Notes

Synthesis of (±)-Nuciferal

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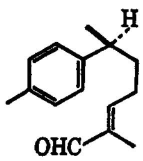
The wood oil Japanese Kaya (*Torreya nucifera* Sieb et Zucc.) contains the sesquiterpene aldehyde nuciferal (1).[1] The structure of nuciferal bears a certain resemblance to those of the two sinensals[2-6] which promise to become important materials for the creation of orange flavors. Consequently it would be of interest to compare the organoleptic properties of nuciferal (1) with those of the sinensals and in the present Note we outline a synthesis of racemic nuciferal (1).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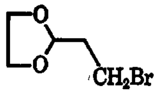
Condensation of acrolein with ethylene glycol in the presence of anhydrous hydrogen bromide gave bromo acetal 2. The tertiary alcohol 3 prepared by Grignard reaction of 2 with 4-methylacetophenone decomposed on attempted distillation and consequently was used in its crude form for further transformations. Hydrogenolysis of 3 was performed over a palladium catalyst and hydrolysis of the resulting acetal 4 to the aldehyde 5[7] was effected with hot aqueous hydrochloric acid. Condensation of the aldehyde 5 with lithio propylidene-*t*-butylimine (6)[6,8,9] yielded an *α,β*-unsaturated aldehyde whose infrared and nuclear magnetic resonance spectra were identical with those of natural nuciferal (1).[10] The chemical shift of the aldehyde proton in the nuclear magnetic resonance spectrum of nuciferal (9.27 ppm, CCl$_4$) is in good agreement with those of other *trans-α,β*-unsaturated aldehydes, *e.g.*, tiglic aldehyde (9.32 ppm, CCl$_4$)[11] and *β*-sinensal (9.33 ppm, CCl$_4$)[6] but not with those of *γ*-substituted angelica aldehydes (10.1 ppm).[5] The *trans* stereochemistry is thus confirmed and in agreement with earlier work;[6,9] the aldol condensation produced the thermodynamically more stable isomer.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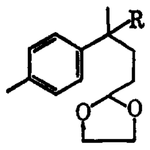
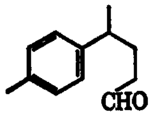

3, R = OH
4, R = H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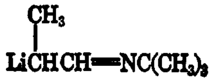
$\overset{CH_3}{\mathrm{LiCH}}CH{=}NC(CH_3)_3$

6

Experimental Section

Microanalyses were performed by Dr. S. M. Nagy and associates of the MIT microchemical laboratory. Boiling points are uncorrected. Vapor phase chromatographic (vpc) analyses were performed on a F & M 720 instrument, using silicon rubber gum SE-30 and Carbowax 20M columns. The following spectrometers and solvents were used: nuclear magnetic resonance (nmr), Varian A-60 (CCl$_4$, TMS as internal standard); infrared (ir), Perkin-Elmer Model 237 (CHCl$_3$); ultraviolet (uv), Cary Model 14 (EtOH). Silicic acid Mallinckrodt 100 mesh was used for column chromatography.

Bromide 2.—To a stirred solution of 240 g (3 mol) of HBr in 400 g (6.5 mol) of ethylene glycol was added, at 5-10°, 112 g (2 mol) of acrolein. After stirring for 1 hr at room temperature the mixture was extracted twice with pentane. The organic layer was washed with 5% NaHCO$_3$, dried over Na$_2$SO$_4$ and evaporated. Distillation of the residue afforded 219 g (61%) of bromide 2: bp 68-70° (8 mm); nmr 2.13 (d of t, 2, J = 4.5 and 7 Hz), 3.43 (t, 2, J = 7 Hz), 3.83 (m, 4), 4.88 ppm (t, 1, J = 4.5 Hz).

Anal. Calcd for C$_5$H$_9$BrO$_2$: C, 33.17; H, 5.01; Br, 44.14. Found: C, 33.23; H, 5.01; Br, 44.18.

Alcohol 3.—The Grignard reagent was prepared by addition of 24.5 g (0.135 mol) of bromide 2 in 100 ml of dry tetrahydrofuran to 3.16 g (0.13 g-atom) of magnesium over a period of 1.5 hr at 30-35°. Stirring was continued for 1 hr at 30°; then a solution of 13.4 g (0.1 mol) of 4-methylacetophenone in 30 ml of dry ether was added dropwise at 30°. The mixture was allowed to stand overnight at room temperature. It was poured into ice-cold aqueous NH$_4$Cl solution, extracted twice with ether, washed with water, dried over Na$_2$SO$_4$ and evaporated. The remaining oil (20.9 g) was hydrogenolyzed without further purification, ir (CHCl$_3$) 3580, 3440 cm^{-1}.

Acetal 4.—Crude alcohol 3 (20.9 g) was dissolved in 120 ml of absolute ethanol and hydrogenated in the presence of 1.5 g of 20% Pd on charcoal. Hydrogen uptake after 10 hr at 20° (750 mm) was 2.78 l. (115%, based on 4-methylacetophenone). The solution was filtered, diluted with pentane and washed with water. The organic layer was dried over Na$_2$SO$_4$ and evaporated. Distillation of the residue afforded 12.1 g (55%, based on 4-methylacetophenone) of acetal 4: bp 103-107° (0.1 mm); ir max (CHCl$_3$) 3000, 2950, 2920, 2870, 1520, 1145, 1125, 1040 and 820 cm^{-1}; nmr (CCl$_4$) 1.18 (d, 3, J = 7 Hz), 2.25 (s, 3), 2.9-1.4 (m, 5), 3.7 (m, 4), 4.65 (t, 1, J = 4 Hz) and 6.94 ppm (s, 4).

Anal. Calcd for C$_{14}$H$_{20}$O$_2$: C, 76.32; H, 9.15. Found: C, 76.55; H, 9.15.

Aldehyde 5.—A vigorously stirred mixture of 80 g (0.36 mol) of acetal 4 and 1 l. of aqueous 0.5 N HCl was refluxed for 45 min. It was then cooled and extracted twice with pentane. The organic layers were subsequently washed with water, 5% NaHCO$_3$, water, dried over Na$_2$SO$_4$ and evaporated. The remaining oil was distilled to give 55.5 g (87%) of aldehyde 5: bp 72-76° (0.07 mm); ir (CHCl$_3$) 2720, 1720 cm^{-1}; nmr (CCl$_4$) 1.21 (d, 3, J = 7 Hz), 2.26 (s, 3), 2.8 – 1.5 (m, 5), 7.0 (s, 4) and 9.47 ppm (t, 1, J = 1.5 Hz).

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(1) T. Sakai, K. Nishimura, and Y. Hirose, *Bull. Chem. Soc. Jap.*, **38**, 381 (1965).

(2) K. L. Stevens, R. E. Lundin, and R. Teranishi, *J. Org. Chem.*, **30**, 1690 (1965).

(3) R. A. Flath, R. E. Lundin, and R. Teranishi, *Tetrahedron Lett.*, 295 (1966).

(4) A. F. Thomas, *Chem. Commun.*, 947 (1967).

(5) E. Bertele and P. Schudel, *Helv. Chim. Acta*, **50**, 2445 (1967).

(6) G. Büchi and H. Wüest, *ibid.*, **50**, 2440 (1967).

(7) An alternate synthesis was described by V. K. Honwad and A. S. Rao, *Current Sci.* (India), **34** (18), 534 (1965).

(8) G. Wittig and H.-D., Frommeld, *Chem. Ber.*, **97**, 3548 (1964).

(9) G. Wittig and H. Reiff, *Angew. Chem.*, **80**, 8 (1968).

(10) We are indebted to Dr. T. Saki, Institute of Food Chemistry Kita-Ku, Osaka, for this comparison.

(11) R. E. Klinck and J. B. Stothers, *Can. J. Chem.*, **44**, 45 (1966).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.85; H, 9.20.

Nuciferal (1).—Dried ether (50 ml) was placed in a 500-ml three-necked flask fitted with a magnetic stirrer, a dropping funnel and a thermometer. The air was swept out of the flask with dry nitrogen and a steady flow was maintained throughout the reaction. Finely cut lithium wire (2.78 g, 0.40 g-atom) was introduced and the stirred suspension was cooled to $-10°$. A solution of 30 g (0.21 mol) of methyl iodide in 150 ml of ether was added in the course of 1 hr at -20 to $-10°$. Stirring was continued for 1 hr at 0°. Diisopropylamine (20. g, 0.20 mol) (distilled over NaH) was added over a period of 20 min at $-5°$ and stirring was continued until methane evolution had ceased ($\sim$20 min). Freshly distilled propylidene-*t*-butylamine[12] (26 g; 0.23 mol) was then added at $-5°$ over a period of 20 min and stirring was continued for 20 min. Finally, a solution of 24.6 g (0.14 mol) of aldehyde **5** in 40 ml of ether was added at -70 to $-75°$ over a period of 1 hr. The mixture was allowed to stand overnight at room temperature. It was then poured into an ice-cold solution of 50 g of oxalic acid in 500 ml of water and stirred vigorously for 30 min. The mixture was extracted with ether twice, and the combined extracts were subsequently washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated. Distillation of the residue afforded 25.3 g (83%) of racemic nuciferal (1), bp 105–115° (0.1 mm). This product contained $\sim$10% aldehyde **5**. An analytical sample was obtained by redistillation through a Vigreux column, followed by chromatography on silicic acid using hexane + 3% AcOEt as eluent. Pure nuciferal had bp 94° (0.05 mm); uv (EtOH) 222 mμ (ϵ 19,000), 231 (18,900), 264 (940), 267 (800) and 273 (710); ir ($CHCl_3$) 2710, 1680, 1640 cm^{-1}; nmr (CCl_4) 1.23 (d, 3, J = 7 Hz), 1.60 (s, broad, 3), 2.29 (s, 3), 2.9–1.4 (m, 5), 6.33 (t, 1, J = 7 Hz), 7.04 (s, 4) an 9.27 ppm (s, 1).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.46; H, 9.43.

Registry No.—**1,** 18744-24-6; **2,** 18742-02-4; **4,** 18742-03-5; **5,** 4895-19-6.

Acknowledgment.—We are indebted to Firmenich et Cie., Geneva, for generous financial support.

[12] R. Tiollais, *Bull. Soc. Chim. Fr.*, **14**, 708 (1947).

Sodium–Liquid Ammonia Reduction of *anti*-1-Phenyl-1-chloro-2,3-*cis*-dimethylcyclopropane[1]

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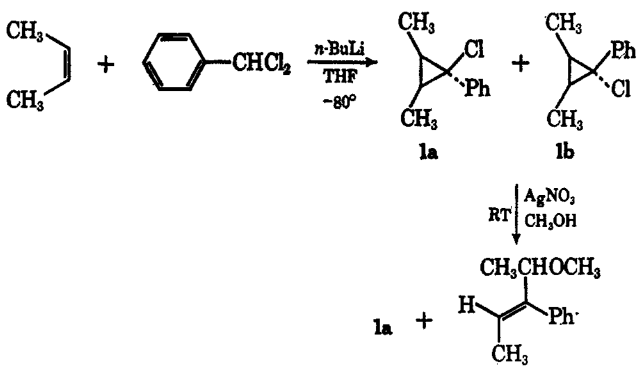
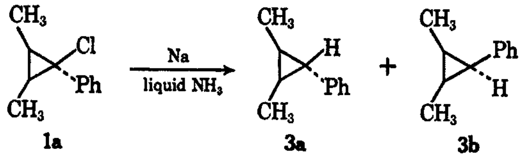
We would like to report the stereoselective reduction of *anti*-1-phenyl-1-chloro-2,3-*cis*-dimethylcyclopropane (**1a**) by sodium–liquid ammonia. A mixture of the two isomeric cyclopropanes **1a** and **1b** was obtained in a 50% yield from the reaction of *cis*-2-butene and benzal chloride with *n*-butyllithium (Scheme I). The two isomers could not be separated by gas chromatography; however, nmr showed **1a** and **1b** to be present in approximately a 3:1 ratio. The stereochemistry of the isomers has previously been assigned by Closs and coworkers on the basis of nmr considerations (isomer **1a** exhibits a multiplet at 1.2 ppm while **1b** has absorption at 0.8 ppm).[2] Treatment of the product mixture with methanolic silver nitrate (0.3 equiv) at room temperature afforded pure **1a** and the olefin **2a** which were readily separated by elution chromatography. The enhanced reactivity of **1b** under these conditions is in agreement with the rules governing electrocyclic transformations proposed by Woodward and Hoffmann[3] and lends credence to the stereochemical assignments made by Closs.

SCHEME I



The structure of olefin **2a** was assigned on the basis of spectral data and a correct elemental analysis. The nmr of **2a** exhibits absorption at 1.07 (doublet, J = 6.5 cps, three protons), 1.58 (doublet, J = 7.0 cps, three protons), 3.28 (singlet, three protons), 3.79 (quartet, J = 6.5 cps, one proton), 5.69 (quartet, J = 7.0 cps, one proton), and 7.17 ppm (multiplet, five protons). The *cis* relationship of methyl and phenyl in **2a** is assumed from consideration of the two disrotatory modes of ring opening which are available to the cyclopropyl halide **1b**.[3]

Reduction of **1a** with sodium–liquid ammonia under paramagnetic conditions[4] afforded *anti*-1-phenyl-2,3-*cis*-dimethylcyclopropane (**3a**) in 63% yield (eq 1).[5]



(1)

The nmr spectrum of **3a** was in complete agreement with that reported by Closs. Gas chromatographic analysis of the product showed it to contain less than 1% isomer **3b**. Reduction of a 3:1 mixture of **1a** and **1b** afforded **3a** and **3b** in a 13:1 ratio. The reduction thus proceeds to give the thermodynamically more stable cyclopropane isomer as the predominent product.[5] It is difficult to reconcile our results with those of Hodgkins and coworkers,[6] who reported that a mixture of the epimeric 7-phenyl-7-chloronorcaranes underwent potassium–liquid ammonia reduction to afford *syn*-7-phenylnorcarane as the major product. Closs and Coyle[2] have questioned the assignments of the epimeric 7-phenylnorcaranes made by Hodgkins,

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[1] Abstracted from the honors thesis of S. MacLean, Middlebury College, 1968.

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[3] R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 395 (1965).

[4] (a) M. C. R. Symons, *Quart. Rev.* (London), **13**, 99 (1959); (b) C. A. Hutchison and R. A. Pastor, *J. Chem. Phys.*, **21**, 1959 (1953).

[5] G. L. Closs and R. A. Moss, *J. Amer. Chem. Soc.*, **86**, 4042 (1964).

[6] J. E. Hodgkins, J. D. Woodyard, and D. L. Stephenson, *ibid.*, **86**, 4080 (1964).