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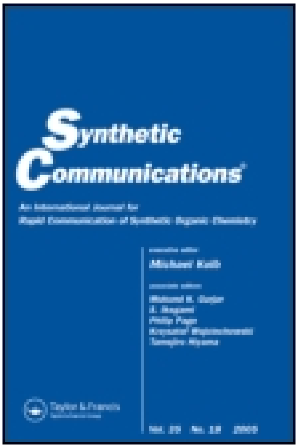

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(1R,5S)-(+)-Nopinone of High Enantiomeric Purity

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(1*R*,5*S*)-(+)-NOPINONE OF HIGH ENANTIOMERIC PURITY

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Abstract: Commercial β-pinene of 87% ee can be upgraded to the 98+% ee level by simple treatment with silver perchlorate. A solid complex is obtained whose formation is more rapid when two like enantiomers are involved. Simple dissolution of this precipitate in water releases the enantioenriched hydrocarbon from which (+)-nopinone of high enantiomeric purity is obtained via ozonolysis.

(1*R*,5*S*)-(+)-Nopinone has often been used as a cheap, chiral starting material for the synthesis of a wide range of optically active compounds and for mechanistic investigations. Unfortunately, commercial (+)-nopinone, $[\alpha]_D^{20}$ +16 (neat), is of insufficient optical purity (84% ee) for useful application in synthesis today. This need has been recognized earlier by Boger,[1] who proceeded to develop a means for optical purification based upon sodium borohydride reduction to (-)-*cis*-nopinol, repetitive crystallization of this alcohol from hexane, and oxidation with pyridinium dichromate. The overall yield was 30%.

Described here is a more direct alternative route to (+)-nopinone that takes advantage of an elegantly simple means for the optical purification of β-pinene.[2] Upon mixing somewhat less than one mole of silver perchlorate (hydrated or

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anhydrous) with two moles of inferior quality β-pinene, a complex forms which is composed of two molecules of olefin to one of the silver salt (Scheme 1). Evidently, the rate of complex formation is more rapid when two like enantiomers are matched than when a racemate is produced. Some post-equilibration leading away from the mismatched combination is also a possibility. In any event, it is necessary only to remove the uncomplexed β-pinene by evaporative distillation in the absence of heat[3] and to treat the salt with water in order to free the higher quality hydrocarbon. The subsequent ozonolysis of this material[4] proceeds uneventfully to deliver nopinone of 98.9% ee, $[\alpha]_D^{21}$ +19.1 (neat),[5] in excellent yield (96%).

The two-step procedure described above constitutes an efficient and operationally simple means for enhancing the enantiomeric purity of β-pinene. Although we have experienced no complications when dealing with the perchlorate salt, the synthesis of this complex must be undertaken with great care, as even modest input of energy could initiate its spontaneous and rapid decomposition.

Experimental Section

Enhancement of the Optical Purity of Commercial (1*S*,5*S*)-β-Pinene. Commercial β-pinene (92.26 g, 0.70 mol), $[\alpha]_D^{21}$ -19.9 (neat) (87% ee) was placed in a 1-L, one-necked, round-bottomed flask and silver perchlorate hydrate (40 g, 0.19 mol) was introduced. Within several minutes, a semi-solid white mass had formed. Admixture of the reagents was somewhat facilitated with a spatula. The reaction mixture was then left to stand at 25 °C for 18 hr. All uncomplexed β-pinene was removed by high vacuum distillation *at room temperature* and collected in a receiver cooled to -78 °C. Recovery levels in excess of 65% were routinely observed.

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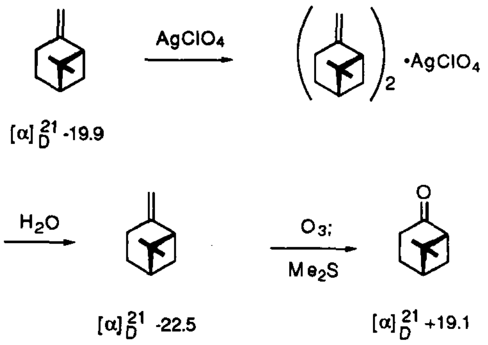

Scheme 1

The residual solid complex was treated with water until dissolution was complete, ether (50 mL) was added, and the mixture was transferred to a separatory funnel where the organic phase was separated, dried, and carefully concentrated *without being heated.* The resulting oil was distilled to give 33.5 g (66%) of optically enriched β-pinene as a colorless liquid, $[\alpha]_D^{21}$ -22.47 (neat) or 98.6% ee. The maximum rotation reported for β-pinene, presumably of ≥ 99% optical purity, is $[\alpha]_D^{26}$ -22.8 (neat).[6]

(1*R*,5*S*)-(+)-Nopinone. A cold (-78 °C), magnetically stirred solution of (-)-β-pinene (33.5 g, 0.242 mol) in 1:1 dichloromethane-methanol (100 mL) was ozonolyzed until a blue color persisted (~ 5 hr), at which point TLC analysis showed no hydrocarbon remaining. The excess ozone was purged from the solution with oxygen for 20 min and the colorless reaction mixture was treated carefully with dimethyl sulfide (100 mL, 1.24 mol) at -78 °C, allowed to warm to rt, and stirred for an additional 36 hr. The volatiles were removed under reduced pressure and the resulting yellow oil was taken up in ether (25 mL) and stirred for

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15 min with 5% aqueous ferrous sulfate solution. The separated organic phase was washed twice with water (100 mL), dried, and concentrated. Distillation of the residue gave 32.0 g (96%) of nopinone as a colorless oil, bp 118-120 °C (22 Torr), having $[\alpha]_D^{21}$ +19.1 (neat) or 98.9% ee.

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2. Comyns, A. E. and Lucas, H. J., *J.* Am. Chem. Soc. **1957**, 79, 4339.
3. (β-pinene)$_2$•AgClO$_4$ *appears to be highly shock sensitive and exhibits extreme exothermic behavior with initiation temperatures below 65 °C.* Consequently, a cautionary note is sounded regarding the safety precautions that must be exercised when working with the potentially hazardous complex.
4. Newman, M. S. "An Advanced Organic Laboratory Course," The Macmillan Company, 1972, Chapter 10.
5. The highest optical rotation reported for (+)-nopinone of $\geq$ 99% ee is $[\alpha]_D^{23}$ +19.11 (neat).[6]
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