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THE TOTAL SYNTHESIS OF (±)α- AND (±)β-PINENE: A GENERAL ROUTE TO BICYCLO[3.1.1]HEPTANES

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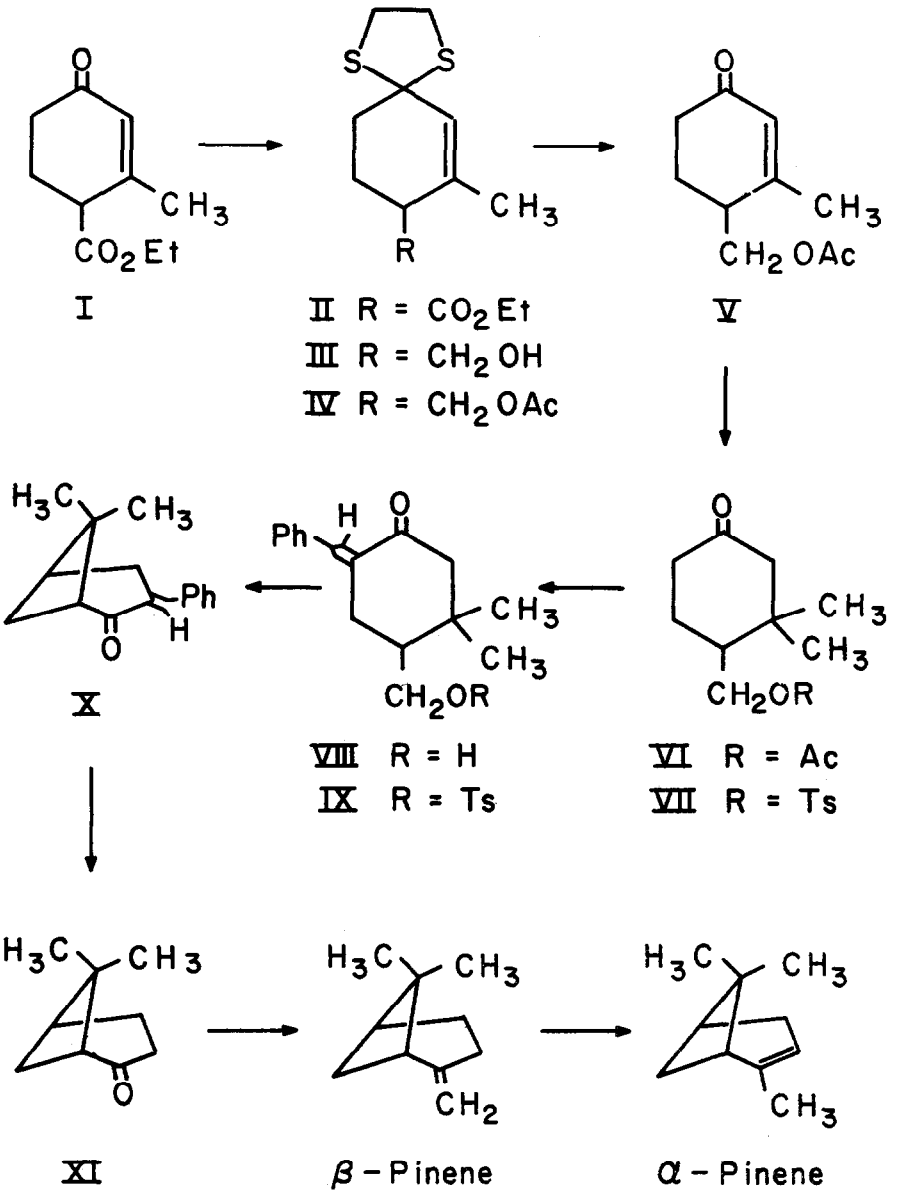
α- and β-Pinene are among the most widely distributed of the monoterpene hydrocarbons and occur in the essential oils of most conifers. In addition they are of industrial importance as solvents and for the commercial preparation of camphor and α-terpineol. Thus it is surprising that no direct total synthesis appears to have been reported although their formal synthesis is established by virtue of degradative and synthetic correlations of long standing.[1] Routes to the pinane skeleton are limited and we report herein a direct preparation of the pinenes by a general scheme involving an intramolecular alkylation which may be adapted to give diverse bicyclo[3.1.1]heptanes including bridgehead substituted compounds of which few examples are known.[3]

Hagemann's ester[4] (4-carbethoxy-3-methyl-2-cyclohexenone, I) was protected as its thioketal derivative using conditions, ethane dithiol containing boron trifluoride etherate at 0° for 18 hours, whereby migration of the double bond into conjugation with the ester function is minimized[5] and subsequent experimental difficulties avoided. The ester II was reduced with $LiAlH_4$ to give III as a viscous oil which crystallized on standing, m.p. 49-51°. The primary alcohol so obtained was protected as its acetate IV, b.p. 164-165°/1 mm., $\nu_{max}^{CHCl_3}$ 1728, 1645, 1210 br.; δ^{CCl_4} 1.73 (3H, d, J = 1 Hz), 2.07 (3H, s), 3.33 (4H, s), 4.11 (2H, m), 5.71 (1H, br. m) and the ketal function removed ($CdCO_3$, $HgCl_2$, CH_3CN)[6] to give cyclohexenone V in 52% overall yield from I.

Conjugate addition to the cyclohexenone with dimethylcopperlithium afforded the saturated cyclohexenone acetate VI, $\nu_{max}^{CCl_4}$ 1738, 1718 cm^{-1}; δ^{CCl_4} 0.87 (3H, s) 1.11 (3H, s), 2.01 (3H, s), 4.17 (2H, complex m). Hydrolysis of the acetate


O
CH3
CO2Et
I
S
S
CH3
R
II R = CO2Et
III R = CH2OH
IV R = CH2OAc
O
CH3
CH2OAc
V
H3C
CH3
Ph
H
O
X
Ph
H
O
CH3
CH3
CH2OR
VIII R = H
IX R = Ts
O
CH3
CH3
CH2OR
VI R = Ac
VII R = Ts
H3C
CH3
O
XI
H3C
CH3
CH2
β - Pinene
H3C
CH3
CH3
α - Pinene

function with base and treatment of the resulting alcohol with tosyl chloride in pyridine gave VII. Cyclization of this material (NaH, DME) afforded both possible bicyclo[3.1.1]heptan-2-one isomers, nopinone(XI) and 4,4-dimethylbicyclo-[3.1.1]heptan-2-one, as a 1/1 mixture which could not be readily separated. It was therefore necessary to prevent cyclization in the undesired direction[7] and it should be possible to take advantage of the steric bulk of the gem-dimethyl function which should hinder attack of a blocking group at C_2 relative to C_6. This was accomplished by preparing the monobenzylidene derivative VIII, under reaction conditions (KOH, ethanol, 23°) which caused concomitant cleavage of the acetate function. The protected tosylate IX, m.p. 130-131°, cyclized smoothly upon treatment with sodium hydride in dimethoxyethane at 83° for 20 hours to give X in 81% yield. The spectra (IR, NMR, MS) of this material were identical with the benzylidene derivative prepared from authentic nopinone (XI)[8]. The benzylidene blocking group was removed using our recently developed procedure[9] by treatment of X in hexamethylphosphoramide-ethylene glycol (5:1) containing potassium hydroxide (7 equiv.) and 4-aminobutyric acid (25 mg, added as a catalyst for the retroaldol step)[10] at 190-195° for 20 minutes to give (±)nopinone. The Wittig reaction ($Na^{\oplus}\overset{\ominus}{C}H_2SOCH_3$, $Ph_3P{=}CH_2$) with nopinone afforded (±)β-pinene whose spectra were indistinguishable from an authentic sample and isomerization to (±)α-pinene using 5% Pd/C saturated with hydrogen[11] completed the synthesis. This also completes the formal total synthesis of several oxygenated pinane derivatives as well as related bicyclo[2.2.1]heptanes due to previous transformations in these series[12].

This work is currently being extended to give the cis and trans-begamotenes and this general approach will serve as the basis for the preparation of various related sesquiterpenes (e.g., sesquifenchene, β-santalene, etc.) by controlled Wagner-Meerwein rearrangement of appropriate synthetic intermedicates.

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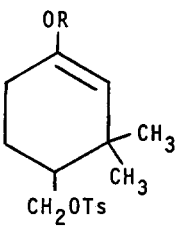

i

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