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CONVERSION OF R-(+)-PULEGONE TO S-(-)-PULEGONE.
A 1,3 KETONE TRANSPOSITION

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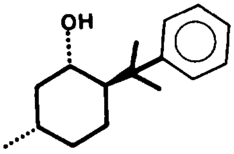
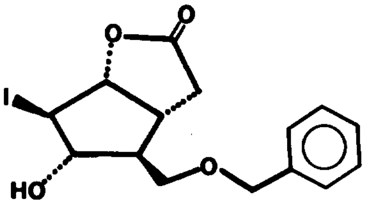
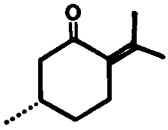
Acrylate esters of the chiral alcohol I show a very high enantioselectivity in Lewis acid catalyzed Diels-Alder reactions. This property has been utilized in a high-yield asymmetric synthesis of the key prostaglandin intermediate II.[1] The alcohol I is conveniently prepared from S-(-)-pulegone (III); however, III is not commercially available.[2] III has previously been prepared by the oxidative cyclization of (-)-citronellol and purification of the (-)-pulegone _via_ fractional recrystallization of the semicarbazone.[3] This paper reports a convenient synthesis of III from its readily available enantiomer, R-(+)-pulegone.



I

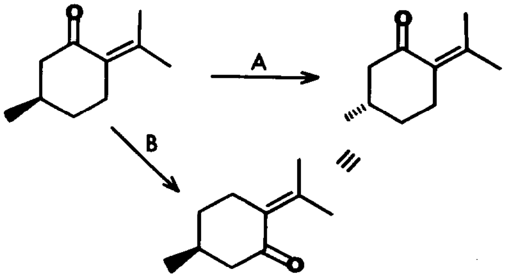


II



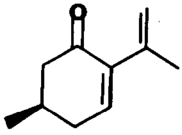
III

Scheme I

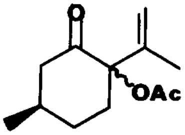


The interconversion of pulegone enantiomers may be perceived in two ways (Scheme I): A) direct conversion _via_ an inversion of stereochemistry at C_5 or B) conversion _via_ a cross conjugative 1,3 ketone transposition. The methods available for path A are very limited; however, path B requires only the introduction of functionality at C_3 and the removal of the carbonyl group at C_1 without the introduction of symmetry in the molecule during the transformation.

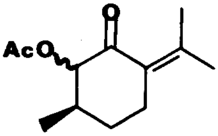
The first method attempted for the introduction of functionality at C_3 was *via* the ketodiene IV. The lead tetraacetate oxidation of pulegone was known to give a mixture of the two α-acetoxyketones V and VI in the ratio 20:1;[4] however, the yield for this reaction was low and the elimination of acetic acid to give IV was complicated by side reactions.



IV



V

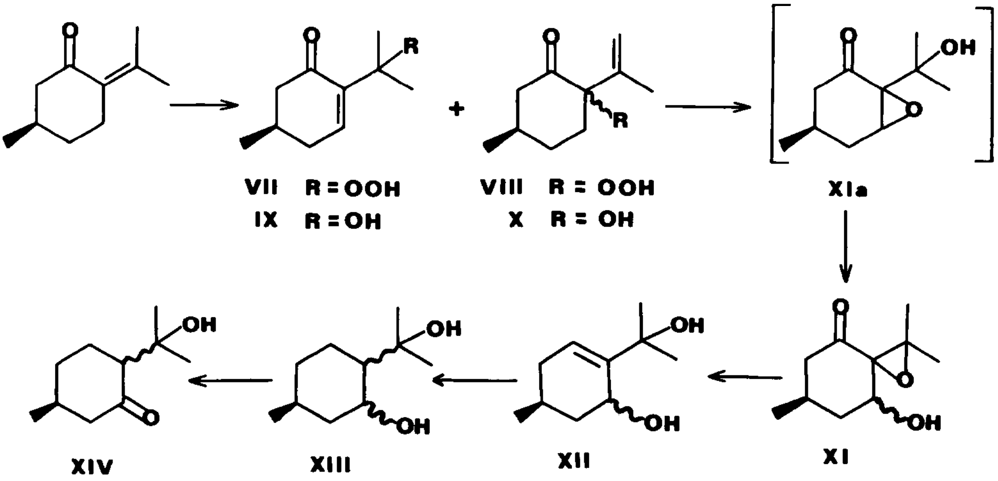


VI

A superior method for the introduction of functionality at C_3 involved the reaction of singlet oxygen with (+)-pulegone.[5] Singlet oxygen is weakly electrophilic and its reaction with α, β-unsaturated ketones has not been extensively studied.[6]

A 2 M solution of (+)-pulegone, $[\alpha]_D^{23}$+ 24° (*c* 2, abs. C_2H_5OH), in methylene chloride, in the presence of 5% (by weight) of Photox,[7] was externally irradiated with a 750 watt DDB-DDW tungsten-halogen lamp at -10° to produce a mixture of the allylic hydroperoxides VII and VIII (Scheme II). The rate of consumption of (+)-pulegone under these conditions was 1 g/hr.

Scheme II



Reduction of this mixture using excess aqueous stannous chloride[8] gave an 87% yield of the alcohols IX and X in the ratio 8:1. Spectral data for IX: $[\alpha]_D^{23}$ - 61.6° (*c* 4, abs. EtOH); uv max (abs. EtOH) 325 (ϵ 43), 234 (ϵ 8600); nmr ($CDCl_3$) δ 7.04 (dd, J_1=2.5Hz, J_2=5.5 Hz, 1 H), 4.33 (s, 1H), 2.62-1.85 (m, 5H), 1.37 (s, 6H), 1.05 (d, J=5.5 Hz, 3H). Although pure IX[9] could be obtained by careful fractional distillation, the presence of a small amount of X was found not to be detrimental and the by-products arising from X were removed conveniently at a later stage. Epoxidation of crude reaction mixture using four equivalents of 30% hydrogen peroxide and 0.4 equivalent of sodium hydroxide in methanol at 0° gave quantitative conversion of IX to the epoxide XI, presumably *via* the base catalyzed rearrangement of the initially formed epoxide XIa.[10] Purification by filtration through silica gel gave XI in 70% yield (from pulegone): $[\alpha]_D^{23}$ + 61.5 (*c* 4, abs. EtOH) nmr ($CDCl_3$) δ 3.72 (s, 1H), 3.21 (m, 1H), 2.75-1.08 (m, 5H), 1.38 (s, 3H), 1.25 (s, 3H), 0.95 (d, J=6.5 Hz, 3H). Treatment of XI with 95% hydrazine (4 equivalents) in methanol at 0° in the presence of a catalytic amount of acetic acid gave the crystalline diol XII in 83% yield:[11] mp 59-60°, nmr ($CDCl_3$) δ 5.83 (dd, J_1=3.0 Hz, J_2=5.5 Hz, 1 H), 4.52 (m, 1H), 3.40 (s, 1H), 2.10-1.05 (m, 5H), 1.41 (s, 3H), 1.36 (s, 3H), 0.96 (d, J=6.5 Hz, 3H). Hydrogenation of XII in a mixture of ethanol and acetic acid (7:1) over PtO_2 at 50 psi gave the known diol XIII as a mixture of isomers in 98% yield.[12]

Oxidation of XIII was best accomplished by addition to a solution of Collins reagent[13] (10 equivalents, generated *in situ*) in methylene chloride at 15° and stirring for 1.5 hr at 25°. The crude β-hydroxyketone (XIV) which was obtained was distilled from a small amount of iodine (bp 123-125° at 30 mm) to give III in 81% yield (from XIII): $[\alpha]_D^{23}$ - 24° (*c* 2, abs. EtOH); nmr ($CDCl_3$) identical to (+)-pulegone.

ACKNOWLEDGEMENT

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NOTES AND REFERENCES

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9. All new compounds reported herein gave satisfactory analytical and spectral analysis.

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