuo, saturated brine (50 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (4 × 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ and saturated brine and then dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure afforded 1.34 g of crude γ-keto aldehyde **14** which was >95% pure by GLC. An analytical sample was obtained by preparative GLC (5% Carbowax 20M, firebrick): IR 1710 and 2735 cm^{-1}; NMR δ 9.68 (s, 1 H), 5.37 (br s, 1 H), 2.79 (s, 2 H), 2.10 (s, 3 H), 1.50–2.50 (complex, 9 H); mass spectrum m/e 180, 123 (base), 122, 107, 93, 68; exact mass (calcd for $C_{11}H_{16}O_2$) 180.1150, found 180.1153.

8-Methylspiro[4.5]deca-1,7-dien-3-one (15). Crude **14** (1.34 g) from above was dissolved in methanol–10% aqueous KOH (10 mL, 1:1), and the resulting solution was stirred at room temperature for 18 h. After acidification of the reaction mixture with 1 N HCl (10 mL), saturated brine (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$), and the excess solvent was removed under reduced pressure to give, after distillation, 0.96 g (64%) of the spiro dienone **15**: bp 79–80 °C (0.6 mm) [lit.[1a] 59–60 °C (0.15 mm)]. An analytical sample was prepared by preparative GLC (5% Carbowax 20M, firebrick): IR 1595 and 1720 cm^{-1}; NMR δ 7.55 (d, 1 H, J = 6 Hz), 6.00 (d, 1 H, J = 6 Hz), 5.40 (br s, 1 H), 2.10 (s, 2 H), 1.69 (s, 3 H), 1.50–2.50 (complex, 6 H); mass spectrum m/e 162, 95, 68 (base); exact mass (calcd for $C_{11}H_{14}O$) 162.1045, found 162.1041.

(*E*)- and (*Z*)-1-Ethylidene-8-methylspiro[4.5]deca-3,7-dien-2-one (17a,b). To a solution of lithium diisopropylamide [generated from diisopropylamine (0.63 g, 6.3 mmol) in anhydrous THF (10 mL) and n-butyllithium (6.3 mmol)] at −78 °C was slowly added a solution of **15** (0.66 g, 4.1 mmol) in anhydrous THF (2 mL). The stirring was continued at −78 °C for 30 min and then at −30 °C for 2 h, whereupon the mixture was again cooled to −78 °C and acetaldehyde (0.84 g, 28.0 mmol) dissolved in anhydrous THF (1 mL) added. After allowing the reaction to proceed at −78 °C for an additional 1.5 h, it was quenched with 10% aqueous acetic acid. The layers were separated, and the aqueous layer was extracted with ether (3 × 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$), and the excess solvent was evaporated under reduced pressure. Flash distillation [oil bath at 180 °C (<0.02 mm)] afforded a mixture of aldol products **16** which was not further characterized. Instead, the crude aldols **16** were dissolved in anhydrous benzene (4 mL) containing a catalytic amount of p-toluenesulfonic acid, and the mixture was heated at reflux for 4 h with continuous removal of water (Dean-Stark trap). Saturated brine (20 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (3 × 40 mL), and the combined organic portions were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of the excess solvent under reduced pressure followed by distillation of the residue gave 0.62 g (80%) of a mixture of E and Z trienones **17a** and **17b** in a 47:53 ratio (determined by GLC and NMR): bp 75–81 °C (0.03 mm). An analytical sample of each isomer was obtained by preparative GLC (5% Carbowax 20M, firebrick). E isomer **17a**: IR 1610, 1660, 1710 cm^{-1}; NMR δ 7.66 (dd, 1 H, J = 6, 0.8 Hz), 6.57 (dq, 1 H, J = 7.5, 0.8 Hz), 6.19 (d, 1 H, J = 6, 0.8 Hz), 5.43 (br s, 1 H), 1.90 (d, 3 H, J = 7.5 Hz), 1.72 (br s, 3 H), 1.50–2.30 (complex, 6 H); mass spectrum m/e 188, 121, 120 (base), 91, 68; exact mass (calcd for $C_{13}H_{16}O$) 188.1201, found 188.1203. Z isomer **17b**: IR 1610, 1660, 1710 cm^{-1}; NMR δ 7.43 (d, 1 H, J = 6 Hz), 6.15 (d, 1 H, J = 6 Hz), 6.03 (q, 1 H, J = 7.5 Hz), 5.42 (br s, 1 H), 2.19 (d, 3 H, J = 7.5 Hz), 1.71 (br s, 3 H), 1.50–2.30 (complex, 6 H); mass spectrum m/e 188, 121, 120 (base), 91, 68; exact mass (calcd for $C_{13}H_{16}O$) 188.1201, found 188.1196.

Reaction of Mixture of *E* and *Z* Trienones 17a and 17b with Lithium Dimethylcuprate. To a suspension of CuI (Fischer) (98 mg, 0.5 mmol) in anhydrous ether (2 mL) at 0 °C was added methyllithium (1.0 mmol) and the resulting mixture stirred at 0 °C for an additional 0.5 h. A mixture of compounds **17a** and **17b** (72 mg, 0.4 mmol) dissolved in ether (0.5 mL) was then added dropwise with vigorous stirring, and the greenish yellow mixture was allowed to stir at 0 °C for 2 h. The reaction was quenched by addition of 0.1 N HCl (20 mL) and the mixture filtered through a Celite pad. After the filtrate was saturated with NaCl, the aqueous layer was extracted with ether (3 × 30 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of the excess solvent under reduced pressure followed by flash distillation of the residue [oil bath at 200 °C (<0.05 mm)] gave 73 mg (93%) of a mixture which consisted primarily of **19** and **20** in an approximately 1:1 ratio: NMR (**19**) δ 7.67 and 7.56 (overlapping d, 0.5 H, J = 6 Hz, –C*H*=CHCO–), 5.98 and 5.97 (overlapping d, 0.5 H, J = 6 Hz, –CH=C*H*CO–); NMR (**20**) δ 6.71 (q, 0.5 H, J = 7.5 Hz, $CH_3CH{=}C<$), 1.82 (d, 1.5 H, J = 7.5 Hz, $CH_3CH{=}C<$).

1-Isopropyl-4,8-dimethylspiro[4.5]dec-7-en-2-one (18). To a stirred solution of lithium dimethylcuprate (2.5 mmol), prepared at 0 °C as described above, was added dropwise a solution of the E/Z mixture of trienones **17a** and **17b** (0.36 g, 1.9 mmol) in anhydrous ether (1 mL). The resulting greenish yellow mixture was stirred at 0 °C for another 2 h, at which time a 5% solution of glacial acetic acid in ether (5.0 mmol) was added, and the stirring was continued at room temperature for 30 min. After cooling at 0 °C, the grey mixture was transferred through a cannula to another flask containing lithium dimethylcuprate (5.0 mmol) in ether (25 mL), and the resulting mixture was stirred at 3–5 °C for an additional 20 h. The reaction was quenched by the addition of 1 N HCl (30 mL). The precipitated solids were removed by filtration through a Celite pad, the layers were separated, and the aqueous layer was then saturated with sodium chloride and extracted with ether (3 × 80 mL). The combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$), and

the excess solvent was removed under reduced pressure to give 0.41 g of **18** as a light brown oil (>95% pure by GLC). An analysis of the carbonyl region of the ^{13}C NMR spectrum of the crude product revealed it to be a mixture (ca. 1:1) of the C-1 epimers (δ 219.03 and 217.67), together with another minor, unidentified component (<5%) (δ 219.75). Although it was not necessary for the synthesis, an apparent thermodynamic mixture of the C-1 epimers could be obtained by base-catalyzed epimerization. Thus, the crude product obtained above was dissolved in 1 N methanolic sodium methoxide (3 mL) and the solution stirred at room temperature for 5 h. After addition of saturated brine (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with saturated NH_4Cl and dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure, followed by distillation of the residue, gave 0.36 g (87%) of **18**, bp 88–89 °C (0.02 mm), which was judged to be an 8:1 mixture of C-1 epimers by ^{13}C NMR. An analytical sample was obtained by preparative GLC (5% Carbowax 20M, firebrick): IR 1740 cm^{-1}; ^1H NMR δ 5.34 (br s, 1 H), 1.71–2.75 (complex, 11 H), 1.63 (br s, 3 H), 1.10 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J = 7 Hz), 0.94 (d, 3 H, J = 7 Hz); ^{13}C NMR, C-2 (major diastereomer, ca. 89%), δ 219.03, C-2 (minor diastereomer, ca. 11%) δ 217.67; mass spectrum *m/e* 220, 178, 150, 121 (base), 110, 97, 96, 82, 68; exact mass (calcd for $C_{15}H_{24}O$) 220.1827, found 220.1828.

Acorone (1) and Isoacorone (2). A solution of diborane in THF (3.4 mmol) was added slowly dropwise with vigorous stirring to a solution of the diastereomeric ketones **18** (0.74 g, 3.4 mmol) in anhydrous THF (30 mL) at 0 °C, and the stirring was continued at room temperature for 2 h. To destroy the excess diborane, water (1 mL) was added, and the mixture was stirred at room temperature for an additional 15 min. A solution of chromic acid [prepared by mixing sodium dichromate (2.10 g, 7.6 mmol), 98% H_2SO_4 (1.75 mL, 3.1 mmol), and H_2O (9.3 mL)] was then added with vigorous stirring over the course of 30 min. After completion of the addition, the reaction mixture was heated at reflux for 2 h and then cooled. Saturated brine (40 mL) was added, the layers were separated, and the aqueous layer was thoroughly extracted with ether (6 × 80 mL). The combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure afforded 0.73 g of a light yellow oil. Analytical GLC and TLC analyses of the crude oil showed it to be a mixture of acorone and isoacorone [ca. 75% by comparison with an authentic sample of neoacorone, which is a mixture of (+)-acorone and (−)-isoacorone], along with several minor unidentified components. Preparative high-pressure liquid chromatography (Waters LC 500) using two Prep PAK columns and ethyl acetate–hexane (1:4) as the eluting solvent and a flow rate of 250 mL/min afforded 0.20 g (27%) of pure (±)-isoacorone (**2**) (6.8 min) and 0.18 g (25%) of pure (±)-acorone (**1**) (10 min). Analytical samples of both (±)-acorone and (±)-isoacorone were obtained by recrystallization from hexane, and these were identical with authentic samples of (+)-acorone and (−)-isoacorone[15] by IR, NMR, MS, GLC, and TLC. (±)-Acorone: mp 101.5–102 °C (lit.[1a] 101.5–103.5 °C); exact mass (calcd for $C_{15}H_{24}O_2$) 236.1776, found 236.1780. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.27; H, 10.33.

(±)-Isoacorone: mp 66–67 °C; exact mass (calcd for $C_{15}H_{24}O_2$) 236.1776, found 236.1777.

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Registry No.—**1**, 61475-94-3; **2**, 61475-97-6; **4**, 4746-97-8; **6**, 64715-23-7; **7**, 64715-24-8; **8**, 64715-25-9; **9**, 64715-26-0; **10**, 64715-27-1; **12**, 7560-64-7; **13**, 64715-28-2; **14**, 61426-19-5; **15**, 61426-14-0; **16**, 64728-47-8; **17a**, 61426-21-9; **17b**, 61426-22-0; **18** (isomer 1), 61475-96-5; **18** (isomer 2), 61426-24-2; **19**, 64715-29-3; **20**, 61475-95-4; diethyl pyrrolidinomethylphosphonate, 51868-96-3; 2,3-dibromopropene, 513-31-5; ethylene glycol, 107-21-1; pyrrolidine, 123-75-1; 2-chloro-3-iodopropene, 39557-31-8.

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New Synthetic Methods. Stereocontrolled Bicycloannulation: an Approach to Gibberellins

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An approach for the stereocontrolled annulation of a bicyclo[3.2.1]nonan-5-one onto a cycloalkanone is delineated. Reaction of 2-(2′-trityloxyethyl)cyclopentanone with diphenylsulfonium cyclopropylide provides the spiro-fused cyclobutanone. Regiocontrolled ring expansion converts the cyclobutanone into a cyclopentanone. This approach serves to create spiro[*n*.4] systems in a stereochemically defined fashion. Sulfinylation, reduction of the β-keto sulfoxide to the β-keto sulfide, and conversion of the trityloxy group to a mesylate allows base-catalyzed cyclization to the desired bicyclo[3.2.1]nonan-5-one. Utilizing the bridgehead sulfur as a control element and Wagner–Meerwein shifts, either stereochemical series of fusion of the bicyclic system is available. Methylenation completed the gibberellin model.

Among the structural types of important natural products that are very common are the bicyclo[3.2.1]octanes fused to another ring. Two examples, gibberellic acid (**1**) and aphidicolin (**2**), illustrate two much sought after important targets that possess this feature. In considering the synthesis of gibberellic acids, the vast majority of methods focus on creating ring D onto a preformed ring C system.[1-4] We report a new approach to the stereocontrolled production of the BCD

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