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METHODS FOR STEREOSPECIFIC SYNTHESIS OF CIS OR TRANS HYDRINDANONES

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Abstract: Methods are described for the stereospecific conversion of hydrindenone 3 either to the corresponding trans fused or cis fused hydrindanone (1 or 2, respectively.)

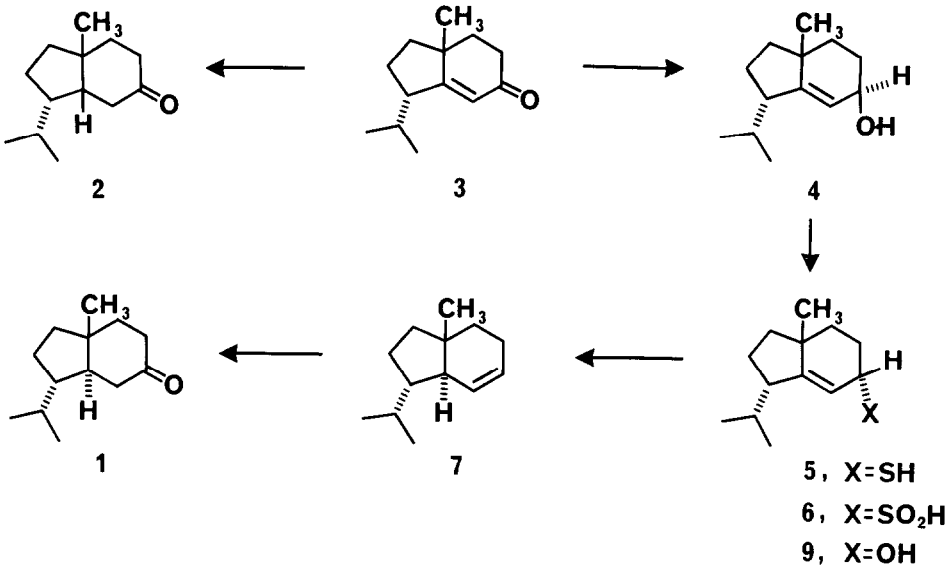
The stereocontrolled generation of either cis or trans fused hydrindanes is a longstanding synthetic problem which continues to receive much attention.[1-3] We now report stereocontrolled syntheses of the trans and cis hydrindanones 1 and 2 (required as part of a larger project) from the hydrindenone 3 which is readily available in 2 steps from 2,6-dimethyl-5-heptenal (melonal) in 76% overall yield.[4]

The conversion of 3 to the trans fused hydrindanone was accomplished by a new method which depends on the internal delivery of hydrogen to the sp^2 carbon at the fusion. Reduction of 3 by $LiAlH_4$ (ether, -20°) affords stereospecifically the allylic alcohol 4 (99%). The β-orientation of the hydroxyl group was shown by its hydrogenation with $[Ir(cod)P\text{-}c\text{-}hx_3(py)]^+PF_6^-$[5] as catalyst (20 mol %, 1 atm. H_2, CH_2Cl_2) to a saturated alcohol which upon oxidation ($Na_2Cr_2O_7$-aq. H_2SO_4, acetone, 0°) produced the cis fused hydrindanone 2.[6] The iridium catalyst is known to direct hydrogen delivery to an allylic alcohol syn to the hydroxyl group.[7] The alcohol 4[8] was converted to the sulfinic acid 6 by the sequence (1) Mitsunobu inversion[9] by thiolacetic acid (1.5 equiv.)-triphenylphosphine (1.3 equiv.) - diethyl azodicarboxylate (1.3 equiv.) at 0° (82%); (2) reduction of thiolacetate to thiol 5 (95%) with $LiAlH_4$ at 23° in ether; and (3) oxidation with 2 equiv. of m-chloroperoxybenzoic acid in CH_2Cl_2 at -90° and filtration of the reaction mixture to remove

m-chlorobenzoic acid.[10] Removal of CH_2Cl_2 from 6 by distillation at atmospheric pressure (40 - 50°) effects concurrent thermal decomposition[11] of 6 to form 7 which can be isolated in >90% purity (80% overall yield from 5) simply by filtration through a plug of silica gel with pentane as eluent. Olefin 7 was converted to the trans fused hydrindanone 1 in 89% overall yield by a three step sequence consisting of: (1) epoxidation with m-chloroperoxybenzoic acid - CH_2Cl_2 at 5°; (2) S_N2 epoxide displacement by $LiAlH_4$ (ether, 23°) to form 3:1 mixture of epimeric alcohols (axial predominating); and (3) oxidation of the 3:1 axial - equatorial alcohol mixture ($Na_2Cr_2O_7$-aq. H_2SO_4, acetone, 0°). The trans fused hydrindanone 1 prepared in this way was free of the cis isomer 2 or other impurities as shown by chromatographic and ^1H nmr (300 MHz) analysis. The stereospecific formation of the trans fused ketone 1 by thermolysis of sulfinic acid 6, expected for a cyclic six-membered transition state,[11] occurs despite strong shielding by isopropyl of the α-face of the fusion sp^2 carbon atom of 6. This finding strongly suggests that the allylic sulfinic acid route to fused ring systems will prove to be a reliable general method for control of geometry of ring fusions. Although this new method entails a number of steps, the present work shows that the individual operations are both simple to perform and efficient.

The enone 3 could be converted easily and stereospecifically into the cis fused ketone 2 by either of two reductive processes which are controlled by the steric screening of the α-oriented isopropyl substitutuent in 3. Catalytic hydrogenation of 3 (Pd-C, 1 atm. H_2, EtOAc) affords cis hydrindanone 2 stereospecifically (>95% yield) as might have been expected on steric considerations. Interestingly, it was observed that the reduction of 3 with 3 equiv. of lithium and 1 equiv. of t-butyl alcohol in liquid ammonia at -78° was also stereospecific and produced the cis fused ketone 2 (76% isolated yield). Metal-ammonia reduction of fused ring enones has been used on many occasions[12] to generate trans ring fusions (purportedly by protonation of thermodynamically more stable radical anion intermediates having trans-like ring fusion). The present observation that 2 is produced stereospecifically by metal-ammonia reduction of enone 3 is especially instructive since it provides a clear indication that the direction of protonation of the reactive intermediate at the fusion atom can be subject to kinetic and steric control.[13]

The trans fused hydrindanone 1 can also be obtained by hydrogenation of the allylic alcohol 9 (prepared from 4 via 9 benzoate by Mitsunobu inversion[14] in 89% yield) with $[Ir(cod)P\text{-}c\text{-}hx_3(py)]^+ PF_6^-$ catalyst[5] (30 mole%, 1 atm. H_2, CH_2Cl_2), followed by chromic acid oxidation. However, the low yield (<20%) and large amount of catalyst required for the hydrogenation step render this process impractical in this form.[15]



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9. R. P. Volante, Tetrahedron Letters, 22, 3119 (1981). Best results were obtained by the addition of the phosphine-azo ester complex to a solution of 4 and thiolacetic acid in dimethoxyethane.

10. For best results, thiol 5 in CH_2Cl_2 was added to a solution of peroxy acid in CH_2Cl_2.

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13. No trans fused ketone 1 could be detected in the lithium-liquid ammonia reduction of 3. It has been reported that the analog of 3 lacking the isopropyl substituent by lithium-ammonia affords a mixture of cis and trans fused products (ratio 9:1); see, D. Caine, Organic Reactions, 23, 33-35 (1976).

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15. This research was assisted financially by the National Institutes of Health and the National Science Foundation.

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