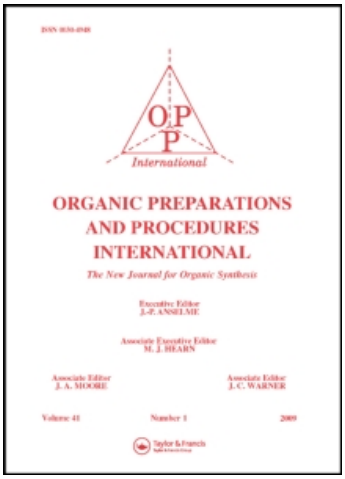

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A CONVENIENT SYNTHESIS OF ISOMERICALLY PURE 1-METHYL-2-VINYLCYCLOHEXENE AND 1-VINYLCYCLOHEXENE

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A CONVENIENT SYNTHESIS OF ISOMERICALLY PURE 1-METHYL-2-VINYLCYCLOHEXENE AND 1-VINYLCYCLOHEXENE

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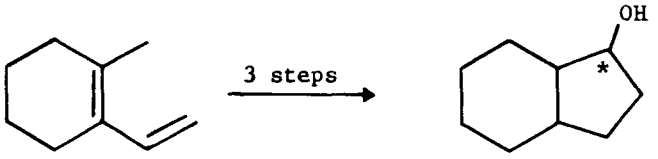
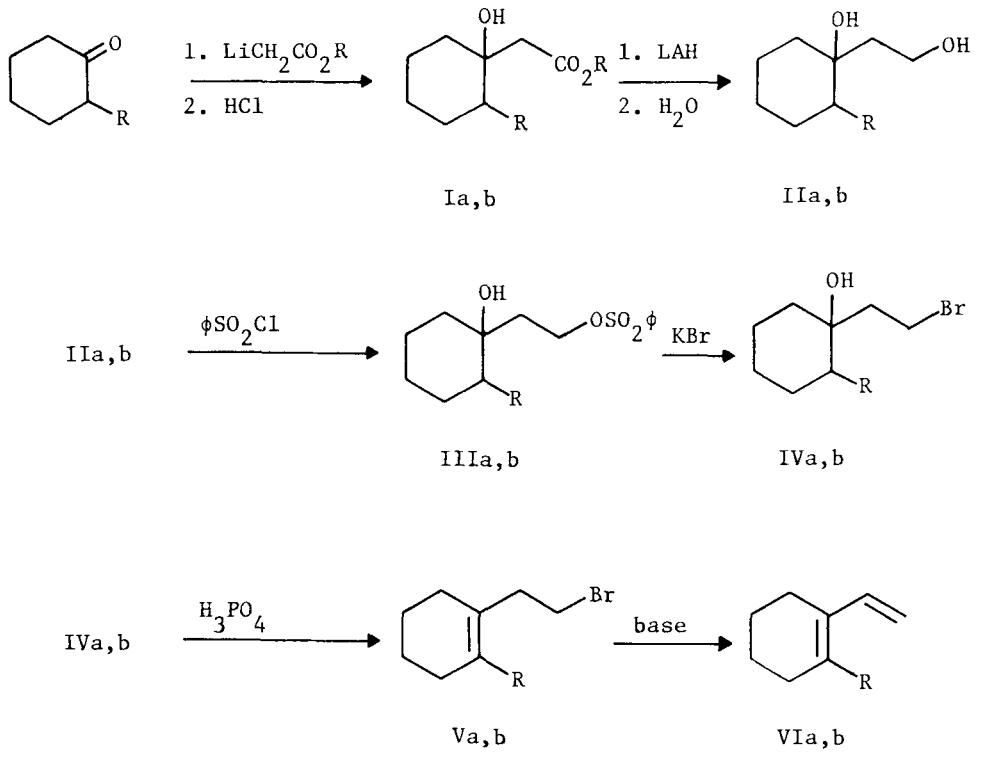
As part of a program to synthesize carbon-11 labeled, 17β-estradiol and related hormones using organoborane chemistry,[1,2] we required isomerically pure 1-methyl-2-vinylcyclohexene and related dienes as model compounds for investigating ring closure reactions. Although a number of synthesis of 1-methyl-2-vinylcyclohexene (VIa) have been reported,[3-8] the desired product is generally contaminated with the isomeric 2-methyl-3-vinylcyclohexene.



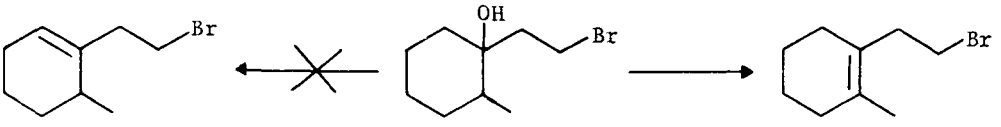
We now report an improved synthesis of 1-methyl-2-vinylcyclohexene (VIa) and 1-vinylcyclohexene (VIb). The products are formed in good yield with regiospecific placement of the internal double bond. The synthetic sequence is summarized in Figure 1.



(a) R = CH_3; (b) R = H

FIGURE I

The procedure (6-steps) produces good yields of the desired product and is more convenient than the previously reported procedures. Under the reaction conditions, the desired intermediate, Va, is formed isomerically pure from IVa.



Vc IVa Va

The position of the double bond was confirmed by off-resonance ^{13}C-NMR; two quarternary carbons at 127.1 and 129.8 ppm were present as expected. No other vinylic carbons were apparent in the ^{13}C-NMR.

The ^{13}C-NMR spectrum of VIa exhibits two resonance lines at 110 and 135.18 ppm due to the sp^2 carbons of the cyclic and acyclic alkenes, respectively. The off-resonance ^{13}C-NMR spectrum for compound VIa has a singlet peak at 110 ppm and a triplet superimposed by a doublet peak at 35.18 ppm.

EXPERIMENTAL SECTION

The ^{1}H and ^{13}C-NMR spectra were obtained on a Jeol FX-90Q Fourier transform NMR spectrometer. Chemical shift values are expressed in parts per million (δ) downfield from TMS. The IR spectra were obtained on a Perkin-Elmer 1330 spectrometer and Digilab Model 20 c/v FTIR. The reaction flasks were dried in an oven at 130°, and then assembled under a dry nitrogen flow while cooling. The reagents were commercial products of the highest purity available and were used directly as received. Tetrahydrofuran and ether were dried over Na/benzophenone and $LiAlH_4$ respectively and distilled under nitrogen before use.

Ethyl 2-(1-Hydroxy-2-methylcyclohexyl)acetate (Ia).- n-Butyllithium (352 mol, 220 ml of a 1.6 M solution in hexane) was added dropwise to a cooled solution (-78°) of diisopropylamine (352 mmol, 50 ml) in 100 ml dry THF under a N_2 atmosphere. After 15 min. of stirring at 78°, ethyl acetate (320 mmol, 31.5 ml) in 40 ml of dry THF was added dropwise to the reaction mixture. After stirring for 0.5 hr at -78°, 2-methylyclohexanone (320 mmol, 35.8 g) in 40 ml of dry THF was added dropwise. The reaction mixture was stirred for an additional 1 hr at -78° and then as hydrolyzed at -78° by the dropwise addition of a mixture of conc. HCl (35.8 ml) and THF (64 ml). After the addition, the mixture was allowed to warm slowly to room temperature and then 200 ml of ether was added. The organic layer was separated, washed with 5% aqueous HCl (2 x 50 ml) and then water (2 x 50 ml). After drying ($MgSO_4$) for $\sim$ 3 hr, the solvent was removed under reduced pressure to yield 63.2 g, (99%) of the hydroxy-

ester as a pale yellow oil, bp. 80-82°/0.4 mmHg (lit.[8] 119-122°/10 mmHg); ^{1}H-NMR ($CDCl_3$): δ 4.2(q,2H), 3.2(s,1H), 2.62(s,2H), 2.37(s,2H), 1.36(m,9H), 1.2(t,3H), 0.96(d,3H); ^{13}C-NMR ($CDCl_3$): δ 14.15, 15.32, 21.6, 25.58, 30.29, 37.01, 39.72, 44.3, 60.47, 71.55, 177.31; (C=O) IR (neat): 3350-3600, 1710 and 988 cm^{-1} (988 cm^{-1} suggests the presence other axial hydroxyl group).

Ethyl 2-(1-Hydroxycyclohexyl)acetate (Ib). - In a parallel reaction, Ib was synthesized by replacing 2-methylcyclohexanone with cyclohexanone. The reaction produced Ib in 98% as a pale yellow oil, ^{1}H-NMR ($CDCl_3$): δ 4.2(q,2H), 3.54(s,1H), 2.5(s,2H), 1.3(t,3H), 1.4-1.8(m,10H); ^{13}C-NMR ($CDCl_3$): δ 13.77, 21.6, 25.28, 37.07, 45.19, 59.98, 69.46, 172.26 (C=O); IR (neat): strong bands at 3600-3400, 3000-2850, and 1740 cm^{-1}.

1-(2-Hydroxyethyl)-2-methylcyclohexanol (IIa). - The crude hydroxy ester Ia (109.5 mmol, 21.9 g) was dissolved in 100 ml of dry ethyl ether and then added dropwise (over a period of 50 min.) to a cold suspension of $LiAlH_4$ (221.1 mmol, 8.4 g) in 500 ml of dry ether. The reaction mixture was refluxed for 45 min and then stirred at room temperature for an additional 1.5 hr. The mixture was cooled to 0°, and then H_2O (12 ml) was added very slowly. Aqueous NaOH (12 ml, 15%) and H_2O (24 ml) were then added and the reaction mixture was filtered. The precipitate was washed with ether (150 ml) and then ethylacetate (100 ml). The combined organic layer was washed once with a saturated aqueous sodium chloride solution (150 ml) and dried over $MgSO_4$. Removal of the solvent under reduced pressure yielded 16.8 g, (98%) of a colorless oil. The oil crystallized upon cooling and was recrystallized from petroleum ether to yield white crystals, mp. 69-70°, (lit.[8] 67-68°); ^{1}H-NMR ($CDCl_3$): δ 3.84(m,2H), 2.8(s,1H), 1.4-1.98(m,12H), 0.91-0.981(d,3H); ^{13}C-NMR ($CDCl_3$): δ 14.94, 21.76, 25.17, 30.32, 35.55, 39.72, 40.59, 58.93, 73.61; IR (KBr)

3600-3200 cm^{-1} (broad).

1-(2-Hydroxyethyl)cyclohexanol (IIb) - In a parallel reaction IIb was synthesized by the above procedure in 97% yield as a colorless oil, bp 136°/4.0 mmHg, ^{1}H-NMR ($CDCl_3$): δ 4.1(s,2H), 3.83(t,2H), 1.71(t,2H), 1.51(m,10H); ^{13}C-NMR ($CDCl_3$): δ 22.03, 25.72, 37.53, 41.43, 58.87, 72.44; IR (neat): centered at 3400 (strong, broad), 2950, 2850 cm^{-1}.

The Benzenesulfonate Ester of Diol IIa (IIIa) - A solution of crude diol (96.3 mmol, 15.0 g) and 120 ml of dry pyridine was cooled to 0° under stream of nitrogen. Benzenesulfonyl chloride (144.6 mmol, 14.4 ml) was added dropwise to the rapidly stirred solution. The reaction mixture was stirred at 0° for 2.5 hr and then the mixture was poured into 300 ml of cold aqueous Na_2CO_3 (5%). After 10 min. stirring the suspension was extracted with 500 ml of ethyl ether and the organic layer washed sequentially with 5% aqueous HCl (4 x 200 ml), 5% aqueous Na_2CO_3 (2 x 200 ml), and H_2O (200 ml). After drying ($MgSO_4$) and removal of the solvent 25.8 g (90%) of the sulfonate ester was obtained as a pale yellow oil. ^{1}H-NMR ($CDCl_3$): δ 7.48-7.97(m,5H), 4.21(t,2H), 1.2-1.92(m,12H), 0.9(d,3H); ^{13}C-NMR ($CDCl_3$): δ 14.78, 21.46, 25.15, 30.19, 35.98, 38.88, 38.99, 67.73, 127.73, 129.22, 133.74, 135.93; IR (neat) 3300-3700, 1360, and 1190(SO_2) cm^{-1}.

The Benzenesulfonate Ester of Diol IIb (IIIb) - In a parallel reaction IIIb was synthesized by the above procedure in 93.7% yield as a pale yellow oil, ^{1}H-NMR ($CDCl_3$): δ 7.6-7.86(m,5H), 4.26(t,2H), 2.4(s,1H), 1.75(t,2H), 1.43(s,10H); ^{13}C-NMR ($CDCl_3$): δ 21.54, 25.07, 37.1, 39.91, 67.38, 69,76, 127.32, 128.9, 133.4, 135.5; IR (neat) 3300-3600 (broad), 3080, 2900, 136 and 1190 (SO_2) cm^{-1}.

1-(2-Bromoethyl)-2-methylcyclohexanol (IVa). - A mixture of crude benzenesulfonate ester IIIa (73 mmol, 21.7 g), acetone (500 ml), solid

KBr (290 mmol, 34.8 g), and 18-crown-6[9] (80 mmol, 21.2 g) was stirred overnight at 50° during which time a flocculant white precipitate was formed. After removal of the acetone, water (100 ml) and ethyl ether 200 ml) were added. The organic layer was washed with H_2O (2 x 50 ml) and dried ($MgSO_4$). Removal of the solvent yielded 13.8 g (92%) of the hydroxy bromide as a pale yellow oil, bp 92°/0.7 mmHg, ^{1}H-NMR ($CDCl_3$): δ 3.4(t,2H)2.15(t,2H), 1.96(s,1H), 1.2-1.6(m,9H), 0.9(d,3H); ^{13}C-NMR ($CDCl_3$): δ 14.94 ,21.6, 25.39, 28.48, 30.37, 35.71, 39.02, 44.24, 73.4; IR (neat): 3400-36 0(broad), 1150-1300 cm^{-1} (due to CH_2 wagging band for CH_2Br group) and 690 cm^{-1} (C-Br).

1-(2-Bromoethyl)cyclohexanol (IVb). - In a parallel experiment IVb was synthesized from IIIb in 92% yield as a pale yellow oil, (lit.[10] bp 65°/0.1 mm Hg), ^{1}H-NMR ($CDCl_3$): δ 3.6(t,2H), 2.65(s,1H), 2.08(t,2H), 1.5(M,10H); ^{13}C-NMR ($CDCl_3$): δ 21.92, 25.44, 28.07, 37.17, 45.25, 71.79; IR (neat) 3200-3600 (broad), 1150-1300and 690 cm^{-1}.

1-(2-Bromoethyl)-2-methylcyclohexene (Va). - A suspension of the crude hydroxybromide, IVa, (20.3 mmol, 4.5 g) and 27.5 ml of 85% H_3PO_4 was stirred at room temperature for 3.5 hr. The resultant dark yellow suspension was poured into 250 ml of cold water. Petroleum ether (30-60°, 250 ml) was added and then the pentane layer was washed sequentially with 5% aqueous Na_2CO_3 (2 x 200 ml) and water (2 x 100 ml). After drying ($MgSO_4$), filtration, and removal of the solvent under reduced pressure, 3.95 g, (96%) of the unsaturated bromide was obtained as a pale yellow oil, (lit.[11] bp 89-90°/8 mm Hg), ^{1}H-NMR ($CDCl_3$): δ 3.36(t,2H), 2.58(t,2H), 1.9(s,4H), 1.63(m,7H)^{13}C-NMR ($CDCl_3$): δ 19.2, 23.14, 23.31, 29.48, 31.19, 31.87, 77.13, 127.13, 129.81; off-resonance ^{13}C-NMR ($CDCl_3$): δ 127.13 and 129.81 (due to two quarternary carbons); IR (neat); 1308 and 1200 cm^{-1} (due to C-Br).

1-(2-Bromoethyl)cyclohexene (Vb). - In a parallel experiment, Vb was obtained in 92% yield as a pale yellow oil: bp 55°/0.5 mmHg, (lit.[12] bp 90°/mm Hg), ^{1}H-NMR ($CDCl_3$): δ 5.49(s,1H); 3.41(t,2H), 2.47(t,2H), 1.96(m,4H), 1.62(m,4H); ^{13}C-NMR ($CDCl_3$): 22.28, 22.82, 25.23,27.94, 31.43, 41.43, 124.02, 134.77;IR (neat); 3040 (s)cm^{-1} (unsaturated C-H stretching) 1308 and 1204 cm^{-1} (C-Br).

2-Methyl-1-vinylcyclohexene (VIa). - To a mixture of freshly distilled diisopropylamine (10.9 mmol, 1.53 ml) and dry THF (5 ml) (cooled to -78° under a nitrogen atmosphere) was added n-butyllithium (11 mmol, 5.9 ml of a 1.6 M solution in hexane.) The mixture was maintained at -78° and the unsaturated bromide Va (9.9 mmol, 2.0 g) in 5.0 ml of dry THF was added dropwise. The resultant pale yellow solution was stirred at -78° for 45 min. and then slowly warmed to room temperature. After 30 min of stirring at room temperature, 20 ml of H_2O and 20 ml of pentane were added. The organic layer was washed with H_2O (2 x 25 ml) and dried over KOH pellets (1 hr). Removal of the solvent under reduced pressure yielded a pale yellow liquid. The crude product was purified by chromatography on a short florisil column with pentane. The diene was collected in the first two fractions. Removal of the solvents under reduced pressure yielded 1.03 g, (87%) of pure diene, bp. 72-75°/18 mm Hg (lit.[4,7] 156-157°), ^{1}H-NMR ($CDCl_3$): δ 6.65-7.0(two d,1H); 4.98(m,2H), 2.0(m,4H), 1.76-1.61(m,7H); ^{13}C-NMR ($CDCl_3$): δ 19.24, 22.9, 23.01, 24.82, 33.0, 110.01 (C=C cyclic), 135.18 (C=C exocyclic). Off-resonance ^{13}C-NMR ($CDCl_3$): a singlet peak at 110 ppm and a triplet superimposed by a doublet peak at 135.18 ppm; IR (neat): 3086, 3020, (=C-H), 2930, 2860 (saturated C-H), 1640, 1450, 1241, 986, 892 cm^{-1}.

1-Vinylcyclohexene (VIb) - In a parallel experiment, VIb was obtained in 85% yield as a colorless mobile liquid. bp. 144-146° (lit.[4,5] 145°), ^{1}H-NMR ($CDCl_3$): δ 6.19-6.5 (two d,1H), 5.75(t,1H), 4.94(m,2H), 2.1(m,4H), 1.6(m,4H); ^{13}C-NMR ($CDCl_3$): δ 22.42, 22.61, 23.8, 25.83, 109.5, 129.74, 136.1 and 140.25; IR (neat): 3083, 3030, 3000, 2927, 2858, 2835, 1640, 1600, 1445, 1435, 987, 890, 843, 804 cm^{-1}.

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