without further purification: ^{1}H NMR δ 4.09 (1 H, s, HC-4), 3.7–3.3 (7 H, m), 2.75 (5 H, m), 2.5–2.2 (12 H, m, CH_3CH_2N), 1.33 (6 H, t, J = 7 Hz, CH_3CH_2NC-4), 1.07 (12 H, t, J = 7 Hz, CH_3CH_2NC-8,15); m/e 441.3325 ($C_{27}H_{43}N_3O_2$ requires 441.3355).

***exo,exo,exo*-4,8,15-Tris(2,2,2-trifluoroethoxy)hexacyclo[7.5.1.0^{3,13}.0^{5,12}.0^{7,11}.0^{10,14}]pentadecane-2,6-dione (46).** A solution of selenide **40** (105 mg, 0.18 mmol) in methylene chloride (30 mL) was ozonized as described earlier. After excess ozone was removed, ethyl vinyl ether (1 mL) and a solution of potassium carbonate (150 mg) in trifluoroethanol (20 mL) were added to the cold solution. The mixture was then allowed to warm to room temperature with stirring over 4 h. The colorless solution was poured into water (50 mL), and the mixture was extracted with methylene chloride (5 × 50 mL). The extract was dried, filtered, and concentrated to leave a light yellow oil (148 mg). The desired product was obtained from this mixture by chromatography on an Altex, 90 × 250 mm, 5-μm silica gel column eluted with 2:1 chloroform–cyclohexane as a low-melting, crystalline material (40 mg, 43%): IR ν 1735 cm^{-1}; ^{1}H NMR δ 4.47 (1 H, s, HC-4), 4.0–3.6 (11 H, m), 3.64 (2 H, q of m, $J \simeq$ 10 Hz), 3.02 (2 H, d, J = 10 Hz), 2.94 (2 H, d, J = 11 Hz), 2.82 (1 H, d, J = 10 Hz, HC-9); m/e 522.1014 ($C_{21}H_{19}F_9O_5$ requires 522.1086).

Acknowledgments. The research programs of the Principal Investigator are supported financially by the National Cancer Institute (Grant PHS-CA-12,961) and the National Science Foundation (Grant CHE-75-04123). Funds for the purchase and operation of the NMR instruments essential to this work were provided, in part, by the National Cancer Institute (Grant PHS-CA-14599) via The University of Chicago Cancer Research Center and by the National Science Foundation. We are grateful for this support. We thank Mr. William Bunnelle for his assistance.

Registry No. **4**, 36269-21-3; **5**, 70179-06-5; **6**, 70179-07-6; **8**, 70179-08-7; **10**, 70179-09-8; **11**, 70223-46-0; **14**, 70179-10-1; **18**, 70179-11-2; **20**, 70179-12-3; **21**, 70223-47-1; **22**, 36269-18-8; **23**, 70179-13-4; **27**, 70179-14-5; **30**, 70179-15-6; **31**, 70179-16-7; **32**, 70179-17-8; **33**, 70179-18-9; **34**, 70179-19-0; **35**, 70223-48-2; **36**, 70179-20-3; **37**, 70179-21-4; **38** isomer 1, 70179-22-5; **38** isomer 2, 70223-49-3; **38** isomer 3, 70223-50-6; **39**, 70179-23-6; **40**, 70179-24-7; **42**, 70179-25-8; **45**, 70179-26-9; **46**, 70179-27-0; diethylamine, 109-89-7; 2,2,2-trifluoroethanol, 75-89-8; furan, 110-00-9; dimethyl malonate, 108-59-8; phenylselenenyl chloride, 5707-04-0; potassium acetate, 127-08-2; (2,2-diacetoxyethyl)phenyl selenide, 70209-07-3; acetylacetone, 123-54-6; methyl nitroacetate, 2483-57-0.

Stereoselectivity in Formation of Spiro[5.5]undecanes by Cationic π Cyclization

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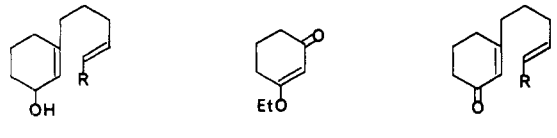
Cationic π cyclization of cyclohexenols **1a–c** leads to spiro[5.5]undecane derivatives in high yield and stereoselectivity. The stereoselectivity of the cyclization is higher with the disubstituted alkenyl side chain (**1b** and **1c**). A rationale for the stereoselectivity of these cyclizations and related heteroatom-substituted analogues is presented.

Biogenetically patterned cationic π cyclizations have been used for synthesis of several spirocyclic sesquiterpenoid systems.[1,2] As part of our continuing study[3] on the general synthetic utility of cationic π cyclization, we have investigated the synthesis of spiro[5.5]undecane derivatives through cyclohexenyl cation initiated π cyclization.[4] The cyclizations of cyclohexenols **1a–c** proceeded in high yield and with a high degree of stereoselectivity.[5] These results provide the basis for development of new stereorational syntheses of a variety of spirocyclic systems via π cyclization.



1a, R = H
1b, R = CH_3
1c, R = Bu

3

2a, R = H
2b, R = CH_3
2c, R = Bu

The cyclohexenones **2a–c** were prepared in good yield by addition of the appropriate unsaturated Grignard reagent or organolithium reagent to 3-ethoxy-2-cyclohexenone (**3**), followed by acid hydrolysis.[8] Reduction of the enones with lithium aluminum hydride in ether at 0 °C gave the allylic alcohols **1a–c** in excellent yield. Treatment of alcohol **1a** with anhydrous formic acid at room temperature for 30 min gave, after normal workup, a mixture of cyclic formates in 80% yield. Cleavage of the formate ester functionality by treatment with lithium aluminum hydride gave a mixture of alcohols **4** and **5**. Although this mixture is not readily separable by VPC (one peak on SE-30 and Carbowax), the presence of two isomers in a ratio of ~4:1 is evidenced by the ^{13}C NMR spectrum. The stereoisomeric relationship of **4** and **5** was proven by catalytic hydrogenation of the mixture to give the known

(1) Spiro[4.5]decanes: J. A. Marshall, S. F. Brady, and N. H. Andersen, *Fortsch. Chem. Org. Naturst.*, 31, 283 (1974), and references cited therein; E. J. Corey and R. P. Balanson, *Tetrahedron Lett.*, 3153 (1973); P. T. Lansbury, V. R. Haddon, and R. C. Stewart, *J. Am. Chem. Soc.*, **96**, 896 (1974).

(2) Chamigranes: D. J. Faulkner, *Pure Appl. Chem.*, **48**, 25 (1976); L. E. Wolinsky and D. J. Faulkner, *J. Org.Chem.*, **41**, 597 (1976); S. Kanno, T. Kato, and Y. Kitahara, *Chem. Commun.*, 1257 (1967); T. Kato, S. Kanno, Y. Kitahara, *Tetrahedron*, **26**, 4287 (1970).

(3) For a recent paper see K. E. Harding, P. M. Puckett, and J. L. Cooper, *Bioorg. Chem.*, **7**, 221 (1978).

(4) For a review of the synthesis of spirocyclic compounds which includes some examples of cationic π cyclization see A. P. Krapcho, *Synthesis*, 383 (1974).

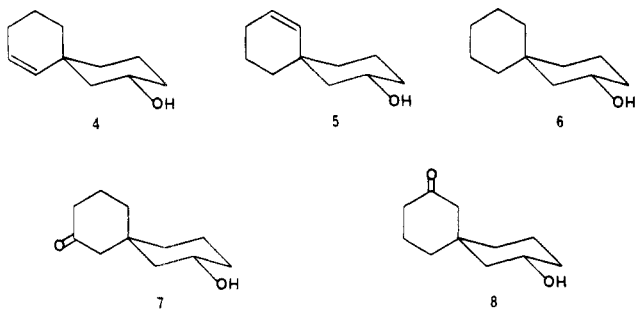
(5) Previous examples of spirocyclization to spiro[5.5]undecanes involving cyclohexyl cations either have not involved stereochemical considerations[6] or have not elucidated stereochemistry.[7]

(6) M. Nojima, T. Nagai, and N. Tokura, *J. Org. Chem.*, **33**, 1970 (1968); N. D. Zelinski and N. V. Elagina, *Dokl. Akad. Nauk SSSR*, **87**, 755 (1952) (*Chem. Abstr.*, **48**, 542 (1954)); A. Nondon, *Justus Liebigs Ann. Chem.*, **585**, 43 (1954).

(7) C. Daisslé and H. Schinz, *Helv. Chim. Acta*, **39**, 2118 (1956).

(8) (a) J.-M. Conia and P. Beslin, *Bull. Soc. Chim. Fr.*, 483 (1969); (b) R. L. Cargill, J. R. Dalton, S. O'Connor, and D. G. Michels, *Tetrahedron Lett.*, 4465 (1978).

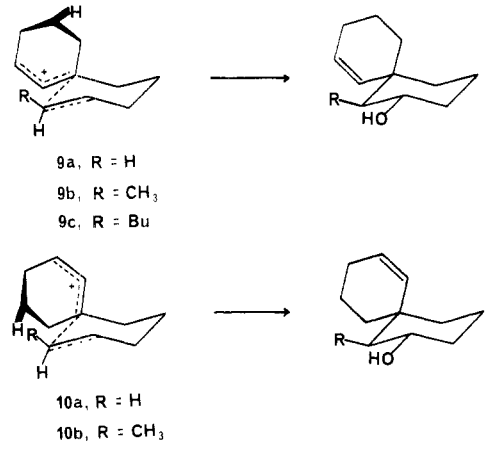
0022-3263/79/1944-2834$01.00/0 © 1979 American Chemical Society



spiro[5.5]undecan-2-ol (**6**) as the sole product. Alcohol **6** was also prepared by direct cyclization of enone **3a** with trifluoroacetic anhydride and trifluoroacetic acid[3,9] to give, after hydrolysis, a mixture of keto alcohols **7** and **8** in 66% yield. Again the presence of two isomers in a ratio of ~3:1 was evidenced by ^{13}C NMR. Deoxygenation of this mixture by sodium cyanoborohydride reduction of the derived tosylhydrazones[10] gave alcohol **6**, identical with the material from hydrogenation of **4** and **5**.

The stereochemical course of the reaction giving **4** and **5** is readily deduced by analysis of the alkene carbon region of the ^{13}C NMR spectrum. Absorption is observed at δ 126.4 and 132.7 for the minor isomer and at δ 125.6 and 138.1 for the major isomer. On the basis of chemical shift theory and analogy,[17,18] the minor signal at 132.7 can be assigned to C-7 of **5** and the major signal at 138.1 to C-7 of **4**. The significant upfield shift in structure **5** is attributed to the well-documented δ effect observed for carbons axial to a cyclohexane ring.[11,12] The chemical shift difference for C-8 in the two isomers is minimal as expected.

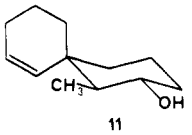
Examination of molecular models suggests that, assuming preferential formation of a pseudoaxial bond in the attack of the double bond on the cyclohexenyl cation,[13] the two transition states leading to **4** and **5** may be represented by structures **9a** and **10a**. The interaction of the out-of-plane methylene with the terminus of the approaching double bond appears greater in **10a** than in **9a**, thus leading to preferential reaction via **9a**. This model suggests that addition of a substituent at the terminus of the double bond (e.g., **9b** and **10b**) would increase the stereoselectivity. Cyclization studies with alcohols **1b**,**1c** were undertaken to confirm this analysis.



9a, R = H
9b, R = CH_3
9c, R = Bu

10a, R = H
10b, R = CH_3

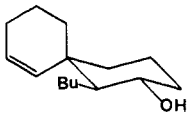
Treatment of cyclohexenol **1b** with anhydrous formic acid at room temperature for 2.5 h gave, after workup and hydrolysis of formate esters, spirocyclic product in 84% yield. The ^{13}C NMR analysis indicates that alcohol **11**



11

constitutes greater than 90% of the material present.[14] The chemical shifts in the alkene carbon region at δ 138.0 and 126.2 demonstrate the equatorial nature of the vinyl group. The cyclization of **1b** thus proceeds to form three adjacent chiral centers with excellent control of relative stereochemistry.

The cyclization of cyclohexenol **1c** proceeded similarly except that more vigorous conditions were required. Refluxing alcohol **1c** in anhydrous formic acid for 11 h gave, after cleavage of formates and removal of hydrocarbon material by column chromatography, spirocyclic alcohols in 54% yield. This material was shown by VPC to consist mainly (80%) of one material with two minor impurities. The major isomer was isolated by chromatography. The ^{13}C NMR spectrum (δ 126.6 and 137.6 for the alkene carbons) indicated that this material is the alcohol **12** with the same stereochemistry as alcohol **11**.[15]



12

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 237B or Beckman Instruments Model IR8 spectrophotometer.

(9) K. E. Harding, J. L. Cooper, and P. M. Puckett, *J. Am. Chem. Soc.*, **100**, 993 (1978); J. L. Cooper and K. E. Harding, *Tetrahedron Lett.*, 3321 (1977).

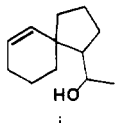
(10) R. D. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).

(11) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.

(12) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **89**, 6612 (1967); E. Wenkert and B. L. Buckwalter, *ibid.*, **94**, 4367 (1972); R. Kutschan, L. Ernst, and H. Wolf, *Tetrahedron*, **33**, 1833 (1977).

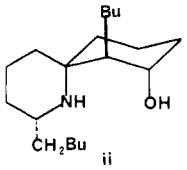
(13) This type of stereoelectronic control in π cyclizations is well documented: W. S. Johnson and K. E. Harding, *J. Org. Chem.*, **32**, 478 (1967); K. E. Harding, E. J. Leopold, A. M. Hudrlik, and W. S. Johnson, *J. Am. Chem. Soc.*, **96**, 2540 (1974); B. E. McCarry, R. L. Markezich, and W. S. Johnson, *ibid.*, **95**, 4416 (1973); D. R. Morton and W. S. Johnson, *ibid.*, **95**, 4419 (1973); R. L. Carney and W. S. Johnson, *ibid.*, **96**, 2549 (1974); K. A. Parker and W. S. Johnson, *ibid.*, **96**, 2556 (1974).

(14) The NMR spectra of this alcohol and of the ketone derived by Jones oxidation conclusively proved that the cyclization had not taken an abnormal course to give the five-membered ring product i, which was suggested to us by Professor D. A. Evans in December 1977.



i

(15) The stereoselectivity exhibited by these cyclizations may be applied to the synthesis of a variety of spirocyclic systems. Subsequent to the completion of our cyclization of alcohols **1a**,**1c** (private communication to D. A. Evans, December 1977; K. E. Harding, J. L. Cooper, B. Dupre, and P. M. Puckett, Abstracts, 176th National Meeting of the American Chemical Society, ORGN 93, September 1978), the application of heterocyclic analogues to the synthesis of perhydrohistrionicotoxin (ii) was reported.[16] The stereochemistry of these cyclizations can be rationalized on the basis of the same conformational principles presented in this paper.



ii

(16) H. E. Shoemaker and W. N. Speckamp, *Tetrahedron Lett.*, 1515, 4841 (1978); D. A. Evans and E. W. Thomas, *ibid.*, 411 (1979).

High-resolution mass spectra were obtained on a CEC Model 21-110 spectrometer under the supervision of Dr. R. Grigsby.

The ^1H NMR spectra were obtained in CCl_4 or $CDCl_3$ solution on a Varian Associates HA-100 or T-60 spectrometer. The ^{13}C NMR spectra were obtained in $CDCl_3$ solution in the Fourier transform mode on a JEOL PFT-100 spectrometer system operating at 25.034 MHz (proton resonance frequency 99.539 MHz) and equipped with a Nicolet 1085 data system. All chemical shifts (^1H and ^{13}C) are reported on the δ scale as parts per million downfield from tetramethylsilane (Me_4Si) as an internal reference.

The vapor-phase chromatographic (VPC) analyses were performed on a Varian Instruments Model 940 chromatograph equipped with a flame ionization detector. Columns used for analyses were $^1/_8$ in. × 6 ft packed with 3% SE-30 on Chromosorb W, 10% Carbowax on Chromosorb W, or 1.5% OV-101 on Chromosorb G. All percentage composition values are reported as relative peak areas without correction for relative detector response. Preparative VPC separations were performed on a Varian Instrument Model 920 instrument equipped with a thermal conductivity detector, using a 0.25 in. × 6 ft column packed with 10% SE-30 on Chromosorb A.

Evaporative distillation refers to bulb-to-bulb (Kugelrohr), short-path distillation. The temperatures cited for these distillations are the maximum temperatures of the oven during the distillation.

The isolation procedure normally consisted of dilution of the product with water and extraction with the solvent indicated. The combined organic extracts were then washed with the stated solutions, dried, and concentrated by using a rotary evaporator to remove solvent at about 30 mm. Acid refers to 10% hydrochloric acid. Bicarbonate refers to a saturated aqueous solution of sodium bicarbonate. Brine refers to a saturated aqueous solution of sodium chloride.

Tetrahydrofuran was distilled from the sodium benzophenone dianion just before use. Anhydrous ether was stored over sodium. Formic acid was distilled from boric anhydride and stored at 3 °C.

3-(4-Pentenyl)-2-cyclohexen-1-one (2a). Ketone **3**[17] (3.08 g, 20 mmol) in 15 mL of anhydrous ether was added dropwise at −78 °C under nitrogen to a Grignard reagent freshly prepared from 20 mmol of 1-bromo-4-pentene and 20 mmol of magnesium metal in 60 mL of ether. After 30 min the solution was warmed to room temperature and stirred for an additional 2 h. The reaction was then cooled to 0 °C, 10% HCl (30 mL) was added, and the solution was stirred for 30 min. The solution was diluted with 50 mL of brine and extracted with ether (3 × 50 mL). The combined extracts were washed (water, bicarbonate, and brine), dried ($MgSO_4$), concentrated, and evaporatively distilled (95 °C (0.4 mm)) to give 2.55 g (78% yield) of enone **2a**: IR (film) 1680 (C=O), 3000, 1600, 990, 900 (C=C) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 4.5–5.2 (m, 2 H, CH=C**H**$_2$), 5.4–6.1 (m, 2 H, CH_2=CH and O=CCH=C); ^{13}C NMR δ 22.8, 26.1, 29.7, 33.2, 27.2 (2 C), 115.2 (C-11), 125.8 (C-2), 137.8 (C-10), 166 (C-3), 199.4 (C-1). The ^{13}C NMR spectrum and VPC analysis (SE-30, 185 °C) indicated a purity of >95%. An analytical sample was obtained by preparative VPC (SE-30, 200 °C). Mass spectrum for $C_{11}H_{16}O$: m/e(calcd) 164.120110; m/e(found) 164.119856.

***trans*-4-Hexenyl Chloride.** A solution of *trans*-4-hexen-1-ol[18] (7.0 g, 70 mmol) in 100 mL of carbon tetrachloride containing 27.5 g (105 mmol) of triphenylphosphine was heated to a gentle reflux.[19] After 12 h the reaction mixture was cooled, filtered, and fractionally distilled (95–115 °C) to give 7.02 g (84% yield) of *trans*-4-hexenyl chloride: IR (film) 995 (C=C), 640 (CCl) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.45 (t, J = 6 Hz, 2 H, CH_2Cl), 5.3–5.6 (m, 2 H, HC=CH).

3-(*trans*-4-Hexenyl)-2-cyclohexen-1-one (2b). Lithium wire (130 mg, 19 mmol) was cut into small pieces and suspended in dry ether. The solution was cooled to −78 °C under argon and then 10% of a solution of *trans*-4-hexenyl chloride (1.13 g, 9.5 mmol) in 20 mL of ether was added. The reaction was stirred for 30 min or until the reaction began (indicated by shiny spots on the metal), and the remainder of the alkenyl chloride was added dropwise over a 30-min period. The reaction was then warmed to 0 °C and stirred for 3 h. The salts were allowed to settle, and the liquid was transferred to a dry round-bottom flask and kept at 0 °C. Ketone **3**[17] (1.33 g, 9.5 mmol) in 20 mL of ether was added dropwise to the lithium reagent and stirring was continued at 0 °C for 1 h. Aqueous 10% HCl (20 mL) was added to the cold solution and the mixture was allowed to stir for 1 h at room temperature. The solution was diluted with 50 mL of water and extracted with ether (3 × 50 mL). The combined extracts were washed (bicarbonate and brine), dried ($MgSO_4$), concentrated, and evaporatively distilled (100 °C (0.25 mm)) to give 1.4 g of a mixture of enone **2b** and a small amount of starting alkenyl chloride. The mixture was separated on silica gel by using 25% ether–75% hexane to give 100 mg of alkenyl chloride and 1.25 g (81% yield) of enone **2b**: IR (film) 1680 (C=O), 3000, 1625, 950 (C=C) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 5.2–5.4 (m, 2 H, HC=CH), 5.7 (bs, 1 H, C=C**H**C=O); ^{13}C NMR δ 17.8 (C-12), 22.8, 26.8, 29.7, 32.0, 37.4 (2 C), 125.6 (C-2 and C-11), 130.3 (C-10), 166.1 (C-3), 199.4 (C-1). The ^{13}C NMR spectrum and VPC analysis (OV-101, 130 °C) indicated a purity of >95%. Mass spectrum for $C_{12}H_{18}O$: m/e(calcd) 178.135760; m/e(found) 178.134901.

***trans*-4-Nonenyl Chloride.** *trans*-4-Nonen-1-ol[20] (3 g, 21 mmol) in 50 mL of carbon tetrachloride was stirred under N_2 at room temperature. Triphenylphosphine (6 g, 23 mmol) was added in one portion and the solution was heated to a gentle reflux for 12 h. The solution was cooled to 0 °C, filtered to remove salts, concentrated, and evaporatively distilled (70 °C (0.25 mm)) to give 3.0 g (95% yield) of *trans*-4-nonenyl chloride: IR (film) 3000, 950 (C=C), 650 (CCl) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.45 (t, J = 6 Hz, 2 H, CH_2Cl), 5.2–5.6 (m, 2 H, HC=CH); ^{13}C NMR δ 13.9, 22.3, 29.7, 31.8, 32.3, 32.5, 44.2, 128.1, 132.1.

3-(*trans*-4-Nonenyl)-2-cyclohexen-1-one (2c). Lithium wire (323 mg, 46 mmol) was cut into small pieces and suspended in dry ether. The solution was cooled to −78 °C under argon and then one-tenth of a solution of *trans*-4-nonenyl chloride (3.7 g, 23 mmol) in 30 mL of ether was added. The reaction was stirred for 30 min or until the reaction began (indicated by shiny spots on the metal), and the remainder of the alkenyl chloride was added over a 30-min period. The solution was then warmed to 0 °C and stirred for 3 h. The salts were allowed to settle and the liquid was transferred to a dry round-bottom flask and kept at 0 °C. Ketone **3**[17] (1.61 g, 11.5 mmol) in 20 mL of dry ether was added slowly to the lithium reagent and stirred at 0 °C for 1 h. Aqueous 10% HCl (20 mL) was added to the solution which was stirred for 2 h at room temperature. The solution was diluted with 50 mL of water and then extracted with ether (3 × 50 mL). The combined extracts were washed (bicarbonate and brine), dried ($MgSO_4$), concentrated, and evaporatively distilled (130 °C (0.2 mm)) to give 2.41 g (95% yield based upon starting ketone) of enone **2c**: IR (film) 1680 (C=O), 3000, 1625, 950 (C=C) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.7–2.4 (m, 21 H), 5.3–5.5 (m, 2 H, HC=CH), 5.6–5.8 (m, 1 H, O=CCH=C); ^{13}C NMR δ 14.0, 22.2, 22.8, 26.9, 29.7, 31.8, 32.1, 32.3, 37.4 (2 C), 125.8 (C-2), 129.0 and 131.5 (C-10 and C-11), 165.9 (C-3), 199.2 (C-1).

3-(*trans*-4-Pentenyl)-2-cyclohexen-1-ol (1a). Enone **2a** (1.4 g, 8.54 mmol) was treated with an excess of lithium aluminum hydride in ether at 0 °C. The reaction mixture was quenched by successive addition of water, 15% sodium hydroxide, and water.[21] Anhydrous magnesium sulfate was added; the mixture was filtered, and the filtrate was concentrated and evaporatively distilled (90 °C (0.1 mm)) to give 1.35 g (95% yield) of alcohol **1a**: IR (film) 3330 (OH), 1660 and 1640 (C=C), 890 (C=C) cm^{-1}, ^1H NMR (60 MHz, $CDCl_3$) δ 4.2 (bm, 1 H, C**H**OH), 4.8–5.2 (m, 2H, HC=C**H**$_2$), 5.4–6.2 (m, 2 H, C**H**=CH_2 and O=CCH=C); ^{13}C NMR δ 19.5, 26.8, 28.5, 31.9, 33.4, 37.0, 65.6 (C-1), 114.5 (C-4′), 124.6 (C-2), 138.6 (C-4′), 140.9 (C-3).

(17) W. F. Bannon and H. O. House, *Org. Synth.*, **40**, 41 (1960).
(18) R. C. Brandon, J. M. Derfei, and C. E. Board, *J. Am. Chem. Soc.*, **72**, 2120 (1950).
(19) I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. Commun.*, 1350 (1968).
(20) Prepared by the addition of butyllithium to dihydropyran: F. L. M. Pattison and R. E. A. Dear, *Can. J. Chem.*, **41**, 2600 (1963). We thank Dr. Harry Ensley, Tulane University, for bringing this procedure to our attention.
(21) V. M. Micovic and M. L. J. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

3-(*trans*-4-Hexenyl)-2-cyclohexen-1-ol (1b). Reduction of enone **2b** (1.16 g, 6.6 mmol) in the same manner as enone **2a** above gave, after evaporative distillation (70 °C (0.25 mm)), 1.15 g (quantitative yield) of alcohol **1b**: IR (film) 3400 (OH), 3000, 1650, 950 (C=C) cm^{-1}; ^1H NMR (100 MHz, CCl_4) δ 3.95–4.22 (m, 1 H, CHOH), 5.2–5.5 (m, 3 H, olefinic protons); ^{13}C NMR δ 17.8 (C-6'), 19.3, 27.4, 28.5, 32.2, 37.0, 65.8 (C-1), 124.0 (C-2), 125.0 (C-4'), 131.2 (C-3'), 142 (C-3).

3-(*trans*-4-Nonenyl)-2-cyclohexen-1-ol (1c). Reduction of enone **2c** (0.95 g, 4.3 mmol) in the same manner as enone **2a** above gave, after evaporative distillation (130 °C (0.25 mm)), 0.92 g (97% yield) of alcohol **1c**: IR (film) 3400 (OH), 3000, 1645, 950 (C=C) cm^{-1}; ^1H NMR (100 MHz, CCl_4) δ 0.94 (t, 3 H, CH_3), 4.1–4.3 (bm, CHOH), 5.34–5.58 (m, 3 H, vinyl); ^{13}C NMR δ 13.9, 19.2, 22.2, 27.5, 27.9, 28.5, 31.8, 31.9, 32.3 (2 C), 37.0, 65.8 (C-1), 123.9 (C-2), 129.8 (C-5'), 130.8 (C-4'), 142.1 (C-3).

Cyclization of Alcohol 1a. Alcohol **1a** (1.30 g, 7.83 mmol) was treated with 30 mL of dry formic acid for 30 min at room temperature. The mixture was poured into CH_2Cl_2/H_2O. The separated aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed (H_2O, bicarbonate, and brine), dried (Na_2SO_4), concentrated and evaporatively distilled 90 °C (0.2 mm)) to give 1.4 g (92% yield) of cyclic formates: IR (film) 3050 (C=C), 1725 and 1175 (O_2CH) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 4.8–5.8 (m, 3 H, CH=CH and CHO_2CH), 8.05 (s, 1 H, O_2CH); ^{13}C NMR δ (major isomer), 18.8 (C-10, 19.8 (C-4), 25.4 (C-9), 31.5 (C-3 and C-11), 36.2 (C-5), 38.2 or 37.7 (C-6), 42.3 (C-1), 70.1 (C-2), 126.1 (C-8), 137.1 (C-7), 160.6 (HCO_2); ^{13}C NMR δ(minor isomer) 18.6 (C-10), 19.5 (C-4), 25.6 (C-9), 31.9 (C-3 and C-11), 36.0 (C-5), 37.7 or 38.2 (C-6), 43.6 (C-1), 70.4 (C-2), 127.0 (C-8), 132.3 (C-7), 160.7 (HCO_2).

A portion of the formate mixture (800 mg, 4.12 mmol) was treated with an excess of lithium aluminum hydride in ether at 0 °C. Normal workup[21] and evaporative distillation (87 °C (0.1 mm)) gave 650 mg (95% yield) of a mixture of alcohols **4** and **5**: IR (film) 3400 (OH) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 3.5–4.0 (bm, 1 H, CHOH), 5.02 (dt, J = 10, 2 Hz, C-7H), 5.75 (dt, J = 10, 4 Hz, C-8H), 6.15 (dt, C-7 of minor isomer); ^{13}C NMR δ(major isomer **4**) 19.0 (C-10), 20.2 (C-4), 25.5 (C-9), 31.4 (C-11), 35.5 (C-3), 36.3 (C-5), 38.9 or 38.1 (C-6), 46.6 (C-1), 125.6 (C-8), 138.1 (C-7); ^{13}C NMR δ(minor isomer **5**) 18.6 (C-10), 20.1 (C-4), 25.8 (C-9), 31.4 (C-11), 35.9 (C-3), 36.3 (C-5), 38.1 or 38.9 (C-6), 48.0 (C-1), 126.4 (C-8), 132.7 (C-7).

Reduction of Alcohols 4 and 5 to Spiro[5.5]undecan-2-ol (6). The cyclic alcohol mixture (400 mg, 2.41 mmol) was reduced with hydrogen over platinum on charcoal in ethanol. The reaction mixture was filtered, concentrated, and evaporatively distilled (90 °C (0.05 mm)) to give 390 mg (96% yield) of a single saturated spirocyclic alcohol: IR (film) 3400 (OH) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 3.5–4.0 (m, CHOH); ^{13}C NMR δ 20.0 (C-4), 21.7 (C-8 and C-10), 26.8 (C-9), 33.2 (C-11, axial), 34.7 (C-6), 35.9 (C-3) 36.3 (C-5), 41.7 (C-7, equatorial), 46.1 (C-1), 67.1 (C-2).

The product was an amorphous solid, mp 50–51 °C (lit.[22] mp 51 °C), which was too soluble to be recrystallized. The *p*-nitrobenzoate was prepared and recrystallized from ethanol to give white crystals, mp 99–99.5 °C (lit.[23] mp 102 °C).

Cyclization of Enone 2a with TFA/TFAA. A mixture of 14 mL of trifluoroacetic acid (TFA) and 7 mL of trifluoroacetic anhydride (TFAA) was added to 700 mg (4.26 mmol) of enone **2a**. The mixture was stirred for 2 h at 25 °C. The TFA and TFAA were removed by concentration and the residue was evaporatively distilled (120 °C (0.25 mm)) to give 1.25 g of spirocyclic product.[24] This material was treated with 25 mL of saturated potassium carbonate in methanol for 1 h. The methanol was removed by concentration, and methylene chloride and $MgSO_4$ were added. The solution obtained after filtration was concentrated and evaporatively distilled (120 °C (0.25 mm)) to give 370 mg of a mixture of keto alcohols **7** and **8** containing some keto olefin. The mixture was separated on silica gel by using methylene chloride to elute the keto olefin (55 mg, 11% yield) followed by elution with methanol to recover the keto alcohols **7** and **8** (315 mg, 52% yield): bp 125 °C (0.3 mm); IR 3400 (OH), 1715 (C=O) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.0–2.3 (m, 16 H), 3.2–4.0 (m, 1 H, CHOH); ^{13}C NMR δ (major isomer) 19.8, 21.8, 32.1, 35.3, 41.2, 45.5 (C-6), 56.1, 66.7 (C-2), 211.5 (C-8). Comparison with signals for the minor isomer indicated a ratio of ~3:1. An analytical sample was obtained by preparative VPC (SE-30, 205 °C). Mass spectrum for $C_{11}H_{18}O_2$: m/e(calcd) 182.130670; m/e(found) 182.131201.

A sample of the keto alcohol mixture (40 mg, 0.22 mmol) was dissolved in reagent grade acetone (20 mL) and cooled to 0 °C. Jones' reagent[25] (diluted fivefold with acetone) was added dropwise until the reaction mixture remained orange. The reaction was then quenched with isopropyl alcohol, diluted with water, and extracted with ether. The combined ether extracts were washed (acid, bicarbonate, and brine), dried ($MgSO_4$), concentrated, and evaporatively distilled (95 °C (0.25 mm)) to give 33 mg (82% yield) of a single diketone: IR (film) 1715 (C=O) cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.4–2.4 (m); ^{13}C NMR δ 21.3, 34.3, 40.7, 43.5, 52.9, 209.5 (carbonyl).

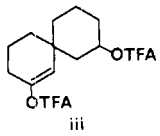
Reduction of Keto Alcohols 7 and 8 to Spiro[5.5]undecan-2-ol (6). The procedure of Hutchins[10] was used. A mixture of keto alcohol (170 mg, 0.93 mmol), *p*-toluenesulfonylhydrazine (217 mg, 1.17 mmol) and a catalytic amount of *p*-toluenesulfonic acid in 30 mL of dimethylformamide/sulfolane (1/1) was heated to 100 °C for 30 min. Then sodium cyanoborohydride (235 mg, 3.74 mmol) was added and heating was continued at 110 °C for 2 h. The mixture was cooled and extracted with pentane (5×). The extract was washed (water, acid, bicarbonate, brine), dried ($MgSO_4$), concentrated, and evaporatively distilled (90 °C (0.05 mm)) to give 100 mg (64% yield) of product. The spectra (IR, ^1H NMR, ^{13}C NMR) were identical with those of alcohol **6** prepared by reduction of alcohols **4** and **5**, and a mixture melting point of the two alcohol samples was undepressed.

Cyclization of Alcohol 1b. Alcohol **1b** (1.15 g, 6.4 mmol) was treated with 50 mL of dry formic acid at 25 °C for 2.5 h. The solution was then diluted with 100 mL of water and extracted with ether. The combined extracts were washed (water, bicarbonate, brine), dried ($MgSO_4$), concentrated, and evaporatively distilled (125 °C (0.2 mm)) to give 1.12 g (84% yield) of cyclic formates: IR (film) 1730 (C=O), 3000 cm^{-1}; ^1H NMR (100 MHz, CCl_4) δ 0.84 (d, J = 6 Hz, CH_3CH), 4.58–4.9 (dq, J = 4 Hz, CHOH), 5.04–5.25 (bd, J = 10 Hz, CH_2CH=CH), 5.52–5.75 (dt, J = 3 Hz, CH_2CH=CH), 7.94 (s, O_2CH); ^{13}C NMR δ 12.4 (C-12), 18.8 (C-10), 19.9 (C-4), 24.0 (C-11), 25.1 (C-9), 32.3 (C-5), 36.0 (C-3), 39.9 (C-6), 45.3 (C-1), 74.8 (C-2), 126.9 (C-8), 137.0 (C-7), 160.7 (C=O).

Cleavage of the formate ester functionality with lithium aluminum hydride proceeded to give, after evaporative distillation (115 °C (0.2 mm)), spirocyclic alcohol **11** in 96% yield: IR (film) 3400 (OH), 3000 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.95 (d, J = 7 Hz, 3 H, CH_3CH), 3.19 (m, J = 5 Hz, 1 H, CHOH), 5.17 (bd, J = 10 Hz, 1 H, CH_2CH=CH), 5.48, 5.79 (dt, J = 4 Hz, CH_2CH=CH); ^{13}C NMR δ(major isomer) 12.5 (C-12), 19.0 (C-10), 20.3 (C-4), 24.2 (C-11), 25.3 (C-9), 36.0 (C-3), 36.3 (C-5), 39.8 (C-6), 48.4 (C-1), 71.7 (C-2), 126.2 (C-8), 138 (C-7). The ^{13}C NMR spectrum and VPC analysis (OV-101, 148 °C) indicted that a single isomer constituted >90% of the product. An analytical sample was obtained by preparative VPC (SE-30, 195 °C). Mass spectrum for $C_{12}H_{20}O$: m/e(calcd) 180.151410; m/e(found) 180.150739.

Alcohol **11** was oxidized to the corresponding ketone by using Collins' reagent according to the procedure of Ratcliffe and Rodehorst.[26] A mixture of chromic anhydride (660 mg, 6.6 mg-atom), 4 mL of dried pyridine, and 50 mL of dried methylene chloride was stirred at 25 °C for 15 min. Then a 200 mg (1.1 mmol) sample of alcohol **11** was added in 1 mL of CH_2Cl_2. The mixture was stirred at 25 °C for 1 h. The methylene chloride was decanted, and the residue was washed with ether. The combined organics

(22) M. Nojima, T. Nagai, and N. Tokura, *J. Org. Chem.*, **33**, 1970 (1968).
(23) W. S. G. P. Norris, *J. Chem. Soc.*, 245 (1926).
(24) This product consisted of a mixture (~5:1) of desired diester iii and ester olefin iv resulting from deprotonation of the intermediate spirocyclic cation.[9]



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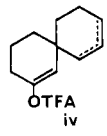

iv

(25) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(26) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

were washed (acid, 5% NaOH, brine), dried ($MgSO_4$), concentrated, and evaporatively distilled (100 °C (0.25 mm)) to give 180 mg (91% yield) of spirocyclic ketone: IR (film) 1715 (C=O), 3100 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.9 (d, J = 6 Hz, 3 H, $CHCH_3$), 5.1–5.4 (d, 1H, CH_2CH=C**H**), 5.5–5.8 (m, 1 H, CH_2C**H**=CH); ^{13}C NMR δ 9.2 (C-12), 18.9 (C-10), 22.4 (C-4), 24.7 (C-11), 25.3 (C-9), 35.8 (C-5), 41.1 (C-3), 43.8 (C-6), 53.9 (C-1), 127.2 (C-8), 136.1 (C-7), 213.0 (C-2).

Cyclization of Alcohol 1c. Allylic alcohol **1c** (370 mg, 1.6 mmol) was combined with 75 mL of dry formic acid and heated to 55 °C under N_2 for 11 h. The cooled solution was diluted with water (200 mL) and extracted with methylene chloride (3 × 100 mL). The combined extracts were washed (water, bicarbonate, brine), dried ($MgSO_4$), and concentrated to give 390 mg of crude formate: IR (film) 1730 (C=O), 1150 (CO), 3040 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 4.6–5.8 (m, 3 H, HC=CH and C**H**OH), 7.9 (s, 1 H, HC=O). Analysis by VPC (Carbowax, 185 °C) showed one major peak with a shoulder and shorter retention time peaks believed to be hydrocarbon.

The above mixture of formates (370 mg) was treated with an excess of lithium aluminum hydride in ether to cleave the formate esters. The resulting mixture was chromatographed on silical gel to give 90 mg of hydrocarbons eluted with hexane and 260 mg of alcohols eluted with methanol. The alcohol mixture was evaporatively distilled (125 °C (0.2 mm)) to give 200 mg of an oil which partially solidified upon standing. Analysis by VPC (Carbowax, 185 °C) showed three peaks with long retention times (>7 min). The first peak, 7.5 min, contained 5.7% of the total area, the second, 9 min, contained 13% of the area, and the third peak, 11.5 min, contained 80% of the area. The mixture of alcohols was partially separated on an alumina column (TLC grade) by using 30% CH_2Cl_2/hexane. The major isomer **12** had the following spectroscopic properties: IR (film) 3400 (OH), 1035 (CO), 3020 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 3.25–3.8 (m, 1 H, C**H**OH), 5.0–5.3 (bd, 1 H, CH_2CH=C**H**), 5.5–5.79 (m, 1 H, CH_2C**H**=CH); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 18.8, 20.3, 23.4, 24.9, 25.3, 29.6, 34.4, 35.7, 36.5, 40.8 (C-6), 54.5 (C-1), 73.1 (C-2), 126.6 (C-8), 137.6 (C-7).

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Registry No. 1a, 70681-88-8; **1b**, 70681-89-9; **1c**, 70681-90-2; **2a**, 70079-75-3; **2b**, 70681-91-3; **2c**, 70681-92-4; **3**, 5323-87-5; **4**, 70681-93-5; **4** formate, 70681-94-6; **5**, 70681-95-7; **5** formate, 70681-96-8; **6**, 16133-76-9; **6** *p*-nitrobenzoate, 70681-97-9; **7**, 70681-98-0; **8**, 70681-99-1; **11**, 70682-00-7; **11** formate, 70682-01-8; **11** ketone, 70682-02-9; **12**, 70682-03-0; **12** formate, 70703-18-3; iii, 70682-05-2; iv, 70682-23-4; 1-bromo-4-pentene, 1119-51-3; *trans*-4-hexen-1-ol, 928-92-7; *trans*-4-hexenyl chloride, 62614-72-6; *trans*-4-nonen-1-ol, 16695-34-4; *trans*-4-nonenyl chloride, 16427-36-4; spiro[5.5]undecane-2,8-dione, 70682-04-1.

Convenient Syntheses of 5,5,9-Trimethyl-*trans*-1-decalone and 6β-Hydroxy-5,5,9β-trimethyl-*trans*-1-decalone

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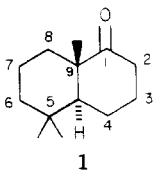
Convenient syntheses of 5,5,9-trimethyl-*trans*-1-decalone (1) and 6β-hydroxy-5,5,9β-trimethyl-*trans*-1-decalone (2) involve (1) the Robinson annelation of 2-methyl-1,3-cyclohexanedione with ethyl vinyl ketone, (2) selective ketalization of 5,9-dimethyl-$\Delta^{5,10}$-octal-1,6-dione at the nonconjugated carbonyl group with ethylene glycol, (3) reductive methylation of 1-ethylenedioxy-5,9-dimethyl-$\Delta^{5,10}$-2-octalone, (4) Wolff–Kishner reduction or dissolving-metal reduction of 1-ethylenedioxy-5,5,9-trimethyl-*trans*-1-decalone, and (5) acid-catalyzed hydrolysis of 1-ethylenedioxy-5,5,9-trimethyl-*trans*-decalin or of 1-ethylenedioxy-6β-hydroxy-5,5,9β-trimethyl-*trans*-decalin to form 1 and 2, respectively.

The value of 5,5,9-trimethyl-*trans*-1-decalone[2] (1) and 6β-hydroxy-5,5,9β-trimethyl-*trans*-1-decalone (2) as



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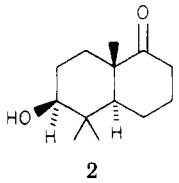

2

synthetic intermediates has been demonstrated in the synthesis of several terpenes.[3] In connection with several projected syntheses in our respective laboratories,[4] we required convenient, stereocontrolled preparations of these bicyclic intermediates. Particularly important, both for our work and for others who might anticipate utilizing these terpene precursors, is the requirement that preparations of racemic 1 and 2 be efficient and exercise highly effective stereocontrol to avoid tiresome and sometimes difficult isomer separations. We now report a short synthetic sequence for the preparation of 1 and 2 in approximately 50% overall yield from 2-methyl-1,3-cyclohexanedione which exercises the requisite stereocontrol while maintaining the C-1 carbonyl oxidation state throughout the sequence. Both the overall yield and

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(2) We are using the common name of the parent compound 1 to avoid the cumbersome 3,4,4aα,5,6,7,8,8a-octahydro-5,5,8aβ-trimethyl-1(2*H*)-naphthalenone. And to avoid confusion, comparable common names and the skeletal numbering system shown for 1 have been used for all related compounds in this study.

(3) For several examples, see ref 5–7 as well as the following: (a) N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron*, **23**, 509 (1967); (b) E. Ghera and F. Sondheimer, *Tetrahedron Lett.*, 3887 (1964).

(4) Several additional manuscripts are now in preparation. See also ref 12a.

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