# The Total Synthesis of (±)-α- and (±)-β-Pinene.
A General Route to Bicyclic Mono- and Sesquiterpenes[1]

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Abstract: A direct total synthesis of racemic α- and β-pinene is described in which a key step is the intramolecular alkylation of a benzalcyclohexanone derivative, **21** to give the requisite bicyclo[3.1.1]heptane ring system **22**. An improved procedure for the one-step removal of the benzylidene blocking function is described and utilized to complete the synthesis. Modification of the functionality of the starting materials will permit the application of this general route to diverse bicyclic systems.

α- and β-pinenes are among the most widely distributed of the monoterpene hydrocarbons and occur in the essential oils of most conifers. They were probably first used in Persia and are currently of industrial importance as solvents and for the commercial preparation of camphor and α-terpinol. Nevertheless, no direct total synthesis of the pinenes has been reported, although the photochemical interconversion of the monoterpene β-myrcene (**1**) into β-pinene (**2**) in 10%
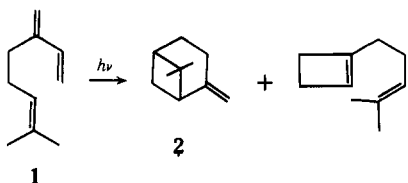

yield (75% purity) constitutes a formal total synthesis,[2] as does the preparation from norpinic acid (**3**).[3]
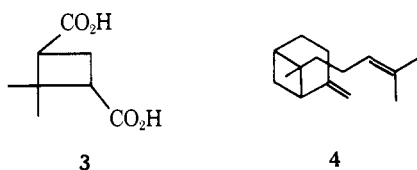
The bicyclo[3.1.1]heptane nucleus is shared in common by the pinene monoterpenes, the bergamotene sesquiterpenes, and highly oxygenated relatives such as paeoniflorin.[4] At the outset of our work, uncertainty existed in the literature concerning the identity of a bicyclic sesquiterpene hydrocarbon from Indian Valerian root oil[5] initially assigned the β-cis-bergamotene (**4**) structure but shown to differ from it by Gibson and Erman.[6] We wished to develop a general route to the bicyclo[3.1.1]heptane system which could be used for terpene synthesis (pinenes in the first instance), to prepare multifunctional derivatives including bridgehead substituted compounds of which few examples are known,[9] and to provide α-cyclobutyl ketones to extend our photochemical studies.[10]

Several possible approaches to the requisite bicyclic nucleus may be envisaged. These include rearrangement of a related bicyclic system,[11] ring contraction of a suitable diazo ketone,[12] cyclization of a substituted cyclobutane[13] or substituted cyclohexane,[14] or photocyclization of a suitable diene or triene.[2] The majority of literature examples are not directly applicable since they give cyclobutanones, and recent direct photochemical approaches to the bergamotenes afforded very low yields.[15] Thus the synthetic pathway selected utilized conjugate addition of the requisite side chain followed by intramolecular alkylation as outlined in Scheme I. This approach should provide entry to the pinenes, the bergamotenes, and by rearrangement, related bicyclo-[2.2.1]heptane terpenes such as α-sesquifenchene, as well as

Scheme 1
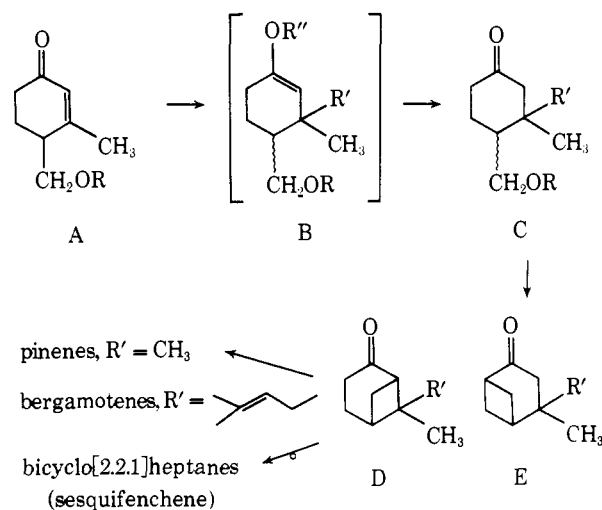
more highly substituted compounds from suitable precursors. It was not possible to ascertain from models which of the two possible isomers (D, E) would predominate in the cyclization step; however, circumvention of this difficulty should be possible by quenching the enolate anion formed during conjugate addition and cyclization of the resulting enol ether B in the desired direction.[16] Alternatively, alkylation could be controlled by using a suitable blocking function.

Results and Discussion

Initial attempts to prepare suitable compounds of type A by Birch reduction of aromatic precursors were disappointing,[17] and 4-carboethoxy-3-methyl-2-cyclohexenone (**5**, Hagemann's ester[18]) was utilized instead. Ketalization with ethylene glycol and p-toluenesulfonic acid caused acid-catalyzed migration of the double bond into conjugation with the ester function to give **6**.[19] Reduction with lithium aluminum hydride afforded the alcohol **7**, and it was intended
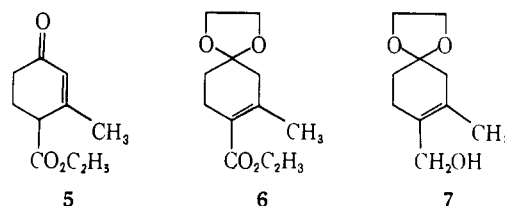

to hydrolyze the ketal under conditions which would also reconjugate the ketone to give **8**. However, in spite of examining several acids, this was not feasible since dehydration occurred readily to give dienone **9** as the major product.

Similar difficulties were encountered by Birch[20] in the hydrolysis of enol ether **10** (R = H). Conjugate addition of


8   9   10
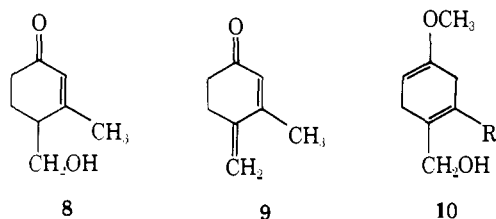
copper complexed methylmagnesium iodide to the ester **6** was unsuccessful, while reaction directly with Hagemann's ester gave a mixture. Thus the thioketal **11** was prepared using boron trifluoride etherate in ethanedithiol at 0° according to the procedure of Marshall and Greene,[21] which minimized double bond migration. The ester was reduced with lithium aluminum hydride and the alcohol **12** so obtained protected as its acetate **13**. Various procedures have been developed in recent years for the regeneration of carbonyl functions from thioketals.[22] Several of these were examined (e.g., NCS, AgNO$_3$, Ce(NH$_4$)$_2$(NO$_3$)$_6$, MeI, Ag$_2$O, Chloramine-T), but the yields were low, and the free ketone was accompanied by the dienone **9** and unidentified polymeric material. However, when the reaction was conducted using mercuric chloride and cadmium carbonate in acetonitrile[23] followed by rapid work-up, the keto acetate **14** was isolated in 74% yield. The infrared spectrum con-


11, R = CO$_2$C$_2$H$_5$ 14   15, R = Ac
12, R = CH$_2$OH   16, R = Ts
13, R = CH$_2$OAc
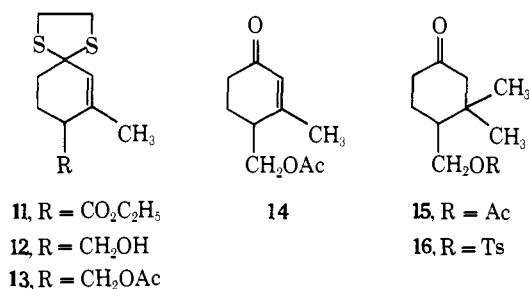
tained carbonyl absorptions at 1740 and 1680 cm^{-1} due to the acetate and enone functions, respectively. The ^{1}H NMR spectrum displayed a multiplet at δ 5.81 ppm assigned to the vinyl hydrogen, while the vinyl methyl and methyl ketone signals were superimposed as a singlet (δ 2.01) representing six hydrogens. This coincidence was removed using a shift reagent [(Eu(fod)$_3$] so that both methyl signals became visible. Conjugate addition of the requisite methyl group with lithium dimethylcuprate afforded the saturated cyclohexanone acetate **15** whose infrared spectrum contained carbonyl absorptions at 1738 and 1718 cm^{-1}, consistent with the assigned structure.

Basic hydrolysis of the acetate and treatment of the resulting alcohol with tosyl chloride in pyridine afforded the keto tosylate **16**. Cyclization of this material was conducted using sodium hydride in dimethoxyethane. The ketonic product isolated was a single peak on GLC, homogeneous to different TLC systems, and possessed an infrared spectrum very similar to that of an authentic sample of nopinone (**17**). However, the ^{1}H NMR spectrum contained three sin-

17   18
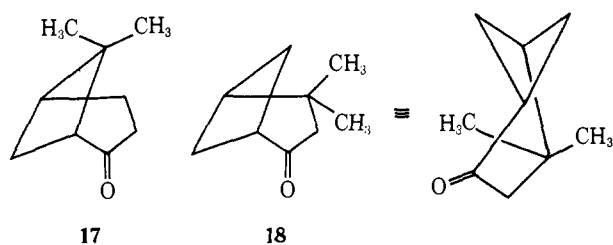
glets at δ 0.83, 1.08, and 1.33 ppm, representing 3, 6, and 3 hydrogens, respectively. The signals at 0.83 and 1.33 are assigned to the syn and anti methyl groups of nopinone on the basis of comparison with an authentic sample prepared by ozonolysis of β-pinene.[24] The remaining singlet arises from the two methyl groups in **18**, groups which are magnetically equivalent as a consequence of their symmetrical environment. Integration of these signals indicated that the cyclization gave a 1:1 mixture of **17** and **18**. These ketones could not be separated, and it was thus necessary to prevent cyclization in the undesired direction.

In order to prevent the unwanted alkylation, it should be possible to utilize the steric bulk of the *gem*-dimethyl function which will hinder attack at C-2 relative to C-6. Considerable attention has been devoted to the development of suitable functions to facilitate selective alkylation.[25] In one approach we examined α-formylation of keto acetate **15** followed by ketalization with 1,3-propanedithiol-*p*-toluenesulfonate to give the dithioketal **19**.[26] However, the yields were disappointing, and the formylation did not proceed with the selectivity required but gave both possible aldehydes. Clearly a larger group is required if the blocking step is to proceed efficiently. Benzaldehyde fits this requirement compared to ethyl formate, and condensation of benzaldehyde in alcoholic potassium hydroxide with **15** caused hydrolysis of the acetate function and afforded the monobenzylidene derivative **20** which was converted to the crystalline tosylate **21** with tosyl chloride in pyridine. The ^{1}H NMR spectrum of this material contained three methyl singlets at δ 0.97, 1.03, and 2.45, the latter due to the "toluene" methyl, in addition to a two-hydrogen singlet at 2.33 assigned to the α-methylene protons and a complex signal at 4.0–4.5 due to the "ester" methylene hydrogens. The complexity of this multiplet is a consequence of the probable presence of both benzylidene isomers and the fact that this side chain is attached to an asymmetric center. The aromatic protons form a multiplet at δ 7.41 which also contains the vinyl hydrogen, while one-half of the AB portion of the ortho protons in the tosyl function are visible, J = 9 Hz, δ 7.77. These features are consistent with structure **21**.

19, R = Ac   20, R = H   22
              21, R = Ts
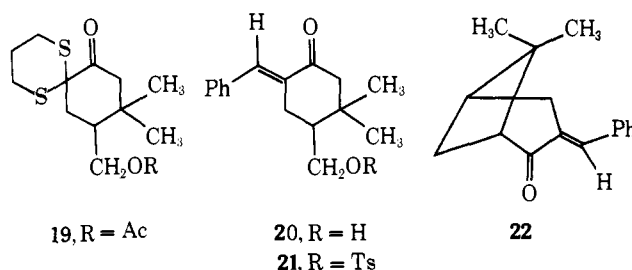
The intramolecular alkylation proceeded smoothly with sodium hydride in refluxing dimethoxyethane (glyme) to give the benzylidene derivative of nopinone **22** in 81% yield. Other bases, such as sodium methylsulfinylmethide and sodium methoxide, were also effective but yields were reduced. The structure of the material so obtained was confirmed by spectral comparison (ir, ^{1}H NMR, MS) with an authentic sample of **22** prepared from nopinone.[27]

House[25] points out that the use of the benzylidene procedure "has the advantage of often producing easily crystallized ketone derivatives, (but) it suffers from the difficulty that the arylidene blocking group is frequently difficult to remove after alkylation". The four-step procedure of Johnson,[28] although it should be applicable to the present case, involves a chlorination step rendering it impractical when an unsaturated side chain is present. It was observed several years ago[29] that the retroaldol reaction of diacetone alcohol may be catalyzed by primary amines. Based on work by

Scheme II
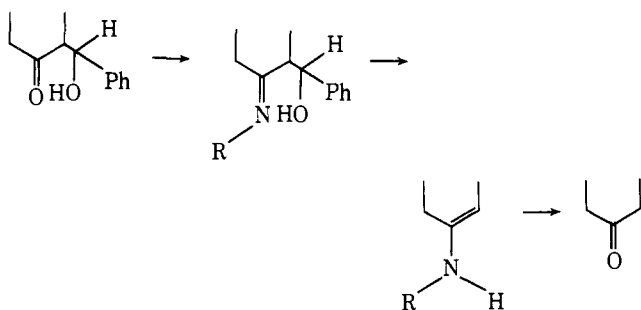
Pallack and Ritterstein,[30] the general mechanism is believed to involve an imine-enamine interconversion as indicated (Scheme II). Thus under conditions where some aldol is formed, it should be possible to catalyze its decomposition. Conditions to accomplish this transformation were developed, and the problem of keeping the amine in the basic solution was overcome using 4-aminobutyric acid. The reaction is, however, not clear-cut and also proceeds in the absence of catalyst although the yield is less, indicating that some product arises via a straightforward retroaldol reaction in dimethyl sulfoxide or hexamethylphosphoramide, the only solvents which suffice. Recently the yields have been improved using a crown ether to solvate the KOH, and the reaction has been applied to other systems.[31]

The synthetic nopinone (17), obtained after removal of the benzylidene function using aqueous KOH in Me$_2$SO containing 4-aminobutyric acid, was converted to (±)-β-pinene (2) in 70% yield using methyl triphenylphosphonium bromide with sodium methylsulfinylmethylide in dimethyl sulfoxide as employed for camphor.[32] Isomerization of the β-pinene so obtained with 5% Pd/C saturated with hydrogen[33] resulted in quantitative conversion to (±)-α-pinene and completed the synthesis.

This also completes the formal total synthesis of several oxygenated pinene derivatives[34] as well as the related bicyclo[2.2.1]heptanes due to previous transformations in these series.[35]

Experimental Section

Melting points were determined in capillary tubes with a Thomas-Hoover "Uni-Melt" apparatus and are uncorrected. Microanalyses were performed by Alfred Bernhardt, West Germany.

Infrared spectra were recorded in carbon tetrachloride solution, unless otherwise indicated, on a Perkin-Elmer 237B grating spectrophotometer and were calibrated with the 2850- and 1601-cm^{-1} bands of polystrene film. Ultraviolet spectra were recorded on a Perkin-Elmer 202 ultraviolet-visible spectrophotometer and were calibrated with the 279.4-nm band of a Holmium filter. Proton magnetic resonance spectra were measured using a Varian Model A-60, Varian Model EM-360, or Varian Model HA-100 spectrometer in carbon tetrachloride solutions, unless otherwise stated, containing tetramethylsilane as an internal standard. Band positions are reported in parts per million downfield from Me$_4$Si (δ scale). Mass spectra were determined on a Hitachi Perkin-Elmer EMU 6E instrument using an ionization energy of 70 eV.

The GLC analyses were conducted on a Varian Aerograph gas chromatograph Model 1720 with helium as carrier gas on an 8 ft × $\frac{1}{4}$ in., 13% SE-30 column supported on Chromosorb W (AW-DMCS) (70-80 mesh) or on a 8 ft × $\frac{1}{4}$ in., 20% Carbowax 20M column supported on Chromosorb W (AW-DMCS) (70-80 mesh).

Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvent with a Büchi rotary evaporator connected to a water aspirator.

Ethyl 3-Methylcyclohex-3-en-1-one-4-carboxylate Ethylene Ketal (6). Hagemann's ester (5) (19.6 g, 0.17 mol, Aldrich) was dissolved in dry benzene (200 ml) containing ethylene glycol (20 ml) and p-toluenesulfonic acid (0.2 g) and the mixture heated under reflux in a Dean-Stark apparatus until 2.2 ml of water had been collected. The reaction mixture was cooled and poured into

water, the benzene layer separated, and the aqueous layer extracted with benzene. The combined extracts were washed with 2% aqueous sodium bicarbonate solution, dried, and filtered; the solvent was removed and the residue distilled, bp 121-122° (0.8 mm), to give the ketal, 34.6 g (90%): ir 1712 (C=O), 1635 (C=C) 1245, 1150, 1065 (C—O) cm^{-1}; ^{1}H NMR δ 1.27 (3 H, t, J = 7 Hz, CH$_3$—CH$_2$), 1.65 (2 H, t, J = 6.5 Hz, CH$_2$—COO), 1.98 (3 H, br s, CH$_3$C=C), 3.88 (4 H, s, OCH$_2$CH$_2$O), 4.13 (2 H, q, J = 7 Hz, CH$_3$CH$_2$O).

3-Methyl-4-hydroxymethylcyclohex-3-en-1-one Ethylene Ketal (7). This alcohol was prepared by lithium aluminum hydride reduction of the ester 6 according to the procedure of Baggiolini, Hamlow, and Schaffner[19] in 95% yield. The crude product was homogeneous to GLC and was used without further purification: ir 3590 (OH), 3440 br (OH), 1150, 1090, 1070, (C—O) cm^{-1}; ^{1}H NMR δ 1.67 (5 H, s + m, CH$_3$C=C, -CH$_2$-), 2.17 (4 H, m, CH$_2$, s), 3.08 (1 H, s, OH), 3.88 (4 H, s, OCH$_2$CH$_2$O), 4.00 (2 H br s, CH$_2$-O).

Hydrolysis of Ketal Alcohol 7. Treatment of 7 under acidic conditions (HCl, oxalic acid, etc.) at room temperature gave a mixture, the major component of which was dienone 9: ir 1685 (C=O); ^{1}H NMR δ 2.07 (3 H, d, $J \sim$ 1 Hz, CH$_3$C=C), 2.2-2.9 (4 H, complex CH$_2$CH$_2$), 5.33 (2 H, s, H$_2$C=C), 5.85 (1 H, br s, HC=CCH$_3$).

Ethyl 3-Methylcyclohex-2-en-1-one-4-carboxylate Ethylene Thioketal (11). Hagemann's ester (5) (9.1 g, 0.05 mol) was added to ethanedithiol (11.6 ml) and boron trifluoride etherate (2.8 ml) in acetic acid (24 ml) and stirred at 0° for 2 h followed by a further 16 h at ~5°. The reaction mixture was poured into ice-water and extracted with ether; the combined extracts were washed with brine and aqueous 10% sodium bicarbonate solution, dried, filtered, and evaporated. The residue was distilled, bp 151-152° (0.4 mm) to give the thioketal 11, 11.5 g (89%): ir 1730 (C=O), 1650 (C=C), 1160 (C-S) cm^{-1}; ^{1}H NMR δ 1.25 (3 H, t, J = 7 Hz, CH$_3$CH$_2$), 1.71 (3 H, br s, CH$_3$C=CO), 1.9-2.3 (4 H, m, CH$_2$CH$_2$), 2.83 (1 H, m, CHCO$_2$C$_2$H$_5$), 3.28 (4 H, s, SCH$_2$CH$_2$S), 4.11 (2 H, q, J = 7 Hz, OCH$_2$CH$_3$), 5.65 (1 H, m, J $\sim$ 1, CH=C).

Anal. (C$_{12}$H$_{18}$O$_2$S$_2$) C, H, S.

3-Methyl-4-hydroxymethylcyclohex-2-en-1-one Ethylene Thioketal (12). The thioketal ester 11 (17 g, 0.06 mol) was added dropwise to a stirred mixture of lithium aluminum hydride (6 g) in anhydrous ether (250 ml) and stirring continued for a further 16 h at room temperature. The excess hydride was destroyed by the addition of moist ether followed by water (5 ml). The ether layer was filtered, the residue thoroughly wasd with ether, the ether portion washed with brine, dried, and filtered, and the alcohol so obtained purified by distillation, bp 165-166° (0.3 mm), 12 g (83%). This viscous material partially crystallized on standing in the cold and was further purified by crystallization from benzene-petroleum ether (80-100°): mp 49-51°; ir 3600 (OH), 3250 (OH) cm^{-1}.

Anal. (C$_{10}$H$_{16}$OS$_2$) C, H, S.

3-Methyl-4-acetoxymethylcyclohex-2-en-1-one Ethylene Thioketal (13). The alcohol 12 (2.6 g, 12 mmol) was dissolved in pyridine (25 ml), and acetic anhydride (5.1 g, 48.5 mmol) was added to the solution which stood at room temperature for 15 h. The reaction was heated on a steam bath for 15 min, cooled, poured into ice-water, and extracted with ether. The ether extracts were washed with brine, 10% aqueous sodium bicarbonate and brine and dried. The residue remaining after removal of the solvent was distilled, bp 164-165° (1 mm), to give the acetate, 2.8 g (89%): ir (CHCl$_3$) 1728 (C=O), 1645 (C=C), 1210 br (C—O) cm^{-1}; ^{1}H NMR δ 1.73 (3 H, d, J = 1 Hz, CH$_3$C=C), 2.07 (3 H, s, CH$_3$C=O), 3.33 (4 H, s, SCH$_2$CH$_2$S), 4.11 (2 H, distorted d of d, $J \sim$ 4.5, 6.5 Hz, CH$_2$O), 5.71 (1 H, br m, CH=C).

Anal. (C$_{12}$H$_{18}$O$_2$S$_2$) C, H, S.

3-Methyl-4-acetoxymethylcyclohex-2-en-1-one (14). Thioketal 13 (9.5 g, 36.8 mmol) was dissolved in aqueous 80% acetonitrile (50 ml) and added to an aqueous 80% acetonitrile solution (250 ml) containing cadmium carbonate (8.5 g) and mercuric chloride (22 g). The reaction was kept at 50° for 7 h, cooled, and filtered through "Celite"; the Celite was washed with hexane-dichloromethane (1:1) and the solvent removed. The residue was immediately dissolved in ether and filtered through a short column of neutral alumina, and the product was distilled, bp 102-103° (0.6 mm), to give the ketoacetate 14, 4.95 g (74%): ir 1740 (C=O),

1680 (C=CC=O), 1225 (C—O) cm⁻¹; ¹H NMR δ 2.01 (6 H, s, CH₃C=C, CH₃C=O), 2-2.7 (5 H, complex), 4.20 (2 H, d, J = 5.5 Hz, CH₂O), 5.81 (1 H, m, CH=C).

3,3-Dimethyl-4-acetoxymethylcyclohexan-1-one (15). Finely divided cuprous iodide (1.9 g, 10 mmol) was suspended in anhydrous ether (35 ml) cooled to 0° in a serum stoppered flask maintained under nitrogen equipped with a condenser and stirring magnet. Methyllithium (2 molar equiv) in hexane (Alfa) was introduced by syringe, causing the initially formed yellow precipitate to dissolve to give a clear solution. The enone **14** (0.91 g, 5 mmol) dissolved in anhydrous ether (40 ml) was added dropwise, stirring was continued for 3 h and the reaction mixture was poured into a saturated aqueous solution of ammonium chloride. The ether layer was separated and the aqueous phase extracted with ether; the combined extracts were washed with brine and dried. The product was purified by column chromatography on silica gel (25:1). Elution with 10% ether-benzene afforded the saturated ketone, 0.7 g (70%) [on a larger scale the product was purified by distillation, bp 105-107° (0.5 mm)]: ir 1738 (C=O) cm⁻¹; ¹H NMR δ 0.87 (3 H, s, CH₃), 1.11 (3 H, s, CH₃), 2.01 (3 H, s, CH₃C=O), 3.87 (1 H, m, CH—O), 4.21 (1 H, m, CH—O).

3,3-Dimethyl-4-hydroxymethylcyclohexan-1-one. The keto acetate **15** (2.0 g, 0.01 mol) was added to 95% ethanol (10 ml) containing aqueous 10% sodium hydroxide (1 ml) and warmed on a steam bath for 30 min, cooled, concentrated, and extracted with ether. These extracts were washed with brine and dried, and the product was distilled, bp 106-107° (0.6 mm), to give the alcohol, 1.4 g (90%): ir 3610 (OH), 3470 (OH), 1720 (C=O) cm⁻¹; ¹H NMR δ 0.83 (1 H, s, CH₃), 1.08 (1 H, s, CH₃), 3.1 (1 H, s, OH), 3.41 (1 H, m, HC—O), 3.80 (1 H, m, HC—O).

3,3-Dimethyl-4-tosylmethylcyclohexan-1-one (16). The keto alcohol (0.31 g, 2 mmol) from hydrolysis of **15** was dissolved in dry pyridine (5 ml), the solution cooled in ice, and p-toluenesulfonyl chloride (0.46 g, 2.4 mmol) in dry pyridine (2 ml) added. The reaction mixture was kept at 0° for 0.5 h, followed by 24 h at room temperature, poured onto ice, and extracted with ether; the extracts were washed with dilute hydrochloric acid and brine and dried. The solvent was removed and the viscous oil remaining crystallized from ether-hexane by cooling to −20° to give the tosylate as fine needles, 0.52 g (84%): ¹H NMR δ 0.78 (3 H, s, CH₃), 1.03 (3 H, s, CH₃), 2.47 (3 H, s, CH₃Ar), 3.88 (1 H, m, HC—O), 4.21 (1 H, m, HC—O), 7.37 (2 H, d, J = 8.5 Hz, ArH α to CH₃), 7.83 (2 H, d, J = 8.5 Hz, ArH α to SO₃).

Cyclization of Tosylate 16: 6,6-Dimethylbicyclo[3.1.1]heptan-2-one (17) (Nopinone) and 4,4-Dimethylbicyclo[3.1.1]heptan-2-one (18). Sodium hydride (0.110 g, 50% emulsion) was washed with dry hexane and added to dry dimethoxyethane (10 ml) in which the tosylate **16** (0.62 g, 2 mmol) was previously dissolved. The solution was refluxed for 5 h, cooled, poured onto ice, and extracted with chloroform; the extracts were washed with water and dried. The yellow oil (0.203 g) obtained after removal of solvent was purified by TLC on silica gel (20% ether-petroleum ether) to give a 1:1 mixture of **17** and **18**, 0.138 g (50%). The ratio was determined by integration of the methyl signals in the ¹H NMR spectrum: ir 1712 (C=O) cm⁻¹; ¹H NMR 0.83 (3 H, s, CH₃), 1.08 (6 H, s, (CH₃)₂), 1.33 (3 H, s, CH₃).

Preparation of Benzylidene Keto Tosylate 21 via Alcohol 20. The cyclohexanone **15** (0.2 g, 1 mmol) was added to ethanol (3 ml) containing benzaldehyde (0.232 g, 2.2 mmol) and aqueous 10% sodium hydroxide (0.5 ml). The solution was allowed to stand at room temperature overnight, diluted with water, extracted with ether, and dried. The alcohol **20**, 0.24 g (100%), obtained after removal of solvent, was partially characterized [ir 3560 (OH), 3400 br (OH), 1675 (C=O) cm⁻¹; ¹H NMR δ 1.00 (3 H, s, CH₃), 1.11 (3 H, s, CH₃), 1.61 (2 H, br s, CH₂), 2.37 (2 H, s, CH₂ α to C=O), 3.5-4.0 (2 H, m, CH₂—O), 7.43 (6 H, m ArH, HC=C)] and dissolved in dry pyridine (5 ml) containing excess p-toluenesulfonyl chloride. After 2 h at 0° and 23 h at room tmeperature, the reaction was diluted with water and extracted with ether; the extracts were washed with dilute hydrochloric acid and water and dried. Removal of the solvent afforded a viscous oil which was crystallized from 95% ethanol to give the tosylate **21**, 0.35 g (88%), mp 130-131°; ¹H NMR δ 0.97 (3 H, s, CH₃), 1.03 (3 H, s, CH₃), 2.33 (2 H, s, CH₂ α to C=O), 2.45 (3 H, s, CH₃Ar), 4.0-4.5 (2 H, m, CH₂—O), 7.41 (8 H, m, ArH, PhCH=C), 7.77 (2 H, d, J = 9 Hz, ArH α to SO₃).

Anal. (C₂₃H₂₆O₄S) C, H, S.

Cyclization of Benzylidene Tosylate 21: Nopinone Benzylidene Derivative (22). Sodium hydride (0.288 g, 12 mmol, 100% Kock-Light) was added to dry dimethoxyethane (100 ml) containing the keto tosylate **21** (3.98 g, 10 mmol) and the mixture refluxed under nitrogen for 20 h. The solvent was concentrated and the mixture poured onto ice and extracted with ether; the extracts were washed with water and dried. The residue remaining after removal of solvent was chromatographed on silica gel (20:1). Elution with 5% ether-petroleum ether afforded a viscous oil which crystallized from hexane, mp 79-80°, 1.83 g (81%): ir (CHCl₃) 1680 (C=O), 1600 (C=C) cm⁻¹; ¹H NMR δ 0.91 (3 H, s, CH₃), 1.37 (3 H, s, CH₃), 7.1-7.7 (6 H, m, PhCH=C).

These spectral data were identical with those from an authentic sample of nopinone benzylidene derivative, mp 105-106°, prepared from nopinone according to the procedure of Wallach.²⁷

6,6-Dimethylbicyclo[3.1.1]heptan-2-one (17) (Nopinone). The benzylidene derivative of nopinone (0.226 g, 1 mmol) was dissolved in dimethyl sulfoxide (14 ml). The solution was flushed with nitrogen, and water (1 ml) containing KOH (0.39 g, 7 mmol) and 4-aminobutyric acid (0.025 g) was added. The reaction was kept at 150 ± 5° for 2 h under a nitrogen atmosphere, cooled to room temperature, diluted with water (50 ml), and extracted with ether-petroleum ether (1:1). The combined extracts were washed thoroughly with water, dried, and purified by TLC (5% ether-hexane) to give nopinone, 0.054 g (40%): ir 1715 (C=O) cm⁻¹; ¹H NMR δ 0.85 (3 H, s, CH₃), 1.35 (3 H, s, CH₃).

These spectral features were identical with those of an authentic sample prepared by ozonolysis of β-pinene according to the procedure of Meinwald and Gassman,²⁴ and the mass spectral fragmentation patterns of the semicarbazones were indistinguishable: M* 195, m/e 179, 153, 151, 134 (base peak), 118, 108, and 82.

The yield increased to 50-55% when the above reaction was conducted in the presence of 4-aminobutyric acid (0.025 g), dibenzo-18-crown-6 (0.025 g), and 3-4 equiv of KOH at 110° for 90 min. These reactions utilized authentic benzalnopinone, not the totally synthetic material.

(±)-β-Pinene (2). Sodium hydride (0.24 g, 5 mmol, 50% dispersion previously washed with hexane) was added to dry dimethyl sulfoxide (14 ml) under nitrogen and stirred at 65-70° until hydrogen evolution ceased (~40 min). The solution was cooled to room temperature, and methyl triphenylphosphonium bromide (1.8 g, 5 mmol) in dimethyl sulfoxide was added. After the ylide had formed, this was followed by nopinone (0.45 g, 3.3 mmol), and the reaction was maintained at 55 ± 5° for 4 h. The dark reaction mixture was poured onto ice, extracted thoroughly with petroleum ether, and dried. The residue after careful concentration was distilled, bp 165-166° (lit.³⁶ bp 166°), on a spinning-band column to give (±)-β-pinene, 0.312 g (70%): ¹H NMR δ 0.71 (3 H, s, CH₃), 1.25 (3 H, s, CH₃), 4.57 (2 H, m, H₂C=C).

(±)-α-Pinene. (±)-β-Pinene was isomerized quantitatively using 10% Pd/C³³ to (±)-α-pinene, bp 153-155° (lit.³⁶ bp 156°); ¹H NMR δ 0.85 (3 H, s, CH₃), 1.28 (3 H, s), 1.65 (3 H, d of d, J ~ 4, 1.5 Hz, CH₃C=C), 5.18 (1 H, m, CH=C).

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Substituent Effects of Alkoxy and Amino Groups Directly Bonded to Cationic Carbon in the Perpendicularly Twisted Geometry. 2-Oxa- and 2-Aza-1-adamantyl Tosylates[1]

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Abstract: In order to provide evidence on the possibility of resonance stabilization of carbocations by α-alkoxy and α-amino substituents which are constrained to the perpendicular geometry (90° twisted from the optimum parallel geometry in which the lone pair p orbital is parallel to the vacant p orbital), we have prepared a series of analogues of adamantyl tosylate in which the methylene group at C-2 has been replaced by an oxygen or an N-methyl group. (Some of the tosylates contain a cyano substituent at C-3.) Relative rates of solvolysis in 80% aqueous ethanol at 25° are: for the 2-oxa-3-cyano, 7.43×10^{-8}; for the 2-methyl-2-aza-3-cyano, 3.56×10^{-2}; for the 3-cyano, 9.97×10^{-5}; for the 2-oxa, 3.68×10^{-3}; and for unsubstituted adamantyl tosylate, 1. These data were considered along with earlier data on solvolysis of adamantyl tosylates in which a methylene group at position 2 was replaced by a cyclopropylidene group, 4.93×10^{-3}, an ethenylidene group, 4.23×10^{-5}, or an isopropylidene group, 2.68. The rate constants are correlated with $\sigma_{eff} = \sigma_I + \delta\sigma_R^+$ with the fractional contribution of resonance, δ, being varied to maximize the correlation coefficient. In the geometry of the adamantyl system, the resonance stabilization of a 1 cation by a 2 substituent is 0.18-0.29 of the maximum resonance stabilization for an unconstrained substituent. The implications of this finding are discussed in terms of hyperconjugative resonance interactions in the perpendicularly twisted geometry. In the perpendicular geometry, carbocation stabilization by electron-donating resonance from filled skeletal orbitals with heteroatom p_x and p_z character is concluded to be 0.18-0.29 as large as that resulting from electron donation from the p_y lone pair in the parallel geometry.

A substituent directly bonded to a carbon which is developing positive charge in an ionization reaction can influence the rate of the reaction by donating or withdrawing electrons from the reaction center by (a) a resonance effect or (b) a polar effect, with the latter often discussed in terms of a composite of field (through-space) effects and inductive (through-bond) effects. Much effort has recently been devoted to the differentiation[2] and quantitative understanding of field effects[3] and inductive effects.[4]

The angular dependence of resonance interactions, particularly the steric inhibition of resonance, has been the object of long-term interest[5] to organic chemists. The availability of NMR methods to measure energy barriers to internal rotations has provided a major impetus to studies of

such angular dependence. The carbon-oxygen double bond character in α-alkoxycarbinyl cations[6,7,8] is reflected in a barrier to rotation (ΔG^*) of 18.4 kcal/mol at 82° for cation 1,[8,9] for example.

1 ("parallel")
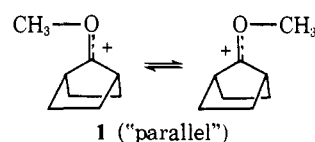
This barrier to rotation represents the difference in energy between the conformations which maximize double bond character, such as the two pictured structures for **1** in which the vacant p orbital on carbon and the lone-pair p orbital on