3, 25109-95-9; 4, 25109-96-0; 4 oxime, 25158-23-0; 6, 25109-97-1.

Acknowledgment.—The author is indebted to Dr. Ralph Dougherty for assistance in obtaining the mass spectrum and to Miss Florence Kraft and Mr. Marvin Pflaumer for technical assistance.

Synthesis of *cis,cis*-2,6-Dimethyl-*cis*-9-oxabicyclo[5.3.0]decane. A Novel Stereospecific Synthetic Route to Bicyclic Systems Containing *cis*-1,4-Dimethylcycloheptane Rings

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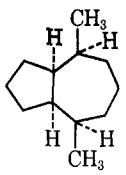
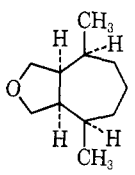
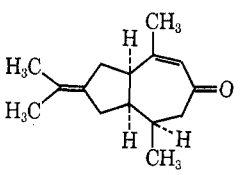
In a projected synthetic sequence leading to bicyclo[5.3.0]decane systems possessing methyl substituents as formulated in **1**, we wish to report a stereospecific synthesis of **2**, a model heterocyclic analog of **1**.[2]



1

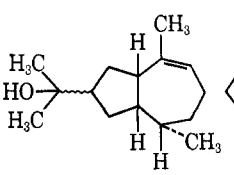


2



3

At the inception of this research synthetic routes to methyl-substituted bicyclo[5.3.0]decane systems of the type **1** were sought in order to develop a total synthesis of β-vetivone and hinesol. The sesquiterpene β-vetivone had been formulated as **3** in 1941.[3] Hinesol had been converted into the enantiomer of β-vetivone and it was therefore assigned structure **4**.[4]



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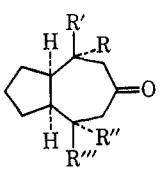

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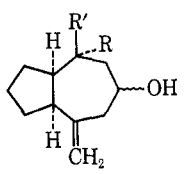


6

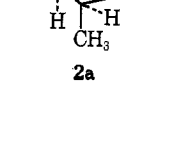
a, R = R″ = CH_3; R′ = R‴ = H **a**, R = CH_3; R′ = H

b, R = R‴ = CH_3; R′ = R″ = H **b**, R = H; R′ = CH_3

c, R′ = R‴ = CH_3; R = R″ = H

(1) (a) Abstracted in part from a thesis presented to the Graduate College of the University of Vermont, Aug 1969, in partial fulfillment of the requirements for the Ph.D. degree; (b) National Aeronautics and Space Administration Predoctoral Traineeship, 1965–1968.

(2) A keto analog **2a** has been prepared by A. P. Krapcho and B. P. Mundy, *J. Org. Chem.*, **32**, 2041 (1967).

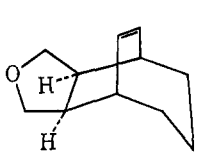


2a

The recent investigations of Marshall and coworkers have necessitated a structural revision of **3** and **4** to spiro[4.5]decane skeletons.[5] The total synthesis of β-vetivone[6] and hinesol[7] has unambiguously supported this structural revision.

Marshall and coworkers have reported a *stereoselective* route to bicyclo[5.3.0]decanes of type **5**.[5] This synthetic sequence leads to methyl isomers. Catalytic hydrogenation of **6a** followed by chromic acid oxidation led to the ketones **5a** and **5b** and a similar reaction sequence on **6b** led to **5b** and **5c**.

The accessibility of compounds such as **7** led us to investigate the stereospecific conversion of the carbon atoms of the double bond into methyl groups to lead to **2**. A route of this type had obvious potential for systems with carbocyclic skeletons.



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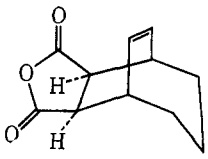

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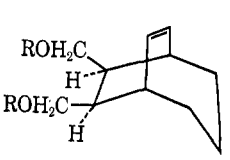
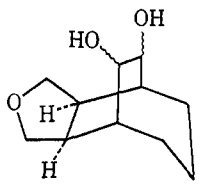


9

Results and Discussion

The reaction of cycloheptadiene with maleic anhydride led to the adduct **8** in an excellent yield.[8] This adduct **8** was reduced to the diol **9** (R = H) using lithium aluminum hydride in refluxing 1,2-dimethoxyethane. If the reduction was performed in ether, the formation of the lactone occurred along with the diol **9** (R = H).[9] The diol **9** (R = H) was converted into the cyclic ether **7** by addition of *p*-toluenesulfonyl chloride to a refluxing pyridine solution of the diol.[10] The ether **7** was treated with osmium tetroxide in pyridine to form the osmate ester which was cleaved by (1) a basic mannitol solution or (2) reaction with lithium aluminum hydride to yield a *cis*-diol **10** of undetermined stereochemistry.[11] This *cis*-diol **10** was cleaved to the dialdehyde **11** by reaction with sodium metaperiodate in an aqueous solution.[2,12] Compound **11** was not obtained analytically pure, but the alde-



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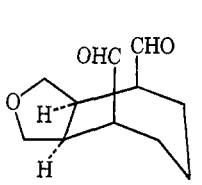
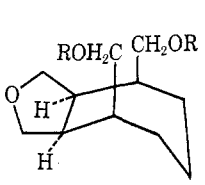


11



12

(3) (a) Y. R. Naves and E. Perrottet, *Helv. Chim. Acta*, **24**, 3 (1941); (b) for a summary of the experimental data, see J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol III, Cambridge University Press, London, 1952, pp 224–232.

(4) I. Yosioka and T. Kimura, *Chem. Pharm. Bull.*, **13**, 1430 (1965).

(5) (a) J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Amer. Chem. Soc.*, **89**, 2748 (1967); *J. Org. Chem.*, **35**, 186 (1970); (b) J. A. Marshall and P. C. Johnson, *J. Amer. Chem. Soc.*, **89**, 2750 (1967); *J. Org. Chem.*, **35**, 192 (1970).

(6) J. A. Marshall and P. C. Johnson, *Chem. Commun.*, 391 (1968).

(7) J. A. Marshall and S. F. Brady, *Tetrahedron Lett.*, 1387 (1969).

(8) K. Alder and H. H. Molls, *Chem. Ber.*, **89**, 1960 (1956).

(9) B. E. Cross and J. C. Stewart, *Tetrahedron Lett.*, 3589 (1968).

(10) A. P. Krapcho and B. P. Mundy, *J. Heterocycl. Chem.*, **2**, 355 (1965).

(11) F. D. Gunstone, *Advan. Org. Chem.*, **1**, 103 (1960).

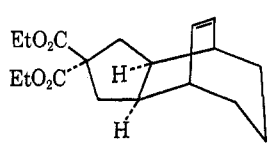
(12) C. A. Bunton, "Oxidations in Organic Chemistry, Part A," K. Wiberg, Ed., Academic Press, New York, N. Y., 1965, Chapter 6.

hydic protons exhibited a singlet at δ 9.15 in the nmr spectrum indicating that coupling with the adjacent α proton had not occurred. One might attribute this lack of splitting to a hindered rotation of the aldehyde groups and the adoption of a conformation for minimal like dipole–dipole repulsions of the >C=O of the aldehyde groups in which the dihedral angle between the aldehydic proton and the adjacent α proton is about 90°.

A more direct method for the preparation of the dialdehyde **11** was ozonolysis of **7**.[13] A solution of **7** in methylene chloride was treated with ozone at a temperature of −78°. Decomposition of the reaction mixture with dimethyl sulfide led to crude **11**.

The dialdehyde **11** was reduced with lithium aluminum hydride to a crude diol (**12**, R = H),[2,14] which was then converted to the ditosylate **12** (R = Ts).[2] The tosylate groups were displaced by hydride in the reaction of **12** (R = Ts) with lithium aluminum hydride in 1,2-dimethoxyethane to yield **2**.[14] Compound **2** exhibited only one doublet in the nmr for the C-2 and C-6 methyl groups (δ 0.93; J = 6.5 Hz). This supports the *all-cis* stereochemistry of the protons at C-1, C-2, C-6, and C-7.

During the course of this work the ditosylate **9** (R = Ts) was prepared by reaction of the diol **9** (R = H) with *p*-toluenesulfonyl chloride in pyridine at 0°. The reaction of this ditosylate with the anion of diethylmalonate in refluxing 1,2-dimethoxyethane led to the carbocyclic geminal diester **13**. Intermediate **13** was of possible utility for the synthesis of systems of type **1** possessing a functional group at C-9. Research on the development of the carbon atoms of the double bond of **13** into methyl groups was terminated when the carbocyclic skeletones of β-vetivone and hinesol were revised.



13

Experimental Section

Cycloheptadiene–Maleic Anhydride Adduct 8.—Cycloheptadiene (22.8 g, 0.25 mol) and maleic anhydride (23.8 g, 0.24 mol) in 100 ml of dry *m*-xylene were refluxed for 24 hr. At the end of this reflux period the uv spectrum of an aliquot of the reaction mixture indicated the absence of unreacted diene. The solvent was removed by distillation under reduced pressure of the water aspirator. The crude solid which remained was recrystallized from carbon tetrachloride to yield 39.0 g (81%) of **8**, mp 110–111° (lit.[8] mp 114°).

Reduction of 8 to 9 (R = H).—The adduct **8** (15.0 g, 0.078 mol) was dissolved in 20 ml of dry 1,2-dimethoxyethane, placed in an addition funnel, and added dropwise to lithium aluminum hydride (4.0 g, 0.105 mol) in 200 ml of dry 1,2-dimethoxyethane. On completion of the addition the mixture was refluxed for 36 hr. At the end of this period, water was slowly added until the mixture turned white, and the salts were filtered. The solvent was removed with the rotary evaporator and the residual oil solidified on standing to give 10.1 g (71%) of **9** (R = H): ir (KBr) 32.0 (O—H), 3030 (=C—H), and 1023 cm^{-1} (C—O); nmr ($CDCl_3$) δ 6.02 (m, 2, H—C=C—H), 4.80 (s, broad, 2, -OH) and 3.64 (m, 4, $-CH_2-O-H$). The analytical sample was prepared by three crystallizations from ether–pentane, mp 70.5–72.0°.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.51; H, 9.96. Found: C, 72.48; H, 10.11.

Preparation of Ether 7.—The diol **9** (R = H) (8.9 g, 0.049 mol) was dissolved in 60 ml of dry pyridine and the solution was placed under a nitrogen atmosphere. The solution was heated to 80° and a solution of *p*-toluenesulfonyl chloride (9.4 g, 0.049 mol) in 40 ml of dry pyridine was added dropwise over a 2-hr period. On completion of the addition heating was continued for 1 hr. The reaction mixture was cooled to room temperature and then poured over a sulfuric acid–ice mixture (100 g/100 g) and extracted with four 100-ml portions of methylene chloride. The methylene chloride extract was washed with a saturated sodium bicarbonate solution and water, and then dried over anhydrous sodium sulfate. The tricyclic ether was distilled to yield 7.3 g (91%): bp 46–47° (0.1 mm); ir (neat) 3045 (=C—H) and 1098 cm^{-1} (C—O—C); nmr (CCl_4) δ 6.05 (m, 2 H, vinyl), 3.92 and 3.21 (each a multiplet similar to a triplet for 2 H, $-CH_2-O-CH_2-$), 2.65 (m, 2), 2.22 (m, 2), and 1.55 (m, 6). The analytical sample was obtained by redistillation and taking a center cut, bp 46–47° (0.1 mm).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.43; H, 9.82. Found: C, 80.66; H, 9.84.

Preparation of *cis*-Diol 10.—The ether **7** (0.20 g, 0.0012 mol), dry pyridine (0.25 g, 0.0032 mol), and osmium tetroxide (0.31 g, 0.0012 mol) were added to 6 ml of anhydrous ether. The flask was fitted with a calcium chloride drying tube and the mixture was stirred for 1 hr. The brown solid was filtered and two procedures were employed for working up the osmate ester.

A.—The osmate ester was transferred to a 50-ml erlenmeyer flask containing 20 ml of a 10% potassium hydroxide solution and 1.0 g of mannitol. This mixture was allowed to stir for 12 hr. The aqueous hydroxide solution was extracted with three 20-ml portions of methylene chloride. The methylene chloride extracts were combined, washed with water, and dried over anhydrous sodium sulfate. The organic material was concentrated and the oil crystallized to give 160 mg (70%) of the diol, mp 116–119°.

B.—To a 250-ml two-necked round bottom flask was added 0.7 g (excess) of lithium aluminum hydride and 25 ml of dry 1,2-dimethoxyethane. To this mixture the osmate ester (1.25 g, 0.003 mol), dissolved in 150 ml of dry 1,2-dimethoxyethane, was added dropwise. The salts were filtered and the organic layer was dried over anhydrous sodium sulfate. The material on concentration gave 440 mg (75%) of dark brown crystals. One crystallization from ether gave slightly colored crystals: mp 118–120°; ir (KBr) 3445, 3365, 3245, and 3180 cm^{-1}; nmr ($CDCl_3$) δ 4.17 (m, 2, -O—C<H), 3.78 (m, 4, $-CH_2-O-CH_2-$), 3.42 (s, 2, -OH), and 2.65–1.2 (m, 10).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.63; H, 9.15. Found: C, 66.57; H, 9.29.

Preparation of 11.—To a 10-ml round-bottom flask were added sodium metaperiodate (0.1 g, 0.0040 mol), 3 ml of water, and *cis*-diol **9** (0.077 g, 0.0035 mol). The mixture was stirred at room temperature for 1 hr. At this time, the reaction mixture was extracted with three 7-ml portions of methylene chloride. The organic layers were combined, washed with water, then dried over anhydrous sodium sulfate. The methylene chloride was removed with the rotary evaporator yielding 0.07 g (92%) of a crude oil (this material was not distilled): ir (neat) 2720 (-CHO) and 1720 cm^{-1} (HC=O); nmr (CCl_4) δ 9.51 (s, 2, -CHO) and 3.50 (m, 4, $-CH_2-O-CH_2-$).

Preparation of 12 (R = H).—To a 50-ml flask was added 10 ml of dry 1,2-dimethoxyethane and lithium aluminum hydride (0.03 g, 0.0007 mol). To this was added dropwise **11** (0.15 g, 0.00077 mol) dissolved in 10 ml of dry 1,2-dimethoxyethane. The mixture was allowed to reflux for 20 hr. At this time, water was added to the mixture until the mixture turned white. The salts were filtered by suction and washed with small portions of methylene chloride. The organic phase was concentrated to give 0.125 g (82%) of an oil: ir (neat) 3280 cm^{-1} (O—H); nmr ($CDCl_3$) δ 3.68 (d, 4, J = 6 Hz), 3.33 (d, 4, J = 7 Hz), 2.93 (s, 2, -OH), 2.63 (m, 2), and 2.07–1.0 (m, 8).

Ozonolysis of 7 to the Dialdehyde 11.—The ozone generator was a commercial Welsbach apparatus. The ether **7** was dissolved in methylene chloride. The solution was cooled to −78° and then the ozone–oxygen mixture was bubbled through the solution for the appropriate period of time. The system and reaction mixture were then purged with oxygen for about 15 min.

(13) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

(14) N. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956.

The methylene chloride solution was drained from the reaction buret and the ozonide was decomposed with dimethyl sulfide. The organic layer was concentrated to give a nearly quantitative yield of the crude dialdehyde.

Preparation of 12 (R = Ts).—To a 10-ml flask, *p*-toluenesulfonyl chloride (0.4 g, 0.0021 mol) was added and to this was added dropwise a solution of **12** (R = H) (0.1 g, 0.0005 mol) dissolved in 3 ml of dry pyridine. The mixture was cooled by means of an ice water bath. After addition was complete, the mixture was placed in the refrigerator for 18 hr. The mixture was then poured over ice water and the aqueous mixture was extracted three times with 20-ml portions of methylene chloride. The organic layers were combined and washed with 10% HCl, saturated $NaHCO_3$, and water, respectively. The extract was dried with sodium sulfate and concentrated to give 0.1 g (39%) of the ditosylate **12** (R = Ts) after one recrystallization from methylene chloride–petroleum ether (30–60°). The analytical sample was obtained after five recrystallizations: mp 147–149°; ir (KBr) 1600 (aromatic C=C), 1170 (S—O), and 956 cm^{-1} (C—O); nmr ($CDCl_3$) δ 7.60 (A_2B_2 centrosymmetric quartet, 8, J = 8 Hz, aromatic protons), 3.80 (d, 4, J = 7 Hz, $-CH_2-$OTs), 3.54 (m, 4, $-CH_2-O-CH_2-$), 2.47 (s, 6, $-CH_3$), and a pattern spread over 2.6 to 1.1 for 10 H for the ring envelope hydrogens.

Anal. Calcd for $C_{25}H_{32}O_7S_2$: C, 59.04; H, 6.34. Found: C, 58.71; H, 6.57.

Preparation of 2.—To a 10-ml flask was added lithium aluminum hydride (0.05 g, 0.0014 mol), 1 ml of dry 1,2-dimethoxyethane, and **12** (R = Ts) (0.1 g, 0.0002 mol) dissolved in 4 ml of dry 1,2-dimethoxyethane. The reaction mixture was refluxed for 20 hr and then cooled. Water was added to destroy the excess lithium aluminum hydride. The salts were filtered by suction and washed with methylene chloride. The organic material was concentrated to give 0.021 g (60%) of an oil. The analytical sample was obtained after this material had been chromatographed on alumina (activity I) and eluted with petroleum ether–benzene (1:1), then distilled: bp 70–75° (0.5 mm); nmr ($CDCl_3$) δ 3.60 (m, 4, $-CH_2-O-CH_2-$), 2.4–1.1 (m, 10, ring hydrogens), and 0.93 (d, 6, J = 6.5 Hz, $-CH_3$).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.63; H, 11.79.

Preparation of Ditosylate 9 (R = Ts).—The *p*-toluenesulfonyl chloride (10.5 g, 0.055 mol) was dissolved in 5 ml of dry pyridine and the solution was cooled in an ice bath. A solution of **9** (R = H) (5.0 g, 0.027 mol) in 25 ml of dry pyridine was added dropwise to the cold toluenesulfonyl chloride solution. After the addition was complete, the mixture was placed in the freezer for 24 hr. The reaction mixture was poured over ice water and allowed to stir for 20 min to insure the hydrolysis of any excess *p*-toluenesulfonyl chloride. The heterogeneous mixture was extracted with three 30-ml portions of methylene chloride. The organic layers were combined and washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, and water, respectively. The organic phase was dried overnight with anhydrous sodium sulfate. The organic phase was concentrated with the rotary evaporator to give 9.4 g (85%): ir (KBr) 1600 (aromatic C=C), 1180 (S—O), and 952 cm^{-1} (C—O); nmr ($CDCl_3$) δ 7.63 (centrosymmetric A_2B_2 quartet, 8, J = 8 Hz, aromatic protons), 5.87 (m, 2, H—C=C—H), 3.92 (m, 4, $-CH_2OTs$), 2.47 (s, 6, aromatic CH_3), 2.35 (m, 4, tertiary protons), and 1.45 (m, 6, $-CH_2-$ of ring). The analytical sample was obtained after four recrystallizations from ether, mp 93–94°.

Anal. Calcd for $C_{25}H_{30}O_6S_2$: C, 61.20; H, 6.16. Found: C, 61.59; H, 6.35.

Preparation of 13.—To a 100-ml three-neck round-bottom flask was added 1.0 g (0.024 mol; 58.6% mineral oil dispersion) of sodium hydride. This was washed with four 10-ml portions of dry 1,2-dimethoxyethane. After washing, 15 ml of dry 1,2-dimethoxyethane was added and the system placed under nitrogen. To this mixture diethylmalonate (3.8 g, 0.024 mol) was added. After the hydrogen evolution had ceased, **9** (R = Ts) (3.6 g, 0.0074 mol) dissolved in 30 ml of dry 1,2-dimethoxyethane was added dropwise. After the addition was complete, the mixture was refluxed for 72 hr with stirring. The reaction mixture was allowed to cool and most of the salt was filtered by suction. The residue was washed with two 30-ml portions of hot 1,2-dimethoxyethane. The organic phase was concentrated with the rotary evaporator. To this residue, 20 ml of water was added and the mixture extracted with four 20-ml portions of methylene chloride. The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was distilled to give 0.78 g (33%): bp 135–140° (0.5 mm); nmr (CCl_4) δ 4.07 and 4.16 (2 q, 4, J = 7 Hz, $-O-CH_2-$), 1.18 and 1.22 (2 t, 6, J = 7 Hz, $-CH_3$), 6.12 (m, 2, H—C=C—H), and 2.4–1.5 (several peaks, 14). The analytical sample was obtained after a portion of this material had been chromatographed on an alumina column (activity III). The *gem* diester was eluted from the column with an ether–benzene mixture (1:9). The material was then redistilled, bp 135–140° (0.5 mm).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.83; H, 8.72.

Registry No.—**2**, 25090-89-5; **7**, 25090-90-8; **9** (R = H), 25090-91-9; **9**, (R = Ts), 25090-92-0; *cis*-**10**, 25090-93-1; **12** (R = Ts), 25090-94-2; **13**, 25090-95-3.

Acknowledgment.—This research was generously supported by Research Grant GM-08241 from the U. S. Public Health Service.

Conformational Analysis. LXVII. The Effect of Solvent on the Conformational Energy of the Carbethoxy Group[1,2]

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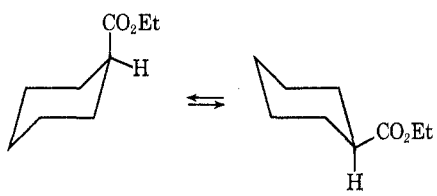
Received January 30, 1970

In recent years, conformational equilibria of the type



have been the subject to many investigations.[4] These investigations have resulted in the determination of numerous $-\Delta G°$ values (termed "conformational energies,"[5] "G values,"[5] or "A values"[6]) for a large variety of substituents.[7] These values are often thought of as constants related to the steric "size" of the particular substituent, and in a recently compiled table of conformational energies,[7] only two substituents (hydroxyl and amino) were listed as having more than one "best value." In these two cases, it is well known that hy-

(1) Paper LXVI: N. L. Allinger, I. Lillien, C. L. Neumann, H. Sugiyama, and N. A. Pamphilis, *J. Org. Chem.*, **35**, 1255 (1970).

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(3) (a) Catholic University; (b) University of Georgia.

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