# Synthesis of *dl*-Sirenin and *dl*-Isosirenin

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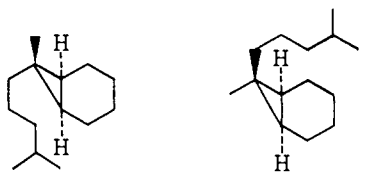
**Abstract:** A synthetic route to *dl*-sirenin and *dl*-isosirenin was achieved using the following sequence. 5-Bromovaleric acid on treatment with triphenylphosphine gave the phosphonium salt; Wittig reaction using this salt and 6-methyl-5-hepten-2-one gave the $C_{13}$-diene acid, 6,10-dimethyl-5,9-undecadienoic acid, as a mixture of *cis* and *trans* isomers. Conversion to acid chloride and treatment with diazomethane gave the diazo ketone which, in refluxing cyclohexane in the presence of cupric sulfate, afforded both the *endo*- and *exo*-methyl isomers of 7-methyl-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptan-2-one. Small amounts (*ca.* 1%) of the corresponding ten-membered ring systems were also isolated. Condensation of the bicyclic ketone with dimethyl carbonate gave a quantitative yield of $\beta$-keto ester which was reduced to an isomeric mixture of $\beta$-hydroxy esters by sodium borohydride. These $\beta$-hydroxy esters were dehydrated *via* the xanthate procedure or better by a base-catalyzed elimination of the pivaloyl derivatives to give a quantitative yield of the desired $\alpha,\beta$-unsaturated ester. Reduction of the esters with $LiAlH_4$ gave monodeoxysirenin and monodeoxyisosirenin. Monodeoxysirenin also was obtained by treatment of natural *l*-sirenin with *p*-toluenesulfonyl chloride in pyridine, followed by reduction with $LiAlH_4$. Oxidation of the unsaturated esters with selenium dioxide in ethanol gave in high yield and stereospecifically the *trans*-aldehydes. Finally, reduction of the aldehydes with $LiAlH_4$–$AlCl_3$ gave *dl*-sirenin and *dl*-isosirenin. *dl*-Sirenin was identical spectrally and chromatographically with natural *l*-sirenin. Bioassays on *dl*-sirenin, *dl*-isosirenin, and the monodeoxy derivatives are also reported.

The chemotactic hormone sirenin is a powerful sperm attractant produced by the female gametes of the water mold *Allomyces* and is active[2] at concentrations of $10^{-10}$ *M*. The production, isolation, and characterization of sirenin and its 4-(4-nitrophenylazo)-benzoate (NABS) esters have been described,[3] and recently its structure has been established.[4] Sirenin, the structural elucidation of which represents the first complete characterization of a plant sex hormone, differs significantly from mammalian sex hormones which are steroids.[5] Also, sirenin and sesquicarene[6] are the first and only known isoprenoid homologs of 2-carene. These facts, combined with sirenin's unique structure, which contains two primary allylic alcohols with one of them a vinylogous cyclopropylcarbinyl system, make it an interesting synthetic objective. We now report the details of the total synthesis of *dl*-sirenin (**15**) and *dl*-isosirenin (**16**).[7]

Our interest in the biological evaluation of various sirenins prompted the utilization of a synthetic method through which both of the isomers a (sirenin) and b (isosirenin) containing the bicyclo[4.1.0]heptane ring system could readily be prepared. The well-documented, intramolecular $\alpha$-ketocarbene addition reaction[8] nicely met this criterion. Moreover, this




a b

method would allow the formation of the bicyclic ring system containing 14 of the 15 carbon atoms of sirenin to be effected in one step from an acyclic precursor. Our synthetic attack therefore was directed to the preparation of the olefinic diazo ketones **3d** and **4d**, with the plan of functionalizing the side chain and introducing the remaining carbon atom after cyclization.

The Wittig reaction was chosen as the method to make the acyclic dienic system since both *cis* and *trans* isomers are formed.[9] Phosphonium bromide salt **2** was readily prepared from 5-bromovaleric acid and triphenylphosphine, and reaction of the ylide of $\delta$-triphenylphosphonovaleric acid (**2**) and excess 6-methyl-5-hepten-2-one (**1**) in dimethyl sulfoxide–tetrahydrofuran gave a 2:3 mixture of the diene acids **3a** and **4a** in 86% yield. No attempt was made to influence the isomer distribution by changing reaction conditions. The corresponding phosphonium salt of the valeric ester cannot be used in the Wittig reaction due to cyclization of the intermediate ylide;[10] however, protection of the carboxyl function as the carboxylate ion allows formation of olefin in the normal manner with retention of carboxyl functionality in the product.

Treatment of the isomeric mixture of 6,10-dimethyl-5,9-undecadienoic acids **3a** and **4a** with dimethyl sulfate in the presence of tris(2-hydroxypropyl)amine[11] gave the

(1) National Institutes of Health Predoctoral Fellow.
(2) L. Machlis, *Physiol. Plant*, 11, 181 (1958).
(3) L. Machlis, W. H. Nutting, M. W. Williams, and H. Rapoport, *Biochemistry*, 5, 2147 (1966).
(4) L. Machlis, W. H. Nutting, and H. Rapoport, *J. Amer. Chem. Soc.*, 90, 1674 (1968); W. H. Nutting, H. Rapoport, and L. Machlis, *ibid.*, 90, 6434 (1968).
(5) Subsequently, a structure for the first steroidal plant sex hormone, antheridiol, was proposed [G. P. Arsenault, K. Biemann, A. W. Barksdale, and T. C. McMorris, *ibid.*, 90, 5635 (1968)] and confirmed by synthesis [J. A. Edwards, J. S. Mills, J. Sundeen, and J. H. Fried, *ibid.*, 91, 1248 (1969)].
(6) Y. Ohta and Y. Hirose, *Tetrahedron Lett.*, 1251 (1968).
(7) A preliminary account of this work has appeared; J. J. Plattner, U. T. Bhalerao, and H. Rapoport, *J. Amer. Chem. Soc.*, 91, 4933 (1969). Syntheses by other routes have also been reported: E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *ibid.*, 91, 4318 (1969); P. A. Grieco, *ibid.*, 91, 5660 (1969).
(8) (a) G. Stork and J. Ficini, *ibid.*, 83, 4678 (1961); (b) M. M. Fawzi and C. D. Gutsche, *J. Org. Chem.*, 31, 1390 (1966).
(9) (a) A. Maercker, *Org. Reactions*, 14, 270 (1965); (b) S. Trippett, *Quart. Rev.* (London), 17, 406 (1963); (c) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1960, pp 132–171; (d) W. Foerst, Ed., "Newer Methods of Preparative Organic Chemistry," Vol. III, Academic Press, New York, N. Y., 1964, pp 111–150.
(10) L. D. Bergelson and M. M. Shemyakin, *Angew. Chem.*, 76, 113 (1964).
(11) F. H. Stodola, *J. Org. Chem.*, 29, 2490 (1964).

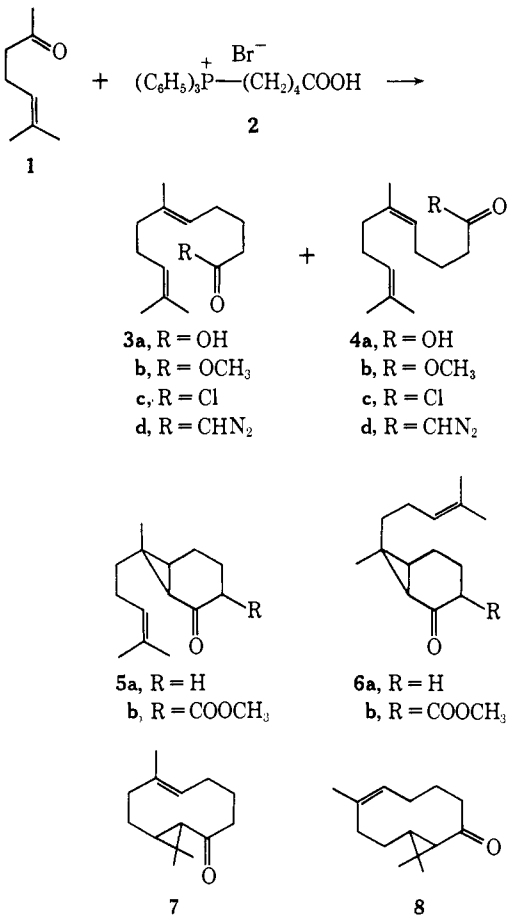
corresponding methyl esters. These were separated by preparative gas chromatography on Carbowax 20M into the pure *cis* and *trans* isomers **4b** and **3b**, respectively. Hydrolysis of each methyl ester then afforded the pure *cis*- and *trans*-diene acids. Assignment of the stereochemistry at the $\Delta^5$-double bond was based on the longer retention time of the *trans*-methyl ester in glpc and the nmr spectra of the separated diene acids. The vinyl methyl group of the *cis*-diene acid was deshielded 5 Hz relative to the methyl group of the *trans* isomer.[12] The process involving the conversion of the *cis,trans*-diene acid mixture to methyl esters, separation on glpc, and hydrolysis, was accomplished in an overall yield of 80%.

The diazo ketones **3d** and **4d** were prepared by a standard reaction sequence. Thus, each diene acid was converted to its sodium salt with sodium methoxide in methanol and thence to the acid chlorides **3c** and **4c** with a tenfold excess of oxalyl chloride in benzene. Smaller amounts of oxalyl chloride resulted in the formation of the symmetrical anhydride.[13] Reaction of the acid chlorides with excess diazomethane gave the *cis*- and *trans*-diazo ketones.

The decomposition of the diazo ketones to give the bicyclic ring system was effected in refluxing cyclohexane solution in the presence of suspended copper sulfate. Employing high dilution and short reaction time, overall yields of 63–68% were obtained from diene acids **3a**, **4a** to bicyclic products **5a**, **6a**. In this manner the *cis*-diazo ketone **4d** was cyclized to the bicyclic ketone **6a**, and the *trans* isomer **3d** to the bicyclic ketone **5a**, thus confirming the stereospecific nature of the intramolecular $\alpha$-ketocarbene reaction.[14] As a result of an extremely facile glpc separation of the bicyclic ketones **5a** and **6a**, cyclization could be performed on a *cis,trans* mixture of diazo ketones and separation of isomers effected at this stage as an alternative to separation at the ester (**3b**, **4b**) stage.

Reaction of the $\alpha$-ketocarbene with the $\Delta^9$-double bond would be expected to be very slight based upon the known[15] relationship of ring size to probability of cyclization, and the recently published data on this reaction[8b] relating yields in cyclization of an $\alpha$-ketocarbene to its spatial relationship to a double bond. This was further supported by formation of the ten-membered ring ketones **7** and **8** in *ca.* 1% yield. Isolation by a combination of column chromatography and preparative glpc gave the *cis*-bicyclic ketone **8** and the *trans* isomer **7**. *trans* isomer **7** however, was obtained in smaller amount due to its partial decomposition during preparative glpc. Inspection of molecular models suggests that *trans* isomer **7** is strained and this may account for its instability.

Condensation of the bicyclic ketones **5a** and **6a** in refluxing dimethyl carbonate in the presence of 2.2 equiv of sodium hydride gave a quantitative yield of the $\beta$-keto esters **5b** and **6b**. Although the two isomers were indistinguishable by tlc, ir, and mass spectroscopy, they could readily be differentiated by their nmr spectra. The chemical shift of the *endo*-methyl isomer appeared

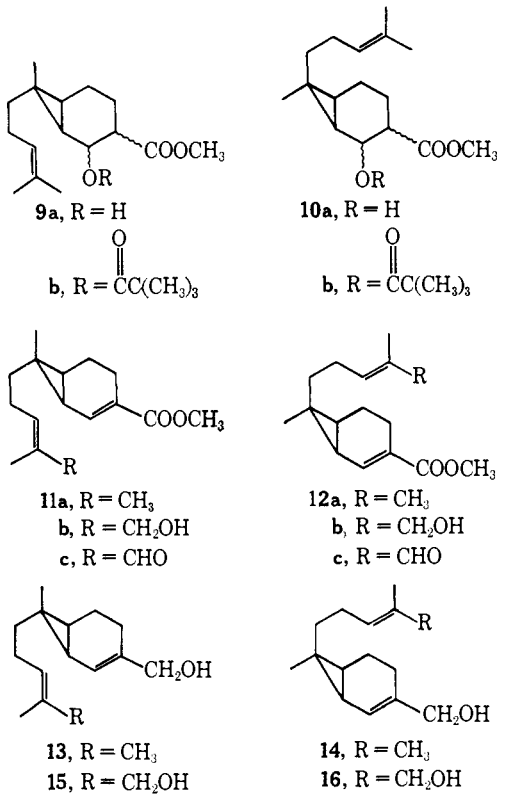



0.12 ppm upfield to that of the *exo*-methyl isomer. This difference in the chemical shifts of the tertiary methyl groups was observed throughout the series.

Reduction of the $\beta$-keto esters with 1.8 equiv of sodium borohydride in isopropyl alcohol at 0° gave a 70% yield of the corresponding isomeric $\beta$-hydroxy esters, but also resulted in the formation of diol (*ca.* 22%). Since diol formation has been ascribed to an intramolecular interaction of the reducing agent, the ester group, and the hydroxyl function,[16] the reaction was investigated at lower temperatures. Reduction in absolute ethanol at −22° for 20 hr afforded the desired product plus unreacted keto ester essentially free from diol. Separation on silica gel and recycling of the recovered starting material gave an 84% yield of the $\beta$-hydroxy esters. In this fashion **5b** and **6b** were converted, respectively, to **9a** and **10a**.

Several methods were tried for dehydration of the alcohol **9a**. Reaction of **9a** with phenyl isocyanate gave, in 50% yield, the corresponding phenylurethan. Pyrolysis of the urethan at 200° for 2 min at 20 mm gave three olefinic compounds, resulting from opening of the cyclopropane ring, as evidenced by glpc and nmr. The elimination was next attempted by the xanthate procedure.[17] A low yield (40%) of the desired unsaturated ester **11a** was obtained; however, tlc examination at different stages of the reaction sequence (treatment of the alcohol with potassium metal, carbon disulfide, and then methyl iodide) indicated that elimination was proceeding during the formation of the potassium alcoholate. Hence, in another experiment

(12) R. B. Bates and D. M. Gale, *J. Amer. Chem. Soc.*, 82, 5749 (1960).
(13) R. Adams and L. H. Ulich, *ibid.*, 42, 599 (1920).
(14) G. Stork and M. Gregson, *ibid.*, 91, 2373 (1969), footnote 6.
(15) P. B. D. de la Mare and W. Klyne, Ed., "Progress in Stereochemistry," Vol. 3, Butterworth and Co., Inc., Washington, D. C., 1962, pp 202–263.
(16) J. E. G. Barnett and P. W. Kent, *J. Chem. Soc.*, 2743 (1963).
(17) C. H. Depuy and R. W. King, *Chem. Rev.*, 60, 431 (1960).




the reaction mixture was examined after treatment with 1.5 equiv of potassium. The products isolated were the hydroxy acid **11d** and the unsaturated ester **11a**. The hydroxy acid **11d** was esterified[11] and subjected again to treatment with potassium. In this case no unsaturated ester was obtained. This result indicated that one of the diastereomers (*trans*) of the hydroxy ester **9a** probably had undergone a base-catalyzed E2 type of elimination. Finally, conversion of the hydroxy ester **9a** to its pivaloyl derivative **9b**, followed by treatment with 2 equiv of potassium *t*-butoxide in dry toluene for 1.5 hr, gave the unsaturated ester **11a** in an overall yield of 87%. During this procedure, a small amount (*ca.* 5%) of the transesterified *t*-butyl ester was formed but could easily be separated by column chromatography. Isomer **12a** was prepared in an analogous manner.

In our earlier experiments on the conversion of natural *l*-sirenin to sesquicarene,[6] *p*-toluenesulfonyl chloride in pyridine followed by lithium aluminum hydride reduction resulted in a monohydroxy compound, which was assigned structure **13** on the basis of its mass spectrum, nmr, ir, and subsequent comparison with synthetic monodeoxysirenin **13**. Repetition of this sequence under more drastic conditions resulted in cleavage of the cyclopropane ring. Synthetic monodeoxysirenin **13** was prepared by reduction of the ester **11a** with lithium aluminum hydride at 0° for 1.5 hr. In a similar fashion ester **12a** on reduction with lithium aluminum hydride gave monodeoxyisosirenin **14**.

Oxidation of the ester **11a** with selenium dioxide[18] in ethanol at 90° for 13 hr gave a mixture of the allylic alcohol **11b** and the aldehyde **11c** as seen by tlc and nmr. Hence the crude reaction product was further oxidized with manganese dioxide[19] in hexane to give in 63% yield the *trans*-aldehyde **11c**. Purification was effected by chromatography on silica gel under nitrogen pressure. The nmr spectrum of **11c** (even as crude material) showed only one singlet at 9.33 ppm for the *trans*-aldehydic proton.[20] Since no *cis*-aldehydic proton was observed, this indicates purity of greater than 95% of the *trans* isomer.[21] Using analogous conditions ester **12a** was oxidized but required a longer reaction time (16 hr) to give the *trans*-aldehyde **12c** in 64% yield.

Reduction of the aldehydes **11c** and **12c** with lithium aluminum hydride–aluminum chloride[22] at 0° for 1.5 hr gave *dl*-sirenin (**15**) and *dl*-isosirenin (**16**), respectively. *dl*-Sirenin was identical spectrally (ir, nmr, mass spectra) and chromatographically (tlc on silica gel) with natural *l*-sirenin. The noticeable difference between *dl*-sirenin and *dl*-isosirenin was the nmr absorption of the tertiary methyl groups which appeared at $\delta$ 0.88 and 1.03, respectively.

Bioassays[23] were performed on *dl*-sirenin (**15**), *dl*-isosirenin (**16**), *l*-monodeoxysirenin (**13**), *dl*-monodeoxysirenin (**13**), and *dl*-monodeoxyisosirenin (**14**) at $1 \times 10^{-6}$ *M* concentration with natural *l*-sirenin as a standard. All three monodeoxysirenins were inactive. *dl*-Sirenin had activity indistinguishable from *l*-sirenin, whereas *dl*-isosirenin showed low (8%) activity. These results indicate that the side chain allylic alcohol function is essential, *d*-sirenin is not inhibitory, and the stereochemistry of the side chain on the cyclopropyl ring is also a factor of major importance since the *exo*-methyl isomer has very low activity.

## Experimental Section[24]

**6,10-Dimethyl-5,9-undecadienoic Acid.** The phosphonium bromide salt (**2**), mp 205–206°, was prepared by heating a vigorously stirred mixture of 5-bromovaleric acid[25] and triphenylphosphine at 85° for 1 hr. The resulting solid was dissolved in boiling chloroform–ethanol (20:1), precipitated with ether, and dried (100° (0.5 mm)).

The phosphonium salt (115 g) and redistilled 6-methyl-5-hepten-2-one (**1**, 45 g) were dissolved in a mixture of dry THF (525 ml) and dry DMSO (675 ml). The resulting solution was added over a period of 45 sec to 13.0 g of sodium hydride (from which the mineral oil

(18) (a) V. M. Sathe, K. K. Chakravarti, M. V. Kadival, and S. C. Bhattacharyya, *Indian J. Chem.*, **4**, 393 (1966); (b) G. Büchi and H. Wüest, *Helv. Chim. Acta*, **50**, 2440 (1967).

(19) (a) F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **75**, 5930 (1953); (b) O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

(20) K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968).

(21) A small amount of this aldehyde was converted to its methyl ester [E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Amer. Chem. Soc.*, **90**, 5616 (1968)]; uv $\lambda_{max}^{EtOH}$ 225, 250 nm. This ester showed a vinylic proton at $\delta$ 6.72 assignable only to a *trans* ester[18b,20] and the total absence of any *cis* isomer. The stereochemistry of this selenium dioxide oxidation will be discussed in a future publication.

(22) M. J. Jorgenson, *Tetrahedron Lett.*, 559 (1962).

(23) We are indebted to Professor L. Machlis and Dr. Gerry J. Hill of the Department of Botany, University of California, Berkeley, for these assays. A more detailed study of structure–activity relationships in this area will be presented in the future.

(24) All boiling and melting points are uncorrected. Microanalyses were performed by the Analytical Laboratory, University of California; uv spectra are reported as $\lambda_{max}^{EtOH}$ in nanometers and were obtained on a Cary 14 spectrophotometer; infrared spectra were recorded as liquid films on a Perkin-Elmer 237 spectrometer and are reported in reciprocal centimeters ($cm^{-1}$). Nmr spectra are reported as $\delta$ values and were obtained in $CCl_4$ unless otherwise noted on a Varian T-60 or HA-100 spectrometer using internal TMS ($\delta = 0$). Mass spectra were obtained on a Varian M-66 or a CEC 103 spectrometer. High-resolution mass spectra were measured on a CEC 21-110 spectrometer at 70 eV. Glpc analyses were carried out on an Aerograph gas chromatograph, Model A-90-P. Preparative glpc was performed on a Hewlett Packard preparative gas chromatograph, Model 775. Thin layer chromatography was done on silica gel. All evaporations of solvent were performed on a Berkeley rotary evaporator *in vacuo*.

(25) Prepared by hydrolysis of commercial 5-bromovaleronitrile with 48% HBr.

had been previously removed) at 0–5° under a nitrogen atmosphere. After being stirred for 2 hr at 5–10° and then 23 hr at 25°, the DMSO–THF mixture was diluted with water, acidified to pH 3 with 30% phosphoric acid, and extracted with pentane. The pentane extract was concentrated to an oil, taken up in benzene, and extracted with 5% sodium hydroxide and the alkali washings were combined and washed with benzene. After acidification with phosphoric acid, the mixture was extracted with ether and the ethereal extract was washed (brine solution), dried (magnesium sulfate), and evaporated to give the *cis,trans* mixture of diene acids, 47 g (86%).

A portion (6.7 g) of this material was esterified[11] in 94% yield and subjected to preparative glpc (160 × 0.75 in., Carbowax 20M, 151°). In this manner the pure *cis* (**4b**, 3.4 g) and *trans* (**3b**, 2.3 g) methyl esters were obtained (85% collection efficiency).

**Methyl *cis*-6,10-dimethyl-5,9-undecadienoate (4b)** had $R_f$ 0.52, 2% ethyl acetate in benzene; retention time 10 min, 5% SE-30, 10 ft × 0.25 in., 160°, 60 ml/min; nmr 3.60 (s, $OCH_3$), otherwise same as *cis* acid.

**Methyl *trans*-6,10-dimethyl-5,9-undecadienoate (3b)** had $R_f$ 0.52, 2% ethyl acetate in benzene; retention time 11 min, 5% SE-30, 10 ft × 0.25 in., 160°, 60 ml/min; nmr 3.60 (s, $OCH_3$), otherwise same as *trans* acid. Hydrolysis of these esters with ethanolic potassium hydroxide (3.5 equiv, 0.5 *M*, 24 hr, 25°) afforded the pure acids in quantitative yield.

***cis*-6,10-Dimethyl-5,9-undecadienoic acid (4a)** had bp (bath) 145–152° (0.3 mm); nmr 1.60 (br s, 3 H, *trans* C=$CCH_3$), 1.67 (br s, 6 H, *cis* C=$CCH_3$), 1.93–2.10 (m, C=$CCH_2$), 2.30 (t, $CH_2$-$CH_2$COOH, $J$ = 7 Hz), 5.08 (br t, $CH_2CH$=C, $J$ = 7 Hz); ir 1715.

*Anal.* Calcd for $C_{13}H_{22}O_2$: C, 74.2; H, 10.5. Found: C, 74.0; H, 10.6.

***trans*-6,10-Dimethyl-5,9-undecadienoic acid (3a)** had bp (bath) 146–152° (0.3 mm); nmr same as for *cis* acid except for integration in the vinyl methyl region.

*Anal.* Calcd for $C_{13}H_{22}O_2$: C, 74.2; H, 10.5. Found: C, 74.3; H, 10.7.

**7-Methyl-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptan-2-one.** The *trans*-diene acid (**3a**, 2.1 g) was treated with 0.23 g of sodium dissolved in 50 ml of anhydrous methanol. The methanol was removed under reduced pressure and the resulting solid dried overnight at 100° (0.25 mm) after which the salt was powdered in a mortar and redried for an additional 5 hr. To prepare the acid chloride, the dry sodium salt was overlaid with 20 ml of anhydrous benzene containing 100 mg of pyridine, the mixture was cooled to −15°, and 12.7 g of oxalyl chloride was added, followed by stirring for 30 min at 5°, then 30 min at 25°. After filtering the mixture to remove the precipitated sodium chloride, the benzene and oxalyl chloride were evaporated under reduced pressure at 25–30° and fresh benzene was added and removed as before.

The diazo ketone was prepared by adding an ethereal solution of this acid chloride to 65 mmol of ice cold ethereal diazomethane (prepared from 21.5 g of *p*-toluenesulfonylmethylnitrosamide[26] and dried 3 hr at 0° over potassium hydroxide pellets) and keeping the solution at 5° for 1.5 hr and 20° overnight. Removal of the ether with a stream of nitrogen afforded the crude diazo ketone **3d** as an oil; ir 2105, 1642. This material was dissolved in 1100 ml of dry cyclohexane containing 3.0 g of anhydrous copper sulfate and heated with stirring at reflux for 2 hr. The mixture was then filtered and the cyclohexane distilled at reduced pressure. The residue was dissolved in ether, washed with aqueous sodium bicarbonate and aqueous sodium chloride, dried, and evaporated. Chromatography over 250 g of silica gel (elution with benzene, benzene–ethyl acetate mixtures) gave 1.35 g (66%) of the *endo*-methyl bicyclic ketone **5a**: $R_f$ 0.28, ethyl acetate–benzene, 4:96; retention time 14 min, 5% Carbowax 20M, 10 ft × 0.25 in., 165°, 60 ml/min; nmr 1.11 (s, >$CCH_3$), 1.60 (br s, *trans* C=$CCH_3$) 1.67 (br s, *cis* C=$CCH_3$), 5.08 (t, $CH_2CH$=C, $J$ = 7 Hz); ir 1685.

*Anal.* Calcd for $C_{14}H_{22}O$: C, 81.5; H, 10.8. Found: C, 81.3; H, 10.7.

The *exo*-methyl bicyclic ketone **6a** was prepared in an analogous fashion. From the *cis*-diene acid **4a** (2.1 g), 1.34 g (65%) of ketone **6a** was obtained: $R_f$ 0.28, ethyl acetate–benzene 4:96; retention time 12 min, 5% Carbowax 20M, 10 ft × 0.25 in., 165°, 60 ml/min; nmr 1.13 (s, >$CCH_3$), 1.60 (br s, *trans* C=$CCH_3$), 1.67 (br s, *cis* C=$CCH_3$), 5.08 (t, C=$CHCH_2$, $J$ = 7 Hz); ir 1685.

*Anal.* Calcd for $C_{14}H_{22}O$: C, 81.5; H, 10.8. Found: C, 81.6; H, 10.7.

For both cyclizations, glpc of the crude and purified product established the stereospecificity of the α-ketocarbene addition by demonstrating the absence of the other isomer.

As an alternate procedure, the *cis,trans* mixture of diene acids (21 g) was cyclized to the *endo,exo* mixture of the bicyclic ketones (14.2 g, 68%) and then separated by prepreparative glpc (15% Carbowax 20M, 160 × 0.75 in., 185°). The isomeric bicyclic ketones gave an easier glpc separation than the *cis* and *trans* methyl esters making this the preferred method for large scale preparation of bicyclic ketones.

Also isolated from the above cyclization by preparative glpc was the ten-membered ring ketone, (*Z*)-6,11,11-trimethylbicyclo[8.1.0]-undec-6-en-2-one (**8**) (*ca.* 1%): retention time 8 min, 10% QF-1, 5 ft × 0.25 in., 150°, 60 ml/min; ir 1685; nmr 1.05 (s, >$CCH_3$), 1.26 (s, >$CCH_3$), 1.65 (br s, *cis* C=$CCH_3$), 5.00 (t, C=$CHCH_2$); mass spectrum, molecular ion, theoretical 206.1671, found 206.1657.

The *trans* ten-membered ring ketone, (*E*)-6,11,11-trimethylbicyclo[8.1.0]undec-6-en-2-one (**7**), was obtained in smaller amount (*ca.* 0.3%). It underwent decomposition during attempted glpc at 190° but was obtained at 150°: retention time 13 min, 10% QF-1, 5 ft × 0.25 in., 150°, 60 ml/min; ir 1701; nmr 0.82 (s, >$CCH_3$), 1.05 (s, >$CCH_3$), 1.60 (s, *cis* C=$CCH_3$); mass spectrum, molecular ion, theoretical 206.1671, found 206.1661.

**3-Methoxycarbonyl-7-methyl-7-(4-methyl-3-pentenyl)bicyclo-[4.1.0]heptan-2-one.** Sodium hydride (1.18 g of a 56.3% dispersion) was washed with three 10-ml portions of dry ether under nitrogen; then 70 ml of anhydrous dimethyl carbonate was added. The 7-*endo*-methyl bicyclic ketone **5a** (2.5 g) dissolved in 10 ml of dimethyl carbonate was added to the stirred suspension at 50° over a period of 10 min, followed by heating at reflux until hydrogen evolution ceased and then for an additional 15 min. After cooling the reaction mixture in an ice bath, 3 ml of acetic acid in 35 ml of ether was added, followed by 75 ml of water, and the mixture was extracted with ether. The combined organic extracts were washed with sodium bicarbonate and saturated brine, and dried over magnesium sulfate. Removal of the solvent left 3.1 g (97%) of a yellow oil which was used as such for the reduction described below. A pure sample of the 7-*endo*-methyl keto ester **5b** was prepared by short-path distillation: bp (bath) 115–120° (0.25 mm); ir 1745, 1684, 1645, 1608; nmr 1.02 (s, >$CCH_3$), 1.60 (br s, *trans* C=$CCH_3$), 1.65 (br s, *cis* C=$CCH_3$), 3.68 (s, $OCH_3$), 5.06 (t, C=$CHCH_2$, $J$ = 7 Hz).

*Anal.* Calcd for $C_{16}H_{24}O_3$: C, 72.7; H, 9.2. Found: C, 72.5; H, 9.0.

Employing the same conditions as described above, the 7-*exo*-methyl bicyclic ketone **6a** (3.0 g) was converted to the 7-*exo*-methyl keto ester **6b**, 3.54 g (92%): bp (bath) 116–119° (0.2 mm); ir 1745, 1684, 1645, 1608; nmr 1.14 (s, >$CCH_3$), 1.61 (br s, *trans* C=$CCH_3$), 1.65 (s, *cis* C=$CCH_3$), 3.68 (s, $OCH_3$), 5.08 (t, C=$CHCH_2$, $J$ = 7 Hz).

*Anal.* Calcd for $C_{16}H_{24}O_3$: C, 72.7; H, 9.2. Found: C, 72.8; H, 9.1.

**3-Methoxycarbonyl-7-methyl-7-(4-methyl-3-pentenyl)bicyclo-[4.1.0]heptan-2-ol.** The 7-*endo*-methyl keto ester **5b** (2.0 g) was dissolved in 10 ml of absolute ethanol and added dropwise to a stirred solution of 0.517 g of sodium borohydride in 25 ml of absolute ethanol cooled to −25°. The addition required 5 min. Stirring for 20 hr at −22° was followed by addition of aqueous sodium chloride, and the mixture was extracted into ether. The ethereal extract was washed with brine solution, dried, and evaporated. The residue was chromatographed over 225 g of silica gel (elution with ethyl acetate–benzene mixtures) to give 0.693 g of starting keto ester, 44 mg of 1,3-diol, and 1.09 g of 7-*endo*-methyl hydroxy ester **9a** (84% based upon recovered keto ester). Short-path distillation afforded the hydroxy ester as a clear, viscous oil: bp (bath) 125–130° (0.15 mm); ir 3521, 1721; nmr 1.13 (s, >$CCH_3$), 1.60 (br s, *trans* C=$CCH_3$), 4.30 (m, $CHOH$), 5.05 (t, C=$CHCH_2$, $J$ = 7 Hz).

*Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.1; H, 9.8. Found: C, 72.0; H, 10.0.

Similarly, the 7-*exo*-methyl keto ester **6b** (1.6 g) was reduced to the 7-*exo*-methyl hydroxy ester **10a** (0.872 g) accompanied with starting material (0.554 g) and 1,3-diol (35 mg). The distilled product had bp (bath) 125–132° (0.15 mm); ir 3521, 1721; nmr 1.14 (s, >$CCH_3$), 1.60 (br s, *trans* C=$CCH_3$), 1.65 (br s, *cis* C=$CCH_3$), 2.89 (s, OH), 3.64 (s, $OCH_3$), 4.34 (m, $CHOH$), 5.10 (t, C=$CHCH_2$), $J$ = 7 Hz).

(26) Th. J. de Boer and H. J. Backer, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 250.

*Anal.* Calcd for $C_{15}H_{26}O_3$: C, 72.1; H, 9.8. Found: C, 71.9; H, 9.8.

**3-Methoxycarbonyl-7-methyl-2-trimethylacetoxy-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptane.** To the 7-*endo*-methyl β-hydroxy ester **9a** (1.25 g), dissolved in 25 ml of dry pyridine, was added 3.5 ml of freshly distilled pivaloyl chloride. The mixture was stirred for 20 hr at 45° and with ice bath cooling, aqueous sodium bicarbonate was carefully added, and the mixture extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate and brine solution, and dried over sodium sulfate. Removal of the ether left 1.63 g (99%) of the 7-*endo*-methyl diester **9b**. Short-path distillation gave a colorless, viscous oil: bp (bath) 147–156° (0.1 mm); ir 1742, 1733; nmr 1.11 (s, $\geqslant CCH_3$), 1.13 [s, $C(CH_3)_3$], 1.57 (br s, *trans* $C{=}CCH_3$), 1.65 (br s, *cis* $C{=}CCH_3$), 3.58 (s, $OCH_3$), 5.00 (t, $C{=}CHCH_2$), 5.40 (m, CHOCOR).

*Anal.* Calcd for $C_{21}H_{34}O_4$: C, 72.0; H, 9.8. Found: C, 72.2; H, 9.8.

The 7-*exo*-methyl diester **10b** was prepared as above. From 1 g of 7-*exo*-methyl hydroxy ester **10a** was obtained 1.3 g (98%) of **10b**: bp (bath) 145–150° (0.05 mm); ir 1742, 1733; nmr 1.07 (s, $\geqslant CCH_3$), 1.21 [s, $C(CH_3)_3$], 1.60 (s, *trans* $C{=}CCH_3$), 1.65 (br s, *cis* $C{=}CCH_3$), 3.61 (s, $OCH_3$), 5.07 (t, $C{=}CHCH_2$), 5.42 (m, CHOCOR).

*Anal.* Calcd for $C_{21}H_{34}O_4$: C, 72.0; H, 9.8. Found: C, 72.1; H, 9.7.

**3-Methoxycarbonyl-7-methyl-7-(4-methyl-3-pentenyl)bicyclo-[4.1.0]hept-2-ene.** The 7-*endo*-methyl diester **9b** (1.50 g) was dissolved in 70 ml of dry toluene and treated with 0.960 g of sublimed potassium *t*-butoxide under a nitrogen atmosphere. After being stirred for 1.5 hr at 25°, the reaction mixture was cooled in an ice bath and acidified with an ethereal solution of acetic acid. Water was added and the mixture extracted with ether. The organic extract was washed with sodium bicarbonate solution and brine solution, and dried over sodium sulfate. Evaporation of the solvent left a yellow oil which was chromatographed over 150 g of silica gel (elution with 1% hexane in benzene) to furnish 923 mg (87%) of the 7-*endo*-methyl methyl ester **11a** and 57 mg (5%) of the corresponding *t*-butyl ester. A sample of the methyl ester was submitted to short-path distillation and had bp (bath) 102–110° (0.1 mm); ir 1966, 1631; nmr 0.88 (s, $\geqslant CCH_3$), 1.60 (br s, *trans* $C{=}CCH_3$), 1.67 (br s, *cis* $C{=}CCH_3$), 3.67 (s, $OCH_3$), 5.05 (t, $C{=}CHCH_2$, $J$ = 7 Hz), 7.10 (br s, CH=C); uv 252 (ε 10,400).

*Anal.* Calcd for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7. Found: C, 77.0; H, 9.7.

Similarly, from the 7-*exo*-methyl diester **10b** (1.84 g) was obtained 1.12 g (86%) of 7-*endo*-methyl ester **12a**: bp (bath) 103–113° (0.1 mm); ir 1699, 1631; nmr 1.13 (s, $\geqslant CCH_3$), 1.60 (br s, *trans* $C{=}CCH_3$), 1.65 (br s, *cis* $C{=}CCH_3$), 3.63 (s, $OCH_3$), 5.03 (t, $C{=}CHCH_2$, $J$ = 7 Hz), 7.03 (br s, CH=C); uv 252 (ε 10,400).

*Anal.* Calcd for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7. Found: C, 77.2; H, 10.0.

**3-Hydroxymethyl-7-*endo*-methyl-7-(4-methyl-3-pentenyl)bicyclo-[4.1.0]hept-2-ene (Monodeoxysirenin) (13).** The 7-*endo*-methyl α,β-unsaturated ester **11a** (132 mg) was dissolved in dry ether (5 ml) and added to a slurry of lithium aluminum hydride (62 mg) in 35 ml of ether at −15° under nitrogen. With the temperature maintained at −15°, the mixture was stirred for 1.5 hr, at which time excess $LiAlH_4$ was decomposed with wet ether. After filtering the ethereal solution and drying the filtrate over sodium sulfate, the solvent was evaporated to give a light yellow oil. Further purification over neutral alumina (2.5 activity, elution with benzene–chloroform mixtures) afforded 106 mg of *dl*-monodeoxysirenin (**13**) as a clear, viscous oil: ir 3695, 1655; nmr 0.88 (s, $\geqslant CCH_3$), 1.60 (br s, *trans* $C{=}CCH_3$), 1.65 (br s, *cis* $C{=}CCH_3$), 2.58 (s, OH), 3.83 [s, $C{=}C(C)CH_2OH$], 5.08 (t, $C{=}CHCH_2$, $J$ = 7 Hz), 5.73 (br s, CH=C).

*Anal.* Calcd for $C_{15}H_{24}O$: C, 81.7; H, 11.0. Found: C, 81.7; H, 11.2.

The *dl*-monodeoxyisosirenin (**14**) was prepared in an analogous manner. Thus, 7-*exo*-methyl α,β-unsaturated ester **12a** (125 mg) gave 100 mg (90%) of **14** upon reduction: ir 3685, 1652; nmr 1.02 (s, $\geqslant CCH_3$), 1.61 (br s, *trans* $C{=}CCH_3$), 1.68 (br s, *cis* $C{=}CCH_3$), 2.14 (s, OH), 3.63 (s, $C{=}C(C)CH_2OH$), 4.96 (t, $C{=}CHCH_2$, $J$ = 7 Hz), 5.67 (br s, CH=C).

*Anal.* Calcd for $C_{15}H_{24}O$: C, 81.7; H, 11.0. Found: C, 81.8; H, 11.3.

**Conversion of Natural *l*-Sirenin to *l*-Monodeoxysirenin (13).** *l*-Sirenin (46 mg) was dissolved in dry pyridine (5 ml) and treated with 76 mg of *p*-toluenesulfonyl chloride at 0°. After keeping the mixture for 48 hr at 0° under anhydrous conditions, the total material was dissolved in dry THF (25 ml) and added dropwise to a slurry of $LiAlH_4$ (154 mg) in 25 ml of THF at 0° under nitrogen. The mixture was stirred for 4 hr at 0° and then excess $LiAlH_4$ was decomposed with 2% water in THF. The mixture was filtered and the filtrate was dried and evaporated to give a viscous yellow oil. Chromatography over neutral alumina (activity 2.5, elution with benzene–chloroform mixtures) furnished 32 mg of *l*-monodeoxysirenin (**13**): retention time 32 min, 21 sec, 30% QF-1, 10 ft × 0.25 in., 160°, 60 ml/min; ir 3685, 1652; nmr 0.88 (s, $\geqslant CCH_3$), 1.60 (br s, *trans* $C{=}CCH_3$), 1.65 (br s, *cis* $C{=}CCH_3$), 3.81 (s, $C{=}C(C)CH_2OH$), 5.08 (t, $C{=}CH{-}CH_2$, $J$ = 7 Hz), 5.70 (s, CH=C); mass spectrum, molecular ion, theoretical 220.1826, found 220.1825; $[\alpha]^{25}D$ −28° (*c* 1.0, $CHCl_3$).

**3-Methoxycarbonyl-7-*endo*-methyl-7-[(*E*)-4-methyl-3-penten-5-al]bicyclo[4.1.0]hept-2-ene (11c).** A solution of selenium dioxide (603 mg) in 42 ml of 97% aqueous ethanol was added dropwise to the 7-*endo*-methyl methyl ester **11a** (500 mg) dissolved in 8 ml of 97% aqueous methanol. Ten minutes was required for the addition which was done at 55°. The mixture was stirred for 13 hr at reflux, cooled, the selenium was removed by filtration, and the ethanol removed *in vacuo* at 25°. The residue was taken up in ether, washed with sodium bicarbonate solution and brine solution, and dried over sodium sulfate. Evaporation of the ether left a dark orange oil, which, as shown by nmr analysis, consisted of the allylic alcohol **11b** and the α,β-unsaturated aldehyde **11c**. The total material was dissolved in hexane (5 ml) and added to a stirred suspension of freshly prepared manganese dioxide[19] (2.5 g) in 150 ml of hexane. After being stirred for 5 hr at 25°, the mixture was filtered and the filtrate evaporated to give 542 mg of material which was chromatographed over 75 g of silica gel under nitrogen pressure (elution with benzene, then 2% ethyl acetate in benzene) furnishing 328 mg (62%) of pure *trans*-aldehyde **11c**: ir 1709, 1695, 1645; nmr 0.95 (s, $\geqslant CCH_3$), 1.73 (br s, *cis* $C{=}CCH_3$), 3.67 (s, $OCH_3$), 6.35 (t, $C{=}CHCH_2$, $J$ = 7 Hz), 7.08 (br s, CH=C), 9.33 (s, *trans* C=C-(C)CHO); mass spectrum, molecular ion, theoretical 262.1569, found 262.1581; uv 232, 260 (sh).

The 7-*exo*-methyl *trans*-aldehyde **12c** was prepared as above except that heating in ethanol was continued for 16 hr. From 340 mg of **12a** was obtained 196 mg of *trans*-aldehyde **12c**: ir 1709, 1695, 1645; nmr ($CDCl_3$) 1.20 (s, $\geqslant CCH_3$), 1.78 (br s, *cis* $C{=}CCH_3$), 3.70 (s, $OCH_3$), 6.47 (t, $C{=}CHCH_2$, $J$ = 7 Hz), 7.28 (br s, CH=C), 9.36 (s, *trans* C=C(C)CHO); uv 232, 260 (sh); mass spectrum molecular ion, theoretical 262.1569, found, 262.1566.

In another experiment, the allylic alcohol **12b** was isolated by column chromatography: ir 3480, 1700, 1645; nmr 1.23 (s, $\geqslant CCH_3$), 1.50 (br s, $C{=}CCH_3$), 3.70 (s, $OCH_3$), 3.83 (s, $C{=}C(C)CH_2OH$), 5.30 (t, $C{=}CHCH_2$), 7.09 (s, CH=C).

***dl*-Sirenin (15) and *dl*-Isosirenin (16).** A solution of $AlH_3$ in ether was generated *in situ* by addition of $AlCl_3$ (179 mg) to a slurry of $LiAlH_4$ (151 mg) in 55 ml of dry ether under nitrogen. The ethereal solution was cooled to −10° and stirred for 0.5 hr at which time the aldehyde **11c** (230 mg) dissolved in 10 ml of ether was added dropwise over a period of 10 min. After stirring for 1.5 hr at 0° excess $AlH_3$ was destroyed by the careful addition of water and the resulting mixture was extracted with ether. The ethereal extract was washed (brine solution), dried ($Na_2SO_4$), and evaporated to give a yellow, viscous oil. Chromatography over neutral alumina (2.5 activity), eluting with benzene–chloroform mixtures, furnished 185 mg (89%) of *dl*-sirenin (**15**). It had superimposable ir, nmr, and mass spectra, in addition to an identical $R_f$ (0.12, 6% methanol in benzene) with natural *l*-sirenin: nmr ($CDCl_3$) 0.88 (3 H, s, $\geqslant CCH_3$), 1.67 (br s, $C{=}CCH_3$), 3.97 (s, $C{=}C(C)CH_2OH$), 5.39 (t, $C{=}CHCH_2$, $J$ = 7 Hz), 5.80 (br s, CH=C), 2.06 (s, OH); mass spectrum, molecular ion, theoretical 236.1776, found, 236.1770; *m/e* 218, 187, 148, 135 (base peak), 133, 131, 119, 109, 107, 105, 95, 93, 91, 79.

*Anal.* Calcd for $C_{15}H_{24}O_2$: C, 76.2; H, 10.2. Found: C, 75.9; H, 10.2.

Isosirenin (**16**) was prepared in exactly the same manner. Aldehyde **12c** (160 mg) gave 118 mg (82%) of isosirenin: nmr ($CHCl_3$) 1.03 (3 H, s, $\geqslant CCH_3$), 1.58 (s, $C{=}CCH_3$), 3.15 (s, OH), 3.71 (s, $C{=}C(C)CH_2OH$), 5.02 (t, $C{=}CHCH_2$, $J$ = 7 Hz), 5.62 (s, CH=C); mass spectrum, molecular ion, theoretical, 236.1776, found 236.1773.

*Anal.* Calcd for $C_{15}H_{24}O_2$: C, 76.2; H, 10.2. Found: C, 75.7; H, 10.0.