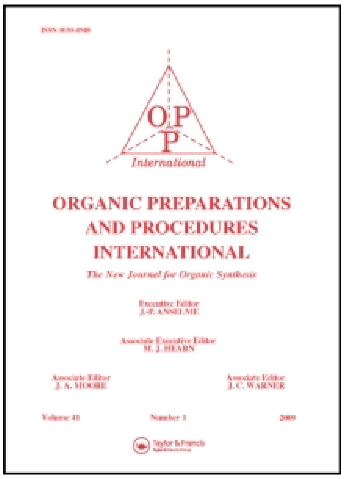

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SYNTHESES AND STEREOCHEMISTRY OF TETRAHYDROFURAN DERIVATIVES FROM α-PINENE

Fu-Chu Liu[a]; Zhen-Qi Mei[a]; You-Chu Wang[a]; Jun Lin[a]
[a] Department of Chemistry, Yunnan University, Kunming, PR China

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SYNTHESES AND STEREOCHEMISTRY OF TETRAHYDROFURAN DERIVATIVES FROM α-PINENE

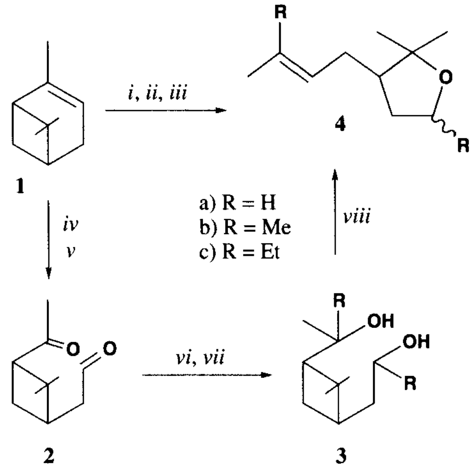
Submitted by (06/28/96)

Fu-chu Liu*, Zhen-qi Mei, You-chu Wang and Jun Lin

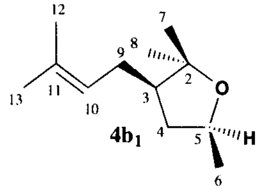
Department of Chemistry
Yunnan University
Kunming 650091, P. R. China

Tetrahydrofuran derivatives have been utilized as intermediates for the synthesis of α-haloesters[1,2] and γ-lactones[3] and terpenoid tetrahydrofuran derivatives have been useful as perfumes. Only a few papers have been reported the synthesis of terpenoid tetrahydrofuran derivatives.[4] In 1985, Kula[5] synthesized 2,2,5-trimethyl-3-(3-methyl-2-butenyl)tetrahydrofuran (**4b**) in several steps *via* diol **3b** derived from α–pinene (**1**) and found it to be endowed with good flowery-woody scent. However, the stereochemistry of **4b** was not investigated.

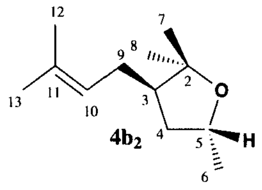
This paper reports a new one-pot method for the synthesis of a terpenoid tetrahydrofuran derivative (**4a**) *via* ozonization of α-pinene (**1**) and sodium borohydride reduction followed by treatment with dilute H_2SO_4 in 56% overall yield. We also synthesized tetrahydrofuran derivatives **4b** and **4c** in three steps, according to Kula's method. Compound **4b** was shown to be a mixture of (**4b**$_1$ and **4b**$_2$) by ^{13}C NMR .



i) O_3, isopropanol
ii) $NaBH_4$
iii) 60% H_2SO_4, heat
iv) O_3, AcOH
v) Zn, AcOH
vi) RMgBr(I)
vii) NH_4Cl, H_2O
viii) 60% H_2SO_4, heat



4b$_1$



4b$_2$

EXPERIMENTAL SECTION

All melting and boiling points were uncorrected. Elemental analysis data were determined on PERKIN-ELMER 2400 CHN Elemental Analyzer. IR spectra were recorded on a Shimadzu 450S infrared spectrophotometer. NMR spectra were measured on a FX-90Q and Finnigan-5410 FT-400Q spectrometers using TMS as an internal standard and $CDCl_3$ as a solvent. Mass spectra were measured on a Finnigan 5410 GC/MC/DS spectrometer. Indexes of refraction were determined on WZS-I Abbe' refractometer. α–Pinene ($[\alpha]_D^{20}$ = +38°) was redistilled before use. Column chromatography silica gel 200-300 mesh (Qing Dao Oceanography Chemical Factory, China).

2,2-Dimethyl-3-(E-2-butenyl)tetrahydrofuran (4a).- A solution of α-pinene **1** (7 g, 51 mmol) in isopropanol (150 mL) was cooled to -2°. A stream of ozonized oxygen containing 5.6 vol.% ozone was bubbled into the solution until an aliquot test portion no longer decolorized a dilute solution of bromine in tetrachloro-methane. Nitrogen was passed through the solution for another 10 min. to drain the excess ozone away. The mixture was added dropwise to a solution of sodium borohydride (2.54 g, 65 mmol) and sodium hydroxide (0.2 g, 5 mmol) in water (100 mL) at 0°, stirred for 6 h at ambient temperature and then concentrated under reduced pressure. A solution of 60% H_2SO_4 (40 mL) was added and the mixture was stirred vigorously at 80-90° for 4 h. After cooling, the mixture was neutralized with sodium carbonate and extracted with ether (3 x 50 mL) and the combined ethereal extracts were washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent by distillation gave crude **4a**, bp. 58.5-61.5°/3 Torr. Further purification by column chromatography (silica gel, light petroleum ether / EtOAc (100:1)) gave 4.4 g (56% based on 1) of **4a**, bp. 59.5°/3 Torr.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.92; H, 11.69. Found: C, 77.76; H, 11.84

$n_D^{20} = 1.4433$. IR(film): 3067, 2987, 1658, 1380, 1375, 1140, 1050, 966 cm^{-1}; ^{1}H NMR($CDCl_3$): δ 0.95, 1.15(2s, 3H, each $C(CH_3)_2$), 1.65(d, 3H, $CH_3CH=$, J = 7 Hz); 1.82-2.21(m, 5H, CH_2CHCH_2), 3.83(t, 2H, OCH_2CH_2, J = 6 Hz), 5.2-5.5(m, 2H, $CH=CH$, J = 16.8, 7, 9 Hz). MS(70 ev, m/z, %): 154 (M$^+$, 10), 152 (34), 135 (43), 125 (16), 106 (64), 55 (21), 43 (100), 41 (22).

***cis*-3-Acetyl-2,2-dimethylcyclobutylacetaldehyde (2)**.- A solution of α-pinene **1** (6.8 g, 50 mmol) in glacial acetic acid (180 mL) and ethyl acetate (20 mL) at -2° and ozonized as above. The mixture was then added dropwise to an ice-cold suspension of zinc powder (6.5 g, 100 mmol) in distilled water (50 mL), and stirred at room temperature for 1.5 h. The solvent was removed under reduced pressure and the residue diluted with distilled water (100 mL), then extracted with benzene (3 x 50 mL). The combined benzene extracts were washed with 10% Na_2CO_3 solution (50 mL) and water, dried over anhydrous sodium sulfate. Removal of the solvent by distillation gave **2** (4.5 g, 54%), bp. 90-95°/1.5 Torr, $n_D^{20} = 1.4610$); semicarbazone, mp. 210°, lit.[6] 209.5°. IR(film): 2720,1760, 1740, 1380, 1375 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88, 1.13(2s, 3H, each $C(CH_3)_2$), 1.2-1.7 (m, 3H, $CHCH_2CH$ and CH_2CHCH_2), 2.06 (s, 3H, CH_3CO), 2.1-2.2 (m, 3H, CH_2CO and $CHCO$), 9.72 (s, 1H, CHO).

3-(1-Hydroxy-1-methylethyl)-α,2,2-trimethylcyclobutylethanol (3b).- A solution of **2** (4.2 g, 25 mmol) in ether (100 mL) was added dropwise under stirring to an ice-cold ethereal solution (100 mL) of CH_3MgI (10.0 g, 60 mmol). The mixture was refluxed on a water-bath for 2 h, then poured into a saturated NH_4Cl solution and extracted with ether (3 x 30 mL). The combined ethereal extracts were washed with destilled water, dried over anhydrous sodium sulfate. Solvent removal gave crude **3b** (4.2 g).

3-(1-Hydroxy-1-methylpropyl)-2,2-dimethyl-α-ethylcyclobutylethanol (3c).- Analogously, **2** (4.0 g, 23.9 mmol) in ether (50 mL) and C_2H_5MgBr (8.0 g, 60 mmol) in ether (80 mL) was converted into crude **3c** (5.8 g). The crude **3b** and **3c** were immediately used in the next step without purification.

(+)-2,2,5-Trimethyl-3(3-methyl-2-butenyl)tetrahydrofuran (4b).- The above crude **3b** (4.2 g, 21 mmol) was added to a 65% H_2SO_4 solution (60 mL) and stirred at 85-90° on a water-bath for 2.5 h. The mixture was then diluted with ice-water (75 mL) and extracted with ether (4 x 25 mL). The combined ethereal extracts were washed with 10% Na_2CO_3 solution (10 mL) and water (2 x 10 mL), dried over anhydrous sodium sulfate. Solvent removal followed by distillation gave 4.1 g (45% based on **2**) of **4b**, bp. 63-65°/5 Torr, $n_D^{20} = 1.4542$, $n_D^{20} = +6.2°$ (c = 0.2, methanol).

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.12; H, 12.09. Found: C, 79.14; H, 12.03

IR(film): 3040, 2930, 2860, 1450, 1380, 1375, 1140, 1050, 820 cm^{-1}. ^{1}H NMR($CDCl_3$): δ 0.95, 1.12 (2s, 3H, each, $C(CH_3)_2$), 1.24 (d, 3H, $CHCH_3$), 1.58, 1.68 (2s, 3H, each, $(CH_3)_2C=$), 1.8-2.3 (m, 5H, CH_2CHCH_2), 4.10 (m, 1H, OCH, J = 7, 9 Hz), 5.08 (br, 1H, $C=CH$, J_1 = 10 Hz, J_2 = 1.5 Hz). MS (70 ev, m/z, %): 183 (M$^+$+1, 16), 182 (M$^+$, 12), 181 (68), 167 (21), 149 (47), 123 (100), 109 (53), 95 (36), 81 (35), 69(41). ^{13}C NMR (see Table 1).

TABLE 1. ^{13}C NMR spectral data of **4b** ($CDCl_3$, δ_c, ppm)

C	2	3	4	5	6	7	8	9	10	11	12	13
4b^1	81.70	48.20	28.90	71.40	21.70	17.70	24.10	39.03	123.41	131.85	25.70	28.30
4b^2	82.30	50.40	29.00	72.90	22.30	17.70	23.20	40.70	123.41	131.85	25.70	28.60

As a result of steric hindrance, the ^{13}C NMR signals of C-6, C-9 as well as asymmetric C-3 and C-5 appear at higher field in **4b**$_1$ than **4b**$_2$.These results are consistent with data given in the literature.[7]

(+)-2,2-Dimethyl-5-ethyl-3-(3-methyl-2-pentenyl)tetrahydrofuran (4c).-Analogously, the above crude **3c** (5.8 g, 25.4 mmol) was converted into 2.6 g(46.5% based on **2**) of **4c,** bp. 82°/3 Torr, $n^{2}{}_{D}{}^{0}$ = 1.4352, n_D^{20} = +7.4°(c = 0.3, methanol).

Anal. Calcd for $C_{14}H_{26}O$: C, 80.00; H, 12.38. Found: C, 80.21; H, 12.16

IR(film): 3080, 1600, 1462, 1380, 1375, 1160, 1040, 810 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.88, 1.02(2s, 3H, each, $C(CH_3)_2$), 1.00 (t, 3H, CH_3CH_2, J = 6Hz), 1.24 (t, 3H, CH_3CH_2=, J = 5 Hz), 1.47 (m, 2H, CH_3CH_2, J = 7 Hz), 1.66 (m, 2H, CH_2C=, J = 4.5, 1.5 Hz), 1.68 (s, 3H, CH_3C=C), 1.76-1.9 (m, 3H, CH_2CH), 2.10 (m, 2H, =$CHCH_2$, J = 9, 14 Hz), 3.7-3.82(br, 1H, OC*H*), 5.52-5.40 (br, 1H, C=C*H*). MS(20 ev, m/z, %): 211(M^++1, 37), 210 (M^+, 20), 195 (15), 193 (36), 137 (55), 125 (91), 123 (55), 83 (100), 81 (76), 55 (93), 43 (70), 41 (69), 29 (36).

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